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Brief Communication

Global research trends on the links between intestinal microbiota and liver diseases: a bibliometric analysis

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Abstract: The number of articles on the relationships between the intestinal microbiota and liver diseases has continued to increase. The aim of this study was to assess publications on this topic, identify research hotspots, and predict trends of future research. Articles on this topic published from 2001 to 2021 were obtained from the Web of Science Core Collection. Bibliometric analysis and visualization were performed to identify research hotspots and trends with the use of the online bibliometric analysis platform, VOSviewer, and CiteSpace. In total, 4415 articles were included for bibliometric analysis. The annual output of research on this topic gradually increased over the past 21 years. China contributed the most publications (1254), while the United States was the core (centrality = 0.35) of the country-cooperation network and Schnabl B published the most articles (n = 80). High-frequency keywords included "gut microbiota", "inflammation", "obesity", "insulin resistance", "disease", "fatty liver disease", "metabolism", and "probiotics". The keywords that have burst in recent years include "intestinal microbiota", "dysbiosis", and "gut-liver axis". The relationships between dysbiosis of the intestinal microbiota and liver diseases, such as nonalcoholic fatty liver disease (NAFLD), cirrhosis, and hepatocellular carcinoma (HCC), are current research hotspots. Treatment for NAFLD, nonalcoholic steatohepatitis, cirrhosis, and HCC via regulation of the intestinal microbiota is predicted as a research hotspot in the following years, especially immunotherapy for HCC. These findings should prove helpful to scholars to direct future research on the relationships between the intestinal microbiota and liver diseases.

Keywords: Intestinal microbiota, liver diseases, bibliometric analysis, CiteSpace, VOSviewer

Introduction

The liver and intestines communicate bidirectionally via the biliary tract and portal vein, which is known as the gut-liver axis [1]. The gut-liver axis has been linked to dysbiosis (compositional and functional changes) of the intestinal microbiota, which has been implicated in a variety of liver diseases. However, it remains uncertain whether dysbiosis of the intestinal microbiota is a cause or rather a consequence of liver diseases. Indeed, dysbiosis of the intestinal microbiota affects the progression of liver diseases through metabolic and immune modulation [2]. Meanwhile, decompensated cirrhosis results in remarkable alterations to the intestinal microbiota [3]. However, additional research is needed to further elucidate the effect of dysbiosis of the intestinal microbiota on the development of liver diseases.

Bibliometric analysis can help investigators to identify research hotspots, track current trends, predict directions of research, and visualize patterns and trends in scientific literature with tools, such as CiteSpace (http://cluster.cis.drexel.edu/~cchen/citespace/) and VOSviewer (https://www.vosviewer.com/). The number of articles on interactions between the intestinal microbiota and liver diseases has continued to increase in recent years. The aim of the present study was to employ bibliometric analysis to assess articles in the literature on the roles of the intestinal microbiota in the development of liver diseases published from 2001 to 2021, identify research hotspots, and clarify the direction of current trends in research.

Materials and methods

Data source and search strategy

The Science Citation Index Expanded™ and Social Sciences Citation Index were chosen to search the literature for all articles on the inter-

actions between the intestinal microbiota and liver diseases published from 2001 to December 31, 2021. The type and language of the publications were limited to "article" and "English", respectively. The literature search and relevant data downloads were conducted on December 1, 2022 to avoid updates of citations and publications. Articles published in 2022 were excluded due to incomplete data.

Data collection

Two of the authors independently searched the Web of Science Core Collection (WoSCC) for relevant articles and the bibliographies were downloaded to assess the titles, authors, institutions, countries/regions, abstracts, keywords, journals, references, and citations. Discrepancies were settled by discussion or consensus with the third author. The impact factor, H-index, and category quartiles were retrieved from the 2021 *Journal Citation Reports*™.

Bibliometric analysis and visualization

The annual volume of publications, distribution by countries/regions and institutions, and number of publications per author were collected in Excel files (Microsoft Corporation, Redmond, WA, USA). Additionally, Excel software was used to fit a regression model to predict the volume of articles published in 2022. The Bibliometric Online Analysis Platform (http://bibliometric.com/) was used to determine the top ten countries/regions with the greatest annual volume of publications. VOSviewer 1.6.17 (Leiden University, Leiden, Netherlands) was used to generate density maps of the co-occurrence of keywords, authors, and organizations. CiteSpace 6.1. R2 (Chaomei Chen, Drexel University, Philadelphia, PA, USA) was used to identify trends and hotspots.

Results

Annual growth trend of publications

In total, 4742 articles of the relationships between the intestinal microbiota and liver diseases were published between 2001 and 2021. After excluding non-English publications (n = 52), meeting abstracts (n = 90), editorial materials (n = 86), conference paper (n = 47), book chapters (n = 37), letters (n = 15), reprints (n = 3), and news items (n = 1), 4415 articles remained. The annual output of research on intestinal microbiota and liver diseases gradually increased from 2001 to 2021 (**Figure 1A**). The number of articles published in the United States was relatively high between 2001 and 2017 (**Figure 1B**), while articles produced in China reached an all-time high between 2018 and 2021.

Countries/regions and institutions analysis

The 4415 articles related to intestinal microbiota and liver diseases from 2001 to 2021 originated in 90 countries/regions. The top ten countries contributed 3909 (88.54%) of the 4415 publications, with China producing the most articles (1254, 28.40%), followed by the United States (1092, 24.73%), Italy (313, 7.08%), Germany (216, 4.89%), Japan (193, 4.37%), England (184, 4.17%), Canada (184, 4.17%), France (174, 3.94%), Spain (156, 3.53%), and South Korea (143, 3.23%). A country-cooperation network of research related to intestinal microbiota and liver diseases is presented in **Figure 1C**. In the country-cooperation network, the United States (centrality = 0.35) was the network core, followed by Italy (centrality = 0.28), China (centrality = 0.24), and England (centrality = 0.24), demonstrating the dominance of these countries in this field.

The University of California San Diego published the highest proportion of the 4415 articles (123, 2.79%), followed by Zhejiang University (103, 2.33%), and Shanghai Jiao Tong University (91, 2.06%). According to the institution-cooperation network presented in **Figure 1D**, the University of California San Diego was the network core (centrality = 0.14), followed by Shanghai Jiao Tong University (centrality = 0.08) and Catholic University of Louvain (centrality = 0.08). The institution-cooperation network revealed that research on the relationships between the intestinal microbiota and liver diseases in the United States and China was dominated by the University of California San Diego and Shanghai Jiao Tong University, respectively.

Author analysis

Authors with more than eight publications and more than 20 citations were used to construct the co-authorship networks shown in **Figure 1E**. Schnabl B published the most articles (n =

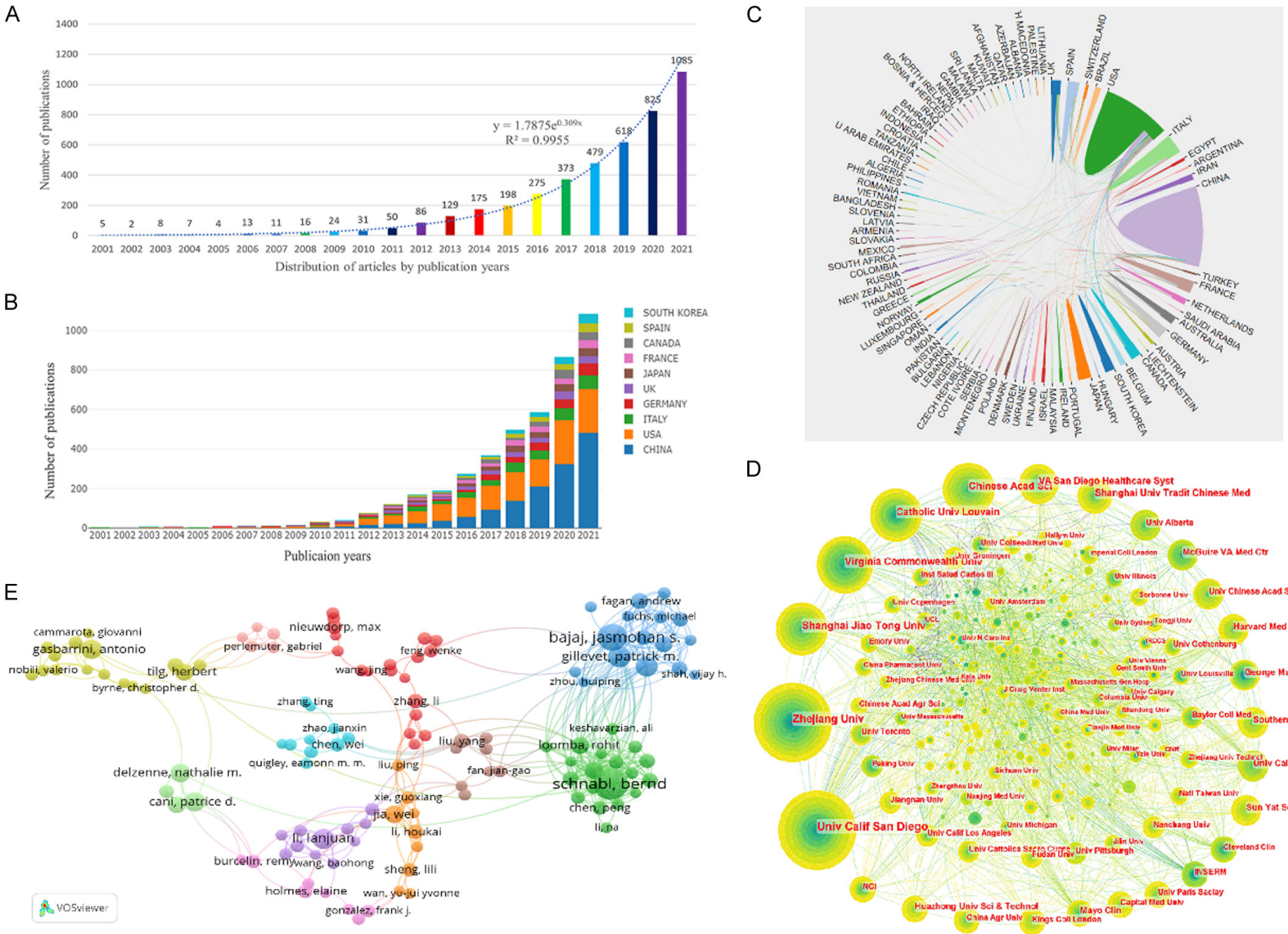

Figure 1. A and B. Annual publications and the country's annual trend publications related to intestinal microbiota and liver diseases; C and D. Co-operation of countries and institutions contributed to publications related to intestinal microbiota and liver diseases; E. Joint mapping of productive authors contributed to intestinal microbiota and liver diseases.

Table 1. The top ten journals contributed to intestinal microbiota and liver diseases

Rank	Journal	Articles counts	Country	JCR (2021)	IF (2021)	Total citations	Average number of citations	H-index
1	Nutrients	140	Switzerland	Q1	6.706	4771	34.08	36
2	Scientific Reports	106	UK	Q1	4.996	3511	33.12	37
3	International Journal of Molecular Sciences	98	USA	Q1/Q2	6.208	2362	24.1	24
4	PLoS One	98	USA	Q2	3.752	4213	42.99	35
5	World Journal of Gastroenterology	88	China	Q2	5.374	4424	50.27	36
6	Food & Function	84	UK	Q1/Q2	6.317	1552	18.48	21
7	Frontiers in Microbiology	72	Switzerland	Q1	6.064	1951	27.1	26
8	American Journal of Physiology Gastrointestinal and Liver Physiology	64	USA	Q1/Q2	4.871	3843	60.05	30
9	Hepatology	58	USA	Q1	17.298	8822	152.1	40
10	Frontiers in Immunology	52	Switzerland	Q1	8.786	1464	28.15	21

JCR: Journal citation reports, IF: Impact factor.

80), followed by Bajaj JS (n = 57), Li Y (n = 53), and Wang Y (n = 47). Based on centrality scores, Wang Y ranked first (0.21), followed by Li LJ (0.09), Schnabl B (0.04), and Li J (0.03). Based on the total number of citations and H-index value, Schnabl B ranked first (5829, 39), followed by Bajaj JS (5077, 34), Gillevet PM (3826, 25), and Li LJ (3447, 22).

Journal and co-cited journal analysis

The 4415 articles on the relationships between the intestinal microbiota and liver diseases from 2001 to 2021 were published in a total of 924 journals. The top ten productive journals are presented in **Table 1**. *Nutrients* published the most articles (n = 140), followed by *Scientific Reports* (n = 106), *International Journal of Molecular Sciences* (n = 98), and *PLoS One* (n = 98). The top ten productive journals published 860 articles, with 318 (36.98%) of the journals located in the United States. According to the *Journal Citation Reports* quartile (2021), of the top ten productive journals, five were classified as Q1, three as Q1/Q2, and two as Q2. Among the top ten productive journals, *Hepatology* had the highest impact factor (17.298), greatest number of citations (8822), and the highest H-index value (40).

Keyword analysis

Cluster analysis of keyword co-occurrence: The results of co-occurrence analysis are presented in the form of a map (**Figure 2A**). According to the co-occurrence analysis map, the most frequent keywords were “gut microbiota” (1713), “inflammation” (782), “obesity” (707), “intestinal microbiota” (609), “microbiota” (575), “insulin resistance” (561), “disease” (512), “fatty liver disease” (434), “metabolism” (369), and “probiotics” (349). In the map, 386 keywords were classified into five clusters shown in green, red, blue, yellow, and purple. The keyword distribution based on occurrence is shown in **Figure 2B**, where the various times of appearance are represented by different colors. “Bacterial translocation” and “cirrhosis” were the most common research topics before the year of 2018, which were replaced by “dysbiosis”, “inflammation”, and “nonalcoholic fatty liver disease” after 2018. VOSviewer was also used to calculate the frequencies of the keywords, which are presented as a density map (**Figure 2C**), where higher density is represented as a brighter color and a higher grayscale level usually represents research hotspots in a specific field.

Keyword burst analysis: The top 20 keywords with the highest citation bursts are shown in **Figure 2D**, where the blue line represents the timeline (begin and end years) and the red line represents the period of bursts in keywords and citations. The keyword “bacterial translocation” had the highest burst strength (6.31) between 2001 and 2016. From 2016 to 2021, the keyword “intestinal microbiota” had the highest burst strength (5.16), followed by “dysbiosis” (4.2) and “gut-liver axis” (3.24).

Co-cited reference analysis

The co-cited references network included 262 nodes and 1329 links (**Figure 2E**). The first author, publication year, journal, and citation frequency of the top ten co-cited articles are shown in **Table 2**. The top-20 references with the strongest citation bursts are shown in **Figure 2G**. The article published by Boursier J et al. [4] in *Hepatology* had the most citations (331), followed by Zhu LX et al. [5] in *Hepatology* (197) and Leung C et al. [6] in *Nature Reviews Gastroenterology & Hepatology* (187). Additionally, five of the top ten co-cited articles were published in *Hepatology*, which is a high-impact journal in the field of liver disease, suggesting that articles published in high-impact journals have positive influences in this field.

The top co-cited references were classified into seven clusters, which include “farnesoid X receptor”, “obesity”, “alcoholic liver disease”, “nonalcoholic fatty liver disease”, “microflora”, “immunotherapy”, and “trimethylamine N-oxide (TMAO)” (**Figure 2F**). In addition, a timeline view of the cluster was constructed to further identify emerging research hotspots (**Figure 2H**). According to the timeline view, “microflora” (cluster 4) was an early (before 2013) hotspot, whereas “obesity” (cluster 1), “alcoholic liver disease” (cluster 2), and “farnesoid X receptor” (cluster 0) were mid-term hotspots (2013-2019), and “immunotherapy” (cluster 5) and “TMAO” (cluster 6) were the latest hotspots (2019-2021).

Discussion

Based on the results of cluster analysis of keyword co-occurrence, the high-frequency key-

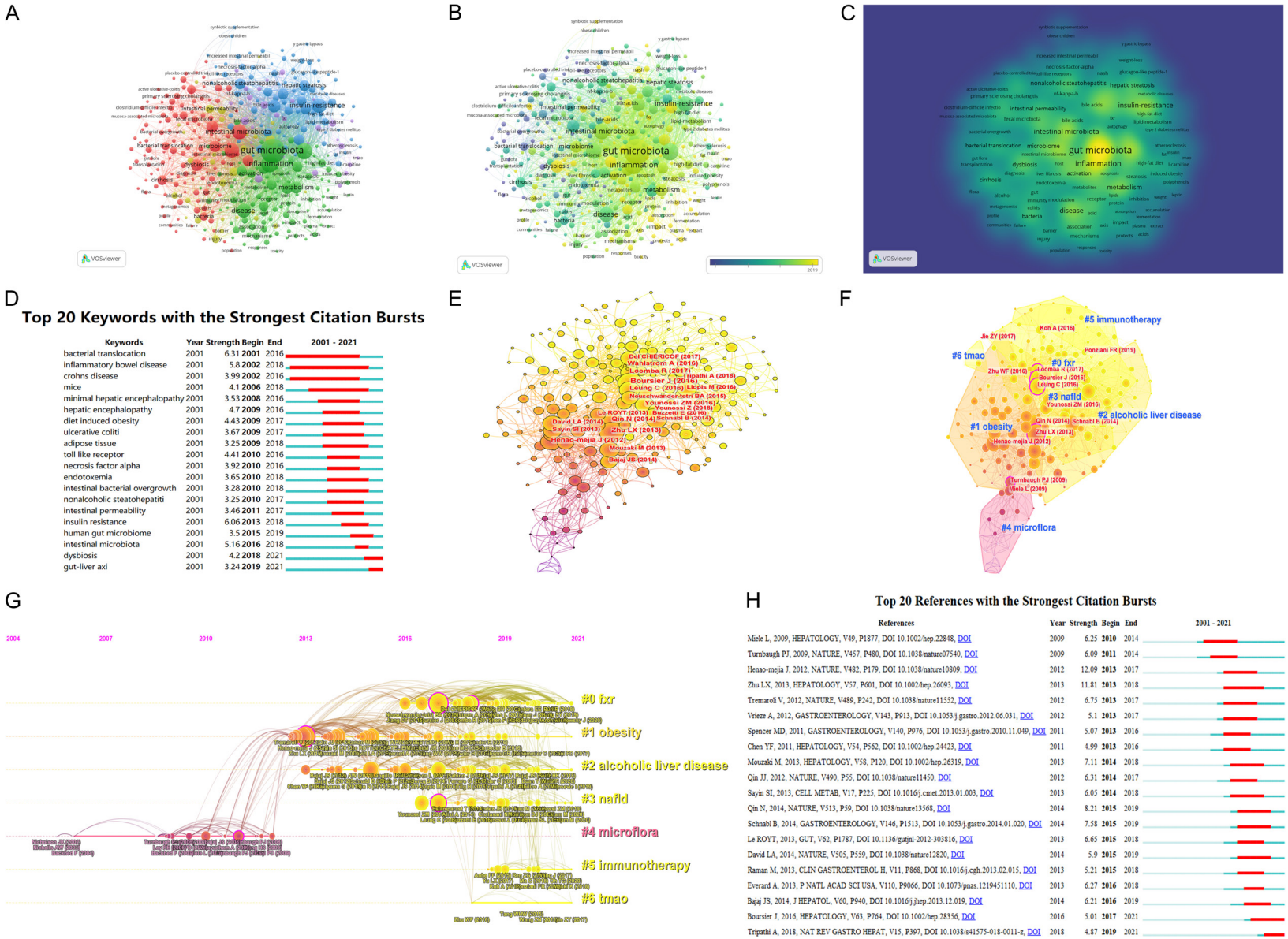

Figure 2. A. Mapping of keywords in the research field; B. Distribution of keywords according to the chronological order of appearance; C. Distribution of keywords according to the mean frequency of appearance; D. Top 20 Keywords with the strongest citation bursts; E and F. Co-cited references map and clustered network map of co-cited references on intestinal microbiota and liver diseases; G. Timeline view of co-cited clusters with cluster labels; H. Top 20 references with the strongest citation bursts.

Table 2. Top ten Co-cited references related to intestinal microbiota and liver diseases

Rank	Title	Author	Year	Journal	Citation frequency
1	The severity of nonalcoholic fatty liver disease is associated with gut dysbiosis and shift in the metabolic function of the gut microbiota	Boursier J	2016	Hepatology	331
2	Characterization of gut microbiomes in nonalcoholic steatohepatitis (NASH) patients: a connection between endogenous alcohol and NASH	Zhu LX	2013	Hepatology	197
3	The role of the gut microbiota in NAFLD	Leung C	2016	Nature Reviews Gastroenterology & Hepatology	187
4	Gut Microbiome-Based Metagenomic Signature for Non-invasive Detection of Advanced Fibrosis in Human Nonalcoholic Fatty Liver Disease	Loomba R	2017	Cell Metabolism	182
5	Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes	Younossi ZM	2016	Hepatology	181
6	Intestinal Crosstalk between Bile Acids and Microbiota and Its Impact on Host Metabolism	Wahlstrom A	2016	Cell Metabolism	171
7	Inflammasome-mediated dysbiosis regulates progression of NAFLD and obesity	Henao-Mejia J	2012	Nature	169
8	Alterations of the human gut microbiome in liver cirrhosis	Qin N	2014	Nature	158
9	Gut microbiota profiling of pediatric nonalcoholic fatty liver disease and obese patients unveiled by an integrated meta-omics-based approach	Del Chierico F	2017	Hepatology	148
10	Interactions between the intestinal microbiome and liver diseases	Schnabl B	2014	Gastroenterology	146

words were divided into five clusters, which were further classified into three categories: diseases, mechanisms, and treatments. The disease category included the terms “obesity”, “fatty liver disease”, “NASH”, and “cirrhosis”, while the mechanism category included the terms “gut microbiota dysbiosis”, “inflammation”, “insulin resistance”, “metabolism”, “intestinal permeability”, and “bile acids”, and the treatment category consisted of the term “probiotics”.

The prevalence of obesity has continued to increase worldwide. Recent studies have found that the gut microbiota is associated with the development of obesity and progression to NAFLD [7]. The close relationship among the gut microbiota, obesity, and NAFLD explains the high frequency of the term “obesity” as a keyword. Regulation of the gut microbiota is a promising strategy to reduce obesity in humans.

NAFLD includes both the milder form of simple steatosis and the more severe form of NASH, which often leads to cirrhosis, liver cancer, end-stage liver disease, and death [8]. The results of epidemiological studies have revealed that obesity is a major risk factor for the development of NAFLD [9]. Many animal studies have indicated that the gut microbiota is also crucial to the pathogenesis of NAFLD by increasing gut permeability, induction of mild inflammation, regulation of the metabolism of bile acids and dietary choline, and synthesis of endogenous ethanol, which can regulate Kupffer cell activity and cytokine production [10]. Based on these findings, future research may focus on the treatment of NAFLD by regulating the intestinal microbiota.

Cirrhosis is defined as the end stage (compensated and decompensated) of liver fibrosis. The formation of cirrhosis is related to systemic inflammation, immunodeficiency, and alterations to the gut-liver axis, which are largely related to dysbiosis of the gut microbiota [11]. The development and progression of cirrhosis are accompanied by gradual changes to the composition and function of the intestinal microbiota, including reductions in the proportions of commensal autochthonous taxa, such as *Lachnospiraceae* and *Clostridia*, and increases in the proportions of pathogenic bacteria, such as *Enterobacteriaceae* and *Streptococcaceae* [12]. Based on these findings, future research may focus on the treatment of cirrhosis via regulation of the intestinal microbiota.

The use of probiotics, as a therapeutic modality to reshape the gut microbiota, has become a research hotspot in recent years. For instance, a recent animal study showed that probiotic treatment reduced the levels of endotoxemia, inflammatory cytokines (tumor necrosis factor-α, interluekin-6), and total cholesterol and triglycerides in a mouse model of NFALD [13]. A randomized controlled trial found that a 6-month intervention with probiotics enriched the intestinal microbiota and improved the

intestinal barrier function of patients with compensated cirrhosis [14]. These results suggest that probiotics regulate the gut microbiota by altering bacterial numbers and composition, reducing intestinal permeability, lowering ammonia levels, and altering the immune response [14]. In general, regulation of the intestinal microbiota is a promising treatment for liver diseases and could remain a research hotspot in the following years.

Although not included in the top ten most frequent keywords, HCC has been linked to NAFLD, NASH, and cirrhosis, and is the sixth most common malignancy [15]. Furthermore, both animal [16] and human [17] studies have demonstrated that changes to the composition of the gut microbiota play an important role in hepatocarcinogenesis, although the underlying mechanism remains unclear. Therefore, further studies are warranted to clarify the roles of the intestinal microbiota in HCC, especially immunotherapy for HCC. Hence, the role of the intestinal microbiota in HCC is another potential research hotspot in this field in the following years.

Conclusion

The United States, the University of California San Diego, and Schnabl B were identified as the most influential country, institution, and author in this field, respectively. *Nutrients* was the most productive journal and *Hepatology* was the most influential journal. The relationships between the intestinal microbiota dysbiosis and liver diseases (NAFLD, cirrhosis, and HCC) are current research hotspots. Treatment of NAFLD, NASH, cirrhosis, and HCC via regulation of the intestinal microbiota is predicted as a research hotspot in this field in the following years, especially immunotherapy for HCC.

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Disclosure of conflict of interest

None.

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