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Historical and Emerging Trends in Hepatitis B Virus Integration: A Bibliometric Visual Analysis

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Purpose: Hepatitis B virus (HBV) infection is a global health concern, linked to chronic hepatitis, cirrhosis, and hepatocellular carcinoma. HBV genome integration into host DNA is critical in disease progression and oncogenesis. Despite advancements in understanding HBV pathogenesis and therapies, the mechanisms and implications of HBV integration remain unclear. This study employs bibliometric analysis to evaluate research trends and collaborations in HBV integration.

Materials and Methods: We utilized the Web of Science Core Collection (WOSCC) as our primary data source, meticulously screening and identifying 972 pertinent articles published between 1980 and November 30, 2024. Bibliometric tools, including VOSviewer, CiteSpace, and Bibliometrix, were employed to analyze publication trends, authorship, institutional contributions, and key research areas. Citation data and keyword clusters were examined to identify research hotspots.

Results: Publications have steadily increased from 1980 to November 30, 2024, with China and the United States contributing the most studies. While China leads in publication volume, the United States has the highest citation impact. The Institut Pasteur in Paris ranks highest in publications. Hino O is the most prolific author, and Koike K the most cited. Hepatology is the most cited journal, and the article "Genome-wide survey of recurrent HBV integration in hepatocellular carcinoma" is the most referenced. Cluster analysis revealed five major research themes.

Conclusion: This study highlights global research trends and key contributors in HBV integration, offering insights into current hotspots and future directions. The findings provide a basis for advancing diagnostic and therapeutic strategies targeting HBV integration.

Keywords: hepatitis B virus, integration, bibliometrics, visualization, genomic instability

Introduction

Globally, hepatitis B virus (HBV) infection continues to pose a significant public health challenge. As one of the most common blood-borne diseases, HBV has infected about one-third of the world's population.[1] It is estimated that nearly 300 million people have serologically detectable chronic HBV infections, which persistently damage the liver due to the virus's continued presence and the chronic immune response against infected cells.[2] This damage often progresses to chronic hepatitis B, cirrhosis, hepatocellular carcinoma, and liver failure, diseases that collectively result in approximately one million deaths annually.[2] Although significant progress has been made in the prevention and management of hepatitis B through vaccines, antiviral therapies, and public health strategies, complete eradication of the virus remains unachievable. This is largely due to the persistence of covalently closed circular DNA (cccDNA) and integrated HBV DNA within hepatocytes, which allow viral components to remain transcriptionally active despite treatment. As a result, increasing attention has been directed toward understanding the pathogenic mechanisms of HBV beyond viral replication. Research indicates that the integration of viral DNA into the host genome is a critical process in HBV-induced liver disease.[3] This process, which involves the incorporation of viral genetic material into the host's genome, results in increased genomic and chromosomal instability, leading to deletions, fractures, or rearrangements that subsequently alter gene expression and transform cellular phenotypes.[4,5] Since the discovery of HBV DNA integration in the 1980s,

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molecular biology and genetics studies have gradually elucidated the significant role of these integration events in the virus's lifecycle and pathogenicity.[6–8] In recent years, with advancements in high-throughput sequencing and bioinformatics, researchers have begun to analyze HBV integration events more systematically, transitioning from basic research to clinical applications. They explore the potential of HBV integration as a biomarker and seek new targets and strategies for preventing and treating hepatitis B and its associated diseases.[9–11] Despite substantial progress, research into HBV integration faces multiple challenges, including the diversity and complexity of integration events and variations in research across different ethnic and geographical backgrounds. Therefore, given the expanding volume of HBV integration studies, a structured analysis of the literature is timely and necessary.

Bibliometric analysis[12] utilizes statistical and mathematical tools to scrutinize the volume and citation data within scientific literature, offering a quantitative pathway for researchers to deeply understand the characteristics and emerging trends of literature in specific fields. This methodological approach has been extensively applied in various disciplines to systematically assess the publication output, thereby facilitating the tracking of publishing and citation trends, and delving into the deeper structural knowledge and evolutionary pathways of research domains.[13,14] Employing bibliometrics enables the evaluation of the impact of scientific outputs, exploration of knowledge networks, and dynamics within academic development. Additionally, it provides insights into the changing dynamics of disciplines and forecasts the trajectories of future research directions.

However, there has been no systematic assessment of the literature to date, and a specific scientometric study focusing on HBV integration has yet to be conducted. This paper aims to systematically collect and analyze research publications from the past decades using bibliometric methods and to present the evolution of research foci, key issues, and potential future directions through visualization tools. This will provide valuable insights and references for scholars in the field of HBV integration research.

Materials and Methods

Database and Search Strategy

For our bibliometric analysis of hepatitis B virus (HBV) integration literature, the selection of an appropriate database was paramount. We opted for the Web of Science (WOS) database, primarily for its extensive literature coverage, inclusion of top-tier journals, efficient retrieval capabilities, robust citation analysis tools, and broad recognition within the global academic community. These characteristics are crucial for ensuring the accuracy and credibility of our analysis, as well as for assessing the impact and scholarly value of the literature. To further ensure the credibility of our data source, we utilized the Web of Science Core Collection (WOSCC), specifically the Social Sciences Citation Index (SSCI) and the Science Citation Index Expanded (SCI-Expanded).

Search terms were developed with reference to PubMed's MeSH terminology but adapted to the syntax of the Web of Science Core Collection (WOSCC). Legacy terms such as "Dane particle" and "viruses, Hepatitis B" were included to ensure comprehensive retrieval of early publications, particularly those from the 1980s and 1990s.The search strategy was structured as shown in Table 1. A detailed search of the WOSCC revealed that the earliest literature on HBV integration was published in 1980. Given our focus on HBV integration, we specifically excluded non-research articles such as reviews and only analyzed research articles. The study period was set from January 1980 to November 30, 2024, and was restricted to articles published in English. It is because some non-English records in WOSCC lacked full metadata (eg, abstracts or references), which could have introduced bias in bibliometric analyses. To ensure data quality, consistency, and compatibility with bibliometric tools, we limited inclusion to English-language publications. After

Table 1 Search Strategy

Search	Details
#1	(((((TS=(Hepatitis B viruses)) OR TS=(Hepatitis B virus)) OR TS=(Dane Particle)) OR TS=(Particle, Dane)) OR TS=(viruses, Hepatitis B)) OR TS=(B virus, Hepatitis)
#2	TS=(integration)
#3	#1 AND #2

meticulous screening, a total of 972 eligible research articles were included. To minimize bias potentially caused by database updates and to maintain consistency, all data collection and screening were completed within a single day and a single session. Data were downloaded in text format, including full records and cited references, for subsequent bibliometric analysis. The process of data collection and screening is illustrated in Figure 1.

Bibliometric Analysis

Bibliometric analysis involves the use of multiple tools; in this study, VOSviewer (1.6.20), CiteSpace (6.2.R4), and Bibliometrix (4.4.2) were the primary tools employed. VOSviewer,[15–17] developed by van Eck and Waltman, was employed to construct and visualize bibliometric networks. The software was run with default layout and clustering parameters, and it was used primarily for generating co-authorship and institutional collaboration maps, co-citation analysis of journals and keyword co-occurrence and density visualizations. CiteSpace,[13,18,19] developed by Synnestvedt and et.al, stands as one of the most popular and recognized tools for bibliometric visualization currently available. In our study, CiteSpace was configured with a 1-year time slicing, Log-Likelihood Ratio (LLR) as the clustering algorithm, and pathfinder as the pruning method, and it was primarily utilized to analyze co-occurrence and centrality in networks of countries, authors, and institutions, to perform dual-map overlays of journals, to identify the strongest citation bursts in cited articles, and to conduct timeline clustering and emergence analysis of keywords. Bibliometrix,[20,21] an R-based package, is principally used for statistical analysis of publication counts and citation data as well as trend analysis of themes. The combined use of these tools enabled a comprehensive, multidimensional assessment of research output and trends.

Results

Analysis of the Number of Publications and Citations

From January 1980 to November 2024, a comprehensive study was conducted on the integration of the hepatitis B virus (HBV), resulting in the publication of 972 research articles. These articles were a collaborative effort involving 5,684 researchers from 1,388 institutions across 69 countries worldwide. Collectively, these articles have garnered an impressive total of 46,119 citations, averaging approximately 47.45 citations per article. Figure 2a illustrates the annual publication and citation statistics. The temporal distribution of publications and citations reveals notable peaks corresponding to significant scientific advancements. In 1991, a marked increase in both publications and citations was observed. This surge aligns with pivotal discoveries regarding the HBV X protein (HBx), notably its role in transactivating oncogenes such as c-Myc, thereby

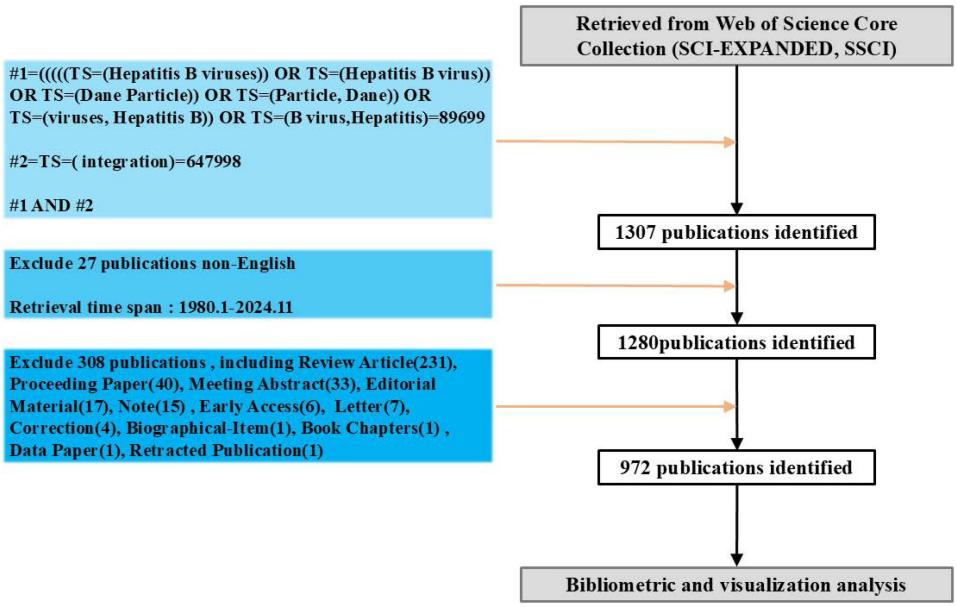

Figure 1 Flow chart for inclusion and exclusion of hepatitis B virus integration publications.

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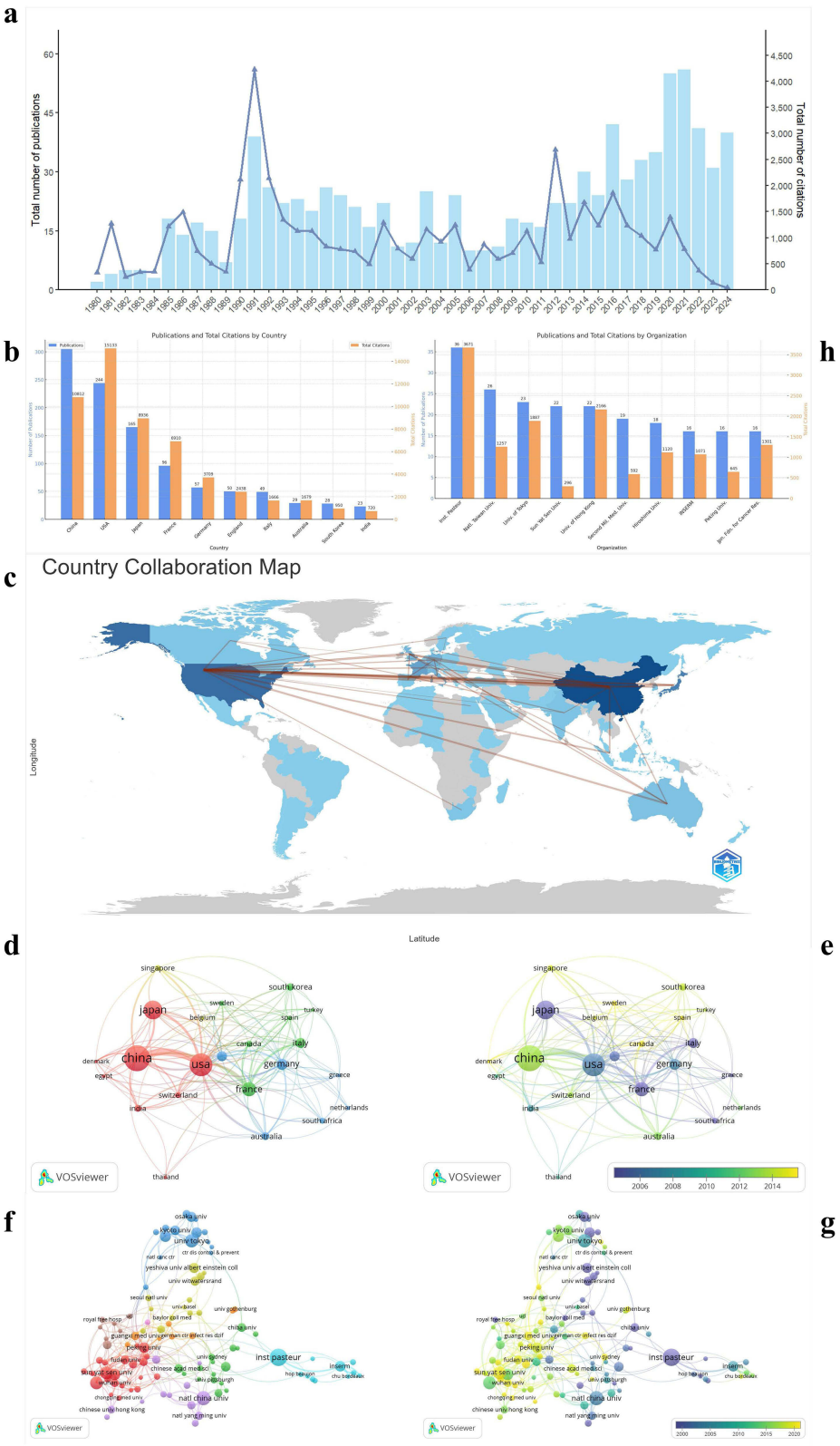

Figure 2 (a) The annual number of publications and citations on Hepatitis B Virus integration from 1980 to 2024. **(b)** Publications and total citations of countries. **(c)** Geographic distribution of global publications on Hepatitis B Virus integration. **(d)** Network visualization map of 23 countries. **(e)** Overlay visualization map of 23 countries. **(f)** Network visualization map of 106 institutions. **(g)** Overlay visualization map of 106 institutions. **(h)** Publications and total citations of institutions.

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implicating HBx in hepatocarcinogenesis. Additionally, the early 1990s saw the widespread adoption of polymerase chain reaction (PCR) techniques in virology research, significantly enhancing the sensitivity of HBV DNA detection and facilitating more detailed studies on HBV integration and replication.

A sustained increase in publications and citations is evident post-2008, aligning with the advent of high-throughput sequencing technologies. These advancements facilitated comprehensive analyses of HBV DNA integration sites across the genome, leading to a deeper understanding of HBV's role in hepatocellular carcinoma (HCC) development. The increased research output and citations during this period reflect the scientific community's growing interest in the molecular mechanisms of HBV integration and its clinical implications.

Furthermore, the correlation between publication and citation trends suggests a general rise in the field's influence rather than reliance on a few highly cited papers. This indicates a broadening interest and recognition of HBV integration research within the scientific community.

Analysis of Contributions of Countries

The distribution of scholarly outputs on hepatitis B virus (HBV) integration reflects international collaboration, with 69 countries contributing to the research in this area. Figure 2b and Table 2 list the top ten countries by publication count in this field, with China leading significantly with 306 publications, followed by the United States and Japan, which have published 244 and 165 articles, respectively. France, Germany, the United Kingdom, Italy, Australia, South Korea, and India have also made notable contributions. Notably, while the United States leads in total citations (TC = 15,133), France exhibits the highest average citations per article (AC = 71.98). This discrepancy may be attributed to differing research strategies. For example, France's key institutions have focused on high-impact molecular and oncogenic studies, often published in prestigious journal, which results in greater citation visibility despite fewer publications. In contrast, China's contribution, while impressive in volume, has a relatively lower average citation rate. This may reflect the broader range of journal types and a more recent surge in publication output that has not yet accumulated substantial citations. The USA, with its long-standing investment in HBV-related research and broad collaborative networks, demonstrates strong academic influence globally. The international collaboration pattern is further illustrated in Figure 2c, which maps global publication distribution and co-authorship networks. A network of 23 countries with at least five publications was constructed (Figure 2d, 2e), revealing particularly strong connections between high-output countries.

Analysis of the Contributions by Institutions

Research on hepatitis B virus (HBV) integration has been conducted across 1,388 institutions globally. We identified 106 institutions that have each published at least five articles. These institutions' collaborative networks were further visualized, and based on the similarity of their research foci, they were categorized into nine clusters, as illustrated in Figure 2f, 2g. In these figures, each node is color-coded, where the size of a node represents the publication output of the institution, the color

Table 2 Top 10 Most Productive Countries

Rank	Country	Publications	TC (Total Citations)	AC (Average Citations)	TLS (Total Link Strength)
1	China	306	10812	35.33	138
2	USA	244	15133	62.02	179
3	Japan	165	8936	54.16	45
4	France	96	6910	71.98	75
5	Germany	57	3709	65.07	51
6	England	50	2438	48.76	62
7	Italy	49	1666	34.00	34
8	Australia	29	1679	57.90	38
9	South Korea	28	950	33.93	18
10	India	23	720	31.30	22

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variance indicates different research clusters, and the thickness of the lines between nodes denotes the closeness of collaboration. The largest cluster, marked in red and centered on Sun Yat-sen University, demonstrates strong domestic and international collaboration. However, citation patterns reveal disparities in academic impact. As shown in Figure 2h and Table 3, Institut Pasteur, Paris ranks first in both total publications and total citations (TC = 3,671), while Sun Yat-sen University, despite a high publication volume, has a comparatively lower citation count (TC = 296). This discrepancy may be attributed to differing research strategies. Institut Pasteur has focused on high-impact topics such as HBV integration and hepatocarcinogenesis, frequently publishing in leading journals, thereby achieving higher citation visibility. In contrast, Sun Yat-sen University's broader research scope and diverse publication outlets may have diluted its citation impact, reflecting a more volume-driven approach. These findings underscore the importance of not only research quantity but also the strategic focus and dissemination channels in shaping institutional influence within the HBV integration research landscape.

Analysis of Contributions of Prolific Authors

A total of 5,684 researchers have been involved in the study of hepatitis B virus (HBV) integration. Using the VOSviewer tool, we constructed a collaborative network for 166 authors who have published four or more articles, forming 30 research clusters as depicted in Figure 3a, 3b. In these networks, Hino, O emerged as the author with the most publications, featuring a prominently significant node, followed by Rogler, CE and Brechot, C, indicating strong collaborative relationships among the authors. Particularly noteworthy is the largest cluster centered around Chayama, K and Kew, MC, which has established inter-cluster collaborations with at least two other groups. Figure 3c and Table 4 list the top ten most prolific authors in the field, revealing not only their contributions within their respective clusters but also their central roles and influence across the entire research network.

Analysis of the Contributions of Journals

In our study, a total of 358 journals contributed to the publication of literature in the field. Among them, 86 journals published three or more articles, indicating their active role in academic dissemination. Through cluster analysis, these journals were categorized into 11 different groups, highlighting the diversity of the research areas and interdisciplinary collaborations, as shown in Figure 3d. Figure 3e and Table 5 present the top ten journals in this domain based on publication count. Leading the list is the journal Hepatology, which has published 43 articles and received 3223 citations, giving it an impressive impact factor of 12.9 and highlighting its prominent position in the field. Following closely behind are the Journal of Virology and Journal of Medical Virology, with 40 and 37 articles, respectively. The top three journals in terms of citation counts are Hepatology (TC=3223), Nature (TC=2414), and Journal of Hepatology (TC=2386). Nature and Journal of Hepatology have impact factors of 50.4 and 26.8, respectively, highlighting the high-quality impact of their research. We noticed that the total citation frequency of Journal of Hepatology is higher than that of Nature, even though the latter has a higher impact factor. This difference may be due to the difference in journal

Table 3 Top 10 Most Productive Institutions

Rank	Organization	Country	Publications	TC (Total Citations)	AC (Average Citations)
1	Institut Pasteur, Paris	France	36	3671	101.97
2	National Taiwan University	China	26	1257	48.35
3	University of Tokyo	Japan	23	1887	82.04
4	Sun Yat Sen University	China	22	296	13.45
5	University of Hong Kong	China	22	2166	98.45
6	Second Military Medical University	China	19	592	31.16
7	Hiroshima University	Japan	18	1120	62.22
8	Institut National de la Sante et de la Recherche Medicale (INSERM)	France	16	1071	66.94
9	Peking University	China	16	645	40.31
10	Japanese Foundation for Cancer Research	Japan	16	1301	81.31

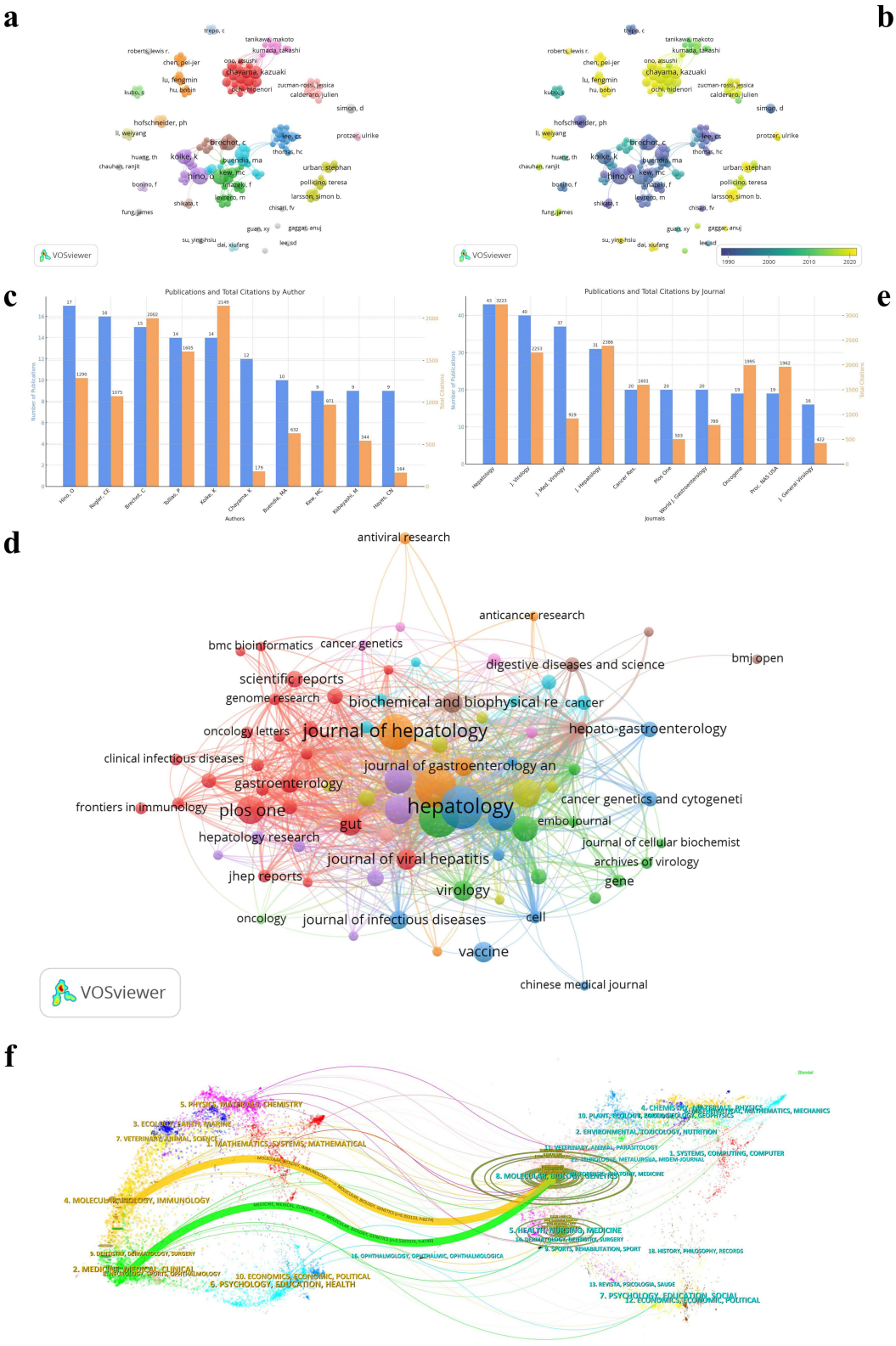

Figure 3 (a) Network visualization map of 166 core authors. **(b)** Overlay visualization map of 166 core authors. **(c)** Publications and total citations of authors. **(d)** Network map of journal cluster. **(e)** Publications and total citations of journals. **(f)** The dual-map overlay of journals.

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Table 4 Top 10 Most Productive Authors

Rank	Authors	Country	Publications	TC (Total Citations)	AC (Average Citations)
1	Hino, O	Japan	17	1290	75.88
2	Rogler, CE	USA	16	1075	67.19
3	Brechot, C	France	15	2002	133.47
4	Tiollais, P	France	14	1605	114.64
5	Koike, K	Japan	14	2149	153.50
6	Chayama, K	Japan	12	179	14.92
7	Buendia, MA	France	10	632	63.20
8	Kew, MC	South Africa	9	971	107.89
9	Kobayashi, M	Japan	9	544	60.44
10	Hayes, CN	Japan	9	164	18.22

Table 5 Top 10 Most Productive Journals

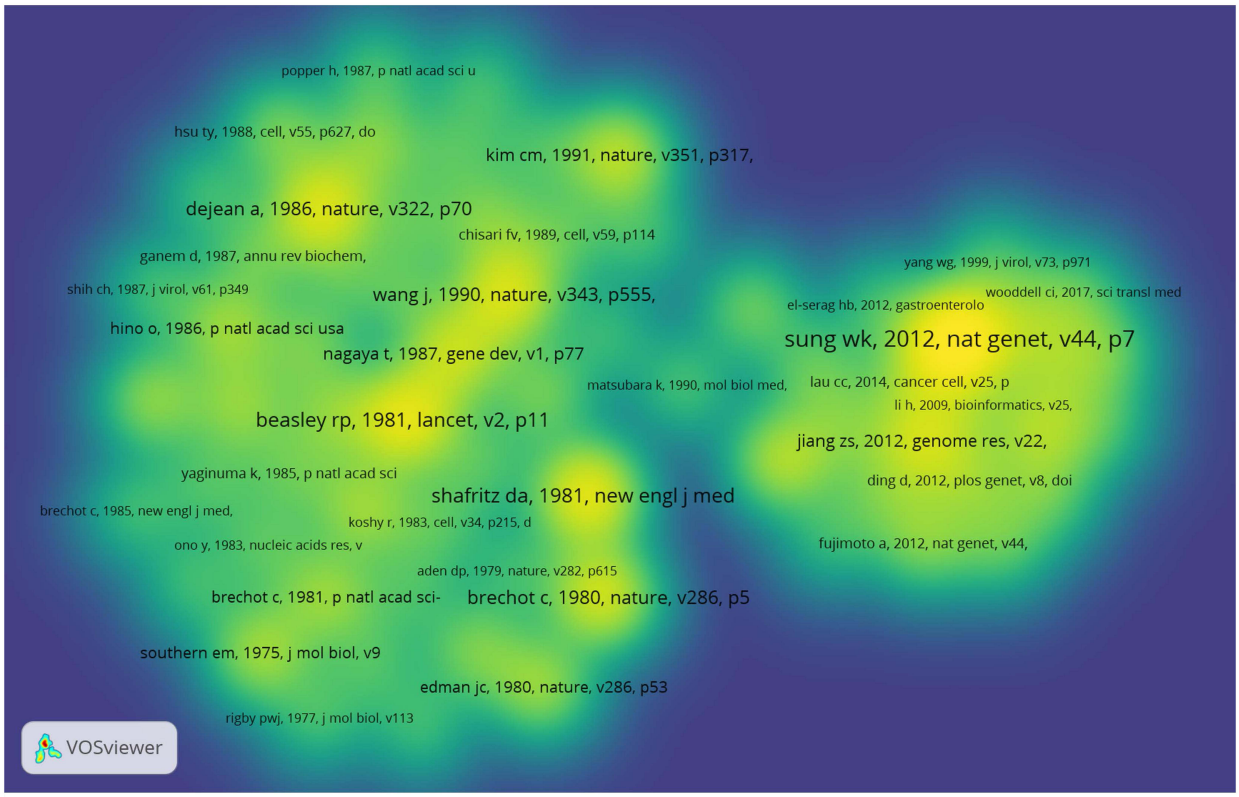
Rank	Journals	Publications	IF-2024	JCR	TC (Total Citations)
1	Hepatology	43	12.9	Q1	3223
2	Journal of Virology	40	4	Q1	2253
3	Journal of Medical Virology	37	6.8	Q1	919
4	Journal of Hepatology	31	26.8	Q1	2386
5	Cancer Research	20	12.5	Q1	1601
6	PLoS One	20	2.9	Q1	503
7	World Journal of Gastroenterology	20	4.3	Q1	789
8	Oncogene	19	6.9	Q1	1995
9	Proceedings of The National Academy of Sciences of The United States of America	19	9.4	Q1	1962
10	Journal of General Virology	16	3.6	Q2	422

positioning and publication strategy between the two. Journal of Hepatology is a professional journal for liver disease research, while Nature is a comprehensive high-impact journal.

To visually illustrate the thematic distribution of citing and cited journals, we utilized a dual-map overlay atlas. This atlas shows citation relationships between the citing journals on the left and the co-cited journal clusters on the right through colored paths, as shown in Figure 3f. The orange path represents the primary citation pathway, indicating that studies published in molecular/biology/genetics journals are predominantly cited by literature in molecular/biology/immunology journals. Meanwhile, the green path illustrates the main document flow pathway, indicating that research published in molecular/biology/genetics journals is primarily cited by studies in medical/clinical medicine journals.

Analysis of Contributions of Co-Cited Reference

Co-cited references are those that have been cited by more than one article included in this study. To delve deeper into the background and knowledge base of hepatitis B virus (HBV) integration, we conducted an analysis of co-cited references using VOSviewer and CiteSpace. Figure 4a displays a density visualization map that shows the distribution of 69 references out of 24,412 co-cited references, each cited 30 times or more. Citation bursts, representing a sudden surge in the citation of these references within the field, indicate articles that have been frequently cited by scholars over a specific period. This type of analysis helps explore how research hotspots evolve over time. The top 25 articles with the strongest citation bursts are shown in Figure 4b, with red bars indicating high citation frequency and blue bars indicating fewer citations. The reference with the strongest burst strength (strength = 36.27, burst period = 2013–2017) is "Genome-wide survey of recurrent HBV integration in hepatocellular carcinoma" by Sung WK et al.[22] This article, which reports on the genome-wide analysis of HBV integration,



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Top 25 References with the Strongest Citation Bursts

References	Year	Strength	Begin	End	1980 - 2024
CHAKRABORTY PR, 1980, NATURE, V286, P531, DOI 10.1038/286531a0, DOI	1980	11.54	1980	1985	
EDMAN JC, 1980, NATURE, V286, P535, DOI 10.1038/286535a0, DOI	1980	11.06	1981	1985	
SHAFRITZ DA, 1981, NEW ENGL J MED, V305, P1067, DOI 10.1056/NEJM198110293051807, DOI	1981	12.29	1983	1986	
DEJEAN A, 1983, P NATL ACAD SCI-BIOL, V80, P2505, DOI 10.1073/pnas.80.9.2505, DOI	1983	11.31	1984	1988	
ROGLER CE, 1985, SCIENCE, V230, P319, DOI 10.1126/science.2996131, DOI	1985	14.45	1986	1990	
TIOLLAIS P, 1985, NATURE, V317, P489, DOI 10.1038/317489a0, DOI	1985	13.89	1986	1990	
DEJEAN A, 1986, NATURE, V322, P70, DOI 10.1038/322070a0, DOI	1986	16.94	1987	1991	
NAGAYA T, 1987, GENE DEV, V1, P773, DOI 10.1101/gad.1.8.773, DOI	1987	12.12	1988	1992	
HINO O, 1986, P NATL ACAD SCI USA, V83, P8338, DOI 10.1073/pnas.83.21.8338, DOI	1986	12.05	1988	1991	
HSU TY, 1988, CELL, V55, P627, DOI 10.1016/0092-8674(88)90221-8, DOI	1988	12.02	1989	1993	
KEKULE AS, 1990, NATURE, V343, P457, DOI 10.1038/343457a0, DOI	1990	13.2	1990	1995	
WANG J, 1990, NATURE, V343, P555, DOI 10.1038/343555a0, DOI	1990	24.96	1991	1995	
KIM CM, 1991, NATURE, V351, P317, DOI 10.1038/351317a0, DOI	1991	16.27	1991	1996	
FOUREL G, 1990, NATURE, V347, P294, DOI 10.1038/347294a0, DOI	1990	12.39	1991	1995	
Jiang ZS, 2012, GENOME RES, V22, P593, DOI 10.1101/gr.133926.111, DOI	2012	18.81	2012	2017	
Sung WK, 2012, NAT GENET, V44, P765, DOI 10.1038/ng.2295, DOI	2012	34.27	2013	2017	
Fujimoto A, 2012, NAT GENET, V44, P760, DOI 10.1038/ng.2291, DOI	2012	12.4	2013	2016	
Ding D, 2012, PLOS GENET, V8, P0, DOI 10.1371/journal.pgen.1003065, DOI	2012	12.12	2014	2017	
Toh ST, 2013, CARCINOGENESIS, V34, P787, DOI 10.1093/carcin/bgs406, DOI	2013	11.39	2014	2018	
Lau CC, 2014, CANCER CELL, V25, P335, DOI 10.1016/j.ccr.2014.01.030, DOI	2014	12.72	2015	2019	
Mason WS, 2016, GASTROENTEROLOGY, V151, P986, DOI 10.1053/j.gastro.2016.07.012, DOI	2016	13.83	2017	2021	
Tu T, 2017, VIRUSES-BASEL, V9, P0, DOI 10.3390/v9040075, DOI	2017	19.1	2018	2022	
Zhao LH, 2016, NAT COMMUN, V7, P0, DOI 10.1038/ncomms12992, DOI	2016	17.33	2018	2021	
Tu T, 2018, J VIROL, V92, P0, DOI 10.1128/JVI.02007-17, DOI	2018	15.61	2018	2024	
Wooddell CI, 2017, SCI TRANSL MED, V9, P0, DOI 10.1126/scitranslmed.aan0241, DOI	2017	12.15	2018	2022	

Figure 4 (a) Density visualization map of the top 69 co-cited references. **(b)** Top 25 references with the strongest co-cited bursts in the field of HBV integration.

has had a significant impact in the field, and its citation burst highlights its critical role in advancing the domain. Table 6 lists the top 10 most co-cited references, half of which were published in Nature, and more than half were published before 2000. These articles[6,7,22–29] showcase genome-wide analyses of HBV integration and the integration sequences of HBV in hepatocellular carcinoma cell DNA, elucidating the integration patterns, mechanisms of HBV DNA, and the impact of HBV DNA integration on the genomes of hepatocellular carcinoma patients. These findings provide multiple perspectives on the influence and clinical progression in this research field.

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Table 6 Top 10 Co-Citation References

Rank	Title	First Author	Year	Journal	Citations
1	Genome-wide survey of recurrent HBV integration in hepatocellular carcinoma[22]	Wing-Kin Sung	2012	Nature Genetics	172
2	Integration of Hepatitis B Virus DNA into the Genome of Liver Cells in Chronic Liver Disease and Hepatocellular Carcinoma — Studies in Percutaneous Liver Biopsies and Post-Mortem Tissue Specimens[7]	David A. Shafritz	1981	New England Journal of Medicine	125
3	Hepatocellular carcinoma and hepatitis B virus: a prospective study of 22707 men in Taiwan[23]	R.Palmer Beasley	1981	The Lancet	120
4	Hepatitis B virus DNA integration in a sequence homologous to v-erb-A and steroid receptor genes in a hepatocellular carcinoma[24]	Anne Dejean	1986	Nature	108
5	Hepatitis B virus integration in a cyclin A gene in a hepatocellular carcinoma[6]	Jian Wang	1990	Nature	107
6	Presence of integrated hepatitis B virus DNA sequences in cellular DNA of human hepatocellular carcinoma[25]	Christian Brechot	1980	Nature	105
7	HBx gene of hepatitis B virus induces liver cancer in transgenic mice[26]	Chang-Min Kim	1991	Nature	88
8	The mode of hepatitis B virus DNA integration in chromosomes of human hepatocellular carcinoma[27]	Nagaya T	1987	Genes & development	87
9	The effects of hepatitis B virus integration into the genomes of hepatocellular carcinoma patients[28]	Zhaoshi Jiang	2012	Genome research	81
10	Large scaled analysis of hepatitis B virus (HBV) DNA integration in HBV related hepatocellular carcinomas[29]	Y Murakami	2005	Gut	80

Analysis of Keywords

Keywords represent the core content of articles. Keyword co-occurrence analysis is employed to identify research hotspots in a given field. By extracting and clustering a total of 3,475 keywords from 972 documents, we identified the top 94 most frequently occurring keywords, each appearing at least 15 times, and categorized them into five clusters (see Figure 5a). We analyzed four of these clusters: Cluster 1 (red cluster) concerns the epidemiology and prevention of hepatitis B virus, featuring keywords such as prevalence, epidemiology, prevention, and risk. Cluster 2 (green cluster) focuses on the relationship between hepatitis B virus integration and the mechanisms of hepatocarcinogenesis, including keywords like Hbx, p53, mutation, apoptosis, and expression. Specifically, HBV integration can disrupt the p53 tumor suppressor pathway, leading to impaired apoptosis and increased risk of hepatocellular carcinoma. The HBV X protein (HBx) has been shown to bind to p53, inhibiting its transcriptional activity and promoting cytoplasmic sequestration, thereby abrogating p53-mediated apoptosis. Additionally, p53 can downregulate HBx via E6AP-mediated proteasomal degradation, influencing HBV replication and pathogenesis. Cluster 3 (blue cluster) explores the sites of HBV integration and the mechanisms of its genomic insertion, with terms such as insertion, integration site, nucleotide-sequence, region, and polymerase chain-reaction. Cluster 4 (yellow cluster) relates to the outcomes of HBV integration and treatments, including hepatocytes, in-vivo, and hepatocellular carcinoma.

We used CiteSpace to create a keyword timeline to analyze the temporal evolution of high-frequency keywords (refer to Figure 5b). The analysis revealed that terms such as activation, gene expression, infection, integration, and hepatocellular carcinoma have consistently been research focal points. Additionally, Figure 5c displays a citation burst analysis of the top 25 most cited keywords in the field of HBV integration, highlighting peaks of research interest over time. This analysis also shows a shift from early studies focusing on HBV integration sites and mechanisms to a focus on the mechanisms and treatment of diseases such as hepatocellular carcinoma associated with HBV integration. Finally, a trend analysis (refer to Figure 5d) illustrates the progression of research trends and forecasts emerging topics, highlighting HBV integration and its connection to hepatocellular carcinoma and treatment as current focal points. These analytical figures collectively showcase the research trends in HBV integration, offering insights into addressing diseases such as liver cancer and hepatitis caused by HBV through both fundamental research and clinical innovation.

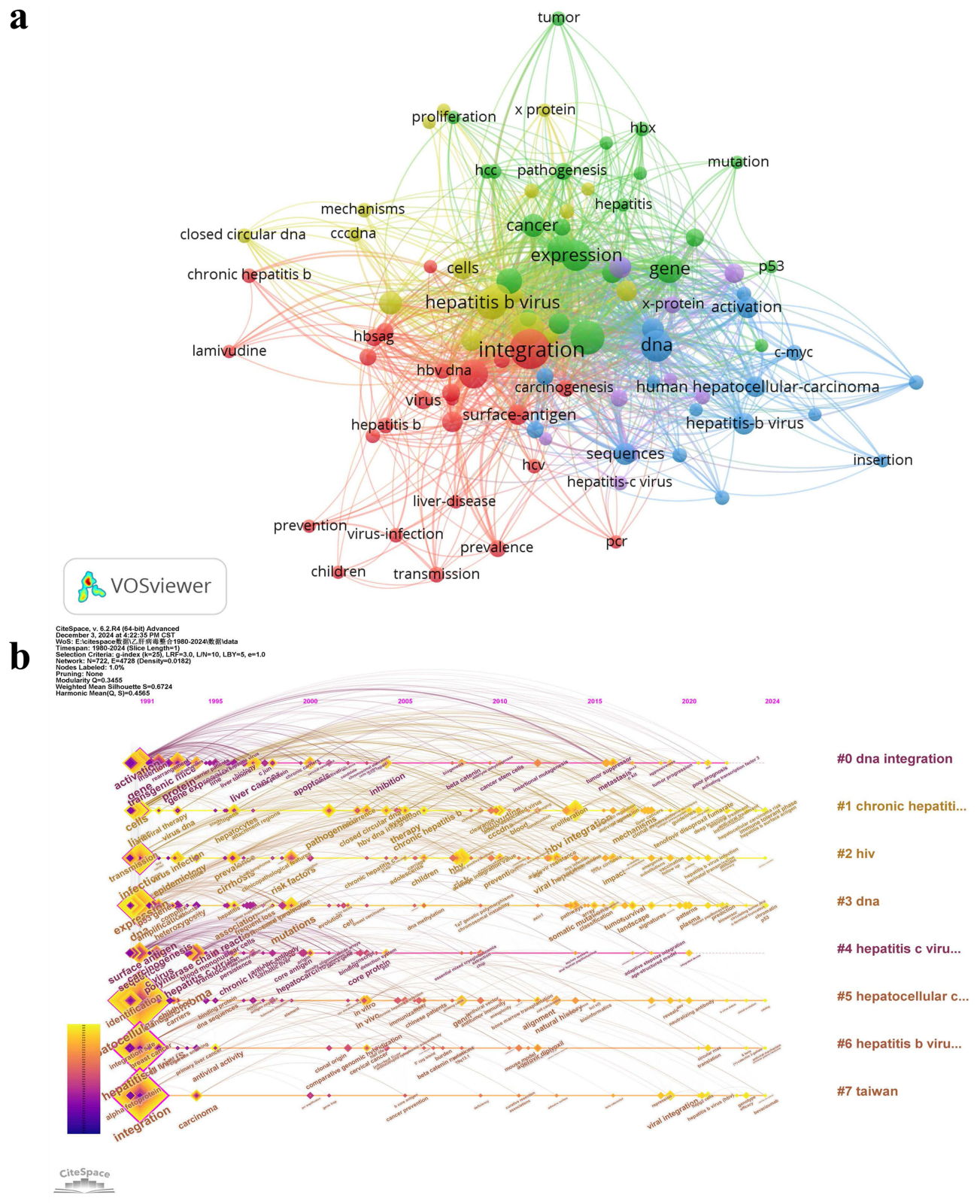

Figure 5 Continued.

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c

Top 25 Keywords with the Strongest Citation Bursts

Keywords	Year	Strength	Begin	End	1980 - 2024
human hepatocellular carcinoma	1991	8.2	1991	2000	
c myc	1991	5.24	1991	1998	
nucleotide sequence	1991	5.12	1991	1998	
viral dna	1991	4.97	1991	1999	
sequences	1991	9.83	1992	2005	
transgenic mice	1992	8.06	1992	2004	
insertion	1992	4.88	1992	1996	
heterozygosity	1993	4.41	1993	1999	
polymerase chain reaction	1994	9.03	1994	2005	
tissue	1991	4.68	1994	1996	
hepatitis c virus	1994	7.54	1996	2003	
cirrhosis	1996	4.96	1996	2007	
mutations	1999	5.6	2012	2024	
x protein	1991	6.67	2013	2017	
risk	2008	6.42	2013	2024	
epidemiology	1993	4.79	2013	2019	
natural history	2013	4.78	2013	2017	
hbv integration	2014	11.87	2014	2024	
liver cancer	1997	4.74	2015	2022	
genm	2008	4.55	2016	2020	
hbv	2008	5.32	2017	2022	
mechanisms	2017	4.97	2017	2024	
viral integration	2019	5.05	2019	2022	
hepatitis b	2000	4.76	2020	2024	
genome	1991	4.62	2021	2024	

d

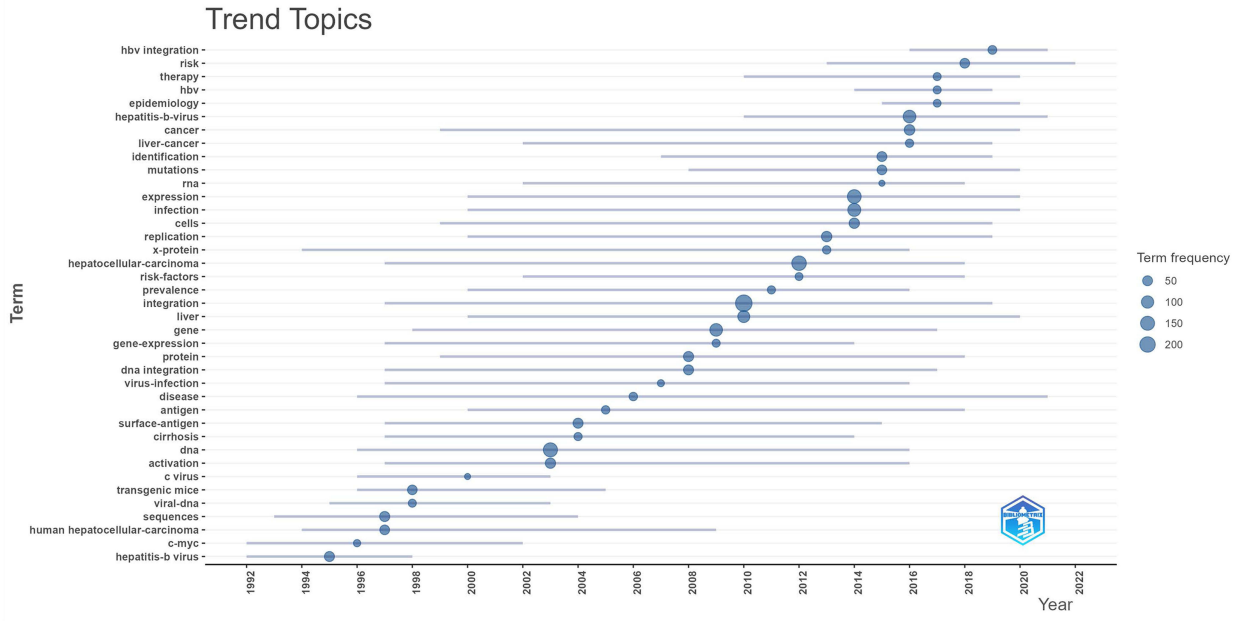

Figure 5 (a) Network map of top 94 keywords with 5 clusters. **(b)** A timeline and keyword clustering display. **(c)** Top 25 keywords with the strongest citation bursts in the field of HBV integration research. **(d)** Trend topics.

Discussion

The Integration of Hepatitis B Virus Has Garnered Increasing Attention

This study conducted a systematic literature search on articles concerning HBV integration published in the WOSCC from 1980 to 2024. Furthermore, a bibliometric visualization analysis was performed based on 972 research papers published across 358 journals by 5,684 researchers from 69 countries.

Since the initial discovery of HBV DNA integration in human hepatocytes in the 1980s, the field of HBV integration has evolved over 44 years. With advancements in technology,[22,28,30–32] the volume of publications related to HBV integration have increased significantly and a significant surge in research occurred post-2010. Early studies on the mechanism of HBV integration[7,25,33,34] provided preliminary insights into how the virus integrates into the host cell genome and proposed foundational theories of virus-host interactions. Afterwards, HBV integration research gradually transitioned from basic science to clinical applications,[35–39] providing valuable theoretical support for clinical treatments. Additionally, the strengthening of interdisciplinary collaborations and close cooperation among leading research institutions and scholars worldwide have further propelled the rapid development of HBV integration studies. The citation counts in the bibliometric analysis reflect this trend, demonstrating the academic impact of research in this field. Therefore, HBV integration research holds the potential to provide new theoretical bases and technical support for personalized treatment of chronic hepatitis B and early screening for liver cancer.

The Integration of HBV Has Established a Rich Global Network That Has Been Enriched Through International Collaboration

Creating co-authorship and collaboration graphs with HBV integration authors, institutions, and worldwide research efforts enables the visualization of academic networks and their dynamics. These graphs provide insights into key contributors, collaboration patterns, and knowledge dissemination, ultimately facilitating more effective and targeted research collaborations.

The field of HBV integration is characterized by a tightly interconnected global network where authors, institutions, and nations collaborate to advance research in this area. Japanese researchers and institutions play a leading role, forming a key cluster within this global network. Prominent among them are Professor Hino O from the Japanese Foundation for Cancer Research and Professor Koike K from the University of Tokyo, with a primary research focus on hepatocellular carcinoma, particularly in the mechanisms of liver cancer and HBV. Professor Hino O's team concentrates on the molecular genetics and pathophysiology of liver cancer,[40–42] exploring the mechanisms behind its development[43,44] including the activation of oncogenes through HBV integration.[45–47] Their studies have elucidated the link between HBV and liver cancer,[48–50] particularly the role of HBV DNA integration in the progression of hepatocellular carcinoma. Moreover, Professor Hino O's group also focuses on how altering the hepatic microenvironment and signaling pathways can prevent and treat liver cancer.[51–53] Professor Koike K, on the other hand, holds a leadership position in the study of viral hepatitis and its carcinogenic mechanisms.[43,54] His research centers on how HBV, through viral protein integration into and interactions with the host genome, influences cell proliferation and death signals, thereby promoting the development of hepatocellular carcinoma.[55,56] Their work involves studying the expression of viral proteins in liver cells and their impact on liver cell growth regulation and immune response.[57] In addition to Japanese scholars, researchers from other countries have significantly advanced HBV integration research. Professor Christian Bréchot (France) identified HBV integration near fragile genomic sites and its role in genomic instability and HCC development Frequent somatic mutations of the p53 gene in human liver cancer.[25] Professor CE Rogler (USA) focused on how hepatitis B virus integration activates host oncogenes through viral enhancer elements and induces chromosomal rearrangements, particularly involving deletions and translocations at integration sites.[58] The research by these professors not only deepens our understanding of the pathophysiology of liver cancer but also drives the development of new prevention and treatment strategies, providing a scientific basis for the development of novel therapeutic approaches targeting HBV-induced liver cancer. Additionally, France's Institut Pasteur, Paris, and China's University of Hong Kong have also played leading roles in this field, providing robust support for the research.

Globally, China, the USA, and Japan lead in the field of HBV integration research, with significant contributions from European countries like France and Germany, reflecting the broad diversity of international cooperation. In terms of

publication volume, China leads significantly; the USA holds the top position in total citations; and France excels in average citations per publication, highlighting the dual importance of quality and quantity in the research world. Contribution of China, while substantial in volume, has a relatively lower average citation rate. This may be attributed to a broader range of publication venues, a recent surge in output with limited time for citation accumulation, as well as factors such as funding policies emphasizing quantity, language barriers, and methodological differences that may limit visibility in high-impact journals. These observations underscore the need to enhance both the quality and international integration of HBV integration research. Analysis of the integration among authors, institutions, and nations reveals that the development of the HBV integration field relies on cross-border cooperation, the valuing of expertise, and the leveraging of collective institutional power. This further underscores that strategic alliances among nations are crucial for breaking through research barriers and translating knowledge into practical therapeutic approaches. Such international collaboration facilitates the progression of the field towards a more comprehensive and globally-oriented research agenda.

Top-Tier Journals and Highly Cited Papers Propel Advances in Hepatitis B Virus Integration

The synergistic interaction between top-tier journals and their highly cited papers has driven progress in the study of HBV integration. Prestigious journals such as Hepatology and Nature have played a pivotal role in advancing HBV integration research. As primary platforms for high-impact research, they not only demonstrate their academic influence and reputation but also successfully attract pioneering work in the field. Highly cited papers often represent significant scientific discoveries or technological innovations. For instance, the groundbreaking work by Wing-Kin Sung et al,[22] marked by a notable surge in citations, has played a crucial role in guiding HBV integration research. It particularly highlights the resolution of complex biomedical issues through high-throughput sequencing techniques, revealing the recurrent integration patterns of HBV in hepatocellular carcinoma and providing deep insights into the molecular mechanisms linking viral integration and cancer development. More importantly, an analysis of the most-cited papers (Table 5) reveals that many of these originate from top-tier journals. This significant overlap suggests a dynamic dialogue between highly cited papers and their journals, not only emphasizing the journals' role in advancing research and breakthrough studies but also highlighting the importance of strategic publication choices and the role of journals as gatekeepers of scientific quality and innovation. Maintaining such high standards in research dissemination is crucial for advancing the study of HBV integration.

Trends and Hotspots in HBV Integration Research—From Basic Science to Clinical Practice

From 1980 to 2024, research on HBV integration has seen considerable development. With continuous technological advancements, the field has progressively moved from basic research to clinical application, generally categorized into three stages, each building on previous discoveries and providing valuable insights for future research.

Early Exploration—DNA Hybridization Detection Methods

In the early 1980s, researchers such as Brechot C et al[25] first reported the integration phenomenon of HBV DNA in human hepatocytes. Using HBV as a probe, Southern blot hybridization detected this phenomenon in tissues of HCC patients and the PLC/PRF/5 cell line, marking the beginning of exploration in this field. Subsequent studies employed Northern blot and in situ hybridization techniques to further investigate the integration process of HBV DNA.[8,59] The primary objective during this stage was to confirm the presence of HBV DNA in the host's liver cells and to propose the hypothesis that HBV might directly participate in the development of liver cancer. Researchers revealed the integration of HBV DNA in liver tissues of patients with HBV-related diseases, such as HCC, acute HBV hepatitis, chronic HBV infection, and HBV-related cirrhosis.[7] These studies provided a foundational framework for understanding how HBV leaves permanent genetic information within the cellular genetic material.

Intermediate Progress—PCR-Based Detection Methods

By the late 1980s, the study of Hepatitis B Virus (HBV) integration entered a new phase with the advent of cloning viral-cell junctions, nucleotide sequencing, and the development of Polymerase Chain Reaction (PCR) technology. The development of various PCR-based strategies, including Alu-PCR and inverse nested PCR (invPCR), enabled researchers to more precisely detect and quantify specific integration sites of viral DNA within the host genome.

This stage focused on detailed exploration of the integration events and their impact on host gene expression, including how integration events could activate nearby oncogenes or disrupt tumor suppressor genes. During this phase, researchers proposed several models of HBV integration to elucidate the molecular mechanisms. These included the "single-stranded gap" model based on the transition of DNA polymerase from human genome DNA to a nearby HBV genomic single-stranded area during cell DNA replication,[33] models related to the DR sequences (direct repeat sequences, short repeated motifs in the HBV genome involved in reverse transcription and integration), where integration into the host genome occurs following the deletion of the first two nucleotides of DR sequences, conserving DR1/DR2 polarity, and the existence of both virus-specific and nonspecific integration sites,[60,61] and models based on site-specific recombination mechanisms.[62] Furthermore, some studies suggested that HBV integration could cause insertional mutations, thereby inducing hepatocellular carcinoma by modulating cancer-related genes. For instance, research[63] on Woodchuck Hepatitis Virus (WHV) indicated that in woodchuck liver tumors, proto-oncogenes from the Myc family (especially N-myc2) were frequently integrated (and subsequently transcriptionally activated). Studies on integration breakpoints revealed that the most common integrated genes in the genomes of HCC patients were the X and C genes, where integration of the X gene could directly activate oncogenes (like Myc, Ras, Src, CyclinD1) and suppress tumor suppressor genes (like P53, Rb), thus participating in the development of HCC.[64–66] Other common integration sites included hTERT and MLL4, with telomerase reverse transcriptase dysregulation by hTERT in somatic cells linked to carcinogenic effects, and the activation of telomerase and its role in maintaining telomere length were key events driving liver cancer development.[29,67] These models and integration events opened new pathways for studying HBV integration at the molecular and genetic levels, laying a foundation for subsequent research.

Moreover, PCR-based diagnostic methods began to be applied clinically. PCR could more accurately quantify levels of HBV DNA in patients, providing a means to monitor the HBV integration status in chronic hepatitis B patients and being crucial for assessing the replication phase and the efficacy of antiviral treatment.[68]

Recent Trends—Detection Methods Based on High-Throughput Sequencing Technologies

High-throughput sequencing (HTS), also known as next-generation sequencing (NGS), has revolutionized the study of HBV integration by allowing millions of reads to be sequenced in a single run without prior knowledge of the target sequence. This technology enables the simultaneous analysis of thousands of integration events, providing unprecedented integration maps and detailed genetic information. Depending on the specific strategy and target, NGS can be utilized for whole-genome sequencing (WGS), whole-exome sequencing, RNA sequencing (RNA-seq), single-cell sequencing, and capture/enrichment NGS.[69] In 2012,[22] WGS and RNA-seq were first employed to detect HBV integration in hepatocellular carcinoma (HCC) patients, proving to be both sensitive and comprehensive in identifying and quantifying viral integrations across the human genome and transcriptome, significantly accelerating HBV integration research thereafter.

Mechanisms of Integration

Current research not only focuses on the mechanisms of integration but also explores the specific associations between integration and liver cancer development, such as the selectivity of integration sites and their correlation with the pathological progression of liver cancer. Recent studies based on HTS have proposed likely mechanisms of HBV integration, notably the non-homologous end-joining (NHEJ), a DNA repair pathway that ligates double-strand breaks without sequence homology) and microhomology-mediated end-joining (MMEJ) DNA repair pathways.[70–72] These pathways facilitate the joining of DNA ends during repair processes, thereby allowing HBV DNA fragments to integrate into the host genome. Concurrently, advanced technologies have enabled researchers to identify more integration sites and propose several viewpoints on how integration leads

to liver cancer development: (1) One viewpoint is chromosomal instability induced by integrated DNA. Chromosomal instability is a key characteristic of liver cancer, closely linked with poor prognosis, metastasis, and resistance to therapy.[73] Studies have shown that HBV integration is closely related to increased levels of chromosomal structural breakpoints and copy number variations.[22] Analysis using HTS of tumor and adjacent non-tumor tissues from HCC patients has revealed that HBV DNA fragments preferentially integrate at fragile sites of the host genome (intergenic regions, repetitive areas, CpG islands, and telomeres) and functional areas (including genes related to cell survival, metabolism, and cell cycle regulation). These areas of integration are prone to rearrangements and genetic alterations, leading to cancer development.[72–74] (2) Mutual promotion with hepatitis. The interaction between HBV DNA and hepatitis further exacerbates the accumulation of damage in the host liver cell genome, leading to genetic alterations.[75] Multiple studies have reported a positive correlation between the extent of integration of hepatotropic DNA viruses and oxidative damage,[73] and HBV-specific cytotoxic T lymphocytes (CTLs) selectively target and eliminate liver cells replicating HBV, leading to preferential clonal expansion of HBV-integrated hepatocytes.[76] Additionally, integrated HBV DNA is considered a potential source of HBsAg, whose presence plays a crucial role in the pathogenesis of hepatitis. It is widely believed that increased production of HBsAg leads to T-cell exhaustion, resulting in limited or impaired T-cell responses, even eliminating T-cells that recognize specific epitopes, thus leading to inflammatory responses and eventually progressing to HCC.[3,72,77] (3) Continuous expression of HBV genes mutated by integration, such as telomerase reverse transcriptase (TERT), mixed-lineage leukemia 4 (MLL4), cyclin E1 (CCNE1), and mutated HBV genes, which influence epigenetic modifications affecting cell proliferation, differentiation, apoptosis, metastasis, and angiogenesis, ultimately leading to the development of HCC.[78,79] In support of these mechanistic findings, previous reviews have also summarized the molecular consequences of HBV integration, including insertional mutagenesis, genomic instability, and dysregulation of oncogenes and immune modulators, all contributing to hepatocarcinogenesis.[80] These perspectives reinforce the biological and translational significance of our bibliometric observations.

Clinical Biomarkers and Diagnostic Innovations

Furthermore, integration research has expanded into precision medicine applications, including the development of therapeutic strategies and predictive models targeting specific integration events, and studying how integration affects immune evasion.[11,81–83] A recent analysis identified 396 genes related to HBV integration in tumor samples, with 28 genes frequently found in at least ten patients, highlighting these sites as hotspots related to the development of hepatocellular carcinoma (HCC).[84] The identification of these genes not only provides potential new targets for liver cancer diagnosis but also serves as a basis for early detection and prediction of HCC occurrence and recurrence.[85] Based on this, multiple studies have explored the feasibility of using HBV integration sites as non-invasive biomarkers for early diagnosis of liver cancer. For example, Chambal LM et al[86] confirmed that HBV DNA and its integration sites in blood can serve as non-invasive viral integration biomarkers for detecting liver cancer. Additionally, Zheng B et al[87] validated with novel circulating single-molecule amplification and resequencing technology that most integration events detected in cell-free DNA samples originated from tumor tissues, further confirming the potential of using HBV DNA integration as a circulating tumor marker. Yang Z et al[9] also indicated that viral integrations in cell-free DNA could offer new strategies for early diagnosis and monitoring. However, recent findings have raised important questions about the specificity of these markers. For instance, Salpini et al[84] emphasized variability in integration patterns across patients and limited reproducibility across clinical samples, suggesting that further validation and methodological standardization are needed before these approaches can be translated into routine diagnostics.

These research findings not only deepen our understanding of the relationship between HBV integration and liver cancer development but also open new pathways for utilizing these biomarkers in clinical practice for early diagnosis and treatment monitoring.

Research Hotspots

Mechanistic and Diagnostic Trends

By analyzing keyword bursts, keyword time clustering graphs, and trend topics, we can effectively identify current hotspots in HBV integration research and predict future research directions. These analytical tools have revealed

sustained high interest in keywords such as "mechanisms" "mutations" "liver cancer" "risk" and "HBV integration" indicating that research in the HBV integration field is primarily focused on exploring new mechanisms of HBV integration, identifying and validating the functional significance of new integration sites through innovative methods, and understanding how these integrations induce carcinogenesis in hepatocytes. Notably, research in this area is progressively moving towards precision treatment for liver cancer. Researchers are increasingly exploring how HBV integration events can be used as biomarkers to predict disease progression or response to treatment. This biomarker-based approach promises more personalized treatment strategies, potentially improving outcomes and survival rates.

Immune-Related and Therapeutic Innovations

The interaction between HBV integration and the host immune system has emerged as a cutting-edge issue. Current studies are investigating how the virus utilizes integration events to evade host immune surveillance, providing vital clues for the development of new immunotherapeutic strategies. Specifically, HBV integration can lead to the clonal expansion of hepatocytes harboring integrated viral DNA, even during the immune-tolerant phase of chronic infection, indicating ongoing immune-mediated selection pressures. Furthermore, HBV infection modulates immune checkpoints, such as PD-1 and CTLA-4, leading to T cell exhaustion and impaired antiviral responses.[76] Understanding how HBV affects host immune responses through these mechanisms will aid in developing new therapies, particularly in enhancing host immunity against viral integration and associated carcinogenesis. Although immune-related mechanisms are clearly relevant, specific terms such as "cytotoxic T lymphocytes (CTLs)" or "immune evasion" did not appear among the top burst keywords in our bibliometric analysis. This may be due to the current dispersion of such studies across different subfields and the use of diverse terminology, resulting in lower citation concentration. This discrepancy highlights the importance of complementing bibliometric findings with expert interpretation to fully capture emerging biological significance. It is noteworthy that, as described by Li CL et al, TERT and MLL have not only been identified as biomarkers of HBV integration-induced hepatocellular carcinoma, but also play important roles in oncogene activation and immune evasion.[88] Overall, HBV integration research not only deepens our understanding of viral carcinogenic mechanisms but also drives innovation in liver cancer diagnostics and treatment approaches. As these studies progress, we expect more diagnostic tools and therapeutic strategies based on HBV integration features to emerge, bringing new hope to liver cancer patients.

Strengths and Limitations

The bibliometric analysis of HBV integration research exhibits several significant strengths. Firstly, this study comprehensively analyzes the research trends in HBV integration using bibliometric methods, providing valuable guidelines and references for researchers in the field. Secondly, the use of multiple bibliometric tools for data analysis ensures the objectivity and accuracy of the results. Additionally, compared to traditional literature reviews, bibliometric analysis more comprehensively reveals research hotspots and frontier areas, thereby better guiding future research directions. However, this study also has some limitations. Firstly, the data are exclusively derived from the WOS database, which might not cover all relevant research, potentially leading to selection bias in the literature. Secondly, non-English papers were not included, possibly underestimating the contributions of non-English-speaking countries to HBV integration research. Future studies could consider multilingual corpora once tools for accurate cross-linguistic bibliometric mapping are more widely available. Moreover, one limitation of this study is the potential timeframe bias caused by delayed indexing of recent publications. As data collection was finalized on November 30, 2024, some 2023–2024 studies may not yet have been available in the database. Future bibliometric updates are encouraged to reassess trends once indexing is complete. Finally, bibliometric analysis mainly focuses on quantitative metrics such as publication volume and citation counts, especially for early-stage innovations that have not yet accumulated high citation counts, such as novel integration detection techniques.

Conclusion

The bibliometric analysis of HBV integration reveals the profound impact and ongoing progress in the field. From 1980 to 2024, leading researchers and institutions such as Professor Hino O, Professor Koike K, Institut Pasteur, Paris, and the

University of Hong Kong have significantly propelled the development of this field. In the current genomics-driven era, significant international collaboration, including China, the USA, Japan, and France, has collectively driven major breakthroughs in HBV integration-based liver cancer research. This has led to innovative treatment strategies, particularly in using integration sites as biomarkers to predict disease progression and treatment response. The collective work of key research clusters led by the above researchers has produced a substantial number of publications, many of which are published in high-impact journals such as Hepatology, Journal of Hepatology, and Nature, playing a crucial role in disseminating important findings. These studies not only deepen our understanding of the relationship between HBV integration and liver cancer but also set the tone for future research directions. Future studies will increasingly focus on refining the dynamics of HBV integration using high-throughput sequencing technologies and exploring how to optimize liver cancer treatment strategies by targeting these integration events. In particular, emerging directions include the integration of artificial intelligence (AI) to analyze complex genomic patterns, the establishment of longitudinal patient cohorts to track integration-driven disease progression, and the consideration of regulatory and ethical implications surrounding HBV integration testing in clinical practice. This continuous innovation in liver cancer treatment strategies ensures that scientific discoveries can be translated into practical clinical applications, ultimately improving treatment outcomes for patients globally.

Highlights

- This study represents the first bibliometric analysis in the field of hepatitis B virus integration.
- Utilizing leading bibliometric methodologies, this analysis explores the current research landscape and hotspots in the field of HBV integration, predicting future research trends.
- The main research directions in this field include prevention and epidemiology of HBV integration, integration sites and mechanisms, associations with hepatocellular carcinoma, and the consequences and treatment of integration.

Data Sharing Statement

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding authors.

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Author Contributions

JL, YB and YX conceived the study; JL, LX and XM acquired, analysed, and interpreted the data; JL prepared the manuscript; YB and YX edited the manuscript. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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