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Emerging trends and research landscape of the tumor microenvironment in head-and-neck cancer: A comprehensive bibliometric analysis

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Abstract

Head-and-neck squamous cell carcinoma (HNSCC) is a complex malignancy characterized by a highly heterogeneous tumor microenvironment (TME) that influences tumor progression, metastasis, and therapeutic resistance. Despite significant advancements in understanding HNSCC at the molecular level, comprehensive analyses of TME-related research within this domain remain limited. Hence, this study presents a bibliometric analysis of TME research in HNSCC, synthesizing data on publication trends, citation patterns, collaborative networks, and emerging research themes. The findings reveal an exponential growth in TME-related publications, reflecting a rising focus on immunotherapy, stromal biology, and molecular biomarkers. Medicine and molecular biology dominate the research output, with interdisciplinary collaborations contributing to innovative therapeutic strategies. Key themes include immune resistance, extracellular matrix modulation, and the role of stromal components, like cancer-associated fibroblasts, in shaping therapeutic outcomes. Emerging topics, such as novel cell death pathways (e.g., cuproptosis and pyroptosis) and artificial intelligence-driven prognostics, highlight future directions. Citation networks emphasize the centrality of immunotherapy and precision medicine, with leading institutions and journals playing pivotal roles in advancing the field. This analysis underscores the importance of interdisciplinary research and highlights critical gaps, offering a roadmap for future investigations to improve clinical outcomes through targeted TME manipulation in HNSCC.

Keywords: Biomarker; Bibliometrics; Scientometrics; Meta-analysis; Cancer

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1. Introduction

Head-and-neck cancer, particularly head-and-neck squamous cell carcinoma (HNSCC), ranks as one of the most prevalent and deadly malignancies worldwide.[1] According to the Global Cancer Report 2020, HNSCC accounts for approximately 6% of all cancer cases globally, with an estimated 650,000 new cases and 350,000 deaths each year.[1-3] It remains a significant public health challenge, especially as the incidence of human papillomavirus-positive cases has risen in recent decades.[4] Despite advancements in understanding its molecular and genetic underpinnings, HNSCC continues to have a high mortality rate, primarily due to late-stage diagnosis, treatment resistance, and recurrence.[5] Treatment

strategies for HNSCC mainly rely on surgery, radiotherapy, and chemotherapy. However, these approaches often have substantial side effects, including functional and esthetic impairments, and fail to prevent recurrence in many patients.[6,7] The complexity of treating HNSCC is compounded by its heterogeneous nature, with variations in genetic profiles and therapy responses based on tumor site, stage, and human papillomavirus status.[8]

The tumor microenvironment (TME) plays a pivotal role in the progression of HNSCC.[9] Conventionally, cancer has been perceived as a disease primarily driven by genetic mutations within tumor cells. However, growing evidence highlights the significant influence of the TME in tumor initiation, growth, metastasis, and resistance to therapy.[10] The TME is a dynamic ecosystem composed of various cellular and extracellular components, including tumor cells, cancer-associated fibroblasts (CAFs), immune cells, and extracellular matrix (ECM) proteins.[11] These elements support tumor growth and facilitate tumor cell survival, invasion, and metastasis through complex signaling networks. The crosstalk between tumor cells and their surrounding microenvironment has profound implications for the development of novel therapeutic strategies.[12] Immune cells within the TME, such as macrophages, T-cells, and myeloid-derived suppressor cells, are critical in regulating the immune response against the tumor.[13] However, in HNSCC, these immune cells often undergo dysfunction, contributing to immune evasion and the progression of the disease.[14]

The immune landscape within the TME of HNSCC is significant in shaping the course of the disease. Tumors have developed sophisticated mechanisms to evade immune surveillance, such as the overexpression of immune checkpoint molecules like programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1), which inhibit T-cell function and allow the tumor to escape immune attack.[15] This immune evasion contributes significantly to tumor progression, metastasis, and resistance to therapies.[16] The approval of immune checkpoint inhibitors, particularly those targeting PD-1/PD-L1, represents a breakthrough in HNSCC treatment, offering hope for improved outcomes, particularly in recurrent or metastatic cases.[1] However, the heterogeneity of immune responses and the limited efficacy of these treatments in a subset of patients underscore the complexity of the TME and the need for a deeper understanding of its role in HNSCC progression.[14]

The significance of the TME in HNSCC has prompted extensive research into its composition and functional dynamics.[17] Recent studies have focused on identifying the key cellular players within the TME, such as CAFs, immune cells, and endothelial cells, and understanding their contributions to tumor progression.[18] Furthermore, research into the metabolic changes within the TME, such as hypoxia-induced angiogenesis and altered metabolic pathways, has revealed new avenues for therapeutic intervention.[19] However, despite significant advances in understanding the molecular mechanisms driving HNSCC, there remains a lack of comprehensive, quantitative analyses that synthesize the breadth of research on the TME in this cancer type.

In this context, bibliometric analyses serve as powerful tools to assess the trends, evolution, and impact of scientific research in specific fields.[20] A bibliometric analysis of the TME in HNSCC offers a systematic approach to understanding the scientific community's focus over time, the emerging research topics, and the connections between different areas of study. By quantifying the number of publications, citations, and collaborations within this field, bibliometrics allows researchers to identify the most influential studies, key authors, and leading institutions. Moreover, a bibliometric approach can uncover the shifts in research focus, helping to highlight underexplored areas and predict future research trajectories.[21]

In recent years, there has been an increasing emphasis on the role of the TME in cancer treatment, with particular attention to how it influences therapeutic responses and resistance mechanisms.[22] The intersection of immunotherapy and the TME has garnered significant interest as researchers explore ways to manipulate the immune landscape to enhance therapeutic efficacy.[23] In addition, the identification of novel biomarkers within the TME has paved the way for personalized treatments, offering the potential for improved patient outcomes.[24] However, despite these promising developments, several challenges remain, including the complexity of the TME, its heterogeneity, and its dynamic nature, which makes it difficult to target effectively with current therapies.[22]

A bibliometric approach to studying the trends in TME research in HNSCC provides a comprehensive overview of the current state of knowledge and the direction of future research. While a previous study provides an overview of immunotherapy trends in HNSCC,[25] it does not explicitly address the TME or its implications in treatment. It focuses on immune checkpoint inhibitors but lacks an in-depth exploration of the TME's role and its interactions with therapies. In contrast, this study uniquely concentrates on the TME and its impact on therapeutic outcomes, offering a novel perspective on how its cellular components influence treatment efficacy. The focus on the TME in HNSCC, integrated with evolving therapies, significantly distinguishes this research and guides future studies in

this field. This analysis can offer valuable insights into the evolving scientific landscape by examining the growth of publications, citation patterns, and thematic clusters within the field. Moreover, it allows the identification of emerging research areas, such as the interplay between the TME and novel treatment modalities, including targeted therapies and immunotherapies. This type of analysis can also highlight the global nature of TME research, with collaborations spanning institutions and countries, facilitating the exchange of ideas and the development of global research agendas.

Furthermore, bibliometric analysis can help identify the gaps in current research on the TME in HNSCC.[26] While significant progress has been made in understanding the cellular and molecular components of the TME, translating these findings into clinical practice remains a significant hurdle. Understanding the trends in research can guide future investigations toward areas that need further exploration, such as the role of specific immune cells in the TME, the impact of the ECM in metastasis, and the potential for combining immunotherapies with other treatment modalities.

The TME is a critical factor in the pathogenesis and progression of HNSCC. Its complex and dynamic interactions with tumor cells contribute to the disease's aggressive nature and resistance to treatment. While research in this area has advanced significantly, there is a need for systematic, quantitative analyses to track the evolution of scientific knowledge on the TME in HNSCC. A bibliometric approach offers an effective method for identifying research trends, uncovering emerging themes, and highlighting areas needing further investigation. By providing a comprehensive overview of the current state of TME research, this analysis aims to contribute to a deeper understanding of the role of the TME in HNSCC and to inform the development of more effective therapeutic strategies.

2. Methodology

2.1. Search strategy

A literature review was carried out to generate appropriate inclusion and search criteria based on the target population, key ideas, content scope, and review goals. Search terms and phrases were combined using Boolean operators "AND" and "OR." The keywords employed were "tumor AND microenvironment AND cancer AND head AND neck AND cancer," and the search was confined to the title, abstract, and keywords sections. Both electronic databases (Scopus and PubMed) and manual techniques, such as reviewing reference lists from selected studies, were utilized for the literature search.

The initial search yielded 6213 results. Only articles published in English were selected to narrow the results, given the widespread use of English in academic research. From these, two types of publications – research articles and review papers – were chosen for further evaluation. This process resulted in 4743 publications retained for further analysis (Figure 1). No additional exclusion criteria were applied.

2.2. Data analysis

Bibliometric data were collected from the Scopus database, a well-established bibliometric research platform offering comprehensive details about academic publications. A search was conducted on Scopus on December 15, 2024, covering the period from 1979 to 2025. The bibliometric analysis was partially carried out using VOSviewer[27] (version 1.6.2), a specialized tool designed to analyze large publications datasets, which helped construct networks for collaboration, co-citation, and co-occurrence. The full counting approach was applied, treating each co-authorship, co-occurrence, bibliographic coupling, and co-citation connection with equal importance. In addition, Microsoft Office Excel 2019 was used to conduct various analyses of the publication data.

3. Results and discussion

3.1. Temporal evolution of research

The temporal evolution of research in the TME in HNSCC reveals significant shifts in scientific attention over the past few decades, as depicted in the provided graph. The data span from 1979 to approximately 2027, offering insights into the changing trends of publication frequency in this field (Figure 2).

From 1979 to 2010, research on the TME in HNSCC was virtually non-existent, highlighting the underexplored TME nature of this area. This early period was characterized by a predominant focus on more conventional cancer research, emphasizing oncogenic pathways, tumor biology, and treatment approaches while largely neglecting TME. The limited attention to the TME during this time can be attributed to technological constraints and a lack of substantial evidence linking the microenvironment to cancer progression and therapy resistance. Methodological limitations in studying the complex interactions between tumor cells and their surrounding microenvironment further hindered research in this area.

The landscape began to shift around 2015, with a noticeable rise in publications, signaling a growing awareness of the TME's critical role in HNSCC. This upward trend coincides with significant advancements in

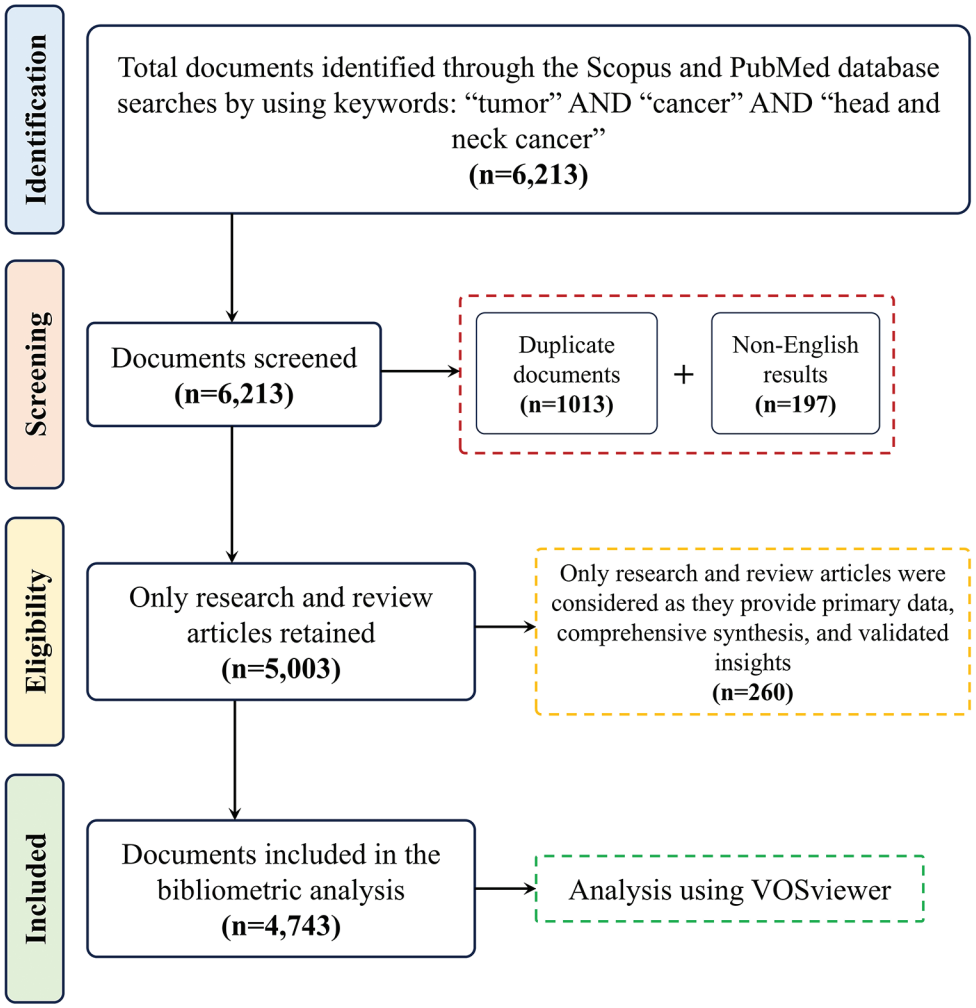

Figure 1. A PRISMA-style flow diagram illustrating the systematic selection process for bibliometric analysis of head-and-neck cancer research

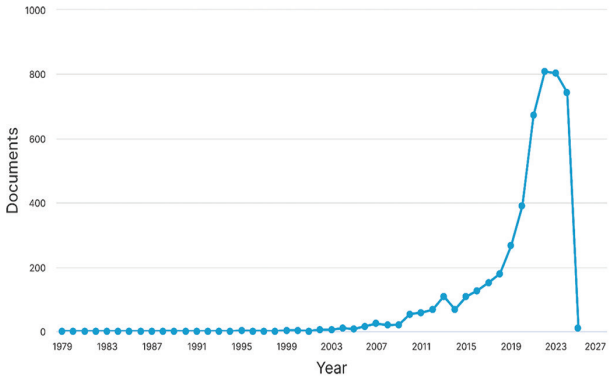

Figure 2. The number of documents published per year

omics technologies, including genomics, transcriptomics, and proteomics, which equipped researchers with the necessary tools to delve deeper into the complexities of the TME. During this phase, studies began to elucidate the contributions of stromal cells,[28] immune cells,[29] ECM components,[30] and signaling molecules[23] in modulating tumor progression, metastasis, and therapeutic resistance in HNSCC. Moreover, the success of immune checkpoint inhibitors and other immunotherapies reinforced the TME as a central target for therapeutic intervention, further accelerating research efforts.

The period between 2017 and 2021 witnessed the most dramatic surge in publications, with a steep rise in research output. This exponential growth underscores the increasing importance of TME in HNSCC research. Several key factors likely contributed to this increment in publications. First, clinical evidence highlighting the role of TME components, such as tumor-associated macrophages, myeloid-derived suppressor cells, and regulatory T cells, in mediating immunosuppression and treatment resistance became more robust. Second, technological breakthroughs, particularly in single-cell

RNA sequencing, spatial transcriptomics, and advanced imaging techniques, allowed for unprecedented insights into the spatial and functional heterogeneity of the TME. Finally, the advent of personalized medicine, which emphasizes tailoring treatments based on patient-specific TME profiles, further fueled the rapid growth in this research area.

However, an interesting trend emerges after 2021 – 2022, where the number of publications plateaued, followed by a sharp decline extending into 2027. This decline may not necessarily reflect a diminishing interest in the field but could be attributed to several factors. One possibility is that it represents an artifact of data collection, as future years may not yet be fully indexed. Given that it is 2025, many publications for these years are still being processed and have not yet been included in the database. This is most certainly the case, as there will undoubtedly be many more papers as the years pass, and the number of publications will likely increase as they are eventually indexed. Another reason could be a shift in focus toward translational and clinical research as the field transitions from basic discovery-driven studies to more applied research aimed at clinical implementation. In addition, the decline may suggest that researchers are expanding their focus beyond HNSCC, exploring broader TME studies encompassing multiple cancer types or novel therapeutic strategies.

The graph illustrates a clear trajectory of increasing interest and activity in TME research in HNSCC, especially from 2011 onwards. The period of rapid growth between 2017 and 2021 reflects the convergence of technological innovations, a deeper understanding of TME biology, and the clinical promise of targeted therapies. Despite the recent decline in publications, the field remains poised for continued progress, particularly in areas such as combination immunotherapies, stromal-targeting agents, and the identification of predictive biomarkers for patient stratification based on their TME profiles. Future research directions are likely to focus on exploring the interplay between the microbiome and TME and understanding how environmental and lifestyle factors influence the modulation of TME in HNSCC.

Table S1 provides a comprehensive list of the top 50 publications on TME in head-and-neck cancer, sorted in descending order of citation count. Each entry includes detailed information such as the year of publication, journal name, first author, and the affiliated institute of the first author. This curated compilation serves as a valuable resource for understanding the impact and progression of research in this emerging field, offering insights into influential studies and leading contributors.

3.2. Disciplinary landscape

The distribution of research on the TME in HNSCC across various scientific disciplines, as illustrated in the pie chart (Figure 3), underscores the highly interdisciplinary nature of this rapidly expanding field. The two dominant contributors, medicine (38.0%) and biochemistry, genetics, and molecular biology (32.6%), collectively represent more than 70% of the research output, reflecting the central role of clinical and molecular investigations in advancing our understanding of TME dynamics in HNSCC.

The substantial share of medicine, which leads the chart, highlights the clinical focus of TME research. This emphasis reflects the importance of translating fundamental scientific discoveries into therapeutic interventions. Research within this domain has extensively examined how the TME contributes to immunosuppression, treatment resistance, and tumor progression. Efforts have been directed toward identifying therapeutic targets such as immune checkpoint inhibitors and combining immunotherapies with conventional treatments. Furthermore, the prominence of clinical research underscores the importance of developing predictive biomarkers for HNSCC, improving diagnostic accuracy, and optimizing treatment regimens in clinical settings.

As the second-largest contributor, biochemistry, genetics, and molecular biology focus on the molecular mechanisms underlying TME biology in HNSCC. This area of research is pivotal for understanding the complex interactions between tumor cells, stromal components, immune cells, and ECM proteins. Techniques such as single-cell RNA sequencing, proteomics, and epigenomics[31] are extensively used to explore the molecular crosstalk within the TME that drives tumor progression, immune evasion, and metastasis. The insights gained are invaluable for identifying novel

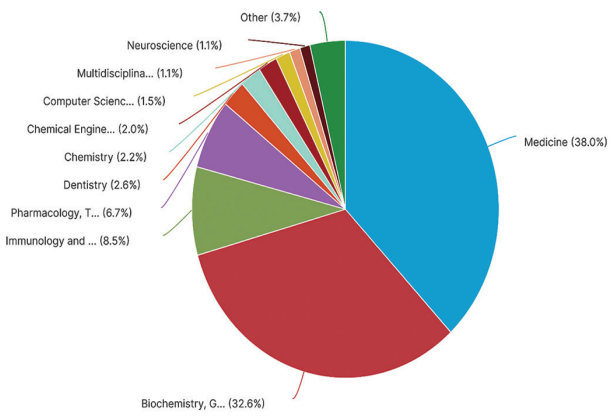

Figure 3. The breakdown of scientific publications by major research fields. Source: www.scopus.com.

therapeutic targets and facilitating the development of targeted treatment strategies for HNSCC.

The significant involvement of immunology and microbiology (8.5%) reflects the increasing recognition of immune modulation within the TME as a critical study area. The immunosuppressive nature of the TME, particularly the role of tumor-associated macrophages, regulatory T cells, and myeloid-derived suppressor cells, is a key focus in this domain. Research in this area informs the growing application of immunotherapies in HNSCC, such as PD-1/PD-L1 inhibitors and cancer vaccines, aimed at reactivating antitumor immunity and overcoming immune evasion mechanisms.

Pharmacology, toxicology, and pharmaceutics (6.7%) also contribute to advancing TME research, particularly in developing new therapeutic agents targeting the TME. This research often addresses challenges related to drug delivery, such as overcoming the physical and biochemical barriers posed by the TME and minimizing off-target effects. Notable advancements include the use of nanocarriers, combination therapies, and TME-specific inhibitors to improve treatment efficacy and reduce side effects.

While smaller in proportion, the contributions from dentistry (2.6%), chemistry (2.2%), chemical engineering (2.0%), and computer science (1.5%) reflect the growing importance of interdisciplinary approaches to TME research. Dentistry's involvement highlights the relevance of regional specificity in HNSCC, considering the unique anatomical and physiological characteristics of the head-and-neck region. Research in this field also explores the impact of oral microbiota and local inflammation on TME characteristics, influencing diagnosis and treatment outcomes.

The contributions of chemistry and chemical engineering are key to developing novel biomaterials, drug delivery systems, and therapeutic agents designed to target the TME. Meanwhile, computer science plays an increasingly important role in data analysis, bioinformatics, and TME interaction modeling through artificial intelligence (AI) and machine learning. These fields are vital for managing the complexity of TME data and for advancing predictive modeling and simulations.

Finally, the category of multidisciplinary and emerging fields (1.1%) emphasizes the continued expansion of TME research through collaborative efforts across various scientific domains, which will undoubtedly drive future innovations in understanding and treating HNSCC.

The disciplinary landscape of TME research in HNSCC is highly diverse and reflects a multi-faceted approach to tackling the challenges posed by the TME. The leading roles of medicine and molecular biology suggest a continued emphasis on clinical applications and mechanistic insights, while the growing contributions from immunology, pharmacology, and computational sciences indicate expanding opportunities for novel therapeutic strategies. Future research may benefit from leveraging AI and exploring the interplay between the microbiome and TME to develop personalized and integrated treatment approaches that span multiple disciplines.

3.3. Mapping the intellectual landscape of TME research in HNSCC

The co-citation network in Figure 4 provides a comprehensive representation of the intellectual landscape of TME research in the context of HNSCC. It reveals the interconnectedness of influential papers, highlighting key thematic clusters and the intellectual cohesion within the field. The size of the nodes within the network corresponds to the citation strength of specific studies, with larger nodes indicating more widely cited or influential works. The edges between these nodes represent connections between research themes, with clusters emerging around seminal works that have shaped the direction of TME research in HNSCC.

At the centre of this network is the highly influential paper by Hanahan and Weinberg, "Hallmarks of Cancer:

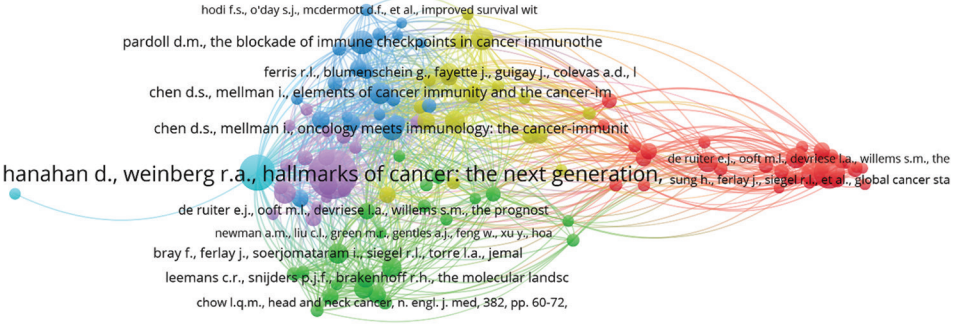

Figure 4. A network visualization of the intricate connections between key publications

The Next Generation," which has become a cornerstone in cancer biology.[32] This foundational work outlines critical biological traits of cancer, many of which are influenced by the TME. Its central positioning in the network, with its large node size, underscores its importance in linking diverse research areas to a unified conceptual framework. The prominence of this paper demonstrates its broad applicability across different subfields of TME research, serving as a critical reference point for understanding the TME in HNSCC.

Surrounding this central node are several key thematic clusters. One prominent group of studies, including works by Chen and Mellman, such as "Oncology Meets Immunology: The Cancer-Immunity Cycle," highlights the growing focus on cancer immunotherapy. These papers emphasize the role of the immune system within the TME and how tumors evade immune surveillance, providing critical insights into immunotherapeutic strategies.[33] The prominence of these works within the network reflects the rising interest in targeting the TME to develop immune-based therapies, such as immune checkpoint inhibitors, which have gained considerable attention in recent years.

Another notable cluster includes studies by Pardoll and Ferris, which focus on immune checkpoint blockade and the clinical translation of immunotherapy in cancer.[34,35] These studies underscore the critical role of the TME in shaping therapeutic responses, particularly in HNSCC, where immune resistance is a significant challenge. The interconnections within this cluster suggest that immunotherapy remains a central and rapidly evolving area of research, with a strong emphasis on overcoming immune resistance in the TME to improve therapeutic outcomes.

The network also highlights important epidemiological and prognostic studies, such as those by Bray *et al.*, which provide valuable insights into the global burden of cancer and its public health implications.[36] While these works do not focus directly on the TME, they are crucial for contextualizing the societal impact of HNSCC and informing strategies for improving treatment outcomes. These studies emphasize the need for a deeper understanding of the TME to address the high morbidity and mortality rates associated with HNSCC.

Furthermore, the network identifies smaller yet significant clusters involving studies on the molecular landscape of HNSCC, such as those by Leemans *et al.* These studies integrate genomic and molecular data with TME research, offering a deeper understanding of how genetic alterations and signaling pathways contribute to the formation and dynamics of the TME.[37] The increasing integration of molecular biology with TME studies points to the growing complexity and sophistication of research in this field as researchers explore the molecular mechanisms that drive the TME.

The figure also reveals emerging research areas, such as the application of computational and bioinformatics approaches to TME studies. Clusters related to single-cell analyses and network modeling indicate that these approaches, while still in the early stages, hold considerable promise for unraveling the complexity of the TME. The sparse connections to chemical and engineering disciplines suggest untapped potential for innovation in drug delivery systems and biomaterial-based interventions targeting the TME. These interdisciplinary areas offer exciting opportunities for future research that could lead to the development of novel therapeutic strategies.

The citation network provides a comprehensive map of the intellectual landscape of TME research in HNSCC, highlighting key themes and identifying emerging trends. The central role of cancer biology, immunotherapy, and molecular biology in shaping the field underscores their importance in advancing our understanding of the TME. Moreover, the network highlights promising growth areas, including computational approaches and interdisciplinary innovations, which could significantly enhance the development of targeted therapies for HNSCC. This analysis not only underscores the foundational works that have shaped the field but also points to the gaps and opportunities that will drive the future of TME research in head-and-neck cancer.

3.4. A network-centric view of the author metrics

Analyzing author metrics in TME research within HNSCC provides valuable insights into the landscape and trends of this rapidly advancing field (Figure 5). Figure 5A visualizes the number of published documents by leading authors and reveals the significant contributions of key researchers. Ferris *et al.*[34,38,39] stands out as the most prolific author, with a substantially higher number of publications than his peers, followed by Sun Z.J., Hoffman T.K., and Karam S.D. Ferris R.L.'s prominence in this field likely reflects his pioneering work in immune modulation, biomarker discovery, and novel therapeutic strategies targeting the TME in HNSCC. While a few authors dominate the field regarding publication output, the broad distribution of publications across multiple researchers demonstrates a growing and dynamic interest in TME-focused studies, indicating a robust field expansion.

In Figure 5B, the citation network presents the interrelationships between top authors based on shared citations, represented by interconnected nodes. The clustering of authors within distinct groups highlights

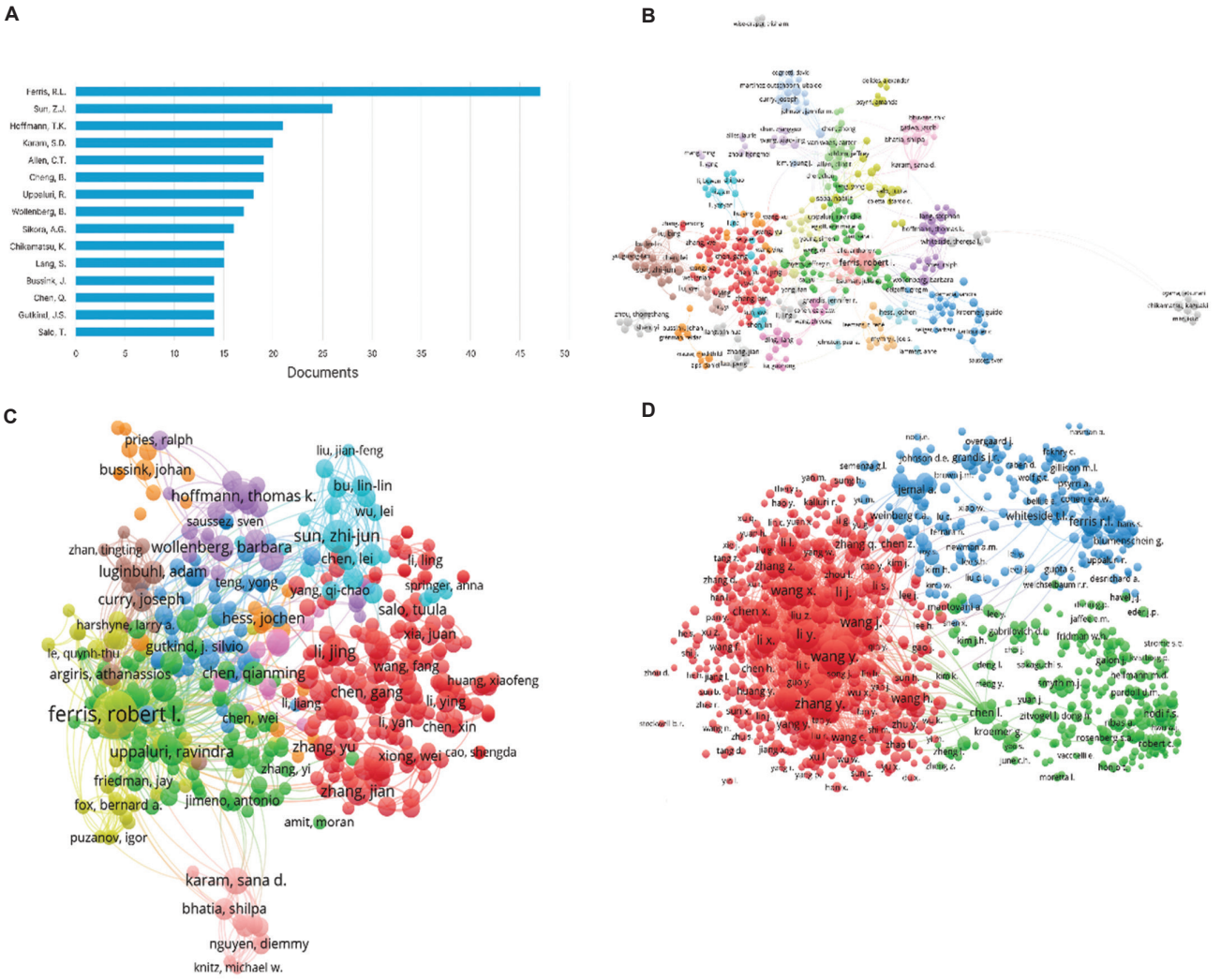

Figure 5. Visualizing scientific collaboration networks. The figure shows (A) author productivity, (B) co-authorship network, (C) bibliometric coupling network, and (D) co-citation network.

strong collaborative or thematic connections, with Ferris R.L. occupying a central position in one of the largest clusters. This centrality underscores his influence in the field, as his work is widely cited. Multiple distinct clusters reflect the diversity of research approaches within TME studies, including immunotherapy, molecular mechanisms, and biomarker discovery. This interconnectedness emphasizes the interdisciplinary nature of TME research, suggesting ample opportunities for further collaboration and integrating different perspectives to advance the field. In addition, the co-authorship network is constructed using a predefined threshold for inclusion, ensuring that only authors with a minimum of five co-authored publications are represented. This threshold enhances the clarity of collaboration patterns and prevents the overrepresentation of infrequent contributors.

Figure 5C illustrates the bibliometric coupling network and builds on this idea by showing how authors are linked through shared references. The clusters in this network are differentiated by color to represent thematic groups, such as immune checkpoints and stromal interactions. Ferris R.L.'s prominent position within a vibrant cluster suggests his research spans multiple subfields and is a pivotal reference for various topics. The proximity of nodes within and across clusters reveals significant overlap in research areas, highlighting the cross-pollination of ideas across thematic domains. This cross-disciplinary synergy points to opportunities for integrative research that unifies fragmented subfields within TME studies.

In Figure 5D, the co-citation network further explores the relationships between authors based on the frequency with which their work is co-cited. The clustering of nodes

in this network reflects thematic alignment, with Ferris R.L. and other leading researchers forming the core of the red cluster. This indicates that their work is frequently cited in studies addressing immune evasion, therapy resistance, and other hallmark features of the TME in HNSCC. The blue and green clusters likely represent other significant research areas, such as molecular profiling and therapeutic development. The dense interconnections within and between clusters highlight the shared intellectual foundation of the research community, illustrating the importance of collaborative or complementary studies in driving the field forward.

The overall analysis of the figure reveals several key trends in TME research within HNSCC. First, the dominance of authors like Ferris R.L. indicates a core group of researchers at the forefront of the field, driving advances in immunotherapy, precision medicine, and immune modulation. Second, the dense clustering in Figure 5B-D highlights the highly interdisciplinary and collaborative nature of the field, with researchers coming from diverse backgrounds, such as immunology, molecular biology, and clinical research. This collaborative framework is crucial for addressing the complex challenges posed by the TME, which involves various cell types, molecular signaling pathways, and therapeutic interactions.

Moreover, the diversity of clusters observed in Figure 5C and D suggests that some research areas, such as immune modulation and biomarker discovery, are well-established, while others may still be emerging. These underexplored areas, such as the role of the microbiota in the TME or the impact of metabolic reprogramming on tumor progression, present significant opportunities for new researchers to contribute to the field. The interconnectedness of the networks also points to the potential for further growth through cross-disciplinary collaborations. Integrating computational modeling with experimental studies could provide deeper insights into therapeutic outcomes while leveraging big data to help identify novel druggable targets within the TME.

Analyzing the bibliometric networks provides a comprehensive view of the author landscape in TME research within HNSCC. It highlights both well-established areas of strength and emerging opportunities for innovation. This dynamic and collaborative research environment offers exciting prospects for the future of TME research and therapeutic strategies for head-and-neck cancer.

3.5. The immune response in head-and-neck cancer: A network of keywords

The network visualization of top author keywords in this research segment provides a detailed snapshot of the evolving landscape surrounding the TME in HNSCC (Figure 6). The centrality of keywords such as "immunotherapy," "head–and-neck cancer," "prognosis," and "biomarkers" signals the increasing focus on translational research aimed at improving clinical outcomes by better understanding and manipulating the TME in HNSCC. This highlights the ongoing shift toward precision medicine, with an emphasis on integrating immune-based and molecular strategies into treatment regimens.

At the heart of the network, the prominence of "immunotherapy" underscores the critical role of immune modulation within the TME. The continued focus on immune checkpoint inhibitors such as PD-1/PD-L1 and cytotoxic T-lymphocyte-associated protein 4 blockers – evident from their recurrent appearance in the figure – reflects a significant research trend exploring their therapeutic potential in HNSCC. Recent clinical successes, particularly with agents such as pembrolizumab and nivolumab, have bolstered this interest, reinforcing the potential of immune checkpoint blockade as a cornerstone of treatment. Furthermore, keywords such as "tumor-infiltrating lymphocytes," "immune infiltration," and "cytokines" indicate substantial efforts to define the immune landscape within the TME, aiming to identify predictive biomarkers that could guide patient stratification and therapeutic decision-making.

The close association of the keyword "prognosis" with terms like "prognostic signature" and "gene signature" reveals an ongoing emphasis on molecular and genetic profiling to tailor treatments. The inclusion of terms such as "long non-coding RNAs," "DNA methylation," and "gene expression" suggests the growing impact of high-throughput techniques in unraveling epigenetic and transcriptomic alterations in the TME. These molecular signatures are critical for prognostication and offer valuable insights into potential therapeutic targets, addressing the inherent heterogeneity of HNSCC and paving the way for personalized approaches.

Tumor biology emerges as a significant area of focus, with terms like "metastasis," "invasion," "epithelial-mesenchymal transition," and "angiogenesis" underscoring the complex interplay between TME and cancer progression. The network highlights the role of stromal components, including CAFs and mesenchymal stem cells, in supporting tumor growth, migration, and resistance to treatment. The strong connections to terms such as "radiation resistance," "chemoresistance," and "hypoxia" reflect the challenges posed by the TME in limiting the effectiveness of conventional therapies, suggesting that further research into overcoming these barriers is crucial for improving treatment outcomes.

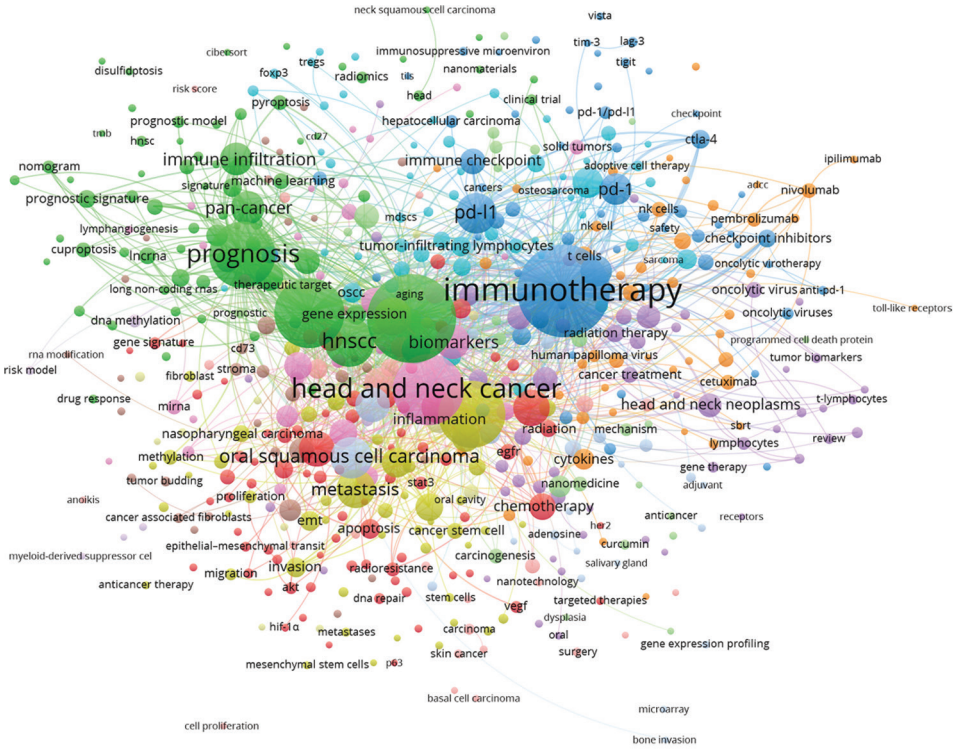

Figure 6. Network visualization of author keywords related to tumor microenvironment in head-and-neck cancer research

Emerging therapeutic avenues are highlighted by the presence of keywords such as "nanomedicine," "targeted therapies," and "oncolytic viruses," pointing to innovative strategies designed to overcome the limitations posed by the TME. The exploration of advanced modalities, including "adoptive cell therapy," "gene therapy," and "oncolytic virotherapy," emphasizes the growing interest in enhancing immune activation and targeting tumors more effectively. These approaches are at the forefront of research aimed at exploiting the unique characteristics of the TME for therapeutic gain, offering promising avenues for future clinical application.

The keyword "pan-cancer" suggests that research into the TME is becoming increasingly integrated across different cancer types, fostering a broader understanding of universal and cancer-specific TME features. This cross-pollination of ideas between HNSCC and other cancers will likely lead to more comprehensive insights into TME dynamics and therapeutic strategies applicable to multiple tumor types.

The network also points to emerging research areas, such as exploring novel cell death pathways such as "cuproptosis" and "pyroptosis." These cell death pathways may have profound implications for TME biology and therapeutic interventions, reflecting the growing interest in non-traditional cell death mechanisms. In addition, the inclusion of "machine learning" highlights the increasing role of computational tools in analyzing large datasets, identifying patterns, and predicting clinical outcomes – tools that are becoming indispensable in the age of precision oncology.

The network analysis reveals the multifaceted nature of TME research in HNSCC, emphasizing key themes such as immunotherapy, molecular biomarkers, and the mechanistic interactions between the tumor and its microenvironment. Future research should focus on overcoming therapy resistance, developing novel therapeutic approaches, and leveraging computational tools to understand TME heterogeneity better. These efforts will be crucial in advancing the clinical management of HNSCC and improving patient outcomes.

3.6. Trends and network of influential journals

The scientometrics of journal publications in TME research for HNSCC (Figure 7) highlights key trends, citation patterns, and collaborations. Figure 7A shows a sharp rise in publications post-2015, reflecting the growing focus on immunotherapy and tumor biology. Journals such as *Cancers*, *Frontiers in Immunology*, and *Clinical Cancer Research* have seen notable growth, paralleling advancements in immunotherapy. The post-2022 decline likely stems from

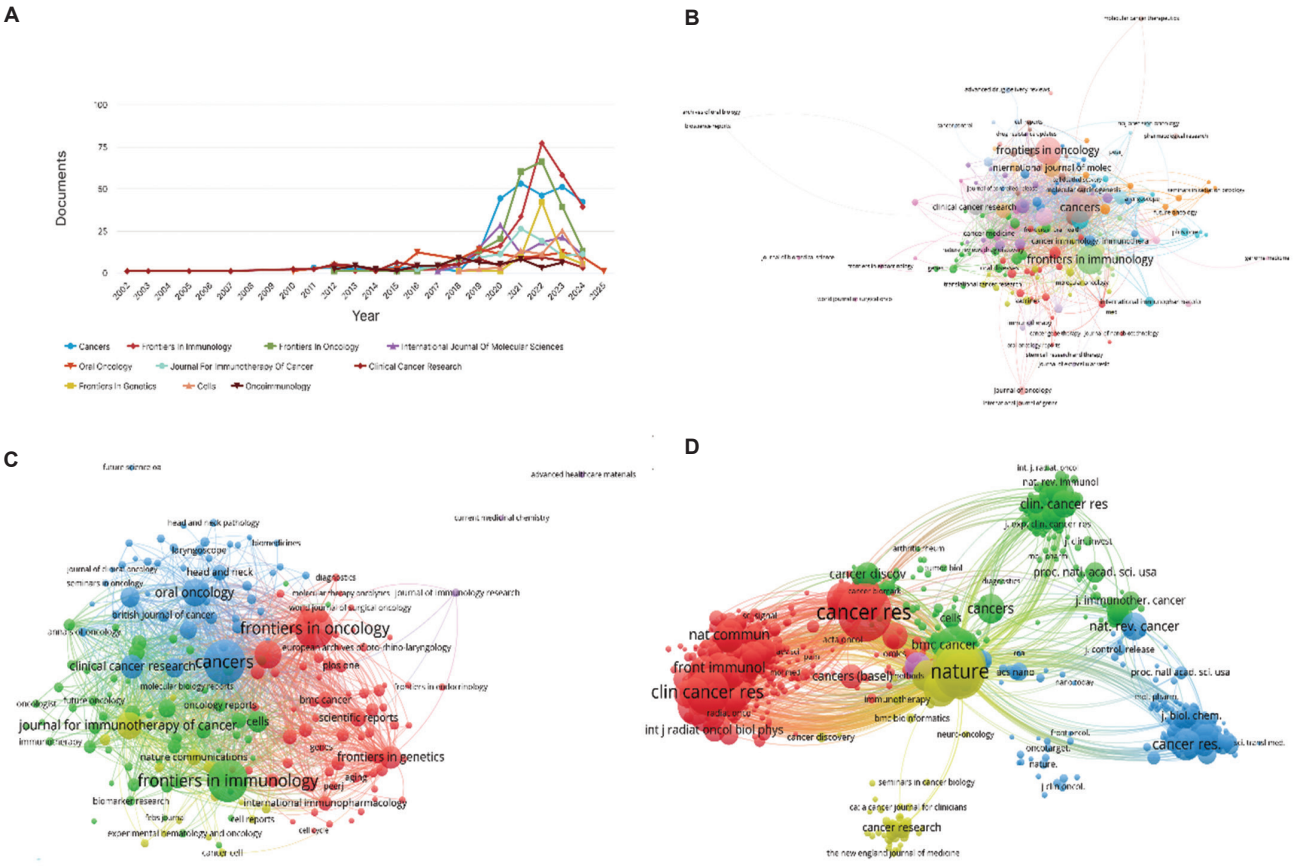

Figure 7. Trend and network analysis of top journals. (A) Publication trends of key journals over time. The journals' interconnectedness highlights influential hubs and emerging areas based on (B) citation network, (C) bibliometric coupling network, and (D) co-citation network.

data limitations rather than reduced interest. Spikes in journals such as the *Journal for Immunotherapy of Cancer* and *Oncoimmunology* align with checkpoint inhibitors (PD-1/PD-L1) breakthroughs. This rapid expansion underscores TME's role in precision therapies, biomarker discovery, and therapeutic target identification while highlighting gaps in stromal biology and epigenetics.

The citation network in Figure 7B illustrates journal interconnectivity through shared references, with *Cancers*, *Frontiers in Oncology*, and *Clinical Cancer Research* as central nodes shaping the research landscape. Thematic clustering reflects overlaps in immunotherapy, prognostic biomarkers, and molecular mechanisms. This multidisciplinary network, linking immunology, oncology, and molecular sciences highlight TME research's interdisciplinary nature and collaborative potential. The broad citation distribution underscores emerging opportunities in underrepresented areas such as nanotechnology and cell death mechanisms within the TME.

Figure 7C's bibliometric coupling network reveals journal relationships through shared references, with *Frontiers in Oncology*, *Frontiers in Immunology*, and *Cancers* forming a tight cluster, indicating overlapping research themes and audiences. These journals consistently publish studies on TME in HNSCC, covering immunological mechanisms, checkpoint blockade therapies, and stromal interactions. The network also suggests expansion opportunities in nanotechnology (*Advanced Healthcare Materials*) and stem cell research for innovative TME-targeting strategies. The rise of the *Journal for Immunotherapy of Cancer* signals a shift toward translational research, emphasizing clinical applications to improve patient outcomes.

The co-citation network analysis presented in Figure 7D underscores the shared influence of frequently co-cited journals, including *Nature*, *Clinical Cancer Research*, and *Cancer Research*, which form central hubs in this network. These journals are recognized for their authority in oncology and immunotherapy, serving as foundational references for subsequent research. The strong co-citation links between *Clinical Cancer Research* and *Nature Communications* highlight the integration of molecular biology and experimental oncology in applied cancer

research. The co-citation network reveals distinct clusters corresponding to different research domains: Red clusters represent immunological studies, green clusters focus on clinical and translational oncology, and blue clusters center on molecular and cellular mechanisms. These clusters not only reflect established areas of research but also identify gaps in the field, such as the potential for incorporating computational approaches, like AI-based prognostics,[40] and exploring novel therapeutic modalities, such as adoptive cell therapies[41] or epigenetic reprogramming.[31]

The analysis reveals that TME research in HNSCC is expanding and diversifying by integrating immunology, oncology, and molecular biology. Trends in journal publications emphasize immunotherapy and biomarker discovery as key drivers of progress. This growing literature enhances TME understanding and paves the way for targeted therapies. Future research could explore stromal biology's role in therapy resistance, innovative treatments such as nanomedicine and combination immunotherapies, and AI-driven predictive modeling. Emerging cell death mechanisms, including pyroptosis and cuproptosis, offer new therapeutic targets. This bibliometric analysis highlights the importance of interdisciplinary collaboration and the potential for translational and precision oncology to improve patient outcomes.

3.7. Beyond boundaries: The network institutional research collaboration

The analysis of the figure reveals the evolving dynamics of institutional research collaboration in the field of TME in HNSCC. Figure 8 comprises four parts: the number of published articles by affiliated institutes, the citation network among top institutes, the bibliometric coupling network, and the co-citation network analysis. Each of these subfigures provides valuable insights into the contributions, collaborations, and intellectual influences within the TME research landscape of HNSCC, offering a comprehensive view of institutional roles and networks in this field.

Figure 8A depicts the number of published articles by affiliated institutes, presenting a bar chart that ranks institutions based on their publication output. This chart highlights the level of engagement of different institutions in TME and HNSCC research. The Ministry of Education of the People's Republic of China emerges as the most prolific contributor, reflecting China's growing emphasis on oncology research and its government-supported academic initiatives. Chinese institutions, such as Sichuan University and Shanghai Jiao Tong University School of Medicine, also appear prominently in the chart,

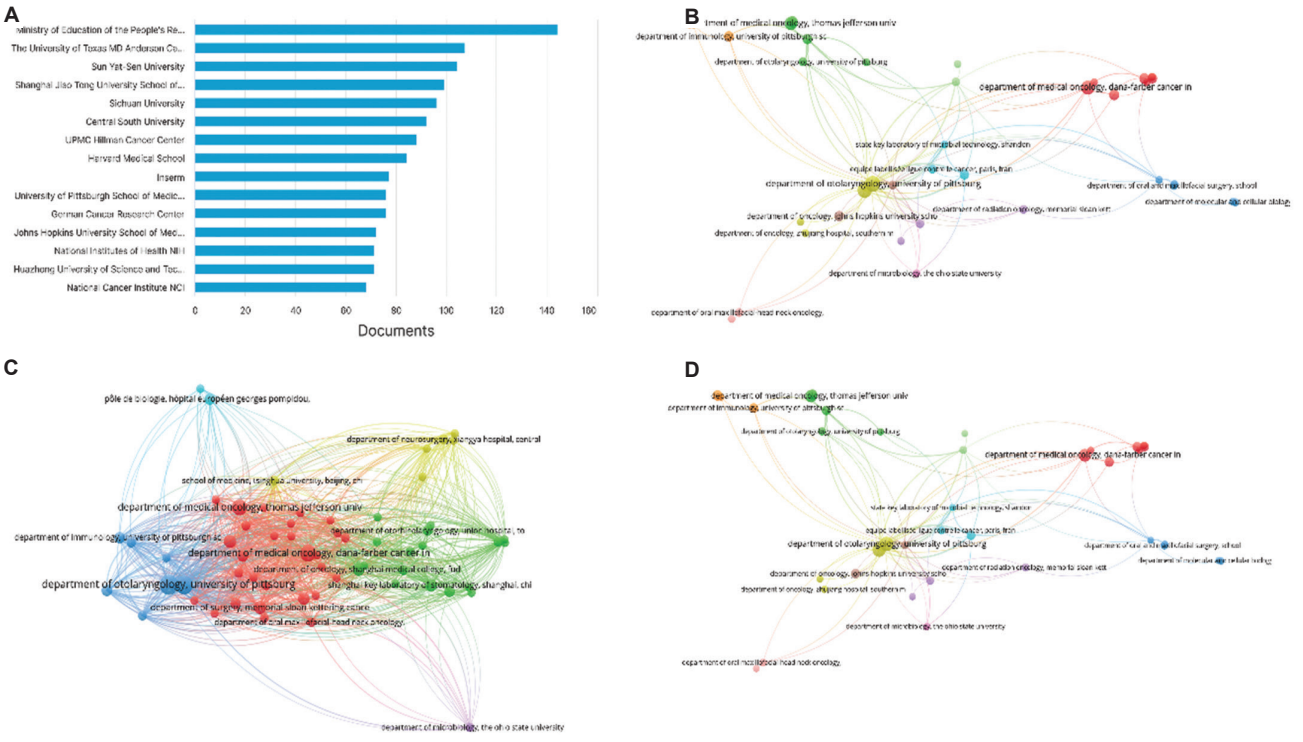

Figure 8. (A) Top 15 institutions contributing to the research, (B) network visualizations depicting collaborations between institutions and departments, (C) bibliometric coupling network, and (D) co-citation network

suggesting a coordinated national effort to advance TME research. Institutions such as the University of Texas MD Anderson Cancer Center and UPMC Hillman Cancer Center are among the top contributors in the United States, underscoring their long-standing leadership in cancer research. European institutions, such as Inserm and the German Cancer Research Center, are also well represented, demonstrating robust international efforts in this domain. The chart reveals a disparity between the major contributors and smaller institutes, suggesting that leading centers disproportionately drive research output. This unequal distribution may limit the diversity of perspectives in the field, thus offering an opportunity for emerging institutions to collaborate with established centers to enhance their contributions.

Figure 8B, the citation network among institutes, visually represents the influence and interconnectedness of leading institutions based on their citation impact. The size of the nodes indicates the volume of citations received by each institution, while the connecting lines and their thicknesses illustrate the strength of citation relationships. The United States and Chinese institutions dominate the network, with significant contributions from Europe. The University of Texas MD Anderson Cancer Center and UPMC Hillman Cancer Center occupy central positions, signifying their intellectual leadership and the widespread citation of their foundational research. The color-coded clusters in the network reveal distinct citation communities, with green clusters representing collaborations between United States institutions and red and yellow clusters reflecting international citation relationships involving European and Chinese institutes. The thinner connections between smaller nodes suggest a limited citation influence, indicating that some institutions may benefit from strengthening citation ties through collaborative publications, which could improve their visibility and integration into the global research network.

The bibliometric coupling network in Figure 8C reveals thematic overlaps between institutions, with node size reflecting shared references and connections indicating research alignment. UPMC Hillman Cancer Center and MD Anderson Cancer Center emerge as central hubs, closely linked to global institutions, particularly in the United States and China, around key themes such as immune microenvironment modulation and biomarker discovery. Peripheral clusters indicate niche research areas with opportunities for greater alignment. The multicolored connections highlight cross-disciplinary and international collaborations, though weakly connected nodes suggest underexplored research areas.

Figure 8D's co-citation network maps intellectual collaboration, with larger nodes representing highly cited institutions. MD Anderson Cancer Center and UPMC Hillman Cancer Center again dominate, reinforcing their leadership in TME research. The network shows United States, European, and Chinese institutions forming distinct, interconnected clusters. The presence of underdeveloped collaborations suggests opportunities for stronger ties to unify research efforts.

The combined analysis of all four panels underscores TME research in HNSCC as a rapidly growing field led by key institutions in China, the United States, and Europe. Their dominance reflects strong infrastructure, funding, and collaborations while emerging institutions can expand their impact through co-authored publications and thematic alignment with global trends. Strengthening international partnerships and exploring underrepresented areas such as immune modulators and therapeutic resistance could enhance inclusivity and innovation.

3.8. Global landscape of research

Figure 9 provides a comprehensive analysis of the global research landscape in the TME of HNSCC, illustrated through four distinct parts. The data presented underscore the trends, research output, and collaborative dynamics within this field. Figure 9A illustrates the number of published articles by country, with China and the United States leading in publication output, significantly surpassing other nations. Germany, the United Kingdom, and Italy follow as strong contributors, reflecting their well-established research infrastructure and sustained focus on TME in HNSCC. Countries such as India, Japan, and France show notable contributions on a smaller scale, pointing to regional disparities in research activity. This distribution highlights the growing gap between leading nations and others, especially in developing regions, which presents an opportunity for growth in underrepresented countries.

Figure 9B focuses on the citation network among countries, revealing the interconnectedness and influence of nations based on citations. China and the United States are central to this network, forming prominent nodes with thick connecting lines, signaling their dominant role in influencing global research. The proximity of Germany, the United Kingdom, and Japan further supports the idea of strong collaborative tendencies between these nations. Meanwhile, peripheral countries with thinner connections, such as Brazil and South Korea, show less citation impact, indicating a need for greater integration into global research efforts. The color-coding in this network highlights China's and the United States' central position, while other countries appear in more diverse color clusters, reflecting differentiated but less influential networks. The position

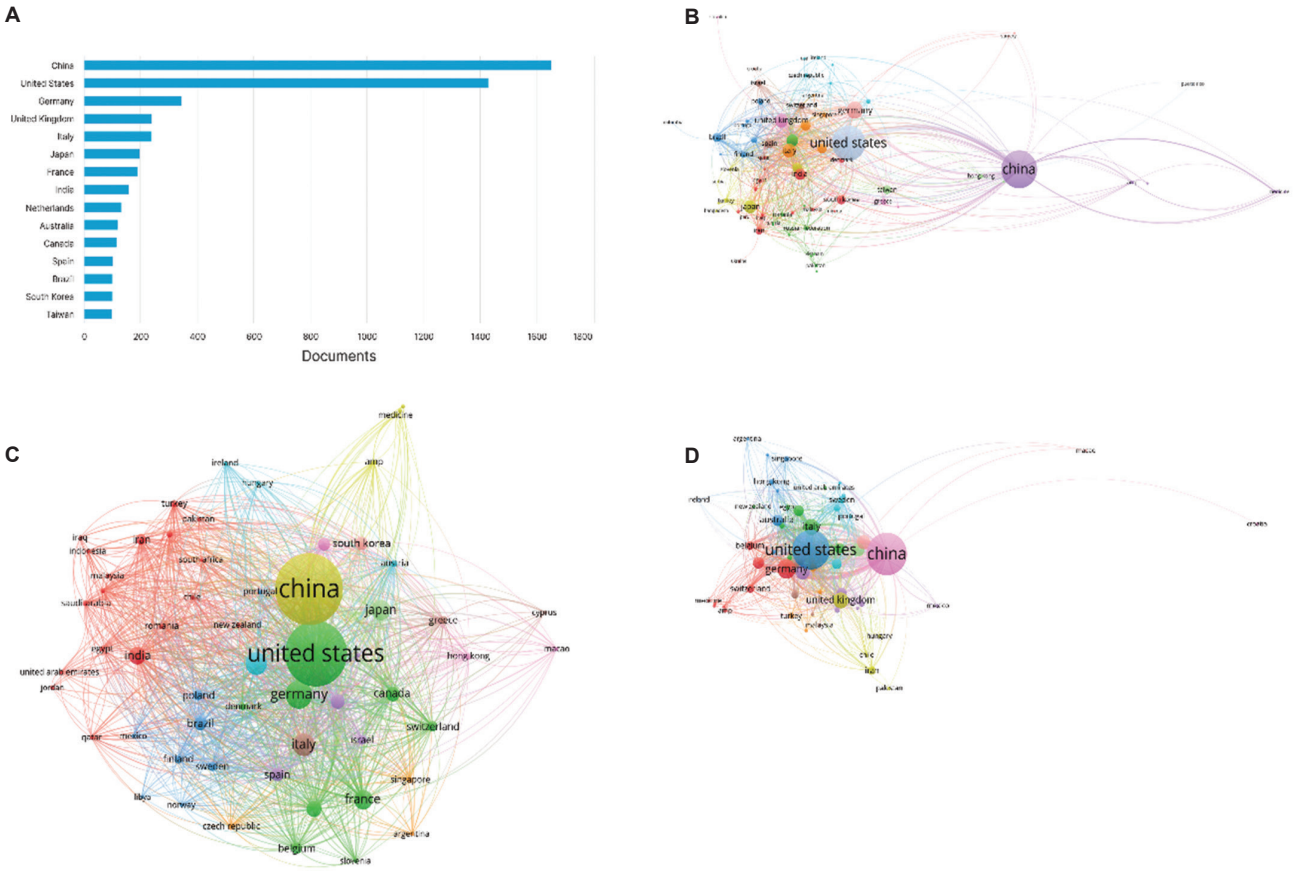

Figure 9. Co-authorship network of countries. The figure shows (A) the number of documents published by the top 15 countries, (B) a citation network, (C) the bibliometric coupling, and (D) the co-citation network.

of countries such as Brazil and South Korea, which are further from the central hub, emphasizes their potential for deeper involvement in global research networks.

The bibliometric coupling network in Figure 9C, which shows countries citing the same references, illustrates thematic similarities in research. China, the United States, and Germany dominate this network, signified by large, central nodes and vibrant colors, underlining their leadership in generating foundational research. The dense clusters around these nations represent robust thematic collaboration, while smaller nodes, such as India, Brazil, and South Korea, mark emerging contributors. The proximity of nodes within clusters reflects substantial thematic overlaps. In contrast, countries such as Cyprus and Hong Kong, located further from the central nodes, are characterized by more specialized or niche research contributions. This network highlights the leading countries' role in steering research agendas and allows emerging nations to align their research with global trends.

In Figure 9D, the co-citation network maps countries frequently cited together, reflecting shared intellectual collaboration. The United States and China are once again dominant, with large, central nodes and dense connections to other nations, particularly Germany, the United Kingdom, and Japan, suggesting shared research interests and methodological approaches. The separation of peripheral countries such as Pakistan, Croatia, and Ireland from the central network indicates their lower integration into the dominant research framework. These nations may either focus on niche areas or have limited international collaborations, presenting opportunities for greater engagement with leading research hubs.

The combined analysis of these four components reveals a growing interest in TME in HNSCC, with China and the United States leading in publication volume, citation impact, and global collaboration. The prominence of European countries, including Germany and the United Kingdom, underscores their historical strengths in oncology research. However, the figure highlights gaps in contributions from regions such as Africa, South America (outside Brazil), and Southeast Asia, which suggests untapped potential for research growth in these

areas. The trends emphasize the importance of fostering collaborations between dominant and emerging countries to broaden the research base and stimulate innovation. Expanding international networks, particularly for underrepresented nations, could diversify perspectives and enhance global research output. Thematic alignment, as seen in the bibliometric coupling analysis, presents a clear pathway for smaller contributors to integrate into global research trends, enhancing their visibility and impact. In summary, Figure 9 illustrates the dominance of established research powerhouses in TME and HNSCC while identifying significant opportunities for growth through international collaboration, thematic alignment, and better integration of underrepresented countries into global research networks. These insights reflect the field's current state and suggest strategic priorities for advancing research in this area.

3.9. Bankrolling the science: An overview of top research funding sources

The bar chart illustrating the top funding organizations for research in TME and HNSCC highlights the global scale and multidisciplinary nature of this rapidly advancing field (Figure 10). It identifies major contributors to research, with funding predominantly led by national science foundations, governmental research bodies, and private organizations. These contributions reflect the prioritization of cancer research and the recognition of the TME's critical role in understanding cancer pathogenesis and improving therapeutic strategies.

The National Natural Science Foundation of China is the most significant contributor, demonstrating China's growing investment in cutting-edge biomedical research. The substantial presence of China in TME research suggests an emphasis on combining molecular biology, bioinformatics, and immunotherapy. China's focus on integrating innovative technologies, such as AI-driven bioinformatics and single-cell sequencing, to analyze TME complexities signals opportunities for international collaborations to accelerate HNSCC research breakthroughs.

The National Institutes of Health and its subdivisions, including the National Cancer Institute, also emerge as prominent funders. This reflects the United States' leadership in TME and cancer immunotherapy research. The National Institutes of Health and National Cancer Institute have been pivotal in supporting foundational and translational research, particularly in developing immune checkpoint inhibitors and understanding the immunological landscape of the TME. The substantial funding from these organizations has contributed to groundbreaking discoveries, such as the role of PD-1/PD-L1 pathways in immune evasion, suggesting that United States-led initiatives will continue to drive immunotherapy and precision oncology approaches in HNSCC.

Other key contributors to TME research include ministries of science and technology from countries like Japan and South Korea, as well as the European Commission, underscoring the global nature of this research and the increasing participation of Asian and European countries. Japan and South Korea are particularly known for integrating advanced technologies, such as 3D tumor modeling and nanotechnology-based drug delivery systems, essential for understanding and targeting the TME. The involvement of the European Commission highlights the region's emphasis on collaborative, interdisciplinary research, supported by initiatives like Horizon Europe, which often foster international partnerships.

The inclusion of private organizations such as AstraZeneca further underscores the pharmaceutical industry's growing interest in translating TME-focused research into therapeutic interventions. AstraZeneca's efforts in developing next-generation immunotherapies and combination treatments reflect the commercial viability and clinical importance of targeting the TME in cancers like HNSCC. This points to opportunities for academia-industry collaborations, bridging the gap between basic research and clinical application and accelerating the development of novel therapeutics.

Smaller but significant contributions from foundations such as the China Postdoctoral Science Foundation and the Deutsche Forschungsgemeinschaft highlight the increasing involvement of early-career researchers and multidisciplinary teams. This growing trend emphasizes the importance of fostering young talent and supporting innovative, high-risk projects that could lead to paradigm-shifting discoveries in TME biology and its implications for HNSCC.

Regarding future opportunities, the chart suggests that additional investment could be directed toward integrating big data analytics, AI, and systems biology approaches to address the complexities of the TME. A notable development in this domain is the AI model "HistoTME," which analyzes routine pathology slides to predict patient responses to immunotherapy by examining the TME's molecular characteristics.[42] This cost-effective method exemplifies how AI can integrate diverse datasets to guide personalized treatment strategies. Furthermore, deep learning techniques have been employed to integrate histopathological, genomic, and transcriptomic data, improving patient outcome predictions by incorporating microbial profiles within the TME. Such advancements

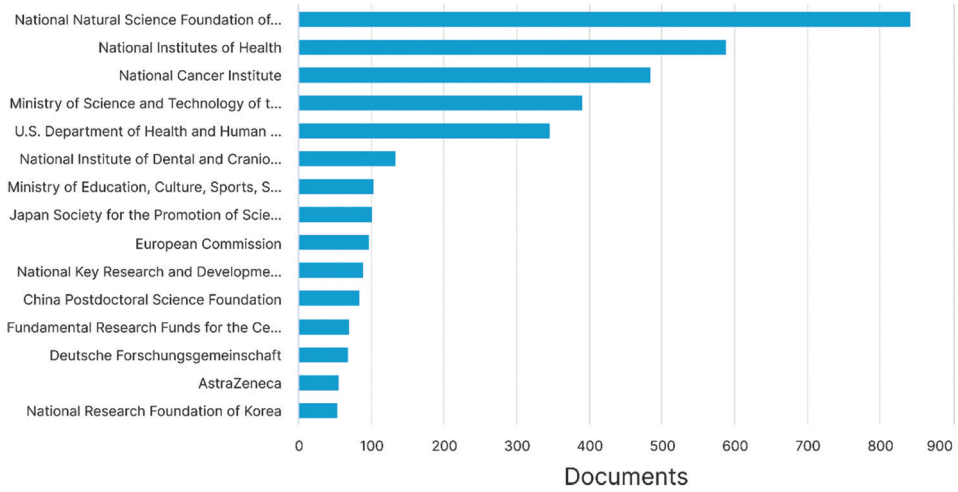

Figure 10. Top 15 funding agencies in this research segment by the number of funded articles. Source: www.scopus.com.

underscore the potential of AI in providing a holistic understanding of TME heterogeneity.

In addition, AI-driven single-cell RNA sequencing analyses, facilitated by tools like scCancer2,[43] enhance the annotation of cellular compositions within the TME, ensuring consistency across studies. AI models have also been applied to highly multiplexed imaging, identifying novel TME elements crucial for patient classification and biomarker discovery. In the realm of personalized medicine, platforms like TumorScope employ AI-driven simulations of individual tumors and their microenvironments, allowing clinicians to explore treatment options and optimize therapeutic strategies computationally.[44]

Expanding funding for collaborative research between high-funding countries and regions with emerging research capabilities could further accelerate these innovations. International collaborations could specifically focus on exploring TME heterogeneity across diverse populations, leveraging AI-driven multi-omics approaches to uncover novel biomarkers and therapeutic targets.

The funding landscape for TME and HNSCC research is characterized by substantial investments from leading national and international organizations, emphasizing the scientific and clinical importance of the field. The dominance of government-funded science foundations and the increasing involvement of private entities suggest a collaborative, translational approach to tackling TME complexities. Potential growth areas include enhancing global collaborations, integrating advanced technologies, and fostering interdisciplinary research to address unmet needs and advance the field.

4. Conclusion

The study highlights the evolving landscape of TME research in HNSCC, emphasizing its interdisciplinary nature and growing focus on immunotherapy, biomarker discovery, and molecular mechanisms. Despite a recent decline in publications, the field remains vibrant, driven by advances in combination immunotherapies, stromal-targeting agents, and predictive biomarkers. Key contributors, particularly in medicine and molecular biology, underscore the centrality of clinical and mechanistic insights, while emerging areas such as computational modeling, nanomedicine, and novel cell death pathways, such as cuproptosis and pyroptosis, signal promising therapeutic strategies. Citation and co-citation analyses reveal the pivotal roles of foundational works and collaborative networks in shaping the intellectual landscape, highlighting established domains such as immune modulation and underexplored areas, such as stromal biology and epigenetics. However, we acknowledge potential limitations inherent in bibliometric analyses, including database selection bias, exclusion of non-English articles, and possible publication biases that may influence the representation of research trends. Despite these constraints, integrating big data, AI, and interdisciplinary innovations is poised to drive breakthroughs, offering opportunities to address challenges like therapy resistance and improve outcomes in HNSCC treatment.

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Conflict of interest

The author declares no conflicts of interest.

Author contributions

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Data will be made available on reasonable request from the corresponding author.

Further disclosure

The writing of this meta-analysis paper involved the use of generative AI and AI-assisted technologies only to enhance the clarity, coherence, and overall quality of the manuscript. The authors acknowledge the contributions of AI in the writing process while ensuring that the final content reflects the author's insights and interpretations of the literature. All interpretations and conclusions drawn in this manuscript are the author's sole responsibility.

References

1. Badola A, Mehta P, Mehra S, Sood S. Epidemiology and survival analysis of head and neck cancer: Results from comprehensive care center in North India. *Oral Oncol Rep.* 2023;6:100022.

   doi: 10.1016/j.oor.2023.100022

2. Das U, Chandramouli L, Uttarkar A, Kumar J, Niranjan V. Discovery of natural compounds as novel FMS-like tyrosine kinase-3 (FLT3) therapeutic inhibitors for the treatment of acute myeloid leukemia: An *in-silico* approach. *Aspects Mol Med*. 2025;5:100058.

   doi: 10.1016/j.amolm.2024.100058

3. Das U, Chanda T, Kumar J, Peter A. Discovery of natural MCL1 inhibitors using pharmacophore modelling, QSAR, Docking, ADMET, molecular dynamics, and DFT analysis. *bioRxiv*. 2024.

   doi: 10.1101/2024.10.14.618373

4. Sathish N, Wang X, Yuan Y. Human papillomavirus (HPV)-associated oral cancers and treatment strategies. *J Dent Res*. 2014;93(7 Suppl):29S-36S.

   doi: 10.1177/0022034514527969

5. Johnson DE, Burtness B, Leemans CR, Lui VWY, Bauman JE, Grandis JR. Head and neck squamous cell carcinoma. *Nat Rev Dis Primer*. 2020;6(1):92.

   doi: 10.1038/s41572-020-00224-3

6. Cognetti DM, Weber RS, Lai SY. Head and neck cancer: An evolving treatment paradigm. *Cancer*. 2008; 113(S7):1911-1932.

   doi: 10.1002/cncr.23654

7. Das U, Banerjee S, Sarkar M, *et al*. Circular RNA vaccines: Pioneering the next-gen cancer immunotherapy. *Cancer Pathog Ther*. 2024;S2949713224000892.

   doi: 10.1016/j.cpt.2024.11.003

8. Li Q, Tie Y, Alu A, Ma X, Shi H. Targeted therapy for head and neck cancer: Signaling pathways and clinical studies. *Signal Transduct Target Ther*. 2023;8(1):31.

   doi: 10.1038/s41392-022-01297-0

9. Qin Y, Zheng X, Gao W, Wang B, Wu Y. Tumor microenvironment and immune-related therapies of head and neck squamous cell carcinoma. *Mol Ther Oncolytics*. 2021;20:342-351.

   doi: 10.1016/j.omto.2021.01.011

10. De Visser KE, Joyce JA. The evolving tumor microenvironment: From cancer initiation to metastatic outgrowth. *Cancer Cell*. 2023;41(3):374-403.

    doi: 10.1016/j.ccell.2023.02.016

11. Wright K, Ly T, Kriet M, Czirok A, Thomas SM. Cancer-associated fibroblasts: Master tumor microenvironment modifiers. *Cancers*. 2023;15(6):1899.

    doi: 10.3390/cancers15061899

12. Oshimori N, Guo Y, Taniguchi S. An emerging role for cellular crosstalk in the cancer stem cell niche. *J Pathol*. 2021;254(4):384-394.

    doi: 10.1002/path.5655

13. Gabrilovich DI, Nagaraj S. Myeloid-derived suppressor cells as regulators of the immune system. *Nat Rev Immunol*. 2009;9(3):162-174.

    doi: 10.1038/nri2506

14. Liu S, Wang R, Fang J. Exploring the frontiers: Tumor immune microenvironment and immunotherapy in head and neck squamous cell carcinoma. *Discov Oncol*. 2024;15(1):22.

    doi: 10.1007/s12672-024-00870-z

15. Mandal R, Şenbabaoğlu Y, Desrichard A, *et al*. The head and neck cancer immune landscape and its immunotherapeutic implications. *JCI Insight*. 2016;1(17):e89829.

    doi: 10.1172/jci.insight.89829

16. Vinay DS, Ryan EP, Pawelec G, *et al*. Immune evasion in cancer: Mechanistic basis and therapeutic strategies. *Semin Cancer Biol*. 2015;35:S185-S198.

doi: 10.1016/j.semcancer.2015.03.004

17. Wang G, Zhang M, Cheng M, *et al*. Tumor microenvironment in head and neck squamous cell carcinoma: Functions and regulatory mechanisms. *Cancer Lett*. 2021;507:55-69.

doi: 10.1016/j.canlet.2021.03.009

18. Joshi RS, Kanugula SS, Sudhir S, Pereira MP, Jain S, Aghi MK. The role of cancer-associated fibroblasts in tumor progression. *Cancers* (*Basel*). 2021;13(6):1399.

doi: 10.3390/cancers13061399

19. Tufail M, Jiang CH, Li N. Altered metabolism in cancer: Insights into energy pathways and therapeutic targets. *Mol Cancer*. 2024;23(1):203.

doi: 10.1186/s12943-024-02119-3

20. Öztürk O, Kocaman R, Kanbach DK. How to design bibliometric research: An overview and a framework proposal. *Rev Manag Sci*. 2024;18(11):3333-3361.

doi: 10.1007/s11846-024-00738-0

21. Arokiasamy ARA, Tan RSE, Deng P, *et al*. A bibliometric deep-dive: Uncovering key trends, emerging innovations, and future pathways in sustainable employability research from 2014 to 2024. *Discov Sustain*. 2024;5(1):450.

doi: 10.1007/s43621-024-00664-x

22. Xiao Y, Yu D. Tumor microenvironment as a therapeutic target in cancer. *Pharmacol Ther*. 2021;221:107753.

doi: 10.1016/j.pharmthera.2020.107753

23. Babar Q, Saeed A, Tabish TA, Sarwar M, Thorat ND. Targeting the tumor microenvironment: Potential strategy for cancer therapeutics. *Biochim Biophys Acta Mol Basis Dis*. 2023;1869(6):166746.

doi: 10.1016/j.bbadis.2023.166746

24. Passaro A, Al Bakir M, Hamilton EG, *et al*. Cancer biomarkers: Emerging trends and clinical implications for personalized treatment. *Cell*. 2024;187(7):1617-1635.

doi: 10.1016/j.cell.2024.02.041

25. Cai XJ, Zhang HY, Zhang JY, Li TJ. Bibliometric analysis of immunotherapy for head and neck squamous cell carcinoma. *J Dent Sci*. 2023;18(2):872-882.

doi: 10.1016/j.jds.2023.02.007

26. Das U, Banerjee S, Sarkar M. Bibliometric analysis of circular RNA cancer vaccines and their emerging impact. *Vacunas*. 2025;500391.

doi: 10.1016/j.vacun.2025.500391

27. Van Eck NJ, Waltman L. Software survey: VOSviewer, a computer program for bibliometric mapping. *Scientometrics*. 2010;84(2):523-538.

doi: 10.1007/s11192-009-0146-3

28. Denton AE, Roberts EW, Fearon DT. Stromal cells in the tumor microenvironment. *Adv Exp Med Biol*. 2018;1060:99-114.

doi: 10.1007/978-3-319-78127-3_6

29. Lei X, Lei Y, Li JK, *et al*. Immune cells within the tumor microenvironment: Biological functions and roles in cancer immunotherapy. *Cancer Lett*. 2020;470:126-133.

doi: 10.1016/j.canlet.2019.11.009

30. Henke E, Nandigama R, Ergün S. Extracellular matrix in the tumor microenvironment and its impact on cancer therapy. *Front Mol Biosci*. 2019;6:160.

doi: 10.3389/fmolb.2019.00160

31. Yang J, Xu J, Wang W, Zhang B, Yu X, Shi S. Epigenetic regulation in the tumor microenvironment: Molecular mechanisms and therapeutic targets. *Signal Transduct Target Ther*. 2023;8(1):210.

doi: 10.1038/s41392-023-01480-x

32. Hanahan D, Weinberg RA. Hallmarks of cancer: The next generation. *Cell*. 2011;144(5):646-674.

doi: 10.1016/j.cell.2011.02.013

33. Chen DS, Mellman I. Oncology meets immunology: The cancer-immunity cycle. *Immunity*. 2013;39(1):1-10.

doi: 10.1016/j.immuni.2013.07.012

34. Ferris RL, Blumenschein G Jr., Fayette J, *et al*. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. *N Engl J Med*. 2016;375(19):1856-1867.

doi: 10.1056/NEJMoa1602252

35. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer*. 2012;12(4):252-264.

doi: 10.1038/nrc3239

36. 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):394-424.

doi: 10.3322/caac.21492

37. Leemans CR, Snijders PJF, Brakenhoff RH. The molecular landscape of head and neck cancer. *Nat Rev Cancer*. 2018;18(5):269-282.

doi: 10.1038/nrc.2018.11

38. Agrawal N, Akbani R, Aksoy BA, *et al*. Integrated genomic characterization of papillary thyroid carcinoma. *Cell*. 2014;159(3):676-690.

doi: 10.1016/j.cell.2014.09.050

39. Argiris A, Karamouzis MV, Raben D, Ferris RL. Head and neck cancer. *Lancet*. 2008;371(9625):1695-1709.

doi: 10.1016/S0140-6736(08)60728-X

40. Xie T, Huang A, Yan H, Ju X, Xiang L, Yuan J. Artificial intelligence: Illuminating the depths of the tumor microenvironment. *J Transl Med*. 2024;22(1):799.

doi: 10.1186/s12967-024-05609-6

41. Albarrán V, San Román M, Pozas J, *et al*. Adoptive T cell therapy for solid tumors: Current landscape and future challenges. *Front Immunol*. 2024;15:1352805.

doi: 10.3389/fimmu.2024.1352805

42. Patkar S, Chen A, Basnet A, *et al*. Predicting the tumor microenvironment composition and immunotherapy response in non-small cell lung cancer from digital histopathology images. *NPJ Precis Oncol*. 2024;8(1):280.

doi: 10.1038/s41698-024-00765-w

43. Chen Z, Miao Y, Tan Z, *et al*. scCancer2: Data-driven in-depth annotations of the tumor microenvironment at single-level resolution. *Bioinformatics*. 2024;40(2):btae028.

doi: 10.1093/bioinformatics/btae028

44. Cole JA, Peterson JR, Earnest TM, *et al*. SimBioSys TumorScope: Spatio-temporal modeling of the tumor microenvironment to predict chemotherapeutic response. *J Clin Oncol*. 2020;38(15_suppl):e12650.

doi: 10.1200/JCO.2020.38.15_suppl.e12650