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Research article

Knowledge mapping of AURKA in Oncology : An advanced Bibliometric analysis (1998–2023)

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ABSTRACT

AURKA, also known as Aurora kinase A, is a key molecule involved in the occurrence and progression of cancer. It plays crucial roles in various cellular processes, including cell cycle regulation, mitosis, and chromosome segregation. Dysregulation of AURKA has been implicated in tumorigenesis, promoting cell proliferation, genomic instability, and resistance to apoptosis. In this study, we conducted an extensive bibliometric analysis of research focusing on Aurora-A in the context of cancer by utilizing the Web of Science literature database. Various sophisticated computational tools, such as VOSviewer, Citespace, Biblioshiny R, and Cytoscape, were employed for comprehensive literature analysis and big data mining from January 1998 to September 2023. The primary objectives of our study were multi-fold. Firstly, we aimed to explore the chronological development of AURKA research, uncovering the evolution of scientific understanding over time. Secondly, we investigated shifting trends in research topics, elucidating areas of increasing interest and emerging frontiers. Thirdly, we delved into intricate signaling pathways and protein interaction networks associated with AURKA, providing insights into its complex molecular mechanisms. To further enhance the value of our bibliometric analysis, we conducted a meta-analysis on the prognostic value of AURKA in terms of patient survival. The results were visually presented, offering a comprehensive overview and future perspectives on Aurora-A research in the field of oncology. This study not only contributes to the existing body of knowledge but also provides valuable guidance for researchers, clinicians, and pharmaceutical professionals. By harnessing the power of bibliometrics, our findings offer a deeper understanding of the role of AURKA in cancer and pave the way for innovative research directions and clinical applications.

1. Introduction

Cancer, a significant global public health concern, poses formidable challenges due to its widespread prevalence and high mortality rates [1]. Therefore, it is of utmost importance to prioritize efforts aimed at discovering effective interventions to mitigate its detrimental impact on human health [2]. Aurora Kinase A (AURKA), a pivotal molecule involved in the regulation of cellular processes, has

Abbreviations: AURKA, Aurora Kinase A; WOS, Web of Science; AKIs, AURKA Inhibitors; Chemo, Chemotherapy; Immune, immunotherapy; HDACi, Histone Deacetylase Inhibitors Vascular Endothelial Growth Factor Inhibitors; ARIs, Androgen Receptor Inhibitors.

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emerged as a key player in cancer research [3].

Belonging to the Aurora kinase family, which encompasses AURKA, AURKB, and AURKC, AURKA, also known as STK15 or BTAK, is a serine/threonine kinase primarily associated with the precise control of mitosis and has garnered substantial attention in cancer research [4]. This attention stems from its critical role in maintaining genome stability and ensuring accurate cell division. AURKA exerts its biological function by governing chromosome alignment and segregation during mitosis [5]. Through phosphorylation of various mitotic proteins, including histone H3 and TPX2, AURKA orchestrates the progression of mitosis and guarantees the faithful separation of chromosomes into daughter cells [6]. Dysregulation of AURKA can lead to chromosomal instability, aberrant cell division, and aneuploidy, all of which significantly contribute to the initiation and progression of tumors [7–9]. Beyond its fundamental involvement in mitosis, AURKA has been implicated in diverse cellular processes, such as centrosome maturation regulation, spindle assembly checkpoint signaling, DNA damage response, and cell migration [10,11] The abnormal expression or activity of AURKA has been detected across various types of cancer, including breast, lung, colorectal, pancreatic, hepatocellular, and ovarian cancers, rendering it an attractive target for anticancer therapies [12–15]. Nevertheless, while the transformative potential of AURKA is increasingly recognized, its clinical application spectrum remains relatively limited [16]. Furthermore, despite the extensive research conducted on AURKA, there remains a dearth of systematic curation and quantitative analysis regarding its impact on cancer. Consequently, synthesizing the existing body of literature surrounding AURKA could yield valuable insights into the current state of research on AURKA, its notable contributions, and future directions.

Bibliometrics, as a scientific discipline, assumes a crucial role in analyzing and quantifying scientific publications [17]. It employs mathematical and statistical methods to evaluate various facets of scholarly literature, such as publication trends, citation patterns, collaboration networks, and research focal points [18]. In line with this, our study aims to comprehensively analyze the available literature on AURKA's involvement in cancer from 1998 to 2023 by leveraging bibliometric techniques. Through an exploration of the characteristics of these publications, we seek to elucidate the hotspots and evolutionary trends of AURKA in cancer research utilizing knowledge mapping methodologies. This endeavor not only promises to enhance our understanding of this molecule but also serves as a guiding resource for future investigations in this field.

By conducting a rigorous bibliometric analysis, our study endeavors to bridge the existing knowledge gap and generate novel insights into AURKA's intricate involvement in cancer. Additionally, this comprehensive analysis will equip researchers, clinicians, and policymakers with a panoramic view of the current landscape of AURKA research, facilitating informed decision-making and fostering further advancements in cancer therapeutics.

2. Materials and methods

2.1. Data acquisition and selection

Web of Science (WOS), a robust digital repository known for high-quality academic articles and widely recognized as suitable for bibliometric analyses, served as our primary data source in this study. To ensure comprehensive and accurate data retrieval, the indices selected were SCI-EXPANDED and SSCI. Our final search strategy encompassed a set of synonymous terms including AURKA, STK15, STK6, BTAK, and ARK1. These terms were combined with search parameters related to cancer such as "cancer*", "tumor*", "oncology", and various relevant subtypes (e.g., "neoplasm*", "carcinoma*", "lymphoma*", "sarcoma*", "leukemia*") to capture a wide range of publications. The time span covered from January 1998 to September 2023, with the cut-off for data retrieval set on September 1, 2023. The literature types were confined to 'Articles' and 'Reviews.' By utilizing the Topic Search (TS) field, we aimed to retrieve literature that contained the specified terms (AURKA) within the titles, abstracts, keywords, or other relevant sections. This approach allowed us to cover various aspects of AURKA molecular research in a broader range of publications. The initial search yielded 2212 journal articles. After rigorous data cleaning and selection processes, a total of 1921 valid papers were identified, comprised of 1751 original research articles and 170 review articles. Detailed information regarding these processes is provided in Table 1 and Fig. 1.

Table 1
Summary of data source and selection.

Category	Specific Standard Requirements
Research database	Web of Science core collection
Citation indexes	SCI-EXPANDED; SSCI
Searching period	January 1998 to September 2023
Language	"English"
Searching keywords	(TS= ("Aurora Kinase A" OR "Aurora-A kinase" OR "Aurora A kinase" OR "AURKA" OR "STK15" OR "serine/threonine kinase 6 (STK6)" OR "breast tumor amplified kinase (BTAK)" OR "aurora-related kinase 1 (ARK1)") AND TS= ("cancer*" OR "tumor*" OR "oncology" OR "neoplasm*" OR "carcinoma*" OR "lymphoma*" OR "sarcoma*" OR "leukemia*")
Subject categories	AURKA & CANCER
Document types	"Articles" & "Review"
Data extraction	Export with records and cited references in plain text format
Sample size	1921

2.2. Data analyses and visualization

In this study, we applied a combination of bibliometric analysis, bioinformatics techniques, and meta-analysis to investigate the research landscape surrounding AURKA in the field of oncology. The tools utilized included Vosviewer, CiteSpace, R package "bibliometrix," and Stata (version 15.1) for data integration and visualization. First, through bibliometric techniques, a comprehensive review and quantitative analysis of existing literature on AURKA in oncology were conducted. Various aspects such as authorship,

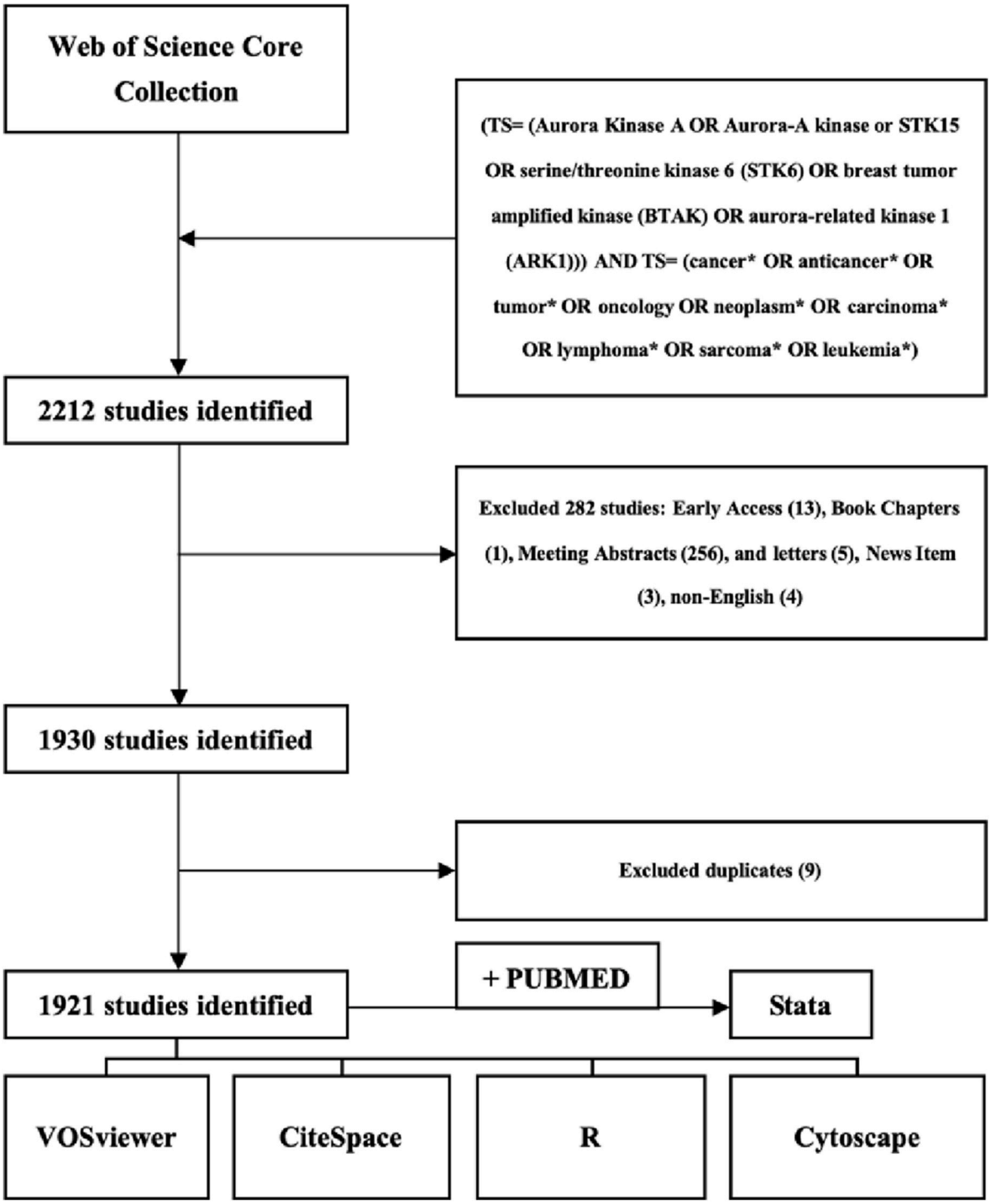


Fig. 1. Publications screening flowchart.

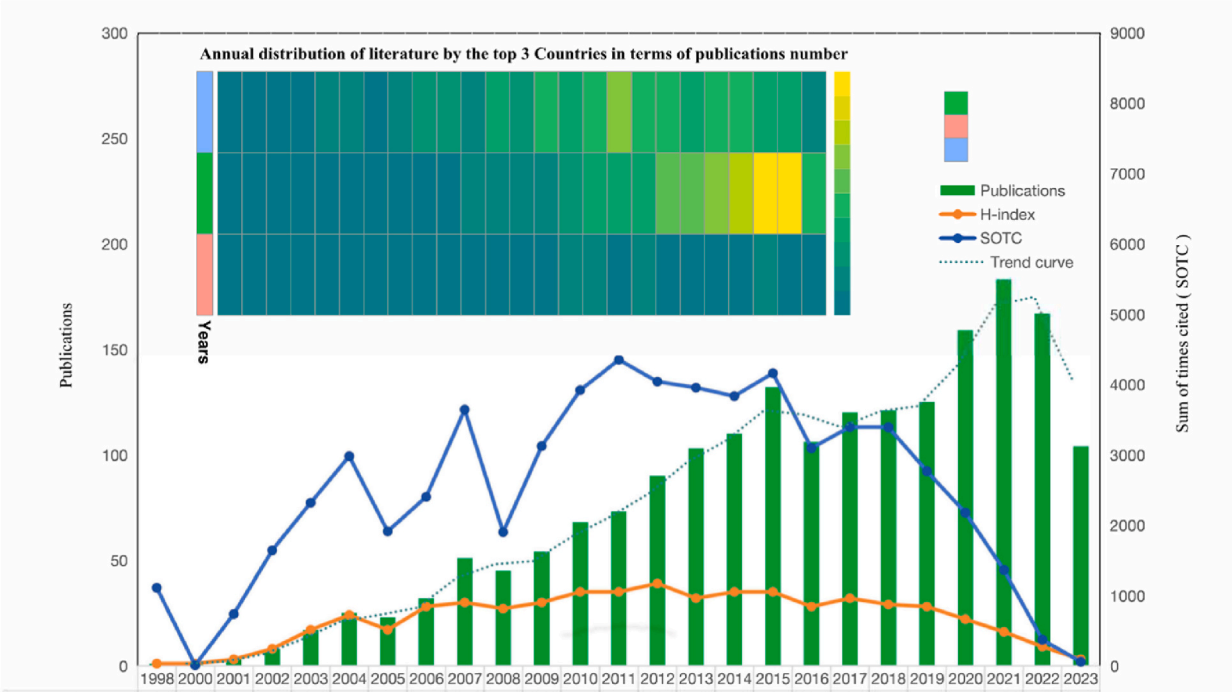
keywords, publications, countries, institutions, and references were examined to gain insights into the evolution and intrinsic connections of AURKA research within the oncological landscape. To explore the biological significance of co-occurring molecular keywords with AURKA, VOSviewer was employed to extract total keywords from 1921 articles. These keywords were then compared with human genome data to identify biologically relevant associated genes. Subsequently, GO/KEGG clustering analysis was performed using the R package clusterProfiler to further understand the functional implications of the identified keywords and associated genes [19]. Additionally, protein-protein interaction (PPI) networks were constructed using Cytoscape software (version 3.10.1) to elucidate the interactions and relationships among proteins related to AURKA. Furthermore, we conducted a meta-analysis utilizing prognostic data pertaining to AURKA and cancer patients, which is thoroughly outlined in Supplementary Table 1. In order to ensure comprehensive analysis, with a specific focus on prognosis-related data associated with AURKA, we extensively integrated data from PubMed. This integration allowed us to expand our dataset and bridge any potential gaps in article coverage that may exist when relying solely on the Web of Science database. By employing these comprehensive methodologies, we were able to gain profound insights into the multifaceted role of AURKA in cancer research and identify potential avenues for future exploration.

3. Results

3.1. General overview of included studies

This study provides a rigorous analysis of 1921 research articles with an H-index of 116 focusing on the Aurora kinase A (AURKA) in the field of oncology. The annual average publication rate was 77 articles, involving contributions from 12,602 authors, 512 institutions, and 68 countries. These publications were distributed across 614 different journals and accumulated a total of 59,942 citations from 5185 distinct journals. From the trend curve depicting the overall publication trend, it is evident that the volume of publications in this field exhibits a steady growth pattern. Notably, there were two minor peaks in publication activity observed in 2015 (132 studies) and 2021 (183 studies), with a consistent increase in publication output before 2015, as depicted in Fig. 2. This indicates that research related to AURKA in the field of oncology has experienced continuous and robust development.

In 2021, the number of publications reached its highest point, with the United States, China, and Germany emerging as the three most influential countries in terms of publication output. However, it is important to note that the United States and Germany have played pioneering roles in studying the significance of this molecule in cancer from an early stage. On the other hand, China has demonstrated consistent growth in publication volume over the past decade, injecting new research vigor into this field. To surpass the impact of earlier literature, as measured by metrics such as H-index and SOTC, further advancements are necessary. Therefore, we



	1998	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
Publications	1	1	3	8	17	25	23	32	51	45	54	68	73	90	103	110	132	106	120	121	125	159	183	167	104
H-index	1	1	3	8	17	24	17	28	30	27	30	35	35	39	32	35	35	28	32	29	28	22	16	9	3
SOTC	1109	7	733	1638	2314	2977	1907	2398	3639	1896	3120	3916	4349	4038	3951	3830	4158	3091	3391	3387	2765	2173	1360	368	56

Fig. 2. Annual distribution of literature in AURKA research in cancers.

anticipate that more in-depth investigations will unveil profound breakthroughs associated with AURKA in the domain of oncology.

3.2. Distribution of countries and institutions

Analyzing the countries and institutions contributing to the published literature (as seen in Fig. 3 and Table 2), the findings reveal that the United States contributed 661 articles, China contributed 681, and Germany contributed 139. However, it is important to note that the United States and Germany have been involved in research in this field for a longer period, leading to higher citation rates, particularly with a focus on highly cited articles. Examining the top 10 institutions in terms of publication volume, Sun Yat-Sen University (China), University of Texas MD Anderson Cancer Center (USA), and Millennium Pharmaceuticals Inc. (USA) were the top three contributors. Additionally, it can be observed from Fig. 3 that countries and institutions with higher publication output also exhibit stronger collaboration intensity.

3.3. Analysis of journals and authors

The field of oncology has experienced a growing research focus on the AURKA molecule, as evident from an increasing number of dedicated high-quality journals. Fig. 4 presents that a total of 614 journals have contributed to disseminating research related to AURKA in oncology. Our analysis further supports adherence to Bradford's Law [20], with fewer core journals having a higher publication volume, as demonstrated by the distribution of publications across different zones detailed in the Supplementary Table 2. Table 3 showcases the top 10 journals that have made significant contributions in this area. Among these journals, "Oncotarget" stands out as the leading publication with 48 articles, representing approximately 2.5 % of the total publication output. This underscores the journal's dedication to publishing cutting-edge research on AURKA. Following closely behind, "Clinical Cancer Research" and "Oncogene" rank second and third, respectively, with 45 and 39 articles each. These journals have also played a pivotal role in fostering advancements in our understanding of the AURKA molecule within the field of oncology.

To further explore the representative scholars and core research forces of AURKA in oncology research, we performed an analysis of the author collaboration network as shown in Fig. 4. Among the 12,602 authors, the author with the highest number of publications has accumulated 37 papers. According to Price's law, authors with more than 5 publications are considered core authors in this field [21]. There are a total of 114 core authors who have published a total of 834 papers, accounting for 43.4 % of the total publication output. This is close to the "half" (50 %) standard proposed by Price, indicating that a relatively stable author collaboration group has formed in this field. Additionally, applying Lotka's inverse square law to evaluate core authorship (the 114 authors with five or more publications accounted for approximately 1 % of the total of 11,014 authors with one publication, close to the expected proportion of $1/5^2$), it is also in line with Lotka's inverse square law. Consistent with Lotka's Law, our study found that around 87.4 % of the authors published only one paper, indicating that the majority of scholars adhere to the principle of having a single publication [22]. Interestingly, this scarcity of highly prolific authors in the field of AURKA research within oncology suggests a significant presence of newcomers exploring this specific area. Among the highly productive authors, the first-ranked author is Jeffrey A. Ecsedy from Millennium Pharmaceut Inc, Dept Translat Med, Cambridge, MA USA. As of September 2023, he has published a total of 37 papers, with 2631 citations and an average citation count of 71.11 per paper. The second-ranked author is Quetin Liu from Sun Yat Sen Univ, State Key Lab Oncol South China, with 25 publications and 902 citations, averaging 36.08 citations per paper. The third-ranked author is Subrata Sen from the University of Texas M.D. Anderson Cancer Center, with a cumulative publication count of 25 and a citation frequency of 3950 (see Table 3).

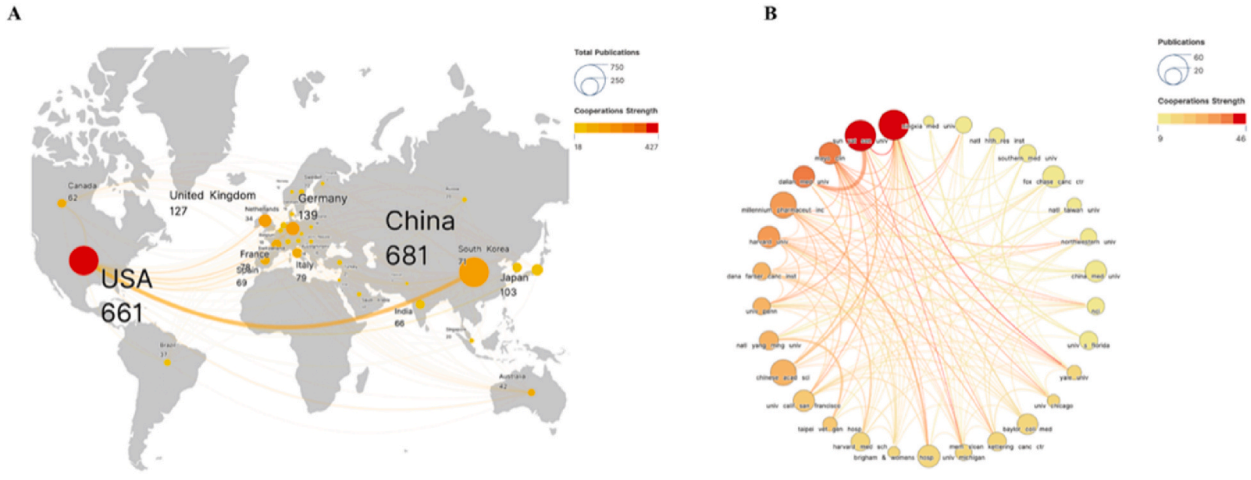


Fig. 3. The geographical distribution and cooperation relationships of countries (A) and institutions (B) on research of AURKA of cancers.

Table 2
TOP10 Countries and Organizations in AURKA of cancers research field.

Rank	Country	Documents	Citations	C/P	Organization	Documents	Citations	C/P
1	China	681(35.5 %)	13273	19.49	Sun Yat-Sen University	60	1678	27.97
2	USA	661(34.4 %)	32936	49.83	University of Texas MD Anderson Cancer Center	58	2672	46.07
3	Germany	139(7.2 %)	7536	54.22	Millennium Pharmaceuticals Inc.	43	3258	75.77
4	UK	127(6.6 %)	5614	44.20	Chinese Academy of Sciences	42	1162	27.67
5	Japan	103(5.4 %)	5393	52.36	Vanderbilt University	31	1831	59.06
6	Italy	79(4.1 %)	2435	30.82	Dalian Medical University	30	976	32.53
7	France	78(4.1 %)	4459	57.17	Fox Chase Cancer Center	30	1587	52.90
8	South Korea	71(3.7 %)	1195	16.83	Harvard University	30	3137	104.57
9	Spain	69(3.6 %)	2871	41.61	Mayo Clinic	30	1253	41.77
10	India	66(3.4 %)	1489	22.56	China Medical University	29	587	20.24

Source: Web of Science. C/P, average number of citations per article

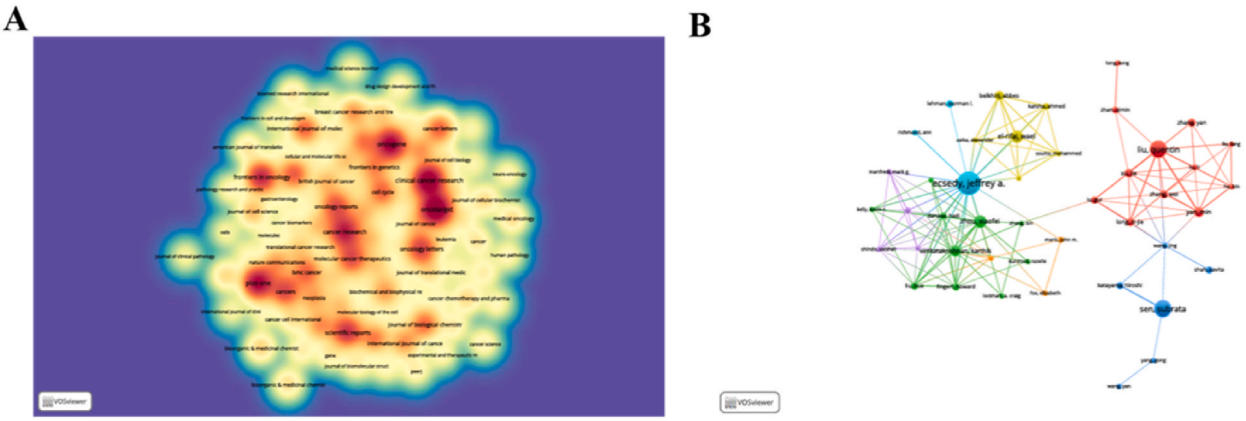


Fig. 4. The top journals (A) and cooperation relationships of authors (B) in AURKA of cancers research field.

Table 3
TOP10 Journals and Authors in AURKA of cancers research field.

Rank	Source	Documents	Author	Documents	Citations
1	Oncotarget	48	Ecsedy, Jeffrey a.	37	2631
2	Clinical Cancer Research	45	Liu, Quentin	25	902
3	Oncogene	39	Sen, Subrata	25	3950
4	Plos one	38	Golemis, Erica a.	19	952
5	Cancer research	32	El-rifai, Wael	16	1006
6	Frontiers in Oncology	31	Zhou, Xiaofei	16	558
7	Scientific Reports	28	Prigent, Claude	14	278
8	Oncology Letters	25	Venkatakrishnan, Karthik	14	428
9	Cancers	24	Bayliss, Richard	12	561
10	Molecular Cancer Therapeutics	23	Yan, Min	12	674

Source: Web of Science.

3.4. Co-cited references and reference burst

In order to gain insights into the highly cited papers in this field, a total of 28 references that received at least 100 citations were identified from the pool of 59,942 cited references. Among these highly cited references, Table 4 presents the top 10 articles that accumulated more than 137 citations. Notably, the article published by Hongyi Zhou as the first author and Subrata Sen as the corresponding author in "Nature Genetics" in 1998 (n = 362) emerges as the most frequently co-cited paper among all the references analyzed. Moreover, within the top 10 list, three articles are review papers while six are research articles.

We utilized Citespace's reference analysis to partition the entire network map into 8 clusters based on different research themes. Each cluster was assigned a distinct term label, corresponding to the distribution of time periods shown in Fig. 5A. As illustrated in Fig. 5B, the clusters include Cluster #7 (STK15), Cluster #6 (polymorphism), Cluster #3 (alternative splicing), Cluster #4 (centrosome), Cluster #0 (AZD1152), Cluster #1 (alisertib), Cluster #5 (bioinformatics analysis), and Cluster #2 (therapeutic target). The literature within different time periods not only focuses on specific research hotspots during those periods but also lays the foundation for future studies. It is evident that targeting AURKA for therapeutic purposes is a current research hotspot. For citation burst analysis,

Table 4
Top 10 co-cited references related to AURKA of cancer.

Rank	Title	citations	Year
1	Tumour amplified kinase STK15/BTAK induces centrosome amplification, aneuploidy and transformation [23]	362	1998
2	A homologue of Drosophila aurora kinase is oncogenic and amplified in human colorectal cancers [24]	337	1998
3	Aurora-A - a guardian of poles [25]	221	2005
4	Phosphorylation by aurora kinase A induces Mdm2-mediated destabilization and inhibition of p53 [26]	209	2004
5	The cellular geography of aurora kinases [5]	194	2003
6	AURORA-A amplification overrides the mitotic spindle assembly checkpoint, inducing resistance to Taxol [27]	178	2003
7	VX-680, a potent and selective small-molecule inhibitor of the Aurora kinases, suppresses tumor growth in vivo [28]	165	2004
8	Aurora-A and an interacting activator, the LIM protein Ajuba, are required for mitotic commitment in human cells [29]	164	2003
9	Roles of Aurora kinases in mitosis and tumorigenesis [30]	152	2007
10	Mutations in aurora prevent centrosome separation leading to the formation of monopolar spindles [8]	137	1995

Source: Web of Science.

a total of 398 references were included, representing significant growth in citations during specific time frames. Fig. 5C presents the top 25 entries, with one paper titled "Targeting AURKA in Cancer: molecular mechanisms and opportunities for Cancer therapy" published in Molecular Cancer in 2021 by Ruijuan Du et al., exhibiting the highest burstness (strength = 36.69) from 2021 to 2023 [3].

3.5. Investigation of keywords and trend topics

To gain further insights into the hot topics and frontiers of AURKA in cancer research, we conducted co-occurrence network analysis using VOSviewer on the keywords that encapsulate the core and essence of the literature. A total of 160 keywords, with a frequency exceeding 5, are visualized in the clustering view of Fig. 6A. The size of each circular node corresponds to the frequency of occurrence of the respective keyword, reflecting its significance as a research hotspot in the field. The connecting lines between nodes indicate the strength of association, with thicker lines indicating a higher frequency of co-occurrence in the same publications. To provide a detailed understanding of specific keywords, we compiled high-frequency keywords with frequencies exceeding 19 in Table 5. Interestingly, the distribution of high-frequency keywords in AURKA cancer research exhibited similarities to Zipf's Law, with a small number of keywords having high frequencies and the majority having lower frequencies (see Supplementary Fig. 1) [31]. Additionally, to capture the evolution of hot topics and frontiers in this domain over time, we employed R biblimatrix to create a trend-topic map (Fig. 6B).

3.5.1. Association gene clustering analysis

To explore the biological significance of the molecular keywords co-occurring with AURKA in the literature, we utilized VOSviewer to extract a total of 6513 keywords from 1921 articles. Among these, 682 keywords had a frequency exceeding 5 times. By comparing them with human genome data, we identified 316 biologically relevant associated genes. Next, we employed the R package clusterProfiler for GO/KEGG clustering analysis. The GO/KEGG functional enrichment results are presented in Fig. 7A and B, which displays bar charts and dotplots of the top 10 enriched biological processes (BP), molecular functions (MF), cellular components (CC) and KEGG pathways related to AURKA in cancer research, based on their P-values.

3.5.2. Protein-protein interaction network related to AURKA in cancer research

To investigate the protein-protein interaction (PPI) patterns of AURKA in cancer research and unravel the complex biological processes and regulatory mechanisms within tumor cells, we initially utilized the STRING online database (https://string-db.org/) to construct a PPI network using a molecular list of AURKA-associated keywords. Subsequently, we imported the network data into Cytoscape for further analysis. Within Cytoscape, we employed the cytoNCA plugin (version 2.1.6) to calculate the betweenness centrality and ranked the interacting molecules based on this measure. Fig. 8 visualizes the top 10 and top 50 molecules, color-coded accordingly. Notably, TP53, HSP90AA1, MYC, AKT1, STAT3, JUN, CDK1, SRC, GSK3B, and BUB1B emerge as potentially core proteins through which AURKA exerts its role in tumorigenesis.

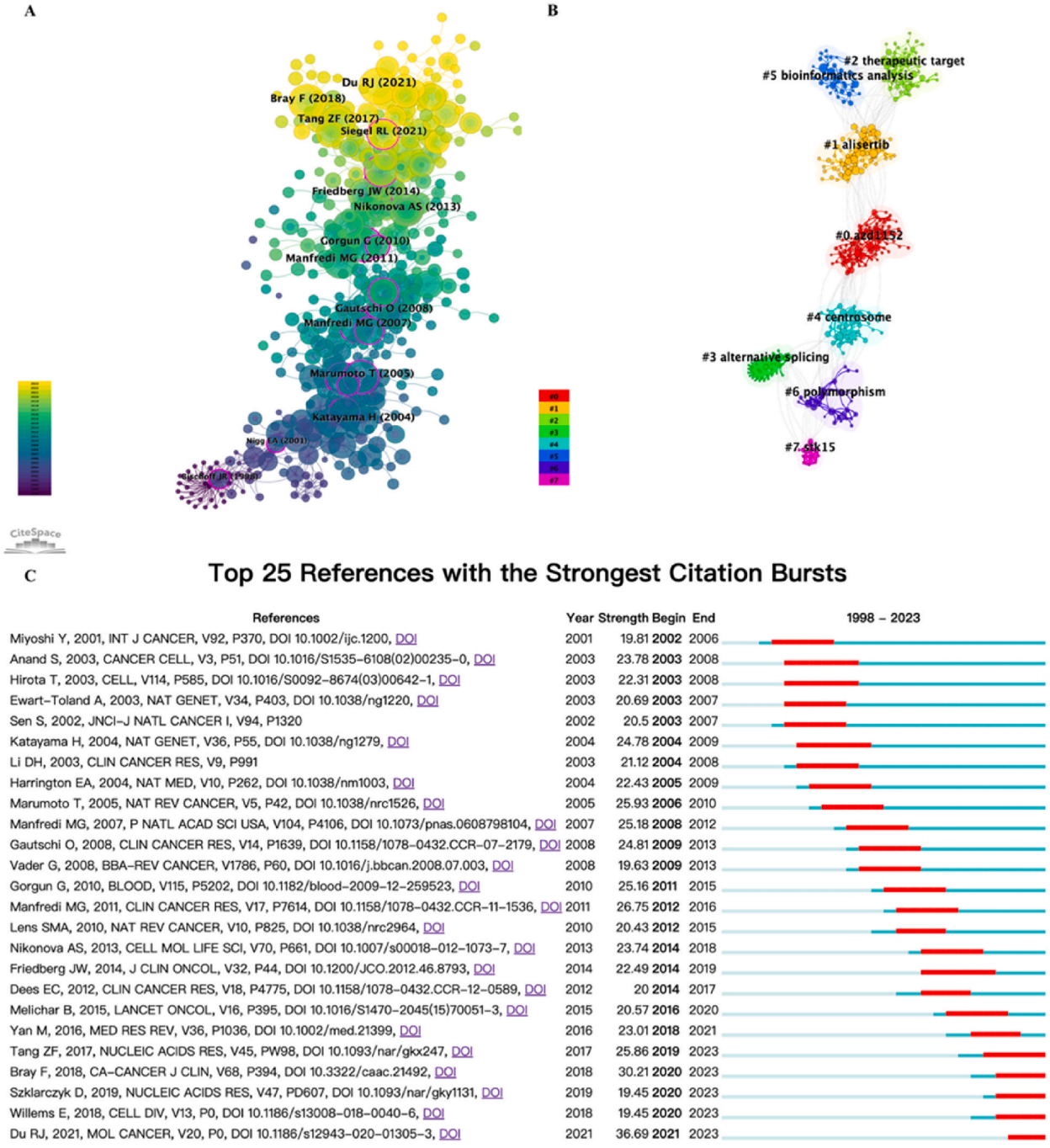
3.5.3. Prognostic meta-analysis of AURKA expression in cancer patients

A comprehensive meta-analysis was conducted to assess the prognostic significance of AURKA expression in cancer patients. A total of 33 studies were identified through an extensive search on PubMed and WOS databases, involving 3973 patients across 18 different tumor types [32–64]. These studies examined the association between AURKA expression levels, measured by immunohistochemistry or RT-PCR, and overall survival outcomes. Using Stata software (version 15.1), a random-effects model forest plot (Fig. 9) was generated to analyze the heterogeneity among the tumor subgroups.

4. Discussion

4.1. General overview

Before 2003, the number of relevant papers was in single digits each year, indicating that the field was in its infancy. Research on



References	Year	Strength	Begin	End	1998 – 2023
Miyoshi Y, 2001, INT J CANCER, V92, P370, DOI 10.1002/ijc.1200, DOI	2001	19.81	2002	2006	
Anand S, 2003, CANCER CELL, V3, P51, DOI 10.1016/S1535-6108(02)00235-0, DOI	2003	23.78	2003	2008	
Hirota T, 2003, CELL, V114, P585, DOI 10.1016/S0092-8674(03)00642-1, DOI	2003	22.31	2003	2008	
Ewart-Toland A, 2003, NAT GENET, V34, P403, DOI 10.1038/ng1220, DOI	2003	20.69	2003	2007	
Sen S, 2002, JNCI-J NATL CANCER I, V94, P1320	2002	20.5	2003	2007	
Katayama H, 2004, NAT GENET, V36, P55, DOI 10.1038/ng1279, DOI	2004	24.78	2004	2009	
Li DH, 2003, CLIN CANCER RES, V9, P991	2003	21.12	2004	2008	
Harrington EA, 2004, NAT MED, V10, P262, DOI 10.1038/nm1003, DOI	2004	22.43	2005	2009	
Marumoto T, 2005, NAT REV CANCER, V5, P42, DOI 10.1038/nrc1526, DOI	2005	25.93	2006	2010	
Manfredi MG, 2007, P NATL ACAD SCI USA, V104, P4106, DOI 10.1073/pnas.0608798104, DOI	2007	25.18	2008	2012	
Gautschi O, 2008, CLIN CANCER RES, V14, P1639, DOI 10.1158/1078-0432.CCR-07-2179, DOI	2008	24.81	2009	2013	
Vader G, 2008, BBA-REV CANCER, V1786, P60, DOI 10.1016/j.bbcan.2008.07.003, DOI	2008	19.63	2009	2013	
Gorgun G, 2010, BLOOD, V115, P5202, DOI 10.1182/blood-2009-12-259523, DOI	2010	25.16	2011	2015	
Manfredi MG, 2011, CLIN CANCER RES, V17, P7614, DOI 10.1158/1078-0432.CCR-11-1536, DOI	2011	26.75	2012	2016	
Lens SMA, 2010, NAT REV CANCER, V10, P825, DOI 10.1038/nrc2964, DOI	2010	20.43	2012	2015	
Nikonova AS, 2013, CELL MOL LIFE SCI, V70, P661, DOI 10.1007/s00018-012-1073-7, DOI	2013	23.74	2014	2018	
Friedberg JW, 2014, J CLIN ONCOL, V32, P44, DOI 10.1200/JCO.2012.46.8793, DOI	2014	22.49	2014	2019	
Dees EC, 2012, CLIN CANCER RES, V18, P4775, DOI 10.1158/1078-0432.CCR-12-0589, DOI	2012	20	2014	2017	
Melichar B, 2015, LANCET ONCOL, V16, P395, DOI 10.1016/S1470-2045(15)70051-3, DOI	2015	20.57	2016	2020	
Yan M, 2016, MED RES REV, V36, P1036, DOI 10.1002/med.21399, DOI	2016	23.01	2018	2021	
Tang ZF, 2017, NUCLEIC ACIDS RES, V45, PW98, DOI 10.1093/nar/gkx247, DOI	2017	25.86	2019	2023	
Bray F, 2018, CA-CANCER J CLIN, V68, P394, DOI 10.3322/caac.21492, DOI	2018	30.21	2020	2023	
Szklarczyk D, 2019, NUCLEIC ACIDS RES, V47, PD607, DOI 10.1093/nar/gky1131, DOI	2019	19.45	2020	2023	
Willems E, 2018, CELL DIV, V13, P0, DOI 10.1186/s13008-018-0040-6, DOI	2018	19.45	2020	2023	
Du RJ, 2021, MOL CANCER, V20, P0, DOI 10.1186/s12943-020-01305-3, DOI	2021	36.69	2021	2023	

Fig. 5. The reference co-citation analysis maps (A) in cluster view (B) and visualization map of the top 25 references related to AURKA of cancer with the strongest citation bursts (C).

AURKA in the field of oncology was relatively new, lacking sufficient literature and research findings. From 2003 to 2015, the average annual publication rate was 63.3 papers, suggesting increased attention and research on AURKA in oncology. This may be attributed to the rising incidence and mortality rates of cancer, leading more researchers to focus on exploring AURKA as a potential therapeutic target or biomarker. During the period from 2016 to 2023, the annual publication rate of AURKA research in oncology exceeded 100 papers, indicating widespread attention and extensive investigation into the gene/protein. This reflects in-depth research on the functions, regulatory mechanisms, and potential roles of AURKA in tumor development and treatment. The high publication rate also suggests a certain degree of accumulation and maturity in the field, with a wide range of research teams and collaborative networks providing a solid foundation for further research.

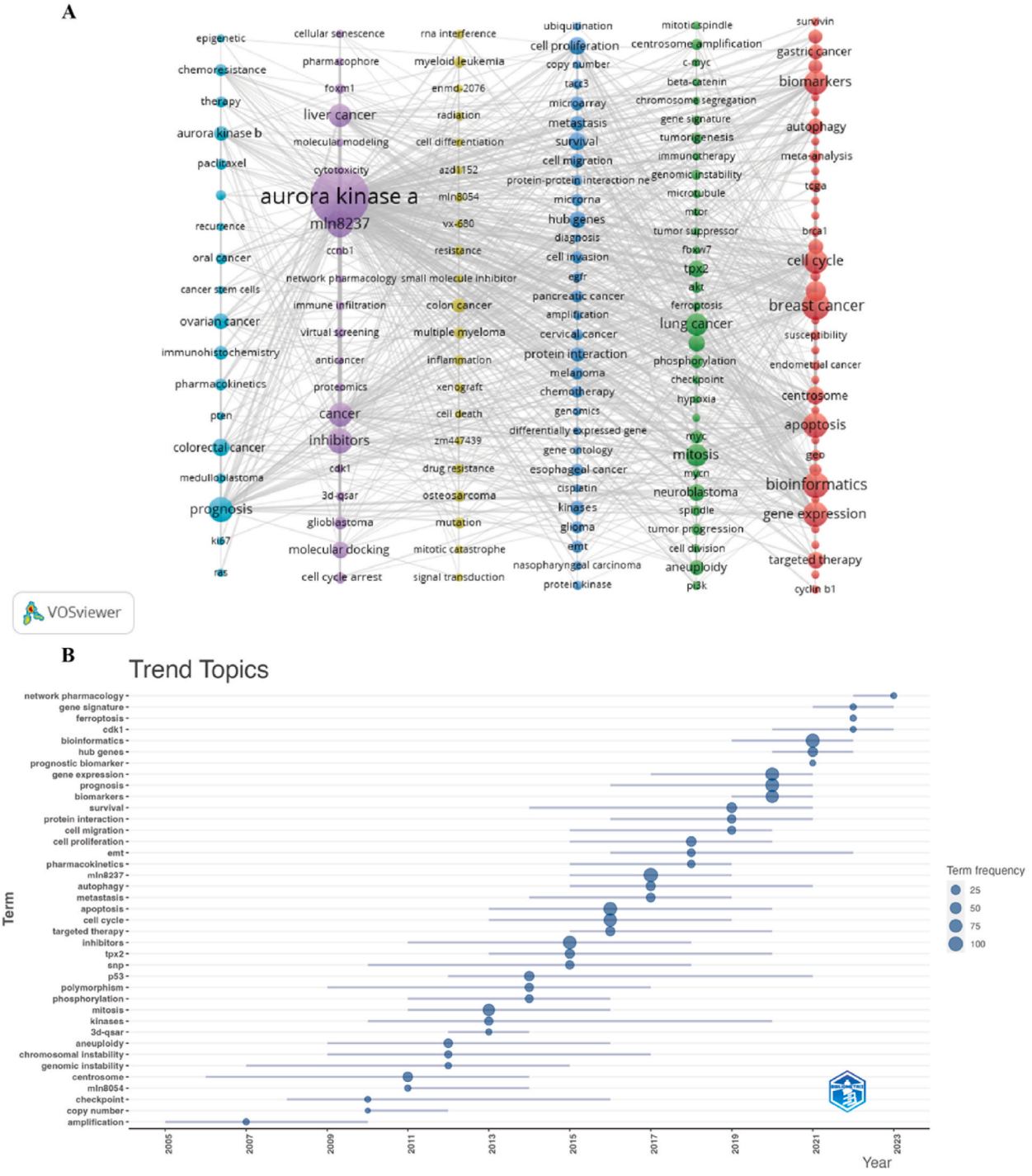


Fig. 6. Keyword cluster analysis (A) and trend topic analysis (B).

China, the United States, and Germany are the major countries conducting AURKA research in oncology, with six out of the top 10 research institutions located in the United States and four in China. There exists close collaboration between China and the United States. However, there is relatively limited connection between Germany and other countries or institutions, which poses limitations on jointly promoting AURKA research in oncology. Therefore, strengthening and expanding cooperation among various countries and research institutions is necessary.

Based on publication rates, we ranked journals publishing AURKA-related research in oncology. We found that Clinical Cancer Research (IF = 11.5, Q1) and Cancer Research (IF = 11.2, Q1) were the two highest-ranked journals in terms of impact factor among

Table 5
High-frequency keywords in AURKA of cancers research field.

Rank	keyword	occurrences	total link strength	Rank	keyword	occurrences	total link strength
1	aurora kinase a	623	1112	19	centrosome	31	75
2	breast cancer	102	189	20	hub genes	30	69
3	mln8237	89	198	21	p53	30	76
4	bioinformatics	84	194	22	molecular docking	28	55
5	apoptosis	80	214	23	neuroblastoma	28	49
6	inhibitors	76	145	24	targeted therapy	27	54
7	prognosis	74	166	25	tpx2	27	63
8	cell cycle	73	185	26	autophagy	26	77
9	gene expression	73	143	27	ovarian cancer	24	44
10	cancer	71	157	28	bladder cancer	23	35
11	biomarkers	69	152	29	metastasis	23	45
12	liver cancer	63	144	30	aneuploidy	22	39
13	mitosis	56	124	31	aurora kinase b	22	48
14	lung cancer	55	95	32	gastric cancer	22	47
15	prostate cancer	48	71	33	protein interaction	20	57
16	colorectal cancer	34	61	34	kinases	19	42
17	survival	34	86	35	microarray	19	37
18	cell proliferation	32	88	36	polymorphism	19	49

Source: Web of Science.

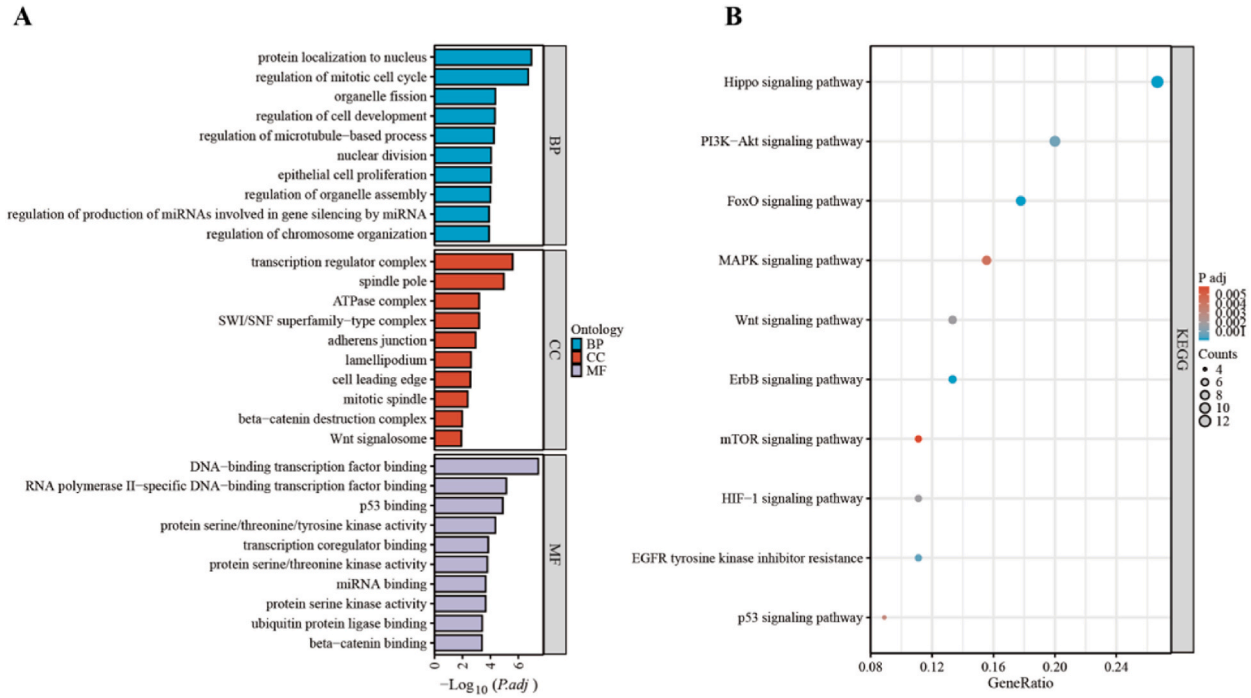


Fig. 7. Enrichment analysis of biofunctions and pathways associated with genes co-occurring with AURKA. (A) Gene Ontology (GO) analysis, and (B) Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis.

the top 10 journals. These two journals have high prestige and influence in AURKA research in oncology, as they can widely disseminate research findings and attract attention and citations from colleagues. However, other journals with impact factors below 10 still play an important role and make unique contributions in specific research directions or subfields. Nevertheless, we encourage higher-quality papers to be published in top-tier journals in the field of oncology to drive progress and innovation. We also encourage researchers to conduct more in-depth studies and contribute further to the field of oncology.

Looking at the top three authors deeply involved in this field, Jeffrey A. Ecsedy's team is dedicated to studying the pharmacological mechanisms of AURKA molecular targeted drugs and conducting preclinical and translational research [65–67]; Professor Quetin Liu's research focuses on the basic and translational research of cell cycle-related proteins and the mechanisms related to the development of tumor stem cells. He has made significant contributions in exploring the regulation of AURKA in cell mitotic cycle and tumor drug resistance [68–71]; Subrata Sen conducts functional characterization of genes regulating mitotic chromosome segregation in

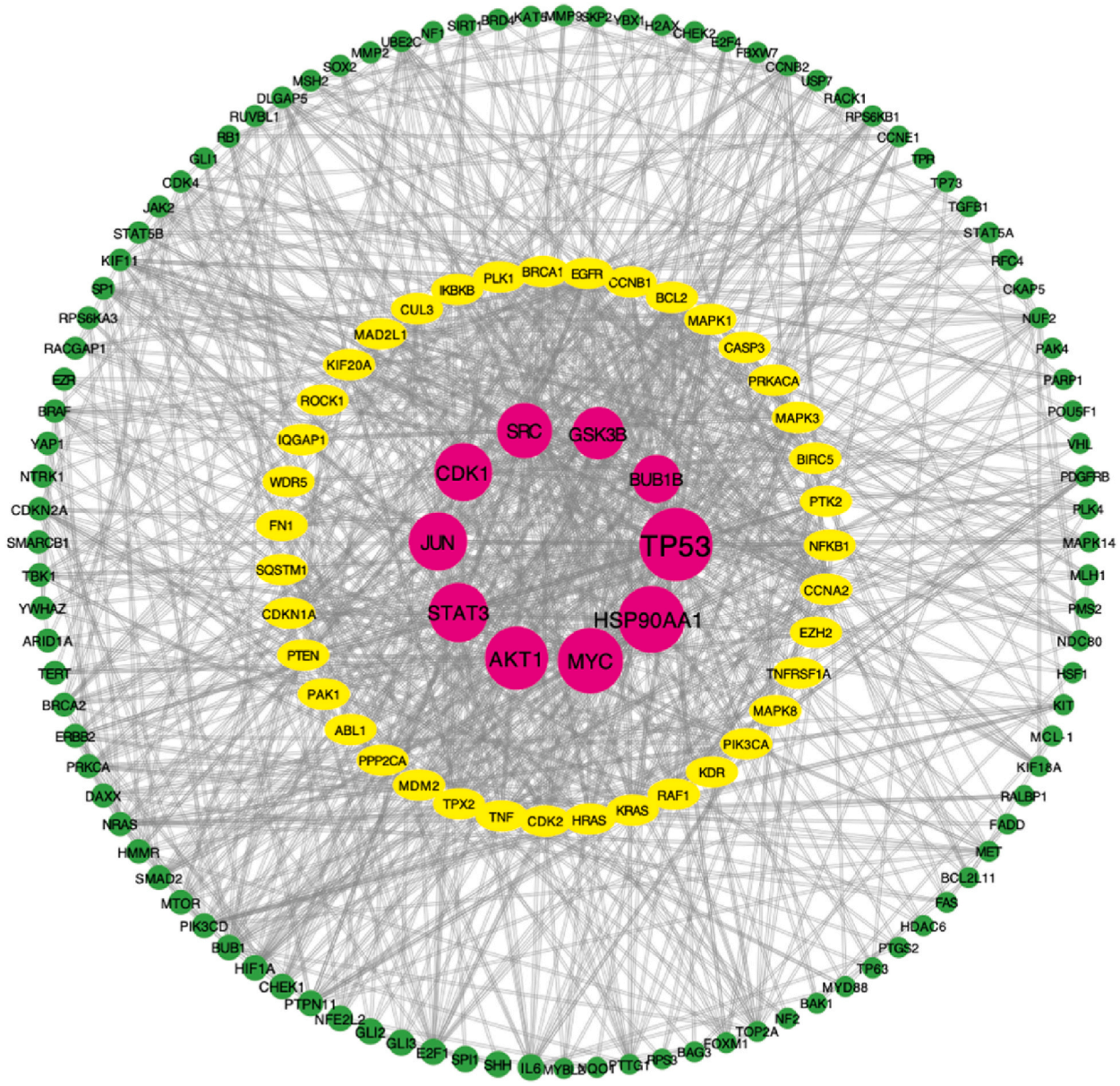


Fig. 8. Visualization of the protein-protein interaction (PPI) network associated with AURKA.

mammalian cells, elucidating their role in inducing chromosomal instability in cancer and exploring the functional interactions of critical mitosis-regulating genes in the Aurora kinase family, while also collaborating closely with Professor Quetin Liu [7,26,72–74].

In conclusion, regarding the research on AURKA in the field of oncology, it is evident that by sharing research findings and engaging in collaboration, we can accelerate our understanding of AURKA and its related signaling pathways. This, in turn, can provide more effective strategies and drug targets for cancer treatment and prevention.

4.2. Knowledge foundation

Considering that the formation of knowledge often relies on the organic combination of co-cited literature, we employed co-citation analysis to explore the knowledge foundation of AURKA in cancer research [75]. Through an examination of the top 10 co-cited articles, we identified a significant accumulation of knowledge between 1995 and 2005.

In 1995, Huw Parry et al. investigated aurora gene mutations in Drosophila, revealing the failure of centrosome separation and the formation of monopolar spindles [8]. This study laid the groundwork for understanding the functional implications of aurora gene mutations. Furthermore, Gregory D. Plowman et al. (1998) identified two human homologous genes of aurora kinase, with aurora2

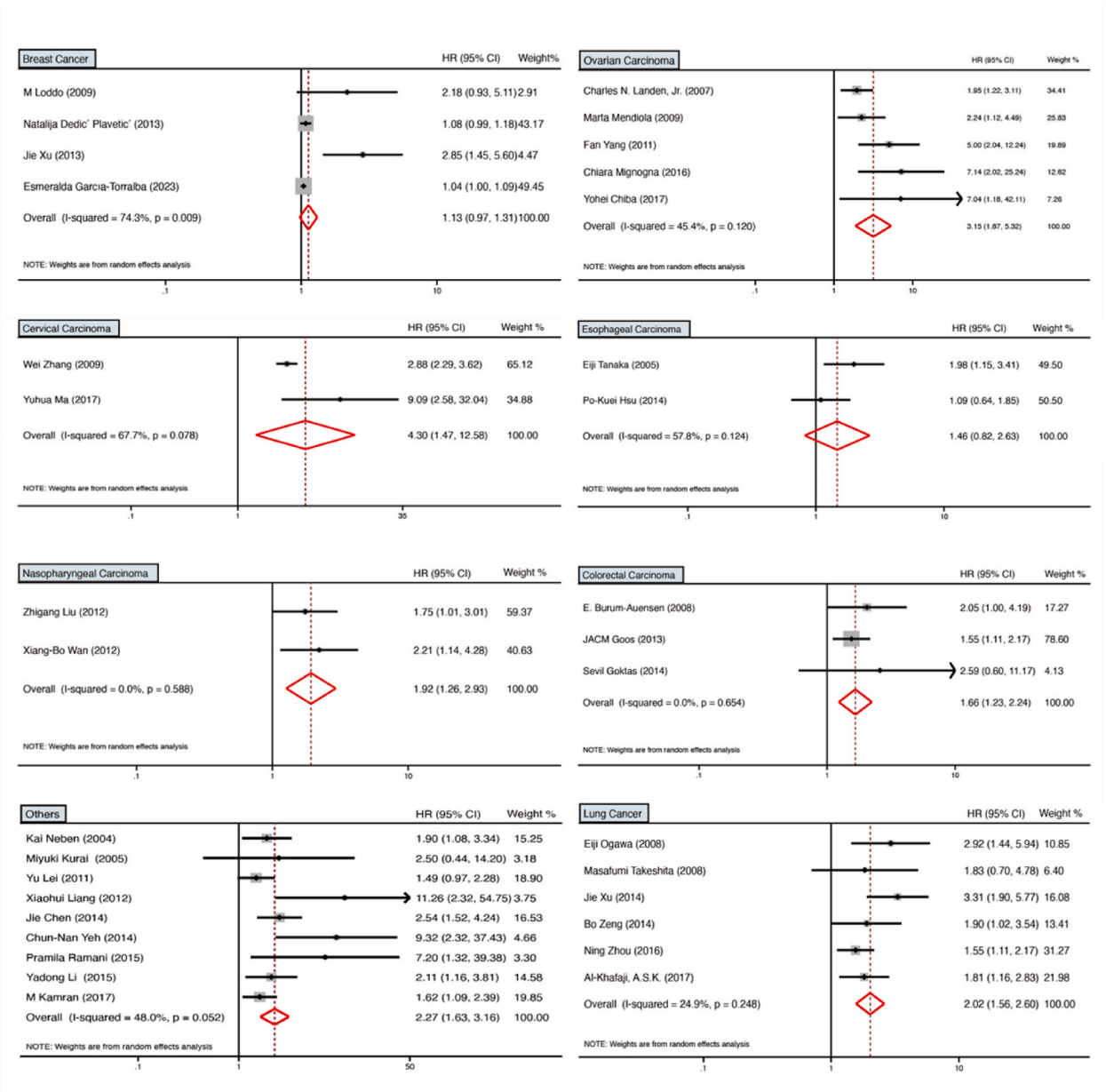


Fig. 9. Forest plot for overall survival in different subgroup of cancers.
Source: Web of Science and PubMed.

being overexpressed and amplified in various tumors, indicating its potential as an oncogene and highlighting centrosomal-associated proteins as potential targets for cancer therapy [24]. During the same period, Subrata Sen et al. (1998) demonstrated STK15 gene amplification in multiple cancers, suggesting its critical role in centrosome amplification, chromosomal instability, and cellular transformation [23]. Moving forward to 2003, Ashok R.Venkitaraman found that amplification of the AURORA-A gene in epithelial malignancies leads to overexpression and resistance against paclitaxel, resulting in abnormal mitosis and cell multinucleation [27]. In the same year, Hideyuki Saya et al. discovered the interaction between Aurora-A and Ajuba in regulating mitosis, underscoring its significance in initiating mitotic processes [29]. Additionally, Subrata Sen's team in 2004 revealed that Aurora kinase A phosphorylates p53, promoting its degradation and facilitating carcinogenic transformation by downregulating cell cycle regulation and checkpoint responses [26]. Karen M. Miller et al. (2004) identified VX-680 as a highly selective small molecule inhibitor of Aurora kinases, demonstrating its effectiveness in inhibiting tumor growth and inducing regression of various tumors at tolerable doses [28]. The remaining three co-cited articles, published in 2003 [5], 2005 [25] and 2007 [30], are comprehensive reviews. William C. Earnshaw et al. (2003) provided a comprehensive overview of the regulatory mechanisms of Aurora kinase family members during

different stages of cell division, highlighting their association with cancer. Hideyuki Saya (2005) focused on the regulation of key events by Aurora-A and Aurora-B during the G2 to M phase transition in the cell cycle, summarizing the aberrant molecular mechanisms of Aurora-A in tumorigenesis. Chuanmao Zhang et al. (2007) summarized the latest research progress on the Aurora kinase family in cell division, tumor occurrence, and targeted therapy.

In summary, these 10 co-cited articles offer profound insights into the normal and abnormal biological functions of AURKA in cell division, molecular mechanisms of its expression and functional perturbations in tumorigenesis, as well as potential molecular targeted therapeutic strategies for cancer treatment. Undoubtedly, these studies serve as essential clues and theoretical foundations for further investigations into AURKA in the field of cancer research.

4.3. Research front and hotspot

The utilization of co-citation clustering and burst detection algorithms provides valuable tools for unraveling the frontiers of AURKA research [76]. The emergence of biological informatics analysis and targeted therapies centered around AURKA signifies significant advancements within the field of oncology. Furthermore, by utilizing omics studies to investigate the interplay between AURKA and other molecules, as well as pathway crosstalk, researchers gain critical insights into the biological mechanisms driving tumor development. These findings contribute to the translational research efforts aiming to bridge the gap between preclinical studies and clinical trials, highlighting the primary research focus on AURKA within the field of oncology.

Additionally, keyword-based text mining serves as a recognized approach for unveiling emerging trends and hot topics in scientific research [77]. From the analysis of Fig. 5 and Table 6, it is evident that the keywords primarily fall into five different categories, namely molecules, diseases, phenotypes, drugs and methodologies. Among the high-frequency keywords associated with AURKA, the top three molecules mentioned are p53, TPX2, and AURKB. The most commonly mentioned cancer types are breast cancer, liver cancer, lung cancer, prostate cancer, and colorectal cancer. The closest phenotypes related to AURKA are apoptosis, cell cycle, cell proliferation, mitosis, and centrosome. The most frequently mentioned drug is mln8237 (also known as Alisertib), a selective inhibitor of AURKA. In recent years, there has been a significant emphasis on various methodologies, including bioinformatics, molecular docking, and network pharmacology.

Through bioinformatics analysis, we can delve into the multidimensional data and complex networks associated with the keywords of molecules related to AURKA. Consistent with the aforementioned phenotype keywords, AURKA is involved in regulating processes related to cell cycle progression, mitotic kinase activity regulation, and protein-protein interaction complex formation. Fig. 7B demonstrates the top 10 enriched Hallmark pathways obtained from the KEGG enrichment analysis. These pathways include Hippo, PI3K-AKT, FOXO, MAPK, and other signaling pathways closely associated with tumor occurrence and development. Overall, this gene clustering analysis provides insights into the biological context of the molecular keywords co-occurring with AURKA, highlighting their involvement in essential cellular processes and signaling pathways implicated in tumorigenesis. PPI protein interaction analysis reveals that p53 acts as a hub gene in the molecular interactome of AURKA, which is consistent with the findings reported by Subrata Sen's team [78]. The functional interactions between Aurora kinases and p53 family proteins modulate the activity and subcellular localization of each other and their downstream effector proteins, thereby coordinating diverse cellular pathways [26]. Dysregulation of these interactions in cells undergoing tumorigenic transformation has significant functional consequences on inducing chromosome instability and developing various tumor-associated phenotypes, including therapy resistance [79–81].

Based on the rigorous meta-analysis of 33 original articles investigating the relationship between AURKA expression and overall survival prognosis in various cancer types, our findings highlight the promising potential of AURKA as a prognostic marker. Despite observing considerable heterogeneity among different tumor types, the consistent association between AURKA overexpression and unfavorable prognosis in cancer patients is evident. This meta-analysis emphasizes the importance of AURKA as a potential indicator for assessing patient outcomes and target therapy in various types of cancer.

In summary, these findings have significant implications for advancing personalized medicine and improving patient outcomes in oncology, highlighting the diverse aspects and research focus related to AURKA in molecular, disease, phenotype, drug, and methodological studies.

4.4. Promising role of AURKA inhibitors (AKIs) in cancer treatment

AURKA, an oncogene that is commonly overexpressed in various cancers, exerts its effects by modulating multiple molecular targets and signaling pathways, leading to genomic instability and promoting various hallmarks of cancer such as increased cell proliferation, survival, migration, invasion, and stemness [82–87]. As a result, AURKA represents a promising therapeutic target. Numerous AURKA kinase inhibitors have been identified, including specific inhibitors targeting Aurora-A kinase, pan-Aurora kinase inhibitors, and naturally derived AKIs [5]. Many of these inhibitors are currently undergoing preclinical and clinical evaluations, with some displaying encouraging findings (*for review, see Refs.* [3,88]). Among these inhibitors, MLN8237, also referred to as alisertib, stands out as a second-generation highly selective small molecule inhibitor of Aurora-A kinase developed by Millennium Pharmaceuticals. MLN8237, which evolved from its predecessor MLN8054 [89], attenuates the activity of Aurora-A kinase by binding to it within cells, thereby impeding spindle assembly and chromosome segregation during mitosis. Notably, MLN8237 has demonstrated significant anti-tumor activity in diverse xenograft tumor models [90–93]. Alisertib, being the only AKI that has progressed into Phase III clinical trials, holds promise for the treatment of cancers. Detailed information regarding the clinical trials involving MLN8237 can be found in Table 6. The data presented in Table 6 indicates that beyond the use of alisertib as a standalone therapy, combination approaches involving AKIs exhibit potential as effective anti-tumor strategies. These combinations encompass AKIs combined with

Table 6
Alisertib in clinical trials.

NCT No.	Regimen	Cancer Cohort	Cases	Phases	End Year	Ref
NCT01154816	Alisertib	Advanced Malignancies	118	II	2019	Ref [94]
NCT01045421	Alisertib	Advanced Solid Tumors	273	I|II	2014	Ref [12]
NCT01512758	Alisertib	Advanced Malignancies	36	I	2013	Ref [95]
NCT01653028	Alisertib	Advanced/Metastatic Sarcoma	72	II	2015	Ref [96]
NCT02444884	Alisertib	Relapsed/Refractory Solid Tumors	54	I	2011	Ref [97]
NCT00807495	Alisertib	Lymphoma	48	II	2013	Ref [98]
NCT01466881	Alisertib	Lymphoma	42	II	2015	Ref [99]
NCT02293005	Alisertib	Mesothelioma	28	II	2021	Ref [100]
NCT00853307	Alisertib	Ovarian Carcinoma	31	II	2011	Ref [101]
NCT01799278	Alisertib	Prostate Cancer	60	II	2017	Ref [102]
NCT01637961	Alisertib	Relapsed Uterine Sarcoma	23	II	2017	Ref [103]
NCT00697346	Alisertib	Hematological Malignancies	58	I	2016	Ref [104]
NCT02186509	Alisertib + Radiotherapy	High-Grade Gliomas	17	I	2018	Ref [105]
NCT00962091	Alisertib + Radiotherapy	Advanced Solid Tumors	53	I	2014	Ref [106]
NCT02109328	Alisertib + Chemo	Bladder Cancer	22	II	2016	Ref [107]
NCT01923337	Alisertib + Chemo	Advanced Solid Tumors	17	I	2016	Ref [108]
NCT01779843	Alisertib + Chemo	Acute Myelogenous Leukemia	22	I	2016	Ref [109]
NCT02038647	Alisertib + Chemo	Small Cell Lung Cancer	178	II	2017	Ref [110]
NCT01091428	Alisertib + Chemo	Breast Cancer and Ovarian Cancer	191	II	2017	Ref [111]
NCT01677559	Alisertib + Chemo	Advanced Solid Malignancies	34	I	2017	Ref [112]
NCT01601535	Alisertib + Chemo	Neuroblastoma	54	I|II	2018	Ref [113]
NCT02560025	Alisertib + Chemo	Acute Myeloid Leukemia	42	II	2018	Ref [114]
NCT01397825	Alisertib + Chemo + Immune	Lymphoma	45	I|II	2016	Ref [115]
NCT01482962	Alisertib + Chemo + HDACi	Lymphoma	271	III	2017	Ref [16]
NCT01567709	Alisertib + HDACi	Lymphoid Malignancies	34	I	2018	Ref [116]
NCT01639911	Alisertib + VEGFi	Advanced Solid Tumors	28	I	2016	Ref [117]
NCT01848067	Alisertib + ARIs	Prostate Cancer	9	I|II	2016	Ref [118]

Source: https://clinicaltrials.gov/

radiotherapy or chemotherapy, targeted therapy, and immunotherapy. Additionally, research efforts are focused on developing even more selective AKIs and multi-target inhibitors, posing both opportunities and challenges in the field of AURKA molecular targeted drugs [88]. In summary, AURKA inhibitors provide a potent tool for investigating the intricate connections between molecular mechanisms, clinical manifestations, and disease treatments.

4.5. Strengths and limitations

Bibliometrics is a research methodology that plays a crucial role in the evaluation and understanding of scholarly literature. By quantitatively analyzing bibliographic data, such as citation counts, co-authorship patterns, and journal rankings, bibliometrics provides insights into the impact and significance of academic publications. This methodology enables researchers to identify influential works, track trends in research fields, and assess the overall scholarly contribution of individuals or institutions.

In our study, we have taken bibliometrics to new heights by integrating advanced bioinformatics techniques. These techniques, including functional clustering and network analysis, allow us to uncover deeper layers of meaning behind key keywords. By exploring the interrelationships between different concepts, we gain a more comprehensive understanding of how ideas and knowledge are interconnected within the scientific literature. It is worth mentioning that we have qualitatively and quantitatively evaluated our research findings using the major laws of bibliometrics (see Supplementary Table 3). Furthermore, we enhance the clinical relevance of our findings by incorporating data from the PubMed database for quantitative meta-analysis related to prognosis. Specifically, our research focuses on investigating the prognostic value of AURKA overexpression across various tumor types. This integration of bibliometrics with bioinformatics and clinical data adds significant value to the field by providing valuable insights that can inform both researchers and clinicians. It also has implications for pharmaceutical development professionals who seek evidence-based guidance in their work.

However, it is important to acknowledge the limitations of our research. One potential limitation is that our search strategy may inadvertently omit relevant literature. Meanwhile, the use of multiple Boolean operators (such as OR) in our search strategy may introduce bias by including irrelevant or tangentially related publications, despite our efforts to develop comprehensive search strategies and conduct rigorous screening. Additionally, our bibliometric analysis relies heavily on data obtained solely from the Web of Science (WoS) database, which may limit the generalizability of our findings to other databases or sources.

5. Conclusion

AURKA plays a critical role in the development and progression of cancer. This study presents an objective analysis using bibliometric methods to comprehensively evaluate the research on AURKA in the context of cancer, encompassing both hematological malignancies and solid tumors. The increasing number of publications reflects the growing interest among researchers worldwide

regarding the involvement of AURKA in cancer biology. Leading countries in this field include China, the United States, and Germany, emphasizing the importance of collaboration and knowledge sharing between nations and institutions. Understanding the mechanisms through which AURKA contributes to cancer development provides valuable insights into the underlying etiology and facilitates the identification of molecular markers for early diagnosis and prognostic prediction. Additionally, the translation of selective AURKA inhibitors from preclinical studies to clinical research offers promising strategies for personalized cancer treatment. Whether utilized as monotherapy or in combination with conventional anti-cancer modalities, AURKA-targeted inhibitors hold potential advantages in improving therapeutic outcomes for various types of cancer. Moreover, leveraging bioinformatics tools to conduct comprehensive molecular exploration of AURKA within the framework of big data enhances our understanding of its biological significance. Therefore, based on current knowledge and cutting-edge advancements in AURKA research within the field of oncology, undertaking further investigations in basic biology and clinical translation will significantly contribute to refining our comprehension of AURKA's role in the pathogenesis and therapy of cancer.

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Ethical approval and consent to participate

Not applicable.

Data availability statement

The datasets utilized and/or analyzed during the current study can be obtained from the corresponding authors upon reasonable request. For additional inquiries, please contact the corresponding author.

Consent for publication

All the authors have read the manuscript and agreed to give their consent for the publication in Biomedicine & Pharmacotherapy.

CRediT authorship contribution statement

Qiong Zhou: Writing – original draft, Methodology, Data curation. **Chunyu Tao:** Visualization, Investigation. **Jiakai Yuan:** Validation, Software. **Fan Pan:** Supervision. **Rui Wang:** Writing – review & editing, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e31945.

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