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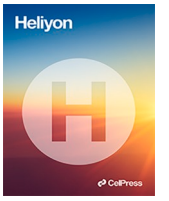

Research article

Bibliometric insights into drug resistance in bladder cancer: Two decades of progress (1999–2022)

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ABSTRACT

Aims: To provide a comprehensive bibliometric overview of drug resistance in bladder cancer (BC) from 1999 to 2022, aiming to illuminate its historical progression and guide future investigative avenues.
Methods: Literature on BC drug resistance between 1999 and 2022 was sourced from the Web of Science. Visual analyses were executed using Vosviewer and Citespace software, focusing on contributions by countries, institutions, journals, authors, references, and keywords.
Results: From 2727 publications, a marked growth in BC drug resistance studies was discerned over the two decades. Prominent among all institutions is the University of Texas System. The majority of top-ranked journals were American. In authorship significance, McConkey DJ led in publications, while Bellmunt J dominated in citations. Research topics predominantly spanned cancer demographics, drug efficacy evaluations, molecular features, oncology subtypes, and individualized treatment strategies, with a notable contemporary emphasis on molecular mechanisms behind drug resistance and nuances of ICIs.
Conclusions: Our bibliometric analysis charts the landscape of BC drug resistance research from 1999 to 2022. While the study of resistance mechanisms has been robust, there's an evident need for deeper exploration into the molecular intricacies and the potential of ICIs and targeted therapeutic strategies.

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1. Introduction

Bladder cancer (BC) is the most common malignant tumor in the urinary system [1]. Pathological types of most bladder tumors are urothelial carcinoma, which can be divided into non-muscular invasive bladder cancer (NMIBC) and muscular invasive bladder cancer (MIBC) according to the depth of muscle invasion. While NMIBC encompasses approximately 75–85 % of the new cases, MIBC and its metastatic counterpart represent about 25 %, often portending an unfavorable clinical trajectory [2,3].

The transurethral resection of bladder cancer (TURBT) in conjunction with intravesical Bacillus Calmette-Guerin (BCG) instillation is the clinically recommended initial treatment for NMIBC [4–6]. Despite the potential for cure in 35 % of BCG patients, treatment resistance will cause 40–60 % to experience tumor relapse within two years [7]. Cisplatin-based chemotherapy, manifested as MVAC, CMV, or GC regimens, is the gold standard for people suffering from MIBC or metastatic stage [8]. Cisplatin is rapidly being employed as a neoadjuvant, adjuvant, and radiation treatment [9]. However, the underlying challenge persists: A significant proportion of patients who develop resistance, recurrence, or metastasis have an extremely grim prognosis for cisplatin drug as the cornerstone of treatment [8,10]. This chemoresistance critically modulates the therapeutic outcomes and the future trajectory for BC patients.

The quagmire of BC resistance is multifaceted, encompassing cisplatin-centric resistance, gemcitabine-mediated resistance, adaptive immune backlash to intravesical BCG, and resistance against targeted therapeutic agents [11]. Thus, Understanding the mechanisms of medication resistance is essential for improving the treatment regimen and prolonging the lifespan of BC patients. The rising prevalence of drug-resistant BC poses a significant challenge in clinical oncology, underlining the urgency for in-depth research in this area. Epigenetic alterations exert a substantial influence on the development of drug resistance and the prognosis of BC patients. These alterations, including the expression of specific microRNAs, have been increasingly recognized as key factors in the resistance mechanisms. Improved prognosis is associated with increased sensitivity to cisplatin, which is caused by increased expression of miR-374a, and overexpression of miR-424 reduces cisplatin sensitivity and predicts an unfavorable outcome in bladder cancer [12]. In BC cells, cisplatin sensitivity is correlated with the expression of the gene heterogeneous nuclear ribonucleoprotein U (HNRNPU), and suppression of HNRNPU could be a potential strategy to improve the prognosis of cisplatin-resistant BC patients [13]. These insights underline the critical need for continued research into the molecular underpinnings of drug resistance in BC, which our bibliometric analysis aims to illuminate. Some scholarly endeavors postulate that adaptive immune resistance might be the linchpin behind the inefficacy of intravesical BCG [14]. Concurrently, several studies propose that cisplatin resistance is primarily caused by accelerated DNA rectification, enhanced drug efflux, decreased influx, and incompetence in inflicting DNA damage [15].

Recently, bibliometrics has burgeoned as an incipient discipline, leveraging mathematical and statistical tools to quantitatively dissect the vast expanse of literature [16]. This approach, supplemented by visualization modalities such as cluster analyses and mapping, offers insights into the pivotal contributions from nations, academic institutions, individual researchers, and esteemed journals in specific scientific arenas. Such methodologies shed light on research epicenters and evolving trends [17–19]. VOSviewer and CiteSpace are commonly used software for bibliometric visual analysis [17,19]. Notably, a glaring lacuna exists: the absence of a visual bibliometric analysis focused on BC drug resistance. There is an undeniable imperative to holistically comprehend the intricate tapestry of BC resistance and the associated research momentum.

In this light, our study embarks on an endeavor to harness tools like VOSviewer and CiteSpace, aiming for a panoramic bibliometric

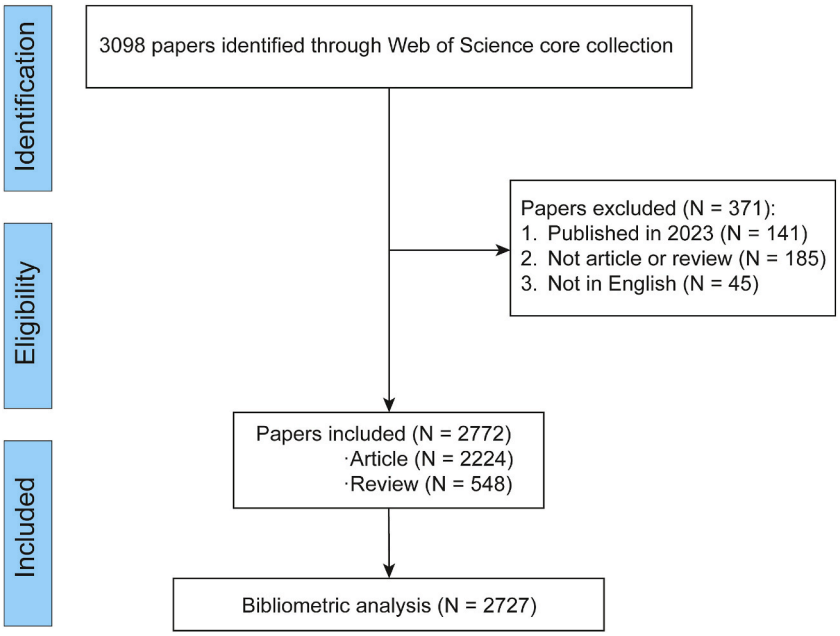

Fig. 1. Flow chart of the literature extracted from the database.

visualization of publications spanning from 1999 to 2022 on BC drug resistance. We aspire to illuminate the contemporary findings, zero in on research epicenters, and carve a roadmap for future explorations in this domain.

2. Methods

2.1. Data acquisition and analytic framework

To conduct this bibliometric investigation, we sourced scholarly articles from the Web of Science Core Collection (WoSCC). Our choice of WoSCC as the primary database is substantiated by its extensive representativeness and fidelity, especially concerning its applicability to visual bibliometric analyses, as corroborated by existing literature [20].

2.2. Search strategy and query formulation

The searching terms are as follow: Topic = ((bladder) NEAR/1 (cancer* OR tumor* OR tumour* OR oncology OR neoplasm* OR carcinoma*)) AND Topic = ((resist*) OR (drug resist*) OR (medicine resist*) OR (agent resist*)). To ensure the data's the accuracy and the research's consistency, the data was downloaded and analyzed by two separate researchers on July 9, 2023. Initially, 3098 results were obtained by analyzing the search terms related to bladder cancer drug resistance from 1999 to 2022 in the Web of Science Core Collection database. We excluded conference abstracts, editorials, letters, and non-English articles, aiming for a comprehensive collection of original research articles and reviews. This was done to ensure that our analysis was focused on comprehensive and substantive contributions to the field. Finally, a total of 2727 articles were collected and analyzed (Fig. 1).

2.3. Quantitative assessment and forecasting models

The yearly distribution of the publications was scrutinized and quantified utilizing Microsoft Office Excel 2019 (Microsoft, Redmond, WA, USA). We employed a polynomial regression model to project the future trajectory of publications in this domain. A coefficient of determination (R^2) closer to one was interpreted as indicative of a robust model fit. Furthermore, the H-index was utilized as a composite metric for gauging both the volume and the impact of the academic contributions, with higher H-index values denoting a greater scholarly influence [21].

2.4. Network visualization and interconnection analysis

For the generation of network visualizations and to examine latent relationships within the dataset, two bibliometric mapping software systems were employed. CiteSpace (Version 6.2.4) was deployed for constructing visual analytics focusing on institutional affiliations, journal distribution, and citation bursts with significant impact. Concurrently, VOSviewer (Version 1.6.19) was used to create visual networks of nations, author/co-citation author matrices, journals, key terminologies, and co-citation references.

3. Results

3.1. Temporal evolution of BC drug resistance publications

As depicted in Fig. 1, a total of 3098 articles were collected through WOSCC, and our primary documents are article and reviews written in English. A total of 2727 articles were obtained for the next bibliometric analysis.

Using sophisticated analytical techniques, a temporal trajectory of publications between 1999 and 2022 was plotted ($R^2 = 0.9669$). Fig. 2 showcases an uptick in publication volume, with a modest growth between 1999 and 2015, subsequently catapulting from 2016 onwards, peaking noticeably in 2016. The significant increase in the number of publications in 2016 can be attributed to several pivotal developments in the field of bladder cancer (BC) treatment and research. Primarily, this surge was catalyzed by the FDA

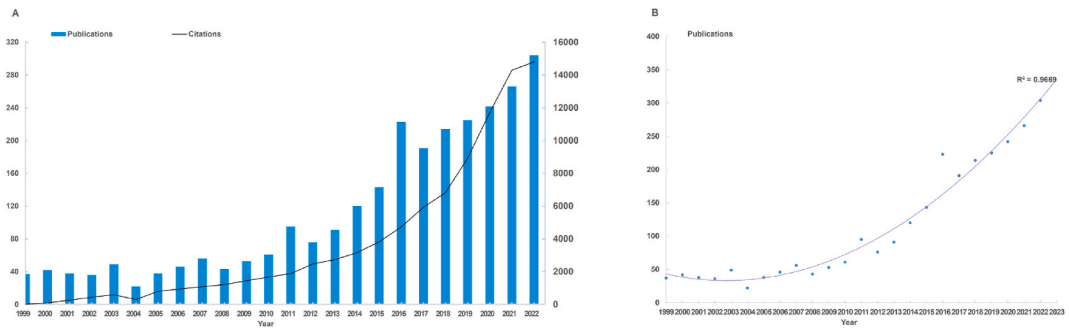

Fig. 2. Global annual patterns in publications and citations (A). The growth trend of the number of publications from 1999 to 2022 (B).

approval of Tecentriq (atezolizumab), the first immunotherapy drug for BC, in 2016. This milestone set off a research upsurge in BC drug treatment and concurrently spurred investigations into BC drug resistance [22]. Additionally, this period marked an increasing focus on personalized medicine and targeted therapies in oncology, particularly in the realm of BC, further driving research interest in understanding and overcoming drug resistance. The advent of next-generation sequencing (NGS) technologies and their increasing application in cancer research around this time also likely contributed to the heightened research activity, as these technologies have enabled more in-depth studies into the genetic and molecular underpinnings of drug resistance in BC. This ascension in publication and citation frequency corroborates the escalating prominence of BC drug resistance in contemporary research circles, suggesting a fertile landscape for future inquiries into therapeutic resistance mechanisms in BC.

3.2. Geographic dispersion and collaborations in BC drug resistance

Table 1 enumerates the top 10 prolific countries/regions steering BC drug resistance research. China's colossal contribution is underscored by 949 papers from 1999 to 2022, underlining BC drug resistance as a burgeoning research paradigm within the nation. Evidently, China's research corpus boasts the most citations and a commendable total link strength (TLS), signifying China's authoritative stance in this domain. The US, besides being prolific, also possesses superior academic traction reflected by its impressive citations, TLS, and H-index. UK and France also merit attention given their influential citations and academic credence.

Fig. 3 offers a visual representation of international collaborations and year-on-year publication trends. Fig. 3A shows the international cooperation map in the field of BC drug resistance, with China and the USA exhibiting a relatively high cooperating. In the annual analysis (Fig. 3B), the quantity of articles published in China has increased annually and surpassed USA in 2017. The increase in China's contributions can be attributed to a combination of factors. These include heightened scientific research investments, the cultivation of scientific research personnel, enhanced promotion of university institutions, and a marked increase in international collaborations. China's research advancements have been particularly notable in the study of the mechanisms underlying drug resistance and strategies for its reduction. This includes seminal work on resistance to cisplatin and immune checkpoint blockade (ICB), where studies have identified key molecular players such as metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), exosome derived from cancer-associated fibroblasts (CAF-Exo), and BCAT2. Furthermore, innovative approaches to reduce drug resistance have been proposed in highly cited Chinese research, including Lysosome-targeting self-assembling prodrugs and Knockdown of IGF-IR [23–27]. These contributions underscore China's growing influence in the global landscape of BC drug resistance research, driven by its strategic focus on oncology and increasing integration with the international scientific community. In other countries, the data also showed an upward trend, indicating that the research in this field is increasing globally. Fig. 3C shows that countries have a concentrated research cooperation network in this field, among which the United States has a large number of publications, and its cooperation network with other countries is closer and more frequent, indicating that the United States severs as a link role. Globally, an upward trajectory in publications speaks volumes about the global commitment to unraveling the complexities of BC drug resistance.

3.3. Institutional prowess in BC drug resistance research

Table 2 reveals that the top 10 institutions are from China and the USA, and USA institutions occupies a position of dominance. University of Texas System has published the most articles in the field, and it also has the highest Central (0.22) and total citations (8445). The top Chinese institution was Sun Yat Sen University, with a total of 1265 citations. Fig. 4 illustrates the co-occurrence of cooperative networks among the institutions. Intensive cooperation network can be seen between institutions. University of Texas System, University of California and Harvard University have a certain bridge effect.

3.4. Journal landscape in BC drug resistance research

The top ten journals in this field were listed in Table 3, they were mainly from the United States. Among them, Oncotarget had the largest number of publications (71). The journal with the highest IF is Clinical cancer research, so it has relatively high reference value.

Table 1
Top 10 productive countries/regions related to bladder cancer drug resistance.

Rank	Country/regions	Count	TLS	Total citations	H-index	Average citation per paper
1	China	949	205	23666	69	24.91
2	USA	800	566	44455	95	55.49
3	Japan	256	122	7450	45	29.29
4	Germany	174	201	6671	37	38.34
5	United Kingdom	173	199	11641	44	67.28
6	Italy	142	206	6412	36	45.15
7	Canada	114	167	5227	40	45.55
8	South Korea	96	51	3019	30	31.45
9	France	77	159	5636	27	73.19
10	Spain	65	114	2942	23	45.26

TLS: total link strength.

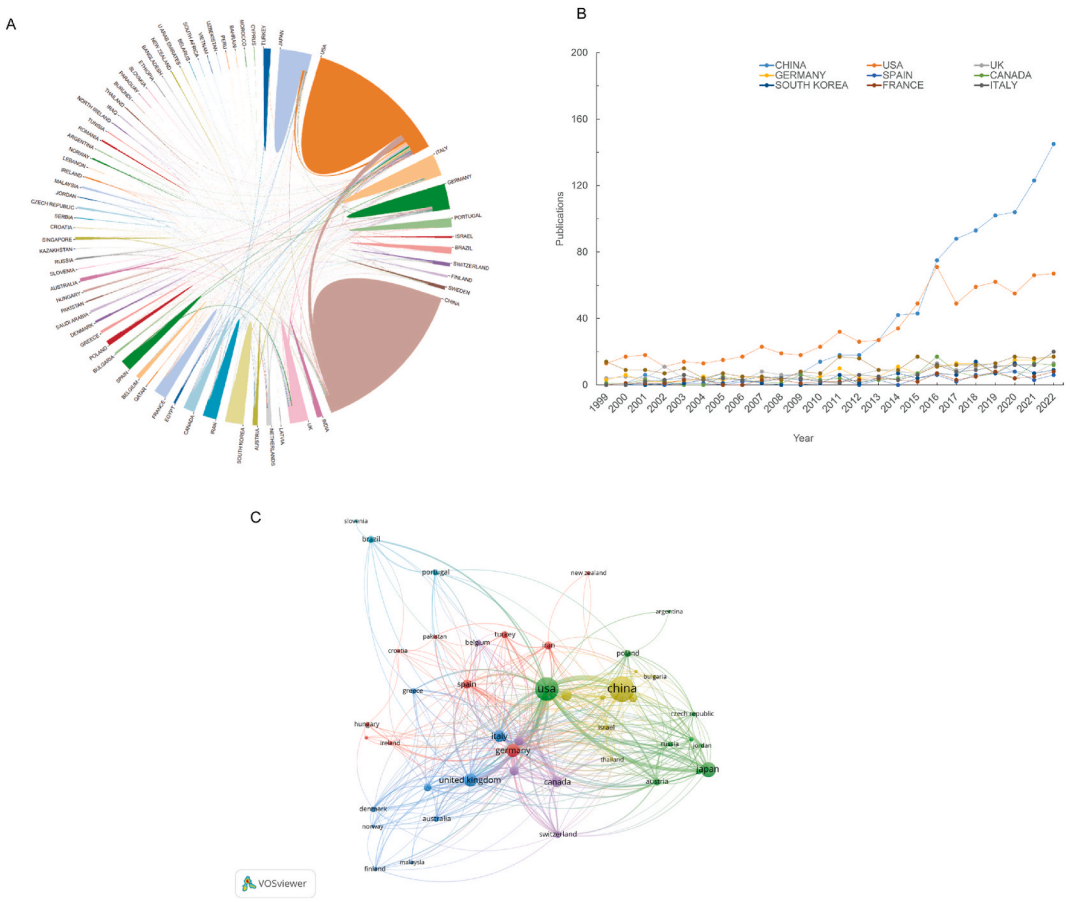

Fig. 3. The visualization of National article publication and cooperation network (A). Statistics of annual publication volume of top10 countries from 1999 to 2022 (B). The visualization of the co-publications network (C). (A) Different colored fan shaped parts represent different countries. The area of the fan shaped region represents the number of publications. The lines between countries reflect their collaborative relationships. (C) Minimum number of documents of a country are 5. The size of a node represents the number of occurrences. countries with the same node color are a small group. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 2
Top 10 institutes related to bladder cancer drug resistance.

Rank	Institutions	Countries/regions	Count	Central	Total citations
1	University of Texas System	United States	142	0.22	8445
2	UTMD Anderson cancer center	United States	106	0.06	6704
3	University of California	United States	77	0.22	5192
4	Sun Yat Sen University	China	49	0.02	1265
5	China Medical University	China	49	0.00	1119
6	Johns Hopkins University	United States	48	0.06	1661
7	Harvard University	United States	44	0.15	2187
8	Cornell University	United States	33	0.01	901
9	Memorial Sloan Kettering cancer center	United States	32	0.05	4059
10	Shanghai Jiao Tong University	China	32	0.02	1191

As shown in Fig. 5A, oncotarget, international journal of molec and clinical cancer research have close cooperative relationships with other major journals. Fig. 5B is the dual map of journals, showing the relationship between citing journals (left) and cited journals (right) via ($z = 7.0878725$, $f = 38598$) and ($z = 3.4534636$, $f = 19486$) respectively. The papers that appeared in molecular/biology/genetics or health/nursing/medicine journals were cited by molecular/biology/immunology or medicine/medical/clinical, and suggested that BC resistance researches are primarily focus in the mechanism research.

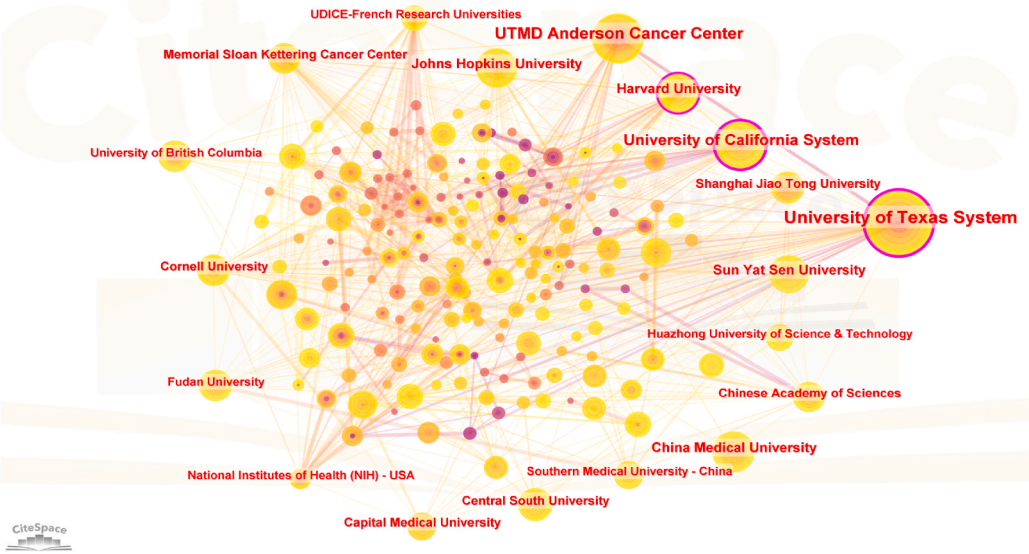

Fig. 4. The visualization of institution's cooperation network. Each node represents an institution. The size of node indicates how much the institution has published. The lines between Institutions reflect their collaborative relationships. Institutions with purple circles indicate that their betweenness centrality is high, and they have a certain bridge effect. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 3
Top 10 Journals related to the research of bladder cancer drug resistance.

Rank	Journal title	Countries	Count	IF (2022)	JCR	TLS	Total citations
1	Oncotarget	United States	71	0.000	Q2	203	2617
2	International journal of Molecular sciences	United States	66	6.208	Q1	225	950
3	Cancers	Switzerland	64	6.575	Q2	181	754
4	Clinical cancer research	United States	56	13.801	Q1	226	5745
5	Journal of urology	United States	53	7.600	Q1	173	1642
6	Urologic oncology-seminars and original investigations	United States	47	2.954	Q2	151	627
7	Oncology reports	Greece	44	4.136	Q2	125	775
8	Plos one	United States	43	3.752	Q2	110	1278
9	Frontiers in oncology	Switzerland	39	5.738	Q2	104	452
10	Anticancer research	Greece	39	2.435	Q4	100	695

TLS: total link strength.

3.5. Authorial and Co-citation insights

A total of 15114 authors contributed to the writing of these 2727 articles, and the relevant information is shown in Table 4. McConkey DJ has published the most articles (28) and has produced the most citations (2,770) in terms of the quantity of articles publication. As shown in Fig. 6A, the cooperative network among the authors is not as tight as we might expect. Among them, McConkey DJ and Black PC published 28 and 21 articles respectively, and TLS was 91 and 81 respectively. Their publication quantity and TLS exhibited a notable performance, which enabled them to become the link in the author cooperation network. Co-cited authors were further analyzed, and the results are shown in Fig. 6B. Bellmunt J is the most cited author with 392 citations, and its TLS is also the highest (6877). In addition, both Won der maase H and Powles T were cited more than 250 times, and their TLS was similarly excellent.

3.6. Citation landscape analysis

The documents commonly cited in papers in this field is called co-cited references. The top 10 cited literatures are shown in Table 5. The article with the most citations was "Cancer statistics, 2014", which was published by Rebecca Siegel MPH in "CA - A Cancer Journal for Clinicians" in 2014 and had 235 citations. Its primary focus was on cancer statistics, which paved the way for research into BC drug resistance. It is observed that the top 10 most cited articles were from CA-A Cancer Journal for Clinicians, Nature, Clinical Oncology, Cell, Lancet, New England, Cancer Cell and European Urology.

As shown in Fig. 7, VOSviewer software was used to analyze co-cited references. It can be observed that the citation between references was frequent and intense. "Comprehensive molecular characterization of urothelial bladder carcinoma", which was

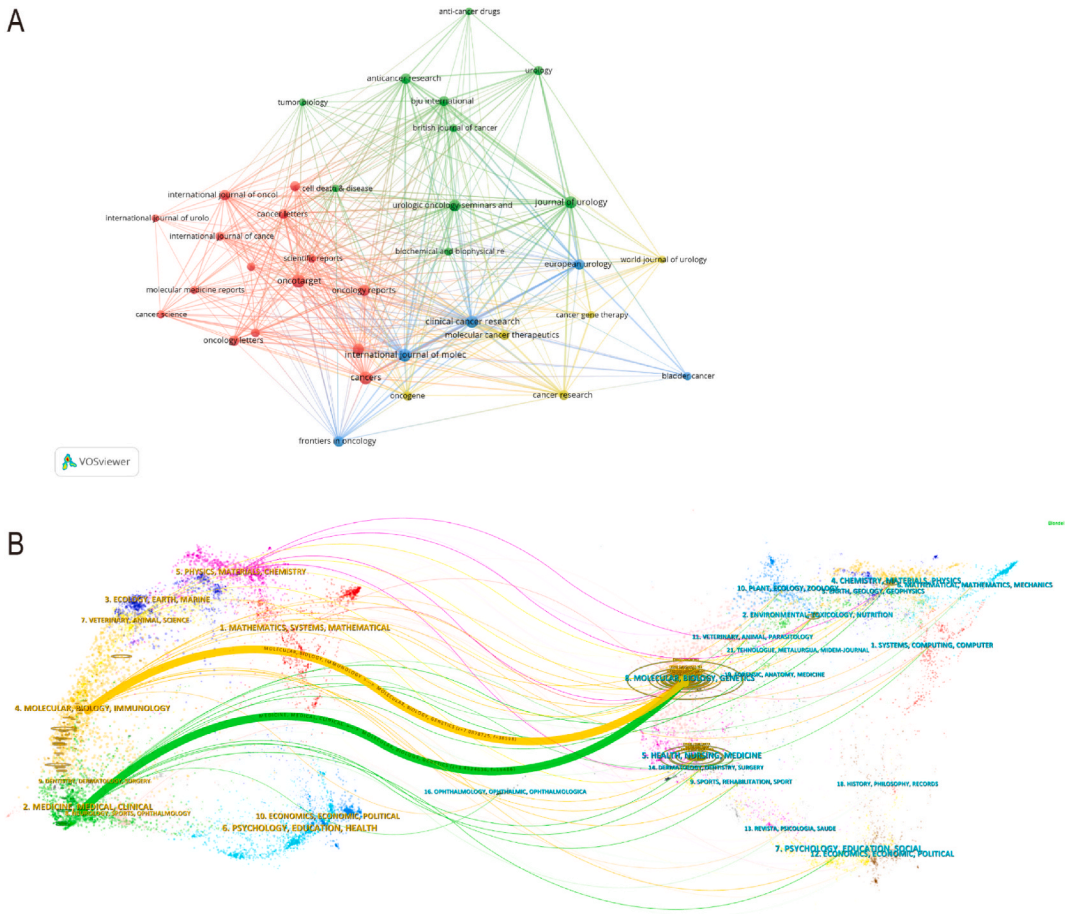

Fig. 5. **(A)** The visualization map of cooperation among journals and, the minimum number of papers published was 15. **(**B) Citespace's dual-map overlap of BC resistance. The citing journal on the left, and the cited journals are the right. Their cited connections are shown as different colors. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 4
The 10 authors and the top 10 co-cited authors related to bladder cancer drug resistance.

Rank	Author	TLS	Count	Total citations	Co-cited author	TLS	Total citations
1	McConkey DJ	91	28	2770	Bellmunt J	6877	392
2	Black PC	81	21	460	Siegel RL	3334	322
3	Theodorescu D	20	19	544	Won der maase H	3490	294
4	Rosenberg JE	40	18	475	Powles T	5806	276
5	Chol W	57	17	2330	Sharma P	4222	194
6	Miyamoto H	62	17	336	Sternberg CN	3050	194
7	Galsky MD	55	17	607	Witjes JA	2221	190
8	Kamat AM	32	16	731	Motzer RJ	5454	187
9	Pan CX	33	16	272	Camat AM	2387	183
10	Chen W	16	15	956	Weinstein JN	2768	182

TLS: total link strength.

published in Nature by Weinstein JN, has the highest TLS, playing a role of bridge in these references. Although the number of citations of the articles published by Robertson JE, Bellmunt J and Choi W were relatively low, the frequency of co-occurrence with other references was relatively high.

3.7. Analysis of keyword co-occurrence and burst

Keywords represent the research hotspot and direction in this field. We use VOSviewer for co-occurrence analysis of keywords in this field. As shown in Fig. 8, keywords co-occurrence network is relatively dense. Keywords such as bladder cancer, apoptosis,

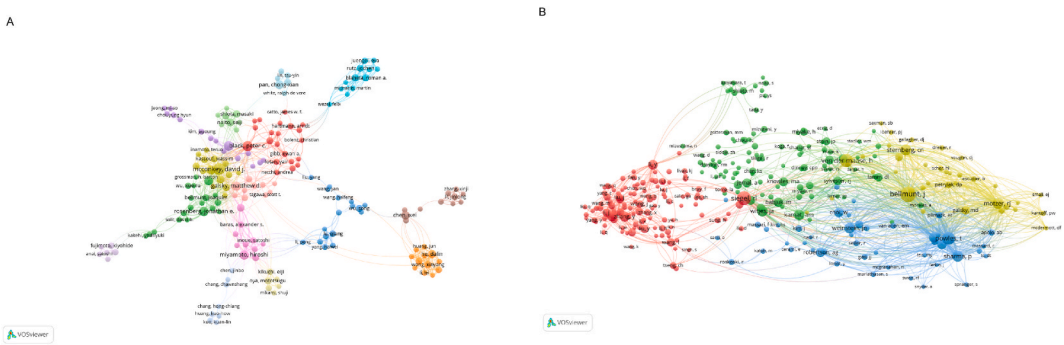

Fig. 6. The visualization of author's cooperation network (A) and co-cited authors network (B) ralated to BC drug resistance. (A) Minimum number of documents of authors are 5, and each node represents an author. The size of the node indicates the number of articles published by the author. The lines between the authors reflect their collaborative relationship. Authors with the same node color are a small group. (B) Minimum number of documents of co-cited authors are 30, and each node represents an author. The size of a node represents the number of total citations. Authors in the same node color are a small group. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 5
Top 10 co-cited references concerning bladder cancer drug resistance.

Rank	Journal	Author	TLS	Citations	Doi
1	A Cancer Journal for Clinicians	Siegel RL	566	235	10.3322/caac.21208
2	Nature	Weinstein JN	929	175	10.1038/nature12965
3	Clinical Oncology	Von der maase H	541	145	10.1200/jco.2000.18.17.3068
4	Clinical Oncology	Von der maase H	535	135	10.1200/jco.2005.07.757
5	Cell	Robertson AG	716	131	10.1016/j.cell.2017.09.007
6	Lancet	Robertson JE	802	120	10.1016/s0140-6736(16)00561-4
7	New England	Bellmunt J	763	116	10.1056/nejmoa1613683
8	Cancer Cell	Choi W	689	116	10.1016/j.ccr.2014.01.009
9	European Urology	Antoni S	378	112	10.1016/j.eururo.2016.06.010
10	New England	Grossman HB	421	93	10.1056/nejmoa022148

TLS: total link strength.

cisplatin, prognosis, drug resistance, chemotherapy, urothelial carcinoma, autophagy, biomarker were highly cited and were research hotspots.

Fig. 9 depicts the top 25 keywords with burst strength by citespace, in which "transitional cell carcinoma" (21.36) had the highest burst strength. "migration" (15.84), "cell proliferation" (15.16) and "epithelial mesenchymal transition" (15.10) have weights above 15, thereby signposting emerging research avenues.

4. Discussion

4.1. General information

From 1999 to 2022, the ever-increasing number of publications and citations related to bladder cancer (BC) drug resistance has become a testament to the world's escalating focus on this critical issue. It reveals the growing acknowledgment within the medical community regarding the importance of not only identifying but also addressing the intricacies of BC drug resistance. As the prevalence of bladder cancer continues to rise, the parallel progression of drug resistance has magnified the importance of early detection and innovative therapeutic interventions. These could bring transformative benefits to global health, especially given the severity of suffering that bladder cancer patients endure.

The United States, with its monumental contributions to this field, has showcased an indomitable research spirit. TLS, H-index, and Average citation per paper of USA are all the highest in the world, and the Central from three American institutions all exceed 0.1, indicating that the USA performs an indispensable bridge role in this field. In addition, there are three Chinese universities that are ranked among the top 10 institutions. In the coming years, China will emerge as one of the leading research countries in the BC drug resistance field.

The number of articles published by other nations also exhibits a rising trend, and 150 article have been published by Japan, Germany, and UK. Among them, UK Total citations ranks second at 11,641. There are six American journals in the top 10 journals, along with two Swiss and two Greek publications. Further observation of the number of publications and the author collaboration network revealed that the cooperation between authors is mainly concentrated among the institutions, and collaboration among authors between countries is a feasible measure to promote research progress. Their increasing collaborations offer hope that through

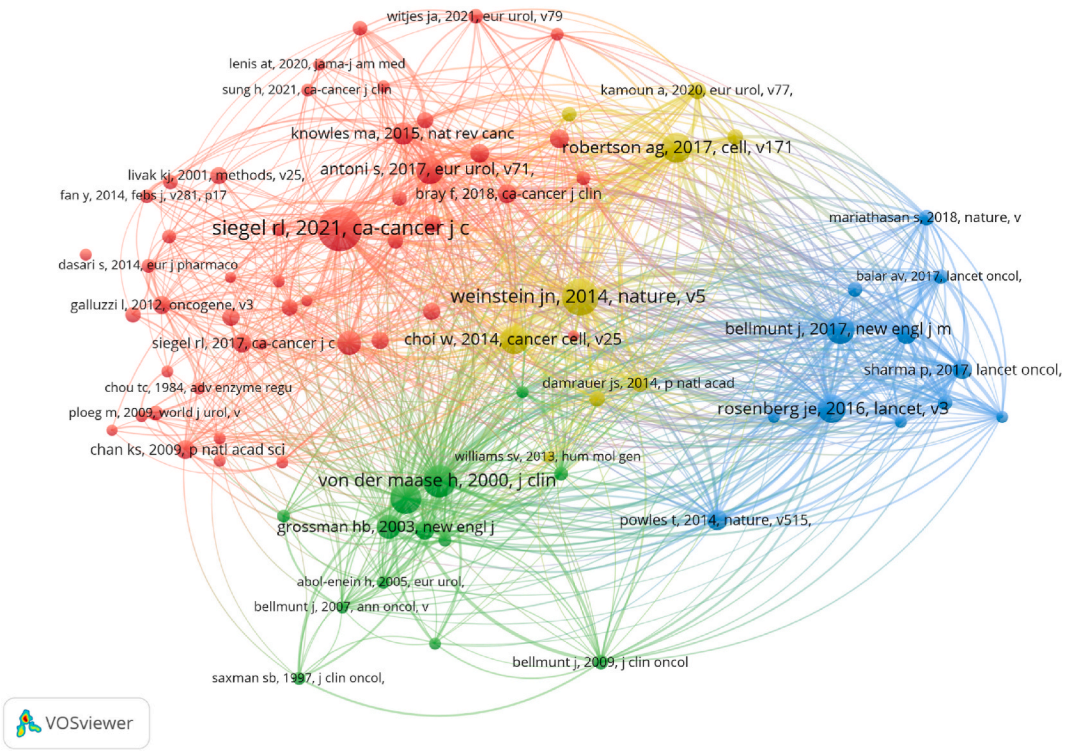

Fig. 7. Visualization of the co-cited reference network. Each node represents an article. The size of nodes represents the number of citations. Articles with the same node color describe a small group. Articles cited 30 times are shown in the figure. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

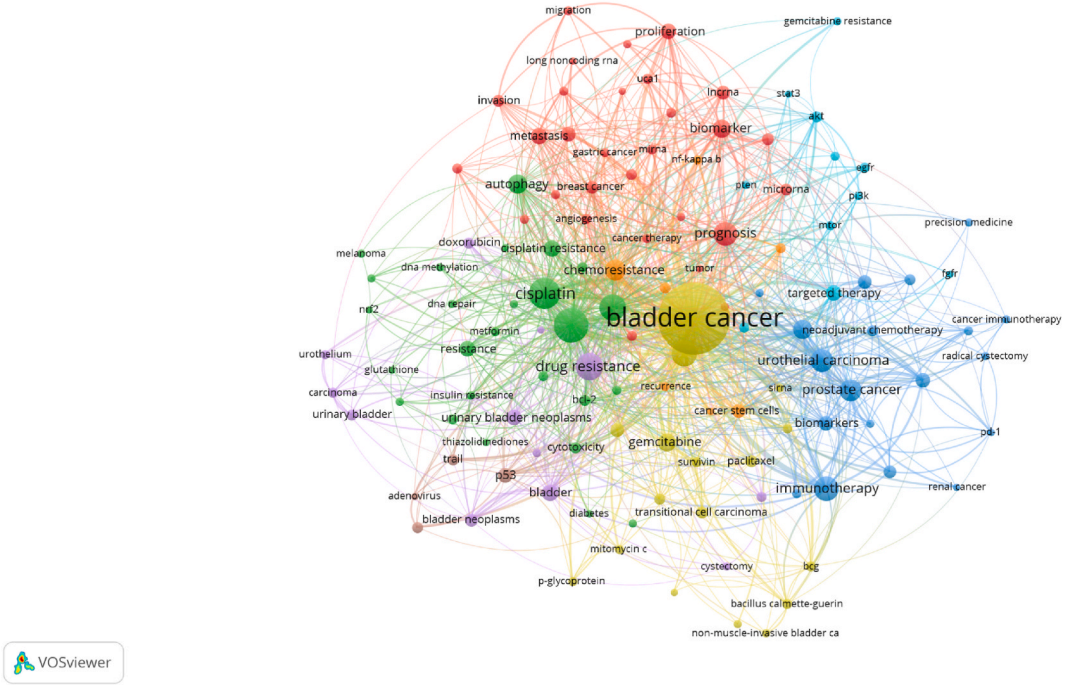

Fig. 8. The visualization of the co-occurrence keywords network. Each node represents a keyword. The size of a node represents the number of occurrences. keywords with the same node color are a small group. keywords with occurrences 10 are shown in the figure. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

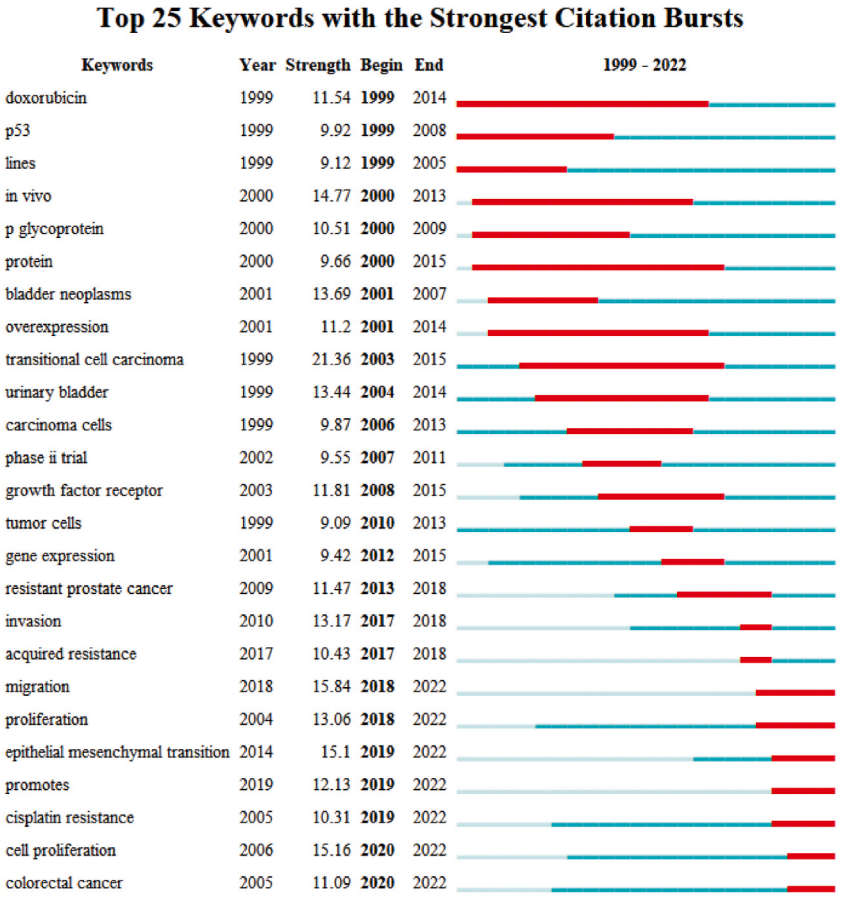

Fig. 9. Top 25 keywords with the strongest citation burst related to bladder cancer drug resistance. The keywords were ranked according to the burst strength. The higher the heat of the keyword, the larger the burst strength.

international synergy, we can unravel the various aspects of BC drug resistance endemic to different populations and environments.

A noteworthy contributor, McConkey DJ, has become synonymous with in-depth studies focused on the molecular mechanisms underpinning BC drug resistance. The principal contents of the three articles with a high number of citations include: the mechanism of bladder cancer resistance to BCG may be adaptive immune resistance, and PD-L1 has a certain predictive value for BCG resistance [14]. There are other the mechanisms of drug resistance research. For example, uncoupling of EGFR with mitogenic pathways is a mechanism by which bladder cancer becomes resistant to EGFR inhibitors, and activation of GSK-3β and of nuclear cyclin D1 can predict the occurrence of drug resistance [28], Furthermore, investigated the mechanism by which gefitinib, an EGFR inhibitor, reverses resistance to TRAIL (tumor necrosis factor-related apoptosis-inducing ligand) in bladder cancer [29].

In our analysis of the articles, we found a lack of strong correlation between the number of citations/TLS of the journal in which the articles were published. This challenges the previous consensus that articles published in journals with high impact factors always receive more citations. This is consistent with many recent analyzes [30–32]. In addition, open access articles accounted for the vast majority of TOP10 journals, and the citations and TLS of non-open access articles were low. Therefore, open access publications may promote the research progress in the field of BC drug resistance by increasing the dissemination and use of research results. Consistent with the analysis of some previous studies [33,34].

4.2. Mechanisms of drug resistance

Through the analysis of highly cited documents, we can get a general understanding of the research topics in this field. Among the top 10 most cited documents, 2 articles analyze cancer-related data [35,36], 5 articles conduct experiments on drug efficacy and compare the efficacy of different drug regimens [22,37–40], 2 articles describe the molecular characteristics of bladder cancer [41,42], and 1 article on bladder cancer subtypes and personalized treatment [43]. Given that the top-ranked article in our analysis was predominantly associated with tumor data and did not delve into the mechanisms of drug resistance, we shifted our focus to the second-ranked article with the highest TLS for a more relevant analysis of drug resistance mechanisms in bladder cancer. This approach aligns with the essence of our bibliometric study, centering on the most impactful literature in the field. Statistically significant recurrent mutations were observed in genes, including TP53, ERCC, EGFR, RB1, PPARG, highlighting their involvement in key

pathways like PI3K/AKT/mTOR, CDKN2A/CDK4/CCND1, and RTK/RAS [42]. This information, extracted from the highly cited literature, underscores the complexity of molecular interactions contributing to BC drug resistance. Through the regulation of energy generation, mitochondrial homeostasis, and metabolic profile, it was noted that TP53 knockdown cells could acquire the potential to be sensitive to tropomyosin receptor kinase (TRK) inhibitors, potentially leading to transcriptional activity alterations [44]. Patients with higher EGFR expression may have a worse prognosis than those with little to no EGFR expression [45]. However, our bibliometric review of the top-cited articles suggests that the specific mechanisms that bladder tumors develop resistance to cisplatin remain largely unknown. This gap highlighted by our bibliometric analysis points to potential areas for future research. Inhibiting the cisplatin-induced excision repair cross-complementation group-1 (ERCC-1) could enhance the sensitivity of resistant ovarian cancer cells to cisplatin by reducing the capability to repair the DNA damage caused by cisplatin, as indicated by our analysis of influential publications [46]. The dysfunction of the retinoblastoma susceptibility gene (RB1) was reported to contribute to enzalutamide drug resistance in prostate cancer, a finding that emerged from our review of highly-cited literature [47]. This illustrates the cross-cancer relevance of such genetic dysfunctions.

Digging deeper into the molecular mechanisms of BC drug resistance brings forth a multifaceted picture. Resistance mechanisms, whether against common drugs like cisplatin and gemcitabine or more specialized agents such as BCG and targeted therapies, vary widely [48–50]. They span from traditional biochemical pathways like nucleotide excision repair to the more nuanced realms of non-coding RNA modulations. These findings, aside from elucidating the molecular pathways, also shed light on potential diagnostic and therapeutic biomarkers. As the research community further deciphers these mechanisms, there's anticipation that this knowledge will form the foundation of more targeted and individualized therapeutic strategies. The mechanisms of drug resistance are very complex and have not yet been fully understood. Francesco Massari concluded that the molecular mechanisms of cisplatin resistance mainly include: 1.expression of ERCC1 protein activates the nucleotide excision repair (NER) system and removes cisplatin-DNA adducts; 2. RARP (a kind of DNA repair mechanisms) repair the cisplatin-DNA adducts; 3. Nrf2 accelerates drug efflux; 4. The decrease of CTR1 leads to the decrease of Cu2+ influx, which in turn leads to the decrease of cisplatin intake; 5. miRNA-27A induces cisplatin resistance by negatively regulating SLC7A11; 6. In the process of EMT, the cells lose their epithelial characteristics and acquire the interstitial phenotype of migration, and then the tumor cells metastasize and escape the antitumor effect of cisplatin; 7. p53 [15]. In recent years, some new molecular mechanisms of drug resistance have been discovered one after another, such as maladjustment of PAX5/PTGS 2 cascades, high expression of formyl peptide receptor 1, functional abnormalities of non-coding RNA (miRNA and lncRNA), the change of multiple signal pathways leads to the enhancement of CSCs (cancer stem cell) characteristics, autophagy of cancer cells, high expression of NAT-10 induces epithelial-mesenchymal transformation (EMT), Up-regulation of N4-acetylcytidine (ac4C), semi-squamatization of cancer cells, MiR-146a-5p with high expression of CAF in bladder cancer microenvironment regulates cancer cell stemness, Circ0008399/WTAP complex inhibits apoptosis by promoting the expression of TNFAIP3 in bladder cancer cells [51]. The above studies not only explain the mechanism of drug resistance, but also provide more reliable biomarkers for accurate treatment screening, and provide new targets for personalized targeted therapy of drug resistant patients, which indicates that a deeper understanding of the molecular characteristics and molecular mechanism of BC drug resistance will promote the recognition of prognostic and predictive markers as well as the development of BC personalized cancer therapy. It can also be observed in our journal topic cluster analysis that the center of research is increasingly focused on molecular, biology, and genetics. In the future, research on molecular mechanisms will become a hot topic and frontier.

4.3. Potential future directions and implications

Conventional chemotherapies, with their innate limitations, have necessitated the exploration of novel therapeutic vistas. Immune checkpoint inhibitors (ICIs) stand out in this new wave of therapeutic approaches [52], which greatly improved the treatment pattern of patients with advanced cancer including bladder cancer. Immune checkpoint inhibitors have been approved by the FDA for second-line treatment for metastatic and locally advanced urothelial cancer, as well as first-line treatment for patients who are not suitable for cisplatin treatment. In recent years, five PD-1/PD-L1 inhibitors have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of advanced UC patients: atezolizumab, pembrolizumab, nivolumab, durvalumab and avelumab [53]. In addition, the combination of ICIS and targeted therapy, chemotherapy, radionuclide therapy, cytokines and vaccines has also attracted some attention and research [54]. New ICIS for TIM-3、LAG-3、B7–H3、B7–H4、Vista、CEACAM1、BTLA、CD200-CD200R、Siglec15 and TGIT are under development [11,55].

Targeted therapies, especially those centering on the Fibroblast growth factor receptor (FGFR), represent another frontier in BC treatment [56]. Their potential is evident in the recent FDA approval of erdafitinib for specific bladder cancer cases [57]. Currently, Research on targeted therapies targeting BC stem cells is still ongoing [58]. How to obtain more therapeutic targets and develop targeted drugs with better effects and fewer adverse reactions has become a hotspot.

Additionally, the researchers identified five different BC subtypes, each with different sensitivity to specific treatments, leading to the development of personalized treatments in the future [41].

5. Limitations

We acknowledge the limitation due to our exclusive use of the Web of Science Core Collection database. While comprehensive, its coverage is not exhaustive, potentially leading to a selection bias. The restriction to English-language articles might have resulted in an incomplete representation of global research efforts. Our use of VOSviewer and CiteSpace, while popular, could lead to somewhat biased results, as different bibliometric tools may yield varied outcomes. Additionally, the potential impact of publication bias has

been recognized, as it could influence the trends and themes identified in our analysis.

6. Conclusion

Our study's analysis from 1999 to 2022 underscores a dynamic shift in bladder cancer (BC) drug resistance research. The leadership roles of the USA and China highlight the importance of fostering international research collaborations to pool knowledge and resources. Institutions like the University of Texas System demonstrate the significant impact of dedicated research centers in advancing the field. Our findings point towards a growing focus on molecular-based therapies and personalized medicine as promising avenues to combat BC drug resistance. The rise in immune checkpoint inhibitors and targeted therapy research signals an urgent need to develop new biomarkers for early detection and tailored treatment plans. These insights suggest a clear path forward: invest in collaborative research to unravel complex resistance mechanisms, and prioritize personalized treatment approaches to improve outcomes for BC patients.

Data availability statement

Reasonable inquiries might be made by contacting the corresponding author to obtain the relevant data.

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Ethics statement

The data of our study were obtained from public databases. Ethics committee permission was not required.

CRediT authorship contribution statement

Yi Huang: Writing – original draft, Software, Methodology, Conceptualization. **LiGang Chen:** Writing – original draft, Software, Methodology. **Yitong Zou:** Software, Methodology. **Hao Yu:** Investigation, Formal analysis. **Weibin Xie:** Investigation, Formal analysis. **QingHua Gan:** Validation, Software. **YuHui Yao:** Data curation. **ChengXiao Liao:** Software. **Junjiong Zheng:** Writing – review & editing. **Jianqiu Kong:** Writing – review & editing, Writing – original draft, Software, Methodology. **Tianxin Lin:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

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

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