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

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Abstract

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. 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. 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. The 100 top-cited articles are marked with the leading countries, institutions, journals, hotspots, and development trends in the PBC field that could provide the foundation for further investigations.

Keywords Bibliometric · Primary biliary cholangitis · Primary biliary cirrhosis · Citation analysis

Introduction

Primary biliary cholangitis (PBC) was formerly known as primary biliary cirrhosis [1], first described by Addison and Gull in 1851 and Hanot in 1876 [2]. 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 [3, 4]. 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 [5]. 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 [6].

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
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 [8].

Multiple medical fields have used a rank list to determine the impact of articles and journals within their specialty [9]. Robert et al. [10] 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.

Methods

Data source and search strategy

Relevant articles were extracted from the Web of Science Core Collection (WoSCC) Database (Clarivate Analysis, Boston, USA) [11]. Because this research did not involve intervention or data collection in animal experiments or clinical trials, approval from an ethical committee was not required. 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.

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 do 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.

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 [12].

Statistical analysis was performed using the IBM SPSS version 25.0 software (IBM Corp., Armonk, NY, USA). The suitability of the data to normal distribution was checked using the Shapiro–Wilk–Francia test. The Pearson and Spearman’s rho test was used to examine the correlations among variables. A p value of < 0.05 was considered statistically significant with 95% confidence interval (CI).

Results

Citation range

A total of 6818 articles were extracted from WoSCC Database. The T100 articles are listed in Table 1 (Supporting Information). The citation count of articles ranged from 60 to 900 (total number of citations, 13,455). The number of citations ranged from 900 for Lindor et al. [13] (“Primary Biliary Cirrhosis”) to 60 for Moritoki et al. [14] (“B Cells Suppress the Inflammatory Response in a Mouse Model of Primary Biliary Cirrhosis”). The mean number of citations for all articles was $134.55 \pm 111.13$.

Year of publication

The T100 articles were published between 1983 and 2019. Data are input in the flow diagram (Fig. 1A). 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 et al. [15] (“Primary biliary cirrhosis: geographical clustering and symptomatic onset seasonality.”). We observed a strong negative association between the citation score and Year of publication (Fig. 1B, $r = -0.848$, $p < 0.001$).

**Distribution and contribution of global countries and institutions**

A total of 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 (Fig. 2A). The USA 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 are listed in Table 2 (Supporting Information). Cooperation between countries was an important factor in promoting technological development. Figure 2B presents the cooperative relationships among all countries in this field. We can intuitively observe that the USA, 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) reveals the top ten institutions with the most publications. Due to the difficulty, many clinical trials are completed by many different institutions worldwide. According to the overlay visualization map made by VOSviewer, Univ Calif Davis and Univ Birmingham had the most intense publication density (Fig. 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 (Fig. 3B).

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. There was no statistically significant relationship between the impact factor and the number of articles, and the number of citations (p = 0.870, and p = 1.000, respectively). However, there was a strong positive correlation (r = 0.975) between the number of articles in a journal and the number of citations, which was statistically significant (p < 0.05).

Analysis of authors

A total of 809 authors participated in the T100 articles. Gerzshwin 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 (Fig. 4).

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 number of publications (n = 24), followed by ursodeoxycholic acid (n = 22). The results showed that “cholestasis, biochemical response, autoimmune” was highly central.

Article of type analysis

The T100 articles included 32 observational studies, 29 basic research articles, 15 reviews, eight meta-analyses, 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%) (Fig. 5A). Moreover, Fig. 5B shows 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 USA and the UK made the main contributions. Although the
number of RCTs was minor, all were published by American researchers.

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 [16]. 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 [16]. 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 et al. [17], and Corpechot et al. [18]. The high interest of these researches suggested the promising academic influence in the foreseeable future.

In the T100 list, the article with the highest citation count was published in Hepatology (2009) by Lindor et al. [13]. The article received a total of 900 citations count. The
authors have comprehensively reviewed PBC from epidemiology, pathogenesis, clinical manifestations, diagnosis, treatment, prevention, and management perspectives. It is not surprising that a landmark article such as this, published in a high-impact journal, was the most cited article on PBC. This study has been pivotal in subsequent management and research strategies for the disease. In fact, several other articles in the top 100 have cited this study as well.

Some bibliometric studies have reported that journals with high impact factors, such as NEJM or Nature, were the leading journals within their respective fields [19]. 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 [16].

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 [20]. PBC is a typical autoimmune disease with a T-cell signature, characterized by an HLA-DR associated loss of immune tolerance to a crucial enzyme of oxidative phosphorylation, the E2 component of the pyruvate dehydrogenase complex (PDC-E2) [21]. T helper (CD4) T-cell antigen receptor-ab and CD8 T cells are most commonly seen in portal tracts, in particular around damaged bile ducts in the liver tissue of PBC patients, strongly suggesting the involvement of cellular immune mechanisms in biliary damage [22]. 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 PBC susceptibility in HLA and non-HLA loci [23]. Among them, IL-7, 13q14, and IL-12 are star loci [24–26]. Multiple of these PBC risk loci were also shared risk loci in other autoimmune diseases [27]. The existence of shared autoimmune susceptibility loci could contribute to the frequent appearance of additional autoimmune diseases in individuals with PBC and their families [28]. Although it is almost certain that PBC susceptibility is conferred by an unknown genetic factor(s), gene alteration is not sufficient to trigger the disease. Exposure to certain environmental factor(s), even not harmful per se, could result in immune tolerance breakdown and is therefore necessary for PBC onset [29]. Prince et al. [30] confirmed that among environmental risk factors, smoking and the use of some cosmetics as well as urinary infections appear important. Although the insight into pathogenetic aspects of PBC has grown enormously during the recent decade, the precise pathogenesis remains enigmatic [13]. Therefore, whether it is now or in the future, exploring the initiating factors that trigger the autoimmune response of the intrahepatic bile duct epithelium, search for new therapeutic targets has always been the focus of mechanism research of PBC.

There is a wide range in incidence and prevalence rates for PBC in Europe, North America, Asia, and Australia. The highest incidence rates to date have been found in USA and UK (40.2 per 100,000 and 32 per 100,000, respectively); the prevalence rate in the Chinese population was almost twice as high as in the Malay population (4.1 per 100,000 and 2.3 per 100,000, respectively) [31]. Its prevalence is 100 times higher in first-degree relatives than in the general population [32], pointing toward possible geographic or genetic risk factors. Improvement in diagnostic tools, increasing disease awareness, and digitalized patient registration likely contributed to the rising incidence and prevalence rates.

The diagnosis of PBC is based on three widely accepted criteria [33]: biochemical signs of cholestasis (elevated levels of serum alkaline phosphatase and gamma-glutamyl transpeptidase), diagnostic histological features, and presence of disease-specific autoantibodies, particularly against mitochondrial antigens. 1965, antimitochondrial antibodies (AMA) were identified as the most important serological marker for PBC [34]. AMAs are present in about 95% of PBC cases, with a disease specificity close to 100% [29]. Retrospective analysis of PBC who were diagnosed clinically and histologically, Li et al. [35] found that 76% of Chinese patients with PBC were positive for serum AMA. Invernizzi et al. [36] detected that the positive of Italian patients is 92%, and Witt-Sullivan et al. [37] detected that the positive of Canadian patients is 91.6%. These studies revealed differences in the positive rate of diagnosis between countries, particularly between China and Italy (76% VS 92%, p = 0.002). The presence of specific anti-nuclear antibodies (ANAs) or anti-centromere antibodies (ACA) (or anti-gp210 or sp-100 by ELISA) can frequently be sufficient to diagnose AMA-negative PBC. A meta-analysis by Zhang et al. [38] indicated no significant differences in the pooled sensitivities and specificities in various ethnicities among the total ANAs (23% vs. 28% and 97% vs. 99%). However, the sensitivities of anti-gp210 exhibited 31% (95% CI: 16%, 50%) in the Asian group and 18% (95% CI 9%, 33%) in the Caucasian group. On the contrary, anti-sp100 appeared to possess a sensitivity of 20% (95% CI 6%, 44%) in the Asian group and 30% (95% CI 16%, 50%) in the Caucasian group. It is of interest to note that among female patients with urinary tract infections but no liver disease, 80% is AMA-positive. Among PBC patients, about 74% of patients with urinary tract infections were positive for anti-sp100, whereas the positivity was only 4.8% in PBC patients without urinary tract infections [39]. These findings support the hypothesis that some infections such as Escherichia coli are involved in the induction of PBC-specific autoimmunity [40]. The true autoantibody-negative disease exists and can only be
diagnosed on biopsy [4]. Histologically, PBC is characterized by non-suppurative cholangitis and the destruction of the small intrahepatic bile ducts. Although liver histology can be used for prognostication, non-invasive risk assessment is usually preferred [41].

Common clinical symptoms of PBC include fatigue, pruritus, weakness, daytime sleepiness, loss of weight, upper abdominal discomfort, osteodystrophy, osteoporosis, cholelithiasis, and extrahepatic manifestations of an autoimmune nature, although roughly 50% of PBC patients are asymptomatic at diagnosis [42]. Fatigue and/or pruritus at onset identify a subset of patients who preferentially are women, younger, with particularly active illness, a suboptimal response to UDCA therapy [43]. A comparative study of three independent international PBC cohorts by Hegade et al. [44] suggests 70% UK, 68% USA, and 60% Italy patients had experienced itch at some point in their illness. Of these, persistent itch was reported by 32% (UK), 34% (USA), and 27% (Italy) patients and severe itch by 15% of UK & USA and 13% of Italy patients. Treatment of itch in PBC patients appeared unsatisfactory in all three cohorts as more than half of patients with severe itch had not received the first-line therapy. Compared to asymptomatic PBC patients without pruritus, symptomatic PBC patients with pruritus more frequently suffer from hepatic cirrhosis and its related complications \( (p = 0.004) \) [43]. Fatigue is the symptom with the greatest apparent impact on the quality of life of PBC patients. Newton et al. [45] found that 60% PBC patients described moderate or severe fatigue in the UK. Gu et al. [46] detected that 72.4% of Chinese patients with PBC had experienced fatigue. Al-Harthy et al. [47] reported that fatigue was noted in 48% Canadian PBC patients. It is associated with excessive daytime sleepiness and autonomic dysfunction. There is currently no specific treatment for fatigue [48].

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. UDCA is currently the only FDA-approved medical treatment for PBC [49]. However, about a third of patients are not sufficiently controlled with UDCA monotherapy, which drives the search for additional therapeutic approaches [50]. Of the 20 articles on treatment, 15 described second-line treatment for PBC. Two RCTs, one on obeticholic acid (OCA) [17] and the other on bezafibrate [18], 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 [4]. In addition, Corpechot et al. [18] 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 [51]; it can even worsen the severity of IBD patients [52].

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 [4]. 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 [53, 54]. Survival of those with advanced PBC with biochemical response to UDCA is significantly better than for non-responders. Prognostic information, based on bilirubin and albumin levels, is superior to that provided by alkaline phosphatase (ALP) levels [55]. 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 [56].

This study has several limitations. First, we performed our search using only the WoSCC database. Second, owing to the exponential increase in the number of studies, the list of the top cited articles is expected to change over time. Lastly, citation count is only an indirect measure of scientific impact and may be influenced by other factors, such as journal accessibility and reputation.

In conclusion, this paper summarized the current findings from the analysis of the top 100 cited articles in PBC field. It is the first global look at the history and current situation of PBC research to assess the performances of leading countries/territories and institutes and research hotspots of this disease. The study described the epidemiological, genetic, immunological, diagnostic, and therapeutic aspects of PBC. Although the research of PBC has made some progress in recent years, the field still faces many problems and challenges. Exploring new treatment targets for the key pathogenesis of PBC, thereby providing theoretical basis and experimental basis for new drug research and development, is still facing many problems. The ultimate challenge for physicians is reducing UDCA non-responders and recurrent PBC after liver transplantation.
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Author contributions HC, YZ, and ZY designed the study. YZ and ZY conducted the literature search and analyzed the data. YZ drafted the manuscript. HD and KH drew the pictures. YZ and FZ prepared the tables. HC and YZ reviewed and revised the manuscript. All authors contributed to the article and approved the submitted version.

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Declarations

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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