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Global research trends in the tumor immune microenvironment of esophageal cancer from immune infiltration to clinical translation

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Abstract

Objective

To systematically analyze the global research landscape, knowledge base, evolution of research hotspots, and clinical translational trends in the field of the tumor immune microenvironment in esophageal cancer, and to provide a reference for future mechanistic studies and precision diagnosis and treatment.

Methods

English-language publications related to the immune microenvironment in esophageal cancer were retrieved from the Web of Science Core Collection and Scopus databases from inception to 2025. The document types were limited to articles and reviews. After merging records from the two databases and removing duplicates, 886 publications were included. Bibliometrix/Biblioshiny, VOSviewer, and CiteSpace were used to perform bibliometric and visualization analyses of annual publication trends, countries/regions, institutions, journals, author collaboration, co-cited references, highly cited documents, and keyword hotspots.

Results

From 2007 to 2019, the annual publication output in this field remained relatively low, followed by rapid growth after 2020, indicating that research on the immune microenvironment in esophageal cancer has entered a phase of accelerated development. China dominated the field in terms of publication output, and high-yield institutions were mainly Chinese universities and research institutes. The major publication sources were journals related to oncology, immunology, and translational medicine. Co-citation and highly cited document analyses showed that the knowledge base of this field was derived not only from general theories of tumor immunology, cancer biology, and immunotherapy, but also from an emerging disease-specific research foundation centered on the immune microenvironment and clinical translation in esophageal cancer. Keyword analysis showed that research hotspots have gradually shifted from early studies of immune cell infiltration, cytokines, and molecular expression toward the immunosuppressive microenvironment, tumor-associated macrophages, cancer-associated fibroblasts, immune checkpoint inhibitors, neoadjuvant therapy, single-cell sequencing, and bioinformatics analysis.

Conclusion

Research on the immune microenvironment in esophageal cancer has developed rapidly in recent years. Its core value is gradually shifting from explaining tumor immune phenomena toward guiding clinical

stratification, predicting therapeutic response, and optimizing comprehensive treatment strategies. In the future, multi-omics, spatial profiling, dynamic molecular residual disease monitoring, and digital pathology are expected to further promote the application of this field in precision diagnosis and treatment for esophageal cancer.

1. Introduction

Esophageal cancer is one of the gastrointestinal malignancies with a substantial global disease burden. According to GLOBOCAN 2022, esophageal cancer remains among the major contributors to global cancer incidence and cancer-related mortality, with marked geographic disparities in both incidence and mortality rates [1]. Histologically, esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC) differ in epidemiological distribution, risk factors, and molecular characteristics, with ESCC being particularly prevalent in East Asia [2]. Recent studies on the global burden of esophageal cancer further suggest that population aging, regional differences in exposure, and disparities in access to diagnosis and treatment will continue to shape future patterns of esophageal cancer prevention and control [3]. Despite advances in surgery, radiotherapy, chemotherapy, and multimodal treatment, the overall prognosis of esophageal cancer remains unsatisfactory. Therefore, novel biological indicators that can guide risk stratification, therapeutic response prediction, and individualized treatment are urgently needed in clinical practice [4].

In recent years, immunotherapy, particularly immune checkpoint inhibitors, has substantially changed the treatment landscape of esophageal cancer. This has also made the tumor immune microenvironment (TIME) an important research focus for explaining differences in therapeutic efficacy and mechanisms of treatment resistance. Existing evidence indicates that molecular characteristics of ESCC, the PD-1/PD-L1 axis, tumor mutational burden, immune infiltration status, and various immune-related biomarkers may influence patient responses to immunotherapy and targeted therapy [5]. Meanwhile, the development of neoadjuvant chemotherapy combined with immunotherapy and perioperative immunotherapy has shifted TIME research beyond basic mechanistic exploration and toward clinical scenarios such as pretreatment patient selection, post-treatment pathological response assessment, and postoperative recurrence risk evaluation [6, 7].

The TIME is a complex ecosystem composed of tumor cells, immune cells, stromal cells, cytokines, vascular structures, and extracellular matrix components. In esophageal cancer, tumor-infiltrating lymphocytes, tertiary lymphoid structures, tumor-associated macrophages, cancer-associated fibroblasts, metabolic reprogramming, and genomic mutation features may all contribute to the formation of local immune states and further influence tumor progression, prognosis, and sensitivity to immunotherapy [8–12]. In particular, recent studies have shown that the spatial distribution and maturation status of tertiary lymphoid structures may be associated with neoadjuvant treatment response and patient survival [8, 9]. Metabolic subtypes, genomic mutation features, and multi-omics signals have also been used to characterize the immune landscape of ESCC and to explore potential therapeutic stratification [10–12]. At the same time, studies on immune checkpoint resistance further

suggest that PD-L1 expression alone is insufficient to fully explain differences in immunotherapy response. A more comprehensive assessment framework integrating tumor cell states, immune cell composition, stromal barriers, and spatial interactions is therefore needed [13, 14].

With the rapid increase in related studies, a large body of literature has accumulated in the field of the immune microenvironment in esophageal cancer. However, its overall knowledge structure, distribution of research forces, evolution of hotspots, and clinical translational trends remain insufficiently summarized. Previous bibliometric studies have mainly focused on immunotherapy for esophageal cancer, revealing research progress in immune checkpoint inhibitors, combination therapy, and clinical trials [15]. However, immunotherapy represents only one important clinical application scenario of TIME and cannot fully reflect the overall developmental trajectory of immune infiltration, prognostic stratification, tumor microenvironment remodeling, biomarkers, single-cell technologies, and spatial omics in esophageal cancer TIME research. Therefore, based on the Web of Science Core Collection and Scopus databases, this study used bibliometrix, VOSviewer, and CiteSpace to perform a bibliometric and visualized analysis of publications related to the immune microenvironment in esophageal cancer from 2007 to 2025. This study aimed to systematically reveal the global research landscape, knowledge base, thematic evolution, and clinical translational frontiers of this field, providing a reference for future mechanistic studies and precision diagnosis and treatment.

2. Materials and Methods

2.1 Data sources and search strategy

The data used in this study were retrieved from the Web of Science Core Collection (WoSCC) and Scopus databases. The search time span was set from database inception to 2025. To ensure the academic quality and comparability of the included records, document types were limited to articles and reviews, and the language was restricted to English. The search topic focused on the “immune microenvironment in esophageal cancer.” The search strategy consisted of two components: the first component was used to identify esophageal cancer-related publications, including terms such as esophageal/oesophageal cancer, esophageal squamous cell carcinoma, and esophageal adenocarcinoma; the second component was used to identify immune microenvironment-related topics, including broad conceptual terms such as tumor immune microenvironment, immune microenvironment, immune landscape, immune contexture, immune infiltration, and immune cell infiltration. The complete search strategies are shown in Table 1.

Table 1
Search strategies for the WoSCC and Scopus databases

Database	Search query
WOS	TS=(((esophag* OR oesophag*) NEAR/3 (cancer* OR carcinoma* OR neoplasm* OR tumor* OR tumour* OR malignan* OR adenocarcinoma*)) OR "esophageal squamous cell carcinoma" OR "oesophageal squamous cell carcinoma" OR "esophageal adenocarcinoma" OR "oesophageal adenocarcinoma" OR ESCC OR EAC) AND TS= ("tumor immune microenvironment" OR "tumour immune microenvironment" OR "immune microenvironment" OR "tumor immun* microenvironment" OR "tumour immun* microenvironment" OR "immune landscape" OR "immune contexture" OR "immune infiltration" OR "immune cell infiltration" OR ("immune cell*" NEAR/3 infiltrat*) OR ("tumor microenvironment" NEAR/5 immun*) OR ("tumour microenvironment" NEAR/5 immun*) OR ("tumor infiltrat*" NEAR/3 immun*) OR ("tumour infiltrat*" NEAR/3 immun*))
Scopus	TITLE (((esophag* OR oesophag*) W/2 (cancer* OR carcinoma* OR neoplasm* OR tumor* OR tumour* OR malignan*)) OR "esophageal cancer" OR "oesophageal cancer" OR "esophageal carcinoma" OR "oesophageal carcinoma" OR "esophageal squamous cell carcinoma" OR "oesophageal squamous cell carcinoma" OR "esophageal adenocarcinoma" OR "oesophageal adenocarcinoma") AND TITLE-ABS-KEY ("tumor immune microenvironment" OR "tumour immune microenvironment" OR "immune microenvironment" OR "tumor immun* microenvironment" OR "tumour immun* microenvironment" OR "immune landscape" OR "immune contexture" OR "immune infiltration" OR "immune cell infiltration" OR ("immune cell*" W/3 infiltrat*) OR ("tumor microenvironment" W/5 immun*) OR ("tumour microenvironment" W/5 immun*) OR ("tumor infiltrat*" W/3 immun*) OR ("tumour infiltrat*" W/3 immun*))

To reduce search bias, conceptual and higher-level terms were primarily used for the immune microenvironment component. Specific molecules, immune cell subsets, or technical terms, such as PD-1, PD-L1, Treg, TAM, MDSC, and single-cell RNA sequencing, were not used as core search terms, in order to avoid artificially overrepresenting any specific research direction. A total of 849 records were retrieved from WoSCC and 454 records from Scopus. After merging the records from the two databases and removing duplicates, 886 publications were finally included for subsequent bibliometric analysis. The literature retrieval and data processing workflow is shown in Fig. 1.

2.2 Data processing and bibliometric analysis

The bibliographic data exported from WoSCC and Scopus included titles, authors, institutions, countries/regions, journals, abstracts, keywords, references, publication years, and citation counts. After merging and deduplication, the records were uniformly converted into WoS format for subsequent analysis. To improve the accuracy of keyword analysis, author keywords and Keywords Plus were standardized by unifying capitalization, British and American spellings, abbreviations and full terms, singular and plural forms, and common synonyms. For example, TIME was standardized as tumor immune microenvironment, TME as tumor microenvironment, PD-L1-related variants as pd-l1, and expressions such as single cell RNA sequencing and scRNA-seq as single-cell RNA sequencing. Keyword cleaning was performed only to standardize term expressions and did not remove any original publications.

Bibliometric analysis was performed using bibliometrix/Biblioshiny, VOSviewer, and CiteSpace. Bibliometrix/Biblioshiny was used to describe general bibliometric characteristics, including annual publication trends, average annual citations, country/region distribution, institutional distribution, journal sources, and highly cited documents. VOSviewer was used to construct collaboration and co-occurrence networks of countries, institutions, authors, journals, co-cited references, and keywords, with node size and link strength representing research output, collaboration relationships, and thematic associations. CiteSpace was used to analyze keyword clustering, timeline evolution, and burst terms, in order to identify the knowledge structure, hotspot changes, and emerging frontiers in this field. The visualization results were interpreted comprehensively by considering publication output, citation frequency, cluster labels, burst strength, and temporal distribution.

3. Results

3.1 General characteristics and annual publication trends

A total of 886 publications related to TIME in esophageal cancer were included from database inception to 2025, with the earliest relevant study published in 2007. These publications were derived from 307 journals or sources and involved 5,202 authors. Only four documents were single-authored, indicating that research in this field was mainly conducted through multi-author collaboration. The average number of authors per document was 8.6, and the proportion of internationally co-authored publications was 0.3386%. The included publications contained 41,138 cited references and 1,516 author keywords. The average document age was 3.41 years, and the average number of citations per document was 18.35.

As shown in Fig. 2A, the annual publication output remained relatively low and stable from 2007 to 2019. After 2020, the number of publications increased markedly, exceeding 100 in 2021 and continuing to rise thereafter, reaching the highest level in 2025. This trend suggests that TIME research in esophageal cancer has entered a phase of rapid growth in recent years.

The average annual citation frequency showed a different pattern (Fig. 2B). Before 2016, it fluctuated slowly with an overall upward trend and reached a peak during 2017–2018, followed by a gradual decline. The relatively low average annual citation frequency in recent years may be partly attributable to the shorter citation accumulation time of newly published studies.

3.2 Country/region distribution and collaboration network

The country/region collaboration network showed that TIME research in esophageal cancer was characterized by marked geographic concentration and centralization. In the CiteSpace country collaboration network, China had the largest node and occupied a central position, with collaborative links to the United States, Japan, Germany, the United Kingdom, and other countries, indicating that China made the most prominent contribution to publication output and had a high level of network participation in this field (Fig. 3A). The United States, Japan, Germany, and the United Kingdom also represented important nodes in the network and participated in international collaboration in this area.

The VOSviewer country collaboration network further illustrated the collaboration structure among countries (Fig. 3B). China, the United States, Japan, Germany, the United Kingdom, and the Netherlands constituted the main collaborative groups, with relatively frequent links between China and the United States, Japan, and several European countries. Overall, an international collaboration network has been preliminarily formed; however, it remains centered on a limited number of high-output countries, whereas the participation of other countries is relatively limited. From the perspective of global geographic distribution, relevant studies were mainly concentrated in East Asia, North America, and Europe, with China showing the most prominent publication contribution (Fig. 3C). In contrast, research output from South America, Africa, and some Asian countries was relatively limited, suggesting that the global distribution of research in this field remains uneven.

Table 2 further quantifies the research output and academic impact of the major countries. China ranked first in publication output, with 696 publications, accounting for 78.6% of all included documents and far exceeding other countries. The United States and Japan ranked second and third, with 41 and 38 publications, accounting for 4.6% and 4.3%, respectively. They were followed by Ireland with 16 publications, Germany with 14, the United Kingdom with 12, the Netherlands with 10, Australia with 8, India with 8, and Sweden with 6.

Table 2
Publication output and collaboration characteristics of major countries and regions

Country	Articles	Articles %	TC	Average Article Citations	SCP	MCP	MCP %
CHINA	696	78.6	8182	11.80	696	0	0
USA	41	4.6	1675	40.90	41	0	0
JAPAN	38	4.3	1050	27.60	38	0	0
IRELAND	16	1.8	309	19.30	16	0	0
GERMANY	14	1.6	228	16.30	13	1	7.1
UNITED KINGDOM	12	1.4	2333	194.40	11	1	8.3
NETHERLANDS	10	1.1	124	12.40	10	0	0
AUSTRALIA	8	0.9	79	9.90	8	0	0
INDIA	8	0.9	74	9.20	8	0	0
SWEDEN	6	0.7	224	37.30	6	0	0

In terms of citations, publications from China had the highest total citation count, with 8,182 citations, followed by the United Kingdom with 2,333, the United States with 1,675, and Japan with 1,050 (Table 2). Notably, although the United Kingdom contributed a relatively small number of publications, it had the highest average citations per article, reaching 194.4 citations per publication. The average citations per

article for the United States and Japan were 40.9 and 27.6, respectively, both higher than that of China, which was 11.8. Regarding international collaboration, most high-output countries showed relatively low MCP ratios, suggesting that although a cross-national collaboration network has been established to some extent, deeper international collaboration among high-output countries still needs to be strengthened.

3.3 Institutional and journal source analysis

Institutional analysis showed that TIME research in esophageal cancer was mainly driven by Chinese universities and research institutes. In the VOSviewer institutional collaboration network, Sun Yat-sen University, Zhengzhou University, Fudan University, Nanjing Medical University, the Chinese Academy of Medical Sciences/Peking Union Medical College, Shandong University, and Fujian Medical University were located in the core area of the network and formed relatively dense collaborative links (Fig. 4A). In terms of publication output, Sun Yat-sen University ranked first with 130 publications, followed by Zhengzhou University with 101, the Chinese Academy of Medical Sciences/Peking Union Medical College with 96, Fudan University with 90, and Nanjing Medical University with 89 (Fig. 4B). Overall, high-yield institutions were highly concentrated in China, indicating a clear publication advantage of Chinese research institutions in this field.

Journal source analysis showed that publications in this field were mainly distributed across journals related to oncology, immunology, genetics, and translational medicine. The VOSviewer journal network indicated that Frontiers in Immunology, Frontiers in Oncology, Cancers, Scientific Reports, BMC Cancer, and Cancer Immunology, Immunotherapy constituted the major publication platforms (Fig. 4C). Among them, Frontiers in Immunology had the highest publication output, with 62 articles, followed by Frontiers in Oncology with 45 articles. Discover Oncology and Frontiers in Genetics each published 20 articles, while Cancers and Scientific Reports published 18 and 17 articles, respectively (Fig. 4D). These findings suggest that studies in this field were mainly published in open-access journals and specialized journals related to tumor immunology.

3.4 Author collaboration, co-cited references, and highly cited documents

The author collaboration network showed that TIME research in esophageal cancer has formed several relatively independent research groups, although the overall collaboration pattern remains dispersed. In the VOSviewer author collaboration map, different colors represent different collaboration clusters. The groups led or represented by Li Feng, Wang Wei, Yang Hong, Liu Yang, John V. Reynolds, and Joanne Lysaght were relatively prominent and formed stable collaborative links within their respective networks (Fig. 5A). Overall, this field has not yet formed a highly centralized core author group, but instead shows a pattern of parallel development among multiple research groups. These groups may focus on different directions, such as immune infiltration, mechanisms of the TME, immunotherapy response, and bioinformatics analysis.

The co-cited reference network further indicated that the knowledge base of this field is not limited to esophageal cancer itself, but is jointly constructed by tumor immunology, cancer biology, molecular features of esophageal cancer, and clinical studies of immunotherapy (Fig. 5B). In this network, classic studies in cancer biology, such as Hanahan D 2011 [16], provided a fundamental theoretical framework for TME research. Epidemiological studies, such as Sung H 2021 [17], offered background evidence regarding the disease burden of esophageal cancer. Studies by Zheng YX 2020 [18], Huang TX 2019 [19], and Huang TX 2022 [20] more directly advanced the understanding of TIME features, immune cell composition, and molecular characteristics in esophageal cancer. Meanwhile, clinical immunotherapy studies, including Kato K 2019 [21], Kojima T 2020 [22], and Kelly RJ 2021 [23], also occupied important positions in the co-citation network, suggesting a close connection between TIME research and immunotherapy translation in esophageal cancer.

The analysis of highly cited documents also reflected this dual knowledge structure, consisting of both a general tumor immunology foundation and esophageal cancer-specific research. According to Fig. 5C and Table 3, the study by McGranahan N 2017 [24] published in Cell had the highest citation frequency, followed by the review by Baracos VE 2018 [25] published in Nature Reviews Disease Primers. These findings suggest that broader oncological issues, such as tumor heterogeneity, immune recognition, and cancer-associated systemic conditions, have exerted an important influence on this field. Among studies more directly related to TIME in esophageal cancer, Zheng YX 2020, Baba Y 2020, Huang TX 2019, Huang TX 2022, and Tong Y 2021 showed high citation frequencies or high normalized citation performance (Fig. 5C; Table 3). These studies had substantial influence on the construction of immune atlases, characterization of TIME features, elucidation of immunotherapy-related mechanisms, and bioinformatics-based analyses in esophageal cancer. Taken together, Fig. 5 and Table 3 indicate that the core knowledge base of this field is derived not only from classic theories of tumor immunology and cancer biology, but also from an emerging disease-specific research foundation focused on TIME characteristics and clinical translation in esophageal cancer.

Table 3
Globally highly cited documents

Paper	DOI	Total Citations	TC per Year	Normalized TC
MCGRANAHAN N, 2017, CELL	10.1016/j.cell.2017.01.018	2105	210.50	10.03
BARACOS VE, 2018, NAT REV DIS PRIMERS	10.1038/nrdp.2017.105	1280	142.22	6.50
ZHENG YX, 2020, NAT COMMUN	10.1038/s41467-020-20019-0	367	52.43	7.81
BABA Y, 2020, CANCER SCI	10.1111/cas.14541	225	32.14	4.79
RAYES RF, 2019, JCI INSIGHT	10.1172/jci.insight.128008	217	27.13	2.38
SCHWARTZ M, 2016, J IMMUNOTHER CANCER	10.1186/s40425-016-0145-x	217	19.73	2.85
HUANG TX, 2019, CANCER COMMUN	10.1186/s40880-019-0427-z	206	25.75	2.26
HUANG TX, 2022, GUT	10.1136/gutjnl-2020-322924	173	34.60	12.81
TONG Y, 2021, THERANOSTICS	10.7150/thno.56157	166	27.67	8.08
STAIRS DB, 2011, CANCER CELL	10.1016/j.ccr.2011.02.007	161	10.06	2.50

3.5 Keyword hotspots and thematic evolution

Keyword analysis revealed the major developmental trajectory of TIME research in esophageal cancer from four dimensions: thematic structure, temporal trends, hotspot density, and cluster evolution. The thematic map showed that no clearly defined motor themes with both high centrality and high density had yet emerged, suggesting that the field remains in a stage of rapid development and ongoing integration (Fig. 6A). Among the identified themes, prognosis, ESCC, and esophageal cancer were located in the basic themes quadrant, indicating that prognostic evaluation and esophageal cancer, particularly ESCC, remain the main disease-related foundation of this field. In contrast, terms such as human, humans, and esophagus tumor were located in relatively peripheral areas and mainly reflected background or descriptive information rather than independent research hotspots.

Trend topic analysis showed that early keywords mainly included natural killer cells, IFN-gamma, messenger RNA, and ligand, suggesting that early studies focused more on basic immunological issues, such as immune effector cells, cytokines, and molecular expression. Subsequently, regulatory T cells, TME, immune microenvironment, esophageal cancer, and ESCC gradually became high-frequency

themes, reflecting a shift in research focus toward esophageal cancer-specific TIME features, immunosuppressive cells, and TME characteristics. In recent years, terms such as combination, chemotherapy, mechanism, and single-cell have continued to emerge, indicating that the field is expanding from descriptive characterization of TIME toward combination therapy, mechanistic investigation, and refined immune profiling at the single-cell level (Fig. 6B).

The keyword density map further showed that current research hotspots were mainly concentrated around cancer, expression, prognosis, immunotherapy, biomarkers, immune infiltration, ESCC, PD-L1, and TME (Fig. 6C). These high-density keywords collectively formed the main research framework of this field. On the one hand, immune infiltration, TME, and immune microenvironment reflected sustained attention to immune infiltration and microenvironmental structure. On the other hand, PD-L1, biomarkers, and expression pointed to molecular biomarker and immune phenotype studies. Meanwhile, immunotherapy, prognosis, and survival highlighted the close connection between this field and clinical translation as well as prognostic evaluation.

CiteSpace timeline clustering further supported these findings from the perspective of evolutionary pathways. As shown in Fig. 6D, the major keyword clusters included #0 esophageal cancer, #1 tumor-associated macrophages, #2 cancer vaccine, #3 ESCC, #4 TME, #6 EAC, #8 immune infiltration, #9 cancer-associated fibroblasts, and #10 IL-10. Consistent with the high-frequency hotspots shown in the density map, these clusters indicated that TIME research in esophageal cancer has gradually extended from general disease- and microenvironment-related concepts to more specific microenvironmental components and regulatory factors, including TAMs, CAFs, immune infiltration, inflammatory cytokines, and cancer vaccines. Overall, the research hotspots in this field are shifting from early studies of immune cells and molecular expression toward immune infiltration profiling, microenvironmental cell composition, molecular biomarkers, immunotherapy translation, and single-cell technology-driven refined characterization.

4. Discussion

4.1 The era of immunotherapy has driven TIME research in esophageal cancer from basic description toward clinical questions

This study showed that publications related to TIME in esophageal cancer increased rapidly after 2020, suggesting that this field has gradually shifted from a relatively scattered mechanistic research direction to an active research topic in precision diagnosis and treatment for esophageal cancer. Notably, the average annual citation frequency showed a clear peak during 2017–2018, which may have been driven mainly by a small number of highly influential publications. The study on tumor clonal heterogeneity and evolution published by McGranahan and Swanton in Cell in 2017 provided an important theoretical basis for understanding tumor heterogeneity, immune selection pressure, and treatment resistance [24]. The review on cancer-associated cachexia published by Baracos et al. in Nature Reviews Disease Primers in 2018 further suggested that systemic tumor status, inflammatory responses, and metabolic

abnormalities also represent important external knowledge sources for TME-related research [25]. Therefore, the early citation peak did not arise entirely from esophageal cancer-specific studies, but more broadly reflected the theoretical input of general tumor immunology, tumor heterogeneity, and systemic cancer biology into this field.

In contrast, esophageal cancer-specific TIME research has increased substantially since 2020. Zheng et al. used single-cell sequencing to reveal the cellular composition and immune regulatory features of the immunosuppressive microenvironment in human ESCC, promoting a shift in this field from conventional tissue-level analyses toward high-resolution immune profiling [18]. Baba et al. systematically summarized the relationship between the TIME and immune checkpoint inhibitors in ESCC, further highlighting the importance of TIME in explaining differences in immunotherapy response [26]. At the same time, clinical studies such as ATTRACTION-3, KEYNOTE-181, CheckMate 577, KEYNOTE-590, and CheckMate 648 have successively promoted the application of immunotherapy in advanced disease, postoperative adjuvant therapy, and first-line combination treatment settings [21–23, 27, 28]. These clinical data have shifted the research focus from whether immunotherapy is effective to which patients benefit, which patients develop resistance, and how microenvironmental features can be used to guide treatment selection. Accordingly, the core value of TIME research in esophageal cancer is gradually shifting from explaining tumor immune phenomena toward supporting clinical stratification, predicting therapeutic response, and optimizing comprehensive treatment strategies.

4.2 From immune infiltration to prognostic stratification: the complementary value of TIME beyond conventional staging

The keyword clustering and thematic evolution results both indicated that immune infiltration, prognosis, diagnostic, prognostic model, prognostic biomarkers, and immune cell infiltration were important themes in this field. This suggests that the early clinical value of TIME research in esophageal cancer was mainly reflected in prognostic evaluation and risk stratification. Conventional TNM staging remains the foundation for prognostic assessment and treatment decision-making in esophageal cancer; however, substantial heterogeneity in survival and recurrence risk still exists among patients with the same stage. TIME features, particularly TILs, Tregs, TAMs, CAFs, and immunosuppressive cytokines, may complement conventional pathological staging from the perspective of tumor–host interactions.

From a clinical perspective, immune infiltration is not merely a pathological phenomenon, but may serve as an integrated indicator reflecting local antitumor immune activity, the degree of immunosuppression, and potential recurrence risk. Previous studies on the immune landscape of esophageal cancer have suggested that immune-related factors, including TILs, TAMs, MDSCs, Tregs, and PD-1/PD-L1, are closely associated with prognosis and sensitivity to immunotherapy [19]. Further single-cell studies have shown that the TIME of ESCC contains complex states of T cells, NK cells, macrophages, dendritic cells, and stromal cells, indicating that immunosuppression is not driven by a single cell type but is jointly shaped

by multicellular interactions [18, 29, 30]. Therefore, future clinical prognostic stratification should not rely solely on individual immune biomarkers. Instead, interpretable risk models integrating immune cell composition, spatial distribution, immune activation or exhaustion states, and molecular expression profiles should be further explored.

This trend also explains why themes such as bioinformatics analysis, gene signature, prognostic signature, and drug sensitivity have become increasingly active in recent years. Models based on transcriptomic data and immune infiltration algorithms can help screen candidate biomarkers from large-scale datasets, but their clinical application remains limited by differences in algorithmic sources, sample types, detection platforms, and insufficient external validation [31]. A more clinically valuable direction would be to integrate bioinformatics-derived risk scores with pathological sections, immunohistochemistry, multiplex immunofluorescence, ctDNA/MRD, and clinical variables to establish stratification tools applicable to real-world clinical settings. In other words, the clinical endpoint of TIME research should not remain at the level of identifying “high-risk” or “low-risk” genes, but should ultimately support postoperative recurrence risk assessment, follow-up intensity planning, and adjuvant treatment selection.

4.3 From single PD-L1 expression to an integrated immune ecosystem: a shift in predicting immunotherapy response

The clinical application of immunotherapy has been a key driver of the rapid development of TIME research in esophageal cancer. The PD-1/PD-L1 axis is one of the most established immunotherapeutic targets in clinical practice, and related clinical trials have demonstrated the therapeutic value of PD-1 inhibitors in advanced esophageal cancer, neoadjuvant/adjuvant treatment, and chemotherapy-based combination strategies. However, in clinical practice, PD-L1 expression alone cannot fully explain differences in therapeutic efficacy. Some patients with PD-L1-positive tumors still exhibit primary resistance, whereas some patients with PD-L1-negative or low-expression tumors may also derive benefit. This suggests that the response to immunotherapy in esophageal cancer is not determined by a single molecule, but rather depends on a more complex immune ecosystem.

Themes identified in the keyword clusters, including immune checkpoint inhibitors, tumor mutation burden, neoantigens, T cell receptor, regulatory T cells, CD8 + T cells, tumor-associated macrophages, and cancer-associated fibroblasts, indicate that this field is shifting from single checkpoint molecule-centered research toward integrated immune ecosystem assessment. Tumor mutation burden and neoantigens may influence tumor immunogenicity, T cell receptor clonal expansion may reflect antigen-specific T cell responses, and CD8 + T cell exhaustion together with Treg enrichment may indicate suppressed antitumor immunity. Meanwhile, non-lymphoid components such as TAMs and CAFs can also affect T cell infiltration and immunotherapy sensitivity through chemokines, extracellular matrix remodeling, and ligand–receptor interactions [18–20].

Recent single-cell and spatial omics studies have further strengthened this understanding. A 2024 single-cell study showed that, among ESCC patients receiving neoadjuvant immunochemotherapy,

treatment response was closely associated with microenvironmental features such as CXCL13 + CD8+ T cells, Treg expansion, LRRC15 + CAFs, and SPP1 + macrophages, suggesting that treatment resistance may arise from an immunosuppressive niche that is formed or reinforced after therapy [32]. Another single-cell study of neoadjuvant chemoimmunotherapy similarly indicated that tumor cell differentiation states and microenvironmental composition were associated with pathological response, suggesting that response prediction should consider both intrinsic tumor cell states and the external immune ecosystem [33]. The association between SPP1 + macrophages and resistance to neoadjuvant chemoimmunotherapy was further supported by integrative analyses of bulk RNA-seq and single-cell RNA-seq data [34]. In addition, spatial proteomic studies have begun to dissect immune determinants of neoadjuvant chemoimmunotherapy response at the tissue spatial-architecture level, providing new insights for developing prediction systems that are more closely aligned with clinical pathology settings [35]. Together, these findings suggest that future prediction of immunotherapy response should move beyond the single PD-L1 marker toward an integrated assessment framework incorporating tumor cell states, immune cell composition, stromal barriers, and spatial interactions.

4.4 Microenvironmental remodeling guides neoadjuvant and combination treatment strategies

The keyword trends and clustering results of this study showed that themes such as neoadjuvant, chemoradiotherapy, combination, chemotherapy, immune checkpoint inhibitors, and single-cell RNA sequencing have become increasingly prominent in recent years, suggesting that TIME research in esophageal cancer is moving into the level of treatment strategy design. For locally advanced ESCC, neoadjuvant chemotherapy, chemoradiotherapy, and immunotherapy-based combination strategies have become important research directions. However, several clinical challenges remain, including unstable pathological complete response (pCR) and major pathological response (MPR) rates, ineffective treatment in some patients, and difficulty in predicting postoperative recurrence risk. Therefore, one of the key tasks of TIME research is to explain the heterogeneous responses to neoadjuvant therapy among different patients and further guide the optimization of treatment combinations, treatment sequencing, and postoperative adjuvant strategies.

Mechanistically, radiotherapy and chemotherapy are not merely cytotoxic treatments; they may also reshape tumor immune status by promoting antigen release, immunogenic cell death, dendritic cell activation, T cell infiltration, and myeloid cell remodeling. The rationale for combining immunotherapy with radiotherapy or chemotherapy lies in the possibility of converting some immunologically “cold” tumors into “hot” tumors. However, this process does not necessarily lead to enhanced antitumor immunity. In some patients, treatment may induce CAF enrichment, an increase in SPP1 + macrophages, Treg recruitment, T cell exhaustion, and strengthening of stromal barriers, thereby forming a therapy-induced immunosuppressive microenvironment [36]. Therefore, the clinical question is not simply whether immunotherapy should be combined with other treatments, but rather which patients have a TIME that can be activated by combination therapy and which patients may require additional targeting of TAMs, CAFs, TGF-β, WNT2, or other immune exclusion mechanisms.

This trend has become particularly evident in recent studies. CAF-secreted WNT2 can suppress dendritic cell-mediated antitumor immunity, and targeting this axis may restore immune responses and improve the efficacy of immunotherapy [20]. The spatial dynamics of CD39 + CD8+ exhausted T cells and TLS-related immune structures further suggest that local organized immune architecture may influence the response to PD-1 blockade [37]. Predictive models based on the TIME for the efficacy of neoadjuvant chemoimmunotherapy have also begun to emerge, indicating that this field is moving from mechanistic interpretation toward the development of clinically applicable prediction tools [38]. In addition, dynamic MRD monitoring has started to enter the field of response prediction for neoadjuvant chemoimmunotherapy. A 2026 study showed that baseline genomic alterations and post-treatment MRD status could be used to predict pathological response, suggesting that blood-based molecular monitoring may complement tissue-based TIME assessment [39]. Residual disease subtyping and TLS status have also been used to predict survival and recurrence risk in patients without pCR and may help guide postoperative adjuvant immunotherapy selection [40–42]. Therefore, future clinical pathways may shift from a one-time pretreatment assessment toward a continuous decision-making model integrating pretreatment immune stratification, on-treatment dynamic monitoring, and postoperative residual-risk re-stratification.

4.5 Single-cell analysis, spatial omics, and clinically actionable immune classification: future directions

In recent years, the emergence of themes such as single-cell RNA sequencing, bioinformatics analysis, spatial transcriptomics, and multi-omics has indicated that TIME research in esophageal cancer is entering a stage of high-resolution characterization. However, the ultimate goal of future studies should not be limited to generating increasingly complex immune atlases, but should be to translate these atlases into clinically actionable immune classifications. An ideal immune classification system should be able to address key clinical questions: whether a patient has an immune-active status; whether CAF/TAM-driven immune exclusion is present; whether there is a residual immune niche predictive of recurrence; and whether the patient is suitable for immunotherapy combined with chemotherapy, radiotherapy, anti-angiogenic therapy, or therapies targeting stromal or myeloid components.

Recent studies have begun to move in this direction. GPR116 + pericytes have been found to participate in ESCC metastasis and immunotherapy resistance, suggesting that pericytes and spatial stromal niches may also represent clinically relevant intervention targets [43]. A single-cell multi-stage spatial evolutionary map further indicated that ESCC development is not driven solely by tumor cell mutations, but is accompanied by the co-evolution of epithelial cell states, immune infiltration, and the spatial microenvironment [44]. TLS-related studies have shown that locally organized immune structures may be closely associated with antitumor immune responses, treatment response, and recurrence risk [37, 40, 42, 45]. Meanwhile, SPP1-related studies have further strengthened the role of TAMs in ESCC progression, immunosuppression, and treatment resistance, suggesting that myeloid cells may become important targets for future combination therapies [34, 46]. A 2026 study using single-cell and spatial transcriptomic approaches further showed that interactions between LAMA3 + malignant cells and

SPP1 + macrophages may shape an immune-excluded microenvironment and are associated with poor response to anti-PD-L1 therapy [47].

From the perspective of clinical translation, three directions deserve particular attention in future research. First, reproducible and interpretable immune classification systems should be established, such as immune-inflamed, immune-excluded, myeloid/CAF-enriched, TLS-high, and MRD-high-risk subtypes. Second, tissue-based multi-omics findings should be translated into clinically accessible assays, including multiplex immunofluorescence, spatial immunohistochemistry, targeted RNA panels, ctDNA/MRD monitoring, and digital pathology models. Third, the value of immune classification in guiding treatment selection should be validated in prospective clinical cohorts, particularly for neoadjuvant immunochemotherapy, postoperative adjuvant immunotherapy, combined chemoradiotherapy, and salvage treatment after resistance. Only by completing the translational loop from mechanistic discovery to measurable biomarkers and then to therapeutic decision-making can TIME research in esophageal cancer be truly integrated into clinical diagnosis and treatment.

4.6 Limitations

This study has several limitations. First, the data were mainly retrieved from WoSCC and Scopus; therefore, some non-English publications, conference papers, preprints, and studies not indexed in these databases may have been missed. Second, bibliometric results depend on bibliographic records, keywords, and citation data provided by databases. Although deduplication and keyword cleaning were performed, residual synonym variations, inconsistent institutional names, and noise from Keywords Plus could not be completely avoided. In addition, citation analysis is subject to a time-lag effect. The actual impact of recently published high-quality studies, especially those related to single-cell sequencing, spatial omics, dynamic MRD monitoring, and prediction of response to neoadjuvant immunotherapy, may not yet be fully reflected. Finally, bibliometric analysis can reveal research trends and knowledge structures, but it cannot directly validate the clinical effectiveness of specific TIME-related indicators. These findings still require further confirmation through prospective cohorts, multicenter studies, and clinical trials.

5. Conclusion

This study systematically analyzed the global research landscape and thematic evolution of TIME research in esophageal cancer from database inception to 2025. The results showed that this field has grown rapidly since 2020, with China playing a dominant role in research output. High-yield institutions and publication sources were mainly concentrated in areas related to oncology, immunology, and translational medicine. Knowledge base and keyword analyses indicated that TIME research in esophageal cancer is gradually shifting from early studies of immune cell infiltration, cytokines, and molecular expression toward the immunosuppressive microenvironment, TAMs, CAFs, immune checkpoint inhibitors, neoadjuvant therapy, single-cell sequencing, and bioinformatics analysis. Overall, the core value of this field is evolving from explaining tumor immune phenomena toward guiding clinical stratification, predicting therapeutic response, and optimizing comprehensive treatment strategies. In

the future, multi-omics, spatial profiling, dynamic MRD monitoring, and digital pathology are expected to further promote the application of TIME research in precision diagnosis and treatment for esophageal cancer.

Abbreviations

CAFs
Cancer-associated fibroblasts
CD
Cluster of differentiation
ctDNA
Circulating tumor DNA
CXCL13
C-X-C motif chemokine ligand 13
EAC
Esophageal adenocarcinoma
ESCC
Esophageal squamous cell carcinoma
GPR116
G protein-coupled receptor 116
IFN-gamma
Interferon-gamma
IL-10
Interleukin-10
LAMA3
Laminin subunit alpha 3
LRRC15
Leucine-rich repeat containing 15
MCP
Multiple-country publications
MDSCs
Myeloid-derived suppressor cells
MPR
Major pathological response
MRD
Molecular residual disease
NK cells
Natural killer cells
pCR
Pathological complete response

PD-1
Programmed cell death protein 1
PD-L1
Programmed death-ligand 1
RNA-seq
RNA sequencing
scRNA-seq
Single-cell RNA sequencing
SCP
Single-country publications
SPP1
Secreted phosphoprotein 1
TAMs
Tumor-associated macrophages
TCR
T-cell receptor
TC
Total citations
TGF-β
Transforming growth factor beta
TILs
Tumor-infiltrating lymphocytes
TIME
Tumor immune microenvironment
TLS
Tertiary lymphoid structures
TMB
Tumor mutational burden
TME
Tumor microenvironment
TNM
Tumor-node-metastasis
Tregs
Regulatory T cells
WoS
Web of Science
WoSCC
Web of Science Core Collection
WNT2
WNT family member 2

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors agree to the publication of this article.

Availability of data and materials

The datasets supporting the findings of this study have been deposited in Zenodo and are publicly available at https://doi.org/10.5281/zenodo.20625049. The deposited files include the original bibliographic records exported from the Web of Science Core Collection and Scopus databases, the merged and deduplicated dataset used for bibliometric analysis, and the keyword cleaning files, including the keyword cleaning package, thesaurus, stopword list, protected terms, and workflow documentation. The Zenodo DOI for this dataset is 10.5281/zenodo.20625049. Use of records derived from the Web of Science Core Collection and Scopus should comply with the subscription and licensing policies of Clarivate and Elsevier.

Clinical trial number

Not applicable.

Competing Interests

The authors declare no competing interests.

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Authors' contributions

J.W. performed the data analysis and drafted the main manuscript. Y.Z. was responsible for data screening and visualization. Z.L. reviewed and revised the manuscript. B.L. supervised and coordinated the overall study and manuscript preparation. All authors read and approved the final manuscript.

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Figures

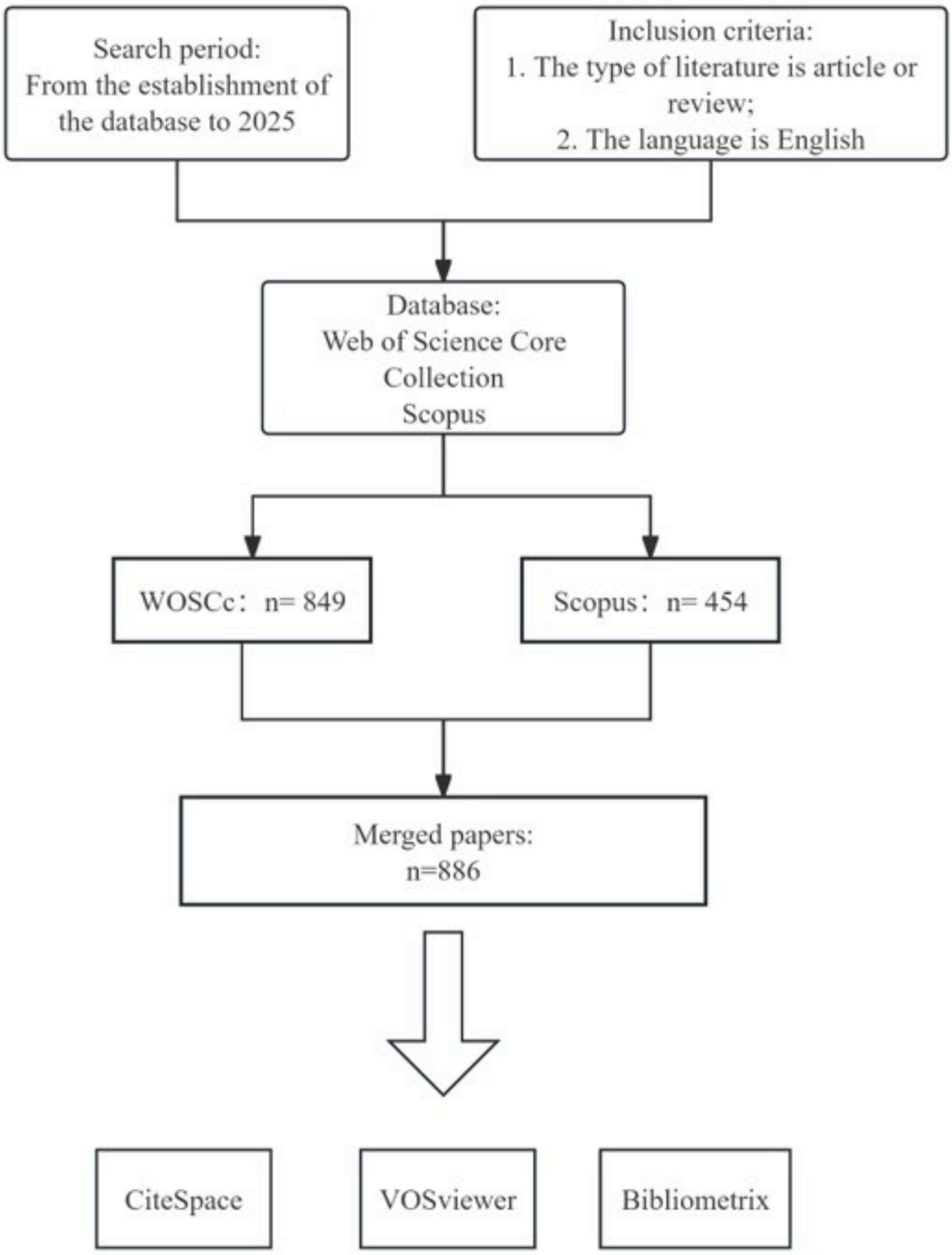


Figure 1

Literature retrieval and inclusion flowchart

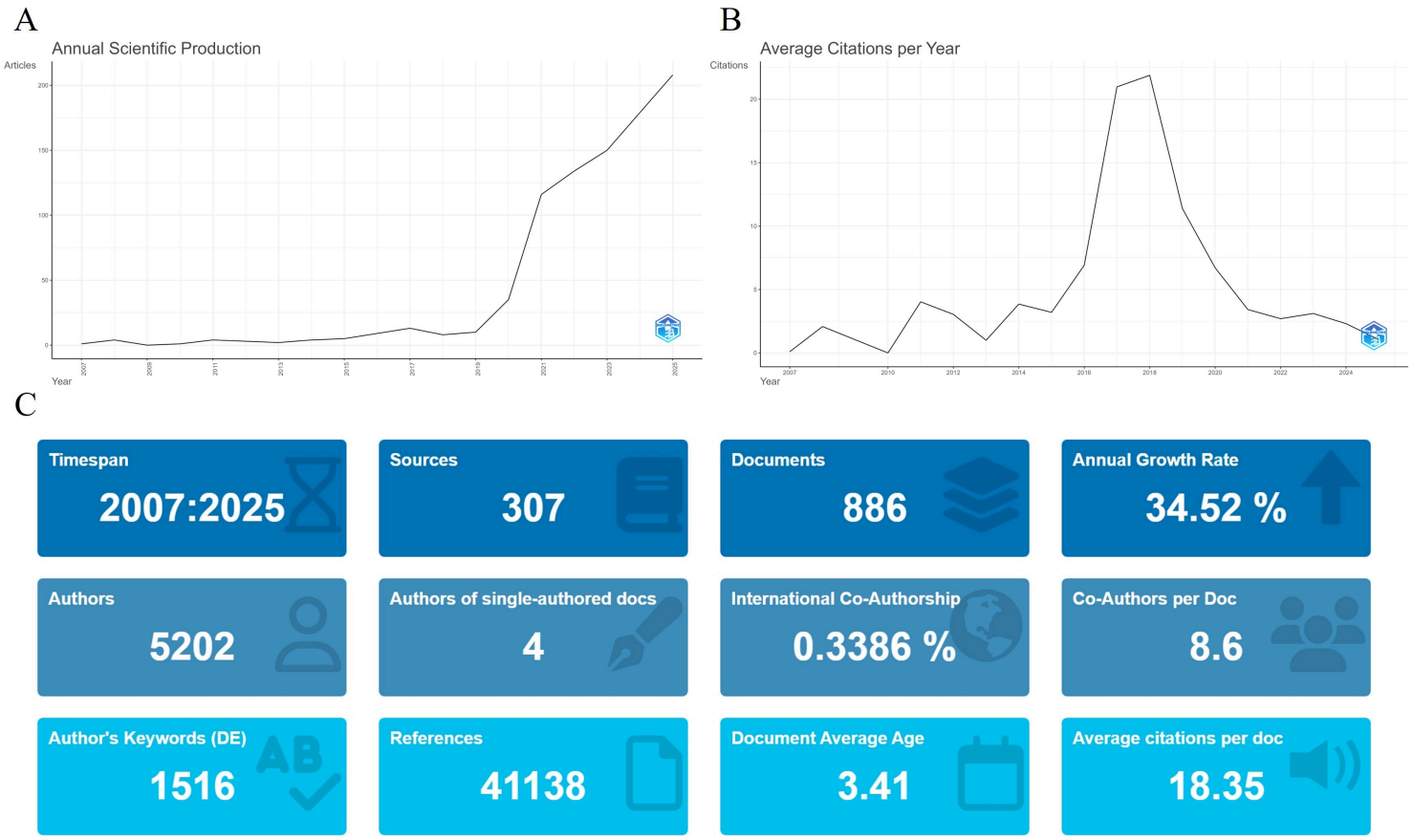


Figure 2

Annual publication output and average annual citation trends

（A）Annual publication output from 2007 to 2025

（B）Average annual citations by publication year

（C）General characteristics of the included publications

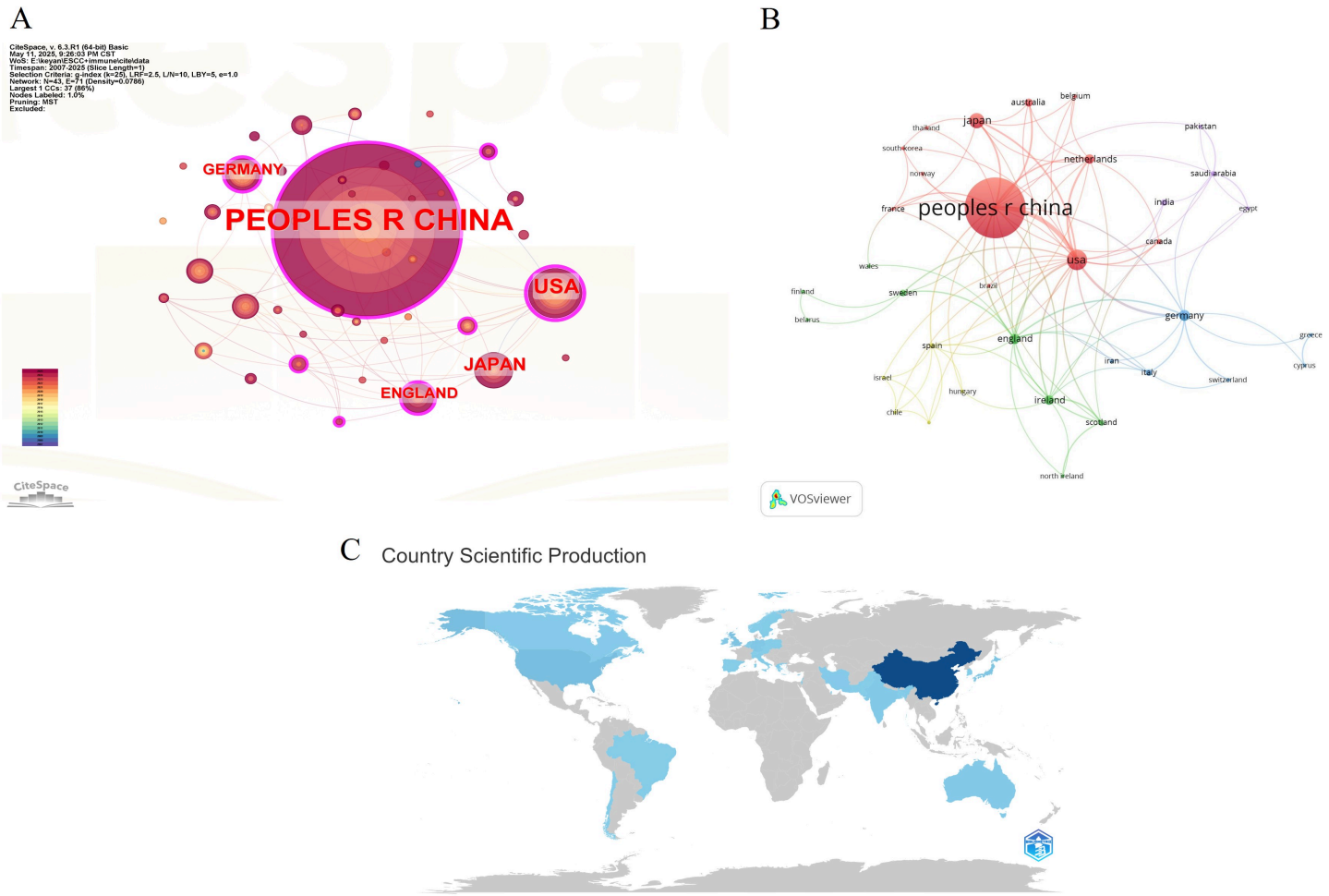


Figure 3

Country and region distribution and collaboration network

（A）CiteSpace country and region collaboration network

（B）VOSviewer country and region collaboration network

（C）Global geographic distribution of publications

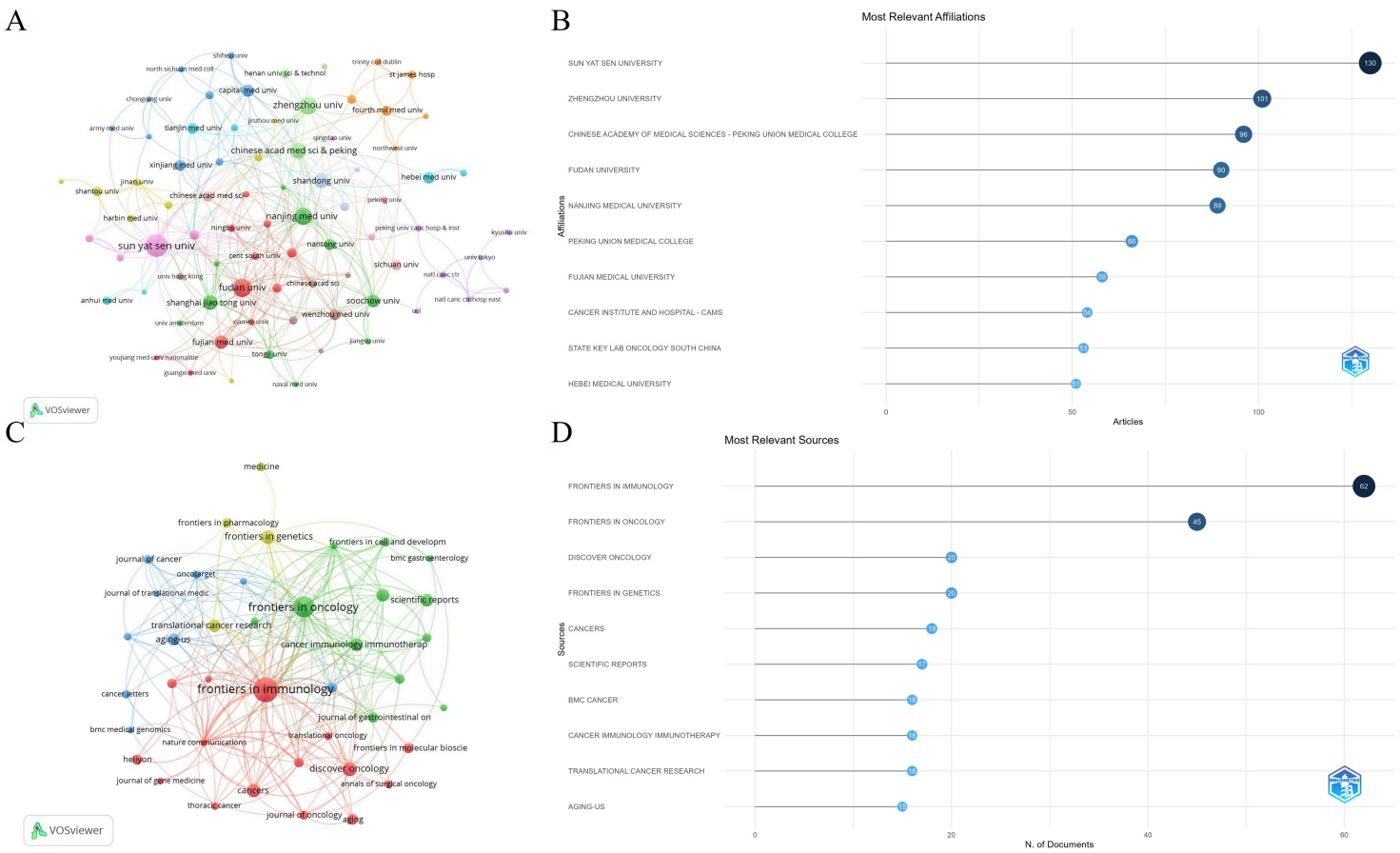


Figure 4

Institutional and journal source analysis

（A）Institutional collaboration network

（B）Distribution of high-yield institutions

（C）Journal and source network

（D）Distribution of high-yield journals and sources

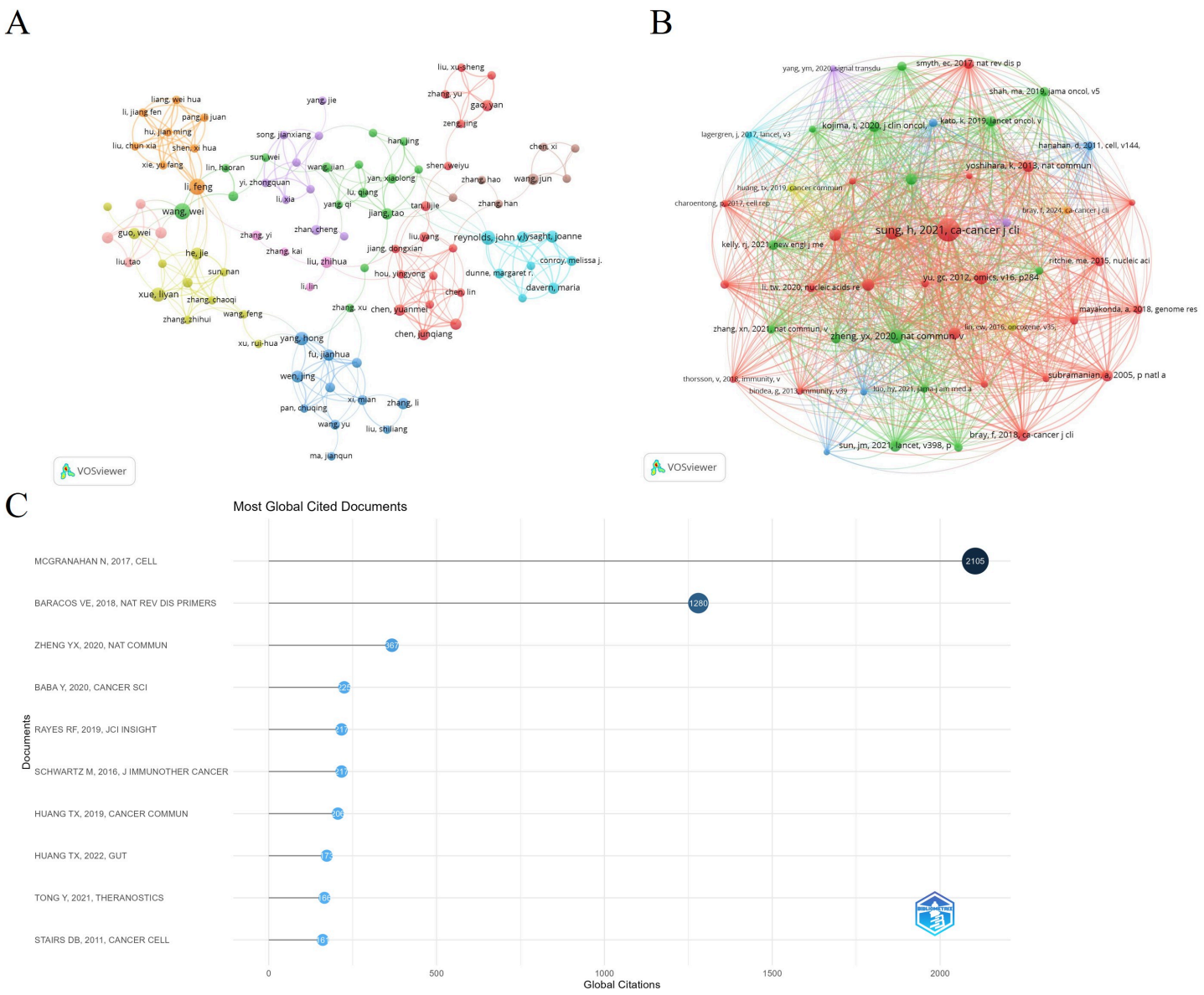


Figure 5

Author collaboration, co-cited references, and highly cited documents

（A）Author collaboration network

（B）Co-cited reference network

（C）Distribution of globally highly cited documents

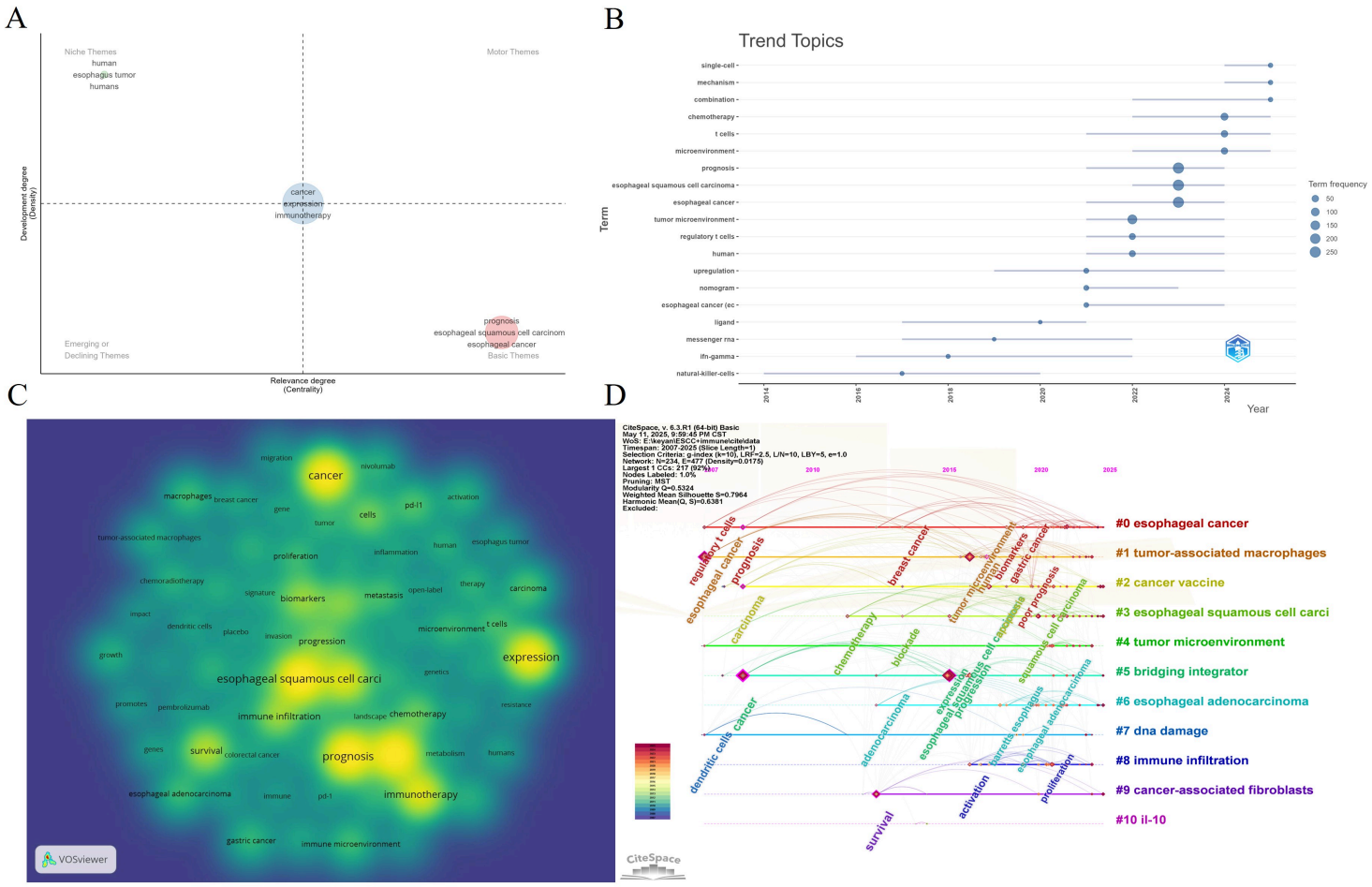


Figure 6

Keyword hotspots and thematic evolution

（A）Keyword thematic map

（B）Trend topic map

（C）Keyword density map

（D）Keyword timeline clustering map