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Research

The role of programmed cell death in renal cancer: a bibliometric perspective (1998–2024)

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Abstract

Objective This bibliometric study aimed to map the global research landscape of programmed cell death (PCD) in renal cancer, delineating publication trends, influential authors, contributing regions, and thematic shifts between 1998 and 2023 year.

Methods We retrieved 5, 134 records from the Web of Science Core Collection (1998–2023) using comprehensive keywords encompassing "renal cancer," "programmed cell death," and related synonyms. After applying inclusion and exclusion criteria, we conducted co-citation, keyword, and cluster analyses with CiteSpace (v.6.3.R2) and VOSviewer (v.1.6.20) to identify major research fronts, collaboration networks, and thematic clusters.

Results Findings revealed a progressive increase in publications, notably accelerating after 2010 in tandem with the rise of immunotherapeutic strategies and targeted molecular interventions. China and the United States emerged as leading contributors, while journals such as Cancer Research and Clinical Cancer Research dominated in both publication frequency and citation impact. Authors including Kwon Taeg Kyu and Dahiya Rajvir significantly shaped foundational apoptosis research. Keyword and cluster analyses demonstrated a shift from earlier apoptosis- and angiogenesis-focused studies toward intersections of metabolic reprogramming, immune infiltration, and newer cell death modalities (e.g., ferroptosis, pyroptosis). High-impact papers underscored immunotherapy's pivotal role in modulating cell death pathways and informing novel combination regimens.

Conclusion PCD research in renal cancer has evolved into a dynamic, interdisciplinary domain integrating immunology, molecular targeting, and multi-omic profiling. Future development of the field aimed at refining precision therapies that exploit diverse cell death mechanisms and thereby improve clinical outcomes.

Keywords Programmed cell death · Renal cancer · Apoptosis · Immunotherapy · Molecular targeting · Tumor microenvironment

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1 Introduction

Programmed cell death (PCD) represents a tightly regulated biological process critical for maintaining tissue homeostasis and preventing uncontrolled cell proliferation [1–3]. In renal cancer alterations in these cell death pathways enable cancer cells to evade cytotoxic signals, contributing to tumor initiation, progression, and treatment resistance [4–7]. Traditionally, apoptosis has been regarded as the prototypical form of programmed cell death in oncological research, but emerging studies underscore the importance of other cell death mechanisms—such as autophagy, necroptosis, ferroptosis, pyroptosis, cuproptosis, anoikis, and immunogenic cell death—in shaping the tumor microenvironment and influencing therapeutic outcomes [8–10]. Collectively, these processes highlight the multifaceted nature of RCC and underscore the need for integrative research approaches that elucidate how various PCD pathways intersect within the complex landscape of renal tumor biology.

Beyond the molecular intricacies, the global burden of renal cancer and its rising incidence have spurred a concerted, international research effort to better characterize the function and modulation of programmed cell death in this malignancy. Several countries—led by the United States, China, and those in Europe—are driving high-impact studies that converge on immunotherapy, targeted therapies, and novel biomarkers designed to potentiate PCD in tumor cells [11–15]. This worldwide momentum reflects a broader shift away from conventional cytotoxic chemotherapies toward more nuanced strategies that manipulate distinct cell death programs [16–20]. Findings on these mechanisms are increasingly translated into clinical practice: for instance, immunotherapeutic interventions that enhance tumor-specific T-cell responses often function, in part, by stimulating or restoring critical death pathways within cancer cells [21, 22]. As a result, understanding how PCD underlies therapy response or resistance has become a linchpin for improving patient outcomes globally.

Against this backdrop of expanding literature, bibliometric analyses offer a structured means of synthesizing and visualizing research trends, collaborations, and thematic evolutions in the field. By statistically quantifying publications, citations, and keywords, bibliometrics can map the intellectual architecture of research on programmed cell death in renal cancer, revealing hidden linkages and identifying pivotal studies that have propelled the discipline forward. In this article, two specialized tools—CiteSpace and VOSviewer—are deployed to discern co-citation networks, collaborative clusters, and emergent themes [23–25]. CiteSpace excels in highlighting research fronts and cluster formations over time, while VOSviewer provides complementary graphical depictions of keyword co-occurrences and institutional partnerships [26–28], thereby yielding a multidimensional picture of the field's development.

Building on these methodologies, the purpose of this bibliometric study is to present a comprehensive overview of how programmed cell death research in renal cancer has evolved, ultimately serving as a knowledge base to guide future investigations. By systematically exploring publication outputs, author and country collaborations, thematic clusters, and top-cited works, the analysis illuminates the key factors that have shaped current scientific understanding and identifies potential directions for subsequent research. Through this integrative lens, we aim to offer a valuable reference for clinicians, researchers, and policymakers seeking to harness the therapeutic potential of PCD pathways and to advance the design of innovative treatment regimens in renal oncology.

2 Method

2.1 Data sources and search strategies

The literature measurement process is shown in Fig. 1. We obtained all bibliographic records from the Web of Science Core Collection (WOSCC), selected for its broad cross-disciplinary coverage and comprehensive citation data in biomedical research. To ensure a sufficiently long timeframe, we searched for publications from 1998 through 2023. This window was chosen to capture both early developments and more recent progress on programmed cell death (PCD) in renal cancer. All data were retrieved on the same day to minimize discrepancies caused by routine database updates. Our search formula used a combination of standardized Medical Subject Headings (MeSH) terms, common keywords, and recognized abbreviations for both renal cancer and multiple PCD pathways. Specifically, we included "renal cancer," "kidney cancer," "renal cell carcinoma," "kidney tumor," "renal neoplasm," and "RCC/ccRCC," in tandem with "programmed cell death," "apoptosis," "autophagy," "ferroptosis," "necroptosis," "pyroptosis," "cuproptosis,"

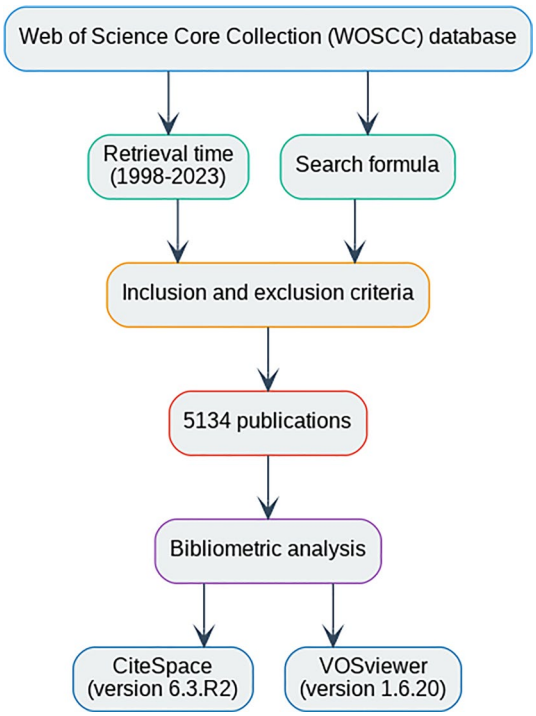

Fig. 1 Methodological workflow for bibliometric analysis of programmed cell death in renal cancer

"anoikis," and "immunogenic cell death." Each term was searched in the title, abstract, and keywords (Topic Search) to maximize the retrieval of potentially relevant articles.

2.2 Inclusion and exclusion criteria

We conducted a multi-stage screening of the initial search results to arrive at the final dataset of 5, 134 articles. Two independent reviewers first evaluated each retrieved record by title and abstract to confirm its relevance to both PCD and renal cancer. Publications were initially included if they presented scientific data, clinical or experimental findings, or substantive mechanistic discussions related to cell death pathways in renal tumors. Materials such as conference abstracts, commentaries, letters, purely theoretical essays, or articles unrelated to either PCD or renal cancer were excluded to ensure focus on robust, data-driven studies. A second group of reviewers then assessed any uncertain or borderline items by examining full texts, further removing articles that did not specifically address PCD mechanisms (e.g., studies mentioning renal cancer but focusing solely on epidemiology without discussion of cell death pathways). During this stage, papers that lacked experimental or clinical data were also excluded. Any disagreements were discussed and resolved by consensus. We limited our scope to articles indexed in WOSCC, recognizing that certain journals or proceedings might not appear in this database; we acknowledge this as a potential limitation affecting citation counts and trends. Only publications written in or translated into English were retained, reflecting the predominant language of the biomedical literature and ensuring clarity of text for subsequent analysis.

2.3 Duplicate removal and data processing

All retrieved records were checked for duplicates using title, author names, and digital object identifiers (DOIs). When two entries were confirmed to describe the same publication, one was retained and the other removed. This process helped maintain a clean dataset, free from overlapping references that might inflate publication or citation counts. After deduplication and final inclusion checks, we obtained 5, 134 unique, English-language papers. To capture the impact of national research programs noted in the final dataset, we included studies from all countries without geographic or funding-source restrictions. This approach allowed us to observe how major funding initiatives may have influenced publication trends.

2.4 Bibliometric and network analysis

We used CiteSpace (version 6.3.R2) and VOSviewer (version 1.6.20) to conduct the bibliometric analyses and visualize collaboration patterns. CiteSpace was employed to generate co-citation networks, identify burst words, and delineate thematic clusters. In this software, the Q value represents the modularity of the network (i.e., how well it can be decomposed into distinct clusters), and the S value (or silhouette) assesses the homogeneity of those clusters. In our cluster analysis, the Q value was 0.8994, suggesting a strongly modular network, and the S value was 0.9641, indicating high internal consistency within each cluster. VOSviewer was used to construct co-occurrence networks based on author affiliations, institutional partnerships, and keyword frequencies. Nodes in the resulting maps represent authors, institutions, or keywords, with node size reflecting frequency (e.g., publication count or term occurrence) and link thickness denoting the strength of co-authorship or thematic similarity. Through these complementary methods, we sought to provide a multi-dimensional perspective on how research subfields have evolved over time, as well as how collaborative relationships have shaped the discipline. To track emerging trends, we applied the burst-detection algorithm in CiteSpace, which identifies sudden increases in keyword usage frequency over specified time intervals. These "burst words" help pinpoint shifting research priorities and reveal how concepts such as immunotherapy, metabolism, or novel forms of PCD have gained prominence within the literature. By highlighting when and for how long a particular term experienced a surge in attention, burst detection offers insight into how the field's thematic focus has shifted in relation to clinical or technological advances.

3 Results

3.1 The trend of publication outputs

As shown in Fig. 2, the publication output in the field of programmed cell death in renal cancer from 1998 to 2024 reveals a marked upward trajectory, reflecting both deepening scientific insights and expanding clinical applications in oncology. This pattern can be viewed in several phases: an early, relatively modest rise from 25 publications in 1998 to 51 in 2002, corresponding with initial breakthroughs in apoptosis research and targeted therapy trials; a more sustained climb from 2003 (83 publications) through 2010 (135 publications), coinciding with the introduction of tyrosine kinase inhibitors, broader global funding initiatives (e.g., Europe's early Framework Programmes), and a surge in molecular biology

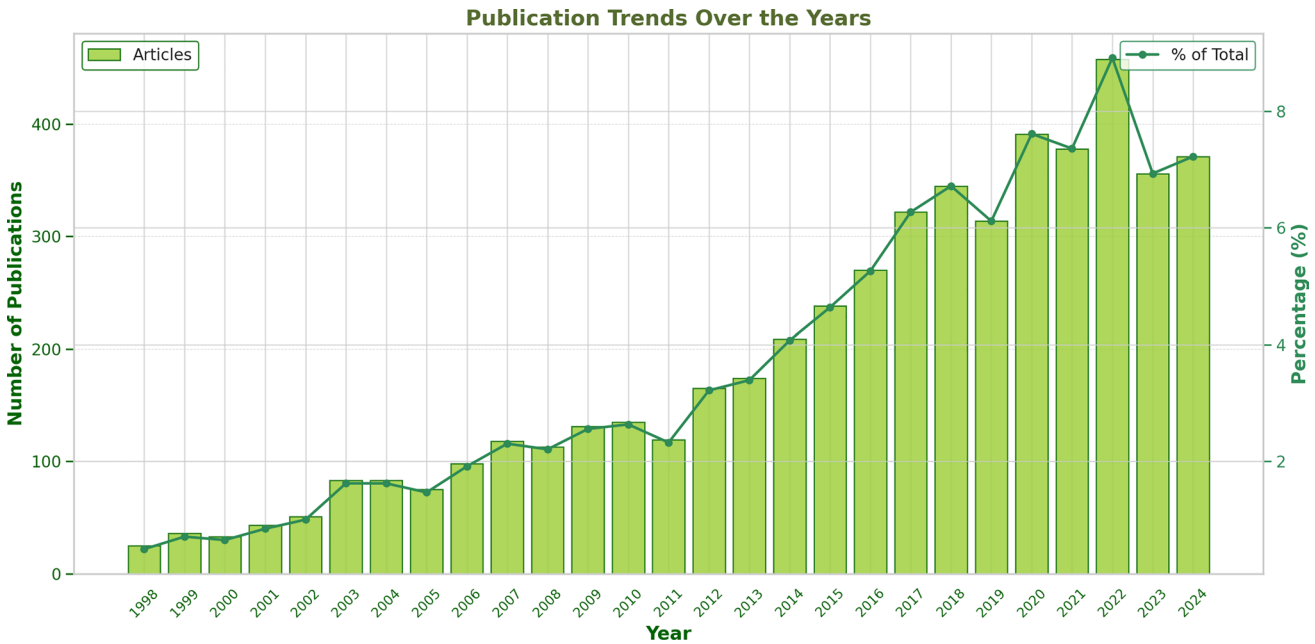

Fig. 2 Annual publication output in programmed cell death in renal cancer (1998–2024)

techniques that allowed researchers to dissect cell death pathways more precisely; a robust expansion from 2011 to 2022, evidenced by an ascent from 119 to a peak of 458 publications, driven by major national and international programs such as the U.S. 21 st Century Cures Act, China's strategic biomedical endeavors, and philanthropic projects like the Cancer Moonshot, all of which fostered cross-disciplinary collaborations and propelled novel research into autophagy, ferroptosis, and immunomodulatory treatment strategies; and a subsequent recalibration in 2023 (356 publications) and 2024 (371 publications), which, while lower than the 2022 zenith, reflects a return to more balanced medical investment in the aftermath of COVID-19's emergency-driven focus—an effect noted worldwide as research expenditures shifted back toward routine and diversified portfolios. Despite this recent stabilization, the overarching trajectory remains upward, underscoring the sustained regional and global commitment to unraveling cell death mechanisms and translating these discoveries into targeted therapeutic innovations for renal cancer.

3.2 Distribution of authors

As shown in Fig. 3, the distribution of authors in the field of programmed cell death in renal cancer was analyzed through a co-occurrence network using VOSviewer, enabling a detailed visualization of collaboration patterns across multiple research clusters. In this network visualization, each node corresponds to an individual author, with node size reflecting publication frequency and node color signifying distinct collaborative subgroups. Table 1 lists the top ten authors by publication frequency, revealing that Kwon Taeg Kyu, with 68 documents and a total link strength of 254, emerges as a particularly influential figure in uncovering the molecular underpinnings of cell death pathways and informing targeted therapeutic strategies. Dahiya Rajvir, who leads the table in citation impact (2170 citations) while producing 30 documents, underscores the longevity of foundational work in apoptotic and genetic mechanisms of renal carcinoma. Other prolific contributors, such as Hirata Hiroshi and Majid Shahana, have shaped the evolving discussion around autophagy and necroptosis as key modulators of treatment resistance, reflecting broader shifts in the discipline toward more nuanced, multi-pathway explorations of tumor biology. The presence of renowned clinical researchers, including Atkins Michael B. and Choueiri Toni K., highlights the increasingly translational orientation of the field, whereby discoveries on programmed cell death find application in immunotherapy protocols and combination treatments. Collectively, this network underlines that multidisciplinary collaborations—spanning molecular biology, clinical oncology, and translational medicine—have propelled the emergence of robust research consortia dedicated to advancing therapeutic innovation in renal cancer.

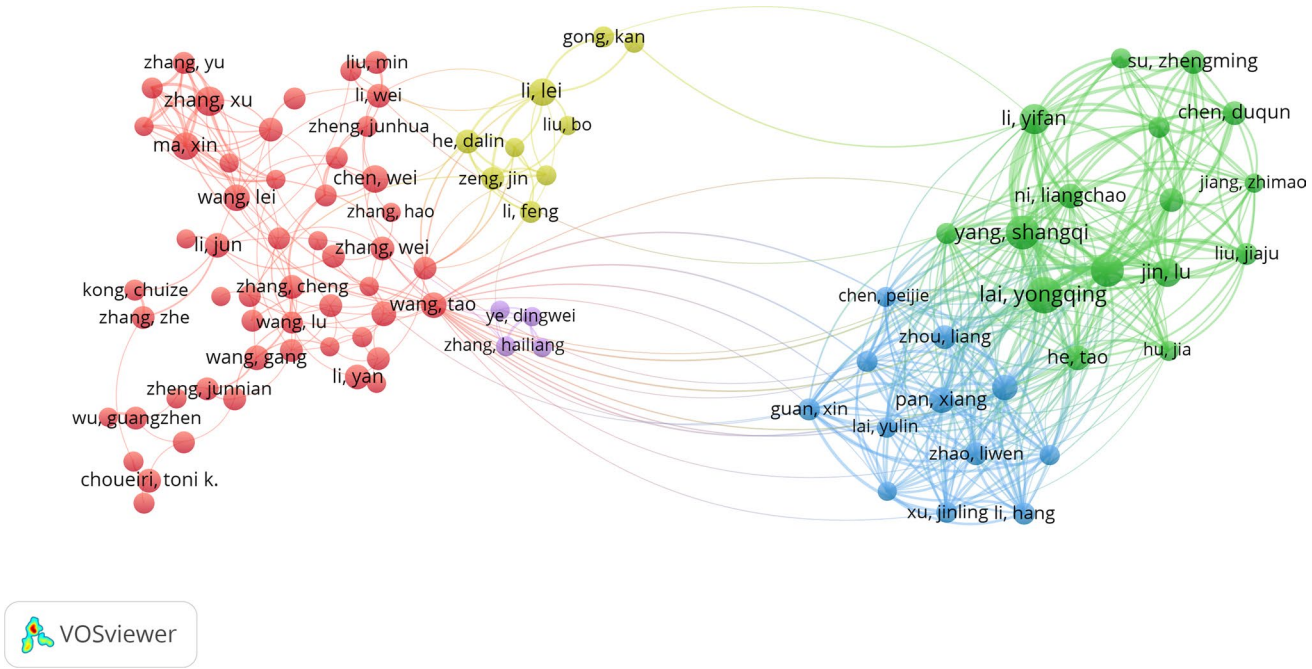

Fig. 3 Co-occurrence network of authors in programmed cell death in renal cancer

Table 1 Top 10 Authors by Publication Frequency in targeted therapy for multiple myeloma

No	Author	Documents	Citations	Total link strength
1	Dahiya, Rajvir	30	2170	212
2	Kwon, Taeg Kyu	68	1763	254
3	Hirata, Hiroshi	19	1741	139
4	Majid, Shahana	24	1492	186
5	Shahryari, Varahram	14	1453	132
6	Atkins, Michael B	8	1442	17
7	Ballabio, Andrea	8	1428	10
8	Kwon, Eugene D	7	1348	32
9	Saini, Sharanjot	19	1235	155
10	Choueiri, Toni K	16	1215	67

3.3 Distribution of countries/regions

As shown in Fig. 4, the geographical distribution of research in programmed cell death in renal cancer was examined using CiteSpace with parameters including a Slice Length of 1, g-index (k = 7), LRF = 3.0, and e = 1.0, yielding a clear view of how scientific collaborations are dispersed globally. According to Table 2, the People's Republic of China emerges as a leading contributor, reflected in a notably high citation frequency (60, 294) and a centrality of 0.30, with 2006 marking a pivotal year of intensified impact. The United States also occupies a dominant position, accruing 30, 082 citations and

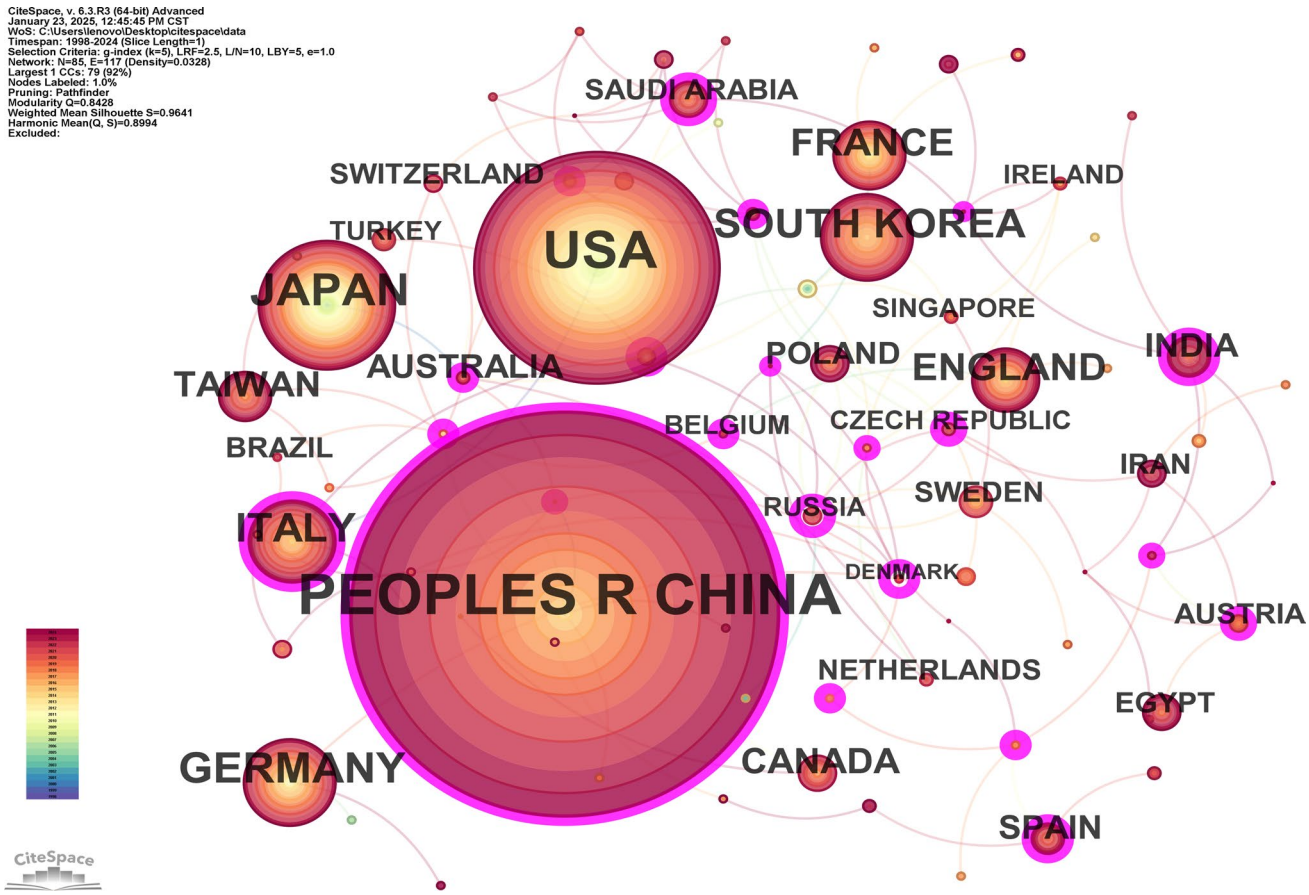

Fig. 4 Geographical distribution of publications in programmed cell death in renal cancer

Table 2 Top Contributing Countries/Regions in targeted therapy for multiple myeloma

No	Country	Citation Frequency	Centrality	Years with the highest number of citations
1	PEOPLES R CHINA	60294	0.30	2006
2	USA	30082	0.28	2014
3	JAPAN	4915	0.15	2008
4	GERMANY	11028	0.18	2002
5	ENGLAND	7626	0.22	2003
6	ITALY	15523	0.10	2008
7	FRANCE	9205	0.06	2005
8	SOUTH KOREA	7168	0.05	2010
9	CANADA	6507	0.19	2009
10	SPAIN	6739	0.06	2006

a centrality score of 0.28, particularly evident around 2014, when molecular and immunotherapeutic initiatives gained substantial traction. Other major players, such as Japan (citation frequency = 4, 915, centrality = 0.15) and Germany (11, 028, centrality = 0.18), highlight the breadth of foundational and translational research in autophagy, apoptosis, and emerging cell death pathways, often supported by robust national funding frameworks. England, Italy, and France all demonstrate significant influence, with respective peaks in citation activity around the mid-2000 s to early 2010 s, reflecting a collective European effort to decode intricate tumor microenvironments. South Korea and Canada likewise display a steady upward trajectory, underscoring the increasingly global pursuit of collaborative renal cancer studies that span basic science to clinical trials. Spain's inclusion among the top contributors further emphasizes the widespread interest in applying novel insights into ferroptosis, necroptosis, and combination therapies for renal tumors. Overall, this distribution underscores the truly international nature of inquiry into cell death mechanisms, wherein multidisciplinary teams across continents collectively shape the current and future landscape of renal cancer research.

3.4 Distribution of published journals

The distribution of academic journals publishing on programmed cell death in renal cancer was examined via VOSviewer, as shown in Fig. 5, revealing that high-impact, Q1-ranked outlets dominate this research area and reflect the field's strong translational emphasis. According to Table 3, Cancer Research stands out with 102 articles and 8259 citations (IF 12.5), indicating its central role in disseminating both foundational and clinical insights. Clinical Cancer Research follows with 79 articles and 6356 citations (IF 10.4), further underscoring the integration of preclinical findings with patient-focused studies. Proceedings of the National Academy of Sciences (14 articles, 4939 citations; IF 9.4) signifies the continued importance of high-level basic science investigations, while Cancer Cell (12 articles, 2125 citations; IF 48.8) highlights the value of advanced molecular research in elucidating emerging cell death mechanisms. PLOS ONE also features prominently, with 87 articles and 3301 citations despite a more moderate IF of 2.9, reflecting the journal's broad scope and inclusive publication policy. The Journal of Urology (109 articles, 2543 citations) demonstrates how domain-specific journals foster clinical translation, complementing multidisciplinary outlets like the International Journal of Cancer and Molecular Cancer Therapeutics. Together, these findings underscore the multifaceted nature of renal cancer cell death research—ranging from benchside molecular discoveries to bedside clinical implementations—and reflect the dynamic exchange of knowledge among high-profile journals committed to advancing both theoretical and therapeutic frontiers.

3.5 Distribution of top-cited publications

As shown in Fig. 6 [29–38], the top-cited publications in programmed cell death in renal cancer were investigated using CiteSpace and the ten most influential studies are presented in Table 4. Klionsky et al.'s (2016) work [29] in AUTOPHAGY emerges with the highest citation count (5071), reflecting the pivotal role of autophagy monitoring guidelines in elucidating tumor biology and therapeutic targets. Sivan et al. (2015) in SCIENCE (2686 citations) [30] underscores how gut microbiota can modulate antitumor immunity, foreshadowing the deepening synergy between host immune mechanisms and immune checkpoint strategies. Topalian et al. (2016) in Nature Reviews Cancer (2017 citations)[31] and Chan

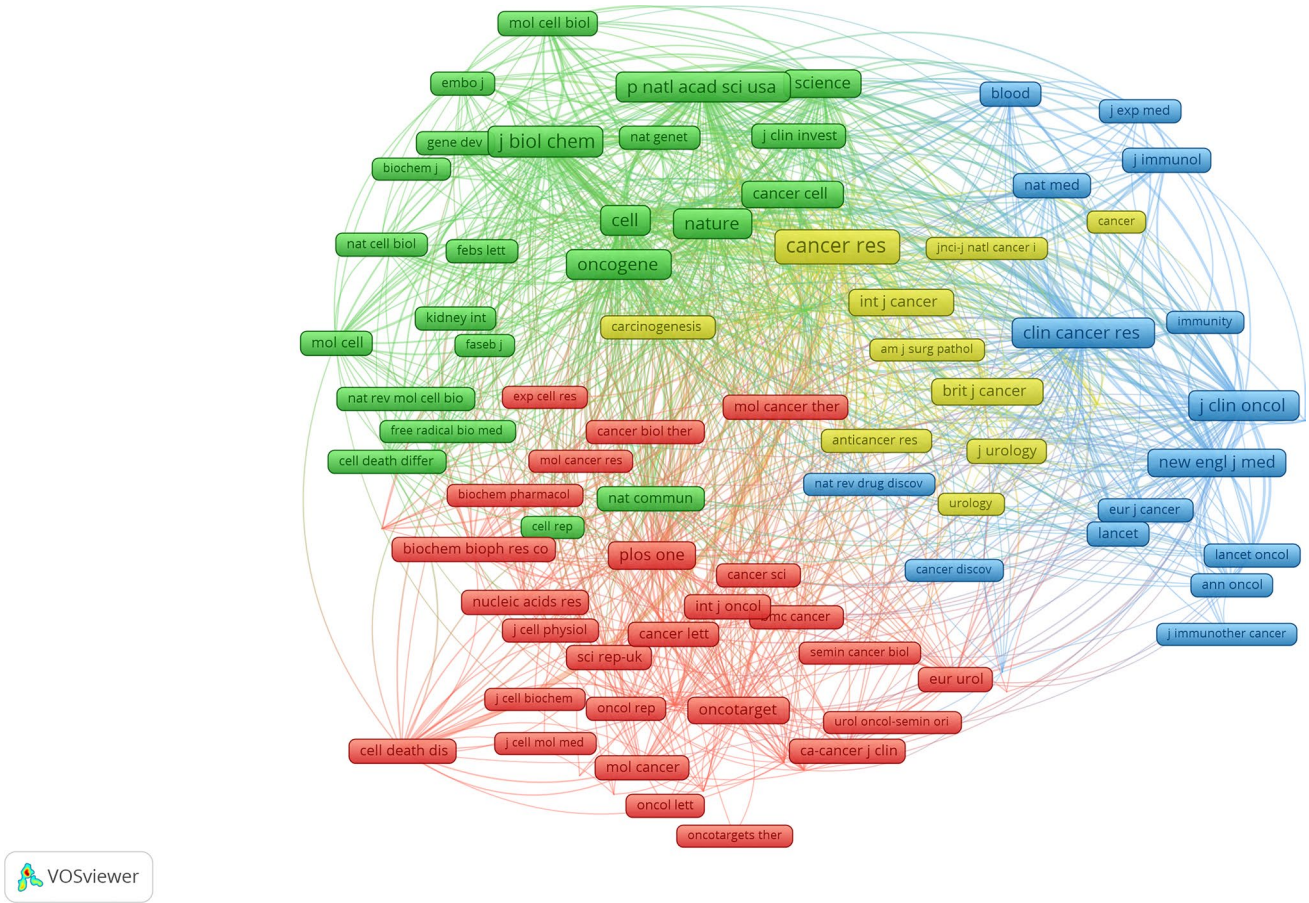

Fig. 5 Distribution of journals publishing in programmed cell death in renal cancer

Table 3 Top Journals Publishing in targeted therapy for multiple myeloma

No	Journal	Article number	Citations	IF (2023)	JCR
1	CANCER RESEARCH	102	8259	12.5	Q1
2	CLINICAL CANCER RESEARCH	79	6356	10.4	Q1
3	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES	14	4939	9.4	Q1
4	PLOS ONE	87	3301	2.9	Q1
5	ONCOGENE	45	3089	6.9	Q1
6	JOURNAL OF UROLOGY	109	2543	6.4	Q1
7	INTERNATIONAL JOURNAL OF CANCER	45	2436	5.7	Q1
8	MOLECULAR CANCER THERAPEUTICS	36	2398	5.4	Q1
9	CANCER CELL	12	2125	48.8	Q1
10	BRITISH JOURNAL OF CANCER	33	1850	6.4	Q1

et al. (2019) in Annals of Oncology (1771 citations) [32] advance biomarker-oriented approaches—such as tumor mutation burden—to enhance the precision of immunotherapy. Patel et al. (2015) detail the predictive significance of PD-L1 expression (1753 citations) [33], while Mahoney et al. (2015) highlight combination immunotherapy as an emerging paradigm (1002 citations) [34]. Meanwhile, Hollingsworth et al. (2006) in JNCI-J Natl Cancer I (911 citations) [35] points to the clinical relevance of the rising incidence of small renal masses, heralding new diagnostic and treatment challenges. Miao et al. (2018) in SCIENCE (863 citations) [36] and Barata et al. (2017) in CA-Cancer J Clin (614 citations) [37] emphasize the genomic drivers and comprehensive management strategies in renal carcinoma, respectively, and Brahmer et al. (2021) in Journal of Immunotherapy Cancer (428 citations) [38] provides SITC guidelines for managing immune

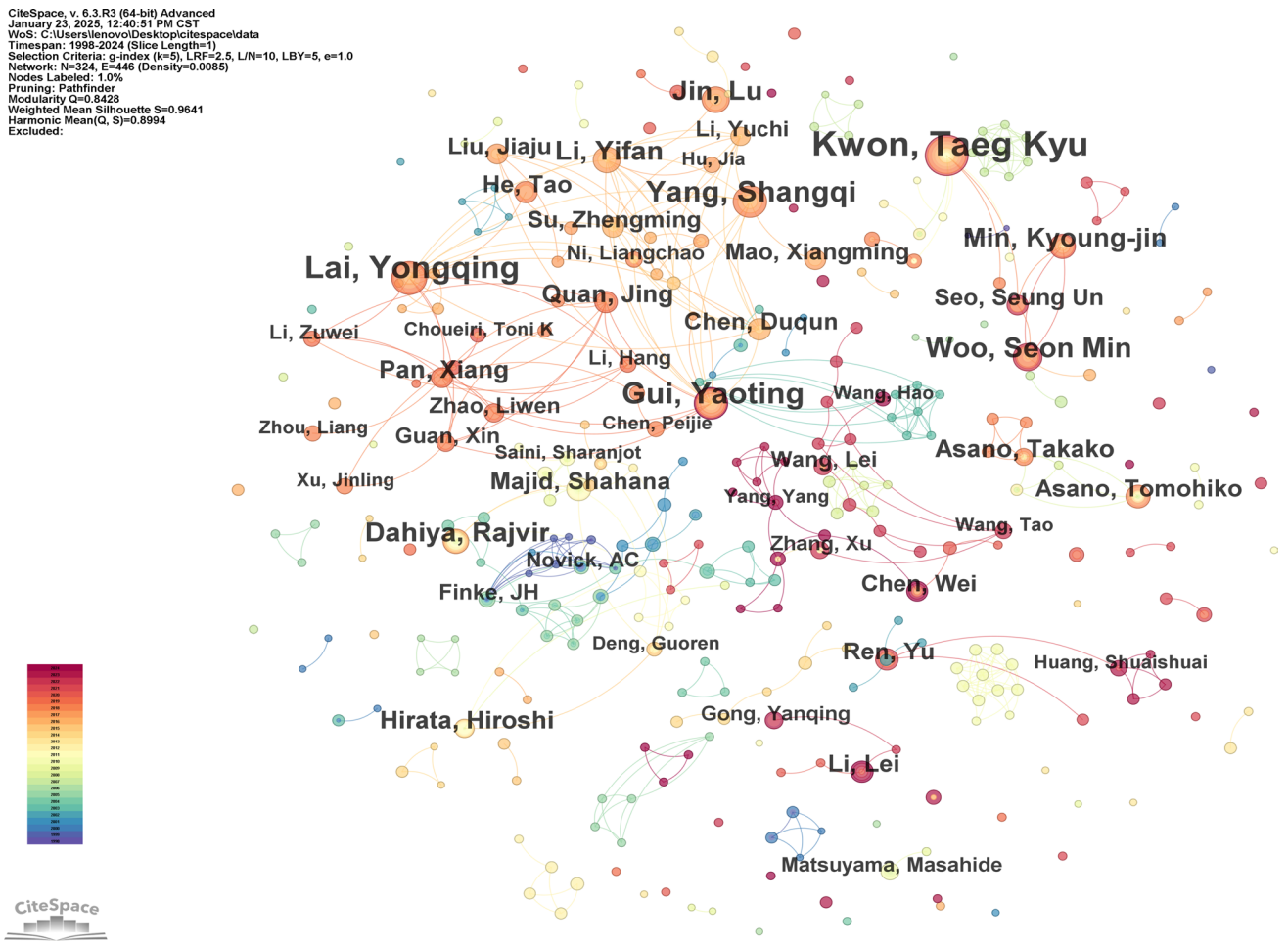

Fig. 6 Top-cited publications in programmed cell death in renal cancer

checkpoint inhibitor-related toxicities. Collectively, these high-impact publications mirror the field's transition toward multidisciplinary, immunologically informed frameworks for understanding cell death pathways and optimizing renal cancer treatment.

3.6 Analysis of keywords

Keywords distilled from the included literature provide a succinct encapsulation of research themes and evolving focal points in programmed cell death in renal cancer, reflecting both foundational mechanisms and emerging translational interests. As shown in Figs. 7 and 8, terms appearing more than 40 times were mapped into 54 nodes divided into three distinct clusters. The red cluster, centered around "apoptosis," "death," and "inhibition," emphasizes canonical cell death pathways and underscores the influence of regulatory molecules such as p53, NF-κB, and Bcl-2. The green cluster, dominated by "renal cell carcinoma," "autophagy," and "immunotherapy," points to ongoing efforts to combine cell death regulation with immune-based strategies, particularly as targeted therapeutics (e.g., sunitinib, everolimus) are increasingly recognized for their interplay with T-cell activation and the tumor microenvironment. The blue cluster, featuring keywords like "proliferation," "metastasis," and "migration," highlights more recent interest in dynamic processes driving tumor progression, including the roles of microRNAs, methylation, and epigenetic modifications in shaping cell fate decisions. Over time, as shown by the color gradient in the overlay visualization, earlier investigations focused on basic apoptosis and chemotherapy-induced cell death, whereas newer research trends emphasize immunomodulation, metabolic reprogramming, and emerging death modalities, such as ferroptosis. Collectively, the keyword analysis demonstrates a progression from fundamental apoptotic studies toward multifaceted, translational research aimed at leveraging diverse programmed cell death pathways for more effective renal cancer therapies.

Table 4 Top 10 Cited publications in targeted therapy for multiple

No	Title	Centrality	Year	Authors	Source title	Cited by
1	Guidelines for the use and interpretation of assays for monitoring autophagy (3rd edition)	0.35	2016	Klionsky et al. [29]	AUTOPHAGY	5071
2	Commensal Bifidobacterium promotes antitumor immunity and facilitates anti-PD-L1 efficacy	0.18	2015	Sivan et al. [30]	SCIENCE	2686
3	Mechanism-driven biomarkers to guide immune checkpoint blockade in cancer therapy	0.09	2016	Topalian et al. [31]	NAT REV CANCER	2017
4	Development of tumor mutation burden as an immunotherapy biomarker: utility for the oncology clinic	0.22	2019	Chan et al. [32]	ANN ONCOL	1771
5	PD-L1 Expression as a Predictive Biomarker in Cancer Immunotherapy	0.15	2015	Patel et al. [33]	MOL CANCER THER	1753
6	Combination cancer immunotherapy and new immunomodulatory targets	0.14	2015	Mahoney et al. [34]	NAT REV DRUG DISCOV	1002
7	Rising incidence of small renal masses: A need to reassess treatment effect	0.28	2006	Hollingsworth et al. [35]	JNCI-J NATL CANCER I	911
8	Genomic correlates of response to immune checkpoint therapies in clear cell renal cell carcinoma	0.17	2018	Miao et al. [36]	SCIENCE	863
9	Treatment of renal cell carcinoma: Current status and future directions	0.10	2017	Barata et al. [37]	CA-CANCER J CLIN	614
10	Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events	0.06	2021	Brahmer et al. [38]	J IMMUNOTHER CANCER	428

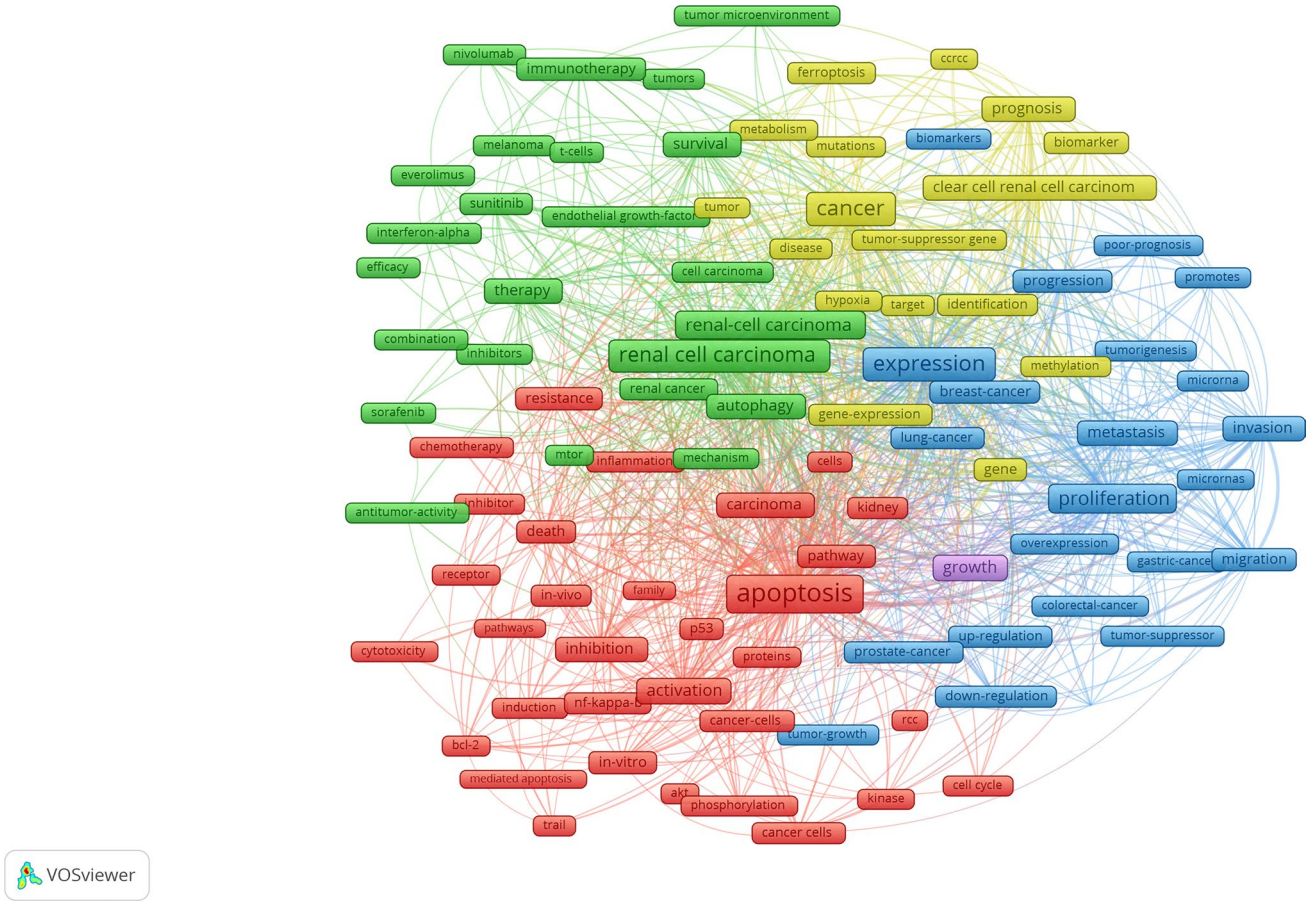

Fig. 7 Keyword co-occurrence network in programmed cell death in renal cancer

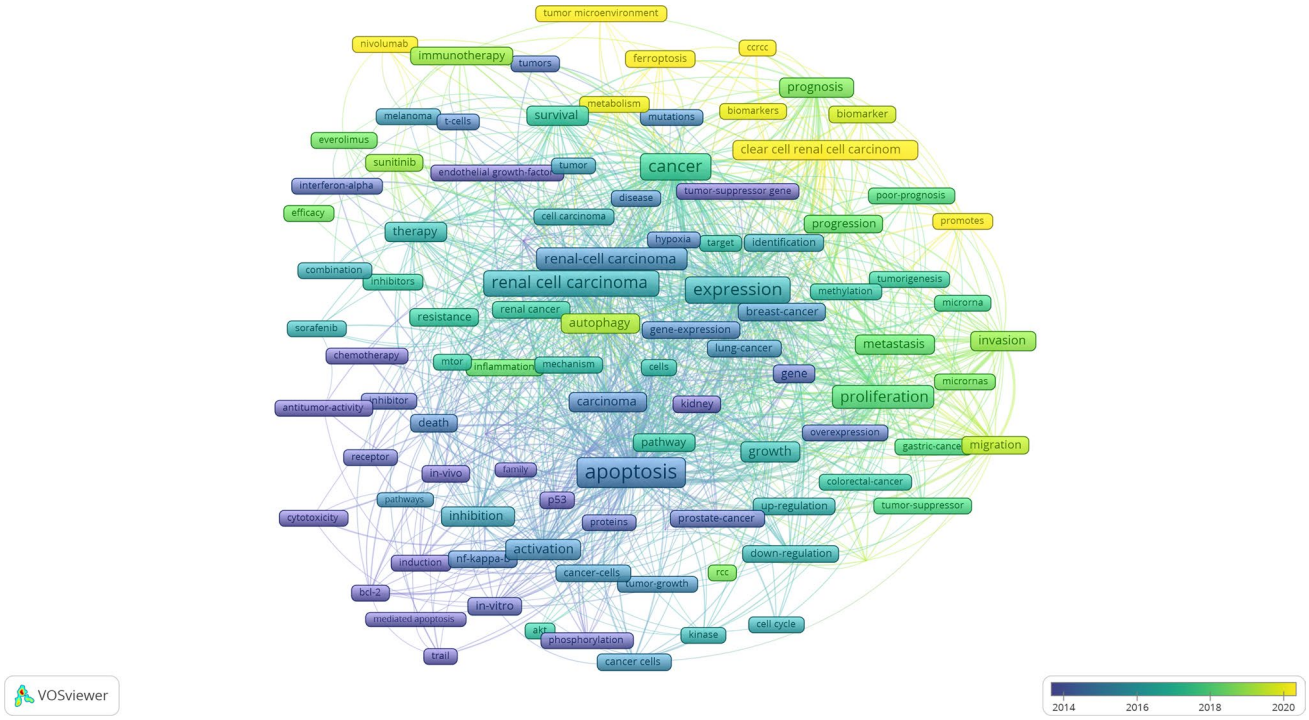

Fig. 8 Temporal evolution of keywords in programmed cell death in renal cancer

3.7 Cluster analysis

Each cluster generated by the CiteSpace analysis represents a cohesive keyword grouping that illuminates prevailing themes and emerging directions in programmed cell death research within renal cancer, as demonstrated by a Q value of 0.8428 and an S value of 0.9641. As depicted in Fig. 9, these ten clusters embody a broad spectrum of scientific inquiry, ranging from fundamental disease identification to advanced immunological strategies. Cluster #0 (t cells) spotlights the expanding interest in harnessing adaptive immune responses for therapeutic benefit, reflecting advances in checkpoint inhibitors and combination regimens. By contrast, Cluster #1 (renal cell carcinoma) and Cluster #7 (kidney cancer) underscore a long-established focus on disease-specific markers and cellular mechanisms, while Clusters #2 (inhibition), #4 (immune infiltration), and #5 (death) capture the evolving recognition of targeted therapies, immune-driven tumor dynamics, and the interplay of various cell death pathways. Clusters #3 (lung cancer) and #8 (renal cancer) indicate an interdisciplinary perspective, wherein lessons gleaned from one solid tumor type often inform treatment strategies in another. Moreover, Cluster #6 (protein) reflects molecular-level investigations probing signal transduction and regulatory networks, whereas Cluster #9 (angiogenesis) highlights ongoing efforts to disrupt vascular supply and modulate the tumor microenvironment. Together, these clusters reveal a research landscape increasingly oriented toward integrated immunotherapy, molecularly informed interventions, and a nuanced understanding of cell death mechanisms, ultimately guiding innovative treatment paradigms for renal cancer.

3.8 Burst word analysis

Burst-word analysis reveals dynamic shifts in research emphasis over time, capturing emerging hotspots in programmed cell death and renal cancer. As shown in Fig. 10, earlier bursts revolved around angiogenesis (strength = 11.05, 2004–2008) and endothelial growth factor (13.99, 2005–2012), highlighting the role of vascular modulation in tumor development. Similarly, "in vivo" (19.14, 2006–2014) gained considerable traction in foundational experimental frameworks. Subsequent

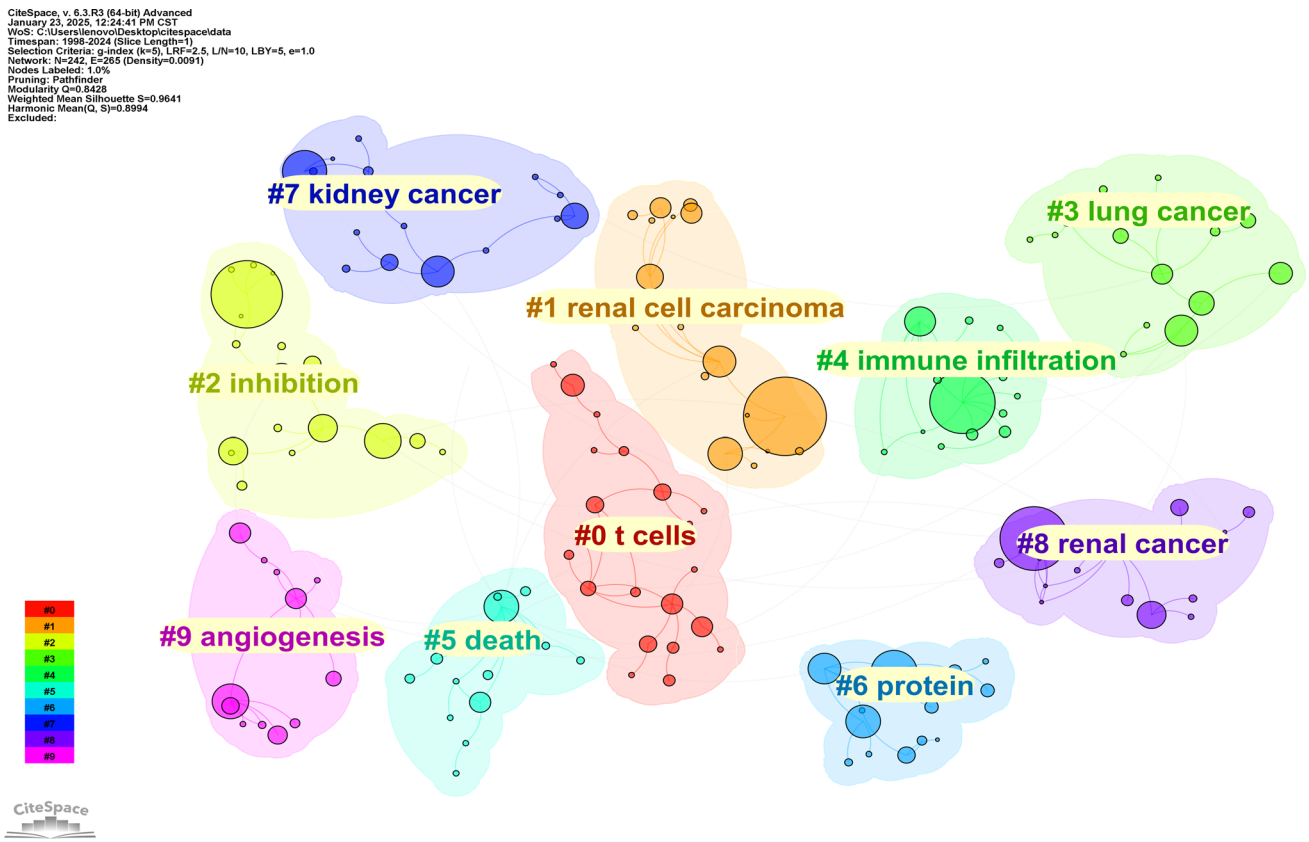

Fig. 9 Keyword cluster analysis in programmed cell death in renal cancer

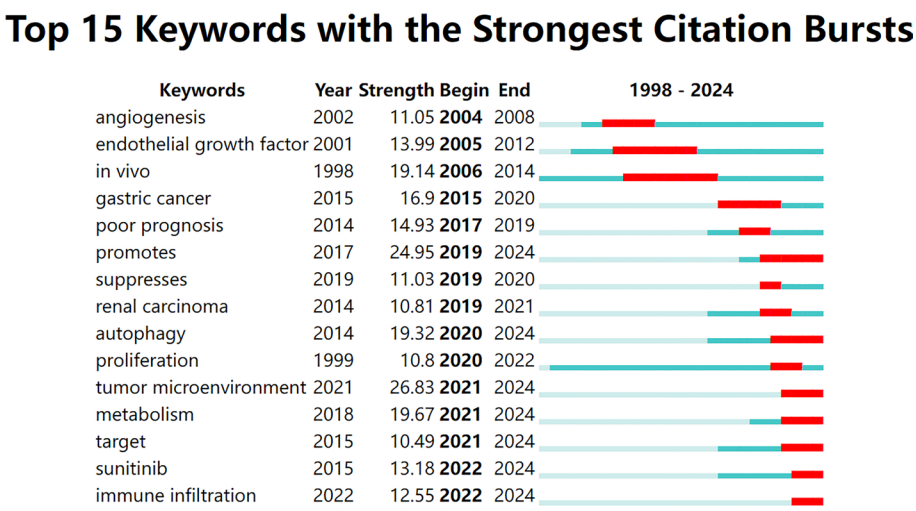

Fig. 10 Burst word analysis in programmed cell death in renal cancer

bursts, such as "poor prognosis" (14.93, 2017–2019) and "gastric cancer" (16.9, 2015–2020), demonstrate broader oncological intersections and clinical relevance of aggressive phenotypes. More recent and powerful bursts—including "promotes" (24.95, 2019–2024), "tumor microenvironment" (26.83, 2021–2024), and "immune infiltration" (12.55, 2022–2024)—underscore the growing importance of immunobiology, wherein immune cells, inflammatory mediators, and the tumor niche converge to influence cell death pathways. The emergence of terms like "sunitinib" (13.18, 2022–2024) and "metabolism" (19.67, 2021–2024) emphasizes a current shift toward targeted agents and metabolic reprogramming as cornerstones in controlling renal cancer progression. Intriguingly, "autophagy" (19.32, 2020–2024) continues to surge, reflecting its complex interplay with apoptosis and immunomodulatory processes in tumor suppression or survival. These burst trends illustrate the field's transition from angiogenesis-centered exploration to an increasingly nuanced inquiry into immune regulation, metabolic vulnerabilities, and the intricate interplay of programmed cell death mechanisms.

3.9 Co-occurrence time zone map analysis

The co-occurrence time zone map (Figs. 11, 12) demonstrates a clear temporal progression of research emphasis in programmed cell death and renal cancer, mapping how key concepts and methodologies have evolved from 2003 to 2023 in roughly biennial increments. Early investigations (2003–2006) were dominated by foundational keywords such as "apoptosis," "cancer," and "death," reflecting an initial drive to characterize essential molecular and cellular mechanisms. Between 2007 and 2012, interest began to shift toward targeted therapies and stress responses, evidenced by the prominence of keywords like "resistance," "therapy," and "oxidative stress," as attention turned to the interplay between tumor cells and their microenvironment. From 2013 to 2016, the emphasis broadened to include autophagy and other intracellular pathways—underlined by terms such as "autophagy," "ER stress," and "microRNAs"—revealing growing recognition of the multifaceted ways in which cells regulate survival and death. In the most recent period (2017–2023), a marked focus on immunomodulatory strategies and metabolic reprogramming emerges, with keywords including "immune infiltration," "tumor microenvironment," and "metabolism" gaining significant visibility. This chronological trajectory underscores the field's shift from basic apoptotic frameworks to more integrative perspectives, wherein immune mechanisms, metabolic vulnerabilities, and molecular signaling pathways collectively shape innovative therapeutic avenues for renal cancer.

4 Discussion

4.1 Progress and development in the field

Over the past two decades, research in programmed cell death within renal cancer has traversed multiple conceptual and technical milestones, revealing a complex interplay between fundamental molecular pathways, immunological mechanisms, and translational therapeutic applications. At the outset, initial explorations into apoptosis-driven tumor suppression and the genetic regulation of renal cell carcinoma helped establish a knowledge base that fostered the

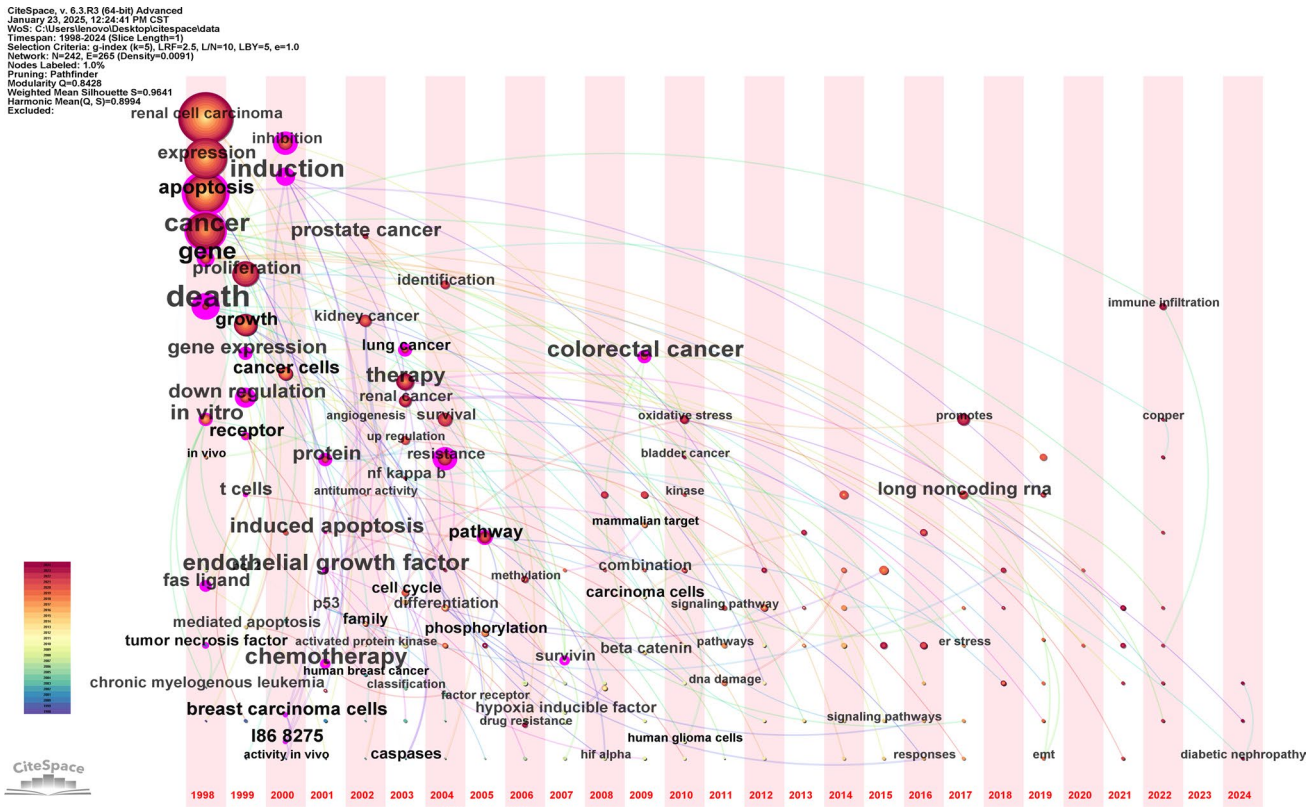

Fig. 11 Co-occurrence time zone map of keywords in programmed cell death in renal cancer

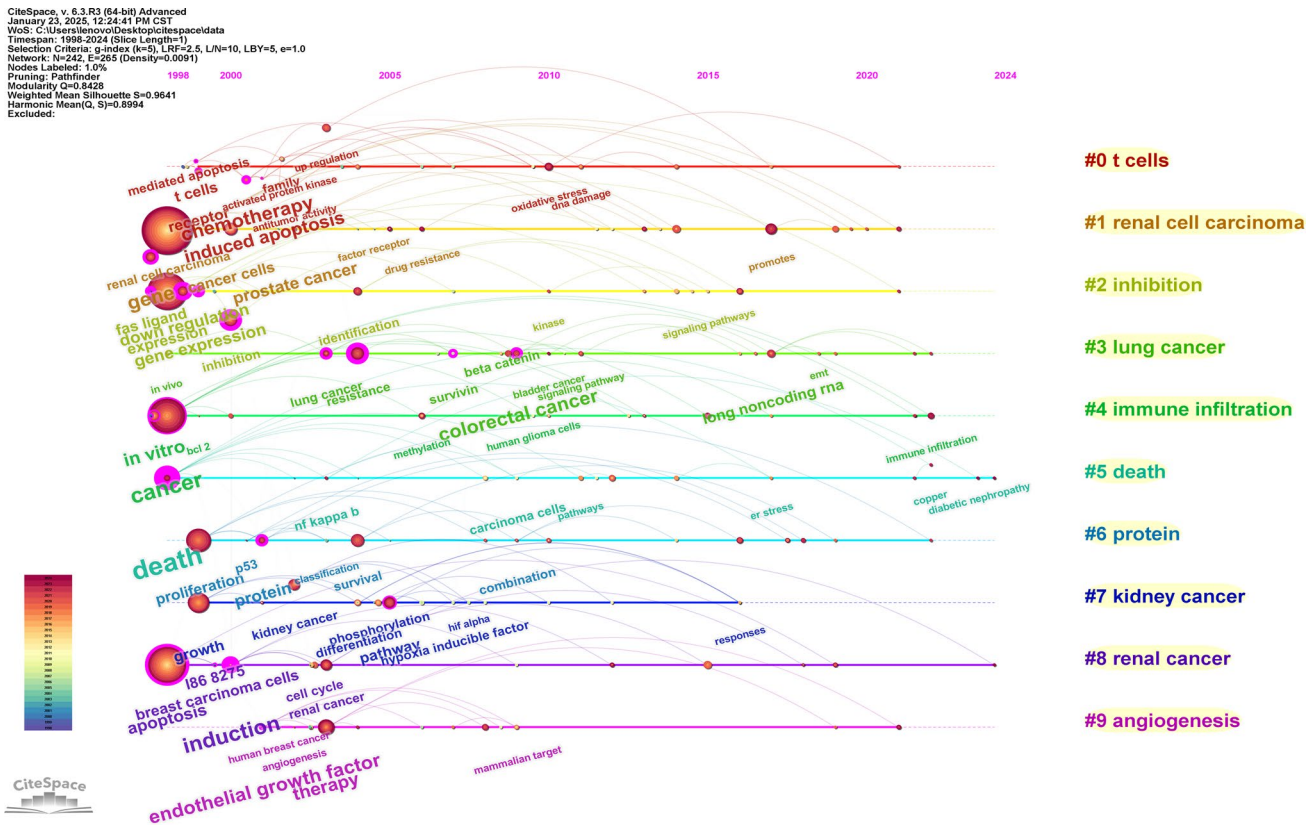

Fig. 12 Evolution of keywords over time in programmed cell death in renal cancer

subsequent proliferation of targeted strategies. Yet as the field matured, studies rapidly broadened their scope to accommodate additional cell death paradigms, including autophagy, necroptosis, and more recently ferroptosis and cuproptosis, thereby illuminating the multilayered crosstalk through which renal tumor cells either succumb to or circumvent cytotoxic stimuli. In tandem, the rapid embrace of tyrosine kinase inhibitors and early immunotherapies prompted a surge in global collaborations and high-impact publications, particularly as mechanistic insights into the tumor microenvironment sharpened clinical interest in next-generation combination regimens. The bibliometric evidence points to a clear progression whereby canonical apoptosis research gave way to a more integrated approach that encompasses metabolic reprogramming, epigenetic modifications, and immune modulation as equal, if not interdependent, drivers of tumor progression and therapy resistance.

This pivot can be attributed not only to a growing appreciation for the heterogeneity of renal carcinoma subtypes—most notably clear cell RCC, which itself exhibits marked variability in immune infiltration and angiogenic factors—but also to the proliferation of advanced molecular profiling tools that enabled precise deconvolution of cell death pathways at single-cell resolution. Consequently, the discipline has increasingly focused on harnessing both intrinsic and extrinsic regulators of programmed cell death, with immunotherapy-based strategies (e.g., PD-1/PD-L1 and CTLA-4 blockade) gaining traction alongside metabolic targets like mTOR, HIF, and AMPK. Such shifts are mirrored in the citation bursts and cluster analyses, which reveal that the field expanded beyond its early fascination with growth factor–driven angiogenesis to encompass the complexities of immunologic crosstalk and metabolic vulnerabilities. By the mid-2010 s, landmark findings on tumor mutation burden and checkpoint blockade in clear cell renal carcinoma catalyzed a wave of translational research, resulting in potent immunotherapeutic combinations that leverage synergy between T-cell–mediated killing and cell-cycle or metabolic inhibition. This evolution toward integrative therapies is further evidenced by an upsurge in studies employing multi-omic approaches, thereby highlighting new biomarkers—such as long noncoding RNAs and specific microRNA signatures—that interact with classical cell death effectors like p53, NF-κB, and Bcl-2. Ongoing investigations now point to an intricate tapestry of signals whereby cell death can be modulated or even hijacked by the tumor to subvert immune recognition, leading researchers to probe deeper into phenomena such as immunogenic cell death and cellular dormancy [39–41]. Regional analyses underscore a significant global commitment—from China's robust contribution to fundamental research in ferroptosis and necroptosis to the United States' emphasis on high-profile immunotherapy trials—while multinational consortia and philanthropic funding initiatives continue to push the boundaries of therapy optimization. At the same time, domain-specific journals like the Journal of Urology and more general high-impact outlets such as Cancer Research and Clinical Cancer Research have served as key platforms for disseminating both mechanistic insights and clinical trial outcomes, illustrating the breadth of expertise required to translate cell death-based strategies into tangible patient benefits.

Notably, top-cited works range from guidelines for monitoring autophagy to breakthrough studies linking gut microbiota to immunotherapy responsiveness, hinting at the intricate interplay between fundamental biology and systems-level influences on treatment efficacy. The strong presence of combination regimens involving tyrosine kinase inhibitors, immune checkpoint inhibitors, and targeted small-molecule modulators of cell survival underscores the field's collective shift from single-agent cytotoxic treatments to a more nuanced palette of therapeutic options that converge upon multiple cell death pathways. With the discipline now homing in on advanced topics such as metabolic rewiring (e.g., Warburg effect manipulation), the tumor microenvironment, and predictive biomarkers, the aim is to refine personalized medicine approaches that exploit each tumor's particular vulnerabilities. Thus, while the overall publication trajectory may have settled into a somewhat less explosive growth phase in the wake of COVID-19–related funding realignments, the long-term research arc indicates a continually strengthening consensus that programmed cell death underlies many of the most promising strategies for combating renal cancer. This perspective is enhanced by the increasing frequency of high-level reviews, meta-analyses, and guidelines that distill core scientific breakthroughs into actionable insights for clinicians, enabling a pipeline in which new molecular findings can be swiftly translated into novel diagnostics, prognostic tools, and combination regimens.

4.2 The hotspots and frontiers

Building upon the momentum of expanded publication outputs and increasingly collaborative networks, the field of programmed cell death in renal cancer has charted out several prominent hotspots and frontiers that reflect both scientific ingenuity and the dynamic nature of translational research. At the molecular level, there is a pronounced shift toward dissecting non-canonical cell death pathways, with ferroptosis, pyroptosis, and cuproptosis garnering growing attention as potentially exploitable weaknesses in the survival machinery of renal tumor cells. Indeed, although apoptosis remains

foundational, emerging evidence points to a broader landscape in which multiple forms of regulated necrosis, including necroptosis, actively interplay with immune components. This has drawn significant focus to the tumor microenvironment, where immunomodulatory strategies—evidenced by a surge in publications linking T-cell activation to checkpoint blockade—are progressively contextualized alongside metabolic vulnerabilities: recent research strongly suggests that targeted inhibition of mTOR, HIF, or AMPK pathways can synergize with PD-1/PD-L1 or CTLA-4 inhibitors to yield improved clinical outcomes. From a more mechanistic standpoint, the interplay between autophagy and immune infiltration has taken center stage, driven by discoveries implicating autophagy in either tumor immunoescape or immunogenic cell death, depending on the cellular context. This dual role underscores the intricacy of crosstalk within the tumor niche, a revelation that has spurred calls for deeper investigation using systems biology tools.

At the same time, advanced "omics" technologies—single-cell RNA-seq, mass spectrometry-based proteomics, and high-throughput CRISPR screens—now enable researchers to pinpoint critical effectors of cell death with unprecedented granularity, forging a path toward personalized therapies tailored to specific mutational or metabolic profiles. Recent burst analyses highlight the continued ascendance of immunotherapy-related keywords and a rising interest in metabolic reprogramming, signaling that the next wave of breakthroughs may revolve around harnessing metabolic checkpoints to enhance immunogenicity. This aligns with real-world advances in combination treatment protocols—e.g., pairing immune checkpoint inhibitors with small-molecule inhibitors (such as sunitinib) or with epigenetic modulators that can potentiate T-cell infiltration and activation. The success of these regimens relies on identifying robust biomarkers, prompting a surge in efforts to develop predictive assays based on circulating tumor DNA, microRNAs, and exosomal cargo that reflect the dynamic state of tumor cell death processes.

Furthermore, the geographic expansion of research hubs in Asia, Europe, and North America, documented in collaborative network analyses, has accelerated large-scale clinical trials aimed at validating next-generation agents—particularly those that bridge immunotherapy and novel cell death pathways. While certain frontiers, such as ferroptosis-based therapies, are still in their relative infancy, the high citation strength of related keywords suggests that they will remain a focal point for experimental therapeutics in the near term. Similarly, the advent of tumor microenvironment–targeting strategies, including anti-angiogenic molecules in conjunction with immune infiltration modulators, points to a holistic paradigm in which vascular normalization, reprogrammed cancer metabolism, and T-cell enhancement coalesce to tip the tumor toward irreversible cell death. At the same time, big-data analytics and machine learning approaches are carving out a niche in predictive modeling, offering the prospect of real-time therapy optimization by mining vast patient datasets to identify patterns of resistance and sensitivity tied to distinct modes of programmed cell death. This systems-level perspective not only enriches basic biological understanding but also shapes clinical decision-making—facilitating the design of tailored regimens that exploit each tumor's unique metabolic and immunologic vulnerabilities. Additionally, long noncoding RNAs (lncRNAs) and other noncoding elements have emerged as key orchestrators of cell death regulation; the high citation bursts associated with these molecules testify to their likely importance as future diagnostic or therapeutic targets, especially in synergy with immunomodulatory agents. Another burgeoning area is the study of hypoxia-inducible factors (HIFs) in modulating cell death under the hypoxic conditions typical of renal carcinoma, a direction further catalyzed by the success of HIF-targeting therapeutics in clinical trials. Thus, a consensus appears to be forming that the frontiers in this field lie at the interface of advanced molecular dissection and forward-thinking translational design, bridging the gap between lab-based mechanistic insights and personalized medicine solutions for patients worldwide. Ultimately, these convergent streams—encompassing immunology, metabolism, cell death subtypes, and large-scale data analytics—herald a future in which refined therapeutic regimens systematically dismantle the survival machinery of renal cancer cells. Overcoming current hurdles will likely depend on innovative cross-disciplinary collaborations, robust clinical trial infrastructures, and continued investment in integrative "omics" technologies. By strategically orchestrating multiple cell death pathways, next-generation therapies have the potential to yield not only higher response rates but also more durable remissions, thereby reshaping the clinical landscape of renal cancer treatment.

5 Conclusion

This bibliometric analysis demonstrated a steady growth of research on programmed cell death (PCD) in renal cancer from 1998 through 2024, with a notable surge after 2010 accompanying advances in immunotherapy and targeted molecular interventions. The field's focus has shifted from foundational apoptosis studies to multifaceted investigations that highlight the synergy between immune checkpoint blockade and metabolic reprogramming. These insights are increasingly guiding therapeutic innovations, as harnessing pathways such as ferroptosis, pyroptosis, and autophagy

opens avenues for combination regimens capable of overcoming resistance. Clinicians can translate this knowledge into practice by using biomarkers that reflect distinct PCD mechanisms—thereby refining therapy selection and timing—to enhance response rates and mitigate adverse effects. Looking ahead, continued integration of immunological strategies with multi-omic profiling and metabolic targeting is poised to refine precision treatments and improve long-term patient outcomes in renal cancer.

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Declarations

Competing interests The authors declare no competing interests.

Ethics and consent to participate declarations Not applicable.

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