

Trends in chronic hepatitis B treatment-related research from 1973 to 2018: a bibliometric and visual analysis

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Abstract

Objective: Chronic hepatitis B (CHB) is a worldwide disease and the most common cause of liver cancer. This study aimed to identify specific areas of research activity concerning CHB treatment between 1973 and 2018 and to aid in identifying new areas for future development.

Methods: The literature was searched from the GoPubMed and Web of Science databases using terms related to CHB treatment, analyzed with bibliometric methods and visualized using VOSviewer.

Results: A total of 9486 and 5883 papers were collected from PubMed and Web of science, respectively. The studies focused on two clusters of topics: antiviral therapy for CHB and progressive diseases, and drug resistance. Studies related to *antiviral drugs* concentrated on *lamivudine* (n = 788), *entecavir* (n = 390), and *adefovir dipivoxil* (n = 376). Studies addressing conditions developing from CHB highlighted *hepatocellular carcinoma* (n = 403) and *cirrhosis* (n = 223). China (n = 1978) contributed the most publications. The 10 most quantitatively prolific organizations were in France. All 20 of the most cited papers investigated antiviral treatments for CHB or CHB-associated cirrhosis.

Conclusions: Research on CHB treatment over the past 45 years has concentrated on antiviral therapy, CHB-associated progressive conditions, drug resistance and immunization. Although work on CHB treatment has made considerable progress, new approaches must be explored.

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Keywords

Chronic hepatitis B, treatment, trend, literature, bibliometric analysis, cirrhosis, antiviral drugs

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Introduction

CHB is a worldwide disease caused by hepatitis B virus, despite the implementation of preventive vaccines.^{1,2} Schweitzer and colleagues reported that up to 248 million individuals were seropositive against hepatitis B surface antigen (HBsAg) in 2010, by reviewing and analyzing the literature from 1965 to 2013 on the prevalence of CHB virus from databases such as MEDLINE and Web of Science.³ Uncontrolled CHB contributes to cirrhosis and even cancer.⁴ This disease was the major cause of liver cancer deaths (265,000 individuals [33%]) globally between 1990 and 2015.⁵

By 2030, the World Health Assembly's goal is decrease new viral hepatitis infections by 90% and decrease the number of deaths from viral hepatitis by 65% globally.⁶ Extensive work on therapeutic strategies for CHB has been performed. A growing body of literature on treatment of CHB has been collected in PubMed, a free resource provided by the National Center for Biotechnology Information in the United States for readers to explore, as well as the Web of Science database, including the Science Citation Index expanded database. Nevertheless, studies on the status quo, focus areas, and future prospects of research toward CHB treatment are still absent.

Bibliometric methods have expanded the focus of topics, publications, countries, authors, institutions and journals in many research fields.⁷⁻¹¹ A large number of studies have applied bibliometric methods to identify research trends in various fields.^{7,10,12-18} Although a few articles related to hepatitis have been bibliometrically

analyzed,¹⁹ there is a lack of comprehensive bibliometrics for CHB treatment. The aims of this study were to apply bibliometric methods to identify specific areas of research activity concerning CHB treatment and to facilitate the identification of new areas for future development.

Materials & methods

Using GoPubMed as a retrieval tool,²⁰ we searched PubMed for literature on the treatment of CHB. The search strategy in GoPubMed (www.gopubmed.org) was as follows: "Hepatitis B, Chronic" [mesh] AND Therapeutics [mesh]. The earliest available literature was from 1973. Relevant literature was also mined from the Web of Science database using the following search strategy: TI=(("Chronic hepatitis B" AND (therap* OR treat* OR cure* OR remedy*)) from 1973 to 2018. The search was conducted on October 29, 2018.

A network visualization map based on data searched from the Web of Science Core Collection database was created using VOSviewer (www.vosviewer.com) to analyze all keywords, as well as collaborations between countries, organizations, and authors, related to research on CHB treatment. The search strategy for the Web of Science Core Collection database was as described above.

All data were analyzed using Microsoft Excel 2003 (Microsoft Corp., Redmond, WA, USA). Bar graphs were prepared using OriginPro 2018 (OriginLab, Northampton, MA, USA).

Results

Annual publications on CHB treatment

From 1973 to 2018, PubMed indexed 9486 papers on the treatment of CHB, while Web of Science indexed 5883 papers. The results from GoPubMed showed that the number of published papers on treatment of CHB increased from 1973 to 2015, with one paper published in 1973 and 683 papers published in 2015, a 683-fold increase. In 2016 and 2017, slightly fewer papers were published than in 2015 (Figure 1). These results suggested that the interest of researchers in CHB treatment generally rose from 1973 to 2015 and that there was a slight drop from 2016 to 2018.

Top topics addressed in CHB treatment-related literature

The results (data collected from Web of Science; Figure 2) demonstrated that the co-occurrence of all keywords (except for

chronic hepatitis B, hepatitis B, or therapy) focused on *lamivudine* (788, 19.70%), *hepatocellular carcinoma* (403, 10.07%), *entecavir* (390, 9.75%), *adefovir dipivoxil* (376, 9.40%), *virus infection* (340, 8.50%), *infection* (333, 8.32%), *hepatitis B virus* (273, 6.82%), *virus* (254, 6.35%), *management* (248, 6.20%), *antiviral therapy* (246, 6.15%), *cirrhosis* (223, 5.57%), *efficacy* (213, 5.32%), *interferon* (209, 5.22%), *resistance* (207, 5.17%), *e-antigen* (190, 4.75%), *natural-history* (184, 4.60%), *peginterferon alpha-2a* (180, 4.50%), *trial* (174, 4.35%), *combination* (164, 4.10%), *tenofovir* (162, 4.05%), *surface-antigen* (152, 3.80%) and *lamivudine therapy* (151, 3.77%). Each of these topics was addressed by at least 150 studies, and together were broadly interpreted as “antiviral therapy for CHB and its progressive diseases”, and “antiviral drug-related resistance” using cluster analysis. This suggested that research on the treatment of CHB concentrated on antiviral drugs, especially lamivudine, entecavir and adefovir dipivoxil. Consistent with the

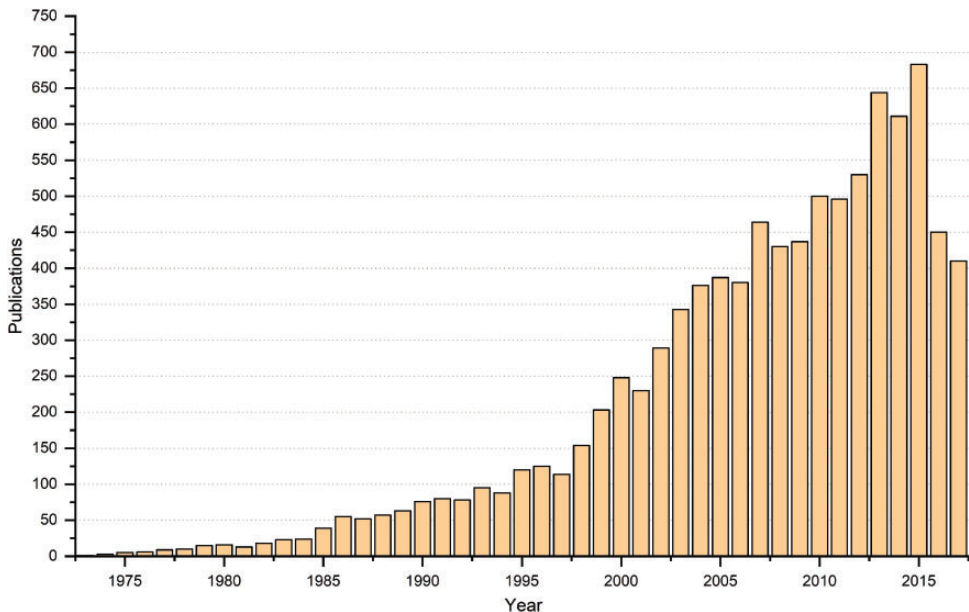


Figure 1. Annual publication on the treatment of chronic hepatitis B.

results from the Web of Science database, antiviral drugs were also frequent topics related to CHB treatment in studies from PubMed (Table 1). In addition, development of this disease, including cirrhosis and hepatocellular carcinoma, as well as drug resistance were also frequent topics in research on CHB treatment over the past decades.

Country/regions, city distribution and collaborations on CHB treatment-related research

According to the world map from GoPubMed related to treatment of CHB, the literature was concentrated in Europe,

East Asia, and North America (data not shown). The 10 leading countries in publications related to CHB treatment were China (n=1978, 20.85%), the United States (n=1258, 13.26%), Japan (n=496, 5.23%), Germany (n=457, 4.82%), Italy (n=443, 4.67%), France (n=433, 4.56%), South Korea (n=413, 4.35%), Turkey (n=284, 2.99%), the United Kingdom (n=266, 2.80%), and Spain (n=229, 2.41%). Figure 3 shows the collaborations between the top-publishing countries/regions. Among 75 countries, 23 countries were responsible for more than 30 publications. The map was divided into four collaboration clusters: 10 countries surrounding the United States (red), five

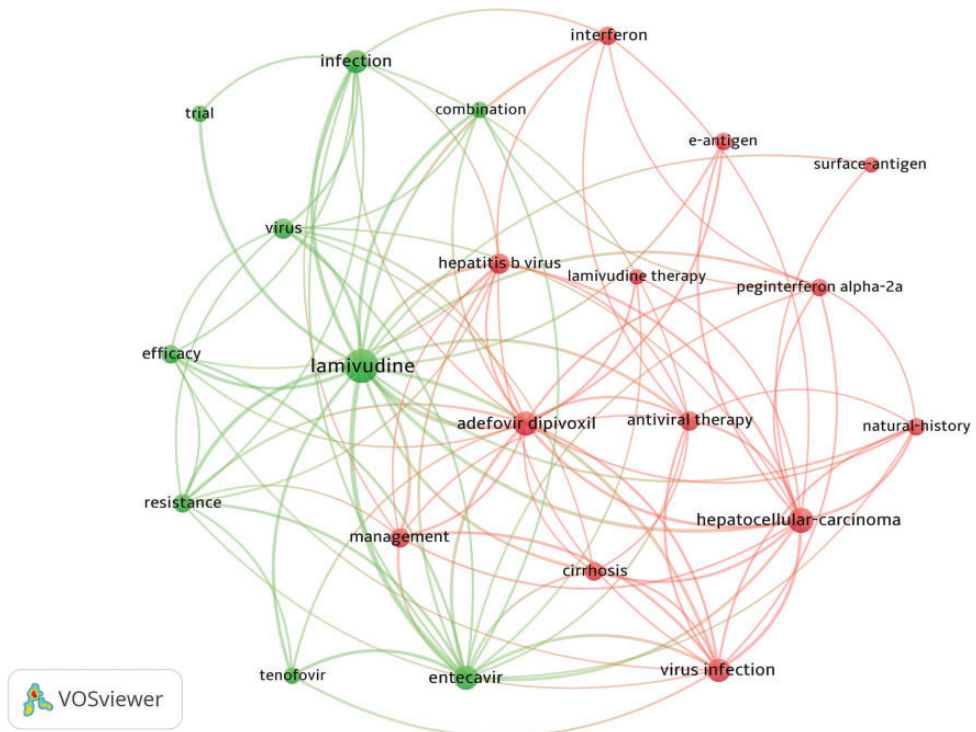


Figure 2. Network visualization map showing co-occurrence of all keywords analyzed by VOSviewer. The map was created using a threshold of $n=150$ for analyzing papers from Web of Science. Twenty-two keywords appear on the map. More occurrences of each keyword result in larger circles. A color represents a cluster. The red cluster can be broadly interpreted as “antiviral therapy for CHB and its progressive diseases”, while the green cluster can be interpreted as “antiviral drug-related resistance”. CHB, chronic hepatitis B.

Table 1. Top 15 terms in publications concerning treatment of CHB from GoPubMed.

Top terms	Frequency	%/total
Humans	8073	85.10%
Patients	7131	75.17%
Hepatitis B virus	6191	65.26%
Male	4961	52.30%
Female	4613	48.63%
Adult	4342	45.77%
Antiviral agents	3950	41.64%
Middle aged	3487	36.76%
Hepatitis B e antigens	3255	34.31%
DNA	2739	28.87%
Immunization	2672	28.17%
Immunity	2654	27.98%
Antigens	2591	27.31%
Serum	2463	25.96%
Fibrosis	2395	25.25%

CHB, chronic hepatitis B.

countries surrounding China (green), four countries surrounding England (blue), and four countries surrounding Australia (yellow) (Figure 3). The results suggested that the most prolific countries collaborated strongly with one another on research related to CHB treatment.

The top nine cities producing CHB publications were Beijing (n = 423, 4.46%), Taipei (n = 320, 3.37%), Shanghai (n = 299, 3.15%), Hong Kong (n = 284, 2.99%), Seoul (n = 278, 2.93%), Guangzhou (n = 223, 2.35%), London (n = 181, 1.91%), Paris (n = 156, 1.64%), and Rotterdam (n = 135, 1.42%). This demonstrates that the most prolific cities producing CHB treatment-related research were concentrated in China.

Top authors and organizations for research on the treatment of CHB

The co-authorship network map from VOSviewer (Figure 4) showed the publications and collaborations between authors. Seventeen authors had at least 40

publications, and Patrick Marcellin was the most active author (102 papers, 1.7%).

Table 2 shows the most productive organizations, with the most prolific organization being *Assistance Publique Hopitaux Paris* (264 papers, Table 2).

The 10 most productive journals and the 20 most influential papers for research on treatment of CHB

Table 3 shows the 10 most prolific journals publishing research on CHB treatment. The three most prolific journals were *Journal of Hepatology* (314 papers, 3.31%), *Hepatology* (313 papers, 3.30%), and *Chinese Journal of Hepatology* (278 papers, 2.93%).

As shown in Table 4, the most highly cited papers were primarily concerned with the effects of antiviral drugs, especially lamivudine, adefovir dipivoxil, interferon, and entecavir, on CHB and associated diseases including fibrosis and cirrhosis, consistent with the results of the top topics for CHB treatment. These results further suggested the major theme of antiviral therapy as a central topic for CHB and CHB-associated research.

Discussion

We analyzed literature on CHB treatment, involving 9486 papers retrieved from PubMed and 5883 papers from Web of Science database, by applying quantitative and qualitative bibliometric methods. Through bibliometric analysis, our results provided an overview of the development of CHB treatment and issues of special interest based on literature over the past 45 years.

According to the increasing amount of literature in PubMed and Web of Science over the past 45 years, great progress has been made in the therapy of CHB. The results highlighted frequent topics in CHB

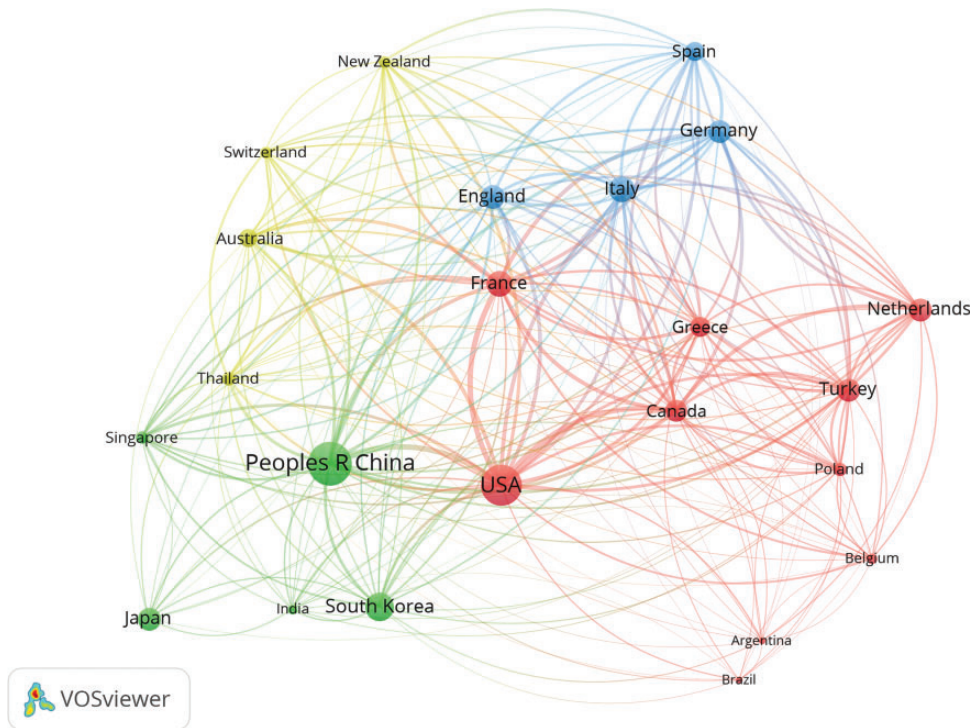


Figure 3. Network visualization map for top publication countries/regions. The map was created using a threshold of $n = 30$ for analyzing the papers searching from Web of Science. Twenty-three countries/regions appear on the map. The more publications, the larger the circle. The thickness of the line represents link strength of collaboration between the countries, and the collaboration cluster between the countries is shown as four colors.

treatment including a focus on *antiviral drugs*. There was a large body of literature that described antiviral therapies for CHB, especially lamivudine, entecavir, adefovir dipivoxil, interferon, peginterferon alpha-2a (PegIFN α -2a) and tenofovir. These highlights were likely related to the discovery and development of antiviral agents. Between 1990 and 2013, several antiviral agents were successively approved for CHB treatment.⁴¹ Six antiviral agents (peginterferon-2a, lamivudine, telbivudine, entecavir, adefovir, and tenofovir) were approved for the treatment of CHB in adults, and five antiviral agents (IFN-A-2B, lamivudine, entecavir, adefovir, and tenofovir) were used for treatment of

CHB in children.³² These approved antiviral agents were classified into interferons and nucleotide/nucleoside analogues, including lamivudine, adefovir, entecavir, telbivudine and tenofovir.³² Our results for both types of antiviral agents were correlated, with studies on interferon and nucleoside analogues both being areas of high interest for CHB treatment over the past decades. In addition, *drug resistance* was also one of the top topics in CHB treatment, which may suggest that new therapeutic strategies for CHB need to be explored.

Progressive conditions associated with CHB, including *cirrhosis* and *hepatocellular carcinoma*, were also frequently described in

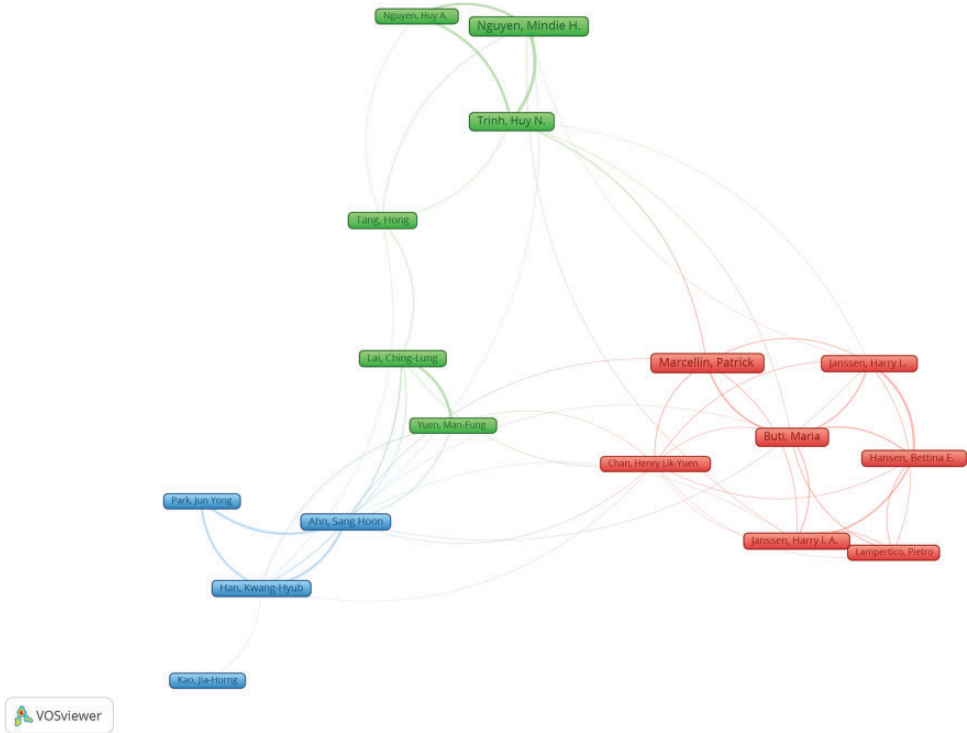


Figure 4. Network of top authors on the treatment of CHB analyzed from VOSviewer. The map was created using a threshold of 40 for analyzing papers identified from Web of Science. The thickness of the line represents collaborations between authors. CHB, chronic hepatitis B.

Table 2. Top 10 organizations producing CHB-related publications.

Organization	Country	Publications	%/total papers
Assistance Publique Hopitaux Paris	France	264	4.49%
Erasmus University Rotterdam	Netherlands	243	4.13%
Erasmus University Medical Center	Netherlands	226	3.84%
University of Toronto	Canada	197	3.35%
Gilead Sciences	USA	191	3.25%
Hopital Universitaire Beaujon Aphp	France	190	3.23%
Institut National De La Sante Et De La Recherche Medicale Inserm	France	189	3.21%
University of Hong Kong	China	183	3.11%
University of London	UK	163	2.77%
Capital Medical University	China	140	2.38%

CHB, chronic hepatitis B.

the literature on CHB treatment, suggesting that CHB treatment also focused on cirrhosis and hepatocellular carcinoma, consistent with previous studies.⁴¹ The risk of

progression to cirrhosis and liver cancer is elevated in patients with CHB. CHB is the most frequent of hepatocellular carcinoma. A recent study reported that patients with

Table 3. Top journals publishing papers on the treatment of CHB identified from GoPubMed.

Journal	Publications	%/total
<i>Journal of Hepatology</i>	314	3.31%
<i>Hepatology</i>	313	3.30%
<i>Chinese Journal of Hepatology</i>	278	2.93%
<i>World Journal of Gastroenterology</i>	258	2.72%
<i>Journal of Viral Hepatitis</i>	229	2.41%
<i>Journal of Medical Virology</i>	194	2.05%
<i>Journal of Gastroenterology and Hepatology</i>	181	1.91%
<i>Liver International</i>	149	1.57%
<i>Gastroenterology</i>	134	1.41%
<i>Antiviral Therapy</i>	132	1.39%

CHB, chronic hepatitis B.

hepatitis B virus-associated hepatocellular carcinoma receiving antiviral drugs display attenuated hepatocarcinogenesis.⁴² Moreover, three of the 20 most cited papers on CHB treatment investigated antiviral therapy, including tenofovir disoproxil, entecavir and lamivudine, for CHB-associated cirrhosis, further indicating that antiviral therapy for cirrhosis has been of high interest to researchers. A meta-analysis demonstrated that antiviral therapy reduced the risk of cirrhosis and hepatocellular carcinoma in patients with chronic hepatitis B viral infection.⁴³

There was also a great deal of work indexed in PubMed showing the possible therapeutic effects of immunization treatment on CHB. This result is consistent with previous reports.^{1,44-46} Activation of innate immunity is a novel strategy for treatment of CHB by directly targeting hepatitis B virus.⁴⁶ For immune-active CHB in adults, peg-IFN, entecavir, or tenofovir were the preferred antiviral agents recommended by the American Association for the Study of Liver Diseases.³² Taken together with the results from Web of Science database, these findings showed that treatments for

CHB focused not only on antiviral therapy, but also on immunization. Interestingly, few terms related to traditional Chinese medicine were discovered in the terms or keywords from GoPubMed and the network from VOSviewer, even though China is the country with the most publications on CHB treatment. This finding is likely related to the databases we retrieved studies from. More work needs to be done to develop novel treatments for CHB.

Our results also showed the contributions of countries, organizations, and authors to CHB treatment research. We presented a network visualization map in productive countries by applying VOSviewer. Research related to the treatment of CHB varied greatly globally but was mostly produced in Europe, Asia, and America. China contributed the most publications related to CHB treatment, consistent with the results of a literature review reporting high prevalence of this disease in China.⁴⁷ These advances may benefit from a vast network of collaborations between countries, and between researchers. All contributions from countries, institutions and researchers promoted the development of CHB treatment.

Approximately 75% of papers with high influence were related to antiviral agents, which was consistent with the analysis of top terms or keywords. Interestingly, from a productivity and citation perspective, only three journals published the top twenty most highly cited articles (Table 3 and 4) between 1973 to 2018. These three journals were *Gastroenterology*, *Hepatology* and *Gut*. *Gastroenterology* accounted for 20.1% of the top-20 manuscript citations. Two papers were related to adefovir dipivoxil, and the other two were related to lamivudine in *Gastroenterology*. *Hepatology* accounted for 16.4% of the top-20 manuscript citations. Two papers were related to lamivudine, and the others were related to entecavir and guidelines, respectively.

Table 4. Top 20 cited articles on CHB treatment.

Title	Author	Journal	Year	Total Cited
Lamivudine as initial treatment for chronic hepatitis B in the United States ²¹	Dienstag JL, Schiff ER, Wright TL, et al.	<i>New England Journal of Medicine</i>	1999	1105
Adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B ²²	Marcellin P, Chang T, Lim SG, et al.	<i>New England Journal of Medicine</i>	2003	1057
Effect of alpha-interferon treatment in patients with hepatitis-B e-antigen-positive chronic hepatitis-B – a meta analysis ²³	Wong DKH, Cheung AM, Orourke K, et al.	<i>Annals of Internal Medicine</i>	1993	865
Adefovir dipivoxil for the treatment of hepatitis B e antigen-negative chronic hepatitis B ²⁴	Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, et al.	<i>New England Journal of Medicine</i>	2003	763
Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B for up to 5 years ²⁵	Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, et al.	<i>Gastroenterology</i>	2006	685
A randomized, controlled trial of interferon alfa-2b alone and after prednisone withdrawal for the treatment of chronic hepatitis B ²⁶	Perrillo RP, Schiff ER, Davis GL, et al.	<i>New England Journal of Medicine</i>	1990	684
Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study ²⁷	Marcellin P, Gane E, Buti M, et al.	<i>Lancet</i>	2013	682
Long-term follow-up of HBeAg-positive patients treated with interferon alfa for chronic hepatitis B ²⁸	Niederma C, Heintges T, Lange S, et al.	<i>New England Journal of Medicine</i>	1996	670
Long-term safety of lamivudine treatment in patients with chronic hepatitis B ²⁹	Lok ASF, Lai CL, Leung N, et al.	<i>Gastroenterology</i>	2003	621
Effects of extended lamivudine therapy in Asian patients with chronic hepatitis B ³⁰	Liaw YF, Leung NWY, Chang TT, et al.	<i>Gastroenterology</i>	2000	620
Persistence of cccDNA during the natural history of chronic hepatitis B and decline during adefovir dipivoxil therapy ³¹	Werle-Lapostolle B, Bowden S, Locarnini S, et al.	<i>Gastroenterology</i>	2004	602
AASLD guidelines for treatment of chronic hepatitis B ³²	Terrault NA, Bzowej NH, Chang K-M, et al.	<i>Hepatology</i>	2016	597

(continued)

Table 4. Continued.

Title	Author	Journal	Year	Total Cited
Extended lamivudine treatment in patients with chronic hepatitis B enhances hepatitis B e antigen seroconversion rates: Results after 3 years of therapy ³³	Leung NWY, Lai CL, Chang TT, et al.	Hepatology	2001	542
Long-term entecavir therapy results in the reversal of fibrosis/cirrhosis and continued histological improvement in patients with chronic hepatitis B ³⁴	Chang TT, Liaw YF, Wu SS, et al.	Hepatology	2010	541
Prevalence and clinical correlates of YMDD variants during lamivudine therapy for patients with chronic hepatitis B ³⁵	Lai CL, Dienstag J, Schiff E, et al.	Clinical Infectious Diseases	2003	518
Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B ³⁶	Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, et al.	New England Journal of Medicine	2005	453
Lamivudine and alpha interferon combination treatment of patients with chronic hepatitis B infection: a randomised trial ³⁷	Schalm SW, Heathcote J, Cianciara J, et al.	Gut	2000	427
Lamivudine treatment can restore T cell responsiveness in chronic hepatitis B ³⁸	Boni C, Bertolotti A, Penna A, et al.	Journal of Clinical Investigation	1998	380
A treatment algorithm for the management of chronic hepatitis B virus infection in the United States: 2008 update ³⁹	Keefe EB, Dieterich DT, Han S-H, et al.	Clinical Gastroenterology and Hepatology	2008	376
Lamivudine treatment for decompensated cirrhosis resulting from chronic hepatitis B ⁴⁰	Villeneuve JP, Condreay LD, Willems B, et al.	Hepatology	2000	374

CHB, chronic hepatitis B.

Gut published one paper among the top twenty most highly cited manuscripts, accounting for 3.4% of all citations. That paper was related to lamivudine and alpha interferon, which further confirmed that antiviral agents, especially lamivudine, were very interesting to researchers.

Our study had some limitations. We qualitatively and quantitatively analyzed the literature related to CHB treatment over the past 40 years, but the literature databases used were limited to MEDLINE and Web of Science. Other databases, such as Scopus and Embase, also can index relevant papers. Although MEDLINE is one of the most authoritative biomedical databases in the world, and Web of Science is the core database of Science Citation Index Expanded, the papers indexed both two literature databases in this study are still not comprehensive. In addition, we may not have searched comprehensively based on the search terms used, and use of other search terms may also affect the results. Therefore, all the results and conclusions of this study should be interpreted in light of these limitations.

Conclusions

This study illustrated the features of publications on CHB treatment from 1973 to 2018 by applying bibliometric analysis. Great progress has been made in the treatment of CHB over the past 45 years. Overall, our study found that a large amount of research on treatment of CHB concentrated on antiviral therapy, CHB progressive conditions including cirrhosis and hepatocellular carcinoma, immunization, and antiviral drug resistance. Although work on CHB treatment has made considerable progress in the past 45 years, many unresolved issues such as drug resistance and inability to eliminate all HBsAg, remain. New therapeutic strategies

and approaches for CHB remain to be explored.

Authors' contributions

Quansheng Feng and Li Wen designed the study. All authors analyzed the data. Guiyu Li and Jiyong Lin drafted the manuscript. Guiyu Li and Jiyong Lin contributed equally to this work. Quansheng Feng and Li Wen revised and reviewed the manuscript. All authors approved the final version of the manuscript.

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Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Ethical approval

Not required.

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