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Global trends and hotspots of treatment for nonalcoholic fatty liver disease: A bibliometric and visualization analysis (2010-2023)

Trends of treatment for NAFLD

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Abstract

BACKGROUND

Nonalcoholic fatty liver disease (NAFLD) is chronic, with its progression leading to liver fibrosis and end-stage cirrhosis. Although NAFLD is increasingly common, no treatment guideline has been established. Many mechanistic studies and drug trials have been conducted for new drug development to treat NAFLD. An up-to-date overview on the knowledge structure of NAFLD through bibliometrics, focusing on research hotspots, is necessary to reveal the rational and timely directions of development in this field.

AIM

To research the latest literature and determine the current trends in treatment for NAFLD.

METHODS

Publications related to treatment for NAFLD were searched on the Web of Science Core Collection database, from 2010 to 2023. VOSviewers, CiteSpace, and R package "bibliometrix" were used to conduct this bibliometric analysis. The key information was

extracted, and the results of the cluster analysis were based on network data for generating and investigating maps for country, institution, journal, and author. Historiography analysis, bursts and cluster analysis, co-occurrence analysis, and trend topic revealed the knowledge structure and research hotspots in this field. GraphPad Prism 9.5.1.733 and Microsoft Office Excel 2019 were used for data analysis and visualization.

RESULTS

In total, 10829 articles from 120 countries (led by China and the United States) and 8785 institutions were included. The number of publications related to treatment for NAFLD increased annually. While China produced the most publications, the United States was the most cited country, and the United Kingdom collaborated the most from an international standpoint. The University of California-San Diego, Shanghai Jiao Tong University, and Shanghai University of Traditional Chinese Medicine produced the most publications of all the research institutions. The *International Journal of Molecular Sciences* was the most frequent journal out of the 1523 total journals, and *Hepatology* was the most cited and co-cited journal. Sanyal AJ was the most cited author, the most co-cited author was Younossi ZM, and the most influential author was Loomba R. The most studied topics included the epidemiology and mechanism of NAFLD, the development of accurate diagnosis, the precise management of patients with NAFLD, and the associated metabolic comorbidities. The major cluster topics were "emerging drug," "glucagon-like peptide-1 receptor agonist," "metabolic dysfunction-associated fatty liver disease," "gut microbiota," and "glucose metabolism."

CONCLUSION

The bibliometric study identified recent research frontiers and hot directions, which can provide a valuable reference for scholars researching treatments for NAFLD.

Key Words: Bibliometrics; Treatment; Therapy; Nonalcoholic fatty liver disease; Metabolic dysfunction-associated fatty liver disease; Historiography analysis

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Core Tip: A total of 10829 articles published between 2010-2023 were identified through a bibliometric analysis to explore the trends and hotspots of treatment for nonalcoholic fatty liver disease (NAFLD). Replacing NAFLD/nonalcoholic steatohepatitis with metabolic dysfunction-associated fatty liver disease has been shown to greatly promote transformation of the treatment strategy of the disease. Research on gut microbiomes and traditional medicine will continue to be a short-term research hotspot. Obeticholic acid (phase 3 clinical validation) and semaglutide (under study) are likely to become the first approved drugs for NAFLD treatment.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) was first proposed by Ludwig in 1980 to describe fatty liver disease without a history of alcoholism[1]. NAFLD is further divided histologically into nonalcoholic fatty liver and nonalcoholic steatohepatitis (NASH)[2]. NASH can progress to fibrosis, eventually leading to cirrhosis and cirrhosis-related complications such as end-stage liver disease and hepatocellular carcinoma (HCC)[3]. In the United States, NASH cirrhosis is the leading indicator and fastest-growing cause of candidates waiting for liver transplantation (LT)[4] and is expected to become the prevalent indication for LT by 2030[5]. Currently, NAFLD is an epidemic among chronic diseases, threatening the health of nearly 1.7 billion people worldwide and placing a huge burden on individuals, families, and healthcare systems[6].

The clinical burden of NAFLD extends beyond liver-related morbidity and mortality as there is growing evidence suggesting its association with various metabolic

comorbidities, including obesity, type 2 diabetes, cardiovascular disease, chronic kidney disease, hypertension, and hypercholesterolemia[7]. The global epidemics of obesity, diabetes, and metabolic syndrome (MetS) have led to an increasing prevalence of NAFLD[8]. The presence of multiple metabolic comorbidities increases the risk of NAFLD and the risk of progressive liver disease. The primary liver pathology in NAFLD affects liver structure and function, increasing the risk of morbidity and mortality associated with cirrhosis, end-stage liver disease, and HCC, with cardiovascular disease accounting for the most deaths in patients with NAFLD[9]. Therefore, Eslam *et al*[10], representing the International Consensus Group in 2020, recommended renaming NAFLD/NASH to metabolic-associated fatty liver disease (MAFLD) to more accurately reflect its pathogenesis and accelerate the transition to novel therapeutics.

The most effective strategy for addressing chronic disease is to reduce the disease burden through prevention. However, this goal has not been achieved for NAFLD. Lifestyle changes focused on weight loss remain the cornerstone of NASH treatment, with a 10% weight loss able to resolve steatohepatitis or improve fibrosis and portal vein inflammation[11]. Nonetheless, achieving significant weight loss in clinical practice is challenging, as its effects are slow and can easily be reversed. Studies have shown that only 30% of patients can lose more than 5% of their weight through lifestyle changes after 13 mo[12].

New drug research and development for NAFLD treatment has been slow. Currently, clinical phase 2b and phase 3 studies have achieved certain efficacy. It is anticipated that new drugs will be available in the near future. However, no drugs have been approved yet, and the efficacy of the various compounds under development is not deemed satisfactory. The response rates for the investigational drugs in current studies range from 20%–40%, with no significant difference from the placebo response rate of 10%–20%[10].

Bibliometric analysis is a statistical method of literature analysis that examines the publication status of studies in a specific field from both quantitative and qualitative

perspectives. It includes various factors such as authorship, country of origin, affiliated institutions, journal publications, and keywords[13]. Bibliometric tools such as VOSviewer, the R package "bibliometrix"[14], and CiteSpace[15] were used to visualize the results of this literature analysis, and these tools are gradually being used more frequently in the medical field. The application of bibliometrics to analyze research in the treatment of NAFLD/MAFLD is exceedingly helpful for identifying hotspots and research trends in this field of study, and in identifying those countries, institutions, and researchers that contribute the most. The advantages of this research methodology also include the possibility of analyzing and summarizing the evolution of research directions and content for a given institution or individual, as well as of quantitatively analyzing the collaboration between them. However, there are not many bibliometric statistical analyses in the field of liver disease, with few articles related to NAFLD[16-20]. In analyzing research that focuses on the possible causes of classical liver diseases, the research hotspots are mainly viral hepatitis and alcoholic liver disease. In recent years, with the overall decline in the prevalence of viral hepatitis and the annual increase in the incidence of NAFLD, there has been a growing interest in the latter. Indeed, the collective research and resultant advancement in knowledge of the disease ¾ from the proposal of "NAFLD" in 1980[1], to the proposed renaming of the disease to "MAFLD" in 2020[10], to the recent publication of the "multi-society Delphi consensus statement on new fatty liver disease nomenclature"[21] ¾ is serving as a signal to the end of the diagnosis and research into NAFLD and the entry into a brand new era of the more accurately termed "metabolic dysfunction-associated steatotic liver disease (MASLD)". Therefore, at the time of this new naming of the disease, it is necessary to analyze and summarize the research results for the treatment of this disease through the method of bibliometric statistical analysis, so as to accurately analyze the research hotspots and the trend of future development through a more objective approach and global perspective.

As mentioned earlier, NAFLD is widespread and harmful, and new treatment strategies are urgently needed to halt the progression of hepatic steatosis and fibrosis.

Since the renaming of NAFLD to MAFLD in 2020, a major shift has been observed in the direction of its treatment. With the publication of research results in the past 2 years, it is crucial to conduct a statistical analysis of relevant literature, identify key contributors and the current research status in this field, pinpoint current research areas of focus, and outline future research trends and development prospects.

MATERIALS AND METHODS

Search strategy

We conducted a literature search on the Web of Science Core Collection database (https://www.webofscience.com/wos/woscc/basic-search) on April 10, 2023 to collect all literature data related to therapy for NAFLD. We completed the search and retrieval of data within 1 d in order to reduce the bias caused by frequent database updates. The search formula was set to (TS = ((Nonalcoholic Fatty Liver) OR (non-alcoholic fatty liver disease) OR (NAFLD) OR (MAFLD) OR (metabolic dysfunction-associated fatty liver disease) OR (metabolic associated fatty liver disease)) AND TS = ((therapy) OR (treatment)) AND LA = (English)). The type of documents was set to "articles" and "review" (editorials, proceeding papers, abstracts, and book chapters articles were excluded) with a timespan ranging from January 1, 2010 to April 12, 2023 (Figure 1).

Bibliometric analysis

VOSviewer (version 1.6.19) is a bibliometric analysis software released in 2010 by van Eck *et al*[22]. VOSviewer can extract the key information and show the results of cluster analysis based on network data for generating and investigating maps[23, 24]. Country and institution analysis, journal and co-cited journal analysis, author and co-cited author analysis, and author keywords co-occurrence analysis were performed by the VOSviewer software[25]. Of note, reference co-citation cluster and keyword co-occurrence analysis have the ability to recognize the knowledge structure and research hotspots in a field[26].

The R package "bibliometrix" (version 3.2.1) (https://www.bibliometrix.org) was applied for a thematic evolution analysis and to construct a global distribution network of publications of therapy for NAFLD[27]. CiteSpace (version 6.2.R2 Advanced) is the most popular and recognized bibliometric visualization tool[28] developed by Synnestvedt *et al*[15]. In our study, the CiteSpace map primarily completed the dual-map overlay of journals' analysis and the timeline cluster analysis of keywords. GraphPad Prism 9.5.1.733 and Microsoft Office Excel 2019 were used for data analysis and visualization.

RESULTS

Quantitative analysis of publication

According to our search strategy, there were a total of 10829 studies on therapy or treatment for NAFLD since 2010, including 7826 articles and 3003 reviews. The annual number of publication increased year over year, and it showed explosive growth from 2019 to 2022. Although only a quarter of 2023 was available, there were more than 352 articles, suggesting a continuation of the upward trend (Figure 2A).

Country and institution analysis

These publications came from 120 countries and 8785 institutions. More than half of the publications came from China and the United States (54.9%). The United States had the most publications until 2020 when publications from China increased massively (Figure 2B and C). The top 10 countries were distributed in Europe, Asia, and North America (Figure 2D).

China had the highest single-country publications (SCP) ratio of all countries (total of 3160 papers; SCP: 2763; SCP ratio: 87.4%). The SCP ratio in the United States was 75.0%, with 1978 papers. Of note, there was an abundance of active cooperation between different countries and regions (Figure 2E). Germany and the United Kingdom placed the greatest emphasis on international cooperation; their multiple country publication ratios were 42.1% and 43.3%, respectively (Figure 2D).

Subsequently, we filtered and visualized 76 countries based on the minimum number of five publications and constructed a collaborative network based on the number and relationship of publications in each country. In 2018, the United States was the most important and biggest research center in the world, which was transferred to China in 2020 (Figure 2F).

Then, we selected 1173 institutions based on the minimum number of five publications for visualization and constructed a collaborative network based on the number and relationship of publications of each institution (Figure 2G). The top 10 institutions were located in two countries; seven of the institutions were located in China (Figure 2H). The three institutions that published the most relevant papers were University of California-San Diego, Shanghai Jiao Tong University, and Shanghai University of Traditional Chinese Medicine. University of California-San Diego was the leader in publication output and maintained a high level of publications in recent years (Figure 2I and 2J). In the past 3 years, Chinese institutions have increasingly published NAFLD research. In particular, Shanghai Jiao Tong University ranked second and Shanghai University of Traditional Chinese Medicine ranked third, publishing frequently since 2020 and showing expansive growth in 2022.

Journals and cited and co-cited journals

Publications related to therapy for NAFLD were published in 1523 journals. The *International Journal of Molecular Sciences* published the most papers (n = 281, 2.6%). The top three journals with the most citations were *Hepatology* (n = 21451), *Journal of Hepatology* (n = 20843), and the *World Journal of Gastroenterology* (n = 12454). Among the top 20 journals of total link strength, the journal with the highest impact factor (IF) was *Nature Reviews Gastroenterology & Hepatology* (IF = 73.082).

Among the top 20 co-cited journals, five journals were cited more than 10000 times. *Hepatology* (co-citation = 49058) was the most cited journal, followed by the *Journal of Hepatology* (co-citation = 26782), *Gastroenterology* (co-citation = 21448), *Journal of Biological Chemistry* (co-citation = 12220), and *PLOS ONE* (co-citation = 12083). In

addition, the IF of *The Lancet* was the highest (IF = 202.731) followed by the *New England Journal of Medicine* (IF = 176.079).

The dual-map overlay of journals can show the citation relationships between citing journals on the left and the clusters of co-cited journals on the right through the colored paths[29]. As shown in Figure 3A, the orange path is the main citation path, which represents the studies published in molecular/biology/immunology journals primarily cited by literature in molecular/biology/gene and health nursing/medicine journals. The green path is the main document flow path, which represents the research published in molecular/biology/gene and health nursing/medicine journals primarily cited by studies published in medicine/medical clinical journals.

Historiography analysis

Through historiography analysis by R package "bibliometrix," we observed that the publications with the highest importance in chronological order in the dataset were Sanyal *et al*[30], Neuschwander-Tetri *et al*[31], Rinella *et al*[32], and Younossi *et al*[33] (Figure 3C and Table 1). Table 1 clearly showed that the vast majority of important studies (local cited documents and global cited documents were both high) were randomized controlled trials[30, 31, 34-36]. In addition, two important reviews in 2018 were "Mechanisms of NAFLD development and therapeutic strategies"[37] and "Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention"[33].

Reference with citation bursts and cluster analysis

Reference with citation bursts refers to those references that are frequently cited by scholars in a certain field over a period of time. In our study, the details of 25 references with strong citation bursts by R package "bibliometrix" were listed in Table 2. As shown in Table 2, every bar represents a year, and the red bar represents strong citation burstiness. Citation bursts for references appeared as early as 2010 and as late as 2023. The burst strength of these 25 references ranged from 49.79 to 161.62, and endurance strength was from 2-5 years.

A total of eight major clusters (Q = 0.519; S = 0.8789; Q/S = 0.6532) were generated from the co-citation networks of references after cluster analysis by CiteSpace (Figure 3D). The cluster nomenclature may reflect the study hotspots and frontiers in treatment of NAFLD. The largest cluster was emerging drug, followed by glucagon-like peptide-1 (GLP-1) receptor agonist, liver diseases, metabolic dysfunction-associated fatty liver disease, gut microbiota, hepatologists points, glucose-induced glucagon-like peptide, and glucose metabolism.

Authors and cited and co-cited authors

A total of 51987 authors participated in research on the therapy for NAFLD. Among the top 10 authors, 5 (who were from the United States, the United Kingdom, Italy, and France) each published more than 50 papers (Figure 4A). We built a collaborative network based on authors whose number of published papers was ³ 5 (Figure 4B). Sanyal AJ, Loomba R, and Ratziu V had the largest nodes due to publishing the most related publications. In addition, we observed close collaboration among multiple authors.

Sanyal AJ was considered one of the most distinguished scholars because of his prolific research output (Figure 4A) and the highest number of citations (Figure 4B). His research on fatty liver encompassed a multidisciplinary interactive approach, covering areas such as apoptosis, cancer research, obesity, and microRNA. He hypothesized that NASH was associated with altered liver microRNA expression and alterations in the human gut microbiome were associated with cirrhosis and its complications[38]. He has committed to the field of effective therapeutic development for NASH and has provided summaries of new drugs under development or key ongoing research[39]. These include highly anticipated treatments such as farnesoid X receptor agonists, peroxisome proliferator-activated receptor agonists, GLP-1 receptor agonists, C-C chemokine receptor type 2 and 5 inhibitors, caspase inhibitors, lysyl oxidase-like 2 inhibitors, galectin-3 inhibitors, and others.

According to the H-index, which is a measure used to assess the scientific productivity and impact of researchers, the most influential scientists in this field of NAFLD are Loomba R, Sanyal AJ, and Harrison SA. Loomba R has focused on various aspects of NAFLD, including aging, epidemiology, genetic and environmental susceptibility, natural history, and the treatment of NASH. His research has also explored the efficacy of metformin[40], ezetimibe[41], obeticholic acid (OCA)[31], sitagliptin[42], cenicriviroc[43], selonsert[44], polyethylene glycol[45], and semaglutide[46] in the treatment of NAFLD.

Among the 163234 co-cited authors, five authors were co-cited more than 2000 times. The most co-cited author was Younossi ZM (n = 4007) followed by Chalasani NP (n = 2363) and Sanyal AJ (n = 2088). Younossi ZM concluded that lifestyle modifications to achieve weight loss remains a first-line intervention for patients with NAFLD[47]. He also found that a dosage of 25 mg of OCA significantly improved fibrosis and NASH disease activity scores in patients with NASH[34, 48]. Chalasani NP suggested that bariatric surgery may be a viable option for patients with cirrhosis and extreme obesity[49]. Furthermore, Chalasani NP was involved in research on the treatment of NASH using saroglitazar[50], belapectin[51], and OCA[34, 48] .

Co-cited references

There are 309771 co-cited references on research on the therapy for NAFLD over the past 12 years. In the top 10 co-cited references, all references were co-cited more than 550 times. We selected references with co-citation ^{3} 20 for the construction of the co-citation network map (Figure 4C). Four articles occupied an important position and became the center of the co-citation network diagram. They were Kleiner *et al*[52], Younossi *et al*[53], Sanyal *et al*[30], and Chalasani *et al*[3]. The most cited country is the United States (Figure 4D).

Keywords with citation bursts and clustered network

Keywords with citation bursts refers to those keywords or topics that are frequently discussed in a certain field over a period of time. In our study, 25 keywords with strong citation bursts were identified by R package "bibliometrix" (Figure 4F). Judging from the top 25 keywords with the strongest citation bursts, the whole period can be divided into two: Period I (2010-2017) and Period II (2019-2023). Keywords in Period I primarily included MetS, insulin resistance, lifestyle intervention, and focus on pathogenesis such as lipid peroxidation. Subsequently, keywords in Period II primarily included traditional Chinese medicine, network pharmacology, lifestyle modification, autophagy, and gut microbiota. Cluster analysis of the keyword timeline graph built by CiteSpace showed the evolution of high-frequency keywords (Figure 3B).

Co-occurrence analysis of author keywords

Through the co-occurrence analysis of author keywords (n = 12665), we could quickly capture research hotspots in a certain field. Table 3 showed the top 20 high-frequency keywords excluding the name of the disease (such as NAFLD, MAFLD, NASH, *etc*) for publications regarding therapy for NAFLD. Among these keywords, obesity, insulin resistance, inflammation, and MetS appeared more than 500 times, which represented the main research direction of therapy for NAFLD. We filtered keywords with the number of occurrences ^{3} 20 and performed cluster analysis through VOSviewer (Figure 4E). We obtained five clusters representing five research directions. The keywords in red clusters consisted of inflammation, oxidative stress, lipid metabolism, high-fat diet, lipogenesis, macrophages, *etc*. The keywords in yellow clusters consisted of gut microbiota, probiotics, bile acids, *etc*. The keywords in blue clusters consisted of vitamin E, weight loss, diet, *etc*. The keywords in purple clusters consisted of obesity, MetS, insulin resistance, metformin, adiponectin, diabetes, liraglutide, *etc*. The keywords in green clusters consisted of hepatocellular carcinoma, fibrosis, cirrhosis, live transplantation, immunotherapy, *etc*.

Trend topic analysis

The trend topic analysis of the keywords showed that from 2010 to 2016, the research focused on diet, lifestyle intervention, vitamin E, *etc*. Since 2017, researchers have begun to focus on MetS and actively explore the precise diagnosis and effective treatment for NAFLD. Since the suggestion of renaming NAFLD to MAFLD in 2020, the main keywords were insulin resistance, obesity, inflammation, microbiome, OCA, *etc*. It is worth noting that gut microbiota, gut-liver axis, and traditional Chinese medicine are the latest trending topics (Figure 4G).

DISCUSSION

General information

Since 2010, the annual publications regarding NAFLD treatment have increased, particularly in the past 5 years. The number of related studies has also grown rapidly, indicating that research on NAFLD treatment is in an explosive period, and China and the United States are the leading countries studying the treatment of NAFLD. The United States has been the largest center for publications on the treatment of NAFLD worldwide. However, 2020 was a turning point when the number of publications from China exploded. The cumulative number of publications from China surpassed those from the United States in 2022. China accounts for 70% of the top 10 research institutions regarding publication volume, and the remaining institutions are in the United States. University of California San Diego has been a leader in the NAFLD field; however, research institutions in China have developed rapidly in recent years.

China is developing rapidly in the NAFLD field, surpassing the United States in the number of related publications. There are several reasons for this, which we analyzed below.

The first reason is that the incidence of NAFLD is increasing in China. The global prevalence of NAFLD is 25.2%[53] and 29.2% in China. This has increased rapidly (2008-2010: 25.4%; 2015-2018: 32.3%)[54]. Over the past 20 years, the economic development, urbanization, and dietary patterns in China have changed (*e.g.*, increased consumption of animal-derived foods, refined grains, and highly processed, high-sugar, and high-fat

foods)[55]. This has led to sedentary lifestyles and overnutrition, undergirding obesity and the NAFLD epidemic[56].

The second reason is that the burden of NAFLD in China will continue to increase. With the development of the global economy, the global prevalence of NASH will increase by 15%-56%, and the highest prevalence of NAFLD is expected to occur in China[6]. The Chinese population is large, and the burden of the disease increases exponentially[57, 58]. In a NAFLD disease burden modeling analysis, it was estimated that by 2030, the NASH population in China is expected to increase by 48% compared to that in 2016 (48.26 million), with an 86% increase in HCC (14090)[59].

The third reason is that MetS is a significant public health problem in China[60]. MetS is the strongest risk factor for NAFLD and NASH. The association between NAFLD and MetS may be bidirectional, particularly for diabetes and systemic hypertension, while traditional Chinese culinary culture (high in fat, salt, and fiber) adversely affects these diseases. Given the two-way causal relationship between NAFLD and type 2 diabetes mellitus, a rapid increase in diabetes and obesity rates directly leads to an increase in the prevalence of NAFLD[61].

The fourth reason is that the prevalence of hepatitis B in China has decreased. China has the highest prevalence of hepatitis B. However, government control measures, effective hepatitis B virus vaccination, and standardized anti-hepatitis B virus treatment have had a positive impact on decreasing the prevalence. Hepatitis B in China has been largely controlled, making chronic liver disease caused by NAFLD increasingly prominent.

The fifth reason is that the government attached importance to scientific research and improved the level of scientific research. In 2010, China spent less than half the amount on research and development as the United States (208280000 USD *vs* 444709000 USD) (https://data.oecd.org/rd/gross-domestic-spending-on-r-d.htm). Recently, due to economic development and robust government support, China has become the world's second-largest industry research and development center, with its total research and development expenditure reaching 80% of that of the United States'

research and development expenditure (631845000 USD) in 2019 (https://www.oecd.org/sti/msti-highlights-march-2021.pdf). Over the years, basic and clinical research on liver disease in China has been listed as a priority investment area by the National Natural Science Foundation of China (NSFC). From 2010 to 2022, the total number of research projects related to fatty liver funded by the NSFC was 7515, with a total funding of 535000000 USD. The number of projects and funding provided by the NSFC has increased annually. During the same period the National Institutes of Health in the United States funded 3304 projects (1267000000 USD) in the field of fatty liver disease. Although the investment gap between China and the United States is still significant, the number of NSFC-funded projects has surpassed that of the United States.

The final reason is the emphasis on traditional medicine. The NSFC has funded 960 projects related to traditional Chinese medicine and integrated traditional Chinese medicine and Western medicine, while there are few funded projects related to traditional medicine in the United States. This also reflects the advantages and characteristics of the fatty liver research field in China. For example, Shanghai University of Traditional Chinese Medicine systematically and comprehensively analyzes the multitarget mechanism of action of traditional Chinese medicine compounds[62-64] and explores the metabolite-target-disease network of traditional Chinese medicine[65-67] in the treatment of NAFLD. The concept of multitarget therapy with traditional Chinese medicine compounds is consistent with the multiple pathogeneses of NAFLD. It is challenging for a single drug to address the diversity of the pathogenesis of NAFLD. Therefore, traditional Chinese medicine and compound multitarget active ingredients may usher in a new era in the treatment of NAFLD.

Although the number of publications in China has grown rapidly in recent years, the citation volume is still relatively low. Possible causes are: (1) Insufficient international cooperation in China. China's SCP ratio was as high as 87.4%, the highest among all countries; (2) The international discourse of China in this field needs to be improved. The top experts in this field are all American scholars who have decades of

experience in the field. Their research directions are focused and deep, which allows the publication of their research in top journals. Conversely, researchers in China lack international academic authority and have few articles published in top journals; (3) The quality and innovation of publications needs to be improved. Research in China is primarily basic, and there is a lack of multicenter randomized controlled trials and large-sample prospective cohort studies with high clinical evidence levels.

Although Chinese scientists are not ranked high regarding personal influence, they are ranked second only to the United States in the ranking of cited countries, which indicates that the overall scientific research strength in China cannot be underestimated. The top 30 cited Chinese studies focused on epidemiology[59, 61, 68, 69], basic research, particularly pathogenesis[70-76], the search for therapeutic targets[77-89], *in vitro* tests[76, 82, 86], animal experiments[87-89], and review articles[81, 83]. At present, most data on drug treatment originate from foreign research, and there is a lack of research on the Chinese population. This is an important direction that needs to be addressed in future research on NAFLD treatments in China.

Most studies on NAFLD treatment have been published in the *International Journal of Molecular Sciences* (IF = 6.208, second quartile), indicating that it is currently the most popular journal in this field of research. Among the top 20 journals, *Nature Reviews Gastroenterology and Hepatology* (IF = 73.082) had the highest IF. For co-cited journals, we found that most were high-impact top quartile journals. These high-quality international journals provide research support for the treatment of NAFLD. Among them, *Hepatology* and *Journal of Hepatology* are the most popular co-cited journals, indicating the high quality of the journal in the field of NAFLD research. Additionally, the research results in molecular/biology/immunology journals mainly flow to molecular/biology/genetic and health care/medical journals, which also indicates that the development of therapeutics is inseparable from basic research fields such as molecular biology, genetics, and immunity. The articles in the field of NAFLD treatment research have been cited by medical/clinical journals, which illustrates the clinical application value of treatment research.

Historiography analysis

Co-cited references are regarded as the basis of research in a certain field, and the development and evolutionary dynamics of a discipline can be explored by studying co-cited networks[90]. We selected the 10 most co-cited articles to determine the research basis for the treatment of NAFLD. Among the 309771 cited publications, the design and validation of the histology scoring system for NAFLD published by Kleiner *et al*[52] in 2005 was the most cited study. The top 10 citations covered five main topics: diagnosis; epidemiology[33, 53]; pathogenesis; therapeutic drug development[30, 31]; and review of NAFLD[91]. Epidemiology is the exploration of disease prevalence and incidence[33], global burden trend prediction and prevention[53], and the overall understanding of the disease. The standardization of diagnostic methods[3, 52, 58] is a prerequisite for disease management and guiding treatment. The exploration of pathogenesis[37, 92] is conducive to the development of new drugs and individualized and precise treatment. Vitamin E, pioglitazone[30], and OCA[31] are the most promising NAFLD therapeutics in development. These main topics also reflect the evolution of NAFLD drug research directions.

Historiography analysis is commonly described as "the history of history" and seeks to explain origins and evolution providing a clearer understanding of the future. Results from the first randomized controlled trial in 2010 of adult NASH patients using lifestyle modification as an active therapeutic intervention suggested that lifestyle changes focused on diet, exercise, and behavioral changes could successfully improve overall histological activity, degree of steatosis, and liver chemistry of NASH[35]. Weight loss, physical activity, reduction of a sedentary lifestyle, and dietary changes should be treated as the first-line treatment of NAFLD/NASH and assessed after 6 mo. If this is not effective, then additional treatment options, such as medication, may be considered[29].

Simultaneously, it was hypothesized that oxidative stress dealt a second "blow" to the liver, and there was a strong correlation between the severity of NASH and the

degree of oxidative stress. However, the results from antioxidant treatment are inconsistent in the treatment of NAFLD[93]. Only vitamin E, through inhibiting fatty acid oxidation, is superior to placebo in the treatment of NAFLD[30]. NAFLD/NASH is closely related to the global diabetes and obesity epidemics. Some hypoglycemic drugs, such as metformin, can improve aminotransferase levels, and pioglitazone can improve steatohepatitis (recommended NASH regimen: pioglitazone or vitamin E combined with high-dose ursodeoxycholic acid)[29]. However, in 2011, it was found that neither vitamin E nor metformin was superior to placebo for the primary outcome of a sustained reduction in alanine aminotransferase levels in children with NAFLD[94]. A 2012 meta-analysis noted that vitamin E improved histological indices after 2 years of use, but increased insulin resistance and plasma triacylglycerol were observed. Long-term use may increase the risk of prostate cancer, and there is a lack of efficacy in reducing liver fibrosis[37]. In patients who did not respond to lifestyle interventions, pioglitazone improved histological disease activity, slowed fibrosis progression, and broadly improved the cardiometabolic endpoints[95]. However, the use of thiazolidinediones has been limited by adverse effects, such as weight gain, fluid retention, increased risk of fractures (particularly in older women), and bladder cancer.

OCA is a semi-synthetic derivative of human cholic acid, which is a natural agonist of farnesoid X receptors. Farnesoid X receptors are nuclear hormone receptors that regulate glycolipid metabolism, can block the conversion of cholesterol to bile acids, increase serum cholesterol concentration, and promote the reverse transport of cholesterol from tissues. A phase 2 trial in 2013[96] and a multicenter randomized controlled trial in 2015 confirmed that OCA was well tolerated in the treatment of NAFLD, increased insulin sensitivity and weight loss, and reduced markers of liver inflammation and fibrosis[31]. An interim analysis of a phase 3 clinical trial in 2019 concluded that 25 mg/day of OCA resulted in significant histological improvements in NASH[34] and unfortunately in itching and a moderate increase in low-density lipoprotein cholesterol.

The 2016 "two-hit" hypothesis became obsolete, and the "multiple blows" hypothesis more accurately explained the pathogenesis of NAFLD, which includes insulin resistance, hormones secreted by adipose tissue, nutritional factors, gut microbiota, and genetic and epigenetic factors[97]. In 2016, Buzzetti *et al*[97] evaluated the association between intestinal dysbiosis and liver fibrosis in human NAFLD and found that animal diets favor the accumulation of branched-chain fatty acids of *Bacteroides*, thereby promoting insulin resistance and increasing the risk of NASH. The diet of agricultural societies is rich in fiber, starch, and plant polysaccharides, which promotes the abundance of *Prevobacterium*, and its abundance decreases with an increase in liver lesions. A gut microbiota analysis provided a theoretical basis for NAFLD patients to regulate diet structure and intestinal microbial preparations[98].

In 2018, probiotics containing endotoxin antibodies and bovine colostrum were evaluated for their efficacy in the treatment of NASH by enhancing brown adipose tissue to burn glucose and ameliorate obesity and glucose abnormalities[37]. Insulin resistance has long been considered an important component of the pathogenesis of NAFLD and worsens as the disease progresses. GLP-1 analogs reduce hepatic steatosis, liver enzyme concentrations, and insulin resistance by inducing insulin secretion and reducing glucagon secretion in a glucose-dependent manner. Armstrong *et al*[36] reported the effects of GLP-1 analogs on liver histology in patients with NASH in a randomized, placebo-controlled trial. Liraglutide was well tolerated in this study, improving several key components of MetS, including weight and glycemic control, and improving NASH histology.

The pathogenesis of NAFLD involves multiple drivers, and no more than 40% of patients in clinical trials have shown benefits from monotherapy, which is likely insufficient to prompt regulatory approval of monotherapy for long-term treatment of NAFLD. Current research favors combination therapies including drug combinations, single-agent searches for multitarget effects, and comorbidities in patients with NAFLD. We hypothesize that NAFLD has progressed to become the most common cause of chronic liver disease worldwide[57]. The global burden of NAFLD and NASH is growing

rapidly. Future research should focus on accurate non-invasive measurement of biomarkers and clarification of pathogenic pathways, which will facilitate the development and effective evaluation of the efficacy of new drugs. Simultaneously, we continue to actively explore effective treatments, including the development of effective treatments for patients with NASH and prevention methods for individuals at high risk of progression[56].

Research trends and hotspots

Citation bursts represent emerging topics in a particular field of study[99]. Based on the main research content[5, 30, 97, 100, 101] of the strongly cited burst references (Table 2), we found that renaming NAFLD to MAFLD[10, 102] and the development of semaglutide for NAFLD treatment[103] may represent the main hotspots of current NAFLD treatment research. Both of these topics were cited in 2021. As shown in Table 2, 16 of the 25 citations were reviewed, and high-quality reviews reflected understanding of the disease at a certain time. With the exploration of the pathogenesis of NAFLD, the naming and diagnosis of the disease have been gradually updated and standardized[104], and its treatment strategy has gradually evolved from vitamin E, weight loss, and lifestyle interventions for the management of metabolism-related diseases.

In addition to citation bursts, keywords can also quickly capture the distribution and evolution of hot topics in our research field. The top keywords from the last 2 years included gut microbiota, traditional Chinese medicine, network pharmacology, OCA, and clinical practice guideline. In keyword trend topic analysis, it was evident that MAFLD, traditional Chinese medicine, gut-liver axis, and gut microbiota were the most frequently discussed keywords. Interestingly, insulin sensitizers such as pioglitazone for the treatment of fatty liver were popular in 2012, reached their peak from 2014 to 2016, and gradually faded in 2020.

Due to the complex pathogenesis of NAFLD, it is challenging to treat. Effective treatment requires precise localization based on the patient's phenotype and genetic

background[10]. The study of treatment strategies, epidemiological knowledge, pathogenesis, and precise diagnosis (including non-invasive diagnostic techniques) may all be integrated into the consideration of heterogeneity in disease treatment. The current mainstream view is to replace the diagnosis of NAFLD/NASH with MAFLD. Hence, this name change has greatly promoted the transformation of the treatment strategy of the disease. The previous treatment plan mainly included two directions: (1) Correction of insulin resistance and reduction of fat mass with a focus on lifestyle changes for weight loss, including physical activity, diet, insulin sensitizers, and anti-obesity surgery; and (2) Prevention/reversal of lipotoxicity-induced hepatocellular damage by inhibiting lipid peroxidation and oxidative stress or by using anti-inflammatory, anti-apoptotic, or other hepatoprotective agents.

Future therapeutic research on NAFLD/MAFLD should focus on comprehensive therapies tailored to individual patients, considering the above two therapeutic directions, and targeting multitarget and multiaction mechanisms[29]. Research on gut microbiomes and traditional medicine will continue to be a short-term research hotspot. OCA, which has entered phase 3 clinical validation, and semaglutide, which is currently under study, are likely to become the first approved drugs for the treatment of NAFLD.

Advantages and shortcomings

This study had several advantages. First, we systematically analyzed the research on NAFLD/MAFLD treatment through bibliometrics, which provided comprehensive guidance for scholars who are interested in related research. Second, we used three bibliometric tools simultaneously for the survey, hence our data analysis process was objective. Third, bibliometric analysis provided a more complete insight into hot topics and frontiers than traditional reviews.

This study also had some shortcomings. First, the data for this study was extracted from the Web of Science Core Collection database only. Other databases were not searched, and some relevant studies may have been missed. This may increase the risk of bias in the selection of the literature. Second, we filtered studies published in English,

which means that non-English language papers were underestimated. In addition, the 2023 publication data was not fully included, resulting in insufficient statistics for 2023. The research directions of NAFLD/MAFLD therapeutic research, cluster analysis, and trend topic analysis may not be comprehensive and may not cover marginal and emerging topics. Last but not least, bibliometric analysis is an analytical method of bibliometrics that focuses on the analysis of measures such as the number of articles issued, cited and quoted, with particular consideration of research countries, institutions and individuals, but pays less attention to the content of the articles themselves; as such, it may not be able to detect and temporally count research for a new type of topic, especially for the beginning stage of a certain research field that may become a hot spot in the future.

CONCLUSION

The treatment of NAFLD has important research value and application prospects, as indicated by the rapidly increasing number of documents. The study of treatments and therapies for NAFLD, particularly NASH, is highly valued worldwide. The leading countries publishing NAFLD research are the United States and China. NAFLD research in China is developing rapidly, with their number of published articles quickly surpassing the United States in recent years. However, it is worth noting that most of the top scientists in the field are from the United States. Conducting an in-depth study of the pathogenesis can foster the development and research of new drugs, while accurate diagnosis, specifically through non-invasive diagnostic technology, contributes to better patient management and efficacy evaluation. The multiple-hit pathogenesis of NAFLD and the renaming of NAFLD to MAFLD require enhanced multidisciplinary and multicenter cooperation. Mechanism studies provide guidance for therapeutic strategies, while clinical application and treatment research represent the transformation of basic research.

ARTICLE HIGHLIGHTS

Research background

Nonalcoholic fatty liver disease (NAFLD) is a chronic disease that threatens the lives of numerous people globally. However, there are limited bibliometric statistical analyses on NAFLD. In this study, we conducted a bibliometric analysis to examine previous research on NAFLD, aiming to identify key contributors and assess the current research status in the field of liver health. Moreover, we identified prospects for future research trends and development.

Research motivation

The progression of NAFLD leads to liver fibrosis and end-stage cirrhosis. However, no treatment has been established. Many mechanistic studies and drug trials have been undertaken for the development of new drugs for NAFLD treatment. In particular, NAFLD was renamed metabolic dysfunction-associated fatty liver disease, and there was a major shift in treatment strategy. It is necessary to understand the knowledge structure of NAFLD through bibliometrics, focusing on research hotspots in order to explore the direction of development in this field.

Research objectives

The treatment of NAFLD has important research value and application prospects. It is anticipated that drugs may become available in the near future. However, no drugs are currently approved. Clinical phase 2b and phase 3 studies have achieved certain efficacy. While trends and hotspots can be clearly studied through bibliometric analysis, clues can reveal possible future therapeutic strategies for scholars in the field.

Research methods

Bibliometric analysis was applied to provide a comprehensive understanding of the knowledge structure of a research field, and visualization analysis was used to visualize the results. Historiography analysis, bursts and cluster analysis, co-occurrence analysis,

and trend topic analysis were also utilized to reveal the knowledge structure and research hotspots in this field.

Research results

The bibliometric study identified recent research frontiers and hotspot directions, which will provide a valuable reference for scholars researching treatments for NAFLD. The leading countries publishing NAFLD research are the United States and China. The NAFLD research field in China has developed rapidly in the past 3 years.

Research conclusions

Research on the treatment and therapeutics of NAFLD, especially nonalcoholic steatohepatitis, is highly valued by the global academic community. It is likely that obeticholic acid, which has entered phase 3 clinical validation, and semaglutide, which is currently under study, will become the first approved drugs for the treatment of NAFLD.

Research perspectives

The multiple-hit pathogenesis of NAFLD and the renaming of NAFLD to metabolic dysfunction-associated fatty liver disease requires enhanced multidisciplinary and multicenter cooperation. More clinical trials are needed to verify the safety and efficacy of drugs and to discover new ones.

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