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Analyzing MASLD interventional clinical trial registration based on the ClinicalTrials.gov database

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Abstract

Objective With the rising incidence of MASLD, extensive drug research has been conducted in clinical trials. The study examined the design principles and research objectives of MASLD therapeutics, in order to offer guidance to clinical trial participants and decision makers.

Methods By searching the clinical research trial data registered on clinicaltrials.gov platform, 1209 interventional clinical trials were screened. These trials were subsequently evaluated based on clinical stage, trial design, intervention modalities, outcome metrics, and other pertinent factors.

Results A total of 1,209 trials were included, of which 199 were registered from 2000 to 2012 (16.46%) and 1010 were registered from 2013 to 2024 (83.54%), reflecting the growing body of research on MASLD. Regarding the intervention model type, single-group designs were employed in 232 (19.19%) trials, and parallel designs were employed in 873(72.21%). A total of 13 trials were early phase 1 (1.08%), 152 (12.57%) were phase 1, 34 (2.81%) were phase 1/phase 2, 301 were phase 2 (24.90%), 19 (1.57%) were phase 2/phase 3, 72 (5.96%) were phase 3, and 84 (6.95%) were phase 4. Within these trials, the three primary clinical outcomes for drug interventions were hepatic histological improvement, hepatic fat content and adverse events. Furthermore, 140 drug interventional trials with results for therapeutic purposes (This accounted for 88.61% of the 158 drug interventional trials with results) primarily aimed to improve MASLD through mechanisms such as metabolic and energy balance, inflammatory and immunomodulatory, and lipid reduction, targeting primarily PPAR, FXR, ACC and GLP-1.

Conclusion This study suggests the basic characteristics of global MASLD clinical trial design, and the current global interventional clinical trials are mainly focused on drug-related treatments, and drugs to improve inflammation and metabolism are still the first choice for MASLD drug intervention studies.

Keywords MASLD, ClinicalTrials.gov, Clinical trials, Primary endpoints

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Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as Non-alcoholic fatty liver disease (NAFLD), encompasses isolated hepatic steatosis (ILS) or metabolic dysfunction-related fatty liver disease (MASL), Metabolic dysfunction-related steatohepatitis (MASH) and associated fibrosis and cirrhosis. It is a chronic liver disease closely associated with metabolic dysfunction, insulin resistance (IR), inflammatory response and genetic predisposition. The pathophysiology of MASLD involves excessive liver fat accumulation, hepatocyte dysfunction, inflammation, and fibrosis, with subsequent risk of hepatocellular carcinoma (HCC) [1]. With the deepening of research, the 'multiple-shock theory' is now used to explain its pathogenesis. This theory posits that MASLD pathogenesis is multifaceted, encompassing fat accumulation, insulin resistance, inflammatory response, liver-gut axis dysregulation, intestinal microbiota alterations, dietary, and genetic factors [2, 3]. There is evidence that intestinal dysbiosis and barrier breakdown are associated with systemic inflammation and disease progression. The gut, as a triple barrier composed of mechanical, immune, and microbial components, maintains a constant link with the liver [4]. When intestinal barrier function is impaired, intestinal permeability increases, which significantly promotes the initiation and progression of intrahepatic and extrahepatic injury in MASLD [5]. THR-β (thyroid hormone receptor β) is a nuclear receptor involved in multiple metabolic processes that improve the occurrence and development of MASH by regulating fatty acid beta oxidation, regulating inflammation and immunity, and influencing the composition and function of the gut microbiota [6].

Global statistics indicate a prevalence of 30% for MASLD [7], and the projected prevalence in 2040 is 55.7% [8]. Due to the escalating prevalence of obesity and metabolic syndrome (MetS), MASLD has emerged as the primary chronic liver disease in China and the primary cause of liver biochemical abnormalities during health screenings [9]. MASLD has also become the chronic liver disease with the highest incidence among children worldwide [10].The current prevalence among children is 7–14% [11]. Consequently, the diagnosis and treatment of MASLD have garnered significant attention in metabolic disease research, yet there remains a dearth of targeted therapeutic drugs. The exploration of MASLD-specific therapeutic drugs thus remains a pivotal research focus.

Materials and methods

Research data

Data were derived from global MASLD programs that have successfully registered in the ClinicalTrials.gov database since its inception through August 31, 2024.

Search strategy

A comprehensive computerized search of the ClinicalTrials.gov database was performed in the Disease Status Search field. The search term was 'MASLD', 'NAFLD', 'MAFLD', 'NASH', 'MASH', with no other limits.

Inclusion of data

An Excel sheet was utilized to enter the retrieved data on an entry-by-entry basis in the original language of the database registry entry. Extracted data included information such as registration number, study population, sample size, study type, trial design, use of blinding, clinical staging, and intervening factors. All clinical trials were independently reviewed by three investigators and disagreements were resolved by discussion among the two review authors.

Statistical analysis

Statistical analysis was performed using SAS version 9.4 (SAS, Cary, NC), using frequencies and percentages to describe categorical variables.

Results

General information on clinical trials

Through a search of the Home-CinicalTrials.gov database using the keywords 'MASLD' 'NAFLD' 'MAFLD' 'NASH' and 'MASH', we conducted a deduplication process to eliminate identical clinical trial records arising from varying search parameters. Consequently, we obtained a dataset comprising 1,622 unique records. Subsequently, after excluding observational clinical trials, we narrowed our focus to 1,209 interventional clinical trials (Clinical trial number: not applicable.) for inclusion in this study (Fig. 1).

We analyzed 1209 interventional clinical trials that were initiated between 2000 and 2024 (see Fig. 2). We segmented the 1,209 clinical trials by year of registration. Specifically, a total of 199 clinical trials were registered between 2000 and 2012, with an average annual growth rate (AAGR) of 50%; 1,010 studies were registered between 2013 and 2024, with an AAGR of 12%. The overall number of studies increased sharply, from 1 in 2000 to 77 in 2024, for an AAGR of 29%. Additionally, during the period from 2019 to 2023, more than 90 clinical trials per year were registered. The global distribution of the trials is depicted in Fig. 3, (specific values in supplementary Table 1). This distribution includes multinational trials, while some trials lack information regarding their conduct location. The United States conducted the highest number of trials, with a total of 467. Mainland China has a total of 89 trials. Hong Kong and Taiwan, listed separately as high-income economies, have 43 and 28 trials respectively. It is worth noting that there is an absence of data on MASLD trials in low-income countries.

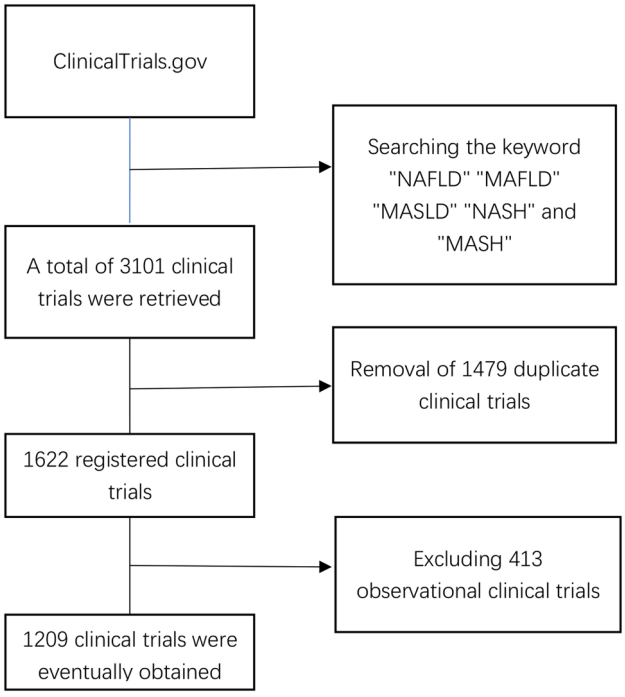

Fig. 1 Filtering process and search results

The basic characteristics of these 1,209 MASLD interventional clinical trials are summarized in Table 1. A total of 199 trials were posted from 2000 to 2012, of which 143 (71.86%) were completed, 23(11.56%) were terminated, and 5(2.51%) were withdrawn. Of the 1010 trials posted between 2013 and 2024, nearly half (479, 47.43%) were completed, 207(20.50%) were recruiting, and 129(12.77%) were unknown. A total of 1011 (83.62%) did not post summary results in the ClinicalTrials.gov results database. In total, 198 (16.38%) trials publicized their findings, of which 54 were initiated before 2013.

A total of 1,139 (94.21%) trials recruited both men and women, whereas 23 trials (1.90%) exclusively recruited female patients, and 47 trials (3.89%) exclusively recruited male patients. Additionally, 62 trials (5.13%) enrolled both children and adults, 39 trials (3.23%) enrolled only children, and 1108 trials (91.65%) enrolled only adults.

Apart from trials of indeterminate stages, the greatest number of clinical trials (301, or 24.90%) were in phase 2, followed by those in phase 1, phase 4, and phase 3, with 152 (12.57%), 84 (6.95%), and 72 (5.96%), respectively. The numbers of studies in various phases also varied over time: The percentage in phase 1 increased from 0.50 to 1.19%, the percentage in phase 2 decreased from 29.65 to 23.96%, the percentage in phase 3 decreased from 9.05 to 5.35%, and the percentage in phase 4 decreased from 9.55 to 6.44%.

Of the evaluated trials, 905 (74.86%) used randomization methods, 97 (8.02%) were nonrandomized, and 207 (17.12%) did not specify whether they were randomized. A total of 873 (72.21%) used parallel controls, and 232 (19.19%) trials were single group. In terms of blinding settings, 517 (42.76%) clinical trials were not blinded. Blinding methods were single-blind (114,9.43%), double-blind (175,14.47%), triple-blind (133,11.00%), and quadruple-blind (266,22.00%). A total of 520 clinical trials (43.01%) enrolled between 1 and 50 patients, 333 (27.54%) enrolled between 51 and 100 patients, 214 (17.70%) enrolled between 101 and 200 patients, 91 (7.53%) enrolled between 201 and 500 patients, 22 (1.82%) enrolled between 501 and 1000 patients, and 26 (2.15%) enrolled more than 1,000 patients. The majority of trials (891, 73.70%) were designed for therapeutic purposes, followed by basic research (102, 8.44%), diagnostic purposes (68, 5.62%), and prevention (52, 4.30%). Of the 1,209 intervention trials, 654 (54.09%) involved drug

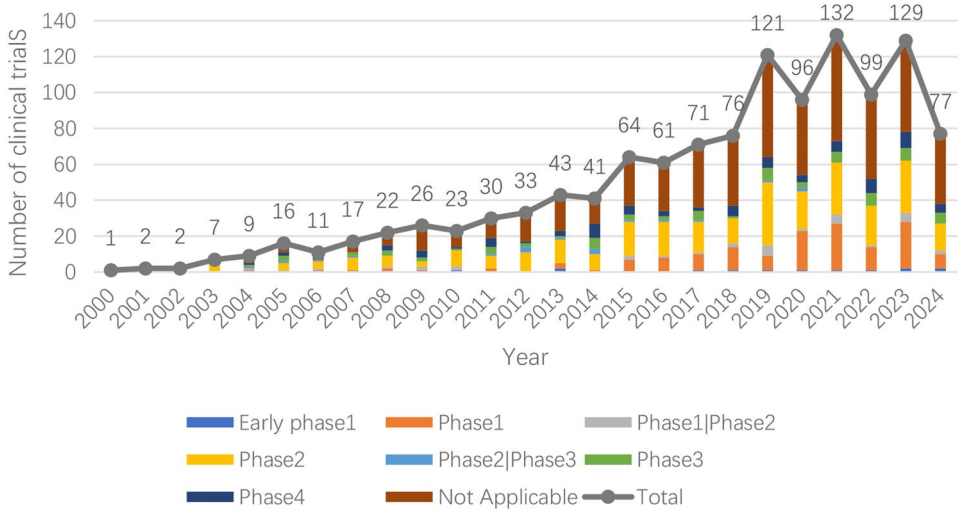

Fig. 2 Starting time and staging of 1209 interventional NAFLD clinical trials

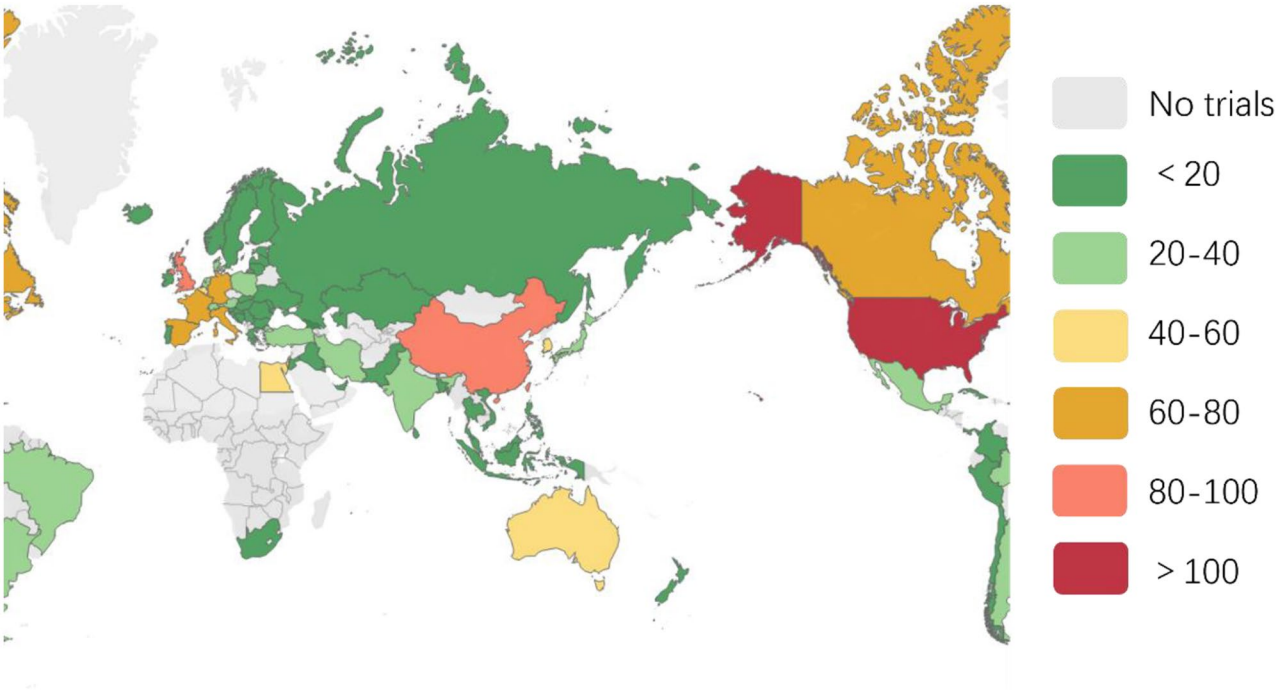

Fig. 3 A map of the global distribution of clinical trials

interventions, 166 (13.73%) dietary supplement interventions, 106 (8.77%) behavioral interventions, 56(4.63%) experimental device interventions, and 127 (10.50%) other interventions.

Subsequently, we conducted an analysis of the drug intervention trials, excluding those that were withdrawn, resulting in a total of 630 trials. The fundamental characteristics of these trials are presented in Table 2. A total of 110 trials were posted from 2000 to 2012, of which 80 (72.73%) were completed, 18 (16.36%) were terminated. Of the 520 trials posted between 2013 and 2024, nearly half (277, 53.27%) were completed, 103(19.81%) were recruiting, and 47(9.04%) were terminated. A total of 1011 (83.62%) did not post summary results in the ClinicalTrials.gov results database. In total, 158 (25.08%) trials had results, while 472 (74.92%) trials not.

592 trials without restrictions on enrollment sex, accounting for 93.97% of total enrollees. 25 trials (3.97%) enrolled only male participants, while 13 trial (2.06%) enrolled only female participants. Additionally, 22 trials (3.49%) enrolled both children and adults, 14 trials (2.22%) enrolled only children, and 594 trials (94.29%) enrolled only adults.

Among the 630 interventional clinical trials with distinct phasing, phase II trials comprised the majority, with a total of 269 cases (42.70%). Additionally, phase I trials had 136 cases (21.59%), phase III trials had 58 cases (9.21%), and phase IV trials had 78 cases (12.38%). In terms of blinding settings, Quadruple-blind trials constituted 30.16% (190 cases), while open-label trials accounted for 30.63% (193 cases). Among the intervention models employed, parallel allocation dominated, accounting for 77.14% (486 cases) of all models. Crossover allocation represented 2.22% (14 cases), single-group allocation comprised 13.02% (82 cases), sequential allocation accounted for 5.56% (35 cases), and factorial allocation accounted for 1.43% (9 cases). With regard to the allocation type, randomized trials constituted 82.06% (517 trials), while non-randomized trials accounted for 6.83% (43 trials). In terms of participant enrollment, 234 clinical trials (37.14%) enrolled between 1 and 50 patients, 186 (29.52%) enrolled between 51 and 100 patients, 133 (21.11%) enrolled between 101 and 200 patients, 53 (8.41%) enrolled between 201 and 500 patients, 11 (1.75%) enrolled between 501 and 1000 patients, and 12 (1.90%) enrolled more than 1,000 patients.

Furthermore, the maximum sample size of 2,480 participants, trial NCT02548351, is a Phase III trial conducted by Intercept Pharmaceuticals. This trial evaluated the efficacy and safety of obeticholic acid in subjects with compensated cirrhosis caused by nonalcoholic steatohepatitis, and the drug is currently available on the market.

Clinical trial targeting

An extensive analysis was conducted on 140 drug interventional trials with results for therapeutic purposes, which accounted for 88.61% of the 158 drug interventional trials with results. The fundamental characteristics of these trials are presented in Table 3. A total of 135

Table 1 Basic characteristics of 1209 interventional NAFLD clinical trials

	2000–2012 (*n* = 199)	2013–2024 (*n* = 1010)	total (*n* = 1209)
Study Status			
Active Not Recruiting	3 (1.51%)	45 (4.46%)	**48 (3.97%)**
Enrolling by Invitation	0 (0.00%)	11 (1.09%)	**11 (0.91%)**
Not Yet Recruiting	0 (0.00%)	47 (4.65%)	**47 (3.89%)**
Recruiting	2 (1.01%)	207 (20.50%)	**209 (17.29%)**
Completed	143 (71.86%)	479 (47.43%)	**622 (51.45%)**
Suspended	1 (0.50%)	2 (0.20%)	**3 (0.25%)**
Terminated	23 (11.56%)	61 (6.04%)	**84 (6.95%)**
Unknown	22 (11.06%)	129 (12.77%)	**151 (12.49%)**
Withdrawn	5 (2.51%)	29 (2.87%)	**34 (2.81%)**
Study Results			
Yes	54 (27.14%)	144 (14.26%)	**198 (16.38%)**
No	145 (72.86%)	866 (85.74%)	**1011 (83.62%)**
Sex			
Female	3 (1.51%)	20 (1.98%)	**23 (1.90%)**
Male	10 (5.03%)	37 (3.66%)	**47 (3.89%)**
All	186 (93.47%)	953 (94.36%)	**1139 (94.21%)**
Participant			
Children	9 (4.52%)	30 (2.97%)	**39 (3.23%)**
Adults	172 (86.43%)	936 (92.67%)	**1108 (91.65%)**
Both	18 (9.05%)	44 (4.36%)	**62 (5.13%)**
Phase			
Early phase1	1 (0.50%)	12 (1.19%)	**13(1.08%)**
Phase 1	8 (4.02%)	144 (14.26%)	**152(12.57%)**
Phase1/2	8 (4.02%)	26 (2.57%)	**34(2.81%)**
Phase 2	59 (29.65%)	242 (23.96%)	**301(24.90%)**
Phase 2/3	9 (4.52%)	10 (0.99%)	**19(1.57%)**
Phase 3	18 (9.05%)	54 (5.35%)	**72 (5.96%)**
Phase 4	19 (9.55%)	65 (6.44%)	**84 (6.95%)**
NA	77 (38.69%)	457 (45.25%)	**534 (44.17%)**
Masking			
Single	22 (11.06%)	92 (9.11%)	**114 (9.43%)**
Double	26 (13.07%)	149 (14.75%)	**175 (14.47%)**
Triple	31 (15.58%)	102 (10.10%)	**133 (11.00%)**
Quadruple	33 (16.58%)	233 (23.07%)	**266 (22.00%)**
None	83 (41.71%)	434 (42.97%)	**517 (42.76%)**
NA	4 (2.01%)	0 (0.00%)	**4 (0.33%)**
Assignment			
Parallel	131 (65.83%)	742 (73.47%)	**873 (72.21%)**
Crossover	7 (3.52%)	35 (3.47%)	**42 (3.47%)**
Single Group	54 (27.14%)	178 (17.62%)	**232 (19.19%)**
Sequential	0 (0.00%)	45 (4.46%)	**45 (3.72%)**
Factorial	2 (1.01%)	9 (0.89%)	**11 (0.91%)**
NA	5 (2.51%)	1 (0.10%)	**6 (0.50%)**
Allocation			
Randomized	140 (70.35%)	765 (75.74%)	**905 (74.86%)**
Non-randomized	18 (9.05%)	79 (7.82%)	**97 (8.02%)**
NA	41 (20.60%)	166 (16.44%)	**207 (17.12%)**
Sample Size			
1–50	105 (52.76%)	415 (41.09%)	**520 (43.01%)**
51–100	50 (25.13%)	283 (28.02%)	**333 (27.54%)**
101–200	29 (14.57%)	185 (18.32%)	**214 (17.70%)**
201–500	8 (4.02%)	83 (8.22%)	**91 (7.53%)**

Table 1 (continued)

	2000–2012 (*n* = 199)	2013–2024 (*n* = 1010)	total (*n* = 1209)
501–1000	1 (0.50%)	21 (2.08%)	**22 (1.82%)**
>1000	3 (1.51%)	23 (2.28%)	**26 (2.15%)**
NA	3 (1.51%)	0 (0.00%)	**3(0.25%)**
Purpose			
Treatment	144 (72.36%)	747 (73.96%)	**891 (73.70%)**
Diagnostic	12 (6.03%)	56 (5.54%)	**68(5.62%)**
Basic science	19 (9.55%)	83 (8.22%)	**102(8.44%)**
Supportive care	3 (1.51%)	21 (2.08%)	**24(1.99%)**
Health Services Research	1 (0.50%)	5 (0.50%)	**6 (0.50%)**
Prevention	10 (5.03%)	42 (4.16%)	**52 (4.30%)**
Screening	1 (0.50%)	17 (1.68%)	**18 (1.49%)**
Other	3 (1.51%)	39 (3.86%)	**42 (3.47%)**
NA	6 (3.02%)	0 (0.00%)	**6 (0.50%)**
Interventions			
drugs	113 (56.78%)	541 (53.56%)	**654 (54.09%)**
Behavioral	18 (9.05%)	88 (8.71%)	**106 (8.77%)**
Biological	3 (1.51%)	14 (1.39%)	**17 (1.41%)**
Device	10 (5.03%)	46 (4.55%)	**56 (4.63%)**
Dietary Supplement	29 (14.57%)	137 (13.56%)	**166 (13.73%)**
Diagnostic Test	0 (0.00%)	42 (4.16%)	**42 (3.47%)**
Combination Product	0 (0.00%)	6 (0.59%)	**6 (0.50%)**
Procedure	7 (3.52%)	27 (2.67%)	**34 (2.81%)**
Genetic	0 (0.00%)	1 (0.10%)	**1 (0.08%)**
others	19 (9.55%)	108 (10.69%)	**127 (10.50%)**

NA: Not applicable. Some trials do not provide information about the phase, so they are classified as 'NA'

(96.43%) trials recruited both men and women, whereas 5 trials (3.57%) exclusively recruited male patients. Additionally, 6 trials (4.29%) enrolled both children and adults, 7 trials (5.00%) enrolled only children, and 127 trials (90.71%) enrolled only adults. Among the 140 interventional clinical trials with distinct phasing, phase II trials comprised the majority, with a total of 101 cases (72.14%). In total, 33 (23.57%) clinical trials were not blinded, whereas 107 (76.43%) were blinded. Among the intervention models employed, parallel allocation dominated, accounting for 79.29% (111 cases) of all models. Crossover allocation represented 2.14% (3 cases), single-group allocation comprised 14.29% (20 cases), sequential allocation accounted for 2.14% (3 cases), and factorial allocation accounted for 1.43% (2 cases). With regard to the allocation type, randomized trials constituted 82.14% (115 trials), while non-randomized trials accounted for 2.86% (4 trials). Notably, 21 trials (15.00%) did not specify the type of allocation. In terms of participant enrollment, 54 clinical trials (38.57%) enrolled between 1 and 50 patients, 30 (21.43%) enrolled between 51 and 100 patients, 34 (24.29%) enrolled between 101 and 200 patients, 17 (12.14%) enrolled between 201 and 500 patients, 3 (2.14%) enrolled between 501 and 1000 patients, and 2 (1.43%) enrolled more than 1,000 patients. There were a total of 10 trials(7.14%) whose duration of drug intervention was ≤4 weeks, 35 trials (25.00%) had durations ranging from 4 weeks to 12 weeks, 36 trials (25.71%) spanned from 12 weeks to 24 weeks, 23 trials (16.43%) were between 24 weeks and 48 weeks, 29 trials (20.71%) extended from 48 weeks to 156 weeks, and 7 trials (5.00%) exceeded 156 weeks.

The classification of the main targets of drugs is shown in Fig. 4, mainly through improving energy metabolism, regulating inflammation and immunity, and improving fat deposition. As detailed in Table 4, the highest number of targets relate to energy metabolism regulation, comprising 37 trials, targeting adenosine 5'-monophosphate-activated protein kinase (AMPK), glucagon-like peptide-1 (GLP-1), acetyl-CoA carboxylase (ACC), fibroblast growth factor 21 (FGF21), and others. Among these 140 trials, the earliest drug to start the trial was Metreleptin, which began in 2001. The latest end time of the related trials was in 2020. By directly supplementing leptin and targeting leptin receptors (LEPR), it regulates metabolism and energy balance in the body, and can improve insulin sensitivity, blood glucose levels, and lipid metabolism [12]. Among the clinical trial targets, Farnesoid X Receptor (FXR) and peroxisome proliferators-activated receptors (PPARs) were the most prominent, with 20 and 18 trials, respectively. Among these 140 trials, the experimental drug targeting FXR that first started in 2007 is obeticholic acid, which has achieved good clinical efficacy in improving insulin resistance and

Table 2 Design characteristics of 630 drug interventional NAFLD clinical trials

	2000–2012 (*n* = 110)	2013–2024 (*n* = 520)	total (*n* = 630)
Phase			
Early phase1	1 (0.91%)	8 (1.54%)	**9 (1.43%)**
Phase 1	7 (6.36%)	129 (24.81%)	**136 (21.59%)**
Phase1/2	6 (5.45%)	19 (3.65%)	**25 (3.97%)**
Phase 2	47 (42.73%)	222 (42.69%)	**269 (42.70%)**
Phase 2/3	6 (5.45%)	3 (0.58%)	**9 (1.43%)**
Phase 3	12 (10.91%)	46 (8.85%)	**58 (9.21%)**
Phase 4	17 (15.45%)	61 (11.73%)	**78 (12.38%)**
NA	14 (12.73%)	32 (6.15%)	**46 (7.30%)**
Participant			
Children	5 (4.55%)	9 (1.73%)	**14 (2.22%)**
Adults	97 (88.18%)	497 (95.58%)	**594 (94.29%)**
Both	8 (7.27%)	14 (2.69%)	**22 (3.49%)**
Study Status			
Active Not Recruiting	1 (0.91%)	25 (4.81%)	**26 (4.13%)**
Enrolling by Invitation	0 (0.00%)	3 (0.58%)	**3 (0.48%)**
Not Yet Recruiting	0 (0.00%)	26 (5.00%)	**26 (4.13%)**
Recruiting	0 (0.00%)	103 (19.81%)	**103 (16.35%)**
Completed	80 (72.73%)	277 (53.27%)	**357 (56.67%)**
Suspended	1 (0.91%)	1 (0.19%)	**2 (0.32%)**
Terminated	18 (16.36%)	47 (9.04%)	**65 (10.32%)**
Unknown	10 (9.09%)	38 (7.31%)	**48 (7.62%)**
Study Results			
Yes	43 (39.09%)	115 (22.12%)	**158 (25.08%)**
No	67 (60.91%)	405 (77.88%)	**472 (74.92%)**
Sex			
Female	2 (1.82%)	11 (2.12%)	**13 (2.06%)**
Male	3 (2.73%)	22 (4.23%)	**25 (3.97%)**
All	105 (95.45%)	487 (93.65%)	**592 (93.97%)**
Masking			
Single	12 (10.91%)	27 (5.19%)	**39 (6.19%)**
Double	20 (18.18%)	91 (17.50%)	**111 (17.62%)**
Triple	23 (20.91%)	72 (13.85%)	**95 (15.08%)**
Quadruple	21 (19.09%)	169 (32.50%)	**190 (30.16%)**
None	32 (29.09%)	161 (30.96%)	**193 (30.63%)**
NA	2 (1.82%)	0 (0.00%)	**2 (0.32%)**
Assignment			
Parallel	77 (70.00%)	409 (78.65%)	**486 (77.14%)**
Crossover	1 (0.91%)	13 (2.50%)	**14 (2.22%)**
Single Group	28 (25.45%)	54 (10.38%)	**82 (13.02%)**
Sequential	0 (0.00%)	35 (6.73%)	**35 (5.56%)**
Factorial	1 (0.91%)	8 (1.54%)	**9 (1.43%)**
NA	3 (2.73%)	1 (0.19%)	**4 (0.63%)**
Allocation			
Randomized	83 (75.45%)	434 (83.46%)	**517 (82.06%)**
Non-Randomized	5 (4.55%)	38 (7.31%)	**43 (6.83%)**
NA	22 (20.00%)	48 (9.23%)	**70 (11.11%)**
Sample Size			
1–50	56 (50.91%)	178 (34.23%)	**234 (37.14%)**
51–100	28 (25.45%)	158 (30.38%)	**186 (29.52%)**
101–200	19 (17.27%)	114 (21.92%)	**133 (21.11%)**
201–500	5 (4.55%)	48 (9.23%)	**53 (8.41%)**
501–1000	0 (0.00%)	11 (2.12%)	**11 (1.75%)**

Table 2 (continued)

	2000–2012 (*n* = 110)	2013–2024 (*n* = 520)	total (*n* = 630)
>1000	1 (0.91%)	11 (2.12%)	**12 (1.90%)**
NA	1 (0.91%)	0 (0.00%)	**1 (0.16%)**

NA: Not applicable. Some trials do not provide information about the phase, so they are classified as 'NA'

hepatic steatosis [13]. Among them, the first drug to target PPAR in trials was pioglitazone, which began in 2003. Another notable drug, Elafibranor, an α/δ-PPAR agonist, was first tested in 2012 [14]. Three trials examined herbal medicines and their extracts, specifically silymarin extract and Korean red ginseng. These herbs are popular because they are common and effective. Extracts of the milk thistle plant contain flavonoids, which have been proven to be liver protectants [15]. Red ginseng improves liver functions in a naturally aged mouse model [16], and can effectively improve insulin resistance and liver steatosis [17].Numerous drugs possess multiple targets of action, and the development of novel drugs tends to favor co-regulation for enhancing metabolism and reducing inflammation.

Clinical trial outcomes

The Principles for Clinical Trials of Drugs for the Treatment of Nonalcoholic Steatohepatitis (Trial), released in China, specify clinical outcomes as endpoint indicators and liver histopathology as a surrogate endpoint [18, 19]. Table 5 presents the main clinical endpoints of 140 interventional clinical trials spanning from phase I to IV. Some trials had more than one primary clinical outcome. Among these endpoints, hepatic fat content was the most frequently used primary endpoint, with 45(23.68%) trials. Most clinical trials (80.00%, 36/45) employed Magnetic Resonance Imaging (MRI) techniques to assess hepatic fat content, with nearly two-thirds (61.11%, 22/36) explicitly stated the use of magnetic resonance imaging-derived proton density fat fraction (MRI-PDFF) to quantify hepatic steatosis. And a few (17.7%, 8/45) used hydrogen proton magnetic resonance spectroscopy (^{1}H-MRS) for precise voxel-specific lipid quantification. Notably, one trial used a valid formula to calculate liver fat content. The formula is as the followings: Liver fat content (%) = 10(-0.805 + 0.282 * metabolic syndrome (yes = 11 no = 0) + 0.078 * type 2 diabetes (yes = 2 / no = 0) + 0.525 * log fasting serum insulin (mU/L) + 0.521 * log fasting serum AST (U/L) – 0.454 * log (AST/ALT).Subsequently, hepatic histology suggesting improvement in NASH or fibrosis was the next most frequent primary endpoint, with 40(21.05%) trials, while adverse events were the primary endpoint in 34(17.89%) trials. 7(46.67%) phase I trials utilized pharmacokinetic parameters as the primary clinical endpoints. In phase II trials, hepatic fat content was the most common primary endpoint (35, 27.34%). Among phase III trials, 6(37.50%) studies employed hepatic histology indicating improvement in NASH or fibrosis as the primary clinical endpoint, while in phase IV trials, it was the endpoint in 3(33.33%) trials. This alignment was consistent with the objectives of the trial staging process.

Although liver biopsy remains the gold standard for diagnosing MASLD, several trials have explored noninvasive methods for detecting NASH or fibrosis improvement, indicating an increasing concern for minimizing liver biopsy-related patient harm in research. Consequently, the development of noninvasive tests to elucidate liver histopathological changes is imperative, such as the Enhanced Liver Fibrosis (ELF) score, which serves as a robust predictor of adverse clinical and patient-reported outcomes [20]. An artificial intelligence-based measurement (AIM) tool was developed for scoring MASH histology (AIM-MASH). Relevant research results suggest that AIM-MASH may assist pathologists in histologic review of MASH clinical trials, reducing inter-rater variability on trial outcomes and offering a more sensitive and reproducible measure of patient responses [21, 22]. The LiverMultiScan is CE marked as a class IIa medical device. Corrected T1(cT1) is a Magnetic Resonance(MR) relaxation parameter/measure from the device. The measure cT1 can be compared across different MRI systems and sites. It is noteworthy as an emerging biomarker for rapid quantification of hepatic fibro-inflammatory diseases [23]. Drug safety is a pivotal concern in clinical trials, encompassing adverse events such as laboratory abnormalities and vital sign irregularities. Drug concentration and half-life can provide insights into its efficacy, and have been employed as key clinical outcome indicators in trials. Three trial(1.58%) utilized a composite outcome encompassing all-cause mortality, cirrhosis, and liver-related clinical regression as the primary endpoint, yet its standardization remains inconsistent. Secondly, liver enzymes (alanine aminotransferase mainly) and blood lipids (consisting of cholesterol, triglycerides, and low-density lipoprotein) are frequently employed as outcome indicators in clinical trials. In the context of cirrhosis stemming from MASLD, particular attention is accorded to the hepatic venous pressure gradient and symptoms of cirrhosis loss. Furthermore, occasional mention is made of other glucose metabolism-related indices, such as glucose, glycated hemoglobin and insulin resistance.

Table 3 Design characteristics of 140 drug interventional trials with results for therapeutic purposes

	2001–2012 (*n* = 38)	2013–2021 (*n* = 102)	total (*n* = 140)
Phase			
Early phase1	0 (0.00%)	1(0.98%)	**1(0.71%)**
Phase 1	1(2.63%)	6(5.88%)	**7(5.00%)**
Phase 1/2	2(5.26%)	5(4.90%)	**7(5.00%)**
Phase 2	20(52.63%)	81(79.41%)	**101(72.14%)**
Phase 2/3	3(7.89%)	0 (0.00%)	**3(2.14%)**
Phase 3	4(10.53%)	5(4.90%)	**9(6.43%)**
Phase 4	7(18.42%)	1(0.98%)	**8(5.71%)**
NA	1(2.63%)	3(2.94%)	**4(2.86%)**
Participant			
Children	3(7.89%)	4(3.92%)	**7(5.00%)**
Adults	32(84.21%)	95(93.14%)	**127(90.71%)**
Both	3(7.89%)	3(2.94%)	**6(4.29%)**
Study Status			
Completed	32(84.21%)	74(72.55%)	**106(75.71%)**
Suspended	1(2.63%)	0 (0.00%)	**1(0.71%)**
Terminated	5(13.16%)	28(27.45%)	**33(23.57%)**
Sex			
Male	1(2.63%)	4(3.92%)	**5(3.57%)**
All	37(97.37%)	98(96.08%)	**135(96.43%)**
Masking			
Single	4(10.53%)	1(0.98%)	**5(3.57%)**
Double	6(15.79%)	22(21.57%)	**28(20.00%)**
Triple	8(21.05%)	23(22.55%)	**31(22.14%)**
Quadruple	9(23.68%)	34(33.33%)	**43(30.71%)**
None	11(28.95%)	22(21.57%)	**33(23.57%)**
Assignment			
Parallel	26(68.42%)	85(83.33%)	**111(79.29%)**
Crossover	1(2.63%)	2(1.96%)	**3(2.14%)**
Single Group	9(23.68%)	11(10.78%)	**20(14.29%)**
Sequential	0 (0.00%)	3(2.94%)	**3(2.14%)**
Factorial	1(2.63%)	1(0.98%)	**2(1.43%)**
NA	1(2.63%)	0 (0.00%)	**1(0.71%)**
Allocation			
Randomized	27(71.05%)	88(86.27%)	**115(82.14%)**
Non-Randomized	1(2.63%)	3(2.94%)	**4(2.86%)**
NA	10(26.32%)	11(10.78%)	**21(15.00%)**
Sample Size			
1–50	20(52.63%)	34(33.33%)	**54(38.57%)**
51–100	6(15.79%)	24(23.53%)	**30(21.43%)**
101–200	7(18.42%)	27(26.47%)	**34(24.29%)**
201–500	5(13.16%)	12(11.76%)	**17(12.14%)**
501–1000	0 (0.00%)	3(2.94%)	**3(2.14%)**
>1000	0 (0.00%)	2(1.96%)	**2(1.43%)**
Duration			
≤ 4 weeks	3(7.89%)	7(6.86%)	**10(7.14%)**
4-12 weeks	8(21.05%)	27(26.47%)	**35(25.00%)**
12-24 weeks	4(10.53%)	32(31.37%)	**36(25.71%)**
24-48 weeks	7(18.42%)	16(15.69%)	**23(16.43%)**
48-156 weeks	16(42.11%)	13(12.75%)	**29(20.71%)**
>156 weeks	0 (0.00%)	7(6.86%)	**7(5.00%)**

NA: Not applicable. Some trials do not provide information about the phase, so they are classified as 'NA'

Discussion

This study analyzed the enrollment of interventional clinical trials with outcomes for MASLD in the ClinicalTrials.gov database, spanning from its establishment to August 2024. A total of 1,209 clinical trials were included in our analysis. Our findings revealed that these trials were concentrated primarily in the period from 2000 to 2024. The notable alteration in the quantity of trial cases between 2019 and 2024 prompts the assumption that the COVID-19 pandemic has significantly impeded the advancement of clinical trials for MASLD. Furthermore, the absence of relevant trials prior to 2000 may be attributed to MASLD not being a research hotspot at that time, resulting in fewer conducted trials and there may have been clinical trials that were not included in the database. Next we screen for drug intervention trials and rule out withdrawal trials. A total of 630 trials were analyzed. Further screening and analysis of 140 trials with therapeutic outcomes were conducted to explore their main outcome measures and targets.

Regarding the interventional clinical trials, most were phase II trials, indicating that research on MASLD drugs remains in the exploratory phase of elucidating mechanisms, assessing efficacy, and evaluating safety. This suggests that MASLD drug research is currently a potential research area. In terms of trial design, the majority were randomized quadruple-blind trials, enrolling primarily adults without sex stratification. While some studies suggest a higher prevalence in men and a similar prevalence in postmenopausal women [24], this implies a potential hormonal influence on MASLD prevalence. Animal studies have demonstrated that male mice generally accumulate more liver triglycerides (TG) than female mice. Association studies have further shown that this sex difference can be attributed to differences in body fat distribution, plasma HDL levels, and genetic regulation [25]. In vivo experiments in mice demonstrated that hepatocyte PPARα determines a sex-specific response to fasting and treatment with a selective PPARα agonist. Liver molecular signatures in humans also provided evidence of sexually dimorphic gene expression profiles and the sex-specific co-expression network for PPARα. These findings underscore the sex specificity of NAFLD pathophysiology in preclinical studies and identify PPARα as a pivotal, sexually dimorphic, pharmacological target [26]. Thus, analyzing a population without considering potential sex-specific effects or hormonal effects, probably masks important observations. How sex and synthetic hormone use impact disease risk with MASLD deserves further investigation. As the prevalence of MASLD in children increases, lifestyle changes remain the primary treatment [27, 28]. However, a large number of new drugs have not yet been tested in children. Future treatments may include multimodal approaches, such

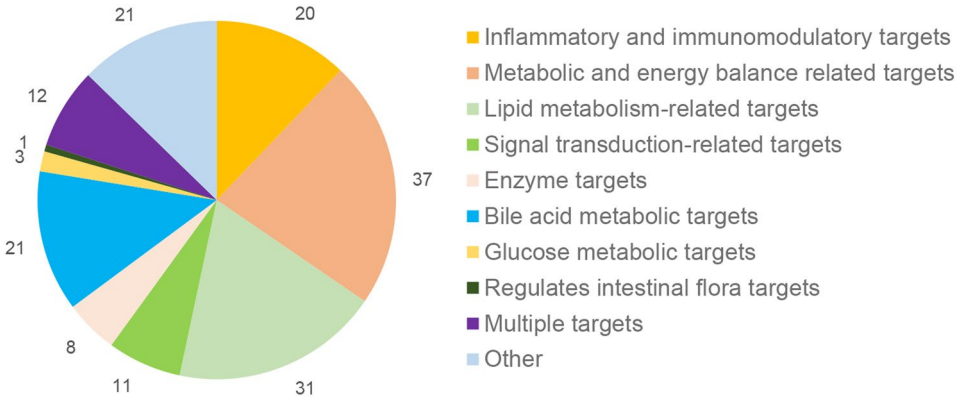

Fig. 4 Drug interventional clinical trials mainly directed at targets

as FXR agonists and bariatric surgery. Therefore, attention should be focused on evaluating the impact of these drugs and other interventions on MASLD in children.

A combined dietary and exercise approach is a crucial method for improving MASLD. Research suggests that exercise can reverse muscle insulin resistance, potentially reducing postprandial hepatic lipogenesis in insulin-resistant individuals, making it a promising therapeutic strategy for treating and preventing atherosclerotic dyslipidemia and MASLD in young insulin-resistant individuals [15]. MASLD, as a metabolic disorder, is intimately linked to lifestyle consequently. A sustained weight loss of 10% is associated with a reduction in hepatic fibrosis [29]. Notably, of the 1,209 clinical trials, 106 (8.77%) involved behavioral interventions and 166 (13.73%) involved dietary supplements, all related to lifestyle. 654 (54.09%) involved pharmacological interventions, about twice as many as lifestyle-focused trials. Future research should continue to investigate the impacts of non-pharmacological interventions on MASLD. This may lead to the development of more effective strategic approaches for MASLD treatment.

In March 2024, Rezdiffra, a liver-targeted thyroid hormone receptor-β(THR-β) selective drug with resmetirom as its primary active ingredient, became the first and only Food and Drug Administration-approved drug for the treatment of MASH [30]. MASH develops from MASLD as hepatic inflammation progresses to hepatic fibrosis and liver dysfunction over time. Currently, there is no specific drug for MASLD, and drug-associated targets, particularly the co-regulation of metabolic and inflammatory pathways, remain a highly sought-after research area [31].

The hepatic de novo synthesis of fatty acids from acetyl-CoA is termed de novo lipogenesis (DNL) [32]. This process plays a pivotal role in fat accumulation, and insulin resistance is a major driver of hepatic DNL in MASLD [33]. Insulin sensitizers, such as PPAR agonists, FXR agonists, and FGF21 and its analogs, are crucial metabolic regulators that decrease fat accumulation by enhancing insulin sensitivity and mitigating insulin resistance. Specifically, FXR activation stimulates the expression of PPARα and its target genes, leading to the promotion of free fatty acid (FFA) oxidation and triglyceride (TG) clearance [34]. Clinical trials have demonstrated the safety and efficacy of FXR-related drugs in inducing hepatic steatosis resolution, improving liver enzymes, and promoting weight loss [35]. PPARs, nuclear receptors with key regulatory functions in metabolism, inflammation, and fibrosis, display limited therapeutic potential when activated individually (PPARα and PPARγ). However, relevant clinical trials suggest that dual and pan-PPAR agonists may exhibit broader and more effective therapeutic benefits [36, 37]. Preclinical and clinical data indicate that FGF21 improves metabolism by modulating adiponectin, possesses antifibrotic properties, and holds potential for the treatment of NASH [38, 39].

The hepatoenteric circulation mechanism of bile acid is shown in Fig. 5. Bile acids are actively reabsorbed via the apical-sodium-dependent bile acid transporter (ASBT) at the ileum and enter the systemic circulation through the basolateral organic solute transporter (OSTα/OSTβ) [26]. The reabsorbed bile acids are subsequently transported into hepatocytes via sodium taurocholate cotransport polypeptide (NTCP) and organic anion transporter (OATP), then resecreted into bile to complete the enterohepatic circulation [27]. FXR is a nuclear receptor activated by bile acids [28], suppresses bile acid synthesis through two mechanisms: when there is too much bile acid in the body, the rate-limiting enzyme cholesterol 7 alpha-hydroxylase (CYP7A1) will bind to FXR and activate small heterodimer partner (SHP) expression, and indirectly inhibit the promotion of CYP7A1 expression. FXR can also directly regulate the expression of fibroblast growth factor-19 (FGF-19) and inhibit the expression of CYP7A1 through c-Jun N-terminal kinase (JNK) dependent pathway [40]. And FGF19 binds to hepatic fibroblast growth factor receptor 4 (FGFR4) /bKlotho receptors,

Table 4 Mainly directed targets of interventional clinical trials of drugs

Categorization	Targets	Drug name	Number
Inflammatory and immunomodulatory targets	ASBT	Volixibat (SHP626)	2
	Caspase	Emricasan (IDN-6556)	2
	Gal-3	GR-MD-02	2
	LTA4H	LYS006	1
	RARs	Fenretinide	1
	RORγt	BMS-986,251	1
	SSAO	BI 1,467,335, TERN-201	2
	TLR-4	JKB-121	1
	CCR	Cenicriviroc, Leronlimab	6
	AT1R	Losartan potassium	2
Metabolic and energy balance related targets	ACC	Firsocostat, PF-05221304, MK-4074	8
	AMPK	PXL770, Glucophage (Metformin)	4
	ANT	HU6	1
	DGAT	Pradigastat (LCQ908), PF-06865571	2
	FGF21	BMS-986,036, Efruxifermin (EFX), Pegozafermin	6
	GLP-1	Efinopegdutide, Exenatide, Semaglutide	8
	GSS	Cysteamine	1
	HPK1	AZ compound	1
	IGF-1	Growth hormone, Somatropin	2
	LEPR	Metreleptin	4
Lipid metabolism-related targets	ANGPTL3	ISIS 703,802	1
	AR	LPCN 1144	2
	FABP6	Colesevelam Hcl	1
	LIPA	Sebelipase Alfa	2
	NPC1L1	Ezetimibe	1
	PPAR	Elafibranor (GFT505), Lanifibranor (IVA337), pioglitazone, PXL065, Seladelpar, Fenofibrate, MSDC-0602 K	18
	SCD1	Aramchol	2
	SGLT	Licogliflozin, Dapagliflozin	3
		Beta Glucosylceramide	1
Signal transduction-related targets	ASK1	Selonsertib (SEL)	5
	GRF	Tesamorelin	1
	JNK	CC-90,001, GWP42003	2
	PDE	Roflumilast, Pentoxifylline (PTX)	3
Enzyme targets	Bacterial RNA polymerase inhibitors	Rifaximin	1
	COX	Aspirin	1
	DPP4	Sitagliptin	2
	HMG-CoA reductase inhibitors	Atorvastatin, pitavastatin	2
	LOXL2	Simtuzumab (SIM)	1
	Transglutaminases inhibitors	DR cysteamine bitartrate capsule	1
Bile acid metabolic targets	FXR	Cilofexor (GS-9674), EDP-305, Nidufexor (LMB763), Obeticholic acid (INT-747), TERN-101, Tropifexor (LJN452), Vonafexor, HTD1801	20
	IBAT	Elobixibat	1
Glucose metabolic targets		ORMD-0801, insulin	3
Regulates intestinal flora targets		Align Probiotic Supplement Capsule	1

Table 4 (continued)

Categorization	Targets	Drug name	Number
Multiple targets	5-LOX, LTRs	MN-001	1
	CCR2/5, PPAR	Gemcabene	2
	GLP-1, GCGR	MEDI0382	1
	Hepatitis B virus structural protein, CYPA	CRV431	1
	IKKε, TBK1	Amlexanox	2
	KLB, FGFR1	BFKB8488A, MK-3655	2
	MR, GR	Miricorilant	1
	NPC1L1, FXR	EZ-Urso combination therapy	1
	PRKAB1, PDE5A	Leu-Met-Sil	1
Other	Vitamin B	Niacin	1
	Vitamin E	4	4
	Proton pump inhibitor	Rabeprazol sodium	1
	thrombin	Dabigatran Etexilate, Eltrombopag	2
	Unsaturated fatty acid	EPA-E, Opti-EPA, Epeleuton, Vascepa, Fish Oil Supplementation, OMACOR, Omega-3 carboxylic acids	9
		KRG (Korea Red ginseng)	1
		IdB 1016 (Siliphos), Silymarin	2
		SAMe	1

Table 5 Primary clinical outcomes of 158 phase I-IV NAFLD interventional clinical trials

Outcome	Early phase1 (*n* = 2)	Phase 1 (*n* = 15)	Phase 1/2(*n* = 9)	Phase 2 (*n* = 128)	Phase 2/3(*n* = 4)	Phase 3 (*n* = 16)	Phase 4 (*n* = 9)	NA (*n* = 7)	total (*n* = 190)
Liver Histology			3 (33.33%)	26 (20.31%)	2 (50.00%)	6 (37.50%)	3 (33.33%)		40 (21.05%)
Safety and Adverse Events (AEs)		6 (40.00%)	2 (22.22%)	25 (19.53%)		1 (6.25%)			34 (17.89%)
Liver Enzymes			1 (11.11%)	13 (10.16%)	1 (25.00%)	1 (6.25%)	2 (22.22%)	1 (14.29%)	19 (10.00%)
Liver Fat	2 (100.00%)	2 (13.33%)	1 (11.11%)	35 (27.34%)			3 (33.33%)	2 (28.57%)	45 (23.68%)
HbA1c				4 (3.13%)					4 (2.11%)
Blood Glucose				1 (0.78%)					1 (0.53%)
Bone Mineral Density				1 (0.78%)					1 (0.53%)
Pharmacokinetic (PK) Parameter		7 (46.67%)	1 (11.11%)	7 (5.47%)		1 (6.25%)			16 (8.42%)
Liver/Spleen Ratio								2 (28.57%)	2 (1.05%)
Insulin Resistance				3 (2.34%)			1 (11.11%)	2 (28.57%)	6 (3.16%)
Low Density Lipoproteins (LDL)				3 (2.34%)					3 (1.58%)
Platelet Transfusion						1 (6.25%)			1 (0.53%)
Comprehensive Outcome						3 (18.75%)			3 (1.58%)
Triglyceride			1 (11.11%)	6 (4.69%)					7 (3.68%)
Hepatic Venous Pressure Gradient (HVPG)				3 (2.34%)					3 (1.58%)
Survival rate					1 (25.00%)	2 (12.50%)			3 (1.58%)
Liver Stiffness				1 (0.78%)		1 (6.25%)			2 (1.05%)

Some trials had more than one primary clinical outcome. NA: Not applicable

co-suppressing the expression of CYP7A1 and Sterol 12-alpha-hydroxylase (CYP8B1) [41]. Animal experiments [42] have shown that FXR agonists activate SHP to reduce bile acid synthesis but may exacerbate cholesterol deposition. Conversely, FXR deficiency allows oxysterols to activate liver X receptor (LXR), up-regulating CYP7A1 to promote bile acid synthesis and maintain homeostasis. Maintenance of cholesterol homeostasis. Peroxisome proliferator activated receptor-γ (PPARγ) is expressed in adipose tissue and is closely related to adipocyte differentiation and insulin resistance. Studies have found that PPARγ can increase the expression of stearoyl-CoA desaturase (SCD) gene in adipocytes and its dependence on PPARγ by activating FXR expression, thus promoting adipogenesis and adipocyte differentiation [43]. Additionally, the FXR-SHP pathway inhibits LXR and SREBP-1c, thereby reducing serum TG levels [44].

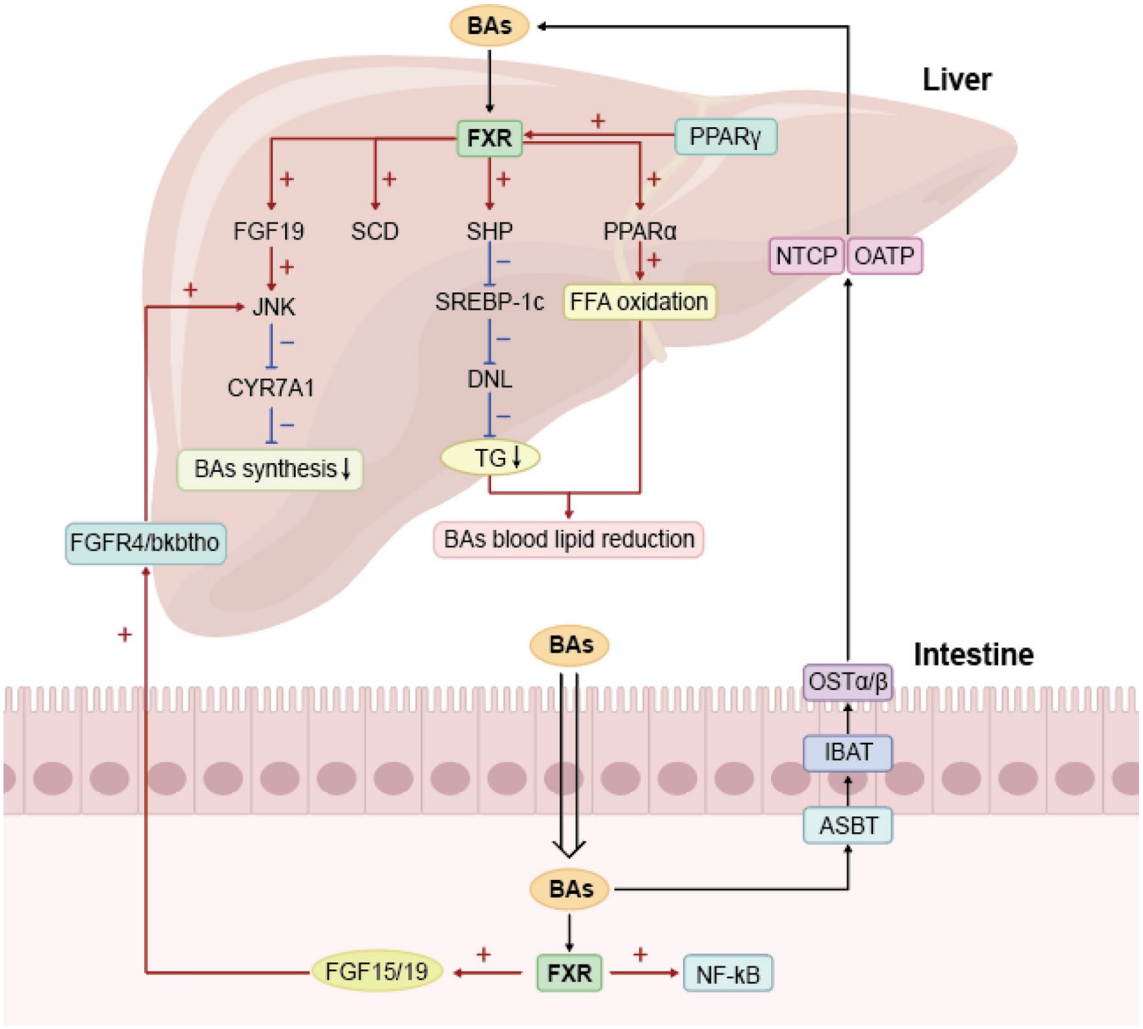

Fig. 5 The hepatoenteric circulation mechanism of bile acid

The three primary outcomes most frequently observed in MASLD-related clinical trials are liver fat content, histologic improvement in NASH or liver fibrosis, and the incidence of adverse events. These outcomes align with the two main pathogenic bases of MASLD: fat accumulation and inflammatory response. Additionally, the focus on adverse events as a key clinical outcome aligns with the objectives of phase II clinical trials, which aim to assess drug safety. Although liver biopsy remains the gold standard for MASLD diagnosis, there is a growing trend in clinical trials toward utilizing noninvasive assays to evaluate improvements in liver fibrosis. We note that although MRI-PDFF technology is widely used, most trials do not mention how much MRI-PDFF reduction is considered therapeutic. One study found that a relative reduction of ≥ 30% (histological response threshold) in MRI-PDFF may be considered a valid threshold for improvement [45]. In the future, we need to clarify the effective threshold of MRI-PDFF and other non-invasive detection methods in improving MASLD. With the rapid rise of artificial intelligence (AI) technology, the use of AI for the assessment of MASLD is also anticipated. Pioglitazone [46] was proved to be effective in improving NASH and decreasing TG without significant adverse reactions in Phase IV trials. In the foreseeable future, we anticipate facilitating the market entry of an increased number of drugs that have undergone rigorous validation through clinical trials.

However, this study has limitations. The ClinicalTrials.gov database, established in 2002, does not contain all existing clinical trial data. Therefore, this study was unable to access data from MASLD-related clinical trials those not registered in the database.

Abbreviations

MASLD	Metabolic dysfunction-associated steatotic liver disease
NAFLD	Non-alcoholic fatty liver disease
ILS	Isolated hepatic steatosis
MASL	Metabolic dysfunction-related fatty liver disease

MASH	Metabolic dysfunction-related steatohepatitis
IR	Insulin resistance
HCC	Hepatocellular carcinoma
MetS	Metabolic syndrome
MAFLD	Metabolic associated fatty liver disease
NASH	Nonalcoholic steatohepatitis
AAGR	Average annual growth rate
AMPK	Adenosine 5′-monophosphate-activated protein kinase
GLP-1	Glucagon-like peptide-1
ACC	Acetyl-CoA carboxylase
FGF21/19	Fibroblast growth factor 21/19
LEPR	Leptin receptors
FXR	Farnesoid X Receptor
PPARs	Peroxisome proliferators-activated receptors
PPAR α/β/γ	Peroxisome proliferators-activated receptor α/β/γ
MRI	Magnetic Resonance Imaging
MRI-PDFF	Magnetic resonance imaging-derived proton density fat fraction
^{1}H-MRS	Hydrogen proton magnetic resonance spectroscopy
ELF	Enhanced Liver Fibrosis score
AIM	Artificial intelligence-based measurement
AIM-MASH	An artificial intelligence-based measurement (AIM) tool to score MASH histology
cT1	Corrected T1
MR	Magnetic Resonance
DNL	De novo lipogenesis
FFA	Free fatty acid
TG	Triglyceride
ASBT	Apic-sodium-dependent bile acid transporter
OSTα/OSTβ	Organic solute transporters
NTCP	Sodium taurocholate cotransport polypeptide
OATP	Organic anion transporter
CYP7A1	Cholesterol 7 alpha-hydroxylase
JNK	c-Jun N-terminal kinase
FGFR4	Fibroblast growth factor receptor 4
CYP8B1	Sterol 12-alpha-hydroxylase
LXR	Liver X receptor
SCD	Stearoyl-CoA desaturase
THR-β	Thyroid hormone receptor-β
AI	Artificial intelligence

Supplementary Information

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Supplementary Material 1

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Author contributions
H.D. and C.W. wrote the main manuscript text and L.H., Y.W. and Y.L. prepared Tables 1, 2, 3, 4 and 5. J.H. and Y.W. prepared Figs. 1, 2, 3, 4 and 5. Y.L. and Q.S. have drafted the work or substantively revised it. All authors reviewed the manuscript.

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Data availability
Data is provided within the manuscript. The datasets generated and/or analysed during the current study are available in the ClinicalTrials.gov repository. The website is https://clinicaltrials.gov.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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