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Global trends in tertiary lymphoid structures: a bibliometric analysis from 2014 to 2023

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Aim and background: Tertiary lymphoid structures (TLS) are increasingly recognized for their role in immunity. Despite growing interest, a systematic bibliometric analysis of TLS-related research has been lacking. To provide a comprehensive overview of current research trends and hotspots, we conducted a bibliometric analysis using data from the Web of Science Core Collection.

Methods: We retrieved TLS-related publications from the Science Citation Index Expanded within the Web of Science Core Collection from January 2014 to December 2023. Co-occurrence analysis with "VOSviewer" identified current status and research hotspots, while "CiteSpace" was used for co-citation analysis to assess knowledge evolution and bursts. Thematic evolution was explored using bibliometrics to identify emerging keyword trends. Additionally, we examined country/region, institutional, and author contributions and collaborations. Tables were created using Microsoft Word.

Results: A total of 785 publications were analyzed, showing a continuous growth trend from 2017 to 2023, indicating escalating interest in TLS among researchers. Leading countries in TLS research were China (231 publications), the United States (212 publications), and France (89 publications). The most productive institution and author were the "Institut national de la santé et de la recherche médicale" (70 publications) and Catherine Sautes-Fridman (21 publications), respectively. Key topics included TLS, B cells, and immunotherapy. Recent research has focused on mechanisms linking TLS with cancers, such as immunotherapy, tumor microenvironment, tumor-infiltrating lymphocytes, prognosis, and immune checkpoint inhibitors, highlighting an expanding area of study. Additionally, TLS' potential as a biomarker for predicting immunotherapy efficacy across different cancer types remains a burgeoning research direction.

Conclusions: This study provides a comprehensive analysis of global TLS-related publications, revealing key literature metrics and identifying influential articles and emerging research concerns. These findings contribute valuable insights into the role of TLS in immunotherapy and suggest future directions for this dynamic field.

KEYWORDS

bibliometric, immunotherapy, tertiary lymphoid structures, research trend, prognostic value

1 Introduction

Immune cells are frequently found in the microenvironment surrounding tumor cells (1). The prognostic impact of these tumor-infiltrating immune cells across different cancer types has long been of interest (2–4). In recent years, immunotherapy, particularly the use of immune checkpoint inhibitors (ICIs), has made remarkable strides in antitumor therapy (5). ICIs primarily enhance antitumor efficacy by reversing the functional exhaustion of lymphocytes infiltrating within or around tumors (6, 7). Consequently, there has been increased attention on the prognostic role and regulatory mechanisms of these tumor-infiltrating immune cells. For instance, patients with enriched intratumoral immune cell populations in non-small cell lung cancer (NSCLC) treated with ICIs often exhibit higher response rates and improved outcomes (8, 9). In chronic inflammatory or tumor environments, a type of lymphocyte aggregate known as tertiary lymphoid structures (TLS) frequently forms (10). TLS develops postnatally in non-lymphoid tissues, also referred to as ectopic lymphoid structures. TLS has been identified in autoimmune diseases and chronic infections (11, 12). Additionally, several studies suggest that the presence of TLS in tumor tissue serves as a promising prognostic marker for immunotherapy (9, 13, 14). However, TLS may not consistently predict positive outcomes in certain tumor subtypes (15, 16). This variability in immunotherapy outcomes has further stimulated research into the functions and regulatory mechanisms of TLS within tumors.

The structure, cellular composition, and regulation of TLS may be different between diseases (10). As a result, investigating the mechanisms of action and the potential therapeutic predictive role of TLS has emerged as a prominent research area, leading to the publication of numerous related studies. Bibliometric analysis, a statistical methodology utilizing public literature databases, quantitatively and qualitatively assesses relevant publications to summarize research trends and hotspots in a specific field (17). Widely applied in scientific research, bibliometrics systematically analyzes various aspects of a research field, including countries/regions, keywords, references, authors, journals, and institutions (18, 19). However, the comprehensive exploration of global trends in TLS through bibliometric analysis remains relatively unexplored.

Therefore, conducting a bibliometric analysis to explore research trends and hotspots related to TLS can significantly aid researchers in quickly grasping essential information, identifying pivotal developments, and discerning future directions in TLS research.

Abbreviations: HEVs, high endothelial venules; ICIs, immune checkpoint inhibitors; NSCLC, non-small cell lung cancer; TLS, tertiary lymphoid structures; WOSCC, Web of Science Core Collection.

2 Materials and methods

2.1 Data collection and extraction

Data from the Web of Science Core Collection database (WOSCC) were utilized for this study. Articles and reviews in English were retrieved from the WOSCC on February 27, 2024. The search terms in this article are derived from the subject terms in the MeSH database (https://www.ncbi.nlm.nih.gov/mesh). We defined the search keywords as: "Tertiary lymphoid structure*", "Lymphoid Structure*, Tertiary", "Ectopic Lymphoid-Like Structure*", "Lymphoid-Like Structure*, Ectopic", "Lymphoid Formation*, Ectopic", "Ectopic Lymphoid Tissue*", "Lymphoid Tissue*, Ectopic", "Ectopic Lymphoid Organ*", "Lymphoid Organ*, Ectopic", "Ectopic Lymph Node*", "Lymph Node*, Ectopic", "Ectopic Lymphoid Follicle*", and "Lymphoid Follicle*, Ectopic".

The terms attached to TLS were searched in the titles (TI), abstracts (AB), or author keywords (AK), a search strategy commonly used in bibliometric analysis (20–22). The detailed search formula is as follows: ((TI=("Tertiary lymphoid structure*" OR "Lymphoid Structure*, Tertiary" OR "Ectopic Lymphoid-Like Structure*" OR "Lymphoid-Like Structure*,Ectopic" OR "Lymphoid Formation*, Ectopic" OR "Ectopic Lymphoid Tissue*" OR "Lymphoid Tissue*, Ectopic" OR "Ectopic Lymphoid Organ*" OR "Lymphoid Organ*, Ectopic" OR "Ectopic Lymph Node*" OR "Lymph Node*, Ectopic" OR "Ectopic Lymphoid Follicle*" OR "Lymphoid Follicle*, Ectopic")) OR AB=("Tertiary lymphoid structure*" OR "Lymphoid Structure*, Tertiary" OR "Ectopic Lymphoid-Like Structure*" OR "Lymphoid-Like Structure*, Ectopic" OR "Lymphoid Formation*, Ectopic" OR "Ectopic Lymphoid Tissue*" OR "Lymphoid Tissue*, Ectopic" OR "Ectopic Lymphoid Organ*" OR "Lymphoid Organ*, Ectopic" OR "Ectopic Lymph Node*" OR "Lymph Node*, Ectopic" OR "Ectopic

Lymphoid Follicle*" OR "Lymphoid Follicle*, Ectopic")) OR AK=("Tertiary lymphoid structure*" OR "Lymphoid Structure*, Tertiary" OR "Ectopic Lymphoid-Like Structure*" OR "Lymphoid-Like Structure*,Ectopic" OR "Lymphoid Formation*, Ectopic" OR "Ectopic Lymphoid Tissue*" OR "Lymphoid Tissue*, Ectopic" OR "Ectopic Lymphoid Organ*" OR "Lymphoid Organ*, Ectopic" OR "Ectopic Lymph Node*" OR "Lymph Node*, Ectopic" OR "Ectopic Lymphoid Follicle*" OR "Lymphoid Follicle*, Ectopic"). Our selection criteria included articles published in English between 1 January 2014 and 31 December 2023. The process of article selection and review is illustrated in Figure 1.

2.2 Data analysis and visualization

The study was conducted by two independent researchers to ensure the reliability of the results. These researchers evaluated the outcomes of independent scans and included studies that met the predefined inclusion and exclusion criteria. Documents retrieved from the search were downloaded in plain text format, and relevant information including author details, country or region, institution, keywords, and references was extracted for subsequent data analysis. In our analysis, we examined various aspects including journals, countries, institutions, cited publications, authors, keyword co-occurrence networks, abstract content analysis, and co-citations. We utilized several software tools for this purpose: "VOSviewer 1.6.17", "CiteSpace 5.8 R3", and the "bibliometrics" function in R Version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org/). Additionally, Tables were created using Microsoft Word.

3 Results

3.1 Annual publications and trends

A total of 589 articles (74.8%) and 198 reviews (25.2%) related to TLS were included in the WOSCC. Of these, 785 publications were written in English. Over the period from 2014 to 2023, there has been a consistent annual increase in publications on TLS (Figure 2A). The growth rate reached its peak in 2023 at 24.076%, indicating a significant rise in interest in TLS within the academic community.

Since 2014, articles originating in the United States (212 documents) have maintained a high percentage, China (231 documents) has seen a dramatic increase in the number of articles published in recent years and was expected to overtake the United States as the most published country after 2022 (Figure 2B). In addition, France, the United Kingdom, Germany, and Japan are also common countries for publication on TLS (Table 1). Single country publications are generally more numerous than multiple country publications. The countries with a high proportion of multiple country publications are mainly the Netherlands, Belgium and the United Kingdom, whereas China has the lowest proportion (Figure 2C). These collaborations have resulted in stronger linkages within the TLS research community in these countries compared to others (Figures 2D, E; Table 1). East Asian countries such as China, South Korea, and Japan have increasingly engaged in joint publications with authors from various nations. Additionally, countries like Brazil, Ireland, and Iran have also begun contributing notable results on TLS in recent years (Figure 2E). These trends underscore the global and collaborative nature of TLS research.

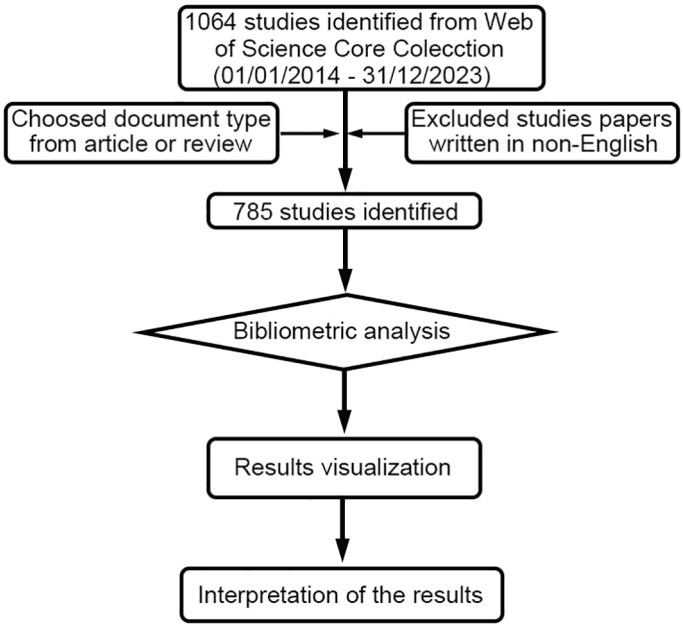

FIGURE 1
The diagram illustrates the process of data filtering and bibliometric analysis.

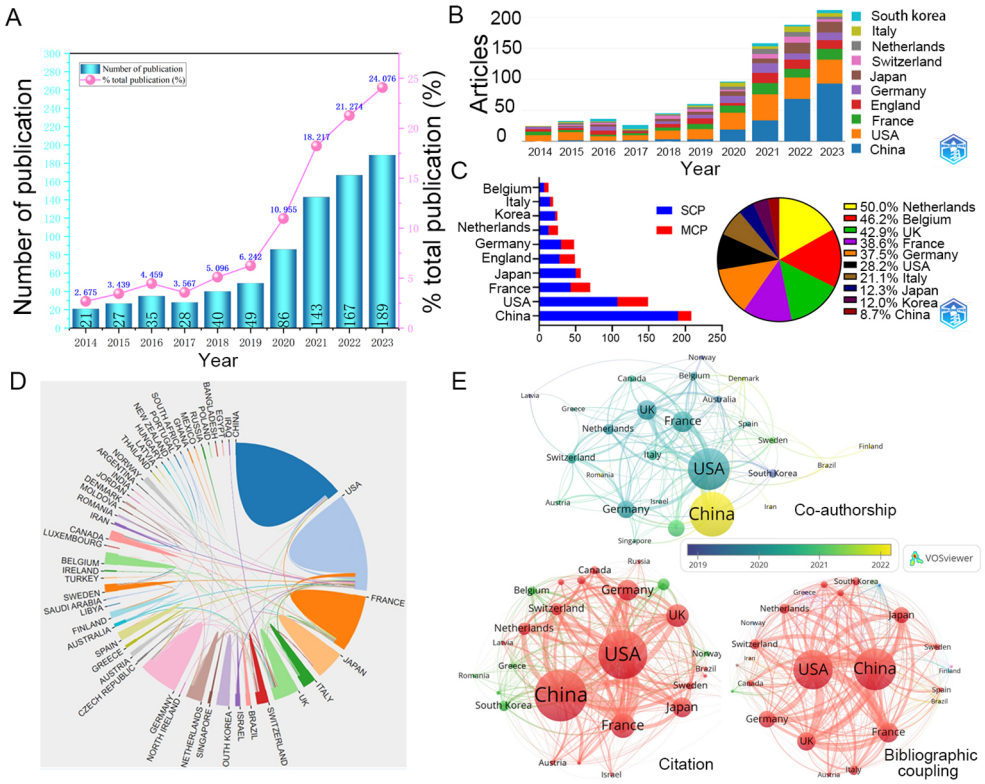

FIGURE 2
Annual publications and interactions between countries. **(A)** The total number and growth rate of TLS-related publications per year during 2014-2023. **(B)** Comparison of the number of articles published in several countries over 10 years. **(C)** The partnerships of different countries. **(D)** Visual map of transnational/regional cooperation. The size of the border lines separating countries indicates the extent of cooperative interaction. **(E)** The networks of cooperation between 53 countries with at least one publication. SCP, Single country publications; MCP, Multiple Country publications; USA, the United States of America; UK, the United Kingdom.

3.2 Analysis of keywords

3.2.1 Gene signature

This keyword clustering map generated by "CiteSpace" reveals several primary research themes identified through keyword clustering in the literature. These themes include gene signature, prognostic significance, inflammation, high endothelial venules (HEVs), and angiogenesis (Figure 3A).

It is interesting to find suitable gene set scores to identify TLS. Of particular interest is the development of gene set scores tailored for identifying TLS. For instance, researchers have utilized a 12-gene expression signature (including CCL2, CCL3, CCL4, CCL5, and others) to assess TLS presence across different cancer types (23, 24). Other gene set scores were also attempted to be applied (15, 25). Given the variability and dynamics in gene expression, immunohistochemistry and hematoxylin-eosin staining continue to be crucial for determining TLS presence and abundance (23, 26). Thus, integrating pathological evaluation with gene signatures may offer a more comprehensive and accurate approach.

3.2.2 Prognostic significance

The prognostic role of TLS in cancer treatment, particularly in immunotherapy, has garnered significant attention. Studies indicate that high intratumor TLS abundance in colorectal cancer, NSCLC, head and neck squamous cell carcinoma, hepatocellular carcinoma, and cutaneous melanoma is associated with improved patient survival and enhanced immunotherapy efficacy (23, 26–30).

However, research also reveals nuances where certain TLS subtypes may not uniformly predict favorable outcomes across all

TABLE 1 The top 10 highly documents countries/regions for TLS research.

Country	Documents	Citations	Total link strength
China	231	3921	58
USA	212	11425	173
France	89	7655	84
UK	80	3834	102
Germany	71	3352	72
Japan	67	1722	35
Netherlands	37	3525	55
Switzerland	37	2621	52
Italy	35	941	42
South Korea	29	859	20

USA, the United States of America; UK, United Kingdom.

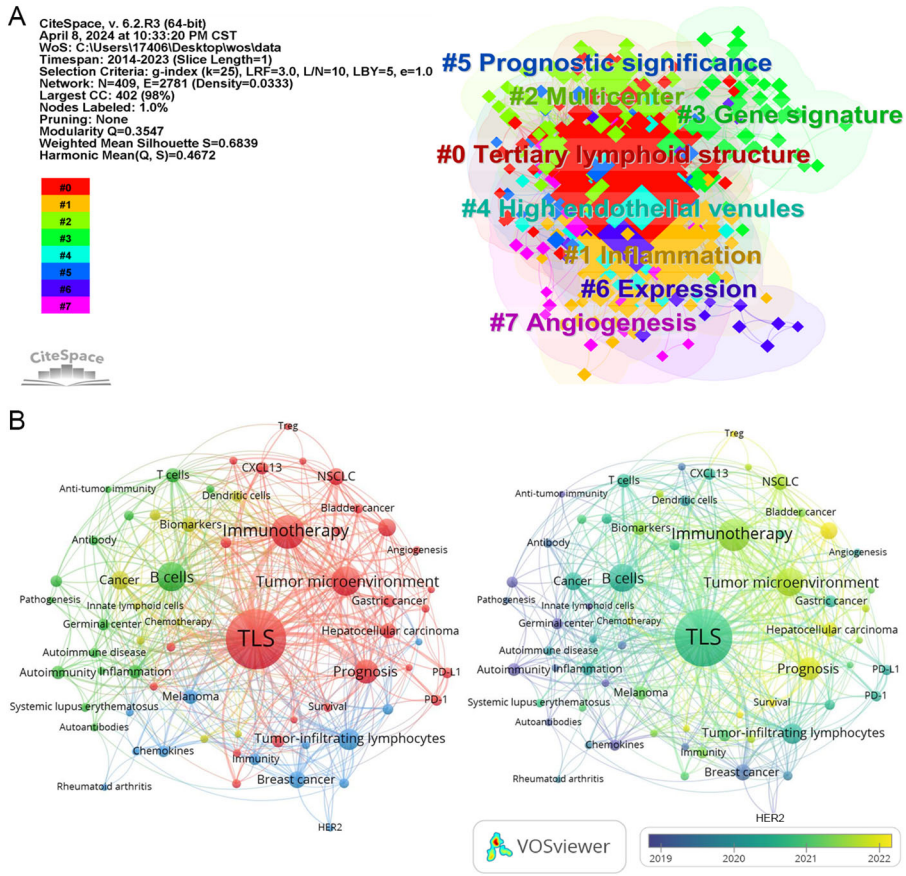

FIGURE 3
The network map of keywords. **(A)** the clustered network map of keywords in the field of TLS. **(B)** Network visualization of keyword co-occurrence which appeared at least 5 times (67 author keywords).

cancer types. For instance, high infiltration (>151) of scattered tumor-infiltrating lymphocytes is identified as a poor prognostic factor in metastatic colorectal cancer (31). Additionally, the level of TLS infiltration did not impact the prognosis of patients with acral melanoma receiving adjuvant anti-PD-1 therapy (15). Moreover, the presence of tumor-distal TLS correlates with poor prognosis in clear cell renal cell carcinoma, whereas tumor-proximal TLS exhibits the opposite effect (32).

These findings underscore the varied predictive value of TLS across different cancer types and even within the same cancer type based on factors such as anatomical location, structure, and abundance of TLS. These factors may influence the tumor immune microenvironment, ultimately impacting patient survival outcomes.

3.2.3 HEVs and angiogenesis

Tumor-associated HEVs play a crucial role in facilitating efficient lymphocyte infiltration into tumors (33). They are also recognized as components of TLS (34, 35). Studies have highlighted that a dense presence of HEVs within tumors correlates with improved efficacy of immunotherapy, chemotherapy, and other treatments (33, 34, 36–38). However, elevated expression of immune checkpoint ligands on tumor-associated HEVs can hinder CD8-positive T cell infiltration, potentially leading to poorer prognosis in patients with NSCLC (39). Conversely, the presence of HEVs indicates effective treatment response in NSCLC patients receiving PD-1 inhibitors combined with anti-angiogenic therapy (40).

The relationship between angiogenesis and TLS is also noteworthy. For instance, intratumoral injection of the STING agonist ADU S-100 in melanoma induced vascular normalization and TLS formation, enhancing control over tumor growth (41). Similar observations have been made in pancreatic neuroendocrine tumors, where vascular normalization and TLS formation attenuated resistance to immunotherapy (42). These findings underscore the critical role of angiogenesis normalization and effective infiltration of antitumorigenic lymphocytes in reshaping the tumor immune microenvironment.

3.2.4 Networks

In the keyword network analysis, TLS, B cells, immunotherapy, survival, and cancer emerge as the most frequently occurring keywords (Figure 3B; Table 2), highlighting TLS as a prominent area of research interest. Over time, additional keywords such as Treg, lung adenocarcinoma, chemotherapy, radiomics, and immune infiltration are gaining prominence in relation to TLS.

For instance, CT-based radiomics nomograms have shown promise in predicting TLS presence in intrahepatic cholangiocarcinoma, while MRI radiomics appears to offer similar capabilities (43, 44). Radiomics' noninvasive approach offers convenience for detecting TLS (43, 45). However, additional clinical evidence is required to validate the reliability of radiomics findings. Notably, "activation" emerged as the keyword with the highest centrality value in Table 2, highlighting a predominant focus on immune cell activation in TLS research.

3.2.5 Citation bursts

To track the evolving research hotspots in TLS, we analyzed the top 25 keywords with the strongest citation bursts (Figure 4), organized by the onset year of their burst. From 2014 to 2018, significant areas of focus included "Breast cancer", "Sjogrens syndrome", "Node like structures", "Rheumatoid arthritis", "Lymphoid neogenesis", "Dendritic cells", "NF-κB", "Lymphotoxin beta receptor", "Antigen", "B lymphocytes", and "Autoantibody production". Recent years have seen a shift towards keywords like "Cells", "Predictive value", "Inflammation", "Infection", and "Pathogenesis".

When sorted by the duration of their burst, the "Sjogrens syndrome", "Rheumatoid arthritis", and "NF-κB " exhibited the longest-lasting impact over a continuous three-year period. In terms of burst strength, which reflects significance, the "Sjogrens syndrome" peaked with a substantial citation spike of 6.85 intensity from 2014 to 2019, while "Pathogenesis" showed a notable spike of 2.29 intensity in 2020. These findings indicate that while early research likely explored the connection between TLS and autoimmune diseases (46, 47), recent trends suggest a growing interest in tumor immunity (12).

3.3 Analysis of references

Burst-detection analysis identifies papers experiencing significant citation surges, pivotal for tracing the evolution of research domains. In the TLS field from 2014 to 2023, notable references were determined (Figure 5A). A standout publication is the 2013 study by Gu-Trantien C et al., "$CD4^+$ follicular helper T cell infiltration predicts breast cancer survival" which exhibited the strongest citation burst (48). This study highlights that $CD4^+$ follicular helper T cells within tertiary lymphoid structure germinal centers can predict survival and response to neoadjuvant chemotherapy in breast cancer. Moreover, it may be the first to identify follicular helper T cells as a subset of tumor-infiltrating T cells in solid tumors.

Another significant article, "Presence of B Cells in Tertiary Lymphoid Structures Is Associated with Protective Immunity in Patients with Lung Cancer" by Germain C et al. in 2014, ranks second in strength value (49). This research demonstrates that a high density of follicular B cells correlates positively with long-term survival in both early and advanced chemotherapy-treated NSCLC patients. Additionally, patients with high densities of intratumoral follicular B cells and mature dendritic cells exhibited significantly better survival outcomes. Furthermore, the article "Tertiary Lymphoid Structures in Cancers: Prognostic Value, Regulation, and Manipulation for Therapeutic Intervention" by Sautès-Fridman C et al., published recently, holds the highest strength value (16.97) (50). These findings underscore the integral role of TLS formation and maturity in tumor progression and response to treatment interventions.

The timeline analysis reveals 710 keywords grouped into 9 large clusters (see Figure 5B), indicating the evolution of co-cited literature by keyword clustering. Recent prominence is observed with keywords like "favorable prognosis" and "sarcoma," suggesting active research engagement in TLS related to these areas. Concurrently, research on "autoimmunity" and "immune cell infiltration" has demonstrated sustained interest over time.

Notably, there has been a notable surge in TLS research related to hepatocellular carcinoma in recent years, coinciding with advancements in ICIs for HCC treatment (51). Recent studies highlight TLS as a reliable predictor of ICIs efficacy and prognosis (52, 53). This trend suggests that the predictive role of TLS in new cancer types will likely garner increased attention amid the expanding landscape of immunotherapy.

TABLE 2 The top 10 keywords for TLS research.

Rank	Count	Keywords	Rank	Centrality	Keywords
1	363	Tertiary lymphoid structures	1	0.1	Activation
2	292	B cells	2	0.09	Neogenesis
3	203	Immunotherapy	3	0.08	Expression
4	187	Survival	4	0.08	Germinal centers
5	187	Cancer	5	0.08	Receptor
6	159	Expression	6	0.07	Breast cancer
7	136	T cells	7	0.07	Antibody
8	117	Dendritic cells	8	0.07	Rheumatoid arthritis
9	109	Tumor-infiltrating lymphocytes	9	0.06	T cells
10	74	Tumor microenvironment	10	0.06	Tissue

Top 25 Keywords with the Strongest Citation Bursts

Keywords	Year	Strength	Begin	End	2014 - 2023
Sjogrens syndrome	2014	6.85	2014	2019	
Breast cancer	2014	6.73	2014	2017	
Node like structures	2014	6.68	2014	2017	
Rheumatoid arthritis	2014	6.15	2014	2019	
Lymphoid neogenesis	2014	4.09	2014	2018	
Dendritic cells	2014	3.21	2014	2017	
NF-κB	2014	3.13	2014	2019	
Lymphotoxin β receptor	2014	3.06	2014	2017	
Antigen	2014	2.89	2014	2018	
B lymphocytes	2014	2.66	2014	2016	
Autoantibody production	2014	2.64	2014	2018	
Lymphocytes	2014	2.4	2014	2016	
Neogenesis	2015	6	2015	2019	
Th17 cells	2015	3.66	2015	2019	
Multiple sclerosis	2015	2.81	2015	2016	
In vivo	2016	3.66	2016	2018	
High endothelial venules	2016	2.99	2016	2018	
Receptor	2016	2.21	2016	2020	
Prognostic significance	2016	3.42	2017	2019	
Immunity	2015	2.66	2017	2019	
Cells	2018	3.44	2018	2020	
Pedictive value	2018	2.93	2018	2019	
Inflammation	2014	2.24	2018	2020	
Infection	2019	3.12	2019	2020	
Pathogenesis	2020	2.29	2020	2023	

FIGURE 4
The top 25 keywords with the strongest citation bursts on TLS field.

A

Top 25 References with the Strongest Citation Bursts

References	Year	Strength	Begin	End	2014 - 2023
Gu-Trantien C, 2013, J CLIN INVEST, V123, P2873, DOI 10.1172/JCI67428, DOI	2013	19.37	2014	2018	
Germain C, 2014, AM J RESP CRIT CARE, V189, P832, DOI 10.1164/rccm.201309-1611OC, DOI	2014	19.23	2014	2019	
Goc J, 2014, CANCER RES, V74, P705, DOI 10.1158/0008-5472.CAN-13-1342, DOI	2014	17.78	2014	2019	
Neyt K, 2012, TRENDS IMMUNOL, V33, P297, DOI 10.1016/j.it.2012.04.006, DOI	2012	12.93	2014	2017	
de Chaisemartin L, 2011, CANCER RES, V71, P6391, DOI 10.1158/0008-5472.CAN-11-0952, DOI	2011	11.89	2014	2016	
Di Caro G, 2014, CLIN CANCER RES, V20, P2147, DOI 10.1158/1078-0432.CCR-13-2590, DOI	2014	11.51	2014	2019	
Cipponi A, 2012, CANCER RES, V72, P3997, DOI 10.1158/0008-5472.CAN-12-1377, DOI	2012	11.24	2014	2017	
Peters A, 2011, IMMUNITY, V35, P986, DOI 10.1016/j.immuni.2011.10.015, DOI	2011	10.7	2014	2016	
Martinet L, 2011, CANCER RES, V71, P5678, DOI 10.1158/0008-5472.CAN-11-0431, DOI	2011	10.7	2014	2016	
Fridman WH, 2012, NAT REV CANCER, V12, P298, DOI 10.1038/nrc3245, DOI	2012	10.67	2014	2017	
Bindea G, 2013, IMMUNITY, V39, P782, DOI 10.1016/j.immuni.2013.10.003, DOI	2013	10.44	2014	2018	
Coppola D, 2011, AM J PATHOL, V179, P37, DOI 10.1016/j.ajpath.2011.03.007, DOI	2011	9.51	2014	2016	
Rangel-Moreno J, 2011, NAT IMMUNOL, V12, P639, DOI 10.1038/ni.2053, DOI	2011	9.51	2014	2016	
Martinet L, 2013, J IMMUNOL, V191, P2001, DOI 10.4049/jimmunol.1300872, DOI	2013	9.39	2014	2018	
Pitzalis C, 2014, NAT REV IMMUNOL, V14, P447, DOI 10.1038/nri3700, DOI	2014	24.9	2015	2019	
Dieu-Nosjean MC, 2014, TRENDS IMMUNOL, V35, P571, DOI 10.1016/j.it.2014.09.006, DOI	2014	18.12	2015	2019	
Salgado R, 2015, ANN ONCOL, V26, P259, DOI 10.1093/annonc/mdu450, DOI	2015	10.85	2015	2020	
Joshi NS, 2015, IMMUNITY, V43, P579, DOI 10.1016/j.immuni.2015.08.006, DOI	2015	15.46	2016	2020	
Hiraoka N, 2015, BRIT J CANCER, V112, P1782, DOI 10.1038/bjc.2015.145, DOI	2015	12.72	2016	2020	
Barone F, 2015, P NATL ACAD SCI USA, V112, P11024, DOI 10.1073/pnas.1503315112, DOI	2015	11.88	2016	2019	
Finkin S, 2015, NAT IMMUNOL, V16, P1235, DOI 10.1038/ni.3290, DOI	2015	11.35	2016	2020	
Fleige H, 2014, J EXP MED, V211, P643, DOI 10.1084/jem.20131737, DOI	2014	9.12	2016	2019	
Sautès-Fridman C, 2016, FRONT IMMUNOL, V7, P0, DOI 10.3389/fimmu.2016.00407, DOI	2016	16.97	2017	2021	
Kroeger DR, 2016, CLIN CANCER RES, V22, P3005, DOI 10.1158/1078-0432.CCR-15-2762, DOI	2016	15.81	2017	2021	
Dieu-Nosjean MC, 2016, IMMUNOL REV, V271, P260, DOI 10.1111/imr.12405, DOI	2016	14.41	2017	2021	

B

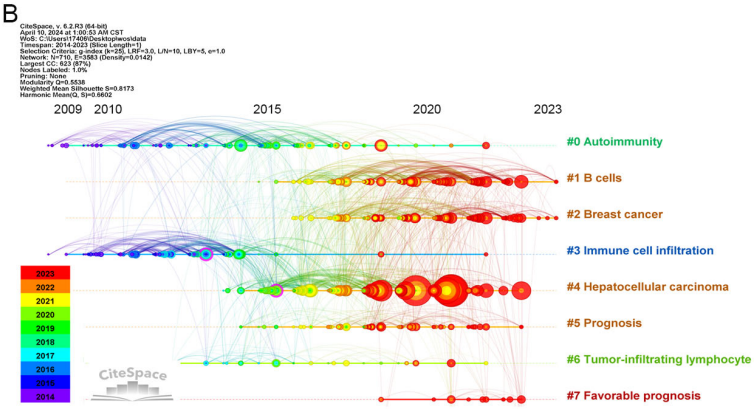

FIGURE 5
Analysis of literature references. **(A)** Top 25 references with the strongest citation bursts (sorted by the beginning year of burst). **(B)** The Timeline of co-cited literature related to TLS.

Analysis of references underscores the dynamic change of TLS research, reflecting both emerging trends and enduring themes in understanding their impact across different cancers and immunotherapeutic strategies.

3.4 Top contributing authors and institutions

A co-authorship network analysis utilizing "VOSviewer" software illustrates collaborative efforts among authors in TLS research spanning from 2014 to 2024. Among 5,739 authors, 224 have contributed three or more publications, resulting in the identification of 6 major network clusters (Figure 6A).

The top three authors by publication count are Catherine Sautes-Fridman (21), Wolf Herman Fridman (19), and Dieu-Nosjean Marie-Caroline (16) (Table 3), all affiliated with French research organizations. Their collaborative efforts have yielded numerous impactful articles in the TLS field (49, 54, 55). Similarly, Soizic Garaud, Denis Larsimont, and Karen Willard-Gallo hold the highest total link strength values (108), representing significant collaborative networks within Belgian research institutions (56, 57). In recent years, Alessandra Vaccaro and Anna Dimberg from Sweden, among others, have made notable

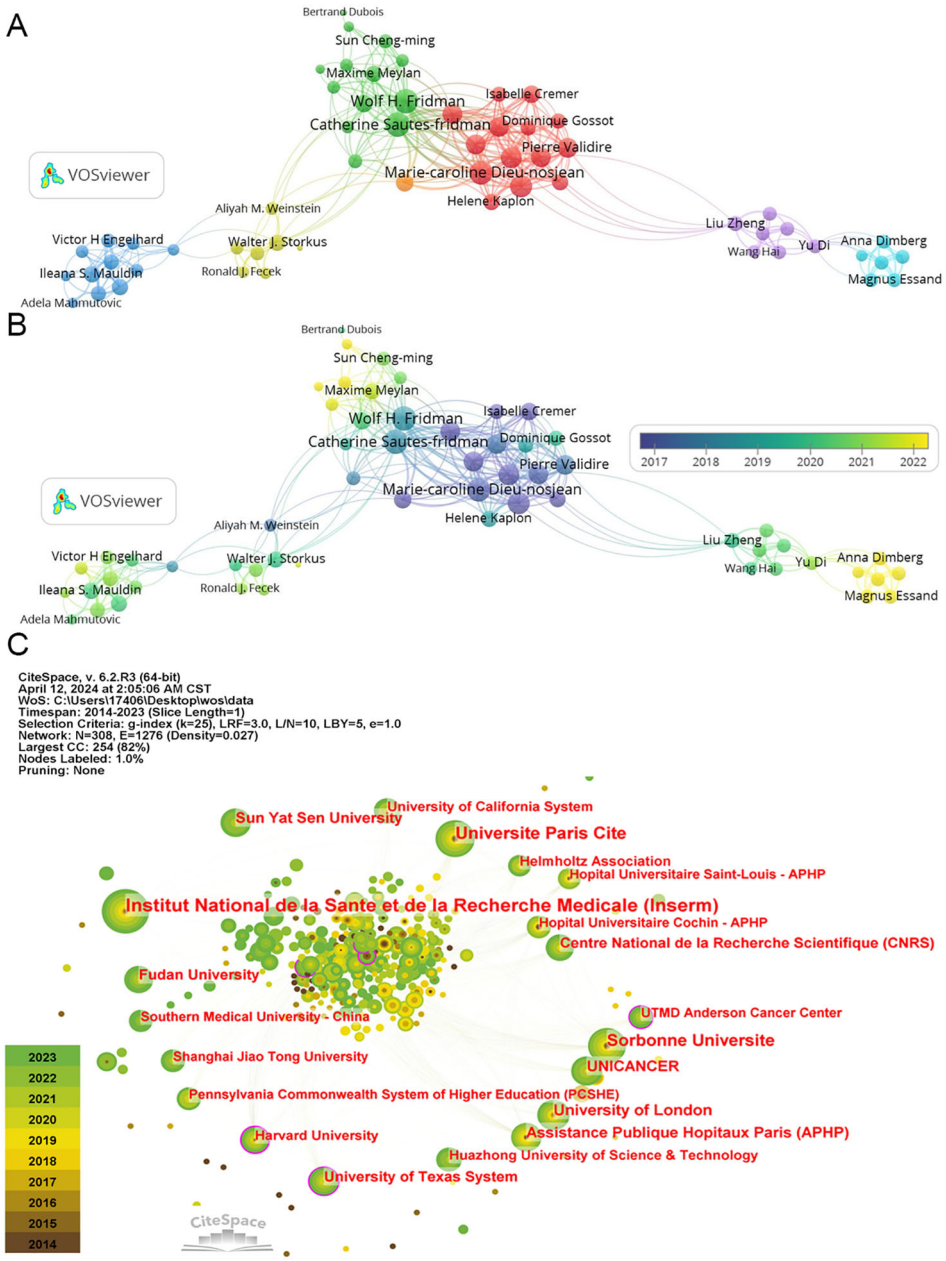

FIGURE 6
The co-authorship of authors and institutions. **(A)** The co-authorship network clusters of authors. **(B)** The co-authorship network timeline of authors. **(C)** The network of institutions.

TABLE 3 The 18 most productive authors for TLS research.

Author	Documents	Citations	Total link strength	Author	Documents	Citations	Total link strength
Catherine Sautes-Fridman	21	3744	104	Denis Larsimont	10	879	108
Wolf-H. Fridman	19	3605	100	Walter J. Storkus	10	412	27
Dieu-Nosjean Marie-Caroline	16	2416	85	Karen Willard-Gallo	10	879	108
Michele Bombardieri	11	911	24	Francesca Barone	9	413	34
Soizic Garaud	11	882	108	Alexandre De Wind	9	866	100
Claire Germain	11	1674	72	In Ah Park	9	521	56
Gyungyub Gong	11	550	64	In Hye Song	9	910	18
Hee Jin Lee	11	550	64	Costantino Pitzalis	9	768	25
Craig L. Slingluff	11	330	35	Karina Silina	9	521	56

contributions with multiple publications on glioma-associated TLS (Figure 6B) (58, 59). While these authors are highlighted, it's important to acknowledge the diverse contributions of others who have propelled TLS research forward.

In terms of institutional contributions, node sizes denote the number of publications, while centrality reflects the influence of links passing through each node. Notably, TLS has garnered substantial attention across numerous research institutions. The top five institutions by publication volume include "Institut National de la Sante et de la Recherche Medicale" (70), "Universite Paris Cite" (49), "Sorbonne Universite" (45), "University of London" (33), and "UNICANCER" (30) (Figure 6C; Table 4). Recent years have seen increasing focus from Chinese research organizations like "Fudan University" (24) and "Sun Yat-sen University" (28), underscoring their emerging role in TLS research.

Moreover, institutions like "Harvard University" and "the University of Texas System", marked with a purple ring denoting high centrality nodes, serve as pivotal connectors in the scholarly communication and collaboration network within this domain. Maybe their influence extends across various research teams, facilitating interdisciplinary advancements in TLS research.

3.5 Distribution of the top cited journals

Using "CiteSpace" software, a dual map overlay of journals reveals the distribution of citing and cited journals in TLS research. On the left side, representing citing journals, prominent disciplines include Molecular/Biology/Immunology and Dentistry/Dermatology/Surgery, which primarily cite publications in Molecular Biology/Genetics journals (Figure 7A).

TLS-related articles have been published across 290 academic journals, with 109 journals contributing two or more articles. Leading the publication count are "Frontiers in Immunology" (119), "Cancers" (30), "Journal for Immunotherapy of Cancer" (28), "Oncoimmunology" (27), and "Nature Communications" (17) (Table 5). "Frontiers in Immunology" stands out as a central

TABLE 4 Top 10 most productive institutions for TLS research.

Rank	Institutions	Count	Centrality	Year
1	Institut National de la Sante et de la Recherche Medicale (Inserm)	70	0.07	2014
2	Universite Paris Cite	49	0.05	2014
3	Sorbonne Universite	45	0.05	2014
4	University of London	33	0.07	2014
5	UNICANCER	30	0.01	2018
6	Assistance Publique Hopitaux Paris (APHP)	29	0.07	2014
7	Sun Yat Sen University	28	0.01	2020
8	University of Texas System	24	0.14	2017
9	Fudan University	24	0.02	2020
10	Centre National de la Recherche Scientifique (CNRS)	24	0.07	2018

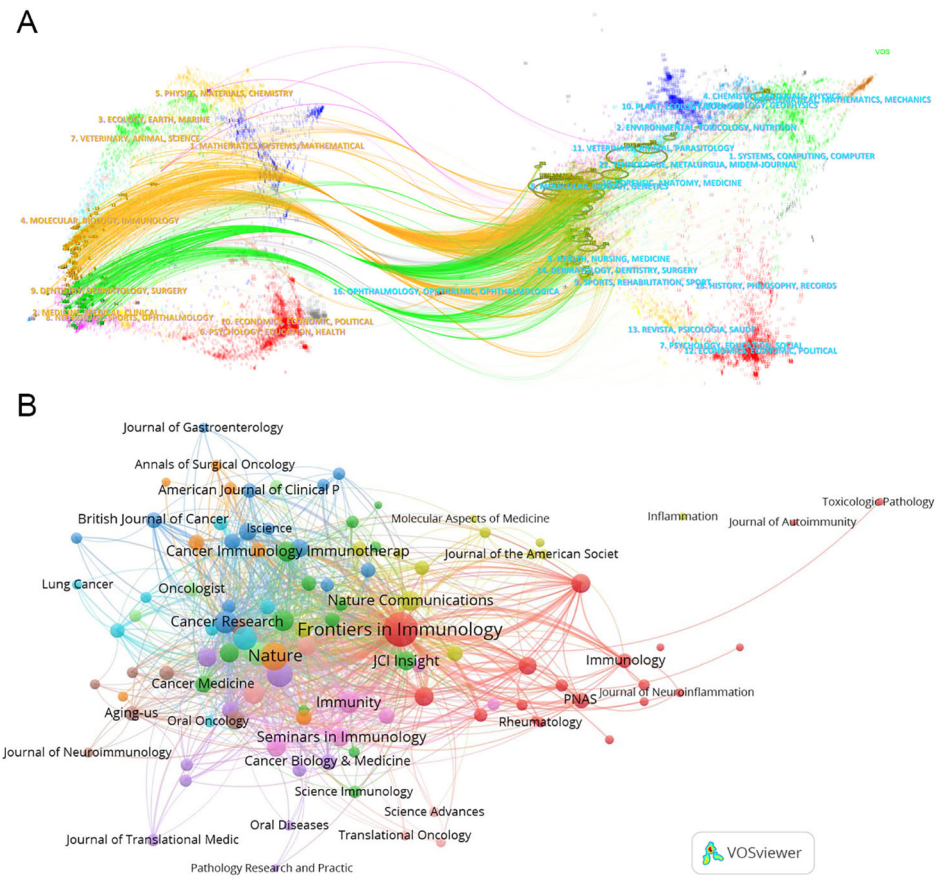

FIGURE 7
Collaboration among journals. **(A)** The dual map overlay of journals. This map uses different colors to symbolize the journals in different disciplines. The map can be divided into two parts, the left side is the distribution of the cited journals, which represents the main disciplines of Science mapping, and the right side is the distribution of the cited journals. **(B)** The network map of cited journals.

player in the network of journal associations (Figure 7B). However, the most cited journal in TLS research is "Nature" (cited 3230 times). The top three most highly cited articles on TLS were all published in "Nature." For instance, Helmink BA et al.'s article titled "B cells and tertiary lymphoid structures promote immunotherapy response" has amassed 1186 citations (60).

This analysis illustrates a complex network of journal relationships in TLS research, highlighting key journals and influential articles that have shaped the discourse and advancements in the field.

4 Discussion

Our findings demonstrate a rapid growth in studies focusing on TLS over the past decade, driven by advancements in immunotherapy, particularly ICIs, which have revolutionized anti-tumor treatments. Concurrently, there is a burgeoning understanding of the tumor immune microenvironment, where TLS plays a pivotal role. Based on the results analyzed above, we will further summarize and discuss the research value of TLS in terms of significant advancements, current status, clinical applications, and challenges.

4.1 Significant advancements and current status

Autoimmune diseases are closely associated with dysregulated immunity, and the formation and maturation of TLS may play a significant role in this process. Furthermore, TLS in various immune disorders may exhibit distinct characteristic cell populations. For instance, Th17 cells are implicated in developing autoimmune encephalomyelitis within the central nervous system (61). Similarly, the enrichment of Th17 cells is closely linked to the progression of follicular pancreatitis (62). Other subtypes of peripheral helper T cells and follicular helper T cells also contribute to the formation and maturation of TLS in immune disease lesions, including rheumatoid arthritis, Sjögren syndrome, and systemic lupus erythematosus (63, 64). Additionally, other immune cell subsets within TLS, such as dendritic cells, B lymphocytes, and macrophages, have been shown to play diverse roles in the development and progression of autoimmune diseases (11, 65). Emerging technologies, such as single-cell sequencing, are increasingly being utilized to analyze cell subsets in TLS associated with autoimmune diseases (11, 66, 67). These advanced techniques may offer valuable insights for identifying a broader range of immune cell subsets and elucidating their mechanisms of action.

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TABLE 5 Top ten produced (left) journals and cited journals (right) related to the research for TLS research.

Rank	Source	Documents	IF-2023	Rank	Source	Citations	Total link strength
1	Frontiers in immunology	119	7.3	1	Nature	3230	646
2	Cancers	30	5.2	2	Frontiers in Immunology	2929	1539
3	Journal for Immunotherapy of Cancer	28	10.9	3	Oncoimmunology	1155	482
4	Oncoimmunology	27	7.2	4	Nature Medicine	1088	124
5	Nature Communications	17	16.6	5	Nature Reviews Immunology	1074	143
6	Frontiers in Oncology	15	4.7	6	Clinical Cancer Research	837	222
7	Cancer Immunology Immunotherapy	11	5.8	7	Cancer Immunology Research	812	190
8	Clinical Cancer Research	9	11.5	8	Nature Communications	811	187
9	Plos One	9	3.7	9	Cancer Research	808	244
10	PNAS	9	11.1	10	Journal for Immunotherapy of Cancer	708	316

Advancements have also been made in understanding the mechanisms of action and predictive value of immune cell subsets in tumors. Early studies have indicated that B cell enrichment in TLS is associated with a favorable prognosis in various cancers, including lung cancer, pancreatic cancer, gastric cancer, and melanoma (49, 60, 68, 69). The application of single-cell sequencing, spatial transcriptomics, and immunohistochemistry aims to identify B cells with specific markers in TLS. For instance, TCL1A-expressing B cells have been linked to oral squamous cell carcinoma, distinct B cell subsets have been identified in nasopharyngeal carcinoma, an interferon-stimulated B cell subtype has been associated with muscle-invasive bladder cancer, and CD20+CD22+ADAM28+ ICI-responsive B cells have also been characterized (70–73).

An increasing number of T cell subtypes within TLS have been analyzed. For instance, TCF1/TCF7-positive T cells located in and around TLS are associated with a better prognosis for oral cancer (74). Chemokine (CXCL13)-high-expressing T cells are also believed to be critical for TLS maturation, thereby influencing tumor progression (75–77). Furthermore, different T cell subtypes within TLS may produce opposing anti-tumor effects (74, 78–80). Additionally, immune cells such as dendritic cells, macrophages, and natural killer cells within TLS play essential roles in shaping the tumor immune microenvironment (81, 82). These immune cells are also continuously being identified and evaluated (65, 83, 84).

Due to their small size, diverse shapes, and multifocal spatial distribution, TLS present a significant challenge for pathologists and physicians in determining their nature. Consequently, researchers are exploring additional markers beyond the commonly used ones, such as CD20, CD4, and CD8. For instance, CD23 expression, a TLS-specific marker, has been found to be positively correlated with disease-free survival and overall survival in breast cancer (85). L1CAM is also recognized as a reliable marker for mature TLS associated with endometrial cancer (86). Furthermore, BCL6-expressing B cells and CD21-positive follicular dendritic cells have been shown to be concentrated in TLS in ovarian cancer (87). Similarly, LGALS2 has been identified as a key marker within TLS in breast cancer, demonstrating a positive correlation with prolonged survival (84). It is likely that more markers will be revealed in the future.

Another point of interest is the relationship between TLS maturity and tumor progression. Several studies have demonstrated that mature TLS is positively correlated with the prognosis of solid tumors treated with ICIs (88–90). This correlation may be linked to the enrichment of immunologically activated cells within mature TLS (13, 91). In contrast, immature TLS appears to be enriched with immunosuppressive immune cells and exhibits immunosuppressive characteristics (32, 83, 92). Immature TLS is likely to contribute to resistance against ICIs (93). For instance, peritoneal metastases derived from gastric cancers are often enriched with tumor-infiltrating macrophages and regulatory T cells, while exhibiting a reduced presence of plasma cells, thereby creating an immunosuppressive microenvironment (83). It is likely that increasing differences between TLS in various cancer types and metastatic lesions will be identified and assessed.

4.2 Clinical applications

The search for reliable prognostic markers for immunotherapy has long been a focus of clinical research. However, dependable markers with broad applicability are still lacking in solid tumors (94, 95). TLS appears to be a promising candidate (96). Results from several clinical trials have demonstrated that TLS is one of the biomarkers associated with responses to neoadjuvant immunotherapy in conditions such as hepatocellular carcinoma, NSCLC, urothelial cancer, and esophageal squamous cell carcinoma (97–100). These findings suggest that effective ICIs treatment may promote TLS maturation, thereby creating a positive feedback loop. Furthermore, several studies have indicated a close association between chemotherapy and TLS, with chemotherapy also capable of inducing TLS maturation, which may enhance the efficacy of immunotherapy (101–104). The results of multiple clinical studies have shown that neoadjuvant immunochemotherapy combinations exhibit superior efficacy compared to either neoadjuvant chemotherapy or neoadjuvant immunotherapy alone (105–107). The maturity of TLS may be one of the influencing factors in this context. It is anticipated that effectively inducing intratumoral TLS maturation will become a focal point of research in the future.

4.3 Challenges of TLS

As previously mentioned, the predictive efficacy of mature TLS and immature TLS against tumors may be contradictory. Furthermore, TLS located in different regions of a tumor may exhibit distinct cellular compositions, resulting in variations in the immune microenvironment. These factors raise concerns about the reliability of using TLS as prognostic biomarkers, particularly given the inherent differences among various cancer types. Therefore, it may be beneficial to identify TLS with specific markers in particular cancers as predictive factors. However, due to the complexity and diversity of TLS structures, standardized diagnostic criteria remain lacking, despite the ongoing application of techniques such as immunohistochemistry, hematoxylin and eosin staining, and gene sequencing. The introduction of new diagnostic methods not only increases the costs associated with learning and treatment but may also hinder their widespread implementation. Lastly, the mechanisms underlying the transformation from immature TLS to mature TLS are not yet fully understood, and the distinctions between TLS in primary lesions and those in metastatic lesions are not completely recognized. These challenges may continue to motivate the scientific community to further investigate TLS, and we anticipate more positive outcomes in the future.

5 Limitation

The study still has a few limitations. First, the data associated with the TLS were sourced from a single database (the WOSCC) so that they would accommodate the data format for bibliometric tools in all "VOSviewer", "CiteSpace", and "bibliometrics". This could have led to selection bias. There are other data sources, such as PubMed or Scopus, that can usually only be used effectively with one of the bibliometric tools (usually "VOSviewer"). To reduce selection bias, we used three bibliometric tools to conduct a comprehensive analysis. In addition, our study only included articles published in English, which may have led to the presence of language bias. In order to obtain a more comprehensive analysis, it might be more appropriate for future investigations to include publications in languages beyond English.

6 Conclusion

This study systematically reviewed global publications on TLS, analyzed their bibliometric characteristics, and identified influential articles. In summary, our bibliometric analysis has traced the evolution of TLS research and highlighted shifting research priorities over the past decade. These findings provide valuable insights into the pivotal role of TLS in immunotherapy and offer glimpses into future directions for this rapidly evolving field.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

YB: Conceptualization, Formal analysis, Methodology, Visualization, Writing – original draft. ZM: Conceptualization, Formal analysis, Methodology, Visualization, Writing – original draft. SW: Conceptualization, Formal analysis, Writing – original draft. JL: Conceptualization, Writing – original draft. HZ: Conceptualization, Writing – original draft. YX: Conceptualization, Writing – original draft. HJ: Conceptualization, Writing – original draft. TQ: Conceptualization, Writing – original draft, Writing – review & editing. ZZ: Funding acquisition, Supervision, Validation, Visualization, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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