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Original Article

Transient Elastography Research Hotspots and Frontiers in Nonalcoholic Fatty Liver Disease: A Bibliometric Study Using CiteSpace

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Abstract

Background and objectives: Transient elastography (TE) has been widely used in nonalcoholic fatty liver disease (NAFLD). The focus of the present study was to provide a reference for researchers and further clarify the research topics, in addition to the frontiers for TE in NAFLD.

Methods: Based on previous studies on NAFLD and TE found in the Web of Science (WoS) database, author, institution, country, journal, and keyword co-occurrence analyses were conducted using CiteSpace 5.8 software.

Results: Through data retrieval and review, 1,685 publications were obtained, and the high-yield countries included the US, China, Italy, Japan, and others. The Chinese University of Hong Kong, the University of California, and Yonsei University were all major research institutions. Wong VWS, Rohit Loomba, and Grace Lai-Hung Wong were among the most prolific authors. The clustering directions of the keywords were divided into NAFLD, nonalcoholic steatohepatitis, hepatocyte steatosis, fibrosis, and noninvasive diagnosis. Biological diagnostic markers, epidemiology, management, and fibrosis degree measurement were all high-intensity burst keywords. The research period in the present field could be split into three stages: the exploration period; the experience summary period; and the promotion and application period.

Conclusions: Applying the quantitative advantages of TE to fat content and fibrosis degree in large-scale epidemiological investigations or disease management could become a trending topic in future research into NAFLD. CiteSpace literature analysis could intuitively display the overall research status of TE in NAFLD and provide references for relevant scholars for the topic and research direction.

Keywords: Nonalcoholic fatty liver disease; Bibliometrics; Instantaneous elastic imaging technique; Visual analysis; CiteSpace.

Abbreviations: CAP, controlled attenuation parameter; CUHK, Chinese University of Hong Kong; LSM, liver stiffness measurement; NAFLD, nonalcoholic fatty liver disease; TE, Transient elastography.

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is one of the most common chronic liver diseases worldwide, which affects approximately 25% of adults,[1,2] and is expected to become the leading cause for liver transplantation.[3,4] The spectrum of NAFLD includes reversible stages (i.e., simple fatty liver disease) and nonalcoholic steatohepatitis, which can progress to fibrosis and hepatocellular carcinoma.[5] At present, liver biopsy remains the gold standard for diagnosing NAFLD patients and determining the severity of steatosis and fibrosis. However, the use of liver biopsy in clinical practice is difficult due to the invasive characteristics, follow-up adverse reactions, and relatively high costs. Therefore, various

noninvasive methods, which are composed of serum biomarkers and imaging techniques, have been developed and advanced.[6,7]

Compared with the traditional noninvasive diagnostic methods of NAFLD in clinical practice (i.e., ultrasound), transient elastography (TE) technology has exhibited high accuracy in diagnosing and staging steatosis and fibrosis in NAFLD patients.[8–10] Recently, TE has been extensively adopted for the assessment of hepatic steatosis and hepatic fibrosis. As two important indexes of TE, the controlled attenuation parameter (CAP) and liver stiffness measurement (LSM) can quantitatively reflect the degree of hepatic steatosis and hepatic fibrosis, respectively. The significantly higher performance of CAP in the detection and staging of steatosis has been reported in numerous biopsy-confirmed NAFLD studies. In addition, LSM could accurately predict the severity grade of liver fibrosis in multiple biopsy-referenced studies.[8,11] The Web of Science (WoS) Core Collection database represents the forefront of natural science research, covers significant scientific and technological research from around the world, and can provide significant data for researchers.[12,13] Through co-occurrence and co-citation analysis of a large number of literature data in a specific research field, CiteSpace can analyze and predict the research frontiers and development trends. In particular, CiteSpace has been extensively applied by Chinese scholars in the field of medicine.[14,15] Recently, there have been numerous reviews in which the research status of TE in NAFLD has been summarized, but there is a scarcity of summaries from the perspective of bibliometric analysis. In addition to being a method to attain the trends and conditions of a specific research field, the bibliometric analysis could affect the progress of these fields in the future.[16] Although Gu *et al*. used this method to summarize the current situation and trending issues for TE, the research was not focused enough to comprehensively reflect the research status of TE in NAFLD.[17] Moreover, the study was published in 2017, and a large amount of the latest research results in the last 4 years was not included.[17] To date, there is a scarcity of professional bibliometric studies in which the focus is on the application status and development trend for TE in NAFLD.

Compared with VOSviewer, CiteSpace can be used to download data directly from databases, such as the WoS, which provides more analysis parameters and more complete diagrams, such as network intermediary centrality and time-sequence analysis. CiteSpace software was used in the present study to analyze TE in NAFLD. This study aimed to enable researchers to quickly grasp the fundamental knowledge and evolution of the present research field through a knowledge map visualization analysis and to assist researchers in identifying research hotspots and future development trends.

Methods and materials

In the present study, TE in the NAFLD field was mined by CiteSpace 5.8.R1 (Chaomei Chen, Philadelphia, PA, USA) software based on the WoS. Further, a visual knowledge map was constructed using methods such as national or regional publication, literature co-citation, and keyword clustering analysis in the software to understand the basic knowledge and evolution of the present field quickly and intuitively. In addition, the main research direction, hot spots, and future development trends were analyzed. The MeSH and entry terms were employed singularly or in combination (Supplementary Fig. 1). The retrieval period was set from the construction of the database to 2021. The present study was limited to the records of types of articles or reviews in English in the Scientific Citation Index Expanded database of the WoS. Since the earliest relevant literature records were from 1997 and the retrieval deadline of the present study was 2021, the time period was between 1997 and 2021.

The parameters of the present study were set as follows: the time slice from 1997 to 2021 was selected as "1"; the subject word source was selected by default; the threshold was maintained by default, and the path was simplified through the critical path method. Data screening was for the top 50. That is, the top 50 co-cited frequency data in each time segment were extracted for display. In the present research, density refers to the density of the network. The actual number of relations in the network was divided by the theoretical maximum number of relations. The centrality of a node was a graph-theoretical property that quantified the importance of the node's position in a network.[14]

Results

Publications

In the present study, 1,704 publications were initially obtained through retrieval, and 1,685 publications were finally included after eliminating duplicate and irrelevant literature (Supplementary Fig. 1). The first document in the present field was found in 1997, and the number of documents reached its peak of 262 in 2019. According to the literature publication trend chart (Fig. 1), the number of TE publications in NAFLD has increased. The number of publications increased significantly from 2013 to 2014, 2014 to 2015, 2016 to 2017, and 2018 to 2019.

Research performance by Countries

Figure 2 shows the co-occurrence map of countries. The map of collaborations between countries consisted of 109 nodes and 421 links, and the network density was 0.0715. The US had the highest number of publications (358), followed by China (222), Italy (171), and Japan (141). In addition, the highest centrality was found in the US (0.40), followed by France (0.18), China (0.16), and Australia (0.15). The list of countries sorted by total publication record and centrality is shown in Table 1. The results indicated that the US was the country with the largest number of publications and one of the countries with the closest cooperation in the present field.

Research performance by institutions

Figure 3 reveals the co-occurrence map of institutions related to TE in the NAFLD field. A total of 584 nodes and 1,160 lines were formed in the co-occurrence map, and the network density was 0.0715. The Chinese University of Hong Kong (CUHK) had the highest number of articles (88). The second most prolific institution was the University of California, with 63 publications. Yonsei University ranked third with 43 papers, and the remaining institutions are shown in Table 1. The University of Palermo had the highest centrality (0.13), followed by the University of Sydney (0.11) and the CUHK (0.10). Therefore, the CUHK was the institution with the largest number of publications and one of the institutions with the closest cooperation in the present field globally.

Analysis of authors and author collaboration

Figure 4 displays the co-occurrence map of authors related to TE

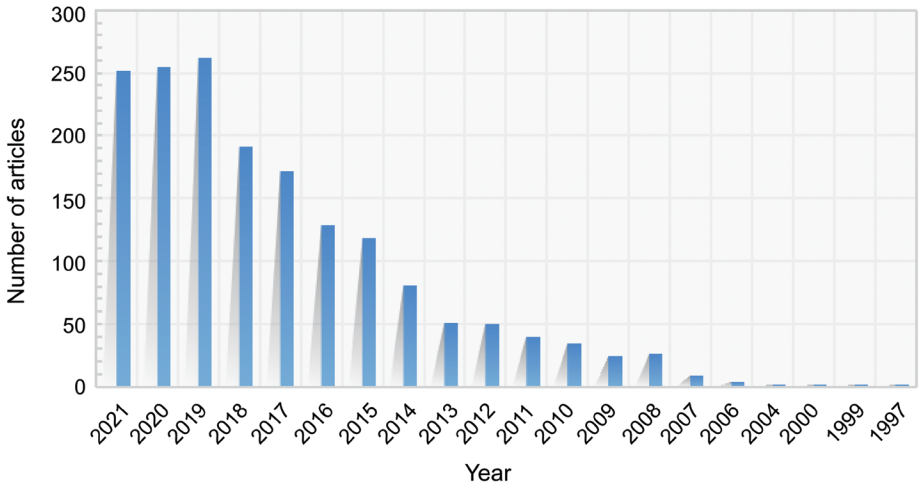

Fig. 1. Time sequence of relevant papers on TE in NAFLD published from 1997 to 2021 in WoS. NAFLD, nonalcoholic fatty liver disease; TE, transient elastography; WoS, Web of Science.

in NAFLD. A total of 795 nodes and 2,338 lines were formed in the co-occurrence map. Professor Wong of the CUHK was the most prolific author, contributing 57 publications. Professor Rohit Loomba of the University of California was in second place with 46 publications, followed by Grace Lai-Hung Wong of the CUHK with 45 publications. The remaining authors are shown in Table 2. Rohit Loomba had the highest centrality at 0.07, followed by Victor DE Ledinghen at 0.05 and Masato Yoneda at 0.05.

Publication performance by journals

The co-occurrence map of journals associated with TE in NAFLD is depicted in Figure 5. A total of 214 nodes and 735 lines were formed in the co-occurrence map, and the network density was 0.032. The most cited journal was *Hepatology*, with 1,428 citations; the second was the *Journal of Hepatol* with 1,302 citations; the third was *Gastroenterology* with 1,217 citations; *Liver International* was fourth with 944 citations; and *Clinical Gastroenterology* was the fifth with 863 citations (Table 3).

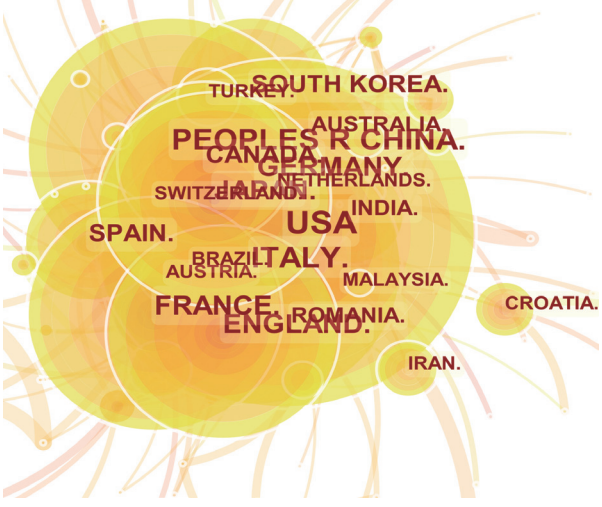

Fig. 2. Map of collaborations between countries related to TE in NAFLD. NAFLD, nonalcoholic fatty liver disease; TE, transient elastography.

Co-citation of reference

Previous research that is cited could be called the knowledge base of the field, through which a stable representation of the essence of a discipline could be provided. Such research could be beneficial in defining and forecasting research frontiers and dynamic trends. The citation map of TE in NAFLD is shown in Figure 6. In addition, the top five cited literatures with high citation frequency were sorted, as shown in Table 4.

Co-occurrence of keywords

Figure 7 represents the co-occurrence map for TE keywords in NAFLD. The top five high-frequency words were TE, fibrosis, diagnosis, NAFLD, and steatosis. The top five places of centrality were TE, insulin resistance, cirrhosis, diagnosis, and chronic hepatitis C (Table 5).

Keyword clustering

Through cluster analysis of English literature on keywords for TE in NAFLD from 1997 to 2021, different cluster labels for TE in NAFLD were identified by the log-likelihood ratio algorithm to identify research hotspots. A total of 189 nodes, 630 links, and a density of 0.0355 were obtained. The modularity Q was 0.6176, between 0–1, and >0.3, which indicated that the community structure was reasonable. The mean silhouette value was 0.8543 > 0.5, which indicated that the clustering was acceptable. Through cluster analysis, seven clusters were obtained, as shown in Figure 8. The seven clusters represented seven crucial aspects of TE in NAFLD.

Emerging trends

When the value of a variable significantly changed within a short

Table 1. 10 Most productive and influential countries and institutions sorted by total publication record and centrality

Sequence number	Countries				Research institutions			
	Sort by number of articles published	Frequency	Sort by centrality	Centrality	Sort by number of articles published	Frequency	Sort by centrality	Centrality
1	USA	358	USA	0.40	CUHK	88	University of Palermo	0.13
2	China	222	France	0.18	University of California	63	The University of Sydney	0.11
3	Italy	171	China	0.16	Yonsei University	43	CUHK	0.10
4	Japan	141	Australia	0.15	Yokohama City University	36	University of Malaya	0.09
5	Britain	133	Italy	0.14	University of Palermo	32	Newcastle University	0.09
6	France	133	Britain	0.14	University of Malaya	28	University of Nottingham	0.08
7	Germany	119	Germany	0.10	McGill University	26	University of California	0.07
8	Korea	87	Romania	0.10	Virginia Commonwealth University	25	University of London	0.07
9	Canada	80	Malaysia	0.08	Newcastle University	25	Shanghai Jiao Tong University	0.05
10	Spain	67	Canada	0.07	Shanghai Jiao Tong University	20	Yokohama City University	0.04

CUHK, The Chinese University of Hong Kong.

period, such occurrence is referred to as burst detection.[18] According to Figure 9, 45 burst keywords were detected. By analyzing the periods of these keywords, studies on TE in NAFLD could be approximately split into three stages: (1) from 1997 to 2012, during which the burst keywords included fibrotic, serum marker, and other; (2) from 2013 to 2016, where the emergent terms included feasibility, meta-analysis, and probes; and (3) from 2017 to 2021, where the emergent terms included epidemiology, management, correlation, and risk factors.

Keyword clustering timeline diagram

The timeline view (Fig. 10) shows the citation year distribution on the *x*-axis and the clustering number distribution on the *y*-axis. The distribution of literature in each cluster can be seen in the graphic, in which the greater the number of studies in a cluster, the more valuable the cluster field. There was a substantial amount of literature on Cluster #0 of nonalcoholic fatty liver disease, #2 elastography, and #3 hepatic steatosis, which demonstrated the importance

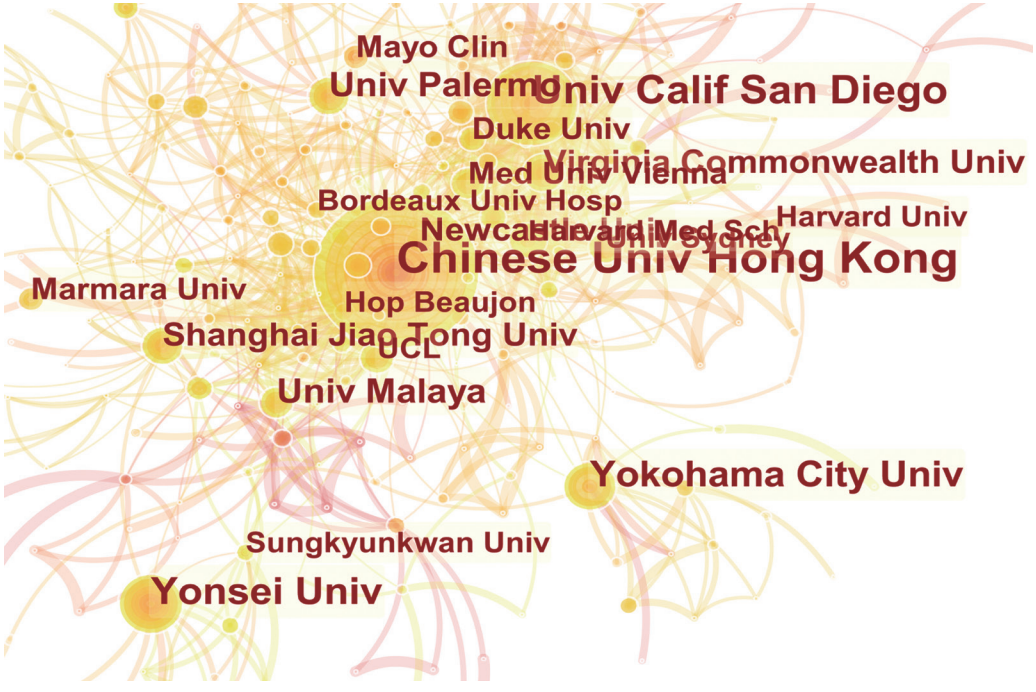

Fig. 3. Map of collaborations between institutions related to TE in NAFLD. NAFLD, nonalcoholic fatty liver disease; TE, transient elastography.

Fig. 4. Map of collaborations between authors related to TE in NAFLD. The larger the node diameter is, the more publications institutions have published. The thicker the line between the nodes, the closer the institutions work together. NAFLD, nonalcoholic fatty liver disease; TE, transient elastography.

of this literature. The timeline view shows the period and research progress for the development and evolution of each cluster. The field represented by Cluster #0 had a relatively large period from the beginning of the research to date.

Discussion

To the best of our knowledge, the present bibliometric study is the first to refer to the application status and development trends for TE in NAFLD. The number of TE publications in NAFLD has steadily increased, which is inextricably linked to the increased recognition and promotion of TE technology in NAFLD. The CUHK and the University of California have developed into world-class research institutes for TE technology in NAFLD and led the field for published papers and collaboration. Based on the keyword clustering, timeline diagram, and burst keywords, the development of TE technology in NAFLD has experienced three periods. The first period was the exploration period, in which TE technology was mainly applied for the noninvasive diagnosis of NAFLD and included determining the fat content and severity of fibrosis and the search for a specific diagnostic threshold.[19–21] Gaia *et al*. reported that TE might be regarded as viable support to identify fibrosis in chronic liver disease due to HCV but should be interpreted carefully in NAFLD patients, in which host or disease-associated variables might alter the accuracy.[19] The second period was the experience summary period, which was based on previous practice and mainly used evidence-based medical evidence, such

Table 2. Top 10 most productive authors sorted by total publication record and centrality

Sequence number	Sort by number of articles published	Frequency	Sort by centrality	Centrality
1	WONG VWS	57	ROHIT LOOMBA	0.07
2	ROHIT LOOMBA	46	VICTOR DE LEDINGHEN	0.05
3	GRACE LAI-HUNG WONG	45	MASATO YONEDA	0.05
4	HENRY LIKYUEN CHAN	41	WONG VWS	0.04
5	MCTOR DE LEDINGHEN	37	SALVATORE PETTA	0.03
6	ATSUSHI NAKAJIMA	34	IOAN SPOREA	0.03
7	KENTO IMAJO	28	CLAUDE B SIRUIN	0.02
8	MASATO YONEDA	26	LAURENT CASTERA	0.02
9	CLAUDE B SIRUIN	26	HENRY LIKYUEN CHAN	0.01
10	GIADA SEBASTIANI	24	GIADA SEBASTIANI	0.01

Fig. 5. Co-journals related to TE in the NAFLD field. NAFLD, nonalcoholic fatty liver disease; TE, transient elastography.

as meta-analysis, to evaluate the accuracy of TE technology in the noninvasive diagnosis of NAFLD.[22,23] In addition, many attempts were made to improve TE technology. Kwok *et al*. conducted a systematic review with meta-analysis and found that the noninvasive diagnostics available were reliable in eliminating advanced fibrosis in people with NAFLD and might be utilized for initial evaluation, but additional research and assessment of NASH biomarkers were required.[22] Mahadeva *et al*. reported that TE was critical for detecting advanced fibrosis and cirrhosis in individuals with NAFLD, and the accuracy was not affected by disease components.[23] The third period was the promotion and application period, during which TE technology was widely applied in large-scale epidemiological investigations, disease management, and more clinical studies.[24–27] Huh *et al*. showed that metabolically healthy obesity was linked with steatosis and fibrosis of the liver as determined by TE.

In addition, the five most cited scholarly articles on the present topic were identified. Among these articles, the European Association for Liver Research's practice guide for noninvasive methods noted that noninvasive methods could be classified as biological methods based on the quantification of biomarkers in serum samples or physical methods based on the measurement of liver hardness. In addition, the practice guide compared the advantages and disadvantages of various noninvasive diagnostic methods in chronic liver disease.[28] According to the report by Vincent *et al*., TE had a high negative predictive value and a

Table 3. Top 10 most productive journals sorted by frequency

No.	Sort by frequency	Frequency
1	*Hepatology*	1,428
2	*Journal of Hepatol*	1,302
3	*Gastroenterology*	1,217
4	*Liver International*	944
5	*Clinical Gastroenterology and Hepatology*	863
6	*American Journal of Gastroenterology*	844
7	*GUT*	835
8	*Alimentary Pharmacology & Therapeutics*	791
9	*World Journal of Gastroenterology*	759
10	*Journal of Gastroenterology and Hepatology*	686

Fig. 6. Document co-citation analysis related to TE in the NAFLD field. NAFLD, nonalcoholic fatty liver disease; TE, transient elastography.

moderate positive predictive value and could be used as a screening test to exclude advanced fibrosis. Liver biopsy could be considered for NAFLD patients with a liver hardness measurement value ≥7.9 kPa.[29] A study by Robert *et al*. indicated that the XL probe of FibroScan reduced TE failure and increased the reliability of the LSM value in obese patients compared with the M probe. Although the probe is highly accurate, when the XL probe is used for a noninvasive examination of liver fibrosis, the cutoff value of the liver hardness measurement must be lowered.[12] Imajo *et al*. suggested that magnetic resonance imaging could more accurately classify steatosis and fibrosis in patients with NAFLD compared with TE.[30] Sasso Magali's study demonstrated that CAP is a noninvasive, quick, objective, and accurate method for detecting and quantifying steatosis.[31]

The present study has several limitations. Due to time, data sources, and staffing constraints, only the WoS database was utilized to include and evaluate the publications in the present study. Therefore, the included data might not be sufficiently thorough, which could affect the accuracy of the results. Second, because the present study was based on previously published material and did not incorporate the most recent research findings, there might be shortcomings.

Prospects

TE is a new ultrasound imaging technology that has been developed recently. With the characteristics of being noninvasive and having rapid examinations, this technology could be quantitatively and repeatably used for ultrasound examination and has advantag-

Table 4. Top 5 document co-citations related to TE in NAFLD

No.	Title	Authors	Number of citations	Published year
1	EASL-ALEH Clinical Practice Guidelines: Noninvasive tests for evaluation of liver disease severity and prognosis	European Association for Study of Liver	778	2015
2	Diagnosis of Fibrosis and Cirrhosis Using LSM in Nonalcoholic Fatty Liver Disease	Wong VWS	728	2010
3	CAP: A Novel VCTE™ Guided Ultrasonic Attenuation Measurement for the Evaluation of Hepatic Steatosis: Preliminary Study and Validation in a Cohort of Patients with Chronic Liver Disease from Various Causes	Sasso M	427	2010
4	Magnetic Resonance Imaging More Accurately Classifies Steatosis and Fibrosis in Patients with Nonalcoholic Fatty Liver Disease Than Transient Elastography	Imajo K	346	2016
5	Feasibility and diagnostic performance of the FibroScan XL probe for LSM in overweight and obese patients	Myers RP	334	2012

NAFLD, nonalcoholic fatty liver disease; TE, transient elastography.

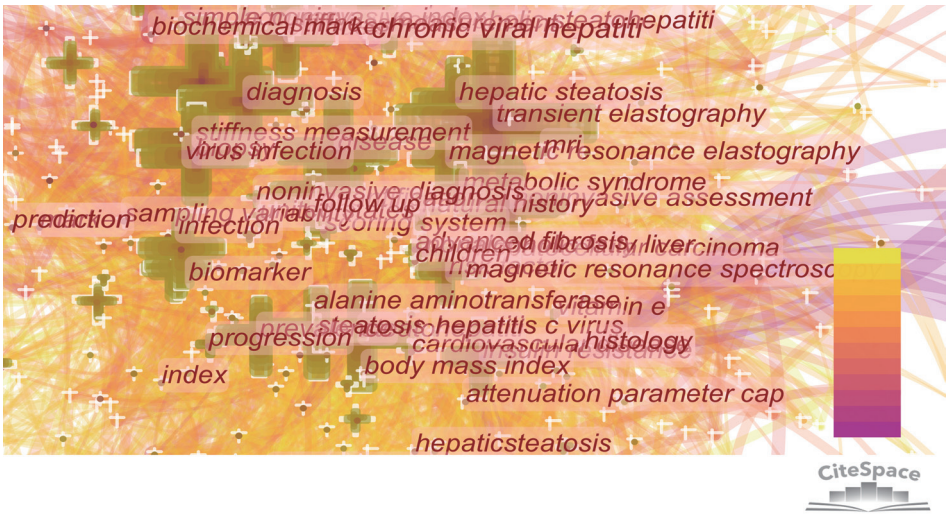

Fig. 7. Co-occurrence map of keywords related to TE in NAFLD. NAFLD, nonalcoholic fatty liver disease; TE, transient elastography.

Table 5. Top 10 keywords related to TE in NAFLD

No.	Frequency	Keywords	Centrality	Keywords
1	749	TE	0.32	TE
2	528	Fibrosis	0.21	Insulin resistance
3	348	Diagnosis	0.18	Cirrhosis
4	339	NAFLD	0.17	Diagnosis
5	317	Steatosis	0.15	Chronic hepatitis C
6	282	CAP	0.14	NAFLD
7	265	Steatohepatitis	0.13	Fibrosis
8	258	Hepatic steatosis	0.12	Steatosis
9	252	Disease	0.12	Noninvasive assessment
10	245	Stiffness measurement	0.1	Hepatic steatosis

TE, transient elastography; CAP, controlled attenuation parameter; NAFLD, nonalcoholic fatty liver disease.

es in the evaluation of liver fibrosis and steatosis in patients with liver disease. The wide application of TE technology in large-scale epidemiological investigations, disease management, and further clinical studies might be the focus and direction of future research. However, the diagnostic efficacy of TE (i.e., FibroScan) could be affected by many factors. In the future, other methods could be combined to improve the diagnostic value of TE.

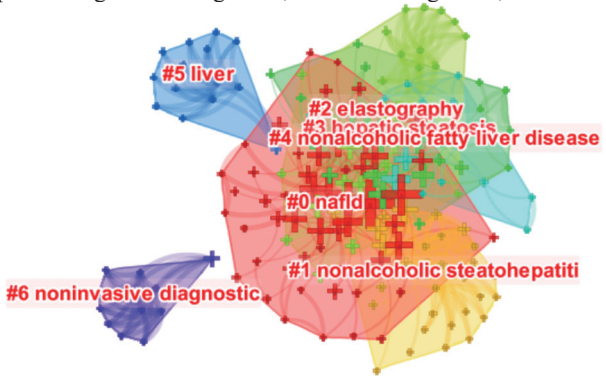

Fig. 8. Keyword clustering. Through cluster analysis, seven clusters were obtained, including NAFLD, nonalcoholic steatohepatitis, elastography, hepatic steatosis, nonalcoholic fatty liver disease, liver, and noninvasive diagnostic. NAFLD, nonalcoholic fatty liver disease.

Conclusions

The use of TE in NAFLD has increased recently. Utilizing the quantitative advantages of TE for fat content and fibrosis degree for large-scale epidemiological investigations or disease management might become a trend in NAFLD. CiteSpace literature analysis could intuitively display the overall research status of TE in NAFLD and provide a reference for relevant scholars for the topic and research direction.

Supporting information

Supplementary material for this article is available at https://doi.org/10.14218/ERHM.2021.00064.

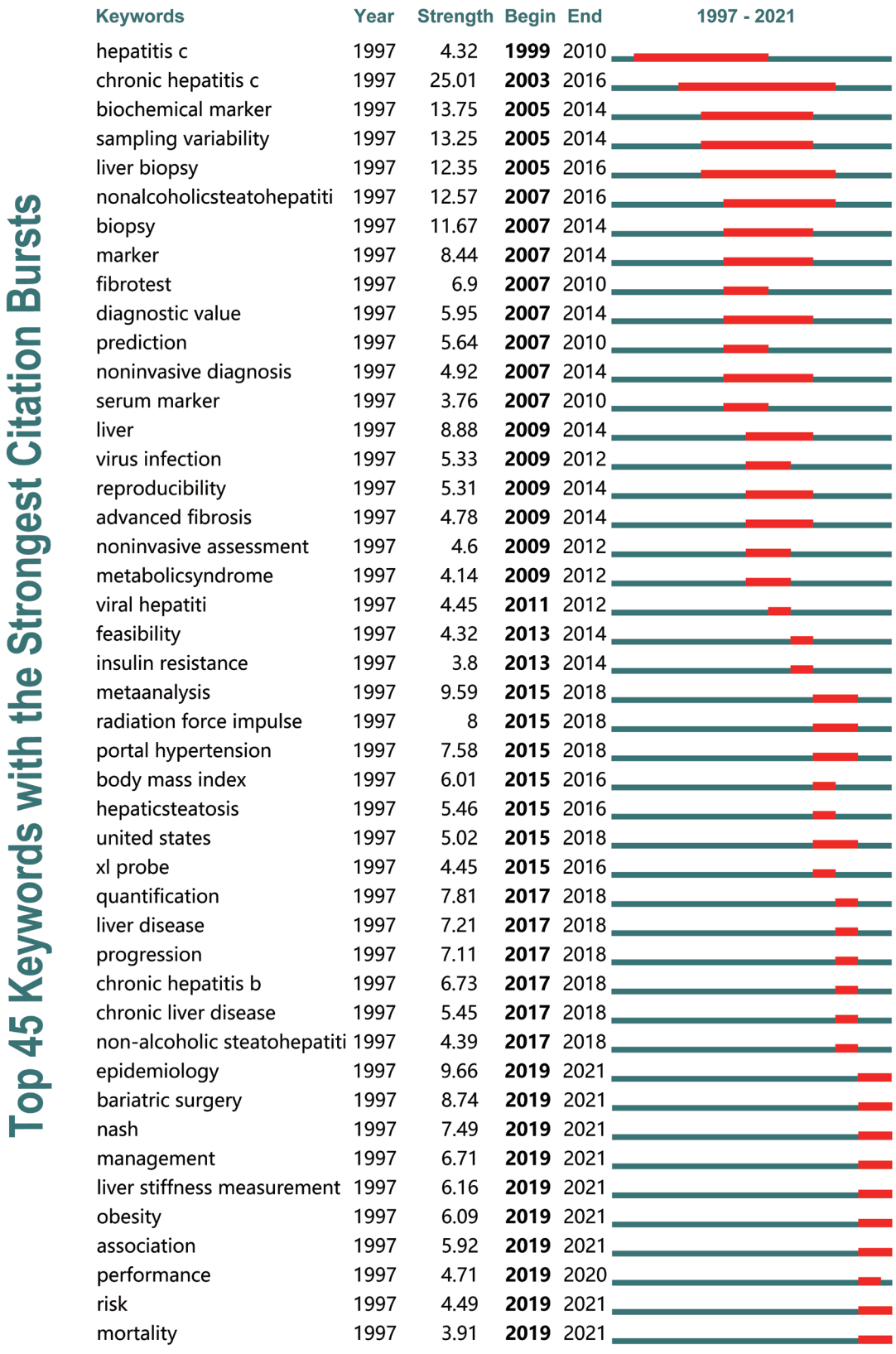

Fig. 9. Top 45 keywords with the strongest citation bursts. The red line indicates the strongest period of the citation burst. For instance, liver biopsy has the longest period of burst, from 2005 to 2016.

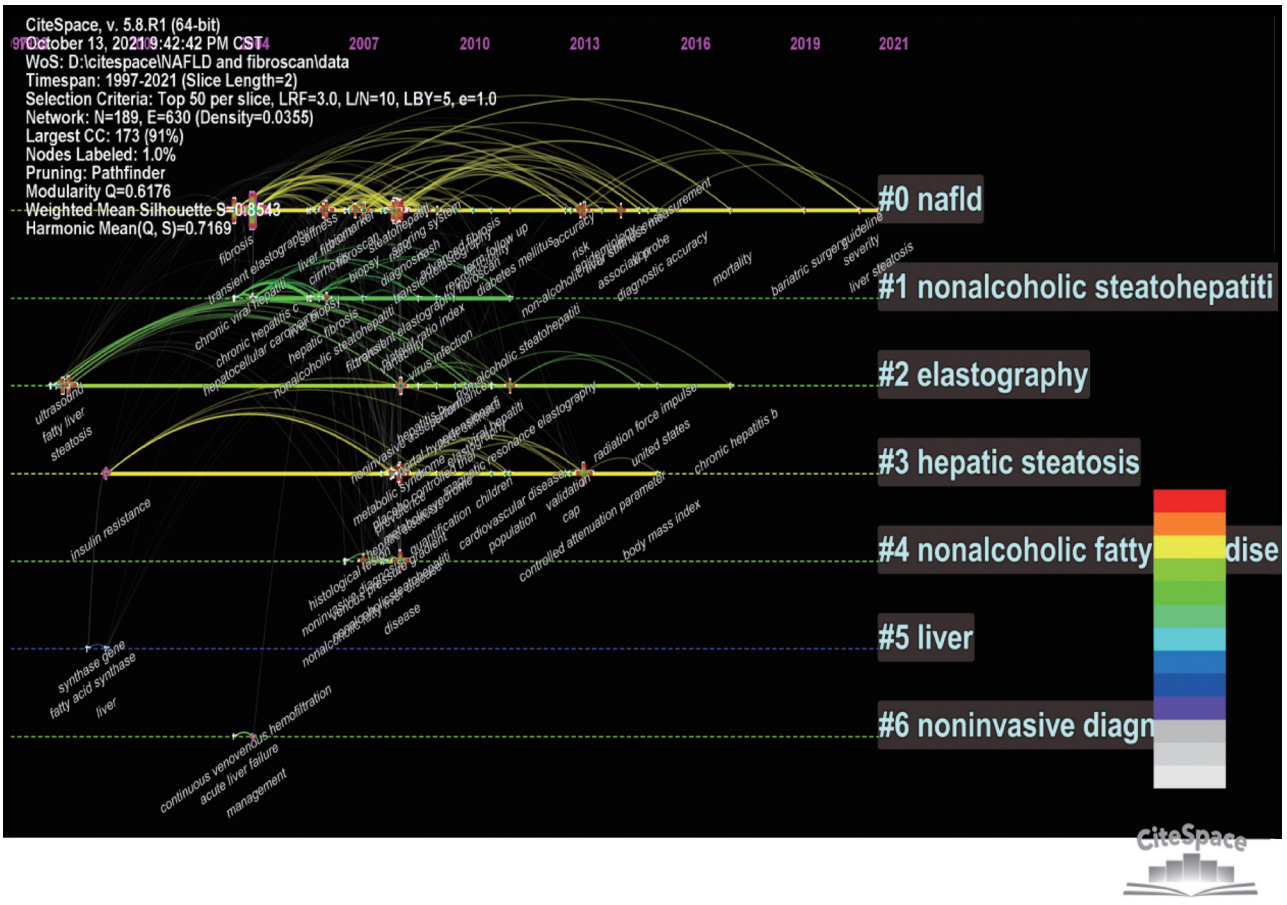

Fig. 10. Keywords clustering timeline graph.

Supplementary Fig. 1. Summary of literature search and selection.

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Conflict of interest

The authors have no conflicts of interest related to this article.

Author contributions

Study design (FG, MM), collected and analyzed the data (FG, NH, RL, XTT), writing and editing the manuscript (FG, NH, QQY, KW, MM). All authors contributed to the manuscript for important intellectual content and approved the submission.

Data sharing statement

No additional data are available.

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