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REVIEW

New biomarkers for diagnosis of bladder cancer: A bibliometric analysis

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Summary ***Background/Objectives: Bladder cancer is a multifactorial disease, ranking as the 10th most common cancer globally and the fourth most common cancer in men and the ninth in women in the Western world. This bibliometric analysis aims to identify and evaluate scientific literature addressing new biomarkers for bladder cancer diagnosis, as well as to identify the most prolific organizations, authors, journals, countries, and keywords within this research domain.***

Methods: An electronic search was conducted using Elsevier's Scopus database. From a total of 940 retrieved papers (published between 2019 and 2024), 493 were selected. For data analysis and visualization, the titles of articles, year of publication, countries, authors, journals, articles, and keywords were analyzed using Microsoft Excel, VOSviewer, and Biblioshiny.

Results: China published the most papers (200 articles) and received the highest number of citations, followed by the USA. While some countries, such as Egypt and India, published exclusively Single Country Publications (SCPs), others demonstrated a higher level of international collaboration, with at least half of their publications being Multi-Country Publications (MCPs). Countries with higher rates of MCPs were Greece (66.6%), Italy (53.8%), Korea, and France (50%). The journals that produced the most publications and received the highest number of citations were Cancers, International Journal of Molecular Sciences, and Frontiers in Oncology, confirming their role in producing high-impact research.

Conclusions: The consistent distribution of publications over the years considered indicates a sustained interest in this field.

KEY WORDS: Bladder cancer; Biomarkers; Diagnosis; Screening; Bibliometric analysis.

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INTRODUCTION

Bladder cancer (BC) diagnosis has traditionally relied upon different diagnostic tests, both invasive and non-invasive, including imaging-based, molecular, urine-based, and histopathological tests. Invasive tests include cystoscopy and fluorescence cystoscopy which remain the gold standard for detecting bladder cancer. Non-invasive tests include urine cytology (a standard test with high specificity but low sensitivity especially for low-grade cancers) (1-3). Urine-based tests are the most common non-invasive methods for detecting bladder cancer, including protein, transcriptomic, and epigenetic markers. Multiple studies have assessed cell-free DNA, DNA mutation, methylated DNA, circulating tumour cells, miRNA, mRNAs, cell-free proteins and peptides in urine specimens and blood (4). Circulating *urinary tumour DNA* (utDNA) has shown a major sensitivity over traditional urine cytology and offers genomic and epigenetic insights (5). Four urinary biomarkers have FDA approval, but they have not replaced cystoscopy and cytology due to limitations in sensitivity and specificity (6). Several studies have identified several proteins in urinary *extracellular vehicles* (EVs) that show potential, such as MASP2, C3, A2M, CHMP2A, and NHERF1 (7).

Advances in next-generation sequencing have highlighted genomic, transcriptomic, and epigenetic markers as promising candidates (8). Furthermore, in the current literature, multitarget biomarker panels offer better diagnostic accuracy compared with single biomarkers (9, 10). Research has focused on identifying new biomarkers capable of reducing the use of invasive diagnostic methods or to be complements of traditional methods (1-3), however, their clinical utility is still under investigation due to varying sensitivity and specificity.

For this reason, the aim of our work is, through a bibliometric analysis of the literature, to evaluate the typology, methods, diffusion, and evolution of published papers to orient towards more aware research of the available material. Currently, bibliometric analysis has turned into an accepted method to present the research patterns of scientific literature (11). It provides evidence regarding the progress of a specific domain, accentuating the most relevant country, journals, authors, and institutes involved in

the research area (12, 13). During these years, the results of bibliometric analyses were used in orthopaedics, gynaecology, and other medical fields (14-17), providing a guide for further research on disease prevention and treatment (18, 19). However, there is a paucity of bibliometric studies examining biomarkers in bladder cancer.
Therefore, this study systematically analyzed the research of biomarkers in BC, to assess frontiers and hotspots in this field. In summary, the aim of this study was to analyze global developments in biomarker studies, providing a valid analysis that projects the researcher towards new directions such as personalized medicine, liquid biopsy or the use of combinations of markers to improve diagnostic accuracy, sensitivity and specificity of tests and personalized treatment of the patient.

Materials and methods

The overall methodology followed to perform the bibliometric analysis has been reported in Figure 1.

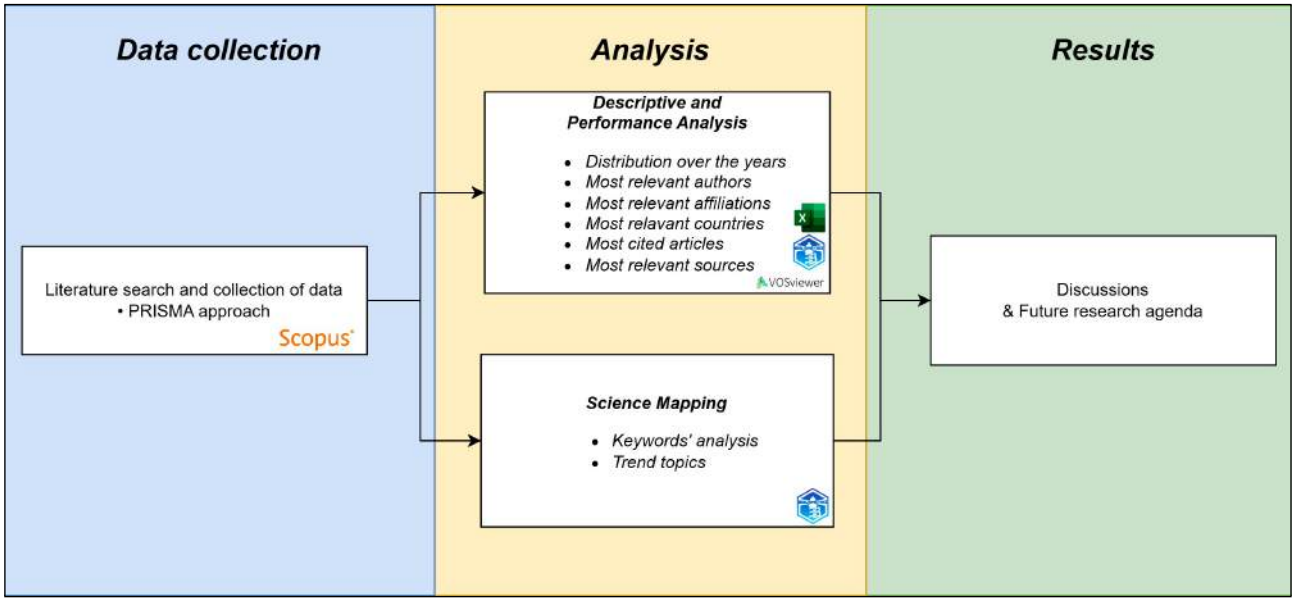
Data collection

The Scopus database, one of the largest peer-reviewed databases of multidisciplinary research publications, was used to search for the relevant literature related to the research topic of this study. The search was conducted in August 2024 and the search string was developed using terms in line with the aim of this research study. Search terms associated with (1) bladder cancer, (2) biomarkers, and (3) diagnosis have been combined using Boolean Operators ("OR", "AND"). The overall string developed is reported below.
TITLE-ABS-KEY(["*bladder cancer*" OR "*bladder carcinoma*") AND (biomarkers OR markers) AND (diagnosis)].
The *Preferred Reporting Items for Systematic Reviews and Meta-analysis* (PRISMA), i.e., a technique that provides a roadmap to study systematic reviews objectively, clearly, and transparently, has been adopted in this research study for the establishment of an eligible set of articles to analyze (20). All articles related to the use of biomarkers for diagnosis of bladder cancer have been considered relevant if they met the following criteria: (1) written in the English language, (2) focused on bladder cancer (3) involving biomarkers for diagnosis and not follow up of bladder cancer. The authors decided to include only research articles from peer-reviewed journals. This choice was mainly related to the quality of publications. The timespan was limited to the last six years (2019-2024). The period has been chosen to provide a detailed analysis of the topic focusing on the most recent publications trying to highlight how the research topic is changing. Two authors conducted the screening process following the PRISMA method as reported in Figure 2 following the inclusion criteria just discussed. In the analysis of the searched works, the following were excluded from the analysis: Articles not relevant to bladder cancer (233 articles), articles related to gallbladder pathologies (43 articles), case reports (23 articles), articles dedicated to the analysis of new biomarkers only for the follow up of bladder cancer (148 articles). Finally, data from the selected articles were gathered and stored in **.csv formats.

Analysis

After having defined the final set of articles, the bibliometric analysis was carried out using Microsoft Excel and two bibliometric tools Biblioshiny and VOSviewer. Biblioshiny is an R statistical programming language tool developed by *Aria and Cuccurullo* (2017) (21) and designed for quantitative evaluation. The user-friendly interface of Biblioshiny makes it simple for users to import, modify, and generate interactive visualizations of data. Also, VosViewer, freely available software developed for constructing and viewing bibliometric maps with significant attention to graphical representation, was employed for some of the analyses carried out.

Figure 1.
Research methodology.



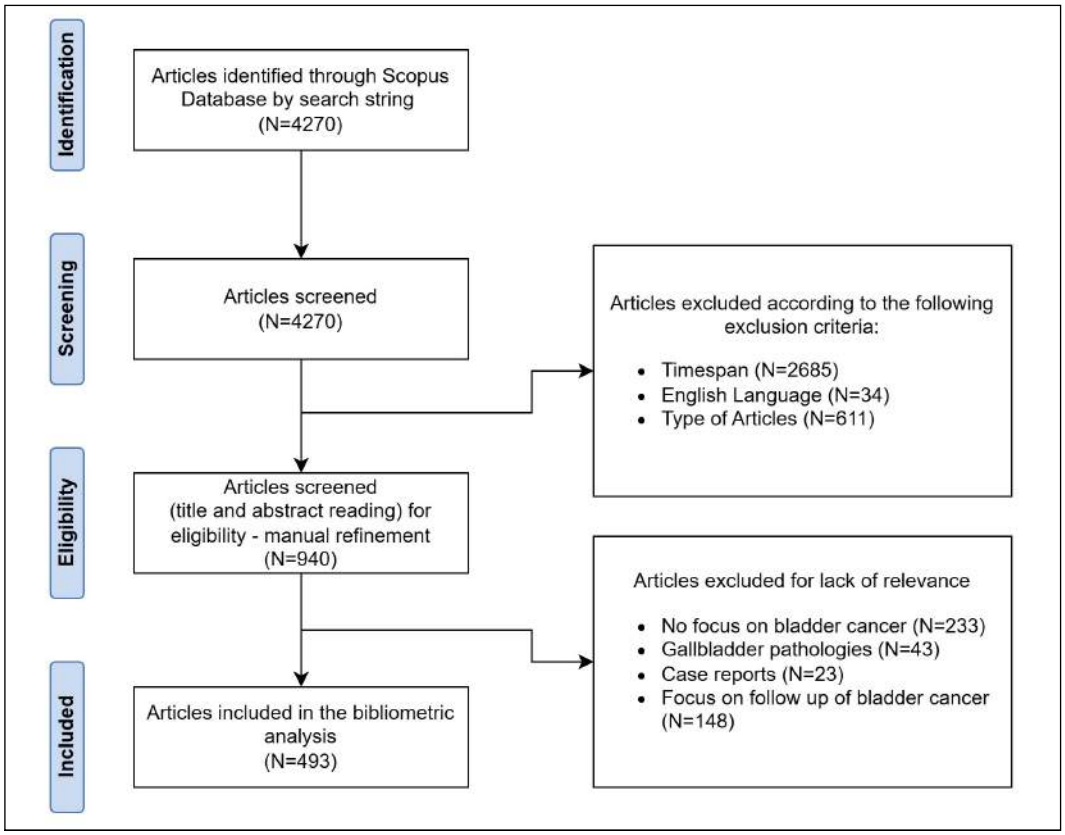


Figure 2.
PRISMA flow chart for the screening process. 493 included articles from a starting value of 4270 papers.

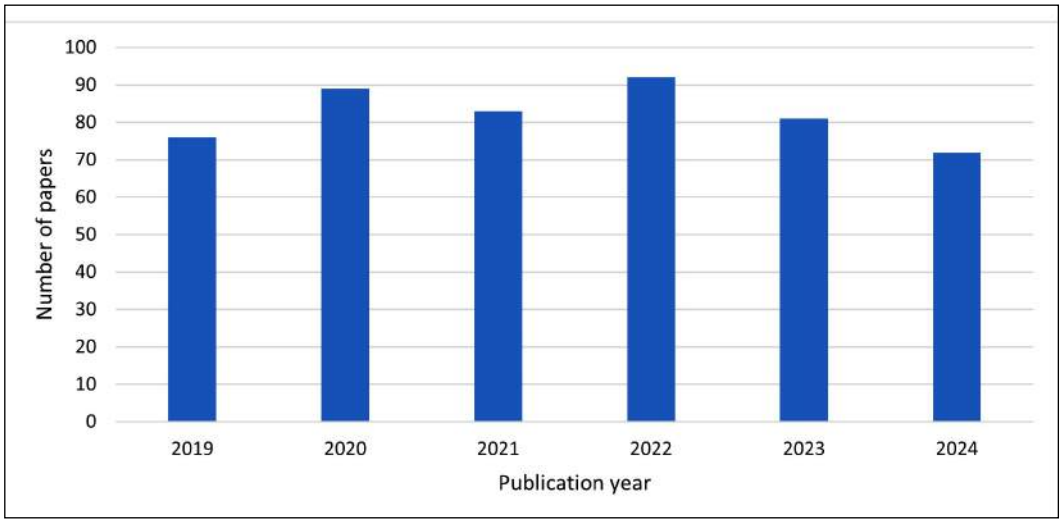


Figure 3.
Distribution of the number of papers per year.

As reported in Figure 1, a descriptive and performance analysis was defined.

This analysis, focused on the publications and their main characteristics, aimed to examine the contribution of researchers in a given field (22). The most relevant authors, sources, affiliations, articles, etc. have been identified objectively. Subsequently, a more detailed analysis in the field of science mapping was performed. Focusing on keywords as a unit of analysis, the existing and possible future relationships between the topics were investigated. Keywords and their trends revealed the main themes on which researchers have focused over the years and that dominate the research landscape.

Results

Figure 3 shows the annual change of studies from 2019 to 2024. The number of papers remains stable overall, highlighting a constant attention to the topic.

The 493 publications identified are distributed across 253 different sources.

Figure 4 exhibits the top 10 journals that contributed to the domain of bladder cancer biomarkers and in Figure 5 the citations received are reported. Cancers, *International Journal of Molecular Sciences and Frontiers in Oncology* published the highest number of articles (17 in the first 2 and 15 in the third), that received a high number of citations (respectively 213, 122 and 174). Urologic Oncology:

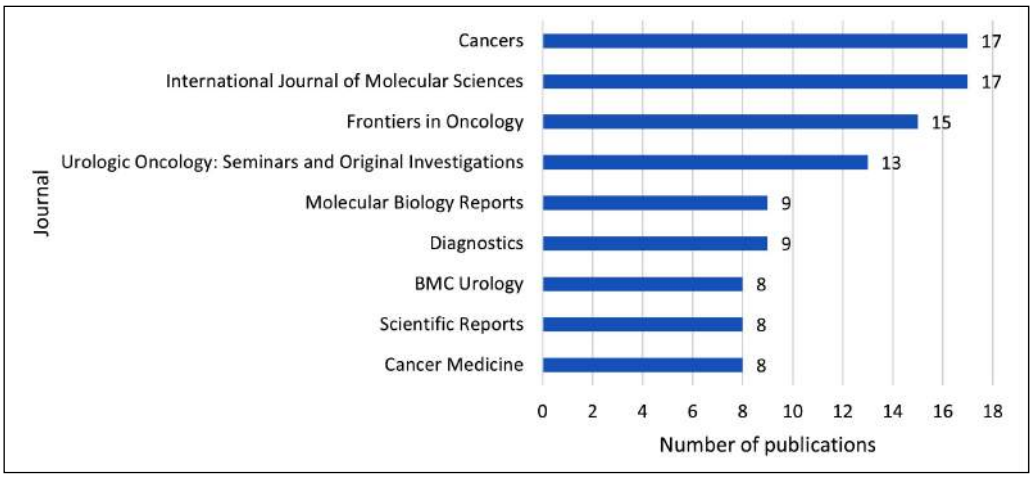


Figure 4.
Journals number of publications over the last 5 years.

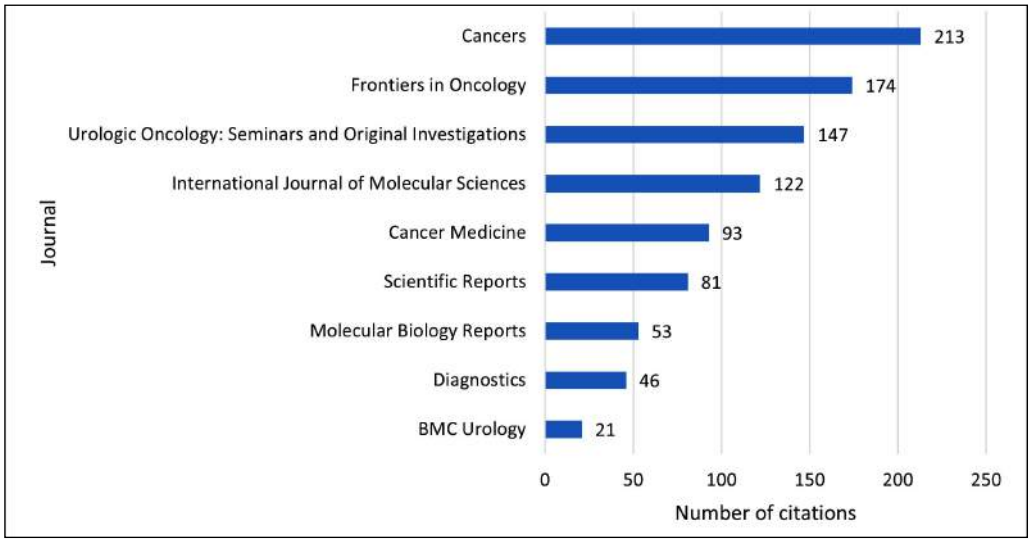


Figure 5.
Journals number of citations over the last five years.

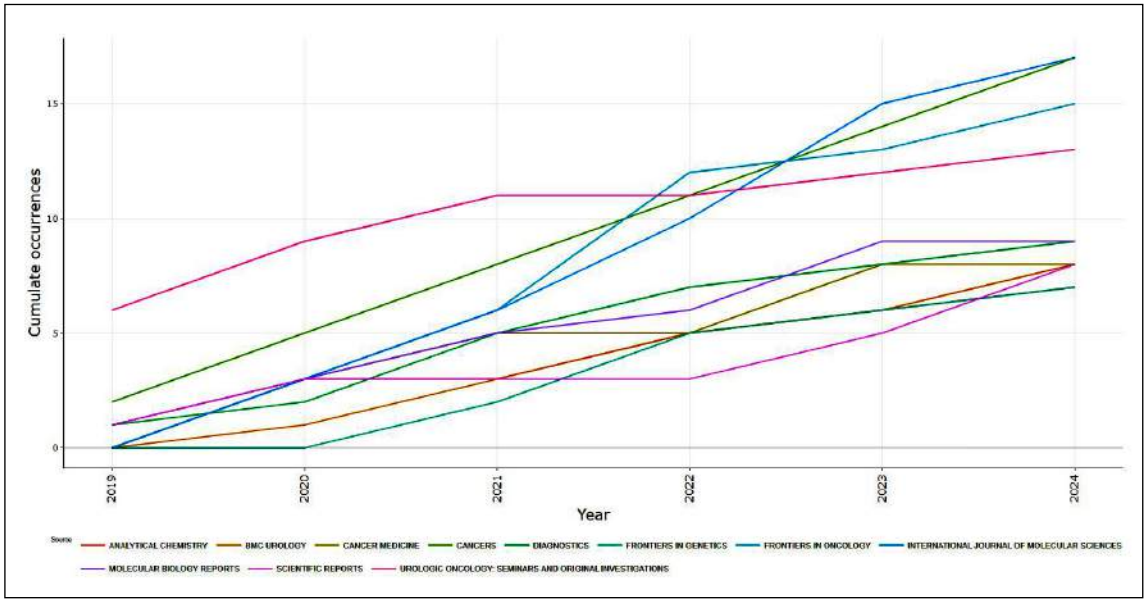


Figure 6.
Distribution of Sources over the last 5 years.

Seminars and Original Investigations is the first journal in the purely urological sector for the number of papers published, that is 13 with 147 citations. With 104 total publications, the top 10 journals published 21% of all publications identified in the last 5 years. Figure 6, instead, shows the evolution over time of publications on leading sources.

Figure 7.
Journals number of citations over the last five years.

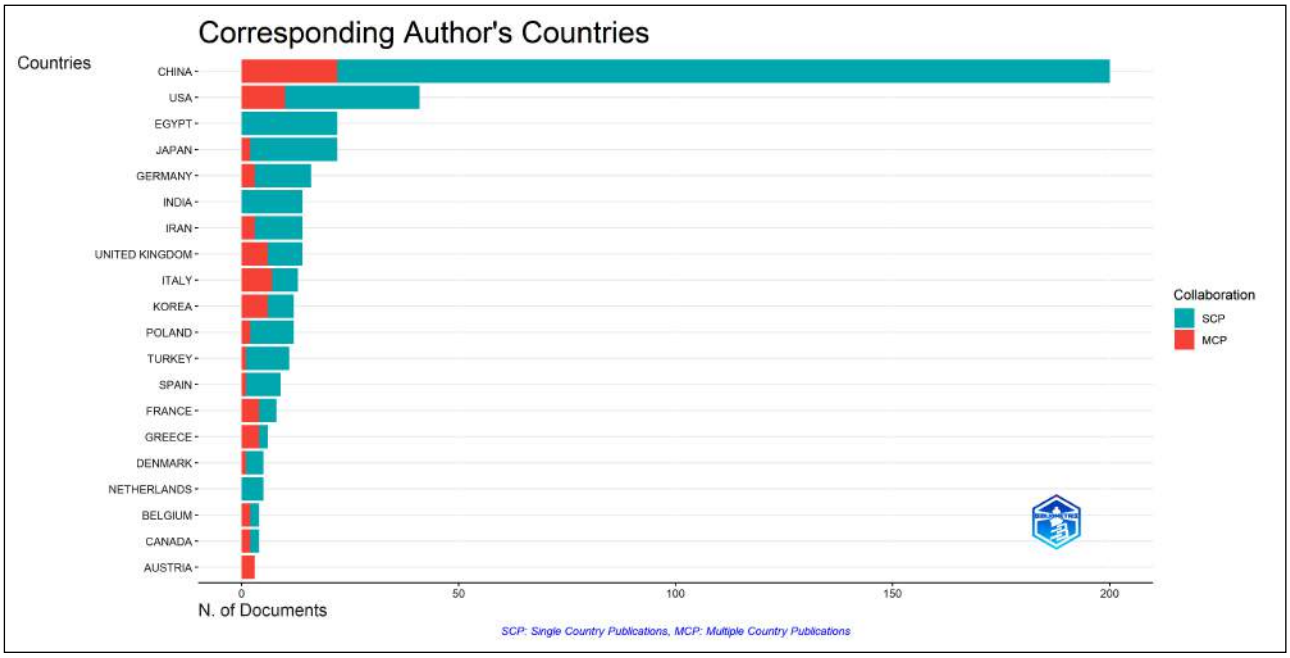


Table 1.
Number of country publications and distribution of SCP and MCP articles in percentage.

Country	Articles*	% Articles on the total sample	SCP	%SCP	MCP	%MCP	Article/Population**
CHINA	200	40.6%	178	89%	22	11%	0.14
USA	41	8.3%	31	75.6%	10	24.4%	0.12
EGYPT	22	4.5%	22	100%	0	0%	0.20
JAPAN	22	4.5%	20	90.9%	2	9.1%	0.18
GERMANY	16	3.2%	13	81.2%	3	18.8%	0.19
INDIA	14	2.8%	14	100%	0	0	0.01
IRAN	14	2.8%	11	78.6%	3	21.4%	0.16
UNITED KINGDOM	14	2.8%	8	57.1%	6	42.9%	0.20
ITALY	13	2.6%	6	46.2%	7	53.8%	0.22
KOREA	12	2.4%	6	50%	6	50%	0.23
POLAND	12	2.4%	10	83.3%	2	16.7%	0.33
TURKEY	11	2.2%	10	90.9%	1	9.1%	0.13
SPAIN	9	1.8%	8	88.9%	1	11.1%	0.19
FRANCE	8	1.6%	4	50%	4	50%	0.12
GREECE	6	1.2%	2	33.3%	4	66.7%	0.58

** Number of articles based on the corresponding authors. ** Population in millions of inhabitants.*

Performance of countries/regions on global output

Table 1 and Figure 7 show the leading countries (the first 15) that published the highest number of papers related to bladder cancer biomarkers based on the nationality of the corresponding author. All articles were analyzed also considering the difference between SCP (Single country publication) and MCP (multi country publication) to indicate in addition to the corresponding authors also the other authors belong to the identified country.

China published the highest number of papers (200) which represents 40.6% of all the articles identified, followed by the USA which published 41 articles (8.3% of the sample), although this primacy goes to Greece, followed by Poland, Korea, and Italy considering the ratio between the articles published and the population (expressed in millions of inhabitants) of the countries considered.

Some countries, such as Egypt and India, published exclusively SCP-type articles. The countries with at least half of MCP articles and therefore greater collaboration at an international level are Greece (66.6%), Italy (53.8%), Korea (50%), and France (50%). With respect to collaborations between authors from different countries, Figure 8 highlights the collaboration network identified in the selected papers. The different colors highlight the main clusters of co-authorship collaborations identified. It is clear that there are countries that have numerous collab-

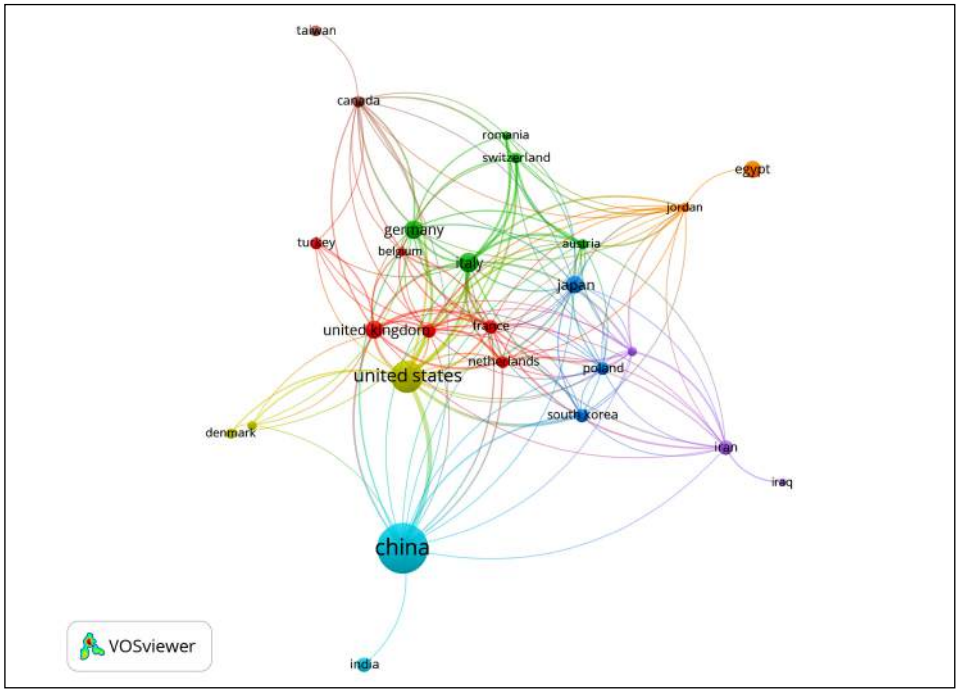
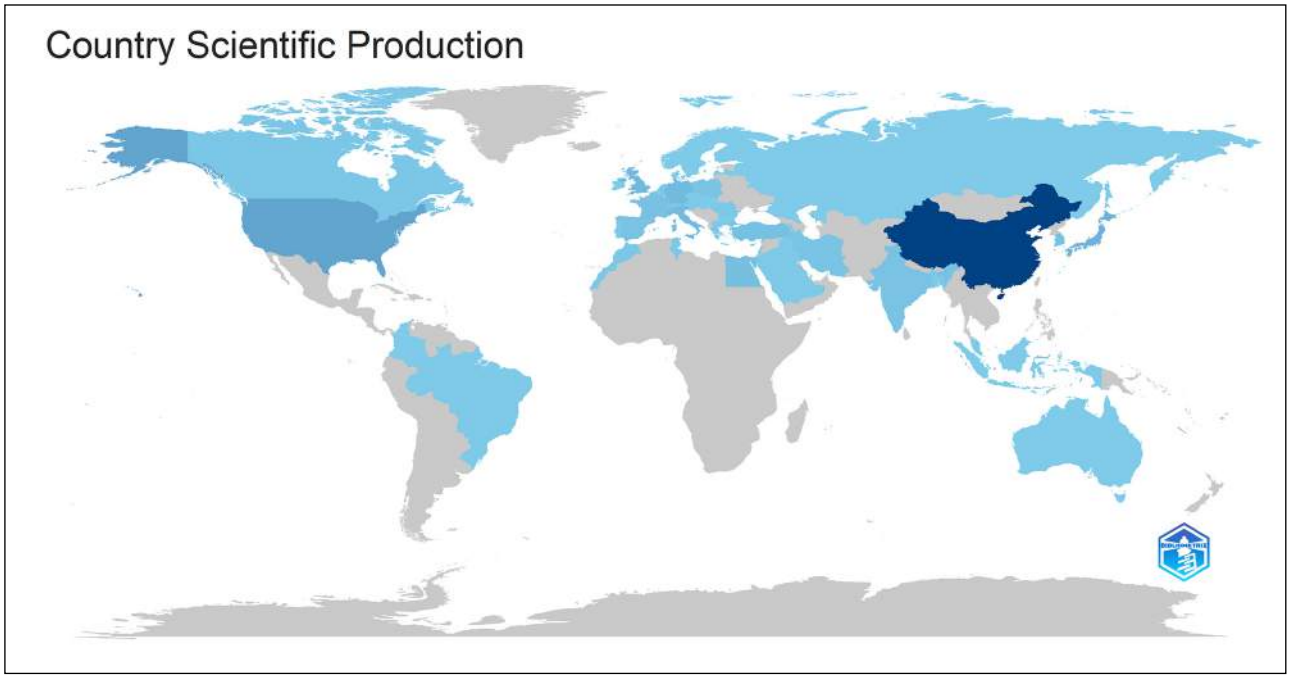


Figure 8.
Clusters of international collaborations.

Figure 9.
Country scientific Production. The highest saturation for the major number of publications.



orations (*China, USA, Italy, Germany, Japan*) and others with very limited collaborations (Egypt only with Jordan; India only with China; Iraq only with Iran; Taiwan only with Canada).

The *Country Scientific Production* (Figure 9 and Table 2) was also calculated by measuring the total number of Authors by country affiliation.

The number was obtained by considering the number of Corresponding Authors plus the number of co-authors of the same nationality who authored each paper.

As a result, the sum of values of Scientific Production of all the countries is higher than the total number of papers considered (each paper contributing with more authors apart from papers with a single authorship).

The results obtained numerically for the first 20 countries are reported in Table 2, where the overall production and total number of citations were also related to the population of the countries (millions of inhabitants in the year 2023). China and the USA are the top countries with respectively 1660 and 430 authors identified, however,

Figure 10.
Countries scientific production over time.

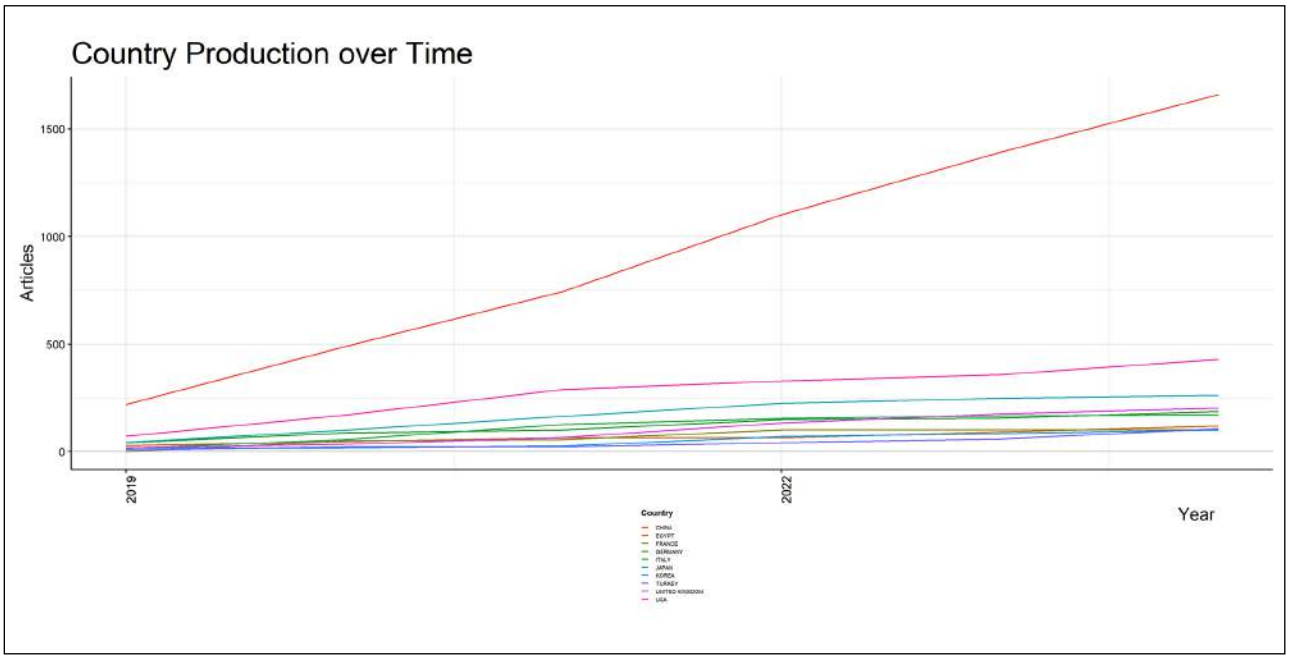


Table 2.
Results of top ten countries based on the country scientific production.

#	Country	Overall production	Total citations	Citations/ overall production	Country scientific production/ population *
1	CHINA	1660	2278	1.37	1.18
2	USA	430	612	1.42	1.28
3	JAPAN	263	347	1.32	2.11
4	UNITED KINGDOM	203	193	0.95	2.97
5	GERMANY	187	219	1.17	2.21
6	ITALY	171	135	0.79	2.91
7	EGYPT	120	201	1.68	1.06
8	TURKEY	107	39	0.36	1.25
9	FRANCE	101	594	5.88	1.48
10	KOREA	101	102	1.01	1.95
11	SPAIN	86	80	0.93	1.78
12	INDIA	84	40	0.48	0.06
13	IRAN	77	198	2.57	0.86
14	POLAND	71	90	1.27	1.94
15	NETHERLANDS	54	185	3.43	3.02
16	CANADA	47	39	0.83	1.17
17	GREECE	45	40	0.89	4.34
18	TUNISIA	43	8	0.19	3.45
19	DENMARK	41	9	0.22	6.89
20	ROMANIA	39	58	1.49	2.05

* *Population in millions of inhabitants.*

considering the Country Scientific production per million inhabitants, Denmark, Greece, Tunisia, Netherlands, UK, and Italy are the countries with the highest scientific production.

Figure 10 shows the trend of publications over time, showing strong growth for China and much slower growth for the remaining countries.

Focusing, instead, on the citations received by the different countries (Figure 11 and Table 2), a different trend is noted. China, the USA and Japan maintain the first positions, followed by countries such as France, or Iran which obtained a high number of citations despite a lower production. This aspect could depend on numerous factors: a greater or lesser quality of the published papers, different possibilities of access to the papers (open access or subscription), or a different temporal distribution of the works with relative impact on the recorded citations.

Table 3 analyses the results of the different countries compared to European and non-European countries. Although with a lower overall number, 94 corresponding authors and 921 Country scientific production for EU-countries and 380 and 3300 for the others, the works published at the European level show a higher ratio between the citations received and the works published (respectively 1.69 *versus* 1.31).

Furthermore, as also highlighted in Table 2 considering

	Articles	Country scientific production	Citation	Average articles/population*	Citations/country scientific production	Average country scientific production/population*
EU-countries	94	921	1554	0.29	1.69	2.19
No EU-countries	380	3300	4321	0.17	1.31	1.33

* *Population in millions of inhabitants.*

Table 3.
Results of the EU- countries and no EU-countries.

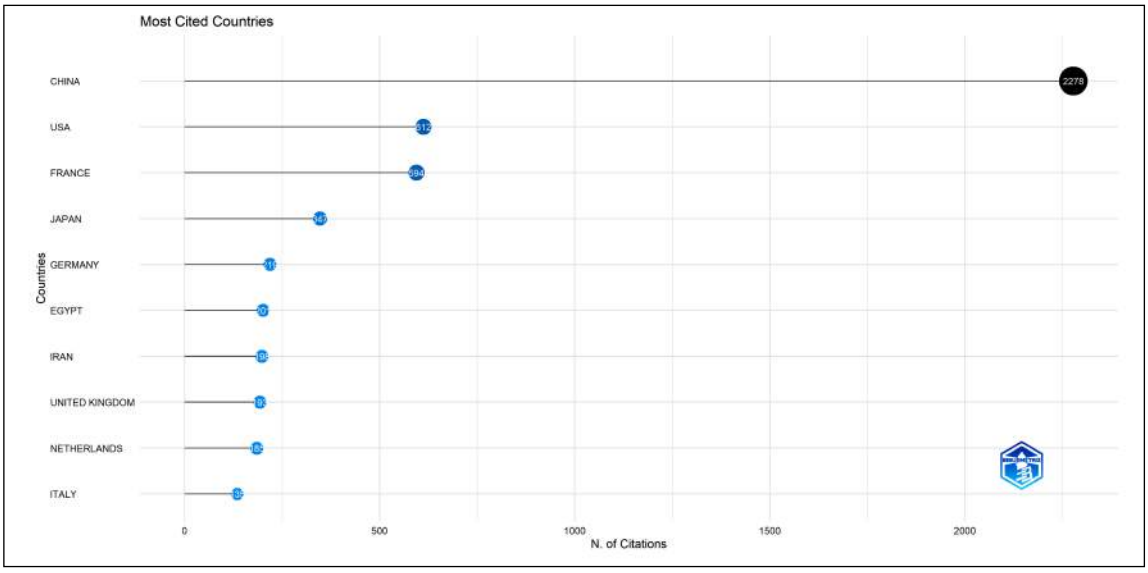


Figure 11.
Country Distribution of the number of citations.

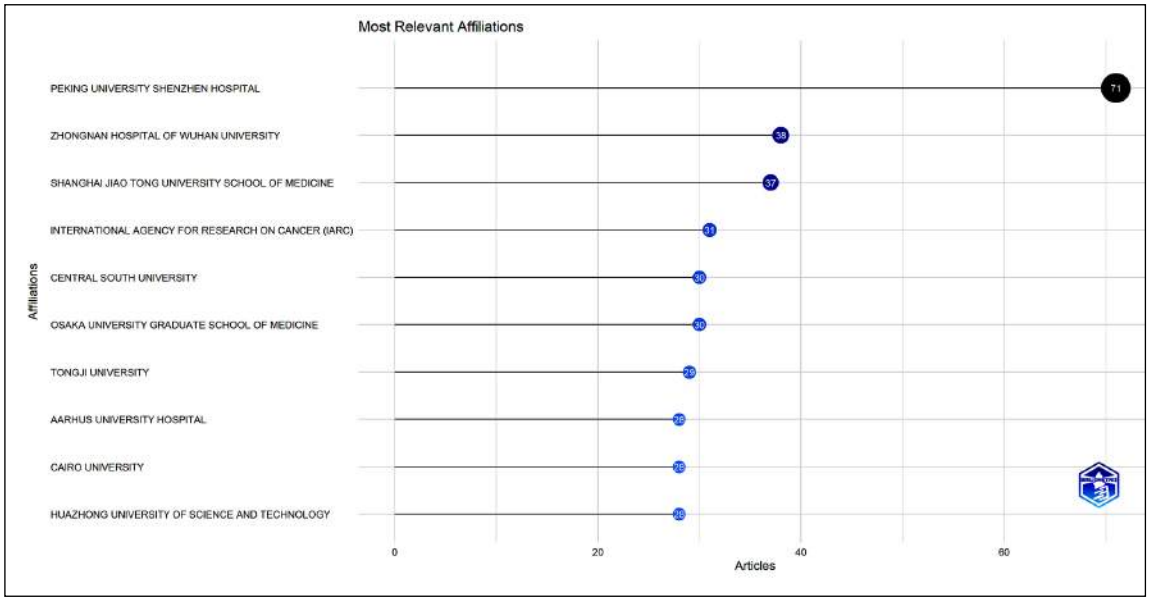


Figure 12.
Most relevant affiliations.

the overall population of the countries considered, at the European level the number of publications and citations received per million inhabitants is higher.

Affiliations performance analysis

Going into the details of the authors' affiliations, 1011 affiliations were identified for the 493 papers.

Figure 12 displays findings of the most relevant institutes, based on the corresponding authors, that are published the most within the field. *Peking University Shenzhein Hospital* published 71 papers, followed by *Zhongnan Hospital of Wuhan University* and *Shangai Jiao Tong University School of Medicine* with 38 and 37 papers respectively. These main institutes also show (Figure 13) an increase in publications in the last 5 years. Extending the evaluation to all the authors of the papers, the first five institutes are reported in Table 4, with evidence also of the increase over time.

Affiliation	Country	2019	2020	2021	2022	2023	2024	Tot
Peking University Shenzhen Hospital	China	0	8	10	31	2	20	71
Zhongnan Hospital of Wuhan University	China	8	9	9	0	0	12	38
Shanghai Jiao Tong University School of Medicine	China	5	2	0	20	10	0	37
International Agency for Research on Cancer (Iarc)	France	0	26	0	5	0	0	31
Central South University	China	9	0	4	8	9	0	30
Osaka University Graduate School of Medicine	Japan	0	16	0	14	0	0	30
Total		22	61	23	78	21	32	

* *Population in millions of inhabitants.*

Table 4.
Affiliations' publications over time - Details.

Figure 13.
Affiliations' production over time.

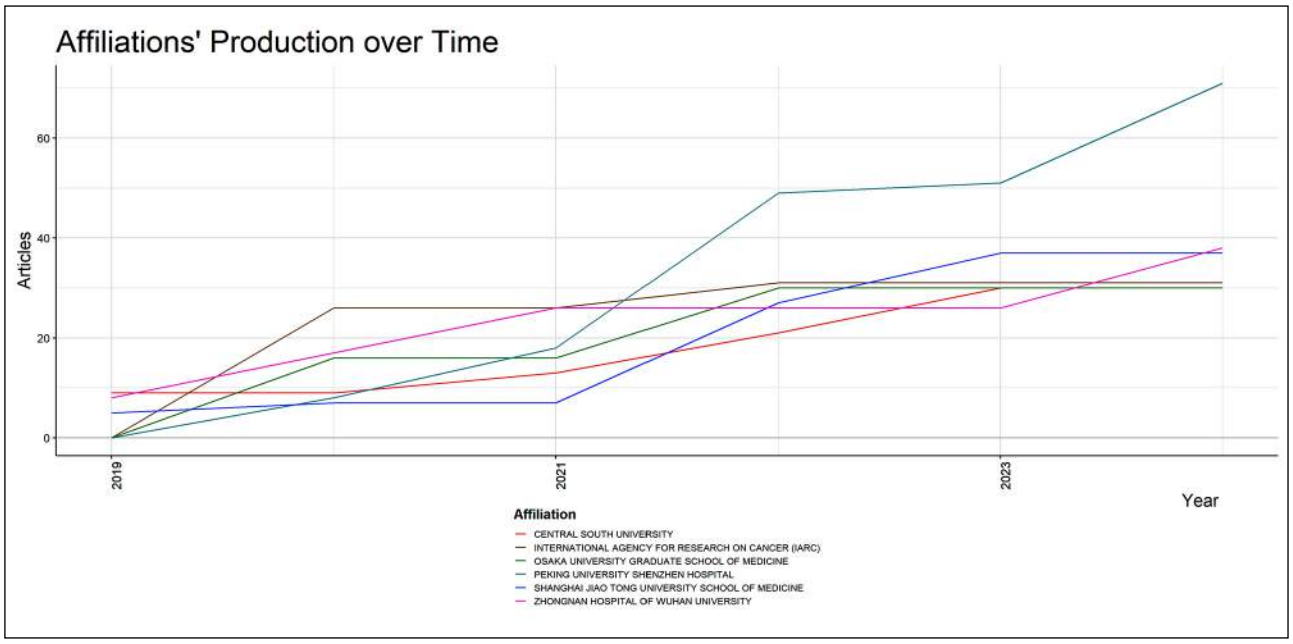
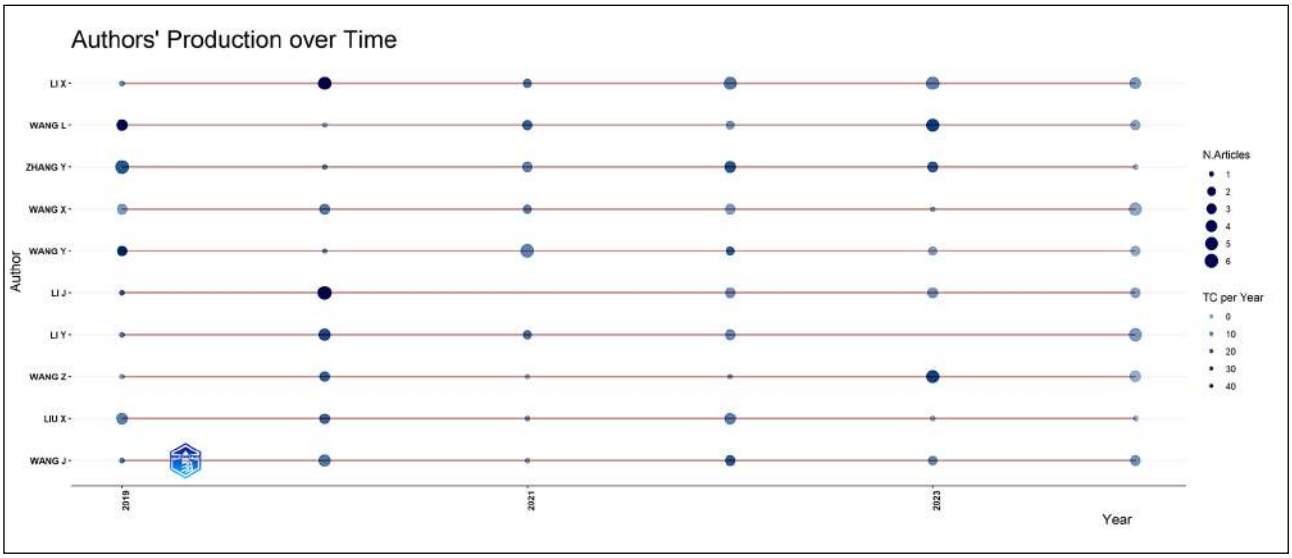


Figure 14.
Most relevant authors based on the number of. document over times.



Authors performance analysis

For 493 papers, a total of 3373 different authors were identified with an average of 9.42 authors per paper. Only 3 articles are published by a single author. Furthermore, the international co-authorship is equal to 20.08%.

Table 5 identifies the leading authors who published papers related to bladder cancer biomarkers in the last 5 years.

Li X. published 21 papers, followed by *Wang L, Wang X. Wang, Y and Zhang Y*, who published 17 articles each. *Li X.* was the highest cited author (345), followed by *Wang C* and *Wang Y*, who received 336 and 333 citations, respectively (Table 5, Figure 14). The co-occurrence of authors is shown in Figure 15.

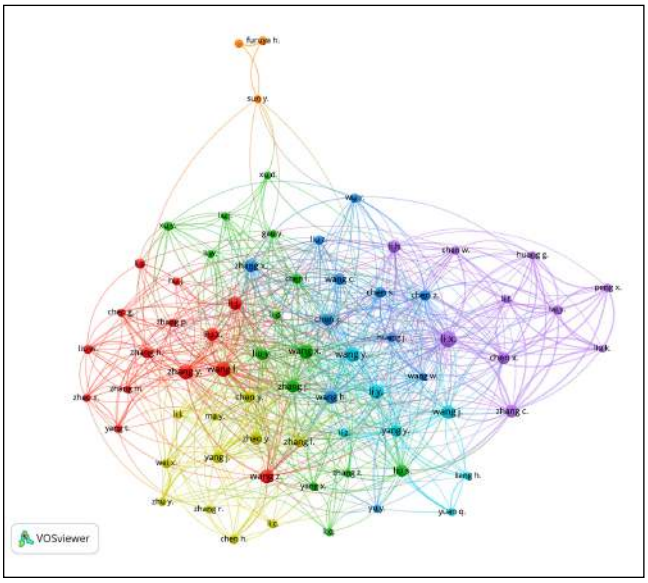
Documents performance analysis

Table 6 displays the highly cited papers on bladder cancer biomarkers. Among these, a paper *Alix-Panabieres C. et al.* published in 2021, received the highest citation (457). The subsequent most highly cited articles were by *Usuba W et al.*'s paper, which was published in 2019 and received 174 citations (Table 6).

Table 5.
Most leading authors (number of papers and citations).

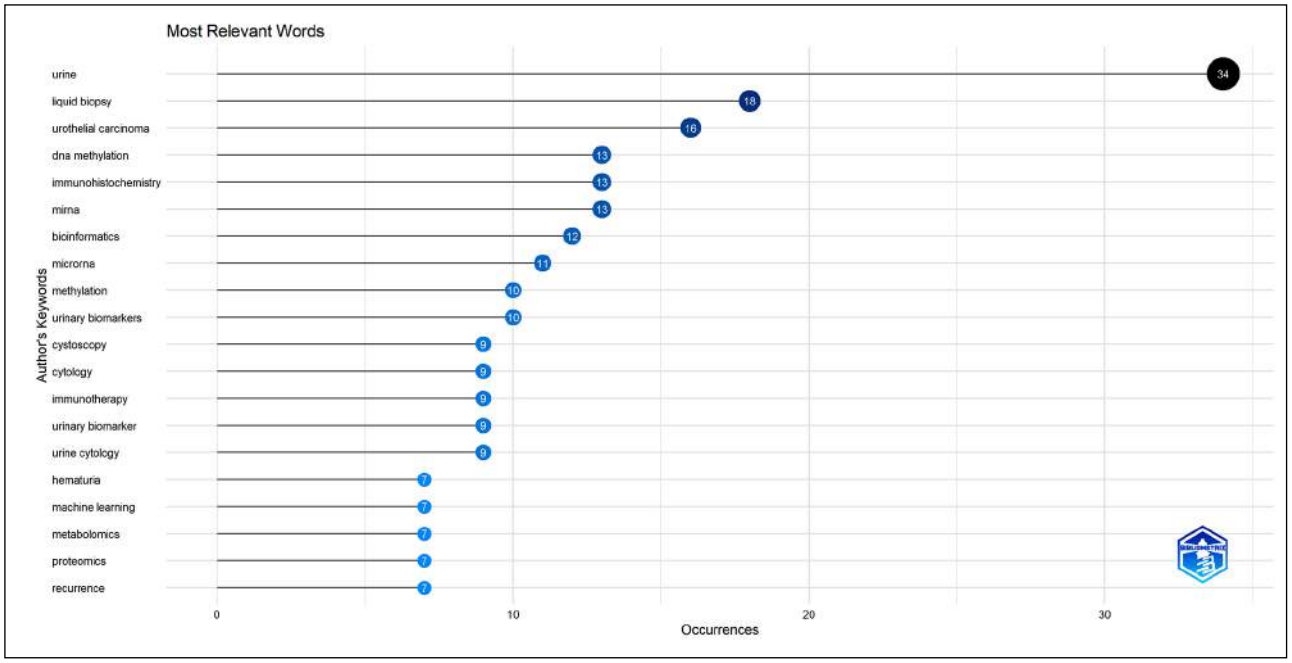
Author	Number of documents	Total citations
Li X.	21	345
Wang L.	17	261
Wang X.	17	139
Wang Y.	17	333
Zhang Y.	17	278
Li Y.	15	249
Wang Z.	15	164
Li J.	14	294
Wang J.	14	206
Wang H.	13	262
Zhang C.	13	91
Zhang J.	13	257
Li H.	12	124
Liu X.	12	141
Zhang X.	12	259
Zhao Y.	12	229
Chen J.	11	311
Chen X.	11	295
Liu S.	11	167
Liu Y.	11	90
Yang Y.	11	221
Chen Y.	10	67
Wang C.	10	336

Figure 15.
Co-authorship distribution.



papers identified (for example review, meta-analysis) were excluded. In this way, the top relevant keywords found in this analysis, according to the level of occurrence, were

Figure 16.
Most relevant keywords.



Keywords performance analysis

In the present analysis, various keywords were used in the domain of bladder cancer diagnostic biomarkers. Keyword performance analysis was carried out excluding the keywords used for primary research for example bladder cancers, biomarker, and all similar.

The keywords related to the methods applied in the urine (34 papers), liquid biopsy (18 papers), urothelial carcinoma (16 papers), DNA methylation (13 papers) and miRNA (13 papers) (Figure 16). Considering the frequency over the years considered, there is a growing use of the world urine, liquid biopsy, methylation, and miRna that confirm the interest in mini-invasive research of novel biomarkers for the diagnosis of BC (Figure 17).

Table 6.
The top ten most cited papers.

Ref.	Title	Authors	Years	Source title	Total citation (TC)	TC per year
(23)	Liquid biopsy: From discovery to clinical application	*Alix-Panabières C., Pantel K.*	2021	Cancer Discovery	485	121,25
(24)	Circulating miRNA panels for specific and early detection in bladder cancer	*Usuba W., Urabe F., Yamamoto Y., Matsuzaki J., Sasaki H., Ichikawa M., Takizawa S., Aoki Y., Niida S., Kato K., Egawa S., Chikaraishi T., Fujimoto H., Ochiya T.*	2019	Cancer Dcience	174	29
(25)	Urine DNA methylation assay enables early detection and recurrence monitoring for bladder cancer	*Chen X., Zhang J., Ruan W., Huang M., Wang C., Wang H., Jiang Z., Wang S., Liu Z., Liu C., Tan W., Yang J., Chen J., Chen Z., Li X., Zhang X., Xu P., Chen L., Xie R., Zhou Q., Xu S., Irwin D.L., Fan J.-B., Huang J., Lin T.*	2020	Journal of Cinical Investigation	139	27,8
(26)	Evaluation of serum exosomal LncRNA-based biomarker panel for diagnosis and recurrence prediction of bladder cancer	*Zhang S., Du L., Wang L., Jiang X., Zhan Y., Li J., Yan K., Duan W., Zhao Y., Wang L., Wang Y., Shi Y., Wang C.*	2019	Journal of Cellular and Molecular Medicine	103	17,17
(27)	The systemic immune-inflammation index is associated with an increased risk of incident cancer – A population-based cohort study	*Fest J., Ruiter R., Mulder M., Groot Koerkamp B., Ikram M.A., Stricker B.H., van Eijck C.H.J.*	2020	International Journal of Cancer	95	19
(28)	A renal-clearable macromolecular reporter for near-infrared fluorescence imaging of bladder cancer	*Huang J., Jiang Y., Li J., He S., Huang J., Pu K.*	2020	Angewandte Chemie - International Edition	78	15,6
(29)	Permutation-based identification of important biomarkers for complex diseases via machine learning models	*Mi X., Zou B., Zou F., Hu J.*	2021	Nature Communications	68	17
(30)	Highly sensitive detection of bladder cancer-related miRNA in urine using time-gated luminescent biochip	*Wang Y., Li Z., Lin Q., Wei Y., Wang J., Li Y., Yang R., Yuan Q.*	2019	ACS Sensors	61	10,17
(31)	LncRNA PVT1 regulates VEGFC through inhibiting miR-128 in bladder cancer cells	*Yu C., Longfei L., Long W., Feng Z., Chen J., Chao L., Peihua L., Xiongbing Z., Hequn C.*	2019	Journal of Cellular Physiology	50	8,33
(32)	Diagnostic accuracy of novel urinary biomarker tests in non-muscle-invasive bladder cancer: A systematic review and network meta-analysis	*Laukhtina E., Shim S.R., Mori K., D'Andrea D., Soria F., Rajwa P., Mostafaei H., Compérat E., Cimadamore A., Moschini M., Teoh J.Y.-C., Enikeev D., Xylinas E., Lotan Y., Palou J., Gontero P., Babjuk M., Witjes J.A., Kamat A.M., Roupret M., Shariat S.F., Pradere B., European Association of Urology-Young Academic Urologists (EAU-YAU): Urothelial Carcinoma Working Group*	2021	European Urology Oncology	49	12,25

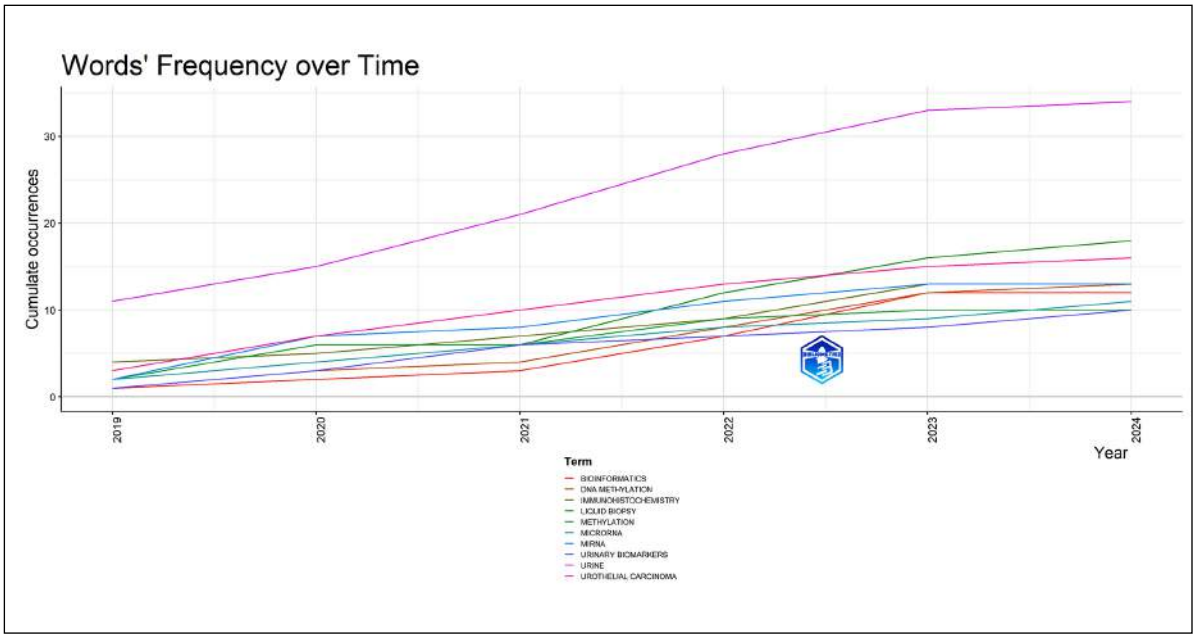


Figure 17. *Keywords frequency over time.*

Discussion

To the best of the authors' knowledge, this is the first bibliometric analysis focusing on research based on new biomarkers in the diagnosis of bladder cancer from 2019 to 2024 over the last 6 years. The Scopus database was used to generate an eligible set of articles related to the topic field including only research articles from peer-reviewed journals to guarantee the high level of the publications analyzed.

The six-year time interval taken into consideration was chosen with the aim of evaluating how research has evolved in the last period, how it is changing, and which are the most important and recent results. Several parameters have been taken into consideration such as journals, the contribution of nations and organizations, citations, leading countries, author's contributions and keywords. With the support of the bibliometric analysis and mapping a better visualization of organizations and dynamics of science domains have been done to make a deep description of this scientific field and to provide predictions for future trends.

The analysis revealed that the distribution of publications over the 6-year interval remained almost constant, highlighting an ever-present interest in the field under study.

An interesting finding of this bibliometric analysis was that most of the papers were published in the most influential and pertinent journals, having a high impact factor, this underlining that the papers published are characterized by a lot of citations.

Even if some countries, like Egypt and India, published exclusively SCP-Type articles, other nations showed at least half of MCP-articles showing greater collaborations at an international level. This is the case of Greece with 66.6%, Italy with 53.8%, and Korea and France with 50% of MCP article. The number of citations of these MCP articles underlined also the strong value of the publications on the field in analysis and the high impact on research.

The main clusters of international collaborations and co-authorship were shown in Figure 8 and underlined how nations like Italy, the USA, China, Germany, and Japan had numerous collaborations while Egypt, Taiwan, Iraq, and India showed limited collaborations, this confirming the results of our analysis on their propension to SCP-articles.

The journals which produced the greatest number of works were Cancers, *International Journal of Molecular Sciences*, and Frontiers in Oncology and they received a high number of citations, confirming their role in producing highly impactful publications. Urologic Oncology: Seminars and Original investigations was the first purely urological Journal for publications in this field, with 13 works and 147 citations. It should be noted that the top ten journals published 21% of all publications identified by our analysis.

Considering the number of national publications (Figure 9), China was the best publisher, with the highest number of papers in this field (200), representing the 40% of all articles. The second country for the number of publications was the USA with 41 articles (8.3%). Considering the pure number of citations, China is in the first place, but considering the country's production over time, Figure 10 showed how China, the USA, and Japan were the first publishers with a growing interest, followed by France and Iran that on the contrary obtained a high number of citations despite a lower production of articles. The explanation for this phenomenon is probably linked to different factors including, better or worse quality of the works, the different possibilities of accessing these works or the different temporal distribution of the articles with a consequent different impact on citations.

However, considering the overall population of the different countries, it is above all the European countries that have the greatest scientific production and also the greatest capillarity and resonance of the published works, as evidenced by the greater number of citations received.

Affiliation Performance analysis details on author's affiliations and most relevant institutes involved in the research. Peking University Shenzhein Hospital was the first publisher with 71 papers, followed by *Zhongnan Hospital of Wuhan University* and *Shangai Jiao Tong University School of Medicine* with respectively 38 and 37 papers, thus confirming that the main institutes correspond to the main country publisher (China). The analysis also confirmed the growing trend of publications of these institutes over the last 5 years, confirming the constant interest in the field of study.

The Authors performance analysis showed the highest cited authors, underlining how there was a correspondence between the author with the greatest number of publications and the one with the greatest number of citations, as shown in Table 5.

A piece of fundamental importance in our research is represented by document performance analysis which showed the most cited works.

In the study of *Alix-Panabierès C et al.* (2021), enormous attention was given to the role of *Circulating Tumor Cells* (CTC) and *Circulating Tumor DNA* (ctDNA) as new biomarkers with clinical application in early cancer detection, improved cancer staging, detection of relapse and monitoring of therapeutic efficacy (23).

Usuba W et al. (2019) underlined the role of miRNa profiles as a tool for liquid biopsy in bladder cancer screening and performed a global miRNA profiling of 392 serum samples of bladder cancer patients with 100 non-cancer samples and 480 samples of other cancers as controls, thus demonstrating that the 7-miRNA panel could be a biomarker for the specific and early detection of bladder cancer (24). In this research study, a careful choice of keywords (bladder cancer; circulating microRNA; diagnosis; early detection; liquid biopsy) has shown the real importance and great impact of the topic of work.

In the third most cited paper, *Chen X et al.* (2020) developed a diagnostic model capable of identifying Bca-specific methylation markers and compared it with cytology and FISH (25). With this model, they showed how urine tumor DNA methylation assessment for early diagnosis but also for minimal residual tumor detection and surveillance in Bca could be proposed as a rapid, noninvasive, and promising approach to reduce the burden of invasive methods.

The keyword performance analysis showed the most relevant words used in the papers and their frequency over time. Considering also the frequency over the years, there was a growing use of the words urine, liquid biopsy,

methylation, and miRna that confirm that the research hotspots are supported by the interest in novel biomarkers for the diagnosis of BC.
In this analysis, the choice to exclude the keywords used in the first search was dictated by the desire to increase the appropriateness of the article selection. In this way, it was possible to highlight keywords such as liquid biopsy, miRNA, and urine, useful for understanding which type of research the various authors were leaning towards.
These results have underlined the trend of research towards non-invasive diagnostic approaches such as urinalysis and liquid biopsy.
The growing use of these words is also confirmed by the analysis of the frequency of their use in literature over the years, thus underlining that the research hotspots are supported by the interest in identifying new diagnostic methods and new biomarkers in the diagnosis of BC.

Conclusions

This bibliometric analysis demonstrated that research on biomarkers in BC is in rapid evolution. Nonetheless, this study has limitations, since we have used only one database, namely the Scopus database which does not represent the entire literature, and some articles not indexed could not be included. However, bibliometric analyses are a precise instrument in the field of medicine, giving us the possibility to better understand the evolution of literature, the collaborations, and the value of the papers published. Furthermore, it highlighted the links between the various nations, institutes, and authors, bringing to light the great value of collaboration between the different structures.
From a clinical point of view, this bibliometric analysis has shown, through the articles taken into consideration, the propensity of the research towards non-invasive methods of diagnosis of bladder carcinoma that could support or replace conventional diagnostic methods. It has also underlined the possibility that the combination of different biomarkers could potentially improve diagnostic accuracy and contribute to increasing the accuracy (sensitivity and specificity) of the tests. Although large-scale clinical trials are necessary to validate the effectiveness of these biomarkers and also evaluation of the costs of developing urinary biomarkers tests should be taken into account.

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Declarations

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