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Review

The 100 most-cited articles in castration-resistant prostate cancer: a bibliometric analysis

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Abstract

Purpose: To assess the present landscape and future research directions, a bibliometric analysis was performed to identify the characteristics of the 100 most-cited articles (T100 articles) on CRPC research. **Methods**: A list of the T100 articles investigating CRPC was generated by searching the Web of Science (WoS) Core Collection database. Different characteristics of the T100 articles, including the countries/territories, journals, authors, and research areas, were analyzed. **Results**: The number of citations of T100 articles published between 1992 and 2017 ranged from 282 to 3594, with an average of 654.9 citations. According to the topic of the article, "Mechanisms related to tumor progression or metastasis" ranked first with 41 T100 articles, while immunotherapy ranked fourth with 7 T100 articles. The T100 articles originated from 31 countries, with more than half originating from the USA (n = 89). Professor Scher HI published the most T100 articles as the first author (4) and as the corresponding author (5), while Pro De Bono JS from the Institute of Cancer Research published 3 articles as the first author and 8 articles as the corresponding author. The journal Cancer Research published 20 T100 articles with a total of 8946 citations. The number of T100 articles ($r = 0.485$, $P = 0.01$) and the total number of citations ($r = 0.626$, $P < 0.001$) were all positively correlated with the IF of the journal. **Conclusions**: This analysis offers a historical perspective on the progress and attempts to reveal future trends in CRPC research using bibliometric analysis. This study's results suggest that immunotherapy and the study of androgen receptors as well as their signaling axes will possibly be hot topics and trends in CRPC research.

Keywords: Castration-resistant prostate cancer (CRPC); Mechanism; Tumor progression; Metastasis; Immunotherapy; Bibliometric analysis

1. Background

Castration-resistant prostate cancer (CRPC) is an aggressive type of prostate cancer with a poor prognosis [1,2]. Considering the high worldwide incidence of prostate cancer, tremendous efforts have been made in this research field. Benefiting from the remarkable progress in understanding the mechanisms related to tumor resistance, progression and metastasis, cytotoxic chemotherapy agents, a new generation of anti-androgen agents, immunotherapies, and PARP inhibitors have been recommended for treating advanced prostate cancers [3,4]. Due to drug development advancements, these patients' survival and quality of life have been improved [3,5]. In summary, large numbers of papers about CRPC have been published, and new discoveries regarding its mechanism and treatment have been studied. The CRPC field has evolved tremendously in the past three decades. Therefore, a retrospective analysis was necessary to identify the important contributors and profound progress in the development of CRPC research.

The number of citations is one important evaluation index used to assess a study's academic influence [6]. Bibliometric analysis (i.e., content and citation analysis) can be used to measure articles' influence, assess status and trends, and even provide ideas and directions for future research in a particular research field [7–9]. Bibliometric studies have been widely applied in medical research and have provided insights for some fields, including neuroimaging [10], palliative oncology [11], psoriatic arthritis [12], urological surgery [13] and nephrology [14].

Although several bibliometric studies on the partial or entire field of prostate cancer have been published in recent years [15,16], a citation analysis estimating the most cited articles that have defined and shaped the CRPC field has never been performed. This study's purpose was to analyze the 100 most-cited (T100) articles on CRPC in an attempt to highlight the most significant improvements made in the field over the past several decades. The publication year, number of citations, publishing journal, research topic, country of origin and other key features of each article were examined to highlight historical and geographic trends and the scientific progression timeline in the CRPC field.

2. Methods

The data were acquired using the Web of Science (WoS) Core Collection database by searching the "topic" field on July 9th, 2019. The search strategy for the WoS database was (TS = "hormone refractory" or "castrat* resistant" or "hormone resistant" or "hormone independent" or "androgen independent" or "hormone insensitive" or "androgen refractory" or "androgen insensitive" or "androgen resistant" or "castration recurrent" or "castration refractory") and ("prostat* Tumor*" or "prostat* Neoplasm*" or "prostat* carcinoma*" or "prostat* Cancer*" or "prostat* adenocarcinoma*" or "CRPC" or "neuroendocrine prostate cancer" or "NEPC"). No time or study type limitations were applied for the investigation. The 100 most-cited articles according to the number of citations were identified by two independent reviewers who evaluated the yielded titles, abstracts and even the full article in cases of disagreement. Data such as titles, authors, journals and citations of the T100 articles were recorded and analyzed. Derwent Data Analyzer (DDA) software was used to acquire the data and analyze countries, international cooperation and to draw a network diagram from a cooccurrence matrix. This study did not require ethical approval.

All data are expressed as the median and interquartile range. The data was tested for normal distribution before correlation analysis, followed by the Pearson or Spearman correlation analysis, which was used to value the strength and direction of the linear relation between the IF of the journal and the number of citations. All data analyses were performed using SPSS software, version 22. All probability values reported were two-tailed, and probability values <0.05 were considered statistically significant.

3. Results

A total of 16,746 papers were identified after an initial search of the period from 1978 to 2019. The number of citations of the 100 most-cited papers published between 1992 and 2017 ranged from 282 to 3594 (mean, 654.89 $\pm$ 569.36; median, 423; IQR, 394.5) as shown in Fig. 1 and **Supplementary Table 1**. The oldest T100 article was published in 1992, with a total citation number of 1027; this article demonstrated that bcl-2 expression is correlated with the progression of prostate cancer from androgen dependence to androgen independence. The most recent article, published in the journal European Urology in 2017 with a citation number of 314, described guidelines for treating CRPC. The most-cited article published in the New England Journal of Medicine in 2004 was written by professor Tannock IF with a total citation number of 3594. In 2004 and 2010, the highest number of T100 articles were published, at 10 for each year. Only 2 T100 articles were published in each of the last 5 years. 40 T100 articles had a total citation number of more than 500 as shown in **Supplementary Table 1**.

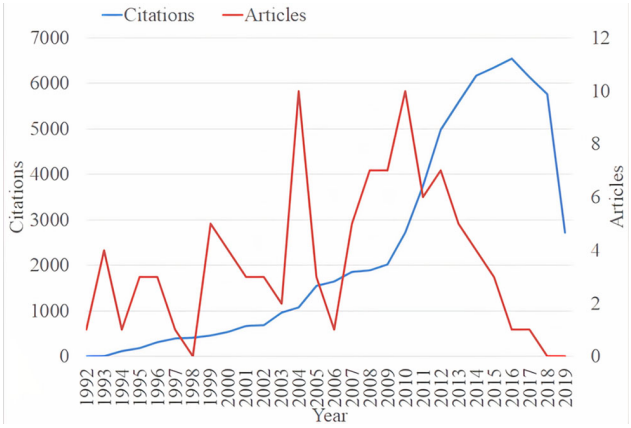

Fig. 1. Numbers of the most-cited articles published from 1992 to 2019.

Fig. 2A presents the distribution of the research areas for the T100 articles. "Oncology" was the dominant research area with a 57% proportion, followed by "General internal medicine" with a 15% proportion. However, the distribution differed for the "topic" category, which Fig. 2B shows. "Mechanisms related to tumor progression or metastasis" ranked first, with 41 T100 articles, and androgen receptor-related research comprised the majority of this topic. "Hormone therapy" ranked second with 15 T100 articles. "Immunotherapy" ranked fourth with 7 T100 articles. In addition, 5 guidelines related to CRPC were found in the T100 articles.

The T100 articles originated from 31 countries. Articles originating from England, Wales, Northern Ireland, and Scotland were classified as belonging to the United Kingdom (UK). Countries with more than 6 publications are shown in Fig. 3A. The USA ranked first, with a total of 89 published articles. The UK ranked second, with 40 T100 articles, followed by Canada (18), France (15), Italy (13) and the Netherlands (11). The academic collaboration network of the top 10 most productive countries is presented in Fig. 3B. The USA was the core of the academic collaboration network and the leader of CRPC research in cooperation with the other countries. The UK, Canada and France were the next three core members of this network, respectively, and had the closest cooperative relationships with the USA.

A total of 1022 scientists contributed to the T100 articles. Authors who published at least 2 articles as first authors are presented in Table 1. Pro Scher HI from Memorial Sloan Kettering Cancer Center published the most T100 articles as first author (4) and as corresponding author (5), followed by Pro De Bono JS from Institute of Cancer Research, who published 3 articles as first author and 8 articles as corresponding author. Pro Small EJ from the University of California San Francisco ranked third, publishing 3 articles as the first author and 3 articles as the corresponding author.

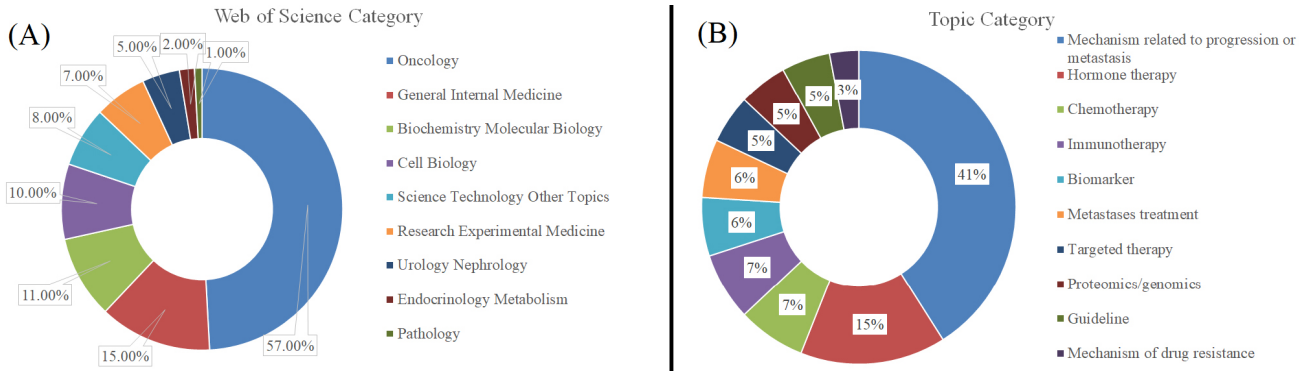

Fig. 2. Contribution of the research areas among the T100 articles. (A) The distribution of the T100 articles according to Web of Science category. (B) The distribution of the T100 articles according to the article topic.

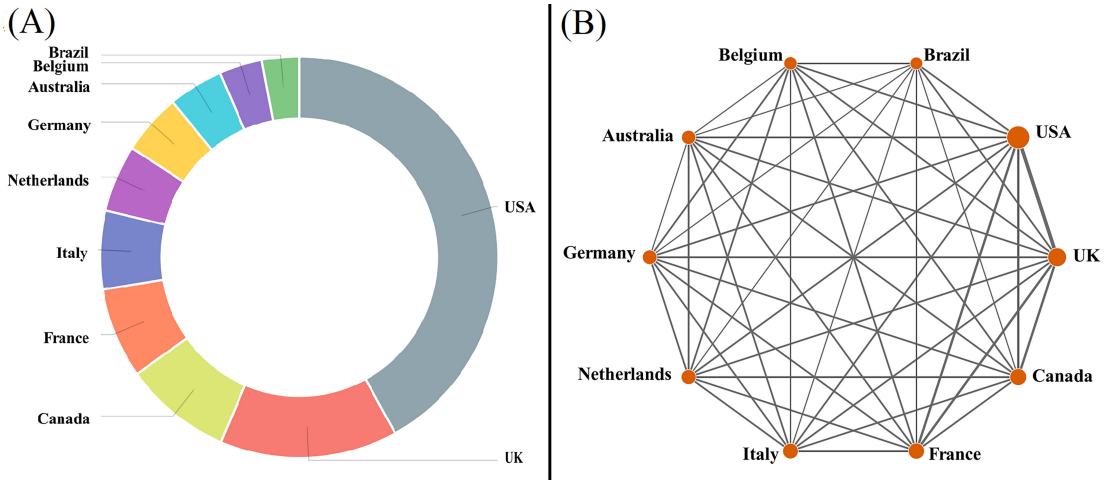

Fig. 3. The top 10 most productive countries among the T100 articles. (A) The distribution of the top 10 most productive countries. (B) Collaborative relationships among the top 10 most productive countries.

Table 1. The most productive authors as first or corresponding author in T100 articles.

Authors	Articles	Authorship				Affiliation	Country
		First author	Corresponding author	Second author	Others		
Scher HI	17	4	1 + 4*	3	9	Memorial Sloan Kettering Cancer Center	USA
De Bono JS	15	3	5 + 3*	0	7	Institute of Cancer Research	UK
Small EJ	11	3	3*	1	7	University of California San Francisco	USA
Kantoff PW	7	3	2*	0	4	Memorial Sloan Kettering Cancer Center	USA
Attard G	6	3	0	1	2	University College London	UK
Sawyers CL	8	0	4	1	3	Memorial Sloan Kettering Cancer Center	USA
Taplin ME	9	2	1*	0	7	Dana-Farber Cancer Institute	USA
Saad F	8	2	2*	1	5	University of Montreal	Canada
Fizazi K	8	2	2*	1	5	Universite Paris Saclay	France
Mostaghel EA	7	2	1*	2	3	VA Puget Sound Health Care System	USA
Ryan CJ	5	2	2*	0	3	University of California San Francisco	USA
Beltran H	3	2	1*	0	1	Weill Cornell Medicine	USA
Tannock IF	3	2	1 + 2*	0	0	Princess Margaret Cancer Centre	Canada
Hu R	2	2	0	0	0	Johns Hopkins University	USA

*: Articles that the first author is both corresponding author.

Table 2. Journal distribution of T100 articles in CRPC research.

Journal	No. of T100 articles	IF as of 2019	5-Year's IF	TC	AC/A
Cancer Research	20	9.727	9.883	8946.00	447.30
Journal of Clinical Oncology	18	32.956	25.597	9593.00	532.94
New England Journal of Medicine	11	74.699	72.098	18913.00	1719.36
Lancet Oncology	5	33.752	35.843	2365.00	473.00
Nature Medicine	5	36.13	36.23	2229.00	445.80
Clinical Cancer Research	4	10.107	10.115	2197.00	549.25
Lancet	4	60.39	59.345	3891.00	972.75
Nature	4	42.779	46.488	2076.00	519.00
JNCI Journal of The National Cancer Institute	4	11.577	11.641	2640.00	660.00
European Urology	3	18.728	16.763	1432.00	477.33
Cell	2	38.637	38.62	1482.00	741.00
Journal of Biological Chemistry	2	4.238	4.237	688.00	344.00
Journal of Clinical Investigation	2	11.864	13.393	717.00	358.50
Proceedings of The National Academy of Sciences of The United States of America	2	9.412	10.62	710.00	355.00
Science	2	41.846	44.374	1552.00	776.00
American Journal of Pathology	1	3.491	4.227	607.00	607.00
Annals of Oncology	1	18.274	15.254	299.00	299.00
Cancer	1	5.772	6.602	349.00	349.00
Cancer Cell	1	26.602	30.237	292.00	292.00
Cancer Discovery	1	29.497	28.298	339.00	339.00
Endocrine Reviews	1	14.661	19.795	959.00	959.00
Journal of Cellular Biochemistry	1	4.237	3.771	282.00	282.00
Molecular Cancer Research	1	4.63	4.76	357.00	357.00
Nature Clinical Practice Urology	1	0	0	337.00	337.00
Nature Reviews Cancer	1	53.03	52.659	1626.00	1626.00
Prostate	1	3.279	3.2884	320.00	320.00
RNA-A Publication of The RNA Society	1	4.32	4.549	291.00	291.00

TC, total citations; AC/Y, average citations per year.

The T100 articles were published in 27 journals, as shown in Table 2. The journal Cancer Research ranked first, publishing 20 T100 articles, with a total 8946 citations, followed by the Journal of Clinical Oncology, with 18 T100 articles and 9593 citations. The New England Journal of Medicine ranked third, with 11 T100 articles and the highest total number of citations at 18,913. The IF and 5-year IF of the journal Nature Clinical Practice Urology were 0 because the journal was dropped by Clarivate Analytics in 2010. According to the Spearman test, the number of T100 articles ($r = 0.485$, $P = 0.01$), total citations (TC) ($r = 0.626$, $P < 0.001$), and average citations per article (AC/A) ($r = 0.629$, $P < 0.001$) were all correlated with the IF of the journal.

Citation analysis is always regarded as a quality factor for evaluating research performance and reflects the scientific community's interest level. The top 10 most cited publications in the CRPC research field during 1992–2017 are presented in Table 3. The number of citations of the top 10 most most-cited papers ranged from 1199 to 3594 and the large number of citations reflected these papers' far-reaching academic impact. 7 of these T100 articles were published in the New England Journal of Medicine and the rest remaining three were published in Lancet, Nature Reviews Cancer and the Journal of Clinical Oncology. 9 of these 10 T100 were related to the therapy, while the remaining one, published in 2001, discusses the mechanisms of CRPC progression.

4. Discussion

As one of the important bibliometric indicators, the number of citations is a useful tool to measure publications' influence [7,15]. In this study, the 100 most-cited articles in the CRPC field were evaluated by assessing the number of times these articles were cited. The results offer a historical perspective on evolving CRPC research. Immunotherapy and the study of androgen receptors and related signaling axes will possibly be hot topics and trends in CRPC research.

Table 3. The top 10 most cited publications in CRPC research.

Rank	Author	Title	Journal	Year	TC	Result
1	Tannock IF *et al*.	Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer	New England Journal of Medicine	2004	3594	Treatment with docetaxel plus prednisone led to superior survival and improved rates of response in terms of pain, serum PSA level, and quality of life, as compared with mitoxantrone plus prednisone.
2	Kantoff PW *et al*.	Sipuleucel-T Immunotherapy for Castration-Resistant Prostate Cancer	New England Journal of Medicine	2010	2854	The use of Sipuleucel-T prolonged overall survival among men with metastatic castration-resistant prostate cancer.
3	Petrylak DP *et al*.	Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer	New England Journal of Medicine	2004	2522	Treatment with docetaxel plus estramustine prolonged median survival of nearly two months among men with metastatic androgen-independent prostate cancer, as compared with mitoxantrone and prednisone.
4	De Bono JS *et al*.	Abiraterone and Increased Survival in Metastatic Prostate Cancer	New England Journal of Medicine	2011	2237	Abiraterone acetate prolonged overall survival among patients with metastatic castration-resistant prostate cancer who previously received chemotherapy.
5	Scher HI *et al*.	Increased Survival with Enzalutamide in Prostate Cancer after Chemotherapy	New England Journal of Medicine	2012	2060	Enzalutamide significantly prolonged the survival of men with metastatic castration-resistant prostate cancer after chemotherapy.
6	De Bono JS *et al*.	Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial	Lancet	2010	1760	Treatment with cabazitaxel plus prednisone has important clinical antitumour activity, improving overall survival in patients with metastatic castration-resistant prostate cancer whose disease has progressed during or after docetaxel-based therapy.
7	Feldman BJ *et al*.	The development of androgen-independent prostate cancer	Nature Reviews Cancer	2001	1626	A review about the mechanism that lead to the development of androgen-independent prostate cancer.
8	Ryan CJ *et al*.	Abiraterone in Metastatic Prostate Cancer without Previous Chemotherapy	New England Journal of Medicine	2013	1360	Abiraterone improved radiographic progression-free survival, showed a trend toward improved overall survival, and significantly delayed clinical decline and initiation of chemotherapy in patients with metastatic castration-resistant prostate cancer.
9	Parker C *et al*.	Alpha Emitter Radium-223 and Survival in Metastatic Prostate Cancer	New England Journal of Medicine	2013	1268	Radium-223 improved overall survival.
10	Tannock IF *et al*.	Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: A Canadian randomized trial with palliative end points	Journal of Clinical Oncology	1996	1199	Chemotherapy with mitoxantrone and prednisone provides palliation far some patients with symptomatic hormone-resistant prostate cancer.

TC, total citations.

As a high-tech powerhouse, the USA is dominant in many research areas [17,18], especially in medicine [19–22]. Similar to other bibliometric publications, most of the 100 articles in this study were from the USA and European countries [23]. This finding may appear because these countries carry a heavy PCa burden [24], and public policy's effective impact on cancer research, scientists and institutions results in abundant financial support from public foundations or private enterprises [25,26]. The USA contributed 89% of the T100 articles, making it dominant in CRPC research. The 10 most productive authors in CRPC research were all from the USA and European countries, regardless of whether they were first authors or coauthors. Furthermore, strong collaborations were identified between the USA and G7 Countries as well as within the USA [15]. It was reported that collaborations might profit the number, impact and quality of the academic outputs. It was suggested that better national and international collaboration were required to resolve complex issues surrounding domestic and worldwide cancer health disparities [27]. More effort and output are expected from developing countries, especially China; however, China only contributed to 2 T100 articles.

The most-cited scientists were Pro Scher HI, Pro De Bono JS and Pro Small EJ, who have contributed greatly to the prostate cancer research and have deeply influenced the entire CRPC research field. Their research areas relate to the development of novel therapies, such as enzalutamide, abiraterone and Sipuleucel-T, which are quite popular in prostate cancer research and have become the standard of PCa treatment [2,28–30]. Judging from the top 10 most-cited publications, 9 of these 10 T100 were related to PCa therapy. Interestingly, the evolution of CRPC treatment was clearly visible among these outstanding papers. From mitoxantrone (1990s) to docetaxel (2000s), from docetaxel (2000s) to Abiraterone (2010s), Sipuleucel-T (2010s) and Enzalutamide (2010s), the novel discoveries of new drugs drastically changed the therapeutic approach to CRPC, improved patients' quality of life and prolonged their lifespan. Additionally, these scientists and top institutions have undertaken some promising and exploratory work in recent years. The biomarker nuclear-localized androgen receptor splice variant 7 protein in CTCs is necessary to better guide treatment selection in MCRPC [31]. Several ongoing clinical trials (i.e., Akt inhibitor Ipatasertib combined with abiraterone, antibody-drug Tisotumab vedotin, next-generation androgen receptor inhibitor Apalutamide) have demonstrated encouraging antitumor activity in CRPC [32–34].

According to the WoS categories, more than half of the T100 articles were related to "oncology", followed by "general internal medicine". However, according to article topic, the mechanism related to tumor progression or tumor metastasis attracted the most attention in the CRPC research field. The androgen receptor and related signaling axes have played a vital role in mechanisms related to tumor progression, tumor metastasis and drug resistance [35–37]. The rapid developments in biological technology, such as high-throughput technologies have greatly advanced the study of CRPC. Judging from the T100 articles, the androgen receptor and related signaling axes will still be the hotspot for future CRPC research in developing new generation hormonal therapy and biomarkers [38,39]. As the understanding of these mechanisms as well as the mutation landscape of PCa grows, novel agents, such as next-generation hormonal therapy, immunotherapeutics, or therapies targeting other oncogenic and genomic pathways are being developed, and prospective identification of predictive biomarkers should be performed, holding great promise for precision medicine [39–41].

A small series of patients with prostate cancer have been reported to have impressive responses to cellular and immunotherapy, making immunotherapy a promising solution for CRPC treatment. According to article topic, immunotherapy ranked fourth with 7 T100 articles (2 about Sipuleucel-T, 2 about Ipilimumab, 1 about Poxviral-based PSA-targeted immunotherapy, 1 about targeting human gamma delta T cells and the last about antigen-loaded dendritic cells). Sipuleucel-T is the first therapeutic cancer vaccine that has shown a survival benefit among men with mCRPC [42], while the CTLA-4 blockade Ipilimumab has been reported to be effective in selective patients [43]. In addition, recent studies suggest that famous PD-1/PD-L1 inhibitors, such as nivolumab and pembrolizumab, have limited effects on prostate cancer, and their combination with other therapies is still in clinical trials [39,44]. Chimeric antigen receptor T-cell (CAR-T) therapy and bispecific antibodies targeting key factors such as PSMA and PCMA have emerged recently as promising new approaches to treat CRPC [45,46]. However, much remains to be understood regarding immunotherapy's role and sequencing in CRPC with regard to existing limitations and renewed promise in immunotherapy clinical trials. Beyond vaccine therapies and checkpoint blockade, combination therapy and new therapies, such as BiTEs and CAR-T therapy, offer intriguing and promising avenues for treating CRPC.

It has been reported that journals with a high IF or high citation numbers would attract scholars who produce highly-cited articles, which in turn maintain the high IF of these journals [47]. In this study, the number of T100 articles, the total citations (TC) and the average citations per article (AC/A) were all correlated with IF. In total, 69 of the T100 articles were published in high IF journals, such as the Journal of Clinical Oncology, the New England Journal of Medicine, Lancet Oncology, Nature Medicine, Lancet, Nature, JNCI Journal of the National Cancer Institute, European Urology, Cell, and so on. However, this study also revealed that several T100 articles were published in journals with a relatively low IF (IF $<$ 5), such as the Journal of Bi-

ological Chemistry, American Journal of Pathology, Journal of Cellular Biochemistry, Prostate, RNA-A Publication of the RNA Society and Nature Clinical Practice Urology. This finding may have emerged because the authors or the editors did not realize-their studies' importance, the authors preferred to publish in specialty journals, or other related studies became more notable.

The study also has some limitations. First, some relatively new "influential" articles may have been excluded because only the most-cited articles were analyzed. The number of T100 articles has decreased over the past several years, along with many classical highly cited articles. Second, many factors could influence the number of citations, including both the journal and author self-citations. Third, the number of citations was only one of the indicators that reflect the value of contributions to the field. Fourth, several articles with a large number of citations were excluded because they discussed additional topics beyond just CRPC. Fifth, the search strategy may not have been comprehensive enough as not searching per category or searching the top journals in the fields of microbiology, infectious diseases, pathology, general medicine, or tropical medicine manually or directly from these journals' websites.

5. Conclusions

This analysis provides a historical perspective on the progress and attempts to reveal the future trend in CRPC research using bibliometric analysis. It aids highlighting contributions from various disciplines and responsible authors within the CRPC field. This study's results suggest that immunotherapy and the study of androgen receptors and related signaling axes will possibly be hot topics and trends in CRPC research. Additionally, journals with a high IF will attract and publish more important articles. On the other hand, papers published in high IF journals will receive more academic attention.

Author contributions

HF, LGH, YHW and CC were involved in conception and design. HF, LGH, HDH, XLW, YYW and HWG were involved in collection and assembly of data. HF, LGH, YHW and CC were involved in data analysis and interpretation. HF and LGH were involved in manuscript writing. YHW and CC were involved in manuscript revising. HF and LGH contributed equally to this work and should be considered co-first author. YHW and CC contributed equally to this work should be considered co-corresponding author. All authors were involved in final approval of the version to be published.

Ethics approval and consent to participate

All analyses were based on previous published studies, therefore no ethical approval and patient consent are required.

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Conflict of interest

The authors declare no conflict of interest.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at https://www.imrpress.com/journal/JOMH/18/1/10.31083/jomh.2021.053.

Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary information files.

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