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RESEARCH ARTICLE

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Visual analysis of global research on immunotherapy for gastric cancer: A literature mining from 2012 to 2022

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ABSTRACT

Gastric cancer (GC) is one of the most common malignancies. Immunotherapy becomes an indispensable part of GC. This study conducts bibliometric analysis of immunotherapy for GC to clarify the research status and identify potential new research directions. VOS viewer and CiteSpace visualization software were used to demonstrate collaborations and correlations. A total of 1141 English publications from 2012 to 2022 were included. The number of publications increased year by year. The publications were mainly from China ($n = 579$, 50.70%), followed by the United States. Fudan University published the most publications ($n = 48$, 4.21%). *Frontiers in Oncology* and *Journal of Clinical Oncology* ranked first in cited and co-cited journals, respectively. Kim Kyoung-Mee published the most publications on immunotherapy for GC ($n = 14$). The clustering of timeline view and co-cited references show the hotspot transformation on immunotherapy for GC. Initially, the hot topic was "cytokine-induced killer cells" and "myeloid-derived suppressor cells." In recent years, the focus has turned to "targeted therapy." "CAR-T" has become the hottest topic, and GC has entered precision therapy phase. Screening patients who can benefit from immunotherapy is key to improving prognosis. The combination of immunotherapy with other treatment options, such as chemotherapy and targeted therapy, is currently the focus of research. Chimeric antigen receptor T cell will be further studied in the future.

RESEARCH HIGHLIGHTS

Bibliometrics is one of the main tools in the current research and hot spots. Immunotherapy becomes an indispensable part of gastric cancer. Chimeric antigen receptor T cells will play an important role for gastric cancer.

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Gastric cancer; immunotherapy; bibliometric analysis; citeSpace; VOS viewer; chimeric antigen receptor T cell; targeted therapy

Introduction

Gastric cancer (GC) is one of the most common cancers worldwide.[1,2] At present, the treatment options for GC include systemic chemotherapy, surgery, radiotherapy and immunotherapy.[3] Most GC patients are diagnosed as advanced disease.[4] Surgery or chemotherapy alone often yields poor results, and new therapy methods are urgently needed.

For metastatic or advanced GC, immunotherapy has become a research hotspot with the development of individualized precision therapy.[5,6] In recent years, the breakthrough achievements of immune checkpoint inhibitors (ICIs), represented by cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) and programmed cell death protein-1 (PD-1) antibody, have promoted the mode transformation of cancer treatment.[7–9] In addition, chimeric antigen receptor T cell (CAR-T) and cytokine-induced killer cells (CIKs) also provide new approaches.[10,11] Immunotherapy prolongs survival by long-lasting immune response.[5,12] Therefore, it is necessary to systematically explore the publications and hotspots of immunotherapy for GC. The global database is updated daily to provide a basis for improving the prognosis of cancer patients.

The number of publications related to immunotherapy for GC has been rising over the past few decades.[13] It is essential to assess the field from a scientific point of view. Bibliometrics is a method or tool to evaluate status and provide reference for clinical medical research.[14] The characteristics of quality and quantity of publications can be provided for researchers by analyzing the measurement indexes. In addition, it is helpful to discover the research hotspot in a certain field.[15,16] At present, the research in the field of immunotherapy for GC is generally limited to the summary of literature and clinical experience.[17] To the best of our knowledge, no publication has conducted a bibliometric analysis of immunotherapy for GC so far.

Therefore, this study systematically searched the publications related to immunotherapy for GC in the past 10 years to analyze the development of this field. In addition, this study also sorted out the research hotspots, aiming to provide an overview for researchers.

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Materials and methods

Data retrieval

As a high-quality digital publications resource database, the Web of Science (WOS) has been widely accepted by researchers for bibliometric analysis.[18,19] We searched the WOS core database on October 31, 2022 for all publications related to immunotherapy for GC from January 1, 2012 to January 1, 2022. The search formula was as follows: TS= ("gastric cancer" OR "gastric carcinoma" OR "stomach cancer" OR "stomach neoplasms" OR "stomach carcinoma" OR "gastric adenocarcinoma" OR "gastric neoplasms" OR "gastric tumor") AND TS= ("immunotherapy" OR "immune therapy" OR "immunization therapy" OR "immunotherapies" OR "immunity treatment" OR "immunotherapeutic"). In the included articles, the title, abstract and keywords should be related to immunotherapy for GC.

Screening process

The inclusion criteria are follows as: (1) The subject focused on immunotherapy for GC, and the full text is available; (2) Written in English; (3) The publication type is limited to "article" and "review;" (4) The publications came from Sciences Citation Index Expanded (SCI-E) and Social Sciences Citation Index (SSCI) database of WOS; (5) Time span was between 2012 and 2022. Exclusion criteria are as follows: (1) Topics not related to immunotherapy for GC. (2) The types of publication are conference abstracts, graduation thesis, reports, etc. The two authors independently evaluated the full text of all publications. Any disagreements were resolved by negotiation (between the two authors YZ-C and T-Z). If disagreements still cannot be resolved, decisions are made under the guidance of the corresponding author. Data is exported as a plain text format.

Variables and analysis

Use bibliometric methods to collect research cutting-edge knowledge and trends.[20] For the included publications, variables of the following data were extracted: articles published annually; open access articles; top 10 authors, countries, institutions and journals; top 10 keywords and burst keywords. In this study, the VOS viewer (version 1.6.18)[21] and Citespace (version 6.1.R3 Basic)[22,23] were used for visualizing data to analyze countries, keywords, coauthors, etc. They combine the three functions of data integration analysis, visualization methods and bibliometrics.[24]

Use CiteSpace to analyze and visualize burst keywords to predict trends on immunotherapy for GC.[25,26] The higher the burst intensity means the higher the frequency of the keyword. Each node in the figure represents an observation result, including keywords, institutions, countries, authors, and co-cited references. Node size indicates frequency of citation or occurrence. Connections between nodes represent collaboration, and co-cited relationships.[27] Nodes with different colors represent different years. Both the 2021 edition of the Journal Citation Report (JCR) and the Impact Factor (IF) were included in the analysis as key indicators of the scientific value of the research.

Results

Annual growth trend of publications on immunotherapy for GC

After careful screening by two authors according to the inclusion criteria (Figure 1), from January 1, 2012 to January 1, 2022, a total of 1141 publications related to immunotherapy for GC were published on WOS, including 806 articles (70.6%) and 335 reviews (29.4%). Publications cover 59 countries or regions. A total of 229 institutions have published 3 or more publications on immunotherapy for GC. The number of publications on immunotherapy for GC from 2012 to 2022 is shown in Figure 2. Before 2016, the research trend line was flat. After 2016, the number of annual publications began to rise rapidly. The fastest growth is between 2019 and 2022. In particular, the number of publications on immunotherapy for GC in 2021 is the most in the past decade.

Analysis of countries/regions and institutions

China is the most published country with 579 publications (50.7% of 1141 publications), followed by the United States (18.0% of 1141 publications), Japan (8.4% of 1141 publications), Germany (6.7% of 1141 publications), and Italy (6.2% of 1141 publications) (Table 1). China alone contributed half of the publications. In addition, as can be seen from the color of the circles, China and the United States, the two countries with the most published publications, have been contributing to immunotherapy for GC from 2012 to 2022 (Figure 3a). The above two countries have close cooperation (Supplementary Figure S1). Likewise, among the top 10 most published countries or regions, China has 11,654 citations, far exceeding all other countries (Figure 3b). But citation/publication ratio (20.13) of China ranks second to last among the top 10 countries (Table 1). Notably, France had the most citation/publication ratio (33.96). Despite the number of publications is relatively small, this also reflects the high quality of publications.

Eight of the top ten institutions with the most publications are from China (Table 2). It can be seen that Chinese institutions are very concerned about immunotherapy for GC. The top 10 institutions published 290 publications, accounting for 25.4% of total publications. Fudan University published 48 publications, followed by Shanghai Jiaotong University (37 publications) and Nanjing Medical University (36 publications) (Figure 4a). Among the top ten institutions, Fudan University has the most citations, reaching 1213 times (Figure 4b). However, the most citation/publication ratio was Zhejiang University (39.17).

Analysis of journals

The journal with the most publications in the field of immunotherapy for GC is *Frontiers in Oncology* (45 publications, 3.94%), followed by *Cancers* (37 publications, 3.24%),

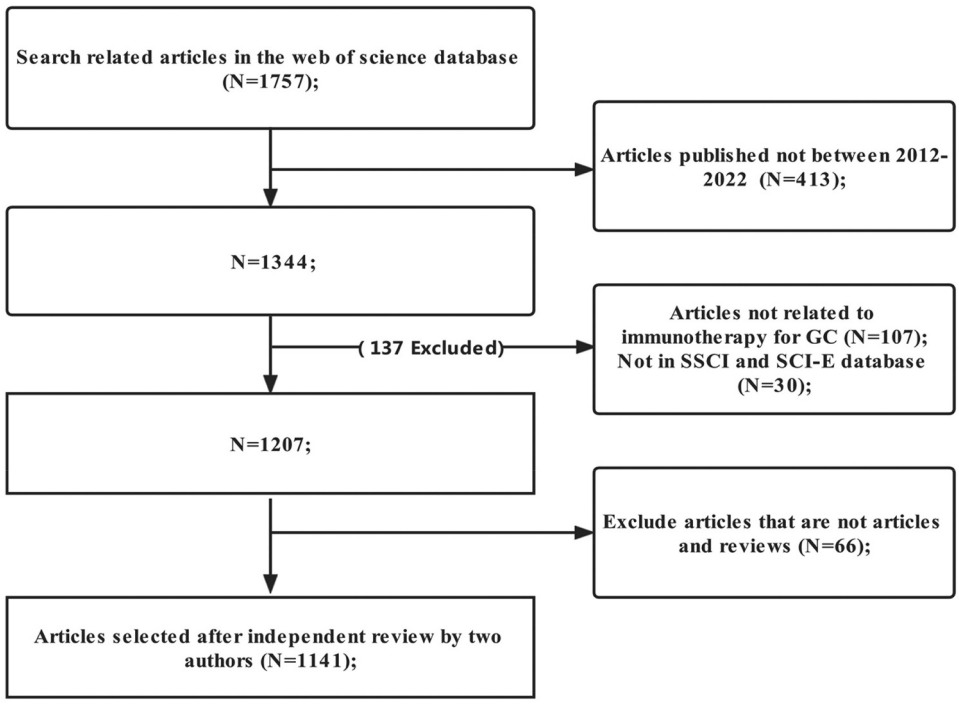

Figure 1. Flowchart of article selection. SSCI: Social Sciences Citation Index; SCI-E: Citation Index Expanded; GC: gastric cancer

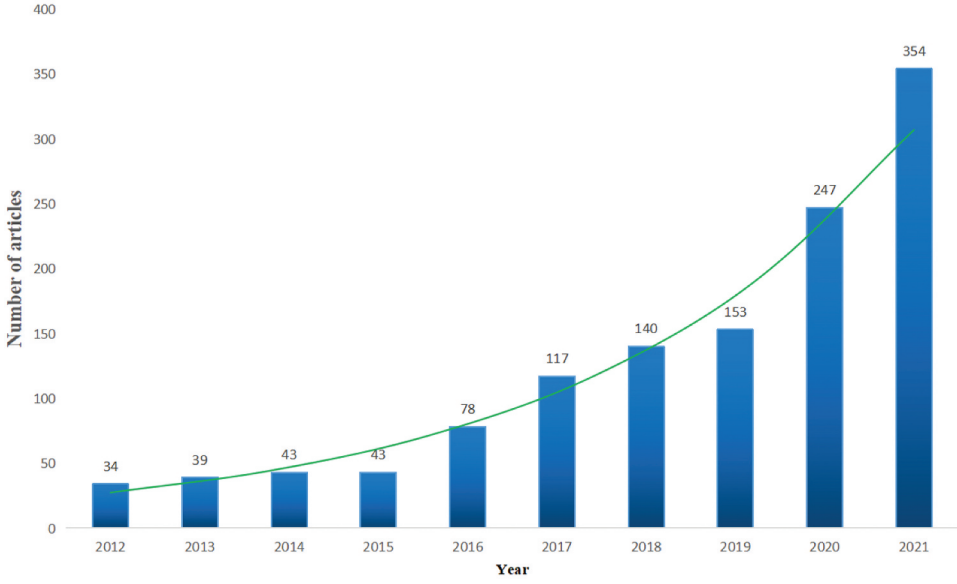

Figure 2. Annual trends of articles published in immunotherapy for GC from 2012 to 2022. GC: gastric cancer.

Oncoimmunology (26 publications, 2.28%), *Frontiers in Immunology* (20 articles, 1.75%) and *Oncotargets and Therapy* (20 publications, 1.75%). Among the top 10 most published journals, *Frontiers* series publishers account for 3 seats (Table 3). Among the top 10 journals, *Frontiers in Immunology* has the highest IF with 8.786, followed by *Oncoimmunology* (7.723). Of the top 5 most published journals, 4 journals are open access, a model that is now getting more attention from researchers. Of the top 10 most published journals, 40% were from Switzerland, followed by United States (30%), England (10%), Greece (10%) and Japan (10%). Of the top 10 most published journals, 60% are classified as Q1, 30% are classified as Q2, and the remaining one are classified as Q3. The most cited journal is *Oncoimmunology* (Figure 5a). Journal with the most citation/publication rate was *Oncotargets and Therapy* (Table 3).

The most co-cited journal was *Journal of Clinical Oncology* (3370 citations), followed by *Cancer Research* (1751 citations), and *New England Journal of Medicine* (1750 citations) (Figure 5b). The top ten co-cited journals were all Q1. And *Lancet* has the highest IF (202.731). A dual-map overlay of the journals describe the subject distribution of academic journals (Figure 6). Color lines represent reference paths.[28] These labels identify the disciplines that journals represent. The map is

Table 1. The top 10 most published countries/regions related to immunotherapy for GC from 2012–2022.

Rank	Country/Region	Article counts	Citation	Citation per articles
1	China	579	11654	20.13
2	United States	205	6418	31.31
3	Japan	96	2938	30.60
4	Germany	76	2319	30.51
5	Italy	71	2008	28.28
6	South korea	65	1264	19.45
7	England	60	1829	30.48
8	France	28	951	33.96
9	Spain	26	631	24.27
10	Sngapore	24	804	33.50

GC: gastric cancer.

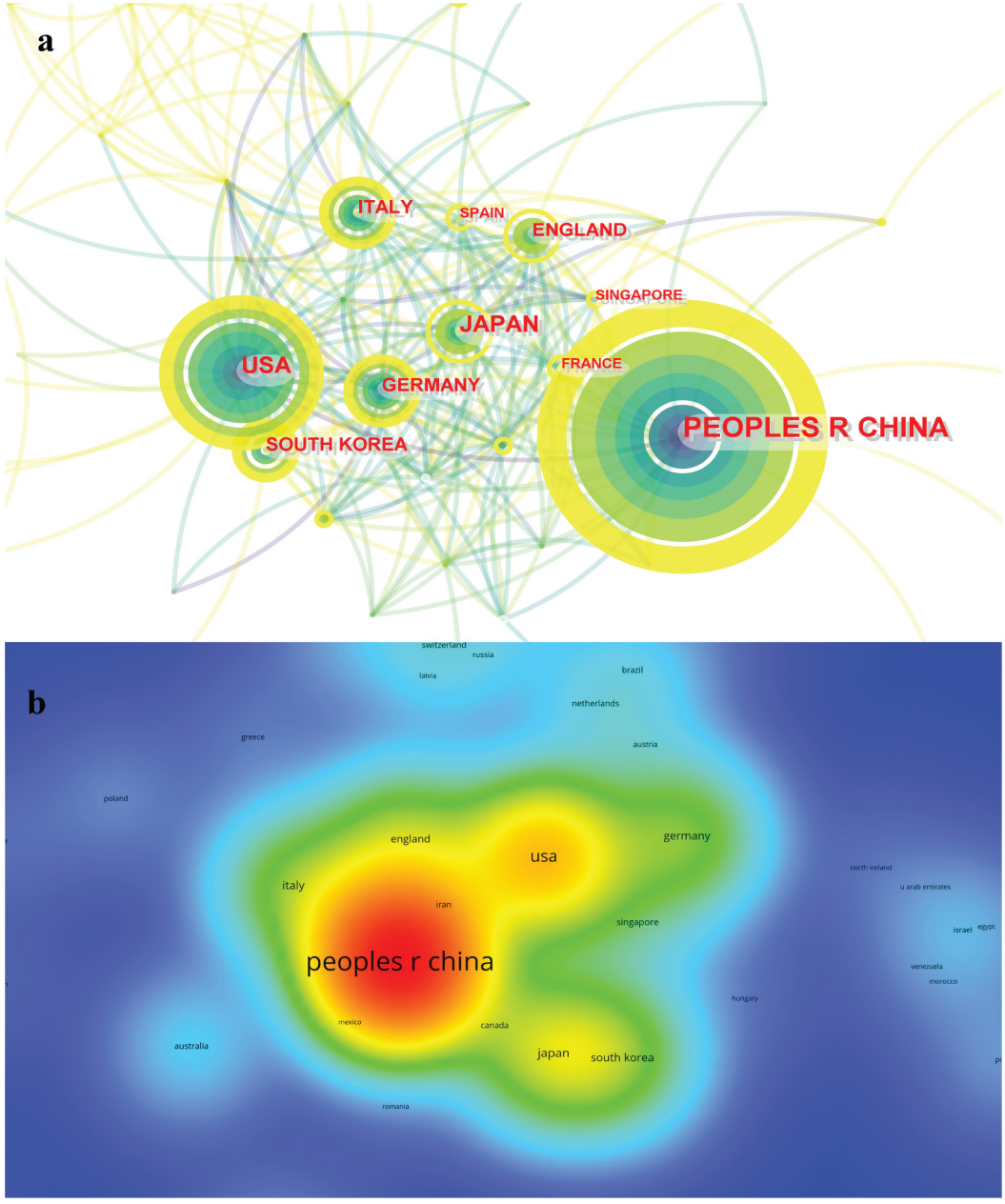

Figure 3. A visualization of countries related to immunotherapy for GC. a:Cooperative network of publications between countries. Countries are represented by nodes. Partnerships are represented by lines. The node area increases with the number of publications. The colors represent different years. The color represents different years. From 2012 to 2022, it changes from dark blue to yellow; b: Number of citations by country. The size and brightness of the nodes indicate the frequency of citations. GC: gastric cancer.

Table 2. The top 10 most published institutions related to immunotherapy for GC from 2012–2022.

Rank	Institution	Article counts	Citation	Citation per articles
1	Fudan University	48	1213	25.27
2	Shanghai Jiao Tong University	37	997	26.95
3	Nanjing Medical University	36	715	19.86
4	Sun Yat-sen University	31	1106	35.68
5	China Medical University	25	688	27.52
6	Zhengzhou University	25	621	24.84
7	Zhejiang University	24	940	39.17
8	Sungkyunkwan University	23	532	23.13
9	Peking University	21	813	38.71
10	National University of Singapore	20	705	35.25

GC: gastric cancer.

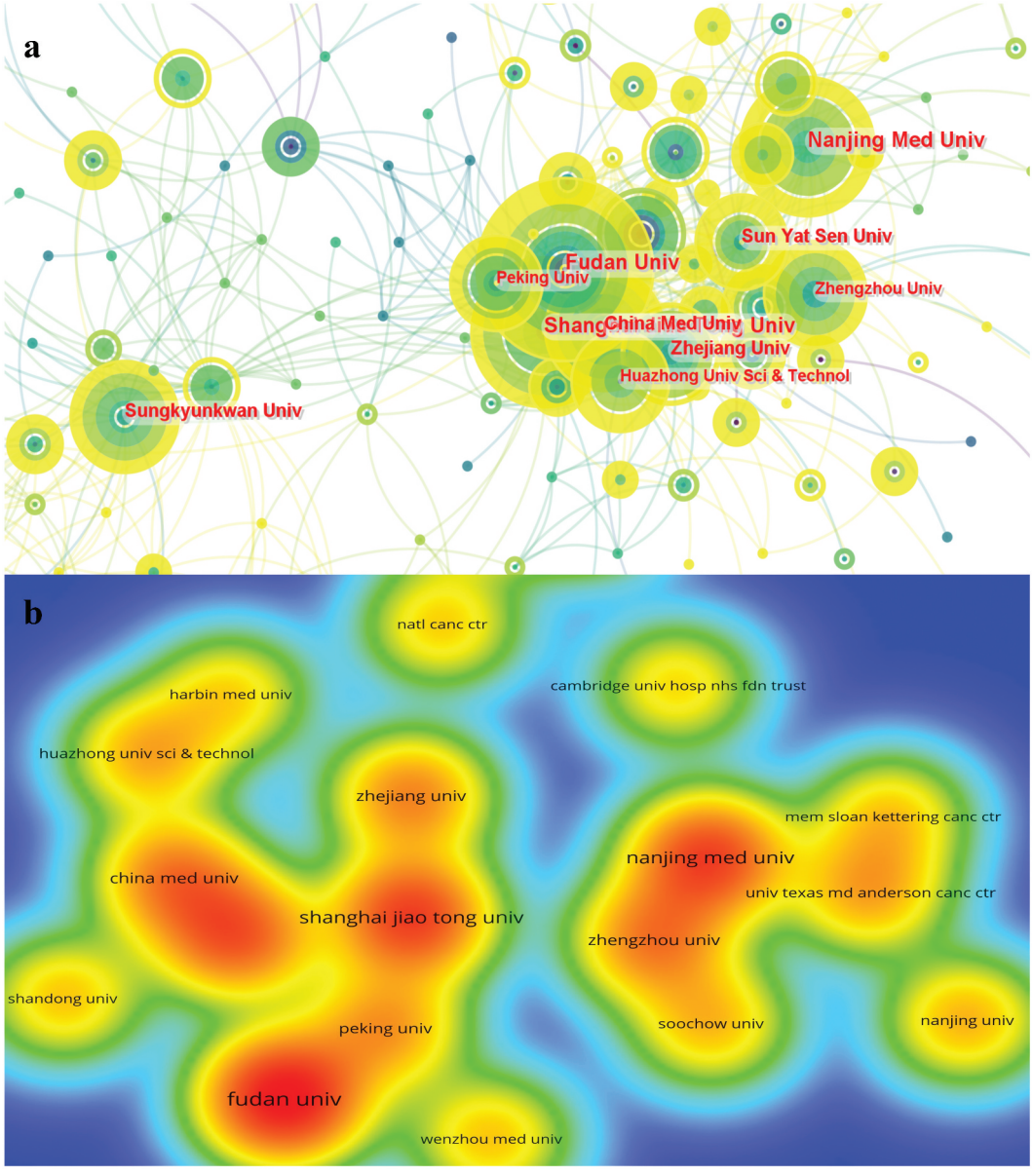

Figure 4. A visualization of institutions related to immunotherapy for GC.a: Cooperative network of publications between institutions. Institutions are represented by nodes. Partnerships are represented by lines. The node area increases with the number of publications. The colors represent different years. The color represents different years. From 2012 to 2022, it changes from dark blue to yellow; b: Number of citations by institution. The size and brightness of the nodes indicate the frequency of citations. GC: gastric cancer.

colored to indicate the two main citation pathways. The orange citation path indicates that research from Molecular/Biology/Genetics is frequently cited by Molecular/Biology/Immunology journal. Green paths indicate that research from Molecular/Biology/Genetics is frequently cited by Medicine/Medical/Clinical journal.

Table 3. The top 10 most published journals related to immunotherapy for GC from 2012–2022.

Rank	Journal	Article counts	Citation	Citation per articles	JCR partition	IF
1	Frontiers in Oncology	45	398	8.84	Q2	5.738
2	Cancers	37	296	8.00	Q1	6.575
3	Oncoimmunology	26	610	23.46	Q1	7.723
4	Frontiers in Immunology	20	367	18.35	Q1	8.786
5	Oncotargets and Therapy	20	560	28.00	Q2	4.345
6	Oncology Letters	19	171	9.00	Q3	3.111
7	Gastric Cancer	18	281	15.61	Q1	7.701
8	Cancer Immunology Immunotherapy	17	331	19.47	Q1	6.630
9	World Journal of Gastroenterology	17	465	27.35	Q2	5.374
10	Frontiers in Cell and Developmental Biology	16	131	8.19	Q1	6.081

GC: gastric cancer; JCR: Journal Citation Reports; IF: Impact Factor.

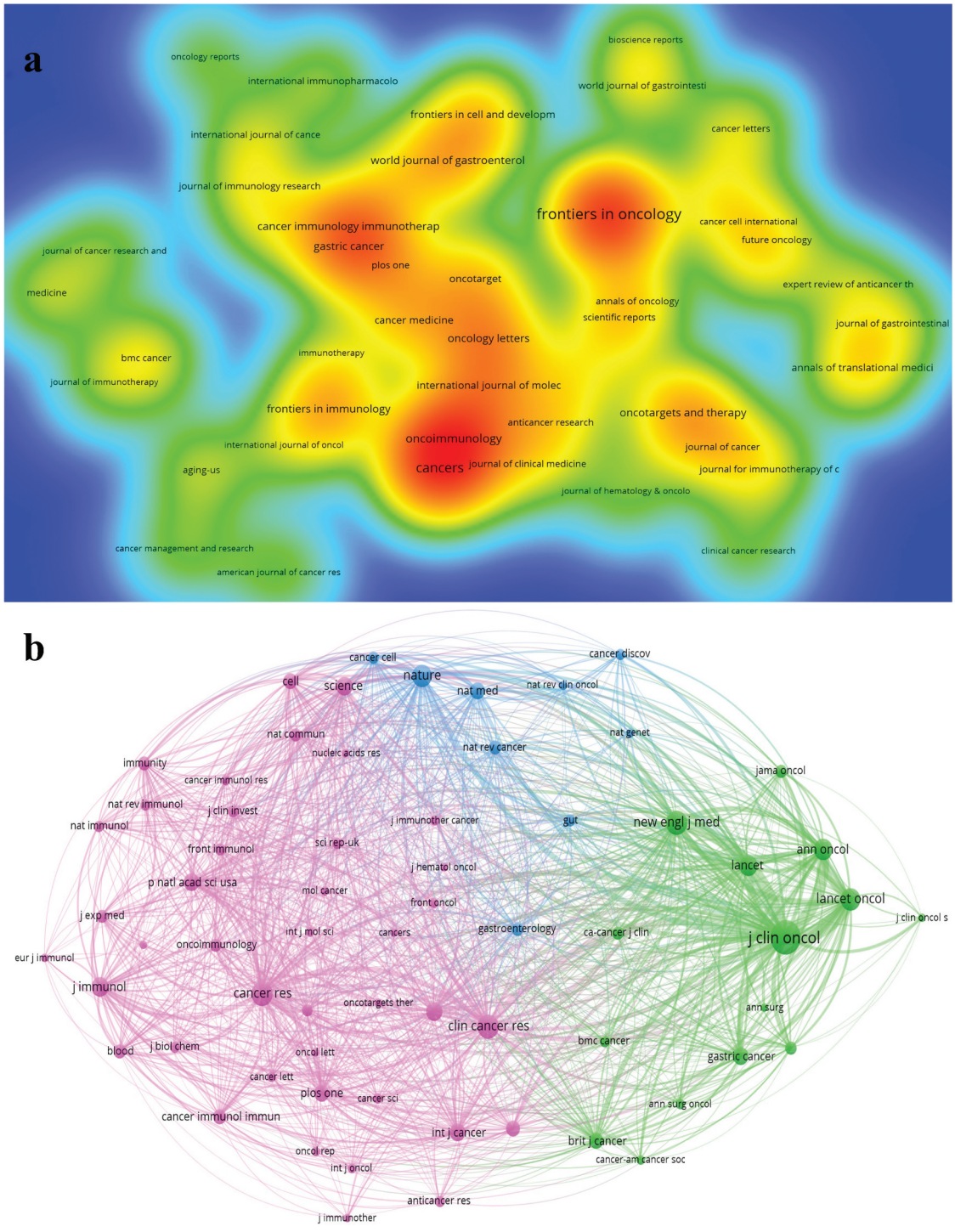

Figure 5. A visualization of journals related to immunotherapy for GC.a: Number of citations by journals. The size and brightness of the nodes indicate the frequency of citations. b: A network visualization of co-cited journals. The size of the circle represents the number of co-cited. GC: gastric cancer.

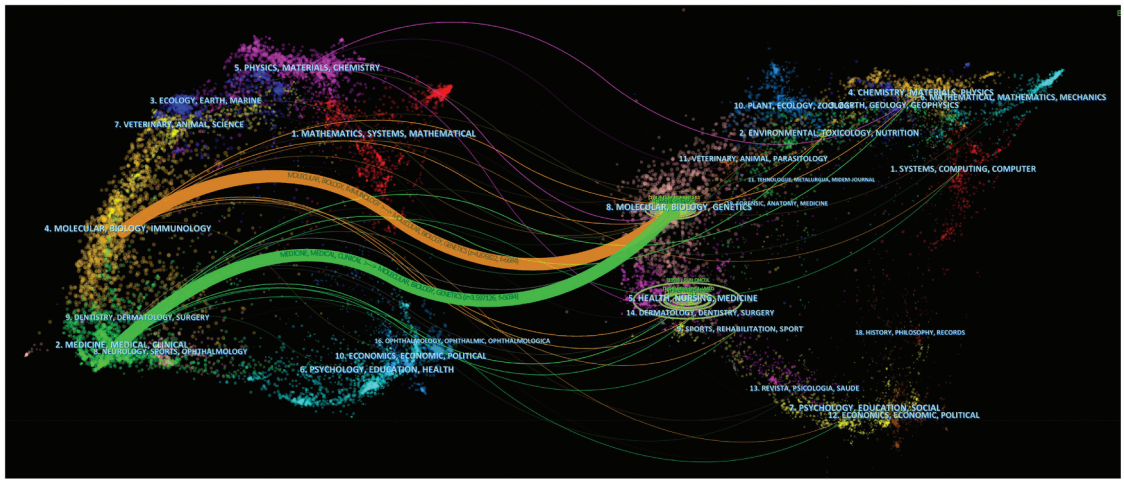

Figure 6. A dual-map overlay of journals related to immunotherapy for GC. Citingjournals on the left and the cited journals on the right, with colored paths indicating citation relationships. GC: gastric cancer.

Table 4. The top 10 most published authors related to immunotherapy for GC from 2012–2022.

Rank	Author	Article counts	Citation	Citation per articles
1	Kim Kyoung-mee	14	272	19.43
2	Lordick Florian	13	259	19.92
3	Liu Baorui	12	160	13.33
4	Liu Hao	12	307	25.58
5	Lee Jeeyun	11	191	17.36
6	Li He	11	126	11.45
7	Shen Lin	11	382	34.73
8	Zhang Heng	11	104	9.45
9	He Hongyong	10	74	7.40
10	Lin Chao	10	74	7.40

GC: gastric cancer.

Analysis of authors

Over the past decade, more than 6,000 researchers have been involved in research related to immunotherapy for GC (Table 4). Kim Kyoung-mee (14 publications) published the most publications, followed by Lordick Florian (13 publications), Liu Baorui (12 publications) and Liu Hao (12 publications). However, the most citation/publication was Shen Lin (34.73), indicating that the publications were recognized by researchers. As shown in Figure 7, the largest node is the author with the most co-cited, including Bang YJ (506 citations), Fuchs CS (442 citations) and Le DT (294 citations). In addition, high-producing authors tend to co-occur more frequently with other authors.

Analysis of co-cited references and timeline

It can be seen that the co-cited references are basically divided into 10 clusters (Figure 8a). Co-cited references refer to those that are frequently cited with other publications, which are considered the basis of research in a field. The smaller the number, the more keywords the cluster contains. "0# Targeted therapy" has the most keywords, indicating that it has been widely studied on immunotherapy for GC. Modularity (Q) >0.3 means significant clustering structure. Weighted mean Silhouette (S) > 0.5 is considered a reasonable value for clustering. In addition, S>0.7 means that clustering is convincing. Two data are valid in this article (Q=0.64 and S=0.88). Clusters "#0 targeted therapy," "#1 Epstein-Barr virus," "#7 car-t" and "#4 chemotherapy" are closely related (Figure 8a). "Comprehensive molecular characterization of gastric adenocarcinoma" (272 citations) published in *Nature* (IF=113.914) by Bass Aj et al is the most co-cited publication (Table 5).[29] It is worth noting that 3 of the top 5 co-cited references are from the *Lancet* journal and its sub-journals. In addition, top-ranked co-cited references tend to be more collaborative (Supplementary Figure S2).

Timeline view is a data visualization method that combines clustering and time slice techniques. In addition to illustrating the distribution of topics in the field, this method can also show the trends and interrelationships of research topics over time.[30] Hence, we draw the timeline view of the co-cited references (Figure 8b). Different colors represent different years. The left side indicates older references. The right represents the newer reference. We found that "# 3 cytokine-induced killer cells" and "# 8 myeloid-derived suppressor cells" were a relatively early hotspot. "#7 CAR-T" has become a new hot spot-on immunotherapy for GC since 2015. Currently, it is still the focus of many researchers. The focus of mid-term period from 2015 to 2018 was on the search for biomarkers, the development of tumor vaccines and the application of immunotherapy in chemotherapy, such as "#1 Epstein – Barr virus," "#4 chemotherapy," and "#6 dendritic cells." Current research focuses on "#0 targeted therapy" and "#5 adjuvant chemotherapy."

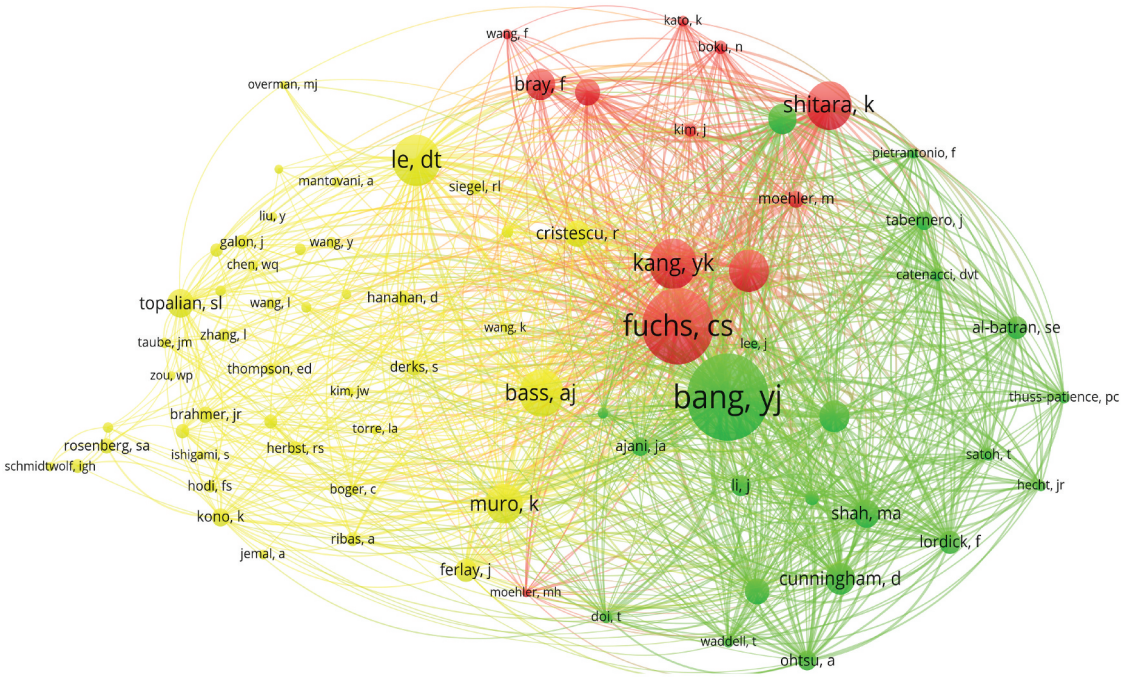

Figure 7. A visualization of co-cited authors related to immunotherapy for GC.The co-citation relationship is represented by the lines between nodes. The node area increases with the increase of co-citation number. GC: gastric cancer.

Analysis of keyword co-occurrence clustering and timeline view

After removing the meaningless keywords through the VOS viewer, we found that the keywords with the most frequency were "Expression," "Prognosis," "Survival," "T-cells," "Microsatellite instability" and "Nivolumab," etc. (Table 6). The development of keywords over time can reflect the evolution of cutting-edge knowledge. This plays an important role in guiding the future research direction in this field. We designed a timeline view using CiteSpace to clearly show the keywords (Supplementary Figure S3). It can be seen that it is roughly divided into 6 clusters. "#0 Microsatellite instability" and "#3 Targeted therapy" reappear. "#0 Microsatellite instability" has not increased or decreased significantly in the last 10 years. The research related to "# 3 Targeted therapy" and "#2 Cytokine induced killer cells" has decreased since 2016. "#4 Immune checkpoint blockade" has been a hot topic for 10 years.

Keyword burst analysis

Detect bursts keywords to identify research fronts. Burst keywords indicates that a certain keyword has been widely cited over a period of time. We focus on the top ten keywords with the highest burst intensity from January 2017 to January 2022 (Figure 9), including "lymphocyte" (Strength=4.43), "adoptive immunotherapy" (Strength=4.1) and "growth factor receptor" (Strength=3.79), etc.

Discussion

Perspective of country

The publications were statistically and visually analyzed to further obtain the research status and hotspots on immunotherapy for GC.[31] There were 1141 publications on immunotherapy for GC in the past 10 years (2012–2022), from 1579 institutions and 59 countries/regions. The number of publications related to immunotherapy for GC is increasing every year. This field has received a lot of attention in recent years. On current trends, the total number of publications in 2022 is set to surpass 2021 and continue to grow rapidly. In terms of the number of total citation frequency and publications, China has made the greatest contribution to immunotherapy for GC in the past decade. In addition to the large population, China also has a high incidence of GC.[32,33] China and the United States, two countries with close cooperation, have made indispensable contributions in the field of immunotherapy for GC. In addition to China, developed countries occupy a mainstream position in the field of immunotherapy for GC. This is related to the large amount of funds and high-tech support needed for research. In the future, the close cooperation between countries is needed to reduce the waste of funds and resources. Of course, this needs to be achieved through the cooperation of institutions and journals.

Perspective of institution

The distribution of institutional rankings is often consistent with countries. China alone accounted for 80% of the top ten institutions that published the most publications. This shows that China has made a great contribution to the academic development in this field. Surprisingly, as the institution with the most number of publications, Fudan University ranked last in citation/publication. The Citation/publication of Zhejiang University is ranked first in the top 10 institutions. It can be seen that the publications published by Zhejiang University in this field are high quality. In addition to the country, close cooperation between institutions has also played a role in

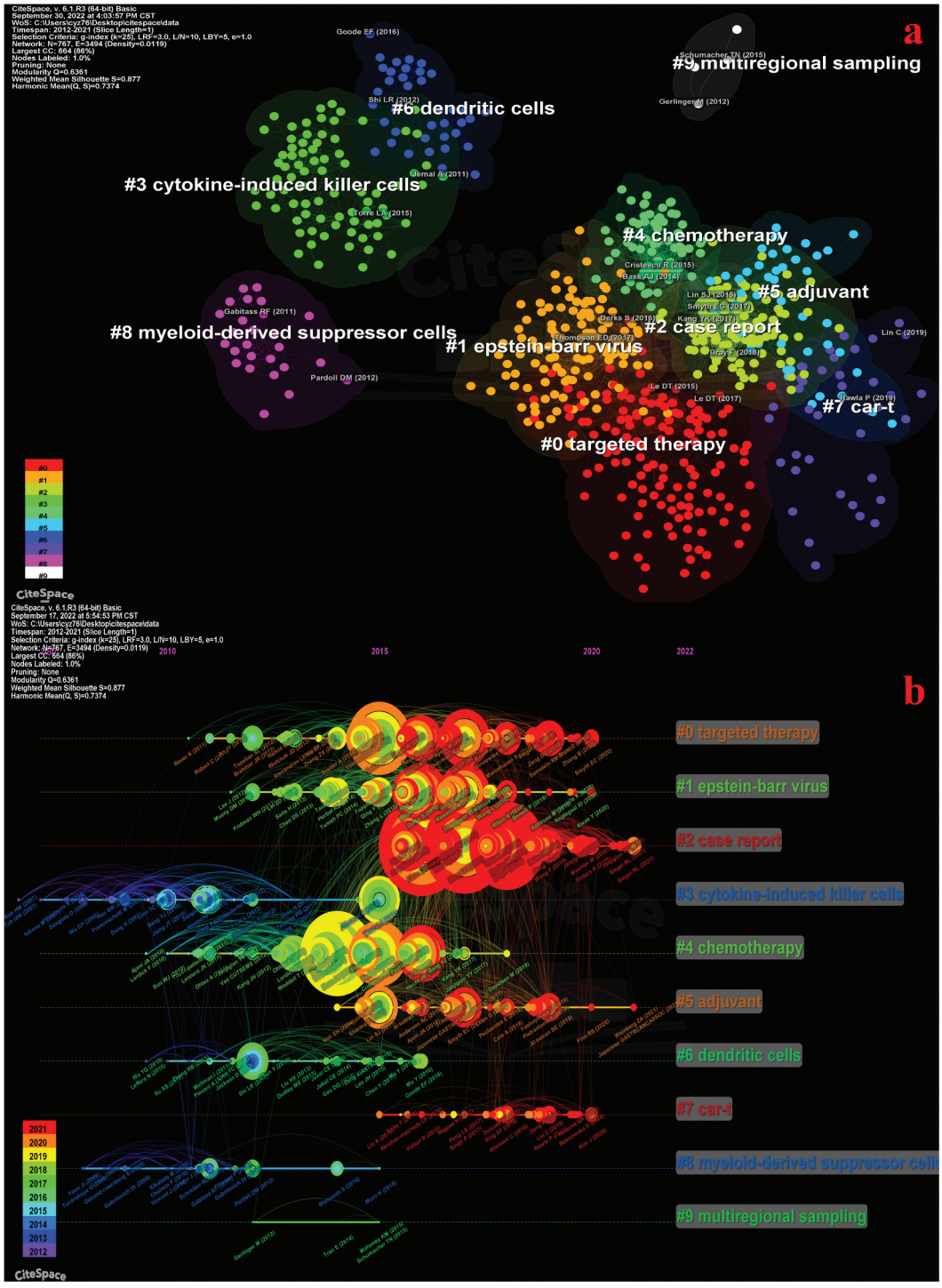

Figure 8. Visualization of co-cited references related to immunotherapy for GC. a:Knowledge map of co-cited references. Different colors represent different clusters. b: Timeline view of co-cited references related to immunotherapy for GC. The position of the node on the horizontal axis represents the time when the reference first appeared. The size of the node is related to the number of co-cited of the reference. Lines between nodes represent co-cited relationships. Redder the color means closer to 2022. GC: gastric cancer.

promoting immunotherapy for GC. Medical research often involves a variety of complex issues, and in-depth cooperation among institutions can better solve these problems.

Perspective of journal

Frontiers in Oncology (45 publications), *Cancers* (37 publications), *Oncoimmunology* (26 publications), *Frontiers in Immunology* (20 publications), and *Oncotargets and Therapy* (20 publications) published more than 20 publications. The most published and high-co-cited journals are Q1 and Q2 (JCR partition). It can be concluded that the above journals are particularly interested in immunotherapy for GC. These will help researchers choose journals when submitting relevant manuscripts. In addition, researchers can follow these journals to get updates on relevant research. It is worth noting that the

Table 5. The top 5 co-cited references related to immunotherapy for GC from 2012–2022.

Rank	Title	Count	IF (2021)	First Author
1	Comprehensive molecular characterization of gastric adenocarcinoma	272	113.914	Bass Aj
2	Nivolumab in patients with advanced gastric or gastro-esophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomized, double-blind, placebo-controlled, phase 3 trial	213	202.731	Kang Yk
3	Safety and Efficacy of Pembrolizumab Monotherapy in Patients with Previously Treated Advanced Gastric and Gastroesophageal Junction Cancer Phase 2 Clinical KEYNOTE-059 Trial	181	33.005	Fuchs Cs
4	Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-esophageal junction cancer (ToGA): a phase 3, open-label, randomized controlled trial	175	202.731	Bang Yj
5	Pembrolizumab for patients with PD-L1-positive advanced gastric cancer (KEYNOTE-012): a multicentre, open-label, phase 1b trial	166	54.431	Muro K

GC: gastric cancer.

Table 6. The top 10 most frequent keywords related to immunotherapy for GC from 2012–2022.

Rank	Keyword	Occurrences
1	Expression	233
2	Prognosis	116
3	Survival	107
4	T-cells	105
5	Microsatellite instability	96
6	Nivolumab	89
7	Cells	87
8	Blockade	85
9	Therapy	84
10	Pd-L1	80

GC: gastric cancer.

top ten most published journals do not appear in the top ten co-cited journals. Most of the top ten most published journals are related to clinical oncology and immunology. And the top ten co-cited journals are related to oncology and biology. Dual-map overlay is consistent with this analysis (Figure 6). Genetics/Molecular Biology research cited by Biology/Molecular/Immunology research and Medical/Medicine/Clinical research. It shows the research of immunotherapy for GC has gradually transformed from basic research to clinical research. This is the current concern of researchers. In addition, journals need to pay more attention to the transformation of basic achievements into clinical drugs.

Perspective of author

Each of the top ten authors who published the most publications have at least ten publications. The top ten most published authors are from China, America, South Korea and Japan. This proves once again that both these countries have made important contributions to the field of immunotherapy for GC. The authors with the most publications, Kim Kyoung-mee, from South Korea, has made significant contributions to immune checkpoints, molecular mechanisms and PD-1 antibodies.[34,35] Kim Kyoung-mee et al explored molecular characteristics associated with the response to pembrolizumab for metastatic GC.[36] The study provided biomarkers relevant to the selection of patients who may benefit from PD-1 inhibition.[36] This article was also one of the most co-cited references. Bang, Yj (506 citations) ranked first among the co-cited authors. Bang, Yj, also from South Korea, published "Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-esophageal junction cancer (ToGA): a phase 3, open-label, randomized controlled trial" in *Lancet* (IF=202.73), which was also one of the most co-cited references in this study.[37] Chemotherapy combined with trastuzumab was considered a new standard option for advanced GC patients with human epidermal growth factor receptor-2 (HER2)-positive.[37] Shen Lin, a researcher from China, had the most citation/publication. Shen Lin was interested in individualized treatment of immunotherapy for GC, mainly explored the efficacy of immunotherapy in Epstein-Barr virus-associated GC,[38] multi-dimensional analyses of tumor immune microenvironment to predict the efficacy of immunotherapy in GC,[39] and plasma extracellular vesicle-derived protein profile to predict the immunotherapeutic outcomes of GC.[40] This suggests that screening suitable patients is one of the priorities of current research. Of course, authors from various countries, especially China and the United States, should strengthen cooperation to promote the development of this field. Researchers focusing on immunotherapy for GC can communicate with the authors who have published the most publications to obtain more resources and experience for research development.

Perspective of reference

The co-cited relationship is defined as two publications being cited jointly by a third publication.[41] The most co-cited references can be regarded as the main focus in the certain field. The top five most co-cited references were composed of four clinical studies and one basic trial, all from top journals. The reference with the most co-cited proposed a molecular classification method.[29] The study divided GC patients into four subtypes: extreme DNA hypermethylation, and amplification of JAK2, CD274 (PD-L1) and PDCD1LG2 (PD-L2); tumors positive for Epstein – Barr virus; microsatellite unstable tumors; and tumors with chromosomal instability.[29] Identification of these subtypes provided guidance for stratification and targeted therapy. Three references with the most co-cited were related to anti-PD-1 antibody.[42–44] This means that anti-PD-1 antibody is indispensable on immunotherapy for GC. ICIs represented by anti-PD-1 antibody played an important role in GC.[45] Although anti-PD-L1 and anti-PD-1 antibodies have clinical activity in GC, only show prognostic advantage in some selected patients.[45–47] This shows that it is important to screen suitable patients according to

appropriate molecular markers for immunotherapy.[48] The latest research has shown that nivolumab is the first PD-1 inhibitor with superior overall survival (OS) and progression-free survival (PFS) for previously untreated, unresectable, non-HER2-positive gastric adenocarcinoma patients.[49] In addition, nivolumab combined with chemotherapy had acceptable safety.[49] This adds to the evidence of combined use of anti-PD-L1 antibodies for GC patients. Interestingly, the four most co-cited references focused on clinical trials in advanced GC.[37–42–44] How to improve the survival of these patients is the focus of many clinicians and researchers. It can also be concluded that nivolumab and pembrolizumab, the representative drugs of immunotherapy for GC, have played an important role in clinical treatment. These co-cited references have showed the development and treatment hotspots of immunotherapy for GC. Researchers focusing on immunotherapy for GC can obtain meaningful information from these articles. The clinical application of these treatments is a hope for advanced GC patients.

In this study, the timeline view of the co-cited references was divided into three periods. The early period is 2012–2014, the middle period is 2015–2018, and the current period is 2019–2022 (Figure 8b). The early period focused on "#3 cytokine-induced killer" and "#8 myeloid-derived suppressor cells." Current study suggested that compared to other immune cells, CIKs have stronger antitumor activity, broader antitumor spectrum and higher proliferation rate.[50] The latest meta-analysis suggested that CIKs or combined dendritic cell (DC)-CIKs has advantages in enhancing immune function, alleviating adverse events and prolonging the survival in GC patients.[51] The early period also focused on myeloid-derived suppressor cells (MDSCs). MDSCs are an important component of Tumor Microenvironment (TME). Exploring TME is crucial for establishing new cancer therapies.[52] The clinicopathological significance of TME in predicting outcomes and therapeutic effects has been demonstrated.[53] Therefore, exploring the characteristics of TME may help explain the efficacy gap of immunotherapy in different GC populations. And it provides new strategies for treatment, also suggests the importance of molecular markers. It is worth noting that these fields in the early period were rarely studied after 2016 (CIKs and MDSCs). These drugs are more likely to be part of combined chemotherapy in the future.

The middle period focused on "#1 Epstein-Barr virus," "#4 chemotherapy" and "#6 Dendritic cells." Epstein-Barr virus (EBV), as a middle period hotspot, indicated that researchers are actively exploring potential markers to screen patients who respond well to ICIs. The infection status of EBV affects the effect of immunotherapy.[1,17,36,54] Of course, exploring how the EBV genome is involved in the development of GC and characterizing the molecular and clinicopathological features of EBV-associated GC are also critical for treatment.[55,56] Thus, no matter in the early or middle stage, screening suitable patients is an indispensable part of precision therapy. "Chemotherapy" in the middle period and "adjuvant chemotherapy" in the current period indicate that the role of immunotherapy in chemotherapy and adjuvant chemotherapy is actively explored. It is clear that the clinical efficacy of immune agents alone is quite limited. At present, multiple clinical trials are exploring combined therapy. A phase II nonrandomized Keynote-059 study in 2017 showed that for advanced GC, chemotherapy combined with pembrolizumab had a higher objective response rate (ORR) than pembrolizumab monotherapy.[57] But the prognosis needs to be further verified. A global multicenter study also showed that chemotherapy combined with pembrolizumab had better efficacy than chemotherapy alone in GC patients.[49] Many clinical trials have demonstrated that the addition of immune agents to chemotherapy or adjuvant chemotherapy achieves better clinical efficacy.[58,59] Chemotherapy combined with immunotherapy is becoming the standard treatment for GC. Which combination of immune drugs and chemotherapy drugs can achieve better prognosis is the focus of future research. In addition, it is also noteworthy whether the side effects between drugs will be superimposed. Tumor vaccines represented by dendritic cells (DC) have been rarely studied on immunotherapy for GC.[17] Among 9 advanced GC patients, one patient achieved partial clinical response after HER2/DC vaccination.[17] Recently, clinical trials are being conducted to verify the efficacy of DC tumor vaccine.[60] More data are expected to demonstrate the role of DC vaccines in GC patients. With the development of technology and in-depth research on immune vaccines, vaccines and drug regimens with different mechanisms may receive more attention in the future.

The current period focuses on "#0 Targeted Therapy" and "#5 Adjuvant." Anti-HER2 antibodies and Vascular Endothelial growth factor (VEGF) inhibitors are the two main options for targeted therapy combined immunotherapy for GC.[17] Trastuzumab is the first monoclonal antibody drug to block HER2 in GC standard treatment protocol. The results of a 2010 phase III randomized controlled trial suggested that trastuzumab in combination with chemotherapy for HER2-positive GC patients had significantly better OS than chemotherapy alone.[37] This publication is also the most cited in this study. The prognostic advantage of combined trastuzumab in GC has also been validated in several prospective trials.[61–63] Several global guidelines (CSCO guidelines of China, NCCN guidelines of United States, and Japanese guidelines) recommend chemotherapy plus trastuzumab as first-line treatment for HER2-positive advanced GC.[1,64,65] Trastuzumab has changed the treatment mode for HER2-positive GC. Immunotherapy combined with targeted therapy is a hot topic in GC research. The prognostic benefits of immunologic agents combined with targeted agents have been demonstrated by various protocols, such as pembrolizumab plus trastuzumab plus chemotherapy, trastuzumab plus pembrolizumab plus capecitabine plus oxaliplatin and pembrolizumab plus trastuzumab plus fluoropyrimidine, etc.[66–68] Targeted drugs have become a critical component of immunotherapy for GC. However, drug resistance hinders the further use of targeted agents,[69,70] which remains a major barrier to clinical treatment. In the future, combination therapy or multi-target antitumor drugs may be the main direction to improve the therapeutic effect and reduce the occurrence of drug resistance. It can be seen from each period that how to combine multiple drugs to improve the prognosis of GC patients is the current and future research trend. Researchers and clinicians can pay more attention to the topic of combination therapy.

The hottest topic is "#7 CAR-T," a new paradigm in cellular immunotherapy. CAR-T is a new revolutionary pillar in cancer treatment.[71] Currently, CAR-T therapy for GC is in early stages. Animal studies have proved that CAR-T has anti-GC efficacy and sustained activity in various targets, such as HER2,[72,73] Folate receptor 1 (FOLR1),[74] Claudin18.2 (CLDN18.2),[75] etc. There are only a few data from phase I clinical trials.[17] It must be noted that although CAR-T cell therapy has shown clinical efficacy in hematological malignancies, there is no convincing data in GC.[76] The latest open-label, single-arm phase I clinical trial in 2022 reported that CLDN18.2 targeted CAR-T cells (CT041) was used for previously treated CLDN18.2-positive digestive system cancer patients.[77] The ORR, disease control rate (DCR) and the 6-month OS rate of GC patients were 57.1%, 75.0% and 81.2%, respectively. These preliminary data indicate that CT041 has good therapeutic efficacy and acceptable safety in CLDN18.2-positive digestive system cancer patients, particularly in GC patients.[77] In addition to focusing on the final results of this trial, there may be more CAR-T clinical trials of other targets in the future. With the discovery of new targeting sites, the better understanding of the tumor microenvironment, and advances in technology, the potential of CAR-T therapy for GC is foreseeable in the near future.

Perspective of keyword

The timeline view of the keywords again proves that it is crucial to screen the GC patients that benefits from immunotherapy (#0 Microsatellite instability). This is essential for personalized treatment. The status of Microsatellite instability (MSI) determines the effect of immunotherapy.[78] Previous studies have confirmed that anti-PD-1 antibodies has shown good efficacy in high-MSI GC patients.[79,80] In addition, significant up-regulation of PD-1 and PD-L1 was also found in MSI-positive GC patients.[81] However, MSI is only detected in a minority of GC patients.[29,82] Therefore, in addition to the development of new therapeutic markers, the combination of multiple markers to screen the beneficiary patients may be a model in the future.

The burst keywords can reflect the research hotspots in the academic field.[83] To highlight the latest hot spots, we drawn the burst keywords of the last five years (2017–2022). From the perspective of the evolution of burst keywords in the past 5 years, different treatment methods are constantly innovating on immunotherapy for GC (Figure 9). Of the all burst keywords, "lymphocyte" has the greatest intensity. This is not surprising, since most immunotherapy for GC relies on lymphocytes and various immune cells to work. For example, a streptococcal preparation (OK-432) enhances the activity of natural killer cells and T lymphocytes.[84] In addition, "adoptive cellular immunotherapy" (ACI) uses various immune cells to induce effective immunity and eliminate cancer cells. Such as, CIK,[85] Tumor-infiltrating lymphocytes (TILs),[86] and Lymphokine Activated Killer cells (LAK),[87] etc. It can be seen that how to better use of immune cells such as lymphocytes is the basis of immunotherapy. ACI will play an important role on immunotherapy for GC in the future due to its unique treatment mode. In addition, the combined use of ACI in chemotherapy also deserves attention.

ACI has proven to be an effective strategy for advanced GC[88], which is also the burst keywords. CAR-T, which appears all in the burst keywords and timeline view of co-cited references, is one of the hottest treatment modalities of ACI in recent years. The specific efficacy of CAR-T in GC has been preliminarily verified.[77] More clinical data supporting CAR-T for GC is expected in the near future. "HER2" also appeared again in the burst keywords, indicating that targeted therapy is indispensable on immunotherapy for GC. Immunotherapy combined with targeted therapy is also a hot topic at present. The "growth factor receptor" in burst keywords is the common therapeutic targets in GC therapy, such as HER2, Endothelial

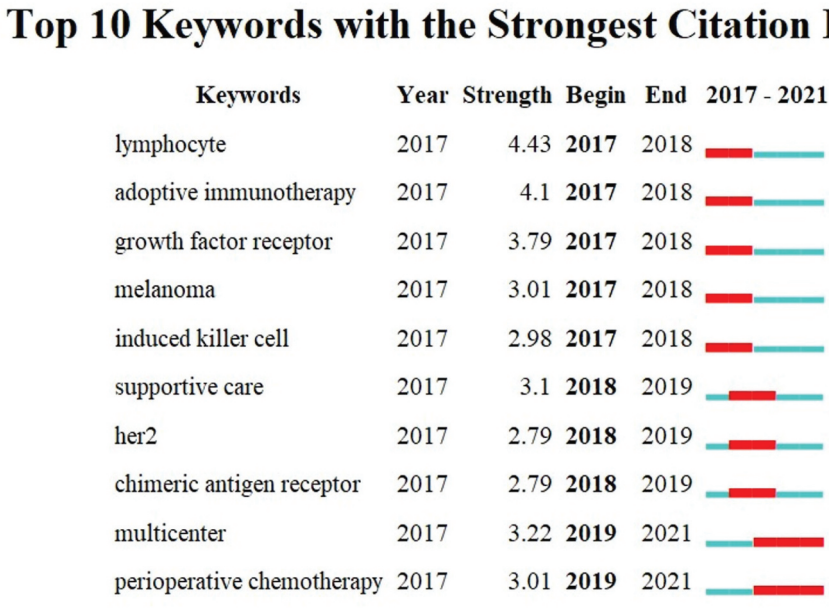

Figure 9. Keywords with the strongest citation bursts related to immunotherapy for GC from 2017 to 2022.The blue line represents the time axis, with the red part indicating the start year, end year, and duration of the burst. GC: gastric cancer.

Growth Factor Receptor (EGFR). The combination of EGFR inhibitors with immunotherapy for GC has also shown preliminary clinical activity.[89,90] Adding VEGF inhibitors to immunotherapy appears to be an effective treatment for advanced GC in the future. It also shows once again that multi-drug immunotherapy is the focus of GC treatment. "Melanoma" appears surprisingly in the burst keywords. In addition to melanoma and GC showing many similar targets in immunotherapy,[91–93] melanoma associated antigen A3 peptide (MAGE-A3) have showed anti-tumor effects for advanced GC patients.[94] To sum up, the burst keywords prove the researchers' concern about CAR-T, targeted therapy and combination therapy in recent years. These can help researchers to select the latest hot spots in the study of immunotherapy for GC.

Limitation

This study inevitably has some limitations. First of all, the publications we included may be missing: ①This study is from a single database; ②The included publications are only in English; ③Publications not related to immunotherapy for GC were manually deleted. Therefore, these publications may not fully represent all studies on immunotherapy for GC. But more than 1,000 publications in this study may address the offset caused by such small deviations.

Conclusion

This study analyzed global academic research on immunotherapy for GC. Through systematic literature search, we found that this study is the first bibliometric analysis on immunotherapy for GC. The rapid growth of publications indicates that immunotherapy for GC is attracting more attention from researchers worldwide. Immunotherapy has become the focus of GC research. Authors and institutions of China and United States should strengthen cooperation and continue to contribute in this field. *Frontiers in Oncology* and *Journal of Clinical Oncology* ranked first in cited and co-cited journals, respectively. The investigator may publish the immunotherapy for GC article in the above journals. Follow these journals to better obtain the research progress in this field.

In general, the treatment of GC has entered the stage of personalized precision treatment. At present, there are many drugs and combination modes on immunotherapy for GC. Selecting appropriate biomarkers for screening suitable patients and monitoring therapeutic efficacy is the first step for the successful of immunotherapy. The combined application of immune drugs and targeted drugs in chemotherapy and adjuvant chemotherapy is the current strategy and the future research direction of immunotherapy for GC. The effect of anti-PD-1 antibody has been verified in immunotherapy for GC. In addition to the prognostic benefits of immune drugs, attention should also be paid to the problems of resistance and side effects caused by these drugs. Researchers also have a strong interest in CAR-T therapy for GC, which is currently a hot spot in this field and will be further studied in the future. The future of immunotherapy for GC may be multi-drug combination and multi-target mode.

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Authors' contributions

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Data availability statement

The datasets used and analyzed during the current article are available from the corresponding author on reasonable request.

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