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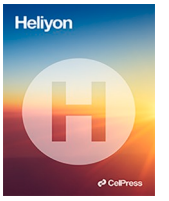

Research article

A bibliometric analysis of macrophages associated with non-alcoholic fatty liver disease research from 2005 to 2023

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) is a prevalent chronic liver condition associated with the risk of progressing to decompensated cirrhosis and hepatocellular carcinoma. While macrophages play a crucial role in the development of NAFLD, their heterogeneity and plasticity allow them to undertake diverse roles in immune response, tissue repair, and maintaining tissue homeostasis. Thus, the exact involvement of macrophages in the onset and progression of NAFLD remains to be further explored. This study aims to employ bibliometric analysis to elucidate the role of macrophages in the pathogenesis of NAFLD, analyze research focal points in this domain, and speculate on future research trends. The literature search, conducted using the Web of Science Core Collection, encompassed articles and reviews related to macrophages and NAFLD published between 2005 and 2023. A bibliometric analysis of 1264 extracted publications was performed using VOSviewer 1.6.17 and Citespace 6.1. R2, evaluating parameters such as spatial and temporal distribution, authors, thematic categories, topic distribution, references, and keywords. The findings revealed a steady global increase in publications in this field, with the United States contributing the most followed by China. The University of California System produced the highest volume of publications, while the Journal of Hepatology had the highest impact factors among the top 10 publishing journals. Tacke Frank emerged as both the most prolific author and the most cited. Co-occurrence and burst analysis of keywords and references highlighted the hotspots in this research area, emphasizing the mechanisms of NAFLD pathogenesis, metabolic regulation, immune modulation, and oxidative stress. Maintaining hepatic homeostasis by liver macrophages and macrophage polarization were identified as trending research directions in this field. Based on the bibliometric analysis, continued attention toward NAFLD therapeutic research involving hepatic macrophages is anticipated. As the mechanisms underlying NAFLD pathogenesis are further elucidated, the development of more treatment approaches related to macrophage immunology and metabolic regulation may expand therapeutic options. This study offers valuable insights into the current state and future trends in the field, providing beneficial guidance to researchers aiming to make significant contributions.

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1. Introduction

Hepatic macrophages, a crucial group of non-parenchymal cells in the liver, play significant roles in maintaining hepatic homeostasis and immune regulation [1]. They also represent the largest population of tissue-resident macrophages in the human body [2,3]. In recent years, mounting evidence has revealed their involvement in the pathogenesis of hepatic diseases, particularly in the development of NAFLD [4]. However, the heterogeneity and plasticity of hepatic macrophages contribute to the complexity of their role in NAFLD and the underlying molecular mechanisms remain elusive. To address this knowledge gap, we conducted a literature-based quantitative study, comprehensively analyzing publications from 2005 to 2023 related to macrophages and NAFLD, along with visualizing the data. The objective of this study was to reveal research characteristics and future directions in this field. Macrophages exhibit diverse functions and impacts in the pathogenesis of NAFLD. For instance, M1 macrophages contribute to liver inflammation and exacerbate NAFLD progression by releasing inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β), leading to hepatic inflammatory damage [5,6]. Conversely, M2 macrophages exert anti-inflammatory and reparative effects. The imbalance between these phenotypes may result in functional dysregulation, thereby impacting disease progression. Moreover, macrophages also regulate lipid metabolism by uptake and clearance of fatty acids, influencing the accumulation of fat within hepatic cells [7]. Moreover, they contribute to the development of liver fibrosis by producing fibrogenic factors like transforming growth factor (TGF), resulting in collagen deposition and changes in liver tissue structure [8]. Finally, macrophages play a crucial role in tumor immune surveillance, being involved in the development and progression of hepatocellular carcinoma (HCC) [9,10]. The diverse phenotypes of hepatic macrophages in the context of NAFLD significantly impact liver inflammation, fibrosis, and the repair process during disease progression. However, the exact mechanisms underlying their roles necessitate further investigation.

Through the analysis of literature metrics, we can identify countries, journals, authors, and institutions that have made significant contributions in this field. Additionally, we can uncover widely cited studies and commonly used keywords, as well as establish collaboration networks among countries, institutions, and authors. By constructing citation networks, we can gain a better understanding of the research dynamics in this field and predict future research hotspots. This literature-based quantitative study yields crucial findings that enhance our comprehension of the correlation between NAFLD and macrophages. It facilitates a comprehensive grasp of the present research landscape and future directions in this domain. Through furnishing valuable references and offering guidance to researchers, this study stimulates advancements and fosters collaboration in the field, thereby providing enhanced strategies for the prevention and treatment of NAFLD.

2. Methods

2.1. Data collection and search strategy

Clarivate Analytics' Web of Science Core Collection (WoSCC) database is widely recognized as a highly authoritative and comprehensive platform dedicated to academic research [11,12]. It encompasses a vast array of more than 12,000 internationally acclaimed scholarly journals [13]. For bibliometric analysis, we have chosen this database to extract worldwide academic information, taking into account previous research studies. We conducted a literature search in the WoSCC database using the following search terms: TS = ("non-alcoholic fatty liver" OR "non-alcoholic steatohepatitis" OR "NAFLD") AND TS = ("macrophage" OR "Kupffer cell"), regardless of language or document type. The search covered the period from January 1, 2005, to January 1, 2023. A total of 1408 articles were identified during the search process. Subsequently, we applied the following selection criteria: excluding conference

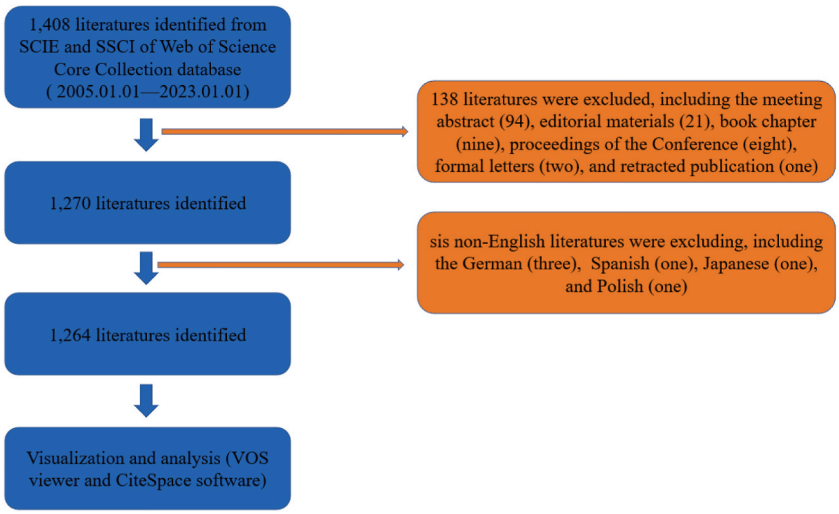


Fig. 1. Screening process flowchart.

abstracts (94 articles), editorial materials (21 articles), book chapters (9 articles), conference proceedings (8 articles), official letters (2 articles), and retracted publications (1 article). This resulted in a final selection of 1270 articles. Furthermore, we excluded 6 non-English articles, yielding a total of 1264 articles for analysis. The screening flowchart is shown in Fig. 1. The relevant literature was exported and saved in the download. txt format, including full-text records and cited references, for further analysis.

2.2. Data analysis

In this investigation, we utilized two bibliometric analysis instruments, namely VOSviewer version 1.6.17 software (developed by Leiden University, Leiden, Netherlands) and Citespace version 6.1. R2 software (developed by Drexel University, Philadelphia, PA, USA). VOSviewer and CiteSpace are two distinct software tools with complementary features that facilitate the visualization and analysis of bibliometric and citation data in academic literature.

VOSviewer serves as a robust tool for bibliometric analysis, facilitating data cleaning, visualization, and analysis through multiple steps. Starting with the collection and cleaning of literature data, importing it into VOSviewer, parameters are set for analysis, generating visual representations of document relationships and thematic distributions. Its primary function involves clustering closely related nodes, identifying higher correlation groups using similar colors. Additionally, it constructs overlay visual maps, depicting node color and distance in a two-dimensional space, aiding in understanding temporal and contextual relationships within the data. During the interpretation phase, researchers can uncover hotspots in the research field, keyword frequencies, among other insights, enhancing comprehension of the literature data and identifying research trends. The versatility of VOSviewer extends to various applications, such as analyzing co-authorship networks to reveal collaborative relationships among authors and institutions. Moreover, co-occurrence networks effectively evaluate the relevance of author keywords. The key lies in ensuring data quality, setting parameters sensibly, and integrating domain knowledge to validate results. This aids researchers in delving deeper into understanding literature data and exploring trends and associations within the research domain.

On the other hand, CiteSpace stands out as an exceptional open-source software designed specifically for the visualization and analysis of citation data in academic literature databases. It excels in presenting dynamic developments within various academic fields through graphical representations, including timelines and network graphs. By accurately identifying collaboration networks among authors and institutions, CiteSpace provides valuable insights into the evolution of research topics. Moreover, its in-depth analysis of citation relationships allows for the identification of pivotal reference articles and assessment of academic impact.

Both VOSviewer and CiteSpace serve as indispensable tools for researchers and academicians in the exploration of scholarly data. VOSviewer's strength lies in its ability to reveal intricate relationships within bibliometric networks, while CiteSpace is particularly adept at capturing the dynamic evolution of research fields through citation data analysis. Together, these software tools complement each other, offering a comprehensive toolkit for researchers to gain a deeper understanding of academic literature, collaboration patterns, and the progress of scholarly knowledge. Their combined use opens up new avenues for scholarly exploration and facilitates informed decision-making in academic pursuits.

3. Results

3.1. Analysis of annual publication outputs

Based on the provided data, analyzing the total number of publications over a period of time allows for an objective and quantitative assessment of the overall development trends in the field of macrophages and NAFLD.

A total of 1264 publications were selected for analysis. Among these, 963 articles (76.19 %) were research papers, 301 articles (23.81 %) were reviews, and 8 articles (0.63 %) were classified as early literature. This distribution indicates a higher preference among researchers in this field for publishing original research papers and review articles, with a relatively lower proportion of early literature.

In Fig. 2A, the annual count of research papers' publications is depicted. The quantity of papers grew from 3 in 2005 to 199 in 2022.

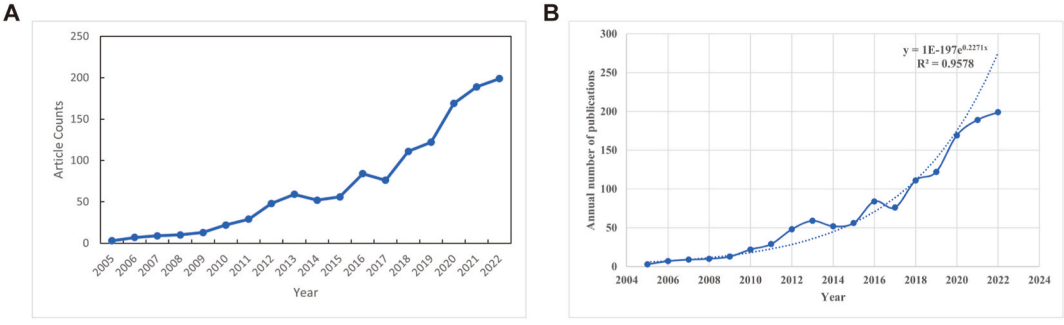


Fig. 2. (A) Line graph of the number of papers published worldwide related to macrophages associated with NAFLD. **(B)** Fitted curve of global publication trends of macrophages associated with NAFLD per year (R2 = 0.9578).

Throughout the preceding 18-year period, a steady upward pattern in the publication of pertinent research papers has been observed. This trend is further supported by the fitted curve shown in Fig. 2B, with an adjusted coefficient of determination (R2) of 0.9578, indicating a steady growth in publication output.

In conclusion, these findings demonstrate a growing interest among researchers in the field of macrophages and NAFLD, which is reflected by the increasing number of publications. The steady growth trend suggests a continuous accumulation of research output and holds potential for further advancements and clinical applications in this field.

3.2. Analysis of the most productive countries/territories

Table 1 presents the top 10 countries/regions with the greatest influence in a specific medical research field, including article counts, percentages, total citations, and citations per article. The table reveals that the United States had the highest number of publications (N = 356), followed by China (N = 347), Japan (N = 148), and Germany (N = 133). The remaining countries each published fewer than 100 articles. Moreover, the United States significantly outperformed other countries in terms of total citations, highlighting its influential role in this research field.

Fig. 3A illustrates the global distribution of publications by countries/territories, showing a concentration of research output in North America, Western Europe, and East Asia.

Furthermore, Fig. 3B presents a VOSviewer visualization map of countries, revealing that the United States has the highest publication volume and maintains close collaborations with China, Japan, and Germany, indicating strong collaborative ties among these nations in medical research.

3.3. Analysis of the most productive institutions

Approximately 1595 institutions contributed to the research on NAFLD and macrophage. Table 2 presents the top 10 contributing institutions, with the highest number of articles attributed to the University of California System (54 articles), followed by Harvard University (34 articles), Maastricht University (29 articles), Shanghai Jiao Tong University (27 articles), and Huazhong University of Science and Technology (26 articles). The most productive institutions on the list were predominantly from four countries: China (5 institutions), the United States (2 institutions), Netherlands (2 institutions) and France (1 institution). Co-authorship analysis can provide insights into the collaborations between different institutions based on the number of co-authored publications. The network visualization of co-authorship analysis is depicted in Fig. 4A. In this representation, the circles' sizes correspond to the number of publications, while the colors indicate diverse clusters, symbolizing collaborations among different institutions. It is evident from the figure that collaborations among different institutions are primarily concentrated within the same country. Fig. 4B displays the average year of publication for each institution in specific research areas. China's research institutions have witnessed a remarkable surge in publications in this particular field over the past few years. This growth signifies the notable progress China has achieved in investigating NAFLD and macrophages.

3.4. Analysis of the higher-impact journals

A total of 387 academic publications have focused on the subject of macrophages in relation to NAFLD. Among these scholarly journals, 54 have published a minimum of 5 papers on this topic. Table 3 presents the top 10 productive journals, their respective article counts, impact factors (IF), and total citation counts. Journal of Hepatology emerged as the most prolific journal, with 60 publications and a total citation count of 7157. Journal of Hepatology attained the highest impact factor (25.7), followed by the Hepatology (13.5). Fig. 5A illustrates that Frontiers series and Biomedicines are at the forefront of research in this field. Fig. 5B delineates two major citation pathways using orange and green lines. Through these pathways, it was observed that articles published in the fields of molecular/biology/genetics are primarily cited by researchers in the molecular/biology/immunology and medicine/medical/clinical journals. The second pathway demonstrates that papers published in the domain of health/care/medicine are predominantly cited by researchers in the molecular/biology/immunology journals.

Table 1
Top 10 countries/territories with the most publications in the field of macrophages associated with NAFLD.

Rank	Country	Article counts	Percentage%	Total citations	Per citations
1	USA	356	28.17	20,835	58.53
2	China	347	27.45	7144	20.59
3	Japan	148	11.71	7245	48.95
4	Germany	133	10.52	5721	43.02
5	Italy	86	6.80	3370	39.19
6	Netherlans	67	5.30	3665	54.70
7	South Korea	64	5.06	1754	27.41
8	France	58	4.59	3827	65.98
9	Spain	53	4.19	1874	35.36
10	England	51	4.04	2629	51.55

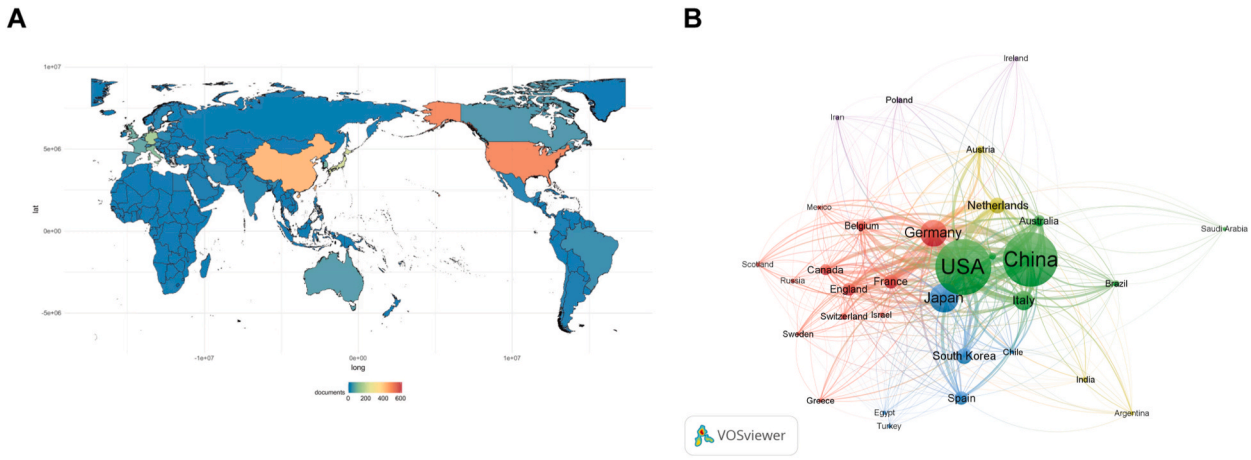


Fig. 3. (A) A world map of the distribution of macrophages relevant to NAFLD research. **(B)** Country/territory collaboration analysis by VOSviewer.

Table 2
Top 10 institutions with the most publications in the field of macrophages associated with NAFLD.

Rank	Institution	Article counts	Country	Total citations
1	Univ Calif System	54	USA	4423
2	Harvard Univ	34	USA	1938
3	Maastricht Univ	29	Netherlands	1138
4	Shanghai Jiao Tong Univ	27	China	1360
5	Huazhong Univ Sci & Technol	26	China	1113
6	Chongqing Med Univ	23	China	963
7	Univ Groningen	22	Netherlands	976
8	Wenzhou Med Univ	20	China	320
9	Inserm	19	France	2707
10	Sun Yat Sen Univ	19	China	542

3.5. Analysis of the most influential authors

According to Table 4, a total of 7937 authors have published papers related to NAFLD and macrophages. The team/lab led by Tacke Franks has the highest number of publications, with a total of 25 papers. They are followed by the Shiri-Sverdlov, Ronit team (20 papers) and Hofker Tim team (14 papers). We found that the average number of citations of Tacke Franks' team and Feldstein, Ariel E. team papers was at the top of the list, suggesting that the team's scientific results are widely recognized in the research field. The collaboration network among researchers is illustrated in Fig. 6, where a minimum publication threshold of 5 papers per author has been set. Among the remaining 124 authors, almost all of them are clustered together, with each cluster closely connected to one or two prolific authors who frequently publish papers. The dense inter-cluster connections indicate strong collaboration among research teams/labs involved in studying NAFLD and macrophages. Tacke Franks' team/lab exhibits the widest range of connections with other researchers, with a total of 151 collaborations. Following closely are the Shiri-Sverdlov, Ronit team (145 collaborations) and the Feldstein AE team (124 collaborations). These findings suggest that the team/lab led by Tacke Franks has established extensive collaborative relationships with other researchers in the field of NAFLD and macrophage-related research.

3.6. Analysis of citation and co-citation

Fig. 7A illustrates that more than 25 citations were obtained for a total of 551 articles within the medical field. Table 5 presents the top 10 most frequently cited papers. The article titled " Glycogen synthase kinase 3-mediated voltage-dependent anion channel phosphorylation controls outer mitochondrial membrane permeability during lipid accumulation" received the highest number of citations, with a total of 607. Following closely is the paper on " Role of obesity and lipotoxicity in the development of nonalcoholic steatohepatitis: pathophysiology and clinical implications," which received 597 citations. Ranking third is the article titled " NLRP3 inflammasome blockade reduces liver inflammation and fibrosis in experimental NASH in mice" with a citation count of 562. Furthermore, Fig. 7B displays the co-cited references, providing an overview of the most influential papers, as analyzed by VOSviewer.

To gauge the interest of scholars in the field over time, citation bursts serve as a valuable indicator. In our study, CiteSpace identified and depicted the top 25 references with the strongest citation bursts in Fig. 7C, showcasing the duration of the citation bursts for these references. Notably, the article "M2 Kupffer cells promote M1 Kupffer cell apoptosis: A protective mechanism against alcoholic and nonalcoholic fatty liver disease," published in 2014, ranked first in terms of strength, with a value of 27.02. Additionally,

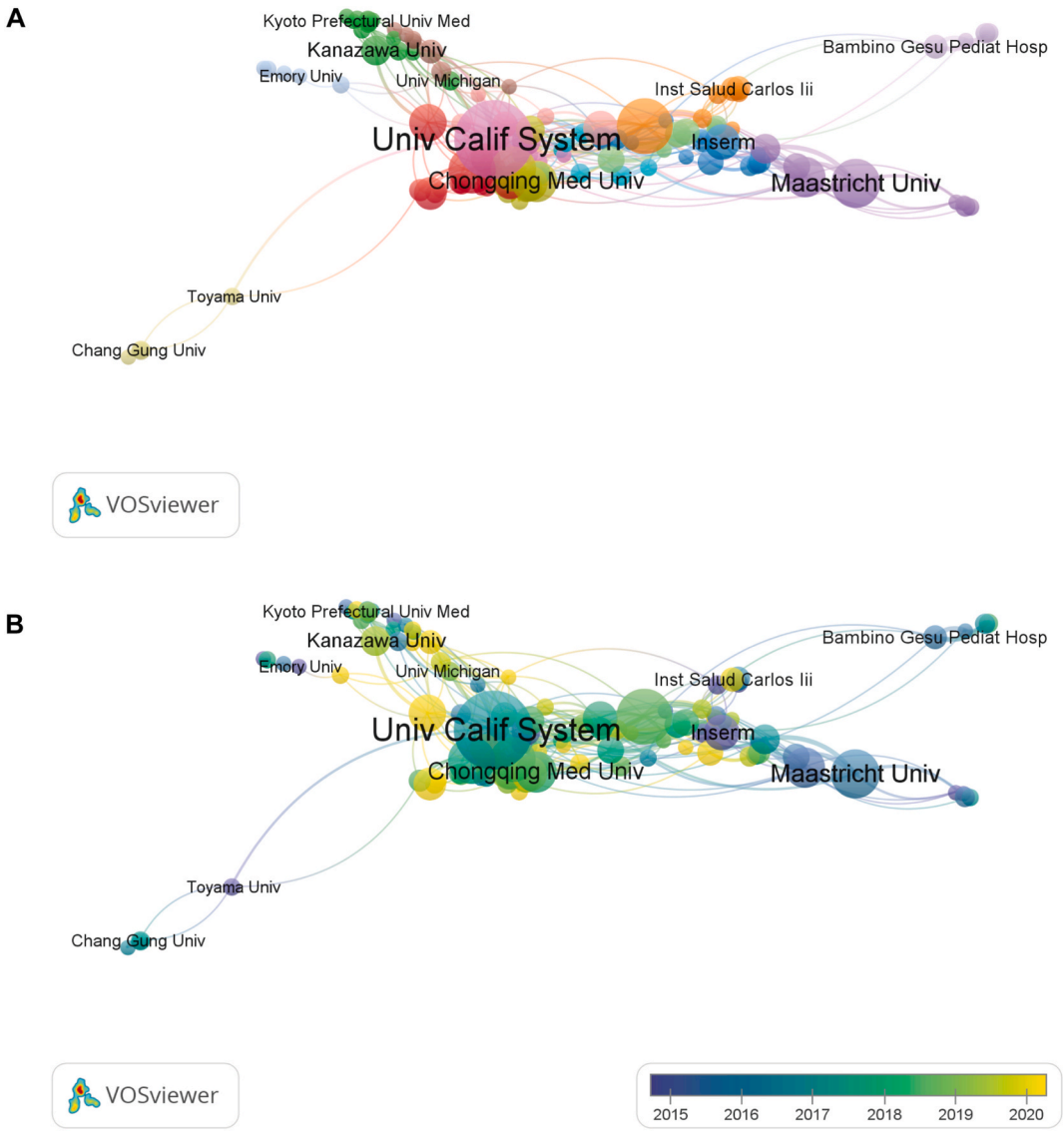


Fig. 4. **(A)** Network visualization for institutional co-authorship analysis by VOSviewer. **(B)** Average year of publication in the field of macrophages associated with NAFLD by institution.

Table 3
Top 10 journals with the most publications in the field of macrophages associated with NAFLD.

Rank	Institution	Article counts	IF (2022)	Total citations
1	Journal of Hepatology	60	25.7	7157
2	International Journal of Molecular Sciences	52	5.6	1308
3	Plos One	52	3.7	2833
4	Frontiers in Immunology	50	7.3	1372
5	Scientific Reports	42	4.6	1187
6	Hepatology	32	13.5	3336
7	World Journal of Gastroenterology	25	4.3	1513
8	Hepatology Research	22	4.2	425
9	Frontiers in Pharmacology	19	5.6	244
10	Nutrients	19	5.9	711

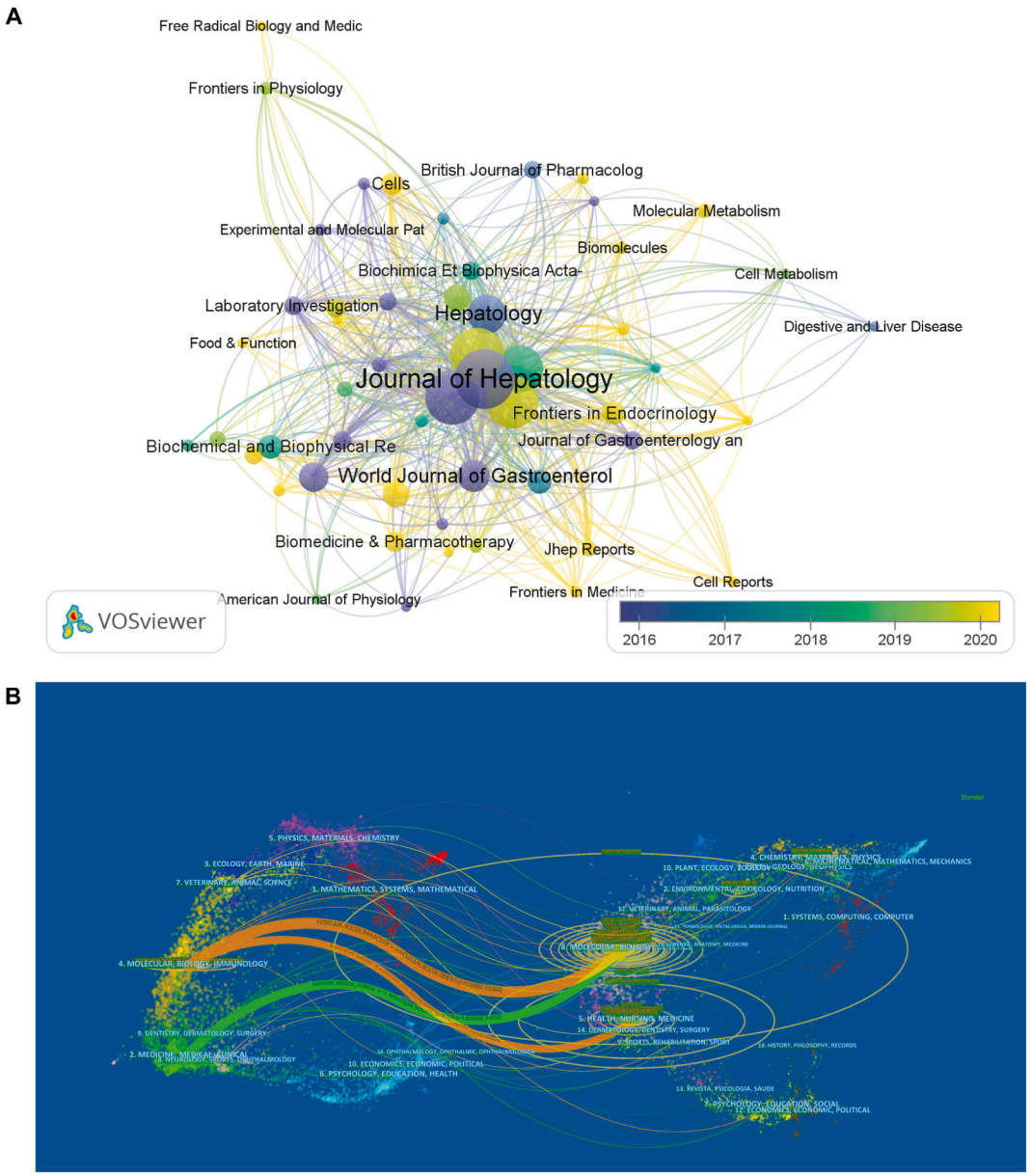


Fig. 5. (A) Average year of publication in the field of macrophages associated with NAFLD by Journal. **(B)** The Dual-Map Overlays in macrophages associated with NAFLD research.

Table 4
Top 10 authors with the most publications in the field of macrophages associated with NAFLD.

Rank	Author	Article counts	Links	Total citations
1	Tacke, Frank	25	687	2517
2	Shiri-Sverdlov, Ronit	20	699	868
3	Hofker, Marten H.	14	546	818
4	Hendrikx, Tim	13	561	511
5	Nobili, Valerio	13	327	583
6	Feldstein, Ariel E.	12	213	1746
7	Gronbaek, Henning	12	422	722
8	Trautwein, Christian	12	198	940
9	Walenbergh, Sofie M. A.	12	472	375
10	Alisi, Anna	11	316	462

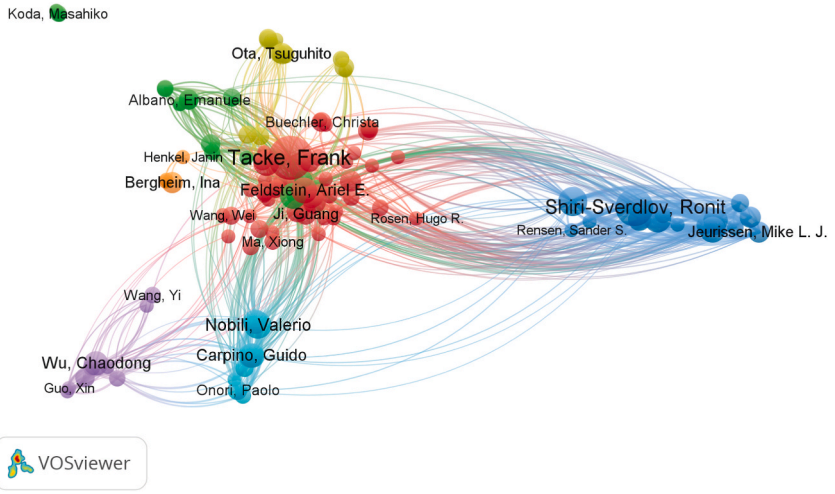
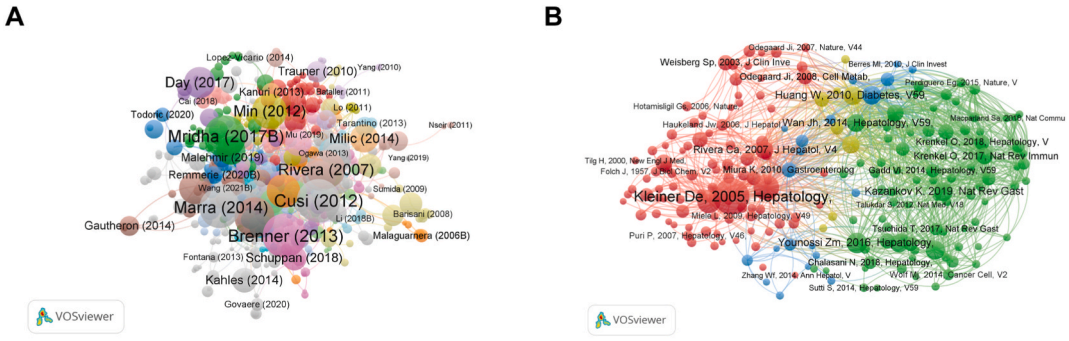


Fig. 6. A collaborative network among researchers in which a threshold of at least five publications per author is set.



C

Top 25 References with the Strongest Citation Bursts

References	Year	Strength	Begin	End	2005 - 2022
Rivera CA, 2007, J HEPATOL, V47, P571, DOI 10.1016/j.jhep.2007.04.019, DOI	2007	12.8	2008	2012	
Wouters K, 2008, HEPATOLOGY, V48, P474, DOI 10.1002/hep.22363, DOI	2008	17.29	2010	2013	
Baffy G, 2009, J HEPATOL, V51, P212, DOI 10.1016/j.jhep.2009.03.008, DOI	2009	14.95	2010	2014	
Huang W, 2010, DIABETES, V59, P347, DOI 10.2337/db09-0016, DOI	2010	14.91	2010	2015	
Tilg H, 2010, HEPATOLOGY, V52, P1836, DOI 10.1002/hep.24001, DOI	2010	26.91	2011	2015	
Stienstra R, 2010, HEPATOLOGY, V51, P511, DOI 10.1002/hep.23337, DOI	2010	13.65	2011	2015	
Sanyal AJ, 2010, NEW ENGL J MED, V362, P1675, DOI 10.1056/NEJMoa0907929, DOI	2010	12.64	2011	2015	
Baeck C, 2012, GUT, V61, P416, DOI 10.1136/gutjnl-2011-300304, DOI	2012	18.39	2012	2017	
Miura K, 2010, GASTROENTEROLOGY, V139, P323, DOI 10.1053/j.gastro.2010.03.052, DOI	2010	18.05	2012	2015	
Miura K, 2012, AM J PHYSIOL-GASTR L, V302, P0, DOI 10.1152/ajpgi.00365.2011, DOI	2012	24.19	2013	2017	
Henao-mejia J, 2012, NATURE, V482, P179, DOI 10.1038/nature10809, DOI	2012	16.23	2013	2017	
Leroux A, 2012, J HEPATOL, V57, P141, DOI 10.1016/j.jhep.2012.02.028, DOI	2012	14.91	2013	2017	
Cohen JC, 2011, SCIENCE, V332, P1519, DOI 10.1126/science.1204265, DOI	2011	14.36	2013	2016	
Farrell GC, 2012, GUT LIVER, V6, P149, DOI 10.5009/gnl.2012.6.2.149, DOI	2012	12.7	2013	2017	
Tosello-trampont AC, 2012, J BIOL CHEM, V287, P40161, DOI 10.1074/jbc.M112.417014, DOI	2012	24.77	2014	2017	
Wan JH, 2014, HEPATOLOGY, V59, P130, DOI 10.1002/hep.26607, DOI	2014	27.02	2015	2019	
Tacke F, 2014, J HEPATOL, V60, P1090, DOI 10.1016/j.jhep.2013.12.025, DOI	2014	16.73	2015	2019	
Marra F, 2014, GASTROENTEROLOGY, V147, P577, DOI 10.1053/j.gastro.2014.06.043, DOI	2014	13.44	2015	2019	
Gadd VL, 2014, HEPATOLOGY, V59, P1393, DOI 10.1002/hep.26937, DOI	2014	12.71	2015	2019	
Younossi ZM, 2016, HEPATOLOGY, V64, P73, DOI 10.1002/hep.28431, DOI	2016	22.14	2018	2022	
Tacke F, 2017, J HEPATOL, V66, P1300, DOI 10.1016/j.jhep.2017.02.026, DOI	2017	12.78	2018	2020	
Friedman SL, 2018, NAT MED, V24, P908, DOI 10.1038/s41591-018-0104-9, DOI	2018	19.69	2020	2022	
Kazankov K, 2019, NAT REV GASTRO HEPAT, V16, P145, DOI 10.1038/s41575-018-0082-x, DOI	2019	17.79	2020	2022	
Ramachandran P, 2019, NATURE, V575, P512, DOI 10.1038/s41586-019-1631-3, DOI	2019	13.48	2020	2022	
Xiong XL, 2019, MOL CELL, V75, P644, DOI 10.1016/j.molcel.2019.07.028, DOI	2019	12.99	2020	2022	

Fig. 7. (A) Literature in the field of macrophages associated with NAFLD with at least 25 citations. **(B)** Analyzing co-cited references provides an overview of the most influential papers. **(C)** Top 25 references with the strongest citation bursts.

Table 5
Top 10 articles with the most citations in the field of macrophages associated with NAFLD.

Rank	Title	The first Author	Journal	Total citations	Publication Year
1	Glycogen synthase kinase 3-mediated voltage-dependent anion channel phosphorylation controls outer mitochondrial membrane permeability during lipid accumulation	Catherine Brenner	Hepatology	607	2013
2	Role of obesity and lipotoxicity in the development of nonalcoholic steatohepatitis: pathophysiology and clinical implications	Kenneth Cusi	Gastroenterology	597	2012
3	NLRP3 inflammasome blockade reduces liver inflammation and fibrosis in experimental NASH in mice	Auvro R Mridha	Journal of Hepatology	562	2017
4	Roles for chemokines in liver disease	Fabio Marra	Gastroenterology	537	2014
5	Targeting hepatic macrophages to treat liver diseases	Frank Tacke	Journal of Hepatology	524	2017
6	Toll-like receptor-4 signaling and Kupffer cells play pivotal roles in the pathogenesis of non-alcoholic steatohepatitis	Chantal A Rivera	Journal of Hepatology	502	2007
7	Increased hepatic synthesis and dysregulation of cholesterol metabolism is associated with the severity of nonalcoholic fatty liver disease	Hae-Ki Min	Cell Metabolism	436	2012
8	The role of macrophages in nonalcoholic fatty liver disease and nonalcoholic steatohepatitis	Konstantin Kazankov	Nature Reviews Gastroenterology & Hepatology	410	2019
9	Pharmacological inhibition of the chemokine CCL2 (MCP-1) diminishes liver macrophage infiltration and steatohepatitis in chronic hepatic injury	Christer Baeck	Gut	392	2012
10	Mechanisms and disease consequences of nonalcoholic fatty liver disease	Rohit Loomba	Cell	385	2021

the citation bursts for articles authored by Younossi ZM persisted from 2018 to 2022, indicating continuous attention towards the author's research direction within the field.

3.7. Analysis of keywords and hotspots

Utilizing the algorithms of CiteSpace, we conducted keyword burst detection to identify emerging trends. Fig. 8 illustrates the top 25 keywords with the strongest citation bursts. Notably, "natural history" exhibited the highest burst strength (7.71), followed by "metabolic syndrome" (7.51). Among these, "endotoxin" had the longest burst duration, spanning a decade from 2007 to 2016. The

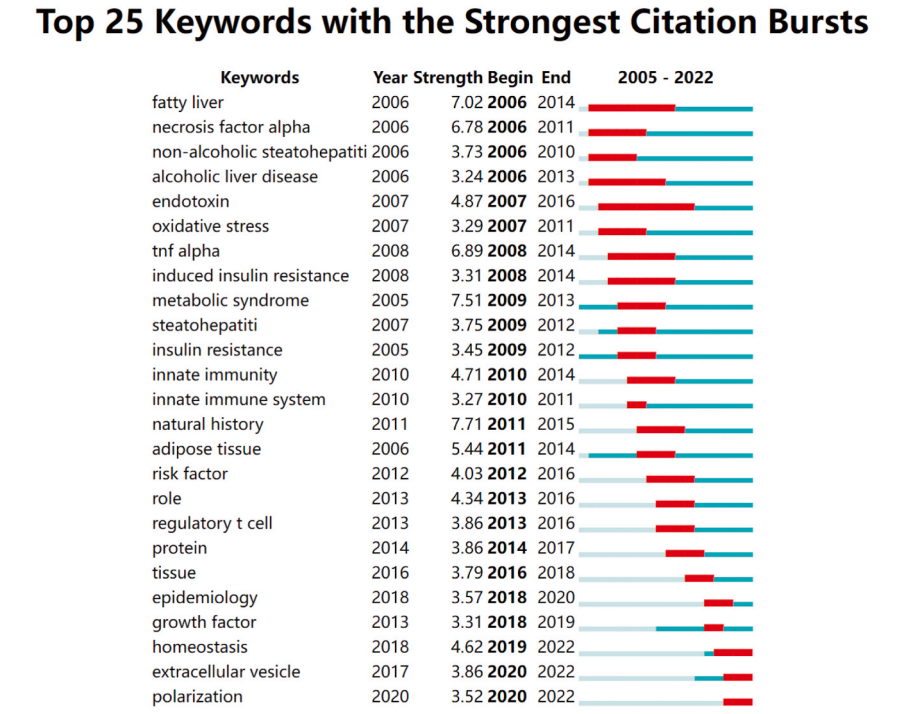


Fig. 8. Top 25 keywords with the strongest citation bursts.

most recently highly cited keywords include “extracellular vesicle," “polarization" (2020–2022), and “homeostasis" (2019–2022), indicating a potential future focus on intercellular communication, subtype variances, and homeostasis maintenance concerning NAFLD and macrophages.

Keyword co-occurrence analysis, a crucial tool in bibliometrics to delineate research hotspots and areas, was employed. In this analysis, 155 high-frequency keywords were identified for VOSviewer analysis after excluding keywords with high frequency but lacking analytical significance. The top 10 frequencies were as follows: NAFLD (517), NASH (506), Inflammation (440), Insulin-Resistance (366), Fatty Liver Disease (313), Hepatic Macrophages (306), Kupffer Cells (271), Fibrosis (270), Obesity (239), and Steatohepatitis (219). Utilizing VOSviewer, a co-occurrence clustering network map (Fig. 9A) was generated, classifying the keywords into five clusters. Cluster 1# (red) involves five of the top 10 keywords and primarily revolves around elucidating the pathogenesis of NAFLD. Cluster 2# (green) predominantly investigates the role of macrophages in metabolic disturbances of NAFLD. Cluster 3# (blue)

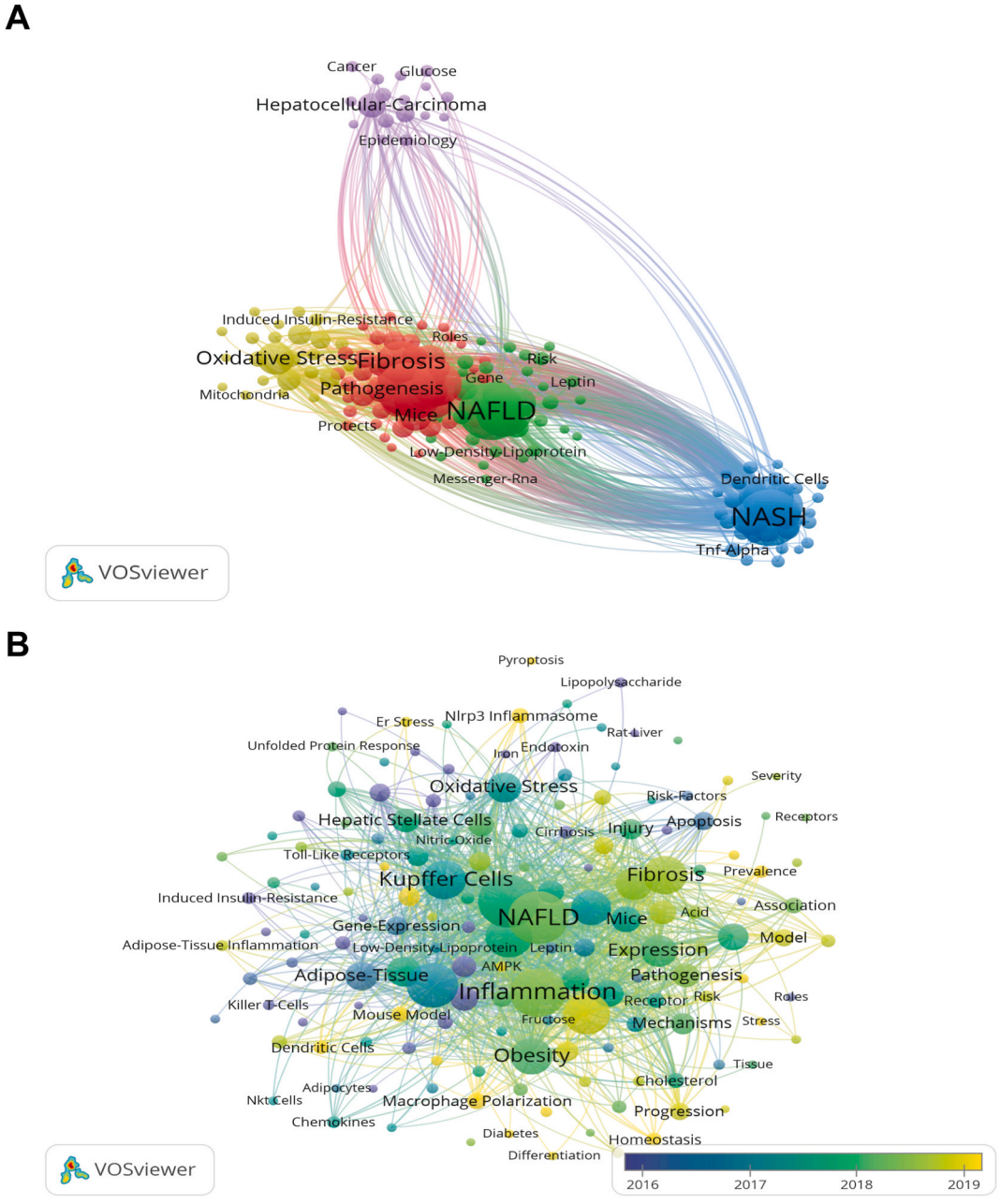


Fig. 9. (A) The research area concerning macrophages in NAFLD is depicted through a keyword mapping approach. Dot sizes represent the frequencies, while the keywords are grouped into six distinct clusters. (B) The average year of citation for keyword-based classification in the field of macrophages associated with NAFLD.

focuses on the immunomodulatory effects of macrophages, impacting liver inflammation and subsequently regulating NAFLD. Cluster 4# (yellow) emphasizes the role of macrophages in oxidative stress during NAFLD pathophysiology. Lastly, Cluster 5# (purple) centers on studying the involvement of macrophages in the progression from NAFLD to hepatocellular carcinoma. These findings showcase the forefront and current hotspots in research concerning macrophages and their relation to NAFLD. Importantly, these research outcomes align not only with the primary research hotspots in the field of macrophages and NAFLD but also provide valuable insights for future investigations.

According to Fig. 9B, VOSviewer utilized coloration based on the average occurrence of all keywords in published papers. Specifically, blue indicates earlier appearances of keywords, while yellow signifies more recent occurrences. The evolving trends in the majority of studies across the five clusters have shifted from elucidating the pathogenesis of NAFLD involving macrophages in mechanisms of disease onset, lipid metabolism, and oxidative stress (Clusters one, two, and four) to focusing on macrophage-mediated immune-inflammatory regulation in NAFLD, disease model interventions, and treatment (Clusters three and five). This shift indicates potential future research areas revolving around the role of macrophages in influencing liver metabolism, immune responses, and subsequently participating in the onset and progression of NAFLD, leading to research on disease diagnosis and treatment.

4. Discussion

The impact of macrophages on NAFLD has become a recent research hotspot, offering novel insights into NAFLD treatment. In essence, Kupffer cells can trigger hepatocyte inflammation through the release of chemokines, inflammatory factors, and recruit monocyte-derived macrophages to the liver [14,15]. These hepatic macrophages assume different activation states, exerting diverse effects on NAFLD. Furthermore, extra-liver adipose tissue macrophages and gut-derived endotoxins, lipids, and metabolites also activate hepatic macrophages, promoting inflammatory responses [16]. These findings provide critical clues for a deeper understanding of NAFLD pathogenesis and the development of new therapeutic approaches. It should be noted that the heterogeneity of macrophages is closely associated with the progression of NAFLD. Macrophage polarization has emerged as a prominent focus of investigation in the hepatic immune microenvironment, as it exerts important regulatory effects on the development and progression of NAFLD. Macrophage polarization refers to the distinct antigen expression patterns exhibited by macrophages in the microenvironment, primarily encompassing classically activated M1 macrophages expressing specific antigens such as CD80, CD86, CD40, and alternatively activated M2 macrophages expressing antigens like CD163, CD206, CD301 [16–19]. Additionally, IL-4 and IL-13 can induce M2 polarization of macrophages, leading to the secretion of IL-10, TGF-β, and their participation in tissue repair [20,21]. However, macrophage polarization is a complex process that is highly susceptible to interference from other factors, exerting extensive effects on hepatic inflammation, lipid metabolism, and even energy homeostasis. Although significant progress has been achieved in the field of NAFLD-related macrophages research, the pathogenesis of NAFLD is characterized by diverse factors and intricate mechanisms, necessitating a comprehensive and systematic analysis to advance the discipline. Therefore, to foster further development in this field, a scientifically oriented analysis using bibliometric methods is warranted to assess the current status of research and identify more valuable research directions, thus propelling the advancement of the discipline.

4.1. An overview of trends in publications in the field of macrophages associated with NAFLD research from 2005 to 2023

From January 1, 2005, to January 1, 2023, the domain of non-alcoholic fatty liver disease (NAFLD)-associated macrophage research has experienced significant growth in research articles globally. The study reveals contributions from approximately 60 countries, with the United States leading in the number of publications (28.17 %), followed by China, Japan, Germany, and Italy. The United States also exhibits the highest total citation count, demonstrating its prominent position in this field due to world-class scholars and scientific institutions. France, Australia, and Germany show high average citation counts, indicating remarkable progress in the quality and impact of their research.

While China ranks second in the number of papers, its total and average citation counts are relatively low, suggesting a need for improvement in research quality. Notably, the University of California system, Harvard University, and Maastricht University are among the top research institutions contributing significantly to macrophage research related to NAFLD. Collaboration between institutions and countries is essential to advance the academic research level further.

In terms of authors, those with more experience in the NAFLD research field receive higher recognition, with Tacke Frank, Feldstein AE, and Shiri-Sverdlov, Ronit being among the most highly cited authors internationally. Journal of Hepatology, International Journal of Molecular Sciences, PLoS One, Frontiers in Immunology, and Scientific Reports are the top journals for publishing macrophages associated with NAFLD research. Among the ten most cited research directions, all were focus on basic research. The most referenced papers explore the physiological and causal mechanisms of NAFLD, with an emphasis on macrophages, metabolic reprogramming and associated cytokines.

In conclusion, the rise in macrophages associated with NAFLD research is evident across multiple dimensions, including contributions from various countries, influential institutions, prolific authors, and prominent journals. The field's focus is on fundamental research investigating NAFLD's pathology, etiology, diagnosis, and treatment, with an emphasis on macrophages' role in disease progression. Collaborative efforts among researchers from different nations are crucial to advancing this area of research and producing high-quality publications in the future.

4.2. Research hotspots and frontiers

The high-frequency keywords identified in Fig. 9A's co-occurrence reveal significant research focal points within the realm of macrophage and NAFLD correlation studies. Among the top 10 highly cited keywords, namely NAFLD (517), NASH (506), Inflammation (440), Insulin-Resistance (366), Fatty Liver Disease (313), Hepatic Macrophages (306), Kupffer Cells (271), Fibrosis (270), Obesity (239), and Steatohepatitis (219), they represent the most frequently referenced terms in macrophage associated with NAFLD research over the past 18 years, thereby indicating key areas of focus in this field during this period.

The cluster 1 comprises the highest number of highly cited keywords, including "Inflammation," "Hepatic Macrophages," "Fibrosis," "Obesity," and "Steatohepatitis," primarily focusing on the pathogenesis of NAFLD. The "two-hit hypothesis," proposed in 1998, delineates the classic theory of NAFLD pathogenesis. The "first hit" refers to hepatic triglyceride accumulation due to insulin resistance, leading to decreased tolerance to endogenous and exogenous insults, ischemia, and hypoxia. The "second hit" occurs when triglycerides accumulate within hepatocytes, resulting in cellular damage under the influence of inflammatory cytokines, oxidative stress, and endoplasmic reticulum stress, ultimately causing inflammation and fibrosis, thus inducing NASH [22]. In recent years, as research into the pathogenesis of NAFLD has deepened, the "two-hit" theory has gradually shifted towards the "multiple-hit" theory, comprehensively considering the influences of genetics, gut microbiota, inflammation, and lifestyle factors on NAFLD development [23]. Particularly, the relationship between gut microbiota and NAFLD has garnered significant attention in research. It has been observed that the gut microbiota plays a pivotal role in the onset and progression of NAFLD through various mechanisms [24–26]. Dysbiosis in the gut microbiota increases intestinal permeability, allowing harmful substances like lipopolysaccharides to enter the bloodstream, triggering hepatic inflammation [27–29]. Furthermore, bacteria in the gut microbiota producing ethanol exacerbate gut barrier damage, further worsening the inflammatory response [30,31]. Simultaneously, studies have revealed the involvement of the gut microbiota in lipid metabolism and immune regulation in NAFLD [32]. The role of the gut microbiota in NAFLD development has become a research hotspot, with modulating the gut microbiota emerging as a novel therapeutic target for treating NAFLD.

The most frequently co-occurring term among the high-frequency keywords is "NAFLD," alongside "Insulin Resistance," both belonging to the same cluster (cluster 2) that predominantly investigates the metabolic regulatory functions of macrophages in NAFLD. Metabolic disturbances in NAFLD not only occur within the liver but are also associated with systemic metabolic syndrome, with lipid metabolism disruption being particularly crucial [33,34]. Macrophages play a crucial role in NAFLD. Insulin resistance leads to triglyceride accumulation within the liver, increasing intrahepatic lipid synthesis. Research indicates that a high-fat diet induces lipid imbalance in Kupffer cells, leading to the accumulation of bioactive lipid metabolites, exacerbating lipid toxicity and liver damage [35,36]. Peroxidation of lipids can induce hepatic inflammatory responses, increase the number of macrophages, and enhance the expression of inflammation-related factors within the liver [37]. Cholesterol-modified lipoproteins absorbed by Kupffer cells through scavenger receptors such as CD36 and scavenger receptor A can reduce lysosomal cholesterol, lipid oxidation, and oxidative stress, thereby reducing liver damage [38,39]. Additionally, leptin levels correlate with the severity of NAFLD, with Kupffer cells participating in lipid metabolism regulation via leptin receptors [40]. Lipid metabolites and regulatory factors directly affect pro-inflammatory macrophage activation, indirectly modulating the release of pro-inflammatory cytokines, thus influencing the pathological progression of NAFLD. Considering the high plasticity of macrophages, they can undergo phenotypic "repolarization" or "reprogramming" upon exposure to specific signals. Hence, metabolic regulation might be at the core of macrophage functional plasticity, with lipid metabolism playing a crucial role in immune cell inflammation and metabolic-driven phenotypic changes. Therefore, further research is needed to elucidate the metabolic characteristics of different macrophage phenotypes, with targeting macrophages for regulating NAFLD lipid metabolism holding promise as a new therapeutic target.

Cluster 3 primarily revolves around elucidating research on how macrophages regulate hepatic inflammation through immune modulation. The high-frequency keywords in this cluster include "NASH"、 "Fatty Liver Disease"、 and "Kupffer Cells." Macrophages, particularly resident Kupffer cells, serve as critical regulatory factors in NAFLD-related inflammation progression. In the early stages of NAFLD, excessive pro-inflammatory polarization significantly promotes hepatic lipid accumulation, initiating inflammation and recruiting various other immune cells [4]. Kupffer cells play a vital role in this process. Furthermore, the lack of monocyte-derived macrophages may contribute to liver fat accumulation and inflammation progression. The interaction between macrophages and other immune cells is also crucial in NAFLD development. Release of bacterial products, toxic lipids, and inflammatory mediators from liver cells triggers hepatic inflammation and NAFLD progression. This process polarizes macrophages and induces the secretion of chemotactic factors, facilitating the recruitment of inflammatory cells, thereby exacerbating chronic low-grade inflammation [41]. Recent studies suggest a decrease in the number of resident Kupffer cells during NAFLD progression, accompanied by increased cell death. Subsequently, monocyte-derived Kupffer cells replace the gradually diminishing resident cells, displaying a more inflammatory phenotype during NASH and actively participating in liver damage [42,43]. In summary, the critical role of macrophages as immune cells in the progression of NAFLD-related inflammation is evident. Exploring methods to regulate macrophages may offer new avenues for treating NAFLD. However, further research is necessary to understand the molecular mechanisms and interactions between macrophages and other immune cells in NAFLD, which will aid in developing more precise therapeutic interventions to alleviate inflammation and slow the progression of NAFLD.

Cluster 4 primarily investigates the role of macrophages in oxidative stress, a pathophysiological process in NAFLD. The onset of NAFLD is accompanied by the appearance of oxidative stress and inflammatory responses, where hepatocytes are the primary parenchymal cells responding to oxidative stress. Additionally, some non-parenchymal cells in the liver, such as hepatic stellate cells, Kupffer cells, and liver sinusoidal endothelial cells (LSECs), also respond to oxidative stress [44]. Oxidative stress activates KC-mediated inflammatory pathways, increasing the release of pro-inflammatory cytokines (such as TNF-α). Oxidative stress and lipid peroxidation can activate HSCs, inducing liver fibrosis. Moreover, lipid-toxicity-induced oxidative stress can directly cause apoptosis

in LSECs [45].

Cluster 5 primarily discusses the role of macrophages in the progression of NAFLD to HCC. HCC represents a severe adverse outcome of NAFLD, and macrophages play a crucial role in the pathological process of NAFLD progressing to HCC. Pro-inflammatory (M1) macrophages often promote inflammation in the early stages of NAFLD, while anti-inflammatory (M2) macrophages participate in liver damage repair and inflammation control during NASH. However, excessive tissue repair inevitably leads to liver fibrosis, which further develops into cirrhosis, forming a critical pathological basis for HCC(4,16). By maintaining macrophage homeostasis and regulating macrophage polarization, strategies could be developed to prevent the occurrence and progression of hepatocellular carcinoma from NAFLD.

Keyword citation burst indicates a sudden surge in the citations of a specific term within a short period. This measurement often signifies the influence and significance of the term within a particular field, reflecting the trends in research. As shown in Fig. 8, peaks for keywords “fatty liver" 、"necrosis factor alpha"、 “non-alcoholic steatohepatitis" and “alcoholic liver disease" emerged in 2006. This indicated a focus on the pathogenesis of NAFLD at that time, with researchers emphasizing liver metabolic disruptions and the impact of associated inflammatory factors on liver damage. Since 2010, the appearance of “innate immunity" and “innate immune system" signified a shift in research focus towards the role of macrophages in immunomodulation concerning NAFLD. Notable keyword bursts including “extracellular vesicle"、 “polarization" and “homeostasis" suggest upcoming trends in macrophage-related studies within the context of NAFLD. Macrophage polarization plays a pivotal role in NAFLD. Studies indicate a close association between MAFLD progression and M1/M2 macrophage polarization within the liver. While M1 polarization correlates with chronic inflammation and disease aggravation, M2 polarization relates to inflammation alleviation and tissue repair [46]. Modulating macrophage polarization might serve as a critical strategy for treating NAFLD. Current research reveals a significant increase in M1 macrophage-related genes and signaling pathways within the livers of NAFLD patients, alongside decreased expression of M2 markers. Drugs and molecules such as nuclear factor-like 2 activators, PPARg activators, and certain non-coding RNAs have been proven to ameliorate NAFLD progression by regulating macrophage polarization [47,48]. Furthermore, gut microbiota and diabetes medications also influence macrophage polarization, thereby affecting NAFLD development [49]. Future trends may delve deeper into understanding the mechanistic impact of various factors on macrophage polarization, including signaling pathways, molecular regulations, and gut microbiota. The relationship between liver homeostasis and macrophages has garnered significant attention. Existing studies elucidate the significance of Kupffer cells and monocyte-derived macrophages in maintaining liver homeostasis. Kupffer cells predominantly arise from embryonic cell precursors, while monocyte-derived macrophages originate from circulating monocytes. Their proportions, characteristics, and functions in the liver are crucial for immune maintenance, waste clearance, metabolism regulation (including iron and cholesterol), and promoting immune tolerance [50]. Future research might focus on a deeper understanding of the roles played by different macrophage subgroups in liver homeostasis, especially in the context of NAFLD development. Advancements in technology, such as single-cell analysis and transcriptomics, will aid in unveiling the diversity and functions of macrophage subgroups. Mesenchymal stem cells (MSCs) are widely sourced multipotent stem cells with immunomodulatory functions [51]. Extracellular vesicles released by MSCs (MSC-EVs) contain active molecules such as mRNAs, miRNAs, cytokines, and growth factors, crucial for regulating immune responses and tolerance [52–55]. In NAFLD research, MSC-EVs demonstrate a regulatory effect on liver inflammation, especially concerning macrophages. Liver inflammation is a key aspect of NAFLD, wherein macrophages and neutrophils play roles [56]. MSC-EVs can inhibit the activation of M1 macrophages, reducing the expression of inflammatory factors, while also promoting the increase of anti-inflammatory M2 macrophages. Moreover, MSC-EVs regulate the metabolic balance of NAFLD and the apoptosis and autophagy processes in liver cells. Overall, MSC-EVs show potential in immune regulation in the liver and in treating NAFLD, particularly in their regulatory effect on macrophages [57].

Given the complexity of NAFLD pathogenesis and the heterogeneity of macrophages, researchers are witnessing a profound transformation in their exploration of this field. With elucidation of related mechanisms and principles, NAFLD treatment strategies based on macrophages are poised to reach new heights.

5. Conclusion

This study conducted a bibliometric and visual analysis of macrophage research in the field of NAFLD over the past 18 years. The overall investigation revealed a consistent, rapid growth in annual publications within this field. Currently, the United States holds a relatively leading position in research, while Chinese researchers have made significant contributions at the forefront of this domain. The pathogenesis of NAFLD, metabolic disorders, immune regulation, oxidative stress, and hepatocellular carcinoma have emerged as major research focal points, reflecting the fundamental research foundations of this field. Simultaneously, our bibliometric analysis indicates that future research trends in this field will predominantly revolve around elucidating the roles of macrophages in liver homeostasis and macrophage polarization. This pursuit aims to regulate or intervene in the progression of NAFLD by targeting hepatic macrophages, thereby devising therapeutic strategies. We can anticipate that future collaborations between nations, institutions, and authors will accelerate the development of research focused on macrophages in NAFLD and ultimately provide practical methods for its diagnosis, treatment, and prevention.

Data availability statement

All data for this study has been included in the article/supplementary materials. Please contact the authors actively if you have any additional questions.

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CRediT authorship contribution statement

Zhen Yang: Writing – review & editing, Writing – original draft, Conceptualization. **Zhiwei Xiong:** Writing – original draft, Visualization, Methodology, Data curation. **Qiuguo Wang:** Writing – review & editing, Visualization, Validation, Methodology, Data curation. **Ning Zhou:** Writing – review & editing, Writing – original draft, Visualization, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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