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BIBLIOMETRICS ANALYSIS

Global research trends in non-alcoholic fatty liver disease

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ABSTRACT

OBJECTIVES: This study aimed to analyze the global profile of the literature in non-alcoholic fatty liver disease (NAFLD) research.

BACKGROUND: Non-alcoholic fatty liver disease is a clinically heterogeneous condition characterized by fat accumulation in the liver and the absence of significant alcohol consumption or underlying genetic disorders. These manifestations are associated with inflammation, steatosis, and fibrosis that can develop into cirrhosis and even hepatocellular carcinoma. However, a study about the research trend in NAFLD has never been reported before.

METHODS: The NAFLD bibliometric analysis was performed on articles indexed in the Scopus database from 1973 to 2022.

RESULTS: The total number of articles published worldwide is 28,673 documents, with an annual average of 561 documents. The United States generated the most articles (n = 6548), followed by China (n = 6180), Italy (n = 2434), and Japan (n = 2032). Since 2013, the number of publications on NAFLD has increased dramatically worldwide. The popular topics in the field include medicine, biochemistry, genetics and molecular biology, pharmacology, toxicology and pharmaceutics, and nursing.

CONCLUSIONS: This study provides a unique composite picture of NAFLD research worldwide and evaluates research productivity from 1973 to 2022. This finding suggests that the prospects for interventions in NAFLD remain promising *(Tab. 5, Fig. 4, Ref. 57)*. Text in PDF *www.elis.sk*

KEY WORDS: bibliometric analysis, NAFLD, Scopus.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a condition characterized by fat accumulation in the liver. This condition can be triggered by obesity, type 2 diabetes, hypertension, dyslipidemia, diet, and unhealthy lifestyle (1, 2). The hepatic metabolic disorders such as fat accumulation in the liver of NAFLD patients can develop into non-alcoholic steatohepatitis (NASH), liver cirrhosis, and hepatocellular carcinoma (3). The risk factors of this disease are gene polymorphisms, genetic mutations, and environmental factors (4).

The highest prevalence of NAFLD from 2016 to 2018 was in South Asia (33 %), the Middle East (32 %), and Central and South America (31 %) (5, 6). NAFLD is also common in Europe, with a prevalence of 23.71 % (7). In South Asia, 30 % of NAFLD cases were caused by obesity and metabolic syndrome (8, 9).

NAFLD can interfere with physiological functions, such as the gut-liver axis. These lead to gut microbiome dysbiosis and metabolic dysfunction, increasing the synthesis of bile acids which then leads to liver inflammation (10). This condition indicates that there are bidirectional interactions between liver health and the digestive tract. Several diagnostic and therapeutic methods have been developed to reduce the prevalence of NAFLD. These include blood tests, steatosis tests, transient elastography, abdominal ultrasound, and liver biopsy (2, 11, 12). A systematic analysis is needed to understand global NAFLD research trends. Bibliometric analysis can be used to find out information on scientific developments and published research (13). This method has been used to determine research trends and patterns, such as in gathering biodiversity data using DNA barcodes, snake venom patterns, and the prevalence of monkeypox worldwide (14–16). In this study, we used bibliometric analysis to evaluate NAFLD research from 1973 to 2022, providing an overview of publication patterns, research collaborations, and authorship profiles to help identify potential areas for future investigation.

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Tab. 1. The highest cited articles on NAFLD.

SCR	Title	Authors	Year	Journal	Vol	Cite score
1	The diagnosis and management of non-alcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases	Chalasani et al (17)	2018	Hepatology	67(1), pp. 328–357	3079
2	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	Chalasani et al (18)	2012	Hepatology	55(6), pp. 2005–2023	2495
3	EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease	Marchesini et al (19)	2016	Journal of Hepatology	64(6), pp. 1388–1402	2386
4	Global burden of NAFLD and NASH: Trends, predictions, risk factors and prevention	Younossi et al (6)	2018	Nature Reviews Gastroenterology and Hepatology	15(1), pp. 11–20	2248
5	Systematic review: The epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults	Vernon et al (20)	2011	Alimentary Pharmacology and Therapeutics	34(3), pp. 274–285	2208
6	Inflammasome-mediated dysbiosis regulates progression of NAFLD and obesity	Henao-Mejia et al(21)	2012	Nature	482(7384), pp. 179–185	1658
7	Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with non-alcoholic fatty liver disease	Angulo et al (22)	2015	Gastroenterology	149(2), pp. 389–397.e10	1622
8	The utility of radiological imaging in non-alcoholic fatty liver disease	Saadeh et al (23)	2002	Gastroenterology	123(3), pp. 745–750	1546
9	Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): A multicentre, randomized, placebo-controlled trial	Neuschwander-Tetri et al (24)	2015	The Lancet	385(9972), pp. 956–965	1472
10	NAFLD: A multisystem disease	Byrne, C.D., Targher, G. (26)	2015	Journal of Hepatology	62(S1), pp. S47–S64	1452

SCR: Standard competition ranking

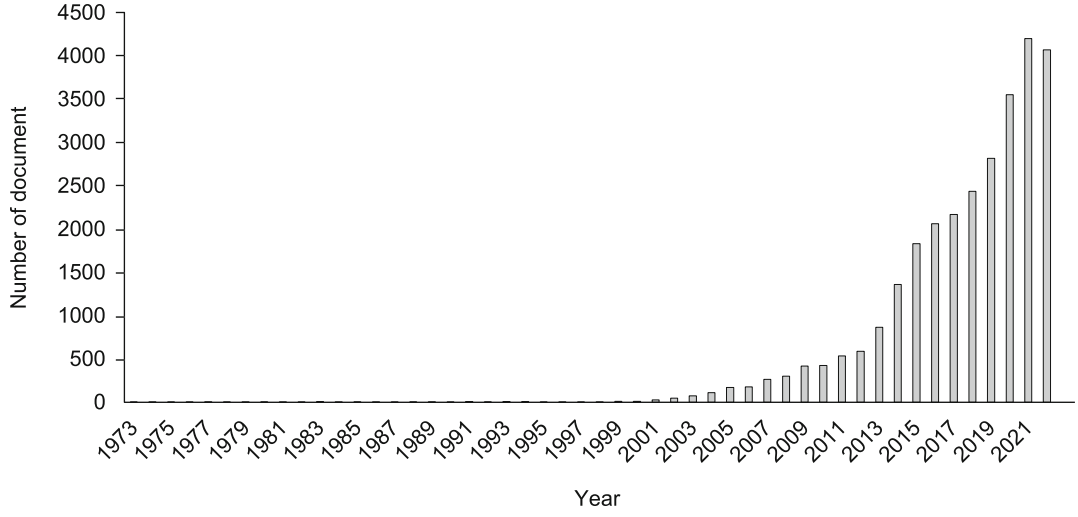

Fig. 1. The profile of NAFLD publications between 1973-2022. The Scopus database yielded a total of 28,673 publications on NAFLD. Research on NAFLD has been gradually increasing since 1973, with most documents being published in 2021.

Material and methods

The Scopus database was used to gather research articles on NAFLD that were published between 1973 and 2022. Scopus is a trusted source for bibliometric analysis across various disciplines, making it an appropriate choice as the primary source for this study. Publications containing the "non-alcoholic", "fatty", "liver", and "disease" key terms in the title and abstract were filtered from the Scopus database in December 2022 to obtain all NAFLD-related publications. Using the VOSviewer software, the data was analyzed to identify and evaluate the key bibliometric indicators such as publication year, institutions, countries, journal titles, citations,

Tab. 2. The ten leading journals in NAFLD research.

SCR	Journal Title	Number of Documents (%)	H-index
1	Journal of Hepatology	743 (2.59)	226
2	PLOS One	562 (1.96)	367
3	Hepatology	535 (1.86)	375
4	Liver International	521 (1.81)	118
5	Scientific Reports	498 (1.73)	242
6	World Journal of Gastroenterology	493 (1.71)	173
7	International Journal of Molecular Sciences	476 (1.66)	195
8	Nutrients	474 (1.65)	143
9	Alimentary Pharmacology and Therapeutics	376 (1.31)	66
10	Journal of Gastroenterology and Hepatology Australia	344 (1.19)	138

SCR: Standard competition ranking

Tab. 3. Institutions with the highest number of publications on NAFLD.

SCR	Institution	Country	Number of Documents
1	University of California, San Diego	United States	498
2	Inserm	France	438
3	Ministry of Education China	China	428
4	Harvard Medical School	United States	407
5	Shanghai Jiao Tong University School of Medicine	China	326
6	Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas	Spain	318
7	Newcastle University	United Kingdom	284
8	Università degli Studi di Milano	Italy	264
9	University College London	United Kingdom	263
10	Chinese University of Hong Kong	Hong Kong	257

SCR: Standard competition ranking

and key words in NAFLD publications. This analysis can provide an understanding of the research trends and patterns, and highlight the prominent contributors to the field (13).

Results

The most cited NAFLD publications

Table 1 illustrates the top ten most cited NAFLD publications as per the Cite Score metric. The publication with the highest Cite Score is "The diagnosis and management of non-alcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases", with a score of 3079, highlighting its significance and impact within the field. This metric provides insight into the most influential works in NAFLD research.

Publication profile of NAFLD between 1973–2022

The temporal trend in the volume of NAFLD publications in nearly five decades is shown in Figure 1. The number of publications showed a notable acceleration in the early 21st century. The data showed that there was a decline in NAFLD publications in 2022 which may not be accurate. It is crucial to keep in mind that all data from 2022 was not yet available for verification. This data point should be viewed as an unreliable prediction. It is also important to note that the quality and relevance of the publications should also be considered, as the publication quantity alone does not always imply an improvement in the understanding of the disease.

The ten leading journals in NAFLD research

Table 2 presents the top 10 journals with the highest volume of NAFLD publications. The Journal of Hepatology has published 743 papers on the topic, while the Australian Journal of Gastroenterology and Hepatology has published 344 papers.

Institutions with the highest number of NAFLD publications

Table 3 lists the institutions with the most NAFLD publications. The University of California, San Diego ranked first with a total of 498 publications. The Chinese University of Hong Kong was the last institution on the top ten list, with a total of 257 publications.

Top ten countries in global contributions and collaborations in NAFLD research

Between 1973–2022, 79 countries with a threshold of at least 20 published NAFLD articles contributed to NAFLD publications (Fig. 2). Visualization of the data using VOSviewer presented seven formed clusters shown in red, yellow, green, dark blue, light blue, purple, and orange (Fig. 2A). Figure 2B shows old to new country-based publications between 2017–2020. The top 10 countries with the most NAFLD publications are listed in Table 4. The country with the most publications was the United States with 6549 publications while Iran had the fewest publications with 828 articles.

Top ten authors in NAFLD publications

A total of 72 authors with a threshold of 100 published NAFLD articles contributed to NAFLD research from 1973–2022, divided into four clusters in VOSviewer visualization (Fig. 3). The clusters formed are red, yellow, green, and blue (Fig. 3A). Figure 3B shows authors with old to new publications between 2017–2019. Table 5 presents the leading contributors to NAFLD research based on the number of publications. The data revealed that Loomba, R was the leading author with 278 publications, while Petta, S had the lowest number of publications in the top 10 with 120 documents. It is noteworthy that a high number of publications is not always an indicator of scientific productivity, relevance, or impact of the work on the field. The quality of the work published, the journal impact factor, article citedness, and other metrics need to be considered to comprehensively understand the authors' impact on the field.

The most common key words in NAFLD publications

Figure 4 illustrates the common key words used in NAFLD publications that have been mentioned for at least 3000 times, divided into 3 clusters (yellow, green, and purple) (Figure 4A). Figure 4B indicates old to new key words used in publications between 2016–2018. Figure 4C shows the density of the key words, with the strong yellow color

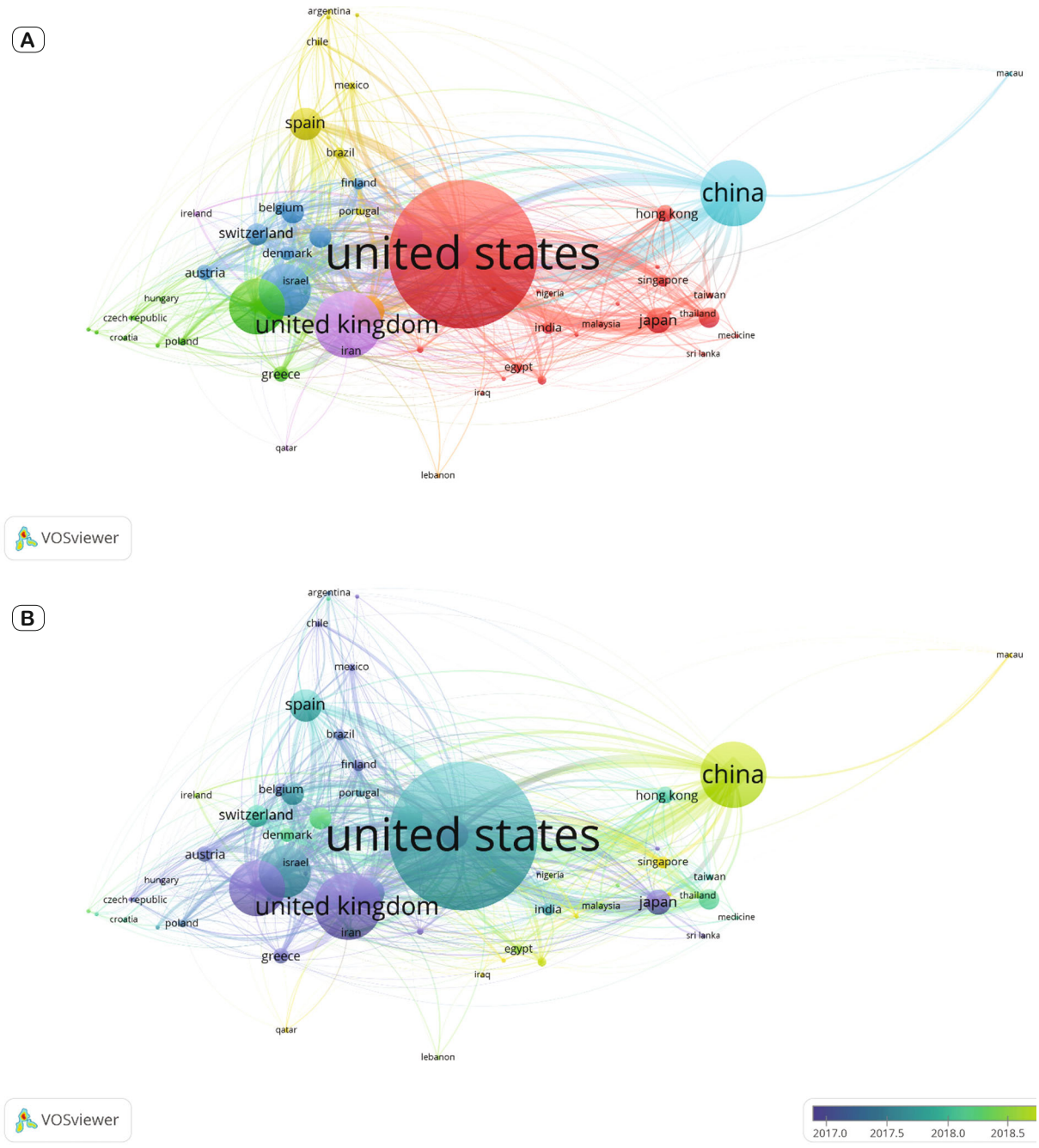

Fig. 2. VOSviewer mapping of the contributing and collaborating countries in NAFLD research. (A) Network visualization; (B) Overlay visualization. The link length indicates the relationship degree with a minimum of 20 publications per country. There were 64 eligible countries.

indicating a higher number of mentions in publications. The most common key words in NAFLD publications included NAFLD, fatty liver, liver, obesity, diabetes mellitus, insulin resistance, and metabolism.

Discussion

This study presents the profile of global NAFLD publications in the last five decades. NAFLD research began in 1973 with antibody activity to *Escherichia coli* in patients with cirrhosis and fatty liver (26). Individuals with liver cirrhosis showed an increase in antibody and immunoglobulin production, compared to those with steatosis. Patients with steatosis have higher levels of Immunoglobulin A (IgA) than healthy individuals (27), indicating that the immune system is more active in those with cirrhosis as a response to inflammation and damage to the liver tissue (28, 29). In addition to antibody and immunoglobulin production, the

Tab. 4. Top ten countries in global contributions and collaborations in NAFLD research.

SCR	Country	No. of Documents	No. of Collaborating Countries*
1	United States	6,549	63
2	China	6,184	54
3	Italy	2,436	59
4	Japan	2,034	49
5	United Kingdom	1,908	58
6	Germany	1,528	57
7	South Korea	1,472	43
8	Spain	1,101	58
9	France	968	57
10	Iran	828	40

SCR: Standard competition ranking; *Number of collaborating countries with a minimum threshold of 50 documents.

Table 5. Top ten authors in NAFLD publications.

SCR	Author	Number of documents	Scopus ID	H-index
1.	Loomba, R.	278	12751805200	94
2.	Targher, G.	199	7003689424	92
3.	Sanyal, A.J.	196	7101788937	131
4.	Nobili, V.	175	13806750500	70
5.	Younossi, Z.M.	174	7005443988	105
6.	Wang, V.W.S.	169	57203018164	99
7.	Anstee, Q.M.	166	12781808200	66
8.	Valenti, L.	143	57217994309	70
9.	Bugianesi, E.	139	6701433364	79
10.	Petta, S.	120	11141625100	64

SCR: Standard competition ranking.

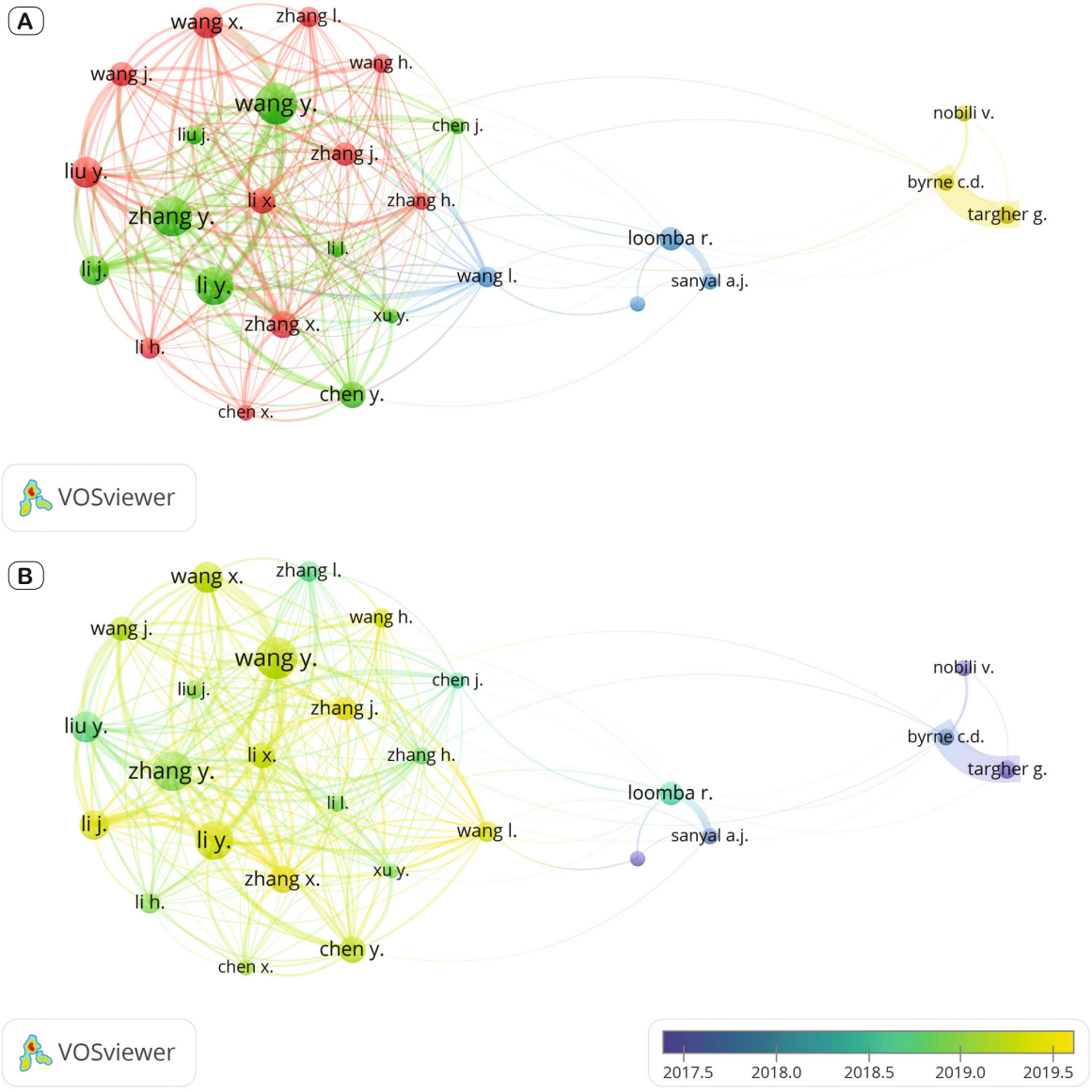

Fig. 3. VOSviewer mapping of authors in NAFLD publications. (A) Network visualization; (B) Overlay visualization. The link length indicates the relationship degree with 100 documents per author threshold.

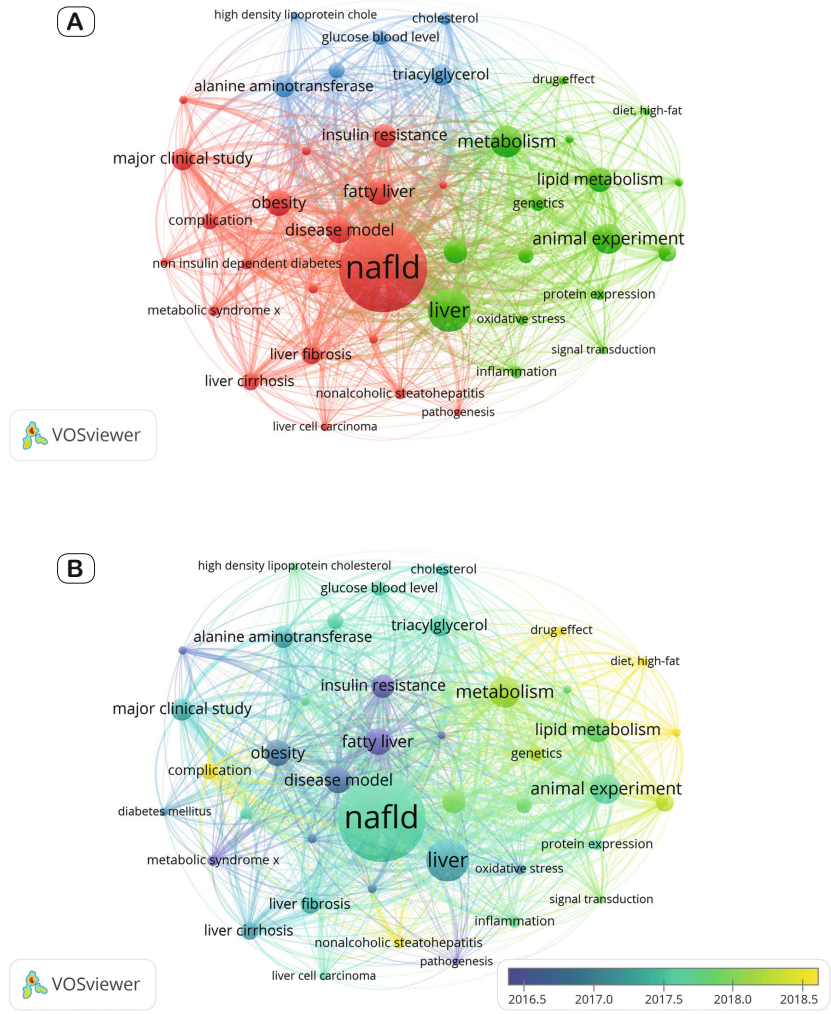

Fig. 4. VOSviewer mapping of the keywords used in NAFLD publications. (A) Network visualization; (B) Overlay visualization; (C) Density visualization. The link length indicates the relationship degree with a minimum of 3000 mentions.

presence and levels of certain gut bacteria, such as *E. coli*, have also been investigated as potential biomarkers for NAFLD diagnosis and disease progression. There are changes in the gut microbiome of patients with NAFLD, such as an increase in *E. coli* in the intestine, suggesting that alterations in the gut microbiome may play a role in the development and progression of NAFLD (30–31).

In 2001, a marked increase in the number of NAFLD publications was observed. This trend is believed to be driven by several factors, including an increase in the number of reported NAFLD cases and advances in molecular disease detection techniques. Studies have shown that NAFLD prevalence has been increasing in recent years, particularly in developed countries such as the United States. These data indicate that NAFLD is becoming a growing public health concern. Furthermore, the development of more sophisticated and accurate diagnostic tools, such as imaging techniques and biomarkers, has also enabled researchers to study NAFLD and its underlying mechanisms more effectively. These situations contributed to an increase in the number of publications on NAFLD (34). Moreover, in the 1990s, molecular diagnostic methods for infectious diseases such as Polymerase Chain Reaction (PCR) and the use of antibiotics began to emerge. In NAFLD research, PCR was used to detect genetic variations so that the copy number variation could be understood. Any NLRP4 copy number loss, ATG7 uncommon mutations, PNPLA3 polymorphisms, and TM6SF2 mutations can increase the risk of developing NAFLD (35–38).

The Journal of Hepatology is among those with a great quantity of NAFLD publications. The number of articles that can be accessed through the Scopus database until 2022 is 743 publications. The first NAFLD publication was “Plasma endotoxin concentrations in patients with alcoholic and non-alcoholic liver disease: re-evaluation with an improved chromogenic test” in 1991 (39). The data indicates that the Journal of Hepatology significantly impacts the growth of NAFLD research. The article “The diagnosis and therapy of non-alcoholic fatty liver disease: Practice guid-

ance from the American Association for the Study of Liver Diseases," published in Hepatology has been cited by 3079 papers (17). Loomba, R. is the author with the most NAFLD publications (278 articles).

Up to 2022, the United States (n = 6,549), China (n = 6,184), and Italy (n = 2,436) have the most publications on NAFLD. The University of California, San Diego (n=498) and Harvard Medical School (n = 407) are two organizations that significantly impact the growth of NAFLD research in the United States. Chinese University of Hong Kong (n = 257), Shanghai Jiao Tong University School of Medicine (n = 326), and the Ministry of Education of China (n = 428) all contribute to the growth of NAFLD research in China, as does Università degli Studi di Milano (n = 264) in Italy. This demonstrates that developed countries conduct the majority of the NAFLD research. NAFLD incidence is high in countries where research on the condition is lacking, emphasizing the need for research and education to improve diagnosis and treatment to reduce the disease burden on public health. Nevertheless, Western Europe, Latin America, and North America experienced the highest NAFLD incidence between 1990 and 2017 (40). Obesity and type 2 diabetes are the leading causes of NAFLD in developed and developing countries (40–42). The United States has a high global prevalence of obesity due to an increase in obesity between 1980 and 2008 (43).

The main key words in NAFLD publications were NAFLD, fatty liver, liver, obesity, diabetes mellitus, insulin resistance and metabolism. These topics indicate a link between fatty liver and NAFLD, with fatty liver being the key factor in NAFLD development (44). Obesity is a major trigger for the accumulation of fat in the liver, which can lead to inflammation, tissue swelling, and eventually cirrhosis (45). Insulin resistance (IR) also plays a role in the development of NAFLD and can lead to diabetes mellitus with impaired glucose homeostasis (46). Insulin resistance is greater in people with moderate chronic hepatitis. IR contributes to hepatic steatosis and fibrosis development in people with hepatitis C virus (47). Elevated alanine aminotransferase (ALT) levels, which indicate metabolic disorders, also have the potential to promote NAFLD (48, 49). People with more severe cases of NAFLD, such as non-alcoholic steatohepatitis (NASH), may be recommended for liver biopsy. A liver biopsy can confirm the existence of cirrhosis, fibrosis, and necroinflammatory activities (50–52). If the biopsy confirms NASH, the patient will be recommended to undergo bariatric surgery if eligible (53). It is important to be concerned that currently, there are still no FDA-approved drugs for NAFLD and NASH. Therefore, the best treatment for NAFLD is to prevent the disease by maintaining a healthy weight, eating a healthy diet, and engaging in regular physical activity (54).

Treatment for NAFLD typically involves lifestyle changes, such as losing weight, eating a healthy diet, and increasing physical activity (55). Medications such as pioglitazone, vitamin E, and ursodeoxycholic acid have also been used to treat NAFLD, but their effectiveness is still debatable. Pioglitazone is a thiazolidinedione drug that improves insulin sensitivity, vitamin E is an antioxidant that can reduce inflammation, and ursodeoxycholic acid is a bile acid that can reduce liver inflammation (56, 57).

Conclusion

This bibliometric analysis revealed that NAFLD has become a more popular research topic. This recent growth in NAFLD research is due to both increasing incidence of the disease and advances in diagnostic and treatment options, leading to better understanding and management of the disease for improved patient outcomes. However, developed countries were still the major contributors to NAFLD research, indicating the need for more NAFLD studies in developing countries where the incidence of the disease is higher. These findings suggest a growing need for further research and development in the field of NAFLD to fully understand the underlying causes of the disease and to identify effective treatment and prevention strategies.

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