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Therapeutic potential of triple-negative breast cancer immune checkpoint blockers

A 21-year bibliometric analysis

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Abstract

Background: Triple-negative breast cancer (TNBC) is an aggressive metastatic subtype of BC that frequently develops chemoresistance. Immune checkpoint blockers (ICB) have led to breakthroughs in TNBC treatment. This study aimed to explore research trends and public interest in ICB interventions for TNBC.

Methods: We searched the Web of Science Core Collection (WoSCC) database for publications related to ICB for TNBC from 2003 to 2024. VOSviewer, CiteSpace, and R package "bibliometrix" were used to analyze the characteristics of ICB publications in TNBC from a quantitative and qualitative perspective and to visualize the results to comprehensively present the research trends in this field.

Results: After removing duplicates, 2698 publications were included. The New England Journal of Medicine may be the leading and influential in the field of ICB in TNBC according to data on the total number of publications, number of citations, and impact factors. Its article entitled "Atezolizumab and Nab-Paclitaxel in Advanced TNBC" is 1 of the most cited articles. Keyword analysis showed that current research hotspots in this field are tumor microenvironment, complete pathological response, neoadjuvant chemotherapy, and PARP inhibitors. Future research hotspots may include the PD-L1 inhibitor durvalumab and antibody-drug conjugates (ADC).

Conclusions: This study revealed that ICB therapy for TNBC is a rapidly evolving and high-profile topic. Future research should focus on the optimal selection of different targets for ICB in combination with neoadjuvant chemotherapy, ADC, and poly ADP-ribose polymerase inhibitors to treat TNBC.

Abbreviations: ADC = antibody-drug conjugates, BC = breast cancer, CTLA-4 = cytotoxic T-lymphocyte-associated antigen-4, FDA = food and drug administration, ICB = immune checkpoint inhibitors, PARP = poly ADP-ribose polymerase, PD-1 = programmed death-1, PD-L1 = programmed cell death ligand 1, PD-L2 = programmed cell death ligand 2, TNBC = triple-negative breast cancer, WoSCC = the web of science core collection.

Keywords: antibody-drug conjugates, bibliometric, immune checkpoint blockade, neoadjuvant chemotherapy, triple-negative breast cancer

1. Introduction

Cancer mortality has declined by 33%, averting an estimated 3.8 million deaths in nearly 30 decades. However, the incidence of breast cancer (BC) is increasing, with BC topping the list of the top 10 cancers with the highest prevalence in women, accounting for 31% by 2024,[1] that is, 31% of cancers diagnosed in women are BC. As a heterogeneous subtype of BC, triple-negative BC (TNBC) was characterized by the estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 were negative, which accounts for 10%

ZS and CL contributed to this article equally.

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This study did not involve human or animal experiments; therefore, ethical considerations were not applicable.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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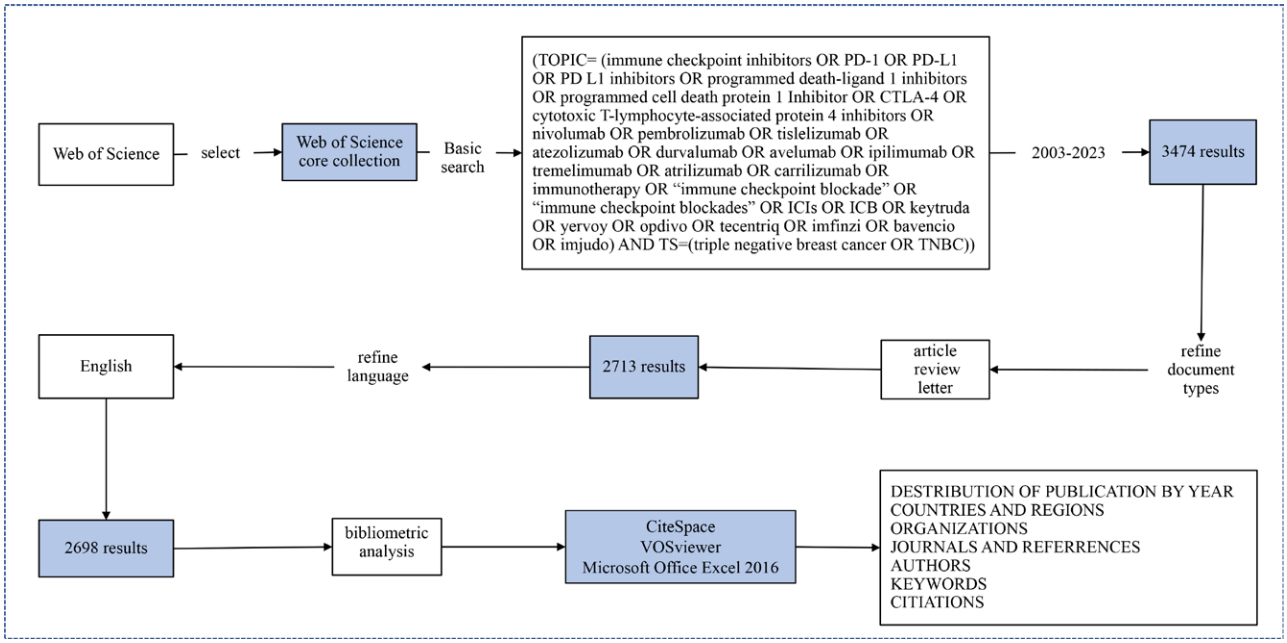

Figure 1. Detailed search flowchart showing steps in the identification and screening of papers. The steps to identify and screen the papers are shown. The year of publication spanned 2003 and 2024. Only literature published in English is included. We use CiteSpace to de-duplicate and extract the publication date.

to 15% of diagnosed BC.[2] TNBC constitutes 1 of the most aggressive malignancies cancer, with high metastatic capacity and low survival rates due to limited use of chemotherapy drugs.[3] Immunotherapy, especially immune checkpoint blockers (ICB), has revolutionized antitumor therapy and rekindled the hope of effective cancer treatment.[4] Researchers found that compared with other subtypes of BC, TNBC has higher immunogenicity due to its high expression rate of programmed death-1 (PD-1) and more tumor-infiltrating lymphocytes. The rapid development of molecular biology tools has furthered our understanding of the molecular mechanisms underlying BC, suggesting that ICB and immune checkpoint inhibitors are better therapeutic options. These findings suggest that ICB and immune checkpoint inhibitors are superior therapeutic options.

The promising antitumor activity of monoclonal antibodies targeting the immune checkpoint proteins cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), programmed death-1 (PD-1), and programmed cell death ligand 1 (PD-L1) has led to regulatory approval of these agents for the treatment of various malignancies. The results of KEYNOTE-355 and KEYNOTE-522 have led to pembrolizumab being recommended as the National Comprehensive Cancer Network guideline recommendation.[5] In addition, other ICBs have also achieved many remarkable results in the treatment of TNBC.[6–9] Recently, ICB treatment efforts in TNBC have improved the prognosis of patients with metastatic disease.[10–12] However, a comprehensive overview of the ICB treatment for TNBCs is lacking.

In this study, we used a visual approach to perform a comprehensive bibliometric analysis of the recent 20 years of research on ICB in TNBC. Bibliometric analysis is a scientific approach that uses methods such as co-occurrence analysis and citation analysis to evaluate research performance, which is used to analyze the characteristics of publications on ICB in TNBC from a quantitative and qualitative perspective.[13,14] During our analysis, we can obtain detailed information about authors, keywords, journals, countries, institutions, references, etc, thus comprehensively illustrating the research trend in this field and providing a valuable reference for subsequent research.

2. Methods

2.1. Data sources and search strategy

Bibliographic data for analysis were acquired from the Web of Science Core Collection (WoSSC, https://www.webofscience.com/wos/woscc/basic-search; https://clarivate.com.cn/solutions/web-of-science). The searches were carried out from January 1, 2003, to August 27, 2024. To perform a comprehensive literature search for immune checkpoint inhibitors in TNBC, a systematic search strategy was designed. The search strategy was as follows: (TS = [immune checkpoint inhibitors OR PD-1 OR PD-L1 OR PD-L1 inhibitors OR programmed death-ligand 1 inhibitor OR programmed cell death protein 1 inhibitor OR CTLA-4 OR cytotoxic T-lymphocyte-associated protein 4 inhibitors OR CD4 OR CD40 OR CD80 OR TNF OR CD86 OR 4-1BB OR CD137 OR B7-H3 OR CD276 OR LMTK3 OR LAG3 OR TIM-3 OR IDO1 OR nivolumab OR pembrolizumab OR tislelizumab OR atezolizumab OR durvalumab OR avelumab OR ipilimumab OR tremelimumab OR atrilizumab OR carrilizumab OR immunotherapy OR "immune checkpoint blockade" OR "ICB" OR ICIs OR ICB OR Keytruda OR yervoy OR opdivo] AND TS = [TNBC]). A total of 2799 documents were retrieved from the WoSCC. The language was restricted to English and the document type was limited to articles, reviews, and letters; 2698 documents remained for bibliometric analysis and visualization. The search details are shown as a flowchart (Fig. 1). To obtain clearer annual results, the time span of the search excluded 2023. The search was completed on August 27, 2024.

2.2. Data extraction and analysis

VOSviewer (version 1.6.18) is a bibliometric analysis software that can extract key information from numerous publications,[15] which is often used to build collaboration, co-citation, and co-occurrence networks. In our study, this software mainly completed the following analyses: country and institution, journal and co-cited author, and keyword co-occurrence. After selecting the literature, it is exported as a text file of "full records and referenced references," and the file name is modified in the download_* format. Click "Create"

in the VOSviewer, then select "Create a map based on bibliographic data" "Read data from bibliographic database files" "Web of Science," import download_* files for quantitative and visual analysis. In the map produced by VOSviewer, a node represents an item such as a country, institution, journal, or author. The size and color of the nodes indicate the number and classification of these items, respectively. The line thickness between nodes reflects the degree of collaboration or co-citation of items.[16]

CiteSpace software (version 6.3. R1) is another software developed by Professor Chen for bibliometric analysis and visualization.[17] In our study, CiteSpace was applied to extract the annual publication data, map the dual-map overlay of journals, and map the co-cited references. After opening CiteSpace software, click "Import" in the menu bar, select "Web of Science," and import the "Input" folder (which contains the download_* format file) at the Input Directory. Import the "Output" folder into the Output Directory, click "Remove Duplicates" to remove duplicates, select "Article" and "Review" in the pop-up dialog box, and then click "Start" to copy the data from the annual published papers and save them to Excel 2016." For the tree-ring map of co-cited references, time slicing was set as January 2003 to December 2024, and the Years Per Slice as 1. With Reference Node Types and TOP 10 Selection Criteria, click "GO" and select "Visualize." When drawing the journal double overlay chart, click "Overlay Maps" in the menu bar, select "JCR Journal Maps," "Overlay," "Add Overlay," "Z Score," click "Refresh," and adjust the background color and parameters as required.

The R package "bibliometrix" (version 4.1.1) (https://www.bibliometrix.org) was applied for a thematic evolution analysis and to construct a global distribution network of publications of ICB in TNBC.[18] The quartile and impact factor of the journal are obtained from Journal Citation Reports 2021.

3. Results

3.1. Distribution of publications

Figure 2 shows the chronological distribution of publications by year as a bar and curve combination graph (Fig. 2A) and a curve diagram (Fig. 2B). ICBs were not detected in a TNBC study until 2008. From 2008 to 2018, the annual number of publications slowly grew; the annual number of publications was <200, and the cumulative number of publications was < 500 on the immune checkpoint blockade for TNBC, with no obvious research trends. The annual number of publications rose sharply from 2019 to 2024; the annual number of publications exceeded 500, and the cumulative number of publications exceeded 2000 to 2024. Studies in this field are ongoing.

3.2. Analysis of country co-occurrence

The country co-occurrence knowledge map clearly shows the research degrees of different countries in the field. Thirty-nine countries (n ≥ 10, where "n" represents the number of publications) were selected from 83 countries for network visualization analysis. Figure 3 shows the average citation overlay visualization diagram of 39 countries, in which each node represents a country; the larger the diameter of the nodes, the more published papers; the lines between nodes represent the connections or cooperative relations between countries; the thicker the lines, the closer the connection; the closer the color is too yellow, the higher the citation score; and the closer the color is too purple, the lower the citation score. The country with the highest number of publications was the United States (836 publications), followed by China (595 publications) and Italy (173 publications) (Fig. 3, Table 1). The United States is the country with the most extensive international cooperation. China has the closest cooperative relationship with the United States.

3.3. Analysis of organizations cooperation

A total of 117 organizations (n ≥ 10, where "n" represents the number of publications of the institution) were selected from 2993 organizations for network visualization analysis (Fig. 4). It is clear that European countries and Australia, led by the United States, are taking the lead and that institutional cooperation between different countries should be further strengthened, especially in Japan.

From the top 10 most productive organizations (Table 2), we can see that the largest number of publications is from the University of Texas MD Anderson Cancer Center (the United States, 54 publications, 12.0%), followed by the Dana-Farber Cancer Institute (the United States, 53 publications, 11.8%), and Fudan University (China, 48 publications, 10.7%). The top 10 institutions were distributed in the United States, China, Australia, and Italy, which corresponds to the country and regional distribution.

3.4. Analysis of co-authorship and core authors

Based on a visual analysis of 13,492 authors from 2168 publications, 117 authors with at least 6 publications were selected and a collaborative network was constructed (Fig. 5). A total of 10 nodes and 82 links were obtained. Each node in the graph represents an author, and the lines between the nodes represent the connections or cooperative relationships between the authors. The thicker the lines, the closer the connection. The 3 most important evaluation criteria for core authors are the number of published documents, total

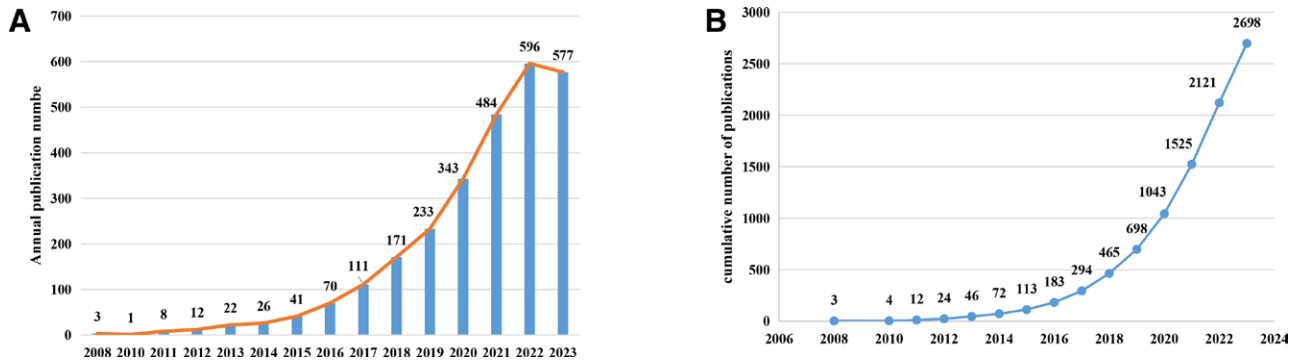

Figure 2. Distribution of publications by year. (A) The annual number of publications and (B) the cumulative number of publications on immune checkpoint blockade for TNBC. The peak of annual publications occurred in 2024. TNBC = triple-negative breast cancer.

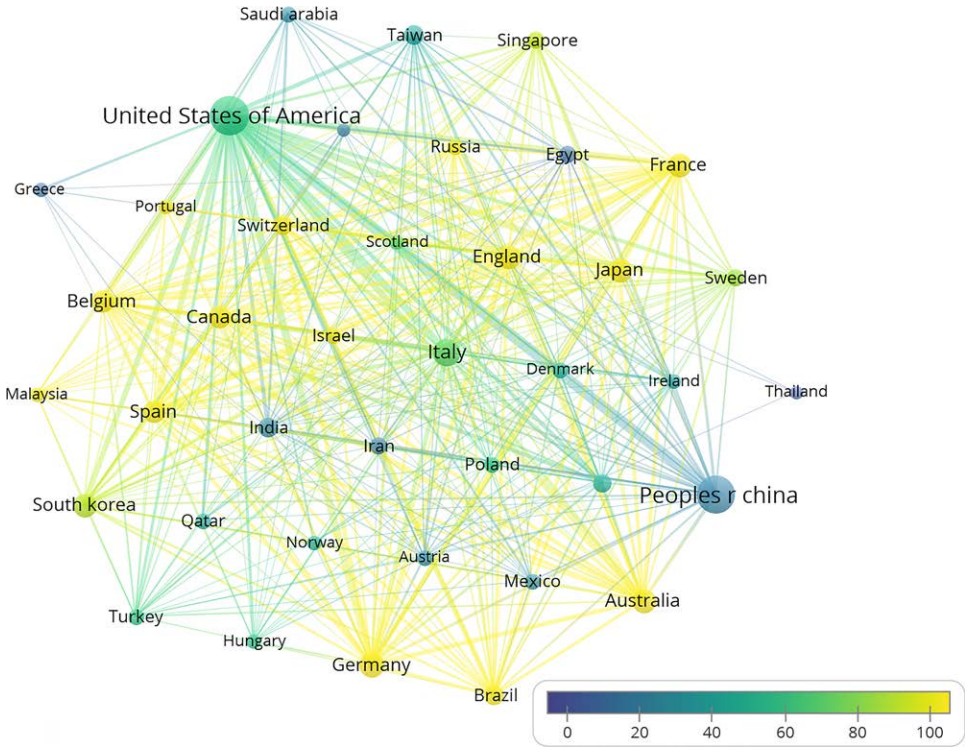

Figure 3. Geographical distribution of global publications. Visualization of the collaboration between countries to study ICBs in TNBC, with thicker lines indicating closer collaboration. The analysis method is Linlog/modularity. The weight is citations. Scores are the average yr of publication. The colors of the circles represent the average yr of publication. ICB = immune checkpoint blockers, TNBC = triple-negative breast cancer.

Table

1 Top 10 most productive countries and frequency of cooperation.

Rank	Country	Counts*	From	To	Frequency
1	USA†	829	USA	China	105
2	China	595	USA	United Kingdom	54
3	Italy	173	USA	Germany	53
4	Germany	135	USA	Italy	53
5	Japan	110	USA	Japan	47
6	Australia	104	USA	Australia	40
7	France	97	USA	France	39
8	England	94	USA	Belgium	36
9	South Korea	86	Australia	Belgium	32
10	Belgium	81	USA	Spain	32

*Number of publications.
†The United States of America.

citations, and the H-index. Therefore, we extracted and visualized the 9 most prolific authors. According to these criteria (Table 3 and Fig. 5), the leader of the Translational BC Genomics and Therapeutics Laboratory, Peter MacCallum Cancer Center, University of Melbourne, Australia, Sherene Loi, was the most productive author in this field, publishing 28 articles and being cited 4025 times in general, whose H-index was also the highest. This adequately explains his authority in this field. This was followed by Professor Giuseppe Curigliano of the University of Milan School of Medicine, with 27 publications and 1194 total citations, and Lajos Pusztai, Director of the Division of Breast Oncology at the Yale School of Medicine, with 24 publications and 3167 total citations. Among the top 9 authors, 4 are from the United States, 2 are from Australia, and 1 each from Italy, the United Kingdom, and Spain. Combined with their previous geographical distribution, these countries also play important research roles in the field. Figure 5 shows an overlay visualization of the co-authorship relationships between the authors, suggesting that most of the most influential authors, such as Sherene Loi, Giuseppe Curigliano, and Roberto Salgado, collaborated closely. In addition, we found that the average year of publication for these authors was between 2018 and 2019, while other authors, such as Paolo Tarantino and Shao Zhi-ming, published more actively after 2021, which suggests that they have the potential to take the lead in the future.

Among the 52,182 co-cited authors, 54 were co-cited more than 150 times (Fig. 6). The most co-cited author was Schmid Peter (n = 1975), followed by Loi Sherene (n = 1033) and Emens, Leisha a. (n = 878).

3.5. Analysis of keywords

Through co-occurrence analysis of keywords, we can quickly capture research hotspots in a certain field. Table 4 shows the top 20 high-frequency keywords in the ICB research in TNBC.

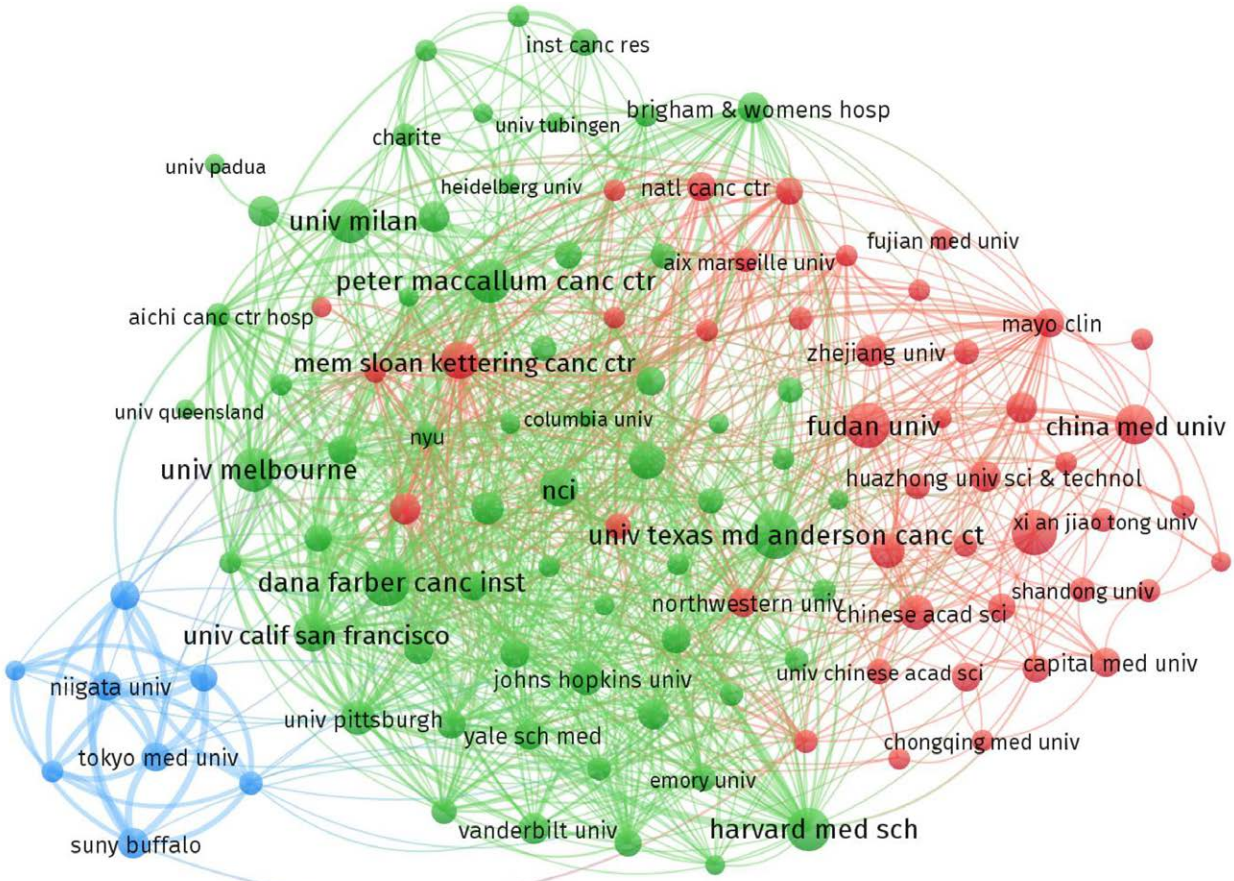

Figure 4. Co-authorship analysis of organizations. The analysis method is Linlog/modularity. The weight is publications. The thickness of the lines indicates the strength of the relationships. The green cluster represents the United States dominated by European countries and Australia. The red cluster represents Asian institutions such as China and South Korea. The blue cluster represents the countries dominated by Japan.

Table 2

Top 10 organizations with the highest number of publications.

Rank	Organization	Country	Publications	Citations	Total link strength
1	University of Texas MD Anderson Cancer Center	USA	54	2716	100
2	Dana-Farber Cancer Institute	USA	53	6934	223
3	Fudan University	China	48	1143	23
4	Sun Yat-sen University	China	46	1442	21
5	University of Milan	Italy	45	1894	86
6	Harvard Medical School	USA	44	1818	105
7	University of Melbourne	Australia	44	5968	129
8	Peter MacCallum Cancer Center	Australia	43	5486	140
9	China Medicine University	China	38	965	37
10	Mem Sloan Kettering Cancer Center	USA	35	1970	88

Among these keywords, PD-L1, tumor microenvironment, and prognosis appeared more than 100 times, representing the main research direction of ICB in TNBC. Fifty keywords with a frequency >15 times were selected from the 3428 keywords, and cluster analysis was performed using VOSviewer (Fig. 7). An overlay of keywords grouped by publication date shows that research hotspots have changed over time, from biomarkers and apoptosis to immunotherapy, to the tumor microenvironment, an assessment criterion, such as pathologic complete response, a new term such as neoadjuvant chemotherapy, and clinical trials of PARP inhibitors.

Trend topic analysis of the keywords (Fig. 8) shows that no trending topics for keywords were found from 2003 to 2013. Until 2014, researchers began to focus on the tumor microenvironment of BC, inflammation, and apoptosis, and basic studies on monoclonal antibodies specific for different molecular subtypes. Since 2018, the research focus has been on clinical studies on the prognosis of immune checkpoint PD-1 and PD-L1 inhibitors in TNBC immunotherapy. In the future, research on the PD-L1 inhibitor, durvalumab, and antibody-drug conjugates (ADC) is very likely to represent research hotspots.

3.6. Analysis of references

The top 10 most highly cited documents were extracted (Table 5).[19–28] Generally, the number of citations ranged from 213 to 554. An article published in the New England Journal of Medicine titled "Atezolizumab and Nab-Paclitaxel

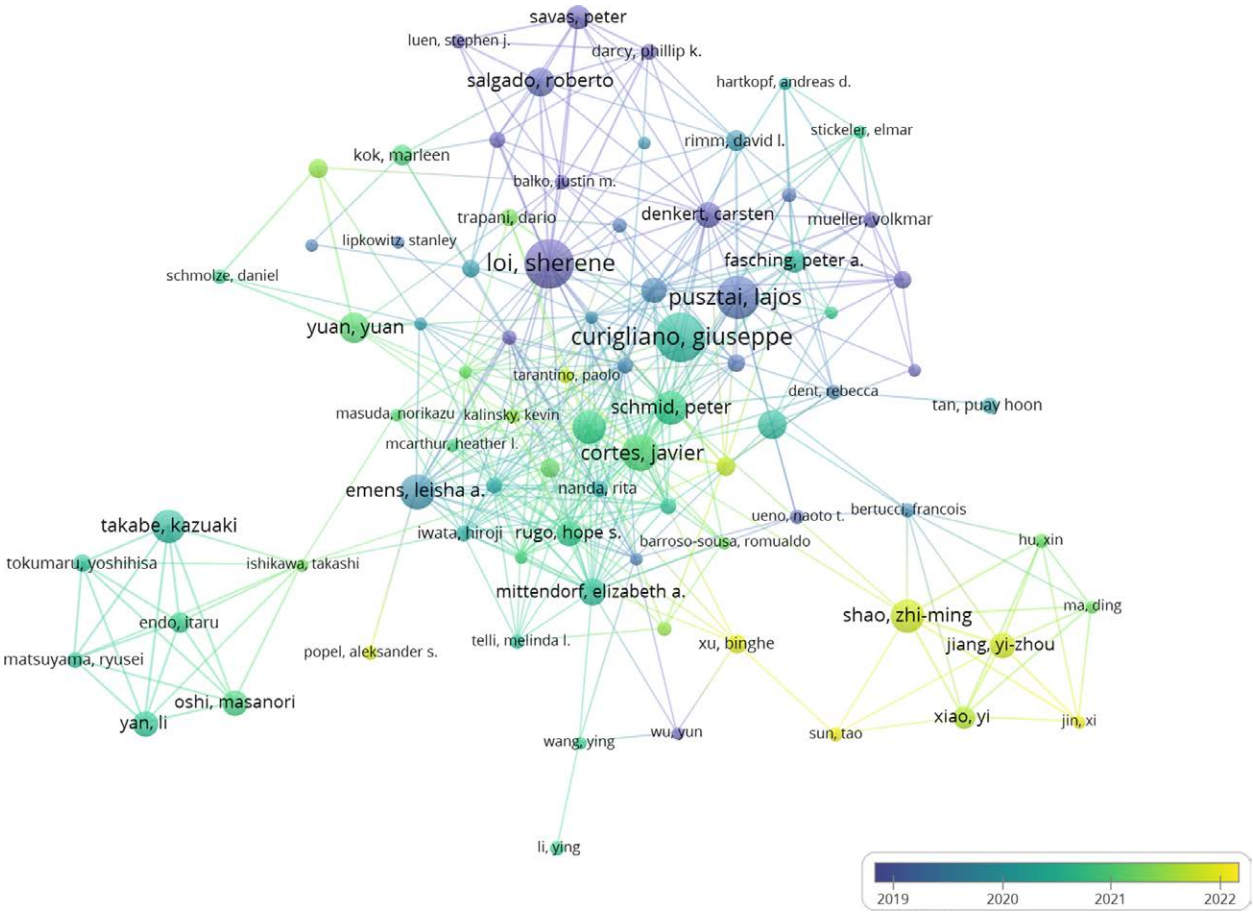

Figure 5. Overlay visualization of co-authorship relationships between authors. The analysis method is Linlog/modularity. The weight is citations. Scores are the average year of publication. The thickness of the lines indicates the strength of the relationships. The colors of the circles represent the average year of publication.

Table 3

Top 9 core authors by number of publications.

Rank	Authors	Organizations	Publications	Citations	H-index
1	Sherene Loi	Translational Breast Cancer Genomics And Therapeutics Laboratory (Australia)	28	4100	36
2	Giuseppe Curigliano	University Milan (Italy)	27	1227	16
3	Lajos Pusztai	Yale School of Medicine (USA)	24	3205	19
4	Kazuaki Takabe	Roswell Park Comprehensive Cancer Center (USA)	20	558	11
5	Leisha A. Emens	Johns Hopkins Cancer Center (USA)	19	2454	19
6	Javier Cortes	International Breast Cancer Center (Spain)	18	1906	14
7	Peter Schmid	Queen Mary University of London (UK)	18	3016	19
8	Sara M.Tolaney	Dana-Farber Cancer Institute (USA)	18	1401	13
9	Roberto Salgado	Peter MacCallum Cancer Center (Australia)	16	1597	18

in Advanced TNBC" ranked first, with 554 total citations. Among the top 10 articles, 7 were related to clinical trials, and the remaining were related to basic research. It is sufficient to state that this pattern of more papers being published in clinical trials than in basic science is indicative of the advancement of immunotherapies for clinical use. The average impact factor of the journals with the top 10 cited references was approximately 67.4575, indicating high research quality. For a comprehensive analysis of the citations, we used CiteSpace (version 6.2. R2) to evaluate the co-citation references (Fig. 9). We performed a co-citation analysis of references from 2008 to 2024. In CiteSpace, the size of the circle indicates the number of documents cited. The purple area in the circle indicates the centrality of the document. The analysis of the documents did not reveal significant centrality, indicating that the literature is largely scattered.

3.7. Analysis of journals

The dual-map overlay of journals shows the citation relationships between journals and co-cited journals, with clusters of citing journals on the left and clusters of cited journals on the right.[29] The length of the vertical axis of the ellipse is proportional to the number of papers published in the journal, and the length of the horizontal axis is proportional to the number of authors. The intermediate line represents the connection between the cited journals and the cited journals in a certain field, and its thickness and density represent the relationship between the frequency and intensity of knowledge

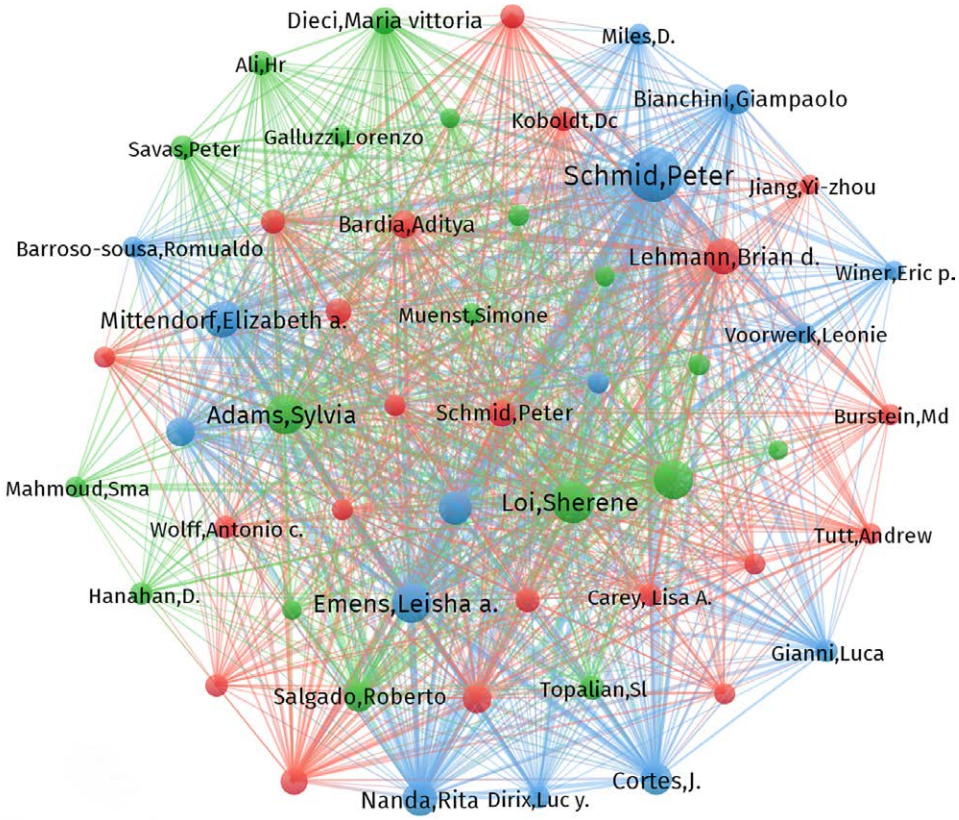

Figure 6. Overlay visualization of co-cited authors. The analysis method is Linlog/modularity. The weight wis citations. The thickness of the lines indicates the strength of the relationships. The colors of the circles represent the clusters.

Table 4

Top 20 high-frequency keywords.

Rank	Keywords	Counts	Rank	Keywords	Counts
1	Immunotherapy	602	11	Tumor-infiltrating Lymphocytes	74
2	Breast cancer	597	12	Metastasis	69
3	TNBC	593	13	Atezolizumab	65
4	pd-l1*	282	14	Chemotherapy	62
5	TNBC	231	15	Biomarkers	60
6	TNBC	185	16	Targeted therapy	58
7	Tumor microenvironment	155	17	Pembrolizumab	52
8	Prognosis	128	18	TNBC	51
9	Immune checkpoint inhibitors	94	19	Immunogenic cell death	48
10	pd-1†	85	20	Neoadjuvant chemotherapy	48

BC = breast cancer, TNBC = triple-negative breast cancer.

*Programmed cell death ligand 1.

†Programmed death-1.

flow between journals. Orange and green paths are the main citation paths, indicating that research published in molecular/biology/genetics journals is mainly cited in the literature in molecular/biology/immunology journals ($z = 4.2375436$, $f = 8100$) (Fig. 10). The z-value is the value of a standardized score used to standardize the reference frequency (f). In simple terms, the Z-value is a measure of how often 1 journal cites another and pharmacy/medicine/clinical research ($z = 5.79207$, $f = 10888$). Clinical cancer research (IF = 13.801) was the most cited journal.

4. Discussion

4.1. General information

First, we analyzed the chronological trends in the publications using a bibliometric method. The results showed that from 2003 to 2007, the annual number of publications was zero, indicating that a research foundation between ICB and TNBC is lacking. From 2009 to 2018, the research in this field remained in its infancy. From 2019 to 2024, the number of publications increased significantly, and the annual publication peaked occurred in 2022.

This chronological trend was reflected in several critical articles and at specific time points, which enabled us to reveal a roadmap for this field. The very first research on ICB was on CTLA-4 blockade, which was conducted in beginning 1987 and was first approved in 2011.[30,31] The recombinant human immunoglobulin G1 and G2 monoclonal antibodies of CTLA-4, known as ipilimumab, respectively, were trialed in TNBC and other advanced cancers, and both showed good efficacy.[32–37] In 1992, Ishida et al found that the activation of PD-1 may be involved in the classical type of programmed cell death.[38] As 1

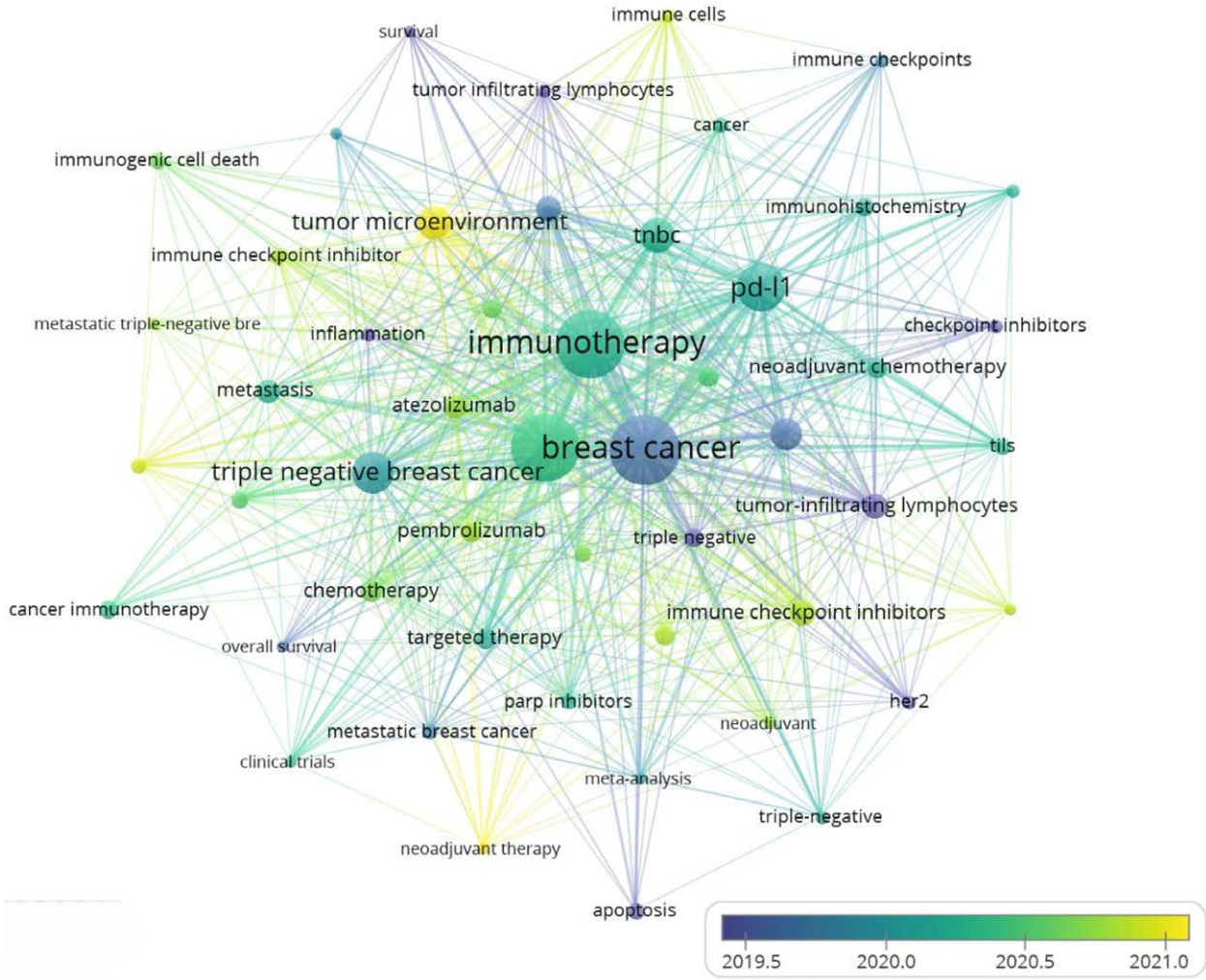

Figure 7. Co-occurrence analysis of keywords. The chosen normalization method is Linlog/modularity. The weight is an occurrence for each plot. The picture shows the 50 top-occurring items among 3428 keywords. Keywords are grouped by year of publication, and the colors of the circles represent the average yr.

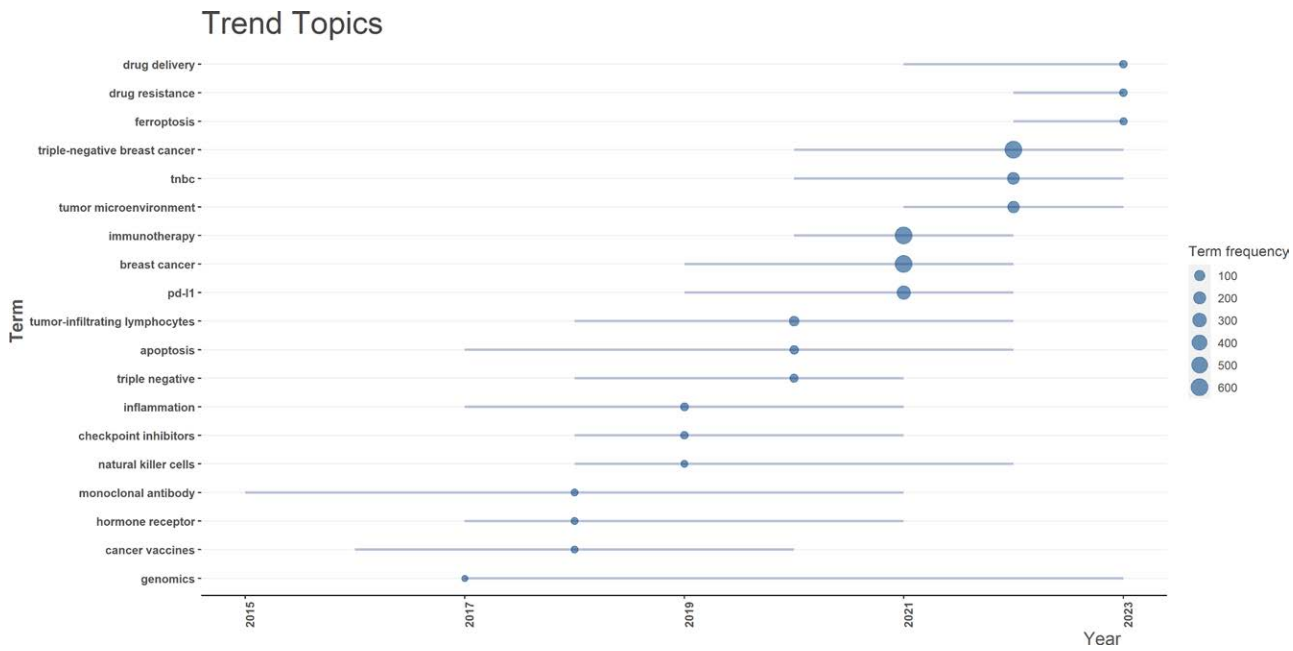

Figure 8. Keyword trend topic analysis. The size of the circle indicates the frequency of occurrence, the position of the circle indicates the year corresponding to the median frequency, and the lines at either end of the circle indicate the positions corresponding to the 25% and 75% frequencies.

Table 5

Top 10 most highly cited publications.

Rank	Title	Source	IF	Citations*	DOI†
1	Atezolizumab and nab-paclitaxel in advanced TNBC	New England Journal of Medicine	176.079	554	10.1056/nejmoa1809615[19]
2	Pembrolizumab in patients with advanced TNBC: phase Ib KEYNOTE-012 study	Journal of Clinical Oncology	50.717	346	10.1200/jco.2015.64.8931[20]
3	Identification of human TNBC subtypes and preclinical models for selection of targeted therapies	Journal of Clinical Investigation	19.456	344	10.1172/jci45014[21]
4	PD-L1 expression in TNBC	Cancer Immunology Research	12.02	340	10.1158/2326-6066.cir-13-0127[22]
5	Pembrolizumab for early triple-negative breast cancer	New England Journal of Medicine	176.079	276	10.1056/nejmoa1910549[23]
6	The evaluation of TILs in breast cancer: recommendations by an International TILs working group 2014	Annals Oncology	51.769	275	10.1093/annonc/mdu450[24]
7	TNBC: clinical features and patterns of recurrence	Clinical Cancer Research	13.801	255	10.1158/1078-0432.ccr-06-3045[25]
8	Atezolizumab plus nab-paclitaxel as first-line treatment for unresectable, locally advanced or metastatic TNBC (IMpassion130): updated efficacy results from a randomized, double-blind, placebo-controlled, phase 3 trial	Lancet Oncology	54.433	224	10.1016/s1470-2045(19)30689-8[26]
9	Prognostic and predictive value of TIL in a phase III randomized adjuvant breast cancer trial in node-positive breast cancer comparing the addition of docetaxel to doxorubicin with doxorubicin-based chemotherapy: BIG 02-98	Journal of Clinical Oncology	50.717	223	10.1200/jco.2011.41.0902[27]
10	Pembrolizumab monotherapy for previously treated metastatic TNBC: cohort A of the phase II KEYNOTE-086 study	Annals Oncology	51.769	213	10.1093/annonc/mdy517[28]

TILs = tumor-infiltrating lymphocytes, TNBC = triple-negative breast cancer.

*Total citations were until the end of 2024.

†Digital Object Identifier.

of the ligands of PD-1, PD-L1 is a type I transmembrane protein with PD-1, which is expressed in antigen-presenting cells, non-lymphocytes.[39] The combination of PD-L1 and PD-1 in tumor cells inhibits the activation, proliferation, and survival of T cells, allowing tumor cells to escape monitoring by the immune system, resulting in immune escape. The concept of TNBC was proposed by Bauer et al in 2007,[40] and no data on ICB for TNBC were retrieved before 2008.

It was not until 2018, when James P. Allison and Tasuku Honjo won the Nobel Prize in Medicine for their work interfering with cancer by suppressing negative immune regulation, that research into TNBC immune checkpoint inhibitors took off. Our time-series distribution results show that the annual number of papers published on ICB in TNBC has increased from 484 to 596 since 2022.This indicates that this field has gradually become a research hotspot and is currently undergoing significant development. During this period, theory developed rapidly, the number of papers increased rapidly, and the growth curve became sharp.

Regarding the geographical distribution, among the 83 countries and regions involved in this bibliometric analysis, the most prolific are listed in Table 1. The United States published most of the papers in this field and is also the country with the most collaborations in this field. China is the second most prolific country, but considering the number of citations, it is still far from taking the lead in this area. Other countries with a large number of publications, such as Japan, Australia, and various European countries, have a good scientific base in this field and most of them are in European countries. This situation is also reflected in the most productive organizations and authors. The top 10 institutions were from the United States, China, Australia, and Italy, which corresponded to the country and regional distribution.

In terms of cooperation between authors, the network analysis showed that Sherene Loi 13 papers revealed clinical studies of ICB, pembrolizumab and atezolizumab alone or in combination with chemotherapy for different subtypes of BC.[41–48] The second author of the H-index, Lajos Pusztai, is a professor at the Yale School of Medicine who investigated the effects of pembrolizumab on event-free survival and pathological complete response in patients with early TNBC and the safety and efficacy of ICB in combination with PARP inhibitors, chemotherapy, and radiotherapy in patients with metastatic TNBC.[23,49–51]

Considering the evidence for the total number of publications, citations, and IF, the New England Journal of Medicine is the most influential journal on this topic, according to my findings. An article published there titled "Atezolizumab and Nab-Paclitaxel in Advanced TNBC" ranked first in terms of total citations.[52] This article demonstrates that nanoparticle albumin-binding (nab)-paclitaxel can enhance the anticancer activity of atezolizumab, thus benefiting patients with metastatic TNBC from progression-free survival. The frequently cited results of this study indicate that the combination of ICB and chemotherapeutic agents to treat TNBC has attracted the attention of many researchers and may be a potential breakthrough in improving its efficacy in this area. Papers published in the New England Journal of Medicine between 2019 and 2024 mainly focused on the long-term outcomes of ICB intervention at different stages of TNBC, the combination of ICB with other therapies, and the application of ICB drug conjugates in metastatic TNBC.[12,53,54]

4.2. Hotspots and frontiers

Immune checkpoint blockers antitumor therapy has made the biggest breakthroughs in the theory and application of tumor immunotherapy for TNBC. In particular, studies have found that ICB combined with other drugs can improve the immune response of the tumor microenvironment in TNBC and the survival rate of patients.[55] Through bibliometric analysis, we know that the current focus of ICB intervention in TNBC is combination therapy, which mainly includes neoadjuvant chemotherapy combined with ICB and ADC therapy combined with ICB.

4.3. Neoadjuvant chemotherapy combined with ICB

Neoadjuvant chemotherapy refers to systemic chemotherapy administered before surgery or radiotherapy to debulk the tumor and inhibit metastasis, followed by treatment of the tumor with

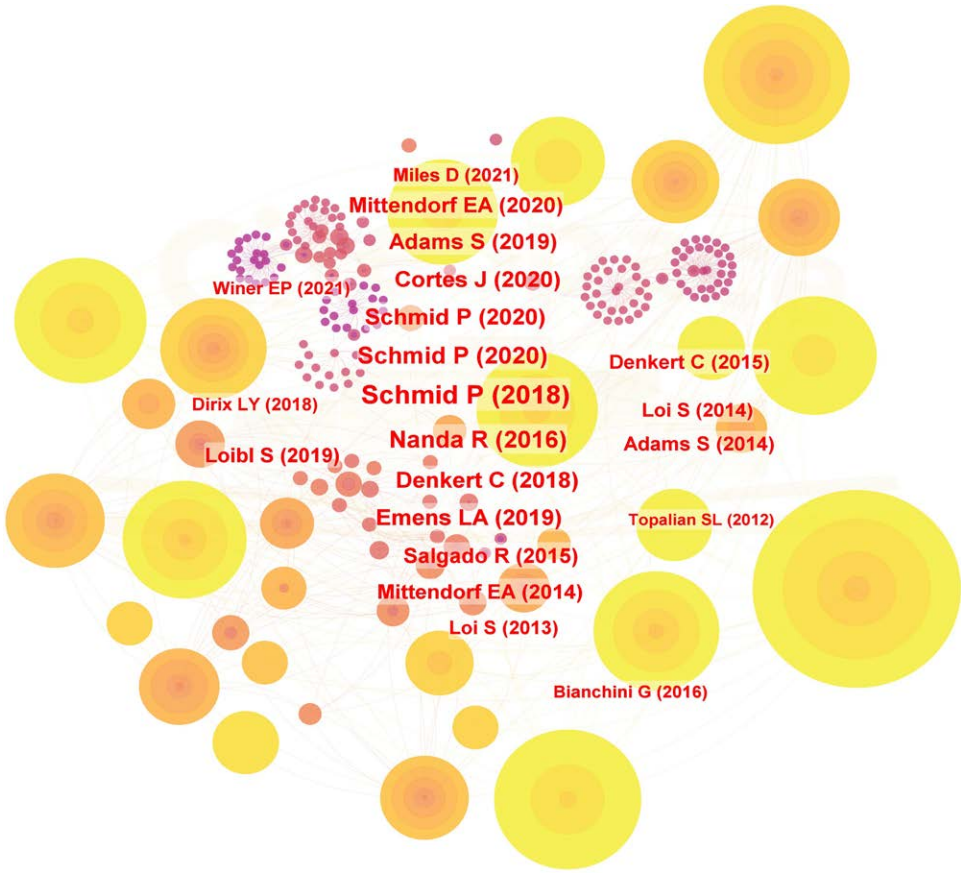

Figure 9. Co-citation analysis of references. Using CiteSpace, we performed a co-citation analysis of references from 2003 to 2024. In CiteSpace, the size of a circle indicates the number of documents cited. The purple area of the circle indicates the centrality of a document. In other words, it indicates the degree of research concentration of the relevant literature.

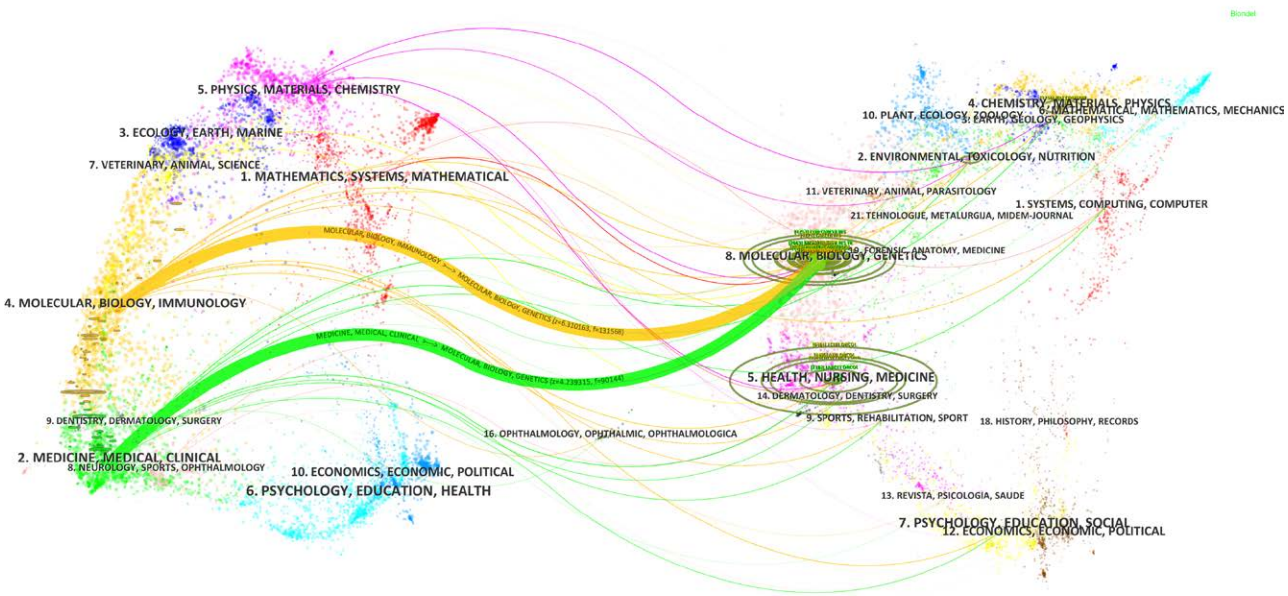

Figure 10. Dual-map overlay of journals that published literature on TNBC ICB from 2003 to 2024. The ellipse in the figure represents the number of publications corresponding to a journal. The longer the horizontal axis of the ellipse, the more authors are represented, and the longer the vertical axis of the ellipse, the more articles are published on behalf of journals. The *Z*-value is the value of a standardized score used to standardize the reference frequency (*f*). In simple terms, the *Z*-value is a measure of how often 1 journal cites another. ICB = immune checkpoint blockers, TNBC = triple-negative breast cancer.

surgery or radiotherapy at a later stage. Previous studies have shown that immunotherapy combined with chemotherapy can achieve a better antitumor effect than monotherapy, and neoadjuvant chemotherapy based on anthracycline-taxane is the standard treatment choice for patients with stage II to III BC.[56,57] Because standard neoadjuvant chemotherapy is prone to poor clinical response associated with a low incidence of pathological complete response, and neoadjuvant anti-PD-L1 therapy can improve the pathological complete response rate of unselected TNBC, upgraded neoadjuvant chemotherapy combined with ICB should be considered to optimize the risk-benefit ratio of drugs notes the importance. Studies have shown that atezolizumab monoclonal antibody combined with neoadjuvant chemotherapy based on anthracycline and paclitaxel also showed an increase in pathological complete response in early TNBC.[35] Furthermore, combined with nab-paclitaxel as the second stage of NAT in adriamycin and cyclophosphamide-resistant TNBC patients single-arm phase II study (NCT02530489), results showed that the residual cancer burden I rate of pathological complete response/increased from 5% to 20%.[58] Another multicenter, prospective single-arm phase II trial NeoImmunoboost (AGO-B-041/ NCT03289819) suggested a pathological complete response of 66.0% after neoadjuvant chemotherapy combined with paclitaxel (nP), an anthracycline and pembrolizumab for TNBC.[59] In the GeparNuevo (NCT02685059) trial, neoadjuvant chemotherapy combined with durvalumab resulted in a 9% increase in pathological complete response, which significantly improved survival.[7] The FDA-approved pembrolizumab monoclonal antibody combined chemotherapy for neoadjuvant therapy based on the results of pathological complete response and event-free survival in KEYNOTE-2.[60] The ongoing GeparDuoze trial (NCT03281954) is investigating the optimal timing, duration and biological mechanism of control response for the addition of Atezolizumab monoclonal antibody (NCT03281954) to neoadjuvant chemotherapy in TNBC.[61] In summary, combined chemotherapy and ICB treatment in neoadjuvant chemotherapy, as an important category of combined therapy, has become a research hotspot in this field. Further research is needed on how to select suitable patients with TNBC, how to choose the appropriate timing of application, duration, and immune response mechanism corresponding to specific ICB, and how to comprehensively assess the impact on patients' subsequent treatment, such as radiotherapy.

4.4. Antibody-drug conjugates therapy combined with ICB

Antibody-drug conjugates are immunomodulators that combine the specificity of monoclonal antibodies (mAbs) and the high potency of small chemical chemotherapeutics to preferentially deliver potent small molecules to cancer cells, with the potential to improve cancer treatment.[62,63] This treatment can specifically target cancer cells while minimizing toxicity to normal tissues, further improving clinical outcomes for patients with TNBC. In 2022, the ADC sacituzumab-govitecan was approved for the first time in metastatic tumors for the treatment of patients with metastatic TNBC,[63] marking a significant advance in immunotherapy for TNBC. To enhance the antitumor activity of sacituzumab-govitecan, a randomized phase 2 trial is testing sacituzumab-govitecan in combination with the monoclonal antibody pembrolizumab (NCT04468061) in patients with PD-L1-negative metastatic TNBC. These results may help overcome resistance to immunotherapy strategies in PD-L1 negative tumors. Another ADC with similar immunomodulatory properties (ladiratuzumab-vedotin) was combined with the monoclonal antibody pembrolizumab as first-line treatment in patients with TNBC in a Phase Ib/II study, and we found that the efficacy of this combination was superior to that of pembrolizumab alone (ORR was 54% at 3 months) and was well tolerated. The successful combination of ADC and ICB depends on the correct classification of the patients while maximizing efficacy and reducing toxicity. However, the reasonable selection of a combination of ADC and ICB with synergistic antitumor activity and sufficient safety remains a challenge.[63]

4.5. Poly ADP-ribose polymerase inhibitors combined with ICB

The response of metastatic BC cells to poly (ADP-ribose) polymerase inhibitors is limited. Many trials have evaluated the combination of PARP inhibitors with various PD-1/PD-L1 checkpoint inhibitors, including pembrolizumab (NCT02657889),[64] avelumab (NCT03330405), and durvalumab (NCT02734004). The results showed that the combination was well tolerated and safe.[65] A number of ongoing clinical trials of PARP inhibitors and checkpoint inhibitors (NCT03101280, NCT02849496, NCT02484404, NCT03544125, PHOENIX/ NCT03740893, NCT03801369, DORA/NCT03167619, NCT03025035, and KEYLINK 009/NCT04191135) will provide more data on PARP inhibitors and checkpoint blocking combination therapy. This combined therapeutic strategy remains an active area of research.

4.6. Strengths and limitations

This is the first study to use bibliometric analysis to investigate the trends and public interest in ICB interventions for TNBC. Because we used systematic retrieval and quantitative statistical analysis, our bibliometric analysis was more comprehensive and intuitive than a literature review. In addition, we used not only CiteSpace, but also VOSviewer and the R package bibliometrix for better data extraction, bibliometric analysis, and visualization. However, this study had some limitations. First, we only extracted literature from the WoSCC database; although it is almost impossible to ignore some studies using this method, this type of literature may be less frequently cited. In addition, the bibliometric analysis method used can only be applied to general data and not to the full text. Consequently, we may have lost important information that is only available in the full text of the article, such as the views of the authors and future perspectives. Second, we only analyzed studies published in English and those written in non-English languages were excluded.

5. Conclusions

This study used the method of bibliometrics to retrieve the core data set of WoSCC; we also used CiteSpace, VOSviewer, R package "bibliometrix" and other software to analyze the bibliometrics data of ICB with TNBC, and visually shows the trend of annual articles, authors, institutions, countries, keywords, journals, references. This shows the main research direction and development trends in ICB for TNBC worldwide. The knowledge graph shows that TNBC ICB is a prolific, rapidly developing, and high-profile topic. Research in this field is mainly concentrated in European countries and Australia and is closely linked to the whole world. Research hotspots range from "biomarker," "apoptosis" to "immunotherapy," to the clinical trials of "tumor microenvironment," evaluation criteria "pathological complete remission," new words "neoadjuvant chemotherapy" and "PARP inhibitors" after 2021. Research on the mechanisms of ICB has gradually matured. In the next few years, the optimal timing, duration, specific response mechanism, and comprehensive evaluation of ICB combined with neoadjuvant chemotherapeutic drugs, ADC, or PARP inhibitors to interfere with the tumor microenvironment may become popular topics in this research field, and efforts to improve the antitumor efficacy of ICB will continue.

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