Clinics in Oncology

Research Article
Published: 27 Nov, 2023

Bibliometric and Visual Analysis of Immunotherapy for Gastric Cancer: A 2012-2022 Study

*Deng H[1#], Zhang K[2,3#], Li Z[1], Lin C[1], Meng H[1], Wei S[4] and Wang J[1]**

[1]Department of Oncology, Liuzhou People's Hospital Affiliated to Guangxi Medical University, China

[2]Guangxi University of Science and Technology, China

[3]Department of Pathology, Second Affiliated Hospital of Guangxi University of Science and Technology, China

[4]Department of Medical, Liuzhou People's Hospital, Guangxi Medical University, China

[#]These authors contributed equally to this work

Abstract

Background: Immunotherapy has emerged as a significant treatment avenue for Gastric Cancer (GC) and has garnered increasing attention within the research community. While recent studies highlight substantial advancements in GC immunotherapy research, a comprehensive bibliometric analysis in this domain remains scarce. This study aims to fill this gap by presenting an overview of research status, key focus areas, and trends in GC immunotherapy from a bibliometric perspective.

Methods: Utilizing the Web of Science Core Collection (WoSCC) database, we gathered and analyzed 1,663 records of GC immunotherapy published between July 1st, 2012, and July 1st, 2022. Employing software tools such as CiteSpace, VOSviewer, and the "Bibliometrix" R package, we conducted analyses on geographical distribution, contributing institutions, prominent journals, prolific authors, and prevalent keywords to prognosticate the latest research directions in GC immunotherapy.

Results: The annual publication count concerning GC immunotherapy demonstrates a consistent increase. China and the USA, together contributing over 70% of the publications, emerge as primary driving forces in this realm. Notably, Fudan University emerges as the most prolific institution with the highest citation frequency. Among journals, "Frontiers in Oncology" garners the most substantial publication count, while the "Journal of Clinical Oncology" emerges as the most frequently co-cited publication. Prolific writer Wang Y and commonly co-cited author Bang YJ stand out. Dominant research areas encompass "Oncology," "Immunology," and "Experimental Medicine". Emerging research hotspots are encapsulated by keywords such as "immunotherapy", "gastric cancer", "expression", "gastric-cancer", and "chemotherapy".

Conclusion: Representing the inaugural comprehensive bibliometric exploration, this study maps the evolving knowledge structure and developmental trajectories in GC immunotherapy over the past decade. The outcomes provide an encompassing synthesis and identification of research frontiers, furnishing valuable insights for scholars engaged in GC-related research pursuits.

Keywords: Gastric cancer; Immunotherapy; Bibliometric; CiteSpace; VOSviewer

OPEN ACCESS

Correspondence:
Wang Jun, Department of Oncology, Liuzhou People's Hospital Affiliated to Guangxi Medical University, No. 8, Wenchang Road, Chengzhong District, Liuzhou, Guangxi, China

Received Date: *04 Nov 2023*
Accepted Date: *22 Nov 2023*
Published Date: *27 Nov 2023*

Citation:
Deng H, Zhang K, Li Z, Lin C, Meng H, Wei S, et al. Bibliometric and Visual Analysis of Immunotherapy for Gastric Cancer: A 2012-2022 Study. Clin Oncol. 2023; 8: 2031.

ISSN: 2474-1663

Introduction

Gastric Cancer (GC) continues to stand as one of the most prevalent and deadly malignancies globally, with a particularly high incidence in eastern Asia. In the United States, the year 2019 witnessed the diagnosis of 27,510 fresh cases of GC, projecting an anticipated 11,140 fatalities, reflecting a 1.4% rise in mortality from the statistics of 2014 [1]. The global landscape showcases over a million new instances of gastric cancer being identified annually, securing its position as the fifth most frequently detected cancer [2]. Despite noteworthy advancements in diagnostic and therapeutic methodologies leading to enhanced survival rates, the age-standardized 5-year net survival rate for gastric cancer remains dishearteningly low, hovering between 20% and 40% across numerous nations [2].

In recent years, the pivotal role of immunomodulation within the tumor microenvironment and the pathogenesis of GC have garnered significant attention. Present-day immunotherapies predominantly encompass the utilization of monoclonal antibodies, cytotoxic immunocytes, and

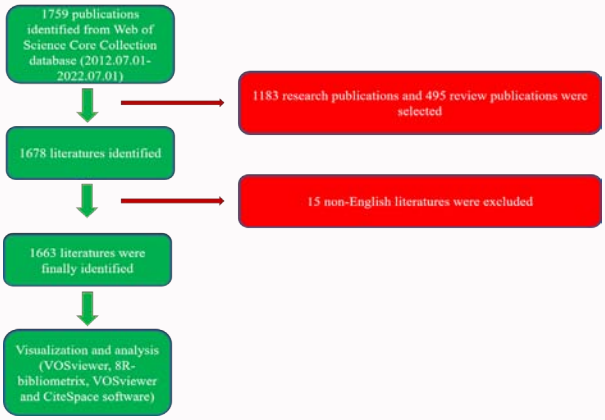

Figure 1: Flowchart depicting the article selection process.

gene-transferred vaccines [3]. Substantiated evidence underscores the therapeutic potential of multiple tumor rejection antigens targeting human tumors. Notably, Melanoma-Associated Antigen 3 (MAGE-3) and HER-2/neu, recognized by cytotoxic T cells, stand out as tumor rejection antigens that exhibit selective expression in gastric cancer, imparting anti-cancer effects [3]. Additionally, research has highlighted the favorable outcomes associated with targeting Tumor-Infiltrating Leukocytes (TIL) bearing CD3+, CD8+, and Granzyme+markers [4], underscoring the potential of cellular immunotherapy as a viable approach for GC treatment.

Furthermore, extending beyond histological considerations, the characterization of GC based on genetic mutations and expression profiles has unveiled its inherent heterogeneity. The Cancer Genome Atlas (TCGA) classification bifurcates GC into distinct categories based on genomic attributes: Epstein-Barr Virus (EBV) infected, microsatellite unstable, Chromosomally Unstable (CIN), and genomically stable [5]. This revelation accentuates the imperative nature of tailoring immunotherapeutic strategies to the specific tumor and patient factors. For instance, findings from the KEYNOTE-059 phase II trial illustrated that pembrolizumab (a PD-L1 inhibitor) monotherapy led to an Objective Response Rate (ORR) of 11.6% and a Complete Response (CR) of 2.3% among 259 GC/Gastro-oesophageal Junction Cancer (GEJ) patients [6].

Despite the accelerated proliferation of publications in the realm of GC immunotherapy, there exists a glaring dearth of comprehensive and insightful information encompassing the escalating publication count, cross-country collaborations, prominent institutions and authors, influential journals, emergent research frontiers, and the prevailing keywords that underscore GC immunotherapy's discourse.

Bibliometric analysis stands as a potent methodology in literature assessment, utilizing publication outputs and citation impact within a specific research domain to gauge research trends from both quantitative and qualitative standpoints [1]. This approach furnishes intricate insights into the contributions of research entities and individual scholars, achieved by extensively scrutinizing authorship, keywords, journal preferences, geographical affiliations, institutional affiliations, references, and more, thus elucidating developmental trajectories within targeted areas [2]. Moreover, it facilitates the identification and scrutiny of prevalent keywords within recent time frames, enabling prognostication of future developmental avenues [3]. Remarkably, despite the existence of bibliometric studies exploring immunotherapies within the context of colorectal cancer [4], there exists a conspicuous dearth of analogous analysis concerning gastric cancer. It is worth underscoring that several instrumental bibliometric tools, including CiteSpace [5], VOSviewer [6], and the R package "Bibliometrix" [7], have been harnessed to visually render specific medical literature domains. To bridge this knowledge void, the current study harnesses the prowess of three pivotal bibliometric software tools, conducting a comprehensive bibliometric analysis and employing visualizations to elucidate the landscape of references germane to immunotherapy for gastric cancer over the past decade (2012-2022). This endeavor strives to discern salient attributes, illuminate notable patterns, and forecast prospective avenues within the realm of gastric cancer immunotherapy research.

Materials and Methods

Data Acquisition and search strategies

For the identification of publications pertaining to GC immunotherapy research, the Web of Science Core Collection (WoSCC) database by Clarivate Analytics emerged as the chosen repository. Following established methodologies [4,8], we conducted a meticulous search for studies germane to GC immunotherapy and subjected the resultant data to rigorous bibliometric scrutiny.

The search spanned from July 1st, 2012, to July 1st, 2022, employing the subsequent query formulation: TS= (Gastric cancer * OR Gastric Tumor* OR Gastric Carcinoma* OR Gastric Neoplasm* OR Stomach Cancer* OR Stomach Tumor* OR Stomach Carcinoma* OR Stomach Neoplasm* OR Cancer of Stomach* OR Carcinoma of Stomach* OR Tumor of Stomach* OR Neoplasm of Stomach) AND TS=(Immunotherapy OR Immunotherapies OR immunotherapeutic). The inclusion criteria encompassed: (1) manuscripts centering on the theme of GC immunotherapy, (2) document types limited to Articles and Reviews, and (3) documents authored in the English language. Conversely, the exclusion criteria encompassed: (1) articles unrelated to GC immunotherapy themes, and (2) articles categorized as briefings, news, meeting abstracts, etc. (Figure 1).

Subsequently, the included research articles underwent meticulous manual evaluation by two reviewers (HBD and KFZ). In instances of discrepancies or uncertainty, consultation with experts facilitated the determination of article relevance, leading to the resolution of any conflicts and the informed decision of inclusion or exclusion within our study.

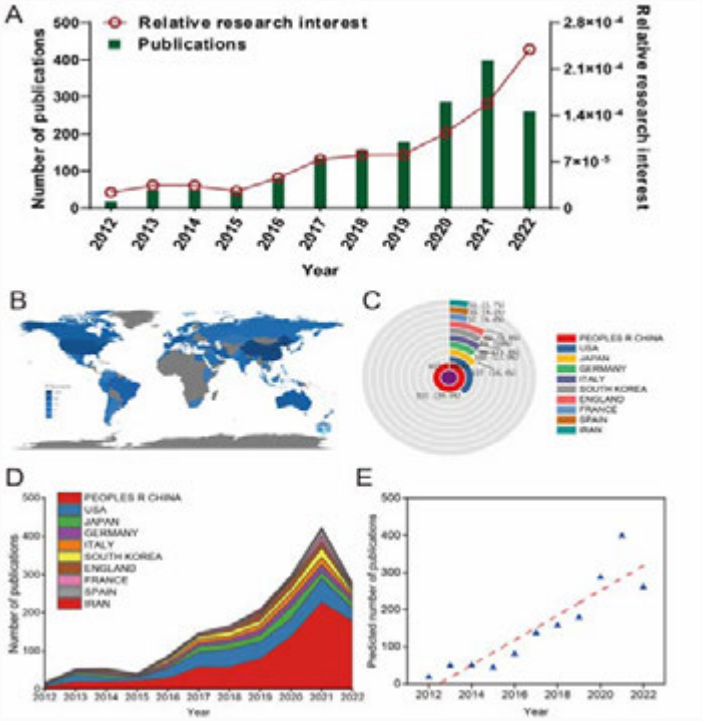

Figure 2: Global trends and countries/regions contributing to the research field regarding gastric cancer immunotherapy. (A) The annual number of publications related to gastric cancer immunotherapy. (B) A world map depicting distribution of gastric cancer immunotherapy. (C) The sum of gastric cancer immunotherapy related publications in the top 10 countries/regions. (D)The annual number of publications in the top 10 most productive countries from 2012 to 2022.(E) Model fitting curves of global trends in publications of gastric cancer immunotherapy.

Bibliometric analysis and visualization

Within this study, a robust array of bibliometric analyses and visualizations were executed, facilitated by three pivotal software tools: R version 4.2.1 [9], VOSviewer [10], and CiteSpace [11]. To commence, the R package "Bibliometrix" was harnessed to undertake the ensuing tasks: 1) visualization of publication counts across different countries, 2) depiction of international collaborations between countries, and 3) creation of a three-field plot through Keywords Plus analysis. Subsequently, CiteSpace (version 6.1. R2), crafted under the guidance of Professor Chen C, assumed a prominent role. It facilitated the generation of collaboration analyses, dual-map overlays for journals, cluster analyses concerning co-cited references and keywords, and identification of references and keywords undergoing pronounced citation bursts. Simultaneously, VOSviewer, an instrument developed by Leiden University, Netherlands, contributed significantly to the study. It was employed to construct and visualize bibliometric networks, yielding a more comprehensive understanding of 1) co-citation patterns and 2) co-occurrence patterns. In the VOSviewer-generated figure, each node signifies an item encompassing countries, institutions, co-cited references, and keywords. Node size correlates with quantities, while colors correspond to distinct years. The thickness of lines between nodes conveys the potency of collaboration or co-citation relationships. Moreover, for the analysis and visualization of annual publication trends, GraphPad Prism v8.0.2 was enlisted. The Impact Factor (IF) of journals was garnered from the Journal Citation Reports of 2021.

Results

Global contribution to the field

Employing the previously outlined literature search strategy, a comprehensive total of 1,663 publications fulfilled the stipulated criteria, thus constituting the dataset for the ensuing analysis (Figure

Table 1: The top 10 productive countries/regions related to gastric cancer immunotherapy.

Rank	Country/region	Article counts	Percentage (N/1663)	Citation	Citation per publication
1	China	837	50.331	12324	14.724
2	USA	331	19.904	10578	31.958
3	Japan	137	8.238	3128	22.832
4	Germany	100	6.013	2479	24.79
5	Italy	99	5.953	2245	22.677
6	South Korea	84	5.051	1508	17.952
7	England	82	4.931	2363	28.817
8	France	37	2.225	1413	38.189
9	Spain	35	2.105	682	19.486
10	Iran	31	1.864	260	8.387

Table 2: The top 10 institutions published literature related to gastric cancer immunotherapy.

Rank	Institution	Country	Article counts	Total citations	Average citation
1	Fudan University	China	65	1268	19.508
2	Nanjing Medical University	China	56	710	12.679
3	Shanghai Jiao Tong University	China	53	958	18.075
4	Sun Yet Sen University	China	45	1155	25.667
5	Zhengzhou University	China	39	577	14.795
6	University of Texas MD Anderson Cancer Center	USA	34	1085	31.912
7	Zhejiang University	China	33	1031	31.242
8	Sungkyunkwan University	South Korea	31	721	23.258
9	Peking University	China	29	832	28.67
10	China Medical University	China	28	629	22.464

Table 3: The top 10 productive journals related to gastric cancer immunotherapy.

Rank	Journal	Article counts	Percentage (N/1663)	Citation per article	IF
1	Frontiers in Oncology	78	4.69	5.128	5.738
2	Cancers	58	3.488	5.621	6.575
3	Frontiers in Immunology	38	2.285	10.421	8.786
4	Oncoimmunology	30	1.804	23.767	7.723
5	Frontiers in Cell and Developmental Biology	29	1.744	3.724	6.081
6	Journal for Immunotherapy of Cancer	27	1.624	20.852	12.469
7	Oncotargets and Therapy	24	1.443	23.583	4.345
8	Oncology Letters	24	1.443	10.292	3.111
7	BMC Cancer	24	1.443	9.958	4.638
10	World Journal of Gastroenterology	20	1.203	25.6	5.374

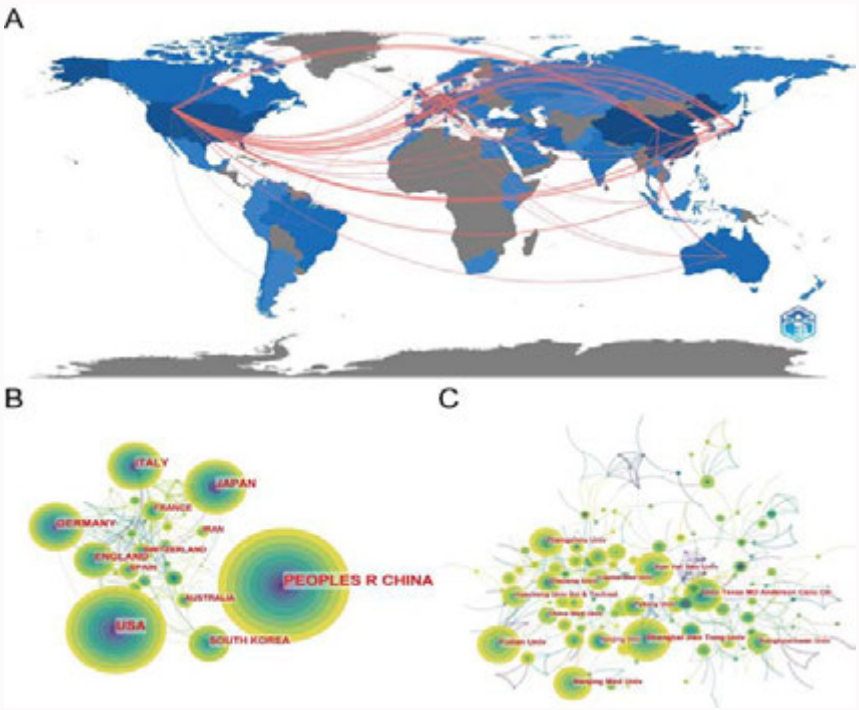

Figure 3: Mapping of countries/regions and institutions associated with gastric cancer immunotherapy. (A) The geographical network map of gastric cancer immunotherapy. (B) Country/regional collaboration analysis. (C) Institutional collaboration analysis. The nodes represent countries/regions or institutions, and the lines connect them. Nodes represent countries/regions or institutions. The number of publications grows proportionally to the size of the nodes. The lines between the nodes represent the cooperation relationship, and the thickness of the connecting lines represents the strength of their cooperation, the closer the cooperation, the thicker and the connecting lines. The nodes with the outermost purple circles have higher centrality. From 2012 to 2022, the color changes from purple to yellow.

1). Spanning the period between 2012 and 2022, the trajectory of annual publications exhibited a noteworthy surge, transitioning from a scant number of articles to surpassing the 400-article mark (Figure 2A). Remarkably, the zenith in Relative Research Interest (RRIs) was attained in the year 2022 (Figure 2A). In totality, a broad spectrum of 73 countries and regions contributed to the corpus of GC immunotherapy research. Of these, China emerged as the most prolific, churning out a staggering 837 papers, constituting 50.331% of the total output. Following suit, the USA accounted for 331 publications (19.904%), trailed by Japan with 137 (8.238%), Germany with 100 (6.013%), and Italy with 99 (5.953%) publications (Figure 2B, 2C and Table 1). Noteworthy is the trajectory of China, characterized by an exponential growth in publications since 2016 (Figure 2D), mirroring the nation's economic ascent. Additionally, a predictive model was constructed employing a generalized additive model, incorporating time and publication counts, to prognosticate the future trend in global publications (Figure 2E). Remarkably, the annual growth trajectory concurred with the fitting curve Y=33.3909 * X-67198.2818 (R^2=0.82996), underscoring a compelling alignment between the actual growth pattern and the predictive model (Figure 2E).

Distribution of countries and institutions

The compilation of these publications was sourced from a diverse array of 73 countries and 481 institutions, with the top 10 countries boasting representation from Asia, North America, and Western Europe (Table 1). The cumulative contributions of the USA and China eclipsed the 70% threshold, significantly surpassing other nations in terms of publication output. Notably, China attained a remarkable citation count of 12,324, a figure notably higher than any other country. However, France exhibited the highest citation-to-publication ratio, reaching an impressive 38.189 (Table 1). Evidently, the USA secured the second-highest citation count at 10,578, accompanied by a citation-to-publication ratio of 31.958, positioning it as a paragon of both quantity and quality within the realm of published papers (Table 1).

The subsequent foray into the realm of global collaboration was effectively visualized in Figure 3A, wherein node sizes were indicative of document numbers. The synergy between China and the USA was palpable, with prominent collaboration emerging between China and the USA, and to a lesser extent, Germany. Simultaneously, the USA exhibited collaboration with multiple countries, including Germany, France, South Korea, Israel, and Switzerland. Noteworthy is China's preeminence in publication output, albeit with a centrality of 0.14, compared to the USA's centrality of 0.23. The network analysis highlighted predominant collaboration centers encompassing the USA, England, Canada, Austria, and China (Figure 3A).

Table 2 encapsulates the most prolific institutions from China, the USA, and even South Korea's Sungkyunkwan University. Fudan University led the pack, churning out 65 papers accompanied by 1,268 citations, followed by Nanjing Medical University (56 papers, 710 citations) and Shanghai Jiao Tong University (53 papers, 958 citations). Among the top 10 productive institutions, the University of Texas MD Anderson Cancer Center displayed the loftiest citation-to-publication ratio, reaching 31.912. Institutional collaboration patterns were also dissected, unraveling cooperative dynamics among institutions (Figure 3A, 3C).

Analysis of journals and research areas

Since 2012, a substantial corpus of 1,663 articles has graced the pages of 481 journals. The most prolific journals are showcased

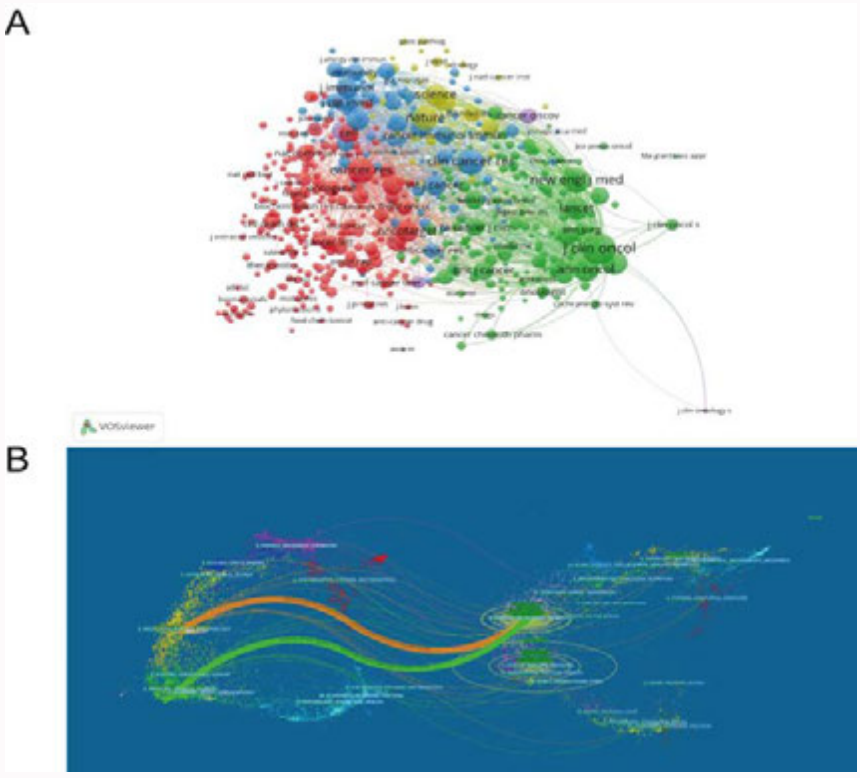

Figure 4: Articles published in different journals on gastric cancer immunotherapy. (A) Network map of journals that were co-cited in more than 20 citations. (B) The dual-map overlay of journals related to gastric cancer immunotherapy.

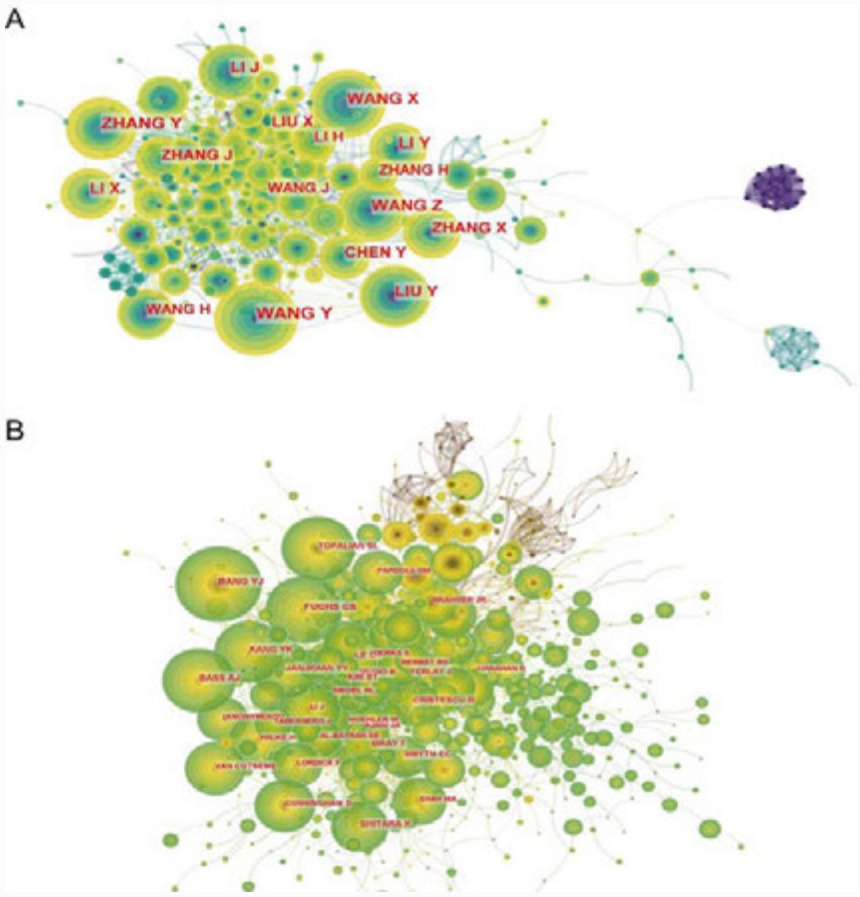

Figure 5: A CiteSpace network visualization of author collaboration analysis and co-cited authors regarding gastric cancer immunotherapy. (A) Author collaboration analysis. (B) Network visualization diagram of the co-cited authors of the Publications. Author collaboration or co-cited authors are indicated by the node. The co-citation relationship is indicated by the line connecting the nodes. The node area grows as the number of co-citations increases. The colors represent different years, in A, the color changes from purple to yellow from 2012 to 2022, and in B, the color changes from brown to green from 2012 to 2022.

Table 4: The top 10 well-represented research areas.

Rank	Research Areas	Records	Percentage (N/1663)
1	Oncology	879	52.856
2	Immunology	212	12.748
3	Research experimental medicine	167	10.042
4	Cell Biology	140	8.419
5	Gastroenterology hepatology	116	6.975
6	Pharmacology Pharmacy	116	6.975
7	Biochemistry Molecular biology	114	6.855
8	Biotechnology applied microbiology	76	4.57
9	General internal medicine	64	3.848
10	Genetics heredity	57	3.428

Table 5: The top 10 co-cited journals related to gastric cancer immunotherapy.

Rank	Cited Journal	Citations	IF
1	Journal of Clinical Oncology	4559	50.717
2	New England Journal of Medicine	2538	176.079
3	Clinical Cancer Research	2509	13.801
4	Cancer Research	2477	13.312
5	Annals of Oncology	2000	51.769
6	Lancet Oncology	1982	54.433
7	Nature	1968	69.504
8	Lancet	1783	202.731
9	Science	1502	63.714
10	Oncotarget	1432	-

in Table 3, elucidating the top 10 publications with the highest publication count, accompanied by their corresponding recent Impact Factors (IFs). Chief among these is Frontiers in Oncology, contributing a noteworthy 78 publications, constituting 4.69% of the entire article collection. This is trailed by Cancers (58, 3.488%) and Frontiers in Immunology (38, 2.285%). Noteworthy is the Journal for Immunotherapy of Cancer, reigning supreme with the highest IF at 12.469, followed closely by Frontiers in Immunology with an IF of 8.786.

Expanding on this, the analysis extended to encompass journals co-cited more than 20 times (Figure 4A), with Table 3 outlining the top 10 co-cited journals involved in the publication of related articles. Leading the roster is Journal of Clinical Oncology, amassing 4,559 citations, followed by New England Journal of Medicine (2538) and Clinical Cancer Research (2509).

Within this scholarly landscape, the publications converge across 55 research domains. Table 4 underscores the top 10 well-represented research areas, with oncology commanding a formidable

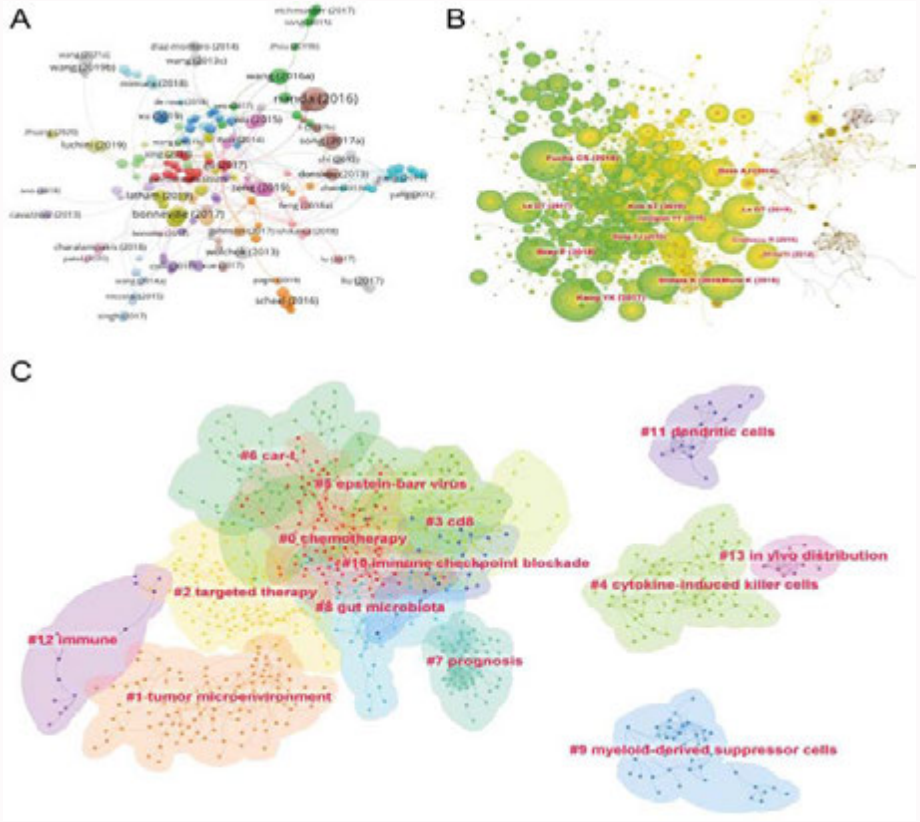

Figure 6: Mapping of documents and references in studies ongastric cancer immunotherapy.(A) Network map of citation analysis of documents with more than 25 citations. (B) Network map of co-citation analysis of references based on CiteSpace. (C) Clustering analysis of the co-citation network based on CiteSpace.

Table 6: The top 10 authors with the most publications and citations on gastric cancer immunotherapy.

Rank	High Published Authors	Country	Article counts	Co-cited Authors	Total citations
1	Wang Y	China	33	Bang YJ	623
2	Zhang Y	China	31	Fuchs CS	549
3	Zhang H	China	26	Le DT	417
4	Li H	China	25	Shitara K	416
5	Liu Y	China	25	Janjigian YY	382
6	Li J	China	23	Kang YK	381
7	Shen L	China	22	Bass AJ	335
8	Li Y	China	21	Bray F	273
9	Liu X	China	21	Muro K	260
10	Yang Y	China	21	Smyth EC	259

presence at 879 records, signifying 52.856% of the entire compilation. It is succeeded by Immunology (212, 12.748%), and Research Experimental Medicine (167, 10.042%) (Table 5).

Furthermore, a dual-map overlay of journals, a method delineated by [12], serves to depict the dynamic citation interplay between citing and cited journals (Figure 4B). The oscillating wave from left to right describes the citation relationships, represented by the colored trajectories. The illustration unveils two prominent citation trajectories demarcated in orange and green, indicative of documents in the molecular/biology/genetics domain being extensively cited by researchers publishing in molecular/biology/immunology and medical/medical/clinical journals.

Authors analysis

Within the realm of gastric cancer immunotherapy literature spanning the last decade, the ten most prolific authors have been succinctly documented in Table 6. Wang Y emerges as the most prolific, having contributed 33 publications, closely followed by Zhang Y (31 publications) and Zhang H (26 publications). A noteworthy revelation is that the entirety of the top 10 authors hails from China. Subsequent analysis delves into author collaboration dynamics, culminating in the visualization of the cooperation interplay between researchers (Figure 5A). The co-cited author network, graphically portrayed in Figure 5B, is an illuminating tapestry of connections between the most co-cited authors. Foremost among these are Bang YJ (623 citations), Fuchs CS (549 citations), Le DT (417 citations),

Table 7: The top 5 documents with the most citations in the field of gastric cancer immunotherapy.

Rank	Title	Corresponding Author	Journal	IF	Publication year	Total citations
1	Pembrolizumab in patients with advanced triple-negative breast cancer: phase Ib KEYNOTE-012 study	Rita Nanda	Journal of Clinical oncology	50.717	2016	1218
2	Landscape of Microsatellite Instability Across 39 Cancer Types	Sameek Roychowdhury	JCO precision oncology	5.479	2017	423
3	Progress in the treatment of advanced gastric cancer	Xuedong Fang	Tumor Biology	-	2017	398
4	PD-L1 expression in human cancers and its association with clinical outcomes	Jinming Yu	Onco Targets and therapy	4.345	2016	371
5	PD-1+ regulatory T cells amplified by PD-1 blockade promote hyper progression of cancer	Hiroyoshi Nishikawa	Proceedings of the National Academy of Sciences	12.779	2019	347

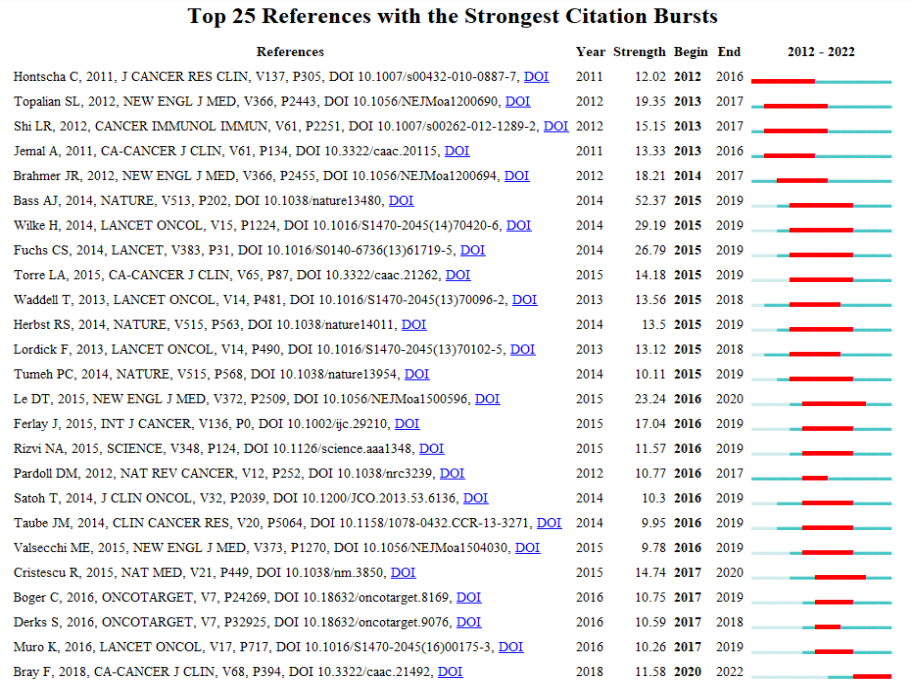

Figure 7: Top 25references with strongest citation bursts of publications related to gastric cancer immunotherapy.

Shitara K (416 citations), and Janjigian YY (382 citations), as enumerated in Table 6.

Citation and co-citation analysis

Within the realm of this field, a substantial cohort of 341 articles has garnered more than 25 citations, as depicted in Figure 6A. The pinnacle of the most cited documents is succinctly encapsulated in Table 7. Foremost is the article titled "Pembrolizumab in patients with advanced triple-negative breast cancer: Phase Ib KEYNOTE-012 study," amassing 1,218 citations. This is followed by "Landscape of Microsatellite Instability Across 39 Cancer Types," accruing 423 citations, and the article titled "Progress in the treatment of advanced gastric cancer," commanding 398 citations.

Delving deeper into the analysis, the co-cited references were meticulously scrutinized through CiteSpace, culminating in the identification of the top 5 references with the highest citation counts (Table 8). Notable inclusions are Bass AJ (2014; 334 citations), Narikazu Boku (2017; 283 citations), Freddie Bray (2018; 267 citations), Charles S. Fuchs (2018; 250 citations), and Yung-Jue Bang (2010; 209 citations).

These co-cited references underwent clustering based on indexing terms, resulting in 14 major clusters. As illustrated in Figure 6C, these clusters encompass various themes, including chemotherapy, tumor microenvironment, targeted therapy, CD8, cytokine-induced killer cells, Epstein-Barr virus, CAR-T, prognosis, gut microbiota, myeloid-derived suppressor cells, immune-checkpoint blockade, dendritic cells, immune response, and *in vivo* distribution.

Moreover, the identification of references with citation bursts unveils the dynamism of their influence over time within a specific domain [13]. Our study pinpointed the top 25 references with the most robust citation bursts, with Figure 7 offering a glimpse into this phenomenon. Topping the chart is the article titled "Clinical trials on CIK cells: first report of the International Registry on CIK cells (IRCC), published in 2011, boasting burst strength of 12.02. Additionally, the citation bursts exhibited by articles authored by Bray F extended from 2018 to 2022.

Co-occurrence analysis of keywords

The exploration of research frontiers was facilitated through VOSviewer, which undertook a co-occurrence analysis of keywords. From this, 125 keywords were identified (with a minimum occurrence threshold of 25). The top five keywords, by occurrence, were discerned as immunotherapy (794), gastric cancer (586), expression (329), gastric-cancer (295), and chemotherapy (272), as delineated in Figure 8A.

A network map was also forged to visualize the distribution of

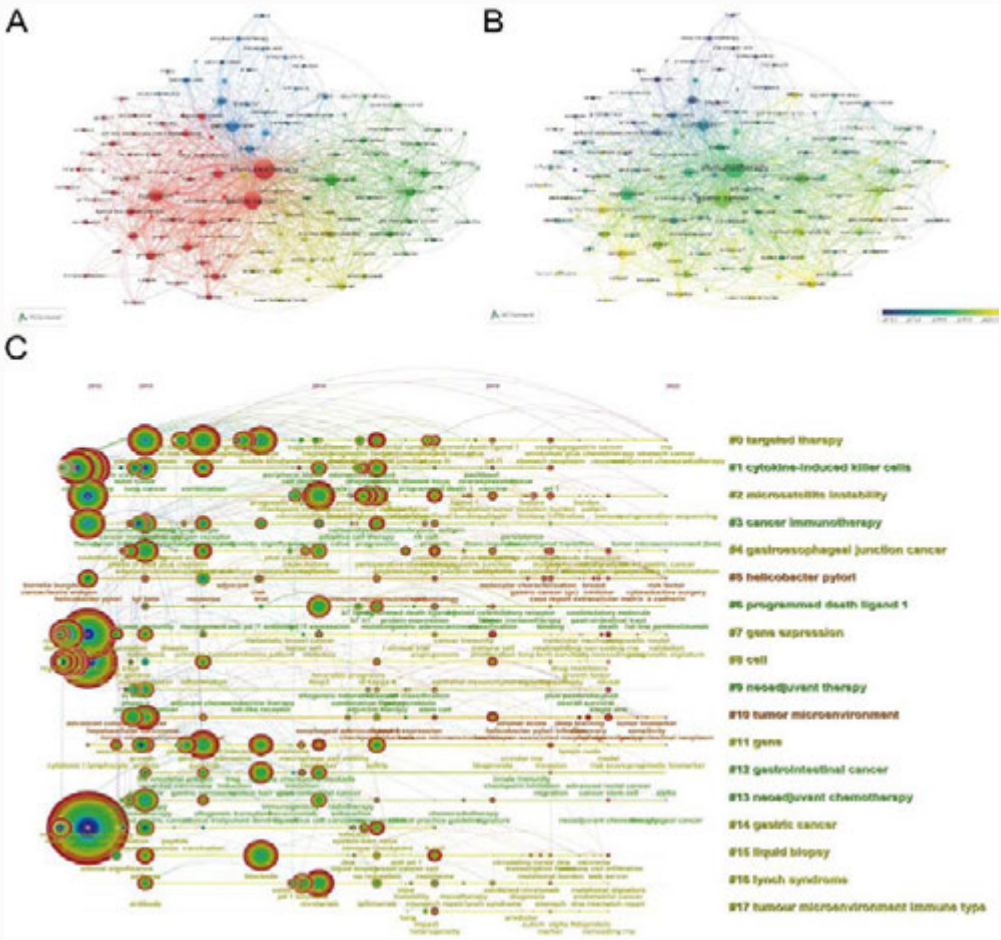

Figure 8: Mapping of keywords in studies on gastric cancer immunotherapy. (A) Network visualization of keywords. (B) Distribution of keywords according to average publication year (blue: earlier, yellow: later). (C) Keyword timeline visualization from 2012 to 2022.

Table 8: The top 5 co-citation analysis of cited reference on gastric cancer immunotherapy.

Rank	Title	Corresponding Author	Journal	IF	Publication year	Total citations
1	Comprehensive molecular characterization of gastric adenocarcinoma	Bass, A, J	Nature	69.504	2014	334
2	Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial	Narikazu Boku	Lancet	202.731	2017	283
3	Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries	Freddie Bray	Ca-A Cancer Journal for Clinicians	286.13	2018	267
4	Safety and efficacy of pembrolizumab monotherapy in patients with previously treated advanced gastric and gastroesophageal junction cancer: phase 2 clinical KEYNOTE-059 trial	Charles S. Fuchs	JAMA oncology	33.006	2018	250
5	Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial	Yung-Jue Bang	Lancet	202.731	2010	209

keywords based on their average publication years, color-coded from dark blue (earlier) to yellow (later) (Figure 8B). Remarkably, a surge in keyword publications transpired in 2019. Notably emerging keywords, such as tumor microenvironment, prognosis, biomarker, and nivolumab, surfaced after the year 2020. The intricate interplay between affiliations, authors, and keywords in the domain of gastric cancer immunotherapy was encapsulated in Figure 9A.

An insightful portrayal of the dynamic evolution of keyword clusters over time is rendered in Figure 8C. This analysis detected 18 distinct clusters, encompassing realms like targeted therapy, cytokine-induced killer cells, microsatellite instability, cancer immunotherapy, gastroesophageal junction cancer, *Helicobacter pylori*, programmed death ligand 1, gene expression, cell biology, neoadjuvant therapy, tumor microenvironment, gene studies, gastrointestinal cancer, neoadjuvant chemotherapy, gastric cancer, liquid biopsy, Lynch syndrome, and tumor microenvironment immune types.

Further employing CiteSpace's algorithm, the burst of keywords was detected, thereby unearthing the top 20 keywords with the most formidable burst strengths (Figure 9). Of particular significance, the keyword "adoptive immunotherapy" seized the spotlight with burst strength of 15.16, trailed by "cytokine-induced killer cell" (11.66) and "CIK cell" (10.4). Noteworthy is the fact that the keyword

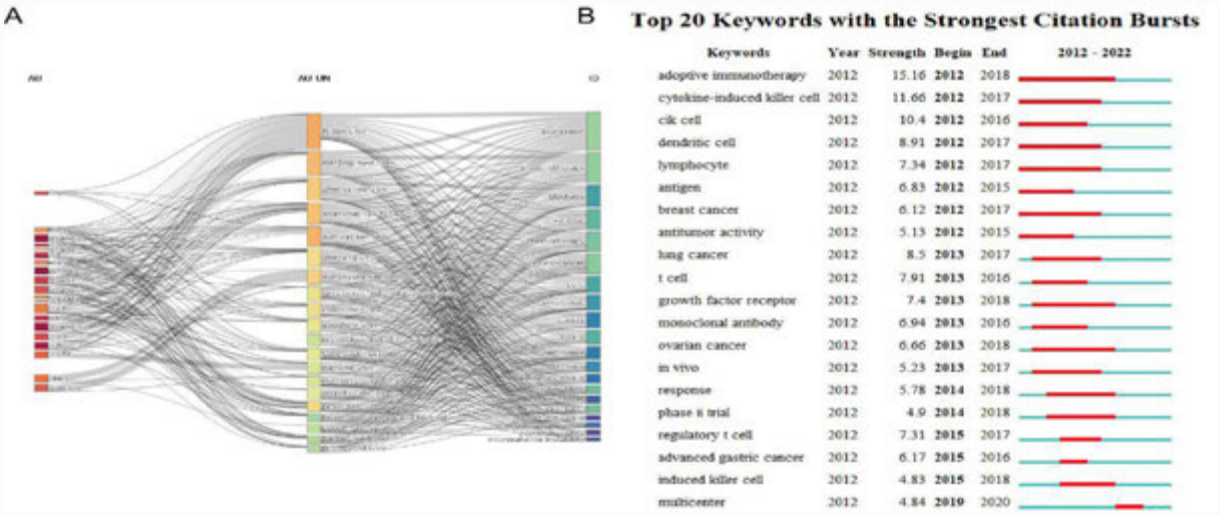

Figure 9: (A) Three-field plot of the Keywords Plus analysis on gastric cancer immunotherapy Notes: three-field plot of the keywords plus analysis: (middle field: affiliations; left field: authors; right field: keywords plus). (B) Top 20 keywords with the strongest citation bursts of publications related to gastric cancer immunotherapy.

"multicenter" experienced recent citation outbreaks spanning 2019 to 2020, implying that the nexus between GC immunotherapy and clinical trials might burgeon into a research hotspot in the near future.

Discussion

Over the course of decades, dedicated endeavors have been channeled into the realm of gastric cancer research, ushering in substantial advancements in the domain of diagnosis and treatment. Yet, the challenge persists in crafting treatment modalities that not only wield optimal effectiveness but also minimize adverse effects. It is within this context that immunotherapy, with its capacity to elicit, enhance, or modulate immune responses, has progressively garnered attention as a promising avenue for GC treatment [14].

Spanning the years from 2012 to 2022, the realm of cancer immunotherapy has substantiated its potential in the treatment landscape, having demonstrated efficacy and safety in diverse malignancies, encompassing melanoma and extending to breast cancer [15], prostate cancer [16], kidney cancer [17], and lung cancer [18,19]. Embarking upon this backdrop, the present study orchestrates a bibliometric analysis, hinging on the utilization of CiteSpace, VOSviewer, and R package "Bibliometrix". Through these tools, an in-depth dissection of the developmental trajectory of GC immunotherapy over the last decade transpires, with a twofold aim: To distill the prevailing research landscape and forecast forthcoming hotspots within the realm of immunotherapies for GC research.

Overview of the development of GC immunotherapy

This study has discerned a substantial upward trajectory in annual publication output spanning the period from July 1st, 2012, to July 1st, 2022. A particularly pronounced surge in publications, exceeding 400 in number, transpired in 2021, and an indicator of the escalating momentum in research endeavors. Moreover, the Relative Research Interests (RRIs) have surged notably in recent years, signifying the burgeoning popularity of the field. These collective trends underscore a heightened focus on GC immunotherapy in recent times.

In terms of global contributions, the expansive reach of this research is evident, with representation from around 73 countries and 481 institutions. China has emerged as the most prolific contributor, accounting for a significant 50.331% of the publications, followed by the USA (19.904%), Japan (8.238%), Germany (6.013%), and Italy (5.953%). Delving deeper, the impact of national contributions extends to total citations, a pivotal parameter shaping the quality and academic influence of various countries. The interplay of contributions and citations portrays China as a particularly influential force in this domain. Curiously, France claims the lead in average citations, trailed by the USA and England. However, an insightful analysis indicates that while China is a leader in publication quantity, it still has room for enhancing the quality of its studies in this sphere, ranking ninth in citations per publication.

Within the scientific institutions landscape, eight out of the top ten establishments hail from China. Fudan University, Nanjing Medical University, and Shanghai Jiao Tong University emerged as dynamic players at the forefront of research. Meanwhile, the University of Texas MD Anderson Cancer Center in the USA secured the highest average citations, an accolade underlining its scholarly impact.

This confluence of evidence signals that collaborative, in-depth investigations are poised to play a pivotal role in propelling the advancement of immunotherapies within the ambit of gastric cancer research. The results galvanize researchers towards conducting high-caliber research and fostering future breakthroughs through effective cooperation.

Influential journals, authors and studies in the GC immunotherapy research

Journals' Landscape: A meticulous exploration into the journal landscape has unveiled intriguing dynamics (Figure 3). Notable frontrunners include Frontiers in Oncology (78 publications), Cancers (58 publications), and Frontiers in Immunology (38 publications). However, it's the Journal of Clinical Oncology that clinches the limelight with the highest citation count. An interesting observation emerges when contrasting the top two journals with the collective publications of the third to sixth-ranked ones. This intriguing pattern posits the top 10 journals as promising contenders for disseminating future high-quality research. Concurrently, the dual-map overlay (Figure 4B) adds another layer of insight, with the co-citation analysis spotlighting journals aligned with oncology and clinical themes. A

bifurcation emerges: Molecular/biology/genetics co-cited journals are linked to counterparts in molecular/biology/immunology and medical/medical/clinical domains. This dual trajectory signifies basic research and clinical translation as the dual engines propelling GC immunotherapy's advancement.

Prolific Minds: The exploration of prolific authors (Table 6) has showcased Wang Y (33 publications) at the forefront, followed by Zhang Y (31 publications) and Zhang H (26 publications). Notably, all top authors are of Chinese origin, underscoring the dominant role China plays. The correlation between highly productive authors and China's prominent institutions further solidifies this impact. These trailblazers, with a robust foundation laid in earlier contributions, hold the promise of propelling GC immunotherapy research into new realms.

Collaborative Co-citations: In the realm of co-cited authors, the network map (Figure 5B) amplifies the influence of Bang YJ (623 citations). Bang YJ's seminal article, "Comprehensive molecular characterization of gastric adenocarcinoma", published in Nature, holds immense significance. This work introduces a molecular classification demarcating four genomic subtypes of gastric cancer [20], paving the way for tailored therapeutic approaches.

Citation Echoes: The network map and co-citation analysis yield insights into publication impact. Notable landmarks are unveiled in Table 7, with the top 5 co-cited articles resonating strongly with Immune Checkpoint Inhibitors (ICIs). These references underscore ICIs' pivotal role in the field. Among these is the globally informed "Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries" [21], contributing a panoramic view of cancer's global prevalence and therapeutic landscape. Additionally, the molecular classification paper mentioned earlier resonates, offering a roadmap for patient stratification and targeted therapies.

Clusters of Focus: The cluster analysis paints a vivid picture of research focal points (Figure 6C). These clusters encompass chemotherapy, targeted therapy, Epstein-Barr virus, and prognosis, reflecting the ongoing interest in routine prognosis and treatment approaches. Concurrently, the emergence of CD8, cytokine-induced killer cells, CAR-T, myeloid-derived suppressor cells, immune-checkpoint blockade, and dendritic cells clusters signals the surge in advanced immunotherapy avenues. A noteworthy highlight is the exploration of Chimeric Antigen Receptor-T Cell Therapy (CAR-T) [23], underlining its significance. Additionally, tumor microenvironment, gut microbiota, immune, and *in vivo* distribution clusters herald new frontiers, signaling a shift towards exploring intricate relationships with the tumor milieu, microbiota, and immune interactions [24-29].

In sum, this comprehensive analysis not only captures the nuances of GC immunotherapy's evolution but also hints at the trajectory ahead. As scholars navigate these research currents, the interplay of cooperation, citation, and exploration promises to illuminate novel horizons in the quest for effective GC immunotherapies.

Research hotspots and frontiers

As showcased in Table 7, the realm of GC immunotherapy traverses a diverse spectrum of research domains, offering a panoramic view of the prevailing directions and frontiers within the field. Notably, the spotlight shines brightly on adoptive cell immunotherapy, commanding widespread attention due to its transformative impact on GC treatment strategies. Specifically, Adoptive Cell Therapy (ACT) has emerged as a formidable player, harnessing genetically-modified, tumor-specific immune cells to fortify the immunogenic response against tumor antigens [30]. Delving into the details, the work of Jiang et al. serves as a testament to the advancements in this terrain. Through a marriage of hybridoma and humanization techniques, they crafted Claudin18.2-specific humanized antibodies. This feat paved the way for the creation of specific CAR T cells *via* lentiviral vector transduction. These engineered cells then demonstrated their mettle, wielding anti-gastric cancer effects both *in vitro* and *in vivo* [31]. Akin to a symphony, the synergy of claudiximab (IMAB362, anti-claudin monoclonal antibody) with chemotherapy has orchestrated promising results as a first-line therapy for advanced GC/GEJ cancer patients. With a spotlight on Claudin18.2 expression, this combination has orchestrated improved Progression-Free Survival (PFS) and Overall Survival (OS), charting a path toward enhanced therapeutic outcomes [32]. Meanwhile, in the domain of Cytokine-Induced Killer cells (CIK), a notable endeavor led by Jiang et al. introduced a groundbreaking fusion of autologous Cytokine-Induced Killer (CIK) cells and chemotherapy. This pioneering amalgamation bore fruit, enriching the survival benefits for patients grappling with advanced gastric cancers [33]. The implications are profound. As the luminous realm of adoptive cell therapy unfolds, its potential to revolutionize GC treatment assumes paramount significance. Yet, the journey ahead beckons for more prospective ACT studies, wielding the power to unveil deeper and more robust evidence in the pursuit of refining GC treatment paradigms.

In the constellation of research clusters depicted in Figure 8, a distinct spotlight is cast upon the terrain of immunotherapy mechanisms. Within this intricate tapestry, the luminary keywords "Microsatellite Instability (MSI)", "*Helicobacter pylori*", and "tumor environment" form a constellation of their own, shedding light on pivotal avenues of exploration. A symphony of studies, as eloquently synthesized by Ratti et al. unveils a subgroup within gastric cancer characterized by microsatellite instability. This subgroup, while modest in size, proves exquisitely receptive to the ministrations of immunotherapeutic interventions like anti-PD-L1 and anti-CTLA4 antibodies [34]. The story further unfolds in an exploratory study, meticulously stratifying patients by their microsatellite status within the nivolumab arm. With molecular profiling unraveling the composition, a resounding 29% Objective Response Rate (ORR) emerges in MSI-High patients, juxtaposed against 11% in MSI-Low counterparts, and 9% in the cohort marked by an enigmatic microsatellite status [35,36]. In the grand saga of gastric tumorigenesis, *Helicobacter pylori* surfaces as a protagonist of profound consequence. A symphony of studies attests to their role as a veritable ringleader in activating oncogenic signaling and orchestrating immunosuppression [37]. This intricate interplay unfolds as vacuolating cytotoxin and the CagA protein emerge as instrumental actors, while the nexus between *H. pylori* and β-catenin along with the transactivation of EGFR paints a vivid mosaic of tumorigenic orchestration [38]. Yet, the tale extends beyond these molecular duets. *Helicobacter pylori*, as a maestro of immunosuppression, orchestrates intricate symphonies with diverse cell types. Take for instance the ballet between bone marrow-derived mesenchymal stem cells and T cells, an endeavor masterfully choreographed by Lin et al. Their harmonious partnership, unveiled within a chronic *H. pylori*-infected mouse GC model, results in the nuanced art of immunosuppression [39]. The narrative weaves a tapestry where immunotherapy mechanisms and environmental

interplays unfurl. As the chapters unfold, the dialogue between these elements promises to reshape our understanding and illuminate pathways to harnessing the innate potential of GC immunotherapy.

Within the lexicon of contemporary research, the keyword "tumor environment" emerges as a beacon of intense fascination. This keyword encapsulates a pivotal avenue of inquiry: the intricate web of interactions woven within the tumor microenvironment. Picture this milieu-a rich tapestry interwoven with inflammatory cells, fibroblasts, nerves, and the delicate architecture of vascular endothelial cells. The extracellular matrix weaves its own story, each thread contributing to the tapestry that is the habitat of cancer cells [40]. Yet, the narrative here extends beyond structural elements. It's a symphony of paracrine interactions, where cells within the tumor environment orchestrate a complex ballet, dictating the behavior of their counterparts [40]. But this environment, while it nurtures cancer cell proliferation and expansion, can harbor darker intentions. Immune escape and therapy resistance are sinister repercussions emanating from this intricate dance. Consider Myeloid-Derived Suppressor Cells (MDSCs), a troupe of myeloid progenitors and immature myeloid cells. In their nuanced performances, they sway the immune response, casting a shadow over CD8+ T cells. In this tango of immunosuppression, MDSCs express PD-L1 and CTLA-4, curating an environment that shields the tumor from immune surveillance [40]. The resonance of their presence reverberates across diverse cancer models, boosting tumor progression and scripting a narrative of chronic inflammation [41]. With these revelations, the narrative takes a crucial turn. The tumor microenvironment, once an enigmatic backdrop, now steps into the spotlight as a pivotal player in the drama of immunotherapy. Emerging from this intricate tapestry are pivotal figures: "tumor microenvironment", "myeloid-derived suppressor cells", "lymphocytes", and "regulatory T cells"- the protagonists of an ongoing saga that resonates deeply in the realm of GC immunotherapy. As researchers delve deeper into these themes, the hope is to rewrite the script, to transform the tumor environment from a fortress of resistance to a haven of therapeutic opportunity.

The landscape of targeted therapy unfolds with a tapestry woven from diverse threads- "immune checkpoint inhibitors", "gene therapy", and "gut microbiota"- a narrative that converges on the clinical horizon, heralding the advancement of gastric cancer treatment. At the heart of this narrative, immune checkpoint inhibitors stand as monumental pillars, pivotal in GC immunotherapy. It's a familiar tale-tumors wielding a potent arsenal to disable T cell guardians through the cunning mechanisms of immune checkpoint pathways [42,43]. But here, science takes up arms. Enter the protagonists: CTLA-4 and PD-1/PD-L1, checkpoints that can be intercepted. Researchers orchestrate checkpoint inhibitors, orchestrating a crescendo that unleashes the anti-tumor prowess of T cells. The symphony plays out- cancer cells are confined, their escape routes blocked, and the immune system reclaims its vigilance [44]. In this saga of innovation, Pembrolizumab emerges as a luminary. The first PD-1-targeted monoclonal antibody, it earned FDA's approval to combat advanced non-small cell lung cancer in 2017 [45]. The tale continues in a phase I clinical trial, the KEYNOTE-012/NCT01848834, where patients with advanced triple negative breast cancer, head and neck cancer, urothelial cancer, and GC step into the limelight. Here, safety and anti-tumor activity are the echoes of Pembrolizumab's journey [46]. But the narrative encompasses more than checkpoints. Gene therapy, a chapter often etched in preclinical trials, unfurls with the promise of oncogenes and tumor suppressor genes- cMYC, s-FLT1, TP53- as protagonists [47-49]. Their impact reverberates across the laboratory, weaving together hopes of targeted precision and the dream of therapies fine-tuned at the genetic level. And amidst these threads, a surprising interlude- "gut microbiota". A seemingly unconventional contributor to the narrative, its presence is marked in the co-occurrence, an intriguing hint at a subplot yet to be fully unraveled. In a tale where every element holds significance, the microbiota too may hold a pivotal role, an unseen influencer shaping the tapestry of GC immunotherapy. As the story of targeted therapy unfolds, it is clear that its pages hold promise, potential, and possibility- a narrative driven by scientific fervor to conquer the formidable realm of gastric cancer.

Indeed, the curtain rises on a new scene in the world of GC immunotherapy- the spotlight now illuminates the enigmatic realm of gut microbiota, a novel and vibrant research hotspot. With every revelation, the intricacies of this microbial world come into focus, revealing its profound role in the intricate dance of tumorigenesis. In this microbial ballet, *Streptococcus Bovis* takes an unexpected turn, moving from its conventional role as an instigator of colorectal cancer to new stage-GC patients. A shift in proportions hints at its involvement in the GC narrative [50]. But it's not alone; another actor, Propionibacterium acnes, takes center stage with its overabundance in GC tissues. It's a role that sparks curiosity, as the hypothesis unfolds that this microbe, armed with the ability to produce short-chain fatty acids, stirs the flames of lymphocytic gastritis [51,52]. Together, they present a tantalizing idea- the presence of specific microbes shaping the trajectory of GC. But the microbiota's influence goes beyond mere development- it wields the power to alter the course of progression. *H. pylori* often a villain in the gastritis saga, finds itself tamed by the presence of other microbes. Enter the helminth, *H. polygyrus*, and the stage is set for a tale of relief. Co-infection with these two actors bestows INS-GAS mice with gift- lower rates of *H. pylori*-associated gastric woes and resistance to colonization, a twist in the tale of pathology [53]. With this revelation, the microbiota stakes its claim as a new frontier in the GC immunotherapy narrative.

But the drama doesn't end there. Bursting onto the scene, the keyword "biomarker" takes a bow. Since 2020, its citation has erupted, a sign that it's poised to seize the spotlight as an emerging research focal point. The need for fresh biomarkers in the GC saga is urgent, their significance reaching far beyond mere diagnosis. They're the markers of clinical stages, the barometers of treatment responses, the sentinels of recurrence [54]. In this intricate plot, PD-L1 and MSI shine as stars, their up-regulated expressions tied to pembrolizumab's efficacy [54-59]. A twist in the narrative reveals that these markers hold sway over the EBV-positive sub-type, illuminating the path for precision treatment with immune checkpoint inhibitors [20]. As the tale unfolds, the intricate threads of gut microbiota and biomarkers interweave, painting a picture of promise and potential. The story of GC immunotherapy is evolving, its protagonists expanding to include not just cells and therapies, but also the unseen microbial actors that influence its course. And in this tale, science takes center stage, guiding the narrative toward a brighter future for GC treatment.

Limitation

Certainly, while this study has illuminated significant insights into the world of GC immunotherapy, it's essential to acknowledge its limitations, ensuring a transparent portrayal of its findings. Foremost among these limitations is the reliance on a single data source- the WoSCC database. This restriction may inadvertently

exclude valuable articles lurking in other corners of the academic realm, such as PubMed, Cochrane, and Embase library databases. The omission of these articles could potentially paint an incomplete picture of the broader landscape of GC immunotherapy research. Additionally, the human touch introduced an element of subjectivity. The manual exclusion of certain publications, while essential to maintain relevance, can inadvertently introduce selection bias. The delicate balance between inclusion and exclusion could influence the composition of the dataset, and thus the conclusions drawn. Language bias, an often-overlooked facet, also has a role to play. By focusing solely on English language publications, there's the possibility of sidelining a wealth of non-English contributions. This could, in turn, lead to an underrepresentation of valuable research from parts of the world where English is not the primary language of publication. The dynamic nature of research is another factor to consider. The WoSCC database, while a valuable resource, isn't a crystal ball into the future. Its snapshot of the academic world might not capture the most cutting-edge research if it's still in its nascent stages, yet to accumulate the citations that place it on the radar. As the curtain closes on this study, it's crucial to cast an understanding light on its limitations. These nuances remind us that every analysis, while informative and enlightening, is a slice of a much larger whole. It's a reminder that the world of research is multifaceted, ever-evolving, and subject to a multitude of variables that can influence its course.

Conclusion

In conclusion, this bibliometric analysis has provided a comprehensive overview of the landscape of GC immunotherapy research over the past decade. The surge in annual publications serves as a testament to the escalating global interest in this field, with China emerging as a dominant contributor. Through this study, prominent authors and institutions in the domain have come to light. While the journal "Frontiers in Oncology" leads in terms of the sheer number of publications, it's "Journal of Clinical Oncology" that stands out in terms of citations. The findings further point towards a promising trajectory, suggesting a continued growth in publications on GC immunotherapy in the future. The keyword and co-citation clustering analyses have pinpointed the research directions that hold significant importance, such as targeted therapy, adoptive cell therapy, and the intricate world of the tumor microenvironment. Moreover, emerging areas like biomarkers and gut microbiota are poised to receive heightened attention in the coming years. In essence, this study provides a roadmap of the past, present, and possible future of GC immunotherapy research. It not only highlights the progress made but also guides researchers towards the uncharted territories that promise breakthroughs and advancements. As the field of immunotherapy continues to evolve, this analysis will serve as a valuable reference for both current and upcoming researchers, guiding them in their quest to combat gastric cancer through innovative and impactful approaches.

Funding

This work was supported by the Startup Foundation for Advanced Talents of Liuzhou People's Hospital (No. LRYGCC202105; LRYGCC202101), the Scientific Research Project of Guangxi Health Commission (No. Z20210018) and Scientific Research Project of Guangxi Provincial Administration of Traditional Chinese Medicine (GXZYB 202220330).

References

1. Chandra R, Balachandar N, Wang S, Reznik S, Zeh H, Porembka M. The changing face of gastric cancer: Epidemiologic trends and advances in novel therapies. Cancer Gene Ther. 2021;28(5):390-9.
2. Rawla P, Barsouk A. Epidemiology of gastric cancer: Global trends, risk factors and prevention. Prz Gastroenterol. 2019;14(12):26-38.
3. Matsueda S, Graham DY. Immunotherapy in gastric cancer. World J Gastroenterol. 2014;20(7):1657-66.
4. Zheng X, Song X, Shao Y, Xu B, Chen L, Zhou Q, et al. Prognostic role of tumor-infiltrating lymphocytes in gastric cancer: A meta-analysis. Oncotarget. 2017;8(34):57386-98.
5. Zhang W. TCGA divides gastric cancer into four molecular subtypes: Implications for individualized therapeutics. Chin J Cancer. 2014;33(10):469-70.
6. Fuchs CS, Doi T, Jang RW, Muro K, Satoh T, Machado M, et al. Safety and efficacy of pembrolizumab monotherapy in patients with previously treated advanced gastric and gastroesophageal junction cancer: Phase 2 clinical KEYNOTE-059 trial. JAMA Oncol. 2018;4(5):e180013.
7. Wang B, Xing D, Zhu Y, Dong S, Zhao B. The state of exosomes research: A global visualized analysis. Biomed Res Int. 2019;2019:1495130.
8. Brandt JS, Hadaya O, Schuster M, Rosen T, Sauer MV, Ananth CV. A bibliometric analysis of top-cited journal articles in obstetrics and gynecology. JAMA Netw Open. 2019;2(12):e1918007.
9. Wang S, Wu K, Zhang Z, Xu Z, Wu J, Xu S. Mapping theme trends and recognizing research hot spots in the use of ultrasound in orthopaedics: A bibliometric analysis of global research. Am J Transl Res. 2021;13(8):9892-911.
10. Ma L, Ma J, Teng M, Li Y. Visual analysis of colorectal cancer immunotherapy: A bibliometric analysis from 2012 to 2021. Front Immunol. 2022:13:843106.
11. Synnestvedt MB, Chen C, Holmes JH. CiteSpace II: Visualization and knowledge discovery in bibliographic databases. AMIA Annu Symp Proc. 2005;2005:724.
12. Yeung AWK, Tzvetkov NT, Balacheva AA, Georgieva MG, Gan R-Y, Jozwik A, et al. Lignans: Quantitative analysis of the research literature. Front Pharmacol. 2020;11:37.
13. Li C, Ojeda-Thies C, Renz N, Margaryan D, Perka C, Trampuz A. The global state of clinical research and trends in periprosthetic joint infection: A bibliometric analysis. Int J Infect Dis. 2020;96:696-709.
14. Zhang X, Lu Y, Wu S, Zhang S, Li S, Tan J. An overview of current research on mesenchymal stem cell-derived extracellular vesicles: A bibliometric analysis from 2009 to 2021. Front Bioeng Biotechnol. 2022:10:910812.
15. Derviş H. Bibliometric analysis using bibliometric an R Package. J Scientometr Res. 2019;8(3):156-60.
16. Eck NJV, Waltman L. Visualizing bibliometric networks. Measuring scholarly impact. 2014;285-320.
17. Chen C. CiteSpace: A practical guide for mapping scientific literature. Nova Science Publishers Hauppauge, NY, USA, 2016.
18. Chen C. Science mapping: A systematic review of the literature. J Data Info Sci. 2017;2(2):1-40.
19. Wu F, Gao J, Kang J, Wang X, Niu Q, Liu J, et al. Knowledge mapping of exosomes in autoimmune diseases: A bibliometric analysis (2002-2021). Front Immunol. 2022:13:939433.
20. Mellman I, Coukos G, Dranoff G. Cancer immunotherapy comes of age. Nature. 2011;480(7378):480-9.
21. Emens LA. Breast cancer immunotherapy: Facts and hopes breast cancer immunotherapy. Clin Cancer Res. 2018;24(3):511-20.

22. Jeong S-H, Kwak C. Immunotherapy for prostate cancer: Requirements for a successful regime transfer. Investig Clin Urol. 2022;63(1):3-13.

23. Xu W, Atkins MB, McDermott DF. Checkpoint inhibitor immunotherapy in kidney cancer. Nat Rev Urol. 2020;17(3):137-50.

24. Couzin-Frankel J. Breakthrough of the year 2013. Cancer immunotherapy. Science. 2013;342(6165):1432-3.

25. To KK, Fong W, Cho WC. Immunotherapy in treating EGFR-mutant lung cancer: Current challenges and new strategies. Front Oncol. 2021;11:635007.

26. Network CGAR. Comprehensive molecular characterization of gastric adenocarcinoma. Nature. 2014;513(7517):202-9.

27. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. Ca-Cancer J Clin. 2018;68(6):394-24.

28. Bang Y-J, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): A phase 3, open-label, randomised controlled trial. Lancet. 2010;376(9742):687-97.

29. Bębnowska D, Grywalska E, Niedźwiedzka-Rystwej P, Sosnowska-Pasiarska B, Smok-Kalwat J, Pasiarski M, et al. CAR-T cell therapy-an overview of targets in gastric cancer. J Clin Med. 2020;9(6):1894.

30. Yang L, Lin PC. Mechanisms that drive inflammatory tumor microenvironment, tumor heterogeneity, and metastatic progression. Semin Cancer Biol. 2017;47:185-95.

31. Wang M, Zhao J, Zhang L, Wei F, Lian Y, Wu Y, et al. Role of tumor microenvironment in tumorigenesis. J Cancer. 2017;8(5):761-73.

32. Llorca-Cardeñosa MJ, Fleitas T, Ibarrola-Villava M, Peña-Chilet M, Mongort C, Martinez-Ciarpaglini C, et al. Epigenetic changes in localized gastric cancer: The role of RUNX3 in tumor progression and the immune microenvironment. Oncotarget. 2016;7(39):63424-36.

33. Liu L, Ning X, Sun L, Zhang H, Shi Y, Guo C, et al. Hypoxia-inducible factor-1α contributes to hypoxia-induced chemoresistance in gastric cancer. Cancer Sci. 2008;99(1):121-8.

34. Chung HW, Lim J-B. Role of the tumor microenvironment in the pathogenesis of gastric carcinoma. World J Gastroenterol. 2014;20(7):1667-80.

35. Stewart OA, Wu F, Chen Y. The role of gastric microbiota in gastric cancer. Gut Microbes 2020;11(5):1220-30.

36. Long B, Qin L, Zhang B, Li Q, Wang L, Jiang X, et al. CAR T-cell therapy for gastric cancer: Potential and perspective. Int J Oncol. 2020;56(4):889-99.

37. Jiang H, Shi Z, Wang P, Wang C, Yang L, Du G, et al. Claudin18. 2-specific chimeric antigen receptor engineered T cells for the treatment of gastric cancer. J Natl Cancer Inst. 2019;111(4):409-18.

38. Al-Batran S-E, Schuler MH, Zvirbule Z, Manikhas G, Lordick F, Rusyn A, et al. FAST: An international, multicenter, randomized, phase II trial of epirubicin, oxaliplatin, and capecitabine (EOX) with or without IMAB362, a first-in-class anti-CLDN18. 2 antibody, as first-line therapy in patients with advanced CLDN18. 2+ Gastric and Gastroesophageal Junction (GEJ) adenocarcinoma. Am Soc Clin Oncol. 2016;34(18).

39. Jiang J, Xu N, Wu C, Deng H, Lu M, Li M, et al. Treatment of advanced gastric cancer by chemotherapy combined with autologous cytokine-induced killer cells. Anticancer Res. 2006;26(3B):2237-42.

40. Ratti M, Lampis A, Hahne JC, Passalacqua R, Valeri N. Microsatellite instability in gastric cancer: Molecular bases, clinical perspectives, and new treatment approaches. Cell Mol Life Sci. 2018;75(22):4151-62.

41. Fink D, Nebel S, Aebi S, Zheng H, Cenni B, Nehmé A, et al. The role of DNA mismatch repair in platinum drug resistance. Cancer Res. 1996;56(21):4881-6.

42. Ott P, Le D, Kim J, Ascierto P, Sharma P, Bono P, et al. Nivolumab (NIVO) in patients (pts) with advanced (adv) chemotherapy-refractory (CT-Rx) esophagogastric (EG) cancer according to microsatellite instability (MSI) status: Checkmate 032. Ann Oncol. 2017;28(Suppl 5):v229-v30.

43. Polk DB, Peek RM. Helicobacter pylori: Gastric cancer and beyond. Nat Rev Cancer. 2010;10(6):403-14.

44. Lin R, Ma H, Ding Z, Shi W, Qian W, Song J, et al. Bone marrow-derived mesenchymal stem cells favor the immunosuppressive T cells skewing in a Helicobacter pylori model of gastric cancer. Stem Cells Dev. 2013;22(21):2836-48.

45. Oya Y, Hayakawa Y, Koike K. Tumor microenvironment in gastric cancers. Cancer Sci. 2020;111(8):2696-707.

46. Ostrand-Rosenberg S, Fenselau C. Myeloid-derived suppressor cells: Immune-suppressive cells that impair antitumor immunity and are sculpted by their environment. J Immunol. 2018;200(2):422-31.

47. Walker LS. Treg and CTLA-4: Two intertwining pathways to immune tolerance. J Autoimmun. 2013;45(100):49-57.

48. Dolan DE, Gupta S. PD-1 pathway inhibitors: Changing the landscape of cancer immunotherapy. Cancer Control. 2014;21(3):231-7.

49. Yang L, Wang Y, Wang H. Use of immunotherapy in the treatment of gastric cancer. Oncol Lett. 2019;18(6):5681-90.

50. Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, et al. Pembrolizumab for the treatment of non–small-cell lung cancer. New Engl J Med. 2015;372(21):2018-28.

51. Muro K, Chung HC, Shankaran V, Geva R, Catenacci D, Gupta S, et al. Pembrolizumab for patients with PD-L1-positive advanced gastric cancer (KEYNOTE-012): A multicentre, open-label, phase 1b trial. Lancet Oncol. 2016;17(6):717-26.

52. Chen JP, Lin C, Xu CP, Zhang XY, Fu M, Deng YP, et al. Molecular therapy with recombinant antisense c-myc adenovirus for human gastric carcinoma cells *in vitro* and *in vivo*. J Gastroen Hepatol. 2001;16(1):22-8.

53. Sako A, Kitayama J, Koyama H, Ueno H, Uchida H, Hamada H, et al. Transduction of soluble Flt-1 gene to peritoneal mesothelial cells can effectively suppress peritoneal metastasis of gastric cancer. Cancer Res. 2004;64(10):3624-8.

54. Ohashi M, Kanai F, Ueno H, Tanaka T, Tateishi K, Kawakami T, et al. Adenovirus mediated p53 tumour suppressor gene therapy for human gastric cancer cells *in vitro* and *in vivo*. Gut. 1999;44(3):366-71.

55. Bik EM, Eckburg PB, Gill SR, Nelson KE, Purdom EA, Francois F, et al. Molecular analysis of the bacterial microbiota in the human stomach. P Natl Acad Sci Usa. 2006;103(3):732-7.

56. Liu X, Shao L, Liu X, Ji F, Mei Y, Cheng Y, et al. Alterations of gastric mucosal microbiota across different stomach microhabitats in a cohort of 276 patients with gastric cancer. EBioMedicine. 2019;40:336-48.

57. Montalban-Arques A, Wurm P, Trajanoski S, Schauer S, Kienesberger S, Halwachs B, et al. Propionibacterium acnes overabundance and natural killer group 2 member D system activation in corpus-dominant lymphocytic gastritis. J Pathol. 2016;240(4):425-36.

58. Whary MT, Muthupalani S, Ge Z, Feng Y, Lofgren J, Shi HN, et al. Helminth co-infection in *Helicobacter pylori* infected INS-GAS mice attenuates gastric premalignant lesions of epithelial dysplasia and glandular atrophy and preserves colonization resistance of the stomach to lower bowel microbiota. Microbes Infect. 2014;16(4):345-55.

59. Matsuoka T, Yashiro M. Biomarkers of gastric cancer: Current topics and future perspective. World J Gastroenterol. 2018;24(26):2818-32.