

The trends of retinoblastoma research in the past decade

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Abstract

• **AIM:** To conduct a bibliometric analysis of retinoblastoma (RB) research to delineate global research trends, identify key research contributors, and highlight emerging research directions in this field.

• **METHODS:** Publications from 2015 to 2024 were collected from the Web of Science Core Collection. Data on publication volume, citations, H-indexes, and collaborative networks were analyzed using CiteSpace.

• **RESULTS:** In total, 1719 publications were included. Annual publication outputs on RB research exhibited an overall upward trend. The United States dominated global RB research with 500 publications (29.09%), 8978 citations and an H-index of 43, followed by China (468 articles, 27.23%) and India. Switzerland and Spain yielded the highest average citation per article, at 29.00 and 27.72, respectively. Institution-wise, Thomas Jefferson University (76 publications) and Memorial Sloan Kettering Cancer Center (70 publications) ranked top in publication quantity. *Indian Journal of Ophthalmology* was the most prolific journal with 52 relevant articles, while Shields

CL was the leading author contributing 67 papers in this domain. Cited-reference analysis identified the article entitled “Global Retinoblastoma Presentation and Analysis by National Income Level” in *JAMA Ophthalmology* as the most frequently cited work with the strongest citation burst. Journals covering molecular biology and genetics constitute the fundamental academic basis for contemporary RB investigations. Keyword analysis demonstrated that “cancer”, “management”, “expression”, and “chemotherapy” were the most recurrent research hotspots.

• **CONCLUSION:** This study performed the first decade-long CiteSpace-based bibliometric analysis of RB. Substantial disparities in publication productivity and clinical practice exist across nations and institutions. Low- and middle-income countries (LMICs) remain burdened by diagnostic and therapeutic limitations for RB, highlighting the necessity of strengthened international collaboration. Future research priorities encompass overcoming chemotherapy resistance, optimizing intra-arterial chemotherapy (IAC) regimens, and translating molecular discoveries into accessible therapies via global partnerships.

• **KEYWORDS:** retinoblastoma; bibliometrics; CiteSpace

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INTRODUCTION

Retinoblastoma (RB) is the most common intraocular cancer in children. Its unique dual origin, involving both inherited genetic factors and acquired somatic mutations, has made it a central focus in translational oncology research^[1-2]. Clinicians traditionally diagnose RB through imaging studies and ophthalmic examinations. In recent years, the increasing use of genetic testing has allowed clinicians to diagnose RB earlier and more accurately^[3-4]. Conventional treatments for RB have mainly included surgery (such as enucleation), chemotherapy, radiation therapy, and local therapies. Today, emerging therapeutic approaches like gene therapy and vitreous surgery are being used more often in clinical practice^[5]. With advancements in medical technology, the treatment approach

for RB has shifted toward ensuring the child's survival and preserving the eyeball while working to keep some visual function, thereby improving the patient's quality of life. As a result, children who are diagnosed and treated early often have better outcomes and an improved quality of life^[6]. Consequently, 5-year survival rates in high income countries (HICs) now exceed 95%, and as a result, attention has shifted towards eye salvage and improving quality of life. However, significant global inequities persist—diagnostic delays in low- and middle-income countries (LMICs) lead to a 5-year metastatic mortality rate that is 10 times or even higher than that of HICs^[5,7], highlighting the imperative for transnational research collaboration^[6].

In this evolving scientific landscape, bibliometric analysis^[8] emerges as a powerful meta-research tool for systematic mapping of intellectual architectures through multi-dimensional assessment of: 1) temporal publication trends, 2) institutional collaboration networks, and 3) conceptual domain evolution. Contemporary bibliometric methodologies, particularly algorithm-driven visualization platforms like CiteSpace^[9], enable sophisticated analysis of: co-citation clustering for seminal paper identification, burst detection for emerging topic recognition, and betweenness centrality calculation for key node determination. This study employs CiteSpace to conduct a bibliometric analysis of RB research over the past ten years, with the goal of revealing the trajectory of the field's development, highlighting impactful studies, and identifying future research directions. We hope that this analysis will offer practical insights to help guide researchers and policymakers in advancing RB research and enhancing patient outcomes globally.

MATERIALS AND METHODS

Data Sources and Search Strategies To conduct a comprehensive bibliometric analysis, we selected the Science Citation Index-Expanded within the Web of Science database (WOS), which is known for its high-quality bibliographic data. We conducted a systematic search within WOS for literature published between 2015 and 2024 using the query: TS=(retinoblastoma) AND TS=(eye OR ocular OR oculus OR optical OR ophthalmic OR ophthalmology OR intraocular OR optic OR retinal OR retina) AND Language=(English). To eliminate potential bias from daily database updates, all searches were completed on February 21, 2025. Only original research articles and reviews from the core database were included. The first two authors independently executed identical search protocols to ensure result consistency, with outputs cross-validated for uniformity. This study analyzed publicly available bibliometric data from the Web of Science database and did not involve human participants or animals. Therefore, ethical approval was not required for this study.

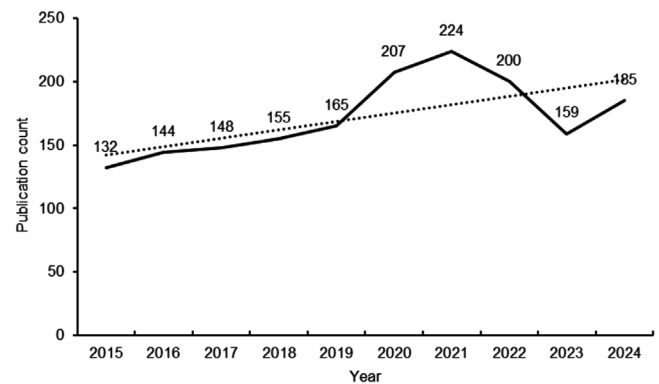


Figure 1 Global trend of annual publications related to retinoblastoma from 2015 to 2024.

Bibliometric Analysis Data extracted from eligible publications included titles, keywords, publication dates, geographic regions, institutions, authors, journals, citation counts, and H-indices. The H-index^[10], quantifying scholarly impact by identifying the number of papers (h) that each received $\geq h$ citations, was employed to evaluate productivity and influence across nations, institutions, and journals. These metrics were analyzed quantitatively and qualitatively using CiteSpace (v6.4.R1). Software parameters included: 1) Time slicing (2015–2024; 1-year intervals); node types (references, keywords); 2) g-index threshold (25), defined as the highest value where the average citation count of the top g publications equals g.

To reduce co-citation network complexity, the Pathfinder algorithm was implemented. This method removes edges violating triangle inequality principles, preserving essential structural relationships while eliminating redundant connections. Default visualization settings in CiteSpace were retained to generate interpretable network maps, enabling precise identification of key research trends and intellectual clusters in RB studies. This approach balanced network simplification with structural fidelity, ensuring robust representation of the field's evolving landscape.

RESULTS

Annual Publication Volume A quantitative analysis of publication volume and timeline can reveal the evolutionary characteristics of academic research in related fields. As shown in Figure 1, the annual publication distribution in RB research over the past decade has shown a general trend of slow growth; however, there has been a noticeable decline in the number of publications in the years following 2021, which may be attributed to the impact of the COVID-19 pandemic and ongoing shifts in research priorities.

Countries or Regions This study analyzed a corpus of 1719 papers published in 526 academic journals, involving 7696 researchers from 2198 institutions spanning 141 countries/regions. USA and China dominated scholarly production with

similar publication counts (500 vs 468, respectively), though differing in proportional contributions (29.09% vs 27.23%, respectively). Subsequent contributors included India (243 articles, 14.14%), Canada (99 articles, 5.76%), and England (93 articles, 5.41%). These countries collectively contributed significantly to the research output in this field.

Citation metrics revealed distinct patterns: The USA led in total citations (8978) and H-index (43), followed by China (7019 citations; H-index 39). Switzerland emerged as the most citation-efficient nation with the highest average citations per paper (29.00), surpassing Spain (27.72), Canada (23.06), France (20.38), and England (19.46), as shown in Table 1. Notably, the United States demonstrated exceptional interdisciplinary connectivity with the highest betweenness centrality (0.12), suggesting its pivotal role as a global research broker (Figure 2).

Institutions The top 10 institutions in terms of publication output are detailed in Figure 3. Collectively accounting for 659 publications, these institutions represent 38.34% of the total scholarly output in this field. Notably, Thomas Jefferson University emerged as the most productive contributor with 76 publications (4.42%), followed closely by Memorial Sloan Kettering Cancer Center (70 articles, 4.07%) and the University of Toronto (68 articles, 3.96%).

Journals and Co-cited Journals A comprehensive analysis of 526 journals publishing on RB revealed distinct patterns in scholarly communication, with 37 core journals each contributing ≥ 10 articles. The top 10 most prolific journals, which account for 22.51% of the overall publication output, are detailed in Figure 4. The *Indian Journal of Ophthalmology* dominated with 52 publications (3.03%), followed closely by *Ophthalmic Genetics* (49; 2.85%) and the *British Journal of Ophthalmology* (46; 2.68%). Co-citation metrics demonstrated enduring scholarly influence, with the *British Journal of Ophthalmology* (1042 citations) maintaining supremacy over *Ophthalmology* (1015) and *Acta Ophthalmologica* (734), followed by *PLoS One* (658) and *Investigative Ophthalmology & Visual Science* (593).

Dual-map overlay analysis revealed four principal knowledge transfer pathways. These pathways indicated that molecular/biology/immunology was predominantly referenced by researchers in the fields of molecular/biology/genetics ($z=6.88$, $f=5812$), medicine/medical/clinical ($z=1.81$, $f=1714$), and neurology/sports/ophthalmology journals ($z=4.87$, $f=4910$). health/nursing/medicine was predominantly referenced by neurology/sports/ophthalmology journals ($z=1.89$, $f=1691$), as visualized through citation trajectory mapping that employed left-to-right gradient pathways to represent cross-disciplinary knowledge flow. This multilayered bibliometric profile underscores the sophisticated intellectual networks sustaining RB scholarship across biological, clinical, and translational

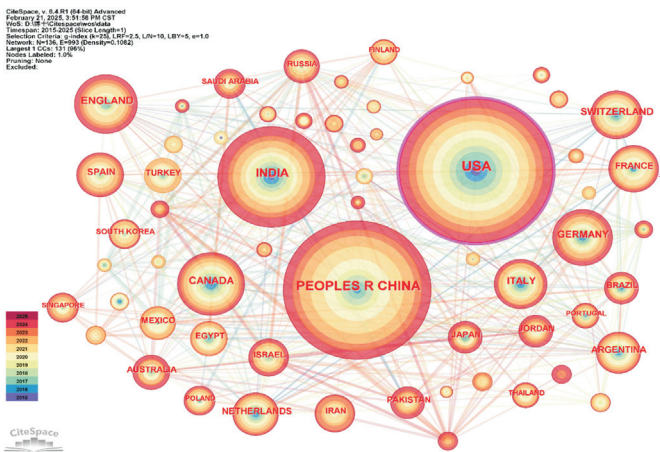


Figure 2 The network map of collaboration between countries/regions based on CiteSpace.

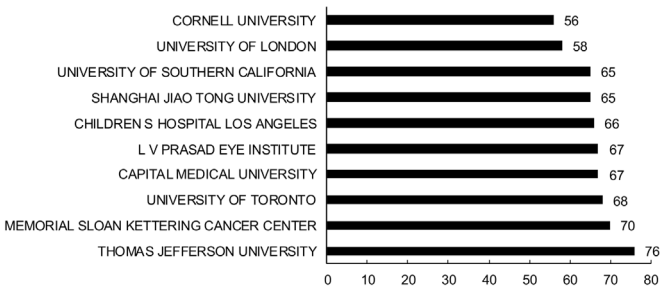


Figure 3 Distribution of the top 10 institutes publishing research on retinoblastoma.

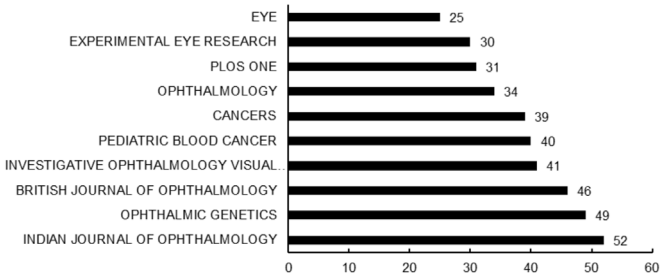


Figure 4 Distribution of the top 10 journals publishing research on retinoblastoma.

research domains (Figure 5).

Authors The scholarly impact of authors in RB research is reflected through their publication output, with the top 10 contributors collectively producing 462 papers, representing 26.87% of the total publications in the field (Table 2). Leading this cohort is Shields CL, whose 67 publications (3.90%) establish them as the most prolific contributor, followed by Abramson DH (62, 3.60%), Kaliki S (59, 3.43%), Francis JH (54, 3.14%), and Berry JL (50, 2.91%). This concentration of productivity among the top five authors alone accounts for 16.88% of the field's total output, underscoring their pivotal role in advancing RB research. Their work spans clinical insights, genetic analyses, and therapeutic advancements central to the field's progress (Table 2).

References with Citation Burst To identify the hotspots in RB study, Citespace software was used to analyze the co-cited

Table 1 The top 10 countries/regions contributing to retinoblastoma

Rank	Countries	Article count	Percentage	H-index	Total citations	Average citation per article
1	USA	500	29.09%	43	8978	17.96
2	China	468	27.23%	39	7019	15.00
3	India	243	14.14%	29	3115	12.82
4	Canada	99	5.76%	22	2283	23.06
5	England	93	5.41%	19	1810	19.46
6	Germany	89	5.18%	22	1595	17.92
7	Switzerland	67	3.90%	20	1943	29.00
8	Italy	66	3.84%	20	1176	17.82
9	France	64	3.72%	19	1304	20.38
10	Spain	54	3.14%	20	1497	27.72

Table 2 The top 10 authors contributing to retinoblastoma

Rank	Author	Countries	Article count	Percentage	H-index	Total citations	Average citation
1	Shields CL	USA	67	3.90%	22	2031	30.31
2	Abramson DH	USA	62	3.60%	24	1814	29.26
3	Kaliki S	India	59	3.43%	14	799	13.54
4	Francis JH	USA	54	3.14%	22	1172	21.70
5	Berry JL	USA	50	2.91%	18	987	19.74
6	Munier FL	Switzerland	40	2.33%	15	1529	38.23
7	Reddy MA	England	34	1.98%	14	748	22.00
8	Yousef YA	Jordan	33	1.92%	13	708	21.45
9	Schaiquevich P	Spain	32	1.86%	16	709	22.16
10	Fabian ID	Israel	31	1.80%	15	703	22.68

references. The top 19 clusters and co-cited articles are shown in Figure 6A. The modularity Q (0.87) and mean weighted silhouette (0.96) indicate highly consistent cluster contents. The largest cluster is labeled by #0 intra-arterial chemotherapy, followed by #1 proliferation, #2 deep learning, #3 aqueous humor, #4 and vitreous seeds, *etc.* The timeline plot depicts the research progress of the field and its twenty subfields over the past decade (Figure 6B).

We identified the top 20 most frequent bursts, as shown in Figure 6C. The blue line indicates the publication period, while the red line marks the duration of the citation surge. The most cited article is “Global retinoblastoma presentation and analysis by national income level”^[5], published in 2020, and has been cited 110 times (intensity=25.15), with a burst intensity of 25.15, reflecting its significant influence on recent research directions.

Keyword Burst Detection and Analysis Keywords are a summary of the research field. Analyzing high-frequency keywords can reveal research hotspots and relationships between various publications. We generated a co-occurrence network containing 421 nodes and 583 links, with a network density of 0.0066. Figure 7A illustrates the keyword co-occurrence network map, with nodes represented as tree-ring diagrams. The ring size in the visualization directly reflects keyword frequency, where broader rings signify terms with

greater prominence in the research landscape. The size of the rings corresponds to keyword frequency, with larger rings indicating higher frequency. Color gradations within the rings represent different years of keyword emergence. The analysis identifies five key nodes “cancer”, “management”, “expression”, “chemotherapy”, and “intraocular retinoblastoma”, which demonstrate extensive radiating connections with other nodes and occupy central positions in the research field.

Burst analysis of relevant keywords can show how a research field has developed over time and where the hotspots are. We picked the top 20 keywords in the RB research area to look at them closely, as shown in Figure 7B. Based on when the research happened, we split it into three parts. Early phase (2015–2017): This part focused on understanding different levels of the disease and how to treat it, like looking at RB in one eye or both eyes, taking out the eye, and using radiation. Middle phase (2017–2020): During this time, there were significant steps forward in learning more about the disease and creating new ways to diagnose it, such as studying how cells grow, stopping certain genes, and using liquid biopsies. Late phase (2020–2024): This part was all about understanding how the disease spreads, managing it in the clinic, and figuring out why some drugs don’t work anymore, with a lot of work being done across different centers and looking at how drugs

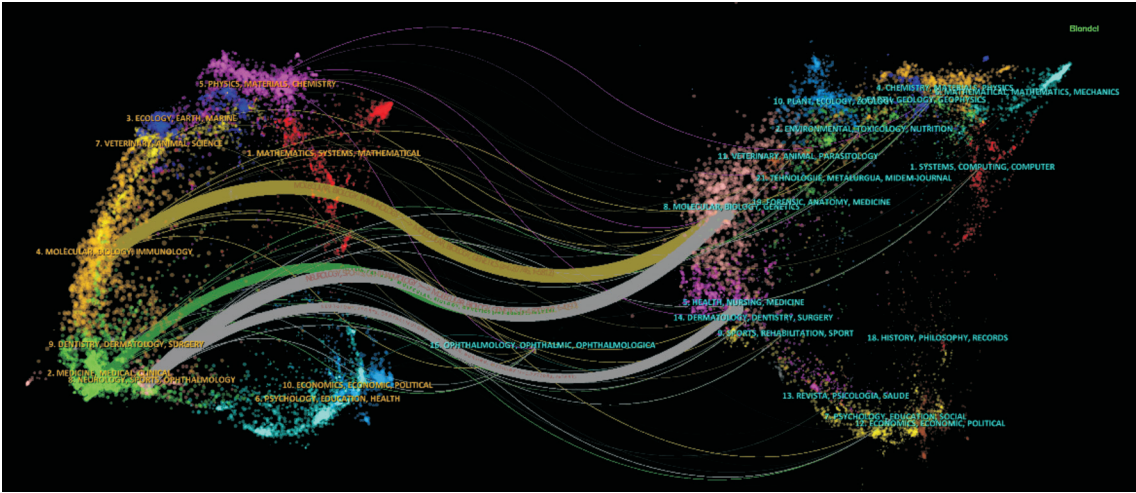


Figure 5 The dual-map overlay of academic journals in the field of retinoblastoma based on CiteSpace software.

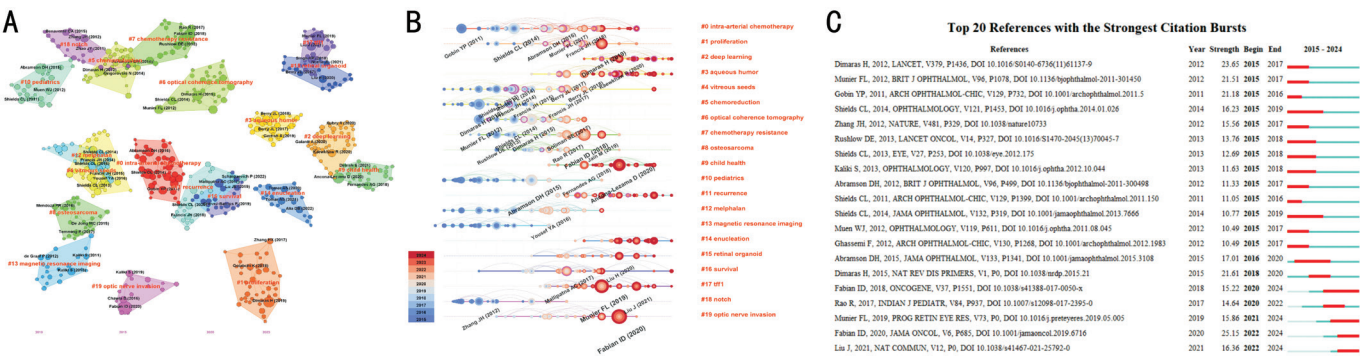


Figure 6 References with citation burst A: Clustered network map of co-cited references; B: Timeline view of clusters of co-cited references; C: Top 20 references with the strongest citation bursts (2015–2024).

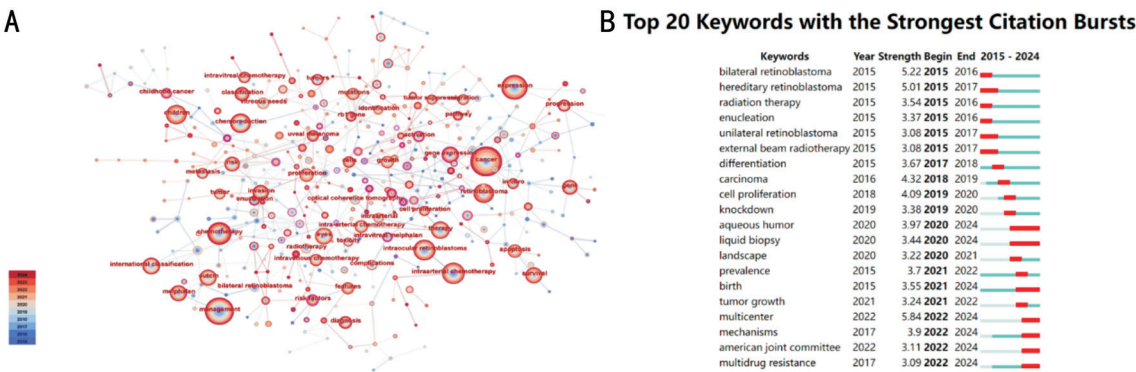


Figure 7 Keyword burst detection and analysis A: Visualization map of co-occurrence keywords; B: The top 20 keywords with the strongest citation bursts.

resist. Looking at how long research has been going on, terms like “liquid biopsy” and “aqueous humor” have been receiving steady attention since 2020. Additionally, from 2022 to 2024, the RB research field saw a surge in activity, with 10 keywords experiencing significant citation bursts in a short period.

DISCUSSION

Research Trends Overview This study systematically examines global RB research trends from 2015–2024 through bibliometric methods. Analysis shows sustained growth in annual publications over the past decade, though a slight decline after 2021 potentially links to COVID-19 pandemic

impacts (Figure 1). USA maintains leadership across multiple indicators: contributing 29.09% of publications, accumulating 8978 total citations, and achieving the highest H-index (43) and centrality score (0.12). While China and India rank second and third in publication output, their comparatively lower citation rates (15.00 and 12.82 per paper, respectively) and minimal centrality scores (both 0.01) indicate room for improving international collaboration impact. Switzerland and Spain demonstrate exceptional research influence with average citations per paper reaching 29.00 and 27.72, respectively (Table 1), likely reflecting their specialized clinical studies.

Institutional analysis identifies Thomas Jefferson University (76 papers), Memorial Sloan Kettering Cancer Center (70 papers), and University of Toronto (68 papers) as global research leaders. The top 10 institutions collectively produced 659 papers, accounting for 38.34% of total outputs, confirming their pivotal role in advancing RB studies. Author networks highlight Shields CL (67 papers) and Abramson DH (62 papers) were identified as key contributors focusing on chemotherapy optimization and molecular mechanisms (Table 2), with most leading researchers affiliated with Western institutions. Journal analysis showed the *Indian Journal of Ophthalmology* (52 papers) and *British Journal of Ophthalmology* (46 papers) lead in publication volume, while the *Journal of Clinical Oncology* (1514 citations) and *New England Journal of Medicine* (1369 citations) dominate citation impact (Figure 4). Dual-map overlay of academic journals reveals molecular research continues serving as the foundation for clinical ophthalmology advancements, with researchers advised to monitor these core journals for emerging developments in ocular melanoma immunotherapy (Figure 5).

Reference Analysis Citation patterns establish the intellectual backbone of research domains, significantly shaping subsequent investigations. Figure 6 details the decade's most cited RB publications. The article "Global retinoblastoma presentation and analysis by national income level"^[5] published in *JAMA Oncology* emerges as the field's cornerstone with 110 citations and peak burst strength, offering critical insights through its multinational comparison of RB patient outcomes. By contrasting clinical trajectories across income levels, the work exposes delayed diagnoses and poorer prognoses in LMICs—findings now widely adopted as standard references that emphasize global cooperation's necessity. Complementing this, The review "Retinoblastoma"^[1] published in *Lancet* (2012) remains pivotal for synthesizing management protocols and proposing actionable strategies to enhance pediatric survival rates, serving as an early-stage clinical guidepost.

Keyword Co-Occurrence Network Central network nodes—"intra-arterial chemotherapy", "chemotherapy", and "enucleation"—encapsulate the field's core challenge: optimizing tumor control with ocular preservation. Current RB chemotherapy advances revolve around three modalities: intravenous chemotherapy (IVC), intra-arterial chemotherapy (IAC), and intravitreal approaches. IAC's targeted ophthalmic artery delivery achieves localized high drug concentrations with reduced systemic toxicity, demonstrating superior ocular salvage rates compared to IVC. Shields *et al*^[11] reported 100% ocular salvage rates for primary Group B/C RB and 94% for Group D RB using IAC, though efficacy dropped to 36% for Group E. Despite precision advantages, IAC faces barriers including technical complexity, elevated costs, and isolated

metastatic incidents post-treatment^[12-13]. For advanced cases with vitreous seeding, intravitreal methods excel by ensuring rapid therapeutic drug levels^[14]. The keyword "multidrug resistance" (intensity: 3.09) highlights chemotherapy resistance as a critical barrier, emerging as a focal research area^[15]. Concurrently, burst keywords "multicenter" (intensity: 5.84) emphasize the growing role of international collaboration in optimizing care for RB patients in LMICs^[16-17].

Keywords like "RB1 mutation" and "cell proliferation" map fundamental research directions. The RB1 tumor suppressor—central to cell cycle control and genomic stability—undergoes biallelic inactivation in about 97% cases^[18], while MYCN amplification drives oncogenesis in RB1-wild-type tumors (about 3%), correlating with aggressive phenotypes^[19]. Cone precursors' unique gene profiles make them susceptible to RB1/MYCN-driven transformation^[20]. Preclinical breakthroughs target MDM2^[21], MYCN^[22], SKP2^[23], and SYK^[24], signaling a molecular therapy era. Tumor evolution involves layered genomic/epigenetic changes—1q+/6p+ copy variations, *BCOR/CREBBP* mutations, and methylation dysregulation^[25-26]. Burst terms "liquid biopsy" and "aqueous humor" spotlight noninvasive diagnostic progress, where aqueous cfDNA analysis dynamically tracks RB1 mutations/MYCN status^[27-28], achieving high sensitivity for early detection, treatment response assessment, and relapse prediction^[3].

While our systematic evaluation of RB literature from WOS database provides comprehensive analysis, three inherent limitations warrant consideration. First, the exclusive inclusion of English-language publications risks omitting significant non-English research findings, particularly from regions with high disease prevalence. Second, observed publication declines post-2020 (-18% vs 2015–2019 baseline) likely reflect COVID-19 pandemic-related disruptions to translational research, potentially distorting contemporary hotspot identification. Third, despite selecting WOS for its superior publication-type classification accuracy, residual misclassification risks persist. While previous analyses offer a broad historical overview^[29], our decade-focused analysis delves deeper into the recent research landscape, uniquely tracing the timeline of hotspot evolution and highlighting key molecular drivers of the field's future.

In conclusion, this analysis highlights the imperative for global collaboration to bridge RB outcome disparities, particularly in LMICs where delayed diagnoses and restricted access to advanced therapies remain prevalent. While IAC and intravitreal chemotherapy mark therapeutic breakthroughs, their optimization for advanced-stage cases and resistance mechanisms requires urgent prioritization. Emerging modalities like liquid biopsy and epigenetic profiling align with precision medicine paradigms, offering early detection

capabilities and personalized treatment pathways. Crucially, developmental biology insights—particularly tumor origins in cone precursors—and genomic evolution patterns (1q+/6p+ alterations) demand deeper exploration to uncover novel targets. Translation efforts should emphasize three pillars: multinational clinical trials validating resource-adaptive protocols, cost-effective LMIC solutions, and multi-omics integration. Through synergistic alignment of these priorities, the research community can concurrently advance survival rates and vision preservation worldwide.

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