Original Article

Research of targeted therapy for renal cancer from 2006 to 2022: a bibliometric and visualized analysis

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Background: This review aimed to analyze the research progress and development trends in targeted therapy (TT) for renal cancer (RC) from 2006 to 2022.

Methods: The Web of Science Core Collection database was searched using the search terms "renal cancer", "kidney neoplasms", "kidney cancer", and "targeted therapy", and all publications were extracted. VOSviewer version 1.6.18 was used to complete the visual analysis based on the information of publications, including author, journal, subject, year, and institution.

Results: A total of 1,136 studies related to TT for RC were found. The top journals in this field were the *Journal of Clinical Oncology*, *Annals of Oncology*, and *European Urology*. Among them, the *Journal of Clinical Oncology* had the highest number of publications (n=35). In terms of country, the United States had the highest number of publications (n=366). The main document type was article, which accounted for 64.26% of the total publications.

Conclusions: To the best of our knowledge, this is the first bibliometric analysis related to TT for RC. The annual number of publications has exhibited a steady growth trend, with the United States having the greatest contribution in this field. Through an analysis of a keyword time density map, we identified that hypoxia-inducing factor-1, drug resistance and therapeutic targets are the research hotspots and trends in this field.

Keywords: Targeted therapy; renal cancer; bibliometric analysis; VOSviewer

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Introduction

Renal cancer (RC) is one of the most common malignant tumors of the urinary system, with high morbidity and mortality rates being reported each year. Among the various pathological types of RC, the most common is renal cell carcinoma (RCC) (1). For patients with early-stage RCC, surgery can be performed to improve survival. However, for patients with advanced metastatic RCC, the 5-year survival rate is only 10% (2).

In the last century, cytokine therapy was the mainstay of RCC treatment, with interleukin-2 and interferon-α being the most widely used in the clinical setting (3,4). However, these two drugs had limited efficacy, low objective response rate, many adverse reactions, and poor patient tolerance (5). In December 2005, the US Food and Drug Administration approved sorafenib for the treatment of advanced RCC (6), and the use of targeted drugs has significantly improved the prognosis of patients with advanced RCC (7). Since then, numerous articles on targeted therapy (TT) for RCC have been published, with the focus being on the

therapeutic effect, side effects, drug resistance, targets, pathways, and the combination of immunotherapy and TT. Therefore, a summary and analysis of these publications via a bibliometric analysis would be helpful in clarifying the research hotspots and trends in this field.

Bibliometrics is the interdisciplinary science of quantitative analysis of all knowledge carriers using mathematical and statistical methods (8). It has been applied in various fields to evaluate the cooperation and contribution among countries and institutions and also to identify research hotspots and research trends in specific areas. In the field of urology, bibliometric analyses on the diagnosis of bladder cancer (9), surgical treatment for RCC (10), immunotherapy for urinary system tumors (11), etc., have been conducted; however, there is no bibliometric analysis on TT for RC at present.

Methods

Source of data and search strategy

The Web of Science Core Collection (WoSCC) of the Thomson Reuters database was selected as the source of literature in this review. To include all studies in the search results, we extracted terms related to RC using the MEDICAL SUBJECT HEADINGS in the PubMed database and entered them into the Web of Science search engine, including the following terms as title content: renal/kidney plus cancer(s)/neoplasm(s). Then, the term "Molecular targeted therapy" was combined with the above search terms as a subject word (see Appendix 1).

Highlight box

Key findings

- In this study, bibliometrics was used to analyze the field of targeted therapy for kidney cancer.

What is known and what is new?

- ICIs is currently a hot topic in this field. Research on drug resistance and hypoxia-inducible factors are potential research trends, and there is a lack of research on NCCRCC in this field.
- VOSviewer software was used to chart the organizations, authors, and keywords in this field. A visualization analysis of all the articles in this field was completed.

What is the implication, and what should change now?

- The current and future research hotspots in this field were analyzed to provide a reference for researchers and clinicians.

Data collection

We limited the time period from January 2006 to December 2022 and downloaded all publication information, including author, journal, subject, year, and institution. The data were collected by 2 independent assessors (Yongxin Fu, Yuanqing Gou). All data were finally imported into Microsoft Excel 2016, and VOSviewer was used for quantitative and qualitative analyses.

Statistical analysis

We used WoSCC to analyze all materials. The cooperation network and keywords were visualized and analyzed using VOSviewer version 1.6.18, which is a free software tool for building and visualizing bibliometric networks (12,13). The workflow is presented in *Figure 1*.

Results

We obtained 1,136 publications that met the search criteria, including 11 document types. The main publication type was article, which accounted for 64.26% (n=730) of the collected literature, followed by review article (n=287) and meeting abstract (n=68), which accounted for 25.26% and 5.98%, respectively. English-language literature accounted for 91.1% of the total publications, whereas other languages only accounted for 8.9%.

Since 2006, the annual number of published articles exhibited a gradual upward trend, and this trend was more obvious in the first 5 years (*Figure 2*). Since then, this trend has become stable. The number of articles published in 2020 was the highest, reaching 95.

The authors of 1,136 articles were from 60 different countries, with the United States being the major contributor (n=366), followed by Italy (n=134), China (n=131), and Germany (n=106) (*Table 1*). Harvard University, University Of Texas System, University of London, and other well-known research institutions were the top 10 institutions in terms of the number of publications (*Table 2*). Harvard University ranked first with 65 publications, followed by the Udice group of French research universities with 54 published articles.

We classified 1,036 articles into 64 research directions according to the journal type. In summary, oncology (627 articles, 55.19%) was the main research direction with the highest number of articles, followed by urology (239 articles, 21.03%) and pharmacology (73 articles). Thus, TT

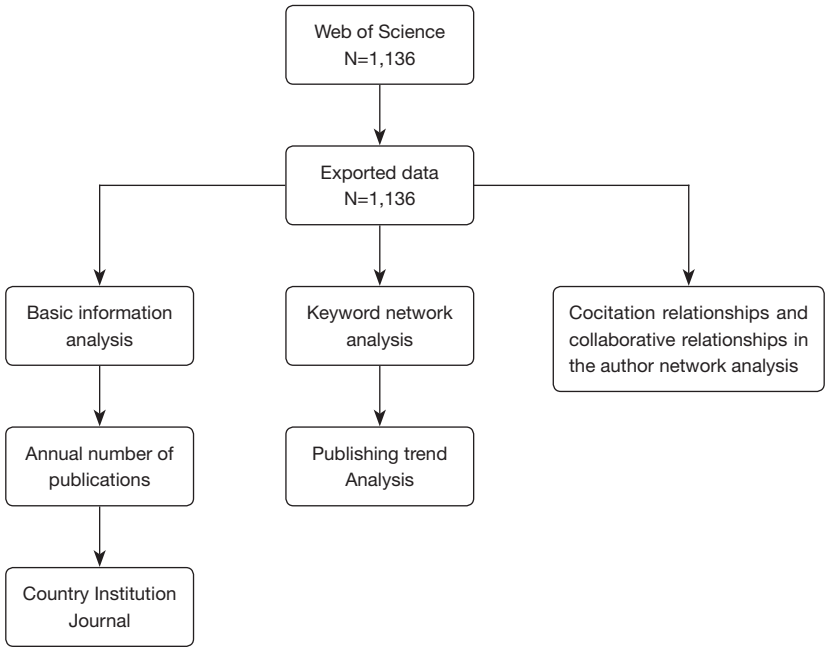

Figure 1 Workflow of the bibliometrics analysis.

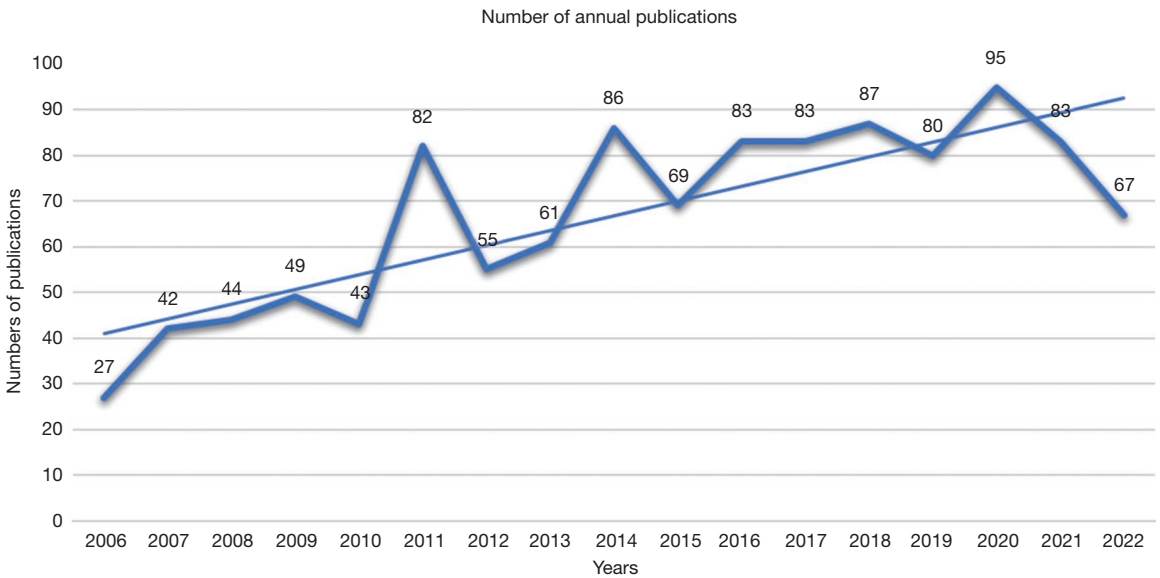

Figure 2 Number of publications on targeted therapy for renal cancer published from 2006 to 2022.

for RC is a multidisciplinary research field dominated by oncology.

The *Journal of Clinical Oncology*, *Onkourologiya*, and *Annals of Oncology* were the most productive journals in this field. The *Journal of Clinical Oncology* published 35 articles, ranking first (*Table 3*). The total number of citations reached 575, and the average number of citations was 16. We ranked the search results by the number of citations and obtained the top 10 most cited articles. All of these articles were published in different journals. Interestingly, we found no articles from the *Journal of Clinical Oncology* ranked in the top 10 most cited articles (14-23). The top-cited article

was published in *Cancer Cell* and was written by Qu *et al.* with 434 citations (14). Other frequently cited articles were also from top journals, including *Nature Medicine*, *European Urology*, and *Radiology*.

More than 5,000 authors participated in studies in the area of TT for RC. Collaboration among authors is presented as a network map in *Figure 3*. In a ranking performed according to the number of articles published, Powles and Choueiri tied for the first place with 24 articles published. Linehan and Bex tied for second place with 23 articles. If multiple authors were cited in 1 or more subsequent papers simultaneously, these authors constituted a cocitation relationship. The authors' citation information was visualized with VOSviewer, and the network diagram was drawn according to the cocitation times of the number of authors (*Figure 4*). From this, we could determine which authors in the field were high-impact ones, which authors had similar research topics, and which authors were the link between different topics.

VOSviewer was used to extract and analyze authors' name from 1,136 publications. We set the minimum occurrence frequency to 5 and manually excluded synonyms and nonsense words. A density map was drawn according to the frequency and correlation degree of the final keywords, as seen in *Figure 5*; a higher density is indicated by a red color, while a lower density is indicated by a blue color; the density depended on the number of elements in the surrounding area and their importance. The density view can be used to quickly determine important domains and the density of knowledge and research. Subsequently, we drew the time view according to the period when the keywords appeared (*Figure 6*).

Table 1 Top 10 most active countries in targeted therapy for renal cancer as measured by the total number of publications from 2006 to 2022

Ranking	Country	Number of documents	%
1st	United States	366	32.21
2nd	Italy	134	11.79
3rd	China	131	11.53
4th	Germany	106	9.33
5th	France	99	8.71
6th	England	87	7.65
7th	Japan	69	6.07
8th	Netherlands	62	5.45
9th	Canada	59	5.19
10th	Spain	57	5.01

Discussion

It has been reported that about 30% of patients with RCC have metastases at the time of initial diagnosis (1). As a first-line treatment for advanced RCC, TT has garnered intense research interest over a long period. Obtaining effective information from the massive and complex information network is an imposing challenge for both researchers and clinicians. Nonetheless, it is critical that scientific researchers and clinical practitioners grasp the current

Table 2 Top 10 most active institutions in targeted therapy for renal cancer as measured by the total number of publications from 2006 to 2022

Ranking	Institute	Country	Number of documents	%
1st	Harvard University	United States	65	5.72
2nd	Udice French research universities	France	54	4.75
3rd	University of Texas System	United States	49	4.31
4th	Unicancer	France	45	3.96
5th	University of California System	United States	45	3.96
6th	Dana Farber Cancer Institute	United States	41	3.60
7th	Assistance Publique Hopitaux Paris	France	38	3.34
8th	University of London	England	37	3.25
9th	Harvard Medical School	United States	36	3.16
10th	Netherlands Cancer Institute	Netherlands	31	2.72

Table 3 Top 10 most active journals in targeted therapy for renal cancer as measured by the total number of publications from 2006 to 2022

Ranking	Journal	Number of Documents	IF	%
1st	*Journal of Clinical Oncology*	35	50.739	3.08
2nd	*Onkourologiya*	32	Unknown	2.81
3rd	*Annals of Oncology*	25	51.769	2.20
4th	*Clinical Genitourinary cancer*	23	3.121	2.02
5th	*European Urology*	23	24.344	2.02
6th	*Urologic Oncology Seminars and Original Investigations*	19	2.954	1.67
7th	*BJU International*	18	5.969	1.58
8th	*Bulletin Du Cancer*	18	1.318	1.58
9th	*Clinical Cancer Research*	18	13.801	1.58
10th	*Journal Of Urology*	18	7.641	1.58

IF (Year 2022), impact factor.

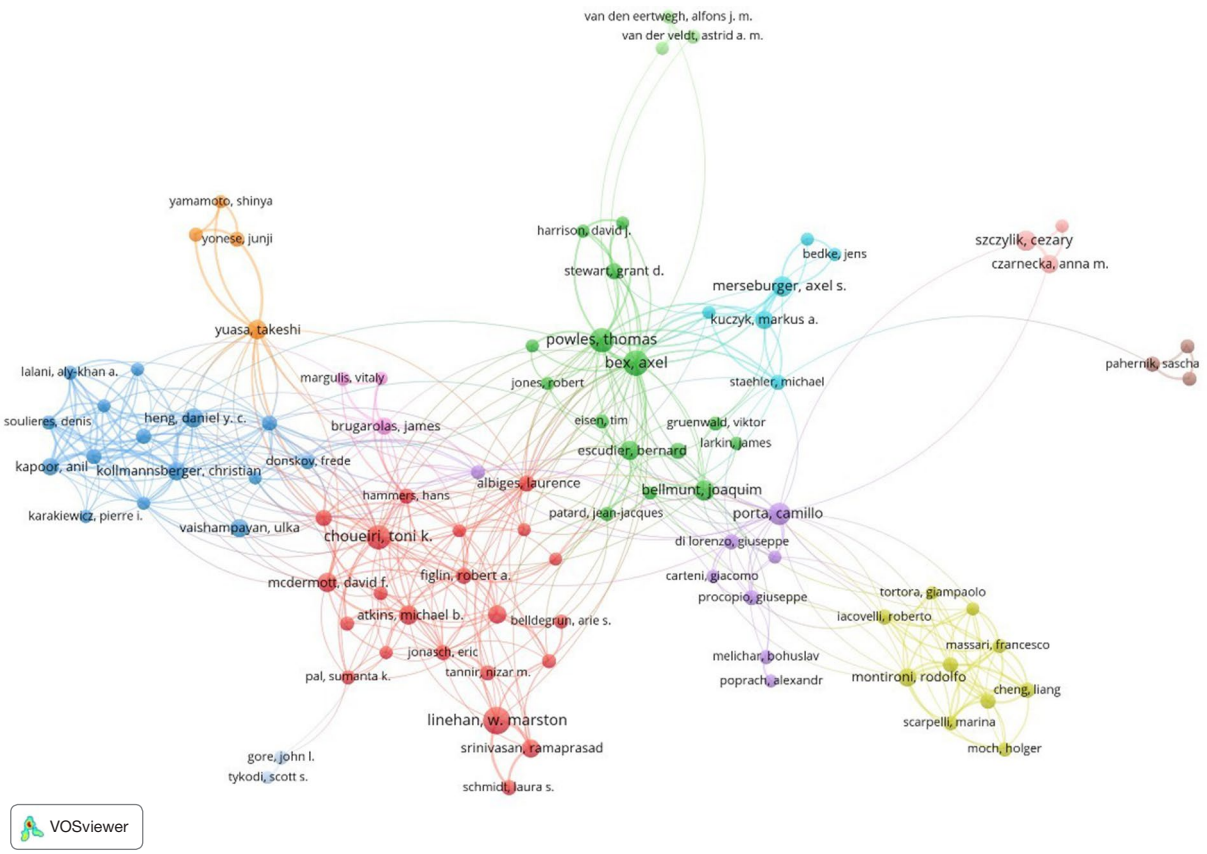

Figure 3 Collaborative relationships among the most active authors in the field.

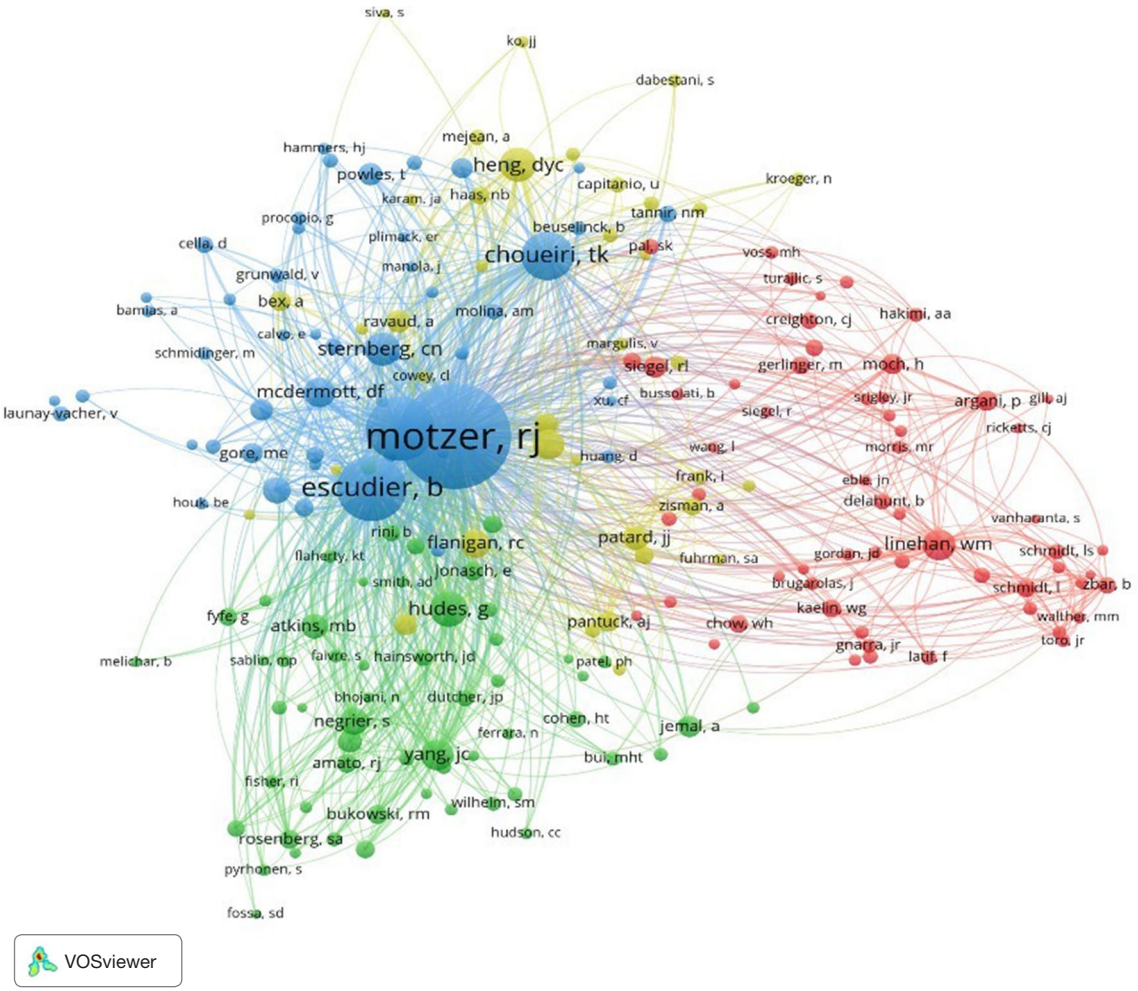

Figure 4 Cocitation relationships among the most active authors in the field.

hotspots in research. Systematic bibliometric analysis is a valuable tool for solving these issues (12). In this review, we present the first bibliometric analysis focusing on the research status and publication topics of TT for RC and provide statistical data visualized through maps.

Impact factor refers to the frequency of article citations in a certain journal during a specific year or period. By comparing the top 10 most cited articles, we can see that the most influential articles are from senior medical institutions and top journals. However, there are also 2 articles from journals with an impact factor of less than 10 (24,25). Impact factor is just one metric and cannot fully reflect the quality of a journal. For example, it only considers the number and frequency of citations of articles published in a journal, but does not consider the quality of the citations, the actual impact of the articles, and the contribution of the journal to society, industry, and academia.

The keyword density map is centered on "renal cell carcinoma" and "targeted therapy", which are surrounded by high-frequency keywords such as "sunitinib", "immunotherapy", "biomarker", and "angiogenesis". Sunitinib was the first agent to be developed that selectively targets multiple receptors of tyrosine kinases and has become the first-line agent for treating advanced RCC. Among the related studies, those reporting sunitinib-related clinical trials, adverse reactions, and drug resistance mechanisms accounted for a considerable proportion. However, the density map only reflected the most frequent keywords in this field and could not reflect the upward trending research directions. Thus, we further plotted the time density map and keyword timeline view map by adding time constraints, and the keywords that appeared

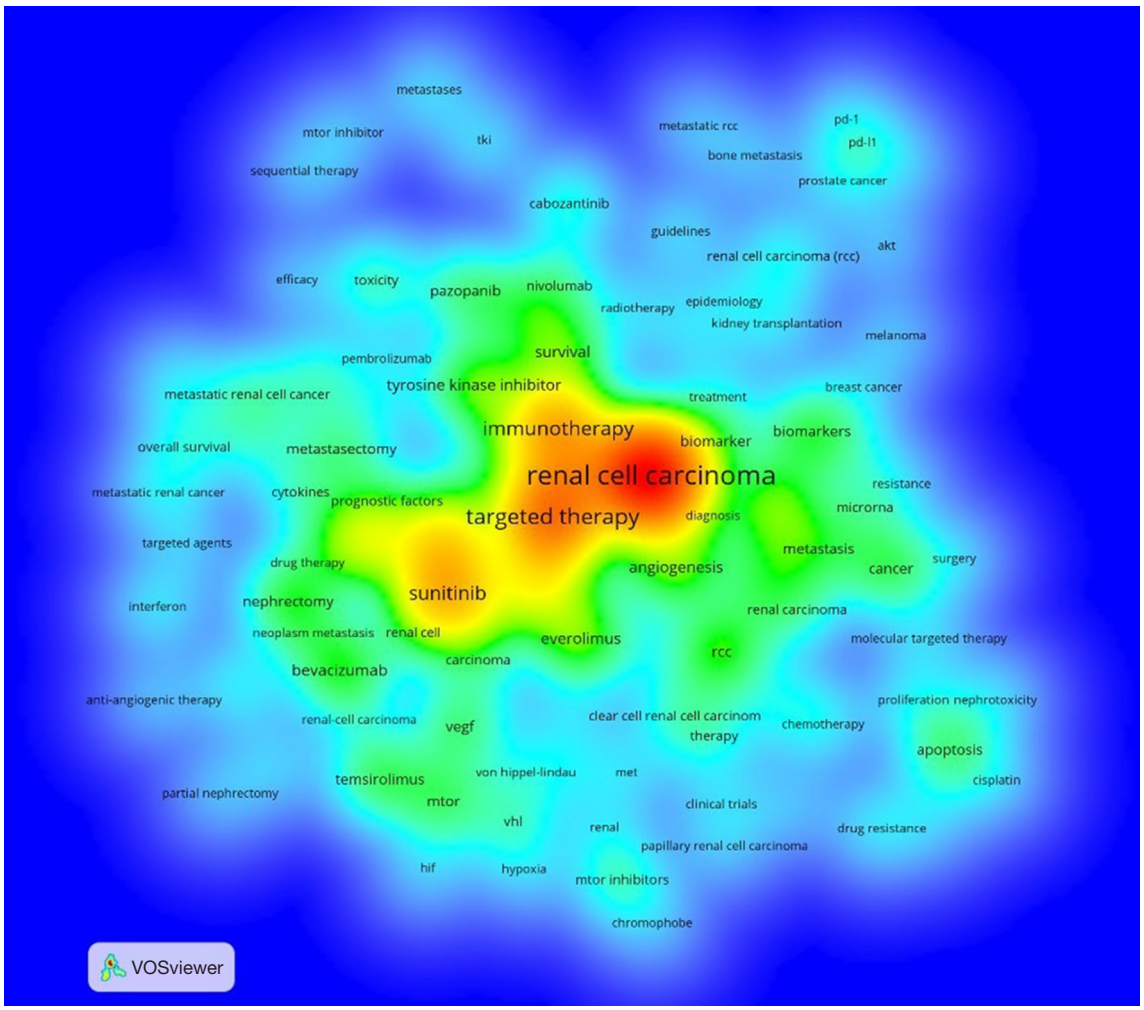

Figure 5 Keyword density map by keyword frequency and co-occurrence times.

more frequently in recent years included "pembrolizumab", "immune checkpoint inhibitors", "cabozantinib", and "hypoxia". From this, we speculated that the following future research hotspots and trends.

Immune checkpoint inhibitors (ICIs) are a type of cancer immunotherapy that works by blocking the activity of checkpoint proteins on immune cells, such as CTLA-4, PD-1, and PD-L1 (26). In recent years, clinical trials focusing on PD-1 drugs combined with TT, such as nivolumab plus pembrolizumab, have become a research trend (27,28). In some studies, the combination of ICIs and targeted therapy has shown significant advantages in overall survival and progression-free survival (29,30). Judging from the number of papers published in the past 2 years, ICIs will continue to be a research hotspot in the future.

Although many molecular targeted drugs have been used for the treatment of advanced RCC, the occurrence of drug resistance still negatively impacts the therapeutic effect to a large degree. At present, angiogenesis escape, target gene mutation, and tumor microenvironment change are believed to be the cause of drug resistance (31). Long noncoding RNA (lncRNA) may also play an important role. The most cited article found that an lncRNA named lncARSR, which promotes the expression of *AXL* and *c-MET* in RCC cells via competitive binding of microRNA (miR)-34/miR-449, can promote sunitinib resistance (14). Recently, some studies have utilized single-cell transcriptomics technology to perform high-throughput sequencing on tumor samples from patients with kidney cancer, revealing the diversity and individual variability of mechanisms of resistance to

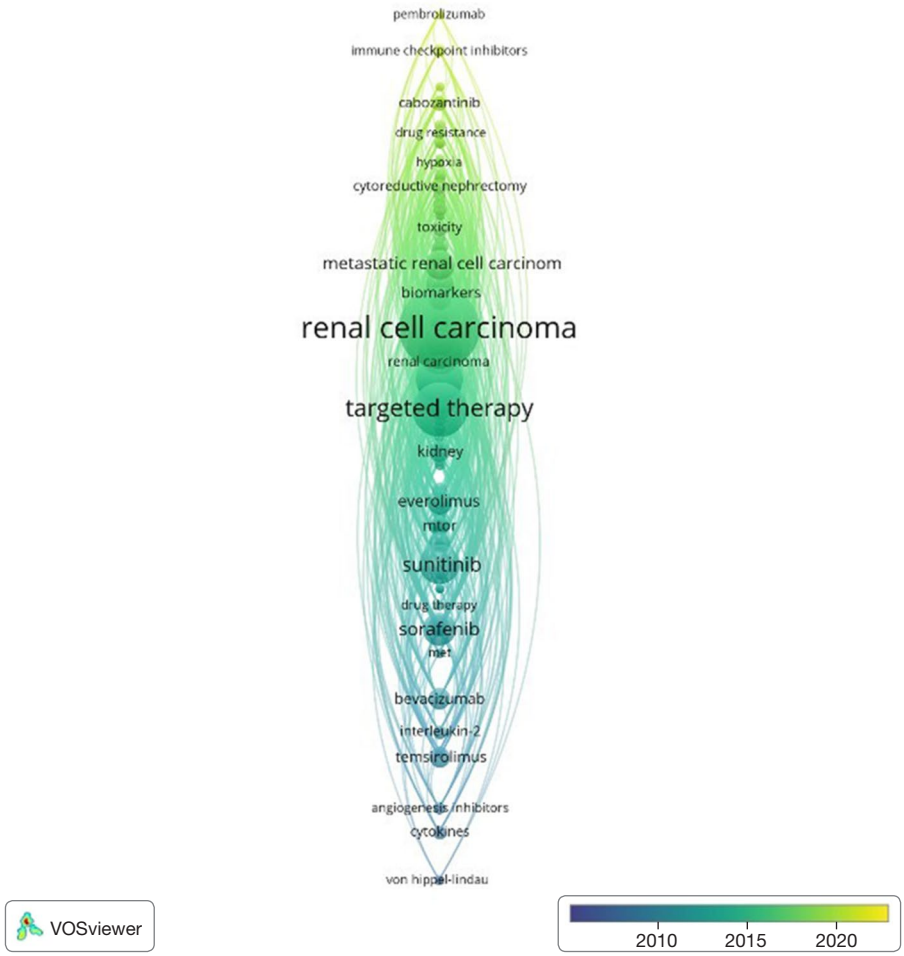

Figure 6 Keyword time density map based on the time period when the keyword appears.

targeted therapies (32,33). Further studies on the molecular mechanisms of resistance to targeted drugs may provide insights into the development of new effective drugs.

Hypoxia-inducible factor 1 (HIF-1) is a transcription factor that can sense low oxygen environments. It consists of two subunits, HIF-1α and HIF-1β. A recent study has demonstrated that high HIF-1α expression is also associated with resistance to antiangiogenic therapy (34). Currently, many HIF-1 inhibitors such as YC-1 have been developed and have shown good anti-tumor effects in preclinical trials. Among them, PT2385, a drug that inhibits the stability of HIF-2α, has entered clinical trial stages. Overall, further research into HIF-1 as a therapeutic target is warranted.

Nonclear cell renal cell carcinoma (NCCRCC) accounts for 25% of RCCs. It is a group of highly heterogeneous RCCs with histopathological diversity and includes papillary RCC, chromophobe RCC, renal collecting duct carcinoma, renal medulla carcinoma, and renal collecting duct carcinoma, among others. However, there are no guideline-recommended targeted drugs for patients with advanced NCCRCC. Sunitinib, everolimus and lenvatinib are commonly used for these patients (35). Recently, HIF-2α inhibitors have shown to be effective in treating non-clear cell RCC. One of the HIF-2α inhibitors, called *MK-6482*, has shown promising results in a phase II clinical trial (36). In our literature search, few relevant studies on NCCRCC were found, and clinical studies with large sample sizes are still lacking. TT for NCCRCC may also be a potential hotspot.

In addition, studies on cuproptosis-, autophagy-, m6a-, and immune-related genes as well as lncRNAs and other related studies in the field of kidney cancer are ongoing.

These studies are important for deepening our understanding of the basic mechanisms of cellular life activities, molecular mechanisms of cancer occurrence and development, and drug development. For instance, Zhu *et al.* confirmed that two genes, *ACO1* and *IREB2*, are strong prognostic biomarkers for patients with RCC, and they were associated with RCC autophagy, ferroptosis, and immune infiltration (37).

Several limitations to this study should be acknowledged. First, there are fewer journals included in the WoSCC than in SCOPUS, suggesting that we might have missed key literature, resulting in selective bias. Second, due to the limited date range, we did not include the newly published literature for analysis. Some literature on TT for NCCRCC uses specific pathological terms, so the literature may not be comprehensive in this regard.

Conclusions

To the best of our knowledge, this is the first bibliometric analysis focusing on TT for RC. We summarized the characteristics of published literatures in this field. With our time density map of keywords, the hotspots and trends of research and development in TT for RC can be more intuitively grasped. We believe that the research on targeted therapy combined with immunotherapy is the current and future hotspot. In addition, the study of hypoxia-inducing factor-1 and drug resistance mechanism is also an emerging research trend. Finally, the exploration of therapeutic targets is also an indispensable part of current basic research. Our study can provide a reference for scientific researchers and clinicians.

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Footnote

Peer Review File: Available at https://tau.amegroups.com/article/view/10.21037/tau-23-128/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-23-128/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Appendix 1 Search strategy

Retrieval formula #1: ((((((((((((((((((TI=(Kidney Neoplasms)) OR TI=(Kidney Neoplasm)) OR TI=(Neoplasm, Kidney)) OR TI=(Renal Neoplasms)) OR TI=(Neoplasm, Renal)) OR TI=(Neoplasms, Renal)) OR TI=(Renal Neoplasm)) OR TI=(Neoplasms, Kidney)) OR TI=(Cancer of Kidney)) OR TI=(Kidney Cancers)) OR TI=(Renal Cancer)) OR TI=(Cancer, Renal)) OR TI=(Cancers, Renal)) OR TI=(Renal Cancers)) OR TI=(Cancer of the Kidney)) OR TI=(Kidney Cancer)) OR TI=(Cancer, Kidney)) OR TI=(Cancers, Kidney))

Retrieval formula #2: (((TS=(Molecular Targeted Therapy)) OR TS=(Targeted Therapy)) OR TS=(Small Molecular)) OR TS=(Monoclonal antibody)

Final retrieval: #1 and #2

Query link: https://www.webofscience.com/wos/woscc/summary/6384a99c-cfc0-4a05-aaa7-98685848a1da-780b2852/times-cited-descending/1

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