The latest research trends in primary biliary cholangitis: A bibliometric analysis

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Abstract

Background and aims: The bibliometric analysis uses the citation count of an article to measure its impact in the scientific community, but no study has been undertaken to determine the most influential papers in the field of primary biliary cholangitis (PBC). This study aimed to investigate the global research interest regarding PBC in dentistry using a bibliometric approach. **Methods:** We searched the Web of Science Core Collection database to find the top 100 most cited (T100) articles focusing on PBC. The information about each article including citations, authors, journals, countries, institutions, and keywords was recorded for bibliometric analysis. **Results:** The T100 articles related to PBC were published from 1983 to 2019 and were originated from 26 countries. A total of 805 different authors were from 342 different institutions, and articles written by them were published in 35 journals. The five most frequently occurring keywords were “biochemical response”, “ursodeoxycholic acid”, “primary biliary cirrhosis”, “antimitochondrial antibody”, and “autoimmunity”. The T100 articles were classified into different research focuses: pathogenesis (41%), treatment (20%), prognosis (12%), epidemiology (9%), diagnosis (8%) and others (10%). These 100 articles included 32 observational studies, 29 basic research articles, 15 reviews, eight meta-analyses, 12 clinical trials, and four clinical guidelines. **Conclusions:** This report presents major advances and changes in research regarding PBC. The single treatment method entered a bottleneck period, and combined treatment with immunosuppressant, local therapy, and surgery will become the next research focus to identify possible beneficial treatment combinations.

1. Introduction

Primary biliary cholangitis (PBC) was formerly known as primary biliary cirrhosis [31], first described by Addison & Gull in 1851 and Hanot in 1876 [1]. PBC is an autoimmune disorder characterized by the destruction of small intrahepatic bile ducts, leading to periportal inflammation, fibrosis, and potential cirrhosis. However, as the disease is increasingly diagnosed through the combination of cholestatic serum liver tests and the presence of antimitochondrial antibodies, most presenting patients are not cirrhotic and the term cholangitis is more accurate [4, 9]. The pathogenesis of PBC is thought to be related to the interaction between genetic predisposition and environmental triggers. PBC is common among women of middle age worldwide. The disease ratio among females to males is 9:1. Patients with PBC can be asymptomatic or may present with jaundice, pruritus, and fatigue, which usually correlate with the stage of disease at presentation [25]. Current guidelines advocate a step-wise approach to the disease-modifying treatment of PBC: all patients begin treatment with ursodeoxycholic acid (UDCA) monotherapy – and those with inadequate biochemical response to UDCA are subsequently considered for second-line therapies [2].

Bibliometric analysis is an increasingly used method that can analyze the basic characteristics of published literature, including, but not limited to, keywords clustering, the citation network of all manuscripts, and the cooperation network of countries, institutions, and authors of all manuscripts in a field. Via bibliometric analysis of manuscripts in a certain field, we can clearly understand the research hotspots and development trends [13]. Citation analysis involves ranking and evaluating an article or

journal based on the number of citations it receives. In addition to determining the most frequently cited articles, this analysis is also used to rank journals in terms of impact [26].

Multiple medical fields have used a rank list to determine the impact of articles and journals within their specialty [22]. Robert et al. [27] conducted a literature analysis of English papers covering PBC published in journals between 2000 and 2010. However, to date, no study has been undertaken to determine the most influential papers in the field of PBC. Therefore, this study aimed to identify and characterize the top 100 most cited (T100) articles that have focused on PBC. The analysis of these data helped us determine the most influential literature in this field, which can enable us to better understand the evolution of the management of PBC.

2. Methods

2.1 Data source and search strategy

Relevant articles were extracted from the Web of Science Core Collection (WoSCC) Database (Clarivate Analysis, Boston, USA) [34]. We searched publications by exploiting keywords “(primary biliary cholangitis) or (primary biliary cirrhosis)” from WoSCC Database. The search was conducted on a single day, 23 September 2021, to minimize adjustments to the number of citations during the search. No language restrictions were imposed. The time span we selected is all years. By this query, 6818 records were generated. Two researchers (Yu Zhao and Zhenjie Yin) screened titles and abstracts independently for qualified papers. The list of the T100 articles was extracted to Microsoft Excel 2010. We extracted data including the title, author, institution, journal, year of publication, total citations, and the type of study. Moreover, “Full record and cited references” were downloaded and raw data were transformed into TXT format which allowed for the analysis of bibliometric tools.

2.2 Criteria for enrolled researches for these studies

Inclusion criteria: 1. The object of study is primary biliary cholangitis or primary biliary cirrhosis; 2. Study designs included: case series, prospective cohort, randomized control trial (RCT), retrospective cohort, retrospective case-control, cross-sectional, and review.

Exclusion criteria: 1. The main body of the research and none of the content does not meet the requirements; 2. Non-academic paper type data included: meeting abstract, editorial material, news item, proceedings paper, book chapter, correction, and other types of data.

2.3 Data display

The distribution and contribution of authors, institutes, countries, and research areas of literature were analyzed, which was retrieved from WoSCC Database. The data were analyzed using CiteSpace (Chaomei Chen, Drexel University, USA) and VOSviewer (Ludo Waltman, Leiden University of Centre for Science and Technology Studies, Netherlands) for comprehensive science mapping analysis of extensive bibliographic metadata.

CiteSpace (Version 5.7.R5W 64-bit), a Java-based computer program designed by professor Chen from Drexel University, served as an indicator of the most active area of scientific community research. Several types of bibliometric studies such as co-word analysis, author co-citation analysis, document co-citation analysis, and text and geospatial visualizations are supported by this software. VOSviewer (Version 1.6.16) was utilized for recognizing association among journals and constructing collaboration networks, which referred to term clustering, countries/institutions/authors, and quotation systems of cited journals [32].

2.4 Ethical Requirements

Because this research did not involve intervention or data collection in animal experiments or clinical trials, approval from an ethical committee was not required.

3. Results

3.1 Citation range

A total of 6818 articles were extracted from WoSCC Database. The T100 articles were listed in Table 1 (Supporting Information). The citation count of articles ranged from 60 to 900 (total number of citations, 13455). The number of citations ranged from 900 for Lindor, KD et al. [19] ("Primary Biliary Cirrhosis") to 60 for Moritoki, Y et al. [21] ("B Cells Suppress the Inflammatory Response in a Mouse Model of Primary Biliary Cirrhosis"). The mean number of citations for all articles was 134.55 ± 111.13 .

3.2 Year of publication

The T100 articles were published between 1983 and 2019. Data is input in the flow diagram (Figure 1). The number of articles published per year had not exceeded five until 2009, but since then it has increased dramatically. The largest number of articles was published in 2009, with a total of 19 articles. The oldest article featured in the T100 articles was published in 1983 by Hamlyn AN, et al. [8] ("Primary biliary cirrhosis: geographical clustering and symptomatic onset seasonality. ").

3.3 Distribution and contribution of global countries and institutions

26 countries in total published researches on PBC, including 17 European countries, three North American countries, five Asian countries, and Australia. The USA, UK, Canada, Japan, and Italy had the highest number of published articles (Figure 2A). The United States contributed the most articles and total citations in the field of PBC, publishing 52 articles and 7095 citations. France ranked nine in the number of articles, but the average number of citations was highest for this nation. Canada published the three most articles, but it had the second-highest average number of citations. Thus, the quality of research in France and Canada was generally high. The average number of citations for the two Asian countries, namely China and Japan, was much lower than those for other countries. The top ten most productive

countries were listed in Table 2 (Supporting Information). Cooperation between countries was an important factor in promoting technological development. Figure 2B presented the cooperative relationships among all countries in this field. We can intuitively observe that the United States, France, Netherlands, Canada, the UK, Australia, and Italy had close cooperation with other countries.

A total of 342 institutions published papers. Table 3 (Supporting Information) revealed the top ten institutions with the most publications. Due to the difficulty, many clinical trials are completed by many different institutions from all over the world. According to the overlay visualization map made by VOSviewer, Univ Calif Davis and Univ Birmingham had the most intense publication density (Figure 3A). The institution with the largest number of papers was led by the of *Univ Calif Davis* the USA (n=34). It is worth noting that the most represented institutions were associated with the highest countries (Figure 3B).

3.4 Analysis of journals of publication

The 100 articles were published in 35 different journals. Although *Hepatology* had a lower impact factor than the *Journal of Hepatology* (17.425 vs 25.083), *Hepatology* published the most papers in the T100 articles and generated the highest number of citations (n = 28; 3397 citations). Journals of 100 articles are listed in Table 4 (Supporting Information) with their impact factors.

3.5 Analysis of authors

809 authors participated in the T100 articles. Gershwin ME, from the USA, has published 32 articles related to PBC, which have been cited 4,007 times. We have compiled the top ten authors' information, which is attached in Table 5 (Supporting Information). Due to the same research finished by multiple authors, we used CiteSpace to analyze co-authorship and citation networks among authors and to reveal the most highly cited researchers and collaboration among researchers (Figure 4).

3.6 Analysis of keywords

Keywords are highly refined research content and important indicator to reflect the research theme and hotspots. We have compiled the top five keywords attached in Table 6 (Supporting Information). The biochemical response was the keyword with the highest amount of publications (n = 24), followed by ursodeoxycholic acid (n =22). The results showed that “cholestasis, biochemical response, autoimmunity” was highly central.

3.7 Article of type analysis

The T100 articles included 32 observational studies, 29 basic research articles, 15 reviews, eight meta-analyses, and 12 clinical trials, and four clinical guidelines. The T100 articles were classified into different research focuses: pathogenesis (41%), treatment (20%), prognosis (12%), epidemiology (9%), diagnosis (8%) and others (10%) (Figure 5A). Moreover, figure 5B showed the topical distribution of the T100 articles by 5-year periods from 1983 to 2020 (the first period is extended to 1983-2005 due to too

little data). After 2006, the proportion of observational studies and basic research studies increased dramatically. Although clinical research articles comprised approximately half of the T100 articles, the mean number of citations was significantly higher for review articles than for other article types. Of all the 52 clinical studies, observational research occupied an overwhelming share (63.46%), to which the authors from the US, and the UK made the main contributions. Although the number of RCTs was minor, all were published by American researchers.

4. Discussion

The bibliometric analysis identifies the most influential articles in the field during the past several decades, highlights contributions that have led to significant advances, and reveals current trends in the field [12]. We ranked these articles by the total number of citations according to the WoSCC database and analyzed the T100 articles in this field. Through the analysis of the most frequently cited articles, we discovered the research hotspots of PBC in recent decades. In addition, we can identify potential future research directions.

From the 1970s to the early 2000s, the number of studies on PBC grew slowly. Over the last 20 years, the amount of research in this field has experienced explosive growth. The number of citations of an article depends partly on when the article was published, as citations accumulate over time [12]. Thus, more than half of the articles in our study were published between 2010 and 2015. These findings are consistent with those of other recent bibliometric analyses. However, several articles with high citation density published in recent five years, which made them accumulate relatively low total citations due to less time, such as Nevens, F et al. [24] (2016), and Corpechot, C et al. [7] (2018). The high interest of these researches suggested the promising academic influence in the foreseeable future.

Some bibliometric studies have reported that journals with high impact factors, such as NEJM or Nature, were the leading journals within their respective fields [29]. However, we found that *Hepatology* and *Journal of Hepatology* were the most productive journals, despite their relatively low impact factors. Indeed, they published 28 and 8 articles in the T100 articles, respectively. This result highlights a growing trend in which highly influential articles are published in specialized journals, and are not limited to the most well-known general medical journals [12].

One-third of the T100 articles were basic science (n = 29), showing the significant role of basic science to PBC in the last decade. The main body of basic science is to explore pathogenesis and optimize the treatment [30]. Although the insight into pathogenetic aspects of PBC has grown enormously during the recent decade and numerous genetic, environmental, and infectious factors have been disclosed which may contribute to the development of PBC, the precise pathogenesis remains enigmatic [19]. In 29 basic studies, a total of 14 articles studied the susceptibility sites of PBC. The genome-wide association studies (GWAS) have identified multiple genes influencing the susceptibility to PBC in HLA and non-HLA loci [18]. Among them, IL-7, 13q14, and IL-12 are star loci [14, 17, 33]. Multiple of these PBC risk loci were also shared risk loci in other autoimmune diseases [28]. The existence of shared autoimmunity susceptibility

loci could contribute to the frequent appearance of additional autoimmune diseases in individuals with PBC and their families [10]. Therefore, whether it is now or in the future, the exploration of new autoimmunity susceptibility loci has always been the focus of mechanism research of PBC.

In recent years, the role of therapy in the management of PBC has considerably increased. In 100 records, an analysis of the research focuses revealed that 20% were related to therapy. Among the T100 articles, therapy was the hot topic (n=20). UDCA is currently the only FDA-approved medical treatment for PBC [11]. However, about a third of patients are not sufficiently controlled with UDCA monotherapy, which drives the search for additional therapeutic approaches [5]. Of the 20 articles on treatment, 15 described second-line treatment for PBC. Two RCTs, one on obeticholic acid (OCA) [24] and the other on bezafibrate [7] were published in top journals (NEJM) and generated high citation rates. National Institute for Health and Care Excellence (NICE) has appraised OCA and recommended OCA within its marketing authorization as an option for treating PBC in combination with UDCA for people whose disease has responded inadequately to UDCA or as monotherapy for those who cannot tolerate UDCA [9]. In addition, Corpechot C et al. [7] found that in patients with primary biliary cholangitis who had had an inadequate response to ursodeoxycholic acid, add-on therapy with bezafibrate for 24 months resulted in a higher rate of complete biochemical response than ursodeoxycholic acid therapy plus placebo. Rituximab, an anti-CD20 monoclonal antibody, selective B-cell depletion with rituximab was safe and associated with a significant decrease in autoantibody production, but had limited biochemical efficacy in PBC patients with an incomplete response to UDCA [23], it can even worsen the severity of IBD patients [20].

PBC is primarily a biliary disease, so when signs of failure of hepatocyte function develop, such as coagulopathy or jaundice, these usually indicate advanced and typically irreversible disease [9]. Therefore, all PBC patients should receive lifelong follow-up and need to make risk predictions. If necessary, they also need to add second-line treatment. In the T100 articles, many studies (n=10) have assessed the prognostic significance of biochemical data collected following UDCA treatment. More risk scores and prognosis models for predicting the prognosis of PBC patients have been developed [3, 16]. Survival of those with advanced PBC with biochemical response to UDCA is significantly better than for nonresponders. Prognostic information, based on bilirubin and albumin levels, is superior to that provided by alkaline phosphatase (ALP) levels [15]. Early-stage patients who show ALP and aspartate transaminase (AST) $\leq 1.5\times$ upper limit of normal, and normal bilirubin level after 1 year of treatment appear to be at very low or no risk of liver failure or progression to cirrhosis [6].

In conclusion, this report presents major advances and changes in research regarding PBC. The single treatment method entered a bottleneck period, and combined treatment with immunosuppressant, local therapy, and surgery will become the next research focus to identify possible beneficial treatment combinations.

Declarations

Author Contributions

Hongbin Chen, Yu Zhao and Zhenjie Yin designed the study. Yu Zhao and Zhenjie Yin conducted the literature search and analyzed the data. Yu Zhao drafted the manuscript. Huang Du and Kangming Huang drew the pictures. Zhenjie Yin and Fajing Zhang prepared the tables. Hongbin Chen and Yu Zhao reviewed and revised the manuscript. All authors contributed to the article and approved the submitted version.

Data Availability

Our data are from the analysis of articles and can be provided when necessary.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Human or animal rights statement

This article does not contain any studies with human or animal subjects.

Compliance with ethical standards

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Figures

Figure 1

Distribution of the 100 top-cited articles per year.

Figure 2

Figure 3

(A) Heat map of publications in the institutions. (B) The co-authorship among the 100 highly cited institutions.

Figure 4

The co-authorship among the top 100 highly cited authors.

Figure 5

(A) The classification of the main points in the content of the T100 articles. (B) Publication trends for specific article types stratified by 5-year intervals from 1983 to 2015.

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