

## Bibliometric Analysis of NK Cell Therapy for Prostate Cancer

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### Abstract

**Objective:** To conduct a visual analysis of the research field of NK cell therapy for prostate cancer using software such as CiteSpace and VOS viewer, and to explore the research hotspots and trends in this field over the past decade. **Methods:** Based on relevant Chinese literature included in the Web of Science Core Collection, China National Knowledge Infrastructure (CNKI) database, and Wanfang Data Knowledge Service Platform, a visual analysis was conducted on the annual distribution, countries, authors, institutions, journals, and keywords of articles published in the past decade (2014-2023) using CiteSpace, VOS viewer, and the Bibliometric website to explore the hotspots and trends in this research field. **Results:** A total of 166 Chinese articles and 380 English articles were retrieved. The overall publication trend showed slight fluctuations but generally exhibited an upward trend. According to the statistical results, the country with the highest number of English publications was the United States. The author with the highest number of Chinese publications was Wang Ting, while the author with the highest number of English publications was Moretta, Alessandro. The top three institutions in terms of Chinese publication output were Shandong University, Zhengzhou University, and Anhui Medical University; the top three institutions for English publications were the National Cancer Institute (USA), University of Washington, and King' s College London. After removing Chinese and English search terms, the top three high-frequency keywords in Chinese literature were macrophages, radiotherapy, and apoptosis; the top three high-frequency keywords in English literature were dendritic cells, immunotherapy, and tumor microenvironment. Analysis of keywords and burst terms revealed that the research hotspots in the field of NK cell therapy for prostate cancer include combination therapy of immune cells with NK cells, the inhibitory effect of the tumor microenvironment on NK cells, and enhancing the proliferation capacity and cytotoxicity of NK cells.

## Full Text

### A Bibliometric Analysis of Literature on NK Cell Therapy for Prostate Cancer

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#### Abstract

**Objective:** To conduct a visual analysis of the field of NK cell therapy for prostate cancer research using software such as CiteSpace and VOS viewer, exploring the research hotspots and trends in this domain over the past decade.

**Methods:** Based on relevant Chinese literature collected from the Web of Science Core Collection, China National Knowledge Infrastructure (CNKI), and Wanfang Data Knowledge Service Platform, we performed visual analysis of articles published from 2014 to 2023 using CiteSpace, VOS viewer, and Bibliometric website. The analysis covered annual distribution, countries, authors, institutions, journals, and keywords to identify hot topics and trends in this research field.

**Results:** The search yielded 166 Chinese articles and 380 English articles, showing a slightly fluctuating but generally increasing publication trend. The United States had the highest number of English publications. Wang Ting ranked first among authors publishing in Chinese, while Moretta, Alessandro was the top author for English publications. The three most productive institutions for Chinese literature were Shandong University, Zhengzhou University, and Anhui Medical University; for English literature, they were the American Cancer Society, University of Washington, and King' s College London. After excluding search terms, the top three high-frequency keywords in Chinese articles were macrophages, radiotherapy, and apoptosis; in English articles, they were dendritic cells, immunotherapy, and tumor microenvironment. Keyword and emerging term analysis revealed that research hotspots in NK cell therapy for prostate cancer include combination therapy of immune cells with NK cells, the inhibitory effect of the tumor microenvironment on NK cells, and enhancing the proliferative capacity and cytotoxicity of NK cells.

[Key words] NK cells; prostate cancer; bibliometrics; VOS viewer; CiteSpace

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## Introduction

According to World Health Organization (WHO) data, prostate cancer ranks as the second most common malignancy among men worldwide [1-2]. Current detection methods primarily include prostate-specific antigen (PSA) testing [3], while treatment options encompass radical prostatectomy and other approaches [4]. Natural killer (NK) cells are a type of innate lymphocyte capable of recognizing and eliminating virus-infected cells, cancer cells, and foreign cells [5]. Over the past decade, NK cells have emerged as a research hotspot in prostate cancer immunotherapy due to their tumor-killing ability and capacity to rapidly release various cytokines and chemokines that recruit other immune cells or promote adaptive immune responses by T and B cells [6]. This study employs CiteSpace and VOS viewer tools to conduct co-occurrence, clustering, and emergence analyses of relevant literature in the field of NK cell therapy for prostate cancer.

## 1. Methods

**1.1 Data Sources** Chinese literature was sourced from CNKI and Wanfang Data Knowledge Service Platform, while English literature was obtained from the Web of Science Core Collection. We retrieved Chinese and English articles published from 2014 to 2023 and downloaded all bibliographic information for analysis.

**1.2 Search Strategy** CNKI and Wanfang employed subject term searching. The CNKI search strategy was: SU=(prostate cancer OR prostate malignancy OR radical prostatectomy) AND SU=(NK cell OR natural killer cells). Time span: 2014-2023; Language: Chinese; Export format: RefWorks. The Web of Science Core Collection search strategy was: #1 TS=( "NK cell" OR "natural killer cells" OR "NK lymphocyte" OR "NK cell subset") AND #2 TS=( "prostatic cancer" OR "prostatic carcinoma" OR "prostatic adenocarcinoma" OR "prostate tumor" OR "prostatic malignancy" OR "prostatic neoplasm" ); Time span: 2014-2023; Document type: Article; Language: English; Index: SCI-EXPANDED; Export type: Full Record and Cited References.

**1.3 Statistical Methods** English literature was exported in "Tab Delimited File" format and imported into the Bibliometric website for visual analysis of annual publication volume and distribution by country. Chinese and English literature were exported in RefWorks format and imported into CiteSpace for deduplication and visual analysis. We performed data mining and analysis on countries, institutions, authors, keywords, and journals to visualize overall trends, distribution patterns, and hotspot changes in this field.

## 2. Results

**2.1 Literature Volume** From 2014 to 2023, 166 Chinese articles and 380 English articles related to prostate cancer and NK cells were published. The overall publication trend showed a gradual increase, with Chinese literature growing slowly while English literature exhibited greater fluctuations, though annual publications exceeded 40 articles in the past four years. The peak publication year was 2022 with 81 articles [Figure 1: see original paper].

**Figure 1** Annual changes in publication volume (2014-2023)

**2.2 Country Network Analysis** A total of 57 countries participated in related research. The top three countries by publication volume were the United States (139 articles, 34.9%), China (111 articles, 27.9%), and the United Kingdom (27 articles, 6.8%). The countries with the top three centrality scores were the United States (0.47), China (0.23), and Iran (0.15). Using VOS viewer with a frequency threshold of 1, we created a country collaboration network map [Figure 2: see original paper] A and 2B, where node size and connection strength represent citation frequency, and colors represent clusters. The network comprised 47 nodes forming 13 clusters with 180 links and a total link strength of 573. The network map reveals that the United States and China are the primary research countries with close collaborative ties. European countries (UK, France, etc.), North American countries (USA), and Asian countries (China) maintain strong cooperative relationships, while some countries such as Thailand, Luxembourg, and certain South American nations show limited collaboration in this field. Among the top ten countries by publication volume, four are from Europe, three from Asia, two from North America, and one from Oceania, indicating that active research in this domain is concentrated in Asia, Europe, and North America, while South America and Africa demonstrate relatively weaker research capacity.

**Figure 2** Country network for Chinese literature (A) and English literature (B)

**2.3 Institution Network Analysis** Institution network analysis identified 125 institutions publishing Chinese literature and 821 institutions publishing English literature. The top three institutions for Chinese publications were Shandong University (10 articles), Zhengzhou University (10 articles), and Anhui Medical University (7 articles). The top three institutions for English publications were NIH National Cancer Institute (29 articles), UTMD Anderson Cancer Center (25 articles), and Memorial Sloan Kettering Cancer Center (18 articles). The institutions with the top three centrality scores were UNICANCER (0.24), Cleveland Clinic Foundation (0.20), and University of Texas System (0.14). The collaboration maps show that universities represent the primary research force with high scientific capacity and vitality. Notably, institutions publishing Chinese literature exhibit relatively limited inter-institutional collaboration, whereas those publishing English literature demonstrate very close cooperative

relationships. U.S. institutions wield strong global influence and maintain extensive collaborations with multiple countries.

**Figure 3** Institution network for Chinese literature (A) and English literature (B)

**2.4 Author Network Analysis** CiteSpace-generated author co-occurrence maps show that the Chinese literature network had  $N=247$  and  $E=347$ , indicating 247 authors published articles in this field between 2014-2023 with 347 collaborations. The top three authors by publication volume were Wang Ting, Gao Weishi, and Wang Jingwei (2 articles each). The English literature network had  $N=291$  and  $E=369$ , representing 291 authors with 369 collaborations. According to the retrieved literature, 2,685 authors published English articles in this field, with the top three being Moretta, Alessandro (4 articles), Dongrong Yang (4 articles), and Chen, Yuhchyan (3 articles). Chinese literature authors showed significantly less collaboration compared to their English literature counterparts.

**Figure 4** Author network for Chinese literature (A) and English literature (B)

## 2.5 Keyword Analysis

**2.5.1 Keyword Co-occurrence Analysis** Keyword frequency statistics are presented in Table 1. After excluding search terms, the top three high-frequency keywords in Chinese literature were macrophages, radiotherapy, and apoptosis, while in English literature they were dendritic cells, immunotherapy, and tumor microenvironment. The high-frequency keyword co-occurrence maps are shown in Figure 5 [Figure 5: see original paper].

**2.5.2 Keyword Clustering Analysis** Clustering analysis of included keywords is illustrated in Figure 6 [Figure 6: see original paper]. Chinese literature formed 7 clusters ( $Q=0.6496$ ,  $S=0.9238$ ), while English literature formed 9 clusters ( $Q=0.3987$ ,  $S=0.7335$ ). Representative keywords in Chinese literature clusters included NK cell proliferation and immune response to tumor cells, while English literature clusters featured cytokines stimulating NK cell proliferation/activation and the effect of tumor microenvironment on NK cells. Research hotspot keywords in this field include metabolic regulation of NK cells, interaction between NK cells and other immune cells, and allogeneic transplantation of NK cells. Timeline views intuitively display the temporal span and research progress of each cluster [Figure 7: see original paper]. The timeline reveals that prostate cancer pathological mechanisms became a research focus in 2015; immunotherapy-related studies gradually increased in 2017, with improving NK cell immunotherapy efficacy emerging as a key research priority; since 2020, enhancing NK cell cytotoxicity has become a hotspot, alongside increased attention to immune checkpoint inhibition and biomarker application.

**Table 1** Top 8 keywords in Chinese and English literature

**Figure 5** Keyword network maps for Chinese and English literature

**Figure 6** High-frequency keyword clustering diagram

**Figure 7** High-frequency keyword clustering timeline

**2.6 Research Trend Analysis** Running CiteSpace' s “Burst” function on keyword clusters identified emerging terms. After excluding search terms, high-frequency emerging keywords included tumor cell recognition, immune escape inhibition, and NK cell combination therapy. Over the past decade, research trends have evolved from NK cell-mediated tumor killing and inhibition → allogeneic NK cell transplantation → interactions between NK cells and other immune cells, with improving NK cell targeting and killing efficacy representing the therapeutic focus of this field [Figure 8: see original paper].

**Figure 8** Keyword emergence map

### 3. Discussion

**3.1 Research Status at Home and Abroad** Based on the bibliometric analysis of Chinese and English papers on NK cell therapy for prostate cancer over the past decade, research output in both domestic and international contexts shows an upward trend. Analysis of recent publication proportions by country reveals a significant increase in English publications from China, indicating China' s growing prominence in this international research field. Examination of authors and institutions shows limited collaboration among Chinese literature authors and institutions, whereas English literature authors and institutions have established close cooperative networks, with strong international collaboration among countries. Keyword analysis indicates that recent research focuses on inhibiting tumor cell immune escape and enhancing NK cell activity and targeting.

**3.2 Bottlenecks and Challenges** NK cell therapy for prostate cancer represents a promising immunotherapy approach, yet faces several challenges and bottlenecks in clinical application. The tumor microenvironment (TME) constitutes a major barrier affecting NK cell activity and tumor infiltration capacity. Immunosuppressive molecules in the TME (such as prostaglandin E2), immunosuppressive cells (including CD4<sup>+</sup>CD25<sup>+</sup> regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs)), and adverse environmental factors (hypoxia, low pH, metabolic waste accumulation) can impair NK cell activity, leading to functional decline and even exhaustion [7-9].

Keyword analysis revealed substantial research attention on macrophages (TAMs) and Tregs in the TME regarding their impact on NK cells. In immunotherapy, TAMs play a crucial role in tumor immune evasion. Studies demonstrate that TGF- $\beta$  (Transforming Growth Factor Beta) secreted by TAMs can induce NK cell dysfunction [10-11]. Additionally, TAMs secrete immunosuppressive chemokine ligands such as CCL5 (Chemokine (C-C motif)

Ligand 5) that recruit Tregs to the TME [12]. Tregs can also inhibit NK cell proliferation and activity while suppressing interferon- $\gamma$  and other inflammatory cytokine secretion through TGF- $\beta$  signaling pathways [13-14].

Obtaining sufficient quantities of high-quality NK cells for therapy presents another challenge, particularly in allogeneic NK cell therapy where safety and efficacy must be ensured [15]. Designing effective clinical trials to evaluate NK cell therapy safety and efficacy, and exploring combination therapies with other treatment modalities [16], are critical steps for advancing NK cell therapy. Despite these challenges, researchers are actively exploring multiple strategies, including: improved cell culture and expansion techniques such as using CD16 antibody combined with five cytokines (rhIL-2, rhIL-12, rhIL-15, rhIL-18, and rhIL-21) to effectively induce peripheral blood mononuclear cell conversion to NK cells [17]; induced pluripotent stem cell-derived NK cells with higher proliferative capacity and greater engineering potential [18]; novel immune checkpoint targets such as GPR34 (G Protein-Coupled Receptor) on lipid metabolite LysoPS (phosphatidylserine) [19]; and innovative NK cell targeting strategies like CAR-NK (Chimeric Antigen Receptor Natural Killer cells) therapy [20].

In summary, this visual analysis identifies research hotspots and trends in NK cell therapy for prostate cancer. Despite significant research achievements, the field has yet to establish stable large-scale research directions, necessitating enhanced collaboration among researchers, institutions, and countries. As research progresses, multiple approaches to improve NK cell therapy efficacy have been explored, with some demonstrating positive results in clinical trials. These developments underscore the significant potential of NK cell therapy for prostate cancer, which is gradually becoming a major research trend in cancer treatment.

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