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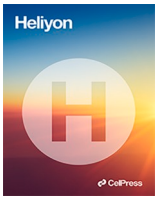

Research article

Knowledge domains and emerging trends in immune-related adverse events from immune checkpoint inhibitors: A bibliometrics and visualized analysis

Jun Zhao [a], Yujie Feng [b], Guang-wei Liu [c,*]

[a] Department of Pharmacy, The Affiliated Hospital of Qingdao University, Qingdao, Shandong, 266003, China
[b] Department of Hepatobiliary and Pancreatic Surgery, The Affiliated Hospital of Qingdao University, Qingdao, shandong, 266003, China
[c] Department of Gastrointestinal Surgery, The Affiliated Hospital of Qingdao University, Qingdao, shandong, 266003, China

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ABSTRACT

Objective: The primary objective of this paper is to investigate the research hotspots and future trends of immune-related adverse events induced by immune checkpoint inhibitors, offering valuable insights for researchers in this field.

Methodology: Using the visual analysis software, this study conducted quantitative statistics and visualization research on the relevant literature concerning immune-related adverse events caused by immune checkpoint inhibitors in the Web of Science Core Collection Database. By evaluating the publication trends, countries, institutions, keywords, research status, cited documents, and document co-citations, among several others, the discussion revolved around the hot spots and future development trends in this field and provided references for future research.

Findings and conclusions: A total of 514 English articles were included, and the top three countries in the research field at the time of this study were the United States, Japan, and China. More specifically, the University of Texas MD Anderson Cancer Center, Dana-Farber Cancer Institute, and Massachusetts General Hospital have been the top three research institutes with more than 10 publications. The frequency of keyword use linked to immune-related adverse events caused by immune checkpoint inhibitors in literature research has been steadily growing over the years. Additionally, the research with respect to the disease focuses on melanoma, cell lung cancer, hepatocellular carcinoma, and breast cancer. In the context of drugs, cancer-related research has mainly focused on the combined use of nivolumab, pembrolizumab, ipilimumab, and immune checkpoint inhibitors. Meanwhile, research on adverse events has delved into the immune checkpoint inhibitors causing vitiligo, thyroid dysfunction, pancreatitis, cholangitis, and rheumatism. Related studies cover acute arthritis, myositis, acute kidney injury, as well as the combination therapy of immune checkpoint inhibitors and docetaxel, management of irAEs in cancer immunotherapy, and biomarkers of immune adverse reactions of immune checkpoint inhibitors. Finally, case report studies of immune adverse reactions caused by immune checkpoint inhibitors could serve as research hotspots in the future.

* Corresponding author.
E-mail address: liuguangwei@qdu.edu.cn (G.-w. Liu).

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1. Introduction

Monoclonal antibodies, known as immune checkpoint inhibitors (ICIs), have proven to be highly effective in tumor treatment by facilitating the signaling cascade of T cell function, resulting in immune activation and tumor tissue damage. While researchers continue to study new immune checkpoint inhibitors, the most mature inhibitors are cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) inhibitors, programmed cell death receptor-1 (PD-1) inhibitors, and programmed cell death ligand-1 (PD-L1) inhibitors. In clinical practice, immune checkpoint inhibitors are currently used for the treatment of various types of malignancies. The efficacy of these drugs, whether used alone or in combination with other anticancer treatments, has revolutionized previous methods and is now the cornerstone of advanced malignancy treatment [1]. With the increasing number of clinical trials proving the significant responses and outcomes of ICIs over monotherapy in cancer immunotherapy [2], the use of ICI combination therapy has also gained recognition and is being gradually applied in clinical settings. The prevalence of immune-related adverse events (irAEs) is rising as the use of these drugs increases [3]. Additionally, immune-related toxicity occurs more frequently and to a greater extent with combination therapy than with either ICI alone [4]. As a result, the safety and management of related adverse reactions of ICI monotherapy and combination therapy have also garnered considerable attention. Owing to the promising efficacy of immune checkpoint inhibitors and the non-negligible incidence of adverse events, multiple investigations are underway to determine the specific patient population that will benefit the most from this approach [5]. As of now, a number of summarized analyses on ICI-induced irAEs have been integrated into published relevant studies, highlighting the considerable attention paid by researchers to the research progress and direction of ICI-induced irAEs. Despite this, the traditional approach to literature search and review is inherently content-driven, resulting in a biased extraction of representative papers from the existing literature. Bibliometrics based on big data and statistical analysis avoids this subjective bias to a certain extent, and the results presented through visualization are more objective and credible. Therefore, this paper used bibliometric analysis and visual processing methods to evaluate the research trends quantitatively and qualitatively in the field of ICI-induced irAEs. It also sought to objectively reveal the research hotspots and development trends in this field, as well as provide literature data support and reference for formulating research strategies and directions.

2. Methodology

2.1. Data source

Screen the literature on ICI-induced immune-related adverse events in the Web of Science (WoS) core collection database, and the search strategy involved keywords (TS=("PD-1″ OR″PD-L1″OR″CTLA-4″OR″Immune checkpoint inhibitors")) AND TS=("immune related adverse event"). The timeline was set from the establishment of the database to 2022-12-31, where a total of 544 articles were retrieved. The papers and review papers were reserved, and the main language was set to English. Ultimately, 514 articles were included in the study. Then, the documents were selected as full records and cited as references before exporting them in.txt format.

2.2. Data processing

The research used CiteSpace 5.8.R3, setting parameters as time slicing (time slicing): January 2008 to December 2022 (research in this field was initially published in 2008). Then, time slicing was set to 1 year; node types (node types): author, institution, keywords. The node was the author: threshold (top N per slice) = 25, pruning (pruning) = None. Next, the node was the institution: threshold (top N per slice) = 25, pruning (pruning) = None. Afterward, the node was the keyword: threshold (top N per slice) = 25, pruning = pathfinder + pruning the merged network. Based on the parameter settings of every node, visual analysis was performed to generate knowledge maps of institutions, countries, and cooperations in the research field of ICI-induced immune-related adverse events. These were knowledge maps of co-occurrence, emergence, and clustering of keywords, and timeline graphs of keywords.

Documents retrieved from the WOS database were recorded using "full records and cited references" and then exported in plain text format. Subsequently, the data were imported into the VOSviewer software, the calculation method was configured to full calculation,

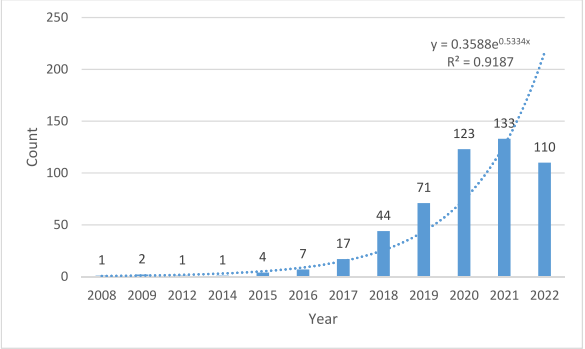


Fig. 1. The number of publications in this field from 2008 to 2022.

and the corresponding threshold was adjusted based on different analysis items. We also drew visual graphs and conducted collaborative network analysis.

3. Results

3.1. Posting trends

In 2008, the first publication on immune-related adverse events of immune checkpoint inhibitors was released. The USA -based Scientist Phan, GQ published CTLA-4 Blockade with Monoclonal Antibodies in Patients with Metastatic Cancer in the journal "Annals of Surgical Oncology": Surgical Issues [6] article had several findings, It revealed that CTLA-4 blockade could lead to sustained tumor regression in patients with metastatic melanoma and other solid tumors. Nevertheless, Grade III/IV autoimmune toxicities, including enterocolitis, dermatitis, hypophysitis, uveitis, and hepatitis, are frequently observed. Among them, enterocolitis was identified as the most common immune-related adverse event, which can result in severe diarrhea. The treatment policy for such patients was also provided, specifically intravenous hydration, high-dose corticosteroids, and infliximab blocking tumor necrosis factor α. Scholars in the US have started to focus on the immune-related adverse reactions of this particular drug since 2008. Fig. 1 demonstrates that the yearly publication output varies and increases over time. After 2020, the annual publication volume was expected to exceed 100 and reach a maximum of 133 in 2021. Despite a slight decline in 2022, it is predicted that the number of publications will persist or rise due to the advancement of research in the field.

3.2. Analysis of national or regional cooperation network

The geographical distribution and cooperation network of countries or regions in the literature included in the study were analyzed (Figs. 2 and 3). The figure clearly shows that the US has the highest number of published research in this field (161 articles), followed by Japan (147), China (62), France (32), and Italy (26). The countries or regions with the most published papers are ranked in Table 1, with the top 10 being highlighted. The US, Japan, and China significantly influence this field. The US was the first to initiate the research. Based on the national cooperation network, the US has a relatively close cooperative relationship with other nations, playing a vital role in this field. In terms of centrality, research holds great significance in Japan, the US, and France, as evidenced by the significant number of impactful research findings published by their researchers in this area. Although Japan started late, its research has the highest importance. China has demonstrated a notable surge in research activity in recent years, despite its delayed entry into this field. Nonetheless, there is still room for enhancing the quality of its research.

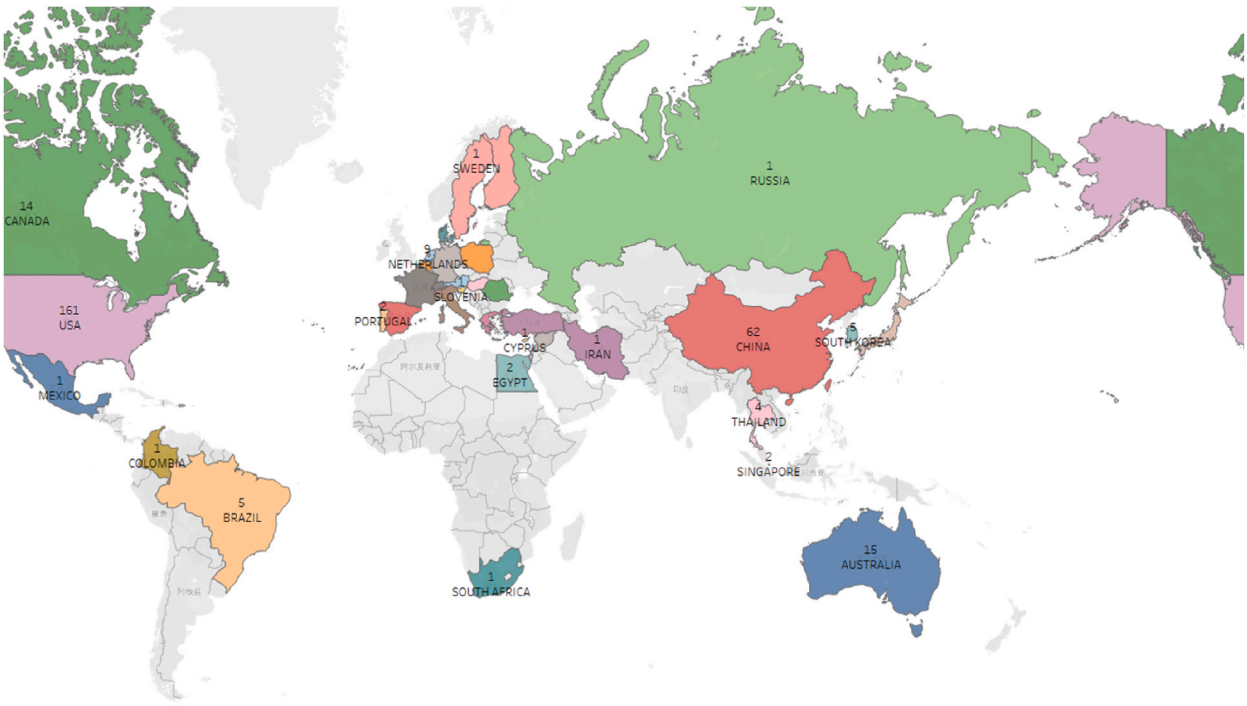


Fig. 2. Geographic distribution of research countries or regions.

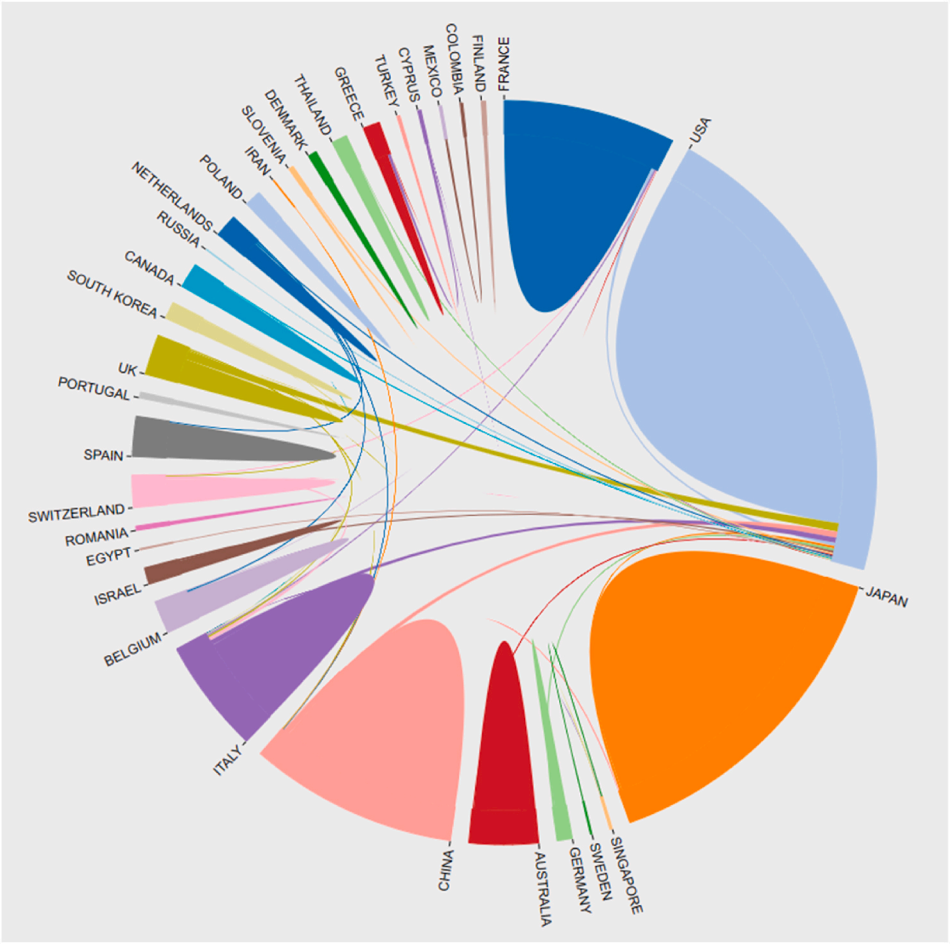


Fig. 3. The relationship diagram of cooperation network among research countries or regions.

Table 1
The top 10 countries or regions in the field of study.

Rank	Country	Count	Percentage	Centrality	Year
1	USA	161	31.323	0.57	2008
2	JAPAN	147	28.599	0.74	2017
3	PEOPLES R CHINA	62	12.062	0.03	2017
4	FRANCE	32	6.226	0.34	2009
5	ITALY	26	5.058	0.30	2009
6	ENGLAND	18	3.502	0.22	2009
7	AUSTRALIA	15	2.918	0.16	2015
8	CANADA	14	2.724	0.10	2009
9	BELGIUM	13	2.529	0.11	2017
10	SPAIN	13	2.529	0.04	2016

3.3. Institutional cooperation network

Citespace was employed to analyze the publishing institutions in the literature included in the study to generate Fig. 4. There were 229 nodes and 443 connections on the map, and the network density was 0.017. Moreover, the research involved a total of 229 institutions. Table 2 details the top 10 institutions in terms of the number of publications. The results exhibit that the University of Texas MD Anderson Cancer Center is the research institution with the largest number of publications (14 frequencies), followed by Dana Farber Cancer Institute (11 frequencies) and Massachusetts General Hospital (10 frequencies). The publishing institutions are primarily cancer research centers, medical schools, and comprehensive universities, among several others. There are certain cooperative relationships among institutions, which may be attributed to the fact that most research institutions are American, making cooperation more convenient. Centrality served as an index to evaluate the position and importance of network nodes in the network, and its value

Fig. 4. Network diagram of research institutions.

Table 2
Top ten institutions in the field of research.

Rank	Institution	Country	Count	Centrality	Year
1	Univ Texas MD Anderson Canc Ctr	USA	14	0.09	2016
2	Dana Farber Canc Inst	USA	11	0.12	2016
3	Massachusetts Gen Hosp	USA	10	0.07	2016
4	Brigham & Womens Hosp	USA	9	0.01	2016
5	Mayo Clin	USA	9	0.02	2016
6	Univ Washington	USA	9	0.02	2009
7	Johns Hopkins Univ	USA	8	0.02	2016
8	H Lee Moffitt Canc Ctr & Res Inst	USA	8	0.07	2008
9	CEA	USA	7	0.01	2017
10	Harvard Med Sch	USA	7	0.05	2020

being $\geq$0.1 indicated its important role in the evolution of the field. This reflects the hot direction of the research [7]. It can be seen from the centrality that the research of Dana Farber Cancer Institute occupies a relatively important position in this field.

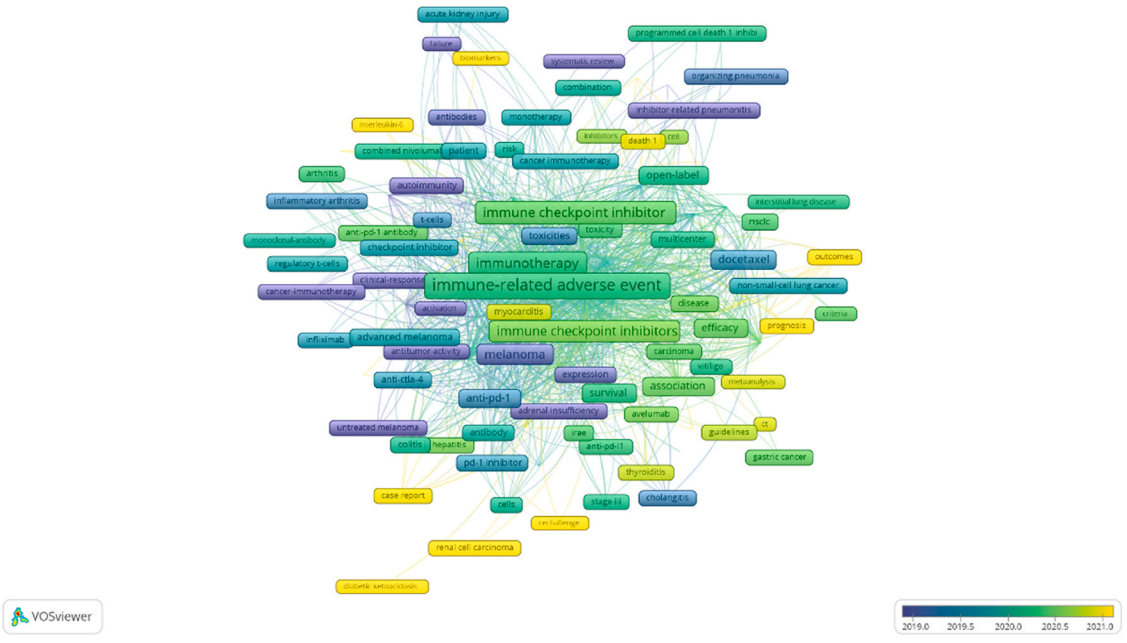
3.4. Keyword network analysis

3.4.1. Keyword co-occurrence network

Keywords serve as a concise overview of the theme of the paper. Co-occurrence analysis refers to a co-occurrence map comprised of nodes and links formed by tailoring keywords as nodes. VOSviewer was utilized for visual analysis, generating keyword co-occurrence network diagrams and overlay visualization diagrams. Among the 1549 keywords in the co-occurrence network (Fig. 5A), a total of 136 were screened and divided into 7 clusters, with a screening threshold of 5 minimum occurrences. Cluster 1 (38 items, red) was ICI-induced immune adverse events and research on risk management. Then, Cluster 2 (31 items, green) covered research on ICI-related immune system diseases like arthritis, myositis, and rheumatoid arthritis. Cluster 3 (27 items, blue) was ICI-induced hypothyroidism, thyroiditis. Cluster 4 (23 items, yellow) focused on related research about ICI multi-center trials and meta-analysis. Following this, Cluster 5 (9 items, purple) was devoted to related literature on the biomarkers of immune-related adverse events caused by ICI. Cluster 6 (7 items, light blue) encompassed research on ICI-induced acute interstitial nephritis and acute kidney injury, and Cluster 7 (1 item, orange) delved into research on ICI-induced cholangitis.

The keyword overlay visualization (Fig. 5B) incorporated the time factor, and different colors corresponded to the year when the keyword appeared, and the greener the color, the earlier the keyword appeared. The redder the keyword, the later it appeared. Based on keyword frequency, there is a notable emphasis in this field on studying immune-related adverse events caused by nivolumab,

A Keyword co-occurrence network diagram



B Keyword Time Overlay Visualization

Fig. 5. A Keyword co-occurrence network diagram, B Keyword Time Overlay Visualization.

followed by ipilimumab and pembrolizumab. Additionally, the treatment, safety, and management of immune-related adverse events caused by ICI are also research hotspots. Table 3 itemizes the top 20 keywords in terms of frequency.

The Carrot2 software was employed to cluster and analyze the keywords in this field to generate a tree map accordingly (Fig. 6). The results highlighted that pembrolizumab has been extensively studied for immune-induced adverse events, serious immune-related adverse events, and as an initial ICI treatment. This is a research hotspot in the field. For prognostic studies that researchers attach great importance to, our study found a total of 9 studies using overall survival (OS) as the keyword for prognosis research. Fig. 7 illustrates the keyword cloud map in this field. As shown by the word cloud map, the high-frequency terms in the field were pembrolizumab, nivolumab, ipilimumab, adverse events, immunotherapy, melanoma, cancer, and docetaxel.

3.4.2. Keyword emergence network

Keyword emergence refers to a notable rise in the frequency of keywords over a brief period. Being knowledgeable about ongoing research can aid in determining the most relevant and cutting-edge areas of study [8]. Fig. 8 displays the keyword emergence analysis of ICI-induced immune-related adverse events research literature. Parameters $\gamma[0,1] = 0.8$ and minimum duration $= 1$ were set, and 12 emergent words were obtained in total. The evidence suggests that the research in this particular field began in 2008, and a growing number of related studies surfaced in 2016. In terms of diseases, the research mainly focuses on melanoma and cell lung cancer. The primary focus of drug research centered on anti-CTLA-4 monoclonal antibodies and anti-PD-1 monoclonal antibodies. Moreover, the emphasis of the study was on adverse events caused by ICI and their relation to vitiligo. The research hotspots in the past five years were predominantly combined therapy with ICI and docetaxel, cancer immunotherapy, ICI-induced vitiligo adverse reactions, ICI immune adverse reaction biomarkers, and ICI-induced immune adverse reactions case report research.

3.4.3. Keyword timeline

The feature "timeline" was selected to draw a timeline map of document clustering, the visual analysis of the time span, and the association of clustering (Fig. 9). Evidently, clusters #1, #3, #4, #7, and #11 all stopped evolving, while clusters #0 (anti-pd-1), #2 (hyperthyroidism), #5 (pancreatitis), as well as the research fields represented by #6 (immune checkpoint inhibitors), #8 (hepatocellular carcinoma), #9 (cancer immunotherapy), #10 (breast cancer), and #12 (cytokines) have a relatively long time span and have continued to this day. These areas have proven to be enduring focal points of research within the discipline.

3.5. Leading journals

Table 4 lists the top 10 journals in this study. A total of 150 papers were published, accounting for 29.18% of the total literature volume. Most of the JCR journals were Q1 and Q2 journals. With 26 articles (5.06%), the "JOURNAL FOR IMMUNOTHERAPY OF CANCER" has the most publications focused on research related to tumor immunotherapy.

3.6. Top 10 cited documents and documents co-cited

3.6.1. Top 10 cited documents

The total number of citations of 514 documents in this field was 9421, the average number of citations per item was 18.33, and the h-index was 46. Table 5 shows the top 10 most cited documents. More specifically, the most cited document (430 times) is the article entitled "A Randomized, Double-Blind, Placebo-Controlled, Phase II Study Comparing the Tolerability and Efficacy of Ipilimumab Administered with or without Prophylactic Budesonide in Patients with Unresectable Stage III or IV Melanoma" [9]. The study acknowledges diarrhea as an irAE that may be caused by ipilimumab, regardless of whether it presents with colitis. With hopeful survival rates and acceptable side effects, ipilimumab exhibits action in advanced melanoma. Grade $>$ or $=$ 2 diarrhea brought on by ipilimumab therapy should not be treated with budesonide as a preventative measure.

Table 3
Top 20 keywords in terms of frequency.

Serial number	Frequency	Centrality	Year	Keywords	Serial number	Frequency	Centrality	Year	Key words
1	215	0.01	2015	nivolumab	11	52	0.02	2014	therapy
2	208	0.03	2015	immune-related adverse event	12	47	0.05	2016	checkpoint inhibitor
3	184	0.02	2015	immune checkpoint inhibitor	13	43	0.03	2015	safety
4	139	0.03	2009	ipilimumab	14	43	0.03	2017	open label
5	132	0.07	2015	immunotherapy	15	43	0.04	2018	management
6	117	0.03	2015	pembrolizumab	16	42	0.10	2009	blockade
7	99	0.12	2012	adverse event	17	41	0.05	2016	toxicity
8	74	0.03	2008	melanoma	18	41	0.03	2017	association
9	65	0.08	2009	cancer	19	38	0.04	2018	efficacy
10	54	0.02	2017	docetaxel	20	38	0.03	2016	chemotherapy

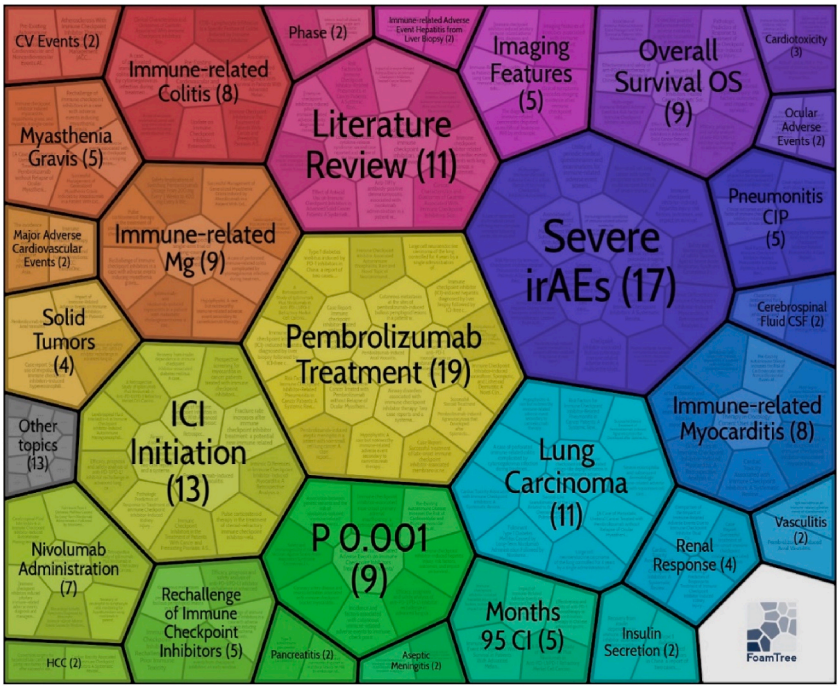


Fig. 6. Keyword treemap in the field.

Fig. 7. Cloud map of keywords in this field.

3.6.2. *Document co-citation network*

VOSviewer was used to analyze a total of 9361 co-cited documents, extract data from documents with at least 20 citations, obtain 70 co-cited documents, and generate documents. In the citation network, the cited documents were divided into 4 clusters according to the color blocks. Table 6 displays the top 10 documents with the most cited frequencies. The highest number of co-cited documents were published in high-level journals, and 6 were published in "New England Journal of Medicine," with an impact factor of 176.079. Fig. 10 depicts the co-cited network diagram of documents. The co-cited documents were divided into 4 clusters. Cluster 1 (25 items, red) was comprehensive high-level medical journal research, and Cluster 2 (15 items, green) covered research on journals related to endocrinology. Then, Cluster 3 (15 items, blue) delved into journals associated with the field of tumors, and Cluster 4 (15 items, yellow) focused on journals linked to diabetes.

3.6.3. *Sankey diagram*

Fig. 11 shows the relationship between cited references (left), authors (middle), and keywords (right). The area of the rectangle was proportional to the number of publications. Based on the figure, the data flow among references, authors, and keywords in the field, as well as the relationship between them, can be observed intuitively.

Top 12 Keywords with the Strongest Citation Bursts

Keywords	Year	Strength	Begin	End	2008 - 2022
lymphocyte associated antigen 4	2008	3.22	**2008**	2016	
melanoma	2008	3.1	**2008**	2017	
autoimmunity	2008	2.89	**2008**	2015	
metastatic melanoma	2008	4.89	**2009**	2017	
untreated melanoma	2008	3.81	**2016**	2017	
cell lung cancer	2008	2.62	**2016**	2017	
anti-pd-1	2008	2.4	**2016**	2017	
docetaxel	2008	5.1	**2017**	2019	
cancer immunotherapy	2008	3.22	**2018**	2018	
vitiligo	2008	2.26	**2020**	2020	
biomarker	2008	2.89	**2021**	2022	
case report	2008	2.67	**2021**	2022	

Fig. 8. Keyword emergence map.

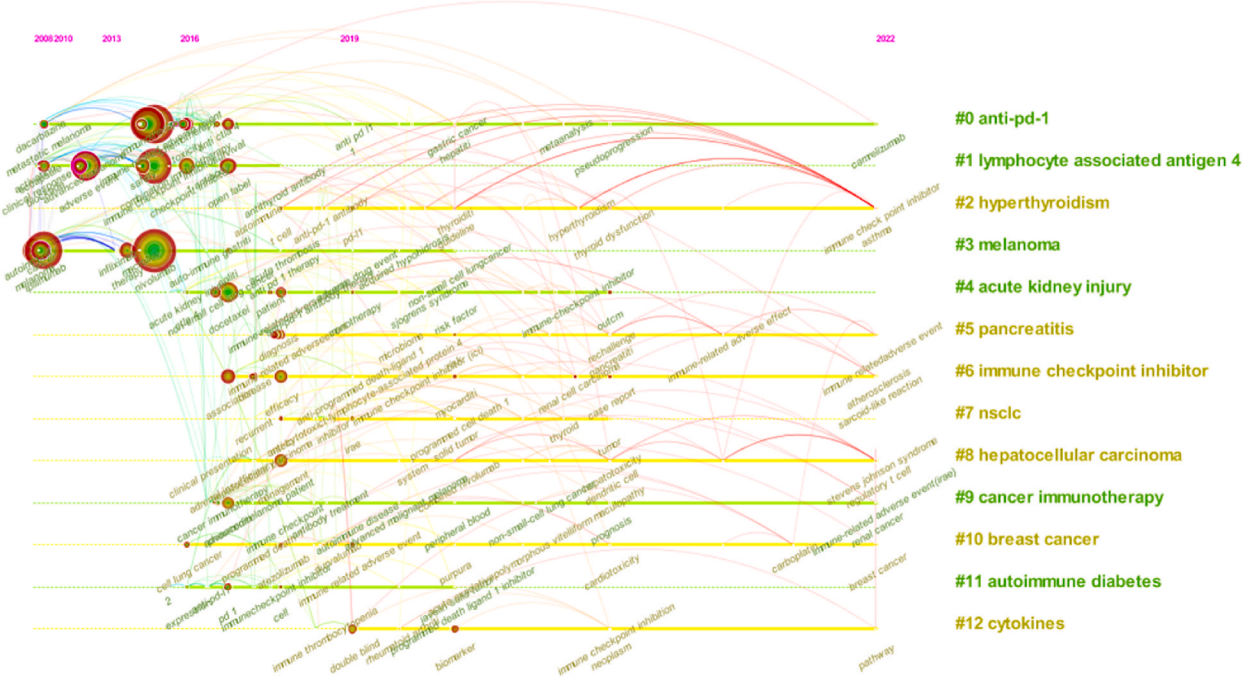


Fig. 9. Keyword timeline diagram.

3.7. Double image overlay

Dual-map overlays are designed to reveal overall scientific contributions and linkages [28] while also displaying interactions between journals. Publications and citations in this field can be described at the discipline level. It is worth noting that citation bimaps were constructed using CiteSpace's bimap overlay function. The left half is the citing document, the right half is the cited document, the curve is the citation relationship line, and the citing document is primarily influenced by the cited document. This connection illustrates the knowledge flow and connections across various research disciplines (Fig. 12). Ranked by their Z-scores, the most commonly covered record domains are Molecular Biology, Genetics, Health, Nursing, and Medicine. The research was influenced by these fields.

Table 4
Top 10 leading journals in the field of research.

Journal of publication	Count	Percentage	IF (2022)	JCR
JOURNAL FOR IMMUNOTHERAPY OF CANCER	26	5.06%	12.469	Q1
FRONTIERS IN ONCOLOGY	19	3.70%	5.738	Q2
FRONTIERS IN IMMUNOLOGY	17	3.31%	8.786	Q1
CANCERS	16	3.11%	6.575	Q1
INTERNAL MEDICINE	14	2.72%	1.282	Q4
JOURNAL OF ONCOLOGY PHARMACY PRACTICE	13	2.53%	1.416	Q4
IMMUNOTHERAPY	12	2.34%	4.04	Q3
THORACIC CANCER	12	2.34%	3.223	Q3
JOURNAL OF IMMUNOTHERAPY	11	2.14%	4.912	Q2
CANCER IMMUNOLOGY IMMUNOTHERAPY	10	1.95%	6.63	Q1

4. Discussion

In recent years, ICIs have been demonstrated to be effective against various solid organ malignancies and have become the mainstay of treatment for advanced malignancies. While these monoclonal antibodies activate cytotoxic T cells to destroy cancer cells, they may result in immune intolerance and irAEs. Equally important, severe irAEs may lead to treatment failure in cancer patients. In order to effectively address this issue, clinicians must possess a comprehensive understanding of the incidence of irAEs, risk factors, biomarkers, and personalized treatment and monitoring strategies to take the necessary steps to protect patients from irAEs and continue to benefit from ICIs or to restart ICIs after irAEs. In this paper, the research hotspots of ICI-induced irAEs were examined and discussed through bibliometric methods and visual analysis charts, serving as a valuable resource for researchers and clinicians in this domain.

4.1. Research status and future development

Between 2008 and 2022, a total of 229 institutions published 514 articles pertaining to this particular field, and the annual publication volume showed a fluctuating growth trend. Since 2020, over 100 articles have been published annually as research in this area continues to progress. By 2021, the maximum number was anticipated to be 133. The CTLA-4 blocker is the first drug in this class to be assessed for irAEs. Phan, GQ, an American scholar, was the first to shed light on the immune-related adverse reactions of CTLA-4 blockers in 2008, drawing attention to the potential risks associated with these drugs. The US has published the most research in this field and is a prominent collaborator with other countries, as evidenced by the number of published papers and collaborative networks. Although Japan is a late starter, the number of published papers is second only to the US, and the importance of research is the highest. From the viewpoint of the issuing institution, the Dana-Farber Cancer Institute's research occupies a more prominent position in this field. It is a specialized oncology research organization located in Boston, Massachusetts, United States. Ever since its establishment in 1947, the Institute has remained dedicated to offering the most advanced treatments for both adults and children, while also pioneering future treatments through innovative research.

This study demonstrated that the treatment of irAEs induced by ICIs in melanoma, cellular lung cancer, hepatocellular carcinoma, and breast cancer has garnered considerable attention from scholars in the field of disease management. The focus of the drug study was on the combination of pembrolizumab, nivolumab, ipilimumab, and docetaxel. Additionally, the investigators were interested in the hot areas of irAEs, including vitiligo, thyroid dysfunction, pancreatitis, cholangitis, arthritis, myositis, and acute kidney injury, among several others. The focus of clinicians should be on these irAEs, and any alterations in relevant indicators during clinical medication should be promptly investigated to determine the cause and identify ICIs-related irAEs.

Furthermore, the treatment, safety, and management of irAEs caused by ICIs are also research hotspots in the field. At present, the harm of irAEs to patients may be minimized with the wide application of tumor immunotherapy in clinical practice, immunotherapy interruption caused by irAEs occurs from time to time, and if the risk of irAEs can be predicted and managed promptly. Scholars have focused on the management of irAEs, which will continue to become a research hotspot in this field in the future. In any case, the management of irAEs is built upon five fundamental pillars: prevention, assessment, detection, treatment, and monitoring. At the forefront of irAEs research currently are the management of irAEs, recording patterns, and pre-screening of patients who are scheduled to receive ICIs. As research on irAEs and their treatment in ICIs nears completion, the inclusion of real-world studies has added significant clinical value to the development of improved biomarkers for predicting irAEs [29]. It is also crucial to further explore monitoring indicators, tools, and scales to provide standardized guidance for the prevention and treatment of clinical irAEs. In this field, scholars and clinicians are actively pursuing this direction.

The safety and efficacy of rechallenging ICIs after irAEs in cancer patients [30] is currently lacking substantial evidence [30]. Specifically, there is a dearth of information on the safety of ICI reuse after irAEs [17], leading to a potential gap in knowledge in this field. In the future, scholars can fortify basic and clinical research concerning the safety and efficacy of ICIs after restarting irAEs. With the gradual increase in clinical trial data, it is anticipated that more substantial clinical evidence will become available to direct clinical practice. Simultaneously, this study found that case reports are also a research hotspot in this field, suggesting that clinicians should actively report clinical cases associated with irAEs and prioritize real-world studies to collect additional clinical data. Case reports from large international pharmacovigilance databases can also be retrieved to provide some experience and clues for the safe and effective

Table 5
Statistics of the top ten cited documents.

Rank	Title	First author	Publication Year	Total Citations	Average per Year
1 [9]	A Randomized, Double-Blind, Placebo-Controlled, Phase II Study Comparing the Tolerability and Efficacy of Ipilimumab Administered with or without Prophylactic Budesonide in Patients with Unresectable Stage III or IV Melanoma	Weber, Jeffrey	2009	430	28.67
2 [10]	Immune-related adverse events and anti-tumor efficacy of immune checkpoint inhibitors	Das, Satya	2019	378	75.6
3 [11]	Durvalumab as third-line or later treatment for advanced non-small-cell lung cancer (ATLANTIC): an open-label, single-arm, phase 2 study	Garassino, Marina Chiara	2018	349	58.17
4 [12]	Clinicopathological features of acute kidney injury associated with immune checkpoint inhibitors	Cortazar FB	2016	333	41.63
5 [13]	Early Immune-Related Adverse Events and Association with Outcome in Advanced Non-Small Cell Lung Cancer Patients Treated with Nivolumab: A Prospective Cohort Study	Teraoka, Shunsuke	2017	254	36.29
6 [14]	Efficacy and Safety of Avelumab for Patients With Recurrent or Refractory Ovarian Cancer Phase 1b Results From the JAVELIN Solid Tumor Trial	Disis, Mary L	2019	216	43.2
7 [15]	Safety of Programmed Death-1 Pathway Inhibitors Among Patients With Non-Small-Cell Lung Cancer and Preexisting Autoimmune Disorders	Leonardi, Giulia C	2018	193	32.17
8 [16]	Safety and Efficacy of Re-treating with Immunotherapy after Immune-Related Adverse Events in Patients with NSCLC	Santini, Fernando C	2018	181	30.17
9 [17]	Immune Checkpoint Inhibitor Rechallenge After Immune-Related Adverse Events in Patients With Cancer	Dolladille C	2020	176	44
10 [18]	Evaluation of Readministration of Immune Checkpoint Inhibitors After Immune-Related Adverse Events in Patients With Cancer	Simonaggio, Audrey	2019	173	34.6

Table 6
Top 10 co-cited references.

Rank	Title	First Author	Year	Journal	IF (2022)	Citations
1 [19]	Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline	Brahmer Jr	2018	J Clin oncol	50.717	139
2 [20]	Immune-Related Adverse Events Associated with Immune Checkpoint Blockade	Postow Ma	2018	New engl j med	176.079	121
3 [21]	Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer	Borghaei H	2015	New engl j med	176.079	88
4 [4]	Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma	Valsecchi Me	2015	New engl j med	176.079	87
5 [22]	Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up	Haanen Jbag	2017	Ann oncol	51.769	85
6 [23]	Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer	Brahmer J	2015	New engl j med	176.079	83
7 [24]	Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer	Reck M	2016	New engl j med	176.079	72
8 [25]	Improved survival with ipilimumab in patients with metastatic melanoma	Hodi FS	2010	New engl j med	176.079	70
9 [26]	Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group	Puzanov I	2017	J immunother cancer	12.469	62
10 [27]	Immune-related adverse events with immune checkpoint blockade: a comprehensive review	Michot Jm	2016	Eur j cancer	10.002	60

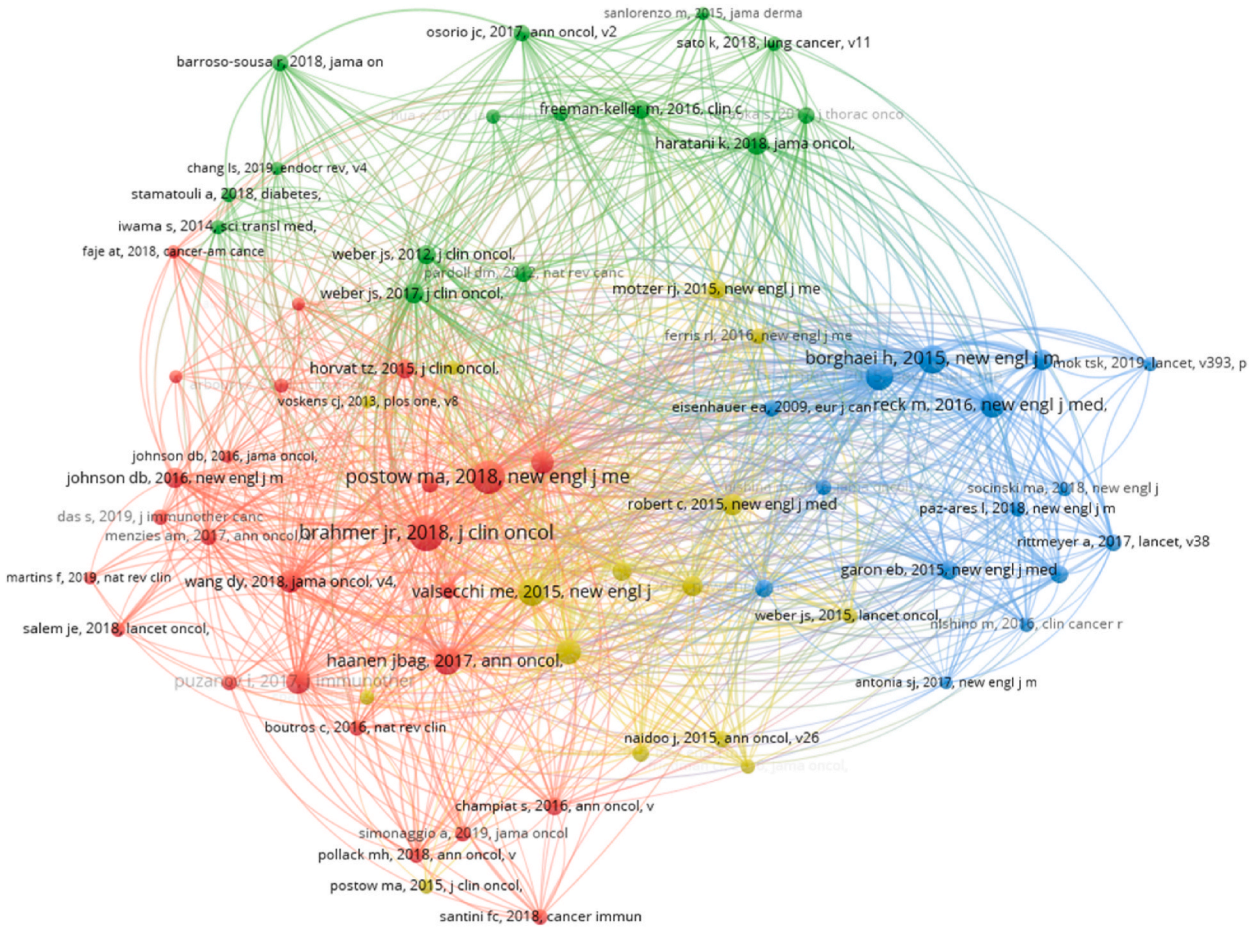


Fig. 10. Document co-citation network diagram.

clinical use of ICIs, particularly the reuse of ICIs after irAEs.

4.2. Hotspot irAEs

Skin and its appendages are frequently affected by irAEs during ICI treatment, with vitiligo-like lesions being a prominent skin manifestation and a major focus of research in the last five years. Moreover, ICI-induced vitiligo occurs predominantly in melanoma patients, with an incidence of up to 25%, which is higher than the normal prevalence of vitiligo [31]. The development of ICI-induced melanoma-associated vitiligo has been reported to be a good clinical marker of treatment response and overall survival [32]. Hence, after the occurrence of vitiligo, ICI treatment can be extended. IrAEs have become a widely discussed topic among scholars due to their correlation with improved prognosis. The findings of this study underlined that the occurrence of an irAE was associated with an improved prognosis, which was thyroid dysfunction due to ICIs. At present, the key research keywords in this field are the clinical features, treatment, and prognosis of thyroid dysfunction caused by ICIs. Thyroid irAEs are frequently observed during anti-PD-1 and anti-PD-L1 antibody therapy and the incidence of combination therapy increases compared with monotherapy. According to previous studies, most patients who undergo ICI treatment experience destructive thyroiditis or hypothyroidism, which can be attributed to the infiltration of inflammatory cells, primarily lymphocytes, into the thyroid gland [33]. ICIs can also cause hyperthyroidism (Graves' disease), although this occurrence is uncommon. Despite its rarity, this study suggests that ICI-induced hyperthyroidism has been a long-standing research hotspot in this field. Existing literature reports that thyroid irAEs are associated with better cancer outcomes, better survival, and better prognosis [34,35]. The mechanism of irAE and cancer prognosis improvement has also become a hot topic among scholars.

ICI-induced immunoassociated pancreatitis is currently a major area of focus in this field, which is a relatively uncommon irAE but has a high likelihood of being severe ($\geq$ grade 3) [36] and potentially fatal [37]. It is characterized by serum amylase or lipase values greater than 3 times the upper limit of the normal value [38]. Since patients with isolated pancreatic enzyme elevations do not require treatment, regular monitoring is not currently practiced. However, those with pancreatitis symptoms should be evaluated for lipase and amylase levels. Additionally, irAE is uncommon but can cause grave consequences, making it a subject of interest for researchers

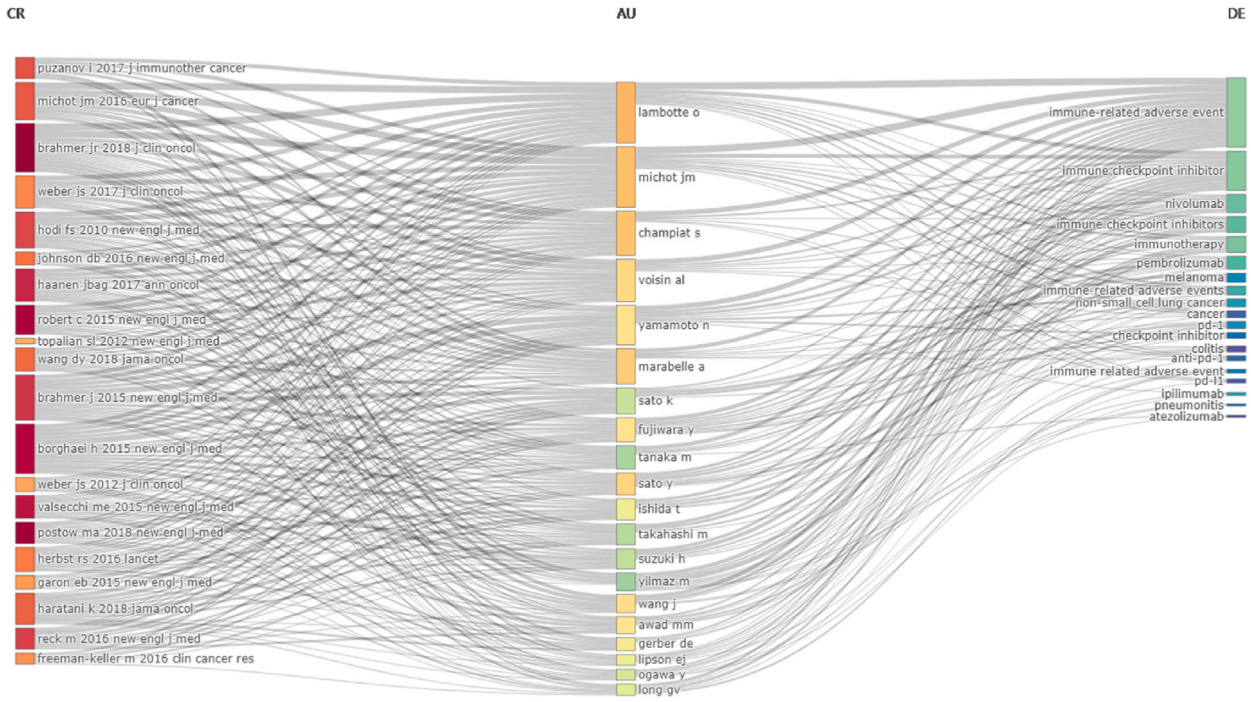


Fig. 11. Sankey diagram.

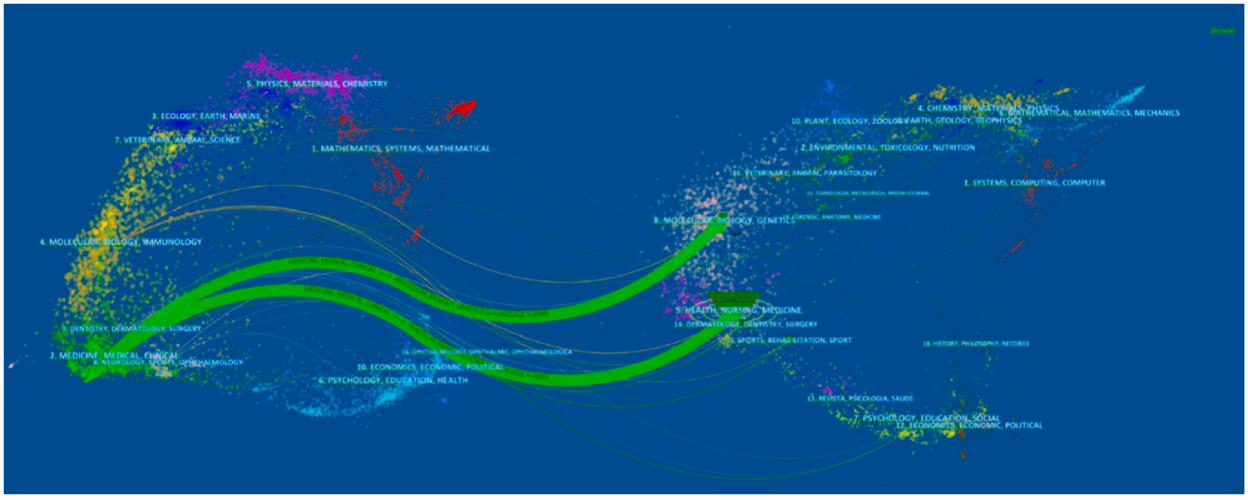


Fig. 12. The function constructs a double graph of citations.

and medical professionals. The rheumatoid immune system is prone to adverse reactions to ICI immunotherapy. Arthritis is the most prevalent type of rheumatic irAE, with approximately 5% of patients undergoing ICI treatment [39]. ICI-associated arthritis can severely impair a patient's quality of life, lead to the discontinuation of ICI treatment, and cause bone destruction due to its inflammatory nature [40]. This type of irAE is a chronic course that necessitates months or even years of long-term immunosuppressive therapy [41].

Inflammatory myopathy is another rheumatic immune system adverse reaction to ICI immunotherapy, and ICI-associated myositis is a rare and potentially fatal disease, particularly when accompanied by myasthenia gravis and myocarditis. Early intervention is crucial in ICI-associated myositis, highlighting the significance of identification. It is imperative to regularly monitor a patient's creatine kinase levels and inquire about any symptoms related to muscle pain, weakness, vision, breathing, or swallowing problems. The incidence of acute kidney injury (AKI) caused by ICIs is on the rise. Acute interstitial nephritis [42] is the leading reported pathology associated with ICI-related AKI, as per existing literature. The incidence of ICI-associated AKI may be underreported due to the

multifaceted and non-specific nature of kidney damage in tumor patients. Therefore, more stringent criteria for disease evaluation and diagnosis must be established [43]. The onset of acute kidney injury (AKI) can range from weeks to months after initial use of ICIs, or even after discontinuation of the drug. As a result, this type of irAE has garnered heightened interest within the field.

4.3. Biomarkers

The utilization of biomarkers in studies can aid in the assessment of ICIs' efficacy and prediction of irAEs, ultimately improving patient outcomes. Previous studies have indicated a lack of prognostic and predictive biomarkers for response to ICIs in current clinical practice [44]. While several potential biomarkers are being assessed, the selection of patients who may benefit from immunotherapy and the effective markers to guide treatment strategies are still far from validated. However, with the increasing incidence of ICIs for the treatment of irAEs, predicting irAEs has become a key factor in improving patient survival and quality of life [45]. The topic of identifying irAEs in advance to prevent disruption in immunotherapy has sparked growing consideration among academics. The findings of this paper suggest that irAE-related biomarkers have been a research hotspot in this field in the past five years. Currently, absolute counts such as absolute lymphocyte count (ALC), absolute eosinophil count (AEC), platelet count (PLT) or neutral lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR) have been of interest to clinicians and researchers, as they offer a straightforward and unbiased approach to identifying irAEs in their early stages. Simultaneously, tracking white blood cell counts (WBCs) and ALC may also be valuable in monitoring patients with ICIs for irAEs. Nevertheless, the majority of published research on blood counts and ratios is retrospective, time-limited, and restricted to particular malignancies, specific irAEs, or certain ICIs, thus resulting in an insufficient chain of evidence. Additional investigation is warranted on the subject of biomarkers such as cytokines, autoantibodies, HLA genotypes, micro-RNAs, and gene expression profiles, as their validity is not yet established [46]. This study observed that cytokines remain a prominent area of research in the future. Since irAEs are the product of overactivation of the immune system, cytokines have been extensively studied and become a hot topic in the field. Mounting evidence suggests that the production of cytokines in response to these treatments enhances the development of irAEs and may be predictive as a biomarker for the onset of irAEs [47]. Furthermore, the administration of therapeutics that inhibit cytokine activity can limit the severity of irAEs, and this approach is being validated in relevant clinical trials to investigate the mechanism of action of cytokine response in cancer immunotherapy and to aid in managing irAEs [48]. As of now, while some biomarkers may assist in clinical decision-making, there is no known biomarker that can accurately predict ICI-related irAEs, which may represent another deficiency in this area of study. Researchers have ample opportunities to further contribute in this area, including utilizing the latest findings from artificial intelligence, big data, and machine learning to develop effective toxicity prediction models [49,50]. These outcomes will provide some basis for the early prediction of irAEs and rational clinical use of ICIs.

Certainly, this paper has some limitations. The data were only retrieved from the WOS database, and the research literature of some countries may have been omitted. Along with that, this study only included relevant literature in English, and studies published in other languages were excluded, which could cause a certain degree of bias in the analysis. Nonetheless, WOS remains the most commonly used database for scientometric analysis, and English is today's international lingua franca. Ultimately, we believe that this will not have a material impact on the overall trend in the field.

5. Conclusion

This paper objectively analyzed the countries, authors, institutions, journals, research hotspots, and future trends associated with the immune checkpoint inhibitor immune-related adverse events. The three main areas of focus in the field were identified as diseases, drugs, and irAEs, and potential future advancements in the field were proposed with regard to managing irAEs. This study will help relevant researchers and clinicians understand the hot spots, trends, and frontiers of ICI-related irAEs, as well as identify the directions that necessitate further research. This is where the potential of this study lies.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent to publish

Not applicable.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

CRediT authorship contribution statement

Jun Zhao: Writing – original draft, Investigation, Funding acquisition. **Yujie Feng:** Visualization, Investigation. **Guang-wei Liu:** Writing – review & editing, Visualization, Methodology, Investigation.

Declaration of competing interest

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

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