Original Article

# Inflammation, tertiary lymphoid structures, and lung cancer: a bibliometric analysis

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**Background:** The intricate interplay between inflammation and lung cancer has long been recognized by large number of studies, yet a comprehensive understanding of this relationship remains elusive. There is a clinical need to elucidate the role of tertiary lymphoid structures (TLSs) in lung cancer, particularly their impact on prognosis and therapy. This study aims to address these gaps by conducting a bibliometric analysis to explore the correlations between lung cancer, inflammation, and TLS, highlighting collaborative networks, publication trends, and emerging research directions.

**Methods:** This study conducted a comprehensive bibliometric analysis of academic literature on lung cancer and inflammation from 2013 to 2023 using the Web of Science Core Collection database. The search strategy "topic (TS) = ('lung cancer') AND TS = (inflammation)" yielded 5,470 records, which were refined through exclusion criteria to 1,284 relevant studies. The inclusion process involved excluding non-English studies and non-original articles or reviews, followed by a relevance check based on titles and abstracts. The bibliometric indicators were calculated based on a transparent and repeatable methodology to ensure the integrity of the findings.

**Results:** The investigation encompassed 1,284 selected studies, revealing an escalating publication trend since 2013. The interdisciplinary scope of research is apparent, with contributions from 54 countries, with China at the forefront. In-depth author and journal analyses exposed key contributors like Zhang L and influential journals like "*Lung Cancer*". Co-citation networks illuminated crucial references, clusters, and evolving themes over time, underscoring the intricate relationship between inflammation, cancer, and TLS. TLS as a key component of immune response and inflammation, studying its mechanism of impact on cancer will be a potential research direction in the future.

**Conclusions:** This study underscores the pivotal role of inflammation in lung cancer progression, mediated by a delicate balance of immune responses. The emerging prominence of TLS as indicator of adaptive immune responses within the tumor microenvironment (TME) offers intriguing avenues for future research and therapeutic interventions. However, limitations in the current research, such as the need for more longitudinal studies and clinical trials, must be addressed. The insights gained from this bibliometric analysis can inform clinical practices and guide future investigations into novel strategies to improve patient outcomes.

**Keywords:** Inflammation; tertiary lymphoid structures (TLSs); lung cancer; microenvironment; immune response

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## Introduction

According to the "Cancer Statistics 2023" report, lung cancer remains the leading cause of cancer-related deaths (1). Although targeted therapies and immunotherapies have benefited some lung cancer patients, the 5-year survival rate for lung cancer remains unsatisfactory, at only 21% (2). Therefore, more effective treatment approaches and early diagnostic methods are still needed. Rudolf Virchow first proposed the correlation between inflammation and cancer in the mid-19$^{th}$ century (3). Approximately 15–20% of cancer cases are linked to infections, chronic inflammation, or autoimmune responses within the same tissue or organ site (4).

Inflammation is a response to heterogeneous stimuli, leading to the activation and recruitment of inflammatory cells through the production of cytokines [e.g., interleukins (ILs)], chemokines [e.g., C-C motif chemokine ligands (CCLs)], and inflammation proteins (e.g., C-reactive protein) (5). However, the development and response to cancer treatment are influenced by inflammation, which acts as a "double-edged sword" by either promoting or inhibiting tumor progression. On the one hand, acute inflammatory responses induce dendritic cell (DC) maturation and antigen presentation, triggering anti-tumor immune responses that help suppress tumor growth (6). On the other hand, during chronic inflammation, inflammatory cells, and cytokines can act as tumor promoters, affecting cell survival, proliferation, invasion, and angiogenesis, all of which are crucial processes in regulating the tumor microenvironment (TME) (7).

Tertiary lymphoid structures (TLSs), also known as tertiary lymphoid organs (TLOs) or ectopic lymphoid structures, include mucosa-associated lymphoid tissue, skin-associated lymphoid tissue, etc., and mainly consist of B cells, follicular DCs (FDCs), and T cells, among others (8). TLS usually appears in the context of chronic inflammation, such as autoimmune diseases, chronic infections, and cancer (9,10). Under sustained chronic inflammation, lymphoid tissues may undergo extranodal seeding and form TLS at inflammatory sites. In the lung cancer microenvironment, inflammatory factors induce anti-tumor immune responses by TLS formation (11) and can also promote malignant cell proliferation and survival, facilitate angiogenesis and metastasis, weaken acquired immune responses, and alter the body's response to chemotherapy drugs and hormones. Bibliometrics, a subfield of informatics, focuses on the study of literature systems and their bibliometric properties through both quantitative and qualitative analysis. This analytical approach allows for a numerical assessment of the distribution, connections, and patterns within a research domain (12), and it has emerged as a key method for evaluating the credibility, excellence, and reach of scholarly outputs (13). The analysis can detail the contributions and impact of various authors, geographical regions, academic institutions, fields of study, and academic journals, as well as provide insights into the dynamics, trends, and leading edges of research endeavors. Tools like VOSviewer and CiteSpace are frequently utilized for bibliometric visualization, aiding in the analysis and graphical representation of data (14,15). These tools are particularly adept at examining the evolution of topics within structured content, enhancing

### Highlight box

**Key findings**

- Growing interest: there is a significant increase in research publications on lung cancer, inflammation, and tertiary lymphoid structures (TLSs) since 2013.
- Role of TLS: TLS are identified as key players in immune responses related to lung cancer, highlighting their potential impact on disease progression.

**What is known and what is new?**

- Previous research has extensively documented the relationship between inflammation and lung cancer, highlighting the role of TLS as a response to chronic inflammation.
- This bibliometric analysis reveals a marked increase in publications about the relationship between inflammation and lung cancer since 2013, particularly from China. The analysis highlights TLS's role in mediating immune responses within the tumor microenvironment (TME), pinpointing it as a crucial area for future research.

**What is the implication, and what should change now?**

- The findings advocate for a shift in research focus towards the mechanisms by which TLS influences lung cancer progression. There is a need for targeted research that could lead to the development of new therapeutic approaches based on the modulation of TLS within the TME, potentially improving patient management and treatment strategies.

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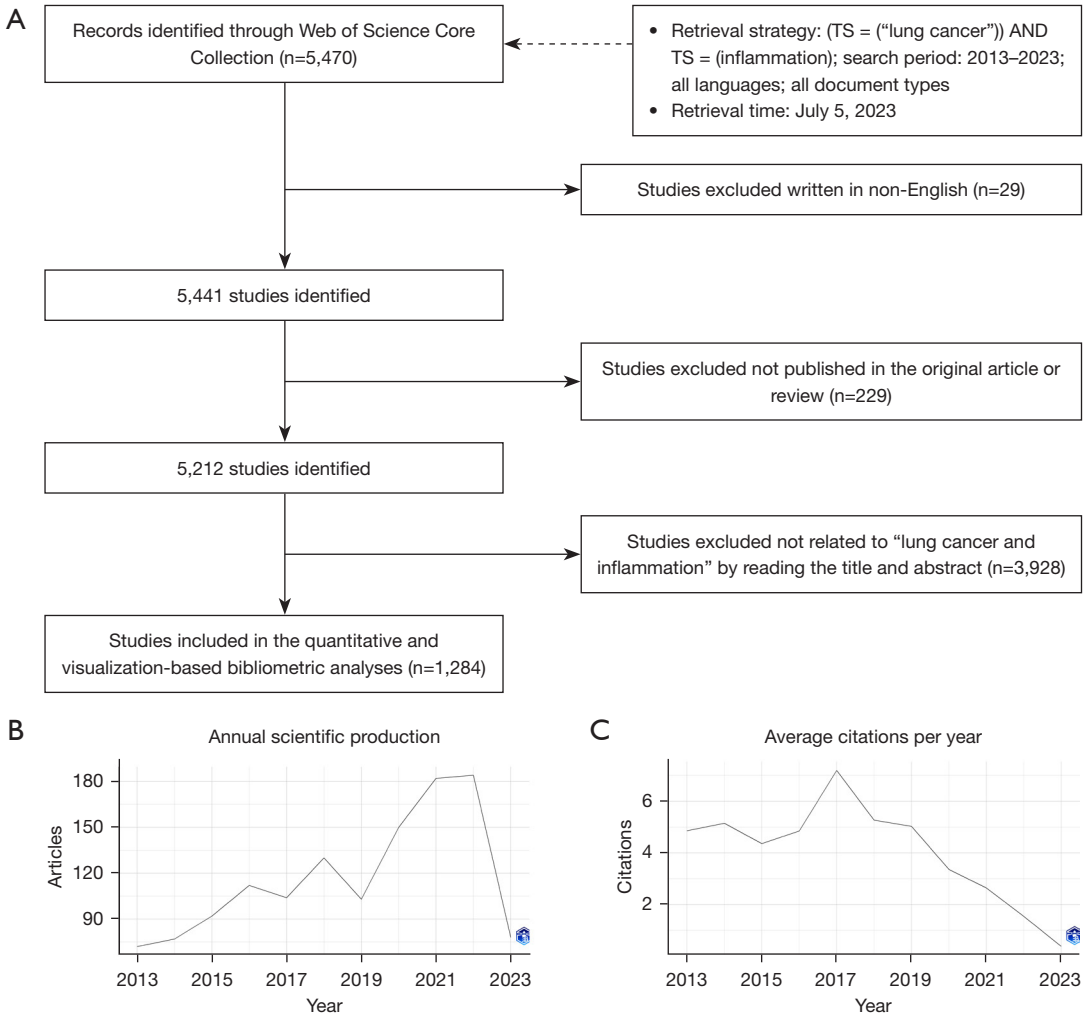


**Figure 1** Overall situation analysis. (A) Document retrieval and screening process. (B) Annual publication volume. (C) Number of citations per year. TS, topic.

the clarity of understanding for readers (16). However, no bibliometric studies have been published on the correlation between lung cancer, inflammation, and TLS. To address this gap, we have conducted a scientometric analysis of the literature on this subject.

## Methods

### *Data acquisition*

The Web of Science platform comprises multiple databases, the most significant being the Web of Science Core Collection, which includes over 12,000 academic journals across more than 250 disciplines. Our study conducted a comprehensive bibliometric analysis using the Web of Science Core Collection database. Using the retrieval strategy "topic (TS) = ('lung cancer') AND TS = (inflammation)", 5,470 records covering the period from 2013 to 2023 were identified. All languages and document types were included, and the retrieval was performed on July 5, 2023. The literature search strategy involved multiple stages. Initially, 29 non-English studies were excluded from the analysis, and studies not published as original articles or reviews were excluded. Furthermore, all identified studies were screened for relevance based on the title and abstract, excluding 3,928 studies that were not directly related to "lung cancer and inflammation". After these exclusions, 1,284 studies were included for the quantitative and visualization-based bibliometric analyses (*Figure 1*).

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**Table 1** The studies of prognosis value and predicting immunotherapy response of TLSs in lung cancer

| Value | Markers | Patients | Main findings | Prognosis value | Reference |
|---|---|---|---|---|---|
| Prognosis | The density of mature DCs | 74 | The density of mature DCs was found to be a better predictor of clinical outcome | Positive | (17) |
| | Mature DC and $CD8^+$ T-cell densities | 458 | TLS represent a privileged area for T-cell recruitment and activation in the primary site of lung tumor | Positive | (11) |
| | The density of follicular B cells | 74 and 122 | A high density of follicular B cells was associated with an increase in median survival | Positive | (18) |
| | TLS+ | 112 | TLS was a favourable prognostic factor independent of PD-1 expression in patients with lung adenocarcinoma | Positive | (19) |
| | $TLS\text{-}B^{high}$ and $Treg^{low}$ | 56 | $TLS\text{-}B^{high}$ $Treg^{low}$ patients had the best clinical outcomes | Positive | (20) |
| | TLS+ | 53 | TLS+ group had a better progression-free survival | Positive | (21) |
| | GC+ TLS | 616 | GC+ TLS was associated with better prognosis in NSCLC | Positive | (22) |
| Predict immunotherapy outcomes | Intratumoral plasma cells | 891 | Increased plasma cell signatures to be predictive of OS in patients | – | (23) |
| | mTLSs | 114 | The mTLS is a specific biomarker of cancer immunotherapy | – | (24) |
| | $CXCL13^+$ cell density | 65 | Improved clinical outcome in NSCLC patients was significantly associated with increased CXCL13 density within TLS | – | (25) |

TLS, tertiary lymphoid structure; DC, dendritic cell; PD-1, programmed cell death protein 1; Treg, regulatory T cells; GC, germinal center; NSCLC, non-small cell lung cancer; OS, overall survival; mTLS, mature TLS; CXCL13, C-X-C motif ligand 13.

### *Data visualization*

This study gathered fundamental data such as authorship, affiliations, countries/regions, journals, keywords, and references. Data visualization was achieved using the R language (R-4.3.1) with the bibliometric package and CiteSpace software. The bibliometric package facilitated data collection, analysis, and visualization. We conducted descriptive statistics on the bibliographic data and performed additional simple calculations at the author level, such as the H-index. Furthermore, based on the bibliographic data, we utilized the bibliometric package and CiteSpace software to construct co-citation and co-authorship networks and conduct cluster analysis.

### *Statistical analysis*

The statistical analysis was conducted using R version 4.3.1, utilizing the bibliometrics package to perform a comprehensive bibliometric analysis and visualize research trends, citation impact, keyword analysis, and synthetic analysis.

## Results

### *Retrieval results*

From 2013 to 2023, 5,470 articles were indexed in the ScienceNet database. After excluding non-English publications (n=29) and publications that were not original articles or reviews (n=229), titles and abstracts were screened. Ultimately, 1,284 studies were included in the bibliometric analysis (*Figure 1A*).

### *Quantity analysis*

Over the past decade, there has been an overall increasing trend in the publication volume of cancer and inflammation research (*Figure 1B*). These articles were published in 459 journals, with the top 50 contributing 617 papers (48.1%). Among them, *Frontiers in Oncology* published the highest number of papers (35 papers) (*Table 1*). A total of

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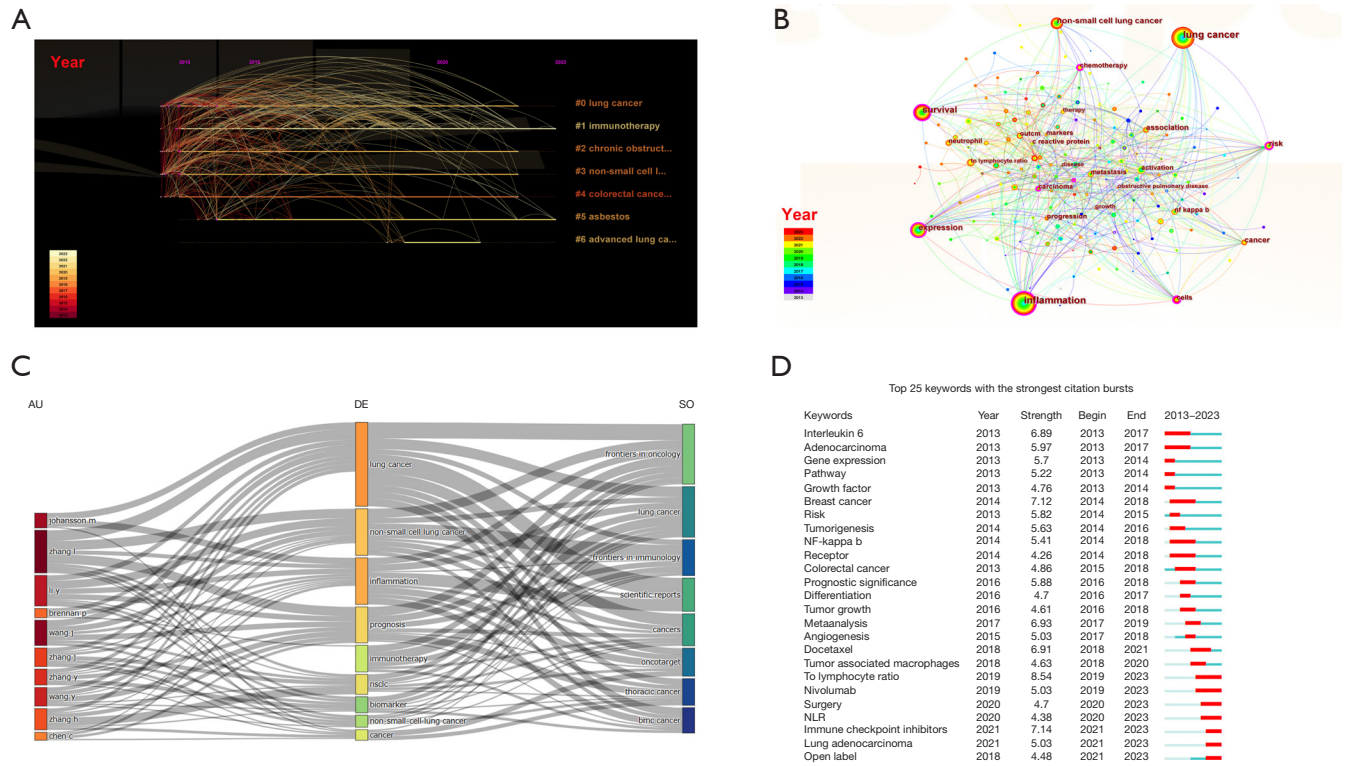


**Figure 2** Keyword analysis. (A) Keyword clustering timeline. (B) Co-occurrence mapping of keywords. (C) Author-keyword-journal three-field plot. (D) Top 25 keywords with the strongest citation bursts. AU, authors; DE, subject terms; SO, journals; NF, nuclear factor; NLR, neutrophil-to-lymphocyte ratio.

7,896 authors were included, with the top five authors being Zhang L (33 papers), Wang J (24 papers), Johansson M (22 papers), Li Y (22 papers), and Wang Y (20 papers), accounting for a total of 121 papers (9.4% of the total) (Table S1). Fifty-four countries have contributed to the publications on lung cancer and inflammation worldwide. The results indicate that China ranked first in publication output with 562 articles, accounting for approximately half of all identified records. The United States ranked second with 176 articles, followed by Japan with 84 (Table S1).

### *Quality analysis*

In 2017, the topic of lung cancer and inflammation had the highest number of citations (*Figure 1C*). The most cited article on this topic was titled "Effect of interleukin-1β inhibition with canakinumab on incident lung cancer in patients with atherosclerosis: exploratory results from a randomized, double-blind, placebo-controlled trial", published in *Lancet*, with a total of 734 citations (Table S2). Two of the top 10 cited articles were from *Lung Cancer*, with the highest citation count of 1,581 (Tables S1-S3). Interestingly, the journal with the highest publication volume, *Frontiers in Oncology*, did not have highly cited articles. China, being the country with the highest publication volume, also had the highest citation count of 10,920, with an average of 19.4 citations per article, indicating significant contributions from China in the research on lung cancer and inflammation (Tables S1,S3).

### *Keyword analysis*

#### Timeline analysis

The keyword timeline analysis aims to understand the development trends in a specific field by examining keywords' temporal and spatial evolution. This study generated a visualization map of the spatiotemporal evolution of lung cancer and inflammation research in China from 2013 to 2023 (*Figure 2A*). Seven relevant clusters were identified, and the keywords were arranged chronologically to demonstrate their evolution. The timeline was divided into three stages: from 2013 to 2015,

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the main focus was on prognosis-related aspects, such as "survival", "risk", "metastasis", and others. From 2015 to 2020, attention shifted to inflammation-related factors, including "neutrophil-to-lymphocyte ratio", "neutrophil", "biomarkers", "lymphocyte ratio", and others. From 2020 to 2023, there was a growing interest in immunotherapy, with keywords such as "immune checkpoint inhibitors", "suppressor cells", "microenvironment", and others becoming more prominent.

**Co-occurrence analysis**

Keywords are highly condensed representations of the research topics and core content of the literature. Based on keyword co-occurrence analysis, research hotspots in the field can be identified. The keyword co-occurrence network depicted in the graph includes 183 nodes and 668 links, with a density of 0.0401. "Chemotherapy" is the keyword with the highest intermediary centrality, crucial in advancing and developing lung cancer and inflammation research. Keywords with a frequency of 100 or more include "survival", "expression", "risk", and others (*Figure 2B*), listed in descending order of frequency. Overall, this keyword timeline analysis provides valuable insights into the evolving research trends and hot topics in lung cancer and inflammation in China over the specified period.

**Three-fields plot**

The passage describes the analysis of the relationship between different bibliometric indicators using the three-field plot method in bibliometrics. The plot depicts the network relationship between authors, subject terms, and journals in English and Chinese literature. According to the results (*Figure 2C*), Zhang L has the highest publication count and focuses on key terms such as "biomarker" and "prognosis".

**Highlighting analysis**

The CiteSpace analysis has identified the top 25 burst keywords in lung cancer and inflammation research (*Figure 2D*). Burst keywords are those with a higher frequency of occurrence in a relatively short period, indicating research frontiers and emerging trends. The visualization map shows the timeline of these burst keywords, with red indicating the years in which the keywords burst, light blue indicating no burst, and dark blue indicating the beginning of the burst. The top 25 burst keywords in the recent 5 years (from 2018 to 2023) are as follows: "to lymphocyte ratio", "nivolumab", "surgery", "NLR", "immune checkpoint inhibitors", and "open-label". These burst keywords represent the emerging research trends and frontiers in lung cancer and inflammation from 2018 to 2023. Researchers are actively exploring these topics and are likely to contribute significantly to advancing knowledge in this area.

### *Co-citation references analysis*

**Cluster analysis**

The analysis of co-cited references can provide insights into the research frontiers in the field. Researchers can better identify key focus areas by clustering the co-cited references from the past 10 years. After performing the clustering analysis on the co-cited references, the results showed a modularity value (Q) of 0.6961, indicating significant clustering, and a silhouette value (S) of 0.8878, indicating the clustering is reasonable. A total of 27 cluster labels were obtained, and the first eight cluster labels from 2013 to 2023 are listed as follows: "prognosis" (cluster 0), "immunotherapy" (cluster 1), "lung cancer" (cluster 2), "immunity" (cluster 3), "COPD" (cluster 4), "systemic immune-inflammation index" (cluster 5), "lung adenocarcinoma" (cluster 6), "chronic inflammation" (cluster 7) (*Figure 3A*). Extracting the keywords from the co-cited references in each cluster helps determine the main topics represented by the cluster labels. Cluster 0 (prognosis) has the largest number of co-cited references, indicating its prominence in the field.

**Timeline and highlight analysis**

The co-cited references timeline graph (*Figure 3B*) shows that "prognosis", "immunotherapy", "immunity", and "systemic immune-inflammation index" are current research hotspots, with "lung cancer" being the earliest identified research hotspot. *Figure 3C* presents the top 25 most bursting references, and the citation burst in this field started in 2013. Many of these references are still frequently cited, indicating that inflammation in the context of lung cancer will remain a significant research hotspot in the coming years.

### *Synthetic analysis*

The most academically influential authors are Wang J (H-index =14), followed by Johansson M (H-index =13) and Li Y (H-index =13). The most academically influential journals are *PLoS One* (H-index =20), followed by *Lung Cancer* (H-index =18) and *Oncotarget* (H-index =17). The journal with the highest publication count, *Frontiers in*

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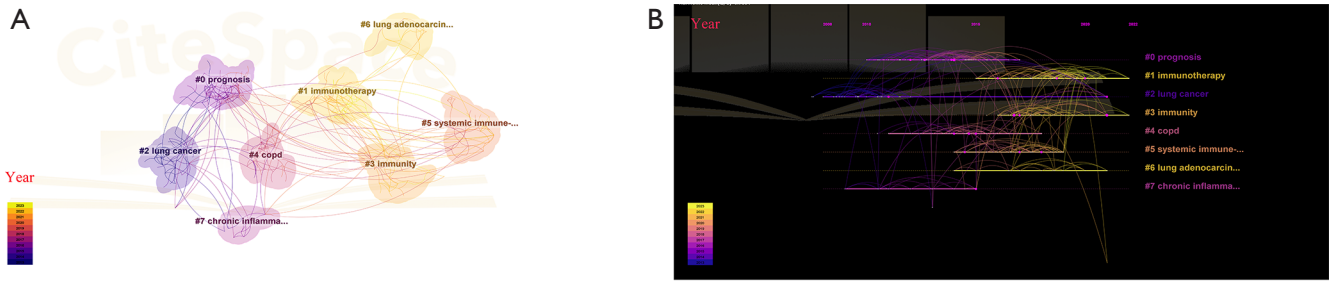


C

Top 25 references with the strongest citation bursts

| References | Year | Strength | Begin | End |
|---|---|---|---|---|
| Hanahan D, 2011, *CELL*, V144, P646, DOI 10.1016/j.cell.2011.02.013, DOI | 2011 | 20.93 | 2013 | 2016 |
| Grivennikov SI, 2010, *CELL*, V140, P883, DOI 10.1016/j.cell.2010.01.025, DOI | 2010 | 13.21 | 2013 | 2015 |
| Siegel RL, 2021, *CA-CANCER J CLIN*, V71, P359, DOI 10.3322/caac.21208, DOI | 2021 | 10.29 | 2021 | 2018 |
| JEMAL A, 2011, *CA-CANCER J CLIN*, V61, P69, DOI 10.3322/CAAC.20107, DOI | 2011 | 9.49 | 2013 | 2016 |
| Pine SR, 2011, *JNCI-J NATL CANCER I*, V103, P1112, DOI 10.1093/jnci/djr216, DOI | 2011 | 8.24 | 2013 | 2016 |
| Cedres S, 2012, *CLIN TRANSL ONCOL*, V14, P864, DOI 10.1007/s12094-012-0872-5, DOI | 2012 | 7.96 | 2013 | 2017 |
| Siegel R, 2012, *CA-CANCER J CLIN*, V62, P10, DOI 10.3322/caac.20138, DOI | 2012 | 7.88 | 2013 | 2015 |
| Siegel R, 2013, *CA-CANCER J CLIN*, V63, P11, DOI 10.3322/caac.21166, DOI | 2013 | 8.71 | 2014 | 2017 |
| Pinato DJ, 2014, *BRIT J CANCER*, V110, P1930, DOI 10.1038/bjc.2014.145, DOI | 2014 | 10.84 | 2015 | 2017 |
| McMillan DC, 2013, *CANCER TREAT REV*, V39, P534, DOI 10.1016/j.ctrv.2012.08.003, DOI | 2013 | 8.74 | 2015 | 2018 |
| Cannon NA, 2015, *J THORAC ONCOL*, V10, P280, DOI 10.1097/JTO.0000000000000399, DOI | 2015 | 8.03 | 2015 | 2018 |
| Kang MH, 2014, *BRIT J CANCER*, V111, P452, DOI 10.1038/bjc.2014.317, DOI | 2014 | 7.57 | 2015 | 2017 |
| Siegel RL, 2016, *CA-CANCER J CLIN*, V66, P7, DOI 10.3322/caac.21332, DOI | 2016 | 9.3 | 2016 | 2018 |
| Torre LA, 2015, *CA-CANCER J CLIN*, V65, P87, DO1 10.3322/caac.21262, DOI | 2015 | 8.01 | 2016 | 2019 |
| Templeton AJ, 2014, *JNCI-J NATL CANCER I*, V106, P0, DOI 10.1093/jnci/dju124, DOI | 2014 | 7.72 | 2017 | 2019 |
| Borghaei H, 2015, *NEW ENGL J MED*, V373, P1627, DOI 10.1056/NEJMoa1507643, DOI | 2015 | 10.43 | 2018 | 2020 |
| Bagley SJ, 2017, *LUNG CANCER*, V106, P1, DOI 10.1016/j.lungcan.2017.01.013, DOI | 2017 | 9.18 | 2018 | 2021 |
| Reck M, 2016, *NEW ENGL J MED*, V375, P1823, DOI 10.1056/NEJMoa1606774, DOI | 2016 | 8.63 | 2018 | 2021 |
| Siegel RL, 2021, *CA-CANCER J CLIN*, V71, P7, DOI 10.3322/caac.21654, DOI | 2021 | 14.32 | 2021 | 2023 |
| Diem S, 2017, *LUNG CANCER*, V111, P176, DOI 10.1016/j.lungcan.2017.07.024, DOI | 2017 | 8.85 | 2019 | 2023 |
| Goldstraw P, 2016, *J THORAC ONCOL*, V11, P39, DOI 10.1016/j.jtho.2015.09.009, DOI | 2016 | 7.68 | 2019 | 2021 |
| Mezquita L, 2018, *JAMA ONCOL*, V4, P351, DOI 10.1001/jamaoncol.2017.4771, DOI | 2018 | 8.15 | 2020 | 2023 |
| Bray F, 2018, *CA-CANCER J CLIN*, V68, P394, DOI 10.3322/caac.21492, DOI | 2018 | 14.36 | 2021 | 2023 |
| Gandhi L, 2018, *NEW ENGL J MED*, V378, P2078, DOI 10.1056/NEJMoa1801005, DOI | 2018 | 9.74 | 2021 | 2023 |
| Mandaliya H, 2019, *TRANSL LUNG CANCER R*, V8, P886, DOI 10.21037/tlcr.2019.11.16, DOI | 2019 | 9.74 | 2021 | 2023 |

**Figure 3** Co-cited literature analysis. (A) Clustering analysis of co-cited literature. (B) Co-cited literature clustering timeline. (C) Top 25 references with the strongest citation bursts. COPD, chronic obstructive pulmonary disease.

*Oncology*, did not appear in the top 10 (Table S4). The results of the journal overlay analysis show that there are three main citation pathways. However, the citing journals must exhibit a clear trend regarding their subject areas. On the other hand, the cited journals are predominantly concentrated in three fields: "molecular, biology, genetics", "veterinary, animal, parasitology", and "environmental, toxicology, and nutrition" (*Figure 4A*). The countries with the closest cooperation relationship are China and the United States (frequency =49), followed by the United States and the United Kingdom (frequency =23), the United States and Italy (frequency =21), Italy and the United Kingdom (frequency =19), the United States and France (frequency =19), and Italy and France (frequency =18), which indicates a trend of globalization in lung cancer and inflammation research (*Figure 4B*). Based on *Figure 4C*, it can be seen that lung cancer has been the main focus of research in the past decade.

### *Areas of special attention: TLSs in lung cancer and inflammation*

Interestingly, when we explored the relationship between 'lung cancer' and 'inflammation', we found that TLSs were described in both. Therefore, we searched further and characterized the current status of inflammation-related TLS in lung cancer. Several clinical studies have found that the presence of TLS could not only assess the prognosis

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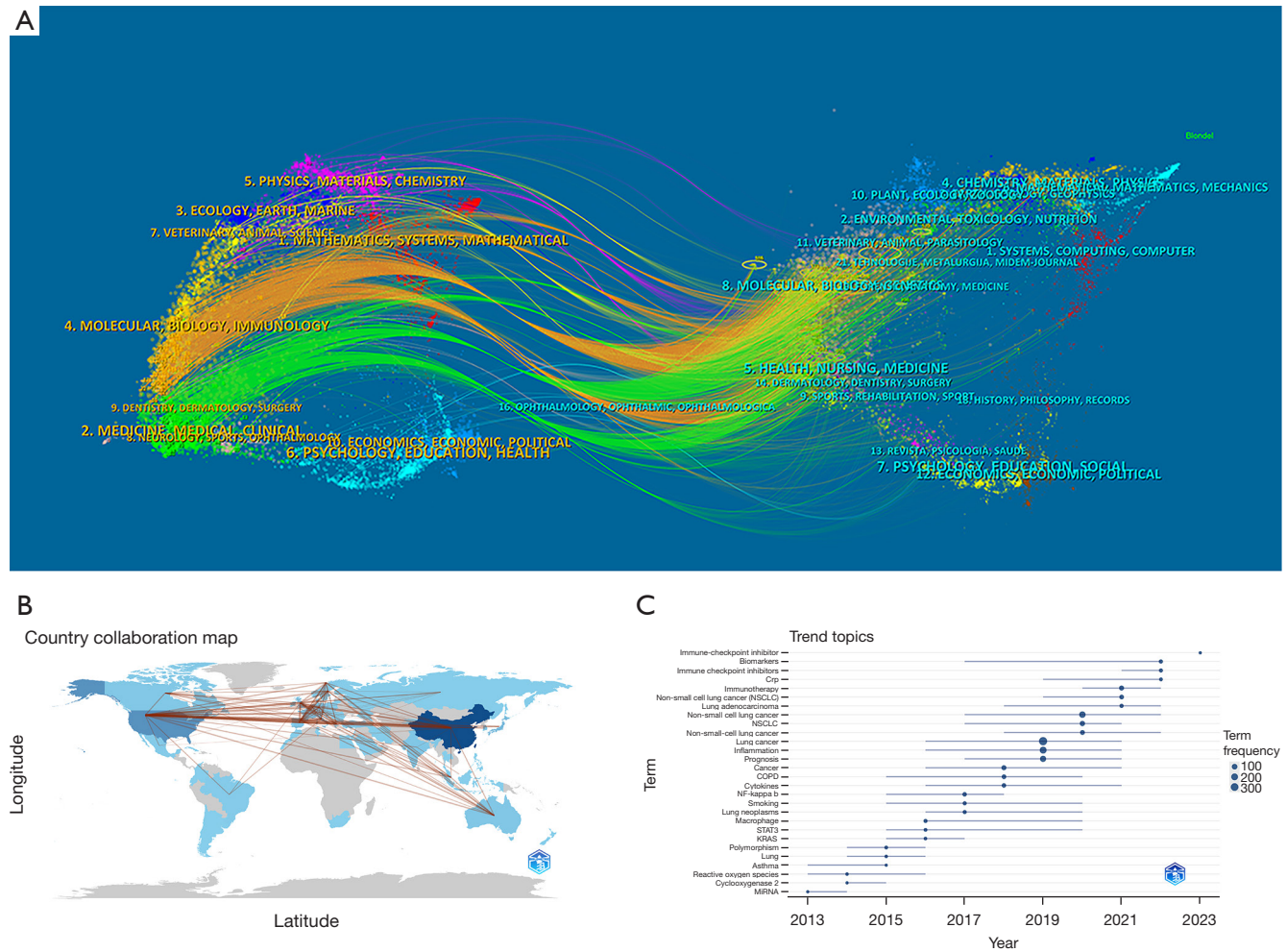


**Figure 4** Synthetic analysis. (A) Double graph overlay analysis of citing and cited journals. (B) Collaborative relationships among different countries. (C) Research trends in the last decade. CRP, C-reactive protein; NSCLC, non-small cell lung cancer; COPD, chronic obstructive pulmonary disease; NF, nuclear factor; STAT3, signal transducer and activator of transcription 3; KRAS, Kirsten rat sarcoma viral oncogene homolog; miRNA, microRNA.

of lung cancer patients (11,17) but also predict the efficacy of anti-tumor therapy (8,10,26). The maturity and cellular composition of TLS influence tumor immunity (18-21) and may be a potential predictor of immunotherapy efficacy (23,24,27). Here we list these studies in *Table 1*.

There are several stages of TLS maturation: early TLS shows clusters of aggregated lymphocytes without FDC and germinal center (GC) or separate T- and B-cell areas. Subsequently, lymphocyte clusters develop into primary follicular-like TLS with a $CD21^+$ FDC network. Secondary follicle-like TLS has activated GCs and $CD21^+CD23^+$ FDCs, in which the presence of GCs is considered to be a marker of TLS maturation (28). Current research does not have a uniform definition of the observed and mature state of TLS. Some researchers have categorized TLS into "mature" and "immature" states by the CD23 positivity observed by immunohistochemistry (IHC) or immunofluorescence (IF). Other researchers have defined the maturation stage of TLS by detecting the maturation of B cells in GC (29) or the abundance of $DC\text{-}Lamp^+$ cells (27). The relationship between TLSs and non-small cell lung cancer (NSCLC) prognosis has not been elucidated in terms of location, density, and maturity. One study showed that intratumorally immature TLS was associated with a favorable prognosis (30). Another study supported that C-X-C motif ligand 13 $(CXCL13)^+$ cells located in TLS

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**Table 2** The studies of TLSs in non-tumor inflammatory diseases in lungs

| Diseases | Year | Main points | Reference |
|---|---|---|---|
| Respiratory syncytial virus infection | 2021 | IL-21 treatment decreased RSV viral load and lung inflammation, inducing the formation of TLOs in the lung | (35) |
| COPD | 2020 | Type 2 conventional DC enable to induce IL-21 Tfh-like cells, suggesting an involvement of these cells in TLO formation | (36) |
| Chronic pulmonary infection | 2018 | Induction of chronic lung infection and TLSs in animals by intratracheal instillation of agarose beads containing *Pseudomonas aeruginosa* or *Staphylococcus aureus* | (37) |
| COPD | 2021 | The secretory IgA containing mucosal immune barrier correlated with lymphocyte accumulation in airway walls and the development of TLS around small airways | (38) |
| Pneumoconiosis | 2024 | Cross-linked water-soluble acrylic acid polymers increases the number of iBALT structures, Th2 cells infiltrated around B cells in the center of the iBALT | (39) |
| Klebsiella pneumoniae lung infection | 2022 | K. pneumoniae exposure increased iBALT structures in size and number with high expression levels of CXCL12 | (40) |
| Influenza | 2021 | They identified a long-lived, Bcl6-dependent population that have termed T resident helper cells | (41) |

TLS, tertiary lymphoid structure; IL-21, interleukin-21; RSV, respiratory syncytial virus; TLO, tertiary lymphoid organ; COPD, chronic obstructive pulmonary disease; DC, dendritic cell; Tfh, T follicular helper; IgA, immunoglobulin A; iBALT, inducible bronchus-associated lymphoid tissue; Th, T helper; CXCL12, C-X-C motif ligand 12.

was associated with favorable prognosis while other location was related to unfavorable prognosis (25). In addition, different tumor driver mutation profiles may also affect the prognostic value of TLS (31).

Recently, a study identified the progressive formation of TLS during lung adenocarcinoma initiation and invasion (32). During tumor initiation, CD4 T cells are the very first to accumulate around alveolar epithelial cells, and CD8 T cells and B cells do not form aggregates. As the tumor invaded, T follicular helper cell like cells expressing CXCL13 appeared, forming a region of mature B and T cells defined as mature TLS (mTLS). mTLS contained GCs, peripheral node addressin (PNAd) high endothelial veinlets, and $CD21^+$ FDCs. These suggest that TLS matured as the tumor progressed (32). TLS in the lung is often referred to as bronchus-associated lymphoid tissue (BALT) and is usually observed in pulmonary infections or inflammation (33,34). These conditions result from chronic exposure to antigens or inflammatory agents, highlighting the significance of TLS in chronic inflammation and immune responses within the lung. This broader understanding of TLS in inflammatory diseases provides a foundation for comprehending their impact on lung cancer progression and patient outcomes. Hence, the study of TLS in other non-tumor inflammatory diseases might provide some useful clues in the tumor immunology (35-41) (*Table 2*).

## Discussion

In recent years, extensive research has investigated the relationship between inflammation and lung cancer. For instance, IL-17 has been shown to promote lung cancer development by recruiting $CD11b^+Gr1^+$ myeloid-derived suppressor cells (MDSCs), which in turn facilitate tumor angiogenesis and suppress the proliferation and activation of $CD8^+$ T cells and natural killer (NK) cells, as well as induce T regulatory (Treg) cells to inhibit immune responses, ultimately promoting lung cancer occurrence and progression (42). Researchers like Zhang *et al.* have demonstrated that CCL7 promotes the infiltration of cDC1 cells into the TME, inducing T cell expansion in lung cancer tissue and bronchial lymph nodes, thereby promoting anti-tumor immune responses (43). These studies collectively emphasize the critical role of inflammation in tumor development.

A bibliometric approach was used to investigate the current status of inflammation and lung cancer in this study. The author with the highest number of citations in this field is Ridker PM, with his article "Interleukin-1β inhibition and canakinumab in patients with lung cancer: exploratory results randomized, double-blind, placebo-controlled trial". By integrating keyword analysis, the overarching trajectory in this domain presently leans toward the domains of "prognosis" and "immunotherapy". According to our

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research, topics related to lung cancer, inflammation, and the prognosis of lung cancer primarily revolve around their relationship with chronic obstructive pulmonary disease (COPD), their role in NSCLC, the influence of neutrophil-to-lymphocyte ratio and their relationship with immunotherapy as well as related markers.

Notably, when exploring the relationship between "lung cancer" and "inflammation", we discovered that TLS is associated with both. Therefore, we aimed to delve deeper into the research status of inflammation-related TLS in lung cancer. In the following discussion, we will explore the possibility of the abovementioned topics.

TLS refers to ectopic lymphoid structures induced in chronic inflammation, originally described in autoimmune diseases, infections and transplant rejection, and playing an important role in the adaptive immune system (44). In autoimmune diseases, TLS is associated with disease progression and poor prognosis (45). For instance, mature inducible BALT (iBALT) consists of numerous B-cell follicles containing GCs and FDCs associated with tissue damage in the lungs of rheumatoid arthritis patients (46). In contrast, T and B cells in TLS play a major protective role in infection and TME (47-49). Earlier, we mentioned the studies of inflammation and lung cancer. There are some characteristics of chronic inflammation in the TME, and it is thought to contribute to chemotherapy and radiotherapy resistance and tumor metastasis (50). An early study showed that the presence of TLS in the TME correlates with better clinical outcomes in NSCLC (17). Chronic inflammation induced by cancer often leads to the development of TLSs, which create a unique inflammatory environment. A study has indicated that the expression of genes associated with TLS formation increases within tumors (51). This correlates with increased TLS markers and the abundance of B cells, T cells, and DCs. TLS in lung cancer control the number of TH1 cells and modulate the immune response of cytotoxic $CD8^+$ T cells within the tumor. Therefore, the presence, location, and maturity of TLSs contribute to the specific TME, thereby regulating tumor growth, progression, and metastasis (50). The complex interactions within the TME significantly impact tumor growth and metastasis (52). Then, TLS was subsequently found to be associated with better prognosis in other solid tumors (29,53), suggesting that TLSs may induce specific anti-tumor immune responses. The internal structural features of TLS are highly similar to those of secondary lymphoid organs (SLOs) such as lymph nodes, which also have unique lymphocyte aggregation areas: B cell follicles with FDCs, follicular reticular cells, GCs and high endothelial venules (HEVs) (54). In contrast to SLOs, TLSs in tumor tissues lack peripheral fibrous envelope allowing immune cells within TLSs to come into contact with surrounding tissues directly. Antigen presentation cells can deliver antigens directly to T and B cells, generating a rapid and efficient long-lasting anti-tumor immune response.

Research (55) has indicated that lymphatic dysfunction in the lungs can lead to a chronic inflammatory state, of which the formation of TLOs is a prominent manifestation. Simultaneously, it can lead to lung damage, thus establishing an association between chronic lung diseases and the formation of TLOs. Moreover, the formation of TLSs in chronic inflammation also influences disease progression. In patients with COPD (56), the number of tertiary lymphocyte follicles (TLFs) increases under the influence of the airway epithelium, along with the elevation of relevant immune factors and an increase in the number of follicular immunoglobulin A (IgA) B cells. These factors are associated with disease severity. A study (57) has revealed a heightened risk of cancer development in individuals with COPD, and in turn, tumor formation can impact the inflammatory response and alter the TME. But it remains unclear whether the formation of TLSs in COPD affects tumor cell proliferation and is involved in the occurrence of lung cancer. The disparity between TLSs in COPD and TLSs in lung cancer necessitates further exploration in subsequent studies.

TLSs in different types of tumors often exhibit varying maturity levels but typically consist of areas with T cell accumulation, B cell GCs, and abundant mature DCs. These DCs act as antigen-presenting cells, promoting the differentiation of helper T cells and effector memory cells. TLSs also harbor cytotoxic cells, memory B cells, and plasma cells. The density of TLSs within a tumor is also associated with the density of $CD8^+$ T cells and $CD4^+$ T cells. Tumors with a high expression of TLSs often exhibit increased levels of activated T cells marked by $CD38^+$ and $CD69^+$ expression and effector memory $CD8^+$ T cells (58,59). In lung cancer, current research primarily focuses on studying the unique composition of TLSs within tumors and understanding their role in predicting prognosis and treatment outcomes (11). However, the detailed mechanisms by which TLSs affect the TME and their impact on tumors require further exploration.

Additionally, researchers need to develop TLS-related marker detection kits and more sensitive methods for identifying the structure and composition of TLSs. Furthermore,

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programmed death receptor-1 (PD-1) inhibitors are widely used to treat NSCLC. Transcriptome analysis of tumors in patients treated with PD-1 inhibitors revealed distinct distribution and expression patterns of B and plasma cells. Tumors with TLSs show enrichment of a plasma cell signature. This plasma cell signature significantly predicts survival benefits following atezolizumab treatment, suggesting that TLS recognition may also predict survival benefits in NSCLC immunotherapy (23). However, further research is necessary to investigate the mechanisms underlying the induction of plasma cells within TLSs and how they can enhance the anti-tumor effects of PD-1 inhibitors.

## Conclusions

This study underscores the pivotal role of inflammation in lung cancer progression, mediated by a delicate balance of immune responses. The emerging prominence of TLS as indicator of adaptive immune responses within the TME offers intriguing avenues for future research and therapeutic interventions. Collaborative networks and publication trends reflect the global pursuit of comprehensive insights into inflammation's dual impact on lung cancer, fostering novel strategies to enhance patient outcomes.

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