

Application of Liquid Biopsy Technology in Lung Cancer: A Bibliometric Study and Visualization Analysis

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Background: Lung cancer is a major global health threat, and traditional treatments are hindered by tumor heterogeneity and drug resistance. Liquid biopsy technology offers new opportunities for precise diagnosis and treatment of lung cancer; however, its clinical application still presents challenges. Therefore, we aimed to elucidate the research progress and future trends of liquid biopsy technology through a bibliometric analysis.

Methods: Literature on liquid biopsy technology in lung cancer research spanning from 1990 to 2024 was retrieved from the Web of Science Core Collection. Various bibliometric tools were employed, including VOSviewer (1.6.20), Cite Space (6.2.R3), RStudio (utilizing the R package bibliometrix), and Scimago Graphica, to explore the current situation and research hotspots in this area. The research covered multiple aspects, including publication counts, contributions from different countries and institutions, journals involved, authorship, co-references, and keywords. By generating corresponding visualization maps, an attempt was made to forecast future development trends within this research field.

Results: We identified 363 articles published in 198 journals, authored by 2518 authors from 266 institutions across 54 countries/regions. The journal, country, institution, and author with the highest number of publications were Cancer, China, Harvard University, and ROLFO C. Over the past 34 years, research on the application of liquid biopsy technology in lung cancer have primarily focused on cancer diagnosis, biomarkers, and treatment monitoring.

Conclusion: Liquid biopsy technology is rapidly evolving in the field of lung cancer. Detecting biomarkers such as circulating tumor DNA, circulating tumor cells, and extracellular vesicles, facilitates early detection and monitoring of treatment response, reveals drug resistance mechanisms, and promotes personalized treatment. With the advancement of technology and international cooperation, liquid biopsy is expected to provide more accurate diagnosis and treatment for patients with lung cancer in the future.

Keywords: liquid biopsy technique, tumor, bibliometric tools, bibliometrics, citespace, VOSviewer

Introduction

Lung cancer remains the leading cause of cancer-related mortality worldwide. Patients are often asymptomatic in the early stages, but as the disease progresses, patients may develop persistent symptoms, such as chronic cough, chest pain, and dyspnea.^{1,2} According to the latest epidemiological data, in 2022, lung cancer ranked first in incidence and mortality among all malignant tumors in China, while in the United States, it remained the leading cause of cancer-related death despite ranking third in incidence.³ Multiple factors influence the prognosis of lung cancer, including histological type, disease stage at diagnosis, patient age, and overall health status.⁴⁻⁶ Consequently, elucidating its pathogenesis is essential for developing novel therapeutic strategies and improving patient outcomes.^{7,8}

Liquid biopsy technology, an emerging non-invasive diagnostic tool, enables early diagnosis, real-time monitoring, and prognostic evaluation of tumors by analyzing biomarkers in the blood, such as circulating tumor cells (CTCs), circulating tumor DNA (ctDNA), and exosomes.⁹⁻¹⁵ Recent studies have shown that liquid biopsy technology has

advanced rapidly in lung cancer research and has become a research hotspot. It can assist in early diagnosis, evaluate treatment effectiveness in real-time, and adjust treatment plans promptly. Its potential application and future development direction in clinical practice have attracted considerable attention.^{12,13,16–20}

Bibliometrics is a method of revealing scientific development trends and research hotspots through quantitative analysis of literature data.²¹ It can reflect the development trends and research hotspots of a certain field by analyzing data on countries, authors, journals, institutions, and keywords in that field. Considering the compatibility with bibliometric analysis tools, such as CiteSpace and VOSviewer, the Web of Science Core Collection (WoSCC) was selected as the sole data source due to its comprehensive coverage, structured records, and standardized indexing. At present, there is no research on the application of liquid biopsy technology in lung cancer using bibliometric methods. Therefore, we aimed to use bibliometric tools to comprehensively analyze the research and application of liquid biopsy technology in lung cancer from multiple perspectives, as well as the current development status, future research trends, and hotspots in this field.

Materials and Methods

Data Sources and Literature Retrieval

All bibliographic data were obtained from the WoSCC database. The search period spanned January 1, 1990, to September 30, 2024. The retrieval strategy combined subject terms for lung cancer and liquid biopsy techniques, using this search formula: (TS=“Lung Neoplasms” OR “Neoplasms, Pulmonary” OR “Neoplastic, Pulmonary” OR “Pulmonary Neoplasms” OR “Neoplasms, Lung” OR “Lung Neoplasms” OR “Neoplastic, Lung” OR “Lung Cancer” OR “Cancer, Lung” OR “Lung Cancer” OR “Cancer of Lung” OR “Pulmonary Cancer” OR “Cancer, Pulmonary” OR “Cancer, Pulmonary” OR “Cancer, Pulmonary” OR “Cancer, Pulmonary Cancer” or “Cancer of the Lung”) and TS= (liquid biopsy techniques).

Eligibility Criteria and Data Standardization

We included original research articles and review papers that focused on the application of liquid biopsy technology in lung cancer, were written in English, and provided complete bibliographic metadata (title, authors, affiliations, country, keywords, and source, amongst others). We excluded non-research documents, such as conference abstracts, patents, news items, and popular health articles, as well as duplicate records identified during screening. The retrieved records were exported in RefWorks and plain-text formats and subjected to a standardized preprocessing workflow comprising removal of special characters and formatting artifacts, harmonization of synonymous terms and abbreviations (standardizing variants such as “NSCLC” and “non-small cell lung cancer”), and conversion to analytics-ready formats using the Data Import/Export function in CiteSpace.

Data Analysis

We conducted a comprehensive bibliometric analysis using Microsoft Excel, VOSviewer (v1.6.20), CiteSpace (v6.2.R3), RStudio (with the bibliometrix package), and Scimago Graphica across a 34-year period from January 1990 to September 2024, with 1-year time slices. We used Excel to quantify annual publication volumes, track country-level outputs over time, and classify records by research category. RStudio/bibliometrix was used to generate visual mappings of journal sources, national contributions, international collaboration, co-cited references, keyword frequencies, and author activity. CiteSpace was used to examine institutional collaboration networks and centrality as well as to detect keyword clusters and burst terms. Node types included keyword and institution co-occurrence, and pruning was kept at default settings. VOSviewer was used to support the analyses of co-cited references, while Scimago Graphica was used to refine author and keyword frequency visualizations. Co-occurrence, clustering, and burst analyses were integrated to produce optimized knowledge maps for visualization-driven interpretation. The overall retrieval and analysis workflow is summarized in [Figure 1](#).

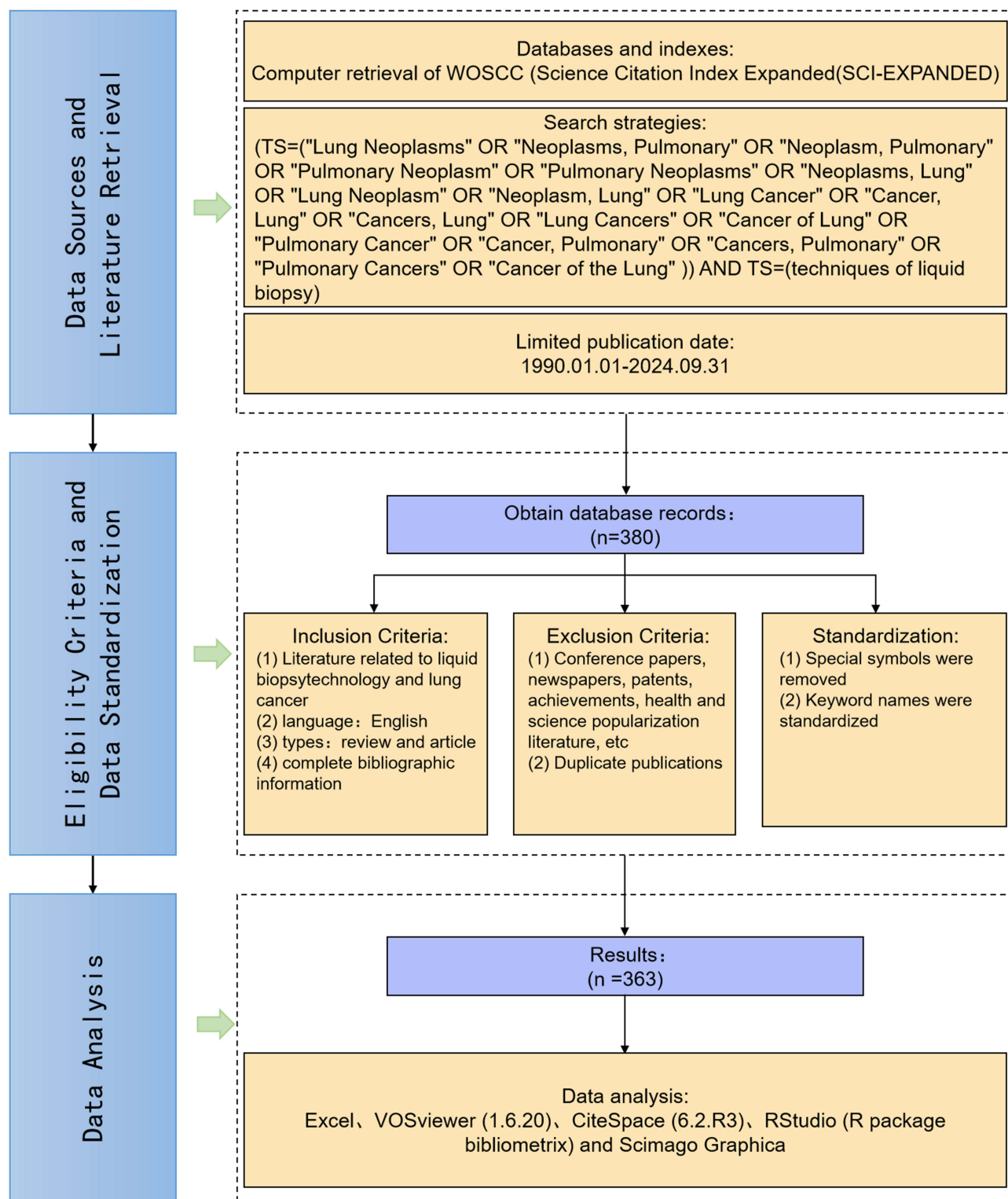


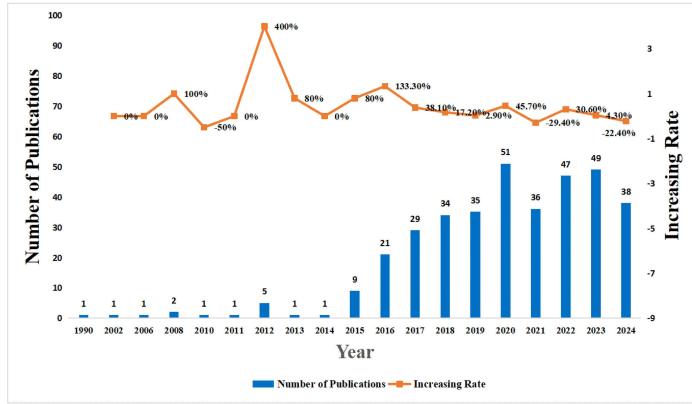
Figure 1 Flowchart illustrating the screening process for literature selection.

Results

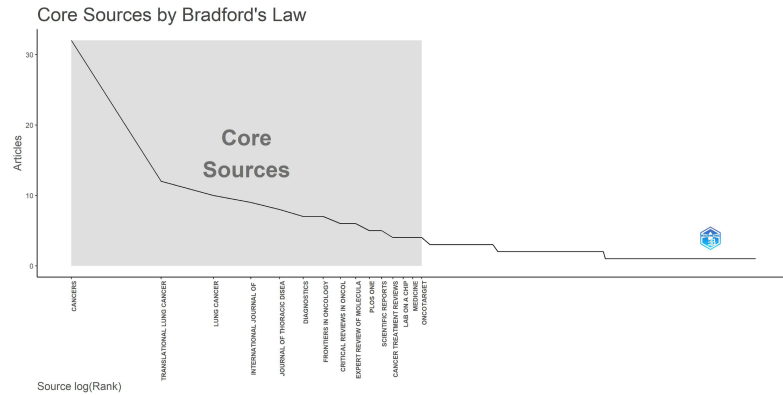
Analysis of Publication Year and Journal Source

Publication activity on liquid biopsy in lung cancer remained modest until 2015 and then increased steadily (Figure 2A). The first article appeared in 1990; annual output remained below 10 until 2015, peaking at 51 in 2020. Two growth spurts

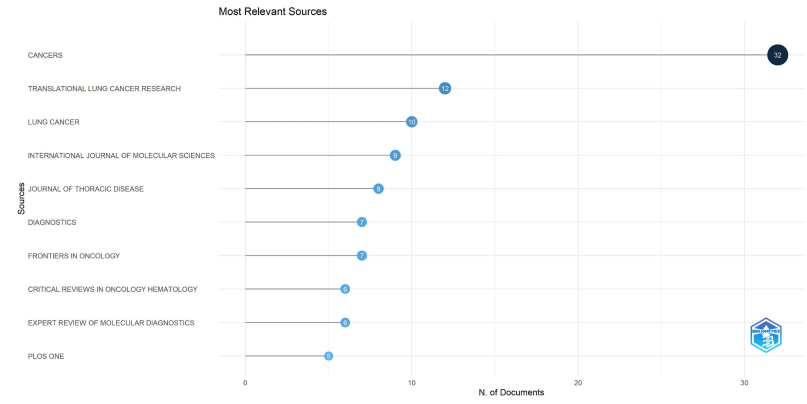
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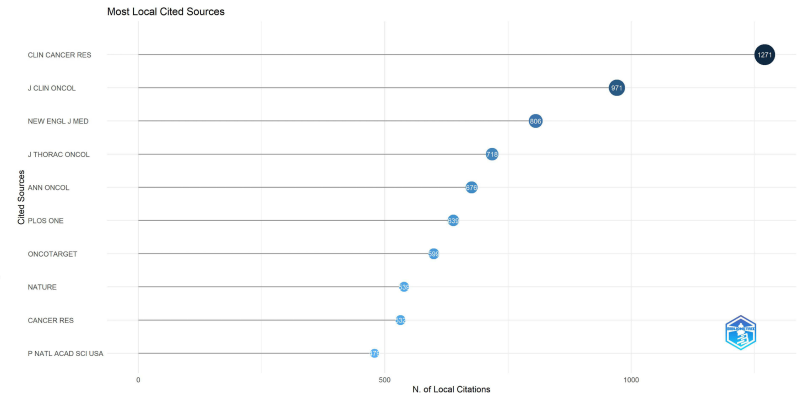


Figure 2 (A) Annual distribution of publications; **(B)** Top 10 journals ranked by the number of published articles; **(C)** Core journals identified according to Bradford's Law; **(D)** Top 10 journals most frequently cited in the included publications.

(2011–2012 and 2014–2016) likely reflect contributions from the Lv Ming and Li Dai-Rong teams. From 2016 to 2024, output maintained an upward trajectory.

Across 198 journals, *Cancers* (n=32), *Translational Lung Cancer Research* (n=12), and *Lung Cancer* (n=10) contributed the largest volumes (Figure 2B). According to Bradford’s law, the core outlets are *Cancers*, *Translational Lung Cancer Research*, *Lung Cancer*, *International Journal of Molecular Sciences*, and *Journal of Thoracic Disease* (Figure 2C). Notably, influence is not fully captured by volume alone: *Clinical Cancer Research* amassed the highest total citations (n=1,271) within our dataset (Figure 2D), illustrating that citation-based indicators (such as citations per paper [CPP] or h-index) provide complementary nuance beyond publication counts. Temporal journal dynamics further show *Translational Lung Cancer Research* peaking in 2016 (n=4) and *Cancers* in 2022 (n=4) (Figure 3A). Dual-map overlays indicate cross-disciplinary citation flows from *Molecular Biology-Genetics* toward *Molecular Biology-Immunology* and *Medicine-Clinical* domains (Figure 3B).

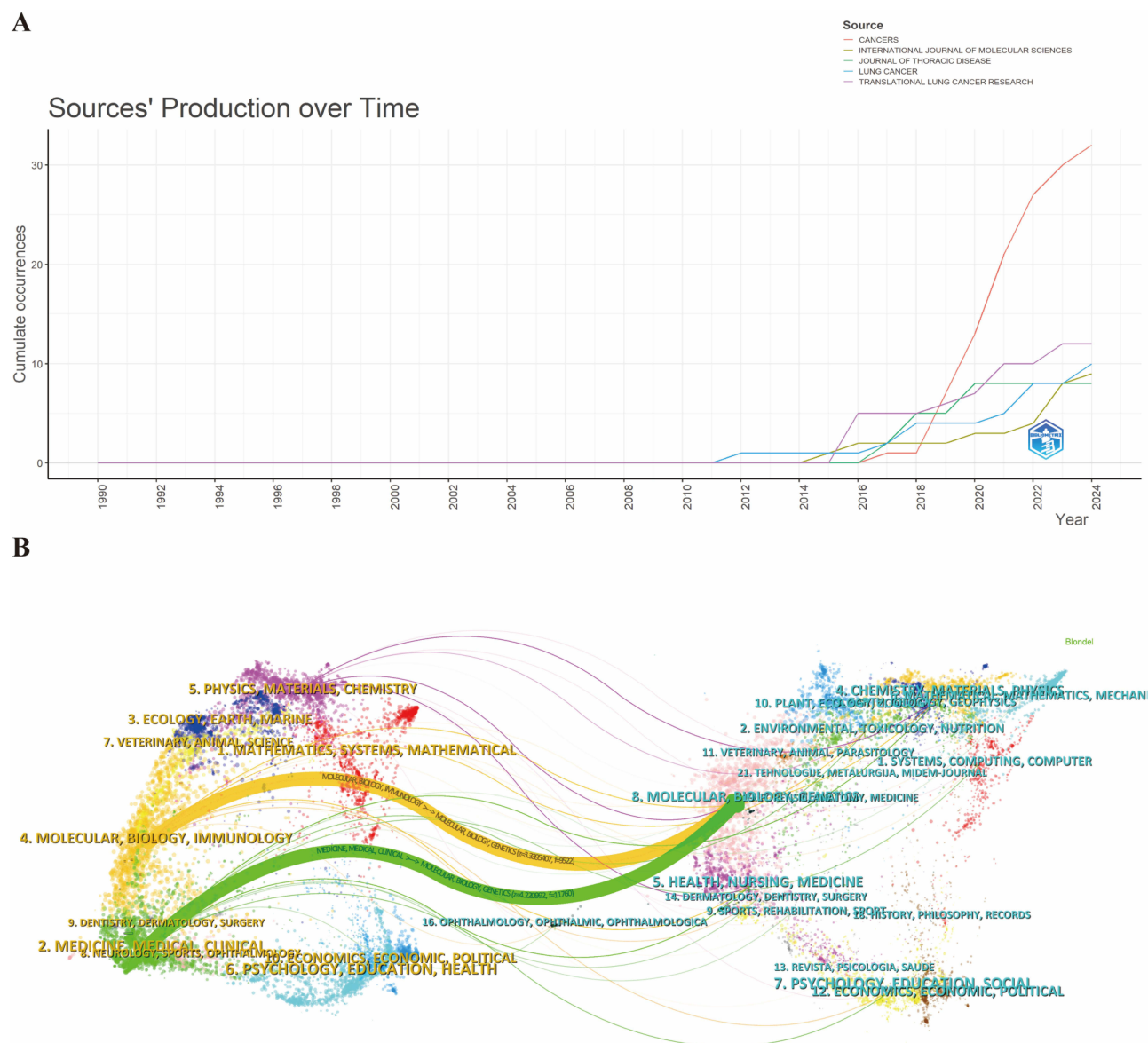


Figure 3 (A) Annual publication trends of the top five journals by volume; (B) Dual-map overlay illustrating citation relationships, showing clusters of citing and cited journals.

Visualization Analysis of International Cooperation

Fifty-four countries/regions contributed to this literature (Figure 4A). By output, the top 10 were China (n=384), USA (n=248), Spain (n=235), Italy (n=159), France (n=94), Belgium (n=61), Germany (n=58), United Kingdom (n=54), India (n=53), and South Korea (n=42) (Table 1). By total citations, the USA ranked first (n=2,683), followed by China (n=1,858) and Italy (n=1,111) (Figure 4B). To avoid conflating productivity with impact, we assessed citation intensity where feasible. For example, CPP was higher for the USA (~10.8; 2,683/248) than for China (~4.8; 1,858/384), underscoring differences in per-article influence that publication volume alone cannot convey.

Collaboration maps (Figures 4C and D) depict international ties; line thickness represents link weight (co-authorship counts). The USA shows multiple high-weight links, indicating broad, intensive collaborations. Figure 4E indicates that

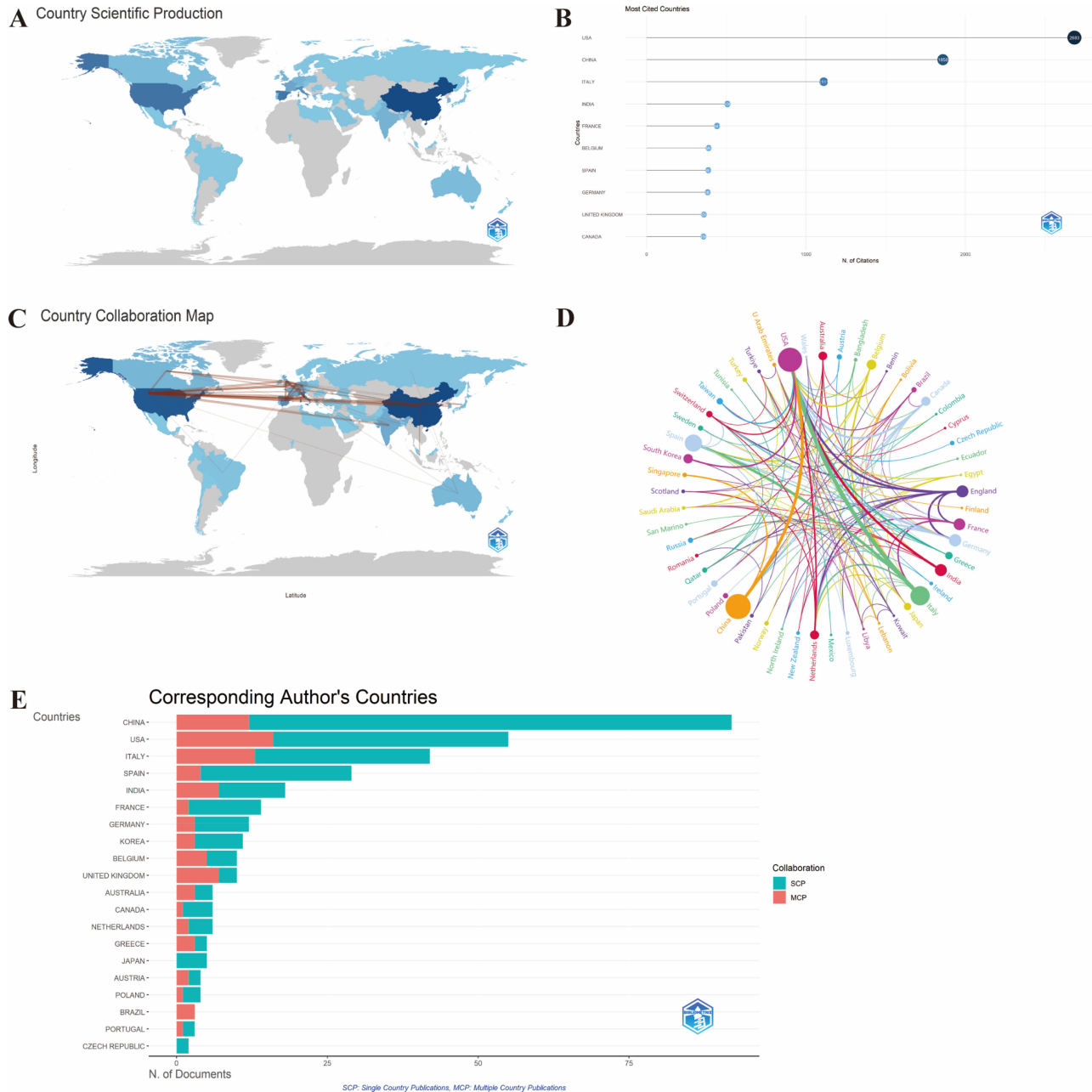


Figure 4 (A) Geographic distribution of publications by country; (B) Top 10 most-cited countries ranked by publication count; (C) Distribution of international collaborative research; (D) Chord diagram illustrating global collaboration patterns; (E) Top 20 countries ranked by the number of corresponding authors.

Table 1 Top 10 Most Productive Countries/Regions

Rank	Country	Frequency
1	China	384
2	USA	248
3	Spain	235
4	Italy	159
5	France	94
6	Belgium	61
7	Germany	58
8	England	54
9	India	53
10	South Korea	42

China accounts for 25.3% of global output, followed by the USA (15.2%) and Italy (11.6%). By collaboration type, China had the most single-country publications (SCP, $n=80$), suggesting predominantly domestic teamwork, whereas the USA showed a higher proportion of multiple-country publications (MCP, 29.1%), reflecting stronger international engagement. MCP% should be interpreted in the context of the denominator: countries with small absolute outputs (Brazil at 100% MCP) can exhibit inflated MCP proportions that overstate reliance on foreign partnerships. Where available, network statistics (such as betweenness centrality and weighted degree) provide more objective assessments of structural importance than MCP% alone.

Visualization Analysis of Authors' and Institutions' Collaboration

The 363 included publications were authored by 2,518 researchers. Rolfo C (Icahn School of Medicine at Mount Sinai) was the most prolific author ($n = 11$) and also the most cited ($n = 25$) (Figures 5A–C). Based on Price's law ($Mp = 0.749 \times \sqrt{Np_{max}} = 2.48$), authors with ≥ 3 publications were designated as core authors, yielding 72 contributors. The co-authorship network (Figure 5E) revealed four major collaborative clusters, led by Rosell Rafel, Rolfo Christian, Provincio Mariano, and Malapele Umberto, with research themes centering on circulating biomarker detection and analysis.²² These collaborations reflect the pivotal role of liquid biopsy in monitoring tumor dynamics, detecting drug resistance, predicting therapeutic response, and supporting personalized treatment, particularly in patients with non-small cell lung cancer (NSCLC).^{15,23,24}

Institutional collaboration mapping identified 266 nodes and 739 links. Table 2 presents the top 10 institutions in lung cancer liquid biopsy research, ranked by publication quantity and network centrality to reflect research productivity and collaborative influence. Harvard University ranked first in publication volume ($n = 14$), with research primarily addressing the clinical potential and technical challenges of liquid biopsy.^{11,25–27} Centro de Investigación Biomédica en Red (CIBER) ranked second ($n = 11$). The Chinese Academy of Sciences and Brigham & Women's Hospital each displayed the highest betweenness centrality (0.19), underscoring their bridging roles in international collaboration. Notably, Harvard University, CIBER, CIBERONC, the Chinese Academy of Sciences, and UNICANCER formed a closely connected network, suggesting the presence of sustained and high-impact cross-regional cooperation.

Analysis of Cited Literature

The most cited articles were authored by Sorber L (2017, Lung Cancer),²⁸ Kapeleris J (2018, Frontiers in Oncology),²⁹ and Cescon DW (2020, Nature Cancer) (Figure 6A),³⁰ all focusing on ctDNA and CTCs for NSCLC management. Citation burst analysis (Figure 6B) revealed six articles with recent surges, pointing to emerging research priorities including minimal residual disease detection,³¹ cell-free (cfDNA) fragmentation/methylation profiling,^{32–34} blood tumor mutational burden (bTMB) prediction for immunotherapy,^{23,35} and advanced early detection approaches.³⁶

Thematic coupling (Figure 6C) identified five clusters: biomarkers, ctDNA, molecular detection strategies, CTCs, and treatment monitoring. Citation clustering (Figures 6D–E) confirmed the prominence of cfDNA in treatment response assessment and monitoring. Persistent clusters, such as “Lung cancer management” and “Liquid biopsy technique” reflect

Table 2 Leading Institutions in Lung Cancer Liquid Biopsy Research: Top 10 by Publication Quantity and Network Centrality

Rank	Institutions	Publications	Rank	Institutions	Centrality
1	Harvard University	14	1	Chinese Academy of Sciences	0.19
2	CIBER - Centro de Investigacion Biomedica en Red	11	2	Brigham & Women's Hospital	0.19
3	Chinese Academy of Sciences	11	3	Feinberg School of Medicine	0.17
4	CIBERONC	10	4	Memorial Sloan Kettering Cancer Center	0.12
5	UNICANCER	9	5	Ann & Robert H. Lurie Children's Hospital of Chicago	0.12
6	University of Naples Federico II	9	6	UNICANCER	0.1
7	Institut National de la Sante et de la Recherche Medicale (Inserm)	9	7	Institut National de la Sante et de la Recherche Medicale (Inserm)	0.08
8	Peking University	9	8	CIBERONC	0.07
9	Harvard Medical School	8	9	Autonomous University of Barcelona	0.07
10	Chinese Academy of Medical Sciences - Peking Union Medical College	7	10	Dana-Farber Cancer Institute	0.06

Notes: Left: Top 10 institutions by publication quantity in lung cancer liquid biopsy research. Right: Top 10 institutions by network centrality in lung cancer liquid biopsy research.

ongoing research pillars, while newer clusters on “Clinical application” and “Phenotypic characterization” suggest a shift toward translational and practice-oriented investigations.

Keyword Visualization Analysis

Keyword visualization analysis revealed 48 high-frequency terms (≥ 10 occurrences) (Figures 7A–D), primarily associated with molecular diagnostics, therapeutic interventions, particularly targeted and immune therapies, tumor biology, and biomarker evaluation, with NSCLC and small cell lung cancer (SCLC) constituting the predominant disease contexts. These co-occurrence patterns underscore the centrality of molecularly driven approaches and biomarker research in shaping the thematic structure of liquid biopsy studies in lung cancer.

Keyword burst (Figure 8A) and time-zone analyses (Figures 8B–D) delineated a clear temporal evolution of research priorities. The initial phase (2006–2011) was characterized by exploratory investigations into biopsy methodologies, cfDNA methylation detection, and liquid-based cytology. The subsequent phase (2012–2021) marked a substantial expansion in molecular diagnostics, focusing on epidermal growth factor receptor (EGFR)/Kirsten rat sarcoma viral oncogene homolog mutation detection through next-generation sequencing (NGS) and digital polymerase chain reaction (PCR), thereby advancing precision oncology. In the most recent phase (2022–2024), attention shifted toward integrating liquid biopsy into personalized NSCLC treatment, exemplified by ctDNA-guided targeted therapy selection, with osimertinib and exosomal DNA emerging as focal areas. Time-zone mapping further demonstrated the progressive transition from the development of early diagnostic methodologies (2002–2007) through biomarker discovery and molecular characterization (2008–2014) to clinical translation emphasizing treatment monitoring and trial design (2015–2024).

Discussion

Global Publication Trends

Consistent with our bibliometric findings of a sharp rise in annual publications, research on liquid biopsy in lung cancer has shown an accelerating trajectory over the past three decades, particularly after 2015. This growth mirrors advances in NGS,^{16,23,37,38} digital PCR,²⁸ and single-cell analysis,¹¹ which have enhanced the sensitivity and specificity of liquid biopsy platforms. Early publications were largely exploratory, focusing on methodological feasibility, whereas recent studies emphasize translational application and clinical integration. This temporal evolution indicates that liquid biopsy has gradually transformed from a conceptual innovation to a critical tool in precision oncology. The increasing

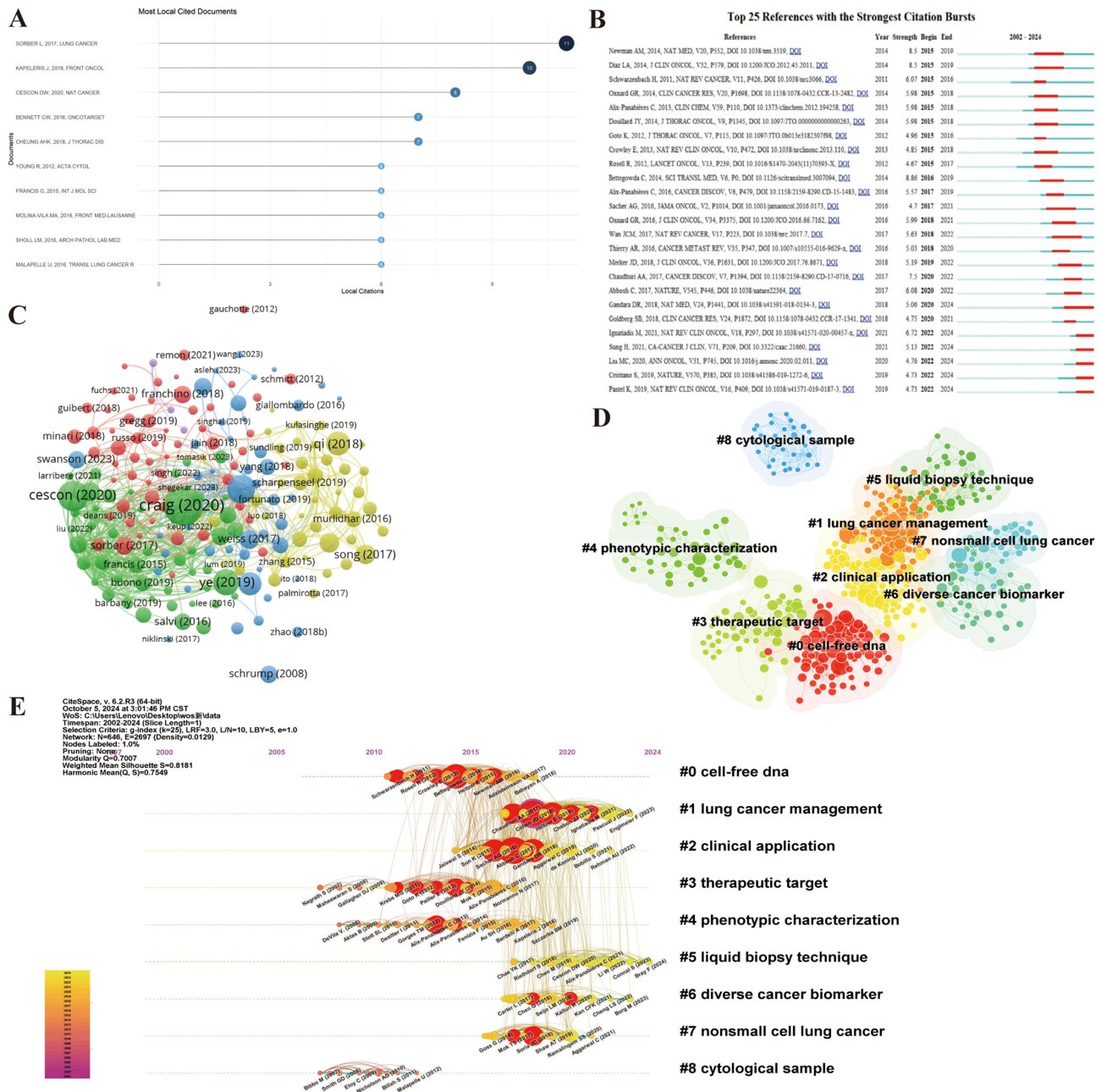


Figure 6 (A) Top 10 references ranked by citation frequency; (B) In-depth analysis of citation bursts; (C) Topic coupling analysis of the research literature; (D) Cluster analysis of cited references; (E) Timeline view of citation patterns.

contribution of high-impact journals and the expanding citation network suggest that liquid biopsy has achieved sustained recognition as a mainstream research frontier in thoracic oncology.

International and Institutional Collaboration

Our collaboration analysis revealed substantial regional imbalances. China produced the largest volume of publications, reflecting its expanding investment in translational oncology research. However, the CPP for China was lower than those of Western countries, implying that the overall scientific influence of Chinese studies is still developing. In contrast, the United States, with fewer publications, exhibited a higher impact and broader international collaboration, as evidenced by elevated MCP ratios. Institutions such as Harvard University, the Chinese Academy of Sciences, and Icahn School of Medicine at Mount Sinai occupied central network positions, bridging different regions and forming high-density

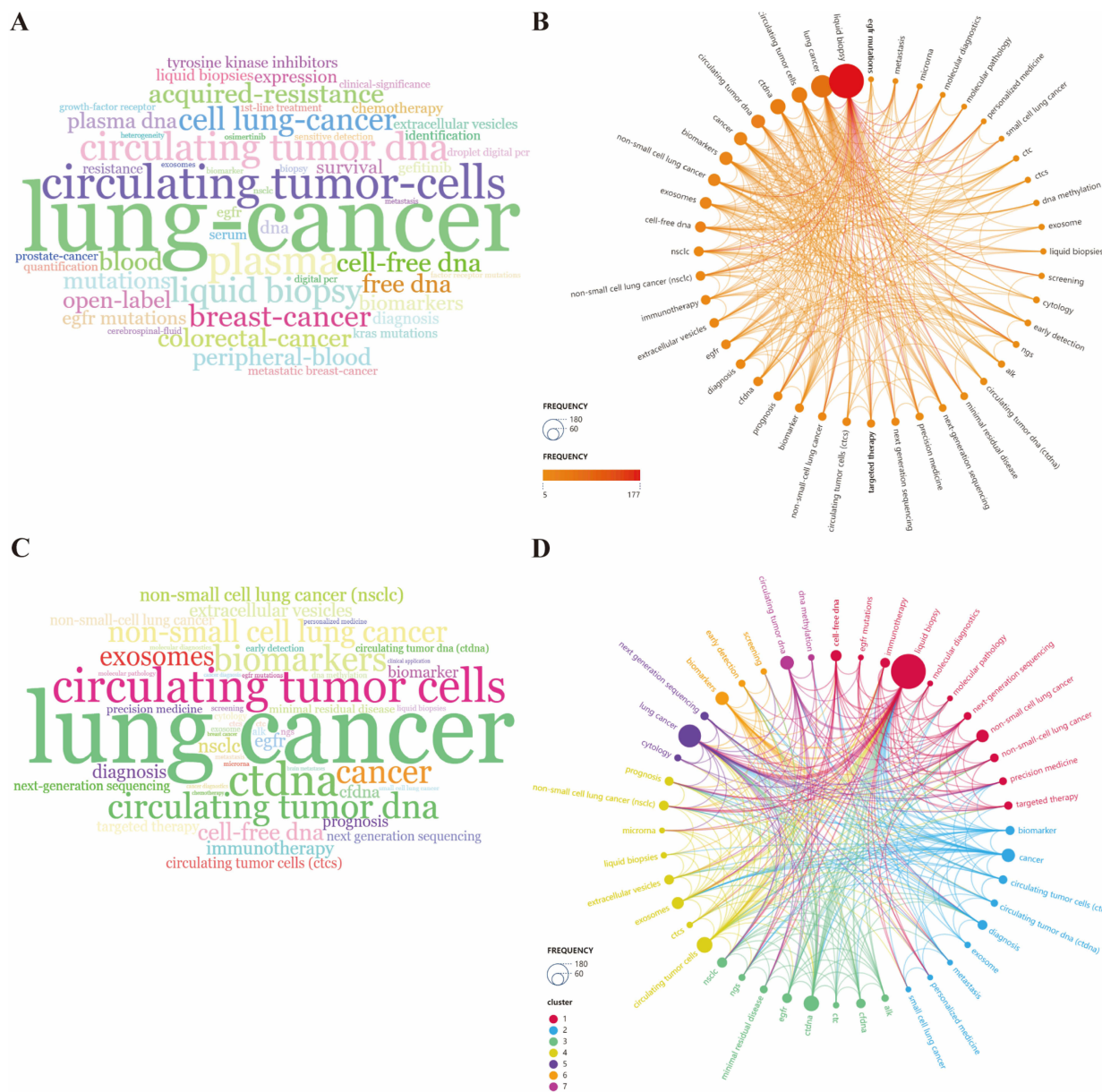


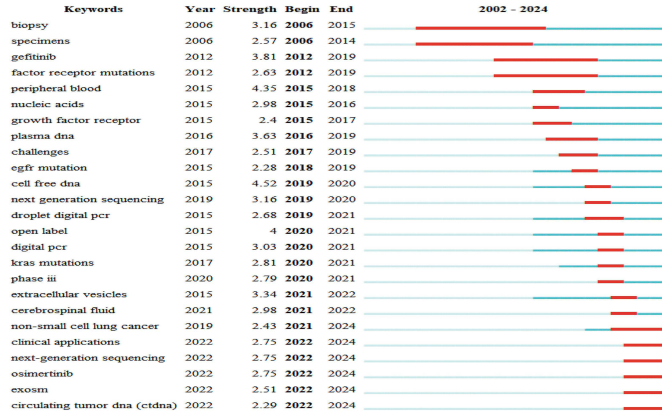
Figure 7 (A) Word clouds of supplementary keywords in local clusters; (B) Frequency distribution of keywords; (C) Word clouds of author-provided keywords; (D) Co-occurrence analysis of keywords.

collaborative clusters. These findings underscore that productivity alone does not guarantee influence; rather, international cooperation and network centrality are critical for amplifying global visibility. For countries with high output but limited impact, strengthening cross-regional partnerships and enhancing methodological rigor are necessary to achieve greater international influence.

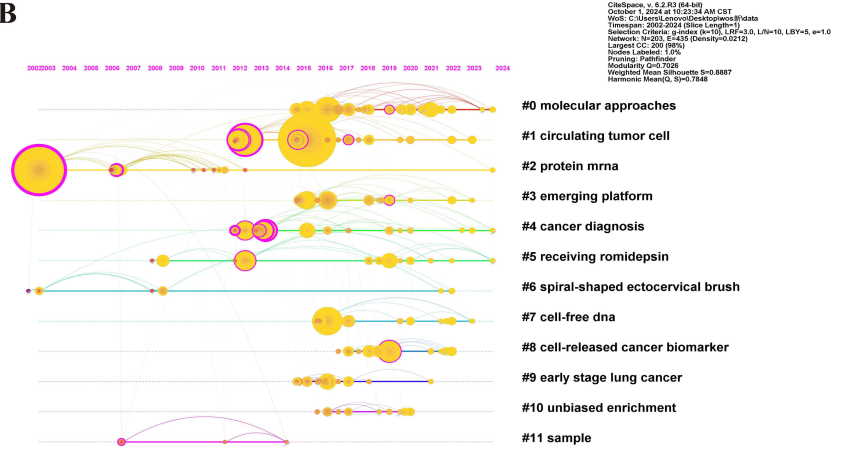
Biomarkers and Clinical Applications

The bibliometric mapping of keywords, co-cited references, and citation bursts highlights biomarkers as the cornerstone of liquid biopsy research in lung cancer. ctDNA^{2,9,12,16,30,39,40} and CTCs^{9–11,19,29,41} remain the most widely investigated analyses, with clinical relevance for early diagnosis, treatment monitoring, and resistance prediction.^{16,37,38,42} Our results revealed that minimal residual disease (MRD) detection, cfDNA methylation profiling, and bTMB are emerging hotspots, aligning with the global shift toward personalized therapy.^{13,18,37,43–46} Notably,

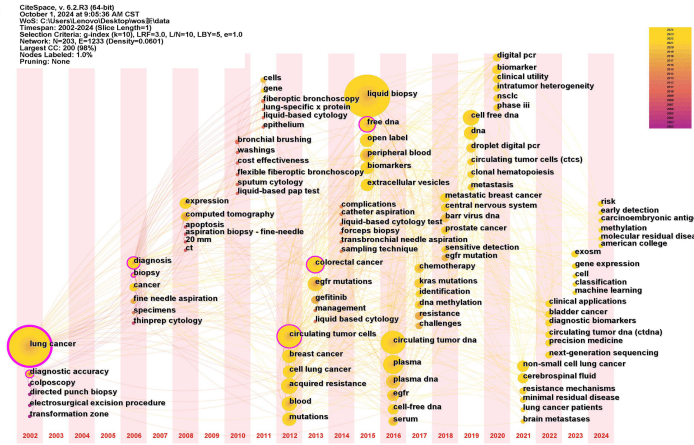
A Top 25 Keywords with the Strongest Citation Bursts



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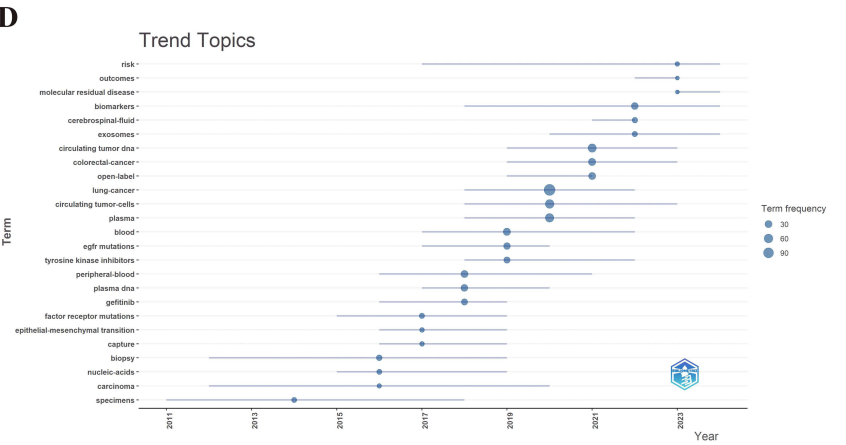


Figure 8 Analysis of keyword bursts and temporal trends. (A) Keyword burst analysis; (B) Keyword timeline; (C) Keyword time zone mapping; (D) Emerging research topics in liquid biopsy for lung cancer (1990–2024).

exosomal nucleic acids,⁴⁷ although at an earlier stage of investigation, demonstrate complementary potential, expanding the biomarker spectrum beyond ctDNA and CTCs. This diversified biomarker portfolio highlights the capacity of liquid biopsy to provide dynamic, real-time insights into tumor heterogeneity, which is especially crucial for managing NSCLC and SCLC.^{12,37,41,48}

Research Hotspots and Emerging Directions

The evolution of thematic clusters suggests a transition from technical innovation to clinical translation. In the early phase, research prioritized optimization of detection platforms, including digital PCR^{13,49} and NGS technologies.^{16,35} More recent studies focus on clinical decision-making, exemplified by ctDNA-guided targeted therapy in EGFR-mutant NSCLC, which validates the translational utility of liquid biopsy in tailoring treatments.¹² Furthermore, integrating immunotherapy-related biomarkers, such as bTMB and immune gene signatures, underscores the expanding scope of liquid biopsy beyond targeted therapy toward immuno-oncology.³⁵ Emerging trends identified in our analysis also point to the incorporation of artificial intelligence,^{17,44} machine learning,^{17,25} and multi-omics approaches,⁵⁰ which hold promise for refining predictive algorithms and stratifying patients with greater precision. These findings collectively reflect a field in rapid transition toward holistic and personalized cancer management.

Challenges and Future Prospects

The clinical promise of liquid biopsy is widely recognized; however, several critical challenges remain unresolved. Technical heterogeneity—encompassing pre-analytical variability, inconsistencies in detection sensitivity, and the absence of universally accepted standardized assays—continues to impede its widespread clinical implementation. Moreover, current research has predominantly concentrated on advanced-stage lung cancer,^{51,52} while applications in early detection and population-based screening remain insufficiently investigated. As indicated by recent citation bursts, expanding investigations into early-stage disease are essential to unlock the full preventive potential of liquid biopsy. In addition, despite the presence of international collaborative networks, establishing a stronger consensus on assay standardization and quality control is urgently required to ensure reproducibility, comparability, and broader clinical translation across diverse research and healthcare settings.

Looking ahead, three research priorities can be distilled from our findings. First, the development of internationally recognized standards for liquid biopsy assays is imperative to ensure methodological consistency and reproducibility across studies and clinical settings. Second, research efforts should be broadened to encompass early diagnosis, longitudinal disease surveillance, and MRD assessment, thereby extending the clinical utility of liquid biopsy beyond advanced-stage management. Third, integrating liquid biopsy with multi-omics platforms, including genomics, transcriptomics, proteomics, and metabolomics, will facilitate the construction of comprehensive biomarker landscapes that more accurately capture tumor heterogeneity. These directions are essential for addressing current limitations and for establishing liquid biopsy as a robust clinical tool that effectively bridges experimental discovery with bedside application, ultimately accelerating the implementation of precision medicine in lung cancer.

Limitations

This study has some limitations. First, the analysis was conducted exclusively using data from the WoSCC, which may have resulted in the omission of pertinent studies indexed in other databases, such as PubMed or Embase. Incorporating multiple databases in future research would improve the comprehensiveness and representativeness of the findings. Second, in the study, we primarily relied on quantitative bibliometric indicators, which are valuable for identifying trends and patterns, but may not fully capture the scientific rigor, methodological quality, or clinical relevance of individual publications. Third, the exclusion of non-English literature may have introduced potential language bias, which could limit the global applicability of the results. Finally, although visualization tools enhance the clarity of bibliometric outputs, interpreting clustering results and temporal trends inevitably involves a degree of subjectivity and may not completely reflect the most recent or ongoing developments in this rapidly evolving field.

Conclusion

We applied bibliometric and visualization tools to systematically map the research landscape, thematic hotspots, and developmental trajectories of liquid biopsy in lung cancer over the past 34 years. This field remains in a dynamic growth phase, with *Cancers* and *Clinical Cancer Research* emerging as leading journals in publication output and citation influence, respectively. Current research primarily focuses on cancer diagnosis, biomarker discovery, and treatment monitoring. Liquid biopsy through the detection of ctDNA, CTCs, and extracellular vesicles offers distinct advantages for early detection, real-time therapeutic assessment, elucidation of drug resistance, and personalized treatment. Despite ongoing technical and standardization challenges, rapid methodological advances and expanding global collaborations highlight its substantial potential to reshape clinical practice. Continued multidisciplinary and translational efforts are expected to accelerate the routine integration of this approach, ultimately improving the outcomes of patients with lung cancer.

Abbreviations

bTMB, blood tumor mutational burden; cfDNA, cell-free DNA; CIBER, Centro de Investigación Biomédica en Red; CIBERONC, Centro de Investigación Biomédica en Red de Cáncer; CPP, citations per paper; CTCs, circulating tumor cells; ctDNA, circulating tumor DNA; EGFR, epidermal growth factor receptor; MCP, multiple-country publications; MRD, minimal residual disease; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; PCR, polymerase chain reaction; SCLC, small cell lung cancer; SCP, single-country publications; WoSCC, Web of Science Core Collection.

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We thank all team members involved in this study.

Author Contributions

All authors contributed significantly to the work reported, including the conception, study design, execution, data acquisition, analysis, and interpretation. They also participated in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

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Disclosure

Yueqi Xu and Biao Huang contributed equally to this work as co-first authors. The authors affirm that the research was conducted without any apparent commercial or financial affiliations that could be construed as potential conflicts of interest.

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