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Exploration of the current status and trends of pancreatic cancer immune cells in the past 30 years: a bibliometric analysis

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Abstract

Objective Immune cells are pivotal in progressing and treating pancreatic cancer. Over the past three decades, the complex interactions between pancreatic cancer and immune cells have garnered much attention, as evidenced by the increasing number of publications in this domain. This bibliometric study maps the global research landscape of pancreatic cancer immune cell interactions, emphasizing evolving trends, collaborative networks, and therapeutic innovation.

Method Using VOSviewer and CiteSpace, we analyzed 2658 articles from the Web of Science Core Collection (2000–2024) to evaluate publication trends, collaborative networks, keyword dynamics, and highly cited works.

Results Annual publications surged from 4 (2000) to 453 (2024), with China (44.9%) and the U.S. (33.6%) dominating output. Key institutions included Fudan University (102 articles) and Zhejiang University (88 articles). Keyword evolution revealed three phases: antitumor mechanisms, clinical translation of checkpoint inhibitors, and recent emphasis on stromal-immune crosstalk. High-impact works by Brahmer (N Engl J Med 366:2455–2465, 2012) and Marabelle (J Clin Oncol 38:1–10, 2020) underscored immunotherapy milestones.

Conclusion This bibliometric analysis highlights the dynamic nature of pancreatic cancer immune cell research, emphasizing the growing global interest and investment in this field. The findings underscore the need for ongoing monitoring of research trends to inform and propel innovative therapeutic strategies, ultimately improving patient outcomes.

Keywords Pancreatic cancer, Immune cells, Bibliometric analysis, Citespace, VOSviewer

1 Introduction

Pancreatic cancer remains one of the most lethal malignancies, with a 5-year survival rate below 10% [1]. Its aggressive progression and resistance to therapy are tightly linked to the unique immunosuppressive tumor microenvironment (TME) [2, 3]. Despite significant advancements in immunotherapy, such as checkpoint inhibitors [4], adoptive cell therapies [5], and cancer vaccines [6], which have transformed the treatment

landscape for numerous cancers, pancreatic cancer remains resistant to immune-mediated control. This therapeutic challenge highlights the critical necessity of elucidating the intricate interactions between pancreatic cancer and immune cells. This research area has experienced exponential growth in scholarly output over the last 30 years.

Medical big data and data mining is used to analyze a large amount of medical data and dig out valuable diagnostic rules to provide reference for the diagnosis and treatment of diseases. Bibliometric analysis provides a powerful framework to map the evolution of scientific knowledge, identify research hotspots, and highlight underexplored areas in complex fields [7, 8]. Despite the critical role of immune cells in pancreatic cancer progression and treatment resistance, no comprehensive bibliometric study has systematically analyzed trends, global collaboration patterns, or emerging themes in this domain. Our findings provide actionable insights to guide future research priorities and optimize therapeutic development in this high-need area.

This study draws upon research related to pancreatic cancer immune cells included in the Web of Science Core Collection. Utilizing the visualization analysis tools CiteSpace and VOSviewer, we constructed a scientific knowledge map. By conducting co-occurrence and cluster analyses of pertinent literature, including research on countries, institutions, journals, authors, keywords, and highly cited works, we investigated the emerging hotspots and frontier trends in pancreatic cancer immune cell research. The findings aim to offer support and reference for future studies in this domain.

2 Methods

2.1 Data collection and search strategy

The Web of Science (WoS) database is widely acknowledged as the most comprehensive and reliable resource for bibliometric analysis, encompassing nearly all high-quality and influential journals and offering an extensive array of citation data. Previous research indicates that the papers included in the Web of Science Core Collection (WOSCC) (https://www.webofscience.com/wos/woscc/) effectively represent the current state of medical science. Consequently, we selected WOSCC as our data source. WOSCC has been extensively utilized for bibliometric analysis and the visualization of scientific literature in numerous studies [9–11]. To enhance data representativeness and accessibility, all data were extracted from WOSCC.

We selected articles about pancreatic cancer immune cells on 24 April 2025. The retrieval formula is as follows (from January 1, 2000 to December 31, 2024): TS = ("Pancrea* Cancer*" OR "Cancer of Pancreas" OR "Pancreatic Carcinoma*" OR "Carcinoma of Pancreas" OR "Pancreatic Adenocarcinoma*" OR "Pancreatic Tumor*" OR "Pancreatic Ductal Adenocarcinoma" OR "PDAC" OR "Pancrea* Neoplasm*") AND ("Immune Cell*" OR "Immunocyte*" OR "Immune Modulation" OR "Cancer Immunotherapy" OR "Tumor Immunotherapy" OR "Tumor Immunology" OR "Cancer Immunology" OR "Checkpoint Inhibitor*" OR "PD-1" OR "PD-L1" OR "CAR-T cell*"). Initially, 3987 studies were retrieved.

The analysis focused on publications from 2000 to 2024 to align with two critical considerations: (1) The WOSCC achieved robust indexing of immunotherapy-related research outputs starting in 2000, ensuring data completeness and reproducibility; (2) This period encompasses transformative milestones in pancreatic cancer immunology. Earlier literature (pre-2000) primarily addressed general tumor immunology concepts

without pancreatic cancer-specific mechanistic insights, as confirmed by our preliminary citation tracing analysis.

2.2 Study selection

The researchers conducted an initial screening of all articles based on their titles and abstracts, selecting those that were pertinent to the topic under investigation. Subsequently, data were independently downloaded and analyzed by two researchers to ensure accuracy and reliability. In instances where discrepancies arose between the two researchers' interpretations, a third researcher was consulted to adjudicate and determine the prevailing viewpoint.

Exclusion criteria: (1) non-English literature; (2) abstracts, editorial materials, corrections, letters, news items, proceedings papers, book chapters, early access and other types of literature.

Ultimately, 2658 articles were retained. All data were sourced from public databases, thus negating the need for ethics committee approval or informed consent. The screening flow chart of the inclusion and exclusion criteria is shown in Fig. 1.

2.3 Statistical analysis

The selection of CiteSpace (version 6.2.R6) and VOSviewer (version 1.6.20) for bibliometric analysis was guided by their complementary capabilities. CiteSpace was prioritized for its capacity to identify emerging trends through burst detection algorithms and timeline visualization, particularly suited for tracking temporal developments in immunotherapy and pancreatic cancer research. In contrast, VOSviewer was employed for its advanced network visualization of high-dimensional co-occurrence relationships among authors, institutions, and keywords, enabling spatial mapping of knowledge structures.

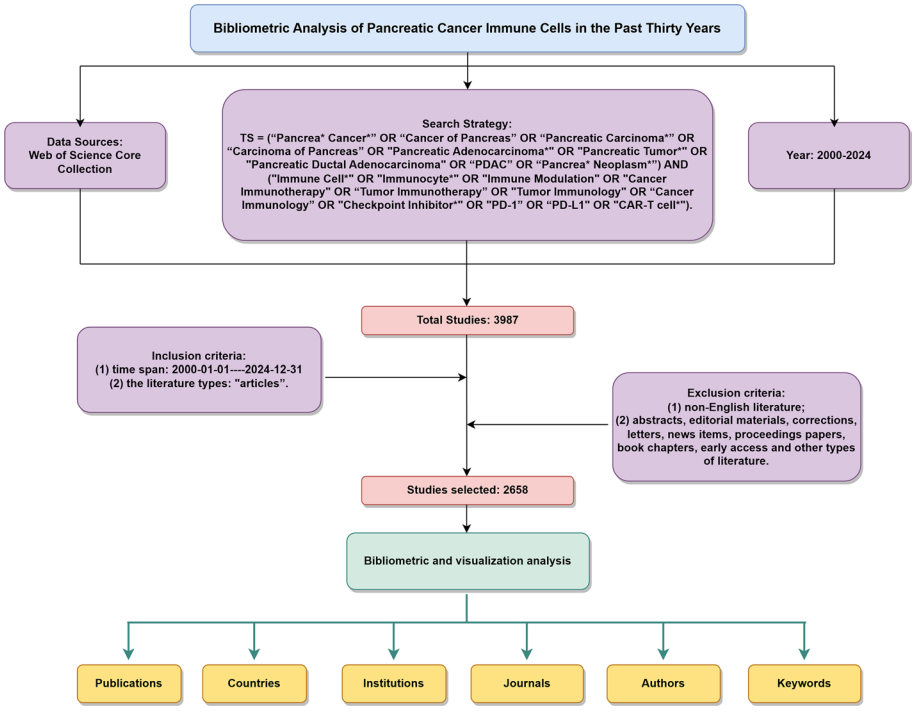


Fig. 1 Flow chart of literature screening

This dual-tool approach aligns with methodological recommendations in oncological bibliometrics, ensuring comprehensive coverage of both temporal evolution and structural dynamics.

For data processing, English literature records from the Web of Science (WOS) database were exported as “plain text” files. In CiteSpace, the "Full Record with Cited References" option was utilized, with parameterization including time slices segmented into 3-year intervals, cosine algorithm-based network strength calculation, and extraction of the top 10% nodes per slice. Node thresholds were set using the k-metric (k = 25), with keyword frequency thresholds fixed at 50. Pathfinder and pruned slice networks were applied to streamline network structures. In VOSviewer, overlay and network visualizations were optimized through dynamic adjustments: the Association Strength method governed co-occurrence analysis, while Attraction/Repulsion parameters and display attributes (Scale, Labels, Lines, Colors) were calibrated to enhance visual clarity. Both tools maintained default settings unless explicitly modified, ensuring methodological consistency across temporal and co-occurrence analyses.

Data on annual publications and journal distributions were sourced from the WoS database, and the corresponding chart was produced using OriginPro 2024. For clustering the keywords of the literature, the LSI algorithm was used to identify the top-ranked title words as cluster labels.

3 Results

3.1 Annual publication outputs and trends

According to Fig. 2, the fluctuations in publication numbers are indicative of evolving trends within the field of pancreatic cancer immune cells. The number of published papers exhibited a steady increase, rising from 4 in the year 2000 to 453 in 2024. During the initial phase (2000 to 2006), the volume of published articles was comparatively low. Between 2007 and 2015, the annual output of published articles remained modest. However, starting in 2017, more than 100 articles were published every year. In the last 5 years, this area has developed rapidly and published 1924 (72.39% of 2658) articles.

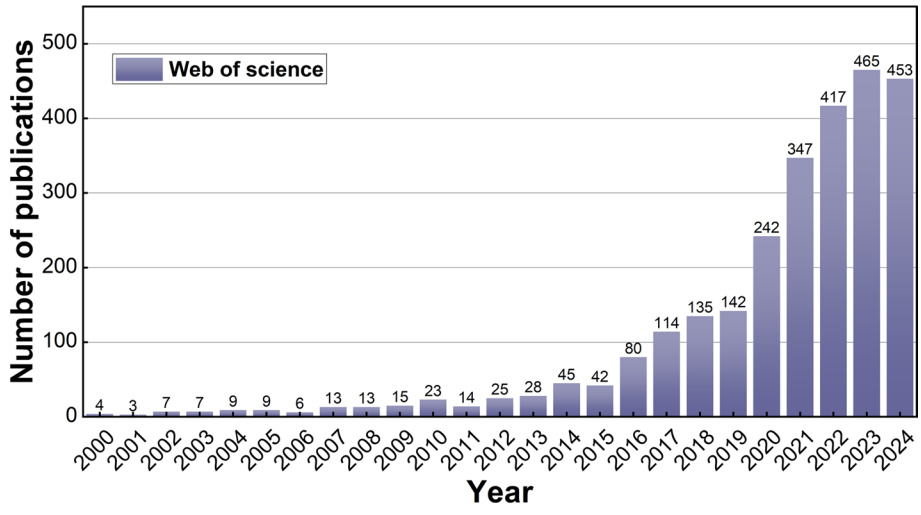


Fig. 2 The annual number of publications and trends

3.2 Detailed analysis of key countries

Table 1 lists the top 15 countries with the highest output of studies. From 2000 to 2024, China had the largest number of publications (1194 articles, 44.92%), followed by the United States (894 articles, 33.63%) and Germany (237 articles, 8.92%). Although China was ranked as the most productive country in terms of publication output, the number of citations was lower compared to the United States. This suggests that Chinese publications may have a relatively lower impact and could indicate a deficiency in high-quality research outputs.

The contributions of various countries played a crucial role in shaping the research landscape in Fig. 3a. The intensity of purple on the world map reflects the number of publications of each country. China and the United States had a deeper purple than any other countries, indicating that the two countries have the largest contributions in this field. Figure 3b, c illustrate the number of publications produced by various countries and the extent of collaboration among them. The circle size represents the number of publications. As the top two countries with the maximum number of publications, China and the United States conducted the most cooperation in this field. And the publications from China were mainly published in recent years, while the United States have more previously published materials.

3.3 Analysis of key institutions

Table 2 lists the top 15 institutions with the highest output of studies. The top 10 institutions are mainly located in China and the United States. And depicted in Fig. 4, various research institutions have contributed significantly to pancreatic cancer immune cell research. Fudan University had the highest contribution, with 102 articles; the second ranking institution was Zhejiang University (88 articles), followed by Shanghai Jiao Tong University (79 articles). Research articles produced by Chinese institutions have been published relatively recently. The collaborative efforts of prominent international institutions have significantly enhanced our comprehension of the pancreatic cancer.

Table 1 Top 15 high-output countries/regions

Ranking	Country	Documents	Citations
1	China	1194	21,627
2	USA	894	65,526
3	Germany	237	10,745
4	Japan	205	10,787
5	England	119	10,503
6	Italy	90	5441
7	South Korea	84	5229
8	Canada	69	5605
9	France	67	7120
10	Netherlands	59	2195
11	Spain	53	4904
12	Australia	38	4208
13	Sweden	38	2489
14	Switzerland	38	2188
15	India	23	1118

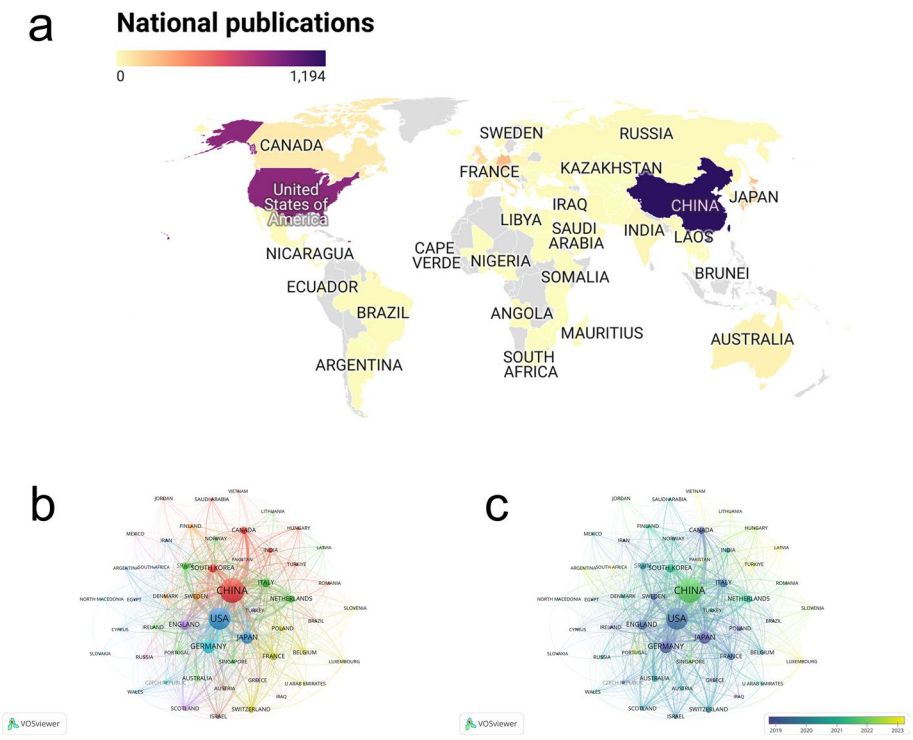


Fig. 3 **a**World map showing the country scientific production and collaboration in pancreatic cancer immune cells field. **b** Country cooperation co-occurrence clustering map. **c** Chronological network of co-occurrence of countries

Table 2 Top 15 high-output institutions

Ranking	Organization	Documents	Citations
1	Fudan Univ	102	2233
2	Zhejiang Univ	88	2183
3	Shanghai Jiao Tong Univ	79	1792
4	Johns Hopkins Univ	70	6706
5	Univ Texas Md Anderson Canc Ctr	66	13,175
6	Sun Yat Sen Univ	62	1393
7	Harvard Med Sch	56	2500
8	Univ Penn	53	6588
9	German Canc Res Ctr	49	2971
10	China Med Univ	47	736
11	Sichuan Univ	43	1200
12	Nanjing Med Univ	42	760
13	Mem Sloan Kettering Canc Ctr	39	8038
14	Huazhong Univ Sci and Technol	38	768
15	Nci	38	2650

3.4 Journal analysis

The basic information of the top 15 journals with the number of published articles is summarized in Table 3. The top three journals with the most published articles were "Frontiers In Immunology," "Clinical Cancer Research," and "Frontiers In Oncology," with 268 articles (10.08%) in total. "Frontiers In Immunology" journal demonstrated the highest publication volume, with 110 documents. "Clinical Cancer Research" also played a pivotal role with 80 publications. "Frontiers in Oncology" contributed 78 publications. "Cancers" and "Journal For Immunotherapy Of Cancer" contributed significantly with

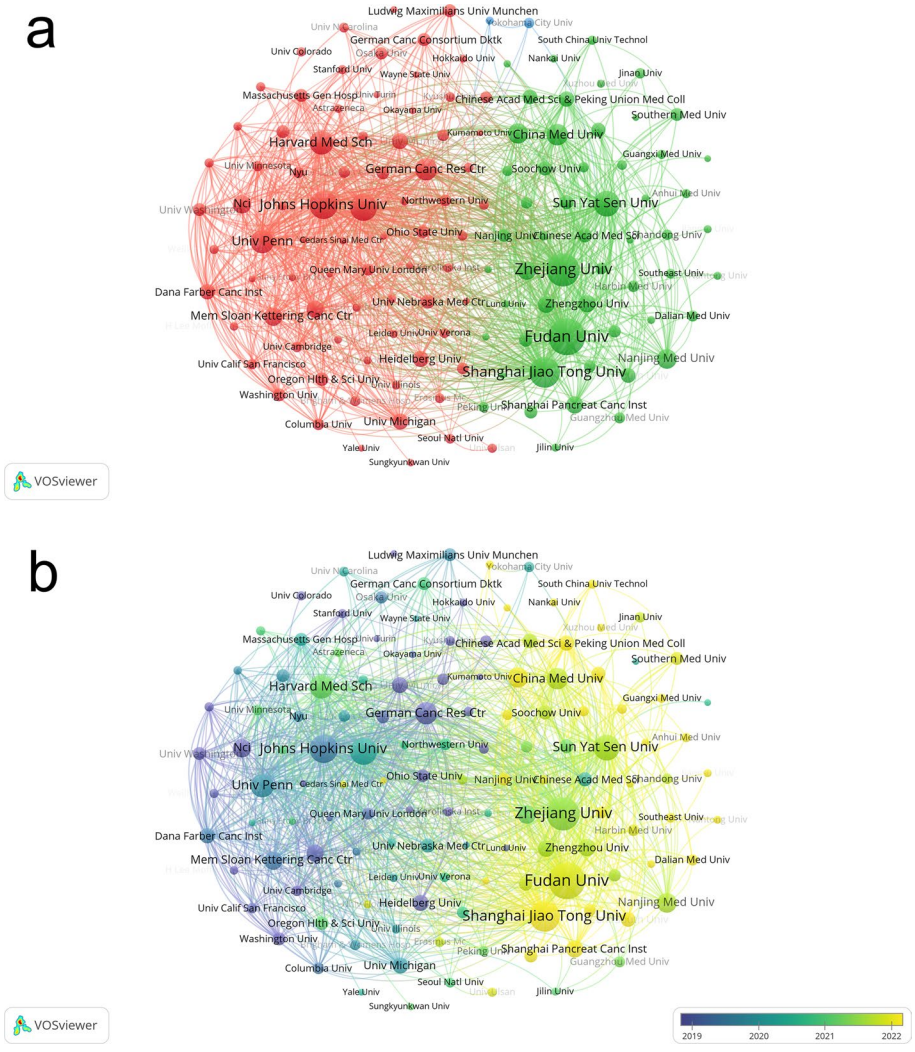


Fig. 4 Institution cooperation co-occurrence map. **a** Institution cooperation co-occurrence clustering map and **b** Chronological network of co-occurrence of institutions

Table 3 Top 15 high-output journals

Ranking	Source	Documents	Citations
1	Frontiers In Immunology	110	1901
2	Clinical Cancer Research	80	8827
3	Frontiers In Oncology	78	701
4	Cancers	74	1445
5	Journal For Immunotherapy Of Cancer	73	2551
6	Scientific Reports	56	951
7	Oncoimmunology	53	2817
8	Nature Communications	46	3495
9	Bmc Cancer	43	1041
10	Cancer Immunology Immunotherapy	42	962
11	Cancer Research	38	4954
12	International Journal Of Molecular Sciences	38	532
13	Cancer Immunology Research	36	2732
14	Cancer Letters	35	860
15	Frontiers In Genetics	34	242

74 and 73 publications, respectively. And Fig. 5a, b show the co-occurrence network of the journals. These journals provided platforms for researchers to publish their latest findings, driving deep exploration of immune cells in pancreatic cancer.

Figure 5c is a double-graph overlay of journals that shows the flow of knowledge between different disciplines in this field. The left side of the graph represents the primary disciplines of the citing journal, whereas the right side illustrates the primary disciplines of the cited journal. Citing journals are positioned as the forefront of knowledge, while cited journals serve as the foundational knowledge base. The labels denote the fields encompassed by each journal, and the colored lines represent distinct citation pathways. The thickness of these lines corresponds to the frequency with which the citing journal references the cited journal. Notably, two predominant citation pathways are identified: the orange pathway and the green pathway. The articles from molecular, biology, genetics, health, nursing and medicine journals were frequently cited by articles from molecular, biology, immunology journals. And the articles from molecular, biology, and genetics journals were also cited by articles from medicine, medical, and clinical journals. This visualizes the interdisciplinary research trends and the emergence of new fields.

3.5 Key author contributions

Several authors have made significant contributions to advance pancreatic cancer immune cell research. Table 4 lists the top 15 authors with the highest output of studies. Wang Wei was the most productive author, with 32 articles, followed by Yu Xianjun, and Elizabeth M. Jaffee, with 29 and 26 articles, respectively. The author, Robert H. Vonderheide, has published a relatively modest total of 16 articles; however, his work has garnered an impressive 2171 citations. Figure 6 illustrates the co-occurrence network of the authors, revealing that Wang Wei, and Elizabeth M. Jaffee each maintain close collaborative ties with other authors.

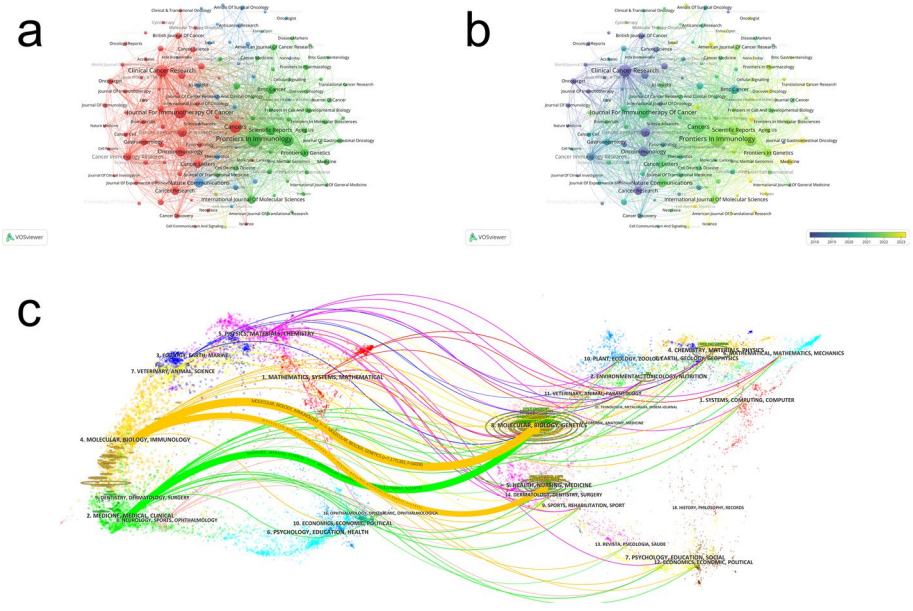


Fig. 5 **a** Journal cooperation co-occurrence clustering map. **b** Chronological network of co-occurrence of journals. **c** Double-graph overlay of journals

Table 4 Top 15 high-output authors

Ranking	Authors	Documents	Citations
1	Wang Wei	32	752
2	Yu Xianjun	29	533
3	Jaffee, Elizabeth M.	26	2677
4	Liang Tingbo	24	531
5	Xu Jin	22	358
6	Zheng Lei	22	1761
7	Zhang Bo	21	325
8	Li Yan	19	498
9	Shi Si	19	395
10	Liu Jiang	17	311
11	Zhang Qi	17	493
12	Li Xin	16	375
13	Liang Chen	16	358
14	Vonderheide, Robert H.	16	2171
15	Van Eijck, Casper H. J.	15	190

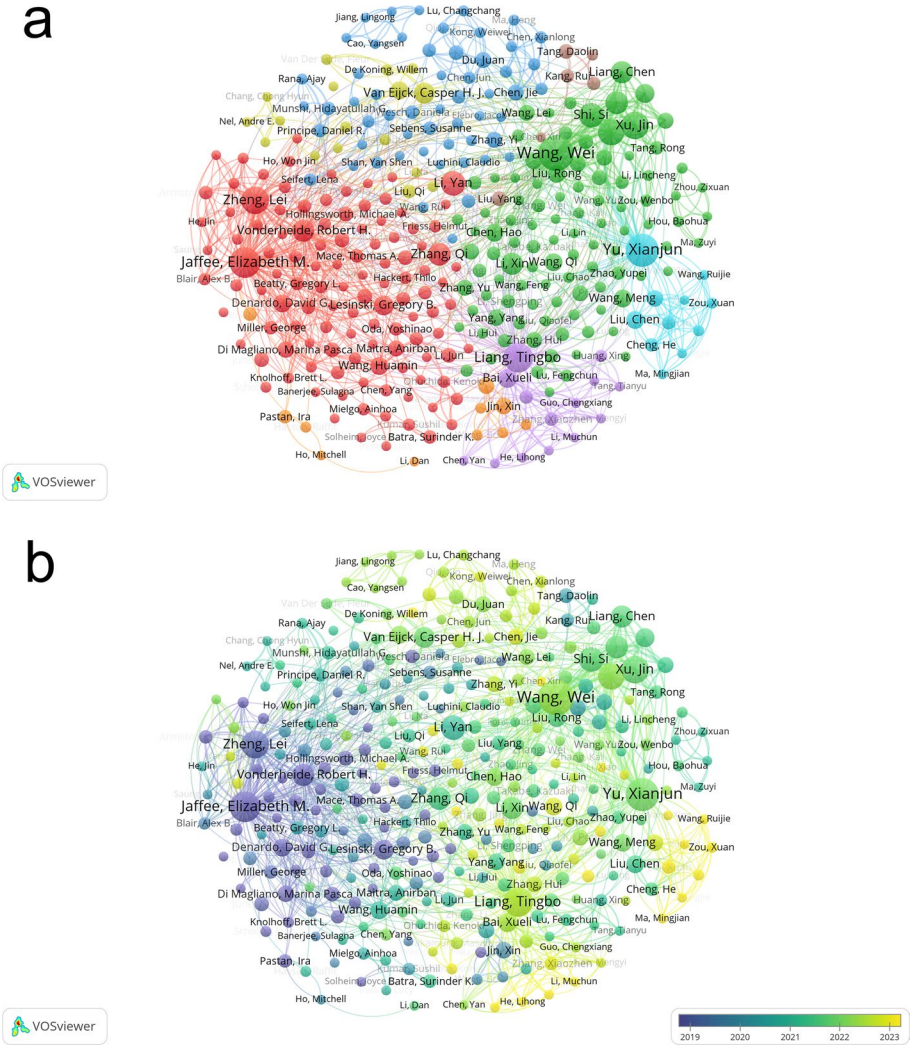
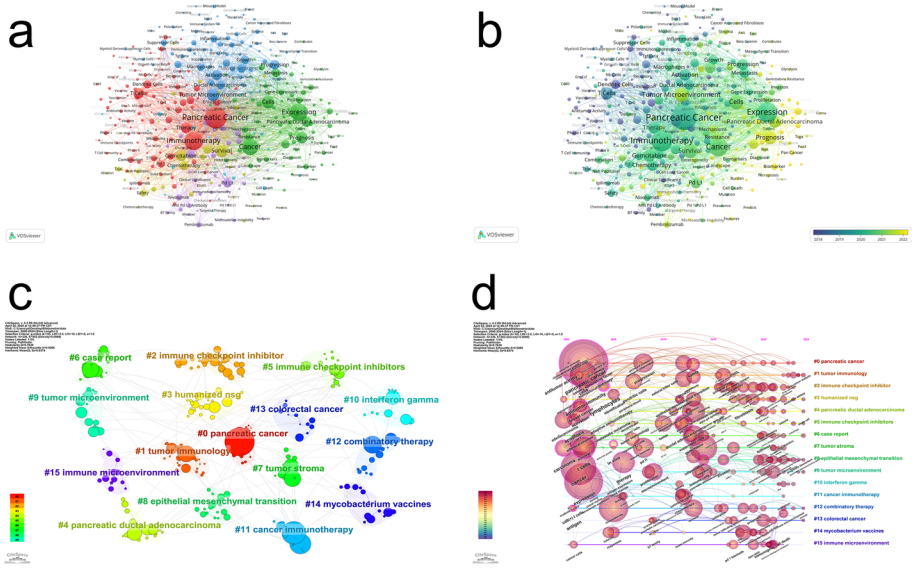


Fig. 6 Author cooperation co-occurrence map. **a** Author cooperation co-occurrence clustering map and **b** Chronological network of co-occurrence of authors

3.6 Keyword analysis

Keyword co-occurrence analysis is a bibliometric method employed to investigate the associations and concurrent appearances of keywords within a specific research domain. In this study, we performed a quantitative analysis of the keywords found in the literature pertaining to immune cells in pancreatic cancer, as illustrated in Fig. 7a. Table 5 displays the fifteen most frequently utilized keywords, which include: "pancreatic cancer," "expression," "cancer," "immunotherapy," "cells," "tumor microenvironment," "survival," "T cells," "therapy," "pancreatic ductal adenocarcinoma," "activation," "gemcitabine," "progression," "PD-L1," and "carcinoma." In Fig. 7b, these keywords are color-coded based on the average year of their appearance in an overlay map. The chronological



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Top 25 Keywords with the Strongest Citation Bursts

Keywords	Year	Strength	Begin	End	2000 - 2024
carcinoma	2000	14.43	2000	2017	
antitumor activity	2000	7.55	2000	2020	
antigen	2001	6.52	2001	2019	
t cells	2002	9.55	2002	2016	
mice	2002	8.69	2002	2018	
antitumor immunity	2002	6.65	2002	2018	
in vivo	2005	11.79	2005	2017	
metastatic melanoma	2005	8.33	2005	2018	
pancreatic cancer	2002	13.25	2006	2015	
dendritic cells	2007	17.2	2007	2018	
cancer immunotherapy	2007	13.48	2007	2018	
b7 h1	2010	10.72	2010	2019	
clinical significance	2010	9.91	2010	2018	
phase i	2012	5.88	2012	2017	
suppressor cells	2013	7.8	2013	2016	
immune cells	2014	7.53	2014	2018	
pd 1 blockade	2017	9.33	2017	2019	
ctla 4 blockade	2017	8.28	2017	2018	
nivolumab	2017	6.77	2017	2020	
anti pd l1 antibody	2017	6.17	2017	2021	
tumor infiltrating lymphocytes	2017	6.08	2017	2018	
ductal adenocarcinoma	2012	5.91	2017	2019	
immune infiltration	2021	8.59	2022	2024	
tumor immune microenvironment	2022	7.25	2022	2024	
pancreatic adenocarcinoma	2014	6.39	2022	2024	

Fig. 7 **a** Keyword cooperation co-occurrence clustering map. **b** Chronological network of co-occurrence of keywords. **c** Cluster diagram of relevant keywords. **d** Timeline chart of relevant keywords. **e** Keyword emergence analysis. Year: the first occurrence of the keyword; strength: the larger the value, the stronger the emergence of the keyword; begin: the start time of the keyword burst; end: the end time of the keyword burst. Red represents the time of the keyword burst, dark green represents the time interval, and light green represents the keyword does not appear

Table 5 Keywords frequency and year

Ranking	Keywords	Frequency	Year
1	Pancreatic cancer	977	2002
2	Expression	626	2002
3	Cancer	500	2002
4	Immunotherapy	370	2005
5	Cells	318	2002
6	Tumor microenvironment	302	2014
7	Survival	302	2002
8	T cells	236	2002
9	Therapy	232	2006
10	Pancreatic ductal adenocarcinoma	226	2013
11	Activation	210	2002
12	Gemcitabine	196	2013
13	Progression	188	2008
14	PD-L1	176	2008
15	Carcinoma	152	2000

trends reveal a gradual transition towards translational and therapeutic themes. Earlier studies predominantly focused on molecular mechanisms, whereas more recent research has shifted towards clinical interventions. A comprehensive analysis of these keywords elucidates the current state and emerging trends in pancreatic cancer immune cell research, thereby indicating potential future research directions.

3.7 Research cluster analysis

A cluster analysis of all literature keywords was performed utilizing the Latent Semantic Indexing (LSI) algorithm, as depicted in Table 6 and Fig. 7c. The analysis resulted in the division of keywords into 16 distinct clusters, each named according to the keyword with the highest frequency within that cluster. It is noteworthy that a smaller cluster ID number corresponds to a larger cluster size. The top three clusters were “pancreatic cancer” (Cluster 0), “tumor immunology” (Cluster 1), and "immune checkpoint inhibitor" (Cluster 2).

We also performed a timeline analysis of all literature keywords to reveal the changes in research hotspots over time in the Fig. 7d. The timeline view of the clustering graph visualizes the period of each cluster formation and the linkage between them, depicting the evolution of research topics. The X-axis of the timeline view represented the year of publication, while the Y-axis corresponded to the cluster number. The keyword timeline diagram shows the current hotspots in this field were mainly focused on the following aspects: “tumor immunology” (Cluster 1), "immune checkpoint inhibitors" (Cluster 5), "epithelial mesenchymal transition" (Cluster 8), “tumor microenvironment” (Cluster 9), and “combinatory therapy” (Cluster 12).

3.8 Keywords with the strongest citation bursts

We employed CiteSpace to identify words that frequently emerge over time, referred to as burst keywords. Figure 7e shows the top 25 strongest burst keywords. The term “antitumor activity” emerges as an early keyword, signifying its importance and close scrutiny during the initial stages of research. Furthermore, “antitumor activity” exhibits the longest duration of focus, first appearing in the year 2000 and persisting as a central topic of interest for researchers over a span of 20 years. Since 2017, the field has

Table 6 Keyword clustering parameters

Cluster ID	Node number	Contour value	Year	Main keywords
0	30	0.954	2008	Pancreatic cancer; tumor immunology; linked tlr; neutrophils; prostate cancer|tumor microenvironment; regulatory t cell; t cell subset; spatial arrangements; nerve fiber density
1	29	0.952	2010	Pancreatic cancer; tumor immunology; checkpoint blockade; car t cells; tumor marker|cells; macrophages; activation; overexpression; in vitro
2	29	0.965	2017	Pancreatic cancer; immune checkpoint inhibitor; reversion; infiltrating lymphocytes; n6 methyladenosine|tumor microenvironment; safety; antibody; immunotherapy; adenocarcinoma
3	24	0.957	2017	Pancreatic cancer; humanized nsg; lineage; immune checkpoint inhibitor; pancreatic neoplasms|growth; pathway; target; resistance; wnt/beta catenin
4	23	0.944	2014	Pancreatic ductal adenocarcinoma; cytotoxic t cells; b lymphocytes; regulatory cells; immune checkpoint inhibitor|pancreatic cancer; immune cell; cancer prevention; immune checkpoint inhibitor; sex difference
5	23	0.837	2012	Pancreatic cancer; immune checkpoint inhibitors; combination therapy; chemokine receptors; sex difference|ductal adenocarcinoma; PD-1; blockade; microenvironment; tumor infiltrating lymphocytes
6	21	0.866	2014	Pancreatic cancer; case report; epithelial mesenchymal transition; spindle cells; hepatocellular carcinoma|tumor microenvironment; pancreatic adenocarcinoma; gene family; nucleotide metabolism; therapeutic target
7	18	0.9	2012	pancreatic cancer; tumor stroma; adam8 protease; immune checkpoint inhibitor; formulation|tumor microenvironment; stromal cells; tumor immunology; adam8 protease; adjuvant chemotherapy
8	18	0.973	2021	Pancreatic cancer; epithelial mesenchymal transition; cell proliferation; survival; activation|pancreatic adenocarcinoma; prognostic biomarker; matrix metalloproteinase; atypical flat lesions; direct anti tumoral effects
9	16	0.959	2017	Pancreatic cancer; tumor microenvironment; regulatory t cell; t cell subset; therapeutic target|pancreatic adenocarcinoma; immune infiltration; transcription factor; immune checkpoint inhibitor; pancreatic neoplasms
10	16	0.916	2014	Pancreatic cancer; interferon gamma; specific t cells; antigen presentation; activation|chemotherapy; therapy; gemcitabine; t cells; double blind
11	16	0.922	2007	Pancreatic cancer; cancer immunotherapy; interferon gamma; programmed death; outcm|pancreatic adenocarcinoma; immune microenvironment; sphingolipid metabolism; tumor biomarker; transcription factor
12	16	0.97	2012	Pancreatic cancer; combinatory therapy; dual stimuli; chemokine receptors; immune checkpoint inhibitor|immunotherapy; tumor microenvironment; safety; antibody; infiltration
13	13	0.867	2014	Pancreatic cancer; colorectal cancer; breast cancer; lung cancer; pro tumoral|gastric cancer; cells; in vitro; overexpression; glycosaminoglycan synthesis
14	13	0.873	2015	Pancreatic cancer; pancreatic ductal adenocarcinoma; cancer immunotherapy; mycobacterium vaccines; immuno oncology|tumor microenvironment; trial; cancer; safety; open label
15	13	0.943	2017	Pancreatic cancer; immune microenvironment; prognostic signature; rna expression; immune checkpoint inhibitor|immune checkpoint inhibitors; tyrosine kinase inhibitor; open label; chemotherapy; pdac

experienced a clinical transformation, characterized by the prominence of terms such as "PD-1 blockade," "CTLA-4 blockade," "nivolumab," and "anti-PD-L1 antibody," which align with advancements in immunotherapy. The terms "immune infiltration," and "tumor immune microenvironment" have emerged in recent years. These terms hold the potential to become focal points of research and catalysts for disciplinary advancements in the study of pancreatic cancer immune cells.

3.9 Analysis of highly cited literature

We constructed a co-citation network of references. Figure 8 reveals that Brahmer's seminal work not only holds the distinction of being the most cited document but also boasts an earlier publication year than other highly referenced studies. Table 7 shows the top ten co-cited references on pancreatic cancer immune cells. "Safety and activity of anti-PD-L1 antibody in patients with advanced cancer" by Brahmer et al. [12] was the highest cited article with 6356 citations. This article mainly found that anti-PD-L1 antibody induced durable tumor regression (objective response rates of 6–17%) with manageable safety (grade 3–4 treatment-related toxicities in 9% of patients) across advanced cancers, validating the PD-1/PD-L1 pathway as a promising target for cancer immunotherapy. The second and third articles were by Marabelle et al. [13] and Feig et al.[14], with 1955 and 1506 citations respectively.

4 Discussion

The bibliometric analysis presented in this study offers a comprehensive overview of the research landscape concerning pancreatic cancer immune cells over the past three decades. The findings highlight a significant and consistent increase in the volume of research output, reflecting a growing global interest and investment in this critical area of oncology. This section discusses the implications of these findings and the

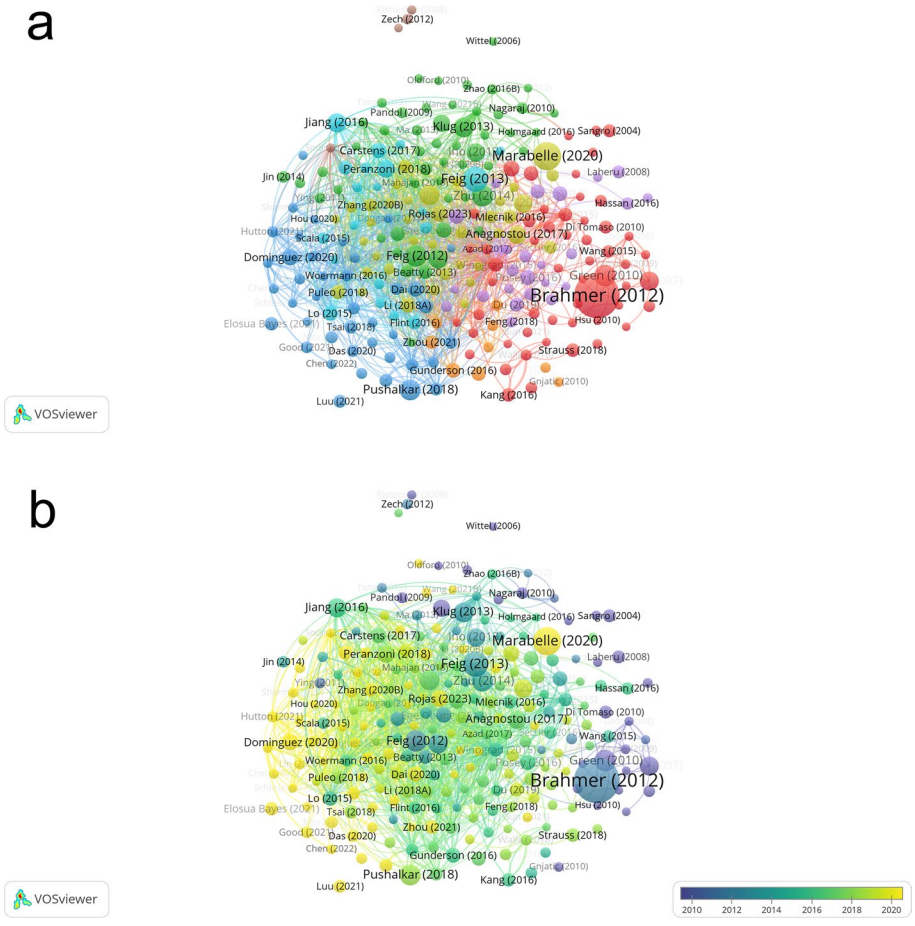

Fig. 8 Highly cited local literature collaboration network. **a** Co-citation network analysis of highly cited references and **b** Chronological network of co-occurrence of co-cited references

Table 7 Top 10 co-cited references

Ranking	Title	First author	Journal	Year	Citations
1	Safety and activity of anti-PD-L1 antibody in patients with advanced cancer	Brahmer	N Engl J Med	2012	6356
2	Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/Mismatch Repair-Deficient Cancer: Results From the Phase II KEYNOTE-158 Study	Marabelle	J Clin Oncol	2020	1955
3	Targeting CXCL12 from FAP-expressing carcinoma-associated fibroblasts synergizes with anti-PD-L1 immunotherapy in pancreatic cancer	Feig	Proc Natl Acad Sci U S A	2013	1506
4	The pancreas cancer microenvironment	Feig	Clin Cancer Res	2012	1036
5	Integrative analysis reveals selective 9p24.1 amplification, increased PD-1 ligand expression, and further induction via JAK2 in nodular sclerosing Hodgkin lymphoma and primary mediastinal large B-cell lymphoma	Green	Blood	2010	1008
6	CSF1/CSF1R blockade reprograms tumor-infiltrating macrophages and improves response to T-cell checkpoint immunotherapy in pancreatic cancer models	Zhu	Cancer Res	2014	977
7	The Pancreatic Cancer Microbiome Promotes Oncogenesis by Induction of Innate and Adaptive Immune Suppression	Pushalkar	Cancer Discov	2018	916
8	Identification of unique neoantigen qualities in long-term survivors of pancreatic cancer	Balachandran	Nature	2017	845
9	Low-dose irradiation programs macrophage differentiation to an iNOS$^+$/M1 phenotype that orchestrates effective T cell immunotherapy	Klug	Cancer Cell	2013	837
10	Targeting tumor-infiltrating macrophages decreases tumor-initiating cells, relieves immunosuppression, and improves chemotherapeutic responses	Mitchem	Cancer Res	2013	770

evolving research focus, providing insights into the future directions of pancreatic cancer immune cell research.

4.1 Global research trends and contributions

The observed increase in annual publication outputs, particularly from 2017 onwards, highlights the growing focus on the intricate interactions between pancreatic cancer and immune cells. This trend is indicative of a maturing research field, driven by advancements in immunology, oncology, and related technologies. The substantial contributions from China and the United States, accounting for a large proportion of the global research output, highlight the importance of these nations in shaping the research agenda. While China produced the highest volume of publications (44.9%), U.S. studies had threefold higher citation impact, partly due to multinational consortia like the Pancreatic Cancer Action Network (PanCAN). Recent Chinese output growth correlates with expanded partnerships with U.S. and European Union (EU) institutions since 2015.

China's significant output in recent years reflects its robust investment in biomedical research and its focus on addressing the high incidence of pancreatic cancer within its population. The United States, with its long-standing leadership in cancer research, has contributed foundational knowledge and innovative therapeutic strategies. These countries' leadership in funding, research infrastructure, and collaborative networks has been pivotal in fostering a rich body of knowledge.

The involvement of leading institutions such as Fudan University and Zhejiang University further emphasizes the role of academic excellence in driving scientific progress. Their contributions have not only expanded the understanding of the disease but also paved the way for translational research and clinical applications.

4.2 Evolving research focus

The shift in research focus from fundamental biology to immunotherapy and the tumor microenvironment is a notable trend identified in this analysis. The increasing prominence of keywords such as " tumor immunology," " immune checkpoint inhibitors," and " tumor microenvironment" reflects the field's progression towards more applied and translational research. This shift is crucial as it aligns with the broader goals of developing effective therapeutic strategies for pancreatic cancer.

The exploration of immunotherapy, including immune checkpoint inhibitors and cancer vaccines, reflects broader oncology trends toward immune-modulating strategies [15–17]. This bibliometric shift toward immunotherapy-related keywords (e.g., "immune checkpoint inhibitors", "PD-L1") directly correlates with landmark clinical trials such as KEYNOTE-158 demonstrating pembrolizumab efficacy in mismatch repair-deficient cancers [13]. However, the persistently low response rates (0–5%) to PD-1/PD-L1 monotherapy in pancreatic cancer [18] explain the concurrent emergence of "combination therapy" as a cluster analysis of keywords, mirroring clinical efforts to overcome resistance through chemo-immunotherapy regimens.

Combination strategies involving immune checkpoint inhibitors and other systemic therapies, such as chemotherapy, vaccines, and radiation, are being explored to overcome resistance to single-agent checkpoint blockade. Recent studies have demonstrated the potential of combining immune checkpoint inhibitors with chemotherapy to enhance treatment efficacy [4, 19]. The rationale for combining immune checkpoint inhibitors with chemotherapy is supported by evidence showing that chemotherapy can induce immunogenic cell death, thereby increasing the presentation of tumor antigens and enhancing the recruitment and activation of immune cells. This process can convert "cold" tumors, which are poorly infiltrated by immune cells, into "hot" tumors that are more likely to respond to immunotherapy [20, 21]. Additionally, certain chemotherapeutic agents have been shown to directly modulate the immune system by depleting regulatory T cells and myeloid-derived suppressor cells, further enhancing the antitumor immune response [22, 23]. Furthermore, targeting specific immune checkpoints like cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) in combination with other therapies has shown promise in enhancing anti-tumor immune responses. However, the efficacy of such strategies in pancreatic cancer remains unsatisfactory, necessitating further investigation into novel combination regimens and the development of new therapeutic targets [24, 25].

While immune checkpoint inhibitors have transformed the treatment landscape for several cancers, their application in pancreatic cancer remains challenging due to inherent resistance. Current research is actively exploring innovative combination strategies, particularly the integration of immune checkpoint inhibitors with chemotherapy, to enhance therapeutic efficacy by modulating the immunosuppressive tumor microenvironment. These efforts are focused on optimizing treatment protocols—including timing, dosing, and sequencing—to maximize clinical benefits while minimizing adverse

effects [22, 23, 26]. The future clinical utility of immune checkpoint inhibitors in pancreatic cancer will depend on successfully translating these multimodal approaches into standardized therapeutic frameworks that address both tumor biology and patient-specific factors [27, 28].

Recent translational work has linked this resistance to dense stromal barriers and immunosuppressive myeloid infiltration [14, 29], driving the keyword shift toward "tumor microenvironment" and "tumor stroma" in our analysis. Furthermore, the rising prominence of "tumor microenvironment" keywords aligns with recent clinical trials targeting stromal-immune interactions. For instance, the combination of CXCR4 inhibitors with PD-1 blockers (NCT04177810) and TGF-β pathway inhibitors with gemcitabine directly addresses the bibliometrically identified need to modulate both stromal and immune compartments [30–32]. These therapeutic innovations validate the observed keyword evolution from basic biology to multimodal clinical strategies. The understanding of the tumor microenvironment's role in immune evasion and tumor progression has opened new frontiers for therapeutic interventions, potentially enhancing the efficacy of existing treatments and offering novel targets for drug development [33, 34].

To overcome these barriers, antifibrotic therapies like halofuginone are used to disrupt stromal structures and improve drug delivery. Halofuginone reduces fibroblast activation and extracellular matrix components, enhancing drug distribution and modifying the immune environment in pancreatic ductal adenocarcinoma [35]. This approach not only boosts drug penetration but also enhances antitumor immunity by increasing the infiltration of immune cells like cytotoxic T cells and inflammatory macrophages into the tumor. Another promising approach targets signaling pathways that control stromal and immune cell interactions. Inhibiting TGFβ signaling can improve tumor perfusion and drug delivery, though tumors may adapt. Combining TGFβ inhibitors with chemotherapy, such as gemcitabine, can potentially suppress tumor growth by reprogramming T regulatory cells and activating CD8 T cells for anti-tumor effects [32].

Additionally, Studies on PK2 antagonists have shown that these agents can inhibit myeloid cell infiltration and angiogenesis, thus suppressing tumor growth in pancreatic cancer models [36]. This highlights the significance of targeting the immune components of the tumor microenvironment to improve treatment effectiveness. Moreover, the activation of pancreatic stellate cells (PSCs) plays a key role in creating a dense extracellular matrix and an immunosuppressive environment in pancreatic cancer. New nanodrugs that block PSC activation and regulatory T cell infiltration are promising for remodeling the tumor microenvironment, reducing the extracellular matrix, and boosting cytotoxic T cell infiltration, potentially enhancing immunotherapy outcomes in pancreatic cancer [37].

Finally, The TMBIM1-YBX1 axis and related gene pathways play a crucial role in creating an immunosuppressive tumor microenvironment. Targeting these pathways can decrease myeloid-derived suppressor cell (MDSC) infiltration and improve immunotherapy effectiveness, presenting new therapeutic options for pancreatic cancer [38]. These studies emphasize the complex stromal and immune interactions in pancreatic cancer and the potential to target these components to overcome treatment resistance, with promising clinical applications.

4.3 Impact of policy and funding

The impact of national policies and research funding on the expansion of this research field is profound. The noticeable rise in publication outputs from 2012 onwards coincides with increased policy support and funding initiatives, both domestically and internationally [39, 40]. In China, the National Natural Science Foundation of China (NSFC) has provided substantial funding for pancreatic cancer research, leading to a significant increase in high-quality publications. Similarly, in the United States, the National Institutes of Health (NIH) has prioritized pancreatic cancer research, driving innovation and collaboration. And U.S. leadership reflects sustained NIH funding for translational immunotherapy trials, exemplified by the prominence of PD-1/PD-L1 research in American cohorts. This correlation suggests that strategic investments in research infrastructure, training programs, and collaborative projects have significantly catalyzed scientific advancements.

Chinese institutions, including Fudan University and Shanghai Jiao Tong University, have developed specialized research centers for pancreatic cancer, supported by government funding. This support facilitates extensive genomic and clinical studies. In the United States, research centers such as Johns Hopkins and the MD Anderson Cancer Center utilize philanthropic contributions and federal grants to lead innovative trials in combination immunotherapy.

The sustained interest and high publication volumes in subsequent years, even amidst global challenges such as the COVID-19 pandemic, further demonstrate the resilience and commitment of the scientific community to this research area. The pandemic itself has heightened the focus on cancer immunology, potentially accelerating research efforts and innovations in this domain [41].

4.4 Future research directions

Looking ahead, the research on pancreatic cancer immune cells is poised to continue its dynamic and evolving nature. The ongoing monitoring of research trends will be essential for informing future studies and guiding the development of innovative therapeutic strategies. The identified research clusters and emerging keywords, such as "immune checkpoint inhibitors" and " tumor microenvironment" suggest that future research will likely delve deeper into the regulatory mechanisms of the tumor microenvironment and the optimization of immunotherapy strategies. The exploration of novel therapeutic targets and the integration of interdisciplinary approaches, including genomics [42], proteomics [43, 44], and nanotechnology [45], will be crucial for achieving breakthroughs in the treatment of pancreatic cancer [46]. For instance, single-cell sequencing technologies are expected to provide detailed insights into the heterogeneity of immune cells within the tumor microenvironment, enabling more precise therapeutic interventions. International collaboration and the sharing of resources and expertise will remain vital in accelerating the pace of discovery and translating research findings into clinical benefits [47, 48].

The role of artificial intelligence (AI) and big data in pancreatic cancer research is increasingly pivotal as these technologies offer transformative potential in addressing the challenges posed by this aggressive disease. AI and big data are being leveraged to enhance early detection, improve diagnostic accuracy, and personalize treatment strategies, thereby potentially improving patient outcomes.

AI technologies, including machine learning and deep learning, are revolutionizing pancreatic cancer research and clinical practice through multifaceted applications. By analyzing diverse datasets such as electronic health records (EHRs), medical imaging, and omics data, AI enables early detection by identifying subtle patterns and biomarkers imperceptible to human analysis. For example, AI-enhanced imaging algorithms have significantly improved the accuracy of detecting pancreatic lesions, supporting earlier diagnosis and optimized treatment planning [49, 50]. Beyond diagnostics, AI-driven predictive models integrate multimodal data to assess cancer risk, predict treatment responses, and monitor disease progression. These models address critical challenges in pancreatic cancer management, such as treatment resistance and recurrence, by enabling personalized therapeutic strategies tailored to individual patient profiles [51, 52]. Additionally, AI's capacity to process large-scale omics datasets accelerates the discovery of novel biomarkers and molecular subtypes of pancreatic cancer, advancing precision oncology efforts to develop targeted therapies and refine patient stratification [53, 54]. This comprehensive integration of AI with biomedical big data not only enhances clinical decision-making but also drives innovation in understanding the disease's molecular complexity, ultimately bridging the gap between research insights and improved patient outcomes.

While AI and big data show promise in pancreatic cancer research, key challenges persist: data quality limitations, model interpretability gaps, and the need for diverse datasets to ensure generalizability. Tackling these issues demands interdisciplinary collaboration to build reliable AI tools for clinical integration [55, 56]. In summary, AI and big data are revolutionizing pancreatic cancer care through earlier detection, precise diagnostics, and personalized therapies. Ongoing innovation could transform patient outcomes, but ethical, legal, and technical barriers must be addressed to maximize their impact [57, 58].

4.5 Limitations and critical analysis

Despite the significant progress, several limitations and challenges remain in the field of pancreatic cancer immune cell research. First, the heterogeneity of pancreatic cancer and its microenvironment poses a significant challenge for the development of effective immunotherapies [59, 60]. The complex interplay between various immune cell subsets and the tumor microenvironment requires a more nuanced understanding to develop personalized treatment strategies [61–63]. Second, the current immunotherapeutic approaches, such as immune checkpoint inhibitors [18], have shown limited efficacy in pancreatic cancer compared to other cancer types. This highlights the need for a deeper understanding of the mechanisms of immune resistance and the development of combination therapies to overcome these challenges. Third, the translation of preclinical findings into clinical success remains a major hurdle. Many promising therapeutic strategies in animal models have failed to demonstrate significant benefits in clinical trials, emphasizing the need for more robust preclinical models and better biomarkers to predict treatment response [64].

Additionally, while the Web of Science Core Collection (WOSCC) is a widely recognized database for bibliometric analysis, it has inherent limitations. First, the WOSCC primarily indexes English-language journals, which may exclude relevant studies published in other languages. This linguistic bias could skew the geographic representation

of research trends, as clinical insights from non-English studies—such as Chinese or Japanese-language research on regional treatment patterns—might be underrepresented in the database. Second, compared to multidisciplinary databases like Scopus or PubMed, WOSCC has less coverage of conference proceedings and preprints, potentially overlooking cutting-edge research. These limitations highlight the need for future studies to integrate multiple databases for more comprehensive analyses. In conclusion, although the Web of Science Core Collection offers comprehensive coverage of high-impact oncology literature, this study was limited to this database to ensure methodological consistency. Future research could enhance its scope by incorporating databases such as PubMed or Scopus, thereby capturing additional clinical trial reports and regional journals.

4.6 Contribution and value of this study

This bibliometric analysis provides valuable insights into the current status and future trends of pancreatic cancer immune cell research. By identifying key research countries, institutions, journals, authors, and keywords, this study offers a comprehensive overview of the global research landscape. The analysis of publication trends and research hotspots helps to inform future research directions and guide the allocation of research resources. Moreover, the identification of emerging keywords and research clusters provides a basis for the development of new research hypotheses and therapeutic strategies. This study emphasizes the importance of sustained investment in research, the fostering of international collaborations, and the continuous adaptation to emerging scientific opportunities. As the field continues to evolve, it holds the promise of transforming the therapeutic landscape for pancreatic cancer, ultimately improving patient survival rates and quality of life.

5 Conclusion

We conducted an in-depth analysis of the research literature in the field of pancreatic cancer immune cells. The research on pancreatic cancer immune cells exhibited exponential growth worldwide from 2000 to 2024. China and the United States made prominent contributions in this field, accounting for 78.55% of total publications, though U.S. studies demonstrated threefold higher citation impact. Specific academic journals like Frontiers in Immunology and Clinical Cancer Research served as pivotal platforms for knowledge dissemination, collectively publishing 18.8% of analyzed articles. The research outputs from institutions and authors reflected vibrant global collaboration patterns, with Fudan University (102 articles) and Zhejiang University (88 articles) emerging as leading Chinese contributors, while U.S. institutions like Johns Hopkins University (70 articles) and MD Anderson Cancer Center (66 articles) maintained long-term research continuity.

Keyword co-occurrence, clustering, and emergence analysis demonstrated a paradigm shift from early exploration of basic biological properties to in-depth investigation of immunotherapy and tumor microenvironment dynamics. The emergent keywords revealed three distinct evolutionary phases: (1) Initial characterization of antitumor activity, (2) Clinical translation of immune checkpoint inhibitors, and (3) Contemporary focus on stromal-immune crosstalk. Notably, tumor immune microenvironment, and combination therapy emerged as persistent research frontiers, aligning with

clinical trial data showing enhanced efficacy of chemo-immunotherapy regimens over monotherapies.

Future research should prioritize four key areas: (1) Deciphering spatial heterogeneity of immune-stromal interactions through single-cell omics and spatial transcriptomics, (2) Optimizing combination therapeutic sequences through AI-driven clinical trial simulations, (3) Developing stroma-modulating nanotherapeutics to enhance immune infiltration, and (4) Establishing standardized biomarkers for immunotherapy response prediction. This bibliometric mapping provides actionable insights for researchers, funding agencies, and policymakers to strategically allocate resources, foster cross-disciplinary collaboration, and accelerate the translation of mechanistic discoveries into clinical breakthroughs against this recalcitrant malignancy.

Acknowledgements
Thank Home for Researchers (www.home-for-researchers.com) for help. Drawing of pathway diagram was performed by Figdraw (www.figdraw.com), and we thank Figdraw for expert assistance in the pattern drawing.

Author contributions
Y.H.: original manuscript, project management, methodology, formal analysis, and conceptualization. S.L.: original manuscript, software, and data organization. Z.Z.: project management, formal analysis and data organization. K.W.: visualization and software. Z.J.: review and editing, validation, supervision, resources, project management, and concepts.

Funding
The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This research received funding from the National Natural Science Foundation of China (no. 52373294, 12226005).

Data availability
The data generated and analyzed during the current study are available from the Web of Science Core Collection database. The search strategy and criteria used to generate the dataset are detailed in the Methods section of this paper.

Declarations

Ethics approval and consent to participate
Review and/or approval by an ethics committee as well as informed consent was not required for this study because this article only used existing data from published studies and did not involve any direct experimentation/studies on living beings.

Consent for publication
All the authors have read and approved the final manuscript and agree with its submission to the Journal of Discover Oncology.

Competing interests
The authors declare no competing interests.

Received: 20 February 2025 / Accepted: 2 June 2025
Published online: 14 June 2025

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