Hepatic Medicine: Evidence and Research

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Mapping the Intellectual Landscape: A 20-Year Bibliometric Analysis of Mechanisms in Metabolic Dysfunction-Associated Steatotic Liver Disease

Jia-Wei Huang[1], Ng Xin Man[1], Hong-Xin Wang[2], Xiang-Ting Ai[1], Dan-Lei Wei[1], Yun-Kai Dai[3]

[1]The Affiliated Guangzhou Hospital of Traditional Chinese Medicine, Guangzhou University of Chinese Medicine, Guangzhou, Guangdong, 510130, People's Republic of China; [2]School of Traditional Chinese Medicine, Jinan University, Guangzhou, Guangdong, 510632, People's Republic of China; [3]Department of Gastroenterology, The Affiliated Traditional Chinese Medicine Hospital, Guangzhou Medical University, Guangzhou, Guangdong, 510130, People's Republic of China

Correspondence: Dan-Lei Wei, The Affiliated Guangzhou Hospital of Traditional Chinese Medicine, Guangzhou University of Chinese Medicine, Guangzhou, Guangdong, 510130, People's Republic of China, Email 939762912@qq.com; Yun-Kai Dai, Department of Gastroenterology, The Affiliated Traditional Chinese Medicine Hospital, Guangzhou Medical University, Guangzhou, Guangdong, 510130, People's Republic of China, Email yun-kaidai@hotmail.com

Background and Purpose: Metabolic dysfunction-associated steatotic liver disease (MASLD), affecting between 20% and 30% of adults around the world, represents a growing public health burden characterized by hepatic steatosis concurrent with cardiometabolic risk factors. Despite two decades of research into its pathophysiology – spanning insulin resistance, gut-liver axis dysregulation, and genetic/epigenetic mechanisms – the vast body of literature has not yet been systematically mapped. A comprehensive bibliometric analysis mapping the field's evolution, collaborative networks, and knowledge gaps remains lacking. Therefore, a 20-year bibliometric analysis (2005–2024) on the mechanism of MASLD was conducted.

Patients and Methods: Publications on the mechanisms of MASLD were retrieved from the Web of Science Core Collection. The search period spanned from January 1st, 2005 to December 31st, 2024. Data were analyzed with CiteSpace (v6.3.R1) and VOSviewer (v1.6.20) to assess publication trends, country/institution contributions, journal influence, author networks, keyword clusters, and reference co-citations.

Results: China (40.75% of publications, n=4368) and the USA (21.18%, n=2270) dominate research output, with the Chinese Ministry of Education, Shanghai Jiao Tong University, and Harvard University as top institutions. International collaboration is prominent, particularly between China and the USA. International Journal of Molecular Sciences, Nutrients, and high-impact journals (Journal of Hepatology, IF=33.0) are key publication venues. Keyword analysis identifies five major research clusters: (1) lipid metabolism/mitochondrial dysfunction, (2) dietary factors/exercise, (3) inflammation/fibrosis, (4) metabolic comorbidities, and (5) gut-liver axis dysregulation. Temporal trends reveal a shift from insulin resistance/oxidative stress toward microbiota and molecular drivers (eg, WDR6-PPP1CB). Influential authors include Nobili Valerio (most productive) and Gerald I. Shulman (most cited; n=7703). Reference bursts highlight seminal works on disease burden (Younossi 2016) and pathogenesis (Powell 2021, Friedman 2018).

Conclusion: This first comprehensive bibliometric analysis of MASLD mechanisms highlights dynamic growth, interdisciplinary collaboration, and evolving research hotspot. Persistent challenges include mechanistic heterogeneity, early diagnostic tools, and targeted therapies. In conclusion, this analysis provides a foundational roadmap for researchers and policymakers, highlighting the imperative to translate mechanistic insights into precision diagnostics and therapies to mitigate the growing global burden of MASLD.

Keywords: bibliometrics, metabolic dysfunction-associated steatotic liver disease, mechanism, therapy

Introduction

MASLD disease (MAFLD), formerly termed non-alcoholic fatty liver disease (NAFLD)(Now Referred to as Metabolic Dysfunction-Associated Steatotic Liver Disease, MASLD), represents a spectrum of hepatic disorders characterized by pathological lipid accumulation in hepatocytes (>5% steatosis) concurrent with cardiometabolic risk factors such as obesity, type 2 diabetes, or dyslipidemia.[1,2] This nomenclature evolution from NAFLD to MAFLD and subsequently to

Received: 21 August 2025
Accepted: 18 November 2025
Published: 3 December 2025

MASLD reflects an ongoing effort to refine diagnostic criteria towards a more positive, pathophysiology-based framework, moving beyond the exclusion of alcohol consumption, though debates continue regarding the optimal classification and its clinical implications. With an epidemiological investigation reporting age-standardized rates and average annual percent change (AAPC) from 1990 to 2021, MASLD, impacting between 20% and 30% of adults, mirrors the concurrent rise of obesity and type 2 diabetes mellitus.[2,3] This disease continuum ranges from simple steatosis to MASLD, fibrosis, and hepatocellular carcinoma (HCC), posing a formidable public health burden exacerbated by the parallel rise in obesity and insulin resistance (IR).[4]

The pathophysiological understanding of MASLD has undergone transformative shifts over the past two decades, converging on several core mechanistic themes. These include, centrally, IR disrupting hepatic lipid homeostasis; dysregulation of the gut-liver axis, involving intestinal dysbiosis, impaired barrier function, and altered signaling via molecules like bile acids and endotoxins; inflammatory pathways driving progression from steatosis to steatohepatitis; and emerging roles of novel cell death mechanisms such as ferroptosis. Early studies emphasized IR as a central driver, yet uncovered a paradox: while hepatic IR impairs insulin-mediated suppression of gluconeogenesis, it paradoxically preserves or even enhances de novo lipogenesis (DNL), leading to lipid deposition.[5] This anomaly was partially resolved in 2023 by Zhao et al, who identified WDR6 as a critical molecular switch that promotes DNL in IR states. Over this period, research has coalesced around several core mechanistic themes. These include: (1) dysregulation of lipid metabolism and associated mitochondrial dysfunction; (2) the influence of dietary factors, such as fructose, and the role of physical exercise; (3) the central pathways driving inflammation and the progression to fibrosis; (4) the interplay with key metabolic comorbidities like obesity, type 2 diabetes, and cardiovascular disease; and (5) dysregulation of the gut-liver axis, encompassing intestinal barrier integrity, microbiota composition, and related signaling molecules like bile acids. Concurrently, the "gut-liver axis" framework gained prominence, highlighting intestinal dysbiosis as a key modulator of MASLD progression.[6] Clinical cohorts revealed MASLD-specific microbial signatures that disrupted intestinal barrier integrity, elevated endotoxin translocation, and dysregulated bile acid (BA) and short-chain fatty acid (SCFA) metabolism, which exacerbated steatosis and inflammation.[7] Genetic and epigenetic investigations further identified polymorphisms in lipid-metabolizing enzymes (eg, FADS1, FADS2, ELOVL2, and ELOVL5) as determinants of individual susceptibility to steatohepatitis and fibrosis, underscoring MASLD as a multifactorial disorder.[8] However, despite extensive research, the heterogeneity of MASLD mechanisms, challenges in early diagnosis, and gaps in targeted therapies remain unresolved.

Bibliometric analysis – a quantitative method for evaluating scientific literature – has become instrumental in mapping research trends, identifying knowledge gaps, and forecasting future directions in medicine.[9] While prior bibliometric studies have delineated evolving paradigms in hepatology, including liver fibrosis treatment and regeneration mechanisms,[10,11] and more general analyses of NAFLD/MAFLD literature, a comprehensive, mechanism-focused bibliometric analysis spanning the full conceptual evolution of MAFLD research over the last two decades remains absent. This gap limits systematic synthesis of interdisciplinary contributions, geographic collaboration patterns, and translational research priorities in MASLD.

We therefore undertake a 20-year bibliometric analysis (2005–2024) to map the intellectual landscape of MASLD research. By examining publication trends, influential authors, institutions, and keyword clusters, we aim to: (1) identify seminal contributions and emerging themes, (2) assess global collaboration networks, and (3) pinpoint translational hurdles and opportunities. Our study is the first to specifically apply bibliometric methods to deconstruct the evolving research fronts and collaborative networks underlying the mechanistic investigation of MAFLD, thereby providing a novel evidence base. Moreover, our findings will provide researchers, clinicians, and policymakers with evidence to guide resource prioritization and innovation strategies in MASLD management.

Materials and Methods

Data Selection

On June 14th, 2025, pertinent information was extracted from the Web of Science Core Collection (WoSCC), a database of significant influence. The search period spanned from January 1st, 2005 to December 31st, 2024, with the language restricted to English. There were some criteria in this analysis. Inclusion: Articles or reviews. Exclusion: Non-English

articles and non-research articles (eg, editorials). Boolean logic operators were utilized to employ search terms including ("metabolic-associated fatty liver disease" OR "metabolic dysfunction-associated steatotic liver disease" OR "MAFLD" OR "MASLD" OR "nonalcoholic fatty liver disease" OR "NAFLD") AND ("mechanism" OR "mechanisms" OR "pathogenesis" OR "pathogenic mechanism"). Detailed search strategy could be found in [Supplementary Material S1]. The outcomes were chosen in the "Full Record and Cited References" format and downloaded as "Plain Text" documents. Consequently, the downloaded files, initially in the "download_*.txt" format, were renamed to be compatible with CiteSpace. Meanwhile, deduplication methods were used by CiteSpace. Furthermore, ethical approval was deemed unnecessary for this research since the data were obtained and exported directly from the WoSCC database.

The WoSCC was selected as the sole database for this analysis due to its comprehensive coverage of high-impact journals, its structured data format which was highly compatible with bibliometric software like CiteSpace and VOSviewer, and its extensive history of use in similar bibliometric studies, ensuring consistency and comparability of findings. While we acknowledged that incorporating additional databases could broaden the scope, the primary aim of this study was to map the core, high-impact research landscape in this field. A single, standardized database was therefore deemed most appropriate to maintain data homogeneity and analytical rigor for this initial comprehensive overview.

Data Analysis and Visualization

Currently, widely utilized bibliometric software comprised CiteSpace, VOSviewer, UCINET, SciMAT, Pajek, and Bicomb.[12] However, there was no agreement on which software was superior. Considering their distinctive features and in accordance with our practical needs, CiteSpace [version 6.3.R1 (64-bit)] and VOSviewer (version 1.6.20) were chosen for bibliometric analysis in this study.[13,14]

CiteSpace, a Java-based citation visualization software developed by Professor Chaomei Chen, functioned not only as a citation visualization tool but also as a bibliometric analysis tool. It had the capability to identify potential research hotspots and trends within a specific field by generating knowledge maps.[15] For the analyses in CiteSpace, the time-slicing was set from January 2005 to December 2024, with a 1-year time slice interval. The selection criteria for each slice was set to the top 50 most cited or occurring items per slice. The pathfinder and pruning sliced networks algorithms were used for network simplification and visualization. In this study, we analyzed and visualized the annual growth trend of publication outputs, countries/regions and institutions, journals and co-cited journals, authors and co-cited authors, the frequency of keyword occurrences, co-cited references, and reference bursts, all with the aim of understanding the mechanism of MASLD.

VOSviewer, a Java-based bibliometric mapping software developed by Leiden University, excelled in the visualization of scientific knowledge and the management of large bibliometric maps derived from network data.[14] For analyses in VOSviewer, a minimum threshold was set for the number of occurrences or citations of an item (eg, a minimum of 5 occurrences for keywords, a minimum of 20 documents for authors) to be included in the maps. The clustering resolution parameter was generally kept at the default setting, which provided a balanced level of detail for cluster identification. The visualization maps were generated using the association strength normalization method. By utilizing bibliographic and text data, this software analyzed and visualized productive journals and authors, relevant knowledge maps, keyword research, and cluster maps, thereby serving as a valuable complement to the capabilities of CiteSpace software. Meanwhile, we performed bibliographic coupling using VOSviewer to identify groups of publications that share common references, thereby highlighting thematic connections and intellectual foundations within the MASLD mechanism research domain. This analysis helped reveal underlying research fronts and emerging thematic specialties that may not be fully captured by co-citation or keyword co-occurrence alone.

Moreover, the database of WoSCC was handled using Microsoft Office Excel 2010, which also served for the analysis and visualization of yearly publications.

Results

A flowchart illustrating the bibliographic retrieval and research steps of this study is presented in Figure 1.

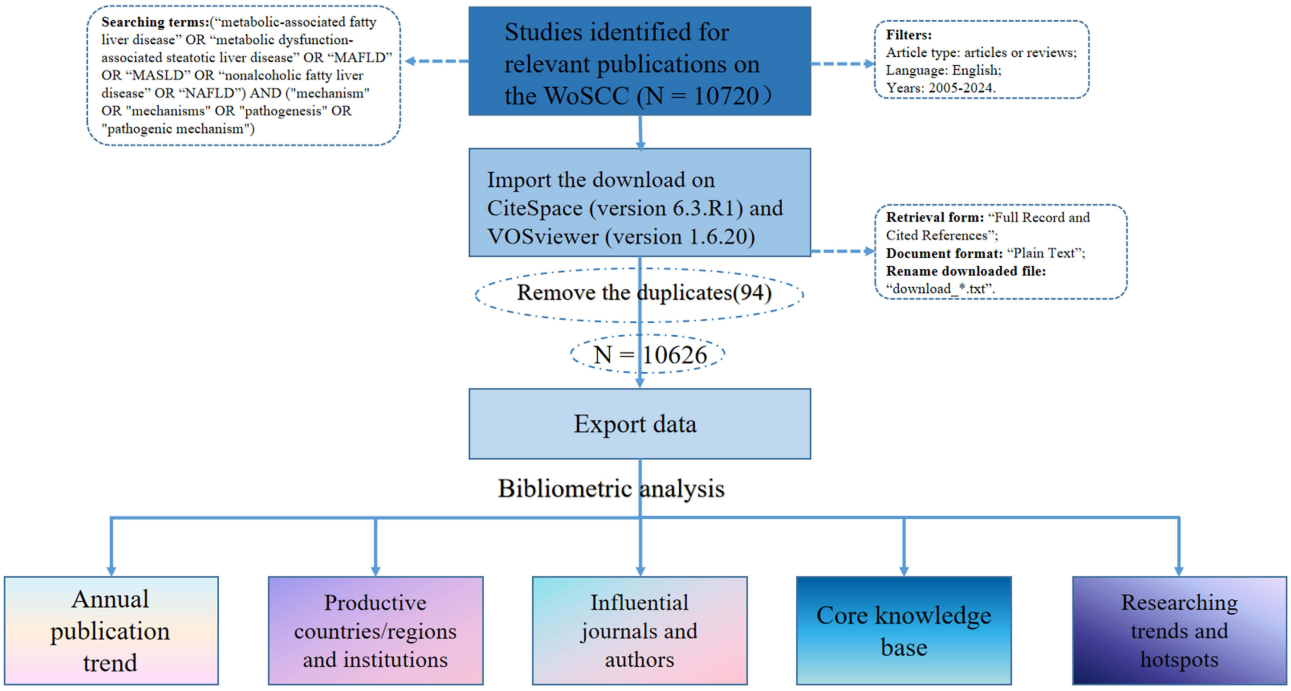

Figure 1 Flowchart of this study.tif.

Annual Growth Trend of Publications

Based on the data selection criteria, a total of 10626 papers on the mechanism of MASLD are retrieved from WoSCC between 2005 and 2024 [Supplementary Material S2]. These include 7668 (72.16%) original articles and 2958 (27.84%) reviews. As shown in Figure 2, the number of publications on the mechanism of MASLD has increased steadily and progressively over the years.

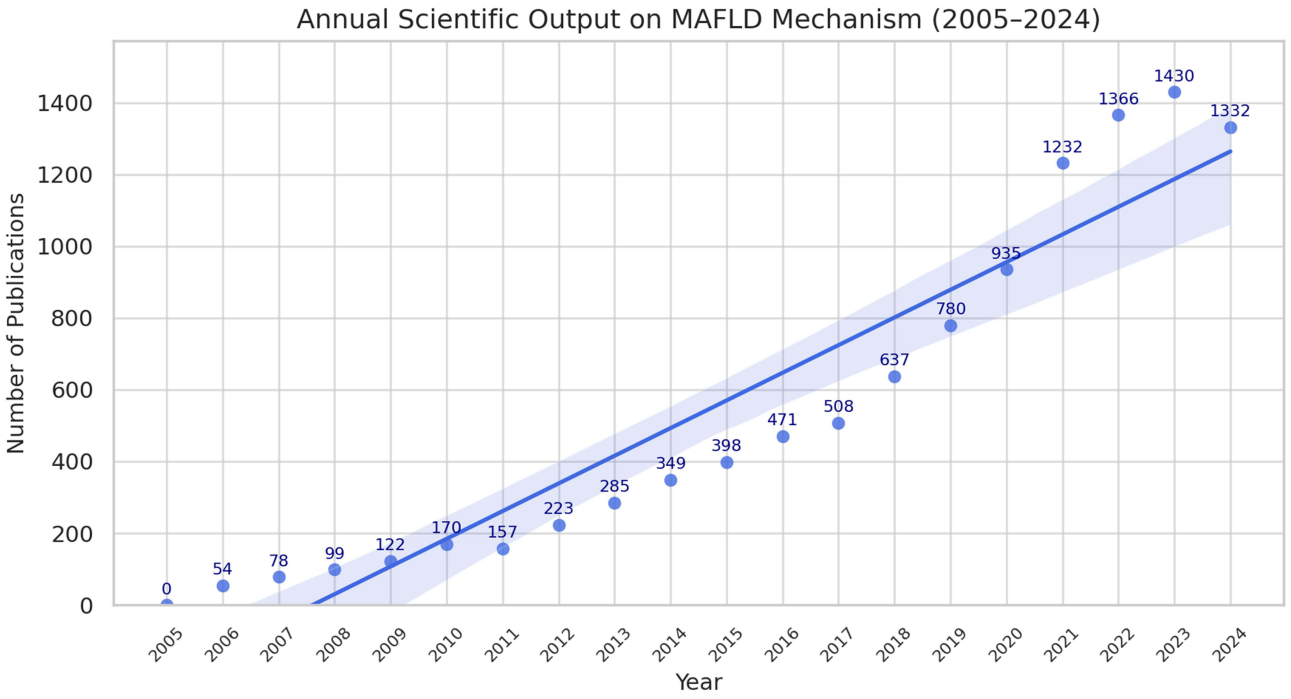

Figure 2 Chronological trend of publications about the mechanism of MASLD research from 2005 to 2024.tif.

Productive Countries/Regions and Institutions

A total of 10626 research papers result from collaboration among 349 institutions across 110 countries/regions. China contributes the most publications (4368; 40.75%), followed by the USA (2270; 21.18%), Italy (856; 8%), South Korea (536; 5%), and Japan (510; 4.80%). The USA demonstrates the highest centrality (0.25), indicating its pivotal role in international collaborations. Among institutions, China's Ministry of Education leads with 408 publications (3.81%), followed by the University of California System (242; 2.26%) and Shanghai Jiao Tong University (228; 2.13%). Detailed rankings are provided in Table 1.

As depicted in Figure 3A, which portrays the countries/regions co-occurrence map, it delineates a dense network of interconnections among nations, with a special emphasis on the numerous collaborations between CHINA and the USA. Turning our attention to Figure 3B, which showcases the institutions co-occurrence map, it becomes evident that the Ministry of Education of China, Shanghai Jiao Tong University, Zhejiang University, and Fudan University have emerged as pivotal players, characterized by their high centrality and frequent collaborative endeavors. On a global scale, institutions like Harvard University, the US Department of Veterans Affairs, and Inserm (Institut National de la Santé et de la Recherche Médicale) have also exerted considerable influence. The color gradient utilized in the map represents the temporal progression of institutional involvement, with warmer hues signifying more recent activities.

Productive Journals and Co-Cited Journals

To scrutinize the journals with the largest number of published articles and co-citations in the field of MASLD, VOSviewer (version 1.6.20) and CiteSpace [version 6.3.R1 (64-bit)] are employed to perform analyses on co-citation and journals being co-cited. The 10626 documents are published across 1398 academic journals. The International Journal of Molecular Sciences has the highest number of publications (n=356), followed by Nutrients (n=252), Hepatology (n=204), Frontiers in Pharmacology (n=189), and World Journal of Gastroenterology (n=188). Among co-cited journals, Hepatology ranks first (47376 citations), followed by Journal of Hepatology (26767) and Gastroenterology (19755). Nine of the top 10 co-cited journals are in Q1 JCR (Journal Citation Reports) category, with Nature having the highest impact factor (IF = 69.504). Full details are available in Table 2.

Table 1 The Top 10 Countries/Regions and Institutions in Bibliometric Analysis of Mechanisms in MASLD

Rank	Country/ Region	Article count (%)	Centrality	Year	Institution (Country/Region)	Article Count (%)	Centrality	Year
1	PEOPLE'S REPUBLIC of CHINA	4368 (40.75%)	0.05	2006	Ministry of Education - China (China)	408 (3.81%)	0.11	2013
2	USA	2270 (21.18%)	0.25	2006	University of California System (United States)	242 (2.26%)	0.16	2006
3	ITALY	856 (8%)	0.14	2006	Shanghai Jiao Tong University (China)	228 (2.13%)	0.05	2013
4	SOUTH KOREA	536 (5%)	0.05	2006	Chinese Academy of Sciences (China)	214 (2.00%)	0.06	2013
5	JAPAN	510 (4.8%)	0.07	2006	Zhejiang University (China)	192 (1.79%)	0.03	2009
6	GERMANY	472 (4.4%)	0.08	2006	Shanghai University of Traditional Chinese Medicine (China)	183 (1.71%)	0.02	2014
7	ENGLAND	449 (4.19%)	0.13	2006	CIBER - Centro de Investigacion Biomedica en Red (Spain)	174 (1.62%)	0.06	2009
8	SPAIN	357 (3.33%)	0.05	2007	Fudan University (China)	170 (1.59%)	0.08	2012
9	FRANCE	247 (2.3%)	0.1	2006	Institut National de la Sante et de la Recherche Medicale (Inserm) (France)	170 (1.59%)	0.05	2008
10	AUSTRALIA	238 (2.22%)	0.05	2006	US Department of Veterans Affairs (United States)	168 (1.57%)	0	2007

https://doi.org/10.2147/HMER.S562237

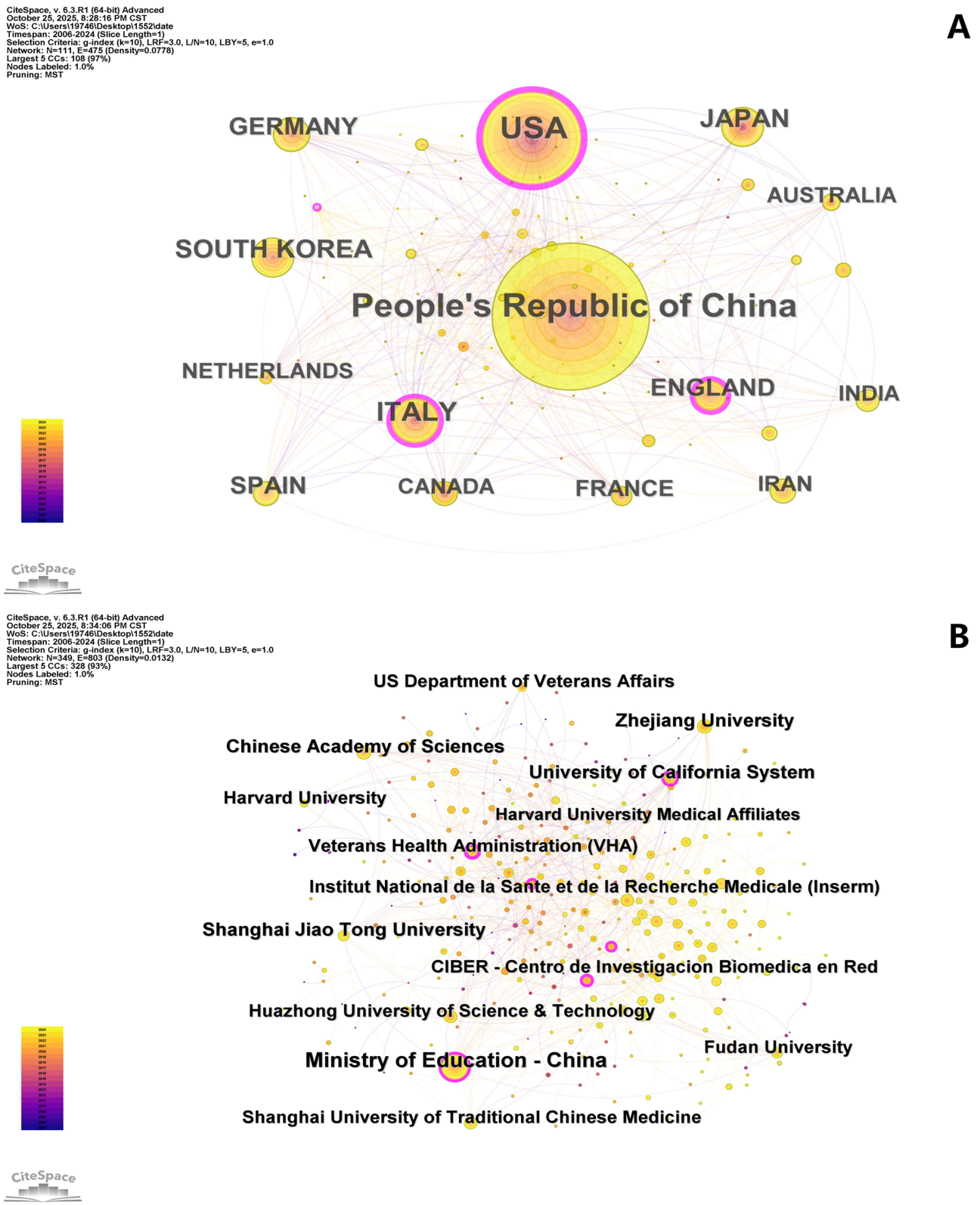

Figure 3 Co-occurrence maps ((**A**) Countries; (**B**) Institutions). Notes: The size of node represents the co-occurrence frequencies while the links reflect the co-occurrence relationships. The color of node and line indicates different years.tif.

Table 2 The Top 10 Journals and Co-Cited Journals in Bibliometric Analysis of Mechanisms in MASLD

Journals	Count	IF (2024)	JCR (2024)	Co-cited Journal	Citations	IF (2024)	JCR (2024)
International journal of molecular sciences	356	6.208	Q1	Hepatology	47376	15.8	Q1
Nutrients	252	4.8	Q1	Journal of hepatology	26767	33.0	Q1
Hepatology	204	15.8	Q1	Gastroenterology	19755	33.883	Q1
Frontiers in pharmacology	189	4.4	Q1	Journal of biological chemistry	14362	4.0	Q2
World journal of gastroenterology	188	4.3	Q1	Plos one	12218	3.752	Q1
Scientific reports	179	3.8	Q1	Journal of clinical investigation	10875	13.3	Q1
Plos one	153	3.752	Q1	Cell metabolism	9975	27.7	Q1
Frontiers in endocrinology	148	3.9	Q1	Nature	9616	69.504	Q1
Journal of hepatology	148	33.0	Q1	Diabetes	9274	4.89	Q1
Liver international	124	6.7	Q1	World journal of gastroenterology	9241	4.3	Q1

From the entire list of journals, the top 300 with the strongest total link strength are chosen to create the overlay map (Figure 4A), which can effectively depict the productive journals based on the color timeline. Journals such as International Journal of Molecular Sciences, Nutrients, Frontiers in Pharmacology, PLOS One, and Liver International exhibit the highest density, signifying their pivotal role in MASLD-related research. A group of journals with high co-citation, ranked by total link strength, is chosen for network visualization with VOSviewer, as depicted in Figure 4B. This analysis highlights the most significant sources in the MASLD research domain.

The dual-map overlay of journals, with citing journals on the left and cited journals on the right, effectively displays the topic distribution of academic journals. The relationship between the journals that cite and those that are cited can be traced along the colored paths. As depicted in Figure 5, four primary reference paths demonstrate that studies published in Molecular/Biology/Immunolog and Medicine/Medical/Clinical journals are predominantly cited by studies published in Molecular/Biology/Genetics and Health/Nursing/Medicine journals.

Productive Authors and Co-Cited Authors

A total of 50471 authors are identified. Nobili Valerio is the most productive author (57 publications), followed by Sanyal Arun J. and Targher Giovanni (54 each). Among co-cited authors, Gerald I. Shulman receives the most citations (7703), followed by Arun J. Sanyal (7655) and Giovanni Targher (7006). Complete rankings are presented in Table 3.

Furthermore, with the set threshold of at least 20 documents per author, a total of 173 authors are finally chosen to build the network map. As depicted in Figure 6A, various colors represent distinct clusters, indicating tight collaboration between clusters, such as those between Shulman Gerald I and PengLiang, Targher Giovanni and Tacke Frank, Song Haiyan and Liu Yang, and so on. Additionally, active collaborations related to the mechanism of MASLD are clearly seen, especially among authors within the same cluster, including collaborations between Zhang Li and Li wei, Zhang Li and Zhang Jing, Zhang Li and Guo Jiao, among others. Additionally, a density map is generated using authors who have at least 20 co-citations (n=6325), which visually represents the frequently co-cited authors with a yellow gradient. Figure 6B clearly shows that the area corresponding to Arun J. Sanyal is the darkest shade of yellow, signifying that this author is the most co-cited in the field.

Keyword Co-Occurrence, Clusters, and Evolution

VOSviewer (v. 1.6.20) provides functionality for keyword co-occurrence and network cluster analysis. A total of 21766 keywords are extracted, with 1473 meeting the threshold of occurring at least 10 times. The most frequent keywords include “NAFLD” (2159 occurrences), “non-alcoholic fatty liver disease” (1574), “nonalcoholic fatty liver disease” (1572), “obesity” (763), and “inflammation” (743). Cluster analysis revealed five major research themes, detailed in Table 4.

https://doi.org/10.2147/HMER.S562237

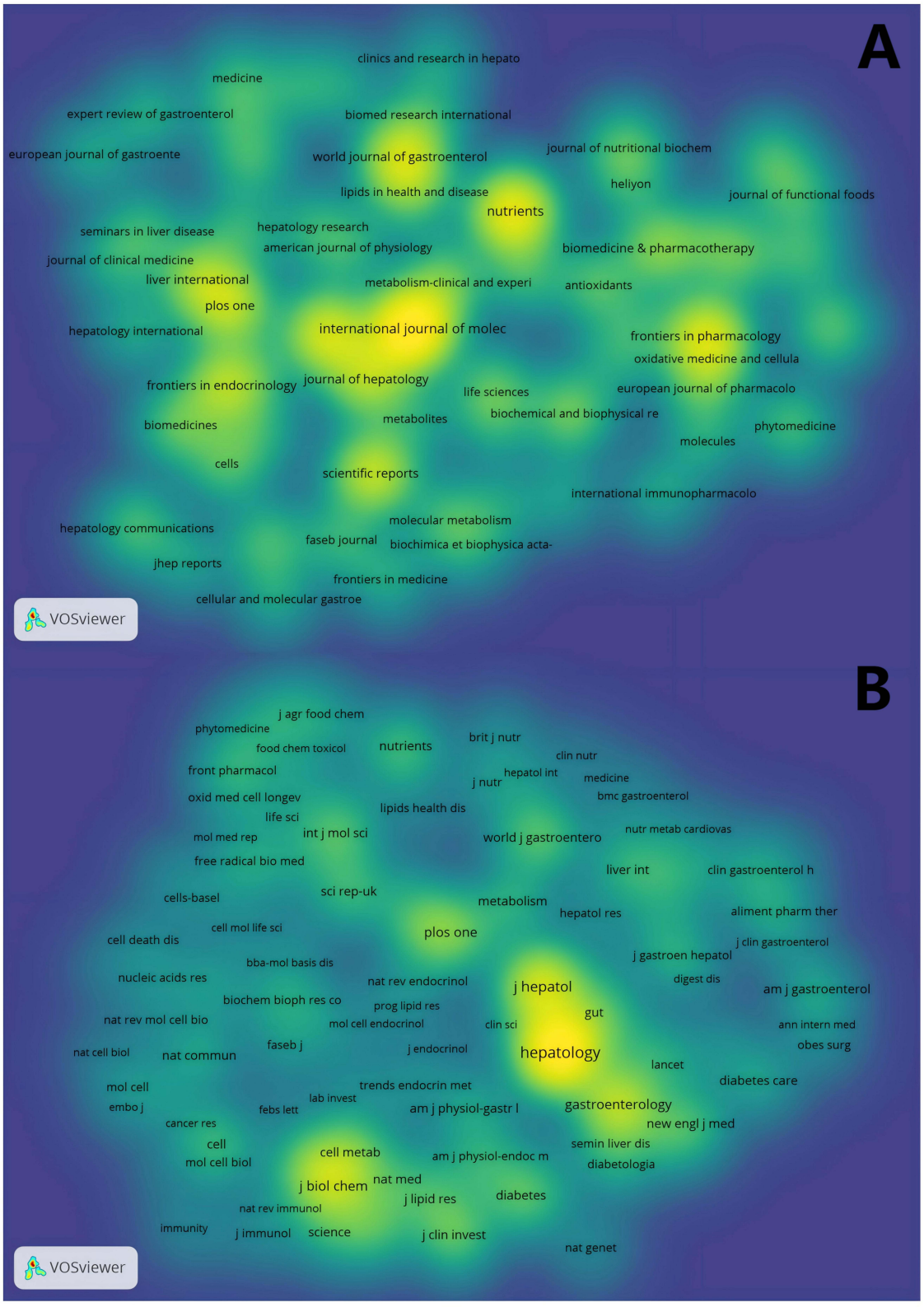

Figure 4 The density maps ((**A**) Journals; (**B**) Co-cited journals). Notes: The size of word and round, and the opacity of yellow are positively associated with the co-cited frequency.tif.

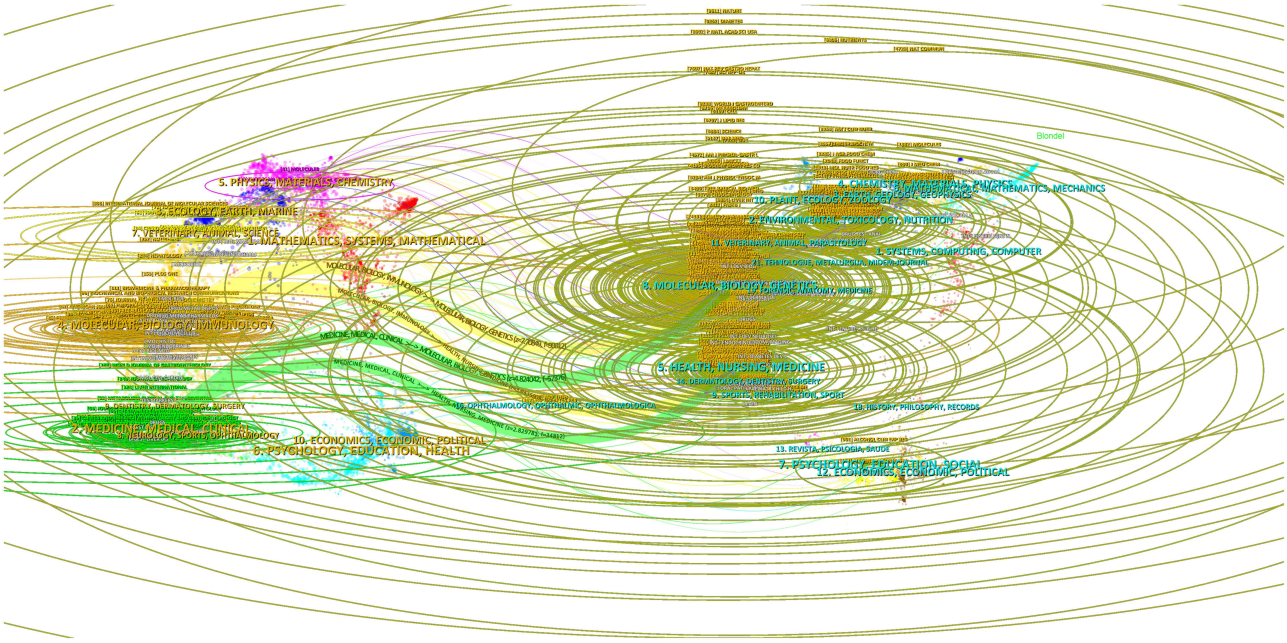

Figure 5 The dual-map overlay of journals associated with mechanism of MASLD (Left: the citing journals; Right: the cited journals).tif.

As shown in Figure 7A, these high-frequency keywords are visually depicted in the density map. Figure 7B also illustrates the outcomes of a network cluster analysis on key terms. This chart displays five clusters, each signifying unique research areas and boundaries. The most extensive cluster, marked in green, is Cluster 1, succeeded by Cluster 2 (yellow), Cluster 3 (red), Cluster 4 (blue), and Cluster 5 (purple). To be specific, Cluster 1 encompasses NAFLD, MAFLD, lipid metabolism, mitochondrial dysfunction, and additional topics. Cluster 2 includes NAFLD, metabolomics, fructose, exercise, and more. Cluster 3 covers inflammation, NASH, fibro, liver, and other subjects. Cluster 4 comprises obesity, insulin resistance, diabetes, hepatocellular carcinoma, and further topics. Lastly, Cluster 5 includes gut microbiota, bile acids, microbiota, gut-liver axis, and other related subjects.

The Keywords Timeline Viewer, developed by CiteSpace, is a tool designed to cluster keywords while taking into account their temporal evolution. It effectively displays the trajectory of high-frequency terms within each cluster, providing valuable insights. Furthermore, this viewer facilitates the identification of the timeline of specific topics and the developmental path of our research field. As illustrated in Figure 8, the focus and evolution of the mechanism of MASLD at each stage are clearly visualized, aiding in a comprehensive understanding of the research progression.

Table 3 The Top 10 Authors and Co-Cited Authors in Bibliometric Analysis of Mechanisms in MASLD

Rank	Author	Document	Co-cited Author	Citation
1	Nobili, valerio	57	Shulman, gerald i.	7703
2	Sanyal, arun j.	54	Sanyal, arun j.	7655
3	Targher, giovanni	54	Targher, giovanni	7006
4	Zhang, li	50	Friedman, scott l.	5781
5	Alisi, anna	49	Feldstein, ariel e.	5421
6	Byrne, christopher d.	48	Byrne, christopher d.	5330
7	Valenti, luca	48	Diehl, anna mae	5321
8	Ji, guang	43	Lonardo, amedeo	4017
9	Zhang, jing	41	Bugianesi, elisabetta	3892
10	Dongiovanni, paola	39	Nobili, valerio	3890

https://doi.org/10.2147/HMER.S562237

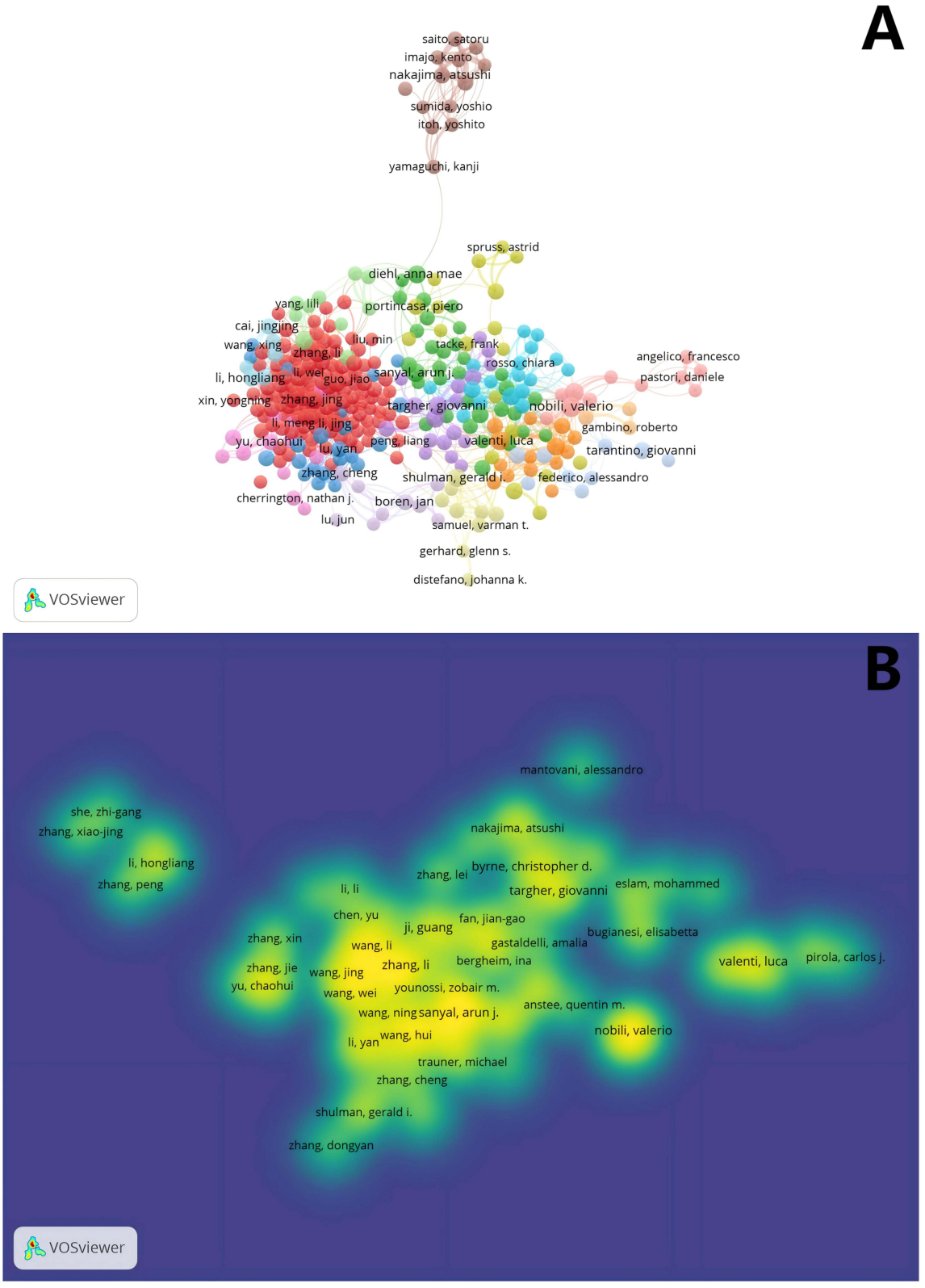

Figure 6 The co-occurrence maps in the mechanism of the MASLD research. ((**A**) Authors; (**B**) Co-authors). Notes: The size of node indicates the author's co-occurrence frequencies while its different colors reflect different clusters, and the links reflect the co-occurrence relationship between authors (**A**). The size of word and round, and the opacity of yellow are positively associated with the co-cited frequency (**B**).tif.

Table 4 The Top 20 Keywords in Bibliometric Analysis of Mechanisms in MASLD

Rank	Keyword	Count	Rank	Keyword	Count
1	Nafld	2159	11	Lipid metabolism	405
2	Non-alcoholic fatty liver disease	1574	12	Steatosis	392
3	Nonalcoholic fatty liver disease	1572	13	Fatty liver	375
4	Obesity	763	14	Gut microbiota	369
5	Inflammation	743	15	Hepatic steatosis	343
6	Insulin resistance	743	16	Fibrosis	338
7	Nash	678	17	Non-alcoholic steatohepatitis	328
8	Oxidative stress	583	18	Liver	316
9	Metabolic syndrome	440	19	Hepatocellular carcinoma	270
10	Nonalcoholic steatohepatitis	412	20	Autophagy	260

Abbreviations: NAFLD, Non-Alcoholic Fatty Liver Disease; Nash, Non-Alcoholic Steatohepatitis.

Citing Article and Co-Cited References

To pinpoint the key citing article and the top co-cited references associated with the mechanism of MASLD, CiteSpace [version 6.3.R1 (64-bit)] is employed for bibliometric analysis. Reference clustering identifies five key research domains, including "Metabolic Syndrome" (392 members) and "Dysfunction-Associated Fatty Liver Disease" (228 members). Seminal works with the strongest citation bursts include publications by Younossi et al (2016), Powell et al (2021), and Friedman et al (2018). A full summary is provided in Table 5. Specifically, cluster A (Metabolic syndrome)[16–19] mainly details the interaction and synergistic promotion of metabolic components such as obesity, insulin resistance, dyslipidemia, and hypertension on the initiation and progression of MASLD. Cluster B (Dysfunction-associated fatty liver disease)[20–23] concentrates on the role of hepatic metabolic dysfunction, intestinal barrier dysfunction, and adipose tissue dysfunction in the pathological process of MASLD, as well as the molecular mechanisms behind these functional abnormalities. Cluster C (Noncoding RNA)[24–27] primarily investigates the regulatory roles of various noncoding RNAs (eg, miRNAs, lncRNAs, circRNAs) in MASLD, including their involvement in hepatic lipid accumulation, inflammation, and fibrosis by targeting key genes. Cluster D (Oxidative stress)[28–31] mainly explains how oxidative stress, resulting from an imbalance between reactive oxygen species production and antioxidant defense systems, contributed to hepatic cell damage, inflammatory response, and steatosis in

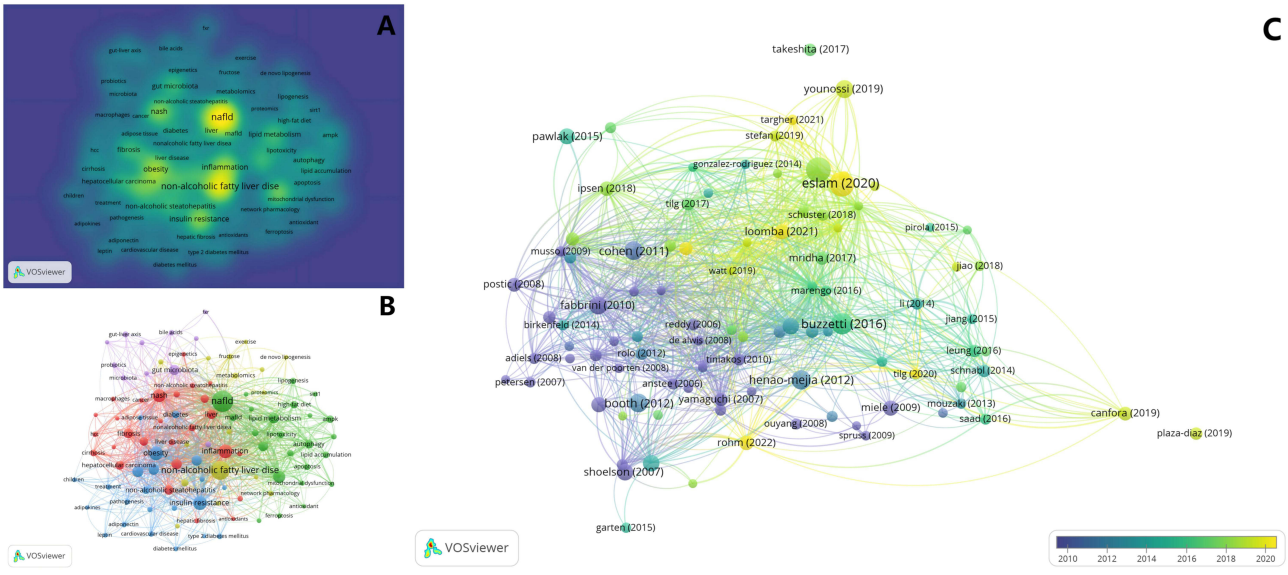

Figure 7 Maps of keywords in the mechanism of MASLD research. ((**A**) The density map; (**B**) Co-occurrence network and clusters; (**C**) The bibliographic coupling map). Notes: The size of word and round, and the opacity of yellow are positively associated with the co-cited frequency (**A**). The size of node and keyword indicates the co-occurrence frequencies while their different colors reflect different clusters, and the links reflect the co-occurrence relationship (**B**). The size of node and reference indicates the co-occurrence frequencies while their different colors reflect different clusters, and the links reflect the co-occurrence relationship (**C**).tif.

https://doi.org/10.2147/HMER.S562237

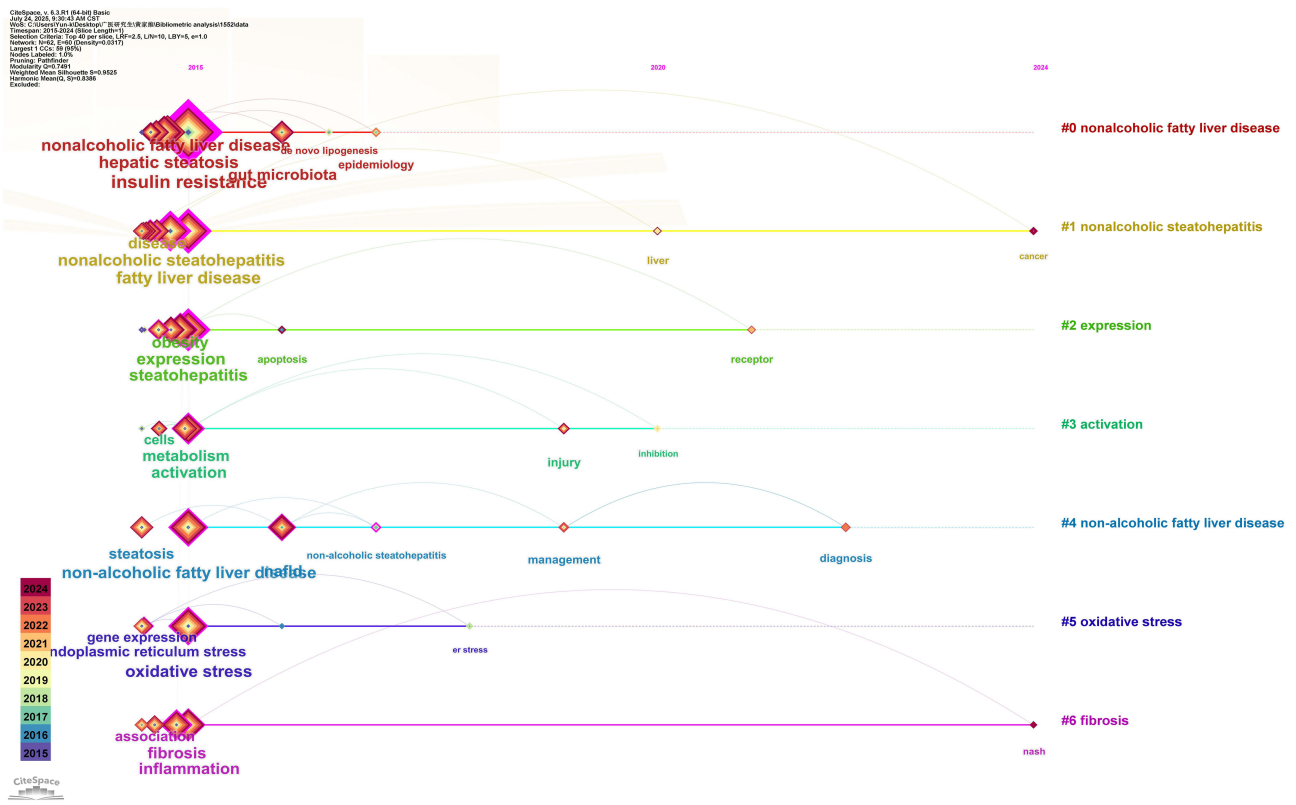

Figure 8 Keywords timeline viewer of the mechanism of MASLD research.tif.

MASLD, and its interaction with other pathological factors. Lastly, cluster E (Nonalcoholic fatty liver disease)[24,32–34] mainly discusses the progression of nonalcoholic fatty liver disease to NASH and liver fibrosis, focusing on the key drivers and potential therapeutic targets in this process, which establishes a foundation for understanding the natural history of MASLD.

Figure 9 showcases the top 30 references exhibiting the strongest citation bursts in MASLD-related research spanning from 2005 to 2024. Each of these references is detailed with its respective burst strength, the year it commences, and the year it concludes. The visual representation consists of red bars, which depicts the specific periods during which the citation bursts occurred. Concurrently, blue lines are utilized to illustrate the comprehensive timespan, encompassing the years from 2006 to 2024. Among the references highlighted, those published by Younossi et al in 2016, Powell et al in 2021, and Friedman et al in 2018, stand out as experiencing the most prominent citation bursts. These particular references witnesses remarkable surges in citations over defined periods, underscoring their temporary yet substantial impact within the field of MASLD-related research.

Discussion

This comprehensive 20-year bibliometric analysis (2005–2024) delineates the evolving intellectual landscape and research trajectories in the field of MASLD mechanisms. By analyzing 10626 publications, we identified evolving research paradigms, key contributors, global collaboration patterns, emerging frontiers, and persistent translational challenges in this field. Our findings also revealed several critical insights.

Regarding the Dominance of China and the USA in Research Output

Interpretation: This finding signifies more than just high productivity; it reflects an alignment between research investment and the significant clinical burden of MASLD in these populations. The high centrality of the USA indicates its role as a major collaborative hub, while China's leading output signals a rapid expansion of its research capacity in this field.

Table 5 Summary of the Largest 5 Clusters Including Citing Articles and Cited References in Bibliometric Analysis of Mechanisms in MASLD

The Summary Highlights Major Clusters	Count	Title	First Author	Year	Journal	DOI
The largest cluster: METABOLIC SYNDROME	392 members	N/A	N/A	N/A	N/A	N/A
The major citing article	N/A	Molecular mechanisms and therapeutic targets in steatosis and steatohepatitis	Anderson, N	2008	PHARMACOLOGICAL REVIEWS	10.1124/pr.108.00001
The most cited references	115	Design and validation of a histological scoring system for nonalcoholic fatty liver disease	Kleiner DE	2005	HEPATOLOGY	10.1002/hep.20701
	84	The natural history of nonalcoholic fatty liver disease: a population-based cohort study	Adams LA	2005	GASTROENTEROLOGY	10.1053/j.gastro.2005.04.014
	81	A placebo-controlled trial of rosiglitazone in nonalcoholic steatohepatitis	Belfort R	2006	NEW ENGL J MED	10.1056/NEJMoa060326
The second cluster: METABOLIC DYSFUNCTION-ASSOCIATED FATTY LIVER DISEASE	228 members	N/A	N/A	N/A	N/A	N/A
The major citing article	N/A	Progression of NAFLD to diabetes mellitus, cardiovascular disease or cirrhosis	Anstee, QM	2013	NATURE REVIEWS GASTROENTEROLOGY & HEPATOLOGY	10.1038/nrgastro.2013.41
The most cited references	197	The diagnosis and management of non-alcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases	Chalasani N	2012	HEPATOLOGY	10.1002/hep.25762
	166	Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults	Vernon G	2011	ALIMENT PHARM THER	10.1111/j.1365–2036.2011.04724.x
	127	Evolution of inflammation in nonalcoholic fatty liver disease: the multiple parallel hits hypothesis	Tilg H	2010	HEPATOLOGY	10.1002/hep.24001
The third cluster: NONCODING RNA	217 members	N/A	N/A	N/A	N/A	N/A
The major citing article	N/A	Peroxisome proliferator-activated receptors and their novel ligands as candidates for the treatment of non-alcoholic fatty liver disease	Fougerat, A	2020	CELLS	10.3390/cells9071638

(*Continued*)

https://doi.org/10.2147/HMER.S562237

Table 5 (Continued).

The Summary Highlights Major Clusters	Count	Title	First Author	Year	Journal	DOI
The most cited references	383	Non-alcoholic fatty liver disease - A global public health perspective	Younossi ZM	2019	J HEPATOL	10.1016/j.jhep.2018.10.033
	194	Nonalcoholic Fatty Liver Disease 2020: The State of the Disease.	Cotter TG	2020	GASTROENTEROLOGY	10.1053/j.gastro.2020.01.052
	184	Obesity and nonalcoholic fatty liver disease: From pathophysiology to therapeutics.	Polyzos SA	2019	METABOLISM	10.1016/j.metabol.2018.11.014
The 4th cluster: OXIDATIVE STRESS	202 members	N/A	N/A	N/A	N/A	N/A
The major citing article	N/A	The interplay between nonalcoholic fatty liver disease and atherosclerotic cardiovascular disease	Finney, AC	2023	FRONTIERS IN CARDIOVASCULAR MEDICINE	10.3389/fcvm.2023.1116861
The most cited references	393	Nonalcoholic fatty liver disease	Powell EE	2021	LANCET	10.1016/S0140-6736(20)32511-3
	328	Global Perspectives on Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis.	Younossi Z	2019	HEPATOLOGY	10.1002/hep.30251
	309	Mechanisms and disease consequences of nonalcoholic fatty liver disease.	Loomba R	2021	CELLS	10.1016/j.cell.2021.04.015
The 5th cluster: NONALCOHOLIC FATTY LIVER DISEASE	200 members	N/A	N/A	N/A	N/A	N/A
The major citing article	N/A	Peroxisome Proliferator-Activated Receptors and Their Novel Ligands as Candidates for the Treatment of Non-Alcoholic Fatty Liver Disease.	Fougerat, A	2020	CELL	10.3390/cells9071638
The most cited references	766	Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention.	Younossi Z	2018	NAT REV GASTRO HEPATEROL HEPATOLI	10.1038/nrgastro.2017.109
	698	Mechanisms of NAFLD development and therapeutic strategies	Friedman SL	2018	NATURE MEDICINE	10.1038/s41591-018-0104-9
	645	Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes.	Younossi ZM	2016	HEPATOLOGY	10.1002/hep.28431

Abbreviations: N/A, Not Applicable; NAFLD, Nonalcoholic Fatty Liver Disease; NASH, Nonalcoholic Steatohepatitis; MAFLD, Metabolic Dysfunction-Associated Fatty Liver Disease; MASLD, Metabolic Dysfunction-Associated Steatotic Liver Disease; HCC, Hepatocellular Carcinoma; T2DM, Type 2 Diabetes Mellitus; PHARMACOL REV, Pharmacological Reviews; CELLGASTROENTER, Cell Gastroenterology and Hepatology; NAT REV GASTRO HEPAT, Nature Reviews Gastroenterology & Hepatology; ALIMENT PHARM THER, Alimentary Pharmacology & Therapeutics.

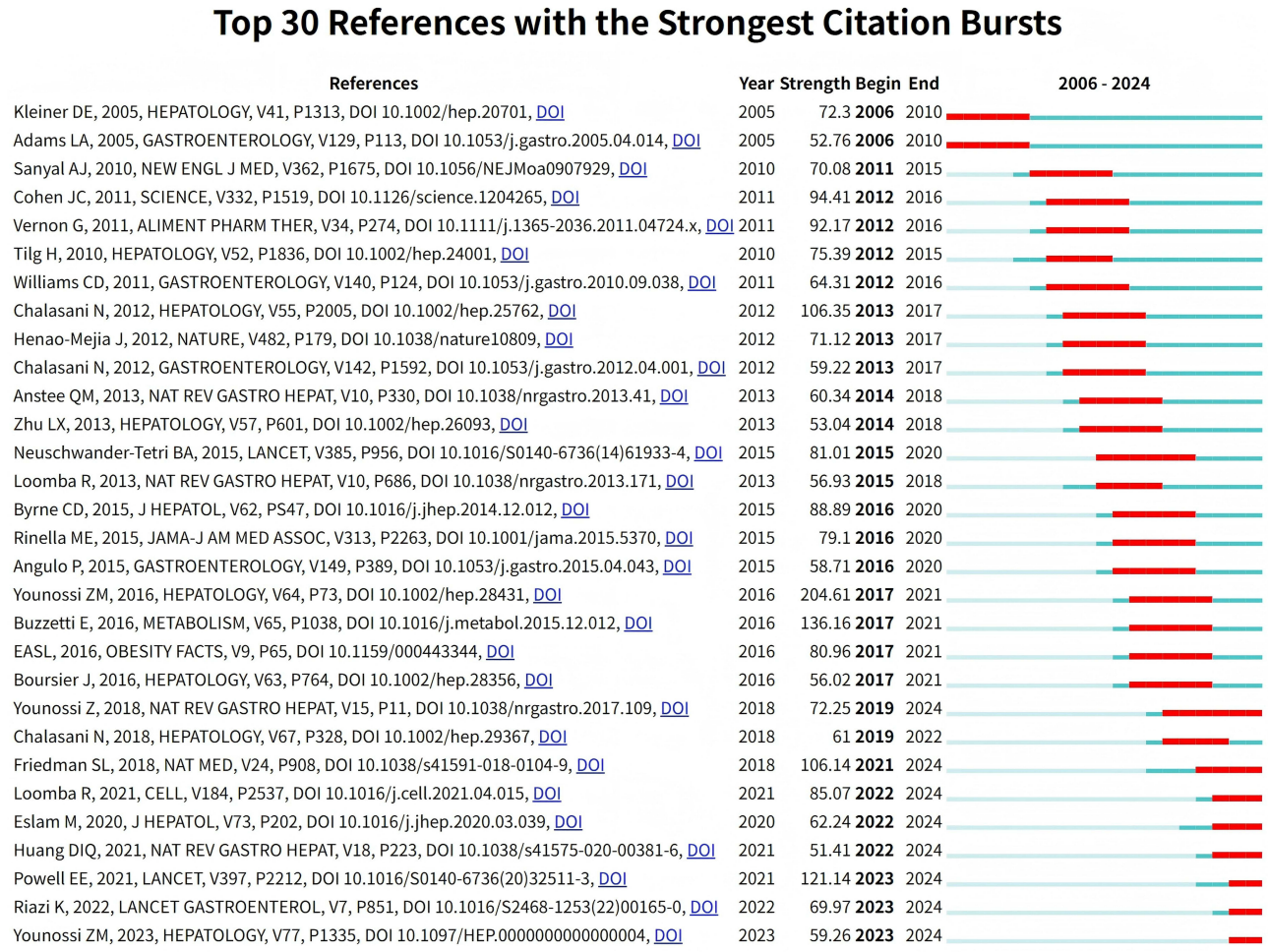

Figure 9 View Citation Burst History. Notes: The blue bars mean the reference had been published; The red bars mean citation burstness.tif.

Importance: This highlights the need for fostering more geographically diverse collaborations. Relying heavily on research from a few countries may limit the generalizability of findings and overlook unique epidemiological or genetic factors in other regions, which is crucial for developing global strategies against MASLD.

Regarding the Identification of Five Major Research Clusters (eg, Lipid Metabolism, Gut-Liver Axis)

Interpretation: This clustering is not merely a taxonomic exercise. It demonstrates that the research community has organically converged on the core, multifactorial pathophysiology of MASLD. The evolution of these themes, visible in the keyword timeline, shows a strategic shift from broad metabolic concepts (eg, insulin resistance) towards more precise molecular and systems-level mechanisms (eg, gut microbiota, specific molecular switches like WDR6-PPP1CB).

Importance: This provides a validated, data-driven map of the intellectual structure of the field. It helps researchers identify the main pillars of knowledge, understand the historical progression of ideas, and pinpoint adjacent fields for potential knowledge transfer. For funders and policymakers, it clarifies the key areas where investment has been concentrated and can guide future strategic priorities.

Regarding the Citation Bursts of Seminal Reviews (eg, Younossi 2016, Powell 2021, Friedman 2018)

Interpretation: The strong citation bursts for these papers indicate that they serve as essential "knowledge-synthesis hubs" or foundational reference points for the field. Their influence coincides with key conceptual shifts, such as the formal recognition of MASLD's global burden and the consolidation of complex pathogenic mechanisms.

Importance: Identifying these papers helps new investigators quickly grasp the core literature. It also underscores that progress in MASLD research is heavily driven by comprehensive reviews that integrate disparate findings, suggesting a continued need for high-quality synthesis to guide future experimental work.

Regarding the Leading Role of High-Impact Journals (eg, Hepatology, Journal of Hepatology)

Interpretation: This signifies that research on MASLD mechanisms is considered high-priority within hepatology and gastroenterology. The dual-map overlay showing knowledge flow from molecular/biological journals to clinical journals indicates a strong translational character in the field.

Importance: It confirms that the field successfully bridges basic science and clinical application. For authors, it identifies the key target journals for high-visibility publications. For the field, it reinforces the credibility and clinical relevance of mechanistic discoveries.

Regarding the Persistent Challenges Identified (Mechanistic Heterogeneity, Diagnostic Gaps)

Interpretation: These are not just restatements of known issues but are highlighted by our bibliometric data as the most significant unresolved frontiers. The sheer volume of literature yet the persistent identification of these challenges indicates their complexity and the limitations of current approaches.

Importance: This directly translates our findings into a clear agenda for future research. It moves the discussion from "what we have done" to "where we must go next", emphasizing the critical need for studies focused on patient stratification, biomarker development, and targeted therapies.

Key Research Trends and Knowledge Evolution

The sustained annual increase in publications (Figure 2) underscores MASLD's escalating global health burden, aligning with epidemiological reports of rising prevalence, particularly in China (AAPC = 1.30) compared to the global average (AAPC = 0.91).[3] The identification of five dominant research themes through keyword analysis (Table 4 and Figure 7) – spanning lipid metabolism, dietary factors, inflammation/fibrosis, metabolic comorbidities, and the gut-liver axis – reflects the multi-factorial pathophysiology of MASLD and underscores the field's progression toward interdisciplinary investigation. This thematic structure highlights how research has evolved from isolated metabolic explorations to integrated models that account for synergistic drivers of disease progression. The recent identification of molecular switches like WD40 repeat-containing protein 6-Serine/threonine -protein phosphatase 1 catalytic subunit beta (WDR6-PPP1CB) in de novo lipogenesis[5] exemplifies the field's progression toward mechanistic precision. Furthermore, the temporal keyword evolution (Figure 8) highlights a paradigm shift from the initial focus on IR[5] and oxidative stress towards gut microbiota[6,7] and genetic/epigenetic determinants (eg, FADS1, ELOVL5)[8] over the past decade. This evolution aligns with the citation bursts of seminal literature (Figure 9). For instance, the rising prominence of keywords related to the "gut-liver axis" and "microbiota" from approximately 2016–2017 onwards corresponds with the high-impact burst of publications by Younossi et al (2016)[34] on disease burden and Friedman et al (2018)[33] on pathogenesis, which extensively discusses these mechanisms. Similarly, the recent keyword emphasis on molecular drivers like "lipogenesis" and specific pathways coincides with the citation burst for Powell et al (2021),[29] whose work consolidates understanding of NAFLD/MASLD mechanisms, including de novo lipogenesis. This consistency between the keyword timeline and reference burst history reinforces that the conceptual evolution in the field is driven by foundational, highly influential studies.

Global Collaboration and Research Leadership

The dominance of China and the USA in publication output not only highlights their significant investment in MASLD research but also suggests a correlation between research productivity and the high prevalence of metabolic disorders in these populations. This distribution underscores the need for more geographically diverse collaborations to address MASLD's global burden (Table 1). China's Ministry of Education, Shanghai Jiao Tong University, and Zhejiang University are among the most productive institutions, reflecting substantial national investment in MASLD research. The high centrality of the USA (0.25) signifies its pivotal role in international networks (Figure 3A). While developed nations (USA, Italy, Japan) dominate the top 10, South Korea represents a significant contributor among developing economies. The dense institutional collaboration network (Figure 3B), particularly between Chinese and US entities, underscore the importance of cross-border partnerships in advancing MASLD science. The increasing prominence of Chinese institutions in the past decade signals a geographic shift in research leadership.

Influential Journals and Knowledge Dissemination

Core journals driving MASLD research includes International Journal of Molecular Sciences, Nutrients, and high-impact clinical journals like Hepatology (IF=15.8) and Journal of Hepatology (IF=33.0) (Table 2 and Figure 4A). Co-citation analysis identifies Hepatology, Journal of Hepatology, and Gastroenterology as the most influential knowledge sources (Table 2 and Figure 4B). The dual-map overlay (Figure 5) reveals primary knowledge flow from Molecular/Biology/Immunology and Medicine/Medical/Clinical journals to Molecular/Biology/Genetics and Health/Nursing/Medicine journals, highlighting the interdisciplinary nature of MASLD research bridging basic science and clinical application.

Leading Authors and Collaborative Networks

Nobili Valerio, Sanyal Arun J., and Targher Giovanni are the most productive authors (Table 3). Co-authorship analysis (Figure 6A) reveals distinct collaborative clusters (eg, Shulman GI & Peng Liang; Targher G & Tacke F; Zhang Li & Li Wei), indicating specialized research communities. Gerald I. Shulman (n=7703 citations) and Arun J. Sanyal (n=7655 citations) are the most co-cited authors (Table 3 and Figure 6B), reflecting their foundational contributions to understanding insulin resistance and MASLD pathophysiology.

Reference Clusters and Bursting Topics

The analysis of the bibliographic coupling map (Figure 7C) highlights a clear shift from metabolic mechanisms toward systemic and conceptual advances in MSFLD research. The five major research clusters derived from co-citation analysis illustrate the conceptual pillars of MASLD mechanistic research (Table 5). These clusters reveal how foundational studies have shaped current understanding, with recent shifts toward molecular mechanisms and microbiome interactions indicating where the field is heading conceptually and clinically. The specific analyses are as follows:

Non-Coding RNA Mechanisms: From Discovery to Translational Potential

Research into non-coding RNAs (eg, miRNAs, lncRNAs, circRNAs) has identified specific molecules such as miR-122, miR-34a, and H19 lncRNA as key regulators of hepatic lipid metabolism, inflammation, and fibrosis.[24–27] In vitro and animal models demonstrate that miR-122 inhibition reduces hepatic steatosis by modulating lipid synthesis genes (eg, SREBP-1c), while miR-34a promotes apoptosis and inflammation via p53 and NF-κB pathways. Human studies corroborate these findings, showing elevated serum miR-122 and miR-34a levels in MASLD patients correlating with disease severity. These RNAs hold promise as non-invasive biomarkers for early steatohepatitis detection and as therapeutic targets; for instance, antisense oligonucleotides against miR-103/107 improve insulin sensitivity in preclinical models. However, major gaps remain in validating their specificity across diverse populations, standardizing detection methods, and developing efficient delivery systems for RNA-based therapies.

Oxidative Stress: Pathways, Biomarkers, and Intervention Strategies

Oxidative stress mechanisms involve key pathways such as CYP2E1-induced ROS production, mitochondrial dysfunction, and NRF2-mediated antioxidant responses.[28–31] Animal studies using CYP2E1 inhibitors or NRF2 agonists show

reduced lipid peroxidation and liver injury, while human evidence links elevated 8-OHdG (a DNA oxidation marker) and decreased glutathione levels to MASLD progression. Potential biomarkers like serum malondialdehyde (MDA) and superoxide dismutase (SOD) activity are being explored for staging fibrosis, and targets such as NOX4 (a ROS-generating enzyme) are under investigation for pharmacologic inhibition. Despite this, challenges persist in distinguishing oxidative stress as a primary driver versus a secondary phenomenon, validating biomarkers against histologic endpoints, and mitigating off-target effects of antioxidant therapies in clinical trials.

Gut-Liver Axis and Microbiota: From Signatures to Therapeutics

Key microbial molecules like lipopolysaccharide (LPS) and bile acids (eg, deoxycholic acid) drive MASLD via TLR4 signaling and FXR receptor modulation. Animal models reveal that fecal microbiota transplantation from healthy donors ameliorates steatosis, while human cohorts show distinct microbiota signatures (eg, increased Escherichia coli, decreased Faecalibacterium prausnitzii) associated with fibrosis. Promising biomarkers include circulating LPS levels and fecal short-chain fatty acids, with targets like FXR agonists (eg, obeticholic acid) advancing to clinical trials. However, heterogeneity in microbiota composition across populations, limited long-term safety data for microbiota-based interventions, and unclear causality in human studies represent critical gaps.[35,36]

Molecular Switches (eg, WDR6-PPP1CB): Precision Mechanisms to Targeted Therapy

The recent identification of WDR6-PPP1CB interaction as a molecular switch for de novo lipogenesis exemplifies pathway-specific advances. In mouse models, WDR6 knockdown improves insulin sensitivity and reduces hepatic fat accumulation by modulating PPP1CB phosphorylation. Human genetic studies suggest WDR6 polymorphisms may influence MASLD susceptibility. This pathway offers a potential target for small-molecule inhibitors, though challenges include optimizing tissue-specific delivery and validating efficacy in human trials without disrupting essential metabolic functions.[37]

Lipid Metabolism Enzymes: From Fundamental Biology to Pharmacologic Targets

Key enzymes in hepatic lipid metabolism, such as Fatty Acid Synthase (FAS) and Acetyl-CoA Carboxylase (ACC), have been extensively studied for their roles in promoting steatosis. Preclinical studies show that inhibitors of FAS (eg, natural compounds like sea cucumber saponins) and ACC (eg, synthetic small molecules) reduce triglyceride accumulation. Human tissue analyses confirm upregulation of these enzymes in MASLD patients. While these enzymes represent well-validated targets, developing liver-specific inhibitors to minimize systemic toxicity remains a primary challenge for clinical translation.[38]

Translational Challenges and Future Directions Despite Progress, Critical Gaps Remain

(1) Mechanistic Heterogeneity: MASLD encompasses diverse etiologies (genetic, metabolic, environmental), underpinned by significant molecular heterogeneity. Future research must prioritize patient stratification based on molecular drivers to enable precision medicine approaches. Recent multi-omics studies have been instrumental in delineating this heterogeneity. For instance, integrated genomic, proteomic, and metabolomic analyses have proposed distinct molecular subtypes of NAFLD/MASLD, which have been validated in external cohorts.[39] Similarly, large-scale multi-omics analyses have systematically revealed key pathogenic pathways and molecular characteristics.[40] Furthermore, multi-omics profiling in animal models has helped characterize the specific molecular mechanisms underlying obesity-associated NAFLD.[41] These findings underscore the critical need to move beyond a one-size-fits-all understanding of MASLD pathogenesis. For instance, FOXO1 inhibition exhibits protective effects in high-fat diet-fed mice;[42] the role of epigenetic modifications such as m6A in the progression of fatty liver disease is becoming increasingly clear;[43,44] and immunological reviews have summarized the inflammatory and immune regulatory pathways in MASLD/MASLD.[45] Additionally, high level reviews systematically discuss metabolic reprogramming, inflammation, and fibrosis mechanisms in MASLD.[31,33]

(2) Early Diagnosis: Non-invasive biomarkers for detecting early steatohepatitis and fibrosis are urgently needed. Integrating multi-omics data (proteomics, metabolomics) with clinical parameters holds promise.

(3) Therapeutic Targets: While WDR6-PPP1CB[5] and gut-microbiota modulators[6,7] represent emerging targets, robust clinical validation is lacking. Combinatorial therapies targeting multiple pathways (eg, lipogenesis, inflammation, fibrosis) may be necessary.

(4) Global Health Equity: Research output disparities persist. Fostering collaborations with underrepresented regions and addressing MASLD in diverse populations are essential for global impact.

Limitations

This study has several limitations inherent to bibliometric methodology. First, our analysis relies solely on data extracted from the WoSCC. While WoSCC is a comprehensive and influential database, it does not encompass all scholarly publications, potentially excluding relevant studies indexed in other databases (eg, Scopus, PubMed). This may introduce selection bias and limit the generalizability of our findings. The bias likely skews the results towards English-language, high-impact journal publications, potentially underrepresenting research from specific regions (eg, non-English speaking countries) or emerging trends published in specialized or local journals. For instance, the dominance of China and the USA in our results may be partially amplified, while contributions from European or Latin American research consortia indexed predominantly in other databases might be less visible. Consequently, the calculated proportions of national contributions and the identified collaborative networks should be interpreted as reflective of the core literature in major international journals rather than the entire global research output. Second, the analysis is restricted to English-language articles and reviews, omitting potentially significant contributions published in other languages. Third, bibliometric tools like CiteSpace and VOSviewer, while powerful for mapping trends and networks, have inherent algorithmic constraints in cluster identification and visualization, which may influence the interpretation of research themes and collaboration patterns. Fourth, our search strategy focuses on specific keywords related to mechanisms, pathogenesis, and related terms; thus, studies using alternative terminology might have been overlooked. Finally, bibliometric analysis quantifies publication output and impact but does not assess the quality or clinical validity of the included studies. Future research could benefit from integrating multiple databases, incorporating non-English literature, and employing complementary qualitative methods to deepen the understanding of MASLD mechanisms and provide a more globally representative perspective.

Conclusion

This bibliometric analysis maps two decades of MASLD mechanistic research, revealing a dynamic field driven by international collaboration, evolving from foundational metabolic studies to cutting-edge molecular and microbiome research. China and the USA lead in productivity, with high-impact work disseminated through premier hepatology journals. While significant progress has been made in understanding MASLD's complexity, unresolved heterogeneity, diagnostic limitations, and therapeutic challenges demand continued interdisciplinary efforts. Prioritizing translational research, biomarker development, and equitable global collaboration will be crucial to mitigate the growing burden of MASLD.

Validate and Translate Key Molecular Mechanisms

Focus on clinical validation of emerging pathways, such as the WDR6-PPP1CB axis in de novo lipogenesis and non-coding RNAs (eg, miR-122, lncRNAs), through longitudinal human studies and targeted interventional trials.

Develop Non-Invasive Biomarker Panels

Integrate multi-omics data (eg, proteomics, metabolomics) with clinical parameters to create accessible, cost-effective biomarker panels for early detection of steatohepatitis and fibrosis, particularly in primary care settings.

Advance Precision Medicine Approaches: Leverage multi-omics stratification to define MASLD subtypes (eg, based on genetic, metabolic, or gut-microbiota profiles) and tailor interventions, such as personalized dietary regimens or microbiota-modulating therapies.

Foster Equitable Global Data Sharing

Establish international consortia to standardize data collection, especially from underrepresented regions, ensuring diverse population representation in mechanistic studies and clinical trials.

Bridge Preclinical-Clinical Gaps

Prioritize combinatorial therapies targeting multiple pathways (eg, lipogenesis, inflammation, fibrosis) in well-designed trials, addressing challenges like tissue-specific drug delivery and long-term safety.

These strategies, grounded in bibliometric trends, can accelerate progress toward reducing the global burden of MASLD. However, our analysis was based primarily on the WoSCC, which may underrepresent literature from regional or non-English journals, and the evolving terminology (from NAFLD to MAFLD to MASLD) may affect the retrieval and interpretation of publications over the 20-year period.

Data Sharing Statement

The datasets used during the current study are available from the corresponding author upon reasonable request.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. The institutions of the first author and the last corresponding author are co-first completing institution.

Funding

This study was supported by National Natural Science Foundation of China (No. 82305100), Guangdong Provincial Association for Science and Technology Youth Science and Technology Talent Cultivation Program 2025-2026 (No. SKXRC2025136), and Young Science and Technology Talents Fund of The Affiliated TCM Hospital of Guangzhou Medical University (No. 2023RC03).

Disclosure

All authors disclosed no competing interests in any aspects.

References

1. Gutiérrez-Cuevas J, Santos A, Armendariz-Borunda J. Pathophysiological molecular mechanisms of obesity: a link between MASLD and NASH with cardiovascular diseases. *Int J Mol Sci*. 2021;22(21):11629. PMID: 34769060; PMCID: PMC8583943. doi:10.3390/ijms222111629
2. Zeng J, Gu C, Wen C, Shen C. The burden of NAFLD (now referred to as MASLD)-related chronic liver disease and cirrhosis from 1990 to 2021 with projections to 2036: a comparative study of global China the United States and India. *Lipids Health Dis*. 2025;24(1):298. PMID: 41024003; PMCID: PMC12482587. doi:10.1186/s12944-025-02750-z
3. Zhao X, Xu D, Ji W, et al. Global and Chinese burden of non-alcoholic fatty liver disease in chronic liver disease: findings from the global burden of disease study 2021. *Chin Med J*. 2025. PMID: 40539304. doi:10.1097/CM9.0000000000003726
4. Haldrup D, Wei C, Holland-Fischer P, et al. Effects of lifestyle intervention on IGF-1, IGFBP-3, and insulin resistance in children with obesity with or without metabolic dysfunction-associated steatotic liver disease. *Eur J Pediatr*. 2023;182(2):855–865. PMID: 36508014. doi:10.1007/s00431-022-04731-1
5. Yao Z, Gong Y, Chen W, et al. Upregulation of WDR6 drives hepatic de novo lipogenesis in insulin resistance in mice. *Nat Metab*. 2023;5(10):1706–1725. PMID: 37735236. doi:10.1038/s42255-023-00896-7
6. Yang Z, Zhang J, Liu X, et al. The liver-gut axis perspective: exploring the pathogenesis of fatty liver. *Eur J Pharmacol*. 2025;1002:177822. PMID: 40484333. doi:10.1016/j.ejphar.2025.177822
7. Zhou T, Jin Z, Jiang R, Li W. Gut microbiota modulation by traditional Chinese medicine: a translational strategy for metabolic dysfunction-associated steatotic liver disease. *Front Pharmacol*. 2025;16:1600439. PMID: 40556760. doi:10.3389/fphar.2025.1600439
8. Ando M, Lee-Okada HC, Yokomizo T. Molecular mechanisms by which polyunsaturated fatty acids suppress the pathogenesis and progression of NAFLD. *Yakugaku Zasshi*. 2025;145(3):177–182. PMID: 40024729, Japanese. doi:10.1248/yakushi.24-00177-2
9. Chen C, Hu Z, Liu S, Tseng H. Emerging trends in regenerative medicine: a scientometric analysis in CiteSpace. *Expert Opin Biol Ther*. 2012;12(5):593–608. PMID: 22443895. doi:10.1517/14712598.2012.674507

10. Dai YK, Zhao ZM, Liu C. Treatment of liver fibrosis: a 20-year bibliometric and knowledge-map analysis. *Front Pharmacol*. 2022;13:942841. PMID: 35903335. doi:10.3389/fphar.2022.942841
11. Qi J, Dai Y, Sun X, Liu C. Mechanism of liver regeneration: 20-year bibliometric analyses. *Front Pharmacol*. 2023;14:1190559. PMID: 37383706. doi:10.3389/fphar.2023.1190559
12. Qin Y, Zhang Q, Liu Y. Analysis of knowledge bases and research focuses of cerebral ischemia-reperfusion from the perspective of mapping knowledge domain. *Brain Res Bull*. 2020;156:15–24. PMID: 31843561. doi:10.1016/j.brainresbull.2019.12.004
13. Xu X, Feng C. Mapping the knowledge domain of the evolution of emergy theory: a bibliometric approach. *Environ Sci Pollut Res Int*. 2021;28 (32):43114–43142. PMID: 34152539. doi:10.1007/s11356-021-14959-3
14. van Eck NJ, Waltman L. Software survey: vOSviewer, a computer program for bibliometric mapping. *Scientometrics*. 2010;84(2):523–538. PMID: 20585380. doi:10.1007/s11192-009-0146-3
15. Chen C. Searching for intellectual turning points: progressive knowledge domain visualization. *Proc Natl Acad Sci U S A*. 2004;101 Suppl 1(Suppl 1):5303–5310. PMID: 14724295. doi:10.1073/pnas.0307513100
16. Anderson N, Borlak J. Molecular mechanisms and therapeutic targets in steatosis and steatohepatitis. *Pharmacol Rev*. 2008;60(3):311–357. PMID: 18922966. doi:10.1124/pr.108.00001
17. Nonalcoholic Steatohepatitis Clinical Research Network; Kleiner DE, Brunt EM, Van Natta M, et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. *Hepatology*. 2005;41(6):1313–1321. PMID: 15915461. doi:10.1002/hep.20701
18. Adams LA, Lymp JF, St Sauver J, et al. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. *Gastroenterology*. 2005;129(1):113–121. PMID: 16012941. doi:10.1053/j.gastro.2005.04.014
19. Belfort R, Harrison SA, Brown K, et al. A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. *N Engl J Med*. 2006;355(22):2297–2307. PMID: 17135584. doi:10.1056/NEJMoa060326
20. Anstee QM, Targher G, Day CP. Progression of NAFLD to diabetes mellitus, cardiovascular disease or cirrhosis. *Nat Rev Gastroenterol Hepatol*. 2013;10(6):330–344. PMID: 23507799. doi:10.1038/nrgastro.2013.41
21. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American association for the study of liver diseases, American college of gastroenterology, and the American gastroenterological association. *Hepatology*. 2012;55(6):2005–2023. PMID: 22488764. doi:10.1002/hep.25762
22. Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. *Aliment Pharmacol Ther*. 2011;34(3):274–285. PMID: 21623852. doi:10.1111/j.1365-2036.2011.04724.x
23. Tilg H, Moschen AR. Evolution of inflammation in nonalcoholic fatty liver disease: the multiple parallel hits hypothesis. *Hepatology*. 2010;52 (5):1836–1846. PMID: 21038418. doi:10.1002/hep.24001
24. Fougerat A, Montagner A, Loiseau N, Guillou H, Wahli W. Peroxisome proliferator-activated receptors and their novel ligands as candidates for the treatment of non-alcoholic fatty liver disease. *Cells*. 2020;9(7):1638. PMID: 32650421. doi:10.3390/cells9071638
25. Younossi ZM. Non-alcoholic fatty liver disease - A global public health perspective. *J Hepatol*. 2019;70(3):531–544. PMID: 30414863. doi:10.1016/j.jhep.2018.10.033
26. Cotter TG, Rinella M. Nonalcoholic fatty liver disease 2020: the state of the disease. *Gastroenterology*. 2020;158(7):1851–1864. PMID: 32061595. doi:10.1053/j.gastro.2020.01.052
27. Polyzos SA, Kountouras J, Mantzoros CS. Obesity and nonalcoholic fatty liver disease: from pathophysiology to therapeutics. *Metabolism*. 2019;92:82–97. PMID: 30502373. doi:10.1016/j.metabol.2018.11.014
28. Finney AC, Das S, Kumar D, et al. The interplay between nonalcoholic fatty liver disease and atherosclerotic cardiovascular disease. *Front Cardiovasc Med*. 2023;10:1116861. PMID: 37200978. doi:10.3389/fcvm.2023.1116861
29. Powell EE, Wong VW, Rinella M. Non-alcoholic fatty liver disease. *Lancet*. 2021;397(10290):2212–2224. PMID: 33894145. doi:10.1016/S0140-6736(20)32511-3
30. Younossi Z, Tacke F, Arrese M, et al. Global perspectives on nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. *Hepatology*. 2019;69 (6):2672–2682. PMID: 30179269. doi:10.1002/hep.30251
31. Loomba R, Friedman SL, Shulman GI. Mechanisms and disease consequences of nonalcoholic fatty liver disease. *Cell*. 2021;184(10):2537–2564. PMID: 33989548. doi:10.1016/j.cell.2021.04.015
32. Younossi Z, Anstee QM, Marietti M, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. *Nat Rev Gastroenterol Hepatol*. 2018;15(1):11–20. PMID: 28930295. doi:10.1038/nrgastro.2017.109
33. Friedman SL, Neuschwander-Tetri BA, Rinella M, Sanyal AJ. Mechanisms of NAFLD development and therapeutic strategies. *Nat Med*. 2018;24 (7):908–922. PMID: 29967350. doi:10.1038/s41591-018-0104-9
34. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology*. 2016;64(1):73–84. PMID: 26707365. doi:10.1002/hep.28431
35. Jiang J, Gao Y, Wang J, et al. Hepatic sphingomyelin phosphodiesterase 3 promotes steatohepatitis by disrupting membrane sphingolipid metabolism. *Cell Metab*. 2025;37(5):1119–1136.e13. PMID: 40015281. doi:10.1016/j.cmet.2025.01.016
36. Tu C, Qian C, Li S, et al. Targeting the chromatin remodeler BAZ2B mitigates hepatic senescence and MASH fibrosis. *Nat Aging*. 2025;5 (6):1063–1078. PMID: 40389730. doi:10.1038/s43587-025-00862-w
37. Yang H, Deng Q, Ni T, et al. Targeted Inhibition of LPL/FABP4/CPT1 fatty acid metabolic axis can effectively prevent the progression of nonalcoholic steatohepatitis to liver cancer. *Int J Biol Sci*. 2021;17(15):4207–4222. PMID: 34803493; PMCID: PMC8579444. doi:10.7150/ijbs.64714
38. Baharuddin B. The metabolic and molecular mechanisms linking fructose consumption to lipogenesis and metabolic disorders. *Clin Nutr ESPEN*. 2025;69:63–68. PMID: 40578484. doi:10.1016/j.clnesp.2025.06.042
39. Ding J, Liu H, Zhang X, et al. Integrative multiomic analysis identifies distinct molecular subtypes of NAFLD in a Chinese population. *Sci Transl Med*. 2024;16(772):eadh9940. PMID: 39504356. doi:10.1126/scitranslmed.adh9940
40. DBDS Genomic consortium; Sveinbjornsson G, Ulfarsson MO, Thorolfsdottir RB, et al. Multiomics study of nonalcoholic fatty liver disease. *Nat Genet*. 2022;54(11):1652–1663. PMID: 36280732; PMCID: PMC9649432. doi:10.1038/s41588-022-01199-5
41. Ægidius HM, Veidal SS, Feigh M, et al. Multi-omics characterization of a diet-induced obese model of non-alcoholic steatohepatitis. *Sci Rep*. 2020;10(1):1148. PMID: 31980690; PMCID: PMC6981216. doi:10.1038/s41598-020-58059-7

42. Ding HR, Tang ZT, Tang N, et al. Protective properties of FOXO1 inhibition in a murine model of non-alcoholic fatty liver disease are associated with attenuation of ER stress and necroptosis. *Front Physiol*. 2020;11:177. PMID: 32218743; PMCID: PMC7078343. doi:10.3389/fphys.2020.00177
43. Chen Y, Zhu Z, Zhang L, Wang J, Ren H. Roles of N6-methyladenosine epitranscriptome in non-alcoholic fatty liver disease and hepatocellular carcinoma. *Smart Med*. 2023;2(3):e20230008. PMID: 39188344; PMCID: PMC11235706. doi:10.1002/SMMD.20230008
44. Wang Y, Wang Y, Gu J, Su T, Gu X, Feng Y. The role of RNA m6A methylation in lipid metabolism. *Front Endocrinol*. 2022;13:866116. PMID: 36157445; PMCID: PMC9492936. doi:10.3389/fendo.2022.866116
45. He Y, Chen Y, Qian S, et al. Immunopathogenic mechanisms and immunoregulatory therapies in MASLD. *Cell Mol Immunol*. 2025;22 (10):1159–1177. PMID: 40494889; PMCID: PMC12480724. doi:10.1038/s41423-025-01307-5