

Global Scientific in Hepatocellular Carcinoma: A Scientometric Analysis

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ABSTRACT

Background: Hepatocellular Carcinoma (HCC), the predominant primary histological subtype of liver malignancy, arises in the context of chronic liver disease. This study aims to construct a scientific map, conduct structural analysis, examine evolutionary trends, and identify emerging trends in the corpus of published research on HCC. **Methodology:** This descriptive survey employs scientometric analysis, using bibliographic records obtained from the Web of Science (WOS) to recognize the core documents central to research topics in the field. **Results:** A total of 98,310 documents, all of which exclusively consist of journal articles, were extracted. Key words frequently associated with hepatocellular carcinoma include "hepatocellular carcinoma," "cirrhosis," "survival," and "management." **Conclusion:** The results of the present study establish a framework delineating the evolution of key research themes in HCC over time, illustrating how researchers have responded to various milestones in its development. Identifying the most efficient methods, with the least prescribed dose yet the most therapeutic impact, remains of paramount importance.

Keywords: Co-word, Hepatocellular carcinoma, Machine Learning, Scientometrics.

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Received: 17-03-2025;

Revised: 08-05-2025;

Accepted: 21-07-2025.

INTRODUCTION

Hepatocellular Carcinoma (HCC), the most prevalent primary histological type of liver malignancy, emerges within the context of chronic liver disease.^[1,2] Recent epidemiological estimates position HCC as the seventh most common cancer globally and the fourth leading cause of cancer-related mortality, particularly prevalent in developing countries.^[3,4] The global burden of hepatocellular carcinoma has witnessed a substantial 40% increase in the incidence of Hepatitis B Virus (HBV)-related HCC from 1990 to 2015.^[5] While potential risk factors, such as chronic hepatitis C infection, cirrhosis, alcohol consumption, fatty liver disease, autoimmune hepatitis, and hemochromatosis, have been implicated in HCC development, further studies are

essential to unravel the impact of factors related to HCC on its initiation and progression.^[6]

HBV, an enveloped DNA virus classified within the Hepadnaviridae family, possesses a genome characterized by double-stranded circular DNA (rcDNA). The pivotal components of its genome comprise four primary genes (C, S, X, and P), with the Hepatitis B X protein (HBx) assuming a crucial role in the virus's tumorigenicity.^[7] This viral agent is accountable for both acute and chronic infections, with a pronounced prevalence of chronic cases globally, affecting nearly 300 million individuals.^[8]

The worldwide repercussions of HBV infection are severe, contributing to a substantial number of deaths annually, exceeding 800,000. These fatalities primarily result from the development of primary liver cancer and cirrhosis. Alarming statistics underscore a significant surge of 42% in liver cancer-related deaths from 1990 to 2015.^[1] This trend necessitates heightened awareness and attention to various aspects of liver cancer, emphasizing the imperative for comprehensive strategies to mitigate the impact of HBV on global health.



DOI: 10.5530/jscires.20251168

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Scientometrics, defined as the "quantitative study of science, communication in science, and science policy".^[9,10] constitutes a scientific analysis designed to explore literature within a specific field and establish connections among various topics.^[11,12] The experimental unit of analysis in scientometrics is text, focusing on text through techniques such as text mining and information mapping.^[10,13] It serves as a tool to assess the evolutionary transformation of scientific achievements and developments across diverse fields, ranging from basic sciences like biology or chemistry to clinical studies such as cognition or neurology.^[14] Depending on the unit of analysis, scientometrics employs various techniques, and one extensively applied method is co-word analysis. Co-word analysis is employed to depict the status of various subject areas by assessing the co-occurrence of keywords in titles, abstracts, or manuscripts of articles.^[15,16] An analysis of the keywords used in articles within a specific field reveals the actual content and themes highlighted in that field.^[17] Following science mapping, social network analysis, along with co-word analysis, helps analyze thematic fields by creating maps based on degree centrality, closeness centrality, and betweenness centrality-fundamental aspects of social network analysis. In this study, these maps facilitate the identification of primary, secondary, and emerging themes in the research data.^[18] Mapping in medicine, using electronic health record data, allows physicians to identify hidden patterns and health trends, which can help improve patient care. Additionally, employing machine learning techniques on this data can provide accurate predictions of future healthcare service needs and optimize resource allocation.^[19]

This study provides a visual representation of the key concepts and their relationships, allowing researchers to quickly identify the main areas of focus and understand the structure and connections within the research field. The motivation for this research is to develop effective tools for analyzing and synthesizing large amounts of research data. By creating these thematic maps, researchers can gain a deeper understanding of the research landscape, uncover hidden patterns and connections, and more efficiently identify important trends and areas for further investigation. This can ultimately lead to more informed decision-making and the advancement of knowledge in the field. We employ data mining techniques to efficiently manage and analyze clinical data, transforming operational databases into a structured data warehouse. This approach enhances decision-making and disease prediction through comprehensive data analysis.^[20]

These studies in the field of machine learning emphasize that the application of these methods significantly improves disease diagnosis, drug development, and personalized treatments. Machine learning can aid in identifying complex patterns and predicting treatment outcomes by analyzing vast electronic data, allowing physicians to provide more accurate diagnoses and design treatment plans tailored to the specific needs of

patients. Additionally, these techniques play a role in optimizing administrative processes and increasing the efficiency of healthcare systems, ultimately leading to improved health outcomes and reduced costs.

LITERATURE REVIEW

In the study conducted by Farooqui *et al.* revealed Healthcare systems and policies are crucial in shaping the provision, utilization, and outcomes of health services, particularly in the context of India's rapid urbanization, which has altered lifestyles and health needs. The integration of machine learning techniques into healthcare is transforming service delivery by leveraging Electronic Health Records (EHRs) for enhanced health risk prediction. This chapter outlines the Indian public healthcare framework, examining past health initiatives while highlighting how machine learning can address deficiencies in health resources, ultimately aiming to improve health outcomes for underserved populations in India.^[19]

Yumnam Gyanajeet *et al.*, (2023) conducted a comprehensive analysis of over 26,000 documents to explore publication trends among leading universities in India. Their findings showed a notable increase in research output, particularly from the University of Delhi. The study emphasized that articles with multiple authors received more citations, underscoring the value of collaborative research. It also highlighted the growing international collaborations between Indian universities and institutions in the U.S., South Korea, and Germany.^[21]

In this research was revealed that the classification of brain tumors is essential for precise diagnosis and treatment. This paper proposes a method that utilizes an ensemble of deep features and machine learning classifiers for this purpose. Automated anomaly detection in clinical imaging, particularly through Magnetic Resonance Imaging (MRI), is crucial for identifying tumors without the lengthy verification process by doctors. Traditional methods are time-consuming and can delay necessary treatment, highlighting the need for automated classification to improve survival rates. Various machine learning techniques are being explored to enhance the accuracy of brain tumor classification. The inherent diversity of brain tumors complicates MRI analysis, but ensemble machine learning models can effectively detect and classify tumor cells. Experimental results indicate that the Random Forest ensemble model outperforms other algorithms like Support Vector Machines (SVM), decision trees, and gradient boosting, especially with larger datasets.^[22]

Another study shows that Early diagnosis of brain tumors is a challenging task for radiologists, as untreated patients often have a survival rate of less than six months. This study focuses on automating the detection of brain tumors using MRI data and advanced learning techniques. Convolutional Neural Networks (CNNs) have shown significant promise in visual feature extraction, allowing for more effective classification

of tumor patients versus healthy individuals.^[22] The research employs deep CNNs to extract comprehensive features for model training, enhancing classification accuracy between tumor and non-tumor cases. Additionally, the study explores five machine learning methods and proposes an ensemble model combining Extreme Gradient Boosting, Ada-Boost, and Random Forest (XG-Ada-RF) to improve binary classification of brain tumors in images. The ensemble approach achieved high accuracy rates of 95.9% for tumor detection and 94.9% for normal cases, outperforming individual methods and demonstrating the potential of automated systems in clinical settings.^[23]

Farooqui and Mehra reported the application of three machine learning techniques-Decision Tree, Support Vector Machine, and Random Forest-for the early diagnosis of breast cancer. The goal is to reduce waiting times and minimize diagnostic errors. By creating a breast cancer prediction model that evaluates risk levels, we aim to improve early detection and treatment options, ultimately assisting healthcare providers and patients in effectively managing this critical disease.^[24]

The study conducted by Hood and Wilson, endeavors that not only enhance our comprehension of the scientific domain but also provide essential insights for policymakers, finding bodies, and educational establishments for effectively distribute resources and promote collaborative initiatives that can drive significant progress across divers research domains. This particular study conducts an exhaustive examination of the literature pertaining to HCC with the spheres of medical sciences, economics, and business, complemented by a through bibliometric analysis. The main objective is to critically evaluate the current body of literature and identify prominent countries, authors, affiliations, and scientometrics aspects related to HCC, a concept pioneered by Eugene Garfield in the 1960s.^[25]

Furthermore, the study aims to delineate research streams and thematic trends within the HCC literature in the medical sciences domain spanning the period from 1961 to 2020. These thematic insights have the potential to steer policymakers, academics, and researches towards future research trajectories and offer solutions to contemporary challenges. Employing a quantitative methodology, this research conducts a methodical review of written publications, with the integration of bibliometric analysis enhancing transparency, organization, and reproducibility in the review process. By utilizing the 'biblioshiny' web-based interface of the R-package 'bibliometrixs 3.0' for bibliometric analysis, the study ensures an important mapping of research fields and influential works, devoid of subjective biases, thereby contributing to more comprehension of the literature.^[26]

The necessity of this research stems from the increasing prevalence and complexity of Hepatocellular Carcinoma (HCC), which significantly affects public health and patient outcomes. By constructing a scientific map and conducting a structural analysis

of published literature, this study aims to elucidate the evolution of research themes related to HCC. Understanding these trends is crucial for identifying effective treatment strategies and improving patient management. Furthermore, with the rise in global mortality rates associated with HCC, particularly due to chronic liver diseases like cirrhosis, there is an urgent need for comprehensive insights into the current state of research. This analysis will not only inform clinicians and researchers but also guide policymakers in resource allocation and strategic planning for HCC management. Ultimately, the findings will contribute to enhancing therapeutic approaches and improving survival rates for patients affected by this malignancy.

OBJECTIVES

The main objectives of this study are to construct a scientific map, conduct structural analysis, explore the evolutionary trajectory, and identify emerging trends in the research on Hepatocellular Carcinoma (HCC). Constructing a scientific map will visually represent the relationships among key topics, authors, and institutions, highlighting influential papers and collaborative networks within the field. Structural analysis will examine the organization of existing literature to understand how studies are interconnected and identify foundational works that have shaped current knowledge. Exploring the evolutionary trajectory will reveal how research themes and methodologies have shifted over time, providing insights into advancements in treatment and diagnosis. Finally, identifying emerging trends will help anticipate future research directions and clinical applications, guiding subsequent investigations and informing evidence-based practices. Together, these objectives aim to enhance our understanding of HCC research dynamics and support impactful developments in clinical settings.

METHODOLOGY

The present study is a descriptive survey conducted through scientometric analysis. This analytical method is employed to amalgamate information within a specified field, with a focus on utilizing quantitative analysis and statistical measures to characterize publication patterns. Bibliographic records were systematically gathered from the Web of Science (WOS) to discern the core documents that encapsulate research topics pertinent to the field under investigation. Notably, the core collection of WOS articles encompasses information from titles, abstracts, and keywords (TS). The novelty of this research lies in its comprehensive approach to understanding Hepatocellular Carcinoma (HCC) through scientometric analysis, which combines the construction of a scientific map with structural analysis and the exploration of evolutionary trends in published literature. This multifaceted methodology allows for a detailed examination of how research themes in HCC have developed over time, revealing not only historical milestones but also emerging trends that may shape future studies and clinical practices.

Data collection

The data collection process for this study includes several steps:

Article Search (2009-2023)

Conduct a systematic search for articles published between 2009 and 2023 across multiple databases, including PubMed, Scopus, and Web of Science (WoS), using predefined keywords relevant to the research focus.

Search Strategy Development

Formulate a comprehensive search strategy by querying titles, abstracts, and keywords utilizing Medical Subject Headings (MeSH) and Emtree databases. Extract the resulting data into a plain text file for further analysis.

Search Terms

The search strategy encompassed specific terms related to HCC, including variations such as "Hepatocellular Carcinoma" OR "Adult Liver Cancer" OR "Liver Cell Carcinoma" OR "Hepatoma."

Inclusion criteria

The inclusion criteria for article selection encompassed a range of document types, specifically Original Articles, Letters, Early Access, Editorial Material, Correction, and Meeting Abstracts. These types of documents were selected because of their relevance and potential contribution to the identified topic.

Exclusion criteria

Some types of documents and their content were excluded from the review based on the defined criteria. Conference abstracts, books, and articles unrelated to the designated topic were purposefully omitted from the selection process (Figure 1).

Machine Learning Implementation

Apply machine learning techniques to identify patterns and relationships within the bibliometric data. Use algorithms

suitable for classification or clustering tasks to analyze citation counts, author affiliations, and keyword frequency.

Bibliometric analysis

In the context of this study, a combination of bibliometric analysis and machine learning techniques was employed to assess the distribution of various factors. The bibliometrix R package served as the primary tool for implementing this methodology. The selected variables for analysis included citation information such as author(s), document title, year, source title, volume, issue, pages, citation count, source and document type, bibliographical information, affiliations, editor(s), keywords, and funding details, including the number, acronym, and sponsor.^[26]

The bibliometric data underwent a thorough analysis using the Bibliometrix Biblioshiny R-package software, accessible at <https://bibliometrix.org/Biblioshiny.html>.^[26] Leveraging the R-Tool, an open-source instrument renowned for its prowess and flexibility in statistical analysis, the data were visualized, identified, and explained. The analysis focused on the following aspects: a. Annual Scientific Output and Year of Publication, b. Sources and Documents from the Field, c. Authors and Institutions in the Field, d. Countries Contributing to Publication, and e. Keywords, Topics, and Themes.

RESULTS

A total of 98,310 documents were meticulously extracted for examination, consisting exclusively of journal articles. This comprehensive collection represents a significant body of academic literature, providing a diverse array of research findings and insights across various disciplines.

Figure 2 section C illustrates the annual production trends, revealing a limited output initially, which gradually increases over time, especially notable from 2020 to 2021.

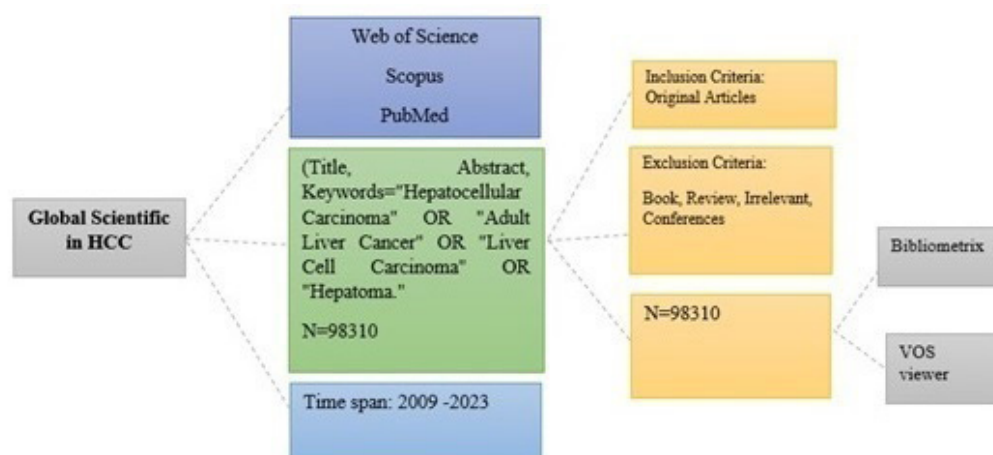


Figure 1: Study flowchart.

Beyond tracking annual production and article citations per year, it becomes imperative to delve into the main topics, geographical distribution, and affiliations associated with HCC publications.

Figure 2 section A encapsulates this comprehensive analysis, presenting a three-fold breakdown. On the left side, keywords and their prevalence are highlighted, while affiliations take center stage on the right. The middle section focuses on the countries contributing significantly to HCC research.

A discernible pattern emerges, with China prominently collaborating with leading affiliations in research related to hepatocellular carcinoma outbreaks. Moreover, Japan, the United States of America, Korea, and Italy emerge as noteworthy contributors, particularly in the realm of medical science topics related to HCC. The overarching theme indicates that issues pertaining to HCC attract widespread study and research attention across various countries.

Main authors, affiliation, institutions, and countries

In the domain of medical sciences within HCC literature, this section sheds light on key figures, including main authors, affiliations, institutions, and countries actively contributing to the field. Tables 1 and 2 highlights the top ten authors who wield a substantial impact on HCC literature, with their ranking determined by the *h*-index. The *h*-index serves as a quantitative measure of an author's scientific impact and provides valuable insights into their impact and contributions to this specialized area of research.

As depicted in Table 2, the United States of America, Japan, and China emerge as the leading contributors in the field of HCC

literature, holding the highest ranks concerning the average number of citations. Figure 3 section B highlights the most relevant affiliations in the field of HCC literature, with the University of Ministry of Education of the People's Republic of China securing the top position. This university has evidently served as a robust foundation for research on hepatocellular carcinoma, emphasizing its significant role and contributions within this domain.

CORE WORDS

Table 3 presents the most frequently used words in the field of medical sciences within hepatocellular carcinoma literature, showcasing an array of keywords and their prevalence.

Throughout the various sections, "hepatocellular carcinoma" stands out as the most prevalent term. The field of medical sciences is intricately linked to keywords like sorafenib, metastasis, and radiofrequency ablation, as evident in the keyword analysis. These keywords are notably associated with hepatocellular carcinoma, forming a crucial part of the literature.

Figure 3 section A illustrates a word cloud generated from keyword plus, wherein words with higher frequency appear larger. Notably, terms such as apoptosis, prognosis, and hepatitis B virus emerge prominently, reflecting their high frequency in the medical sciences literature on hepatocellular carcinoma. Apoptosis and prognosis, in particular, hold significant importance, with the latter having a notable historical context in China and Japan. The literature distinctly emphasizes medical sciences, leading to a wealth of research on societal aspects. Many studies delve into the association of hepatocellular carcinoma

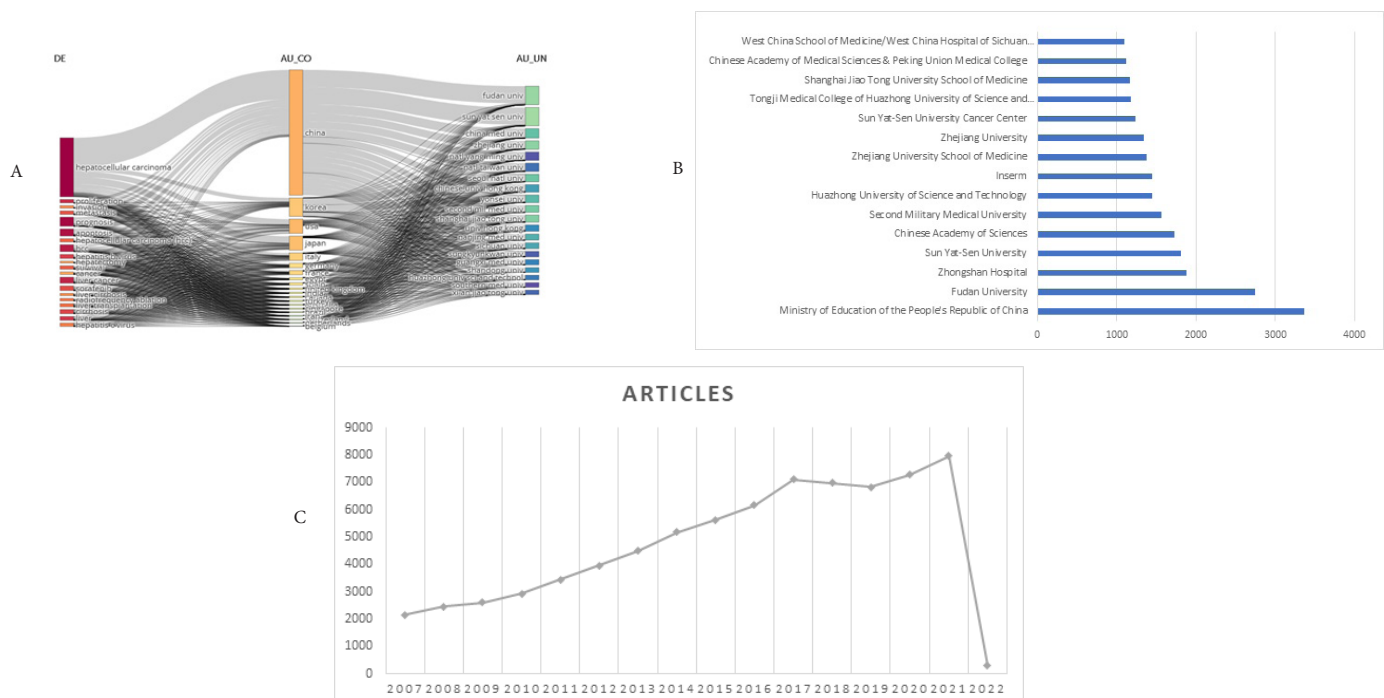


Figure 2: Annual scientific production per year, Three fields analysis, the most relevant affiliation in HCC.

with survival, genetics, therapy, and related themes, underlining the multifaceted exploration within this domain. As evident in the topic dendrogram, the intellectual structure of knowledge in research on liver cancer and relevant measurement fields is delineated into two major clusters. The larger cluster encompasses 36 subjects, while the smaller one comprises 14 subjects, as depicted in Figure 3 section B.

Figure 4 section A, generated using the 'biblioshiny' feature of the R-package 'bibliometrix,' illustrates the co-occurrence network of keywords within the HCC literature in medical sciences. This network reveals a division into three distinct streams. The green cluster takes a central position with high centrality, while the blue and red clusters exhibit interconnected themes. Notably, HCC itself holds the highest centrality.

Each group within this network signifies a division of the HCC literature into various research streams. Survival, therapy, and management emerge as key topics within clinical studies, focusing on the effectiveness of diverse medical and surgical treatments. On the other hand, expression, protein, and gene are prevalent in basic studies that delve into the mechanisms of HCC, aiming to enhance diagnostic and therapeutic strategies.

Thematic map

The thematic map, as depicted in Figure 4 section B, provides a strategic overview of the identified research themes, allowing for a nuanced interpretation of their importance and development.^[27]

This map categorizes themes based on density (y-axis) and centrality (x-axis). Centrality measures the significance of a chosen theme, while density gauges the level of development.

The graph is divided into four quadrants. Themes located in the lower-left part are considered emerging or declining, signifying that they are either new and have the potential to develop further or may be fading from the research area. The lower-right quadrant of thematic map signifies fundamental or cross-cutting themes, characterized by low density yet high centrality. These themes have been the subject of extensive research efforts.

In the upper-left part, themes exhibit high density but lower centrality, indicating that they are highly developed but relatively isolated in terms of research. The upper-right part features themes with both high density and high centrality, signifying their status as developed and essential motor themes.^[27] The size of each theme on the thematic map correlates with the factors associated with that theme, offering a visual representation of the thematic landscape and its intricacies.

In addition to the thematic map, the thematic evolution (Figure 4 section C) provides insights into the historical development of the HCC literature. Utilizing the keywords plus, this visualization traces the evolution of themes over time, illustrating how these themes have progressed. The thematic evolution is generated using 'biblioshiny' and is segmented into three time periods: 2009 to 2014, 2015 to 2018, and 2019 to 2023. These time segments are

Table 1: Important authors based on indicators.

Authors	<i>h_index</i>	<i>g_index</i>	<i>m_index</i>	TC	NP
FAN J	72	123	4.500	20847	432
KUDO M	70	151	4.375	25101	339
WANG Y	65	98		21467	917
ZHOU J	65	108	4.063	17787	523
LLOVET JM	62	98		31970	98
LI Y	61	97	3.813	19320	741
ZHANG Y	61	95		20384	899
LI J	60	86		18451	853
WANG J	60	97		17218	675
WANG L	60	92		16310	663
ZHANG L	59	94	3.688	16410	660
CHAN HLY	57	105	3.563	11514	150
WANG HY	57	99	3.563	12680	312
CHEN Y	56	87	3.500	12809	488
KOKUDO N	54	104	3.375	12142	219
LIU Y	54	87		15730	695
YANG Y	54	96	3.375	14797	507
LI L	53	83		11869	502

As can be seen FANJ is number one on the list of authors with the highest impact.

determined based on subjective judgment, aiming to offer a more nuanced representation of thematic evolution.

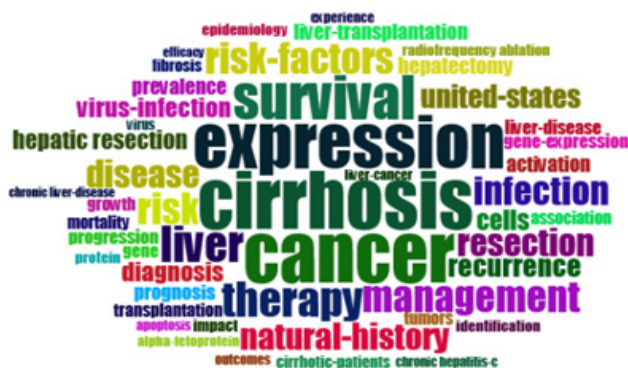
From 2009 to 2014, the literature on HCC primarily focused on themes such as expression, survival, and hepatocellular carcinoma. In the subsequent period from 2015 to 2018, the literature extended its exploration from expression to hepatocellular, survival to nano peptides, and hepatocellular carcinoma to hepatitis B virus. Finally, from 2019 to 2023, the literature continued to delve into themes like hepatocellular carcinoma, survival, and cancer.

Table 2: Important countries based on indicators.

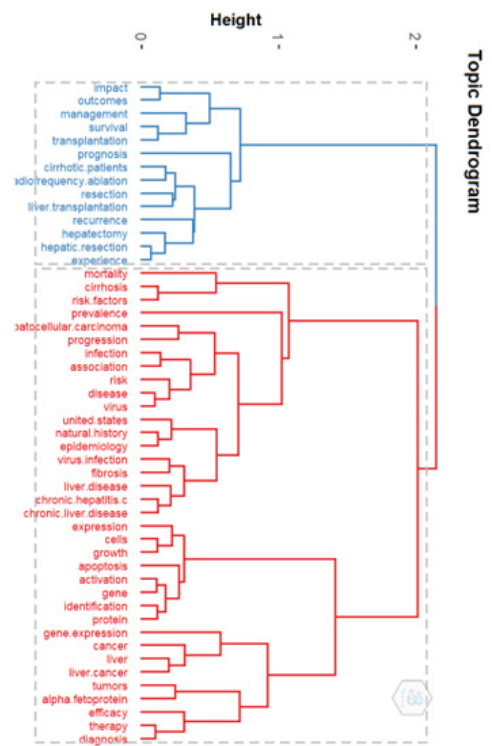
Country	Total citation	Average Article citation
China	676258	19.855
USA	393433	39.561
Japan	169908	21.727
Korea	83904	19.463
Italy	82568	30.445
Germany	72390	29.729
France	63314	39.745
Spain	43328	47.613
United Kingdom	30193	35.190
Switzerland	26117	68.013
Canada	19498	25.963
India	16878	14.651
Singapore	16091	35.133
Egypt	12581	9.891
Australia	11028	21.709
Netherlands	9446	26.459
Sweden	8164	35.190
Austria	7896	27.803
Turkey	7461	10.277
Belgium	7250	26.079

Table 3: The most co-occurrence of keywords.

Row	Keywords	Occurrence
1	Sorafenib	1526
2	Metastasis	1490
3	Radiofrequency Ablation	1152
4	Hepatitis C Virus	1136
5	Invasion	1101
6	Hepatectomy	939
7	Biomarker	926
8	Migration	853
9	Autophagy	701
10	Magnetic resonance imaging	700
11	Transarterial chemoembolization	671
12	Microna	660
13	Immunohistochemistry	622
14	Angiogenesis	615
15	Chronic hepatitis b	600
16	Alpha-fetoprotein	544
17	Epithelial-mesenchymal transition	536
18	Liver resection	527
19	Cell proliferation	522
20	Immunotherapy	478



A



B

Figure 3: The word cloud, the dendrogram of Hepatocellular-Carcinoma.

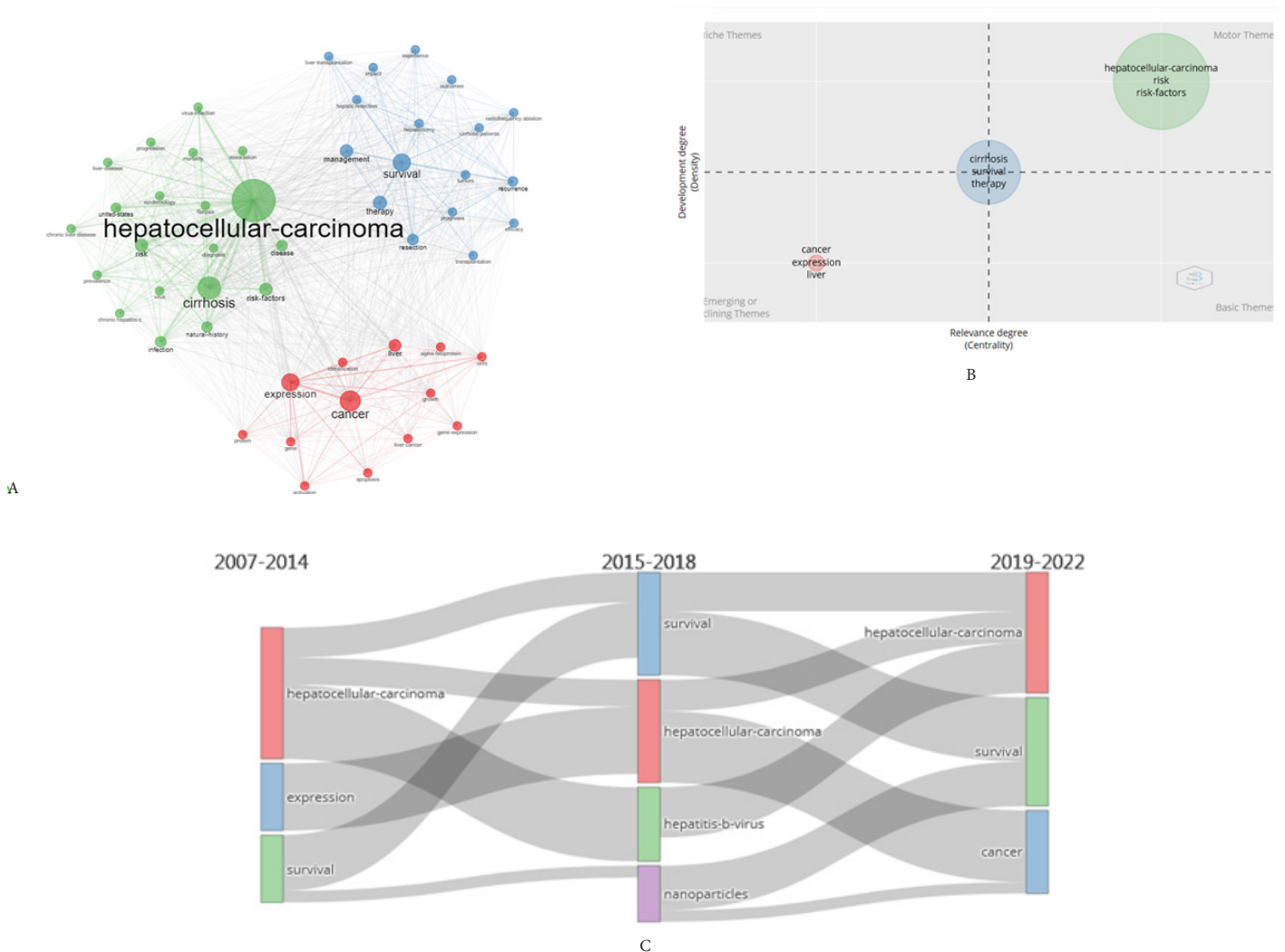


Figure 4: The co-occurrence network, the diagram thematic evolution, the thematic evolution of HCC.

DISCUSSION

This study employed bibliometric and visualization methods to analyze various aspects of published articles related to Hepatocellular Carcinoma (HCC) from 2009 to 2023, focusing on authors, countries, institutions, keywords, key research streams, and themes. During this period, a total of 98,310 articles on HCC were published across 159 scientific journals. The analysis identified a progression of studies over the last 15 years, with varying concentrations in different years. The analysis of Hepatocellular Carcinoma (HCC) research trends from 2009 to 2023 reveals significant insights that can be compared with the findings of Yumnam Gyanajeet *et al.*, (2023), who focused on publication trends among leading universities in India. Both studies employ bibliometric methods to analyze extensive datasets, yet they differ in their scope and focus areas. The study by Farooqui aligns with this direction, emphasizing similar methodologies.

In this study, a total of 98,310 articles were examined, highlighting a notable increase in publications post-2009, primarily attributed

to emerging hypotheses linking Hepatitis B Virus (HBV) antigens to HCC development. This contrasts with Gyanajeet *et al.*'s analysis of over 26,000 documents, which emphasized the growth of research output from specific universities, particularly the University of Delhi. Both studies underscore the importance of collaborative research; however, this study specifically identifies key research themes such as the molecular mechanisms of HCC and the impact of COVID-19 on publication rates.

Furthermore, while this study notes a decline in articles since 2019 due to advancements in antiviral treatments and the pandemic's indirect effects, Gyanajeet *et al.*, highlight increasing international collaborations between Indian institutions and those in countries like the U.S., South Korea, and Germany. This indicates a broader trend toward global cooperation in research efforts.

Both studies also emphasize the significance of keywords in understanding research trends. This literature frequently includes terms like "cirrhosis" and "management," while Gyanajeet *et al.*, focus on collaborative initiatives that drive progress across diverse research domains.

Ultimately, both analyses contribute valuable insights into their respective fields: this study provides a detailed examination of evolving research themes and their implications for clinical practice, while Gyanajeet *et al.*'s work highlights the increasing research output and collaboration among universities, which is essential for informing policy decisions and resource allocation in healthcare research.

Notably, HCC-related publications were less frequent in the first decade but experienced a significant growth rate after 2009, attributed to emerging hypotheses linking Hepatitis B Virus (HBV) antigens to HCC. For instance, the association of hepatitis B x antigen (HBx ag) with the tumor-suppressor protein p53 plays a crucial role in HCC development.^[28] Additionally, the accelerated development of HCC-related studies can be linked to the exploration of molecular mechanisms and novel therapeutic paradigms. The highest number of papers was published in 2017 and 2021, during which there was a notable focus on cellular mechanisms related to HCC. Since 2019, there has been a rapid reduction in the number of HCC-related articles, accompanied by a decrease in total average citations. This decline can be attributed to the discovery of new antiviral drugs that represent significant advancements in HCC management. Moreover, the indirect impact of the COVID-19 outbreak has also played a role in this reduction, leading to fewer newly diagnosed HCC cases and follow-up visits.^[29] The global effects of the coronavirus pandemic extend beyond health and politics, exerting a significant adverse influence on scientific journals and research communities.^[30] Among the top ten countries contributing to HCC research, China emerged as the leading contributor, followed by the United States and Japan. This prominence is largely due to the higher prevalence of HCC in China, primarily driven by widespread chronic HBV and Hepatitis C Virus (HCV) infections.^[31] Notably, China also holds the highest total citations in HCC research due to the substantial burden of this cancer within its borders. Sun Yat-sen University has played a pivotal role in HCC research by publishing the highest number of articles focused on HCC-related topics. The most frequently encountered keywords in HCC literature encompass pivotal aspects of the disease, including "hepatocellular carcinoma", "cirrhosis", "survival", and "management". Of particular significance is cirrhosis, which emerges as a critical element in understanding HCC; its cumulative risk varies significantly based on its etiology. Research findings from large cohorts of cirrhotic patients indicate that HCC occurs most frequently in individuals with chronic viral hepatitis.^[32] Chronic viral infections such as HCV and HBV are identified as predominant causes of cirrhosis, further underscoring their role as potential premalignant conditions for developing HCC.^[33,34] HBV has been reported as a significant factor predisposing individuals to HCC before vaccine immunization became widespread. In contrast, HCV demonstrates a strong association with cirrhosis and HCC during the period from 1999 to 2009.^[35] The challenging

nature of managing HCC reflects the complexities involved in devising effective treatment strategies for individuals with this malignancy. The examination of the topic dendrogram reveals a clear delineation between two primary branches in HCC-related studies: basic studies and clinical studies. Each branch contributes distinct insights into understanding and managing the disease.

Basic Studies encompass a comprehensive array of sub-branches (36 in total), delving into diverse aspects such as physiological parameters, epidemiology, risk factors, diagnosis, biomedicine, and genetics. The prominence of basic studies is underscored by their higher frequency and highlights the pivotal role that molecular and cellular biology plays in unraveling the complexities of malignant diseases. These studies focus on exploring effective and safe diagnostic methods and management techniques while shedding light on fundamental mechanisms underlying HCC.^[36]

In contrast, Clinical Studies focus on practical aspects related to medications, management strategies, and survival outcomes. Although they comprise fewer sub-branches,^[37] clinical studies are essential for translating scientific knowledge into tangible interventions for patient care. Since 2000, there has been a gradual decline in clinical research production relative to overall HCC-related publications. This trend contrasts with an increase in basic research studies, meta-analyses, and clinical guidelines. This shift indicates that cumulative clinical knowledge has prompted additional studies necessitated by more comprehensive analyses of existing data. The increased publication of basic research studies in high-impact journals is attributed to remarkable advancements in molecular biology and genetics related to HCC.^[38]

CONCLUSION

The extensive analysis of HCC-related studies conducted over the past decades has revealed significant insights into the evolving landscape of research in this field. The focus on collaborative networks and scholarly communities highlighted key thematic shifts, starting from topics related to HBV and HBS antigen to a deeper exploration of cirrhosis induced by HBV and HCV, along with investigations into host cellular immune responses. The examination of virus genotypes and personalized epigenetics emerged as crucial subjects in the last decade. Notably, the predominance of basic or pre-clinical studies over clinical investigations in recent decades underscores the need for more comprehensive exploration, especially considering the unsatisfactory survival rates among HCC patients. This study provides a valuable framework for understanding research themes and the response of researchers in this field. Moving forward, identifying effective methods with the lowest prescribed dose is essential for optimal therapeutic outcomes.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

HCC: Hepatocellular Carcinoma; **HBV:** Hepatitis B Virus; **HCV:** Hepatitis C Virus; **DPI:** Dots Per Inch; **EHR:** Electronic Health Record; **MRI:** Magnetic Resonance Imaging; **SEER:** Surveillance, Epidemiology, and End Results; **TC:** Total Citations; **NPF:** National Priority Framework; **AI:** Artificial Intelligence; **ML:** Machine Learning.

AUTHOR'S CONTRIBUTIONS

M.KH, MJ.Z: Supervision, Conceptualization, Methodology, Writing. M.A,M.KH, M.N Data curation, Writing. M. KH,M.N,O.E, A.K Visualization, Validation. All authors read and approved the final manuscript.

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Cite this article: Azimi M, Zahedi MJ, Nakhaie M, Kiskani AK, Eslami O, Khazaneha M. Global Science in Hepatocellular Carcinoma: A Scientometric Analysis. *J Scientometric Res.* 2025;14(2):662-71.