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Global Renal Cell Carcinoma Research Trends Over 30 Years: A PRISMA-Compliant Bibliometric Analysis

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Purpose: Renal cell carcinoma (RCC) is a relatively common malignancy of the urinary tract. Over the past few decades, methodologies for diagnosing and managing patients with RCC have shown various developmental stages. This study was designed to provide insights into RCC research trends over that period.

Materials and Methods: To understand RCC research trends over the past 30 years, we conducted a bibliometric analysis, an appropriate method for evaluating scholarly output. Data were acquired by searching the Web of Science for articles published between 1991 and 2020. Bibliometric analysis and VOSviewer were used to visualize and statistically analyze the research trends.

Results: A total of 18,172 articles were identified. The most productive country was the United States (n=4,461, 26.5%), followed by China (n=3,503, 19.9%), and Japan (n=1,950, 11.9%). During keyword analysis, 3 clusters were identified, relating to gene expression, surgical outcomes, and immunotherapy. Over the last 10 years, research has mostly focused on emerging immunotherapy-related drugs.

Conclusions: Our bibliometric analysis has explained the characteristics of RCC research trends over the past 30 years.

Key Words: Kidney neoplasms, Renal cell carcinoma, Bibliometrics, Trend analysis

INTRODUCTION

Renal cell carcinoma (RCC) is a relatively common malignancy worldwide, accounting for 3%–5% of all oncological diagnoses [1]. Furthermore, its incidence has been increasing by 2% a year over the last 2 decades [2]. RCC is the most common form of solid lesion in the kidneys, with a rate of up to 85% [1]. It is more common in men than women, with an average age at diagnosis of 64 years [3]. These developments in diagnostic trends are mainly due to the use of noninvasive abdominal imaging procedures, such as computed tomography, ultrasonography, and magnetic resonance imaging, which detect incidental renal lesions [4]. Given an increase in early-stage, low-grade diagnoses, surgical treatment for RCC has shifted from radical to partial nephrectomy [5]. Furthermore, over the past 20 years,

medical treatment for advanced RCC transitioned from a nonspecific immune approach (cytokines) to targeted therapy and now on to novel immunotherapeutic agents [6]. Some antiangiogenic agents have shown improved clinical outcomes and have thus replaced cytokine therapy [7]. Recently, immunotherapeutic agents have attracted attention for the treatment of metastatic RCC. Against this background, the foci of RCC-related research have continually changed over time, including aspects such as diagnosis, surgery, and nonsurgical treatment options.

In examining research publication trends in relation to specific diseases, bibliometric analysis can be used to identify aspects such as top authors, journals, and countries, as well as topic changes [8]. Over the past 10 years, diverse bibliometric analyses have been conducted in numerous fields owing to an increase in the number of publications for analysis as well as the availability of user-friendly analytic computer programs. Some authors have applied a bibliometric approach to urology studies [9-11]. These trend analyses have focused on localized RCC treatments, but the overall trends of RCC research have not been investigated using a bibliometric approach [12]. To fill this gap, this study aimed to analyze the characteristics and trends of RCC research over the last 30 years based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for bibliometric analyses.

MATERIALS AND METHODS

As this study was a bibliometric analysis, ethical approval was not required. The study was conducted in accordance with the PRISMA guidelines [13].

1. Source of Research Data

We searched the Thomson Reuters Web of Science (Clarivate Analytics, Philadelphia, PA, USA) database from January 1, 1991, to December 31, 2020. The terms used in the search were "clear-cell cancer," "kidney cancer," "renal cell carcinoma," and "RCC." A total of 34,743 articles published between 1991 and 2020 were identified. Among these, we excluded editorials, reviews, comments, perspectives, and letters, as well as articles not published in English. Finally, 18,172

articles were included in the analysis (Fig. 1).

2. Bibliometric Analysis

Data analysis was performed using the Bibliometrix package in R 4.2.1 software (http://www.bibliometrix.org); the web-based application "Biblioshiny 4.0" was used to visualize the results. The following parameters were collected and analyzed: publication year, country of origin, corresponding author, citation number, publishing journal, title, abstract, and keywords.

VOSviewer (version 1.6.15; Leiden University, Leiden, The Netherlands) was used to evaluate the relationships between keywords and produce a keyword map [14]. Prior to VOSviewer analysis, the authors manually standardized the keywords included in the article titles or abstracts (because different representations of the same keyword can inaccurately increase the total number of keywords) [8]. Each node in the resulting map represents a keyword. Nodes with higher frequencies appear larger, and lines between nodes indicate keyword co-occurrence. Related keywords are grouped into clusters of the same color. An overlay visualization represents developments over time by calculating the average number of appearances per keyword and visualizing them on a network map to demonstrate trends in keyword appearance.

RESULTS

1. Number of Annual Publications

In the 2000s, the number of publications on RCC steadily increased; by 2007, it had increased markedly to more than 500 articles per year. Subsequently, the number of RCC-related articles continued to rise, exceeding 1,000 in 2015 and reaching 2,000 by 2020 (Fig. 2). Therefore, the doubling period of RCC-related publications gradually shortened during the analyzed period.

2. Contribution Trends of Countries and Authors

The articles were categorized according to their country of publication. The United States published the largest
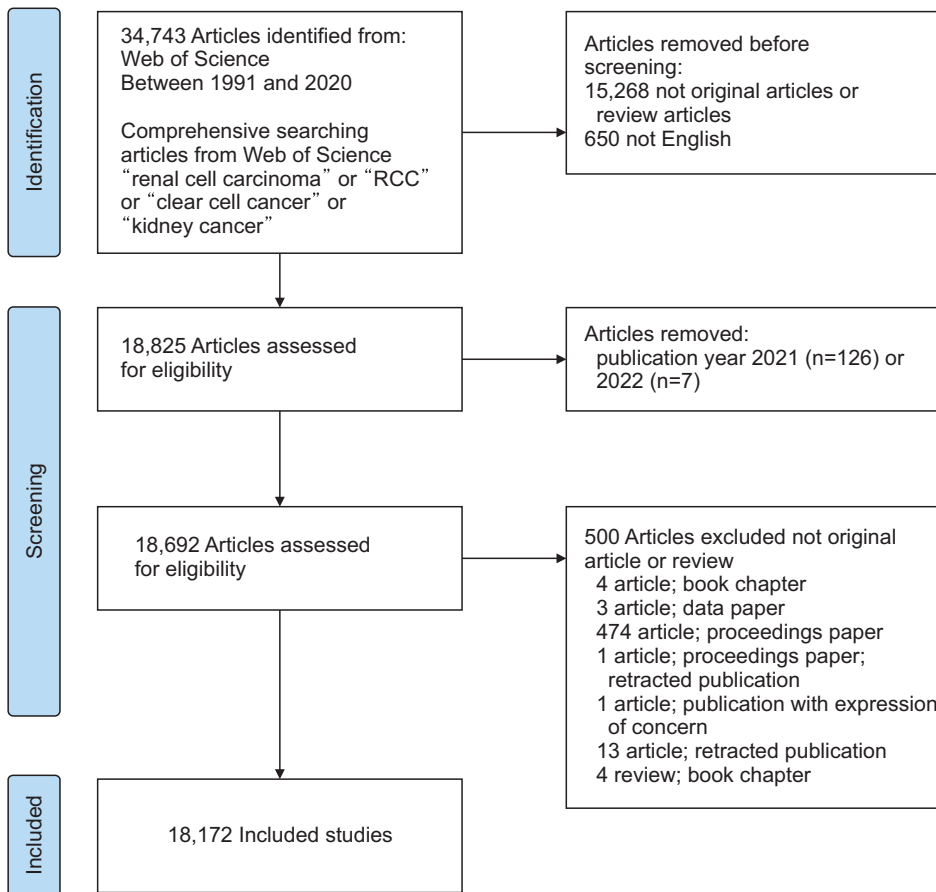
Fig. 1. Data acquisition flowchart.
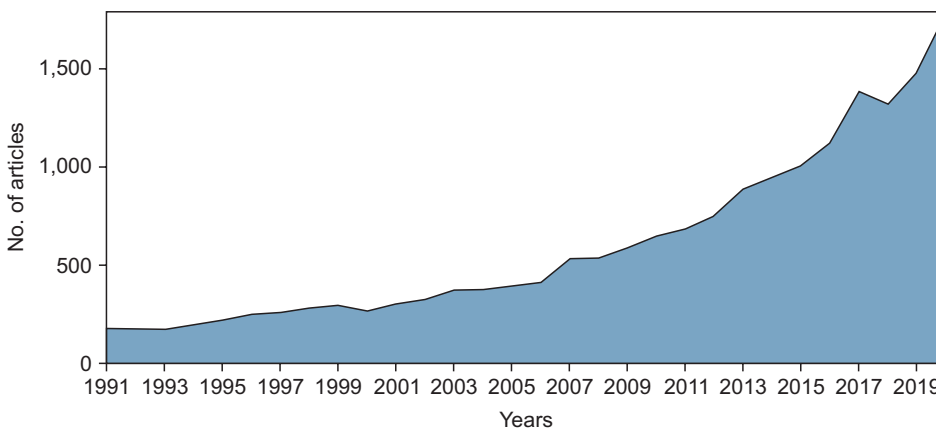
**Fig. 2.** The annual numbers of published articles on renal cell carcinoma.

number of papers (4,661), accounting for 26.5% of the total (Table 1, Fig. 3A). China and Japan published 3,503 (19.9%) and 1,950 articles (11.1%), respectively. We also assessed collaboration tendencies among countries by measuring domestic/international publication ratios. Asian countries such as China, Japan, and Turkey tended to publish articles without international collaboration. In contrast, international publication ratios were higher than 0.10 in Western countries (Canada, 0.44; United Kingdom, 0.31; France, 0.26; USA,

0.18). The characteristics of international collaborations are summarized in Fig. 3B. Looking at the United States' collaborations, the width of ties (i.e., number of connections) with Canada, China, and Japan are very thick; significant collaborations also occurred with Germany, Italy, and France.

The 10 most productive authors participating in RCC studies are summarized in Table 2. Motzer, who works for the Memorial Sloan-Kettering Cancer Center in New York,

Table 1. Top 10 countries by corresponding author and domestic vs. international collaboration

Rank	Country	No. of articles	Frequency	Domestic studies	International studies	Domestic-international ratio
1	US	4,661	0.2648	3,818	843	0.1809
2	China	3,503	0.199	3,228	275	0.0785
3	Japan	1,950	0.1108	1,832	118	0.0605
4	Germany	1,144	0.065	912	232	0.2028
5	Italy	788	0.0448	615	173	0.2195
6	Korea	640	0.0364	589	51	0.0797
7	France	593	0.0337	437	156	0.2631
8	Canada	454	0.0258	250	204	0.4493
9	UK	444	0.0252	308	136	0.3063
10	Turkey	338	0.0192	329	9	0.0266
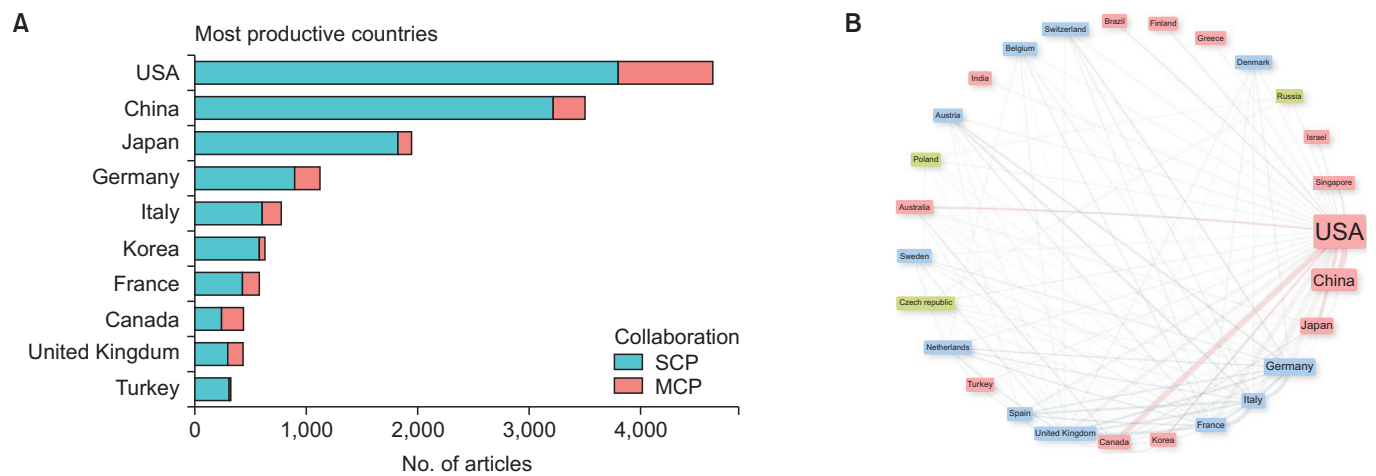
Fig. 3. The distribution of authors' countries and collaborations. (A) The 10 most productive countries according to corresponding author. (B) Specific relationships forming international collaborations. SCP, single-country publication; MCP, multicountry publication. Assigning colors based on the frequency of collaboration or patterns of collaboration in specific research fields can visually compare different relationship formation patterns between countries within the network.

Table 2. Top 10 most prolific authors

Rank	First author	No. of publications	H-index	G-index	M-index (first year)	Local citations
1	Motzer RJ	238	85	221	2.741935	49,072
2	Escudier B	230	75	188	2.5	35,745
3	Rini BI	226	78	168	3.12	28,979
4	Choueiri TK	225	66	161	3.882353	26,580
5	Leibovich BC	151	53	101	2.65	10,864
6	Wood CG	148	49	95	2.45	9,741
7	Figlin RA	141	60	141	1.875	22,970
8	Ljungberg B	141	47	98	1.46875	10,065
9	Cheville JC	139	56	119	1.931034	14,337
10	Porta C	134	38	105	1.461538	11,351

has published the largest number of articles (238 articles, 49,072 citations). Following Motzer, Escudier (n=230), Rini (n=226), and Choueiri (n=225) each published more than 200 articles. We also conducted a time series analysis of the publication status of the top 10 most prolific authors (Fig. 4A). Five authors—Figlin, Ljungberg, Motzer, Escudier, and Cheville—have continuously published articles for

almost 30 years. The most active authors in the last 5 years were Choueiri, Escudier, Motzer, Rini, and Porta. Although Choueiri, Leibovich, and Wood only started publishing their research in the early 2000s, they were included in the list of the top 10 authors.

Citation networks indicate that Motzer and Escudier were strongly connected and made a central contribution to the
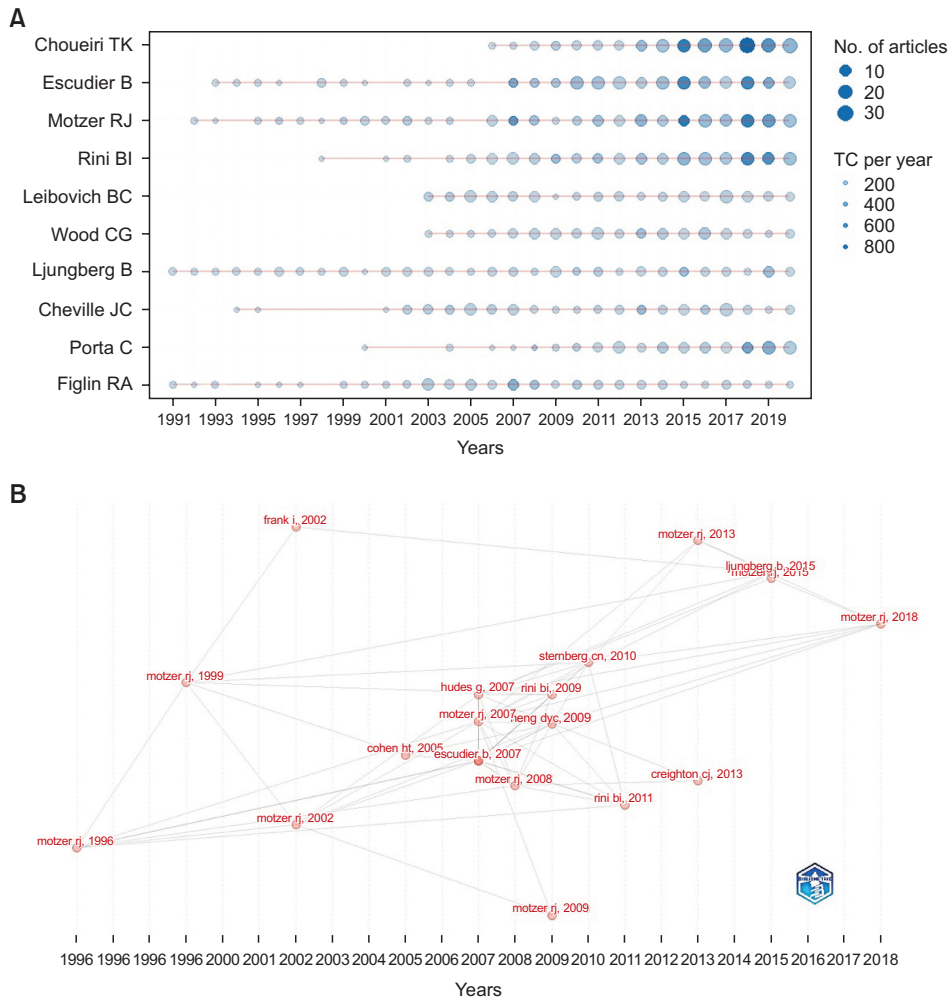
Fig. 4. Characteristics of articles published by top 10 authors. (A) Annual numbers of published articles and citations over time. (B) Historical direct citation network. TC, total citation.

Table 3. The most active journals in terms of publishing renal cell carcinoma-related research

Rank	Journal	No. of publications	IF[†]	5-years IF[†]	Total citations	H-index[‡]
1	*Journal of Urology*	702	7.450	6.413	39,631	100
2	*Urology*	429	2.649	2.564	12,611	54
3	*Clinical Genitourinary Cancer*	347	2.872	2.989	4,514	30
4	*Urologic Oncology: Seminars and Original Investigations*	346	3.498	3.491	4,544	31
5	*BJU International*	342	5.588	5.225	11,246	54
6	*European Urology*	317	20.096	21.259	22,613	79
7	*Cancer*	261	6.860	7.921	15,205	66
8	*International Journal of Urology*	261	3.369	2.986	3,762	29
9	*Oncotarget*[§]	259	5.168	N/A	5,141	34
10	*Clinical Cancer Research*	239	12.531	12.836	18,083	78

[†]Impact factor (IF) of each journal was obtained from Journal Citation Reports. [‡]The H-index is defined as the maximum value of h, such that a given journal has published h papers cited at least once. [§]The IF of *Oncotarget* was obtained from 2016 data because it was deselected from the Science Citation Index-Expanded in 2018.

publication of RCC articles (Fig. 4B). The figure shows that this network of prominent authors—which was most active during 2007–2009—began with an article published by Motzer in 1996. Looking at the chronological direct citation pattern, 4 articles published in 2007 showed a tendency to be widely cited, suggesting they influenced later articles.

3. Journal and Citation Trends

The top 10 journals for RCC research (i.e., most publications) are listed in Table 3. The *Journal of Urology* published the most articles (n=702), followed by *Urology* (n=429), and *Clinical Genitourinary Cancer* (n=347). Although *European*

Table 4. Top 10 most cited publications related to renal cell carcinoma

Rank	First author	Title	Citations
1	Motzer RJ	Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med. 2007 Jan 11;356(2):115-24.	1,854
2	Escudier B	Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med. 2007 Jan 11;356(2):125-34.	1,341
3	Fuhrman SA	Prognostic significance of morphologic parameters in renal cell carcinoma. Am J Surg Pathol. 1982 Oct;6(7):655-63.	1,322
4	Hudes G	Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med. 2007 May 31;356(22):2271-81.	1,154
5	Motzer RJ	Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol. 2009 Aug 1;27(22):3584-90.	865
6	Motzer RJ	Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet. 2008 Aug 9;372(9637):449-56.	851
7	Sternberg CN	Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol. 2010 Feb 20;28(6):1061-8.	832
8	Motzer RJ	Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med. 2015 Nov 5;373(19):1803-13.	793
9	Motzer RJ	Renal-cell carcinoma. N Engl J Med. 1996 Sep 19;335(12):865-75.	785
10	Heng DY	Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. J Clin Oncol. 2009 Dec 1;27(34):5794-9.	782

Urology had the highest impact factor (5-year impact factor=21.259; Journal Citation Reports), its number of RCC publications was relatively small (n=317), ranking it in sixth place.

The most frequently cited articles are presented in Table 4. Among the top 10 most cited articles, the top 4 articles had more than 1,000 citations. Motzer was first author in 5 of the top 10 articles. The ranking demonstrates that interest in therapeutics for RCC has been high; 8 out of the top 10 papers were associated with targeted drugs and immuno-oncologic therapies, such as sunitinib, sorafenib, temsirolimus, everolimus, pazopanib, and nivolumab.

4. Trends of RCC-Related Keywords

The most frequently occurring keywords are listed in Table 5. Among analyzed articles, the keyword "cancer" appeared the most frequently. This was followed by "expression," "survival," and "interferon-alpha." The most frequent treatment drug was "sunitinib," which was mentioned 1,349 times. Excluding old immunotherapeutic agents such as "interferon-alpha" and "interleukin-2," "sorafenib" and "everolimus" appeared with high frequencies. This indicates that RCC research has focused on novel immunotherapeutic agents. Unexpectedly, the keyword analysis identified breast cancer as a frequently occurring keyword. This is probably due to similarities in gene expression and immunotherapy between breast cancer and kidney cancer. Among the keywords related to surgical approaches to RCC, radical

Table 5. List of the most frequently appearing keywords

| Term	Frequency	Term	Frequency
Cancer	5,083	Protein	525
Expression	2,835	Breast cancer	523
Survival	2,647	Apoptosis	514
Interferon-alpha	1,665	Invasion	512
Tumors	1,645	Features	509
Sunitinib	1,349	Disease	505
Therapy	1,331	Everolimus	504
Radical nephrectomy	864	Risk	490
Kidney	808	Masses	488
Growth	800	Impact	472
Classification	733	Targeted therapy	471
Metastasis	732	Experience	469
Management	725	Immunotherapy	468
Gene	705	Diagnosis	459
Identification	684	Interleukin-2	457
Endothelial growth factor	678	Double-blind	449
Proliferation	671	Tumor-suppressor gene	436
Nephrectomy	639	Neoplasms	433
Progression	638	Mutations	427
Sorafenib	614	Prognosis	402
Activation	586	Angiogenesis	400
Kidney cancer	564	Prognostic factors	400
Efficacy	558	Outcomes	398
Trial	558	Surgery	396
Tumor	537	Gene expression	370

nephrectomy appeared 864 times and was ranked in 8th place.
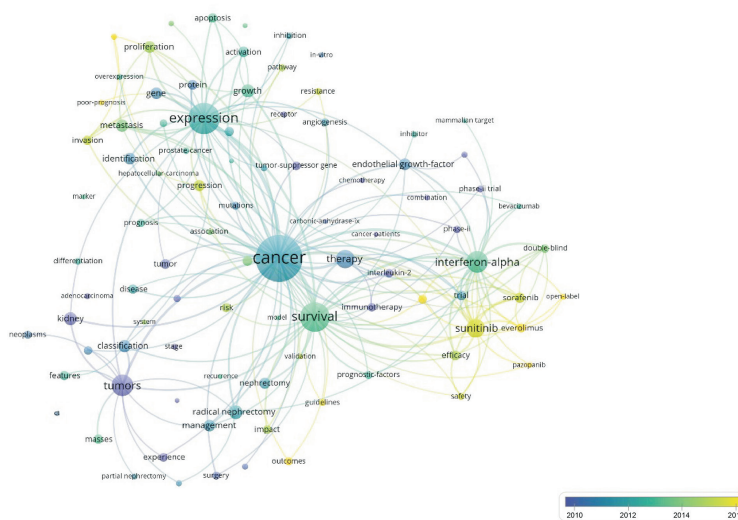
5. Co-occurrence Network Analysis

The co-occurrence network analysis between keywords is shown in Fig. 5A. Co-occurrence analysis aims to evaluate the relationships between core terms based on the number
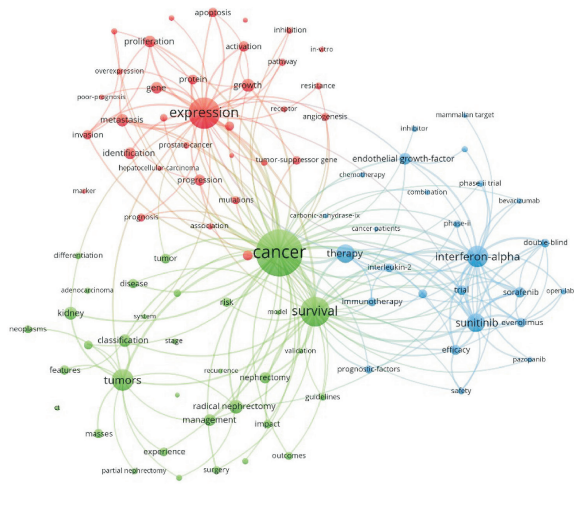
Fig. 5. A co-occurrence network of "keywords plus" from articles on renal cell carcinoma (RCC) from 1991 to 2020. (A) Clustering of keywords in the RCC field. (B) Average year of publication distribution of keywords (purple indicates earlier publication and yellow indicates more recent publication).

of articles in which they appear together. Circle sizes indicate the number of articles in which the terms were presented. We clustered the keywords into 3 major categories according to their correlation and frequency of appearance. Green clusters are related to surgical treatment, such as surgical outcomes, tumor stage, surgical procedures, and survival rates. The blue categories are associated with trends related to medical management. In this category, interferon-alpha and sunitinib had the largest circles. Interleukin-2, pazopanib, everolimus, bevacizumab, and sorafenib were associated with small circular nodes. Finally, the red clusters relate to gene and protein expression or suppression. Keywords with similar topics or meanings are grouped and represented with the same color. This helps visually identify specific thematic areas within the network. Time series analysis (Fig. 5B) showed that keywords related to surgical methods were

more popular in the past, before research interest shifted to treatment drugs for advanced or metastatic RCC, such as immunotherapy and targeted therapy. This is likely to be related to the developmental history of drugs used to treat patients with RCC. Overlay visualization in the figure represents developments over time by demonstrating the network map of the trend topics according to the keywords. While the earliest nodes were painted with purple, the most recent ones were colored with yellow.

DISCUSSION

This study is the largest bibliometric analysis in the field of RCC, including 18,172 articles. We aimed to include all published articles that could be accessed online and included RCC-related keywords. Recently, 2 studies have analyzed

RCC using a bibliometric approach [12,14]. However, these studies limited their investigation to publications on the surgical method of partial nephrectomy in patients with RCC. Hence, our analysis provides a broader overview of the RCC field. In relation to other urological cancers, many bibliometric analyses have been produced. For example, He et al. analyzed the top 100 articles on immunotherapy for urological cancer [15]. Mainwaring et al. [16] reviewed big data relating to more than 40,000 articles and reported the top manuscripts on bladder cancer. Similarly, Shen et al. [17] studied global research patterns on prostate cancer.

The number of RCC manuscripts has been steadily increasing over the past 3 decades, though this increase became much more pronounced after 2007; we suggest this can be explained as follows. In 2007, when the results of a phase III clinical trial related to sunitinib were announced, targeted therapy for metastatic RCC generated a huge amount of interest [18]. Furthermore, the therapeutic effects of sorafenib were first reported in 2007; oral sorafenib prolonged progression-free survival in patients with meta-static RCC [19]. Thus, the success of targeted therapy may have driven the increase in RCC articles since 2007 [20]. Although Xu et al. reported a research trend in the use of tyrosine kinase inhibitors for RCC from 2000 to 2022, they only demonstrated a trend toward focusing on immune checkpoint inhibitors [21]. Furthermore, the development of surgical techniques for the treatment of small RCC has contributed to the rapid growth of RCC-related studies. As laparoscopic and robot-assisted surgeries have become more popular, many studies have compared their surgical outcomes with those of conventional open surgery [22]. Additionally, as diagnostic technologies for small renal masses (SRMs) have developed, surgical skills for partial nephrectomy have also developed and begun to replace conventional radical nephrectomy.

Overall, RCC research can be categorized into surgical and drug treatments. Surgical excision is the gold standard treatment for nonmetastatic RCC, and various surgical techniques have been developed for this purpose. Specifically, trends in surgical strategies have changed as the detection rate of SRMs increased. Previously, all RCCs, including SRMs, were treated with aggressive surgery; however, the scope of partial nephrectomy has recently expanded. Furthermore,

less invasive and conservative treatment modalities have emerged [23,24]. Among the most frequent keywords, those related to surgical methods were "radical nephrectomy" and "surgery." The keywords associated with prognosis were "survival," "progression," "efficacy," "risk," "prognosis," and "outcomes." Keywords such as "SRM," "active surveillance," "radiofrequency ablation," and "cryoablation" were not identified in the ranking list, because they primarily relate to recently emerging research. Hence, the number of articles on novel surgical techniques is relatively low, and the majority of research articles we examined relate to traditional surgical techniques.

Unlike other malignant epithelial tumors, RCC is highly resistant to cytotoxic chemotherapy. Despite their low efficacy, interleukin-2 and interferon-alpha were used to treat metastatic RCC until the early 2000s [25]. Targeted therapeutic agents, including sunitinib, pazopanib, temsirolimus, everolimus, and axitinib, have replaced cytokine therapy for metastatic RCC [26]. Recently, immunotherapeutic agents and combination strategies have been developed for metastatic RCC treatment [7]. Thus, this study successfully demonstrated the trends of changing therapeutic drugs over time. Considering that the latest drug treatment strategies are included among the top-ranked keywords, it can be seen that research on the latest drugs is being actively conducted. This is different to the trends in surgical method-related research.

In summary, the present study makes valuable contributions by analyzing big data on RCC. However, it has some limitations. Although our study reflects RCC-related research trends over the last 3 decades, it does not reflect physicians' decisions regarding the direction of diagnosis and treatment of individual RCC patients. Therapeutic determinations should be made considering not only the RCC size and location but also the patient's renal function, underlying diseases, and even sociodemographic characteristics such as religion or sex [27]. Because bibliometric analysis is a keyword-oriented analytical method, it cannot identify the overall contextual meaning of the identified articles. Since the articles included in the bibliometric analysis were very diverse, it is difficult to understand exactly why each keyword appeared in each article. Additionally, although some keywords had similar

meanings, they were recognized distinctly. To minimize the subjective intervention of researchers, technical improvements, such as contextual or semantic analyses, are required to clearly classify and cluster keywords. Finally, because data acquisition was performed only in relation to English-language articles, some excellent articles published in other languages were not included, leading to selection bias.

With respect to future research prospects, research on RCC is progressing toward the diagnosis and treatment of incidental SRMs. Surgical techniques have continuously improved toward minimally invasive surgeries, such as single-port surgery, small robot devices, flexible instruments, and ablative therapy. Researchers could conduct distinct trend analyses relating to these aspects to obtain more specific and suggestive research results. In advanced or metastatic RCC, various comparative studies of other novel antitumor drugs have been reported. The emerging research topic of publications regarding the treatment of RCC has been related to targeted therapy using vascular endothelial growth factor tyrosine kinase and immunotherapy with immune checkpoint inhibitors [28]. Additionally, various drugs based on targeted and immuno-oncological therapies have been used to treat RCC. Recently, targeted therapies for metastatic RCC have evolved into third-line therapies [29]. Targeted therapies have improved the survival rate of patients with metastatic RCC [30]. Although the number of articles regarding immuno-oncologic therapy in patients with metastatic RCC has a small range (approximately 10 years), a significant therapeutic outcome can be found when analyzing large-scale articles closely.

CONCLUSIONS

This is the largest bibliometric analysis to explain research trends in RCC; accordingly, it provides an overview of kidney cancer articles. Publications on RCC have increased over the last 30 years. Whether conducted domestically or as part of international collaborations, the United States made the largest contribution to kidney cancer research. After 2007, publishing rates markedly increased in response to the development of targeted therapy, immune checkpoint inhibitors, and less invasive minimal surgery. Overall, this bibliometric analysis of RCC provides an understanding of research trends; it may provide insights to practitioners with respect to counseling patients about their disease and treatment plans.

NOTES

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