

ORIGINAL RESEARCH ARTICLE

Knowledge mapping of immunotherapy for colorectal cancer: A bibliometric analysis (2015–2025)

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Abstract

Colorectal cancer (CRC) remains a global health challenge, but immune checkpoint inhibitors (ICIs) have revolutionized its treatment landscape. This study provides a comprehensive bibliometric analysis of ICI research in CRC to bridge current knowledge gaps. A systematic search of the Web of Science Core Collection (January 1, 2015, to October 31, 2025) identified 1,125 qualifying publications. Analyses using VOSviewer, CiteSpace, and the R-package “bibliometrix” evaluated collaborative networks, co-citations, and keyword trends. Results revealed exponential growth in annual output, with China (21.4%) and the United States (10.1%) emerging as dominant research hubs. *Frontiers in Immunology* was the most prolific journal, while the *Journal of Clinical Oncology* garnered the highest co-citations, reflecting its foundational impact. Author Sahin ranked first with an H-index of 8. Central themes included “Microsatellite Instability,” “Tumor Microenvironment,” and “PD-L1”. Citation burst analysis highlighted a shift from initial safety evaluations toward resistance mechanisms and neoadjuvant therapies in rectal cancer. The research landscape integrates specialized molecular oncology with high-impact clinical evidence. Current trends underscore a transition toward precision medicine, emphasizing overcoming resistance in microsatellite-stable tumors and optimizing organ-preservation strategies.

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1. Introduction

Colorectal cancer (CRC) ranks as the third most diagnosed cancer and the second leading cause of cancer mortality globally.^{1,2} Despite advancements in early screening in developed nations, which have improved 5-year survival rates, about 25% of patients are diagnosed with metastatic disease, and 20–25% of early-stage cases eventually metastasize.³ Microsatellite instability (MSI), indicative of mismatch repair deficiency, is observed in 15% of CRC cases, arising from either epigenetic silencing of *MLH1* or germline mutations in mismatch repair genes (*MLH1*, *PMS2*, *MSH2*, *MSH6*).⁴

Colorectal cancer tumors with mismatch repair deficiency (dMMR) and high MSI (MSI-H) show increased tumor neoantigen load and more tumor-infiltrating

lymphocytes than mismatch repair-proficient (pMMR) and microsatellite-stable (MSS) tumors.^{5,6} These immunogenic features drive the effectiveness of immune checkpoint inhibitors in this molecular subgroup.

Immune checkpoint inhibitors (ICIs) enhance antitumor immunity by disrupting inhibitory checkpoint signaling. The first validated target, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), was clinically validated with ipilimumab, an IgG1κ monoclonal antibody that enhances T-cell activation and extends survival in metastatic melanoma.^{7,8} Recent advances have positioned ICIs as first-line therapy for metastatic dMMR/MSI-H CRC.⁹

Bibliometric analysis enables the systematic evaluation of research landscapes by quantitatively assessing scholarly outputs.^{8,10} Tools such as CiteSpace (Version 6.3.R1, Drexel University, USA)¹¹, VOSviewer (Version 1.6.20, Leiden University, Netherlands)¹², the R package “bibliometrix”¹³, and HistCite¹⁴ provide comprehensive mapping of publication trends in medical fields, including oncology^{15,16}, orthopedics^{17,18}, and traditional medicine.^{19–21}

Although bibliometric studies have examined ICIs' applications in melanoma^{22,23}, hepatocellular carcinoma²⁴, and non-small cell lung cancer²⁵, none have specifically focused on CRC, despite proven efficacy. This study presents the first longitudinal bibliometric analysis of ICI-related CRC research (2015–2025), identifying key contributors, emerging trends, and future research priorities.

2. Methods

2.1. Search strategy

On November 27, 2025, a comprehensive literature search was performed using the Web of Science Core Collection database. The search combined the terms: (TS = (“immune checkpoint inhibitor*” OR “ICI” OR “anti-PD-1” OR “anti-PD-L1” OR “anti-CTLA-4” OR “PD-1 blockade” OR “PD-L1 blockade” OR “CTLA-4 blockade” OR nivolumab OR pembrolizumab OR ipilimumab OR atezolizumab OR durvalumab) NEAR/10 (“colorectal cancer*” OR “colorectal carcinoma*” OR “colon cancer*” OR “colon carcinoma*” OR “rectal cancer*” OR “rectal carcinoma*” OR “CRC”))), applying filters for publication dates from January 1, 2015, to October 31, 2025, to ensure the reliability and representativeness of the dataset, the search was strictly limited to English-language publications, recognizing English as the lingua franca of global scientific communication. Furthermore, the document types were restricted to “Articles” and “Review Articles.” This selection criterion was applied to mitigate potential noise, as these formats typically undergo rigorous peer review and contain

complete experimental data or comprehensive theoretical syntheses, unlike meeting abstracts or editorials. While this inclusion strategy may introduce a minor linguistic bias by excluding non-English contributions, it ensures that the analysis is grounded in high-quality, fully validated scientific evidence (Figure 1).

2.2. Data analysis

Bibliometric data, including full records and cited references, were retrieved and exported from the Web of Science Core Collection (WoSCC) in plain text format. Quantitative statistical analysis and data cleaning were initially performed using Excel (2019, Microsoft, USA) to determine the annual publication output and growth trends. Subsequently, a multi-tool approach was integrated to conduct a comprehensive visualization and network analysis of the dataset. VOSviewer¹² was utilized to construct and visualize complex bibliometric networks, facilitating the generation of co-occurrence maps for journals and keywords, as well as co-citation networks for journals, authors, and references; specific thresholds regarding citation counts and occurrence frequencies were applied to optimize the clarity of these networks and are detailed in the respective results sections. To delve into the structural patterns and temporal dynamics of the field, CiteSpace (Version 6.3.3.0)¹¹ was employed to generate co-occurrence maps for countries and institutions, perform cluster analysis of co-cited references using the log-likelihood ratio (LLR) algorithm, and construct timeline views to trace the evolution of research themes. CiteSpace was also used to detect reference and keyword citation bursts to identify emerging trends. Furthermore, SCImago Graphica (Version 1.0.53, SCImago Research Group, Spain) was applied to provide enhanced visualization of geospatial cooperation networks between countries and collaborative relationships among top authors. Finally, the R package “bibliometrix” (Version 5.0)¹³ was utilized to calculate the H-index for both authors and sources, serving as a quantitative metric to evaluate local impact and academic productivity.

3. Results

3.1. Quantification of publications

A total of 1,125 articles on immunotherapy for CRC were identified in the Web of Science database using predefined inclusion and exclusion criteria. As illustrated in Figure 2, annual publication output and average citations per year from 2015 to 2025 revealed a clear upward trajectory in research activity. The field exhibited significant growth, particularly in recent years, with publications from the last five years (2021–2025) comprising 81.2% of the total,

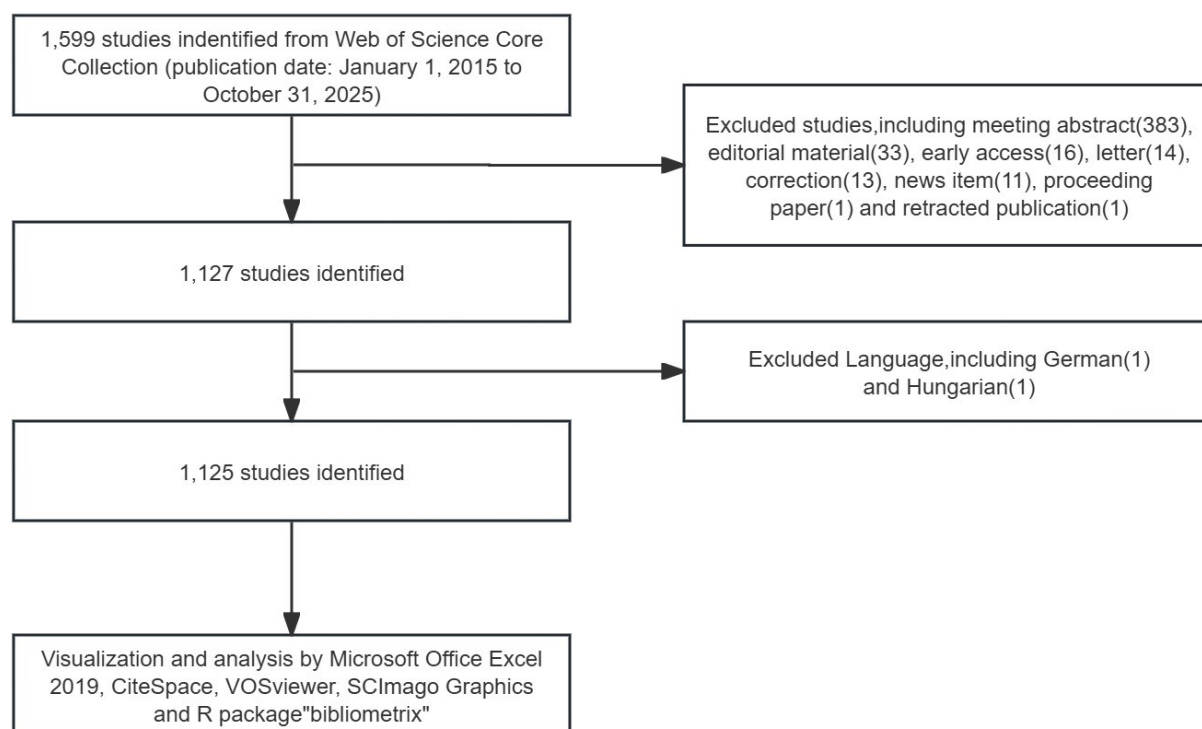


Figure 1. Publications screening flowchart

indicating a sharp acceleration in scholarly interest. The number of annual publications increased steadily from 5 in 2015 to 211 in 2025. Prior to 2019, annual outputs remained below 70 articles; a marked and sustained rise was observed from 2019 onward.

The average number of citations per year further underscored the growing impact of this research. From 2017 to 2022, the mean number of citations per year consistently exceeded 5, reaching a peak of 9.37 in 2018. Although recent publications (e.g., those from 2023 to 2025) demonstrated lower cumulative citations due to shorter exposure times, citation rates in the early years post-publication remained robust. Overall, these findings highlight a rapid expansion in CRC immunotherapy research, characterized by substantial increases in both publication volume and academic influence, reflecting heightened engagement from the scientific community.

3.2. Analysis of national/regional contributions and collaborative networks

Based on the distribution of corresponding authors' countries/regions, a total of 34 countries/regions participated in research on immunotherapy for CRC, indicating that this field has attracted extensive international attention. Figure 3A provides a schematic representation

of the global distribution of these contributing nations, highlighting the worldwide engagement in this research field. As detailed in Table 1, which is based on the corresponding author's country/region, China was the most productive nation, contributing 241 articles and accounting for 21.4% of the total publications. It was followed by the USA (114 articles, 10.1%), Japan (22 articles, 2.0%), France (16 articles, 1.4%), and South Korea (13 articles, 1.2%). Analysis of international collaboration patterns revealed significant variation among countries. The USA demonstrated a substantially higher multiple-country publication ratio (MCP ratio; 25.4%) compared to the most productive nation, China (7.9%). Notably, several countries exhibited exceptionally high MCP ratios, such as Canada (72.7%), Israel (100%), and Switzerland (100%), indicating their roles as pivotal connectors within the global research network despite their moderate total publication output.

The intricate international collaborative landscape was further elucidated through a detailed network analysis, presented in Figure 3B. This network map identifies key nations, including the USA, China, and Spain, as central hubs. It visually confirms that the USA and China serve as the most central and highly interconnected nodes, underscoring their leadership and extensive collaborative

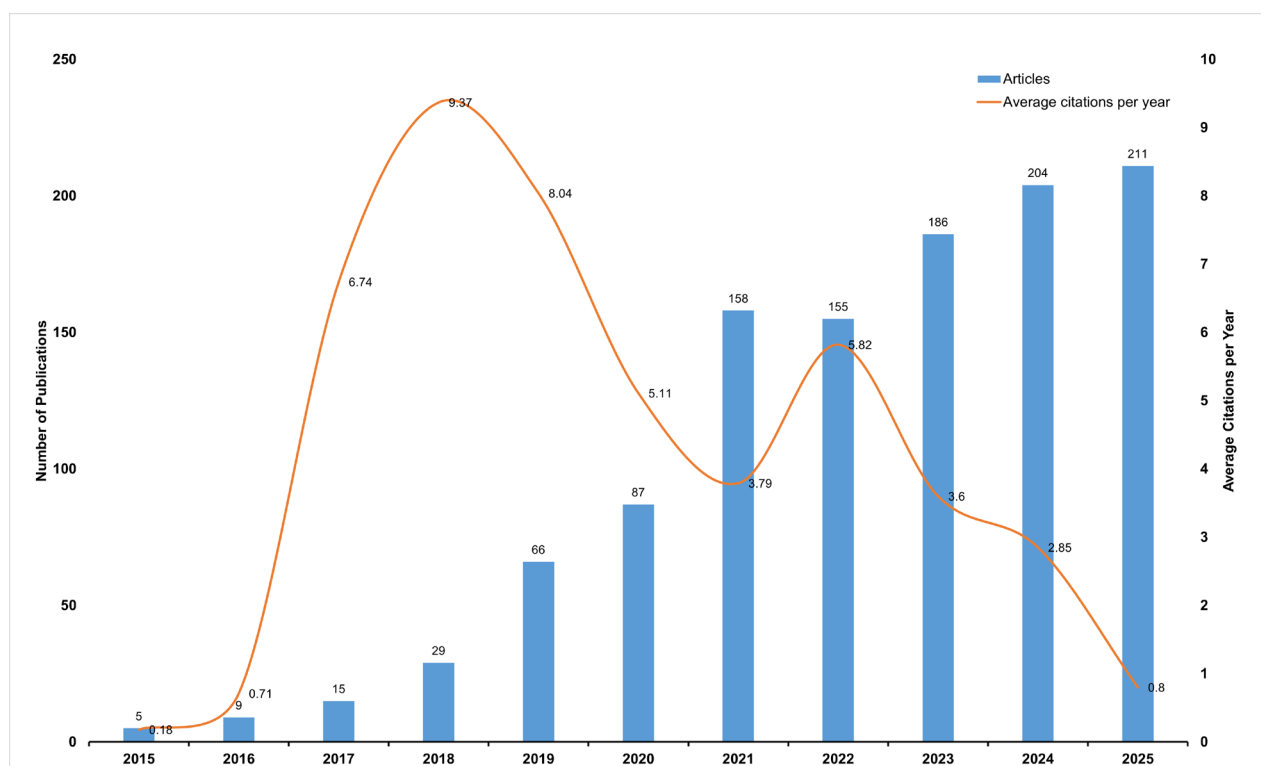


Figure 2. Publications and average annual citations trends

ties. Other nations, such as Spain, France, Italy, Germany, the United Kingdom, and Australia, form strong, interconnected secondary clusters. This network structure reveals a multipolar global research effort, primarily driven by North America, East Asia, and Europe. In summary, the quantitative and network analyses present a nuanced picture of global contributions. While China leads decisively in publication volume, nations like the USA, with their extensive and robust collaborative networks, play a more central role in the global knowledge exchange. Other countries, such as Canada and several European nations, facilitate international connectivity, highlighting the collaborative nature of modern scientific research.

3.3. Analysis of institutional contributions and collaboration networks

Analysis of institutional productivity and collaborative patterns revealed key contributors in the research field. As detailed in Table 2, Sun Yat Sen University emerged as the most productive institution with 39 publications, followed by the University of Texas System (16 publications) and the University of Texas Monroe Dunaway Anderson Cancer Center (11 publications). Chinese institutions dominated the top contributors, occupying six positions among the top ten most productive institutions. Evaluation of

betweenness centrality values demonstrated distinct patterns of institutional influence within collaboration networks. Sun Yat Sen University exhibited both high productivity and strong network connectivity (centrality = 0.42), indicating its dual role as a major knowledge producer and key connector. Similarly, the University of Texas System (centrality = 0.33) and Howard Lee Moffitt Cancer Center and Research Institute (centrality = 0.22) maintained substantial influence as network bridges despite moderate publication output. Conversely, as shown in Table 2, several top-ranked institutions, such as Harbin Medical University and Shanghai Jiao Tong University, displayed a centrality of 0.00 despite their high publication output. This suggests that while these institutions are prolific contributors to the field, their collaboration patterns tend to be intra-institutional or within specific localized clusters, limiting their role as “bridges” in global information flow compared to institutions with high centrality. These findings demonstrate the complex interplay between institutional productivity and network influence in shaping the research landscape.

The institutional co-occurrence network (Figure 3C) visualizes the collaborative landscape and structural hierarchy of research forces in this domain. Sun Yat Sen University emerged as the preeminent node with the largest

Table 1. The 10 most prolific countries/regions regarding studies on immune checkpoint inhibitors for colorectal cancer

Rank	Country	Articles	Articles (%)	SCP	MCP	MCP (%)
1	China	241	21.4	222	19	7.9
2	USA	114	10.1	85	29	25.4
3	Japan	22	2	20	2	9.1
4	France	16	1.4	11	5	31.3
5	Korea	13	1.2	11	2	15.4
6	Italy	12	1.1	9	3	25
7	Canada	11	1	3	8	72.7
8	Germany	8	0.7	6	2	25
9	Australia	7	0.6	6	1	14.3
10	Iran	7	0.6	4	3	42.9

Abbreviations: MCP: Multiple-country publication; SCP: Single-country publication; USA: United States of America.

volume of publications and high betweenness centrality, establishing itself as the central hub of the research network. The analysis reveals a distinct pattern of geographical clustering, while prominent US institutions, such as the University of Texas Monroe Dunaway Anderson Cancer Center and Memorial Sloan Kettering Cancer Center, form the foundational pillars of early research. There is a dense web of domestic collaboration among Chinese institutions, including Fudan University and Shanghai Jiao Tong University. Notably, the temporal dimension of the network highlights a dynamic shift in research leadership. While traditional academic medical centers maintained steady output, the network identifies a surge of activity from emerging contributors in the most recent time slices (2023–2025), such as Zhejiang University and Guangzhou Medical University. This trend suggests rapid diversification of research entities and a potential eastward shift in the locus of innovation in CRC immunotherapy.

The collaboration patterns evident in centrality metrics indicated that while Chinese institutions led in quantitative output, certain US and European institutions maintained crucial roles as knowledge brokers and collaboration facilitators within the global research network. These findings demonstrate the complex interplay between institutional productivity and network influence in shaping the research landscape.

3.4. Analysis of journal contributions and co-citation networks

The dissemination of research findings in CRC immunotherapy was analyzed through publication and co-citation patterns across academic journals. As shown in Table 3, *Frontiers in Immunology* emerged as the most prolific journal with 63 publications, followed by *Cancers*

(48 publications) and *Journal for Immunotherapy of Cancer* (54 publications) (Figure 4A). Co-citation analysis revealed a distinct pattern of influential knowledge sources (Figure 4B), with *Journal of Clinical Oncology* ranking as the most frequently co-cited journal (1,639 citations), demonstrating its foundational role in the field. This was followed by *New England Journal of Medicine* (1,133 citations) and *Clinical Cancer Research* (923 citations), indicating the strong clinical orientation of the research domain.

The analysis identified several specialized immunology and cancer journals among the most productive outlets, including *Cancer Immunology Immunotherapy* and *Journal for Immunotherapy of Cancer*, reflecting the specialized nature of the research field. Meanwhile, high-impact general medical journals, such as *New England Journal of Medicine*, *Lancet Oncology*, and *Nature Medicine*, maintained a strong presence in co-citation networks, indicating the broad clinical relevance and interdisciplinary impact of the research. The substantial citation counts and link strengths observed in both productive and co-cited journals highlight robust knowledge exchange between specialized cancer journals and high-impact clinical publications, creating an integrated academic communication ecosystem that bridges specialized research and clinical application in CRC immunotherapy.

3.5. Analysis of author contributions and co-citation networks

The analysis of authors and co-cited authors identified the most active researchers and the foundational knowledge base in the field of ICIs for CRC. As summarized in Table 4, Thierry André was the most prolific author

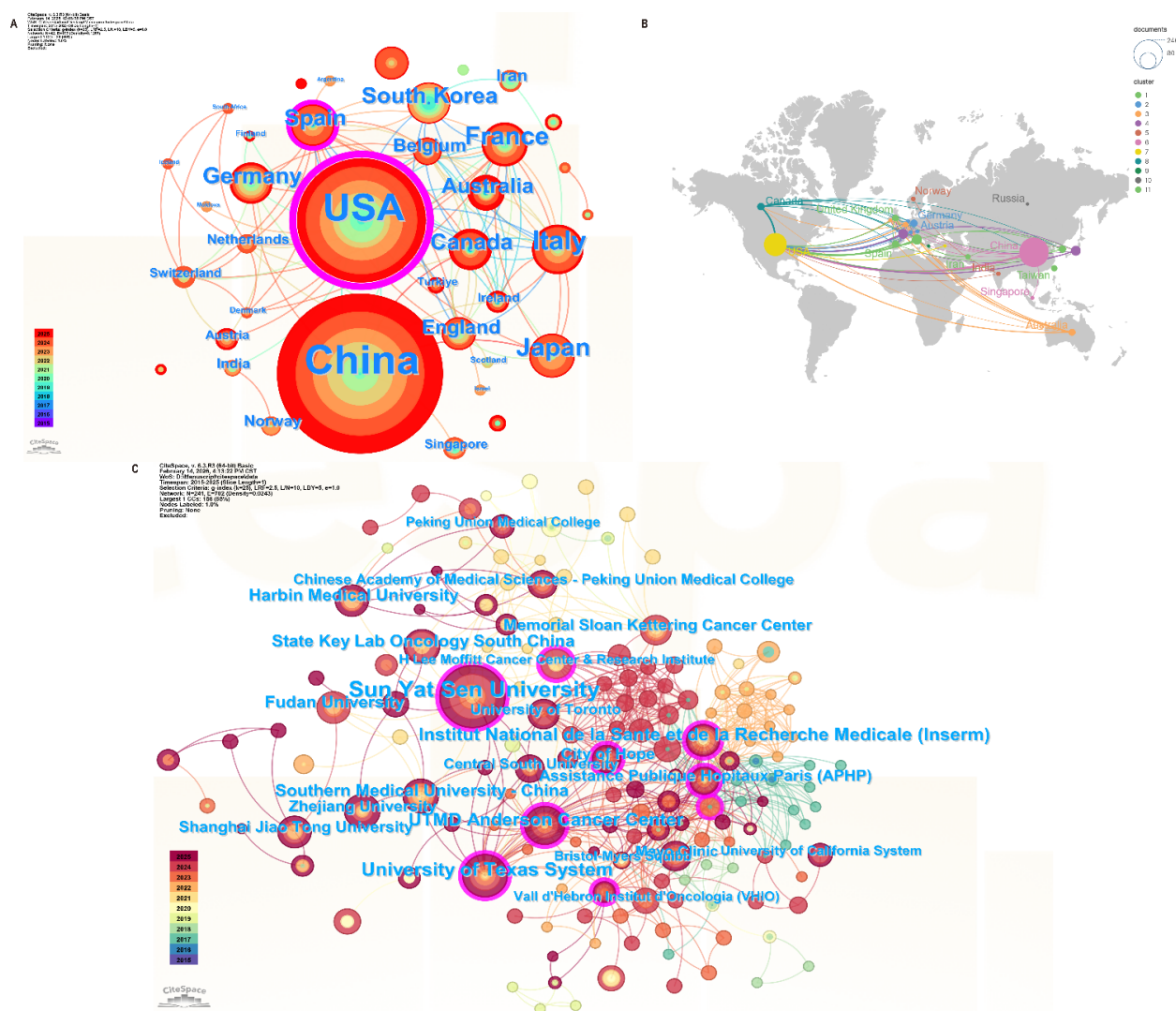


Figure 3. Global distribution and collaborative networks of contributing countries, regions, and institutions. (A) CiteSpace-generated national/regional co-occurrence network map. (B) Cooperation network map between countries/regions created using SCImago Graphics. (C) Research institution co-occurrence network map generated using CiteSpace.

with 23 publications, closely followed by Sara Lonardi (22 publications) and Filippo Pietrantonio and David Tougeron (17 publications each). The international diversity of leading authors, with significant contributions from researchers across Europe and the United States, reflects the global collaborative effort in advancing CRC immunotherapy research. The collaboration network among leading authors, visualized in Figure 5A, shows that Thierry André occupies a central and highly interconnected position, underscoring the team-oriented nature of clinical and translational research in this domain.

In terms of co-cited authors representing the intellectual foundation of the field, Dung T. Le emerged as the most

frequently cited scholar with 410 co-citations, with her seminal work on programmed cell death protein 1 (PD-1) blockade in mismatch repair-deficient tumors constituting a cornerstone of the field. Michael James Overman (309 co-citations) and Thierry André (166 co-citations) also ranked highly, reflecting the significant impact of their clinical trials on ICIs in metastatic CRC. The presence of other co-cited authors, including Karuna Ganesh and Suzanne L Topalian, indicates that the research foundations extend from clinical trials to fundamental mechanisms of tumor immunology and immune checkpoint function (Figure 5B).

The timeline visualization (Figure 5C) illustrates the

Table 2. Top 10 most productive institutions

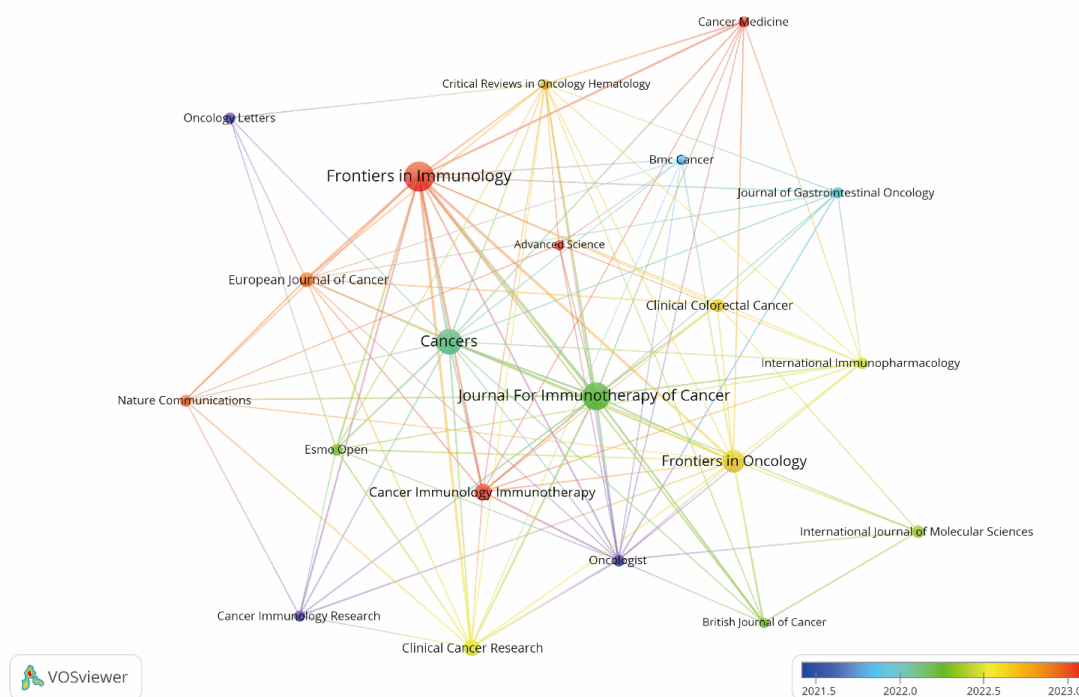
Rank	Institution	Records	Centrality	Year
1	Sun Yat Sen University	39	0.42	2021
2	University of Texas System	16	0.33	2019
3	The University of Texas Monroe Dunaway Anderson Cancer Center	11	0.04	2019
4	Fudan University	9	0.12	2022
5	State Key Laboratory of Oncology in South China	8	0.10	2021
6	Howard Lee Moffitt Cancer Center and Research Institute	8	0.22	2021
7	Harbin Medical University	8	0.00	2022
8	Shanghai Jiao Tong University	7	0.00	2022
9	National Institute of Health and Medical Research (INSERM)	7	0.15	2017
10	Central South University	5	0.00	2016

Table 3. Top 10 journals/co-cited journals for publications on immune checkpoint inhibitors for colorectal cancer

Rank	Journal	Records	JCR/IF (2024)	Rank	Co-cited Journal	Citations	JCR/IF (2024)
1	<i>Frontiers in Immunology</i>	63	Q1/9.5	1	<i>Journal of Clinical Oncology</i>	1639	Q1/42.1
2	<i>Journal for Immunotherapy of Cancer</i>	54	Q1/13.4	2	<i>New England Journal of Medicine</i>	1133	Q1/78.5
3	<i>Cancers</i>	48	Q2/7.2	3	<i>Clinical Cancer Research</i>	923	Q1/10.0
4	<i>Frontiers in Oncology</i>	39	Q2/5.0	4	<i>Science</i>	690	Q1/45.8
5	<i>Cancer Immunology Immunotherapy</i>	24	Q2/5.7	5	<i>Nature</i>	616	Q1/48.5
6	<i>Clinical Cancer Research</i>	22	Q1/10.0	6	<i>Lancet Oncology</i>	626	Q1/41.6
7	<i>European Journal of Cancer</i>	19	Q2/5.8	7	<i>Annals of Oncology</i>	620	Q1/65.4
8	<i>Clinical Colorectal Cancer</i>	16	Q4/1.8	8	<i>Nature Medicine</i>	497	Q1/58.7
9	<i>International Journal of Molecular Sciences</i>	14	Q2/4.8	9	<i>Journal for Immunotherapy of Cancer</i>	514	Q1/13.4
10	<i>ESMO Open</i>	13	Q3/2.5	10	<i>Cancer Cell</i>	358	Q1/66.8

Abbreviations: ESMO: European Society for Medical Oncology; IF: Impact factor; JCR: Journal citation reports.

A



B

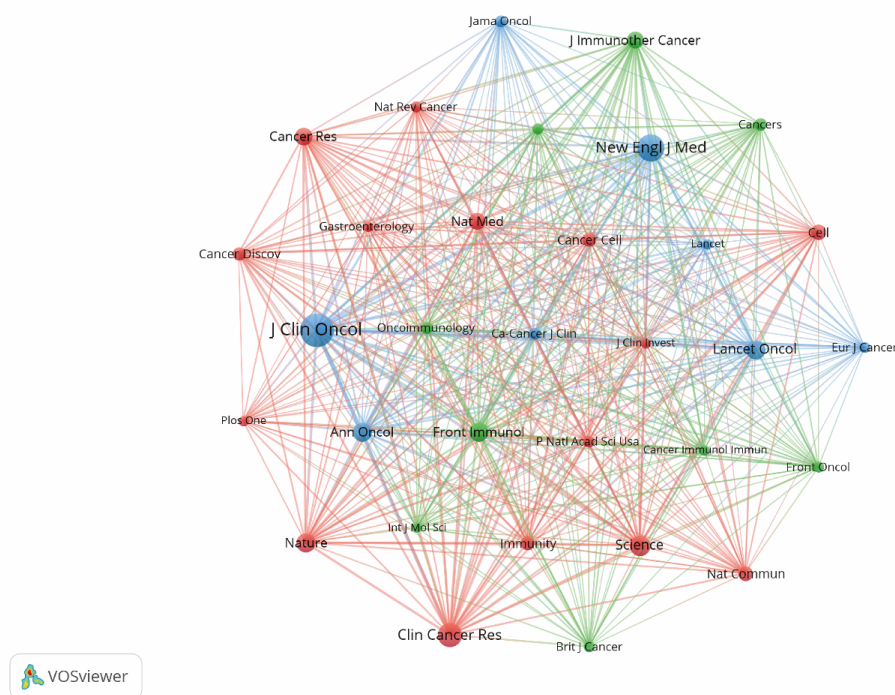


Figure 4. Analysis of journal publication patterns and co-citation networks. (A) Journal co-occurrence network map created using VOSviewer. The threshold was set to a minimum of 10 documents from the source. (B) Journal co-citation network map created using VOSviewer. The threshold was set at a minimum of 200 citations.

evolution and temporal distribution of research hotspots in CRC immunotherapy. The analysis showed robust clustering quality, with a Modularity Q score of 0.4255 and a Weighted Mean Silhouette S value of 0.7254, indicating significant community structure and reliable clustering results. As illustrated in the timeline view, the research focus evolved substantially over the past decade, with seven major clusters identified. The most prominent clusters included #0 Regorafenib, #1 Colon Cancer, and #6 Tumor Immunotherapy. Notably, Cluster #3 dMMR and Cluster #4 PD-L1 highlight the early emphasis on molecular biomarkers. By contrast, the recent prominence of Cluster #0 Regorafenib reflects a shift in clinical attention toward therapeutic strategies for refractory or microsatellite-stable (MSS) subtypes, which remain more challenging to treat than the MSI-H phenotype.

From a temporal perspective, the large nodes with red rings (indicating citation bursts) concentrated in the early period (2015–2018) represented foundational contributions, with key researchers including Le DT, André T, and Overman MJ dominating this phase through seminal clinical trials that established the efficacy of ICIs in dMMR/MSI-H CRC. In contrast, the period from 2020 to 2025 featured emerging active nodes represented by researchers such as Ganesh K and Sung H, with dense interconnections flowing from the earlier influential nodes to these recent clusters. This pattern suggests that contemporary studies are building upon the initial breakthroughs in immunotherapy, now branching into more specific mechanisms, epidemiological trends, and novel therapeutic strategies for resistant tumor types, reflecting both the maturation and expanding scope of the research field.

3.6. Co-cited references and burst references

To visualize the intellectual structure and thematic evolution of the field, a co-citation network was constructed using VOSviewer (Figure 6A), with the top 10 most significantly co-cited references summarized in Table 5. The analysis revealed three distinct clusters, each corresponding to a critical phase in the development of immunotherapy for CRC. The red cluster, located at the center of the network, represents the foundational mechanisms and proof-of-concept studies. The most prominent node in this cluster—and the entire network—is Le *et al.*²⁶ (*The New England Journal of Medicine*), with the highest total link strength. This seminal work established dMMR as a reliable predictive biomarker for PD-1 blockade, fundamentally initiating the era of precision immunotherapy. Radiating from this foundation is the green cluster, which signifies the successful clinical translation and establishment of therapeutic standards for the MSI-H population. Key nodes, such as Overman *et al.*²⁷ (*Lancet Oncology*) and André *et al.*²⁸ (*The New England Journal of Medicine*), correspond to pivotal clinical trials, including CheckMate-142 and KEYNOTE-177. These studies confirmed the robust efficacy of ICIs in dMMR/MSI-H metastatic CRC, establishing them as the first-line or second-line standard of care. In contrast to the MSI-H focus, the blue cluster represents the current research frontier aimed at overcoming resistance in MSS or refractory CRC through combination strategies. This cluster highlights efforts to expand the benefits of immunotherapy to the MSS majority. Notable contributions include Fukuoka *et al.*²⁹ (*Journal of Clinical Oncology*), which reported promising antitumor activity with the combination of regorafenib and nivolumab (REGONIVO

Table 4. The 10 most frequently cited and co-cited authors regarding publications in immune checkpoint inhibitors for colorectal cancer

Rank	Authors	Count	Co-cited authors	Citations
1	Thierry André	23	Dung T Le	410
2	Sara Lonardi	22	Michael James Overman	309
3	Filippo Pietrantonio	17	Thierry André	166
3	David Tougeron	17	Myriam Chalabi	104
5	Romain Cohen	16	Karuna Ganesh	95
5	Marwan Fakih	16	Rebecca L Siegel	94
7	Michael James Overman	15	Heinz-Josef Lenz	93
8	Chiara Cremolini	14	Suzanne L Topalian	89
8	Takayuki Yoshino	14	Julie R Brahmer	82
10	Elena Elez	13	Hyuna Sung	81

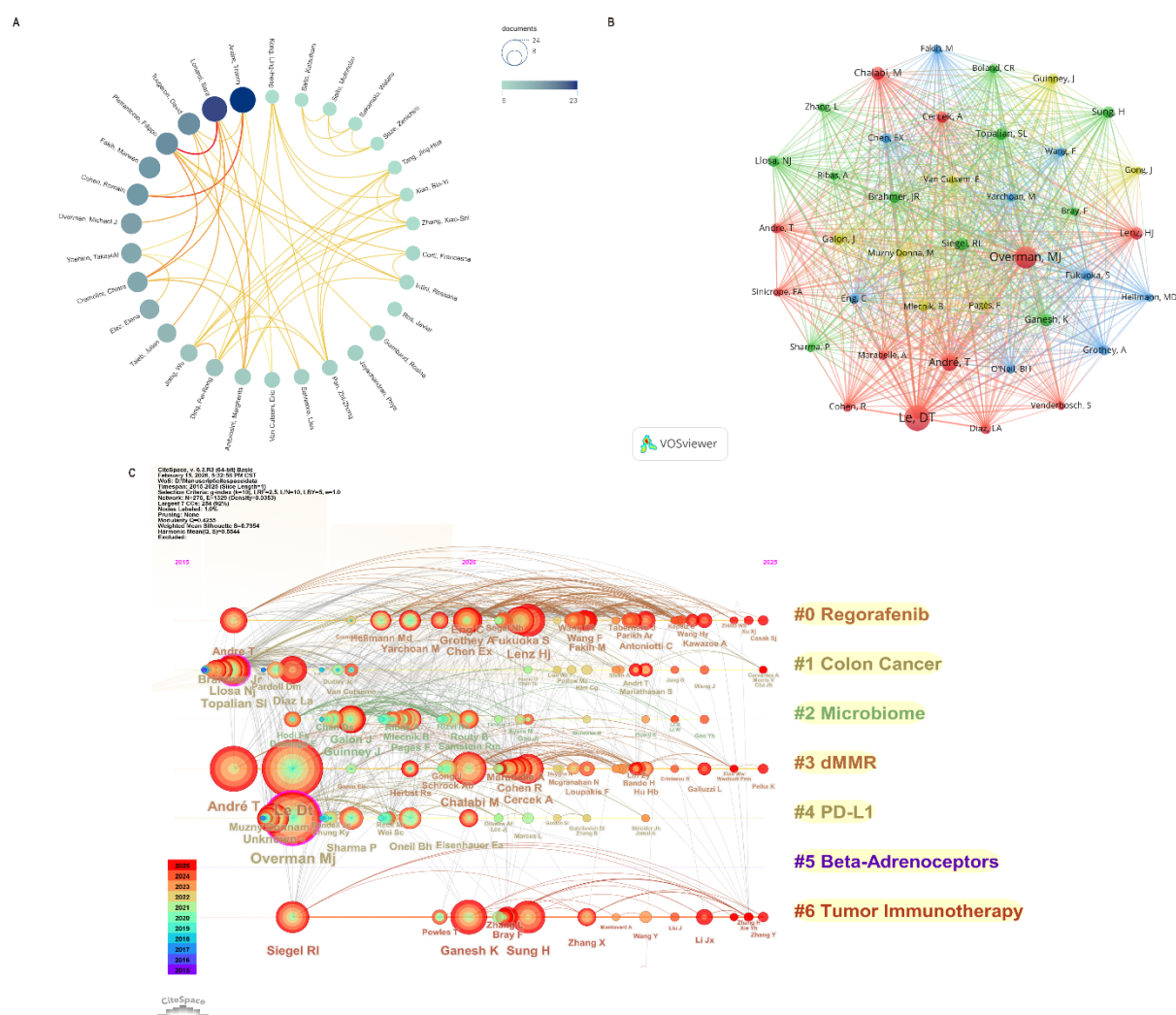


Figure 5. Visualization of author collaboration networks and the temporal evolution of co-citation authors. (A) Top 30 authors' collaboration network map generated using SCImago Graphica. (B) Co-citation authors network map created using VOSviewer. The threshold is set at a minimum of 40 citations from sources. (C) Co-citation authors regarding immune checkpoint inhibitors in colorectal cancer.

Notes: The horizontal axis shows the time of the authors' first appearance, the node size reflects the number of citations, and the color change represents the passage of time.

study), as well as Eng *et al.*³⁰ (*Lancet Oncology*) and Chen *et al.*³¹ (*JAMA Oncology*). These studies reflect the rigorous exploration of novel combinatorial approaches, such as mitogen-activated protein kinase kinase (MEK) inhibitors or dual checkpoint blockade, specifically designed to address therapeutic challenges in the non-MSI-H patient subgroup.

To systematically identify the principal research themes and knowledge structure within the domain of immunotherapy for CRC, a co-citation cluster analysis was performed using CiteSpace (Figure 6B). The resulting network exhibits a high Modularity Q score of 0.5486 and a Weighted Mean Silhouette S score of 0.8478, indicating

a significantly structured network with high internal consistency and credibility. As illustrated in the cluster visualization, the reference network is divided into distinct communities automatically labeled by the LLR algorithm. The most prominent cluster, Cluster #0 "Regorafenib," contains the largest number of nodes. This finding suggests a shift in the field from early emphasis on mismatch repair deficiency, Lynch syndrome, and biomarker identification—represented by Cluster #1 "MSH2" and Cluster #2 "Lynch Syndrome"—toward therapeutic optimization for refractory subtypes. Because regorafenib has been widely investigated in combination strategies to overcome resistance in MSS disease, this cluster reflects

the urgent clinical need to convert immunologically “cold” tumors into more responsive microenvironments. Furthermore, the emergence of clusters such as Cluster #3 “Tumor-Infiltrating Lymphocytes” and Cluster #6 “Tumor Immune Microenvironment” reflects a deepening understanding of the complex cellular interactions within the tumor niche. This evolutionary trajectory suggests that the field is moving beyond broad molecular subtyping toward more granular characterization of immune infiltration and the local microenvironment to identify predictive signatures of response.

To delineate the evolutionary trajectory and temporal characteristics of research hotspots within the field, a timeline visualization of co-cited references was generated. In this layout, clusters are arranged vertically, and references are positioned horizontally according to their publication year, visualizing the flow of knowledge over time (Figure 6C). The analysis reveals a distinct paradigm shift in research focus from 2015 to 2025. Initially, the field was anchored by Cluster #1 “MSH2” and Cluster #5 “Adjuvant Chemotherapy,” in which early high-impact nodes such as Llosa *et al.*⁶ and Le *et al.*²⁶ established the foundational link between MSI and immune checkpoint blockade. As the timeline progressed, research consolidated around Cluster #2 “Lynch Syndrome,” with seminal studies, including André *et al.*²⁸ and Overman *et al.*³², helping establish the standard of care for dMMR/MSI-H metastatic CRC. However, in the post-2020 period, a significant redirection of scientific effort is observed

toward Cluster #0 “Regorafenib” and Cluster #6 “Tumor Immune Microenvironment.” This transition indicates that, after therapeutic strategies had been established for the MSI-H population, the scientific community increasingly turned its attention to the more challenging MSS subtype. The prominence of regorafenib reflects the intensive exploration of combination therapies aimed at modulating the immunosuppressive microenvironment to overcome resistance in MSS tumors. Notably, the appearance of recent high-burst nodes, such as Chalabi *et al.*³³ and Cercek *et al.*³⁴ within Cluster #4 “Rectal Cancer,” highlights emerging frontiers, particularly the breakthrough of neoadjuvant immunotherapy in locally advanced rectal cancer, signaling a transformative trend toward organ preservation and precision oncology.

To identify pivotal turning points and emerging trends within the domain, citation burst analysis was performed to detect references that garnered a sudden surge of attention over a specific period (Figure 7). The analysis highlighted the top 25 references with the strongest citation bursts. Le *et al.*²⁶ exhibited the highest burst strength (23.48), followed closely by Overman *et al.*²⁷ (21.77) and Le *et al.*³⁵ (16.40). The temporal distribution of these bursts reveals a distinct evolution in the research trajectory. The early phase (bursts beginning 2016–2018) was dominated by these landmark studies, which fundamentally established dMMR as a predictive biomarker and validated the clinical efficacy of PD-1 blockade in MSI-H CRC. Significantly, the most recent bursts in the 2021–2023 period indicate

Table 5. The 10 most significantly co-cited references regarding publications regarding immune checkpoint inhibitors for colorectal cancer

Rank	First author	Year	Journal	Vol.	Page	Citations	TLS
1	Le DT ²⁶	2015	<i>N Engl J Med</i>	372	2509	188	927
2	Overman MJ ²⁷	2017	<i>Lancet Oncol</i>	18	1182	160	861
3	André T ²⁸	2020	<i>N Engl J Med</i>	383	2207	147	762
4	Overman MJ ³²	2018	<i>J Clin Oncol</i>	36	773	123	739
5	Le DT ³⁵	2017	<i>Science</i>	357	409	114	633
6	Ganesh K ³	2019	<i>Nat Rev Gastroenterol Hepat</i>	16	361	83	403
7	Sung H ¹	2021	<i>CA Cancer J Clin</i>	71	209	80	299
8	Le DT ³⁹	2020	<i>J Clin Oncol</i>	38	11	78	523
9	Chalabi M ³³	2020	<i>Nat Med</i>	26	566	73	428
10	Llosa NJ ⁶	2015	<i>Cancer Discov</i>	5	43	64	324

Notes: Citations are the number of citations within the retrieved dataset; Total link strength represents the connection strength of the reference within the network.

Abbreviations: *CA Cancer J Clin*: *CA: A Cancer Journal for Clinicians*; *Cancer Discov*: *Cancer Discovery*; *J Clin Oncol*: *Journal of Clinical Oncology*; *Lancet Oncol*: *The Lancet Oncology*; *N Engl J Med*: *New England Journal of Medicine*; *Nat Med*: *Nature Medicine*; *Nat Rev Gastroenterol Hepat*: *Nature Reviews Gastroenterology & Hepatology*; TLS: Total link strength.

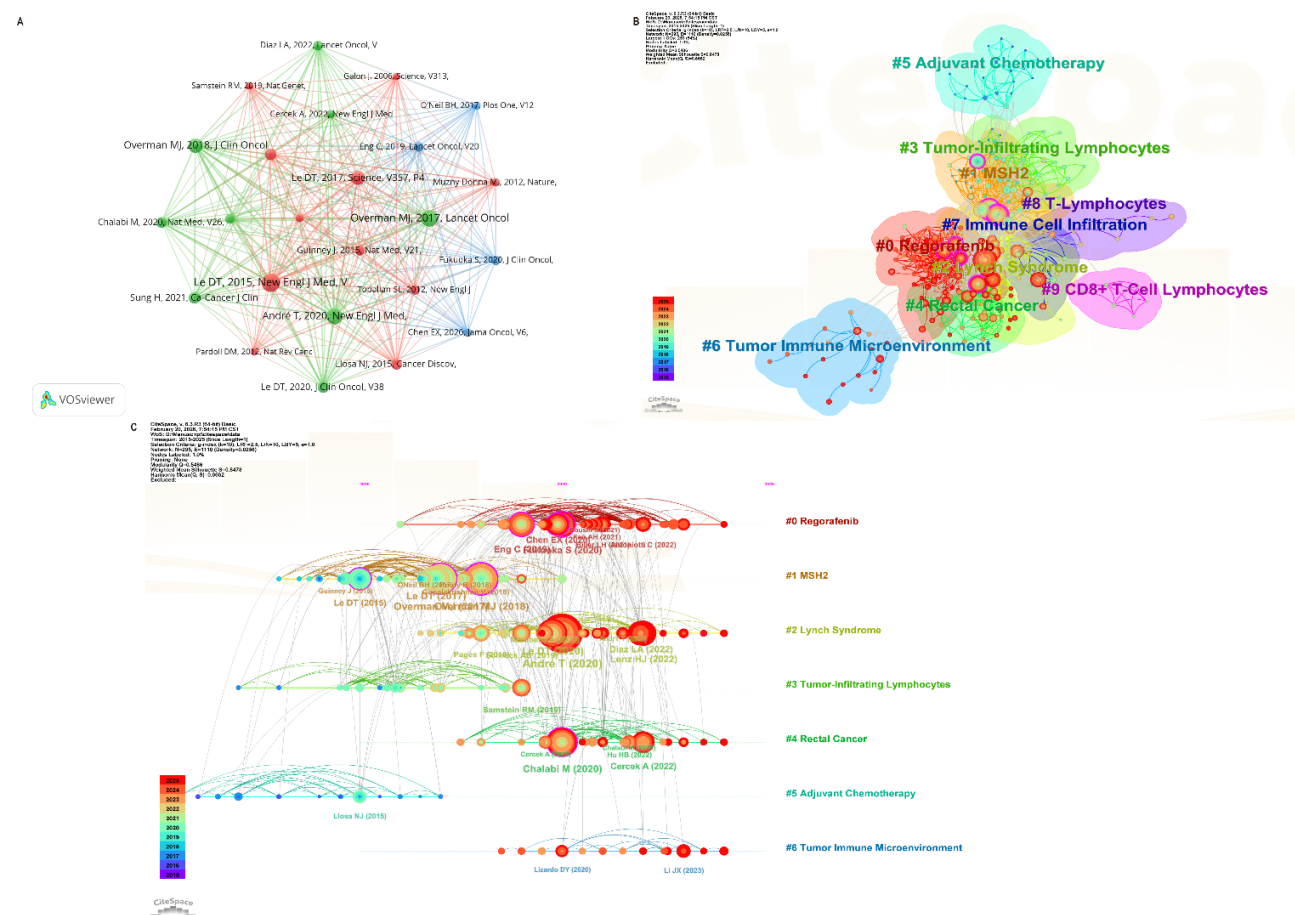


Figure 6. Analysis of the intellectual structure and thematic evolution of co-cited references. (A) Network map of co-cited documents created using VOSviewer. The threshold is set at a minimum of 35 citations for cited references. (B) Cluster map of co-cited references generated using CiteSpace. The colored areas represent distinct research topics labeled using the LLR algorithm. (C) Timeline view of co-cited references. Nodes represent individual cited references, and their horizontal positions indicate the year of publication. Node size is proportional to co-citation frequency, while red rings indicate citation bursts. The figure illustrates the temporal evolution of research themes from early foundational studies (e.g., Clusters #1 and #5, left) to more recent work focused on therapeutic strategies and the tumor immune microenvironment (e.g., Clusters #0, #4, and #6, right).

a shift in the research frontier toward understanding resistance mechanisms and global disease burden. Specifically, Mariathasan *et al.*³⁶ (*Nature*), who identified TGF- β signaling in fibroblasts as a key driver of immune evasion, have garnered recent attention as researchers seek to overcome resistance in immune-excluded tumors. Similarly, Yu *et al.*³⁷ (*Nature Medicine*) are highlighted for their investigation into the liver metastatic niche, which has revealed that liver metastases can siphon activated T cells from systemic circulation, thereby inducing systemic immune suppression. Furthermore, the study by Hu *et al.*³⁸ (*The Lancet Gastroenterology & Hepatology*) reflects the growing focus on the changing epidemiology of the disease, providing updated global statistics on CRC incidence and mortality that underscore the urgency of novel therapeutic strategies. These active bursts suggest

that contemporary studies are moving beyond establishing basic efficacy in MSI-H patients toward tackling deep-seated mechanisms of resistance and addressing the global public health challenge.

3.7. Hotspots and frontiers

To systematically delineate the conceptual landscape and identify the prevailing research hotspots within the field, a keyword co-occurrence network was constructed using VOSviewer (Figure 8A). The resulting visualization reveals a highly interconnected structure divided into three primary clusters, representing the fundamental pillars of immunotherapy research in CRC. The green cluster, anchored by the largest node “colorectal cancer” (203 occurrences) and closely linked with “tumor microenvironment” (36 occurrences) and “PD-L1” (36

Top 25 References with the Strongest Citation Bursts

References	Year	Strength	Begin	End	2015 - 2025
Llosa NJ, 2015, CANCER DISCOV, V5, P43, DOI 10.1158/2159-8290.CD-14-0863, DOI	2015	9.65	2016	2020	
Topalian SL, 2012, NEW ENGL J MED, V366, P2443, DOI 10.1056/NEJMoa1200690, DOI	2012	4.03	2016	2017	
Le DT, 2015, NEW ENGL J MED, V372, P2509, DOI 10.1056/NEJMoa1500596, DOI	2015	23.48	2017	2020	
Larkin J, 2015, NEW ENGL J MED, V373, P23, DOI 10.1056/NEJMoa1504030, DOI	2015	5.64	2017	2020	
Domingo E, 2016, LANCET GASTROENTEROL, V1, P207, DOI 10.1016/S2468-1253(16)30014-0, DOI	2016	3.61	2017	2021	
Overman MJ, 2017, LANCET ONCOL, V18, P1182, DOI 10.1016/S1470-2045(17)30422-9, DOI	2017	21.77	2018	2022	
Le DT, 2017, SCIENCE, V357, P409, DOI 10.1126/science.aan6733, DOI	2017	16.4	2018	2022	
Guinney J, 2015, NAT MED, V21, P1350, DOI 10.1038/nm.3967, DOI	2015	7.96	2018	2020	
Motzer RJ, 2015, NEW ENGL J MED, V373, P1803, DOI 10.1056/NEJMoa1510665, DOI	2015	4.76	2018	2020	
Gopalakrishnan V, 2018, SCIENCE, V359, P97, DOI 10.1126/science.aan4236, DOI	2018	3.46	2018	2021	
ONeil BH, 2017, PLOS ONE, V12, P0, DOI 10.1371/journal.pone.0189848, DOI	2017	9.34	2019	2021	
Yarchoan M, 2017, NEW ENGL J MED, V377, P2500, DOI 10.1056/NEJMc1713444, DOI	2017	4.75	2019	2022	
Mlecnik B, 2016, IMMUNITY, V44, P698, DOI 10.1016/j.immuni.2016.02.025, DOI	2016	4.43	2019	2020	
Chalmers ZR, 2017, GENOME MED, V9, P0, DOI 10.1186/s13073-017-0424-2, DOI	2017	4.14	2019	2020	
Ebert PJR, 2016, IMMUNITY, V44, P609, DOI 10.1016/j.immuni.2016.01.024, DOI	2016	3.63	2019	2021	
Overman MJ, 2018, J CLIN ONCOL, V36, P773, DOI 10.1200/JCO.2017.76.9901, DOI	2018	5.85	2020	2022	
Ribas A, 2018, SCIENCE, V359, P1350, DOI 10.1126/science.aar4060, DOI	2018	4.08	2020	2021	
Matson V, 2018, SCIENCE, V359, P104, DOI 10.1126/science.aao3290, DOI	2018	3.63	2020	2021	
Bray F, 2018, CA-CANCER J CLIN, V68, P394, DOI 10.3322/caac.21609, DOI	2018	7.74	2021	2022	
Luchini C, 2019, ANN ONCOL, V30, P1232, DOI 10.1093/annonc/mdz116, DOI	2019	3.65	2021	2022	
Siegel RL, 2020, CA-CANCER J CLIN, V70, P145, DOI 10.3322/caac.21601, DOI	2020	3.24	2021	2022	
Ayers M, 2017, J CLIN INVEST, V127, P2930, DOI 10.1172/JCI91190, DOI	2017	3.24	2021	2022	
Mariathasan S, 2018, NATURE, V554, P544, DOI 10.1038/nature25501, DOI	2018	4.52	2022	2023	
Hu HB, 2022, LANCET GASTROENTEROL, V7, P38, DOI 10.1016/S2468-1253(21)00348-4, DOI	2022	5.31	2023	2025	
Yu JL, 2021, NAT MED, V27, P152, DOI 10.1038/s41591-020-1131-x, DOI	2021	4.37	2023	2025	

Figure 7. Top 25 references with strong citation bursts. A red bar indicates high citations in that year.

occurrences), underscores the intense focus on elucidating the biological mechanisms and immune contexture that dictate therapeutic response. Bridging this biological foundation is the blue cluster, centered on “immunotherapy” (144 occurrences) and “immune checkpoint inhibitors” (62 occurrences), which represents the broad therapeutic paradigm and clinical evaluation in metastatic settings. Most significantly, the red cluster highlights the specific clinical implementation and patient stratification strategies; it features specific therapeutic agents such as “pembrolizumab” (25 occurrences) and “nivolumab” (23 occurrences) in direct association with “microsatellite instability” (33 occurrences) and “microsatellite stable” (12 occurrences) (Table 6). This clustering pattern vividly illustrates the field’s translational trajectory: moving from understanding the tumor microenvironment to applying checkpoint inhibitors, and ultimately refining these treatments based on specific molecular biomarkers, such as MSI status, to optimize patient prognosis.

Burst detection analysis of keywords was employed to capture rapid changes in research hotspots and emerging trends over the past decade (Figure 8B). Among the top 8 keywords with the strongest citation bursts,

“immunotherapy” demonstrated the highest burst strength (4.66), peaking between 2019 and 2020, which signifies the consolidated acceptance of this modality as a cornerstone of treatment during that period. The evolutionary trajectory of the field can be distinctly categorized into three phases based on these bursts. The initial phase (2017–2019) focuses on clinical validation and drug safety, characterized by keywords such as “therapy,” “PD-1,” “multicenter,” and notably “safety” (strength = 3.99). The prolonged burst of “safety” from 2018 to 2022 underscores the enduring priority researchers placed on evaluating adverse events and toxicity profiles in large-scale clinical trials. Subsequently, the intermediate phase (2019–2021) features keywords such as “phase I” and “inflammation,” indicating a dual focus on early-phase dose-finding studies for novel agents and on deeper mechanistic exploration of how tumor-associated inflammation modulates the immune response. Most significantly, “rectal cancer” represents the sole active burst in the most recent period (2023–2025). This distinct shift points to a specific and critical evolution in current clinical practice: the targeted application of immunotherapy in locally advanced rectal cancer, reflecting the growing paradigm of using neoadjuvant checkpoint blockade to achieve organ

preservation and avoid radical surgery in dMMR/MSI-H patients.

To delineate the evolutionary trajectory of research themes and visualize how the field’s focus has shifted over the past decade, a timeline view of the keyword co-occurrence network was generated (Figure 8C). The clusters are arranged vertically based on their size, with keywords distributed horizontally according to their year of appearance. The analysis reveals an evolution from general efficacy assessments to more specific clinical applications and mechanistic inquiries. The most prominent cluster, Cluster #0 “Immune Checkpoint Inhibitors,” dominates the upper portion of the timeline and extends into the 2023–2025 period, featuring keywords such as “1st line treatment,” “combination,” and “clinical trials.” In parallel, Cluster #1 “Tumor Microenvironment” and Cluster #4 “Rectal Cancer” reflect a deepening translational and disease-specific research focus. While early high-frequency keywords on the left side of the timeline, such as “multicenter” (Cluster #0) and “safety” (Cluster #2), correspond to the initial phase of validating ICIs in large-scale trials, the emergence of mid-to-late timeline keywords such as “resistance,” “tumor microenvironment,” and “antitumor” indicates a shift toward mechanistic investigation and therapeutic optimization.

3.8. Top 20 H-index authors and journals

To quantitatively evaluate the scholarly influence and identify the core sources of knowledge within the field, an analysis of local impact based on the H-index was conducted for both authors and journals. As illustrated in Figure 9A, Sahin IH emerged as the most influential individual researcher with an H-index of 8, followed closely by Overman MJ and Wang Y (H-index = 7), indicating their consistent contribution to high-quality research and their central positions in the academic network. Regarding the publication landscape, the *Journal for Immunotherapy of Cancer* demonstrated the highest local impact, ranking first with an H-index of 13 (Table 7), underscoring its status as the premier specialized venue for this domain. It is worth noting that while *Frontiers in Immunology* exhibited the highest publication volume (number of publications = 63) and a robust H-index of 12, it reflects role in driving the breadth of academic discourse. The *Journal of Clinical Oncology* presented a distinctive high-impact pattern. Despite a moderate local H-index of 6, it garnered the highest total citations (2,950), suggesting that while specialized and open-access journals facilitate rapid knowledge dissemination, top-tier clinical journals remain the repository for the field’s most foundational and highly cited breakthroughs.

Table 6. Top 20 high-frequency keywords in the field of immunotherapy for colorectal cancer

Rank	Keyword	Occurrences	TLS	Rank	Keyword	Occurrences	TLS
1	Colorectal cancer	203	298	1	Nivolumab	23	51
2	Immunotherapy	144	224	12	PD-1	22	42
3	Immune checkpoint inhibitors	62	108	13	Prognosis	18	29
4	Immune checkpoint inhibitor	40	73	14	Microsatellite-stable	12	31
5	Tumor microenvironment	36	68	15	Biomarker	11	25
6	PD-L1	36	63	16	Chemotherapy	11	21
7	Microsatellite instability	33	73	17	Biomarkers	10	19
8	Colon cancer	26	38	18	Immune checkpoint blockade	10	14
9	Metastatic colorectal cancer	25	42	19	Combination therapy	9	27
10	Pembrolizumab	25	36	20	Regorafenib	9	27

Notes: Occurrences are the number of documents in which the keyword appears; Total link strength is an attribute measuring the total strength of the co-occurrence links of a given keyword with other keywords.
Abbreviations: PD-1: Programmed cell death protein 1; PD-L1: Programmed death-ligand 1; TLS: Total link strength.

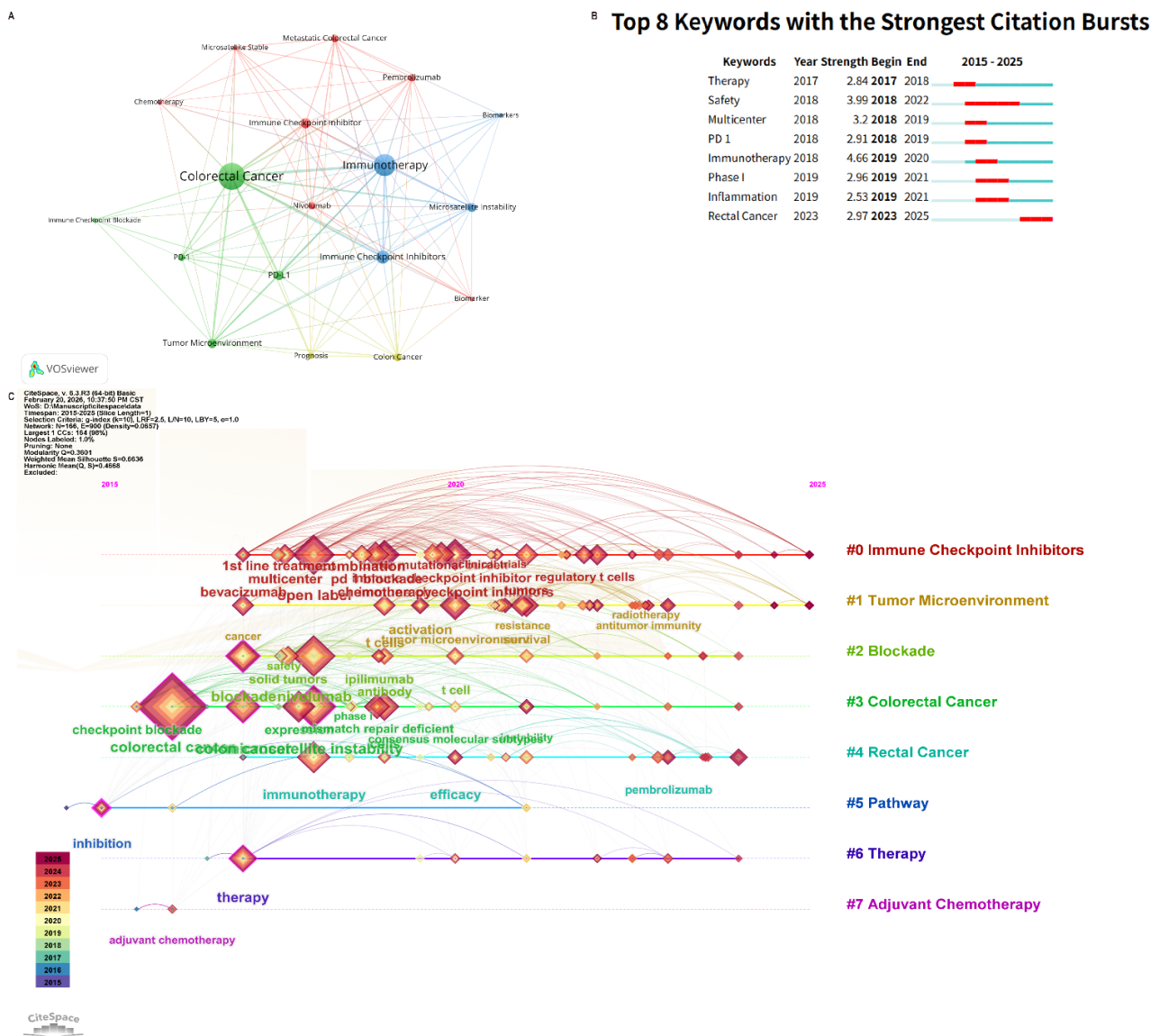


Figure 8. Analysis of research hotspots and the evolutionary trajectory of keywords. (A) VOSviewer visualization of the keyword co-occurrence network. Keywords with a minimum occurrence of 10 were included in the analysis. (B) Top 8 keywords with the strongest citation burst. (C) CiteSpace visualization map of timeline viewer related to keywords.

Table 7. Top 10 high-impact journals in the field of immunotherapy for colorectal cancer

Rank	Source	H-index	Total citations
1	Journal for Immunotherapy of Cancer	13	637
2	Frontiers in Immunology	12	1,189
3	Cancers	10	409
4	Clinical Cancer Research	8	219
5	Frontiers in Oncology	8	240
6	Cancer Immunology Immunotherapy	6	181
7	Cancer Immunology Research	6	262
8	Journal of Clinical Oncology	6	2,950
9	Oncologist	6	246
10	Cancer Cell	5	843

Notes: H-index is an author-level or journal-level metric that attempts to measure both the productivity and citation impact of the publications.

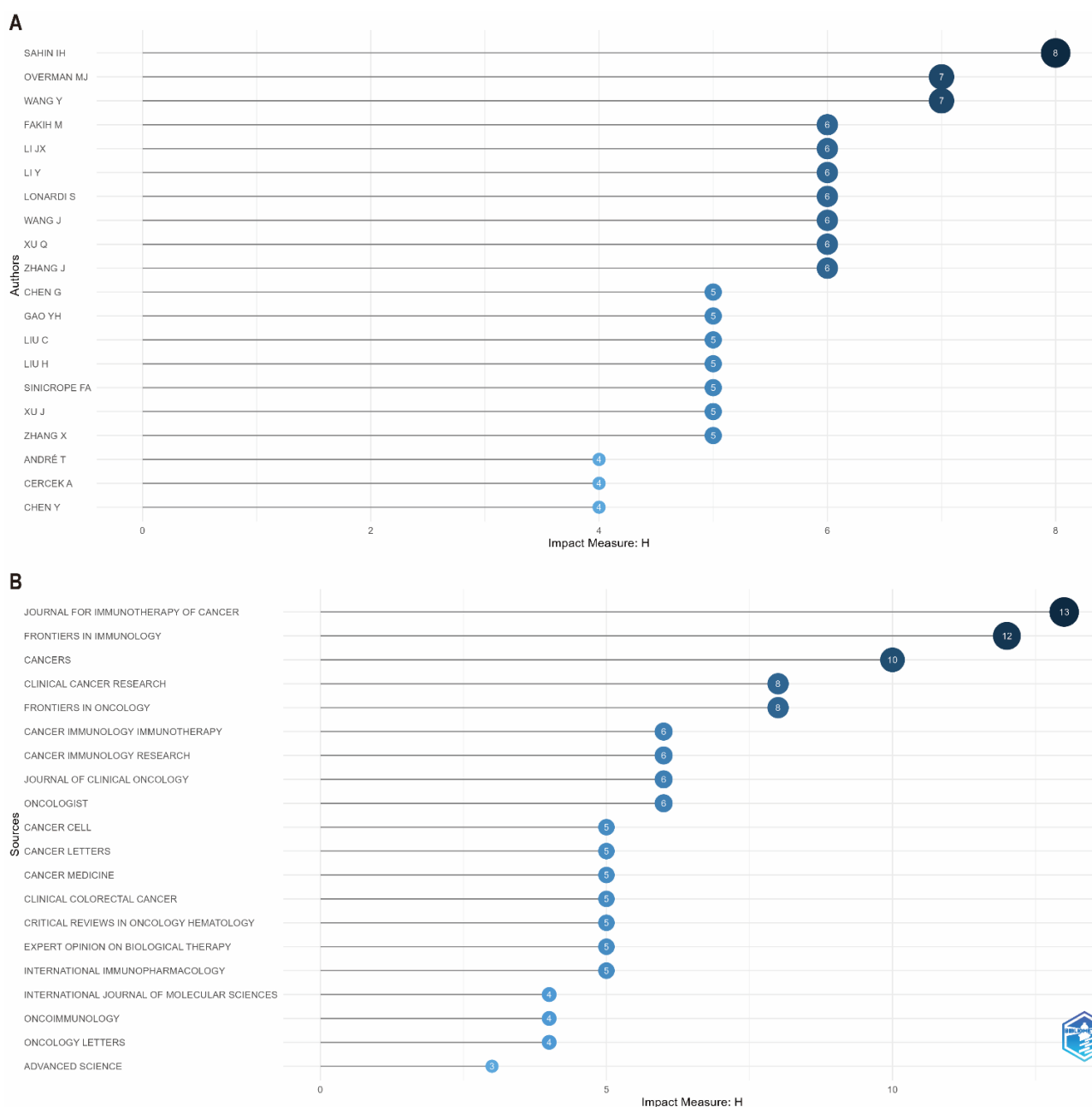


Figure 9. Analysis of local impact by H-index for authors and sources. (A) Top 20 authors ranked by H-index. (B) Top 20 journals ranked by H-index.

4. Discussion

This study represents the first comprehensive bibliometric analysis that systematically maps the global research landscape on ICIs in CRC from 2015 to 2025. Based on 1,125 qualifying publications, including 908 original articles and 217 reviews, our data show exponential growth in annual scholarly output. This surge aligns with the pivotal clinical breakthroughs of PD-1/programmed death-

ligand 1 (PD-L1) blockade⁴⁰, which have transformed ICIs from experimental agents into standard-of-care therapies for MSI-H patients. The rapid accumulation of literature indicates that this field has transitioned from an initial infancy phase to a period of vigorous expansion, attracting multidisciplinary attention from immunology⁴¹, oncology, and molecular biology.

Geographically, the research domain is characterized

by a distinct bipolar dominance driven by China and the United States. As evidenced by publication volume and collaborative network analysis, these two nations constitute the central hubs of global productivity. China's leadership in publication volume reflects its massive patient population and increasing investment in medical research, while the United States maintains a foundational role, contributing seminal clinical trials and high-impact theoretical frameworks. This Sino-American hegemony suggests that future advancements in CRC immunotherapy will likely rely on the continued competition and collaboration between these two scientific powerhouses, although broader international cooperation remains essential to validate findings across diverse ethnic populations.

An in-depth analysis of publication sources reveals significant stratification between “knowledge production” and “knowledge validation” within the field. As shown in Table 3, specialized journals, such as *Frontiers in Immunology* (63 records) and *Journal for Immunotherapy of Cancer* (54 records), have become the primary venues for disseminating new findings, reflecting the field's intensive focus on immunological mechanisms. However, the co-citation analysis paints a different picture regarding academic influence. The *Journal of Clinical Oncology* (1,639 citations) and *New England Journal of Medicine* (1,133 citations) dominate the co-citation network, vastly outperforming high-output journals in terms of citation frequency. This discrepancy indicates that while specialized journals drive the breadth of discourse, top-tier clinical journals remain the bedrock of the field, providing the high-level evidence and clinical guidelines that shape practice.

The evolution of research themes, as traced by keyword co-occurrence and citation bursts, mirrors the clinical maturation of immunotherapy for CRC. In the early stages (2015–2018), high-frequency keywords such as “safety,” “phase I,” and “PD-1 blockade” predominated, corresponding to the initial need to establish dosage safety and preliminary efficacy in diverse solid tumors. Over time, the focus has shifted distinctively toward precision and mechanistic depth. Current research hotspots now center on MSI, tumor microenvironment, and resistance. This thematic migration signifies that the scientific community has moved beyond asking “does it work?” to investigating “why it fails in MSS tumors?” and “how to optimize organ preservation,” marking the entry into the era of precision immuno-oncology.

Identifying these citation patterns highlights dominant themes in CRC immunotherapy and guides future research directions. The core topics in highly cited papers align with key concerns, such as response criteria, innovative

treatments, safety, and adverse effect management. This underscores a focus on refining immunotherapeutic strategies and understanding their clinical implications. A co-citation analysis also demonstrates that the development of effective immunotherapy results from discussions among influential studies on efficacy and safety, which contribute to defining best treatment schemes. Therefore, this analysis provides an important reference point to researchers seeking to interpret complex results in immunotherapy development.

The recent developments in CRC immunotherapy highlight the delicate balance between tumor burden and treatment response.⁴² Between 2015 and 2017, observational studies conducted at the Memorial Sloan Kettering Cancer Center confirmed a sizeable effectiveness for PD-1 inhibitors in metastatic MSI-H CRC, especially among low-burdened patients. In contrast, MSS had limited sensitivity, demonstrating the importance of the tumor molecular setting. Between 2018 and 2020, Johns Hopkins University explored combination therapies using CTLA-4 and PD-1 inhibitors to improve MSS tumor responses, yet challenges remained for patients with high tumor burden. From 2021 to 2023, research at Monroe Dunaway Anderson Cancer Center revealed the promise of combined targeted and immune therapies for high tumor burdens by targeting pathways such as the mitogen-activated protein kinase pathway. The 2023–2024 NICHE-2 trial at Amsterdam University Medical Center confirmed the efficacy of neoadjuvant PD-1 inhibitors for MSI-H CRC in low-tumor-burden cases, while stressing the need for cautious monitoring in high-burden patients to prevent immune-related recurrence. Collectively, these findings enhance our understanding of tumor burden's dual role in treatment outcomes and toxicity, underscoring the need for tailored therapeutic strategies.

Our analysis of co-cited literature underscores the critical link between tumor burden dynamics and immune therapy responses. Overman *et al.*^{27,32} highlighted that patients with MSI-H/dMMR metastatic CRC treated with PD-1 monoclonal antibodies, such as nivolumab and ipilimumab, may initially experience “pseudoprogression,” where tumor burden temporarily increases. Nonetheless, continued treatment results in significant tumor reduction in over 60% of patients, thereby improving overall survival. This phenomenon mirrors findings by Wolchok *et al.*⁴³ in melanoma, where initial tumor swelling due to immune cell infiltration does not indicate treatment failure. Le *et al.*³⁵ showed that MMR-deficient tumors, irrespective of tissue origin, respond well to PD-1 blockade therapy due to high tumor mutational burden and neoantigen production. The KEYNOTE-177 trial by André *et al.*²⁸ reported increased

risk of immune-related adverse effects in patients with significant tumor burdens, emphasizing the importance of balancing efficacy with safety. Collectively, these studies emphasize the importance of considering tumor burden dynamics and immune-related toxicities in optimizing immune therapy strategies.

Immunotherapy, radiotherapy, and chemotherapy are pivotal in cancer treatment. Combining stereotactic body radiotherapy (SBRT) with PD-1/PD-L1 inhibitors significantly improves local control rates in MSS colorectal liver metastases.⁴⁴ This improvement is linked to STING pathway activation and a marked increase in CD8⁺ T cell infiltration.⁴⁵ The transformation of “cold” MSS tumors into immunologically active environments enhances outcome.⁴⁶

Immune checkpoint inhibitors enhance T-cell-mediated antitumor responses. However, infiltration of myeloid-derived suppressor cells (MDSCs) can suppress T-cell activity and disturb the tumor immune microenvironment, potentially diminishing the efficacy of ICIs.⁴⁷ Moreover, modifications such as epidermal growth factor receptor (EGFR) amplification and Wnt/ β -catenin activation in liver metastases are associated with hyperprogressive disease (HPD) and an immunosuppressive tumor microenvironment.^{48–50} These insights highlight the need for alternative strategies, including B-Raf proto-oncogene, serine/threonine kinase (BRAF)/MEK inhibitors, to mitigate HPD risks.⁵¹ This highlights the need for treatment sequencing and the use of real-time circulating tumor DNA (ctDNA) monitoring to optimize personalized treatment for CRC patients.

Term statistics are used to identify key themes in cancer research, and the frequency of terms reflects their relevance. Terms such as “microsatellite instability,” “tumor microenvironment,” “PD-L1,” and “PD-1” were identified in our analysis, indicating interest in this theme and in the mechanisms of immunotherapy and tumor biology. Clustering analysis revealed distinct research domains, such as molecular diagnostics and ICIs. The temporal evolution of these keywords indicates a shift from targeted therapies (2004–2016) to a pronounced focus on ICIs after 2018, with trends emerging in metastatic CRC and prognostic factors from 2022 to 2024. This suggests increasing complexity in therapeutic strategies to improve CRC outcomes.

Citation burst analysis reveals key research trends by identifying references and keywords with notable changes in interest over time. Our study’s review of literature on MSI-H and dMMR tumors underscores a strong focus on the efficacy of ICIs, such as nivolumab and pembrolizumab³⁵, particularly regarding tumor

mutational burden and its role in predicting treatment response.⁵² Between 2015 and 2020, landmark publications highlighted the clinical importance of MSI-H tumors, reinforcing their role in therapeutic strategies.^{28,35} From 2020 to 2022, the focus shifted toward integrating spatial biology markers, such as tertiary lymphoid structures, as predictive factors⁵³, marking a move beyond traditional molecular subtyping. Clinical trials, including NICHE-2⁵⁴ and REGONIVO²⁹, underscore the increasing emphasis on combination therapies to overcome resistance in MSS populations. Beyond 2023, upcoming studies concentrate on hyperprogression biomarkers and toxicity optimization, highlighting the need for improved stratification approaches in clinical trials. This research avenue represents a turnaround in the immunotherapy strategies for CRC, where personalized care becomes increasingly important. Subsequent directions should focus on elaborating integrated biomarker systems, optimizing a combined strategy with reduced toxicity, and real-time monitoring of dynamic changes in tumor burden. This integrated approach is necessary to select the most effective treatment options and to achieve better clinical outcomes in different molecular subtypes.

A literature review of these publications provides critically important information on the relationship of CRC to immunosuppressants. Tumor burden fundamentally influences immunotherapy outcomes in CRC via measurable biological mechanisms and clinically actionable patterns. A lower baseline tumor burden, such as oligometastatic disease with liver metastases under 5 cm³, predicts a superior response to PD-1/PD-L1 inhibitors in MSI-H patients, with an objective response rate exceeding 50%, compared to 30% or less in high-burden cases. This is mainly due to increased T-cell infiltration and improved antigen presentation efficacy.^{55,56} Four response patterns have been identified: (i) immediate regression in 65% of low-burden MSI-H cases, (ii) sustained stabilization (SD >6 months) in MSS patients receiving ICI combinations, (iii) pseudoprogression requiring confirmation after ≥ 16 weeks, occurring in 15% of cases, and (iv) hyperprogression, associated with EGFR amplification and IL-10 levels > 15 pg/mL, which increases mortality risk by 3.2-fold.^{56–58} Elevated tumor burden is significantly associated with grade ≥ 3 immune-related toxicities, such as enterocolitis (8% in low vs. 32% in high burden), and with the remodeling of an immunosuppressive microenvironment. This remodeling is marked by regulatory T cell (Treg)/MDSC expansion (>30% infiltration), PD-1⁺T-cell immunoglobulin and mucin-domain containing molecule-3⁺ T-cell exhaustion (60% functional reduction), and cytokine dysregulation driven by interleukin-6/C-reactive protein.^{57,59} These observations underline the need for burden-stratified

therapies: PD-1 monotherapy for low-burden MSI-H (PFS 16.5 months), ICI combinations like regorafenib/nivolumab for moderate-burden MSS (PFS 7.9 months), and pre-immunotherapy cytoreduction, such as SBRT, for high-burden to reduce HPD risk by 72%.^{55,58,60} Future research should focus on standardizing the integration of liquid biopsy (ctDNA) and radiomics for burden monitoring and on developing Treg-targeted agents to counteract immunosuppression in large tumors.^{57,60}

4.1. Advantages and shortcomings

This study exhibits several distinct methodological strengths. Primarily, it employs a quantitative, data-driven bibliometric analysis to objectively map the knowledge structure of CRC immunotherapy, moving beyond the subjective selection inherent to traditional narrative reviews. By synergizing multiple analytical tools—including VOSviewer, CiteSpace, SCImago Graphics, and the R-package “bibliometrix”—the research successfully visualized complex temporal evolutions and collaborative networks, facilitating the accurate identification of shifting research hotspots from broad efficacy verification to precise mechanistic investigations, such as therapy resistance in MSS tumors. Furthermore, the inclusion of publication data up to 2025 ensures the capture of contemporary trends, including the emerging paradigm of neoadjuvant therapy, providing a timely and comprehensive landscape for the field.

Nonetheless, several limitations warrant consideration when interpreting these findings. First, data retrieval was restricted to the WoSCC. While we recognize that PubMed and Google Scholar are essential repositories for clinical research, they were not included in this study due to technical constraints in bibliometric mapping. Specifically, co-citation analysis—a core component of this study—requires high-quality cited reference data, which WoSCC uniquely provides in a structured format suitable for VOSviewer and CiteSpace. Consequently, this study may inadvertently overlook unique clinical reports indexed solely in other databases. Second, the restriction to English-language publications and specific document types (articles and reviews) may introduce linguistic and publication bias, potentially overlooking valuable contributions published in other languages or presented as conference abstracts. Finally, bibliometric indicators are inherently subject to “citation lag,” meaning that recent high-impact publications (e.g., from 2023–2025) may not have accumulated sufficient citations to be prominently featured in co-citation networks, possibly leading to an underestimation of the latest breakthroughs. Despite these constraints, the core trends and structural patterns identified remain robust and representative of the

dominant global research trajectory.

5. Conclusion

This bibliometric study provides the first comprehensive roadmap of the research landscape concerning ICIs in CRC in the past decade. The exponential growth in publications reflects the transformative impact of immunotherapy on CRC management, shifting from experimental protocols to standard-of-care treatments, with a distinct bipolar dominance in productivity by China and the United States. Scientometrically, the field has evolved through three distinct phases: an initial exploration of PD-1/PD-L1 mechanisms, a subsequent validation of efficacy in MSI-H populations, and a current frontier focused on precision medicine. Based on the burst detection and thematic evolution analysis, the trajectory of future research is poised to pivot toward two critical dimensions. First, elucidating the mechanisms of primary and acquired resistance in MSS tumors remains the paramount challenge, necessitating intensified investigation into the “cold” tumor microenvironment and the development of novel combination strategies, such as integrating ICIs with anti-angiogenic agents or targeted therapies. Second, the paradigm shift toward neoadjuvant immunotherapy for locally advanced rectal cancer underscores a growing emphasis on organ preservation and quality of life. However, significant gaps remain, particularly in identifying robust predictive biomarkers beyond MSI-H status and the long-term management of immune-related adverse events in these emerging combinatorial regimens. Addressing these unmet needs and expanding research into these limited areas will be essential for extending the therapeutic benefits of ICIs to a broader patient population.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: Chengdong Zhu

Formal analysis: All authors

Investigation: All authors

Methodology: Chaochao Liu

Writing–original draft: Chengdong Zhu

Writing–review & editing: Chaochao Liu

Ethics approval and informed consent

Not applicable.

Consent for publication

Not applicable.

Availability of data

All data are available from this article/supplementary material and from the corresponding author.

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