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ORIGINAL RESEARCH

Deciphering the Dynamics of EGFR-TKI Resistance in Lung Cancer: Insights from Bibliometric Analysis

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Video abstract

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Background: EGFR-TKI resistance poses a significant challenge in the treatment landscape of non-small cell lung cancer (NSCLC), prompting extensive research into mechanisms and therapeutic strategies. In this study, we conduct a bibliometric analysis to elucidate evolving research hotspots and trends in EGFR-TKI resistance, offering insights for clinical interventions and scientific inquiries.

Methods: Publications spanning from 1996 to 2024, focusing on EGFR-TKI resistance in NSCLC, were sourced from the Web of Science Core Collection. Utilizing VOSviewer 1.6.19, CiteSpace 6.2. R2, and Scimago Graphica 1.0.35, we analyzed these articles to identify countries/regions and institutions, Journals, publications, key contributors, collaborations, and emerging topics.

Results: An analysis of 8051 articles by 38,215 researchers from 86 countries shows growing interest in EGFR-TKI resistance mechanisms. Since 1996, publications have steadily increased, surpassing 500 per year after 2016, with a sharp rise in citations. Research articles make up 84% of publications, emphasizing scholarly focus. Global collaboration, especially among researchers in China, the US, and Japan, is strong. Leading institutions like Dana-Farber and Harvard, along with journals such as "Lung Cancer", are key in sharing findings. Professors Yi-Long Wu and William Pao are prominent contributors. Keyword analysis reveals core themes, including first-generation EGFR-TKIs, emerging agents like osimertinib, and research on the T790M mutation.

Conclusion: EGFR-TKI resistance remains a critical issue in NSCLC treatment, driving ongoing research efforts worldwide. Focusing future research on clear identification of resistance mechanisms will guide post-resistance treatment strategies, necessitating further exploration, alongside the validation of emerging drugs through clinical trials. Moreover, "chemo+" treatments following EGFR-TKI resistance require more clinical data and real-world evidence for assessing safety and patient outcomes. As research advances, a multidisciplinary approach will be key to overcoming these challenges. Continued innovation in treatment could greatly enhance patient survival and quality of life.

Keywords: EGFR-TKI, resistance, lung cancer, bibliometric, citespace, VOSviewer

Introduction

In April 2024, the World Health Organization reported that in 2022, there were 19.965 million new cancer cases and 9.737 million cancer-related deaths worldwide. Lung cancer was the most common, with 2.48 million cases, making up 12.4% of the total. Data from the International Agency for Research on Cancer (IARC) shows that lung cancer is one of the leading causes of cancer deaths globally, accounting for 20.4% of cancer deaths in the US in 2024, with around 343 daily fatalities. Among early-stage lung cancer patients, EGFR mutations are the most frequent, found in 56% of cases.[1] Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) have revolutionized the treatment landscape of non-small cell lung cancer (NSCLC), particularly in patients harboring EGFR mutations. EGFR mutations, present in approximately 50% of lung adenocarcinomas,[2] are pivotal in driving tumorigenesis by activating downstream signaling pathways involved in cell proliferation and survival.[3] Compared to Western populations, the EGFR mutation rate is significantly higher in Asians, detected in over 50% of advanced lung adenocarcinoma cases, and is considered a "golden

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mutation" in this group.[4] The advent of EGFR-TKIs, such as gefitinib, erlotinib, afatinib, and Osimertinib, marked a paradigm shift in NSCLC treatment, offering targeted therapy tailored to the molecular profile of the tumor. Nevertheless, after 9–13 months of first- and second-generation EGFR-TKI treatment, acquired resistance inevitably develops through various mechanisms, with the T790M mutation in exon 20 being the primary cause, occurring in 50–60% of patients.[5–7] Intrinsic resistance, often attributed to primary mutations like T790M, limits the initial response to EGFR-TKIs. Acquired resistance, on the other hand, manifests through secondary mutations, amplifications, bypass signaling pathways, or histological transformation, leading to disease progression despite initial clinical benefit.[8]

Understanding the dynamics of EGFR-TKI resistance is imperative for optimizing treatment strategies and improving patient outcomes. Bibliometric analysis, a quantitative method in library and information science, offers a systematic approach to evaluating the current state and identifying research hotspots in this field.[9] By analyzing bibliographic material and utilizing quantitative measures, bibliometrics provides insights into publication trends, collaborative networks, and key research directions, thereby guiding experimentation strategies and funding decisions. While bibliometric studies have been applied to various medical fields, including gynecology, orthopedics, and complementary medicine, its application to EGFR-TKI resistance in lung cancer in respiratory medicine remains underexplored. Hence, the aim of the present study is to systematically analyze the research landscape of EGFR-TKI resistance in lung cancer, shedding light on the current state and hotspots in this critical area. Through comprehensive bibliometric analysis, we aim to elucidate the complexities of EGFR-TKI resistance mechanisms, identify novel therapeutic targets, and pave the way for future advancements in the treatment of EGFR-mutant NSCLC.

Materials and Methods

Data Sources and Search Strategy

Acknowledging the broadest coverage, including the oldest literature dating back to 1900, and its prompt data updates, comprehensive nature, and wide-ranging content, we chose to employ the Science Citation Index Expanded (SCI-EXPANDED) and Social Sciences Citation Index (SSCI) from the Web of Science Core Collection for bibliometric analysis.[10] The literature encompassed in this study ranges from July 1996 to March 2024. Recognizing the swift updates within databases, the retrieval of data was accomplished within a single day to ensure accuracy and comprehensiveness. The search methodology employed in this study was TS=(((epidermal growth factor receptor-tyrosine kinase inhibitor or EGFR-TKI or EGFR TKIs or erlotinib or gefitinib or afatinib or osimertinib or dacomitinib) AND (resistance or resistant)) AND (Pulmonary or Neoplasm, Pulmonary or Pulmonary Neoplasm or Lung Cancer or Cancer, Lung or Cancers, Lung or Lung Cancers or Pulmonary Cancer or Cancer, Pulmonary or Cancers, Pulmonary or Pulmonary Cancers or Cancer of the Lung or Cancer of Lung)). Ultimately, a total of 8051 articles were included in the study, with a detailed screening process outlined in Figure 1.

Data Collection and Bibliometric Analysis

Based on the search strategy outlined above, we downloaded the 'full records and cited references' of 8051 articles included in this study from the Web of Science Core Collection (WoSCC) and saved them as text files. Next, we excluded articles categorized as processing papers, book chapters, and early access. This left us with a total of 8068 articles and reviews. From these raw data, we extracted information including the number of publications, citation frequency, countries and regions, publication years, institutions, authors, references, journals, and keywords. To ensure the accuracy of the data to the fullest extent possible, we implemented multiple effective measures. Data filtering was independently conducted by two researchers and reviewed by all researchers. We corrected spelling errors, merged synonymous terms, deleted undisputed terms, and used Citespace to deduplicate and exclude 17 retracted articles, resulting in a final total of 8051 articles included in the study. In order to comprehensively and thoroughly address current research trends and summarize research hotspots, both articles and reviews were included in this study. Finally, the thoroughly processed data was imported into Citespace and Vosviewer for bibliometric analysis.

Bibliometrics is a quantitative approach to the study of scholarly literature, citations, and academic publications, aimed at assessing the impact, visibility, and evolutionary patterns of research outputs within a given field or discipline. It

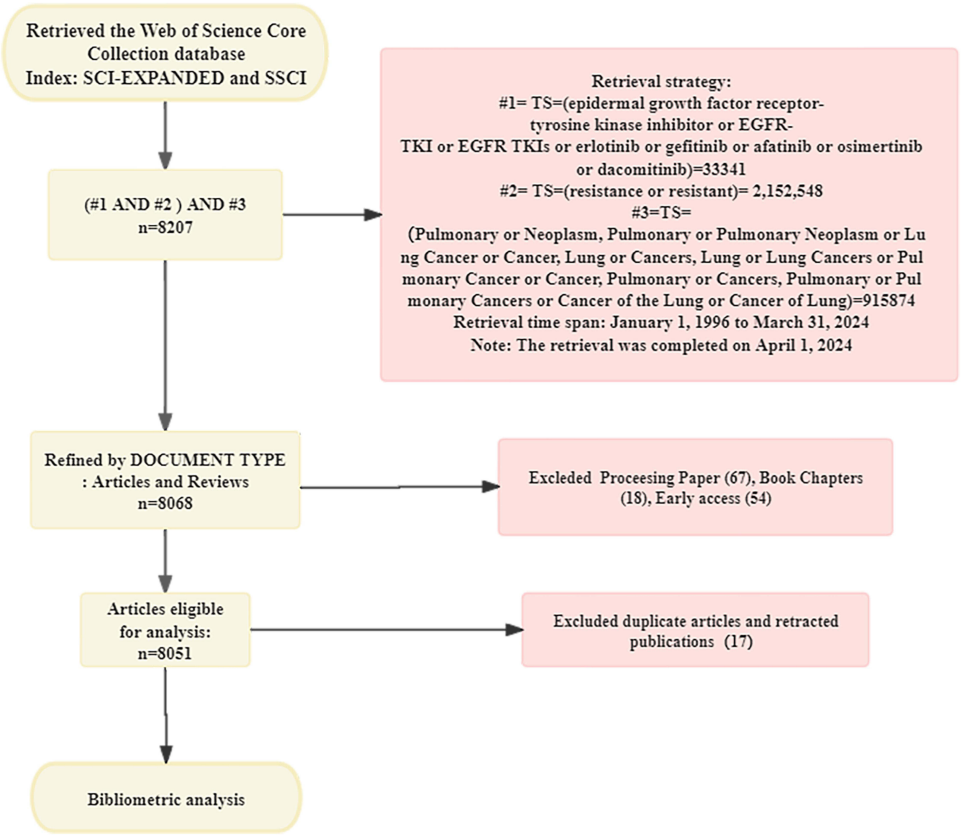

Figure 1 Flowchart of literature screening in this study.

delves into elements such as volume, excellence, citations, authorship, and subject matter to offer understanding on research directions, influence, cooperative efforts, and focal points.[11] Subsequently, we employed VOSviewer for in-depth analyses including cluster analysis, while also utilizing CiteSpace to investigate citation bursts, analyze keyword evolution over time, and delve into factors such as countries and regions, authorship networks, key thematic areas, and citation patterns. This comprehensive approach provided a multi-dimensional view, enabling the creation of visually intuitive representations and facilitating a nuanced exploration of research landscapes, emergent themes, and temporal trends within the scholarly domain.[12,13]

Result

Overview of Publication Status

The analysis of publication and citation trends reveals a substantial growth in scholarly activity and impact within the field over the past few decades. The scatter plots presented in Figure 2A illustrate the annual publication count and cumulative citation count spanning from 1996 to 2024. Accompanied by trend lines representing their respective temporal trajectories, these data provide insights into the evolution of scholarly output and its impact over time. Notably, the publication count demonstrates a gradual ascent, transitioning from a solitary article before 2003 to a sustained yearly increase thereafter. Particularly striking is the trend since 2016, with the annual publication count consistently surpassing 500 articles, indicative of a robust and burgeoning research landscape. Concurrently, the citation count exhibits a sharp escalation in tandem with the surge in publication volume, underscoring the growing influence and significance of the field's contributions. Figure 2B illustrates the percentage distribution of literature types, with research articles comprising the largest proportion (84%).

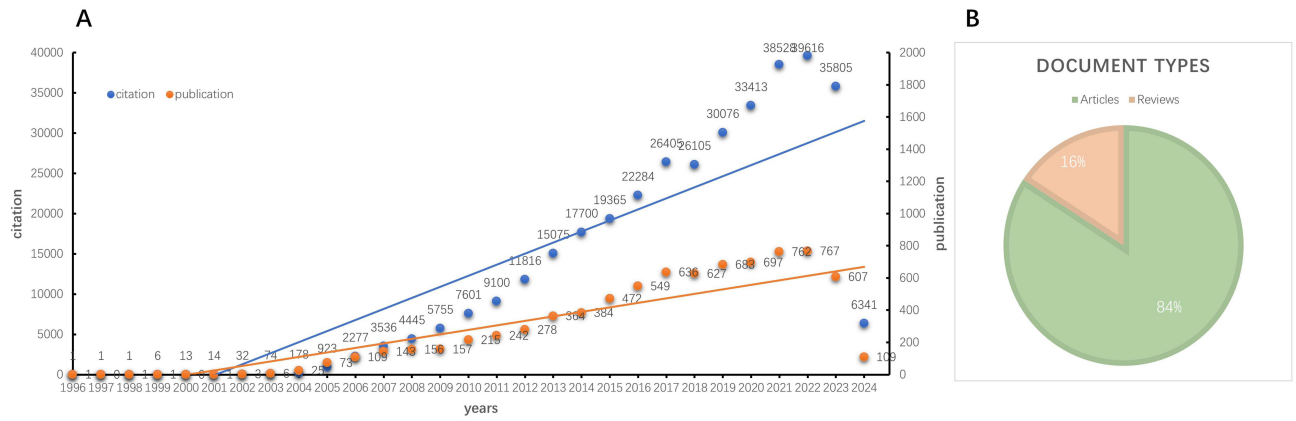

Figure 2 (**A**) The trend of publication outputs; (**B**) article type about EGFR-TKI resistance.

Contributions of Countries/Region and Institutions

The analysis of global research contributions and collaborations highlights the dominant roles of countries such as China, the United States, and Japan, as well as leading institutions like the Dana-Farber Cancer Institute, Harvard University, and Memorial Sloan Kettering Cancer Center, in advancing the field of EGFR-TKI resistance in lung cancer. These entities are distinguished by their significant publication volumes and citation impacts. Researchers from 86 countries contributed articles included in the study. Figure 3 illustrates the collaboration in publishing articles among different countries using VOSviewer and SCImago. The size of the nodes reflects the number of articles published by each country, while the lines connecting the nodes represent the collaboration between countries. Thicker lines indicate more frequent collaboration, and the color of the nodes represents clusters of different countries with similar characteristics. The figure highlights the close collaboration among countries with high publication volumes. Moreover, countries like China, the United States, and Japan stand out with larger nodes, signifying their significant contributions to the majority of publications.

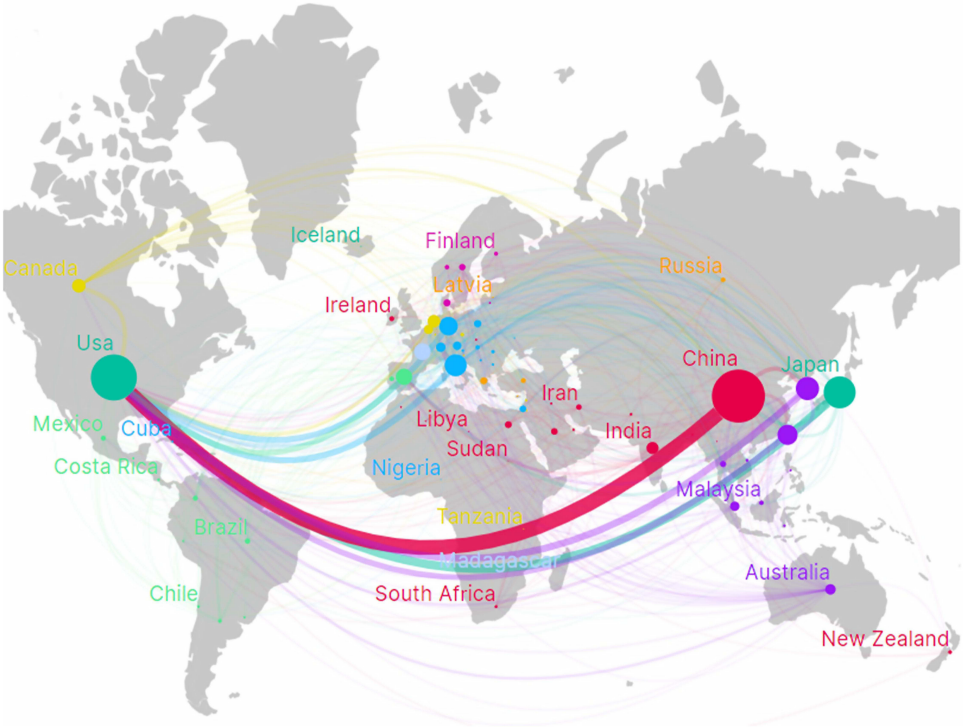

Figure 3 Geographic distribution map based on publications from different countries/regions.

Table 1 Publications in the 10 Most Productive Countries/Regions and Affiliations

Rank	Country/region	Np	Nc	H-index	Affiliations	Documents	Citations	TLC
1	China	2953	78,435	101	DANA FARBER CANC INST	208	36,964	245
2	USA	2225	202,572	212	HARVARD UNIV	204	55,550	196
3	Japan	1076	60,856	110	MEM SLOAN KETTERING CANC CTR	189	33,266	110
4	South Korea	567	35,778	84	SHANGHAI JIAO TONG UNIV	164	3637	57
5	Italy	510	32,868	77	NATL CANC CTR	164	15,068	95
6	Taiwan	427	26,936	66	NANJING MED UNIV	161	2961	44
7	Germany	362	22,611	75	NATL TAIWAN UNIV	151	10,437	159
8	England	297	33,853	80	MASSACHUSETTS GEN HOSP	151	34,390	183
9	France	293	21,754	64	UNIV TEXAS MD ANDERSON CANC CTR	147	14,110	81
10	Spain	282	20,737	64	NATL TAIWAN UNIV HOSP	145	12,297	180

Abbreviation: TLC, Total link strength.

Table 1 presents a comprehensive overview of the top 10 institutions and countries contributing to research on EGFR-TKI resistance in the field of lung cancer. Leading this list are renowned institutions such as the Dana-Farber Cancer Institute, Harvard University, and Memorial Sloan Kettering Cancer Center, holding the top three positions not only in terms of publication count but also in citation rates. It's noteworthy that all three of these prestigious institutions are based in the United States, underscoring their significant contributions and prominent standing in academia. Moreover, the table highlights China's prominence in terms of the sheer volume of publications, boasting 2953 articles, closely trailed by the United States with 2225 publications and Japan with 1076 publications. However, the United States maintains a considerable lead in citations, amassing an impressive count of 202572 citations and an H-index of 212, more than double that of China (78435/101).

Productive Journals and Co-Cited Journals

The analysis of journal influence in EGFR-TKI resistance research underscores the prominence of high-impact journals, particularly those in the first quartile of the Journal Citation Reports. Key platforms like "Lung Cancer", "Clinical Cancer Research", and "Journal of Thoracic Oncology" lead in both publication volume and citation impact, serving as central hubs for advancing the field. To examine research on EGFR-TKI resistance in the field of lung cancer, we utilized CiteSpace and VOSviewer for analysis, identifying journals with the highest citation counts and co-citation frequencies in this domain. From Table 2, it is evident that among the top ten journals by publication volume, five are classified in the

Table 2 Journals and Co-Cited Journals

Rank	Journal	Documents	IF (2022)	JCR	Rank	Co-cited Journal	Citations	IF (2022)	JCR
1	Lung cancer	329	5.3	Q1	1	Journal of Clinical Oncology	25404	45.4	Q1
2	Clinical cancer research	227	11.5	Q1	2	Clinical cancer research	21472	11.5	Q1
3	Journal of thoracic oncology	220	20.4	Q1	3	New England Journal of Medicine	18757	158.5	Q1
4	Frontiers in oncology	197	4.7	Q2	4	Cancer research	15859	11.2	Q1
5	Cancer research	151	11.2	Q1	5	Journal of thoracic oncology	13947	20.4	Q1
6	Clinical lung cancer	142	3.6	Q2	6	Lancet oncology	10192	51.1	Q1
7	Cancers	139	5.2	Q1	7	Annals of oncology	7495	50.5	Q1
8	Molecular cancer therapeutics	131	5.7	Q2	8	Lung cancer	8776	5.3	Q1
9	Thoracic cancer	119	2.9	Q3	9	Proceedings of the National Academy of Sciences of the United States of America	8158	11.1	Q1
10	Scientific reports	115	4.6	Q2	10	Nature	6536	64.8	Q1

first quartile of the JCR, while all the top ten journals by citation count are exclusively from the first quartile of the JCR. The leading journal in terms of article publications in the domain of EGFR-TKI resistance in lung cancer is "Lung Cancer" (IF: 5.3, JCR: Q1), boasting a total of 329 articles. Following closely are "Clinical Cancer Research" with 227 articles (IF: 11.5, JCR: Q1) and "Journal of Thoracic Oncology" with 220 articles (IF: 20.4, JCR: Q1). These journals, renowned for their high impact factors and top-tier classifications, serve as pivotal platforms for disseminating cutting-edge research and insights into overcoming EGFR-TKI resistance in lung cancer. Additionally, nearly one-fourth of the articles (22%, 1770/8051) were published in these top ten journals by publication volume.

Figure 4A and B present visually striking density maps showcasing the distribution of published articles across journals and the co-citation patterns, respectively. In these visualizations, varying colors denote the volume of published articles, with deeper shades of red indicating higher concentrations, while areas shaded in green suggest relatively fewer publications. The intricate interplay between journals is elegantly captured in Figure 4C, where a dual-journal overlay offers insights into thematic clusters and the complex network of citing and cited journals. Positioned on the left side are the citing journals, while their corresponding cited counterparts reside on the right. This depiction unveils two predominant pathways, showing that articles originating from the realms of "medicine, medical, clinical" and "molecular, biology, immunology" are primarily referenced in the "molecular, biology, genetics" sphere of scholarly discourse.

Authors and Co-Cited Authors

The analysis of leading authors in EGFR-TKI resistance research highlights the significant contributions and collaborations within the field, with key figures such as Professor Yi-Long Wu and Professor William Pao standing out for their

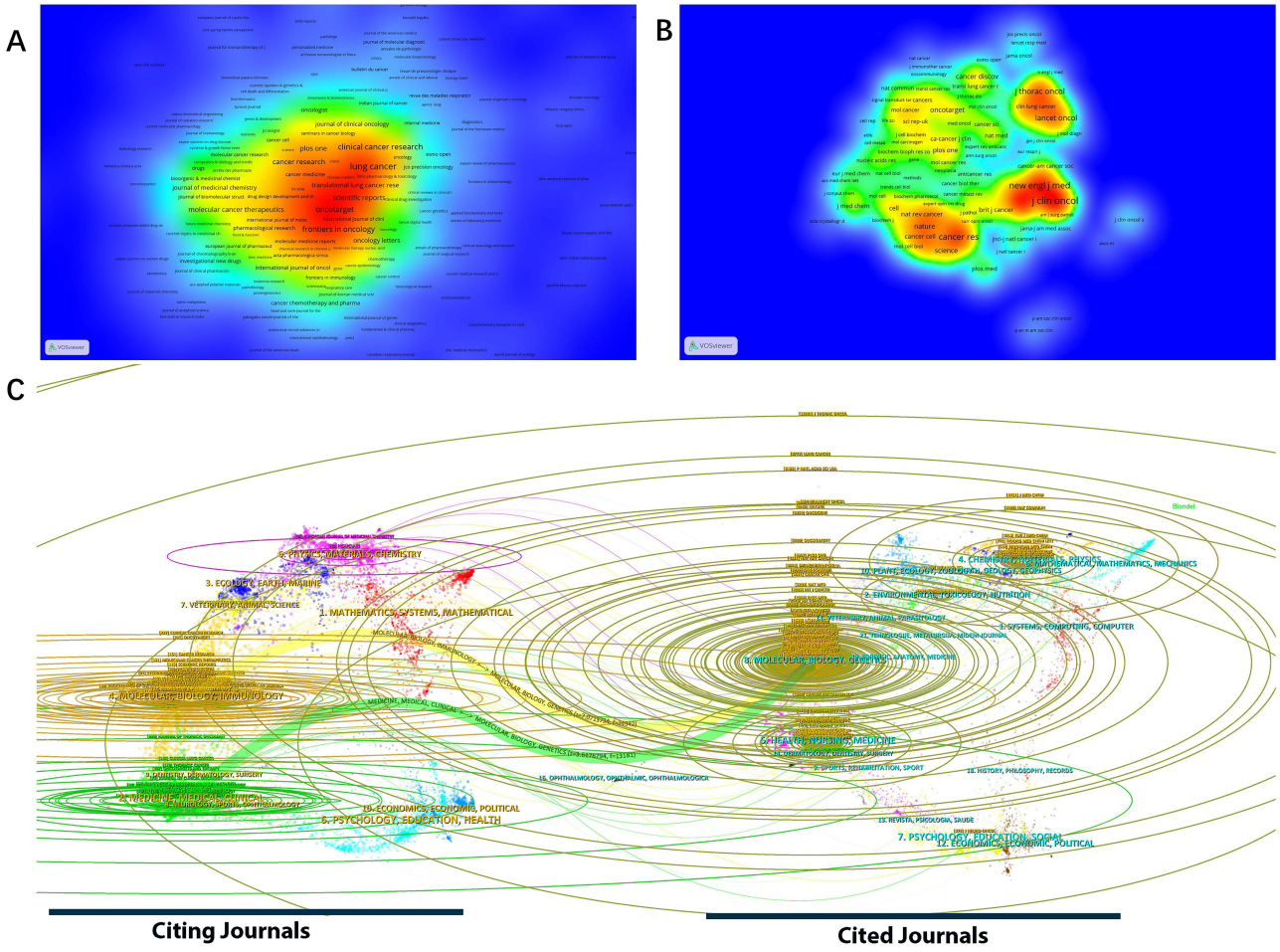

Figure 4 (**A**) The density map of Cited Journals; (**B**) The density map of Co-Cited Journals; (**C**) The dual-map overlay of journals on EGFR-TKI resistance.

Table 3 Author

Rank	Author	Affiliations	Np	Nc	H-index
1	Wu, Yi-long	Guangdong Lung Cancer Institute	75	5177	95
2	Kiura, Katsuyuki	Okayama University Academic Field of Medicine	69	3272	55
3	Park, Keunchil	Samsung Medical Center	68	4776	77
4	Mitsudomi, Tetsuya	Kindai University Faculty of Medicine	67	10,201	39
5	Pao, William	Department of Medicine and Vanderbilt-Ingram Cancer Center	67	15,645	102
6	Nishio, Kazuto	Department of Genome Biology	64	2815	69
7	Rosell, Rafael	Catalan Institute of Oncology	64	2894	76
8	Yang, James Chih-Hsin	National Taiwan University Hospital	62	8713	79
9	Nakagawa, Kazuhiko	From Memorial Sloan Kettering Cancer Center and Weill Cornell Medicine	62	3464	77
10	Ahn, Myung-Ju	Samsung Medical Center	60	5276	85

prolific publication records and citation impact. Table 3 provides a compilation of the top ten authors and their respective affiliations, who collectively contributed 658 articles (8.2%, 658/8051) in this domain. Leading the list is Professor Yi-Long Wu from China, with the highest Np value of 75 publications, while Professor William Pao from the United States holds the highest Nc value at 15,645 citations. Notably, Professor Pao also boasts the highest H-index among these distinguished authors. Additionally, as depicted in the mesh visualization in Figure 5, the size of nodes represents the contribution of authors, while the connecting lines between nodes denote collaboration among authors. Different colors indicate distinct clusters of authors with spontaneous collaboration. It can be observed that several core author groups formed by prolific authors have fewer connections with other clusters. Table 3 provides a compilation of the top ten

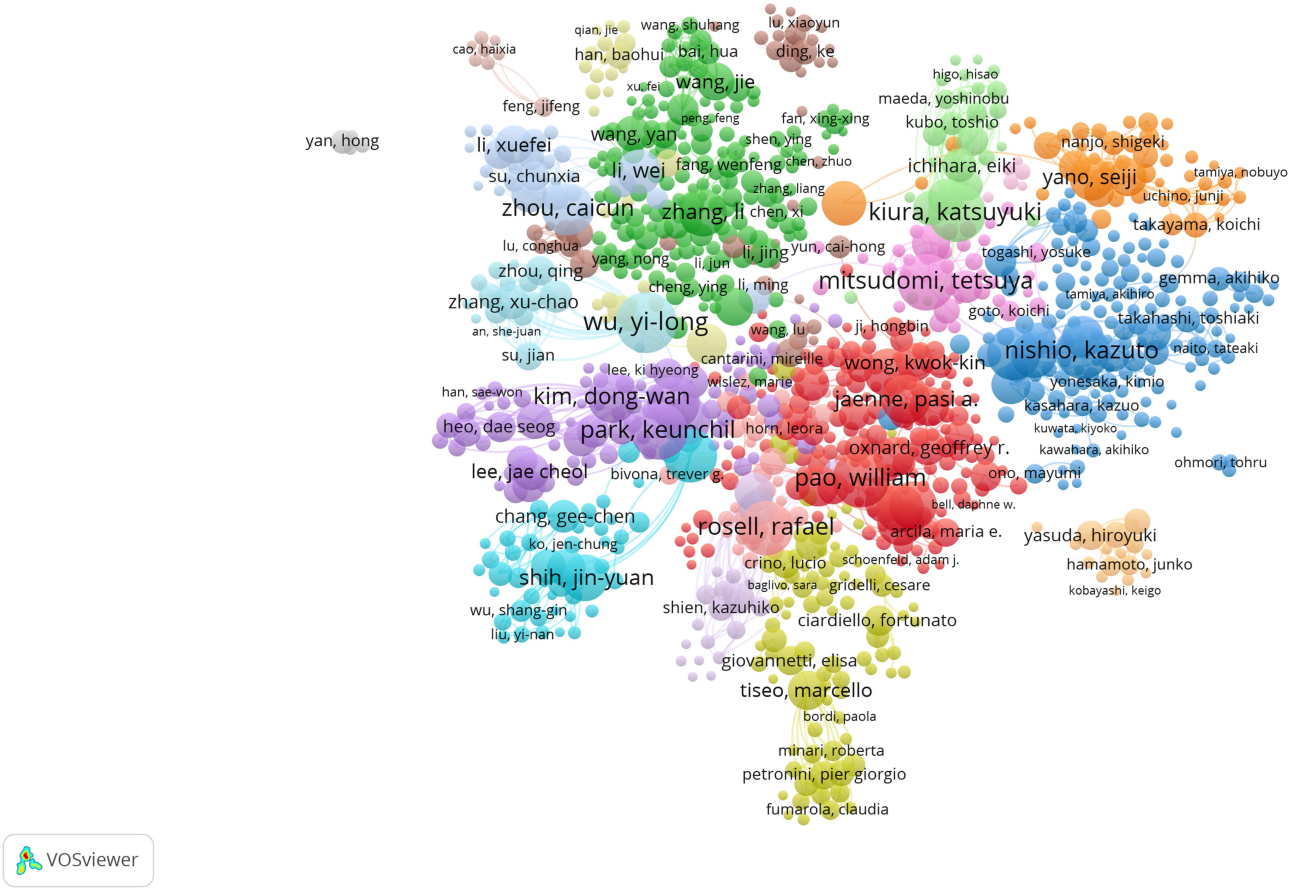

Figure 5 Network visualization map of author co-authorship analysis.

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Most Cited Publications and Citation Bursts

The analysis of highly cited articles in EGFR-TKI resistance research reveals the widespread impact of seminal works published across top-tier journals, with the New England Journal of Medicine, Science, and Lancet Oncology featuring prominently. Additionally, the identification of strong citation bursts highlights recent surges in research interest, particularly in studies on Osimertinib. VOSviewer was utilized to conduct an analysis of the top ten cited articles, as outlined in Table 4. These articles, representing significant contributions to the field, are distributed across reputable journals. Notably, four of the top ten articles were published in the prestigious New England Journal of Medicine. Additionally, two articles found their place in the influential journal Science, while another two were featured in the esteemed Lancet Oncology. This diverse distribution underscores the widespread dissemination and recognition of key research findings across various renowned academic platforms. The article titled "Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib" ranks first with an impressive citation count of 10,184, firmly establishing its prominence in the field.

Figure 6 presents the top 25 citation bursts obtained using CiteSpace, all with burst strengths exceeding 100. The article labeled as "Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer"[24] exhibits the highest burst strength at 305.15, indicating a concentrated surge of interest among researchers in Osimertinib over a short period. Among these, 10 publications show a concentrated burst period between 2014 and 2024, suggesting frequent citations over the past decade.

Table 4 Top 10 Co-Cited Reference Related to EGFR-TKIs

Rank	Year	Author	Title	Journal	Citation	Reference
1	2004	Lynch, T. J.	Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib	N Engl J Med	10184	[14]
2	2004	Paez, J. G.	EGFR mutations in lung cancer: Correlation with clinical response to gefitinib therapy	Science	8815	[15]
3	2009	Mok, T. S.	Gefitinib or Carboplatin-Paclitaxel in Pulmonary Adenocarcinoma	N Engl J Med	7154	[16]
4	2010	Maemondo, M.	Gefitinib or Chemotherapy for Non-Small-Cell Lung Cancer with Mutated EGFR	N Engl J Med	4785	[17]
5	2012	Rosell, R.	Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised Phase 3 trial	Lancet Oncol	4653	[18]
6	2007	Engelman, J. A.	MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling	Science	4256	[19]
7	2005	Kobayashi, S.	EGFR mutation and resistance of non-small-cell lung cancer to gefitinib	N Engl J Med	3681	[20]
8	2010	Mitsudomi, T.	Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial	Lancet Oncol	3475	[21]
9	2005	Pao, W.	Acquired resistance of lung adenocarcinomas to gefitinib or erlotinib is associated with a second mutation in the EGFR kinase domain	PLoS Med	3168	[22]
10	2011	Sequist, L. V.	Genotypic and Histological Evolution of Lung Cancers Acquiring Resistance to EGFR Inhibitors	Sci Transl Med	2896	[23]

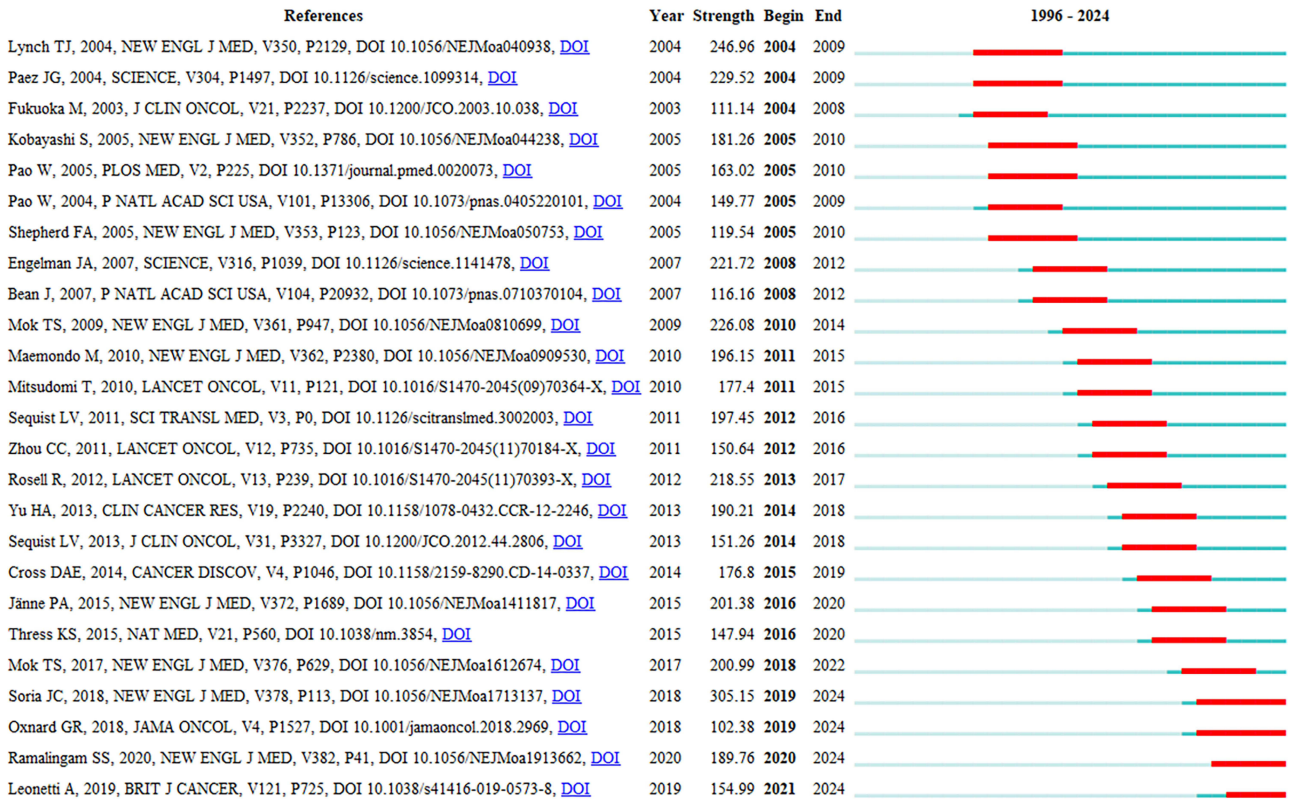

Figure 6 The top 25 references with the strongest citation bursts involved in EGFR-TKI resistance.

Keywords Frequency and Research Hotspots

The keyword analysis uncovers the dynamic progression of research on EGFR-TKI resistance in lung cancer, tracing the transition from early studies on first-generation drugs like gefitinib and erlotinib to more recent focus areas, including the T790M mutation and third-generation therapies like osimertinib. We utilized VOSviewer to conduct keyword analysis on the literature included in our study, presenting the top twenty most frequently occurring keywords in Table 5. We observed that the most frequently occurring keywords were the first-generation EGFR-TKI drug gefitinib, appearing 3324 times, followed by Acquired-resistance at 2507 times, resistance at 2247 times, erlotinib at 1824 times, and EGFR at 1476 times. Following Price's Law, keywords appearing more than 36 times were deemed core, yielding 317 core keywords through VOSviewer analysis. Figure 7A and B showcase the network visualization and density plot of these keywords. In Figure 7A, keywords are clustered into five distinct groups, each denoted by a unique color. The red cluster

Table 5 The Top 20 Keywords Related to EGFR-TKIs

Rank	Keyword	Count	Rank	Keyword	Count
1	Gefitinib	3324	11	Non-small cell lung cancer	1175
2	Acquired-resistance	2507	12	Osimertinib	1053
3	Resistance	2247	13	Expression	936
4	Erlotinib	1824	14	1st-line treatment	905
5	EGFR	1660	15	Lung cancer	856
6	Chemotherapy	1476	16	Therapy	776
7	Growth-factor receptor	1353	17	Adenocarcinoma	729
8	Tyrosine kinase inhibitors	1342	18	Activation	706
9	Open-label	1319	19	Mutation	641
10	Mutations	1272	20	Epidermal growth factor receptor	623

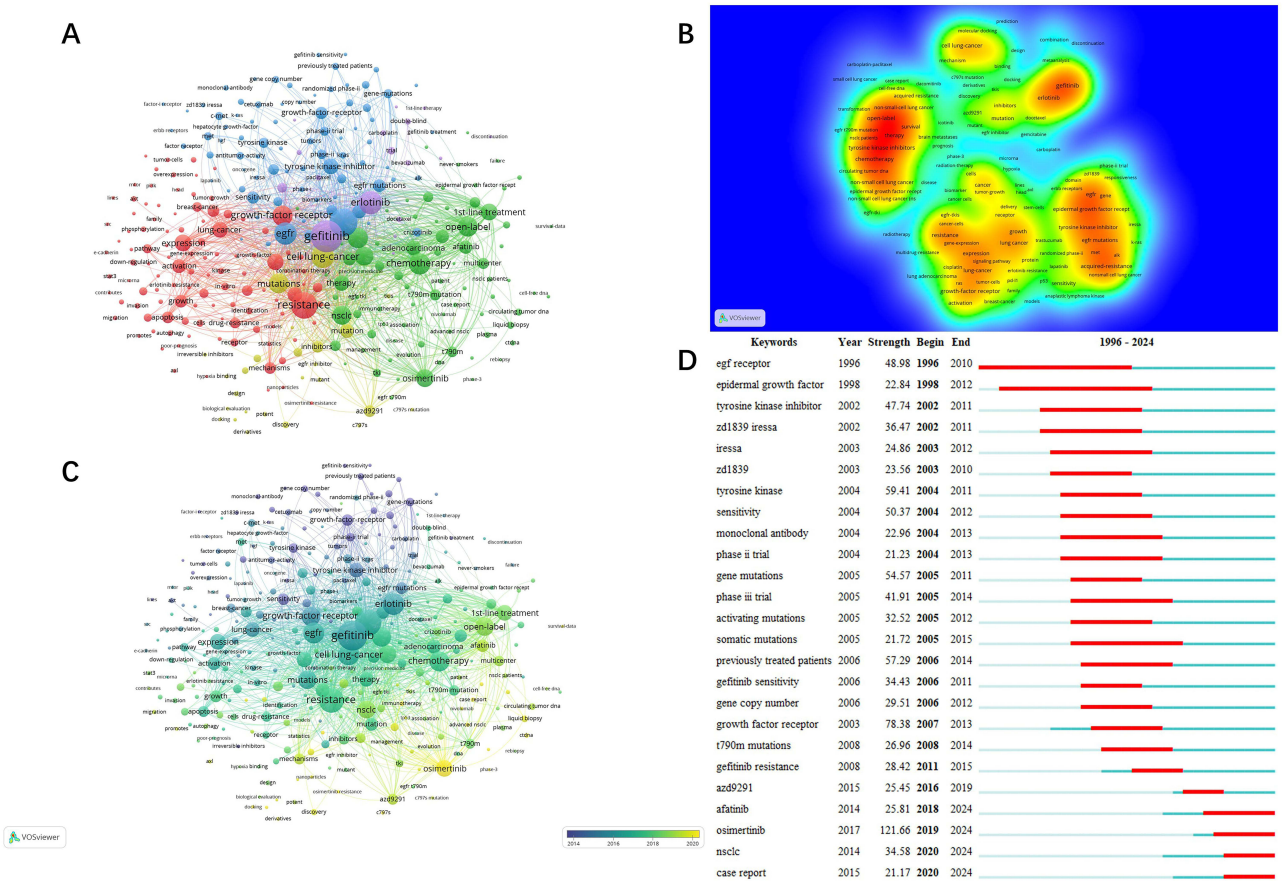

Figure 7 (**A**) The 317 keywords that occurred more than 36 times were divided into five clusters by different colors. (**B**) Density map of the core keywords. (**C**) Visualization of keywords according to the time. (**D**) The top 25 keywords with the strongest citation bursts.

encompasses keywords related to resistance mechanisms and growth factor receptors, indicating a focus on understanding resistance pathways and receptor signaling in lung cancer treatment.In the green cluster, keywords such as "chemotherapy" and "adenocarcinoma" suggest an emphasis on therapeutic interventions and the histological subtype of lung cancer. Terms like "acquired resistance" and "EGFR" found in the blue cluster highlight research into acquired resistance mechanisms specific to EGFR-targeted therapies. Keywords within the orange cluster, such as "clusters" and "expression", indicate a focus on clustering methods and gene expression patterns. Finally, the purple cluster includes terms like "gefitinib" and "erlotinib", indicating a specific focus on first-generation EGFR-TKIs, possibly exploring their efficacy and mechanisms of action in lung cancer treatment. These clusters collectively represent different aspects of research in the field of EGFR-TKI resistance in lung cancer, ranging from mechanistic studies to therapeutic interventions and molecular profiling. These clusters span mechanistic studies, therapeutic interventions, and molecular profiling. Additionally, Figure 7B depicts keyword frequency within each cluster, with the red segment indicating high frequency and the green segment indicating low frequency. To capture the sudden emergence of research hotspots, we employed Citespace to analyze the burst strength of the top twenty keywords. Figure 7D illustrates a concentrated burst period between 2002 and 2011 in the field of EGFR-TKI resistance in lung cancer. Moreover, Figure 7C illustrates the changing research focus over time, accurately reflecting the transition of research hotspots from the discovery and overcoming of resistance mechanisms associated with first-generation EGFR-TKIs such as gefitinib and erlotinib, to the emergence of third-generation agents like osimertinib. This depiction precisely captures how research interests in EGFR-TKI resistance in lung cancer have evolved over time.

Considering that the T790M mutation is the predominant mechanism of resistance to first- and second-generation EGFR-TKIs,[20,25] accounting for 60% of cases, significant attention has been directed towards it

since 2016. This trend is evident in Figure 6A and C. Therefore, we curated relevant studies on T790M and conducted keyword analysis using VOSviewer, as depicted in Figure 8 and Table 6. Gefitinib and erlotinib, as first-generation EGFR-TKIs, are among the most commonly used drugs, as reflected by their high frequency of appearance in Figure 7C. Moreover, alongside T790m, the acquired resistance nodes in Figure 8A are also significant, indicating the importance of TKI resistance mechanisms. When taking into account Figure 8B, terms such as azd9291, Osimertinib, chemotherapy, etc., also appear frequently, and they became prominent relatively late, around 2018.

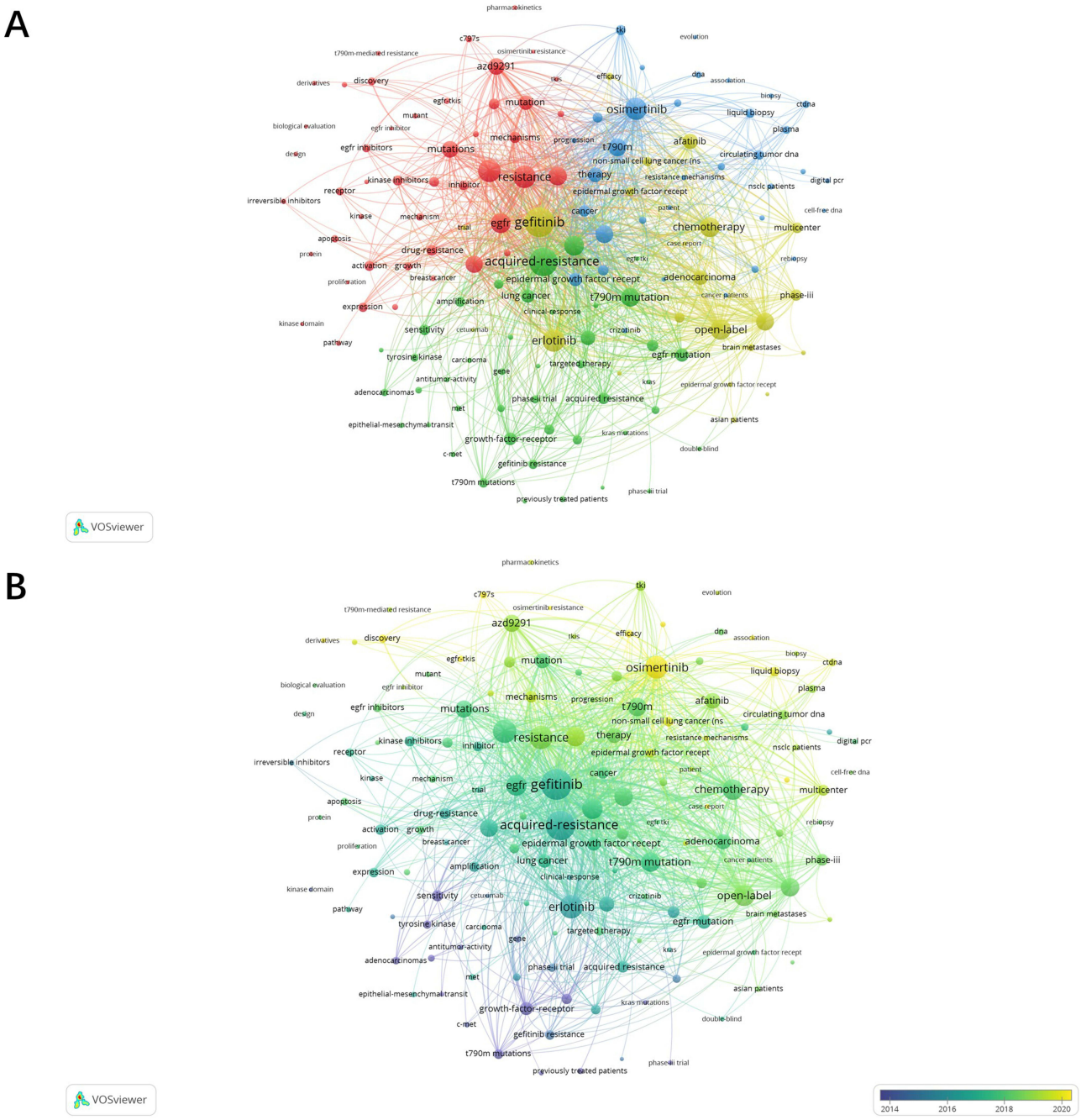

Figure 8 (**A**) The co-occurrence network and clusters of keywords related to T790M. (**B**) Density map of The core keywords.

Table 6 The Top 20 Keywords Related to T790M Mutation

Rank	Keyword	Count	Rank	Keyword	Count
1	Gefitinib	1084	11	NSCLC	442
2	Acquired-resistance	1022	12	t790m mutation	435
3	Resistance	639	13	1st-line treatment	418
4	Cell lung-cancer	637	14	t790m	416
5	Erlotinib	623	15	Non-small cell lung cancer	404
6	Osimertinib	616	16	Growth-factor receptor	373
7	Open-label	545	17	Azd9291	354
8	Egfr	510	18	Mutations	343
9	Chemotherapy	504	19	Afatinib	286
10	Tyrosine kinase inhibitors	482	20	Mutation	275

Discussion

General Information on EGFR-TKI Resistance in Lung Cancer

Through tracking the yearly publication and citation rates, we can discern the overarching developmental trajectory of EGFR-TKI resistance in lung cancer treatment. The emergence of EGFR as a therapeutic target in tumors was first proposed back in 1978.[4] Subsequently, with the FDA's approval of the inaugural EGFR-TKI drug gefitinib in 2003, there's been a notable uptick in both the quantity of published papers and their corresponding citations concerning resistance mechanisms, as evidenced in Figure 2. The surge reflects a growing acknowledgment in the scientific community of the complexities surrounding EGFR-TKI resistance and the urgent need for innovative strategies, that research on EGFR-TKIs resistance has amassed enough knowledge and methodology, inspiring further exploration and expansion in this field. Additionally, the predominance of JCR Quartile 1 journals in both the journal and co-cited journal analysis (Table 3) emphasizes the significance of EGFR-TKI resistance research within the scholarly community. This trend suggests that high-quality journals recognize the importance and impact of studies in this field, potentially driving further advancements and collaborations in the pursuit of novel treatment strategies.

From Figure 3 and Table 1, it is clear that China, the United States, and Japan demonstrate a significant level of collaboration, occupying the top three positions in publication volume. This collaborative spirit across nations highlights the global effort in tackling EGFR-TKI resistance in lung cancer. It's noteworthy that the top three institutions based on publication volume are all from the United States, underscoring their significant contributions and prominent standing in academia. However, while China leads in publication output, the lower H-index compared to the United States and Japan suggests a potential gap in the impact and quality of research. Furthermore, an analysis of highly cited literature from China and the United States reveals distinct focuses in their research. Chinese studies are primarily centered on the potential advantages of new drugs in treating drug-resistant NSCLC. For instance, the FLAURA clinical trial highlighted the clinical efficacy of osimertinib, demonstrating its superiority over traditional EGFR-TKIs through clinical trial data.[24] On the other hand, US publications tend to focus more on uncovering the molecular mechanisms underlying EGFR mutation-induced drug resistance. For example, one of the most highly cited studies identified MET amplification as a key driver of gefitinib resistance through ERBB3 (HER3)-dependent activation of PI3K, offering deep insights into personalized treatment strategies.[19] These research directions are complementary, with the latter emphasizing mechanistic exploration and the former focusing more on clinical application.

Current and Future Trends in EGFR-TKI Resistance Targets for Lung Cancer

In 2015, before the introduction of third-generation EGFR-TKI medication, osimertinib, the question of which EGFR mutation—specifically related to the first-generation drugs gefitinib and erlotinib—yielded better clinical responsiveness in lung cancer patients remained a prominent research focus. Among the top ten cited articles, Professor Lynch's study stands out with the highest citation count.[14] His research revealed that in patients with non-small cell lung cancer responsive to gefitinib, mutations in the EGFR gene were predominantly located in the EGFR tyrosine kinase domain. These mutations led to enhanced cellular response to growth factor signaling, thereby increasing sensitivity to gefitinib.

This finding suggests that targeting mutations clustered within specific regions of the EGFR tyrosine kinase domain may help identify patients responsive to gefitinib therapy. In terms of authorship, William Pao stands out among the top ten cited authors with the highest H-index. His publication "Acquired resistance of lung adenocarcinomas to gefitinib or erlotinib is associated with a second mutation in the EGFR kinase domain"[22] ranking ninth among the top ten cited articles, reports the emergence of resistant subclones containing an additional EGFR mutation, specifically the T790M mutation, following exposure to gefitinib or erlotinib in patients with sensitizing EGFR mutations. After 2015, the FDA approved osimertinib for targeting the T790M mutation, igniting interest in third-generation TKI research. The article with the highest citation eruption index in Figure 8, "Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer"[24] compared osimertinib (80 mg daily) with standard EGFR-TKIs (gefitinib at 250 mg daily, or erlotinib at 150 mg daily) in 556 patients with previously untreated, EGFR mutation-positive advanced NSCLC. The study demonstrated that osimertinib significantly prolonged median progression-free survival compared to standard treatments, confirming its superior efficacy as a first-line therapy in this patient group. This underscores the ongoing relevance of research into EGFR-TKI resistance mechanisms over the years. Expanding on targeted therapies, FGFR-TKIs, like EGFR-TKIs, face challenges with emerging resistance, driven by mechanisms such as gatekeeper mutations, alternative pathway activation, lysosome-mediated sequestration, and gene fusion.[26] While EGFR-TKIs target EGFR mutation-driven signaling, FGFR-TKIs focus on different molecular pathways, providing complementary approaches in precision oncology. Additionally, studies on ANXA2's impact on the lung cancer microenvironment and CASC's role in prognosis further underscore the complexity of resistance mechanisms across TKIs.[27,28] These findings highlight the need for ongoing research and the complementary roles of FGFR-TKIs and EGFR-TKIs in lung cancer treatment.

In the core keyword analysis portrayed in Figure 7A, the blue cluster encompasses pivotal terms like HER2, MET, BRAF, and K-RAS mutations, indicating their relevance in the landscape of EGFR-TKI resistance. They all fall within EGFR-independent, non-target-dependent resistance mechanisms, involving the upregulation of downstream signaling proteins or the activation of one or more bypass signaling pathways following cellular phenotype transformation.[29] When considering Figure 7A and C holistically, it's evident that while these resistance targets receive less attention compared to T790M, their significance predates the emergence of T790M. This precedence, potentially attributable to historical context and lower clinical incidence rates, is exemplified by MET amplification, somewhat more common compared to other mutations, which accounts for only 5% in first- and second-generation TGFR-TKI resistance mechanisms but increases to 15% in the third generation.[30] Moreover, the recent spotlight on the C797S mutation, conspicuously illustrated in the figure following T790M, has sparked significant interest. The C797S mutation, characterized by a serine substitution for cysteine at position 797 in exon 20 of EGFR,[31] stands as a pivotal mechanism of resistance to third-generation TKIs. This highlights the evolving nature of resistance mechanisms and underscores the need for ongoing exploration to develop effective counterstrategies.

Treatment After Resistance to EGFR-TKI

In the keyword analysis presented in Figure 6A, the green cluster clearly highlights the central themes in treatment. It specifies that "1st line treatment" with EGFR-TKI is the preferred choice for lung cancer patients with EGFR mutations. Professor Mitsudomi's open-label, randomized Phase III clinical trial (WJTOG3405),[13] as shown in Table 4, illustrates that gefitinib significantly extends progression-free survival for these patients when compared to a regimen of cisplatin and docetaxel. However, despite the superior efficacy of EGFR-TKI, resistance to this treatment is a significant and unavoidable issue. This reality calls for continuous research into novel therapeutic strategies that could potentially enhance treatment effectiveness and delay the onset of resistance. In Figure 7 keyword analysis, osimertinib (azd9291) emerges as an effective solution for combating resistance primarily driven by the T790M mutation, which is a typical treatment approach for patients resistant to first and second-generation EGFR-TKIs. The third-generation osimertinib is designated as the preferred medication in the American NCCN guidelines,[32] but the use of first-generation followed by third-generation TKIs is also common. Since the emergence of the T790M mutation following EGFR-TKI treatment is typical, some patients may benefit from this approach—experiencing extended progression-free survival (PFS) and overall survival (OS). Therefore, exploring how to better utilize EGFR-TKIs is a question worth considering.

For patients with known resistance mechanisms like MET amplification, HER2 amplification, and C797S mutation, researchers are exploring various dual-targeting strategies. For instance, clinical trials combining MET-TKI and EGFR-TKI for treating NSCLC patients with MET amplification have already shown promising clinical benefits and robust anti-tumor activity.[31,33,34] Additionally, experiments with the fourth-generation drug BLU-945, aimed at overcoming the C797S mutation, are being vigorously pursued.[35]

For other patients, strategies such as Antibody-Drug Conjugate (ADC), Chemotherapy combined with Immunotherapy, and Chemotherapy combined with anti-VEGF therapy are still under exploration.[30,36,37] The ADC is composed of a monoclonal antibody attached to a cytotoxic drug, effectively killing target cells while minimizing toxicity to non-target cells.[38] BL-B01D1, an EGFR × HER3 bispecific ADC linked to a topoisomerase I inhibitor via a cleavable linker, has shown promising Phase I results in heavily pretreated EGFR-mutant NSCLC patients (n = 34), with an ORR of 61% (95% CI, 43.6–77.8) and a DCR of 91.2% (76.3–98.1).[39] Additionally, due to the lack of successful or reliable treatment strategies to overcome EGFR TKI resistance, switching to chemotherapy remains the most widely accepted approach, as supported by current practice guidelines.[40] The Phase II clinical trial of osimertinib combined with chemotherapy (FLAURA2 study) has demonstrated superior efficacy and safety compared to osimertinib alone.[41] This might explain why "chemotherapy" appears as a prominent keyword in both Figures 6A and 7A: patients with EGFR mutations may benefit significantly from a combined regimen of EGFR-TKI and chemotherapy. Furthermore, after patients with EGFR resistance undergo chemotherapy and experience disease progression again, there is a focus on whether re-challenging them with EGFR TKIs, as EGFR-sensitive mutant cell populations may re-emerge, becomes a research priority.[42]

These innovative approaches reflect a significant shift towards precision medicine in lung cancer treatment. The successful development of these targeted therapies may signify a pivotal moment in cancer treatment, potentially setting new standards for managing the complex resistance mechanisms of lung cancer. These areas are expected to become major research focuses in the field in the near future.

Strength and Limitation

Our study on EGFR-TKI resistance in lung cancer treatment employed a meticulous search formula to gather a comprehensive array of relevant research articles. Utilizing advanced bibliometric and visualization analysis tools like CiteSpace and VOSviewer, we not only explored previous research trends and focal points but also gained insights into crucial research nodes. Furthermore, our study made well-founded predictions for future research trajectories, aiding in the advancement of knowledge in this area.

However, despite these strengths, our study has limitations. We confined our search to the Wosc database, potentially excluding pertinent articles from other databases and thereby possibly overlooking critical insights. Additionally, due to access constraints to certain databases, we may have missed recent articles published after our retrieval date, limiting the inclusivity of our findings. These limitations underscore the need for cautious interpretation and suggest avenues for future research exploration.

Conclusion

The landscape of EGFR-TKI resistance in lung cancer treatment has witnessed significant evolution and progress over the past few decades. The annual publication count and cumulative citation count have steadily increased since the approval of the first EGFR-TKI drug gefitinib in 2003, reflecting the growing interest and impact of research in this field. Collaboration among researchers from various countries, with notable contributions from China, the United States, and Japan, underscores the global effort in addressing EGFR-TKI resistance. Renowned institutions such as the Dana-Farber Cancer Institute and Harvard University have played pivotal roles in advancing research, alongside prolific authors like Professor Yi-Long Wu and Professor William Pao. Combining EGFR-TKI with chemotherapy has shown promising results in overcoming resistance and improving patient outcomes. Additionally, ongoing research into novel therapeutic strategies targeting resistance mechanisms like MET amplification and HER2 amplification holds great potential for enhancing treatment efficacy and prolonging survival.

Looking ahead, firstly, clear identification of resistance mechanisms can guide post-resistance treatment strategies, necessitating further detailed exploration of specific resistance mechanisms. Secondly, the emergence of novel clinical drugs provides additional options for addressing resistance issues, yet these new medications require further clinical trials to validate their safety and efficacy. For instance, preliminary success has been observed with combination therapies targeting MET amplification/overexpression, with further research data eagerly anticipated to provide guidance. Thirdly, for "chemo+" treatment approaches following EGFR-TKI resistance, more clinical data and real-world evidence are needed to assess safety and patient outcomes, aiming for improved survival rates.

In summary, while challenges persist, the rapid pace of research in EGFR-TKI resistance in lung cancer holds promise for transformative advancements in the diagnosis and treatment of this disease. By leveraging multidisciplinary approaches and harnessing cutting-edge technologies, the field is poised to usher in a new era of precision oncology, ultimately improving patient outcomes and quality of life.

Data Sharing Statement

The data collected and analyzed in the article are from WOS, an open access database of scholarly articles, and are properly adopted and collected.

Ethics Approval

Ethical approval was not required for this study, as all data were downloaded from public databases and did not involve any human or animal participants.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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