Knowledge-map analysis of bladder cancer immunotherapy

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Abstract

Background

This study aims to conduct the bibliometric and visual analyses in the field of bladder cancer (BC) immunotherapy, and explore the research trends, hotspots and frontiers from 2000 to 2021.

Methods

Data were obtained from the Web of Science core collection database, which collected 2,022 papers related to BC immunotherapy around the world from 1 January 2000 to 31 December 2021. VOSviewer software was used to comprehensively analyze the collaborative relationships between authors, institutions, countries/regions, journals through citation, co-authorship, co-citation, etc., so as to identify research hotspots and frontiers in this research field.

Results

The trend of literature publication was relatively flat from 2000 to 2015, and since 2015, the literature publication showed an overall upward trend. The United States of America has published 643 papers with 27,241 citations, ranked first among the top 10 most active countries, and has the most extensive collaboration with other countries. The University of Texas MD Anderson CANC CTR has published 62 articles, making it the most published articles and active collaborative research institution. Kamat AM and Lamm DL were the most active and co-cited authors with 27 papers and 1,039 co-citations, respectively. Chang yuan and Xu le ranked first with 145 total link strength, becoming the most active collaborative authors. J UROLOGY was the most active and frequently co-cited journal, with 106 papers and 6,764 co-citations. Studies of BC immunotherapy can be divided into three categories: “basic research”, “clinical trial” and “prognosis”.

Conclusions

Our findings provide a comprehensive overview of the research priorities and future directions of BC immunotherapy. Tumor microenvironment and immune checkpoint inhibitors (ICIs) of BC, as well as the combination of ICIs and other drugs may become the main direction of future research.

1. Introduction

According to a cancer statistics, bladder cancer (BC) is the fourth most common and eighth most lethal malignancy in men in the United States of America (United States), with an estimated 81,180 new cases and 17,100 deaths in 2022. The result show that BC seriously affects the health and quality of life of the elderly [1]. Non-muscle-invasive BC (NMIBC) has a high recurrence rate, while muscle-invasive BC (MIBC)
has a poor 5-year survival rate [2]. Although the survival rate of NMIBC was higher, the 5-year recurrence-free survival (RFS) of low-, medium-, and high-risk patients was 43%, 33%, and 23%, respectively [3]. For MIBC, metastasis remains a challenge despite the significant survival advantage provided by neoadjuvant chemotherapy, with a 5-year overall survival (OS) of only 4.8% [4].

Cancer immunotherapy works by stimulating and strengthening the body’s anti-tumor immune response to eliminate cancer cells. Over the past decades, immunotherapy has shown remarkable efficacy and bright prospects in cancer treatment. In particular, the success of cytotoxic T lymphocyte antigen 4 (CTLA-4), programmed cell death protein 1 (PD-1) and programmed cell death ligand 1 (PD-L1), as well as the emerging role of "targeted" immunotherapeutic agents, have led to breakthroughs in tumor immunotherapy [5]. Atezolizumab and pembrolizumab are immune checkpoint inhibitors (ICIs) approved by the Food and Drug Administration (FDA) in April and May 2017 for patients with locally advanced or metastatic urothelial carcinoma (UC) who are not eligible for cisplatin [6]. Atezolizumab showed encouraging durable response rates, survival rate, and tolerability in IMvigor210 study [7]. Pembrolizumab also showed anti-tumour activity and an acceptable safety in patients with advanced UC in phase 1b KEYNOTE-012 study and phase 2 KEYNOTE-052 study [8, 9]. "Non-targeted" immunotherapeutic agents such as Bacille Calmette-Guerin (BCG), interferon (IFN), and interleukin (IL) are also widely used to treat BC [10]. For example, BCG has been used to treat NMIBC for more than 30 years, and this highly effective approach has achieved high successful results in patients [11,12]. Therefore, immunotherapy is of great significance in BC and is expected to revolutionize the landscape of BC therapeutics [13].

Bibliometrics can combine mathematical and statistical methods to quantitatively analyze a large number of literatures in a specific field, and has been widely used in the analysis of research output, as well as the discovery of hotspots and research trends. Bibliometrics helps to understand the knowledge base and research frontiers of a particular research field [14,15]. They are widely used in the field of assessment research and play an important role in the biomedical field. For example, Tang et al. [16] summarized the research trends, hotspots, and frontiers in the field of cyclic adenosine monophosphate in the past decade through bibliometric analysis, which was of great significance. Shen at al. [17] published a global bibliometric analysis of immunotherapy for hepatocellular carcinoma by collecting global literature over the last decade.

In the past decades, many scientific achievements have been made in BC immunotherapy research. However, no bibliometric articles on BC immunotherapy have been published. In this study, we searched the research literatures in the Web of Science (WOS) core collection in the past 22 years and analyzed them using bibliometric methods. VOSviewer software was used to deeply explore the collaboration among authors, institutions, countries/regions, and comprehensively analyze journals, co-cited references, and high-frequency keywords. This study evaluated the literatures on BC immunotherapy from 2000 to 2021 to evaluate the current state of the field and identify new research directions.

2. Materials And Methods
2.1 Data source and search strategy

All publications related to BC immunotherapy were searched in the WOS core collection database from 1 January 2000 to 31 December 2021. The search strategies were as follows: TS = ((“bladder cancer” OR “bladder carcinoma”) AND (“immunotherapy” OR “immunotherapeutic”)). The types of documents were limited to articles, and the language was limited to English. Detailed data retrieval and inclusion procedures were shown in Fig. 1.

2.2 Data collection and analysis

The file information was downloaded from the WOS core collection database. Full records and cited references (titles, keywords, authors, journals, abstracts, references, and citations, etc.) were obtained. The documents were downloaded in TXT format. VOSviewer 1.6.18 software was used to comprehensively analyze the collaborative relationships among authors, institutions, countries/regions, journals through citation, co-authorship, and co-citation. In addition, high-frequency co-cited references and keywords were clustered by VOSviewer. These maps were presented through network, overlay, and density visualisation. In network visualization, different colors indicated different clusters, the size of nodes was positively correlated with the frequency of total link strength or occurrence, and the straight lines between nodes represented the strength of the connection.

Microsoft Excel 2019 was used to analyze and plot the annual number of publications related to BC immunotherapy, as well as the top 10 most active authors, co-cited authors, institutions, and countries/regions, including the number of publications and citations. In addition, major journal information such as number of published papers, countries, total citations, impact factor (IF), and journal citation reports (JCR) partition were also analyzed and plotted. The top 10 co-cited literatures related to BC immunotherapy, including authors, countries, publication years, corresponding journals, and IF, were described in excel tables.

3. Results

3.1 Analysis of the basic situation of the extracted literature

3.1.1 Analysis of publication outputs

In this study, 2,022 publications related to BC immunotherapy between 2000 and 2021 were acquired from the WOS core collection database. As shown in Fig. 2, the lowest number of published papers was 36 in 2006, and the highest was 339 in 2021, with an annual average of 92. A statistically significant relationship between year and number of publications can be observed by fitting a mathematical function to the curve of annual number of publications ($R^2 = 0.9817$). According to the fitting curve, 420 papers related to BC immunotherapy are expected to be published globally in 2022. There was no obvious research trend from 2000 to 2015, but it remained relatively stable. The number of publications has
generally been on the rise since 2015. Therefore, this topic has received great attention in recent years, and the research prospect will be brighter.

### 3.1.2 Analysis of countries/regions

These publications were contributed by 71 countries/regions. The top 10 most active countries/regions of BC immunotherapy were listed in Table 1. The United States is the most active country in this field, with 643 publications and 27,241 citations, far more than any other country. The People's Republic of China (China) ranked second with 360 publications. Japan, Germany, and Italy ranked third to fifth. It was noted that the most productive countries are the developed countries, but not China. This phenomenon revealed that the number of publications was closely related to economic development.

A total of 45 countries/regions with more than five publications were selected for the co-authorship analysis. In the network visualisation map (Fig. 3A), the United States was the most productive contributor and the most extensive collaborator. In the field of BC immunotherapy, the United States has links to 42 countries, for a total link strength of 534. The United States has the closest cooperation with Italy, with 56 link strength, followed by Germany and Canada.

Notably, an article titled “MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer” was published in the journal Nature in 2014 by England, the United States, France, and Spain. It has been cited 1,706 times, making it the most consistently cited and popular article. The study reported the results of a phase clinical trial of anti-PDL1 antibody MPDL3280A in the treatment of metastatic urothelial BC (UBC), which inhibited the interaction of PD-L1 with PD-1 (PDCD1) and B7.1 (CD80). The results showed that MPDL3280A was particularly effective against PD-L1-positive tumors infiltrating immune cells, with a response rate of 11% in PD-L1-negative patients. In addition, MPDL3280A was better tolerated by UBC patients than chemotherapy, and these results suggested that MPDL3280A may play an important role in the treatment of UBC [18].

It was observed that Austria ranked eighth in total link strength, with only 37 publications. China ranked second with 360 publications, but 17th in total link strength. This was worthy of our consideration. Perhaps it was because Austria produced many high-quality articles in cooperation with other countries, while many articles in China were completed by Chinese scholars independently, and the degree of cooperation with scholars from other countries was relatively insufficient. For example, scholars from Austria, Netherlands, Italy and other countries have put forward some constructive suggestions on the optimal dose and duration of intravesical BCG vaccine for NMIBC through clinical trials. The results showed that there were no differences in toxicity between 1/3 dose and full dose. Intermediate-risk patients should receive full dose therapy for one year. In high-risk patients, 3 years of full dose treatment reduced recurrence compared with 1 year [19]. From these findings, it is confirmed that cooperation between countries is a powerful catalyst for knowledge renewal and innovation.
As can be observed in the overlay visualisation map (Fig. 3B), 10 countries/regions, including Germany, Japan, and Belgium, etc., started to study BC immunotherapy before 2012. They were among the first countries/regions to conduct research in this field. Since 2018, only a few countries/regions have joined the research in this field, including China, Russia, Romania, Jordan, and Iran. It was noticed that the trend of cooperation between countries/regions has been on the decline in recent years.

### 3.1.3 Analysis of institutions

There were 2,681 institutions involved in these publications. As shown in Table 2, the institution with the most output was the University of Texas MD Anderson CANC CTR, which published 62 publications. MEM Sloan Kettering CANC CTR, second with 60 publications, was the most cited institution, with 3,784 citations. Of the top 10 institutions, the majority were from the United States, accounting for half.

A total of 89 institutions with more than 10 publications were selected as co-authorship analysis. In the network visualisation map (Fig. 4A), University of Texas MD Anderson CANC CTR was the most enthusiastic institution, linking 39 institutions with a total link strength of 95. Followed by MEM Sloan Kettering CANC CTR with a total link strength of 93. The total link strength of these two institutions was much higher than that of the others. These two institutions have their own research teams and are close partners. One of their studies showed that pembrolizumab monotherapy was tolerable and showed promising antitumour activity in patients with BCG-nonresponsive NMIBC [20]. By calculating the thickness of the connection line between the two institutions in Fig. 4A, we found that the link strength between Shanghai Jiao Tong University and Fudan University was the highest. In a study, they showed that dendritic cell-specific C-type lectin (+) tumor-associated macrophages (TAMs) had immunosuppressive and tumor-promoting functions and can be used as prognostic indicators and therapeutic targets in MIBC [21].

The distribution of institutions in different time periods were presented in Fig. 4B. It was observed that UNIV Iowa, Institut Pasteur, and UNIV Amsterdam, etc. were the major institutions conducting researches in the field of BC immunotherapy before 2012. After 2020, there were also many institutions interested in this field, including Fdn IRCCS Ist Nazl Tumori, Fudan UNIV, and UNIV Washington, etc. Fdn IRCCS Ist Nazl Tumori mainly studied the role of neoadjuvant pembrolizumab in BC and achieved some results. Their findings confirmed the activity of neoadjuvant pembrolizumab in patients with MIBC, squamouscell cell carcinoma, and lymphoepithelioma-like features and may be suitable for neoadjuvant immunotherapy trials [22].

### 3.1.4 Analysis of authors and co-cited authors

These 2,022 articles were produced by 11,045 authors. The information of authors and co-cited authors was analyzed, and the co-cited authors were drawn into a density visualization map by VOSviewer software (Fig. 5A). The number of co-citations authors in the figures was positively correlated with the density. In addition, the top 10 most active authors and the top 10 co-cited authors were listed in the Table 3. Kamat AM has published 27 articles and Shariat SF has published 15 publications with 2,341 citations, and was the most prolific and most cited author, respectively. Among the top 10 co-cited...
authors, Lamm DL ranked first with 1,039 co-citations, much higher than other co-cited authors, followed by Herr HW (513 co-citations), and Sylvester RJ (509 co-citations). It was noticed that two authors were both most active and co-cited authors among the top 10 authors, which were Bohle A and Witjes JA. These excellent authors have made outstanding contributions in the field of BC immunotherapy.

A total of 132 authors who published more than 7 times were selected for network visualisation analysis (Fig. 5B). Chang yuan and Xu le, who ranked first with a combined link strength of 145, belong to a research group. Their team also included Liu li, Wang zewei, and Zeng han, etc., and had a close cooperative relationship, the total link strength of each member was not low. A study by their group showed that TIGIT(+) CD8(+) T-cell abundance can be used as an independent predictor of clinical outcome and a predictive biomarker of poor responsiveness to MIBC adjuvant chemotherapy [23].

It was observed that six authors Albert matthew l, Schlom J, Yao xudong, Wang bo, Chang In ho, and Bunimovich-Mendrazitsky S focused on individual studies and did not form a team. However, they have made some achievements in the field of BC immunotherapy through their own efforts. For example, a study of Albert et al. [24] showed that boosting the BCG response by parenteral exposure prior to initiation of intravesical therapy may be a safe and effective means of improving intravesical BCG-induced clinical responses. Chang et al. [25] designed novel nanoparticles composed of liposome-encapsulated BCG cell well skeleton (BCG-CWS). Compared with nonenveloped BCG-CWS, encapsulated BCG-CWS nanoparticles were more effective in delivering BCG-CWS to the bladder and inhibiting tumor growth. The results indicated that BCG-CWS delivery system was a promising and effective therapeutic strategy for BCG-mediated BC therapy.

From the overlay visualisation map (Fig. 5C), several research teams and individuals have been interested in the field of BC immunotherapy in recent years. For example, it was clearly observed that Chang yuan and Necchi A’s teams were yellow in the figure, indicating that they made a lot of research achievements in this field in recent years. They have certainly brought new blood into the field.

3.1.5 Analysis of journals and co-cited journals

A total of 551 journals have published related articles in the field of BC immunotherapy, including 88 journals with more than five papers. Table 4 listed the top 10 most prolific journals related to BC immunotherapy. J UROLOGY has published 106 papers with 8,017 citations, far more than any other academic journal, and was the journal with the most published papers and citations. In addition, the IF/JCR partition of J UROLOGY was 7.600/Q1 in 2022, which has a high reputation in the field of BC immunotherapy. We observed that 7 of the top 10 prolific journals were from the United States. This indicated that the United States had a high influence in the field of BC immunotherapy, which provided a reliable platform for the publication of related research papers. Meanwhile, we found that the EUR UROL from Netherlands had the highest IF with IF/JCR partition of 24.267/Q1 in 2022. The second was CLIN CANCER RES from the United States, whose IF/JCR partition was 13.801/Q1.
The density visualisation map of co-cited journals was drawn by VOSviewer (Fig. 6A). So far, 10 co-cited journals have been cited more than 1,000 times. The top 10 co-cited journals were plotted in Fig. 6B. We noted that J UROLOGY was the most co-cited journal with a total of 6,764 citations, far more than other co-cited journals. This was followed by EUR UROL (3,913 co-citations) and J CLIN ONCOL (3,141 co-citations) in 2022. To our surprise, J UROLOGY ranked first in both prolific and co-cited journals, indicating that this journal has a high reputation in the field of BC immunotherapy. At the same time, three journals were cited in both prolific and co-cited journals, including J UROLOGY, EUR UROL, and UROLOGY. This result indicated that there was a close relationship between journals and co-cited journals, and prolific journals were more likely to be co-cited. These data will help scientists to select journals when submitting manuscripts related to BC immunotherapy in the future.

3.2 Analysis of the basic content of extracted literature

3.2.1 Analysis of co-cited references

The density visualization map of 62 most co-cited references was drawn by VOSviewer software (Fig. 7). We summarized the top 10 co-cited references, including article title, corresponding author, country, year, count of co-citation, journal, and IF (2022), which were listed in Table 5. In 1976, Morales et al. [26] published a paper in J UROLOGY entitled "Intracavitary Bacillus Calmette-Guerin in the treatment of superficial bladder tumors", which has been cited 273 times. This was followed by articles by Lamm et al. [27] and Rosenberg et al. [28] with 235 and 225 co-cited references, respectively. It was observed that half of the top 10 co-cited references were from the United States, two from England, two from Belgium, and one from Canada. In terms of journals, four were from J Urology, three from Lancet, and another three from NEW Engl J Med, EUR UROL, and NATURE. To our surprise, Sylvester, RJ and Lamm, DL each published two papers among the top ten articles.

So far, these 10 articles had a significant impact in the field of BC immunotherapy. For example, in the BCG study. Morales et al. [26] found favorable changes in recurrence patterns after BCG treatment in nine patients with relapsed superficial BC. This was the first study that found BCG can be used to treat BC, which laid a solid foundation for many scholars to study BCG in the future, and has a milestone significance. Lamm et al. [29] showed that BCG irrigation elicited more local and systemic responses than intravesical chemotherapy. In rare cases, BCG can cause life-threatening or fatal sepsis. No serious side effects were reported in 95% of 2,602 patients who received intravesical BCG treatment. Prompt and appropriate treatment of early side effects can significantly reduce the incidence of severe toxicity.

Another study by Lamm et al. [27] showed that maintenance BCG immunotherapy for BC was beneficial compared with standard induction therapy in patients with carcinoma in situ (CIS) and in patients with stage Ta and T1. The median RFS was twice as long in the 3-week BCG maintenance group (76.8 months) as in the no BCG maintenance group (35.7 months), and disease-free survival was significantly longer. Sylvester et al. [30] found that intravesical BCG injection significantly reduced the risk of progression after transurethral resection in patients with superficial BC receiving BCG maintenance
therapy. The results indicated that BCG was the first choice for patients with intermediate and high risk bladder papillary tumors and CIS.

### 3.2.2 Analysis of keywords

The co-occurrence keywords network visualization map was composed of 138 high-frequency keywords, and the extraction frequency was more than 25 times (Fig. 8A). The keywords can be divided into three categories: cluster 1: “basic research” (red), including expression, proliferation, induction, and growth; cluster 2: “clinical trials” (green), including safety, survival, PD-L1, phase- trial, and pembrolizumab; cluster 3: “prognosis” (blue), including progression, risk, recurrence, complications, and BCG. It was observed that among the numerous high-frequency keywords, the co-occurrence times of the five important keywords were more frequent: BCG, expression, progression, recurrence, and survival. This indicated that these keywords were the key research directions of BC immunotherapy researchers.

According to the overlay visual analysis of the keywords, the research direction of BC immunotherapy researchers may have shifted from basic research and prognosis to clinical research of new drugs (Fig. 8B). It was observed that keywords such as pembrolizumab, atezolizumab, ICIs, tumor microenvironment (TME), landscape, and outcomes have become the research hotspots of BC immunotherapy in recent years. This result showed that there was an urgent need for more effective immune drugs to treat BC, and the clinical research and development of new drugs has been the direction of interest for researchers in recent years.

### 4. Research Hotspots And Frontiers

Based on the above results, we listed some research hotspots and frontiers in the field of BC immunotherapy. Immunotherapy aims to activate the body's immune system and kill cancer cells. According to different sites of action, immunotherapy drugs can be divided into two categories: "non-targeted" and "targeted" [31].

#### 4.1 Non-targeted immunotherapy for BC

BCG is the only FDA approved first-line treatment for patients with NMIBC [32]. Since Morales et al. [26] first reported the use of BCG in the treatment of BC in 1976, the era of BC immunotherapy has begun. In the past decades, a large number of clinical practices have confirmed the important role of BCG in the treatment of BC [33–37]. Sylvester et al. [33] found through meta-analysis that compared with intravesical chemotherapy, intravesical BCG significantly reduced the risk of short-and long-term treatment failure. The results showed that it is considered to be the intravesical agent of choice in the treatment of CIS. Buffen et al. [34] demonstrated that rs3759601 in autophagy gene ATG2B was associated with BC progression and recurrence after intravesical BCG infusion. These findings identify a critical role for autophagy in the nonspecific protective effect of BCG. Rentsch et al. [35] compared the therapeutic effects of two commonly used BCG strains on NMIBC and found that treatment with BCG Connaught was more effective in preventing recurrence than treatment with BCG Tice. They also
compared the immunogenicity of the two strains in mice and showed that the immunogenicity of BCG Connaught was better than that of BCG Tice. Pérez-Jacoiste et al. [36] analyzed 282 BC patients treated with intravesical BCG treatment. The results showed that disseminated (34.4%), urogenital infection (23.4%), and skeletal muscle infection (19.9%) were the most common disease manifestations. Patients aged ≥ 65 years or older with disseminated infection and vascular involvement had higher attributable mortality. Pichler et al. [37] found that BCG failure was associated with low density of CD4⁺ and GATA3⁺ T cells, increased expression of FOXP3⁺ and CD25⁺ regulatory T cells (Tregs), and CD68⁺ and CD163⁺ TAMs. In addition, studies have demonstrated prolonged RFS in patients with increased CD4⁺ and GATA3⁺ T cells counts. TAMs, Tregs, and T-bet⁺ T cells were inversely correlated with RFS. The study showed that TME seems to influence treatment response to BCG, permitting individualized treatment for patients with BC.

IFN has been used intravesical alone for the treatment of superficial BC. However, combined BCG therapy may have unexpected results. Lam et al. [38] showed that intravesical BCG combined with IFN-alpha2B was an effective and tolerable alternative for patients with superficial BC. The benefits of this combination therapy may include a potentially reduction in morbidity and improved clinical efficacy. In the long term, fewer patients receive radical therapy. Alternatively, IL plays an auxiliary role in the treatment of BC. The findings of Bunimovich-Mendrazitsky et al. [39] suggested that the non-responsive subpopulation may benefit from intensive combined BCG and IL-2 maintenance therapy.

4.2 Targeted immunotherapy for BC

Because of the associated toxicity of BCG and the limited population of patients eligible for BCG therapy, alternative immunotherapy for high-risk NMIBC is required [40]. Compared with non-targeted immunotherapy, targeted immunotherapy is more novel. In recent years, it has attracted the attention of researchers, and has achieved good clinical effects in the treatment of BC. CTLA4, PD-1, and PD-L1 are important research directions of targeted immunotherapy [5].

CTLA-4 was the first inhibitory immune checkpoint identified to play a crucial role in modulating T cell responses. There are two monoclonal antibodies (mAbs), ipilimumab (IgG1) and tremelimumab (IgG2), which block the function of CTLA-4 [41, 42]. Jaiswal et al. [43] indicated that the genetic variations of CTLA4 gene (+49A/G, CT60A/G) played a role in BC susceptibility. Liakou et al. [44] found that CD4⁺ T cells in peripheral blood and tumor tissues of all treated patients markedly increased the expression of inducible costimulatory (ICOS). These CD4⁺ ICOS⁺ T cells produced IFN-γ and recognized the tumor antigen NY-ESO-1. The increase in CD4⁺ ICOS⁺ T cells led to an elevation in the ratio of effector T cells to regulatory T cells. These results showed that CTLA-4 influenced human immune responses within the TME, and they may be used to guide the administration and scheduling of this agent to improve clinical responses. Ipilimumab was the first fully human IgG1 mAb against CTLA-4. Carthon et al. [45] conducted the first pre-operative clinical trial of ipilimumab in 12 patients with localized UBC and demonstrated a tolerable safety profile for anti-CTLA-4 therapy in a preoperative setting.
Compared with CTLA-4, PD-L1 and PD-1 have received more attention, especially their representative
drugs, atezolizumab and pembrolizumab, have become research hotspots. PD-L1 is a T cell regulatory
molecule that can be expressed on the surface of tumor and tumor infiltrating immune cells [46]. In 2018,
Tang et al. [47] put forward a different view. Their study demonstrated that PD-L1 was expressed in
antigen-presenting cells, but not on tumor cells. It plays an essential role in checkpoint blockade therapy.
Anti-PD-L1 drugs mainly include atezolizumab, avelumab, and durvalumab. PD-1 is predominantly
expressed on the surface of activated T and B lymphocytes. By binding to PD-L1 and PD-L2, it inhibits
peripheral T cell activation and plays an important role in maintaining the tolerance of peripheral and
central immune cells [48]. Anti–PD-1 ICIs mainly include pembrolizumab, nivolumab, and camrelizumab.
PD-1/PD-L1 signaling pathway in TME can lead to adaptive immune resistance to tumors. Shi et al. [49],
by adding PD-1 blockers to cancer stem cells vaccine (CSCs), increased the amount of CD4(+), CD8(+)
and CD8(+) IFN-γ (+) and induced maximum IFN-γ production. These results showed that PD-1 blockade
can effectively enhance the function of tumor-specific T lymphocytes generated by bladder CSCs.

Currently, 5 ICIs (atezolizumab, pembrolizumab, nivolumab, durvalumab, and avelumab) were approved
by the FDA for the treatment of patients with advanced UC who have progressed after platinum-based
chemotherapy. Two ICIs (atezolizumab and pembrolizumab) were approved for first-line treatment in
patients who were not eligible for cisplatin [50]. Rosenberg et al. [28] based on a single-arm phase 2 study
showed that atezolizumab has durable activity and is well tolerated in patients with locally advanced and
metastatic UC. Increased PD-L1 expression on immune cells correlated with increased response. Balar et
al. [7] reported a phase 2 trial of atezolizumab as first-line therapy in patients with advanced metastatic
UC who were not eligible for cisplatin. The results showed encouraging durable response rates, survival
rates, and tolerability of atezolizumab in patients with untreated metastatic UC. In the IMvigor211 study,
atezolizumab significantly improved OS in the entire study population and was better tolerated than
chemotherapy [51]. Notably, atezolizumab did not significantly improve OS in people with high PD-L1
expression. The PD-L1 biomarker did not work as expected. In people with high PD-L1 expression, the
results were good in both groups [51]. In the ABACUS trial, 27 of 88 patients (31%) in an evaluable cohort
receiving atezolizumab had a pathologic complete remission (pCR), and the pCR rate correlated with PD-
L1 expression [52]. In a phase 2 trial of pembrolizumab, 89 of 370 patients achieved a complete or partial
response, and only one patient died from treatment-related adverse events (AEs). These results implied
that pembrolizumab has great anti-tumour activity and an acceptable safety profile in patients with
advanced UC [9]. Bellmunt et al. [53] showed that pembrolizumab prolonged OS (approximately 3
months) and had a lower incidence of treatment-related AEs in patients with platinum-refractory
advanced UC than chemotherapy as second-line therapy. Necchi et al. [54] indicated that pembrolizumab
may be a valuable neoadjuvant therapy for MIBC patients with PD-L1 positive or high tumor mutation
burden.

In dual ICIs studies of patients with advanced UC, the combination of CTLA-4 and PD-(L)1 was generally
more effective. Dijk et al. [55] showed that CTLA-4 (ipilimumab) combined PD-1 (nivolumab) blockade
may provide an effective preoperative treatment strategy for locally advanced UC. Hooren et al. [56]
demonstrated that local anti-CTLA-4 therapy in combination with anti-PD-1 therapy resulted in complete
responses, which was superior to monotherapy. Gao et al. [57] revealed preliminary safety, efficacy, and biomarker data for neoadjuvant therapy in combination with anti-PD-L1 (durvalumab) plus anti-CTLA-4 (tremelimumab). This provided a further standard of care for patients with localized UC, especially high-risk patients who are not eligible for cisplatin therapy.

In addition, the hot keyword “landscape” attracted our attention, which mainly refers to the metabolic mechanism of tumor immune environment. As a new treatment, it plays an important role in the treatment of cancer. However, at the same time, it is necessary to prevent AEs of immunotherapy. There are many unknown fields of immunotherapy to be explored.

5. Strengths And Limitations

In this study, we conducted a comprehensive and systematic bibliometric analysis of the literature on BC immunotherapy for the first time. It can help researchers to find partners, as well as provide some guidance and suggestion to clinicians and researchers. Inevitably, this study has some limitations. Firstly, the literature in our study was only extracted from the WOS core collection database, which inevitably led to the omission of other literature. Secondly, the type of document selected was only published in English, which may lead to selection bias. Thirdly, publications for 2022 were excluded due to insufficient data. But compared with the volume of literature from 2000 to 2021, new data may have little impact on the final results. Finally, some newly published high-quality papers may not receive as much attention and be cited less frequently than classic papers.

6. Conclusion

In general, this study contributed to our understanding of the current status of BC immunotherapy research from 2000 to 2021. Bibliometric analysis was used to analyze the literature worldwide. The results showed that the trend of literature publication volume was relatively gentle from 2000 to 2015. Since 2015, the amount of literature published has generally been on the rise. The United States has made a great contribution to BC immunotherapy. J UROLOGY was the most active journal and the most frequently co-cited journal. Collaboration between authors, institutions, and countries/regions must continue to be strengthened. Countries should actively create opportunities for communication and cooperation and provide a good platform for researchers and institutions. TME and ICIs of BC seem to be the hotspots in recent years, and the research on the combination of ICIs and other drugs is in full flow, which may become the main research direction in the future.

Abbreviations

factor; JCR: journal citation reports; UBC: urothelial BC; TAMs: tumor-associated macrophages; BCG-CWS: BCG cell well skeleton; CIS: carcinoma in situ; TME: tumor microenvironment; RFS: recurrence-free survival; mAbs: monoclonal antibodies; ICOS: inducible costimulatory; CSCs: cancer stem cells vaccine; pCR: pathologic complete remission; AEs: adverse events.

**Declarations**

**Ethical Approval and Consent to participate**

Not applicable.

**Consent for publication**

Not applicable.

**Availability of data and materials**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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**Authors’ contributions**

KW and YW conceived the manuscript; ZL and JH reviewed the information. ZL wrote the manuscript. ZL and YW prepared the figures. KW critically reviewed the manuscript. All authors read and approved the final manuscript.

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Not applicable.

**References**


Tables

Tables are available in Supplementary Files section.

Figures
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Flow chart of literature screening related to BC immunotherapy research.

Figure 2

\[ y = 0.0126x^4 - 101.03x^3 + 304379x^2 - 4.808x + 2E+11 \]

\[ R^2 = 0.9817 \]
Figure 2

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Figure 3

(A) The network visualization map of countries/regions collaborations in the field of BC immunotherapy.
(B) The overlay visualization map of countries/regions collaborations in the field of BC immunotherapy.

Figure 3

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