Original Article
Mapping trends and hotspots regarding oral carcinoma and macrophages: a bibliometric analysis of global research

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Abstract: Background: In recent years, the incidence of oral carcinoma has been increasing year by year, and the role of macrophages in oral carcinoma cannot be ignored. Many related studies have been published, but until now, there is no bibliometric analysis of these publications. Methods: The global publications about oral carcinoma and macrophages from January 2011 to December 2021 were extracted from Web of Science collection database. Microsoft Excel 2016, GraphPad Prism 8, VOSviewer software and CiteSpace were employed to perform the bibliometric study. Results: China published the most publications in this field and had the most citations as well as H-index. *Oral Oncology* published the most papers relating to the oral carcinoma and macrophages in terms of journals. *Sichuan University* have most publications in terms of institutions and research by *Taams, LS* received the highest number of citations. Conclusion: The squamous cell carcinoma is still the focus of our attention at present. The polarization of macrophages, immunotherapy and the prevention of oral cancer were identified as the emerging topics. However, the collaboration of immunology and oncology has played an important role in the development of this field.

Keywords: Oral squamous cell carcinoma, tumor-associated macrophages, bibliometrics, hotspot, web of science

Introduction

Oral cancer is usually defined as a malignant tumor occurring in the oral cavity and oropharynx, ranging from the tongue, floor of the mouth, oropharynx, etc. It has been reported that 275,000 new cases of oral cancer are identified around the world each year [1]. Among all oral cancer types, oral squamous cell carcinoma (OSCC) is the most common one, accounting for more than 90% of head and neck cancers [2-4]. Although many advances have been made in the research of oral cancer and many treatments have been developed, such as surgery, radiation therapy, chemotherapy drug therapy and integrated sequential therapy, the treatment effect of oral cancer is not satisfactory due to its complex pathogenic mechanism and unclear therapeutic targets, with a 5-year survival rate about 50% [5]. Thus, the mechanism of oral cancer still needs to be further investigated.

Studies have shown that the immune system has a significant impact on the interaction between cancer cells and the tumor microenvironment which regulates tumor initiation, progression, and response to anticancer therapy [6-8]. The tumor microenvironment consists of immune cells, cancer associated fibroblasts (CAF), stromal cells, peripheral vasculature and signaling molecules, among which tumor-associated macrophages (TAMs) are an important class of immune cells that constitute the tumor micro-environment [9-14]. In the tumor microenvironment, TAMs can secrete large amount of CCL17, IL-I0 and other immunosuppressive factors, which suppress T cell- and NK cell-
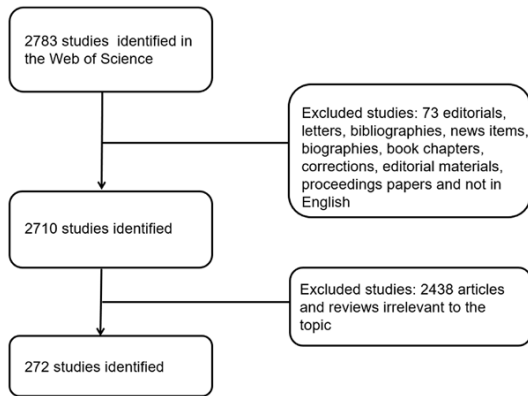
Figure 1. Flow diagram of the inclusion process. The detailed process of screening and enrolment (irrelevant articles were manually screened by two authors through abstracts and full texts, and articles irrelevant to the topic were excluded).

mediated immune responses, leading to tumor immune escape [15]. In oral cancer, TAMs not only trigger tumor immune escape, but also induce tumor angiogenesis via secreting vascular endothelial growth factor (VEGF), epithelial mesenchymal transformation through multiple signaling pathways to promote oral cancer invasion and metastasis, and secrete cytokines to maintain the self-renewal ability of cancer stem cells, etc. [16-18]. Given the close association between oral cancer and macrophages, the related research in oral cancer and macrophages has been always a focus. Therefore, a methodology is needed to summarize the articles in this field and to predict future hotspots.

Bibliometric analysis is a tool that uses rich data to assess as objectively and quantitatively as possible the impact of a paper in its specific field of science [19]. The differential count of citations for an article normally represents its different level of interest to the researcher regarding subject matter. With the help of bibliometric analysis, research hotspots can be presented more visually and clearly to the researcher. Bibliometric analysis is now widely used in clinical studies of COVID-19 [20], heat stroke [21], oral potentially malignant disorders [22], and other research areas.

Several studies have been conducted on the relationship between oral cancer and macrophages, but to best of our knowledge, none has performed a bibliometric analysis on this topic. This bibliometric analysis focused on the oral

cancer and macrophage-related literature published in the past decade, which included article citations, country, journal, submitting institution, highly cited studies, and keywords. In addition, the topics of development history, analysis of posting trends and hotspot prediction were also included. It is expected to help researchers to have a more objective understanding of the research situation in this field and to provide references for further in-depth research.

Materials and methods

Data sources and search strategies

Web of Science, an appropriate database containing a lot of medical information, was used to retrieve the research relevant to oral squamous cell carcinoma and macrophages from January 2001 to December 2021. All the searches we conducted were on December 27, 2020 to avoid bias of database renewal. The search strategy was presented as follows: TS = (oral OR intraoral OR mouth OR tongue OR buccal OR lip OR gingival OR palate) and (cancer* OR carcino* OR tumor* OR tumour* OR malign* OR lesion* OR neoplasm*) and macrophage. Merely original articles were included in the research, excluding book chapters, letters, biographies, bibliographies, corrections, news items, editorials, editorial materials, and proceedings papers. Two authors (Tuan Zhao, Hao Hu) conducted the screening, finally, the experienced corresponding author was responsible for reviewing the included researches and made the final decision. Details of enrolments and selections are detailed in **Figure 1**.

Data collection and processing

The full data for all studies relating to journal, authors, date of publication, country and region of origin, keywords, institution, title, number of citations, H-index were abstracted from identified publications by two authors (YL and XML). CiteSpace version 5.6.R5 64-bit, GraphPad Prism 8, VOSviewer version 1.6.12 and Microsoft Excel 2016 were all used to present, analyze and describe the data.

Bibliometric analysis

Thomson Reuters WOS has collected plenty of researches including biomedicine, which prom-

pted us to choose it as our preferred database. The impact factor (IF), obtained from the journal citation reports (JCRs), is recognized as a key indicator for evaluating articles [23]. The H-index is a method for assessing the academic productivity of a researcher, which represents that H pieces of published papers of a given researcher or a country (or region) has been cited for a minimum of H times in other publications. And there is a general agreement that the H index has a critical importance in the evaluation of the impact of scientific research, especially in the medical field [24]. Meanwhile, the relative research interest (RRI) is related to the total and annual volume of publications in a certain research area, which is meaningful to evaluate the research popularity in this field [25]. The three indicators can help us make a reasonable analysis of the article.

VOSviewer, as a practice-based statistical software, can identify bibliometric properties such as terms, authors, institutions and references by using the relationships among nodes of the map. In fact, the software is not limited to the above, but also capable of extracting keywords and predicting prospective trends for future study [26]. CiteSpace, a handy scientific mapping tool using the Java programming language, is applied extensively in co-citation network analysis and visualization, with its co-occurrence matrix-based implementation for constructing map. And its analysis of cooperative relationship in the research field is unique [27].

Results

Contributions of countries to global publications

Collectively, 272 articles from 2011 to 2021 satisfied the search criteria were included in the evaluation. In the ranking of the number of publications, China (84, 30.88%) ranked first, followed with Japan (55, 20.22%) and the United States (43, 15.80%) (**Figure 2A**). In addition to being the first in terms of the quantity of publications, China also topped in the sum of citations with 1499, followed by the United States in second place with 1441, and Japan in third place with 1084 (**Figure 2A**). Finally, in the H-index ranking, China is also in first place with 20, followed by the United States and Japan in a tie for second place with 19 (**Figure 2A**). In terms of publications, all three countries dominated in the quantities and qualities.

However, when considering publications in all fields, worldwide interest in RRI-measured oral cancer and macrophages have grown modestly in the first 10 years, but peaked in 2021 (**Figure 2B**).

The number of publications from a specific country is shown in **Figure 3A**. A large circle indicates a high quantity of publications, and the five countries with the highest number are China, Japan, the United States, Brazil and Germany. In **Figure 3B**, the red colour represents the region with a large number of articles published. According to the number of articles published, we found that the Asian region represented by China, Japan and India had a large number of publications. The cooperation between different countries was also visualized. China contributed the most publications and had closer ties to other nations, especially USA (**Figure 3C**). Meanwhile, at the same time, cooperation between other countries was not particularly close, which affected the quantity and quality of publications.

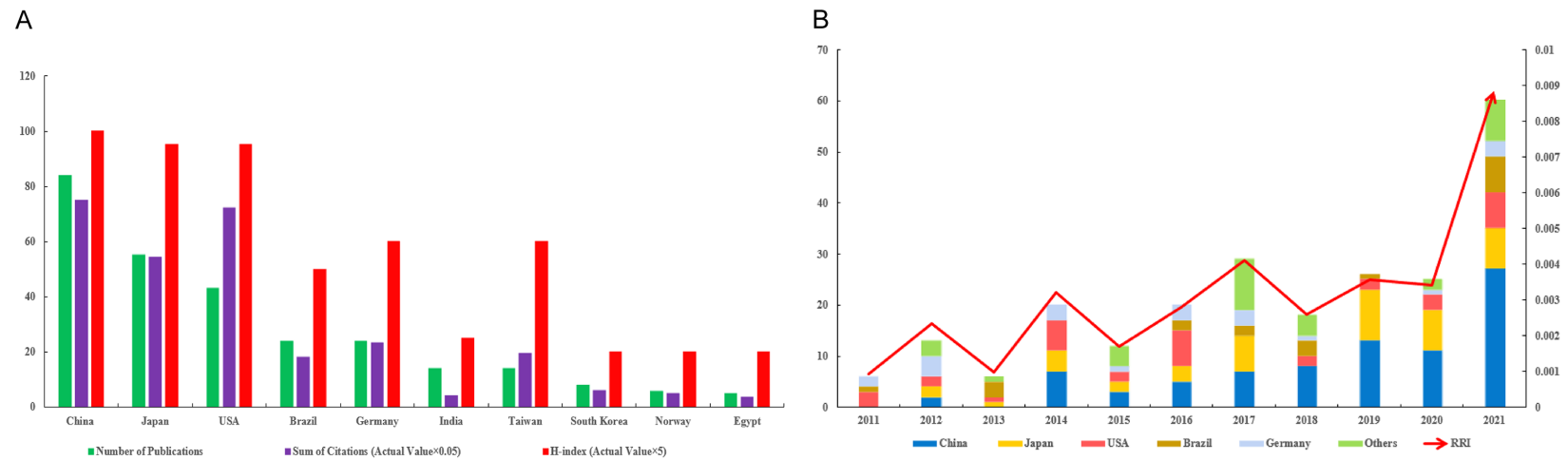*Contributions of different journals to publications*

Oral Oncology (IF = 5.337) published the most studies about oral carcinoma and macrophages, with 17 publications (6.07%). Journal of Oral Pathology & Medicine (5.36%) and Oncotargets and Therapy (3.21%) ranked 2nd and 3rd respectively. Among the top 10 journals that published the most studies, the impact factor of Frontiers in Oncology (IF = 6.244) ranked first. Oral Oncology, which published the most article, placed second with an impact factor of more than 5 points (IF = 5.37). We also found that there were 2 journals related to oral medicine, 8 related to tumor, and 2 related to pathology, which were consistent with our research theme (**Figure 4A**).

The size of the circles in **Figure 4B** represents the quantity of publications. We found that the top three journals in the number of publications were Oral Oncology, Journal of Oral Pathology & Medicine, and Oncotargets and Therapy, all of which are closely related to tumors and Oral medicine, which demonstrated the high degree of expertise in the field.

Contributions of different institutions to publications on oral carcinoma and macrophages

The top ten institutes were responsible for 27.14% of all publications on oral carcinoma

Figure 2. Contributions of different countries/regions to research on oral carcinoma and macrophages. A. Number of publications, citation frequency (×0.05), H-index (×5), and GDP (×5, per trillion dollar) in the top 10 countries or regions; B. Number of publications worldwide and the time course of the RRI in on oral carcinoma and macrophages.
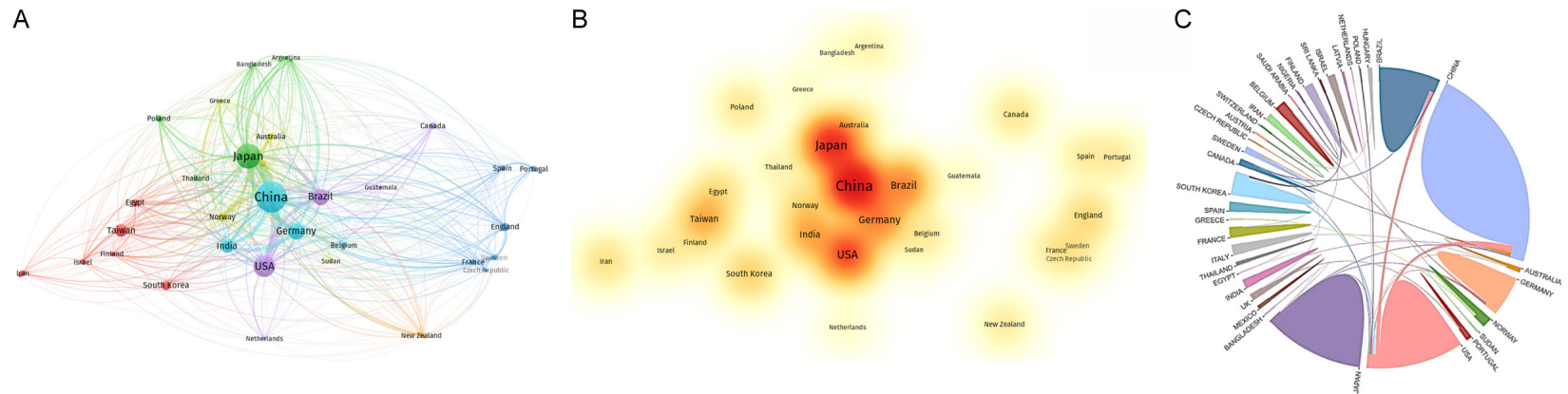
Figure 3. Cooperation network of countries/regions with regard to research on oral carcinoma and macrophages. (A and B) Network of cooperative relations between countries/regions established by VOSviewer and (C) Visualized cooperative relations between countries/regions.

and macrophages. With 11 articles published, Sichuan University in China ranked the first place, accounting for 3.93%. Half of the top ten institutions were from China, while 3 from Japan, 1 from the United States, and 1 from Germany. Notably, three of the top five institutions were from China (**Figure 5A**). As can be seen in **Figure 5B**, the red area connected by Chinese institutions has the deepest color, indicating that China has a leading position in the number of publications. China Med Univ, Wuhan Univ, Sichuan Univ, Zhengzhou Univ, and Shandong Univ have made a contribution to the amount of publications.

Top 10 high-cited articles

Regarding reference quantity, The CD4$^+$CD25$^+$ Foxp3$^+$ regulatory T Cells Induce Alternative Activation of Human Monocytes/Macrophages from Proceedings of the National Academy of the United States of America (IF 11.205) by Taams, LS from England ranked the first with 543 citations, Prognostic Significance of Tumor-Associated Macrophages in Solid Tumor: A Meta-Analysis of the Literature ranked the second with 492 citations, Triggering of Toll-like Receptor 4 Expressed on Human Head and Neck Squamous Cell Carcinoma Promotes Tumor Development and Protects the Tumor from Immune Attack ranked the third with 178 citations. Among the first ten most-cited articles, the United States ranked the first with 4, and Japan ranked second with 3, while China does not have a big advantage. However, the top three countries by volume of publications still lead the way in this respect.

Keyword analysis of oral carcinoma and macrophage publications

VOSviewer was applied to analyze the 272 publications for keywords, which are defined as the words that appeared more than 12 times in titles and abstracts. A total of 79 keywords were identified and grouped into the 3 clusters. In the cluster 1, the keywords with the highest frequency were effect, correlation, head, cytokine. In the cluster 2, the primary keywords were squamous cell carcinoma, patient, treatment, prognosis. In the cluster 3, the main keywords were vitro, tumor cell, tumor growth.

According to the most recent trends, the latest keyword in Cluster 1 was "M2 macrophage" (AAY 2018.2083), with 24 times. In the cluster

2, the new focus was "pdl-1" (AAY 2019.7143) with 14 times. Regarding cluster 3, the new focus was "tumorigenesis" (AAY 2016.0667) with 15 times.

Discussion

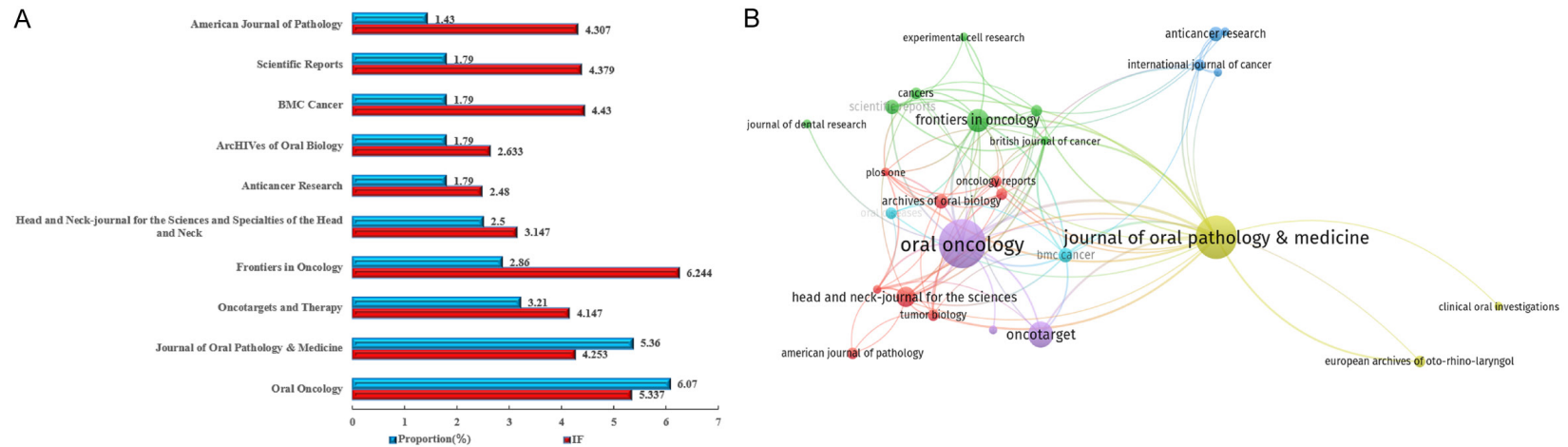*Research trends on publications on oral carcinoma and macrophages*

In terms of the quantity of publications by country, China has the largest quantity of publications, followed by Japan and the United States as the 2nd and 3rd (**Figure 2A**). To investigate the reason, The high incidence of oral cancer in China is mainly because that China has the largest population base in the world. A research has anticipated that the annual incidence of oral carcinoma in China is expected to rise from 2.26 to 3.21 per 100,000 person over the next 20 years [28]. Meanwhile, Japan is the country with the lowest incidence of oral cancer and has conducted in-depth research on this tumor. As early as 1995, it has been demonstrated that the average life expectancy of patients in Japan with oral cancer is 17.2 years shorter than expected, and the understanding had helped the country make a special contribution to the field of oral cancer [29]. Tobacco chewing and smoking and alcohol consumption are the reasons for the high incidence in Brazil and India, which also brings certain enlightenment to the prevention of oral cancer risk factors [30].

In recent years, the proportion of published papers in this field has increased year by year, reaching its peak in 2021 (**Figure 2B**). We believe that it is directly related to the increasing incidence of oral cancer [31]. The recent interest in tumor-associated macrophages has also contributed to the development of this field and its pro-tumor and immunosuppressive functions are relevant to cancer progression and therapeutic responses [32]. At the same time, the development and progress of genomics and molecular medicine have also laid the foundation for the development of this field [33]. We believe that cooperation among China, the United States, Japan and other countries will promote international development and progress (**Figure 3C**).

In terms of institutions, three of the top five universities are from China (**Figure 5A**). Similarly, the most published institutions are focused on

Figure 4. Cooperation network of journals with regard to research on oral carcinoma and macrophages. A. Top 10 journals by number of publications; the blue bar representing proportion and red bar representing IF. B. Network of institutions visualized in VOSviewer; the size of circles reveals the number of publications.
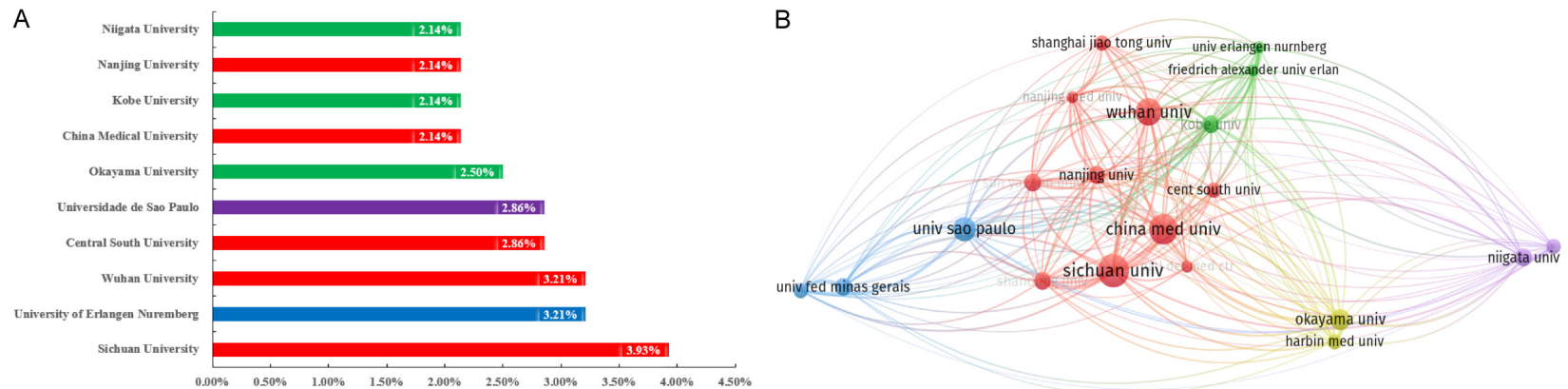
Figure 5. Distribution of institutions engaged in research on oral carcinoma and macrophages. A. Top 10 institutions by number of publications. Numbers represent the percentage of publications, and different colors represent different countries. B. Network of institutions visualized in VOSviewer; the red color of circles reveals more publications of the institution.

the Asian area (**Figure 5B**). Sichuan University ranks first in the number of publications. It is the only institution in China that can effectively complete the screening work of oral cancer by using oral autofluorescence detection system [34], which helps the institution with the highest number of publications.

It is worth noting that 3 of the top ten institutions were from Japan, and Japan has continuously monitored the incidence of oral cancer and compared different types of oral cancer [35]. To a large extent, it provides the research base for the institution, the articles published in this field are mainly concentrated in certain types of journals (**Figure 4A**), which mainly involved oral cavity, tumor and pathology. We believe that the joint exploration of the above-mentioned disciplines is needed in future research.

The most cited papers are linked to the academic impact of a domain. **Table 1** provides details of the ten most frequently cited publications on oral cancer and macrophages. The articles that with the highest number of citations were published in Proceedings of the National Academy of Sciences of the United States of America (IF = 11.205), which focused on CD4(+) CD25(+) Foxp3(+) regulatory T cells [36].

It is not a commonly seen function that regulatory T cells may drive monocyte differentiation toward alternatively activated macrophages, which plays a critical role in oral cancer evasion of immune surveillance [37]. The top ten articles also described CD163, Toll-like Receptor 4 and CXCL14 [17, 38-40], which are closely related to immunity. At the same time, we found that 4 of the top ten articles are related to the prognosis of patients with oral cancer. Therefore, immunological and oral cancer prognosis may be the focus of future research.

Research hotpots on publications on oral carcinoma and macrophages

In **Figure 6A**, in the clustering analysis of all keywords, we found that squamous cell carcinoma (193 times) appeared most frequently. Oral cancer is a broad term for malignant tumors of the oral cavity, with squamous cell carcinoma accounting for 95% of all cases. Every year, 300,000 new cases are reported worldwide, with a recent and dramatic incre-

ase in incidence affecting notably the young [41]. Therefore, it has received more attention.

At the same time, we summarized the latest keywords. The latest keyword in cluster 1 was "M2 macrophage" (AAY 2018.2083), with 24 times in total. Currently, research on macrophages is very hot, depending on the tumor microenvironment cues, it can swing to M2 macrophage, can play an role in anti-inflammatory and pro-tumorigenic in oral cancer, while M1 macrophage acts a pro-inflammatory and antitumor role [42], we call the process polarization of macrophages. Now the relationship between M2 macrophages and oral cancer has entered the molecular stage. Research have shown that while for M2 macrophage-related markers CD68 and CD163, higher concentrations of CD68 and CD163 were associated with worse survival [43]. While in terms of the mechanism of action, signaling pathways involving NF-κB and cytokines emitted from the tumor microenvironment promote a bidirectional cross-talk with M2 and oral squamous cell carcinoma cells, which can lead to an increased proliferation of malignant cells and enhances aggressiveness, thus decreasing the survival time of patients [44]. So, polarization of macrophages is a key factor in the development of oral cancer.

In cluster 2, the new focus was "PD-L1" (AAY 2019.7143), appearing 14 times in total. The mechanism of action lies in the combination of programmed cell death receptor-1 (PD-1) and programmed cell death ligand 1 (PD-L1), which can conduct inhibitory signals and reduce the proliferation of LYMPH node CD8$^+$ T cells, and thus reducing the killing function of CD8$^+$ T cells against tumor [45]. Conventional treatments for oral cancer include surgical therapy, targeted therapy, immunotherapy or combined modality treatments. Anti-PD-L1 is a novel immunotherapy approach that has been shown in studies to enhance disease free survival and overall survival following platinum-based chemotherapy failure [46]. The current combination of anti-PD-1/PD-L1 and other drugs also has bright prospects, and the latest studies also proved that anti-PD-1/PD-L1 lead-in before MAPK inhibitor combination will maximize antitumor immunity and efficacy [47]. Therefore, immunotherapy involving PD-L1 is a new strategy for oral cancer treatment.

Table 1. Top 10 most-cited articles related to oral carcinoma and macrophages

| Title	Corresponding authors	Journal	Total Citations	Corresponding author's country
CD4(+) CD25(+) Foxp3(+) regulatory T cells induce alternative activation of human monocytes/macrophages	Taams, LS	Proceedings of the National Academy of Sciences of the United States of America (IF = 11.205)	543	England
Prognostic Significance of Tumor-Associated Macrophages in Solid Tumor: A Meta-Analysis of the Literature	Liu, L	Plos One (IF = 3.24)	492	China
Triggering of Toll-like Receptor 4 Expressed on Human Head and Neck Squamous Cell Carcinoma Promotes Tumor Development and Protects the Tumor from Immune Attack	Whiteside, TL	Cancer Research (IF = 12.701)	178	USA
Loss of new chemokine CXCL14 in tumor tissue is associated with low infiltration by dendritic cells (DC), while restoration of human CXCL14 expression in tumor cells causes attraction of DC both in vitro and in vivo	Shurin, MR	Journal of Immunology (IF = 5.422)	152	USA
Prognostic factors in oral cavity and oropharyngeal squamous cell carcinoma - The impact of tumor-associated macrophages	Teknos, TN	Cancer (IF = 6.86)	116	USA
Cancer-associated fibroblasts and CD163-positive macrophages in oral squamous cell carcinoma: their clinicopathological and prognostic significance	Shomori, K	Journal of Oral Pathology & Medicine (IF = 4.253)	115	Japan
Cancer-associated fibroblasts promote an immunosuppressive microenvironment through the induction and accumulation of protumoral macrophages	Chikamatsu, K	Oncotargets and Therapy (IF = 4.147)	106	Japan
Infiltrating CD8(+) T cells in oral lichen planus predominantly express CCR5 and CXCR3 and carry respective chemokine ligands RANTES/CCL5 and IP-10/CXCL10 in their cytolytic granules - A potential self-recruiting mechanism	Iijima, W	American Journal of Pathology (IF = 4.307)	105	Japan
CD163+ Tumor-Associated Macrophages Correlated with Poor Prognosis and Cancer Stem Cells in Oral Squamous Cell Carcinoma	Zhang, WF	Biomed Research International (IF = 3.411)	102	China
Neutrophil-to-lymphocyte ratio and overall survival in all sites of head and neck squamous cell carcinoma	Li, ZH	Head and Neck-journal for the Sciences and Specialties of the Head and Neck (IF = 3.147)	92	USA
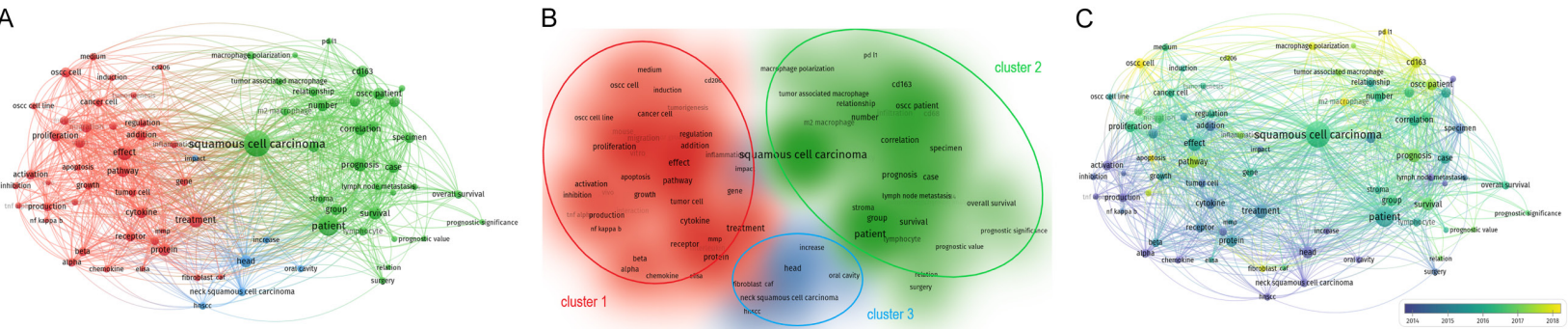
Figure 6. Co-occurrence analysis of all keywords in the publications on oral carcinoma and macrophages: A. Mapping of the keywords in the field of oral carcinoma and macrophages. The size of the circle represents the frequency of keywords. B. Keywords of different classes are divided into three clusters in different colors. C. Distribution of keywords according to the average time of appearance; blue represents an early appearance, and yellow represents a late appearance.

The new focus of cluster 3 was "tumorigenesis" (AAY 2016.0667), which appeared 15 times. Comparing the stage of tumor metastasis with the stage of tumor growth, our current study suggests that the stage of tumorigenesis attracts our attention more in the pathogenesis of oral carcinoma, with tobacco intake, smoking, smokeless tobacco (snuff or chewing tobacco), alcohol, and cuckoo fruit intake, excessive sunlight exposure, passive smoking, and human papillomavirus (HPV) all playing a role in tumorigenesis to a certain extent [41]. And in the early prevention process, studies have shown that melatonin, tea constituents, polyphenols, chemoprevention, Chios mastic gum extract, Poly (ADP-Ribose) Polymerase 1 (PARP1) Targeted optical imaging agent perform their roles in the prevention and therapeutic control of oral cancer [41].

Limitation and prospect

This study was based on publications indexed in the Web of Science to obtain objective and reliable results. However, as the search was limited to English language studies and the Web of Science database is constantly being updated, which may lead to slight discrepancies between our results and the actual results. To achieve more comprehensive results, multiple databases such as Medline, Scopus or Google Scholar can be combined for analysis in further studies.

Disclosure of conflict of interest

None.

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