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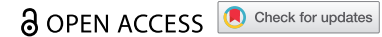


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RESEARCH ARTICLE



# A bibliometric analysis of oncolytic virotherapy combined with immunotherapy

Ting Zhang, Shitao Jiang, Lei Zhang, Yaoge Liu, Han Zheng, Haitao Zhao, Shunda Du, Yiyao Xu, and Xin Lu

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## ABSTRACT

Oncolytic virotherapy in combination with immunotherapy has demonstrated significant survival benefits in some types of cancer. Here, we summarized the development, research hotspots and potential trends of the combination therapy using visual bibliometric analysis. A total of 712 articles were retrieved on June 21, 2023. The USA was the top contributors of any country (325, 45.65%), and the Rluk Research Libraries UK ranked first (43, 6.03%) of any institutions. The Journal for ImmunoTherapy of Cancer was with the largest publications (60, 8.43%). 'Tumor microenvironment' and 'delivery' were citation keywords with the strongest ongoing bursts. Research fronts in the future may focus on the methods of virus delivery and tumor microenvironment modulation. Furthermore, the most extensively studied cancer were melanoma, glioma and hepatocellular carcinoma.

## ARTICLE HISTORY

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immunotherapy;  
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## Background

Oncolytic viruses (OVs) are a promising emerging therapeutic approach that selectively replicate in tumor cells and induce lysis while leaving non-neoplastic cells undamaged, and activate anti-tumor immunity.<sup>1,2</sup> A number of native and genetically engineered viruses have been developed as oncolytic agents, and four OVs have been approved for the cancer treatment. Talimogene laherparepvec (T-VEC) was the first oncolytic virotherapy approved by the US Food and Drug Administration (FDA) to be widely used for the treatment of metastatic melanoma. T-VEC is a genetically modified herpes simplex virus type 1 (HSV-1), and it can significantly improve objective and durable response rates representing a milestone in the field of oncolytic virotherapy.<sup>3</sup> On the basis of the activated antitumor immune response, OVs may be usefully deployed with immunotherapy to extend efficacy in patients with poor response to immune checkpoint inhibitors (ICIs).

Cancer immunotherapy can leverage the immune system to directly eliminate cancer cells and has shown activity against various tumors. To date, novel approaches for immunotherapy have been developed, including ICIs, cytokines, adoptive cell therapy, cancer vaccines and so on.<sup>4</sup> ICIs modulate the immunosuppressive tumor microenvironment (TME) and restores antitumor immunity by targeting immune checkpoints, such as programmed cell death protein 1 and its ligand (PD-1/PD-L1), and cytotoxic T lymphocyte antigen 4 (CTLA-4). ICIs have demonstrated significant increases in survival and objective response rates compared with standard first-line treatment in solid neoplasms.<sup>5-7</sup> However, ICIs monotherapy has limited clinical efficacy and may lead to drug resistance. Oncolytic virotherapy combined with immunotherapy recruit tumor-

infiltrating lymphocytes (TILs) and reinforce immuneresponse to improve therapeutic benefit.




Bibliometrics refers to the quantitative research of existing literatures using mathematical and statistical methods.<sup>8</sup> By analyzing the publication time, author, citation, institution and other factors, it systematically shows the dissemination, influence frontier and hot topics of study over time. In addition, it is of great significance to explore new frontier issues, guide scientific research plan and promote the in-depth development of the field.

This bibliometric study aims to provide a comprehensive overview of the application and developmental trends of oncolytic virotherapy combined with immunotherapy. This research revealed that the combination therapy had shown promising results in preclinical and clinical trials, with some studies demonstrating OVs combined with immunotherapy can overcome ICI resistance. It also highlights the need for further research to fully understand the mechanisms of underlying efficacy of the combination therapy and optimize treatment protocols.

## Materials and method

### Data source and search

Web of Science (WoS) is one of the largest and most prestigious citation databases and incorporates worldwide more than 12,000 of the authoritative, high-impact academic journals.<sup>9</sup> Compared to other databases such as PubMed, Medline, and Scopus, WoS provides the most comprehensive and credible data for bibliometric analysis.<sup>10</sup> The present research project searched all relevant publications in the Web

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of Science Core Collection database (WoSCC) on June 21, 2023. The topic search formula was as follows: [TS = Search: ((Immunotherapy) OR (Immunotherapies)) AND (((((Oncolytic Virotherapy) OR (Oncolytic Virotherapies)) OR (Oncolytic Virus Therapy)) OR (Oncolytic Virus Therapies)) OR (Oncolytic Viruses)) OR (Oncolytic Virus)]. The document type was limited to regular article. The literature language was restricted to English in order to facilitate further analysis of publication content. Complete records and cited references were downloaded and saved.<sup>11</sup> All included papers were independently reviewed by two investigators.

### Data analysis and visualization

R Language version 4.1.2,<sup>12</sup> VOSviewer,<sup>13</sup> and CiteSpace<sup>14</sup> were used in the study for bibliometric analysis. The Bibliometrix R package can calculate the frequency of collaboration between countries. VOSviewer can construct and visualize bibliometric networks based on embedded clustering algorithm.<sup>15,16</sup> Alternatively, the software can build a map of collaboration networks between authors, institutions, or countries, presenting collaboration patterns and research collaboration hotspots.<sup>17</sup> It also reveals the evolution trend of keywords in the research field and help users track the development of the discipline.<sup>18</sup> CiteSpace is a visual citation analysis software and used to spot highly cited literatures and keywords with an outburst of citations.<sup>14</sup> In addition, cooperation between countries was visualized through an online bibliometric website (<https://bibliometric.com/>). Excel uses the exponential growth function to extrapolate the tendency of the number of publications published each year.

## Results

### General analysis of publication status

From 2002 to 2022, a total of 712 conventional articles in the field of oncolytic virotherapy and immunotherapy were collected. Figure 1 demonstrates the annual and cumulative number of literatures related to oncolytic virotherapy and

immunotherapy. The total number of articles has steadily increased from 1 article in 2005 to 133 in 2014. The cumulative number of publications exploded over the next eight years, until the cumulative number of publications reached 3340 in 2022. In addition, the exponential growth model result was consistent with the trend in the number of publications per year ( $R^2 = 0.9619$ ). This strong correlation suggests that oncolytic virotherapy combined with immunotherapy has experienced significant growth and development.

### Analysis of national publications volume

The number of national publications is analyzed to explore the countries that have contributed the most to the field. As shown in Figure 2, the United States (US) ranked first with 325 articles, followed by China (140), Canada (102), and Germany (75). Supplementary Figure S1 showed visibly the collaborative relationships between countries/regions. The most frequent collaboration was between the US and the United Kingdom (UK) (frequency = 45). The following countries were Canada (frequency = 32), China (frequency = 24) and Germany (frequency = 24). All of these national collaborators were from the US. The results indicated that the US has made major contributions in the field of virotherapy and immunotherapy.

The collaboration between countries was investigated from all articles from 49 countries. In the clustering network, the size of the circles indicates the number of publications, and the color of the circles represents the intensity of cooperation. In the time-overlapping network, the size of the circles has the same meaning, and the color of the circles indicates the average productions for each country per year. Supplementary Figure S2a showed the 49 countries divided into five clusters, of which the red cluster had the most countries with seven countries. In Supplementary Figure S2b, the USA was an early pioneer in oncolytic virotherapy combined with immunotherapy, while Belgium scholars' researches were relatively new in this field.

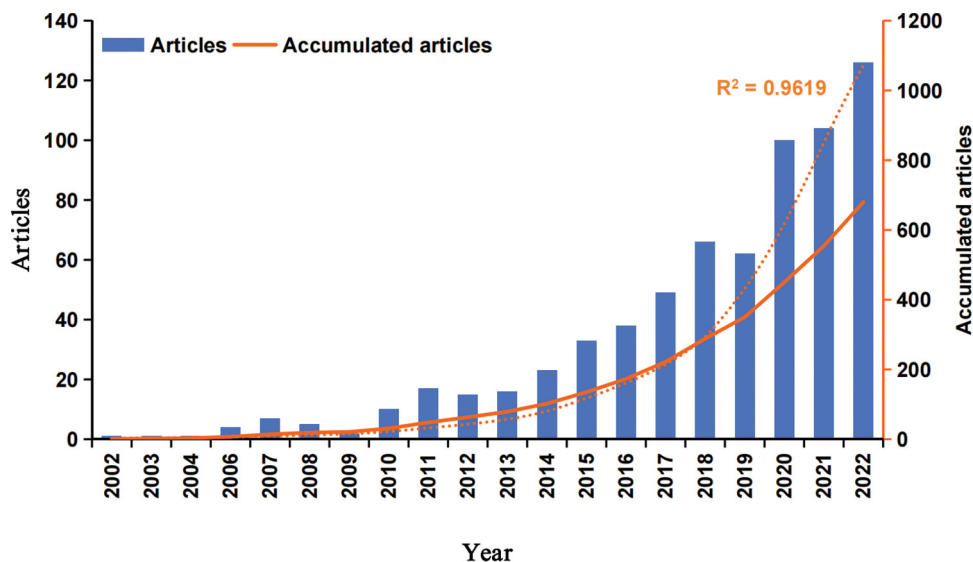
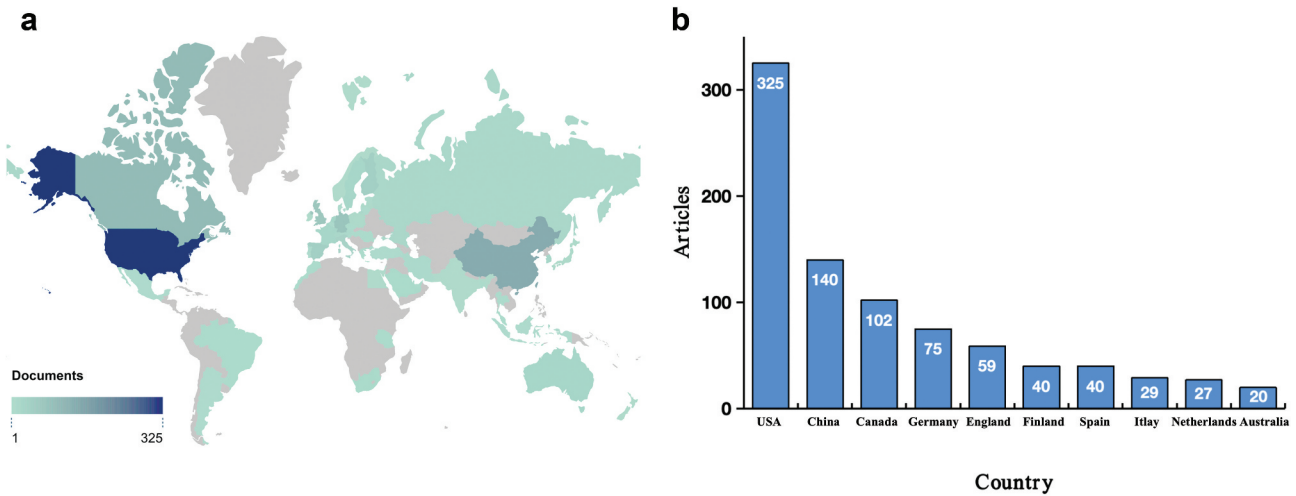


Figure 1. Number of publications per year and the cumulative number.



**Figure 2.** The contributions of each country on the number of publications.

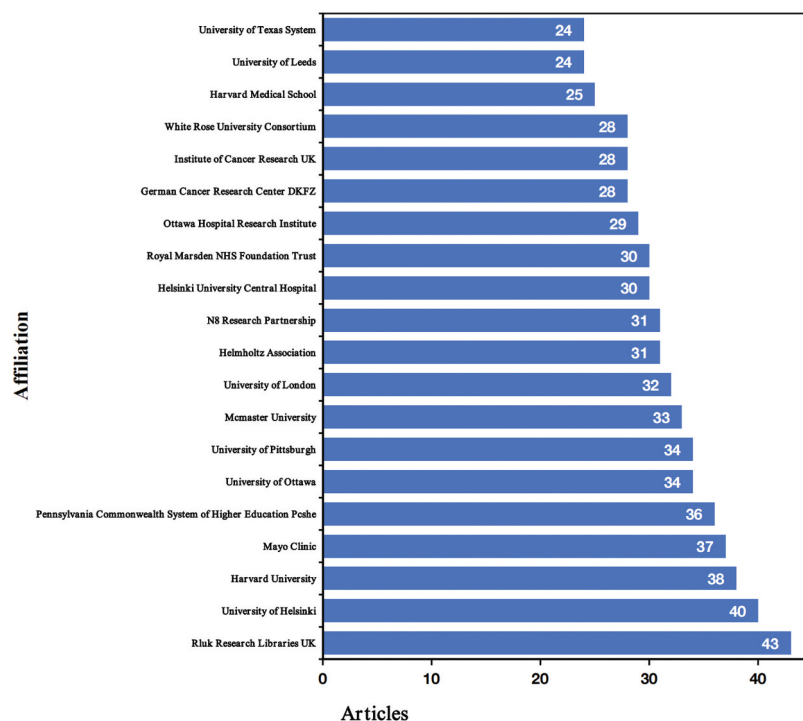
### **Analysis of institutional publications volume**

To explore the contribution of global institutions, the number of institutional publications was analyzed. Total of 1138 institutions participated, with the top 20 institutions publishing 635 articles (Figure 3). There were 7 UK institutions, 6 US institutions, 3 Canada institutions, 2 Finland and 2 Germany institutions. The Rluk Research Libraries of the United Kingdom ranked first with 43 publications. Fifty institutions published at least seven articles, and 190 institutions were grouped into 7 clusters. The red color contains 17 institutions, the largest cluster, most of which were the US institutions (Supplementary Figure S3a). Mayo Clinic was representative of early starters in research on oncolytic virus therapy and

immunotherapy. In contrast, Harvard Medical School conducted relatively recent research in this field (Supplementary Figure S3b).

### **An analysis of the number of publications and impact of journals**

A total of 712 articles included in the study were published on 251 journals. As shown in Table 1, top 10 journals are sorted by volume of articles with their latest impact factors (IF) and Journal Citation Reports (JCR). Nine journals belong to JCR Quartile 1 (Q1). Six periodicals are from the US, and two publishers are from UK and Switzerland, respectively.



**Figure 3.** The top 20 institutions with the most publications in oncolytic virotherapy combined with immunotherapy.

**Table 1.** Top 10 journals in oncolytic virotherapy combined with immunotherapy.

Rank	Source	Article	Country	IF	H-index	JCR-c
1	Journal for ImmunoTherapy of Cancer	60	UK	12.469	46	Q1
2	Molecular Therapy Oncolytics	38	USA	6.311	29	Q2
3	Molecular Therapy	36	USA	12.91	174	Q1
4	Oncoimmunology	27	USA	7.723	26	Q1
5	Cancers	18	Switzerland	6.575	54	Q1
6	Frontiers in Immunology	17	Switzerland	8.786	84	Q1
7	Nature Communications	17	UK	17.694	248	Q1
8	Human Gene Therapy	15	USA	4.791	149	Q1
9	Cancer Immunology Immunotherapy	14	USA	6.63	30	Q1
10	Clinical Cancer Research	14	USA	13.801	292	Q1

### Author influence analysis

Table 2 lists the top 10 authors out of 4626 researchers participated in the study. Akseli Hemminki was the most prolific scholar with 27 articles and H-index of 60, followed by Anna Kanerva (24 articles, H-index = 39) and Howard L Kaufman (19 articles, H-index = 66). The partnership among researchers was illustrated in the clustering diagram and time-overlapping diagram. 77 authors published at least seven publications were grouped into ten clusters. Three clusters were dispersed outside of the concentration area of ten clusters (Supplementary Figure S4a). Scholars represented by Riikka Havunen from Finland, were carrying out relatively new research in this area (Supplementary Figure S4b). Given that teamwork among different communities are insufficient, national and inter-institutional cooperation between research groups must be further strengthened in the field of virotherapy in combination with immunotherapy.

### Research hotspot analysis

#### Most cited publications

The frequency of citations reflects research impact, and the top 10 most cited articles are shown in Supplementary Table S1. Half of publications have been cited exceeding 300 times. The most cited literature was titled 'NF- $\kappa$ B c-Rel is crucial for the regulatory T Cell immune checkpoint in cancer' published in 2017 on Cell.<sup>19</sup> The study reported lack of NF- $\kappa$ B leads to damage maturation and activation of regulatory T cells (Treg), known for inhibiting anti-tumor immune responses in tumor sites. The authors further pointed out that NF- $\kappa$ B inhibitor as a viable option for potentiating the effects of anti-PD-1 immunotherapy. The second was conducted by Heo J et al. titled 'Randomized dose-finding clinical trial of oncolytic immunotherapeutic vaccinia JX-594 in liver cancer' in 2013 on

**Table 2.** Top 10 authors in oncolytic virotherapy combined with immunotherapy.

Rank	Author	Article	H-index
1	Akseli Hemminki	27	69
2	Anna Kanerva	24	39
3	Howard L Kaufman	19	66
4	Vincenzo Cerullo	18	38
5	Alan Melcher	17	59
6	David L Bartlett	15	80
7	Brain D Lichty	14	46
8	Minna Oksanen	14	20
9	John C Bell	13	68
10	Yonghong Wan	13	44

Nature Medicine. It was the first randomized clinical trial to report that an oncolytic virus (JX-594) can significantly improve clinical survival for patients with advanced hepatocellular carcinoma. What's more, it also demonstrated that JX-594 can stimulate the immune reaction by increasing tumor antigens and enhance immune responses.<sup>20</sup> These high cited articles provide robust evidence for the clinical application of oncolytic virotherapy combined with immunotherapy.

#### Reference citation burst analysis

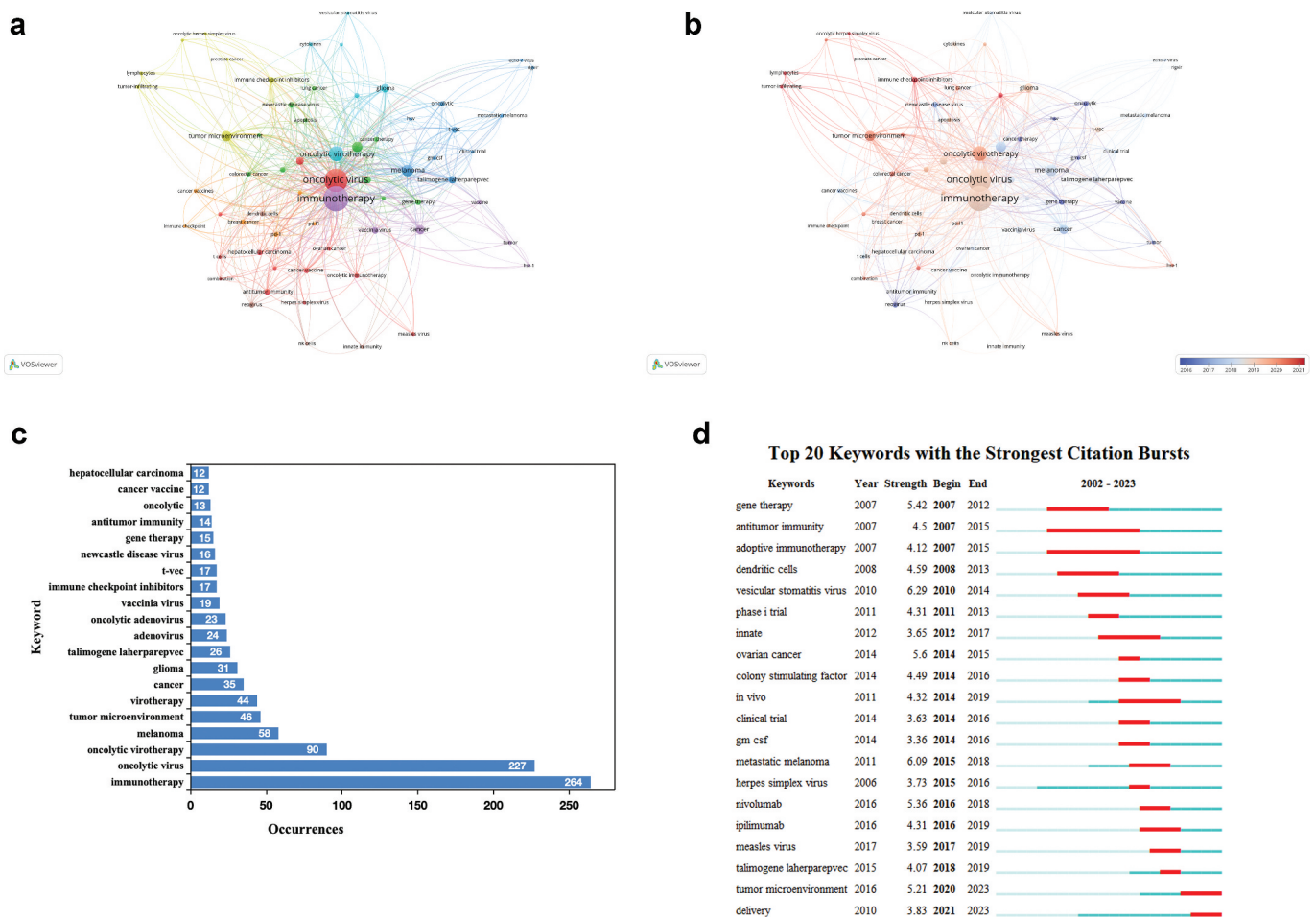
The top 25 references with the strongest citation bursts indicated research directions at different stages (Supplementary Figure S5). The blue line meant the observation period from 2002 to 2023, while the red line remarked the duration of the citation burst. The minimum duration of the burst is one year. The article 'Oncolytic immunovirotherapy for melanoma using vesicular stomatitis virus' published in Cancer Research, had the highest citation burst value of 15.15 from 2008 to 2014.<sup>21</sup> The second was entitled 'Improved survival with ipilimumab in patients with metastatic melanoma'<sup>22</sup> with burst value of 14.95. Additionally, six publications are still experiencing citation burst, including 'Optimizing oncolytic virotherapy in cancer treatment' with strongest burst value of 9.7.<sup>23</sup> In the years to come, this type of direction may be at the forefront of research on oncolytic virotherapy combined with immunotherapy.

#### Frequency of keyword occurrence and clustering analysis

Sixty-three out of 1201 keywords were selected for analysis that the inclusion criterion was the minimum frequency occurrence of 20 (Figure 4a). Keywords were merged when they had similar significance. The same color of the circle indicates a certain correlation, and the size of the circle represents the frequency of keyword occurrence. The distance between the two circles reflects the strength of association, and the stronger the correlation, the shorter the distance. Eight clusters consisting of 63 keywords showed research topics from different aspects of OV and immunotherapy.

Cluster 1 was in red mainly related to OVs of virotherapy and immunotherapy in hepatocellular carcinoma and ovarian cancer, such as 'adenovirus,' 'cancer vaccine,' 'herpes simplex virus,' 'measles virus,' 'adoptive cell therapy,' and 'antitumor immunity.'

Cluster 2 was green and focused on virotherapy combined with chemotherapy in colorectal cancer, lung cancer and pancreatic cancer, with the main keywords 'apoptosis,' 'gene



**Figure 4.** Research hotspots on oncolytic virotherapy combined with immunotherapy (a) Keyword co-occurrence map; (b) Time-overlapping co-occurrence map; (c) The top 20 keywords; (d) The top 20 keywords with the strongest citation bursts).

therapy,’ ‘immunogenic cell death,’ ‘newcastle disease virus’ and ‘oncolytic adenovirus.’

Cluster 3 was in dark blue centralized on clinical trials of OV in the treatment of melanoma, especially metastatic melanoma, with keywords such as ‘ECHO-7 virus,’ ‘GM-CSF,’ ‘HSV’ and ‘T-VEC.’

Cluster 4 in yellow focused on characteristics of immune response after oncolytic virotherapy in combination with immunotherapy, primarily involving ‘lymphocytes,’ ‘oncolytic herpes simplex virus,’ ‘tumor-infiltrating,’ and ‘vaccination.’

Cluster 5 in purple basically related to treatment methods for cancers, including ‘HSV-1,’ ‘vaccine,’ ‘immunotherapy,’ and ‘vaccinia virus.’

Cluster 6 in light blue included primarily combination therapy in glioma, with keywords such as ‘cytokines,’ ‘oncolytic virotherapy’ and ‘vesicular stomatitis virus.’ Some terms, such as ‘mathematical modeling,’ were also included.

Cluster 7 in orange focused on immunotherapy and oncolytic virotherapy in breast cancer, such as ‘cancer vaccine,’ ‘immune checkpoint,’ ‘PD-1’ and ‘PD-L1.’

Cluster 8 in brown concentrated on the function of anti-tumor immunity in OV therapy, with keywords such as ‘dendritic cells,’ ‘innate immunity,’ ‘NK cells,’ and ‘reovirus.’

In the time-overlapping map of keywords, blue represents previous research keywords, and red indicates recent keywords (Figure 4b). Earlier exploration concentrated on ‘oncolytic,’ ‘HSV,’ ‘gene therapy,’ and ‘reovirus,’ while current hotspots are ‘lymphocytes,’ ‘immune checkpoint inhibitors,’ ‘oncolytic virotherapy,’ ‘tumor-infiltrating,’ ‘oncolytic herpes simplex virus,’ and ‘tumor microenvironment.’ The top 20 keywords demonstrated ‘immunotherapy’ was the highest frequency of keyword with 264 times (Figure 4c), followed by ‘oncolytic virus’ (N = 227) and ‘oncolytic virotherapy’ (N = 90). Three cancer types appeared in the top 20 keywords, were ‘melanoma’ (N = 58), ‘glioma’ (N = 31) and ‘hepatocellular carcinoma’ (N = 12).

#### Keywords citation burst analysis

The top 20 keywords with the strongest citation bursts revealed topical issues at different periods (Figure 4d). The keywords ‘antitumor immunity’ (2007–2015) and ‘adoptive immunotherapy’ (2007–2015) have received the most protracted attention over time, while ‘tumor microenvironment’ (2020–2023) and ‘delivery’ (2021–2023) are research themes at the moment. Methods of virus delivery and tumor microenvironment modulation are promising future research directions.

## Discussion

The annual publication trend of research in oncolytic virotherapy combined with immunotherapy was observed by bibliometrics and mathematical from 2002 to 2022. There are two stages of the growth pattern with 2014 as the watershed. A rapid growth phase with over 20 literatures in one year began in 2014, while the annual number of articles has reached 126 by 2022. The potential reason may be that OV combined with immunotherapy provide novel beneficial strategy for patients with immunological cold tumor.<sup>22,24</sup> At same time, the area of research is relative immaturity and still needs to be explored. Hence, research institutions should reinforce investment for the promising direction to facilitate further research.

The US contributed to the major number of publications among all countries (325, 45.65%), while US-centered international teamwork accounts for 70% in the top 10 countries with frequency of collaboration. The above results demonstrate the US has made significant contributions and been a forerunner in the research fronts on account of national financial circumstances and high medical fundings. Meanwhile, top 20 institutions are all from western country and there are extensive cooperation between institutions. It suggested that international cooperation needs to be further strengthened, especially between Eastern and Western countries.

Scholars can choose the appropriate journal to submit manuscripts according to the amount of journal publications in this field. Journal for ImmunoTherapy of Cancer published the most articles with 60. In the top 10 journals by the number of papers, Nature Communications (IF 17.694) is the journal with the highest IF, and Clinical Cancer Research (IF 13.801) comes second. Meanwhile, 90% of periodicals belong to Q1, while journals from the US account for 60% that is parallel to the proportion of institutional and national publications volume.

Citation quantity as an indicator can measure academic influence of scientific papers and highly cited documents are the cornerstones of research field.<sup>25</sup> The 10 most cited articles published in 2006 to 2017, were concentrated on immunological mechanism and clinical practice of oncolytic virotherapy combined with immunotherapy.

In 2014, Zamarin et al. suggested that oncolytic Newcastle Disease Virus (NDV) induces lymphocyte infiltrating in B16 melanoma mouse models. The authors further demonstrated that NDV in combination with CTLA-4 blockade contributed to tumor regression in animal models with poor immunogenicity.<sup>26</sup> At the same time, Engeland et al. also found that measles virus (MV) encoding anti-CTLA-4 and anti-PD-L1 had a favorable immune profile and therapeutic benefits in melanoma murine models.<sup>27</sup> Another study in neuroblastoma reported CAR-T cells combined with oncolytic adenovirus encoding the chemokine RANTES and IL-15, can effectively increase T-cell infiltration into the tumor. Combination therapy also facilitate migration and survival of CAR-T cells.<sup>28</sup> Although these studies does not directly demonstrate that oncolytic virotherapy combined with immunotherapy benefits the survival for tumor patients, preclinical data lays a solid foundation for investigation of such combination treatment in clinic and boosts the investigators' confidence.

In 2015, T-VEC was approved by the FDA for recurrent unresectable melanoma from the pivotal phase III OPTiM trial.<sup>3</sup> In 2016, a phase Ib study showed T-VEC combined with ipilimumab (CTLA-4 blockade) improved durable response and won better survival benefits than monotherapy in patients with advanced melanoma. The overall response rate (ORR) was 50%, the disease control rate (DCR) was 72%, median overall survival (mOS) and median progression-free survival (mPFS) were not reached. The incidence of Grade 3–4 adverse events (AEs) was similar to single-agent.<sup>29</sup>

In 2017, Liu et al. pointed out that oncolytic poxvirus in combination with PD-L1 inhibitor can significantly inhibit tumor growth and prolong survival time in murine colon or ovarian cancer models. The dual therapy can enhance CD4+ and CD8+ effector T cells infiltration and killer cells activity, like IFN- $\gamma$ , granzyme B and perforin. Furthermore, significant decreases in Treg, the subclasses of myeloid-derived suppressor cells and tumor-associated macrophages, and exhausted CD8+ T cells were found in the TME.<sup>30</sup>

Since keywords are the core content of publications, co-occurrence analysis can identify keywords with high frequency, so as to quickly grasp the core problems and emerging research hotspots in the research field. In this study, 'immunotherapy' and 'oncolytic virus' were the most frequent keywords. The most extensively studied cancer were melanoma, glioma and hepatocellular carcinoma. The frequency of 'tumor microenvironment' was 46 times. 'Antitumor immunity' was another frequently appearing keyword with 14 times. The TME exhibits highly complex heterogeneity with acidic and hypoxic conditions, low immunogenicity and immunosuppressive function.<sup>31</sup> Although previous investigations have developed insights of TME and the antitumour immune response to cancer immunotherapy, great challenges still remains in the context of immunosuppressive solid tumors. Oncolytic virotherapy can create immunologically 'hot' tumors,<sup>22</sup> so the arming strategies with OV to enhance systemic anti-tumor immunity have been performed in recent preclinical and clinical researches. The potential combating mechanisms of combination treatment are in four ways: eliminating immune suppression, inducing proinflammatory cytokines, boosting antigen-presenting cells function, and facilitating activity of effector T cells.<sup>32,33</sup>

In the top 20 keywords with the strongest citation bursts, 'tumor microenvironment' and 'delivery' were keywords that continued to burst as of 2023. Research fronts in the future may focus on the changes of tumor microenvironment, and explore the function of antitumour immunity and antiviral immunity under combination strategies. The novel OV-modification strategies for more efficient vascular delivery deserves more in-depth research works.<sup>34</sup>

There are still some limitations in this study. First, our study is limited to English publications listed on the WoSCC database. WoSCC contains the overwhelming majority of high-quality researches, while it has few influence on the overall study trend. In addition, the study included literature within the last 20 years which may result in bias and lack of comprehensiveness. It also only offers a short-term forecast of the field. What's more, latest high-quality trials

may not have mentioned due to deferred citation and need to be updated in the future research.

## Conclusion

In recent years, there has been increasing attention in the field of oncolytic virotherapy in combination with immunotherapy. The substantial increase in publications each year showed the developmental importance of this area. This paper identified the top researchers and institutions worldwide involved in the combination therapy. The Journal for ImmunoTherapy of Cancer was the most active journal, and Akseli Hemminki was the most influential author. Research fronts in the future may focus on the methods of virus delivery and tumor microenvironment modulation. Furthermore, the combination treatment regimen was widely used in melanoma, glioma and hepatocellular carcinoma.

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## Disclosure statement

No potential conflict of interest was reported by the author(s).

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## Notes on contributor

*Yiyao Xu and Xin Lu* are chief physicians in the department of liver surgery in Peking Union Medical College Hospital. They are skilled at diagnosis and treatment of benign and malignant tumors of hepatobiliary system, intra- and extrahepatic bile duct calculi and other diseases.

## Contributors

Study concept and design: Y-YX and XL. Analysis and interpretation of data: TZ and X-TS. Statistical analysis: X-TS and LZ. Administrative, technical, or material support: LZ, Y-GL and HZ. Review and revision of the manuscript: H-TZ and XT-Z. Writing: TZ. Guarantor author: Y-YX. All authors contributed to the article and approved the submitted version.

## Data availability statement

All data of the study are available in the article/Supplementary Material.

## Ethics approval

The study is based on literature research and does not require ethical approval or patient consent.

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