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Letter

A glimpse into the future: mapping global research trends in immunotherapy for rare tumors

Rare tumors, also known as rare cancers, are characterized by extremely low incidence rates, which comprise a group of about 200 cancers.[1] In the United States (US), rare tumors are defined as those occurring in less than 15 cases per 100,000 individuals,[2] while in Europe, the prevalence is even lower, with approximately 6 cases per 100,000 people.[3] Nevertheless, rare cancers collectively account for more than 20 % of all cancer diagnoses in a year, surpassing the incidence of any individual cancer type and imposing a heavy disease burden.[4] Currently, immunotherapy has become a new approach to treating various types of advanced cancers, particularly rare tumors.[5] Recently, the cumulative number of studies of immunotherapy practice in rare tumors has been steadily rising, and there has been a growing focus on research in this area. However, a comprehensive report that provides an overview and aids researchers in understanding the global research trends of immunotherapy in rare tumors is still lacking.

To investigate the underlying mechanisms of immunotherapy in rare tumors and provide new ideas to cure rare tumors by immunotherapy, we applied the bibliometrics,[6] a branch of informatics, to study the development of immunotherapy in rare tumors by qualitative and quantitative analysis of the literature. We collected articles written in English from Web of Science Core Collection database using the selected topic words: rare tumor or rare cancer, and immunotherapy, with a time range from 1992 to 2023. Then, we conducted the literature retrieval and subsequent data download on October 20, 2022. To minimize the discrepancy due to database updates, two independent investigators completed the data search based on given search strategies in parallel. To analyze and visualize the development trends and hotspots of immunotherapy in rare tumors, we used three bibliometric tools, including CiteSpace software, bibliometrics (http://bibliometric.com/), and VOS Viewer software. The flowchart of this study is shown in Fig. 1A.

This study included 1,978 regular articles on immunotherapy in rare tumors, as depicted in Fig. 1A. Fig. 1B showed the annual and cumulative numbers of papers on immunotherapy in rare tumors. The annual number of articles increased steadily. A growth function that increases rapidly was subsequently employed to assess the correlation between total publications and year of publication, aligning with the pattern observed in the total number of publications (R^2 = 0.8668). The significant growth and development of immunotherapy in rare tumors were visualized by this strong correlation. We then analyzed the publication counts at a national level to investigate the countries/regions that were making contributions to this area. According to Fig. 1C, the US held the top position with 585 records, while China had 478, Italy had 131, Germany had 124, and France had 105. Additionally, all other countries/regions published fewer than 100 articles. Moreover, an overview of the global cooperation was also conducted. According to Fig. 1D, the United States had the closest collaborations with Germany and Italy. Among the top 20 institutions that published the most articles worldwide, 11 academic institutions are from the United States, seven from China, and Germany and France each have one (Fig. 1E). The University of Texas MD Anderson Cancer Center in the US published the highest number of articles (n = 80), ranking first. However, most institutions focused on domestic cooperations based on Supplementary Fig. 1A. Meanwhile, Jeffrey S Ross contributed the most articles, followed by Aung Naing and Isaac Brownell. A map visualizing the analysis of co-authorships was conducted in Supplementary Fig. 1B. Fifteen research clusters, distinguished by various colors, were established, with each cluster led by either one or two core researchers. Generally, there were limited connections among authors from various institutions or nations, indicating that global cooperation in this area had not been adequately established.

We next analyzed the published journals, and *Frontiers in Oncology* had the most publications in the area of immunotherapy in rare tumors, followed by *Journal for Immunotherapy of Cancer*, and *Cancers* (Supplementary Fig. 1C and Supplementary Table 1). Regarding the co-cited journals shown in Supplementary Fig. 1D, *Journal for Immunotherapy of Cancer*, *Frontiers in Oncology*, *Frontiers in Immunology* emerged as the three most influential journals in this domain. Furthermore, we collected the top 10 most-cited papers in the field (Supplementary Table 2). All these manuscripts received over 500 citations. Among them, Chalmers *et al.*,[7] had the most citations in Genome Medicine. They first analyzed the genomic landscape of tumor mutational burden in rare tumors.

Keywords are typically the succinct and condensed representation of a study's fundamental content, serving to encapsulate the primary focus of the research paper. In Fig. 1F, the top 20 keywords are presented in order of frequency. The keyword 'immunotherapy' occurred the most commonly, appearing 666 times. The dual-map overlay of journals showcased the distribution of relationships among journals. Fig. 2A reveals that the publications in this area were mainly related to Health/Nursing/Medicine and Molecular/Biology/Genetics, which were frequently cited by Medicine/Medical/Clinical and Molecular/Biology/Immunology journals. Fig. 2B and C present the keywords change tendency from 1992 to 2023. The word 'immunotherapy' (1993–2014) received the most lasting attention. Recently, keywords like 'non-small cell lung cancer' (2021–2023), and 'tumor microenvironment' (2021–2023) have been used, suggesting that upcoming investigations will prioritize these keywords. Besides, three-field plot indicated the interaction network among highly cited papers, highly productive authors, and highly used keywords (Fig. 2D). Supplementary Fig. 1E and F showed the keywords network map and time-overlapping map, which were generated from 630 keywords occurring for at least five times. These results are consistent with the above analysis, suggesting the hotspot changes with new concepts or technologies.

With an in-depth understanding of multiple mechanisms behind the immunotherapeutic strategies, immunotherapies may become more personalized and effective in rare tumors. The elucidation of mechanistic

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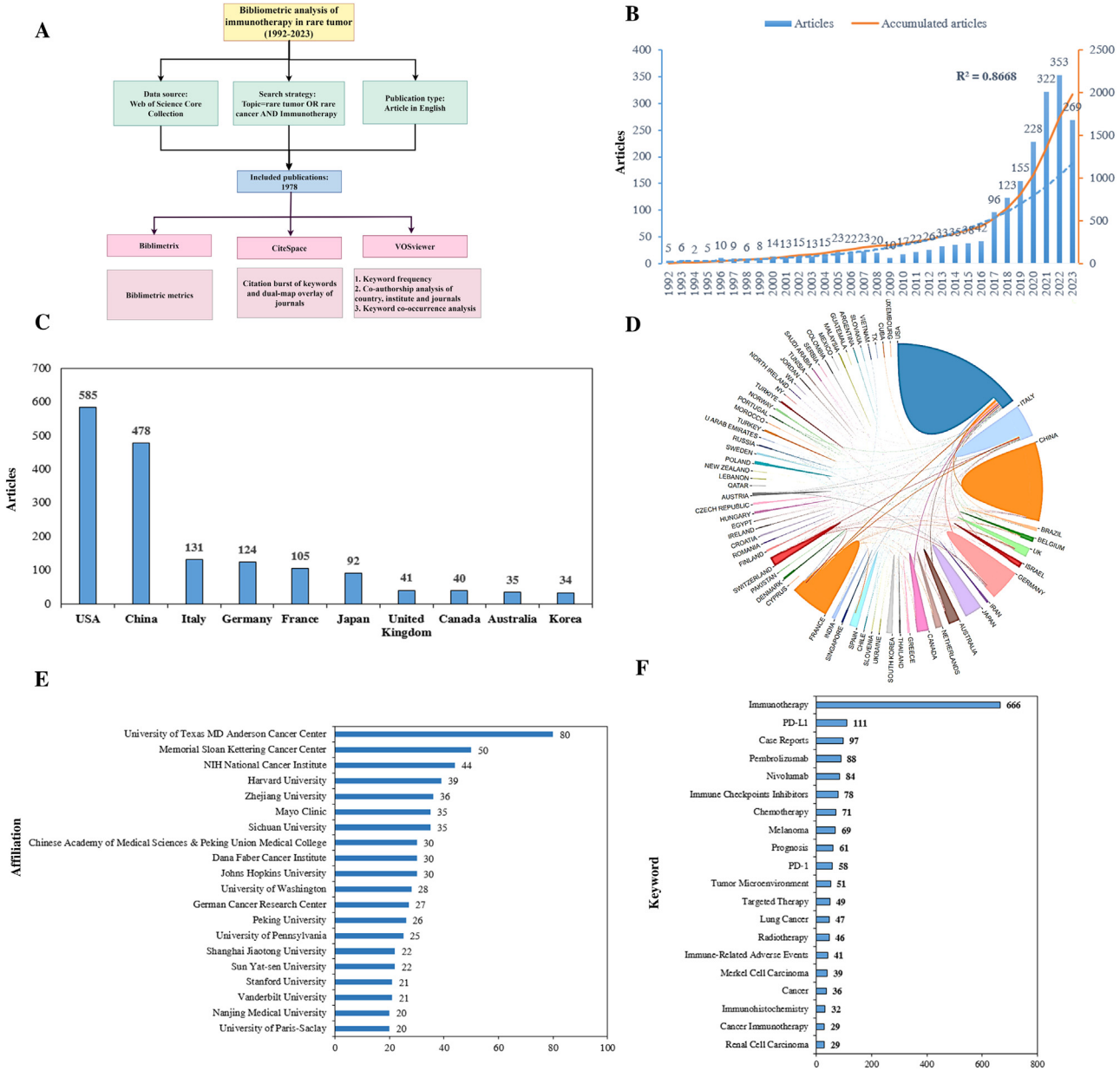

Fig. 1. Overview of immunotherapy in rare tumors from 1992 to 2023. (A) The workflow of this study. (B) Number of publications per year and the cumulative number. (C) Top 10 countrys' contribution to immunotherapy in rare tumors. (D) The network map of countries involved in immunotherapy of rare tumors. (E) The top 20 institutions with the most publications in the field of immunotherapy in rare tumors. (F) A list of the 20 most frequently used keywords.

intricacies pertaining to these strategies is expected to facilitate the development of enhanced therapeutic agents and approaches capable of overcoming the limitations in cancer treatment.[8] Combination therapies with immunotherapy and other cancer treatments also deserve to be explored in the setting of rare tumors in the future.[9] In summary, this paper is the first bibliometric study to provide a comprehensive landscape of immunotherapy in rare tumors. Our discoveries may offer valuable insights for researchers in this area to grasp the basic research frameworks, the current research frontiers, and future directions, and identify future study directions.

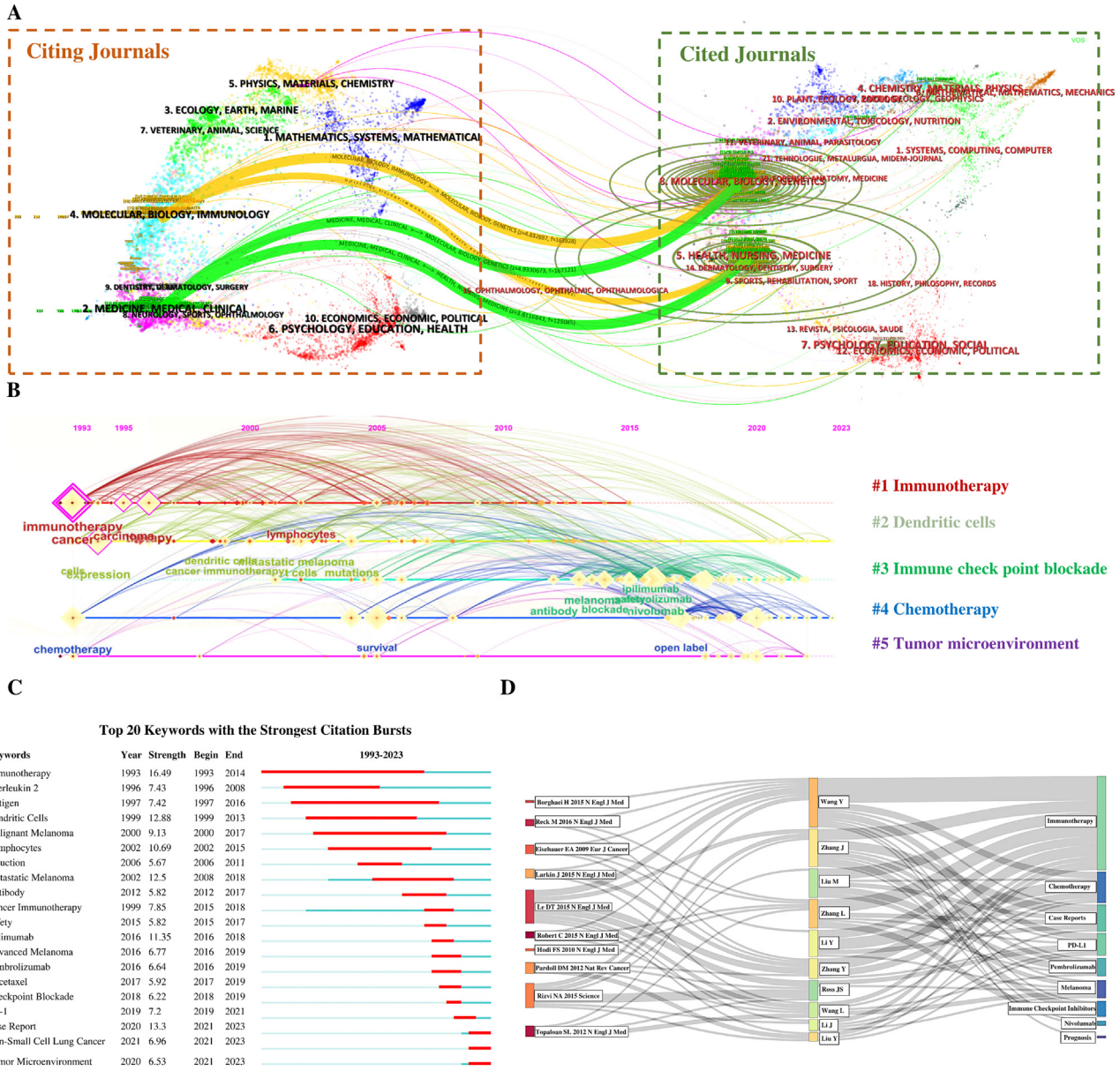

Fig. 2. The hotspots and research frontiers of immunotherapy in rare tumors. (A) The dual-map overlay of journals on immunotherapy in rare tumors. (B) The timeline view of keyword clusters with their cluster-labels on the right. (C) Top 20 keywords with the strongest citation bursts. (D) Three-field plot among highly cited papers, highly productive authors, and highly used keywords.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author contributions

N.L. and S.W. conceived the study and oversaw the project. G.Z. and Y.W. collected and assembled the data. G.Z. and Y.W. analyzed and interpreted data; G.Z. and Y.W. wrote and revised and manuscript; All authors read and approved the final manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jncc.2023.11.002.

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