HUMAN VACCINES & IMMUNOTHERAPEUTICS
2025, VOL. 21, NO. 1, 2505349
https://doi.org/10.1080/21645515.2025.2505349

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REVIEW

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How has the field of immunogenic cell death in breast cancer evolved and impacted clinical practice over the past eleven years?

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ABSTRACT

This study elucidates the research landscape of immunogenic cell death (ICD) in breast cancer through a bibliometric analysis of 457 Web of Science articles. Contributions from China and the USA are particularly prominent, with notable international collaborations. Core journals such as *Biomaterials* published influential studies, while researchers like Huang Y made impactful contributions. High-frequency keyword analysis identified key research hotspots, including immunotherapy, the tumor microenvironment, and nanomedicine. The integration of chemotherapy with immunotherapy and the identification of key proteins have driven recent advancements. Fundamental research on immunotherapy, photodynamic therapy (PDT), and triple-negative breast cancer (TNBC) points to future trends and potential breakthroughs. This study offers a strategic overview of ICD in breast cancer, providing insights into clinical practice and guiding future research in the field.

ARTICLE HISTORY
Received 11 February 2025
Revised 20 April 2025
Accepted 8 May 2025

KEYWORDS
Breast cancer; immunogenic cell death; bibliometric; immunotherapy; clinical practice

Introduction

Breast cancer, the most commonly diagnosed cancer among women worldwide, poses a major threat to women's health and presents serious public health challenges.[1] According to 2022 global cancer statistics, breast cancer accounts for 11.6% of new cancer cases, with 2,308,897 new cases, ranking second in incidence and fourth in cancer-related mortality, with 665,684 deaths (6.9% of all cancer deaths).[2] Due to its rising incidence and the high costs associated with diagnosis and treatment, breast cancer imposes a significant economic burden on patients and healthcare systems.[3] Alarmingly, projections suggest that by 2040, the global incidence may exceed 3 million new cases annually, with approximately 1 million deaths, posing an increasing challenge for healthcare worldwide.[4]

The pathogenesis of breast cancer involves a complex interplay of factors such as age, lifestyle, genetics, gene mutations, and environmental factors.[5,6] Promoting healthy lifestyles, regular exercise, precision prevention strategies, and pharmacological interventions in high-risk groups can help reduce incidence.[5,7] Gene expression profiling has enabled classification of breast cancer into receptor-positive and receptor-negative types.[8] Among these, triple-negative breast cancer (TNBC) – which accounts for 10–20% of cases – is particularly aggressive and difficult to treat, drawing significant research attention.[9–11] In low- and middle-income countries, limited resources and poor health education often delay diagnosis and treatment, worsening patient outcomes.[12] Even with prompt intervention, recurrence, metastasis, and reduced survival remain serious concerns.[13]

Recent advances in systemic therapies – particularly immunotherapy – have transformed the treatment landscape. For example, antibody-drug conjugates (ADCs) such as sacituzumab govitecan and datopotamab deruxtecan have shown safety and efficacy in treating metastatic TNBC (mTNBC), consistent with findings from regulatory trials.[14] These developments promise to redefine treatment paradigms for mTNBC. Moreover, neoadjuvant therapies combining immune checkpoint inhibitors (ICIs) with cytotoxic chemotherapy have shown promise in early-stage TNBC. Studies like KEYNOTE-522, IMpassion031, and GeparNUEVO reported improvements in pathologic complete response (pCR) and event-free survival (EFS) compared to chemotherapy alone.[15,16] However, as immunotherapy continues to evolve, deeper exploration of novel antitumor immune mechanisms is critical to advancing breast cancer treatment.

Immunogenic cell death (ICD) is a form of regulated cell death (RCD) triggered by stress, characterized by its ability to

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/21645515.2025.2505349

initiate specific signaling pathways in dying tumor cells, thereby releasing and exposing damage-associated molecular patterns (DAMPs).[17–20] TheseDAMPs, recognized by pattern recognition receptors (PRRs), activate both innate and adaptive immune responses – particularly CD8+ T lymphocytes – resulting in cancer cell death and proliferation suppression.[19,21] A growing body of evidence suggests that DAMPs such as calreticulin (CALR), ATP, annexin A1 (ANXA1), type I interferons, and high mobility group box 1 (HMGB1)[22]may serve as prognostic and predictive biomarkers across tumor types,[23] providing new therapeutic possibilities for cancer immunotherapy (a schematic diagram of the molecular mechanisms underlying ICD is shown in Figure 1).

Although traditional approaches targeting apoptosis and other RCD modalities have been extensively researched for cancer therapy,[24] particularly in breast cancer, offering novel avenues for overcoming therapeutic resistance,[25] their immunologically silent nature limits their potential to elicit robust immune responses.[26] In contrast, ICD has attracted considerable attention due to its ability to induce strong antitumor immune responses.[26] Numerous studies have shown that chemotherapy, targeted therapy, radiotherapy, and photodynamic therapy can induce ICD, effectively transforming dying cancer cells into vaccines and triggering antigen-specific immune responses and precise immune attacks.[27–29]

Consequently, research on ICD in breast cancer immunotherapy has expanded. For instance, Yin Y et al. demonstrated that the HDAC inhibitor hpy-4a effectively induces ICD in breast cancer by upregulating TUSC2 transcription.[30] Another study found that RIPK1-specific PROTAC degraders achieve potent antitumor effects by enhancing ICD.[31] Celecoxib (CXB), a cyclooxygenase-2 inhibitor, was reported to block the PGE2 synthesis pathway in TNBC cells, thereby enhancing paclitaxel-induced ICD and offering new regulatory strategies for breast cancer treatment.[32] Moreover, ICD can reshape the tumor immune microenvironment, promote tumor cell apoptosis, and support the development of long-lasting antitumor immune memory.[33] Studies exploring the relationship between ICD-related classifications and breast cancer immunotherapy outcomes have enriched theoretical frameworks and provided a solid theoretical and practical foundation for next-generation immunotherapies.[34]

Despite its promise, research on ICD in breast cancer remains fragmented and lacks comprehensive bibliometric analysis. This hinders a full understanding of the current research landscape and future trends. To address this gap, this study employs bibliometric methods to systematically analyze ICD-related breast cancer literature from the Web of Science Core Collection (WoSCC) database. Using VOSviewer and R software packages, we analyze trends in publication year, countries/regions, authorship, journal distribution, highly cited works, and keyword frequency. Our goal is to provide a systematic summary of the current status of ICD research in breast cancer and to highlight emerging directions for future inquiry.

Materials and methods

Data sources and search strategy

The primary data source for this study was the WoSCC. An advanced search was conducted with the time frame set from January 1, 2000, to July 1, 2024. The search query was as follows: ((TS=("Breast Tumor*" OR "Breast Cancer" OR "Mammary Cancer" OR "Cancer, Breast" OR "Malignant Neoplasm of Breast" OR "Cancer of the Breast" OR "Breast Carcinoma") AND TS=("Immunogenic Cell Death" OR ICD OR "Immunogenic Death"))). This search yielded 1,094 relevant documents.

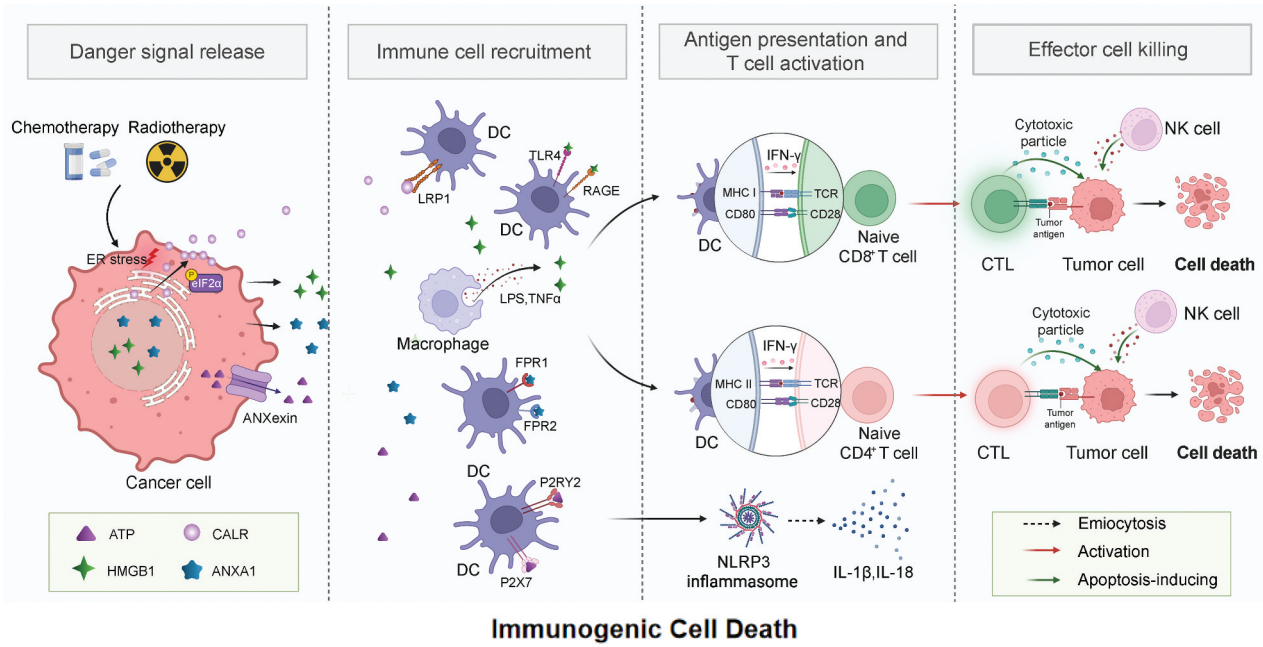

Figure 1. Schematic diagram of the mechanism of immunogenic cell death.

After applying predefined inclusion and exclusion criteria, 885 articles remained for analysis.

All data records included "Complete Records and Referenced Citations" and were exported as plain text (.txt) files. To avoid inconsistencies due to updates in the WoSCC database, all retrieval and export procedures were completed on July 14, 2024. Since all data were obtained from publicly available open-access databases, no ethical issues were involved.

The literature search and screening were independently conducted by Yu-Long Deng and Bang-Teng Chi. Any discrepancies were resolved through discussion with all authors, with Gang Chen, Wei Peng, and Jiayuan Luo making final decisions. The detailed data collection process is illustrated in Figure 2.

Inclusion and exclusion criteria

Inclusion criteria: (1) scientific papers publicly published in scientific journals; (2) papers whose titles include the terms "breast cancer" and "immunogenic cell death," indicating a primary focus on these themes; (3) papers in which the title may not explicitly mention "immunogenic cell death" or "breast cancer," but whose abstracts identify them as a core component of breast cancer and ICD research; and (4) full-text articles that present original research on breast cancer and immunogenic cell death.

Exclusion criteria: (1) non-research literature, including review articles, conference reports, briefs, news reports, editorial materials, letters, and advertisements; (2) literature not written in English; (3) works with duplicate content or incomplete data; and (4) literature that has been retracted by the publishing journal.

Bibliometric methods

The primary software tools used in this study were R (version 4.3.2), VOSviewer (version 1.6.19), Scimago Graphica (version 1.0.44), and Pajek (version 1.0.0). These tools facilitated data processing, bibliometric analysis, and the visualization of results. Specifically, they were used to visualize publication and citation data across authors, journals, and countries/regions. They also supported network clustering, overlay mapping of keywords, keyword evolution over time, and thematic trend charting.

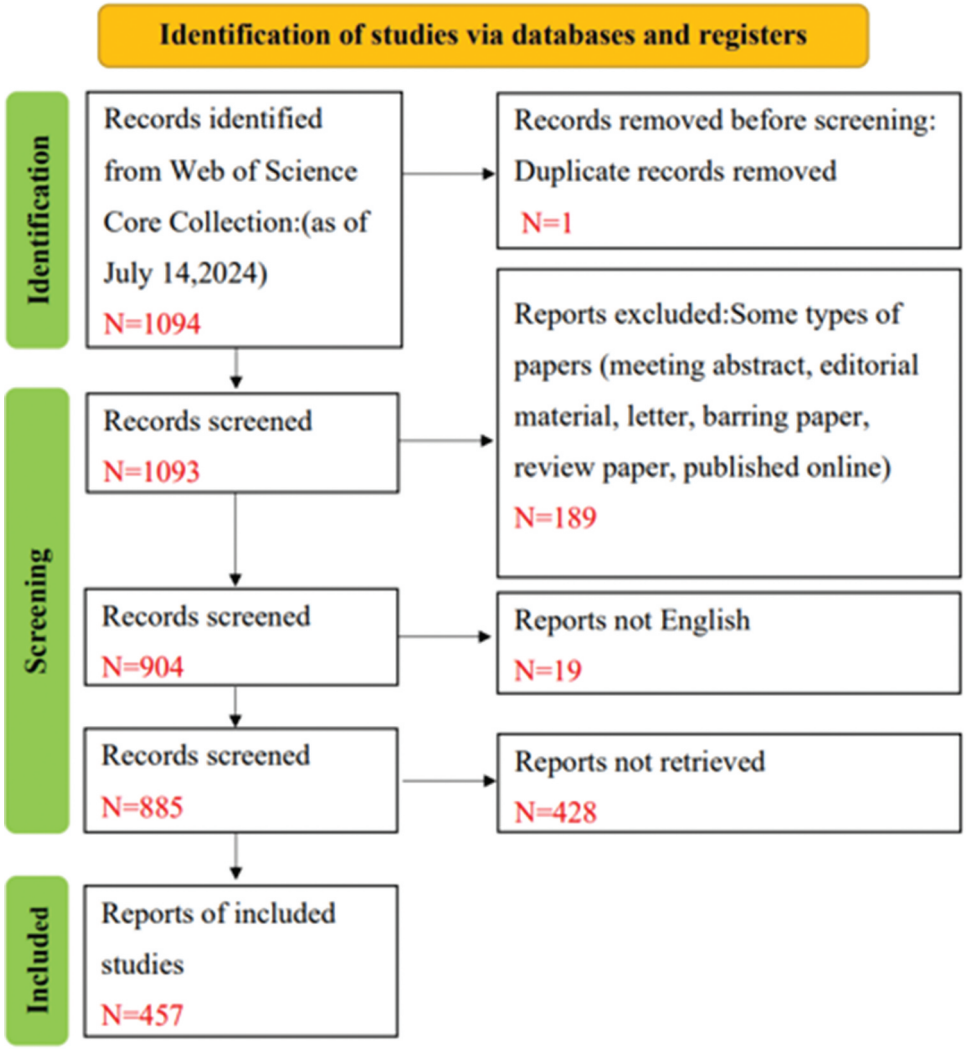

Figure 2. Flowchart of literature data included in this study.

Results

Core information

This study screened 457 papers related to breast cancer and ICD research from 142 journal sources, spanning the period from January 1, 2013, to July 1, 2024 (Figure 3). During this period, the annual growth rate of related research reached 31.45%. The average number of citations per paper was 25.95, and a total of 16,444 references were cited, averaging approximately 36 references per article. The study also compiled 933 author keywords and 831 keywords plus. All papers were the result of collaborative efforts, with an average of 8.85 coauthors per paper, and 19.69% of the papers involved international academic collaboration.

Deep insights into the annual trends and citation impact of breast cancer and ICD research

From 2013 to 2024, cubic function curve fitting ($R^2 = 0.8487$) revealed a significant upward trend in annual publication volume related to breast cancer and ICD research (Figure 4). In the early years, particularly from 2013 to 2016, the number of annual publications was relatively low, with only four relevant papers published in each of 2013, 2014, and 2016, and even fewer – just three papers – published in 2015. Starting in 2018, the growth rate stabilized, indicating a sustained upward trajectory. By 2023, there was a sharp increase, with 134 papers published, marking the peak year (excluding incomplete data from 2024). This represented a significant increase of over 50% compared to 80 papers in 2022 and was more than 30 times the publication volume in 2013.

An analysis of average annual citations for articles published each year revealed fluctuating trends. The highest average citation count occurred in 2018, with articles receiving an average of 15.61 citations. From 2020 to 2023, although research output increased, the average annual citation count per article declined from 11.35 to 3.53.

Deep insights into journal distribution and impact

All articles related to ICD in breast cancer were published across 130 journals indexed by the WOSCC. Supplementary Figure S1A displays the ten most productive journals, with the *Journal of Controlled Release* leading the list ($n = 23$, 5.03%),

Figure 3. Core information of the literature included in this study.

Figure 4. Trend chart of article publications and average annual citation counts in the field of breast cancer and ICD from 2013 to July 1, 2024.

Table 1. Top 10 journals ranked by H index in the field of breast cancer and ICD research.

Rank	Source	h_index	g_index	m_index	TC	$IF_{(2023)}$
1	*BIOMATERIALS*	16	20	2.286	1104	12.8
2	*JOURNAL OF CONTROLLED RELEASE*	11	23	1.833	555	10.5
3	*ACS NANO*	10	19	1.429	1114	15.8
4	*ACS APPLIED MATERIALS & INTERFACES*	9	18	1.5	338	8.3
5	*ONCOIMMUNOLOGY*	9	9	0.818	728	6.5
6	*ACTA PHARMACEUTICA SINICA B*	8	9	1.333	215	14.7
7	*ACTA BIOMATERIALIA*	7	9	1.167	139	9.4
8	*NANO TODAY*	7	13	1.75	330	13.2
9	*ADVANCED FUNCTIONAL MATERIALS*	6	11	1	326	18.5
10	*ADVANCED MATERIALS*	6	9	1.2	482	27.4

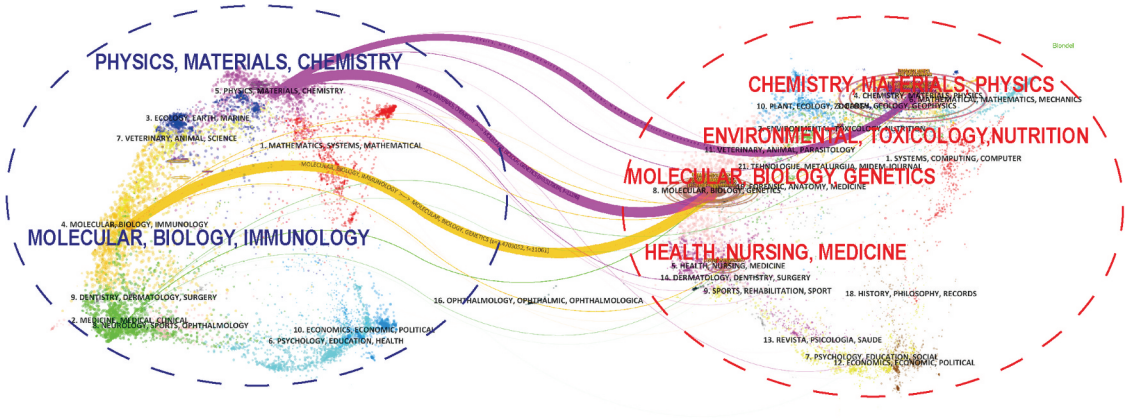

Figure 5. Dual-map overlay of citing journals and cited journals.

making it one of the most active journals in this field. *Biomaterials* and *ACS Applied Materials & Interfaces* followed, ranking second ($n = 20$, 4.38%) and third ($n = 19$, 4.16%), respectively. Between 2018 and 2024, the number of publications in these journals showed an consistent upward trend (Supplementary Figure S1B).

Table 1 presents the top 10 journals ranked by H-index in this field. *Biomaterials* had the highest H-index of 16, an M-index of 2.286, a total citation count of 1,104, and an impact factor (IF) of 12.8. *ACS Nano* had the highest citation count (1,113) and an IF of 15.8. Notably, *Advanced Materials*, a U.S.-based journal, ranked tenth by H-index and had the highest IF (27.4). It had published nine relevant articles and had an H-index of 6.

Figure 5 presents a dual-map overlay analysis of journals, showing journal distribution, the evolving citation patterns, and shifting research foci. This visualization helps elucidate interrelationships within the field of breast cancer and ICD research, emphasizing citation patterns and scholarly progression. Citing journals are shown on the left and cited journals on the right, with colored lines connecting them to represent citation flows. Citing journals primarily belong to fields such as "Molecular, Biology, Immunology, Physics, Materials and Chemistry," reflecting the current frontier directions of research. In contrast, the cited journals mainly originate from disciplines such as "Molecular, Biology, Genetics, Chemistry, Materials and Physics," reflecting the foundational knowledge domains of this research.

Deep insight into the characteristics and influence of core author groups

This study also identified key contributors to the field of breast cancer and ICD research. Table 2 lists the top 10 authors ranked by H-index. These scholars significantly influenced research development through their high-quality publications. Huang Y was the most prominent, with an H-index of 7, an M-index of 1.75, and the highest publication count ($n = 8$). Kroemer G, Li L, and Li Y followed with H-indices of 6.

Table 2. Top 10 authors ranked by H index in the field of breast cancer and ICD research.

Rank	Author	h_index	g_index	m_index	TC	NP
1	HUANG YUAN	7	8	1.75	172	8
2	KROEMER GUIDO	6	6	0.545	566	6
3	LI LIAN	6	7	1.5	101	7
4	LI YAPING	6	7	1.2	254	7
5	ZITVOGEL LAURENCE	5	5	0.455	434	5
6	DEMARIA SANDRA	4	4	0.364	470	4
7	FORMENTI SILVIA C.	4	4	0.364	470	4
8	GAO HUILE	4	6	0.5	326	6
9	HU QIAN	4	4	0.667	244	4
10	KONG LI	4	4	0.667	244	4

Among them, Kroemer G had the highest total citation count (566).

Figure 6a–c provides visualizations of these leading authors, showing their publication volume, average citation strength, and publications timelines. Node size represents publication volume, while the color gradient from light to dark indicates increasing volume or average citation count. Demaria S had the highest average citation count of 117.5, while authors like Kroemer G and Gao HL demonstrated consistent research output over five years, making them among the most active contributors in the field.

Deep insight into national output characteristics and international cooperation patterns

Based on the number of papers published by each country (represented by the size of the nodes) and the strength of international cooperation (represented by the size of the connecting lines), 39 countries were found to have contributed to the literature in this field (Figure 7a). China published its first relevant article in 2015 (Supplementary Figure S2A) and by July 2024 had produced 326 articles, accounting for 71.3% of the total publications – a proportion significantly higher than that of any other country. The United States ranked second with 54 articles (11.8%), followed by South Korea with 14 articles (3.1%). Canada ($n = 8$), France ($n = 7$), and Italy ($n = 6$) had also contributed a noteworthy number of publications.

Analysis of collaboration patterns among leading nations (Figure 7a) showed that the partnership between China and the United States was the most frequent, with 29 collaborative publications. In addition to the United States, China had established cooperative ties with several countries, including Australia and Singapore (both with five collaborations) as well as the United Kingdom and Japan (both with three collaborations). European countries such as France, Germany, Austria, and Belgium also engaged in international cooperation, although the frequency was relatively low. The United States and South Korea collaborated nine times, marking another prominent partnership.

In terms of publication characteristics (Figure 7b), the majority of articles from most countries were single-country publications (SCP), accounting for 80.33% of the total, while multi-country publications (MCP) represented only 19.69%. Although China had the highest number of MCPs ($n = 38$), these accounted for only 11.7% of its total publications. In contrast, the United States had 20 MCPs, comprising 37% of its output.

Regarding the total citation count (TC) per country (Supplementary Figure S2B), China's led with 7,256 citations, followed by the United States with 2,191. France (TC = 613), Canada (TC = 564), and South Korea (TC = 253) had lower totals but still ranked among the top five countries. France had the highest average citation count per article (87.60). China's average citation count per article was 22.30, which was lower than that of the United States (46.6), placing China seventh in this metric.

Characteristics of high-impact articles

Local citations (LC)s reflect the impact of an article within its specific research field, while global citations (GCs) indicate its influence across disciplines. Considering both LCs and GCs, certain articles exhibited significant academic influence at multiple levels. Table 3 summarizes the most highly cited articles. The article titled "*Bioinspired Hybrid Protein Oxygen Nanocarrier Amplified Photodynamic Therapy for Eliciting Anti-tumor Immunity and Abscopal Effect*," published in *ACS Nano*, ranked highest in LCs ($N = 15$) and was also notable in terms of GCs ($N = 284$), yielding an LC/GC ratio of 5.28%. The article "*Photodynamic Therapy Mediated by Nontoxic Core-Shell Nanoparticles Synergizes with Immune Checkpoint Blockade To Elicit Antitumor Immunity and Antimetastatic Effect on Breast Cancer*," published in *Journal of the American Chemical Society*, had slightly fewer LCs ($N = 11$) but garnered 362 GCs, resulting in an LC/GC ratio of 3.04%. A third study, "*Micellar Paclitaxel Boosts ICD and Chemo-immunotherapy of Metastatic Triple-negative Breast Cancer*," published in *Journal of Controlled Release*, received 10 LCs and 47 GCs, yielding a notably high LC/GC ratio of 21.28%.

Deep application and scientific progress tracking of keyword cluster analysis in breast cancer treatment research

Keyword cluster analysis was used as a core method to identify central topics in the literature and to trace scientific developments over time. To improve consistency and accuracy, this study first eliminated terms like "breast cancer" and "ICD" and their variants and then merged related synonyms. Using VOSviewer, 100 frequently occurring keywords were selected and grouped into four thematic clusters based on their conceptual relationships and research focus (Figure 8a–b).

Cluster 1 (red) concentrated on diverse treatment strategies for breast cancer, especially immunotherapy, supplemented by approaches such as photodynamic therapy and chemotherapy. It included 34 keywords, such as "immunotherapy" ($n = 95$), "photodynamic therapy" ($n = 31$), and "doxorubicin" ($n = 21$). Cluster 2 (green) explored novel treatment strategies and drug delivery systems aimed at improving the tumor immune microenvironment, particularly for TNBC. It featured 28 keywords, including "three negative breast cancer" ($n = 60$), "tumor immune microenvironment" ($n = 30$), "combined therapy" ($n = 12$), "drug delivery" ($n = 12$), "autophagy" ($n = 10$), and "nanodrug" ($n = 10$). Cluster 3 (blue) addressed the role of immune modulation in treatment outcomes and prognosis. Its 23 keywords included "immune checkpoint" ($n = 21$), "immunosuppression" ($n = 16$), "ferroptosis" ($n = 13$), "calreticulin proteins" ($n = 10$), "immune response" ($n = 7$), and "prognosis" ($n = 7$). Cluster 4 (orange) examined immune escape mechanisms and strategies to enhance the immune system's anti-tumor capacity. Keywords included "pd-1/pd-l1" ($n = 17$), "reactive oxygen species" ($n = 13$), and "cancer stem cell" ($n = 7$).

Given the 18.6% missing keyword rate reported by the authors, relying exclusively on author-provided keywords could introduce significant errors. To mitigate this, the study incorporated Keywords Plus data, which had a much lower missing rate of 5.47%. This enhanced the reliability of the cluster analysis. The

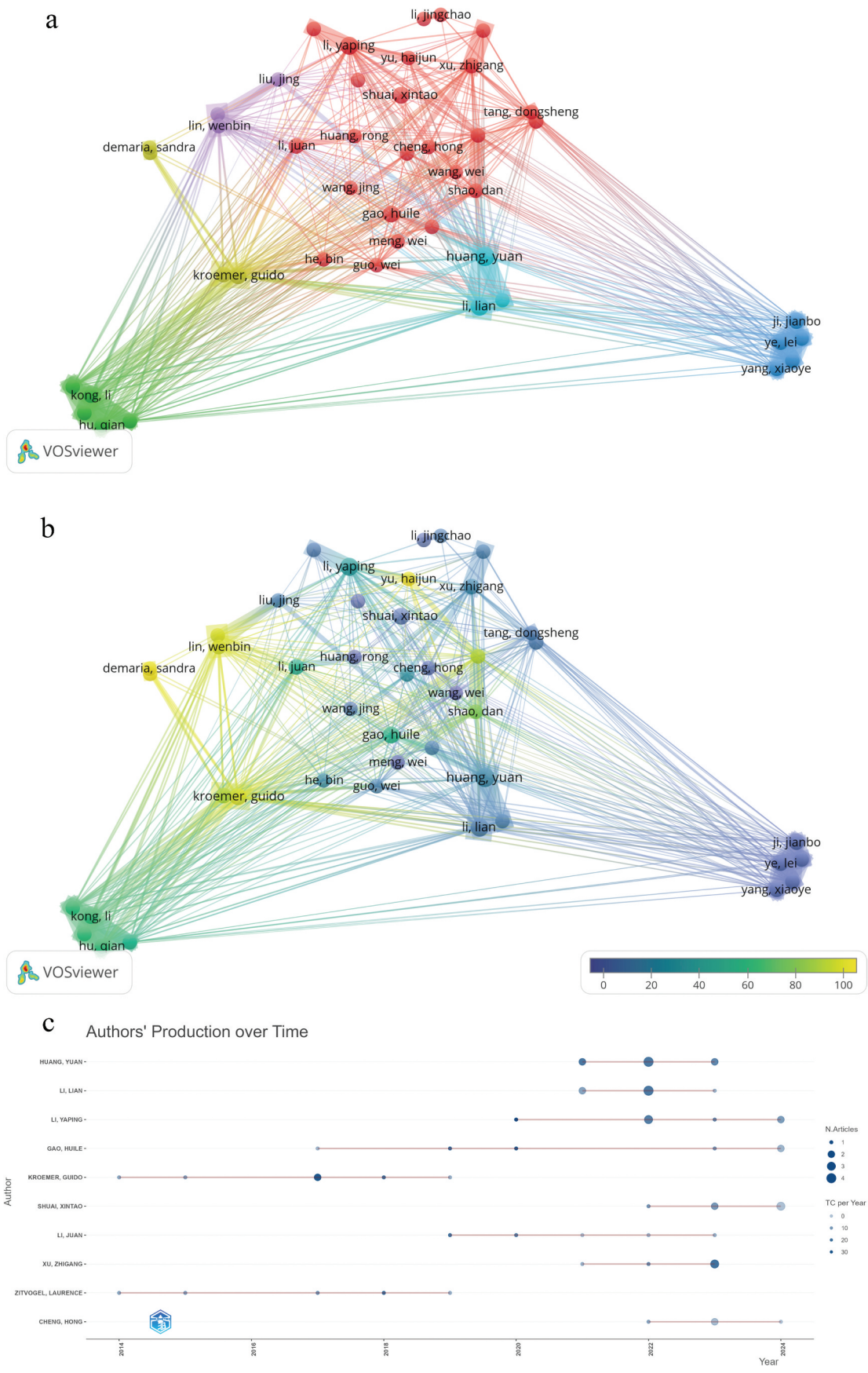

Figure 6. Comprehensive visualization of authors in the field of breast cancer and ICD research. (a) Network visualization map of authors' publication volume; (b) Visualization map of authors' total citations overlay; (c) Authors' publication activity timeline.

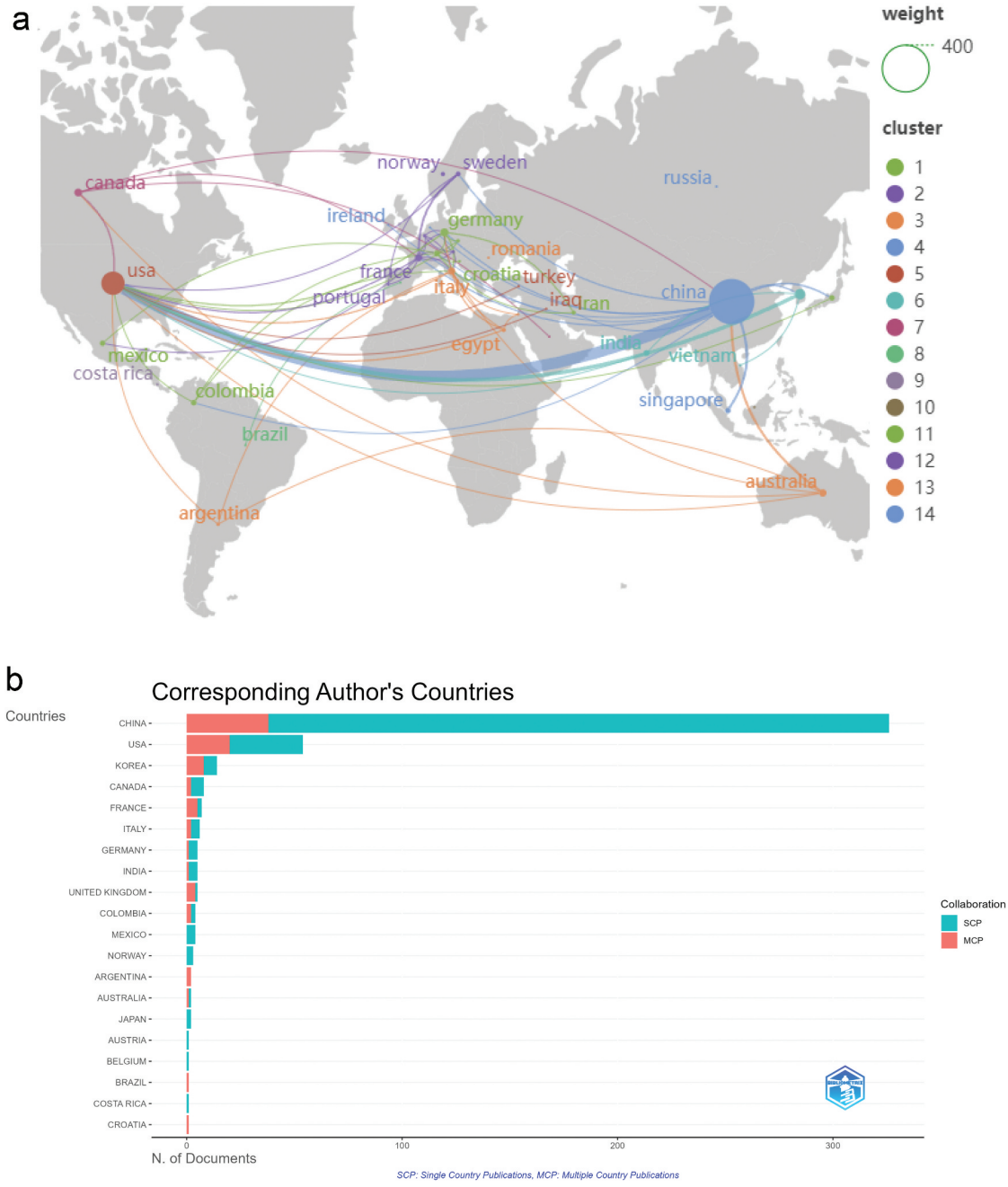

Figure 7. Global perspectives on breast cancer and ICD research fields. (a) Dynamic trend chart of national output in breast cancer and ICD research; (b) Diagram of national collaboration relationships.

Keywords Plus clustering (Figure 9a,b) provided additional classification detail, identifying six main clusters around terms such as "cancer" ($n = 106$), "immunotherapy" ($n = 74$), "chemotherapy" ($n = 66$), "nanoparticle" ($n = 79$), "delivery" ($n = 59$), and "mechanism" ($n = 34$). These results complimented and refined the results of the author keyword analysis.

Deep analysis of keyword evolution and scientific research trends

To trace emerging trends in breast cancer and ICD research, a keyword evolution analysis was performed (Supplementary Figure S3A). The analysis revealed shifting research priorities over time. Although few new keywords appeared in the past five years, most high-frequency terms, such as "immunotherapy," emerged primarily within that timeframe. Between 2018 and 2020, attention was focused on underlying biological mechanisms, reflected in keywords like "endoplasmic reticulum stress," "hypoxia," "calreticulin proteins," and "indoleamine 2,3-dioxygenase." In 2021, interest expanded to include redox balance and autophagy during cell death, as indicated by a temporary increase in terms such as "reactive oxygen species" and "autophagy." From 2021 to 2023, the focus gradually shifted to therapeutic strategies, with popular keywords including "doxorubicin," "photodynamic therapy," and "photothermal therapy." The growing prominence of "immunotherapy"

Table 3. Top 10 articles ranked by local citation counts in breast cancer and ICD research.

Rank	Titel	Year	Local Citations	Global Citations	LC/GC Ratio (%)
1	Bioinspired Hybrid Protein Oxygen Nanocarrier Amplified Photodynamic Therapy for Eliciting Anti-tumor Immunity and Abscopal Effect[35]	2018	15	284	5.28
2	Photodynamic Therapy Mediated by Nontoxic Core-Shell Nanoparticles Synergizes with Immune Checkpoint Blockade To Elicit Antitumor Immunity and Antimetastatic Effect on Breast Cancer[36]	2016	11	362	3.04
3	Micellar paclitaxel boosts ICD and chemo-immunotherapy of metastatic triple negative breast cancer[37]	2022	10	47	21.28
4	Tumors and Their Microenvironment Dual-Targeting Chemotherapy with Local Immune Adjuvant Therapy for Effective Antitumor Immunity against Breast Cancer[38]	2019	9	110	8.18
5	Enhancing Triple Negative Breast Cancer Immunotherapy by ICG-Templated Self-Assembly of Paclitaxel Nanoparticles[39]	2020	9	160	5.63
6	Fighting Immune Cold and Reprogramming Immunosuppressive Tumor Microenvironment with Red Blood Cell Membrane-Cam[40]	2020	9	188	4.79
7	CDK12/13 inhibition induces immunogenic cell death and enhances anti-PD-1 anticancer activity in breast cancer[41]	2020	8	52	15.38
8	GSH depletion liposome adjuvant for augmenting the photothermal immunotherapy of breast cancer[42]	2020	7	134	5.22
9	Acidity-Activatable Dynamic Nanoparticles Boosting Ferroptotic Cell Death for Immunotherapy of Cancer[43]	2021	7	197	3.55
10	Photothermal therapy-induced immunogenic cell death based on natural melanin nanoparticles against breast cancer[44]	2020	6	77	7.79

throughout this period underscored its importance as a leading research theme. Notably, interest in "triple-negative breast cancer" has risen significantly since 2021.

The evolution analysis of Keywords Plus (Supplementary Figure S3B) further enriched this analysis. "Ferroptosis" emerged as a new focus in 2024, while "cancer-infiltrating lymphocytes" appeared consistently from 2017 to 2023, helping to identify both persistent and emerging research directions in this field.

Analysis of major research themes and trends in the field of breast cancer and ICD

An in-depth analysis (Figure 10a) provided a clearer understanding of the major research trends in the field of breast cancer and ICD. In the first quadrant, representing *motor themes*, we identified hotspots such as studies focused on "chemo-immunotherapy," "doxorubicin," and "calreticulin." In the second quadrant, the *niche themes* mainly explored cutting-edge topics like "cancer metastasis." The third quadrant, *emerging or declining themes*, highlighted therapeutic strategies based on various cell death mechanisms, including "photo/immunotherapy," "reactive oxygen species," and "ferroptosis." Finally, in the fourth quadrant, *basic themes* revealed the broader research framework surrounding breast cancer subtypes and immunotherapy, which form the foundation of this research field. Key terms in this quadrant included "triple-negative breast cancer," "immunotherapy," and "photodynamic therapy."

A deeper examination of the thematic words within Keyword Plus (Figure 10b) revealed the emergence of core terms such as "stress," "melanoma," and "copper" under the *motor themes*. The *basic themes* included focal points like "delivery," "nanoparticles," and "combination," offering additional insights for identifying research hotspots and future directions in keyword thematic analysis.

Discussion

In recent years, breast cancer has garnered widespread attention due to its high global incidence and significant impact on women's health.A notable therapeutic strategy in cancer research involves inducing the death of cancer cells through various modalities.[45] ICD, as an emerging approach, promotes cancer cell death via targeted chemotherapy agents, oncolytic viral therapies, physical and chemical treatments, radiotherapy, and combination treatments.[46] Research advancements have enabled ICD to play an increasingly significant role in breast cancer therapy. However, despite ICD's importance in tumor immunology, the current literature remains fragmented and lacks systematic visual analysis.

This study analyzed 457 research articles on breast cancer and ICD from the WoSCC database through a comprehensive bibliometric analysis of authors, journals, countries/regions, citations, and keywords. The objective was to systematically organize the current research status and developmental trends in this domain, providing new perspectives and resources for future researchers studying ICD in the context of breast cancer.Our data analysis revealed a substantial increase in scholarly output related to breast cancer and ICD over the past decade, reflecting growing interest and importance in this area. Trends in publication and citation data – across authors, countries/regions, journals, and highly cited articles – highlight the complexity and evolution of research dynamics in this field. From 2013 to 2023, scientific output exhibited steady growth, with 84 articles already published in the first half of 2024, indicating that annual output will likely continue to rise. This growth may be due to increasing attention on ICD and the expanding potential of immunotherapy in breast cancer treatment. Notably, fluctuations in citation counts in earlier years could reflect shifts in research focus, the emergence of new subfields, or temporary changes in publication and citation behaviors. While the average number of citations per article has declined since 2020, this does not necessarily indicate a drop in quality but may instead result from the higher volume or publications, reducing the average citation frequency per paper.

At the author and country/region levels, significant collaboration between China and the United States reflects the strong academic ties between the two countries. Among contributing authors, the research group led by

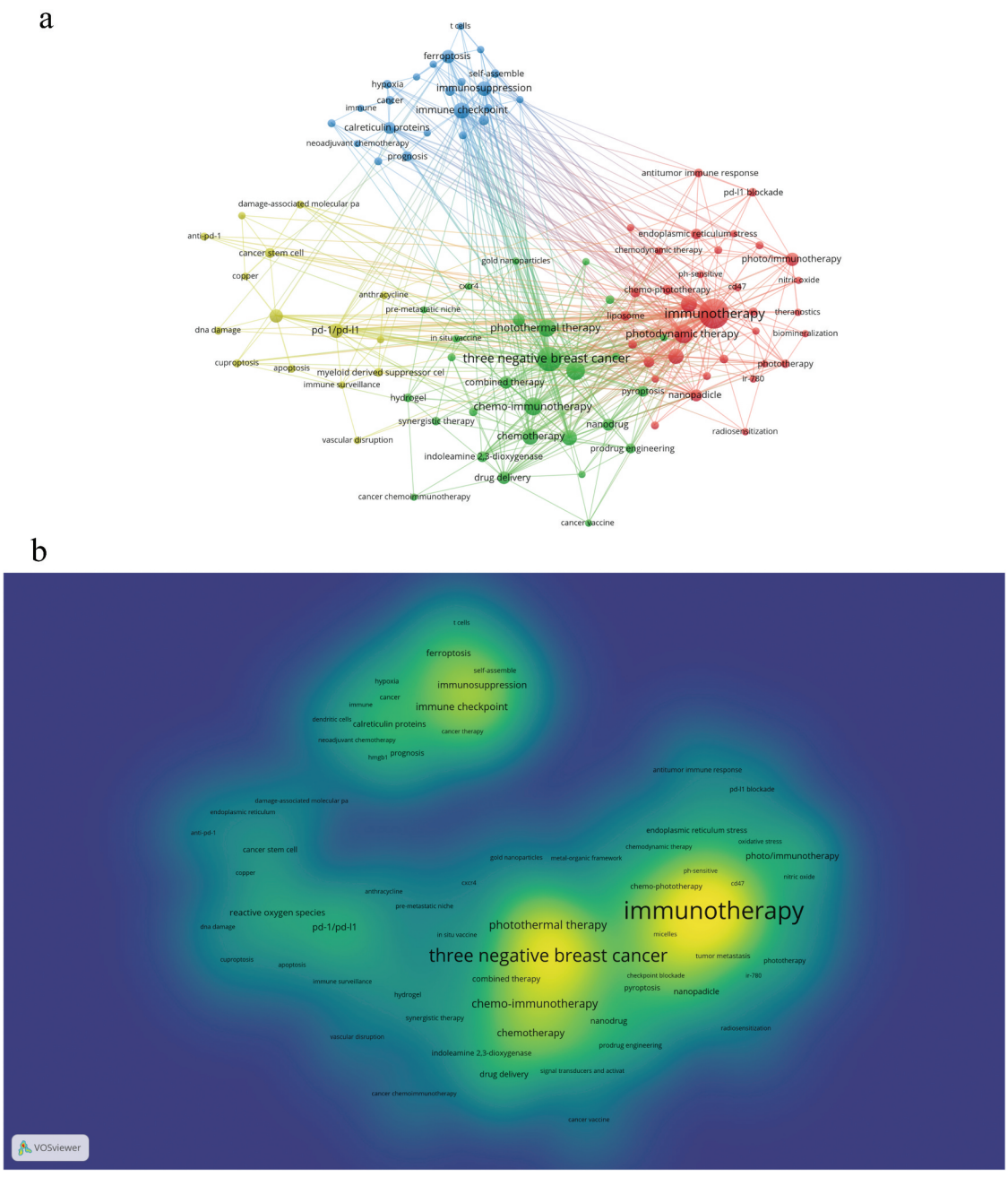

Figure 8. Author keyword clustering visualization in breast cancer and ICD research. (a) Network visualization of author keyword clusters; (b) Heatmap visualization of author keyword clusters.

Huang Y has made substantial contributions, demonstrated by a high H-index. Their work focuses on enhancing ICD efficacy and modifying the tumor immune microenvironment through approaches such as nano-drug delivery, tumor-associated macrophages (TAMs) repolarization, stress granule inhibition, and hydrogel-based drug release. Notably, their studies on autophagy regulation to improve endoplasmic reticulum-targeted therapy offer novel insights with considerable academic and clinical value.[47–54]

In terms of global contributions, a diverse landscape has emerged: China leads in output, the United States offers robust support, and many other countries actively participate. This pattern likely stems from increased policy support, significantly increased research funding, and improvements in research infrastructure across nations. Moving forward, enhancing international cooperation and fostering innovative, high-quality research will be key to the sustainable advancement of this field.

Leading journals have played a major role in disseminating high-quality research on breast cancer and ICD, with the number of related publications growing steadily each year. This trend underscores the academic value and influence of this research area. Our three-field analysis (Supplementary Figure S4) indicates that journals such as *Journal of Controlled Release*, *ACS Applied Materials & Interfaces*, and *Small* are prominent publication channels for Chinese corresponding authors. In particular, immunotherapy targeting TNBC remains a high-priority research

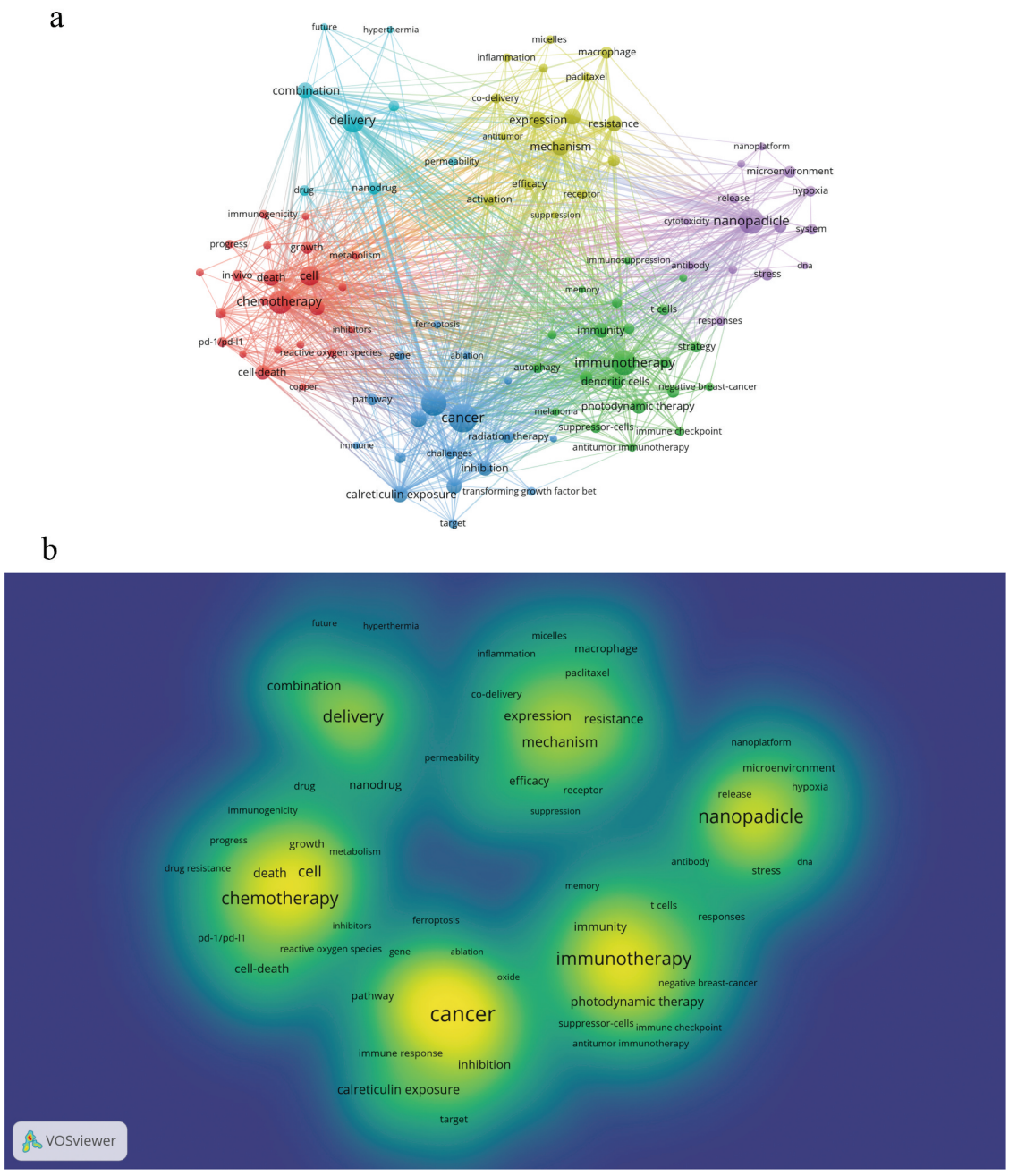

Figure 9. Visualization of keyword PLUS clustering in breast cancer and ICD research. (a) Network visualization of keyword PLUS clustering; (b) Heatmap visualization of keyword PLUS clustering.

direction that attracts considerable attention and investment. Researchers can improve their research positioning, select appropriate journals for submission, and better understand trends and developments by aligning their work with this context.

Furthermore, the dual-map overlay analysis highlighted dynamic changes in academic journal distributions and citation patterns within this field. Cross-disciplinary citation relationships between citing and cited journals emphasize increased knowledge exchange across fields, particularly the growing role of immunology in understanding ICD mechanisms. This trend points to the value of interdisciplinary collaboration in driving further breakthroughs in breast cancer research.

An in-depth review of highly cited papers in this domain revealed three primary research themes. First, many studies investigate the mechanisms and effects of utilizing various nanomedicines to induce ICD in breast cancer.[35–37,39,42–44] Second, enhancing anti-tumor immune responses to trigger ICD is seen as a more efficient strategy, reinforcing the critical role of immunotherapy.[38,40] Third, inhibiting CDK12/13 (cyclin-dependent kinases 12 and 13) has been shown to trigger DNA damage responses, induce ICD, and enhance the effectiveness of anti-PD-1 therapy.[41] Collectively, these highly cited articles

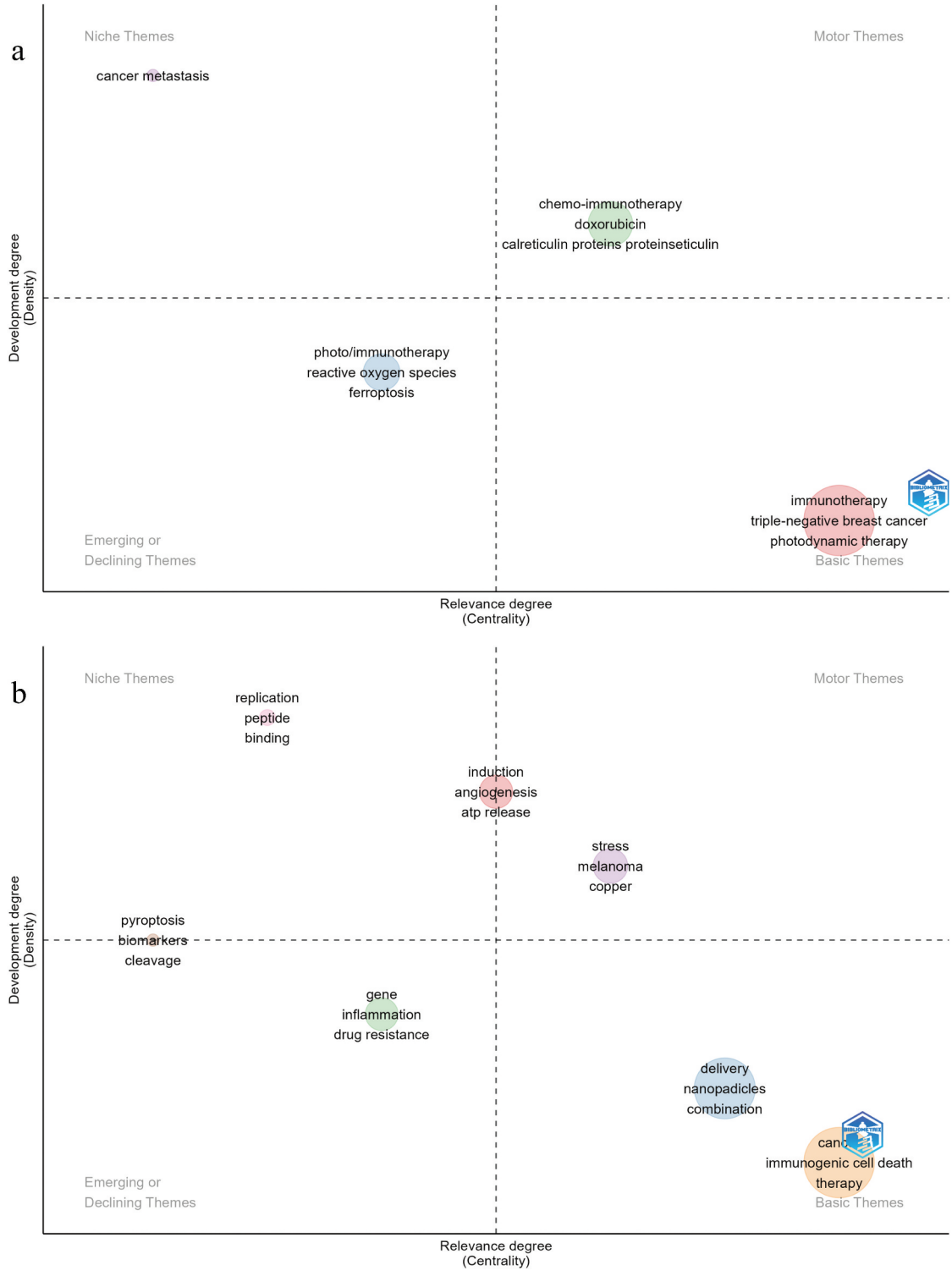

Figure 10. Topic mapping in the research field of breast cancer and ICD. (a) Author keyword topic map; (b) Keyword plus topic map.

deepen our understanding of breast cancer and ICD, not only improving our understanding of this complex disease process but also providing valuable scientific evidence for future clinical treatment and drug development.

The combination of chemotherapy and immunotherapy has emerged as a core strategy in breast cancer treatment, demonstrating remarkable efficacy by inducing ICD to enhance antitumor immune responses. Concurrently, the investigation of key proteins such as calreticulin offers new perspectives for developing highly potent and less toxic combination therapies, marking a prominent area of research requiring further advancement.

Studies have shown that chemotherapy alone still faces numerous challenges, including toxicity to normal cells, multidrug resistance, side effects, and limitations in clinical application.[55] However, chemo-immunotherapy has demonstrated the potential to overcome these issues effectively. Notably, cytotoxic agents such as doxorubicin (DOX) can

enhance immune responses by inducing ICD, establishing themselves as promising agents in breast cancer treatment.[56] To To optimize the combined use of chemotherapy and immunotherapy, various technologies have been developed to reduce toxicity and improve efficacy.[57]

For instance, DOX-loaded nanogels, liposomes, and micelles, when used in combination with immune checkpoint inhibitors (e.g., anti-PD-1/anti-PD-L1), can promote ICD and elicit strong anti-tumor immune responses, showing notable efficacy against TNBC and other breast cancer subtypes.[57,58] One study reported that combining DOX with crizotinib prodrug micelles synergistically induced ICD in breast cancer models.[59] Moreover, a DOX – indocyanine green (ICG) conjugate linked by a hydrazone bond (DOX-ICG) has been observed to induce robust ICD in neoplastic cells. When used in combination with immune checkpoint inhibitors, this conjugated drug can effectively suppress both primary and metastatic tumor growth.[60]

Other promising studies include nano-regulatory strategies targeting PD-L1. For example, PD-L1 inhibitor (FRS) nanoparticles, in combination with DOX, have been shown to reduce PD-L1 expression and induce ICD.[61] Advanced research has also introduced hybrid lipid nanobubbles loaded with drugs (LEV@DOX@REV), formed by fusing cell membranes, phospholipids, DOX, and REV, enabling precise tumor targeting and facilitating chemo-immunotherapy delivery.[62]

Recent studies also support the efficacy of combining paclitaxel with resiquimod, demonstrating potent chemo-immunotherapeutic effects. pH-sensitive nanoparticles further enhance this efficacy, underscoring their potential in multidimensional combination therapy.[63] Paclitaxel-loaded micelles, in particular, have shown great potential in enhancing ICD and improving treatment for metastatic TNBC.[37] Additionally, combining losartan with chemo-immunotherapy significantly improved therapeutic outcomes in TNBC.[64] Zhao Q and colleagues that using doxorubicin hydrochloride liposomes (DOX-L) with losartan (losartan + DOX-L + α-PD1) enhances the effect of α-PD1 by depleting tumor stroma.[64] Meanwhile, genetically engineered oncolytic viruses combined with melittin-CpG have also been investigated as part of viral chemo-immunotherapy for cancer.[65]

Calreticulin has emerged as a critical marker of immune response in breast cancer and represents a key focus in this domain. Its value lies in informing the development of combined chemotherapy and immunotherapy strategies.[66] Research by Luo JQ et al. showed that employing nanoparticles to block CD47-SIRPα interactions and induce calreticulin exposure can significantly boost responses to chemo-immunotherapy.

Overall, these studies illustrate major trends and advancements in breast cancer and ICD research, particularly the integration of chemotherapy and immunotherapy. They also offer valuable guidance for the development of effective, well-tolerated combination therapies, highlighting opportunities for further research. A thorough understanding of influential factors such as chemotherapy, immunotherapy, and ICD can help future researchers better grasp current developments and anticipate future directions in breast cancer treatment. Immunotherapy, photodynamic therapy, and TNBC remain key research foci in this field, offering promising pathways to trigger anti-cancer immune responses, including ICD. These strategies are especially relevant for the treatment of difficult TNBC cases, reflecting emerging research trends. Numerous studies have shown that immunotherapies – including checkpoint inhibitors like anti-PD-1 and anti-CTLA-4 and therapeutic vaccines such as NeuVax, MUC-1, AVX901, INOS-1400, and CEA – can effectively induce ICD and are innovative approaches to breast cancer management.[67,68]

According to research by Li XX et al. combining immune checkpoint inhibitors with oleandrin-induced endoplasmic reticulum (ER) stress could enhance immune-mediated eradication of breast cancer cells via ICD.[69] Dendritic cell (DC) vaccines have also demonstrated significant antitumor effects in clinical trials.[70] As an example, HELA-Exos have been shown to induce ICD in breast cancer cells, unveiling tumor antigens. When paired with Hiltonol, this combination locally activates type 1 conventional dendritic cells (cDC1) in a localized manner and stimulates CD8+ T cell responses, resulting in substantial tumor inhibition in both TNBC xenografts and patient-derived organoids.[71] Additionally, chimeric antigen receptor (CAR)-T cells[72] equipped with genetically engineered receptors can effectively recognize and attack tumor cells expressing specific target antigens. Research by Shivani S et al. suggests that combining Ox/Cy with anti-PD-L1 may synergistically improve CAR-T efficacy and survival outcomes.[73]

Photodynamic therapy is a novel modality, distinct from surgery, chemotherapy, and radiotherapy, which eradicates through unique physicochemical mechanisms. This therapy offers great promise for breast cancer diagnosis and treatment.[74] It works by generating cytotoxic reactive oxygen species, especially singlet oxygen (1O2), to kill tumor cells.[75] Studies have also shown that combining photodynamic therapy with herbal remedies can induce death through multiple mechanisms, including apoptosis, necrosis, autophagy, and cell cycle modulation.[76]

Pan WL et al. developed a nanoscale metal-organic framework coated with cancer cell membranes that integrates photodynamic therapy and chemotherapy for targeted breast cancer therapy, successfully inhibiting tumor growth.[77] Additional research has explored the antiangiogenic and photodynamic effects effects and antiangiogenic activity of parietin liposomes in TNBC,[78] the use of Rose Bengal (RB) with green lasers,[79] and zinc porphyrin (Zn[TPP]) encapsulated in MIL-101 (Zn[TPP]@MIL-101) for photodynamic therapy under red light-emitting diode irradiation to eliminate MCF-7 breast cancer cells.[80] Other studies have used miRNA-guided zinc(II)-protoporphyrin metal-organic framework nanoparticles for image-guided photodynamic therapy.[81] Cen et al. also reported that combining thermally responsive palladium-ruthenium nanoenzymes with photodynamic therapy is highly effective against metastatic breast cancer.[82]

In sum, research is increasingly focused on enhancing breast cancer immunotherapy particularly in TNBC, by inducing ICD. While significant progress has been made in understanding the synergy between immunotherapy and photodynamic therapy, the field remains under developed

and warrants further exploration. These underexplored areas may offer new directions for future research on breast cancer and ICD.

Cancer metastasis, a key prognostic factor, remains the leading cause of mortality in breast cancer patients.[83] However, it remains a relatively underrepresented topic in ICD research. Metastasis often involves spread to lymph nodes or distant organs, driven by mechanisms such as epithelial – mesenchymal transition (EMT) and epigenetic regulation within the tumor microenvironment, which increase the treatment resistance of breast cancer.[84] Currently studies primarily address metastatic breast cancer through targeted ICD induction via nanomedicine.[85–87] Although gaining attention, the topic is not yet a central focus and would benefit from broader exploration.

Meanwhile, phototherapy combined with immunotherapy, reactive oxygen species, and ferroptosis represent emerging or declining peripheral themes. While preliminary research suggests that integrating light-based therapies, oxidative stress, and regulated cell death mechanisms can enhance ICD in cancer,[88–90] the detailed exploration of their combined effects have only been documented in a single study.[91] Whether these themes will gain prominence or fade from future research remains to be seen.

To gain deeper insight into the efficacy and challenges of ICD-based therapies in breast cancer, we analyzed clinical trials registered on ClinicalTrials.gov (https://clinicaltrials.gov/). A search conducted on April 10, 2025, using the terms "[Condition/disease: Breast Cancer]" and "[Other terms: Immunogenic Cell Death]" identified 16 relevant clinical trials, four of which had been completed. One notable completed trial was the "ICE Study" (NCT05727813), which evaluated the efficacy and safety of ultrasound-guided cryoablation for inducing ICD in early-stage breast cancer. The results indicated that cryoablation was well tolerated, effective, and safe, with high patient satisfaction. Magnetic resonance imaging (MRI) and contrast-enhanced mammography accurately predicted the procedure's technical success, suggesting that cryoablation may serve as a viable alternative to surgery in selected patients.[92]

Another completed trial investigated the combination of atezolizumab (anti-PD-L1) with immune-stimulating chemotherapy in patients with mTNBC. Participants received pegylated liposomal doxorubicin and low-dose cyclophosphamide combined with either atezolizumab or placebo. The addition of atezolizumab improved progression-free survival compared to placebo, demonstrating both clinical benefit and tolerability for this combination therapy.[93]

These clinical trial results underscore the potential of ICD-inducing therapies in breast cancer treatment, particularly when used in combination with immunotherapy. However, significant challenges remain, such as drug toxicity, patient heterogeneity, and the emergence of drug resistance.

From the author's perspective, this study highlights the vast potential of ICD-related research in shaping the future of breast cancer therapy. It illuminates current gaps in knowledge – especially concerning the clinical application of novel therapies such as photodynamic and immunotherapies – and explores the evolving understanding of the mechanisms underlying these gaps through rigorous experimental and clinical investigations.

Looking ahead, with growing international cooperation, substantial progress is likely in this field over the next five years. This includes not only closing existing knowledge gaps but also driving translational breakthroughs. Continued advancements in immunotherapy, the integration of diverse therapeutic approaches, and the incorporation of multi-omics data and artificial intelligence are expected to shift the paradigm of breast cancer treatment toward precision medicine. As research deepens, transformative developments in our understanding of ICD are likely, paving the way for the development of more effective and personalized therapeutic strategies for breast cancer patients.

Limitations

While bibliometric analysis serves as a powerful tool for summarizing and integrating research trends, it is not without limitations. First, this study relied primarily on the WOSCC, which may have led to the exclusion of relevant literature, as this database is not specifically optimized for bibliometric purposes. This limitation introduces the potential for systematic errors. Additionally, the analysis included only articles, excluding other publication types such as reviews, conference proceedings, and gray literature, potentially omitting valuable insights.

Second, the study was limited to English-language publications, thus excluding high-quality research published in other languages. Variability in keyword selection may also affect the accuracy and comprehensiveness of the results. Additionally, because the study focused exclusively on breast cancer and ICD within a specific time period, it may not fully reflect the most recent research frontiers or emerging trends. Updates to the database after the search date may further affect the timeliness of the findings.

To address these limitations, future studies should consider combining bibliometric analysis with other approaches such as systematic reviews or meta-analyses. Validation using multiple databases (e.g., PubMed, Scopus, and Google Scholar), broader inclusion criteria for literature types, and multi-language retrieval strategies can expand the literature scope. Regularly updating bibliometric analyses will also help ensure more accurate, comprehensive, and current assessments of developments in breast cancer and ICD research. These methodological refinements will enhance the reliability of future analyses and promote a deeper understanding of the field.

Conclusion

This study is the first to apply bibliometric methods to analyze the rapidly expanding research landscape related to ICD in breast cancer. It reveals a sharp increase in scientific output, marked by notable collaboration between Chinese and American scholars. Influential studies have been published in leading journals such as *Biomaterials*, significantly contributing to theoretical innovation and knowledge accumulation. Core contributors, notably the team led by Huang, have introduced new concepts and research directions for breast cancer treatment.

Despite this progress, substantial challenges persist. The clinical application and mechanistic understanding of

emerging therapies – particularly photodynamic therapy and immunotherapy – remain limited, necessitating systematic investigation and extensive validation. Deepening foundational and clinical research, enhancing interdisciplinary cooperation, and elucidating the mechanisms linking breast cancer and ICD are essential for fostering innovation in treatment strategies and improving therapeutic efficacy.

Acknowledgments

All authors would like to thank the "Guangxi Zhuang Autonomous Region Clinical Medicine Research Center for Molecular Pathology and Intelligent Pathology Precision Diagnosis" for providing relevant technical support.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This work was supported by the Fund of Guangxi Medical University Teacher Teaching Ability Development Project (2202JFA02); Guangxi Medical University Undergraduate Education and Teaching Reform Project (2023Y05); Guangxi Higher Education Undergraduate Teaching Reform Project (2022JGA146); Guangxi Educational Science Planning Key Project (2022ZJY2791); China Undergraduate Innovation and Entrepreneurship Training Program (202410598035); Future Academic Star of Guangxi Medical University (WLXSZX24076).

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Yu-Long Deng, Bang-Teng Chi, and Shang-Yi Lu drafted the manuscript. Yu-Long Deng and Dan-Dan Xiong designed the study. Yu-Long Deng and Bang-Teng Chi were responsible for data collection and statistical analysis. Rong-Quan He, Di-Yuan Qin, Wan-Ying Huang, Xia Yang, Gang Chen, Wei Peng, and Jiayuan Luo revised the manuscript and all authors agreed to be responsible for all aspects of the study. All authors read and approved the final manuscript.

Data availability statement

The data/supplementary materials/citations in the article are sourced from public databases.

Ethics approval

No animal or human studies were carried out by the authors of this article.

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