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ORIGINAL RESEARCH

An Evolutionary Research Framework for the Tumor Microenvironment in Gastric Cancer

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Objective: The tumor microenvironment (TME) plays a central role in the pathogenesis, progression, and therapeutic resistance of gastric cancer (GC). Despite a rapidly expanding body of research, this field lacks a systematic conceptual framework to integrate fragmented knowledge. This study aims to construct an evolutionary framework capable of interpreting the developmental dynamics and future directions of research on the TME in GC, thereby revealing the process of its core paradigm shifts.

Methods: We conducted a systematic synthesis of the knowledge domain regarding the TME in GC and constructed a comprehensive analytical framework to trace the evolution of dominant research themes and identify associated paradigm shifts.

Results: We propose a "two-phase evolutionary framework." Our analysis indicates that the field has transitioned from a basic mechanism exploration phase to the current translational integration phase. Early research focused on deconstructing fundamental inflammatory components, such as stromal fibroblasts and regulatory T cells, and their functions in processes like tumor growth and migration. The current paradigm has shifted decisively toward clinical translation centered on immunotherapy. This phase is characterized by concerted efforts to employ machine learning for quantifying immune infiltration, to develop prognostic models and biomarkers, and to deeply explore mechanisms of immune evasion as well as the unique TME of specific subtypes including gastroesophageal junction cancer.

Conclusion: This study develops an evolutionary framework for the TME in GC, charting its shift from basic research to clinical targeting. We propose that future work should focus on three connected areas: developing multi-omics integration platforms for microenvironment analysis to drive more precise prognostic and predictive models; second, exploring therapies targeting inflammatory pathways to overcome immunotherapy resistance, intensifying research on subtype-specific TME to enable personalized therapy.

Keywords: gastric cancer, tumor microenvironment, inflammatory microenvironment, immunotherapy, research evolution

Introduction

Gastric cancer (GC) remains one of the most lethal malignancies worldwide, posing a significant public health challenge.[1] According to the Global Cancer Statistics 2022, it is the fifth most frequently diagnosed cancer and the fifth leading cause of cancer-related deaths globally, with an estimated 0.97 million new cases and 0.67 million deaths annually.[2] Despite recent advancements in multimodal therapies, including surgery, chemotherapy, targeted therapy, and immunotherapy, the prognosis for metastatic or advanced gastric cancer remains poor. The 5-year survival rate for stage IV GC is lower than 10%, primarily related to tumor recurrence, early metastasis, and acquired therapeutic resistance.[3] This clinical challenge underscores the urgent need to elucidate the biological mechanisms driving GC progression and therapeutic resistance.

Previous studies have revealed that the occurrence and progression of GC are not only associated with the intrinsic characteristics of tumor cells but also closely linked to their tumor microenvironment (TME).[4,5] The complexity and heterogeneity of the TME not only drive the occurrence, progression, and metastasis of GC but also mediate tumor immune evasion and therapeutic resistance.[6] The TME is a heterogeneous milieu. Its inflammatory components, including key cellular actors such as cancer-associated fibroblasts (CAFs) and various immune cells, are particularly critical. The TME also encompasses non-cellular elements like collagen, hyaluronic acid, and growth factors, all of

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which dynamically evolve during tumorigenesis and progression. Within the TME, malignant cells interact with stromal cells, immune cells, and the extracellular matrix (ECM) to collectively shape tumor behavior.[7] CAFs are the main type of the predominant stromal cell that secrete pro-inflammatory cytokines and ECM proteins to promote epithelial-mesenchymal transition in cancer cells.[8] The ECM is one of the critical components of the TME, undergoes remodeling during the malignant progression of GC, thereby facilitating tumor proliferation, migration, and angiogenesis.[9] Currently, the TME has emerged as a critical focus in GC research and therapeutic intervention, and targeting the TME holds promise as an effective strategy to overcome treatment resistance and improve patient prognosis.

Given the central role of the TME in GC, deciphering the field's evolutionary trajectory is crucial for directing future research. However, a conceptual framework capable of integrating fragmented knowledge and systematically interpreting the developmental logic and paradigm shifts within this domain is currently lacking. Moreover, most existing bibliometric analyses only summarize research status and hotspots, rather than constructing an integrated evolutionary framework to demonstrate the developmental dynamics and paradigm transitions. To address this gap, this study aims to construct an evolutionary framework by synthesizing key literature from 2015 to 2024. This framework will explain the major shifts in research focus on the TME and help point out important directions for future studies in this area.

Methods

Literature Retrieval and Screening

We conducted a systematic search of the Web of Science Core Collection database for publications on the TME in GC between 2015 and 2024, and downloaded relevant data. The search strategy used was TS= ("gastric cancer" OR "gastric carcinoma" OR "stomach cancer" OR "stomach carcinoma") AND ("tumor microenvironment" OR "cancer microenvironment"). Limit publication types to articles or reviews, and the publication language to English. Supplementary Figure S1 shows the flowchart of publications search and exclusion process.

Analysis Tools and Methods

In this study, we used Citespace (version 6.4.R1 Advanced edition) and VOSviewer (version 1.6.20) for visual analysis. Firstly, the Citespace was used to generate collaboration networks of countries/regions, institutions and authors, conduct timeline map analysis on keywords, perform burst detection analysis on keywords and cited references, and generate dual-map overlay of journals. The time slicing was set to 1 year, Top N was set to 50, and Pathfinder network scaling was used to simplify and optimize the network structure, which is a common approach to highlight major connections in bibliometric networks.[10] Then, the VOSviewer was employed for co-occurrence analysis of author keywords, co-citation analysis of cited authors and cited references. Only terms or items that appeared at least twice were included to avoid noise from low-frequency occurrences. In the visualization maps generated by VOSviewer, distinct nodes represent different entities, different colors of nodes represent different clusters, with node size proportional to their occurrence frequency. The connecting lines between nodes illustrate relationships between entities, with Total Link Strength (TLS) serving to quantify the connection strength between nodes.

Results

Overview Information and Trend of Publications

Through literature search and screening, our study included a total of 3416 papers, comprising 2542 research articles and 874 review articles. These publications were authored by 21049 researchers from 3071 institutions across 77 countries/regions, and published in 733 academic journals. Figure 1 illustrates the publication trends in research on the TME of GC over the past decade, revealing a progressive increase in annual output from 83 articles in 2015 to 656 articles in 2024. Notably, more than 500 publications have been published annually in the last three years. The above results indicated that increasing scholarly attention to this research domain.

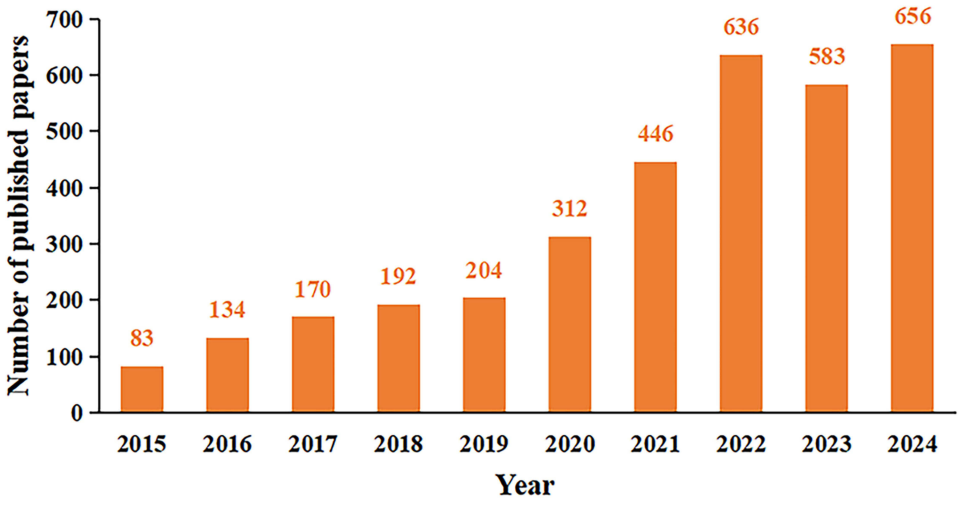

Figure 1 Trends in annual publications over the past decade.

Analysis of Countries/Regions

Supplementary Table S1 shows the top 10 countries/regions with the largest number of publications. China ranked first in both total publications (2227) and total citations (48104), indicating its dominant position in this research field. The USA and Japan ranked the second and third positions respectively in both publication volume and citation counts. Notably, while China led in total citations, its average citations per paper remained relatively low (21.6), suggesting a need to enhance research quality and academic impact. In contrast, the USA achieved the highest average citations per paper (45.62). Supplementary Figure S2A illustrates the countries/regions collaboration network, with centrality values revealing the USA (0.36) and Germany (0.31) occupied central positions in the global collaboration network.

Analysis of Institutions

Supplementary Table S2 summarizes the top 10 institutions with the largest number of publications. All top 10 institutions by publication volume were located in China, demonstrating that Chinese institutions contributed significantly to research in this field. The top three institutions ranked by publication count were Nanjing Medical University (140 publications), Fudan University (133 publications), and Shanghai Jiao Tong University (123 publications). Additionally, the top three institutions with the highest total citations were Shanghai Jiao Tong University (4672 citations), Sun Yat Sen University (3447 citations), and Southern Medical University (3206 citations). Supplementary Figure S2B displays the institutional collaboration network, with a density of 0.0262, indicating a low level of collaboration among institutions and highlighting the need for enhanced cooperation between institutions.

Analysis of Disciplines and Journals

Supplementary Figure S2C illustrates the distribution of publications across the top 10 disciplinary categories ranked by the number of papers in this field. The three most prominent disciplines were Oncology, Cell Biology, and Biochemistry Molecular Biology, collectively accounting for approximately 67% of the total publications.

Supplementary Table S3 lists the top 10 journals ranked by publication volume in this field, which collectively published 778 publications (approximately 22.78% of the total). Among these, *Frontiers in Oncology* (164 publications), *Frontiers in Immunology* (139 publications), and *Cancers* (112 publications) ranked as the top three journals by output, each publishing over 100 publications. Seven of these top 10 journals were categorized in Q1 zone, of the Journal Citation Reports (JCR), with the *Journal of Translational Medicine* achieving the highest Impact Factor (IF) of 6.1 points.

The journal dual-map overlay reveals connections between the thematic domains of citing and cited journals, demonstrating knowledge flow patterns within the TME of GC research field (Supplementary Figure S2D). On the left

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and right sides respectively represented the thematic areas of citing journals and cited journals, with colored paths indicating different citation relationships. Three main citation paths were identified in the journal overlay map, studies published in journals from the molecular, biology and immunology fields were primarily cited by research published in journals from the molecular, biology, genetics, health, nursing, and medicine domains, while studies published in journals from the medicine, medical, and clinical fields were mainly cited by research published in molecular, biology and genetics journals.

Analysis of Authors and Cited Authors

Table 1 lists the top 10 most productive authors and the top 10 most frequently co-cited authors in this field. Yashiro Masakazu (26 publications) from Osaka Metropolitan University, Li Guoxin (24 publications) from Southern Medical University, and He Yulong (22 publications) from Sun Yat-Sen University ranked as the top three productive scholars, with H-indices of 16, 15, and 12 respectively in this research domain, reflecting their significant contributions and high recognition in the field. Notably, eight out of the top 10 most productive authors were Chinese researchers, indicating the outstanding contributions of Chinese scientists in this area.

Supplementary Figure S3A depicts the author co-occurrence and collaborative network based on CiteSpace, with a network density of 0.0068, suggesting relatively loose collaborations among authors. Supplementary Figure S3B depicts the co-cited author network based on VOSviewer. In the co-cited author analysis, 32 out of 87573 cited authors received more than 200 citations. Sung H emerged as the most frequently cited author (647 citations), followed by Hanahan D (495 citations) and Smyth EC (451 citations), with these three scholars exerting substantial influence in the field of TME of GC.

Analysis of High-Cited Studies and High Co-Cited References

Table 2 presents the top 10 studies with the most citations regarding the TME of GC, each with over 540 citations. The 2018 publication "Cancer-associated cachexia" in Nature Reviews Disease Primers emerged as the most cited study, accumulating 1043 citations. This review article comprehensively introduced cancer-associated cachexia and summarized the roles of inflammatory cells, immune cells, and other components within the TME in this condition.[11] Additionally, the 2022 article "Lactate metabolism in human health and disease" published in Signal Transduction and Targeted Therapy achieved the highest annual average citation count (137.25 citations per year). This review article provided a systematic

Table 1 The Top 10 Most Productive Authors and the Top 10 Most Frequently Co-Cited Authors

Rank	Author	Country	Institution	Count	Citation	H-index	Co-Cited Authors	Citation	Total Link Strength
1	Yashiro, Masakazu	Japan	Osaka Metropolitan University	26	715	16	Sung, H	647	2199
2	Li, Guoxin	China	Southern Medical University	24	1,078	15	Hanahan, D	495	1437
3	He, Yulong	China	Sun Yat Sen University	22	532	12	Smyth, EC	451	1811
4	Zhang, Changhua	China	Sun Yat Sen University	21	385	11	Bass, AJ	412	1837
5	Xu, Wenrong	China	Jiangsu University	18	1,264	17	Zhang, Y	381	1450
6	Xue, Yingwei	China	Harbin Medical University	18	196	9	Janjigian, YY	367	2462
7	Liu, Tianshu	China	Fudan University	18	408	12	Liu, Y	355	1279
8	Zhang, Xu	China	Jiangsu University	17	1,312	14	Shitara, K	333	2249
9	Liu, Baorui	China	Nanjing University	17	445	10	Wang, Y	319	1160
10	Kim, Kyoung Mee	South korea	Sungkyunkwan University	17	747	12	Bang, YJ	316	2039

Table 2 The Top 10 Studies with the Most Citations Regarding the Tumor Microenvironment of Gastric Cancer

Rank	Study	Publication Year	Citation	Average Per Year
1	Cancer-associated cachexia. *Nat Rev Dis Primers*. doi: 10.1038/nrdp.2017.105.	2018	1043	130.38
2	Obesity and cancer risk: Emerging biological mechanisms and perspectives. *Metabolism*. doi: 10.1016/j.metabol.2018.11.001.	2019	918	131.14
3	m^6A regulator-mediated methylation modification patterns and tumor microenvironment infiltration characterization in gastric cancer. *Mol Cancer*. doi: 10.1186/s12943-020-01170-0.	2020	732	122
4	CAF secreted miR-522 suppresses ferroptosis and promotes acquired chemo-resistance in gastric cancer. *Mol Cancer*. doi: 10.1186/s12943-020-01168-8.	2020	712	118.67
5	Tumor Microenvironment Characterization in Gastric Cancer Identifies Prognostic and Immunotherapeutically Relevant Gene Signatures. *Cancer Immunol Res*. doi: 10.1158/2326-6066.CIR-18-0436.	2019	711	101.57
6	Cancer Stem Cells-Origins and Biomarkers: Perspectives for Targeted Personalized Therapies. *Front Immunol*. doi: 10.3389/fimmu.2020.01280.	2020	594	99
7	PD-L1 expression in human cancers and its association with clinical outcomes. *Onco Targets Ther*. doi: 10.2147/OTT.S105862.	2016	592	59.2
8	Obesity, Inflammation, and Cancer. *Annu Rev Pathol-Mech*. doi: 10.1146/annurev-pathol-012615-044359.	2016	579	57.9
9	Cyclooxygenase-2 in cancer: A review. *J Cell Physiol*. doi: 10.1002/jcp.27411.	2019	557	79.57
10	Lactate metabolism in human health and disease. *Signal Transduct Tar*. doi: 10.1038/s41392-022-01151-3.	2022	549	137.25

overview of lactate homeostasis, its functions in physiological and pathological processes, and the role of lactylation in cancer.[12]

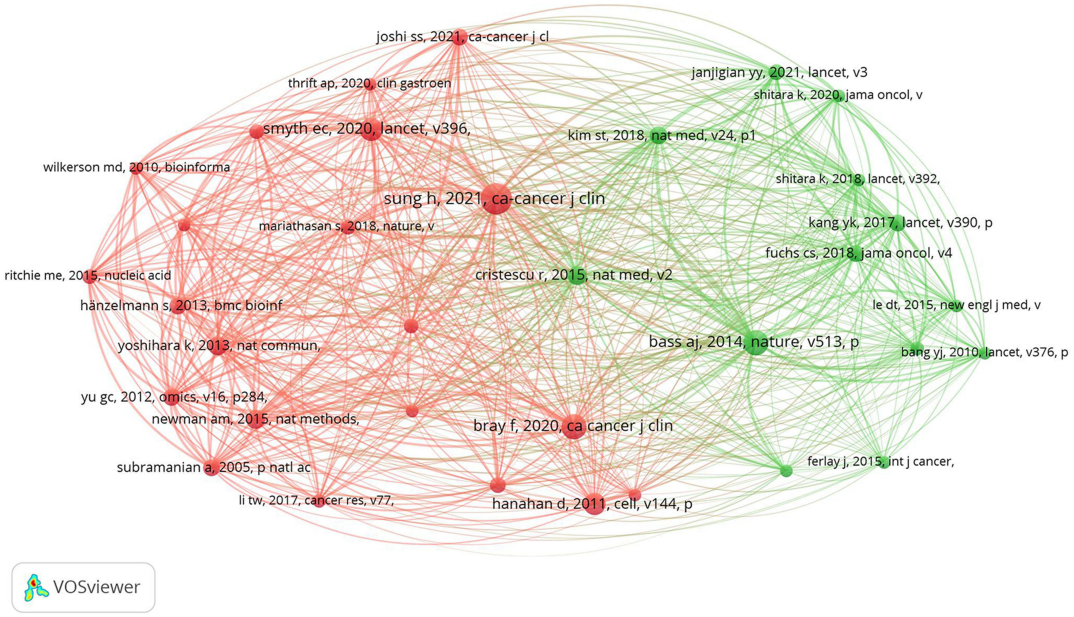
Co-citation references analysis was utilized to identify pivotal studies and research hotspots within the field. Figure 2A illustrates the co-cited references network generated through VOSviewer. In the co-cited references analysis, 34 out of 153,839 references were co-cited more than 200 times. Supplementary Table S4 presents the top 10 references with the most co-citations related to the TME of GC. The most co-cited reference was "Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries" by Sung H et al, which was published in CA-A Cancer Journal for Clinicians in 2021.[13] Figure 2B displays the top 25 references with the strongest citation bursts. Among these, the reference with the longest burst duration (5 years) was "Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012" by Ferlay J et al in 2015.[14] Furthermore, the reference with the highest outbreak strengths was "Comprehensive molecular characterization of gastric adenocarcinoma" (strength=50.58, from 2015 to 2019) published in Nature by Bass AJ et al in 2014, which proposed a molecular classification system dividing gastric cancer into four subtypes.[15]

Analysis of Keywords and the Emergence of an Evolutionary Framework

Keyword analysis of the literature corpus helped identify research hotspots, trends, and emerging directions in this field. We extracted a total of 5588 keywords from the included publications. Supplementary Table S5 lists the top 10 keywords with the most occurrences related to the TME of GC. The five most common keywords were "gastric cancer" (631 occurrences), "tumor microenvironment" (410 occurrences), "prognosis" (391 occurrences), "immunotherapy" (348 occurrences), and "cancer" (302 occurrences).

To visually and rapidly comprehend research hotspots, frontiers, and thematic distributions in field of TME in GC, we conducted co-occurrence analysis and cluster analysis of author keywords using VOSviewer. By setting a minimum occurrence threshold of 20, we analyzed 91 high-frequency keywords and constructed their co-occurrence network (Figure 3A). These keywords were primarily grouped into four distinct clusters, each represented by a different color, indicating that the research on TME of GC could be summarized into four core directions. We determined the primary research directions of each cluster by analyzing keyword frequency and average citation count within each group. The

A



B

Top 25 References with the Strongest Citation Bursts

References	Year	Strength	Begin	End	2015 - 2024
Bass AJ, 2014, NATURE, V513, P202, DOI 10.1038/nature13480, DOI	2014	50.58	**2015**	2019	
Ferlay J, 2015, INT J CANCER, V136, PE359, DOI 10.1002/ijc.29210, DOI	2015	31.67	**2015**	2020	
Hanahan D, 2011, CELL, V144, P646, DOI 10.1016/j.cell.2011.02.013, DOI	2011	18.58	**2015**	2016	
Fuchs CS, 2014, LANCET, V383, P31, DOI 10.1016/S0140-6736(13)61719-5, DOI	2014	14.37	**2015**	2019	
Herbst RS, 2014, NATURE, V515, P563, DOI 10.1038/nature14011, DOI	2014	13.26	**2015**	2019	
Le DT, 2015, NEW ENGL J MED, V372, P2509, DOI 10.1056/NEJMoa1500596, DOI	2015	24.05	**2016**	2020	
Torre LA, 2015, CA-CANCER J CLIN, V65, P87, DOI 10.3322/caac.21262, DOI	2015	23.73	**2016**	2019	
Kim JW, 2016, GASTRIC CANCER, V19, P42, DOI 10.1007/s10120-014-0440-5, DOI	2016	22.13	**2016**	2020	
Cristescu R, 2015, NAT MED, V21, P449, DOI 10.1038/nm.3850, DOI	2015	21.09	**2016**	2020	
Thompson ED, 2017, GUT, V66, P794, DOI 10.1136/gutjnl-2015-310839, DOI	2017	14.14	**2017**	2021	
Llosa NJ, 2015, CANCER DISCOV, V5, P43, DOI 10.1158/2159-8290.CD-14-0863, DOI	2015	13.23	**2016**	2020	
Quail DF, 2013, NAT MED, V19, P1423, DOI 10.1038/nm.3394, DOI	2013	12.02	**2016**	2018	
Muro K, 2016, LANCET ONCOL, V17, P717, DOI 10.1016/S1470-2045(16)00175-3, DOI	2016	31.27	**2017**	2021	
Chen WQ, 2016, CA-CANCER J CLIN, V66, P115, DOI 10.3322/caac.21338, DOI	2016	27.43	**2017**	2021	
Böger C, 2016, ONCOTARGET, V7, P24269, DOI 10.18632/oncotarget.8169, DOI	2016	14.01	**2017**	2019	
Derks S, 2016, ONCOTARGET, V7, P32925, DOI 10.18632/oncotarget.9076, DOI	2016	13.86	**2017**	2020	
Kang YK, 2017, LANCET, V390, P2461, DOI 10.1016/S0140-6736(17)31827-5, DOI	2017	23.17	**2018**	2021	
Van Cutsem E, 2016, LANCET, V388, P2654, DOI 10.1016/S0140-6736(16)30354-3, DOI	2016	21.51	**2018**	2021	
Kalluri R, 2016, NAT REV CANCER, V16, P582, DOI 10.1038/nrc.2016.73, DOI	2016	15.7	**2018**	2021	
Le DT, 2017, SCIENCE, V357, P409, DOI 10.1126/science.aan6733, DOI	2017	11.51	**2018**	2021	
Unknown -, 2020, CA CANCER J CLIN, V70, P313, DOI 10.3322/caac.21492, DOI	2020	45.94	**2020**	2021	
Li TW, 2017, CANCER RES, V77, PE108, DOI 10.1158/0008-5472.CAN-17-0307, DOI	2017	19.86	**2020**	2022	
Tang ZF, 2017, NUCLEIC ACIDS RES, V45, PW98, DOI 10.1093/nar/gkx247, DOI	2017	11.88	**2020**	2022	
Aran D, 2017, GENOME BIOL, V18, P0, DOI 10.1186/s13059-017-1349-1, DOI	2017	11.91	**2021**	2022	
Jiang P, 2018, NAT MED, V24, P1550, DOI 10.1038/s41591-018-0136-1, DOI	2018	16.47	**2022**	2024	

Figure 2 (**A**) Network diagram of the co-cited references based on VOSviewer; (**B**) Map of top 25 references with the strongest citation bursts.

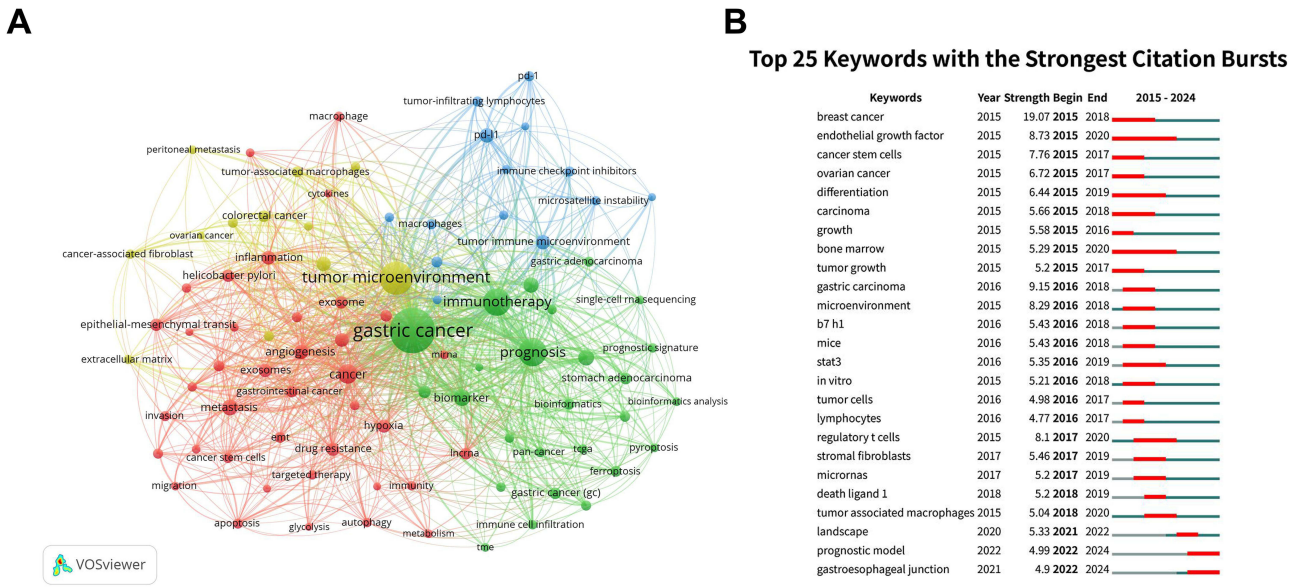


Figure 3 (**A**) Map of keyword co-occurrence analysis and cluster analysis based on VOSviewer; (**B**) Map of top 25 keywords with the strongest citation bursts.

red cluster focused on dynamic regulatory mechanisms of TME and its roles/mechanisms in GC occurrence, progression, and therapeutic resistance, including keywords such as "hypoxia", "immunosuppression", "exosomes", "glycolysis", "proliferation", "invasion", "metastasis", "epithelial-mesenchymal transition", and "drug resistance". The green cluster focused on construction of prognostic models for GC and quantification of the immune microenvironment, including keywords such as "bioinformatics analysis", "biomarkers", "machine learning", "prognostic models", "immune microenvironment", and "immune infiltration". The blue cluster concentrated on GC immunotherapy and efficacy optimization, including terms such as "cancer immunotherapy", "immune checkpoint inhibitors", "immune evasion", "microsatellite instability", and "chemotherapy". The yellow cluster concentrated on TME heterogeneity and cross-cancer research, including terms such as "cancer-associated fibroblasts", "extracellular matrix", "tumor-associated macrophages", and "peritoneal metastasis".

Figure 3B presents the map of the top 25 keywords with the strongest citation bursts. We observed that emergent keywords over the past two years include "prognostic model" and "gastroesophageal junction (GEJ)", which may represent research trends in this field. Figure 4 presents the timeline diagram of keywords in this field, dynamically reflecting the shifts in research hotspots over time. The primary keywords from 2015 to 2019 included "TME", "stromal fibroblasts", "cancer stem cells", "regulatory T cells", "tumor growth" and "migration", whereas the dominant keywords from 2020 to 2024 shifted to "immunotherapy", "immune infiltration", "immune evasion", "machine learning", "biomarker", "prognostic model", and "GEJ".

Based on this clear shift in research focus over time, we propose a "two-phase evolutionary framework" to describe the field's development. The first phase, from about 2015 to 2019, was a period of basic mechanism exploration. The second phase, beginning around 2020, is a period of translational integration, focused on applying new tools and knowledge to clinical challenges.

Discussion

General Information

The exponential growth of publications on the TME of GC over the past decade reflects the global recognition of its pivotal role in tumor progression and therapeutic resistance. With 3416 publications analyzed, this study delineates the evolving landscape of GC TME research, highlighting China's dominant contribution in publication volume and the USA's leadership in academic impact. Despite China's quantitative dominance, the lower average citation rate underscores a critical need to enhance research quality and international collaboration, as evidenced by the sparse institutional

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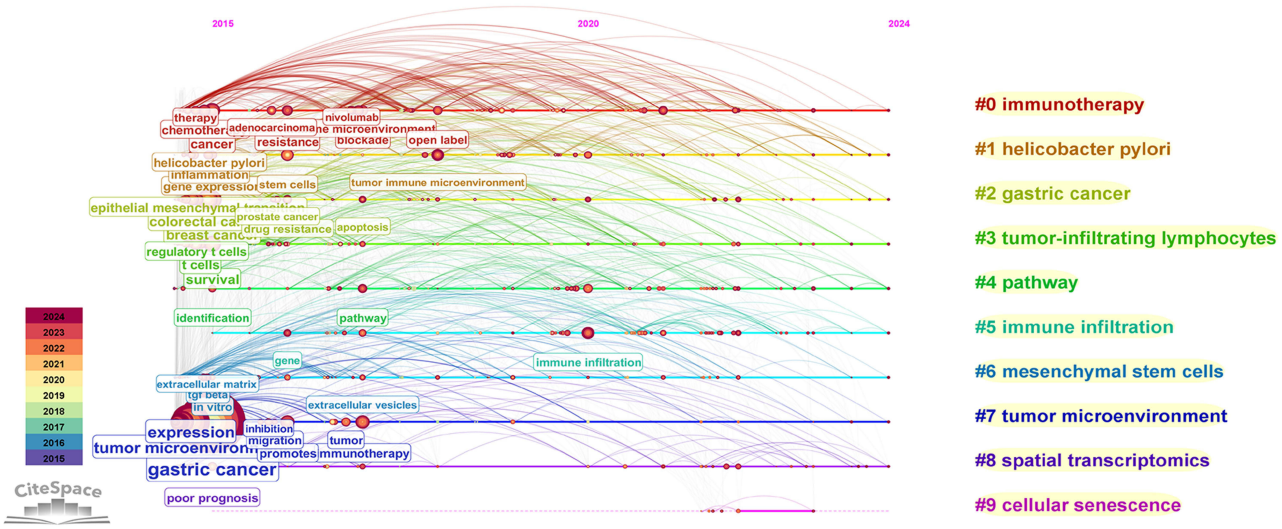

Figure 4 Timeline diagram of keywords.

cooperation network. The disciplinary focus remains anchored in oncology, cell biology, and biochemistry, with *Frontiers in Oncology* and *Frontiers in Immunology* emerging as leading journals for disseminating TME-related research. The dual-map overlay further reveals a bidirectional knowledge flow between molecular/biological research and clinical applications, emphasizing the translational potential of TME studies.

Research Hotspots Within the Two-Phase Evolutionary Framework

Through co-occurrence analysis of author keywords, we identified several hot research directions in the field of GC TME: (1) TME regulation in GC pathogenesis and resistance; (2) Prognostic models and immune microenvironment quantification; (3) Immunotherapy efficacy optimization; and (4) TME heterogeneity and cross-cancer research. Furthermore, the timeline analysis of keywords in this domain revealed that the research focus gradually shifted from basic mechanistic studies to clinical translational investigations. The proposed "two-phase evolutionary framework" provides a coherent structure to understand the shifting prominence of these interconnected themes over time.

During the basic mechanism exploration phase, research was predominantly dedicated to foundational discovery, heavily focused on deconstructing the TME's role in pathogenesis and its inherent heterogeneity. This established the essential mechanistic groundwork. The transition into the translational integration phase marks a decisive turn toward clinical application, where the research emphasis has squarely shifted to building data-driven prognostic tools and developing strategies to overcome barriers to effective immunotherapy. This evolution from understanding the system to targeting it is clearly reflected in the changing keyword landscape, exemplified by the rising prominence of terms such as immunotherapy, machine learning, and prognostic model.

This shift to the translational stage after 2020 is also supported by quantitative results from keyword burst analysis and co-citation clustering. Burst analysis shows that immunotherapy, prognostic model, machine learning, and GEJ cancer became the most prominent emerging topics after 2020, with strong and continuous research interest. Co-citation clusters also confirm that the field has gradually moved from basic mechanism research to clinical translation. These results together support the two-stage evolutionary pattern we proposed.

The TME in GC comprised a complex ecosystem in which hypoxia, metabolic reprogramming, and immunosuppression jointly promoted tumor progression and drug resistance.[16,17] Hypoxia induced HIF-1α–mediated glycolysis and lactic acid accumulation, which suppressed anti-tumor immune responses and promoted immune evasion by upregulating PD-L1 expression. These processes were closely reflected in our keyword clusters related to hypoxia, metabolic reprogramming, and immune suppression.[18,19] Exosomes also mediated intercellular signaling in the TME by transferring non-coding RNAs, thereby remodeling CAFs and promoting epithelial-mesenchymal transition and chemotherapy

resistance.[20,21] Meanwhile, CAF-derived matrix proteins further formed physical barriers that impaired drug penetration.[22] Together, these mechanisms explained the strong association between TME components and drug resistance observed in our analysis, highlighting the clinical importance of targeting TME to improve therapeutic outcomes.

The integration of bioinformatics analysis and machine learning revolutionized gastric cancer prognosis models, enabling precise risk stratification based on immune microenvironment characteristics. By integrating multi-omics data such as TCGA, GEO, researchers identified ferroptosis-related genes and immune infiltration features as robust biomarkers for survival prediction, which were then used to establish precise prognostic models.[23–25] Machine learning algorithms such as random forest constructed prognostic models by integrating these biomarkers, significantly improving prediction accuracy for both survival duration and immunotherapy response.[26] Quantification of the immune microenvironment further optimized these models. Algorithms like CIBERSORT and ESTIMATE played critical roles in immune microenvironment assessment by calculating stromal/immune scores and cell-type proportions, distinguishing PD-1 inhibitor-responsive "immune-hot" tumors from "immune-cold" tumors dominated by CAFs and tumor-associated macrophages.[27,28]

In recent years, the development of immunotherapy represented by immune checkpoint inhibitors (ICIs) has revolutionized treatment strategies for GC. However, immune escape mechanisms including Treg infiltration, PD-L1 upregulation, and metabolic acidosis remained major factors limiting the efficacy of immunotherapy.[29] Previous study demonstrated that blocking PD-1/PD-L1 reactivated cytotoxic T cells, thereby enhancing their immune response against tumor cells.[30] Currently, combining ICIs with chemotherapy or targeted therapies shows significant potential in overcoming drug resistance and improving therapeutic efficacy in GC, becoming a key research focus in immunotherapy. A retrospective study indicated that ICIs combined with chemotherapy significantly prolonged progression-free survival in advanced GC patients.[31] Additionally, a Phase III clinical trial revealed that the combination of CTLA-4/PD-1 bispecific antibody Cadonilimab and chemotherapy exhibited excellent anti-tumor activity with a manageable safety profile and significantly prolonged the overall survival in patients with advanced GC.[32] Previous research also suggested that blocking VEGF/VEGFR signaling inhibited angiogenesis and immunosuppression in the TME, potentially leading to enhanced infiltration of immune effector cells and synergistic enhancement of local immune responses with ICIs.[33] A clinical study demonstrated that the triplet regimen combining ICIs, chemotherapy, and antiangiogenic agents induced TME reprogramming toward a "hotter" phenotype, thereby improving anti-tumor efficacy.[34]

The heterogeneity of the TME in GC became a research hotspot in recent years and was a key factor influencing tumor progression and treatment efficacy. While ICIs combined with chemotherapy improved survival outcomes in advanced GC patients, some individuals exhibited limited durable responses to PD-1/PD-L1 or CTLA-4 inhibitors, which was potentially associated with the genomic status of GC or TME heterogeneity.[35] CAFs were identified as critical drivers in the formation of the heterogeneous TME, participating in suppressing immune cell function, remodeling the extracellular matrix, mediating tumor cell drug resistance, and promoting distant metastasis, demonstrating potential value as prognostic factors and therapeutic targets.[36,37] Scholars proposed that Hydrogen Therapy could reduce intracellular reactive oxygen species in CAFs and reverse their immunosuppressive phenotype, thereby stimulating systemic anti-tumor immunity through TME remodeling.[38] A recently published study conducted a comprehensive analysis of cells from ten cancer types using single-cell spatial multi-omics, and revealed four conserved spatial subtypes of CAFs, indicating shared systemic patterns in CAF manifestations across different cancers while showing tissue-specific variations in abundance and composition. This heterogeneity could affect the level and status of tumor-infiltrating immune cells.[39]

Research Trends

Through burst detection analysis of keywords, we identified that the terms "prognostic model" and "GEJ" exhibited a significant increase in citation frequency over the past two years, indicating these directions may represent future research trends in the field. With advancements in spatial multi-omics technologies and machine learning, prognostic model research has progressed toward multi-modal integration, dynamic monitoring, and molecular classification-driven approaches. These developments not only improved risk stratification for GC patients but also enhanced prediction

accuracy for survival rates, treatment responses, and recurrence risks.[40,41] Liu et al constructed an immune-related risk score model based on six immune genes, which can be used for risk stratification and survival prediction in GC patients.[42] Chang et al established a mitochondria-related risk prediction model that effectively predicts immunotherapy response and prognosis.[43]

GEJ cancer exhibits distinct clinical, pathological, molecular, and immunological characteristics compared to distal GC, with its unique features making it one of the most active research areas in GC studies in recent years.[44] Among patients with GEJ cancer receiving neoadjuvant chemoradiotherapy, those who received adjuvant nivolumab exhibited significantly longer progression-free survival compared to placebo recipients.[45] For patients with GEJ cancer, the addition of the PD-1 antibody tislelizumab to perioperative SOX chemotherapy significantly improved pathological regression with no significant differences in pathological response rates observed between patients with PD-L1 combined positive score (CPS) ≥5 and those with CPS <5.[46]

Limitations

This study has several limitations. First, the exclusive reliance on the Web of Science Core Collection database may overlook relevant publications indexed in other databases, potentially introducing selection bias. Second, the exclusion of non-English publications risks omitting valuable regional insights from high-burden regions like East Asia, where significant research is published in local languages. Third, citation-based metrics tend to favor established research topics, while emerging topics may be underestimated due to their shorter citation history. In future research, searching multiple databases and incorporating multi-language literature would help improve the comprehensiveness of the knowledge graph in this field.

Conclusion

This study develops an evolutionary framework for the TME in GC, charting its shift from basic research to clinical targeting. Guided by this framework, we propose that future work should focus on three connected areas: first, developing multi-omics integration platforms for microenvironment analysis to build more precise prognostic and predictive models; second, exploring therapies targeting inflammatory pathways to overcome immunotherapy resistance; and third, intensifying research on subtype-specific TME to enable personalized therapy.

Abbreviations

GC, Gastric cancer; TME, Tumor microenvironment; GEJ, Gastroesophageal junction; CAFs, Cancer-associated fibroblasts; ECM, Extracellular matrix; Tregs, Regulatory T cells; ICIs, Immune checkpoint inhibitors.

Data Sharing Statement

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

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Author Contributions

Zhenlong Chen: Writing-Original draft, Data Curation and Software; Hang Li: Writing-Original draft, Data Curation, Software and Formal analysis; Xiaosong Li: Writing-Original draft, Formal analysis and Visualization; Lei Zhu: Writing-review & editing, Conceptualization, Methodology, Supervision and Validation. All authors gave final approval of the version to be published and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this article.

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