

Research Hotspots and Trends of Natural Killer Cells in Breast Cancer Immunotherapy: A Bibliometric Analysis

Yue Wang

The 960th Hospital of PLA Joint Logistics Support Force

Jiayu Zhu

The 960th Hospital of PLA Joint Logistics Support Force

Yuanyuan Fu

Shandong First Medical University

Meng Wang

The 960th Hospital of PLA Joint Logistics Support Force

Yuan Liu

The 960th Hospital of PLA Joint Logistics Support Force

Luming Zheng

The 960th Hospital of PLA Joint Logistics Support Force

Qingqing He

19510166505@163.com

The 960th Hospital of PLA Joint Logistics Support Force

Research Article

Keywords: Breast cancer, Natural killer cells, Immunotherapy, Bibliometrics, CiteSpace, VOSviewer, Bibliometric

Posted Date: October 20th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-9504996/v1>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License.
[Read Full License](#)

Additional Declarations: No competing interests reported.

Abstract

Objective

This study employs bibliometric methods to systematically review the research landscape, evolving hotspots, and cutting-edge trends in natural killer cell-based immunotherapy for breast cancer (BC) over the past three decades (1996–2025).

Methods

Relevant literature was retrieved from the Web of Science Core Collection (WoSCC). CiteSpace, VOSviewer and Bibliometrix were used to analyze publication trends, collaboration networks, co-citation, and keyword dynamics, with synonym files applied for keyword standardization.

Results

A total of 603 articles were included. Annual publication volume exhibited exponential growth. The United States is the sole global collaboration hub (176 publications, centrality 0.93), while China leads in output (205 publications) but shows low centrality (0.03). Sun Yat-sen University has emerged as a new core institution (16 publications, centrality 0.26). Five major research teams were identified across the United States, Germany, Argentina, South Korea, and Hungary. Journal co-citation clusters formed four thematic groups, and literature co-citation revealed five foundational knowledge domains. Keyword analysis identified five research themes, with emergent analysis tracing hotspot evolution from early basic studies to current frontiers including tumor-associated macrophages, immune infiltration, and triple-negative BC.

Conclusion

The field has established a complete system from basic mechanisms to clinical translation. Current hotspots focus on microenvironment regulation, immune checkpoint synergy, and precision medicine. China leads in output scale but requires deeper international collaboration to enhance influence. Future efforts should prioritize NK cell-microenvironment interactions, clinical translation of CAR-NK, and biomarker-based precision strategies.

1 Introduction

Natural killer (NK) cells are core effector cells of the innate immune system that can recognize and eliminate tumor cells without prior sensitization, while regulating adaptive immune responses through cytokine and chemokine secretion [1]. In antibody-dependent cell-mediated cytotoxicity, NK cells exert cytotoxic effects by recognizing the Fc fragment of antibodies bound to tumor cells via their surface

FcγRIIIa receptor, a mechanism that closely links targeted therapy with immunotherapy [2, 3]. In recent years, with breakthrough advancements in immune checkpoint inhibitors and adoptive cell therapies, the role of NK cells in tumor immunotherapy has become increasingly prominent, particularly in solid tumors such as BC [4–6].

BC is the most prevalent malignant tumor among women globally, and its treatment strategies have formed a standardized system based on molecular subtyping and multidisciplinary comprehensive therapy. According to the 2025 National Comprehensive Cancer Network (NCCN) guidelines and China Clinical Oncology Society (CSCO) guidelines, local treatment for early-stage breast cancer mainly includes breast-conserving surgery, total mastectomy, and postoperative adjuvant radiotherapy [7, 8]. Systemic therapy is stratified based on molecular subtypes: hormone receptor-positive/HER2-negative breast cancer is primarily treated with endocrine therapy combined with CDK4/6 inhibitors; HER2-positive breast cancer is treated with anti-HER2 targeted therapy (such as trastuzumab, pertuzumab) combined with chemotherapy. Triple-negative breast cancer (TNBC), characterized by the absence of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (HER-2) expression, exhibits poor response to endocrine therapy and HER-2-targeted therapy, resulting in unfavorable prognosis [9, 10]. The advent of immunotherapy has brought new hope for patients with TNBC. Multiple clinical trials have demonstrated that Programmed cell death protein 1/Programmed death-ligand 1 (PD-1/PD-L1) inhibitors combined with chemotherapy significantly improve progression-free survival and overall survival [11–15]. Notably, NK cells function is closely associated with the efficacy of immune checkpoint inhibitors, and the density and activation status of tumor-infiltrating NK cells have been established as independent prognostic factors in TNBC patients [16–18]. Therefore, a systematic review of NK cells research in breast cancer immunotherapy is crucial for elucidating its mechanisms of action, optimizing treatment strategies, and identifying cutting-edge directions.

Bibliometrics, through quantitative analysis of macro-level characteristics of academic literature, can objectively reveal the research status quo, core research forces, and evolutionary trends in specific fields. As mainstream bibliometric tools, CiteSpace and VOSviewer excel in detection and temporal evolution analysis, as well as network clustering and visualization presentation [19, 20]. This study comprehensively utilizes both software tools to conduct an in-depth analysis of relevant literature indexed in the WoSCC from 1996 to 2025, aiming to address the following questions: (1) What are the research trajectories and stage characteristics of this field? (2) How are the global core research forces (countries/regions, institutions, authors) distributed and characterized by collaborative networks? (3) How are knowledge foundations and research hotspots constituted and evolved? (4) What are the current and future frontier directions? Through these analyses, we hope to provide systematic cognitive maps and forward-looking research guidance for scholars engaged in NK cells and BC immunotherapy research.

2 Data Sources and Methods

2.1 Data Sources

The data for this study were sourced from the WoSCC, with the search period spanning March 2026. Retrieval-based design: Utilizes Boolean logic operators and parentheses to control priority levels. The retrieval concepts were categorized into three major modules: natural killer cells, breast cancer, and immunotherapy: TS= (("natural killer cell*" OR "NK cell*" OR "NK-92" OR "CD56 + cell*" OR "CD16 + cell*" OR "CAR-NK" OR "chimeric antigen receptor NK" OR "NK-92MI") AND ("breast cancer" OR "breast carcinoma" OR "breast tumor" OR "breast neoplasm" OR "mammary cancer" OR "TNBC" OR "triple-negative breast cancer") AND ("immunotherapy" OR "immunotherap*" OR "adoptive transfer" OR "adoptive cell therapy" OR "immune checkpoint" OR "checkpoint inhibitor*" OR "PD-1" OR "PD-L1" OR "CTLA-4" OR "CAR Keywords included: "therapy" OR "bispecific antibody" OR "NK cell engager"). Search field description: TS indicates subject-based retrieval, covering titles, abstracts, and author keywords. The Keywords Plus® field was excluded from this study as it reflects literature themes rather than core research content. To avoid introducing semantic noise unrelated to the study subject and ensure keyword analysis accurately reflects research hotspots, literature types were restricted to "Article" and "Review", language was limited to "English", and the time span was set from January 1, 1996 to December 31, 2025. A total of 1,149 articles were retrieved, with deduplication and manual screening (eliminating irrelevant literature) resulting in 603 valid articles. Literature records were exported in "full records and cited references" format as plain text files. Figure 1 illustrates the complete workflow from data collection, data cleaning to bibliometric analysis and result interpretation.

2.2 Bibliometrics and Visualization Analysis

2.2.1 CiteSpace Analysis

The CiteSpace software (version 6.4.R1) was employed to conduct analyses of national collaboration networks, institutional collaboration networks, keyword co-occurrence, and temporal evolution. Key parameter settings included: time slice duration of 1 year, node types selected as keywords, institutions, and countries, with a threshold of Top N = 50. This study utilized these tools for research field identification, literature prominence detection, and keyword prominence analysis. Network pruning was performed using the Pathfinder algorithm to simplify structural complexity while preserving critical connections. To identify dynamic trends in research hotspots, the study implemented timeline visualization and burst detection functionality.

2.2.2 VOSviewer Analysis

In VOSviewer (version 1.6.20), analyses were conducted separately for country/institution/author collaboration networks, journal co-citations, document co-citations, keyword co-occurrence, and clustering analysis. To enhance the accuracy of keyword analysis, we created a thesaurus file to consolidate synonymous terms. The visualization results were presented in three formats: network view (Network Visualization), overlay view (Overlay Visualization), and density view (Density Visualization), respectively, to identify core research themes, track cutting-edge trends, and pinpoint knowledge-intensive areas.

2.2.3 Bibliometric analysis

For in-depth bibliometric analysis, the same dataset was imported into the bibliometrix R package (version 4.5) via its online graphical interface, biblioshiny. This allowed extraction of a comprehensive Excel file containing title, publication year, authors, countries/institutions, journal, author keywords, Keywords Plus, citation counts, reference lists, and abstracts. This structured dataset was further analyzed and interpreted

2.2.4 Flourish Data Visualization Platform

This study utilized the Flourish data visualization platform (<https://flourish.studio>) to generate various interactive charts and network diagrams. These visualizations are used to present core research findings such as national/regional collaboration networks, institutional influence bubble charts, and keyword co-occurrence relationships.

3 Results

3.1 Annual publication trends and phase classification

Overall, the number of publications has experienced exponential growth, and the development of this field can be divided into three phases based on growth rates (Fig. 2). The first phase (1996–2005) was the embryonic stage, characterized by persistently low publication volumes averaging only 3.1 articles annually, with research remaining sporadic. The second phase (2006–2015) marked steady growth, with annual publications increasing significantly to 7.1 articles per year. The first milestone of 9 articles was achieved in 2007, followed by a breakthrough of 10 articles in 2012, signaling the gradual formation of a research framework. The third phase (2016–2025) saw rapid expansion, with exponential growth averaging 50.1 articles annually—a 606% increase from the second phase and accounting for 83.1% of total publications over three decades. In 2021, there was a cliff-like surge to 64 articles (an 113% increase from 2020), followed by sustained growth that reached 99 articles by 2025, approaching the 100-article threshold. This period ushered in a phase of accelerated research development, with breakthroughs emerging at an unprecedented pace.

3.2 National/Regional Distribution and Collaborative Networks

A total of 61 countries/regions worldwide participated in research in this field, with significant variations in contributions across nations (Fig. 3). Table 1 presents the output scale and academic influence of the top 25 countries/regions in terms of publication volume, total citations, average citations per paper, total link strength, and centrality. Among these metrics, publication volume, total citations, average citations per paper, and total link strength were calculated using VOSviewer, while centrality was derived from

CiteSpace. Centrality (0–1) reflects a node's bridging role within collaborative networks, with nodes exhibiting centrality ≥ 0.1 identified as key hub nodes.

Table 1
Country/Region Collaboration Network Analysis

Rank	Country/Region	Documents	Total Citations	Citations per Document	Total Link Strength	Centrality
1	USA	175	8751	50	86	0.93
2	China	205	5197	25.4	33	0.03
3	Germany	36	972	27	26	0.12
4	Canada	27	2145	79.4	27	0.08
5	France	25	1101	44	26	0.19
6	Italy	25	752	30.1	23	0.06
7	Japan	20	1103	55.2	16	0.02
8	Australia	18	1261	70.1	19	0.03
9	United Kingdom	14	917	65.5	33	0.07
10	Argentina	12	1039	86.6	9	0.01
11	Netherlands	12	197	16.4	15	0.01
12	Spain	11	697	63.4	16	0.09
13	Sweden	10	539	53.9	15	0.01
14	Egypt	9	235	26.1	5	0.01
15	Austria	8	279	34.9	6	0
16	Belgium	7	215	30.7	13	0.19
17	Russia	7	76	10.9	9	0.02
18	Serbia	7	387	55.3	1	0.06
19	Iran	16	205	12.8	10	0.03
20	South Korea	33	794	24.1	15	0.01
21	Singapore	6	414	69	12	0.02
22	Switzerland	5	697	139.4	15	0.02
23	India	5	20	4	7	0.1
24	Norway	6	112	18.7	8	0.06
25	Saudi Arabia	6	101	16.8	9	0.04

China and the United States form the first tier, with China leading at 205 articles followed by the United States with 175 articles, accounting for over 60% of the total. Germany, South Korea, and Canada form the second tier (27–37 articles), with Canada's average citation rate reaching 79.4. France, Italy, Japan, and Australia constitute the third tier (16–25 articles), with Japan and Australia having average citation rates of 55.2 and 70.1, respectively.

The United States is the only global cooperation hub with a centrality of 0.93, consistently leading in this field since 1996. China ranks first in the number of publications but has a centrality of only 0.03. Europe has formed a multi-center network, with countries such as France (0.19), Germany (0.12), and Belgium (0.19) exhibiting high centrality. Belgium, India, and Oman leverage high centrality with limited output.

From the perspective of scholarly influence, the United States leads by a wide margin with 8,751 total citations, while China ranks second with 5,197 citations, but its average per paper is only 25.4, lower than that of the United States (50.0), the United Kingdom (65.5), and Australia (70.1). Switzerland stands out with an average of 139.4 citations per paper, followed by Argentina (86.6) and Canada (79.4).

The national bubble chart (Fig. 3F) shows that the United States is located in the upper right corner, with high output and high influence; China is positioned slightly to the left in the center, with large output scale but room for improvement in average citations per paper; Switzerland, Argentina, and Canada are located above or to the right, with extremely high average citations per paper.

3.3 Institutional Distribution and Collaborative Networks

A total of 1,096 institutions participated in the study, with 49 institutions publishing ≥ 4 articles. Among these, 46 institutions had collaborative relationships with other institutions (Fig. 4). Table 2 lists the top 15 institutions by publication volume and their centrality. Analysis was conducted from five dimensions: publication volume, total citations, average citations per article, collaboration intensity, and centrality.

Table 2

Top 20 institutions ranked by publication volume in the field of NK cells in BC immunotherapy.

Rank	Institution	Documents	Total citations	Citations per document	Total link strength	Centrality
1	Sun Yat-sen Univ	16	711	44.4	13	0.26
2	Chinese Acad Sci	14	764	54.6	15	0.06
3	Zhejiang Univ	13	598	46.0	7	0.04
4	Ohio State Univ	12	1029	85.8	4	0.01
5	Nanjing Med Univ	11	155	14.1	3	0.00
6	Fudan Univ	10	130	13.0	10	0.09
7	Shanghai Jiao Tong Univ	10	156	15.6	7	0.00
8	Karolinska Inst	9	538	59.8	9	0.00
9	NCI	9	567	63.0	5	0.00
10	China Med Univ	8	206	25.8	5	0.01
11	Fujian Med Univ	8	63	7.9	3	0.10
12	Southern Med Univ	8	102	12.8	7	0.12
13	Dana Farber Canc Inst	8	151	18.9	9	0.03
14	Univ Chinese Acad Sci	7	738	105.4	10	0.00
15	Univ Kragujevac	7	387	55.3	1	0.00
16	Univ Melbourne	7	524	74.9	6	0.00
17	Univ Minnesota	7	843	120.4	0	0.00
18	Stanford Univ	7	393	56.1	2	0.00
19	Jinan Univ	7	300	42.9	2	0.00
20	Johns Hopkins Univ	7	246	35.1	1	0.03

China institutions dominate, with four of the top five institutions being from China: Sun Yat-sen University (16 papers), Chinese Academy of Sciences (14 papers), Zhejiang University (13 papers), and Nanjing

Medical University (11 papers) ranking at the forefront. Ohio State University (12 papers) is the only non-China institution among the top five.

Regarding academic impact, American institutions demonstrated outstanding performance. Ohio State University achieved 1,029 citations from 12 publications, averaging 85.8 citations per paper; the University of Minnesota published only 7 papers with a total of 843 citations, averaging a remarkable 120.4 citations per paper; the University of Chinese Academy of Sciences recorded an average of 105.4 citations per paper, showcasing high-quality research characteristics.

With respect to collaborative network centrality, Sun Yat-sen University exhibits a high centrality of 0.26, serving as the core hub of institutional collaboration networks in this field. Chinese institutions show divergence: Southern Medical University (0.12), Fujian Medical University (0.10), and Fudan University (0.09) demonstrate higher centrality and active international cooperation; whereas Nanjing Medical University published 9 papers but has a centrality of 0, indicating a closed collaborative network. American institutions exhibit relatively dispersed centrality, with Harvard University (0), the University of Texas system (0.09), and Ohio State University (0.01) failing to form super hubs. European institutions form clustered networks, with stable centrality observed at French Inserm (0.08) and German Helmholtz (0.07). Memorial Sloan Kettering Cancer Center (publishing 5 papers, centrality 0.19) and Cornell University (centrality 0.21) constitute the collaborative hub in the eastern United States.

As for the intensity of international cooperation, Chinese institutions such as Sun Yat-sen University (13), Chinese Academy of Sciences (15), and Fudan University (10) exhibit moderate linkage strength. American institutions like Dana-Farber Cancer Institute (2) and Ohio State University (4) have relatively low linkage strength values, but considering their publication volumes, the proportion of collaborations is not insignificant.

In terms of institutional types, comprehensive universities are the primary contributors to publication output; medical schools and specialized institutions focus on the medical field, with some having closed collaboration networks; research institutions and hospitals demonstrate prominent academic influence; while overseas leading institutions produce fewer publications but exhibit significant impact.

Overall, the field exhibits a pattern where “China institutions dominate the scale of output, while American institutions lead in the quality of influence”. Sun Yat-sen University has rapidly risen in recent years, becoming a new global core hub.

3.4 Author Distribution and Collaborative Networks

A total of 86 core authors with ≥ 3 published papers were identified, who were clustered into five major research teams through author coupling analysis (Fig. 5; Table 3).

Table 3

Top 30 core authors in the field of NK cells in BC immunotherapy (ranked by publication volume)

Rank	Author	Documents	Total citations	Citations per document	Total link strength
1	Mordoh J	6	219	36.5	5
2	Schlom J	5	335	67	9
3	Wels WS	5	250	50	5
4	Hodge JW	4	348	87	5
5	Ahn BC	4	248	62	11
6	Lee J	4	248	62	11
7	Lee SW	4	248	62	11
8	Yu LB	4	237	59.3	4
9	Yoon MS	4	165	41.3	6
10	Li J	4	155	38.8	2
11	Levy EM	4	139	34.8	5
12	Zheng GX	4	136	34	6
13	Arihiro K	4	88	22	18
14	Salih HR	4	74	18.5	6
15	Tonn T	4	69	17.3	6
16	Hegedus C	4	19	4.8	7
17	Virag L	4	19	4.8	7
18	Chouaib S	3	433	144.3	0
19	Burns LJ	3	416	138.7	3
20	Miller JS	3	416	138.7	3
21	Comerma L	3	397	132.3	8
22	Smyth MJ	3	360	120	1
23	Tridandapani S	3	356	118.7	4
24	Benner B	3	341	113.7	4
25	Gameiro SR	3	245	81.7	5
26	Jeong SY	3	231	77	9

Rank	Author	Documents	Total citations	Citations per document	Total link strength
27	Castellano R	3	220	73.3	2
28	Gulley JL	3	211	70.3	6
29	Ashkar AA	3	165	55	6
30	Shenouda MM	3	146	48.7	5

Concerning publication volume, Mordoh J ranked first with 6 articles, making him the highest-output author in this field; Schlom J and Wels WS tied for second place with 5 articles each; Hodge JW, Ahn BC, Lee J, Lee SW, and 13 other authors each published 4 articles, forming a core group of high-output authors.

From the perspective of academic impact, Chouaib S achieved 433 citations from 3 publications, averaging 144.3 citations per paper, making him the author with the highest single-article impact in this field. Burns LJ and Miller JS each contributed 3 papers with 416 citations, averaging 138.7 citations per paper. Authors such as Comerma L (averaging 132.3 citations), Smyth MJ (120.0), and Tridandapani S (118.7) also demonstrated exceptionally high single-article impact. Notably, Mordoh J, the author with the highest publication output (6 papers), received a total of 219 citations, averaging 36.5 citations per paper—a stark contrast to the aforementioned high-impact authors, highlighting two distinct research trajectories: “high productivity” versus “high impact”.

Regarding collaborative network characteristics, authors such as Arihiro K (link strength 18), Cabioglu N (18), and Emiroglu S (18) exhibited the highest total link strength, indicating strong connectivity within international research networks. Notably, three Korean authors—Ahn BC, Lee J, and Lee SW—showed consistent metrics including publication volume, citation frequency, and average citation impact (4 publications each, 248 citations, average impact factor 62.0, link strength 11), suggesting they may belong to the same research team with long-term collaboration. Hegedus C and Virag L each published 4 papers with only 19 citations but achieved a link strength of 7, demonstrating that despite limited influence, their research directions remain closely aligned with mainstream academic trends.

3.5 Journal Citation Network Map and Co-citation Analysis

In this field, open-access journals account for the largest number of publications, traditional authoritative journals hold the highest academic influence, and interdisciplinary journals lead the way in cutting-edge research(Table 4; Fig. 6).

Table 4
citation analysis of the top 10 core journals in natural killer cells research for BC immunotherapy:
Publication volume, academic impact, and network centrality.

Rank	Source	Documents	Citations	Citations per document	Total link strength
1	Frontiers in Immunology	47	1,599	34	79
2	Cancer Research	11	1,180	107.3	18
3	Journal for Immunotherapy of Cancer	25	1,036	41.4	31
4	Cancer Immunology, Immunotherapy	22	702	31.9	30
5	ACS Nano	7	736	105.1	2
6	Oncoimmunology	14	502	35.9	15
7	Biomaterials	7	487	69.6	4
8	Oncotarget	9	453	50.3	17
9	International Journal of Cancer	5	543	108.6	7
10	PNAS	5	607	121.4	4

In the context of publication volume, Frontiers in Immunology ranks first with 47 articles, followed by Journal for Immunotherapy of Cancer (25 articles) and Cancer Immunology, Immunotherapy (22 articles) as the core of professional journals. Regarding academic impact, traditional journals such as PNAS (average citation per article: 121.4) and Cancer Research (107.3) demonstrate exceptionally high average citations per article, while interdisciplinary journals like ACS Nano (105.1) and Biomaterials (69.6) also exhibit outstanding performance, reflecting the frontier nature of nanotechnology-integrated immunotherapy research.

Journals can be classified into four major categories: traditional immunology and oncology journals (e.g., Cancer Research) focus on fundamental mechanism research; open-access specialized journals (e.g., Frontiers in Immunology) concentrate on translational application research; high-impact interdisciplinary journals (e.g., ACS Nano) emphasize technological innovation; and BC-specific journals (e.g., Breast Cancer Research and Treatment) concentrate on disease models. Frontiers in Immunology ranks as the co-citation network hub with a total link strength of 79, followed closely by Journal for Immunotherapy of Cancer (31) and Cancer Immunology, Immunotherapy (30).

CiteSpace journal co-citation analysis revealed that the most frequently cited journals were Cancer Research (416 citations), Journal of Immunology (371 citations), Clinical Cancer Research (353 citations), and Frontiers in Immunology (338 citations) (Fig. 6C). In terms of centrality, the British Journal of Cancer (0.16) ranked highest, while classic journals such as PNAS (0.06), Blood (0.07), and Journal of

Clinical Investigation (0.07) also exhibited high centrality, reflecting their pivotal role in interdisciplinary knowledge integration.

Journal emergence analysis revealed that early emerging journals were predominantly traditional authoritative journals, with Journal of Immunology (impact factor 34.83,1997–2018), Blood (34.46,1998–2018), and Cancer Research (28.51,1998–2018) exhibiting the highest emergence intensity and longest duration, thereby constituting the foundational knowledge base of the field. Mid-term emerging journals included Oncoimmunology (9.82,2014–2020) and Oncotarget (10.74,2018–2020), reflecting the rise of specialized journals in tumor immunotherapy. Recent emerging journals were Journal of Immunology Research (9.74,2022–2023) and Theranostics (8.49,2023–2025), indicating that integrated platforms for immunology research and diagnosis/therapy have become a current frontier. Overall, emerging journals evolved from early traditional authoritative journals to specialized journals and further to interdisciplinary frontier journals, closely aligning with the trajectory of domain research hotspots (Fig. 6D).

3.6 Co-citation and Burst Analysis of Literature

The co-citation network analysis identified 21 highly cited papers with ≥ 20 co-citations, forming five major knowledge bases (Table 5; Fig. 7). These 21 high-cited papers exhibited citation frequencies ranging from 20 to 47 and total link strength values between 20 and 52. These publications constitute the knowledge foundation in the field of “natural killer cells in BC immunotherapy”. The following list is arranged in descending order of Total link strength, an indicator reflecting a paper's centrality within the co-citation network (i.e., the intensity of co-citations with other papers). Higher values indicate a paper's central position within the knowledge base.

Table 5

Core References Citation Analysis: Comprehensive Ranking Based on Citation Frequency, Link Strength, and Research Contribution.

Rank	Cited Reference	Citations	Total link strength	Key Insights
1	Schmid P, 2018, N Engl J Med, v379, p2108	33	52	IMpassion130 trial: atezolizumab plus chemotherapy in TNBC
2	Mamessier E, 2011, J Clin Invest, v121, p3609	36	49	Association between NK cells infiltration and prognosis in BC
3	Sung H, 2021, CA Cancer J Clin, v71, p209	47	46	Global cancer statistics (BC section)
4	Denkert C, 2018, Lancet Oncol, v19, p40	30	44	Tumor-infiltrating lymphocytes and prognosis in BC
5	Vivier E, 2008, Nat Immunol, v9, p503	24	41	Review on NK cells receptors and functions
6	Shimasaki N, 2020, Nat Rev Drug Discov, v19, p200	23	34	Prospects of NK cells in cancer immunotherapy
7	Nanda R, 2016, J Clin Oncol, v34, p2460	24	35	Pembrolizumab in metastatic TNBC
8	López-Soto A, 2017, Cancer Cell, v32, p135	21	32	Role of NK cells in cancer immunoediting
9	Myers JA, 2021, Nat Rev Clin Oncol, v18, p85	20	32	NK cell-targeting strategies in cancer immunotherapy
10	Guillerey C, 2016, Nat Immunol, v17, p1025	22	31	Novel mechanisms of NK cells in antitumor immunity
11	Gennari R, 2004, Clin Cancer Res, v10, p5650	20	31	NK cells activity and prognosis in BC
12	Böttcher JP, 2018, Cell, v172, p1022	25	30	Crosstalk between NK cells and the tumor microenvironment
13	Clynes RA, 2000, Nat Med, v6, p443	37	30	Antibody-dependent cellular cytotoxicity (ADCC)
14	Newman AM, 2015, Nat Methods, v12, p453	24	29	Quantification of immune cell infiltration (CIBERSORT)
15	Binnewies M, 2018, Nat Med, v24, p541	22	28	Immune cell composition in the tumor microenvironment
16	Vivier E, 2011, Science, v331	22	26	Review on NK cells functional regulation
17	Subramanian A, 2005, PNAS, v102, p15545	21	25	Gene set enrichment analysis (GSEA) methodology

Rank	Cited Reference	Citations	Total link strength	Key Insights
18	Mittendorf EA, 2014, Cancer Immunol Res, v2, p361	21	25	Review of clinical trials in BC immunotherapy
19	Liu EL, 2020, N Engl J Med, v382, p545	20	24	Pembrolizumab plus chemotherapy for TNBC
20	Schmid P, 2020, N Engl J Med, v382, p810	23	24	Atezolizumab plus chemotherapy in early TNBC
21	Hanahan D, 2011, Cell, v144, p646	24	20	Hallmarks of Cancer

Highly cited papers form the core knowledge base in this field. Sung H (2021) [21] ranked first with 47 citations, providing a global perspective on cancer epidemiology; Clynes RA (2000)[22] ranked second with 37 citations, first elucidating the ADCC mechanism and bridging targeted therapy with immunotherapy; Mamessier E (2011) [23] followed closely with 36 citations, establishing a direct correlation between NK cells infiltration and BC prognosis; Schmid P (2018)[24] ranked fourth with 33 citations, where the IMPASSION130 trial established immune checkpoint inhibitors as the standard treatment for TNBC.

Citation network centrality analysis revealed that Schmid P (2018) [24] ranked first with a link strength of 52, connecting clinical trials, immune microenvironment, and biomarkers; Mamessier E (2011) [23] ranked second with 49 links, bridging mechanistic research and clinical applications; Sung H (2021) [21] ranked third with 46 links, serving as background literature that extensively connects various disciplines; Denkert C (2018)[25] ranked fourth with 44 links, linking immune microenvironment and clinical prognosis. All four papers exhibited total link strengths exceeding 40, forming the backbone structure of knowledge dissemination.

Literature emergent analysis reveals the three-stage evolution of research hotspots. The first stage (2000–2017) focused on fundamental mechanisms, with studies by Cheng M (2013) [26] and Marcus A (2014) [27] highlighting the central role of NK cells. The second stage (2018–2021) marked the surge in immunotherapy, where Schmid P (2018) [24] emerged with the highest emergent intensity at 7.44, coinciding with simultaneous contributions by Denkert C (2018) [25] and Nanda R (2016) [28], demonstrating synergy between clinical and basic research. The third stage (2022–2025) centered on precision therapy, with continuous emergent studies by Sung H (2021) [21], Shimasaki N (2020) [29], and Myers JA (2021) [30], making NK cell-targeting strategy optimization a cutting-edge frontier.

To summarize, research hotspots in this field have undergone a complete evolution from exploration of the ADCC mechanism to clinical trials of immune checkpoint inhibitors, and further to precision immunotherapy and optimization of NK cell-targeting strategies. Schmid P (2018) [24], Sung H (2021) [21], and Denkert C (2018) [25] represent the core publications with the highest prominence and longest

duration, respectively, embodying the three pillars of clinical trials, epidemiological background, and biomarker research. Current frontiers focus on immunotherapy for TNBC, CAR-NK engineering strategies, and optimization of combination therapies.

3.7 Co-occurrence and Emergence Analysis of Keywords

A total of 49 keywords were included, with a cumulative occurrence frequency of 1,006. Among the 1,290 keywords, the most frequently occurring terms were: breast cancer (205 occurrences), natural killer cells (140 occurrences), and immunotherapy (136 occurrences), which collectively formed the core conceptual triangle of the field (Fig. 8; Table 6).

Table 6

High-frequency keywords in the field: occurrence, total link strength, and CiteSpace centrality.

Rank	Keyword	Occurrences	Total link strength	CiteSpace Centrality
1	breast cancer	205	342	0.36
2	natural killer cells	140	245	0.33
3	immunotherapy	136	253	0.09
4	tumor microenvironment	67	136	0.02
5	triple-negative breast cancer	52	75	0.01
6	adcc	27	56	0.09
7	prognosis	25	48	0.02
8	cancer immunotherapy	28	35	0.07
9	cancer	23	43	0.08
10	trastuzumab	19	41	0.02
11	immune checkpoint	11	21	0.01
12	pd-1	12	19	0.01
13	immunosuppression	14	25	0
14	pd-l1	10	20	0
15	metastasis	10	15	0.02
16	t cells	10	32	0.12
17	immune infiltration	10	13	0.03
18	dendritic cells	9	20	0.06
19	biomarker	9	12	0
20	macrophages	7	22	0
21	cytokines	5	10	0
22	cytotoxicity	7	10	0.02
23	combination therapy	7	10	0
24	immune evasion	7	11	0
25	immune response	9	22	0.01
26	immunomodulation	8	17	0

Rank	Keyword	Occurrences	Total link strength	CiteSpace Centrality
27	myeloid-derived suppressor cells	6	12	0
28	car-nk	5	13	0
29	her2	8	18	0
30	il-15	7	15	0
31	immune cells	9	23	0
32	apoptosis	8	10	0.01
33	antitumor immunity	8	14	0.20
34	chemotherapy	7	13	0.09
35	chimeric antigen receptor	6	16	0
36	doxorubicin	5	11	0
37	flow cytometry	5	10	0
38	immune system	5	11	0
39	immunogenic cell death	5	4	0
40	innate immunity	6	14	0.03
41	lymphocytes	5	6	0.03
42	metastatic breast cancer	9	11	0
43	monoclonal antibody	5	9	0.06
44	pertuzumab	5	15	0
45	bispecific antibody	5	7	0
46	anti-pd-1	5	9	0
47	immune checkpoint inhibitors	5	8	0
48	tumor	5	13	0.02
49	tumor-associated macrophages	5	11	0

Among high-frequency keywords, “breast cancer” (205 occurrences), “natural killer cells” (140 occurrences), and “immunotherapy” (136 occurrences) ranked as the top three, constituting the core domain. “tumor microenvironment” (67 occurrences) and “triple-negative breast cancer” (52 occurrences) respectively reflected significant research frameworks and hot subtypes.

The total link strength analysis revealed that “breast cancer” (342), “immunotherapy” (253), and “natural killer cells” (245) constituted the core hierarchical layer of the network. Although “ADCC” appeared only 27 times, its link strength reached 56, serving as a critical bridging element.

Centrality analysis revealed that “breast cancer” (0.36) and “natural killer cells” (0.33) were absolute cores of the network; “T cells” (0.12) connected innate and adaptive immunity; “antitumor immunity” (0.20) and “ADCC” (0.09) linked basic and clinical aspects; “triple-negative breast cancer” (0.01) exhibited extremely low centrality, presenting a “hotspot island” characteristic; “immunotherapy” (0.09) had centrality slightly below the hub threshold, reflecting limited connectivity among broad terms.

Through CiteSpace keyword clustering analysis, a total of 8 valid clusters (#0- #7) were identified, systematically revealing research hotspots and core themes in the field of BC immunotherapy (Fig. 8E; Table 7). Cluster #0 primarily investigates BC and NK cells therapy, focusing on allogeneic NK cells, hematopoietic stem cell transplantation, and anti-tumor immunity. Cluster #1 further explores the application of NK cells in tumor immunotherapy, encompassing CAR-NK cells, bone marrow transplantation, and combination therapy strategies. Cluster #7 examines the role of T cells and macrophages in the BC immune microenvironment, involving antibody-drug conjugates and cancer progression. In adaptive immunity and antibody therapy, cluster #2 emphasizes the anti-tumor mechanisms of ADCC and monoclonal antibodies (e.g., trastuzumab). Regarding tumor microenvironment and immune checkpoints, cluster #3 delves into the roles of tumor microenvironment, dendritic cells, tumor-infiltrating lymphocytes, and the immune system in TNBC. Cluster #4 focuses on immune checkpoints, cancer stem cells, and receptors associated with tumor progression. In molecular biomarkers and targeted therapy, cluster #5 investigates molecular characteristics such as gene expression, ERBB2, and single-cell RNA sequencing. Additionally, cluster #6 represents emerging cancer immunotherapies and nanomedicine, covering cutting-edge areas including nanomedicines, IL-2, and immunotherapy. These cluster analyses clearly reveal the diversity in breast cancer research, spanning from innate immunity (NK cells, macrophages) to adaptive immunity (antibodies, T cells), from tumor microenvironment regulation to precision targeting and nanotherapy. They demonstrate the comprehensive research landscape of immunotherapy in breast cancer, from fundamental mechanisms to clinical translation.

Table 7
Results of keyword clustering analysis

Cluster ID	Size	Silhouette	Mean (Year)	Top Terms (LSI)	Top Terms (log-likelihood ratio, p-level)
#0 breast cancer	46	0.777	2005	breast cancer; alloreactive nk cell; hematopoietic stem cell transplantation; antitumor immunity; t cells; natural killer cells; antibody- dependent cell- mediated cytotoxicity; immune checkpoint inhibitor; mb15-41bbl cells; pd-l1 inhibitor	breast cancer (22.74, 1.0E-4); human epidermal growth factor receptor 2 (7.09, 0.01); triple-negative breast cancer (7.02, 0.01); antitumor activity (6.52, 0.05); natural killer cell (5.9, 0.05)
#1 natural killer cells	39	0.682	2003	breast cancer; gene expression; polycomb repressive; epigenetic regulation; chromosome inactivation; natural killer cells; recurrent breast cancer; clinical outcome; cancer metabolism; tumor heterogeneity	natural killer cells (19.65, 1.0E-4); therapy (16.74, 1.0E-4); car-nk cells (10.38, 0.005); generation (6.92, 0.01); bone marrow transplantation (6.92, 0.01)
#2 monoclonal antibody	37	0.65	2012	breast cancer; antibody-dependent cellular cytotoxicity; exploratory subgroup discovery; recurrent breast cancer; tumor escape; natural killer cells; combination treatment; free survival; tumor cryoablation; tumor escape	monoclonal antibody (7.67, 0.01); antibody- dependent cellular cytotoxicity (7.45, 0.01); immunity (7.45, 0.01); herceptin (5.85, 0.05); antibody-dependent cellular cytotoxicity (adcc) (5.85, 0.05)
#3 tumor microenvironment	35	0.68	2017	breast cancer; innate immunity; cancer model; tumor immunotherapy; innate lymphoid cells; tumor microenvironment; triple-negative breast cancer; immune cells;	tumor microenvironment (16.15, 1.0E-4); dendritic cells (14.56, 0.001); triple-negative breast cancer (13.17, 0.001); tumor infiltrating lymphocytes (13.04, 0.001); immune system (7.54, 0.01)

Cluster ID	Size	Silhouette	Mean (Year)	Top Terms (LSI)	Top Terms (log-likelihood ratio, p-level)
				traditional chinese medicine; cancer model	
#4 receptors	31	0.66	2016	breast cancer; tumor microenvironment; immune checkpoint inhibitor; cd112r; peptide-drug conjugate; cancer immunotherapy; drug repurposing; immune checkpoint inhibitor; cd112r; peptide-drug conjugate	receptors (7.44, 0.01); cancer stem cells (7.36, 0.01); tumor progression (7.36, 0.01); growth (6.9, 0.01); immune checkpoint (6.29, 0.05)
#5 expression	27	0.621	2011	breast cancer; immune checkpoint inhibitor; transcription; peptide-drug conjugate; tumor-associated glycan antigens; expression; cancer; activation; agents; nanosystem	expression (20.76, 1.0E-4); synthase (7.87, 0.01); erbb2 (7.87, 0.01); disease (7.87, 0.01); single-cell rna sequencing (7.87, 0.01)
#6 cancer immunotherapy	25	0.718	2016	cancer immunotherapy; fusion protein; cellular immunity; endocrine-dependent metastatic breast cancer; oxygen nanocarrier; breast cancer; innate immunity; colorectal cancer; clinical trials; adoptive immunotherapy	cancer immunotherapy (21.25, 1.0E-4); nanomedicine (8.06, 0.005); il-2 (8.06, 0.005); immunochemotherapy (8.06, 0.005); triggers (5.87, 0.05)
#7 t cells	23	0.82	2005	breast cancer; cancer immunotherapy; innate immunity; colorectal cancer; checkpoint; tumor microenvironment; natural killer cell; checkpoint; neoantigen cancer	t cells (10.87, 0.001); macrophages (7.84, 0.01); antibody-drug conjugate (5.22, 0.05); anti asialo gm1 (5.22, 0.05); cancer progression (5.22, 0.05)

Cluster ID	Size	Silhouette	Mean (Year)	Top Terms (LSI)	Top Terms (log-likelihood ratio, p-level)
				vaccine; immune checkpoint inhibitor	

Keyword emergence analysis divides the evolution of research hotspots into four stages (Fig. 8l). The first stage (1996–2005) was the foundational mechanism establishment period, with “antitumor immunity” (1997–2014, intensity 5.5) and “in vivo” (2003–2017, intensity 9.44) as the primary emerging terms. The second stage (2005–2015) marked the targeted therapy and immune crossover period, where “monoclonal antibody” (2005–2017, intensity 6.36) and “ADCC” (2005–2015, intensity 3.28) emerged simultaneously, revealing the rise of the ADCC mechanism. The third stage (2016–2020) was the immunotherapy explosion period, with “immunotherapy” emerging with high intensity (7.64), while “nanoparticles” and “NKG2D” also appeared concurrently. The fourth stage (2021–2025) represented the precision immunotherapy and clinical translation phase, characterized by sustained emergence of terms such as “macrophages” (2021–2025, intensity 3.27), “immune infiltration” (2022–2023, intensity 6.19), and “triple-negative breast cancer” (2023–2025, intensity 5.71), demonstrating a clear clinical translation orientation.

The overall evolutionary trajectory demonstrates that this field has progressed from fundamental mechanism exploration to targeted therapy and immune network modulation, now advancing toward precision clinical translation. Current cutting-edge research focuses on macrophage targeting, immune infiltration analysis, precision treatment for TNBC, and biomarker-guided personalized strategies.

4 Discussion

4.1 Global Research Landscape and Core Competencies

The bibliometric analysis of this study revealed the global research landscape and core force distribution of natural killer cells in the field of BC immunotherapy. At the national level, the United States emerged as the sole global collaborative hub in this field with 175 publications and a centrality of 0.93, a position rooted in its long-term policy support and research ecosystem: The National Institutes of Health provides sustained funding for field development through initiatives like the Cancer Immunotherapy Research Network; meanwhile, the “professional hub + decentralized collaboration” model formed by top institutions such as Memorial Sloan Kettering Cancer Center and Dana-Farber Cancer Institute effectively integrates basic research and clinical translation resources. China leads with 205 publications but a centrality of only 0.03, presenting a dual reality of “output scale advantage” and “international collaboration shortcomings”. This phenomenon reflects China's long-standing tendency to prioritize quantity over quality in scientific evaluation systems, as well as the relatively closed structural characteristics of domestic institutional collaboration networks. Notably, Belgium achieved a centrality of 0.19 with 7 publications, while India obtained 0.10 centrality with 5 publications, demonstrating that

small-scale research efforts can leverage high network status through active participation in international multicenter studies—a model worthy of reference for China.

At the institutional level, Sun Yat-sen University has become a new global core hub with 16 publications and a centrality of 0.26, reflecting China's high research activity and growing international cooperation capabilities in this field. However, Chinese institutions show significant differentiation: Southern Medical University (centrality 0.12) and Fujian Medical University (0.10) exhibit active international collaboration, while Nanjing Medical University (9 publications, centrality 0) is highly productive but closed in collaboration. American institutions demonstrate relatively dispersed centrality, but specialized hubs such as Memorial Sloan Kettering Cancer Center (5 publications, centrality 0.19) play a prominent role, reflecting the professional development model of “small institutions, large hubs”. European institutions form clustered networks, with stable centrality seen in French Inserm (0.08) and German Helmholtz (0.07), showcasing Europe's characteristic of achieving long-term stable collaboration through national research networks.

4.2 Core Author Team and Research Paradigm

Author collaboration network analysis identified five core research teams, each exhibiting differentiated “output-influence” patterns. The United States NCI Immunotherapy Clinical Translation Team (Schlom J, Hodge JW et al.) achieved an average citation frequency of 67–87 per paper, exemplifying the “high-citation-middle-output” model. Their success lies in addressing major scientific questions by integrating basic research, preclinical models, and clinical trial resources to establish a comprehensive research ecosystem. The Spanish NK cells and Immune Checkpoint Team (Albanell J, Comerma L et al.) reported an average citation frequency of 41.7 per paper, demonstrating a “low-output-high-citation” pattern that reflects Europe's strength in capturing cutting-edge concepts and rapidly developing distinctive research features. The Japanese NK Cells Mechanism Research Team (Arihiro K et al.) achieved an average citation frequency of 22 per paper, showcasing a “medium-citation-middle-output” pattern with expertise in mechanistic depth. Their findings provide theoretical foundations for developing ADCC-enhanced antibodies. The Turkish Breast Cancer Clinical Research Team (Cabioglu N et al.) recorded an average citation frequency of 18 per paper, exhibiting a “high-output-low-citation” characteristic. While their clinical resource integration model is noteworthy, the lack of mechanistic depth limits international impact. The Korean NK cells and Cytokine Team (Choi JH et al.) achieved approximately 10 citations per paper, reflecting a “medium-citation-low-output” pattern that underscores the necessity of integrating technological development with mechanistic insights to enhance academic value.

This pattern reveals the impact laws of different research paradigms on academic influence: clinical observational studies are easy to produce but have limited impact, mechanistic in-depth studies can enhance the impact of individual papers, frontier concept research can achieve significant impact with small outputs, and full-chain translational research can maximize impact. The implications for China's researchers are: they should draw lessons from the Spanish team's “frontier focus” strategy, refer to the Japanese team's “mechanistic deepening” model, learn from the United States NCI team's “full-chain” concept, while being wary of the Turkish team's dilemma of “high output but low citations”.

4.3 Journal Ecosystem and Knowledge Dissemination Patterns

Journal analysis reveals a diversified ecosystem of knowledge dissemination in this field. In terms of publication volume, *Frontiers in Immunology* leads with 47 articles, followed closely by *Journal for Immunotherapy of Cancer* (25 articles) and *Cancer Immunology, Immunotherapy* (22 articles), forming the core cluster of open-access professional journals. This pattern reflects how open-access journals have become the primary channel for publishing research findings in emerging interdisciplinary fields, leveraging their rapid publication cycles and broad reader reach. *Frontiers in Immunology*'s total link strength of 79 further confirms its central role as a hub for domain knowledge dissemination.

Regarding academic impact, traditional authoritative journals continue to maintain an irreplaceable leading role. Journals such as *PNAS* (average 121.4 citations per paper) and *Cancer Research* (average 107.3 citations per paper) exhibit limited publication volumes but demonstrate exceptionally high average citations per paper, serving as core platforms for high-quality and groundbreaking research in these fields. The rise of interdisciplinary journals has injected new vitality into the field. The high citation rates of *ACS Nano* (average 105.1 citations per paper) and *Biomaterials* (average 69.6 citations per paper) reflect the cutting-edge nature of interdisciplinary research on nanotechnology and immunotherapy, indicating that NK cells immunotherapy studies are evolving from traditional immunology paradigms toward a multidisciplinary integration paradigm encompassing “immunology-materials-engineering”.

4.4 Structure and Evolution of Knowledge Base

The literature co-citation analysis revealed five major knowledge modules that collectively constitute a complete knowledge chain spanning from fundamental mechanisms to clinical applications in this field. The clinical trial on immunotherapy for TNBC represents the most critical knowledge node in this domain. The IMpassion130 trial by Schmid P (2018) [24] emerged as the most frequently cited and most network-centric core literature, with 33 citations and a total link strength of 52, pioneering the application of immune checkpoint inhibitors in BC. The foundational biology of NK cells and anti-tumor mechanisms, exemplified by Clynes RA (2000) [22], first elucidated the mechanism by which trastuzumab activates NK cells through ADCC, bridging the long-separated fields of targeted therapy and immunotherapy. The analysis of tumor immune microenvironment and infiltration, represented by Mamessier E (2011) [23], systematically described functional deficiencies of NK cells in BC patients and directly correlated NK cells infiltration with BC prognosis for the first time, serving as a pivotal node connecting basic research and clinical practice with a link strength of 49.

From a temporal perspective, this field has undergone four significant paradigm shifts in research: The first shift (2001–2005) marked the transition from chemotherapy dominance to immunotherapy, with NK cells and ADCC mechanisms becoming central. The second shift (2006–2010) shifted focus from individual cells to the entire microenvironment, with attention directed toward tumor immunosuppressive

networks. The third shift (2011–2015) moved from pan-cancer research to subtype-specific approaches, with TNBC emerging as the primary battlefield for immunotherapy. The fourth shift (2016–2025) transitioned from monotherapy to combination strategies, with engineered cell therapies such as CAR-NK entering the exploratory phase. This evolutionary trajectory aligns closely with advancements in clinical practice: In 2011, Hanahan incorporated “immune evasion” as a cancer biomarker; in 2016, immune checkpoint inhibitors were first approved for BC treatment; in 2018, the KEYNOTE-522 trial established pembrolizumab's role in early-stage TNBC; and in 2020, CAR-NK cells therapy entered clinical trial stages.

4.5 Current Research Hotspots and Future Trends

Keyword emergence analysis revealed that current research hotspots are concentrated in four directions: CAR-NK (first identified in 2019), as the next-generation cell therapy technology following CAR-T, exhibits higher safety and generalization potential; immune checkpoint inhibitors (first identified in 2020), which have demonstrated active clinical translation in recent years with continuous optimization of combination therapy strategies; combination therapies (first identified in 2015), where the synergistic mechanisms among chemotherapy, targeted therapy, and immunotherapy are key research focuses; and immunogenic cell death (first identified in 2017), where chemotherapy-or radiotherapy-induced immunogenic cell death can activate NK cells, creating an “in situ vaccine” effect.

Future research trends can be identified from the following directions: First, the clinical translation of CAR-NK therapy[31–33]. Although its current adoption rate remains low, its “spot-type” potential and lower cytokine storm risk make it the most promising development direction. Future efforts should focus on addressing the infiltration and persistence of CAR-NK cells in solid tumors. Second, combination strategies targeting immune checkpoints. The combination therapy of PD-1/PD-L1 inhibitors with other targets (e.g., HER2, ADCC) represents a key optimization direction, alongside exploration of NK cell-specific checkpoint inhibitors (e.g., NKG2A, KIR)[34–36]. Third, precision regulation of the tumor microenvironment [37, 38]. The heterogeneity of the tumor microenvironment determines variations in treatment responses among patients, making microenvironment-based stratified therapy a focal point. Applications of single-cell sequencing and spatial transcriptomics technologies will drive advancements in this field[39–41]. Fourth, biomarker integration. Constructing multidimensional predictive models based on NK cells functional status, immune infiltration characteristics, and gene expression profiles will enable precise patient stratification [42, 43].

4.6 Interaction between NK cells and tumor microenvironment: From immunosuppressive mechanisms to targeted interventions

Keyword emergence analysis revealed that “macrophages” (macrophages) consistently emerged from 2021 to 2025 (intensity 3.27), making it one of the longest-lasting research hotspots. Meanwhile, “tumor microenvironment” (tumor microenvironment) emerged with high frequency (67 occurrences) and centrality of 0.02, establishing it as a key research framework. This indicates that the field is undergoing

a cognitive transition from “single NK cells effect mechanisms” to “NK cell-microenvironment cell interaction networks”.

At the mechanistic level, tumor-associated macrophages (TAMs), as one of the most abundant immune cells in the tumor microenvironment, directly suppress the cytotoxic function of NK cells by secreting inhibitory cytokines such as IL-10 and TGF- β [44–46]. Concurrently, the high expression of PD-L1 on macrophage surfaces can bind to PD-1 on NK cells, inducing NK cells exhaustion [47]. Myeloid-derived suppressor cells (MDSCs) block NK cells activation signals by generating reactive oxygen species and arginase-1 [48, 49]. Analysis of co-cited literature in this study revealed that Mamessier E (2011) [23] became a pivotal node connecting fundamental NK cells biology with clinical prognosis of BC, with 36 citations and 49 link strengths. This study systematically described for the first time functional defects in tumor-infiltrating NK cells in BC patients, which showed negative correlation with macrophage infiltration levels, providing early evidence for understanding NK cell-macrophage interactions.

In the context of therapeutic strategies, targeting tumor-associated macrophages has emerged as a critical approach to overcoming immune therapy resistance. CSF-1R inhibitors can reduce macrophage infiltration and reshape the immune microenvironment [50]; CD47-SIRP α blocking antibodies enhance macrophage phagocytosis of tumor cells while activating adaptive immunity through cross-presenting [50, 51]. Notably, CD47 antibodies have demonstrated preliminary efficacy in clinical trials combining trastuzumab for HER2-positive BC treatment, with mechanisms potentially involving synergistic interactions between macrophages and NK cells [52], suggesting the need for further elucidation of NK cell-tumor-associated macrophage interaction networks to develop combined targeting strategies.

4.7 CAR-NK Engineering Technology: Cutting-edge Breakthroughs from Basic Research to Clinical Translation

As revealed by the keyword burst detection, “CAR-NK” first appeared in 2019 (with a frequency of 5). Although its current frequency is relatively low, as the next-generation cell therapy technology following CAR-T, its “spot-type” potential and lower cytokine storm risk make it the most promising development direction. This trend aligns with the positioning of “senomorphics” as an emerging therapeutic cluster in the reference article.

At the mechanistic level, CAR-NK cells are genetically engineered to express chimeric antigen receptors on their surface, enabling them to specifically recognize tumor antigens and activate cytotoxic functions. Compared to CAR-T cells, CAR-NK cells exhibit multiple advantages: they do not induce graft-versus-host disease, allow allogeneic transplantation, significantly reduce the risk of cytokine storms, and can exert synergistic antitumor effects through various mechanisms (natural cytotoxicity, ADCC, and CAR-mediated killing) [53–59]. Analysis of cited literature in this study revealed that Shimasaki N (2020) [29] emerged as a pivotal review in the field with 23 citations and 34 link strengths, systematically summarizing the application prospects of NK cells in cancer immunotherapy and particularly emphasizing the translational potential of engineered technologies such as CAR-NK.

As for translational challenges, although CAR-NK has achieved preliminary success in hematologic malignancies, its application in solid tumors (including BC) still faces multiple obstacles: immunosuppressive factors in the tumor microenvironment inhibit CAR-NK function; tumor antigen heterogeneity leads to target escape; CAR-NK exhibits limited persistence in vivo; and large-scale production and quality control have not yet been standardized [54, 60]. Key issues to be addressed in the future include: optimizing CAR structure to enhance NK cells function in suppressive microenvironments; developing multi-target CAR-NK strategies to address antigen heterogeneity; exploring combination strategies of CAR-NK with immune checkpoint inhibitors and chemotherapy; and establishing GMP-compliant large-scale production systems. This research direction aligns with the concept of "multi-target homologous drugs for multi-level regulation of the SASP network" described in the reference article, both reflecting future trends in precision intervention and combination therapy.

4.8 Immunogenic cell death: A new bridge connecting traditional therapy with immunotherapy

The results of keyword emergence analysis demonstrate that "immunogenic cell death" first appeared in 2017 (frequency: 5) and has shown continuous increasing attention in recent years. This mechanism elucidates how chemotherapy, radiotherapy, or targeted therapy induce tumor cell death, release damage-associated molecular patterns (DAMPs), activate dendritic cells and NK cells[61, 62].

At the mechanistic level, the hallmark of immunogenic cell death is the exposure or release of DAMPs such as calnexin, high-mobility group box 1 (HMGB1), and ATP during tumor cell death. These molecules promote dendritic cell maturation and antigen presentation, thereby activating NK cells and T cells[63]. Analysis of cited literature in this study revealed that Clynes RA (2000)[22] emerged as one of the foundational works in this field with 37 citations and 30 linkages, having first elucidated the mechanism by which trastuzumab activates NK cells via ADCC. Notably, the ADCC mechanism exhibits synergistic effects with immunogenic cell death: trastuzumab not only directly activates NK cells through ADCC but also induces immunogenic cell death in HER2-positive tumor cells, further amplifying the immune response[64–66].

On the subject of clinical implications, this discovery provides a theoretical foundation for the synergy between traditional therapy and immunotherapy. Chemotherapeutic agents (such as doxorubicin and cyclophosphamide) have been demonstrated to induce immunogenic cell death, and their combined application with NK cells immunotherapy is expected to produce synergistic effects[67, 68]. In keyword frequency analysis, the term "combination therapy" has consistently emerged since 2015 (frequency:7), further confirming that combination strategies have become the mainstream approach in this field. Future research should delve into the molecular mechanisms by which different chemotherapeutic agents and targeted drugs induce immunogenic cell death, optimize the timing window and dose combinations for combination therapy, and explore patient stratification strategies based on biomarkers related to immunogenic cell death to achieve precise "immunochemotherapy" regimens.

4.9 Limitations of the Study

This study has the following limitations: The data were exclusively sourced from the WoSCC, excluding other databases and non-English literature, which may result in the omission of certain significant research findings; the bibliometric methods focused on macro-level characteristics of publications, failing to provide in-depth evaluations of individual studies' scientific value and innovation; citation analysis inherently exhibits temporal delays, as high-quality articles published within the past 1 years might not be included in high-citation rankings due to insufficient citation accumulation; while keyword merging enhanced network clarity, it may have compromised certain semantic details; the study concentrated on NK cells applications in BC immunotherapy without investigating NK cells in other tumor types, necessitating validation of the conclusions' generalizability. This field remains in a phase of rapid development, where future breakthroughs may alter existing trends, requiring continuous analysis updates.

Declarations

- Ethics approval and consent to participate

Not applicable.

- Consent for publication

Not applicable.

- Availability of data and materials

All data generated during this study have been submitted to the journal's online submission system and are available from the corresponding author upon reasonable request.

- Competing Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

- Funding

Key Medical Discipline Project of Joint Logistics Support Force of the People's Liberation Army of China; Key Discipline Project of Shandong Province Medical and Health; Shangdong Provinical Natural Science Foundation General Project (ZR2021MH328); Shandong Province Medical and Health Technology Development Plan (202204011069); 2023 Ji'nan Science and Technology Innovation Development Program (202317016); 2024 Ji'nan Clinical Medicine Science and Technology Innovation Program(202430064).

- Authors' contributions

Yue Wang and Jiayu Zhu wrote the main manuscript text; Yue Wang and Meng Wang prepared figures, Tables; Yuanyuan Fu and Yuan Liu supervised the study; Luming Zheng provided resources and validation; Qingqing He conceptualized the work and supervised the study. All authors reviewed the manuscript.

• Acknowledgements

Not applicable.

References

1. Shihab I, Khalil BA, Elemam NM, et al. Understanding the Role of Innate Immune Cells and Identifying Genes in Breast Cancer Microenvironment. *Cancers (Basel)*. 2020;12(8). 10.3390/cancers12082226.
2. Zambarda C, Guldevall K, Breunig C, et al. CD16A Shedding Regulates Innate Cell Engager-Induced Serial Killing by Natural Killer Cells. *Eur J Immunol*. 2025;55(10):e70078. 10.1002/eji.70078.
3. da Silva Bortoleti BT, Quasem S, Maurer S, et al. A monoclonal antibody that inhibits the shedding of CD16a and CD16b and promotes antibody-dependent cellular cytotoxicity against tumors. *Nat Commun*. 2025;16(1):9915. 10.1038/s41467-025-64862-5.
4. Albarrán V, San Román M, Pozas J, et al. Adoptive T cell therapy for solid tumors: current landscape and future challenges. *Front Immunol*. 2024;15. 10.3389/fimmu.2024.1352805.
5. Zhang T, Tai Z, Miao F, et al. Adoptive cell therapy for solid tumors beyond CAR-T: Current challenges and emerging therapeutic advances. *J Control Release*. 2024;368:372–96. 10.1016/j.jconrel.2024.02.033.
6. Dougé A, Ghazzi NE, Lemal R, et al. Adoptive T Cell Therapy in Solid Tumors: State-of-the Art, Current Challenges, and Upcoming Improvements. *Mol Cancer Ther*. 2024;23(3):272–84. 10.1158/1535-7163.Mct-23-0310.
7. Gradishar WJ, Moran MS, Abraham J, et al. NCCN Guidelines® Insights: Breast Cancer, Version 5.2025. *J Natl Compr Canc Netw*. 2025;23(11):426–36. 10.6004/jnccn.2025.0053.
8. Li J, Jiang Z. Chinese Society of Clinical Oncology Breast Cancer (CSCO BC) Guidelines in 2024: International Contributions from China. *Cancer Biol Med*. 2024;21(10):838–43. 10.20892/j.issn.2095-3941.2024.0374.
9. Garrido-Castro AC, Lin NU, Polyak K. Insights into Molecular Classifications of Triple-Negative Breast Cancer: Improving Patient Selection for Treatment. *Cancer Discov*. 2019;9(2):176–98. 10.1158/2159-8290.Cd-18-1177.
10. Liu Y, Zou Y, Ye Y, et al. Advances in the Understanding of the Pathogenesis of Triple-Negative Breast Cancer. *Cancer Med*. 2024;13(22):e70410. 10.1002/cam4.70410.
11. Ran R, Chen X, Yang J, et al. Immunotherapy in breast cancer: current landscape and emerging trends. *Exp Hematol Oncol*. 2025;14(1):77. 10.1186/s40164-025-00667-y.

12. Jin M, Fang J, Peng J, et al. PD-1/PD-L1 immune checkpoint blockade in breast cancer: research insights and sensitization strategies. *Mol Cancer*. 2024;23(1):266. 10.1186/s12943-024-02176-8.
13. Choi SH, Kim HJ, Park JD, et al. Chemical priming of natural killer cells with branched polyethylenimine for cancer immunotherapy. *J Immunother Cancer*. 2022;10(8). 10.1136/jitc-2022-004964.
14. Schmid P, Oliveira M, O'Shaughnessy J, et al. TROPION-Breast05: a randomized phase III study of Dato-DXd with or without durvalumab versus chemotherapy plus pembrolizumab in patients with PD-L1-high locally recurrent inoperable or metastatic triple-negative breast cancer. *Ther Adv Med Oncol*. 2025;17. 10.1177/17588359251327992.
15. Wang Z, You P, Yang Z, et al. PD-1/PD-L1 immune checkpoint inhibitors in the treatment of unresectable locally advanced or metastatic triple negative breast cancer: a meta-analysis on their efficacy and safety. *BMC Cancer*. 2024;24(1):1339. 10.1186/s12885-024-13105-9.
16. Liu Z, Ding M, Qiu P, et al. Natural killer cell-related prognostic risk model predicts prognosis and treatment outcomes in triple-negative breast cancer. *Front Immunol*. 2023;14:1200282. 10.3389/fimmu.2023.1200282.
17. Ding S, Qiao N, Zhu Q, et al. Single-cell atlas reveals a distinct immune profile fostered by T cell-B cell crosstalk in triple negative breast cancer. *Cancer Commun (Lond)*. 2023;43(6):661–84. 10.1002/cac2.12429.
18. Wang Y, Jiang Y, Ding F, et al. Phenotypes and cytokines of NK cells in triple-negative breast cancer resistant to checkpoint blockade immunotherapy. *Breast Cancer Res*. 2025;27(1):51. 10.1186/s13058-025-02003-y.
19. Ye L, Liang R, Liu X, et al. Frailty and sarcopenia: A bibliometric analysis of their association and potential targets for intervention. *Ageing Res Rev*. 2023;92:102111. 10.1016/j.arr.2023.102111.
20. Roldan-Valadez E, Salazar-Ruiz SY, Ibarra-Contreras R, et al. Current concepts on bibliometrics: a brief review about impact factor, Eigenfactor score, CiteScore, SCImago Journal Rank, Source-Normalised Impact per Paper, H-index, and alternative metrics. *Ir J Med Sci*. 2019;188(3):939–51. 10.1007/s11845-018-1936-5.
21. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin*. 2021;71(3):209–49. 10.3322/caac.21660.
22. Clynes RA, Towers TL, Presta LG, et al. Inhibitory Fc receptors modulate in vivo cytotoxicity against tumor targets. *Nat Med*. 2000;6(4):443–6. 10.1038/74704.
23. Mamessier E, Sylvain A, Thibult ML, et al. Human breast cancer cells enhance self tolerance by promoting evasion from NK cell antitumor immunity. *J Clin Invest*. 2011;121(9):3609–22. 10.1172/jci45816.
24. Schmid P, Adams S, Rugo HS, et al. Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. *N Engl J Med*. 2018;379(22):2108–21. 10.1056/NEJMoa1809615.

25. Denkert C, von Minckwitz G, Darb-Esfahani S, et al. Tumour-infiltrating lymphocytes and prognosis in different subtypes of breast cancer: a pooled analysis of 3771 patients treated with neoadjuvant therapy. *Lancet Oncol.* 2018;19(1):40–50. 10.1016/s1470-2045(17)30904-x.
26. Cheng M, Chen Y, Xiao W, et al. NK cell-based immunotherapy for malignant diseases. *Cell Mol Immunol.* 2013;10(3):230–52. 10.1038/cmi.2013.10.
27. Marcus A, Gowen BG, Thompson TW, et al. Recognition of tumors by the innate immune system and natural killer cells. *Adv Immunol.* 2014;122:91–128. 10.1016/b978-0-12-800267-4.00003-1.
28. Nanda R, Chow LQ, Dees EC, et al. Pembrolizumab in Patients With Advanced Triple-Negative Breast Cancer: Phase Ib KEYNOTE-012 Study. *J Clin Oncol.* 2016;34(21):2460–7. 10.1200/jco.2015.64.8931.
29. Shimasaki N, Jain A, Campana D. NK cells for cancer immunotherapy. *Nat Rev Drug Discov.* 2020;19(3):200–18. 10.1038/s41573-019-0052-1.
30. Myers JA, Miller JS. Exploring the NK cell platform for cancer immunotherapy. *Nat Rev Clin Oncol.* 2021;18(2):85–100. 10.1038/s41571-020-0426-7.
31. Biederstädt A, Rezvani K. Engineered natural killer cells for cancer therapy. *Cancer Cell.* 2025;43(11):1987–2013. 10.1016/j.ccell.2025.09.013.
32. Li H, Song W, Li Z, et al. Preclinical and clinical studies of CAR-NK-cell therapies for malignancies. *Front Immunol.* 2022;13. 10.3389/fimmu.2022.992232.
33. Yang K, Zhao Y, Sun G, et al. Clinical application and prospect of immune checkpoint inhibitors for CAR-NK cell in tumor immunotherapy. *Front Immunol.* 2022;13:1081546. 10.3389/fimmu.2022.1081546.
34. Luo L, Yang P, Mastoraki S, et al. Single-cell RNA sequencing identifies molecular biomarkers predicting late progression to CDK4/6 inhibition in patients with HR+/HER2- metastatic breast cancer. *Mol Cancer.* 2025;24(1):48. 10.1186/s12943-025-02226-9.
35. Zheng G, Guo Z, Li W, et al. Interaction between HLA-G and NK cell receptor KIR2DL4 orchestrates HER2-positive breast cancer resistance to trastuzumab. *Signal Transduct Target Ther.* 2021;6(1):236. 10.1038/s41392-021-00629-w.
36. Bede Á, Váróczy MC, Polgár Z, et al. The Autophagy Inhibitor Bafilomycin Inhibits Antibody-Dependent Natural Killer Cell-Mediated Killing of Breast Carcinoma Cells. *Int J Mol Sci.* 2025;26(13). 10.3390/ijms26136273.
37. Kundu M, Butti R, Panda VK, et al. Modulation of the tumor microenvironment and mechanism of immunotherapy-based drug resistance in breast cancer. *Mol Cancer.* 2024;23(1):92. 10.1186/s12943-024-01990-4.
38. Zhou L, Yu CW. Epigenetic modulations in triple-negative breast cancer: Therapeutic implications for tumor microenvironment. *Pharmacol Res.* 2024;204. 10.1016/j.phrs.2024.107205.
39. Sun X, Xia J, Jiang H, et al. Single-cell and spatial transcriptome profiling identifies cellular heterogeneity and immunosuppressive tumor microenvironment in inflammatory breast cancer. *J Adv Res.* 2026;81:637–56. 10.1016/j.jare.2025.05.061.

40. Tang S, Wang Q, Sun K, et al. Metabolic Heterogeneity and Potential Immunotherapeutic Responses Revealed by Single-Cell Transcriptomics of Breast Cancer. *Apoptosis*. 2024;29(9–10):1466–82. 10.1007/s10495-024-01952-7.
41. An J, Lu Y, Chen Y, et al. Spatial transcriptomics in breast cancer: providing insight into tumor heterogeneity and promoting individualized therapy. *Front Immunol*. 2024;15:1499301. 10.3389/fimmu.2024.1499301.
42. Zhang C, Wu F, Lu X, et al. Peripheral NK cell count predicts response and prognosis in breast cancer patients underwent neoadjuvant chemotherapy. *Front Immunol*. 2024;15:1437193. 10.3389/fimmu.2024.1437193.
43. Muntasell A, Rojo F, Servitja S, et al. NK Cell Infiltrates and HLA Class I Expression in Primary HER2(+) Breast Cancer Predict and Uncouple Pathological Response and Disease-free Survival. *Clin Cancer Res*. 2019;25(5):1535–45. 10.1158/1078-0432.Ccr-18-2365.
44. Xu J, Ding L, Mei J, et al. Dual roles and therapeutic targeting of tumor-associated macrophages in tumor microenvironments. *Signal Transduct Target Ther*. 2025;10(1):268. 10.1038/s41392-025-02325-5.
45. Hu T, Shi R, Gu Y, et al. Cancer-derived non-coding RNAs endow tumor microenvironment with immunosuppressive properties. *Wiley Interdiscip Rev RNA*. 2023;e1822. 10.1002/wrna.1822.
46. Liu X, Jiang R, Xu Y, et al. Dual cytokine-engineered macrophages rejuvenate the tumor microenvironment and enhance anti-PD-1 therapy in renal cell carcinoma. *Int Immunopharmacol*. 2025;156:114725. 10.1016/j.intimp.2025.114725.
47. Su S, Zhao J, Xing Y, et al. Immune Checkpoint Inhibition Overcomes ADCP-Induced Immunosuppression by Macrophages. *Cell*. 2018;175(2):442–e45723. 10.1016/j.cell.2018.09.007.
48. Cantoni C, Falco M, Vitale M, et al. Human NK cells and cancer. *Oncoimmunology*. 2024;13(1):2378520. 10.1080/2162402x.2024.2378520.
49. Lasser SA, Ozbay Kurt FG, Arkhypov I, et al. Myeloid-derived suppressor cells in cancer and cancer therapy. *Nat Rev Clin Oncol*. 2024;21(2):147–64. 10.1038/s41571-023-00846-y.
50. Hu Y, Nie W, Lyu L, et al. Tumor-Microenvironment-Activatable Nanoparticle Mediating Immunogene Therapy and M2 Macrophage-Targeted Inhibitor for Synergistic Cancer Immunotherapy. *ACS Nano*. 2024;18(4):3295–312. 10.1021/acsnano.3c10037.
51. Zhang H, Huo Y, Zheng W, et al. Silencing of SIRPα enhances the antitumor efficacy of CAR-M in solid tumors. *Cell Mol Immunol*. 2024;21(11):1335–49. 10.1038/s41423-024-01220-3.
52. Zhang B, Shi J, Shi X, et al. Development and evaluation of a human CD47/HER2 bispecific antibody for Trastuzumab-resistant breast cancer immunotherapy. *Drug Resist Updat*. 2024;74:101068. 10.1016/j.drug.2024.101068.
53. Yu T, Lu Y, Fang J, et al. Chimeric antigen receptor-based immunotherapy in breast cancer: Recent progress in China. *Cancer*. 2024;130(S8):1378–91. 10.1002/cncr.35096.
54. Peng L, Sferruzza G, Yang L, et al. CAR-T and CAR-NK as cellular cancer immunotherapy for solid tumors. *Cell Mol Immunol*. 2024;21(10):1089–108. 10.1038/s41423-024-01207-0.

55. Niu Z, Wu J, Zhao Q, et al. CAR-based immunotherapy for breast cancer: peculiarities, ongoing investigations, and future strategies. *Front Immunol.* 2024;15. 10.3389/fimmu.2024.1385571.
56. Ahmad GV, Nouri S, Mohammad Gholian A, et al. Breaking barriers: CAR-NK cell therapy breakthroughs in female-related cancers. *Biomed Pharmacother.* 2025;187. 10.1016/j.biopha.2025.118071.
57. Maalej KM, Merhi M, Inchakalody VP, et al. CAR-cell therapy in the era of solid tumor treatment: current challenges and emerging therapeutic advances. *Mol Cancer.* 2023;22(1):20. 10.1186/s12943-023-01723-z.
58. Xie G, Dong H, Liang Y, et al. CAR-NK cells: A promising cellular immunotherapy for cancer. *EBioMedicine.* 2020;59:102975. 10.1016/j.ebiom.2020.102975.
59. Jørgensen LV, Christensen EB, Barnkob MB, et al. The clinical landscape of CAR NK cells. *Exp Hematol Oncol.* 2025;14(1):46. 10.1186/s40164-025-00633-8.
60. Yang R, Yang Y, Liu R, et al. Advances in CAR-NK cell therapy for hematological malignancies. *Front Immunol.* 2024;15. 10.3389/fimmu.2024.1414264.
61. Showalter A, Limaye A, Oyer JL, et al. Cytokines in immunogenic cell death: Applications for cancer immunotherapy. *Cytokine.* 2017;97:123–32. 10.1016/j.cyto.2017.05.024.
62. Amiri M, Molavi O, Sabetkam S, et al. Stimulators of immunogenic cell death for cancer therapy: focusing on natural compounds. *Cancer Cell Int.* 2023;23(1):200. 10.1186/s12935-023-03058-7.
63. Fucikova J, Kepp O, Kasikova L, et al. Detection of immunogenic cell death and its relevance for cancer therapy. *Cell Death Dis.* 2020;11(11):1013. 10.1038/s41419-020-03221-2.
64. Nicolò E, Giugliano F, Ascione L, et al. Combining antibody-drug conjugates with immunotherapy in solid tumors: current landscape and future perspectives. *Cancer Treat Rev.* 2022;106:102395. 10.1016/j.ctrv.2022.102395.
65. Tsao LC, Wang JS, Ma X, et al. Effective extracellular payload release and immunomodulatory interactions govern the therapeutic effect of trastuzumab deruxtecan (T-DXd). *Nat Commun.* 2025;16(1):3167. 10.1038/s41467-025-58266-8.
66. Collins DM, Madden SF, Gaynor N, et al. Effects of HER Family-targeting Tyrosine Kinase Inhibitors on Antibody-dependent Cell-mediated Cytotoxicity in HER2-expressing Breast Cancer. *Clin Cancer Res.* 2021;27(3):807–18. 10.1158/1078-0432.Ccr-20-2007.
67. Wu N, Yang N, Zhang S, et al. Chimeric antigen receptor NK cells for breast cancer immunotherapy. *Cancer Treat Rev.* 2025;137. 10.1016/j.ctrv.2025.102943.
68. Tao B, Du R, Zhang X, et al. Engineering CAR-NK cell derived exosome disguised nano-bombs for enhanced HER2 positive breast cancer brain metastasis therapy. *J Control Release.* 2023;363:692–706. 10.1016/j.jconrel.2023.10.007.

Figures

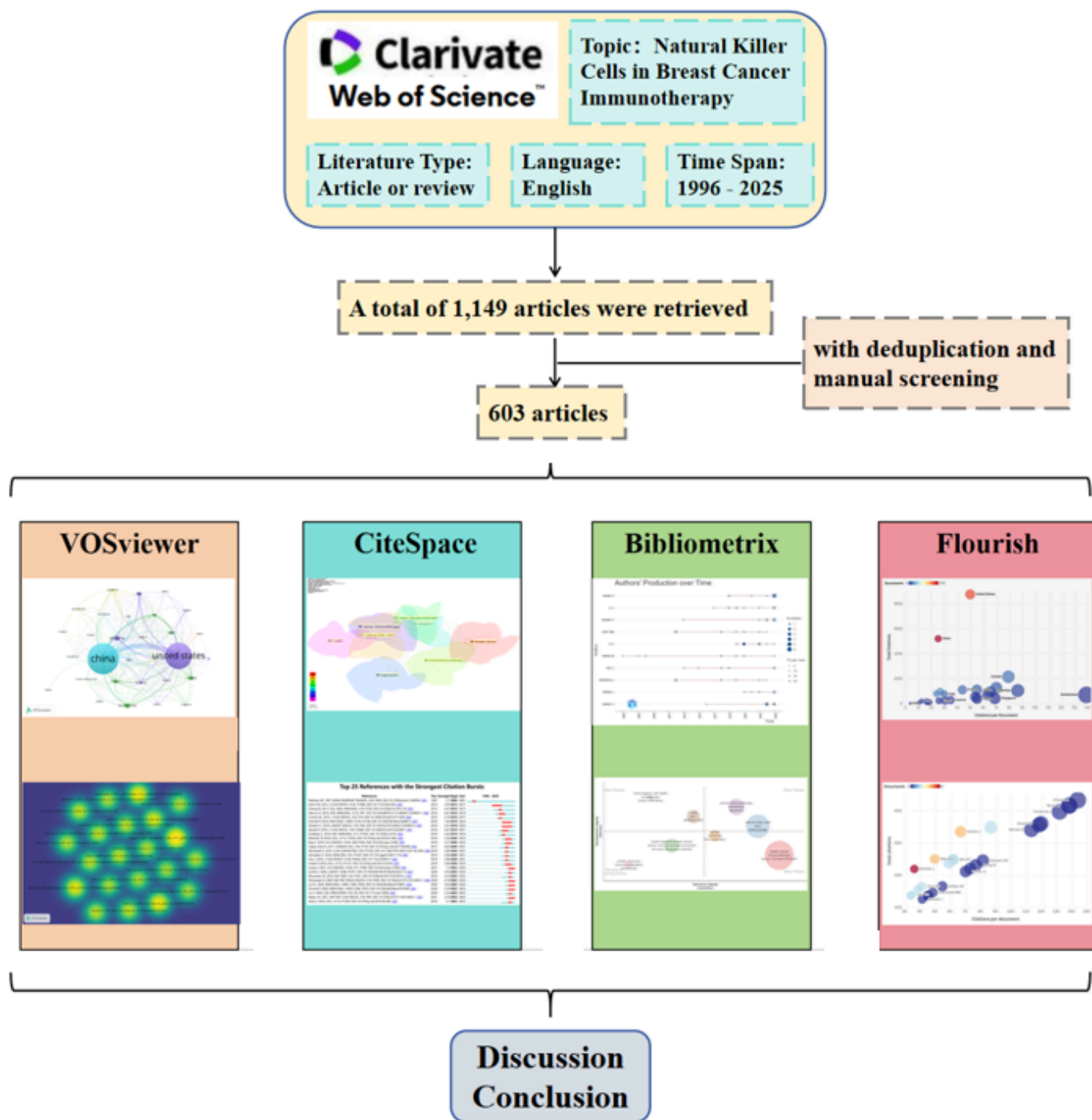


Figure 1

Study Design and Analytical Methods

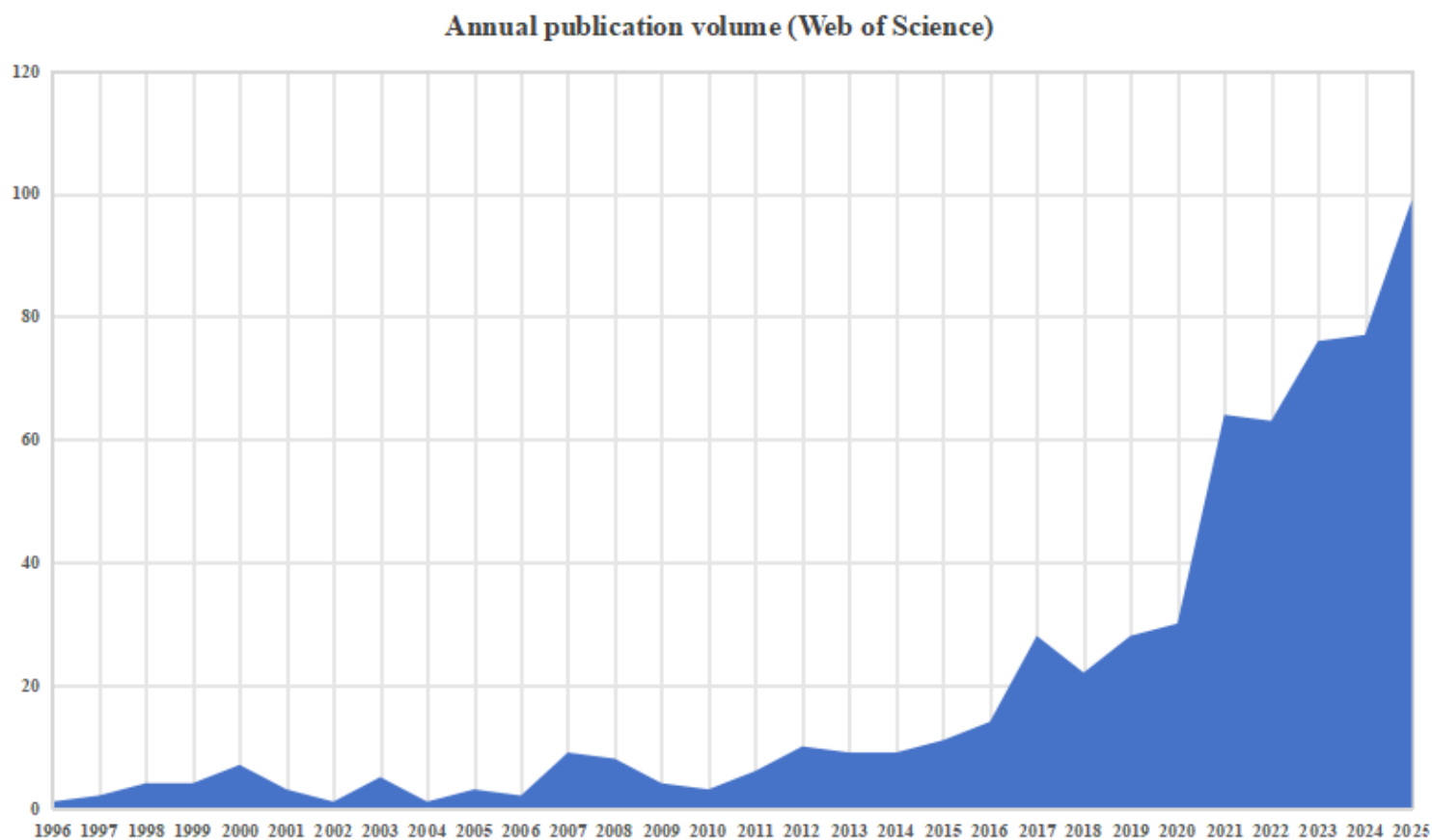


Figure 2

Trends in annual publication volume from 1996 to 2025.

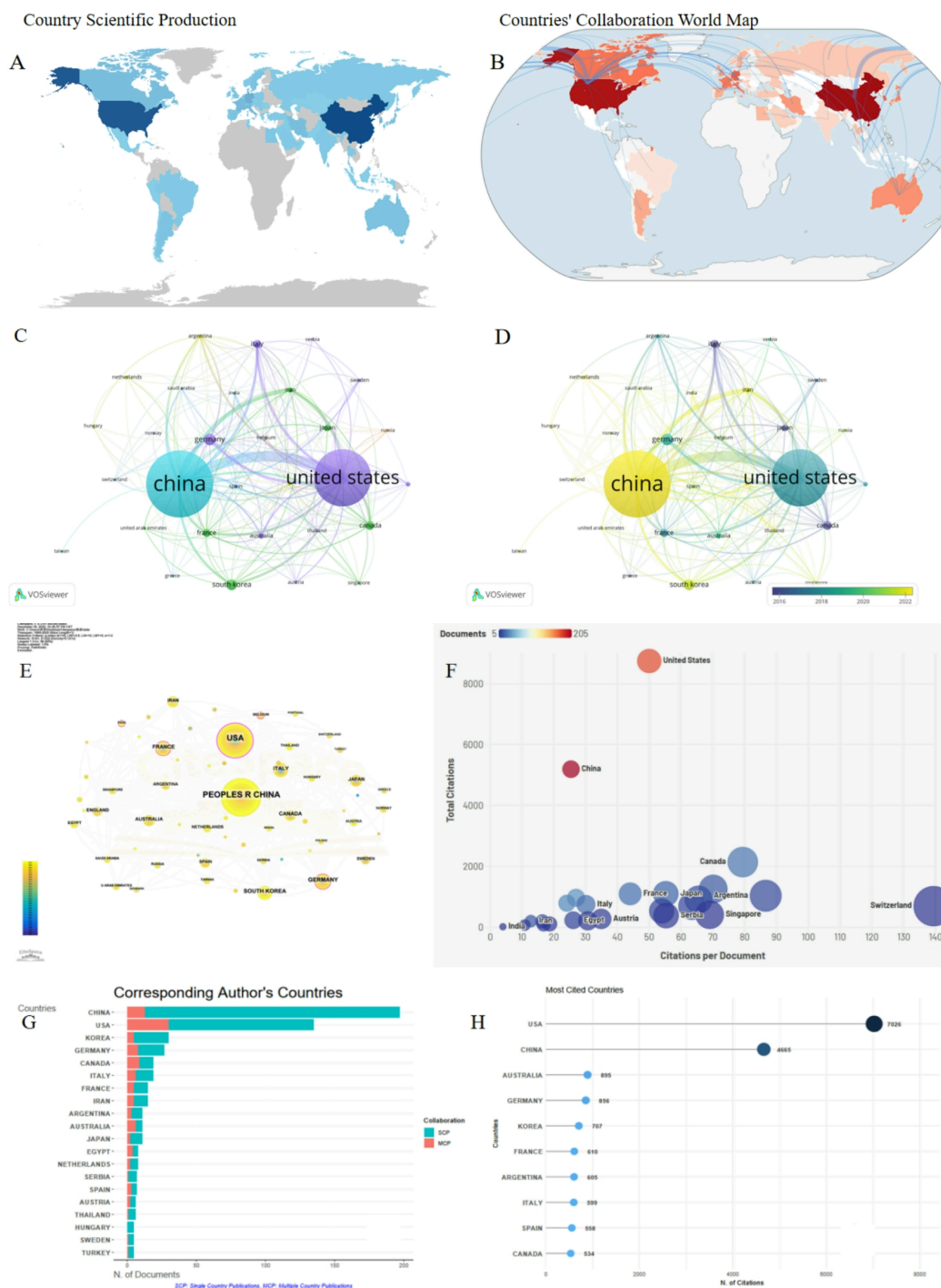


Figure 3

Visualization of national collaboration/regional networks and influence. (A) Country Scientific Production; (B) Countries' Collaboration World Map; (C) Network map of national publication volume, where node size represents publication volume; (D) The national publication timeline; (E) National collaboration density map, where color intensity reflects the density of cooperative relationships between countries; (F) National Academic Impact Bubble Chart, where the horizontal axis represents

average citations per paper, the vertical axis represents total citations, and bubble size indicates publication volume; (G) Corresponding Author's Countries; (H) Most Cited 10 Countries.

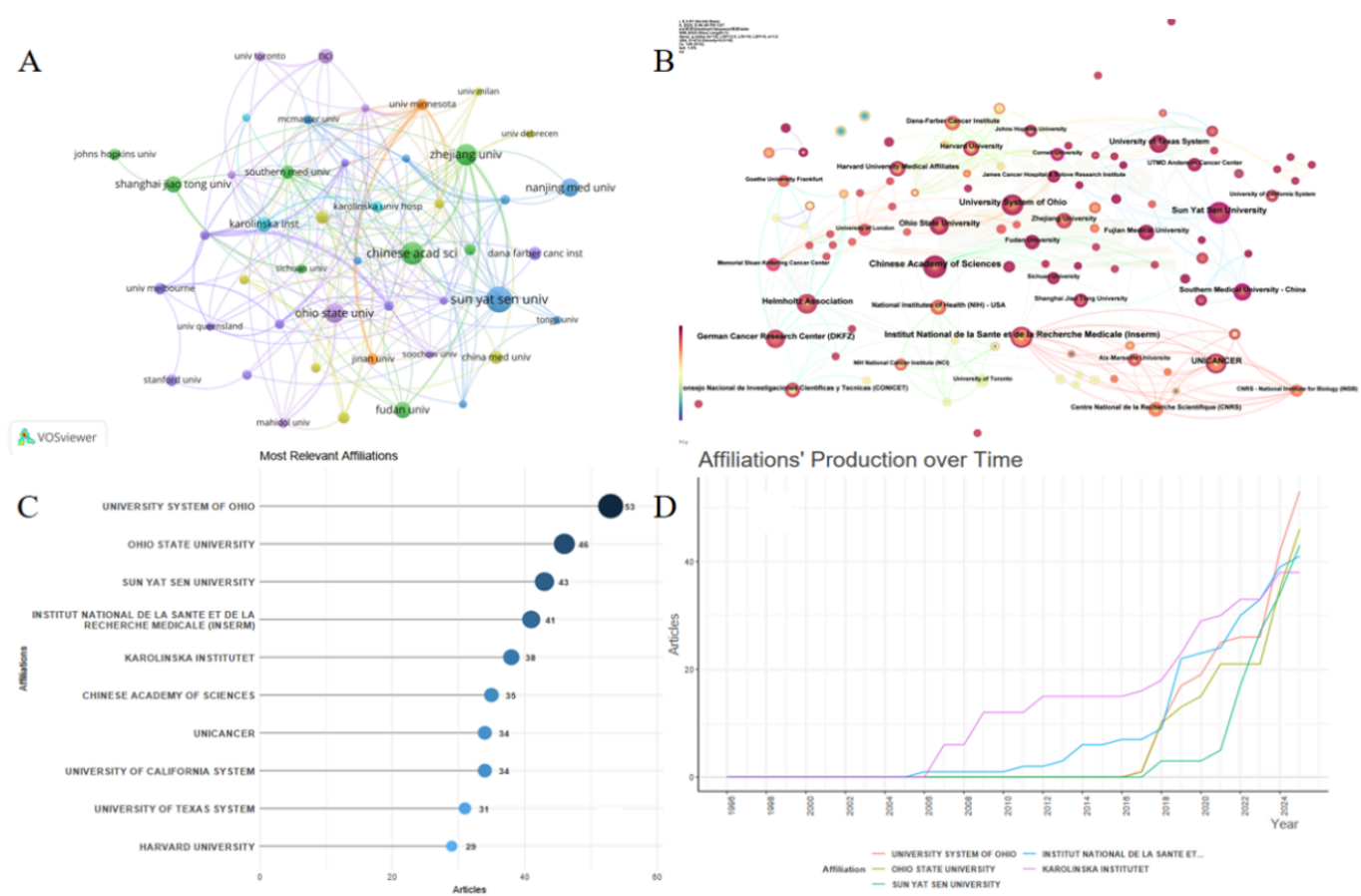


Figure 4

Visual Analysis of Institutional Academic Collaboration Networks and Impact. (A) Institutional paper publication volume network diagram, where node size indicates the number of publications per institution; (B) CiteSpace institutional collaboration network map; (C) Most Relevant 10 Affiliations; (D) Output of 5 affiliated Production over time.

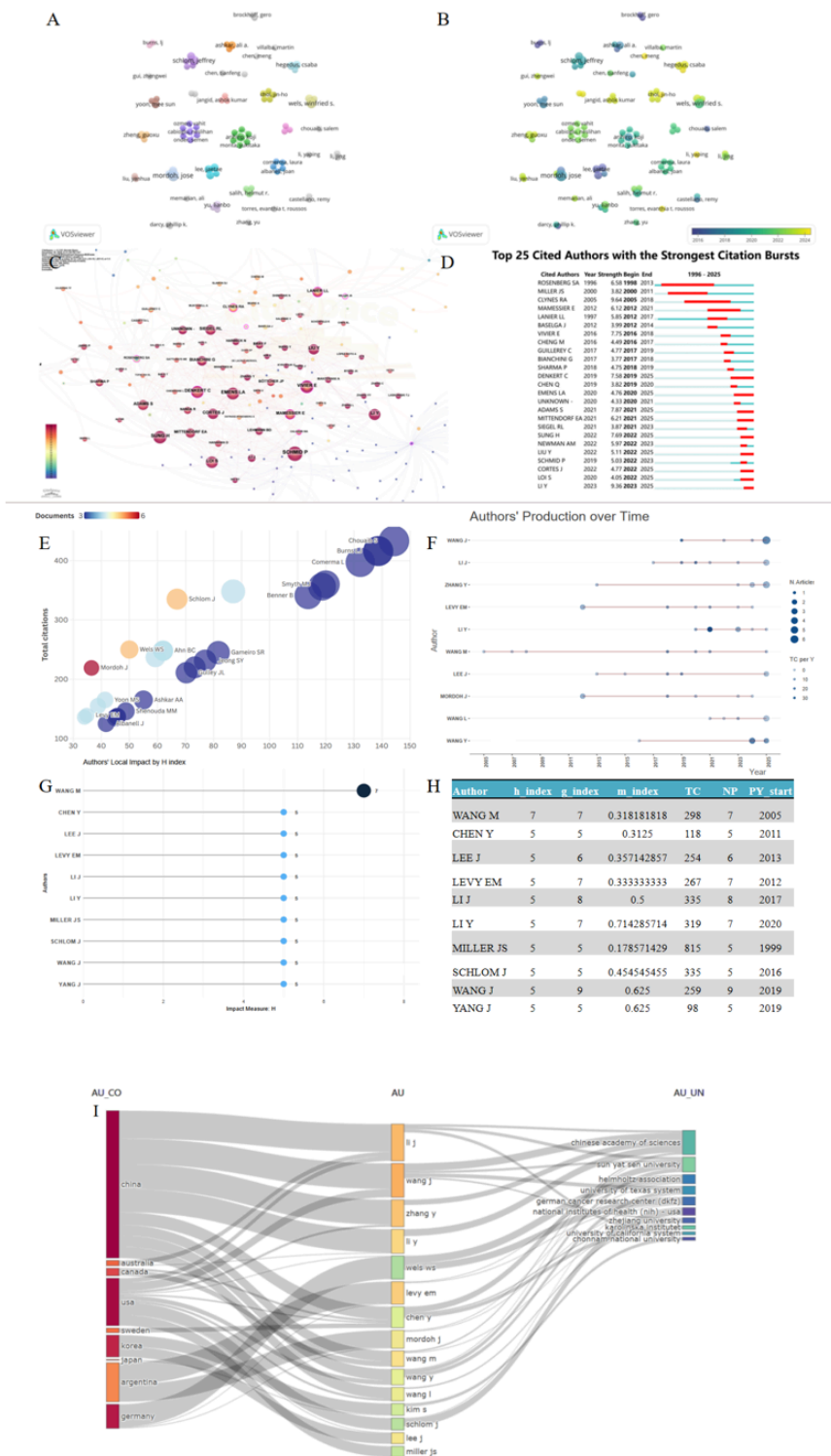


Figure 5

Visual analysis of authors' academic collaboration networks and influence. (A) Publication volume network diagram, where node size indicates the number of publications per author; (B) Publication volume time series chart, with node color reflecting the average publication year of authors' works; (C) Journal collaboration network generated by CiteSpace; (D) Top 25 cited authors with the strongest citation bursts (generated by CiteSpace); (E) Author bubble chart: The x-axis represents average citations

per paper, the y-axis represents total citations, and bubble size indicates the author's publication output; (F) Authors' Production over Time; (G) Authors' Local Impact by H index; (H) Top 10 authors with the highest h-index; (I) Authors from different countries and institutions were shown in Three-Field Plot.

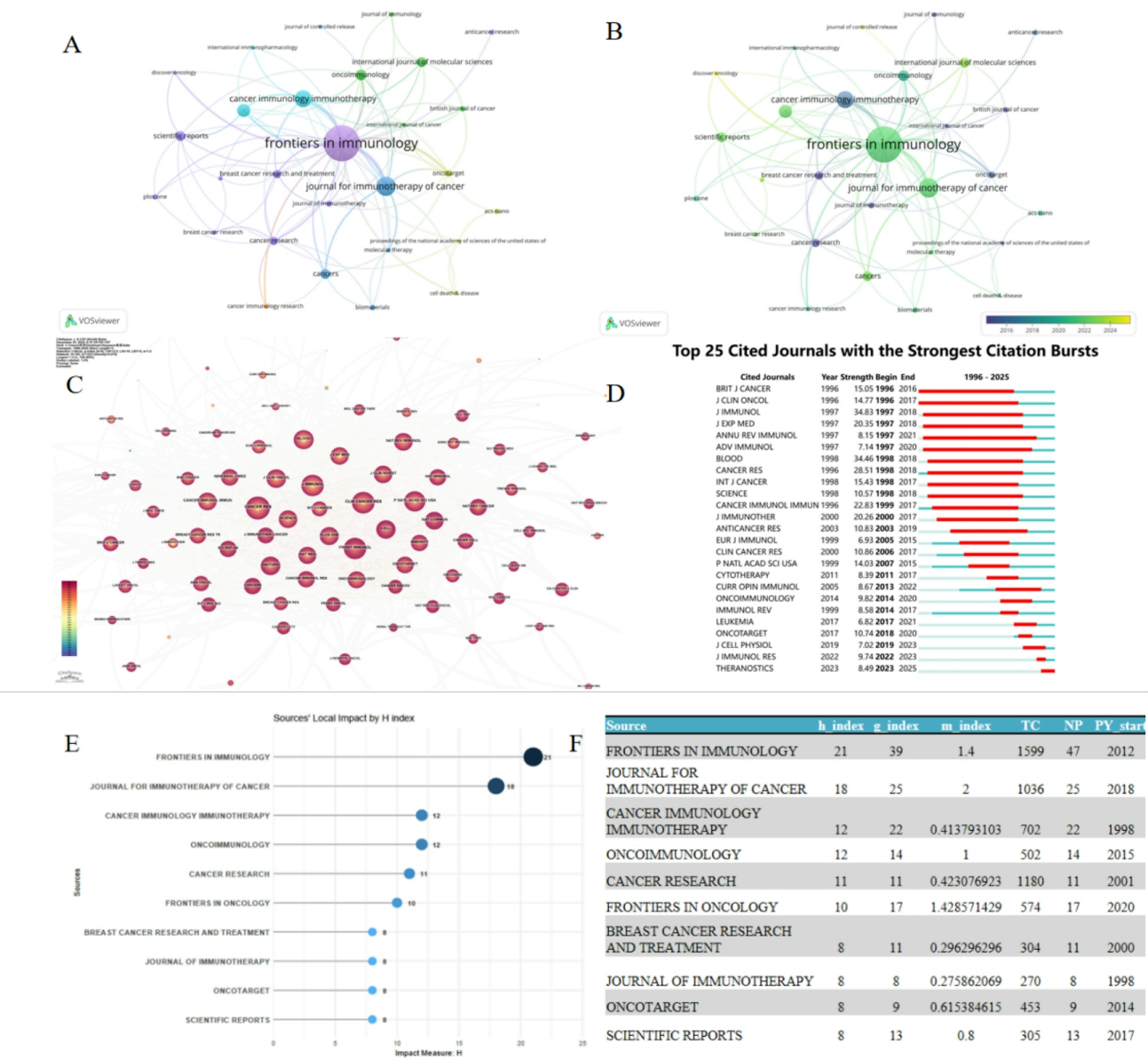


Figure 6

Visualization of journal collaboration networks and influence. (A) Network map of journal publication volume: node size represents the number of documents published by each journal; (B) Network map of journal citations: node size represents total citation count of each journal; (C) Journal co-citation network map: node size represents co-citation frequency, and node color reflects clustering of journal

groups; (D) Top 25 cited journals with the strongest citation bursts (generated by CiteSpace); (E) Sources' Local Impact by H index; (F) Top 10 Sources with the highest h-index.

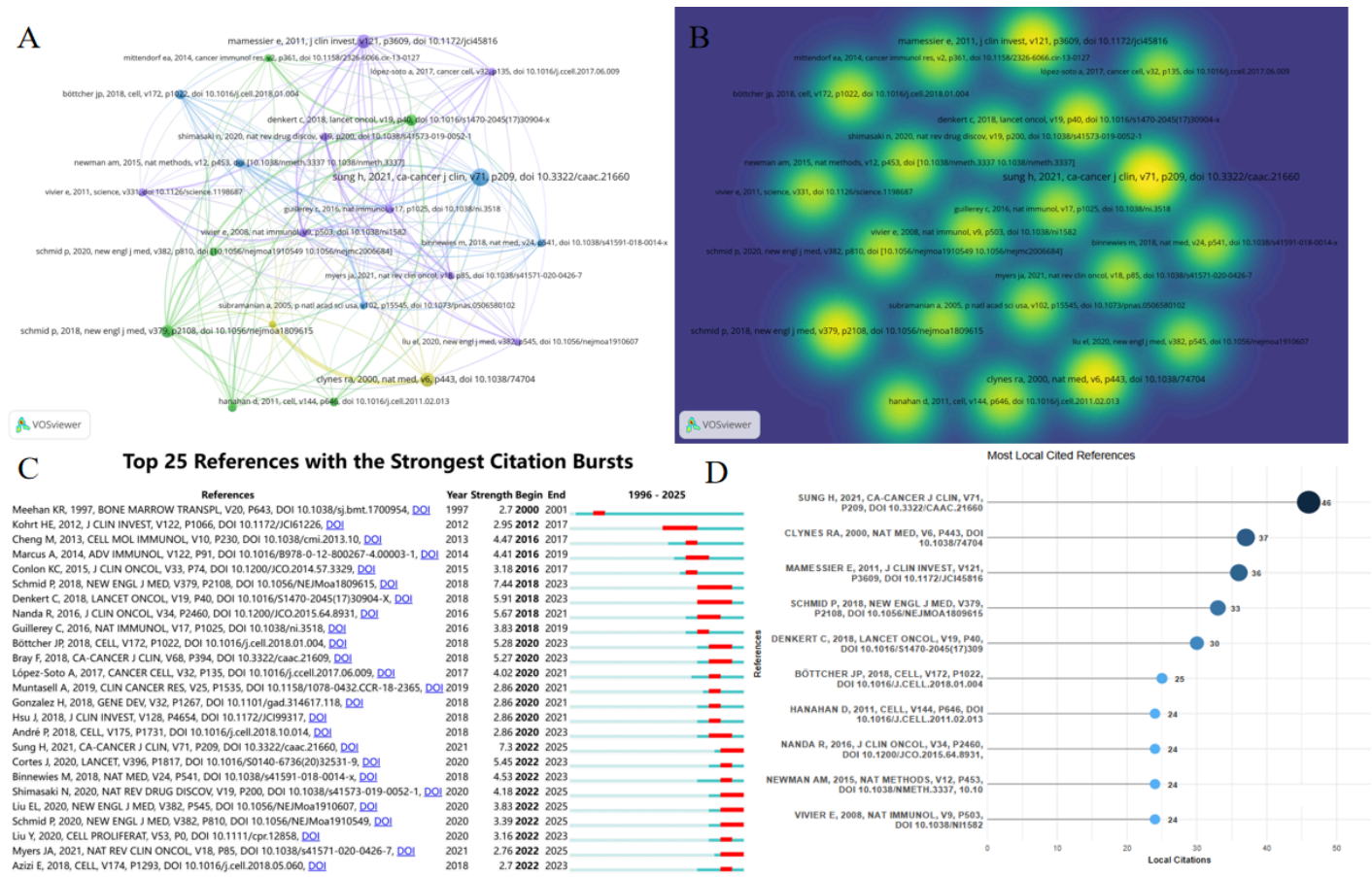


Figure 7

Visualization of References networks and influence. (A) Co-citation network diagram: Node size indicates citation frequency, with node connections representing co-citation relationships; (B) Co-citation density map: Color intensity reflects clustering density of documents within the co-citation network; (C) Analysis of top 25 cited references (CiteSpace): Red bands indicate citation surge periods, reflecting the emergence and evolution of research frontiers; (D) Most Local Cited References.

Keyword Thematic Evolution; (H) Keyword Trend Topics; (I) Top 25 most cited keywords prominence map (CiteSpace): Red bands indicate citation surge periods, reflecting research frontiers.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [BiblioshinyReport1.xlsx](#)
- [BiblioshinyReport2.xlsx](#)
- [BiblioshinyReport3.xlsx](#)
- [BiblioshinyReport4.xlsx](#)
- [BiblioshinyReport5.xlsx](#)
- [BiblioshinyReport6.xlsx](#)
- [BiblioshinyReport7.xlsx](#)