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BRIEF REPORT

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Research hotspots and trends in the field of immune checkpoint inhibitors (ICIs) for cervical cancer: A bibliometric study from 2014 to 2024

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ABSTRACT

In recent years, immune checkpoint inhibitors (ICIs) have emerged as a novel immunotherapeutic approach, offering renewed hope for enhancing cervical cancer patient prognosis. This study represents the inaugural bibliometric analysis of ICIs in the context of cervical cancer, covering the period from 2014 to 2024. A total of 422 articles were identified through the Web of Science Core Collection database, amassing 10,977 citations, with a consistent annual increase in the number of publications. The leading contributors in terms of countries, institutions, journals, and authors included China, the University of Texas System, *Frontiers in Oncology*, and Bradley J. Monk, respectively. The journal with the highest frequency of citation and co-citation was *Journal of Clinical Oncology*. The researchers with the highest number of citations and co-citations were Sarina A Piha-Paul and Krishnansu S Tewari respectively. The keyword cluster analysis identified four main research directions. Furthermore, literature co-citation analysis and burst citation analysis revealed three research hotspots and four potential emerging topics within this domain, respectively. This study provides valuable reference and enlightenment for researchers in this field. As research progresses, ICIs are anticipated to offer significant hope and breakthroughs in the treatment of cervical cancer.

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Introduction

Cervical cancer is one of the most common malignant tumors among women in the world. Recent research indicates that cervical cancer ranks fourth in both incidence and mortality among all female malignancies.[1] Despite the potential for effective prevention through regular screening and HPV vaccination, a significant number of women worldwide do not have access to these interventions, leading to a persistently high incidence of cervical cancer. Conventional therapeutic approaches, such as surgery, radiotherapy, and chemotherapy, often exhibit limited efficacy in patients with advanced or recurrent cervical cancer. Consequently, there is an urgent need to develop novel treatment strategies to enhance patient prognosis.

In recent years, the rise of immunotherapy has brought a new dawn to the treatment of cervical cancer, among which immune checkpoint inhibitors (ICIs) have become a research hotspot. ICIs can relieve the inhibition of tumors in the immune system by blocking the immune checkpoint pathway, thus enhancing the ability of immune cells to attack tumors. Within the domain of cervical cancer, the investigation and application of ICIs have garnered increasing attention, particularly those targeting programmed cell death protein 1 (PD-1),[2,3] programmed cell death protein 1 (PD-L1),[4,5] and cytotoxic T lymphocyte-associated protein 4 (CTLA-4).[6] Currently, no bibliometrics studies in this field have been published. This study provides a comprehensive and objective bibliometric analysis of the field of study, specifically exploring trends, research hotspots, and emerging themes in the field. It aims to provide valuable reference and inspiration for researchers in the field.

Materials and methods

The data utilized in this investigation were sourced from the Web of Science Core Collection (WoSCC) database. Detailed search strategies and search formulas are delineated in Supplementary Table S1.

Bibliometrics and visual analysis in the research field

Our study revealed that a total of 422 articles were published in this research domain from 2014 to 2024, accumulating 10,977 citations. The number of related articles showed a yearly increasing trend (Figure 1a). Utilizing the data on annual publication volumes, we developed a fitting equation ($Y = 9.427*X - 18995$), which demonstrated a strong correlation ($R^2 = 0.9369$, $p \leq .0001$) (Figure 1b). The countries, institutions, journals, and authors contributing the most publications were China ($n = 164$), University of Texas System ($n = 29$), *Frontiers*

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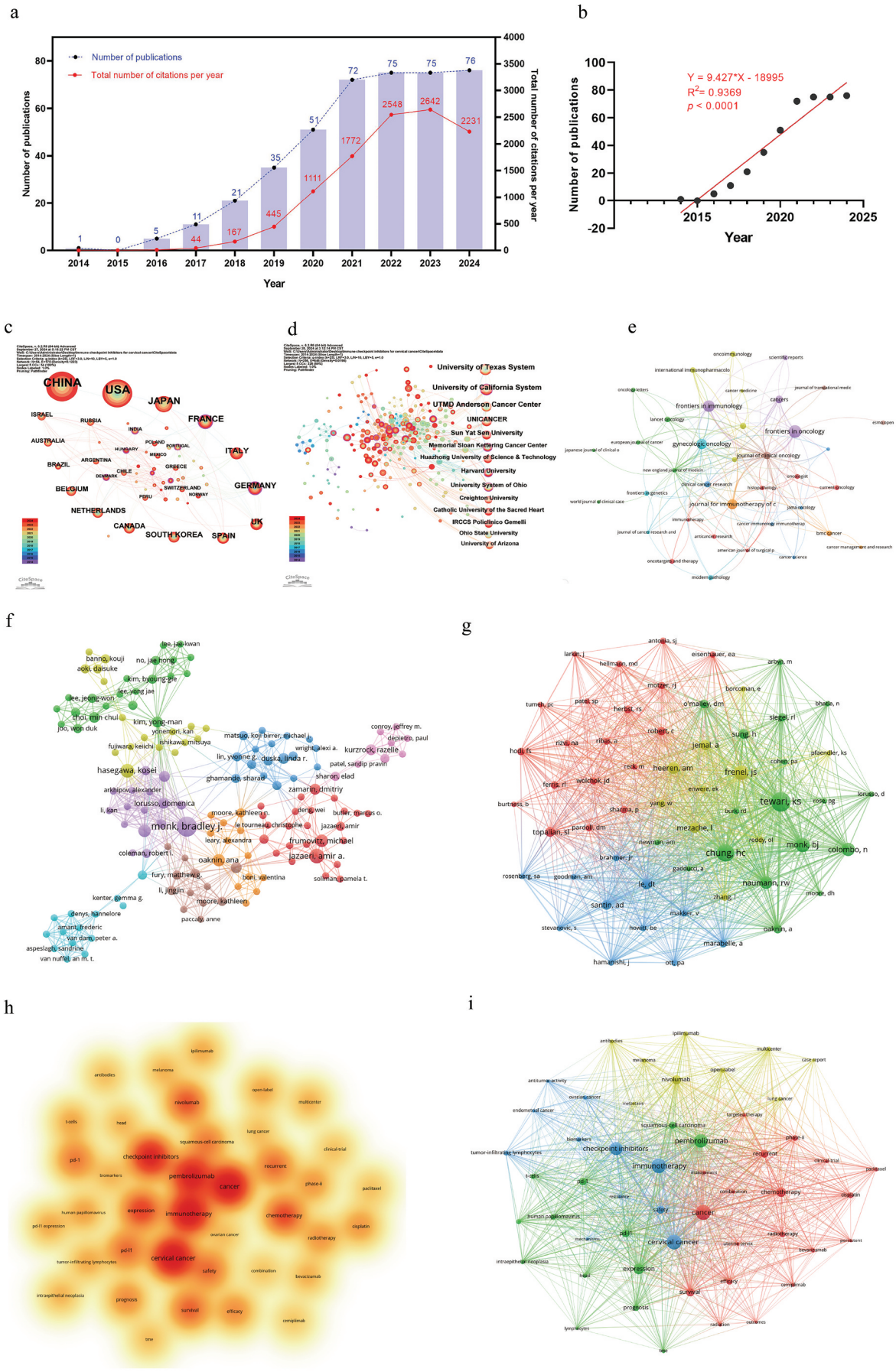

Figure 1. The bibliometrics analysis of ICIs for cervical cancer. (a) Publication output and citation frequency trends in the research field. It shows the number of publications and cited times every year. (b) The fitting equation of annual publication volume. The co-occurrence map of countries (c), institutions (d) and journals (e) about the research field. The visualization map of authors (f) co-cited authors (g) about the research field (Note: Minimum number of documents of an author ≥ 2; Minimum number of citations of an author ≥ 20). The co-occurrence density map (H) of keywords (Note: Minimum number of occurrences of keywords ≥ 15). The network visualization (I) of keywords.

in Oncology ($n = 22$), and Bradley J Monk ($n = 11$), respectively (Table S2 and Figure 1c–e). The journal with the highest number of citations and co-citations was the *Journal of Clinical Oncology* (Table S3). The authors with the highest number of citations and co-citations were Sarina A Piha-Paul ($n = 978$) and Krishnansu S Tewari ($n = 161$), respectively (Table S4 and Figure 1f,g). The most frequent keyword was "cervical cancer ($n = 143$)," followed by "cancer" ($n = 142$), "immunotherapy" ($n = 137$), and "pembrolizumab" ($n = 116$) (Table S5 and Figure 1h). Keyword cluster analysis (Figure 1i) identified four distinct clusters, broadly representing four major research directions, including (a) treatment and prognosis of cervical cancer; (b) immune checkpoints pertinent to cervical cancer; (c) application and safety evaluation of ICIs in cervical cancer treatment; and (d) application of ICIs in the treatment of other solid tumors. A timeline viewer (Figure 2) of the keywords was constructed to show the distribution of the keywords in terms of years, the evolutionary trajectory of the field, and important topics.

Research hotspots and emerging topics in this research field

A co-citation analysis of the literature can quickly summarize the research hotspots in a certain field. We explored and summarized the research hotspots in this field and identified three major research hotspots, including (a) the correlation between immune checkpoint expression in cervical cancer and patient prognosis; (b) the efficacy and safety assessment of ICIs in cervical cancer; and (c) the use and exploration of ICIs in combination with other drugs or therapies in the cervical cancer (Table S6). Furthermore, the burst citation analysis of the literature is important for exploring emerging research themes within a field. The citation burst analysis (Figure 3) shows that there are 12 documents in burst status (Table S7). These documents can help us to explore the emerging themes. Emerging themes within this research domain encompass the following: (a) tumor mutational load may serve as a biomarker of therapeutic response in cervical cancer treated with ICIs; (b) high microsatellite instability/DNA mismatch repair (MSI-H/dMMR) may serve as a biomarker of therapeutic response to ICIs for cervical cancer; (c) to explore the efficacy of different ICIs in cervical cancer; and (d) combination of different ICIs for cervical cancer treatment.

The utilization of tumor mutation burden (TMB) as a biomarker in immune checkpoint inhibitors (ICIs) therapy has garnered significant attention in recent years. TMB is defined as the number of somatic mutations per million base pairs and is generally regarded as a proxy for neoantigen load. Some studies have demonstrated that patients exhibiting elevated TMB levels often experience improved clinical outcomes and prolonged survival when undergoing ICIs treatment.[7,8] In the context of cervical cancer treatment, while PD-L1 expression is currently the predominant biomarker, its predictive

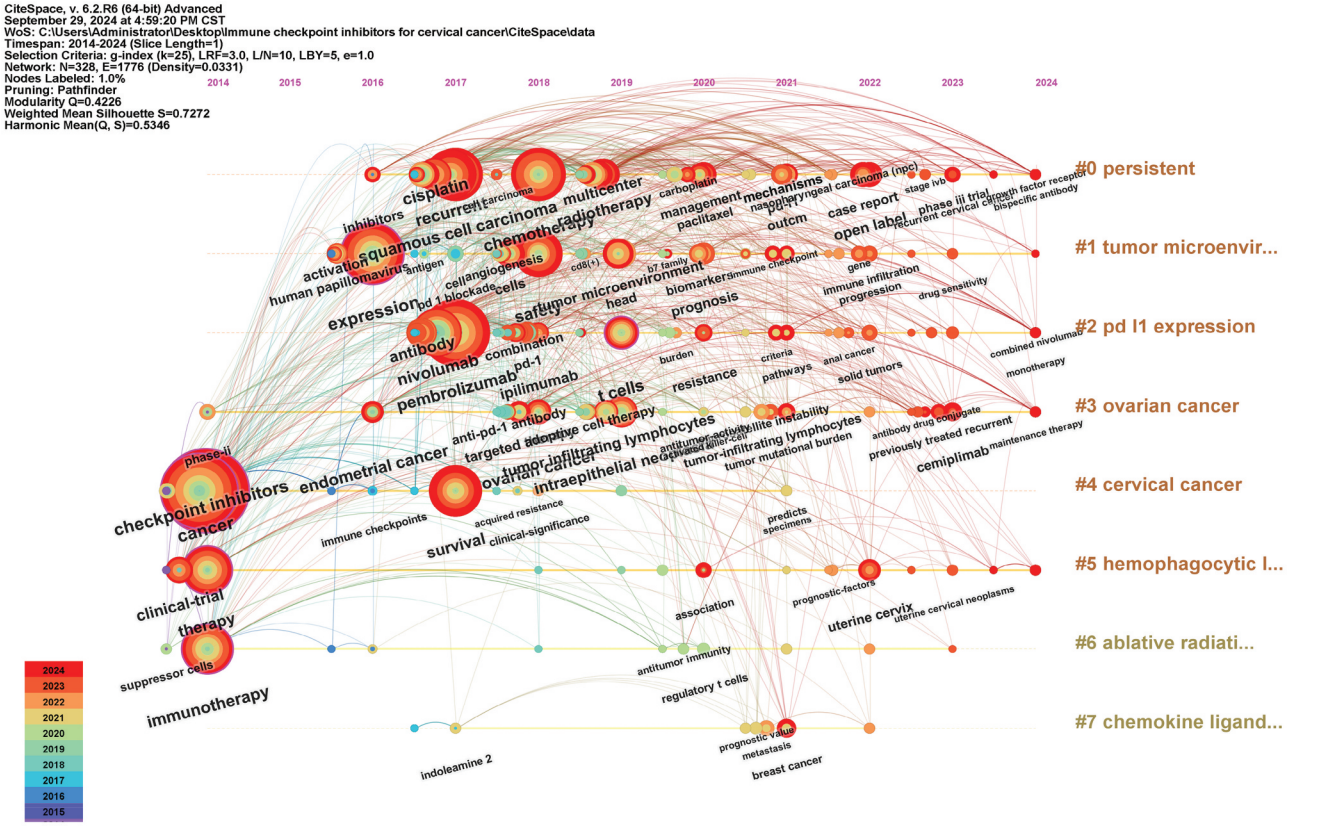

Figure 2. The timeline viewer of keywords. It illustrates the evolution of keywords in the field of ICIs for cervical cancer research from 2014 to 2024. Each node in the diagram represents a specific keyword, and the size of the node indicates the frequency of the keyword in a specific year. Connectors represent the co-occurrence relationship between keywords. The change of color represents the passage of time. Through it, readers can intuitively observe the evolution process of research hotspots in this field. #1: tumor microenvironment #5: hemophagocytic lymphohistiocytosis #7: chemokine ligands

Top 50 References with the Strongest Citation Bursts

References	Year	Strength	Begin	End	2014 - 2024
Le DT, 2015, NEW ENGL J MED, V372, P2509, DOI 10.1056/NEJMoa1500596, DOI	2015	3.01	**2016**	2020	
Taube JM, 2014, CLIN CANCER RES, V20, P5064, DOI 10.1158/1078-0432.CCR-13-3271, DOI	2014	2.7	**2016**	2017	
Herbst RS, 2014, NATURE, V515, P563, DOI 10.1038/nature14011, DOI	2014	2.67	**2016**	2019	
Rizvi NA, 2015, SCIENCE, V348, P124, DOI 10.1126/science.aaa1348, DOI	2015	2.54	**2016**	2020	
Tewari KS, 2014, NEW ENGL J MED, V370, P734, DOI 10.1056/NEJMoa1309748, DOI	2014	3.93	**2017**	2019	
Borghaei H, 2015, NEW ENGL J MED, V373, P1627, DOI 10.1056/NEJMoa1507643, DOI	2015	2.9	**2017**	2020	
Torre LA, 2015, CA-CANCER J CLIN, V65, P87, DOI 10.3322/caac.21262, DOI	2015	2.75	**2017**	2019	
Robert C, 2015, NEW ENGL J MED, V372, P320, DOI 10.1056/NEJMoa1412082, DOI	2015	2.61	**2017**	2020	
Reck M, 2016, NEW ENGL J MED, V375, P1823, DOI 10.1056/NEJMoa1606774, DOI	2016	2.8	**2018**	2021	
Frenel JS, 2017, J CLIN ONCOL, V35, P4035, DOI 10.1200/JCO.2017.74.5471, DOI	2017	15.91	**2019**	2021	
Heeren AM, 2016, MODERN PATHOL, V29, P753, DOI 10.1038/modpathol.2016.64, DOI	2016	8.16	**2019**	2021	
Mezache L, 2015, MODERN PATHOL, V28, P1594, DOI 10.1038/modpathol.2015.108, DOI	2015	6.54	**2019**	2020	
Tewari KS, 2017, LANCET, V390, P1654, DOI 10.1016/S0140-6736(17)31607-0, DOI	2017	5.97	**2019**	2021	
Hollebecque A, 2017, J CLIN ONCOL, V35, P0, DOI 10.1200/JCO.2017.35.15, suppl.5504, DOI	2017	5.93	**2019**	2021	
Ferris RL, 2016, NEW ENGL J MED, V375, P1856, DOI 10.1056/NEJMoa1602252, DOI	2016	4.69	**2019**	2021	
Reddy OL, 2017, DIAGN PATHOL, V12, P0, DOI 10.1186/s13000-017-0631-6, DOI	2017	4.58	**2019**	2021	
Burk RD, 2017, NATURE, V543, P378, DOI 10.1038/nature21386, DOI	2017	4.42	**2019**	2021	
Liu YC, 2019, FRONT PHARMACOL, V10, P0, DOI 10.3389/fphar.2019.00065, DOI	2019	4.27	**2019**	2021	
Pusztai L, 2018, J CLIN ONCOL, V36, P0, DOI 10.1200/JCO.2018.36.15, suppl.586, DOI	2018	4.13	**2019**	2020	
Boussios S, 2016, CRIT REV ONCOL HEMAT, V108, P164, DOI 10.1016/j.critrevonc.2016.11.006, DOI	2016	3.61	**2019**	2020	
Schellens JHM, 2017, J CLIN ONCOL, V35, P0, DOI 10.1200/JCO.2017.35.15, suppl.5514, DOI	2017	3.38	**2019**	2021	
Stevanovic S, 2015, J CLIN ONCOL, V33, P1543, DOI 10.1200/JCO.2014.58.9093, DOI	2015	3.26	**2019**	2020	
Minion LE, 2018, GYNECOL ONCOL, V148, P609, DOI 10.1016/j.ygyno.2018.01.009, DOI	2018	3.26	**2019**	2020	
Le DT, 2017, SCIENCE, V357, P409, DOI 10.1126/science.aan6733, DOI	2017	3.14	**2019**	2021	
Gibney GT, 2016, LANCET ONCOL, V17, PE542, DOI 10.1016/S1470-2045(16)30406-5, DOI	2016	3.11	**2019**	2021	
Garon EB, 2015, NEW ENGL J MED, V372, P2018, DOI 10.1056/NEJMoa1501824, DOI	2015	3.08	**2019**	2020	
Ott PA, 2017, J CLIN ONCOL, V35, P2535, DOI 10.1200/JCO.2017.72.5952, DOI	2017	2.74	**2019**	2020	
Meng Y, 2018, J CANCER, V9, P2938, DOI 10.7150/jca.22532, DOI	2018	5.62	**2020**	2021	
Enwere EK, 2017, MODERN PATHOL, V30, P577, DOI 10.1038/modpathol.2016.221, DOI	2017	4.22	**2020**	2022	
Naumann RW, 2019, J CLIN ONCOL, V37, P2825, DOI 10.1200/JCO.19.00739, DOI	2019	4.09	**2020**	2021	
Borcoman E, 2017, THER ADV MED ONCOL, V9, P431, DOI 10.1177/1758834017708742, DOI	2017	3.49	**2020**	2021	
Yang W, 2017, J OBSTET GYNAECOL RE, V43, P1602, DOI 10.1111/jog.13411, DOI	2017	3.3	**2020**	2022	
Paraghamian Sarah E, 2017, GYNECOL ONCOL RES PRACT, V4, P3, DOI 10.1186/s40661-017-0038-9, DOI	2017	3.1	**2020**	2021	
Chalmers ZR, 2017, GENOME MED, V9, P0, DOI 10.1186/s13073-017-0424-2, DOI	2017	2.63	**2020**	2022	
Cohen PA, 2019, LANCET, V393, P169, DOI 10.1016/S0140-6736(18)32470-X, DOI	2019	3.91	**2021**	2024	
Marth C, 2017, ANN ONCOL, V28, P72, DOI 10.1093/annonc/mdx220, DOI	2017	3.84	**2021**	2022	
Marabelle A, 2020, J CLIN ONCOL, V38, P1, DOI 10.1200/JCO.19.02105, DOI	2020	3.42	**2021**	2024	
Marabelle A, 2020, LANCET ONCOL, V21, P1353, DOI 10.1016/S1470-2045(20)30445-9, DOI	2020	3.4	**2021**	2024	
Goodman AM, 2017, MOL CANCER THER, V16, P2598, DOI 10.1158/1535-7163.MCT-17-0386, DOI	2017	3.14	**2021**	2022	
Li TW, 2017, CANCER RES, V77, PE108, DOI 10.1158/0008-5472.CAN-17-0307, DOI	2017	3.04	**2021**	2022	
Arbyn M, 2020, LANCET GLOB HEALTH, V8, PE191, DOI 10.1016/S2214-109X(19)30482-6, DOI	2020	2.66	**2021**	2024	
Naumann RW, 2019, ANN ONCOL, V30, P898	2019	2.66	**2021**	2024	
Kawachi A, 2018, CANCER SCI, V109, P863, DOI 10.1111/cas.13476, DOI	2018	2.61	**2021**	2022	
Sung H, 2021, CA-CANCER J CLIN, V71, P209, DOI 10.3322/caac.21660, DOI	2021	12.67	**2022**	2024	
Burtness B, 2019, LANCET, V394, P1915, DOI 10.1016/S0140-6736(19)32591-7, DOI	2019	4.35	**2022**	2024	
Lan CY, 2020, J CLIN ONCOL, V38, P0, DOI 10.1200/JCO.20.01920, DOI	2020	3.8	**2022**	2024	
OMalley DM, 2021, GYNECOL ONCOL, V163, P274, DOI 10.1016/j.ygyno.2021.08.018, DOI	2021	3.25	**2022**	2024	
Abu-Rustum NR, 2020, J NATL COMPR CANC NE, V18, P661, DOI 10.6004/jnccn.2020.0027, DOI	2020	2.63	**2022**	2024	
Ferrall L, 2021, CLIN CANCER RES, V27, P4953, DOI 10.1158/1078-0432.CCR-20-2833, DOI	2021	2.63	**2022**	2024	
Hellmann MD, 2019, NEW ENGL J MED, V381, P2020, DOI 10.1056/NEJMoa1910231, DOI	2019	2.63	**2022**	2024	

Figure 3. Top 50 references with the strongest citation bursts in this field. Blue bars indicate that the reference has been published, while red bars represent citation bursts.

capacity is limited. Consequently, TMB, as an independent biomarker, may provide a more powerful predictive basis for immunotherapy of cervical cancer patients. Research indicates that a high TMB is correlated with enhanced immunotherapy response, potentially due to an increased mutation load leading to greater neoantigen production, thereby augmenting the immune system's capacity to identify and target tumor cells.[7,9] Furthermore, the assessment of TMB can be effectively conducted using next-generation sequencing technology, enhancing its practicality in clinical settings. Although the predictive threshold of TMB has not been fully standardized across different cancer types, several studies have proposed specific TMB thresholds for predicting the efficacy of ICIs treatment in certain cancers.[7,9] TMB holds potential value as a biomarker for immunotherapy response in cervical cancer. Nevertheless, to effectively translate TMB into clinical practice, further prospective studies are required to validate its predictive capacity and applicability across various cancer types.[7,9]

MSI-H and dMMR are recognized as effective biomarkers for immune checkpoint inhibitors (ICIs) therapy across various tumors. Recent research indicates that these biomarkers hold potential for application in cervical cancer treatment. Tumors

characterized by MSI-H/dMMR typically exhibit a high mutation burden and increased neoantigen load, facilitating their recognition and attack by the immune system, thereby enhancing the response rate to ICIs therapy.[10] In the context of endometrial cancer, MSI-H/dMMR has been validated as a reliable predictor for ICIs treatment efficacy. Pacholczak-Madej et al. found that a significant improvement in the overall response rate (ORR) for patients with MSI-H/dMMR endometrial cancer following ICIs therapy, along with enhanced progression-free survival (PFS) and overall survival (OS).[10] These findings provide a theoretical basis for considering MSI-H/dMMR as a biomarker in cervical cancer ICIs treatment. Furthermore, research on gastrointestinal cancer has shown that MSI-H/dMMR can predict the therapeutic efficacy of ICIs. Patients with MSI-H/dMMR gastrointestinal cancer have exhibited improved treatment responses and survival rates following ICIs therapy.[11] These results further support the potential of MSI-H/dMMR as a biomarker for the treatment of cervical cancer ICIs. Future research should further verify its effectiveness in cervical cancer and explore its application in clinical practice.

While ICIs as a monotherapy have demonstrated some therapeutic efficacy in patients with cervical cancer, offering new hope to many, significant challenges remain. Firstly, the response rate to monotherapy is limited[12]; Secondly, prolonged use of ICIs may lead to tumor cell resistance, gradually diminishing their therapeutic effectiveness. In response to these challenges, researchers are actively investigating novel treatment strategies. Combination therapies hold promise in overcoming these obstacles and may exert a synergistic effect. For instance, the concurrent use of chemotherapy and ICIs has shown potential in treating cervical cancer. Chemotherapy can enhance the immune system's capacity to recognize and attack cancer cells by killing tumor cells and releasing tumor antigens. Studies indicate that this combination can improve patient survival rates and disease control rates.[13] Additionally, the combination of radiotherapy and ICIs is a widely researched strategy. Radiotherapy not only directly eradicates tumor cells but also enhances the immune response by altering the tumor microenvironment. Radiotherapy may increase the sensitivity of tumor cells to ICIs, thus improving the therapeutic effect.[14] Furthermore, the integration of ICIs with concurrent radiotherapy and chemotherapy has demonstrated a notable impact on cervical cancer treatment. Liu et al.[15] reported that the combination of a PD-1 inhibitor with concurrent radiotherapy and chemotherapy yielded potential benefits for patients with locally advanced cervical cancer, particularly those with pelvic and/or paraaortic lymph node metastasis, as evidenced by improved tumor response rates and progression-free survival. Similarly, the research conducted by Chen et al.[16] indicated that the combination of torepalimab with platinum-based radiotherapy and chemotherapy exhibited significant anti-tumor efficacy and acceptable safety profiles in previously untreated patients with locally advanced cervical cancer. The combination of targeted therapy with ICIs also presents a promising avenue for cervical cancer treatment. Targeted therapies inhibit specific signaling pathways to prevent tumor growth, while ICIs alleviate immunosuppression, thereby enhancing the immune system's anti-tumor activity. This combination can improve the clinical response of patients in certain cases.[17] Finally, the combination of adoptive cell therapy and ICIs is also considered as a potential treatment strategy. Adoptive cell therapy augments the immune system's anti-tumor capabilities by transfusing immune cells, which have been genetically engineered or expanded in vitro, into patients. When combined with ICIs, this approach has the potential to enhance therapeutic efficacy.[13] The combination of ICIs with other therapeutic modalities in the treatment of cervical cancer has emerged as a prominent area of research, offering new hope for improving patient prognosis.

Conclusion

Cervical cancer, as a common malignant tumor in women worldwide, has a high morbidity and mortality rate.[1] Patients with advanced or recurrent cervical cancer have limited effectiveness with traditional treatments. Immunotherapy, especially ICIs, has emerged as a promising avenue of treatment for these patients.[18] This study presents the bibliometric analysis of this research area. The countries, institutions, journals, and authors with the largest number of publications in this field were identified through scientific statistics on relevant measurement indicators. The keyword analysis explores research directions and topic evolution in the field. The co-citation analysis identified four research hotspots. The citation burst analysis revealed four potential emerging topics. These findings could serve as valuable references and sources of inspiration for researchers within this domain.

This study is the first bibliometric analysis of ICIs in the field of cervical cancer treatment. We filled this gap by comprehensively analyzing the relevant literature from 2014 to 2024. Traditional reviews are mostly based on the author's subjective selection of literature and qualitative description, which has certain limitations. Employing rigorous statistical and analytical methodologies, this study aims to objectively and accurately elucidate the current research landscape and trends, providing readers with a thorough understanding of the field and facilitating a rapid comprehension of its overall scope and future directions. Over the past decade, substantial advancements have been achieved, and the intensity of research interest continues to escalate. As investigations persist, ICIs are anticipated to offer increased hope and breakthroughs in the treatment of cervical cancer patients.

Disclosure statement

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

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Author contributions

C.S.: Methodology, formal analysis, investigation, and writing – original draft. J.Z.: Manuscript, investigation, and figure preparation. G.Z.: Manuscript, investigation, and data curation. H.L.: Investigation and data curation. S.Z.: Investigation and data curation. Q.Y.: Investigation and data curation. W.X.: Investigation, methodology and data curation. W.W.: Methodology, formal analysis, and supervision. L.M.: Conceptualization, methodology, and supervision.

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