

# Global research Trends in Tyrosine Kinase Inhibitors: A Co-Word and Visualized Study

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Submitted to: JMIR Medical Informatics  
on: October 29, 2021

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# Global research Trends in Tyrosine Kinase Inhibitors: A Co-Word and Visualized Study

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## Abstract

**Background:** Tyrosinase inhibitors (TKIs) have achieved revolutionary results in the treatment of a wide range of tumors, which have brought out a lot of literature in this field every year. And some reviews provide a great value for us to understand TKIs. However, there is a lack of studies on the knowledge structure and bibliometric analysis in TKIs research.

**Objective:** This paper aims to investigate the knowledge structure, hotspots, and trends of evolution of the field of TKIs by co-word analysis and literature visualization.

**Methods:** We obtained all academic papers about TKIs published in 2016-2020 from the Web of Science. Based on counting keywords from those papers, we generated the co-word networks by extracting the co-occurrence relationships between keywords, and segmented communities to identify the sub-directions of TKIs research by calculating the network metrics of the overall and local networks. We also mapped the association network topology, including the network within and between TKIs sub-directions, to reveal the association and structure among varied sub-directions. Finally, evolution venation and strategic diagram were generated to reveal the trends of TKIs research.

**Results:** We obtained 6,782 unique words (total frequency 26,175) from 5,584 paper captions. Finally, 296 high-frequency words were selected with a threshold of 10 after discussion, the total frequency of which accounted for 65.41%. The analysis of burst disciplines revealed a variable number of burst words of TKIs research every year, especially in 2019 and 2020, such as HER2, Pyrotinib, Next-generation Sequencing, Immunotherapy, ALK-TKI, ALK Rearrangement, etc. By network calculation, the TKIs co-word network was divided into six communities: C1-Non-small Cell Lung Cancer, C2-Targeted Therapy, C3-Chronic Myeloid Leukemia, C4-HER2, C5-Pharmacokinetics, and C6-ALK. The venation diagram revealed several clear and continuous evolution trends, such as Non-small Cell Lung Cancer venation, Chronic Myeloid Leukemia venation, Renal Cell Carcinoma venation, Chronic Lymphocytic Leukemia venation, etc. In the strategic diagram, C1-Non-small Cell Lung Cancer was the core direction located in the first quadrant, C2-Targeted Therapy was exactly at the junction of the first and fourth quadrants that meant C2 was developing, and C3-Chronic Myeloid Leukemia, C4-HER2, and C5-Pharmacokinetics were all immature that all located in the third quadrant.

**Conclusions:** Using co-word analysis and literature visualization, we revealed the hotspots, knowledge structure, and trends of evolution of TKIs research during 2016-2020. TKIs research mainly focused on targeted therapies against varied tumors, particularly against NSCLC. The attention on CML and pharmacokinetics was gradually decreasing, but the heat of HER2 and ALK was rapidly increasing. TKIs research had shown a clear development path: TKIs research was disease-focused and revolved around "gene targets/targeted drugs/resistance mechanisms". Our outcomes will provide sound and effective support to researchers, funders, policymakers, and clinicians.

(JMIR Preprints 29/10/2021:34548)

DOI: <https://doi.org/10.2196/preprints.34548>

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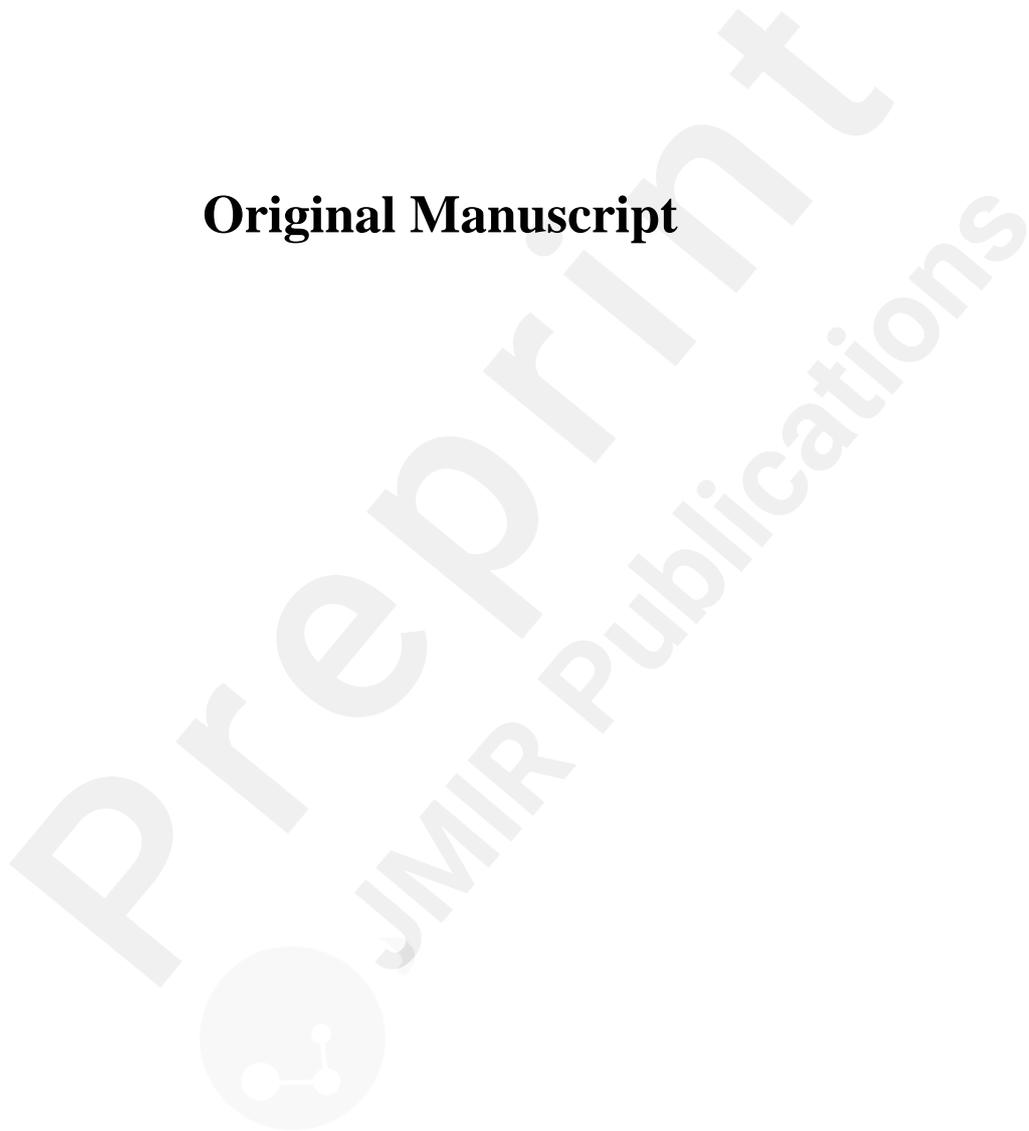
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## Global research Trends in Tyrosine Kinase Inhibitors: A Co-Word and Visualized Study

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## **Abstract**

### **Background**

Tyrosinase inhibitors (TKIs) have achieved revolutionary results in the treatment of a wide range of tumors, which have brought out a lot of literature in this field every year. And some reviews provide a great value for us to understand TKIs. However, there is a lack of studies on the knowledge structure and bibliometric analysis in TKIs research.

### **Objective**

This paper aims to investigate the knowledge structure, hotspots, and trends of evolution of the field of TKIs by co-word analysis and literature visualization.

### **Methods**

We obtained all academic papers about TKIs published in 2016-2020 from the Web of Science. Based on counting keywords from those papers, we generated the co-word networks by extracting the co-occurrence relationships between keywords, and segmented communities to identify the sub-directions of TKIs research by calculating the network metrics of the overall and local networks. We also mapped the association network topology, including the network within and between TKIs sub-directions, to reveal the association and structure among varied sub-directions. Finally, evolution venation and strategic diagram were generated to reveal the trends of TKIs research.

### **Results**

We obtained 6,782 unique words (total frequency 26,175) from 5,584 paper captions. Finally, 296 high-frequency words were selected with a threshold of 10 after discussion, the total frequency of which accounted for 65.41%. The analysis of burst disciplines revealed a variable number of burst words of TKIs research every year, especially in 2019 and 2020, such as HER2, Pyrotinib, Next-generation Sequencing, Immunotherapy, ALK-TKI, ALK Rearrangement, etc. By network calculation, the TKIs co-word network was divided into six communities: C1-Non-small Cell Lung Cancer, C2-Targeted Therapy, C3-Chronic Myeloid Leukemia, C4-HER2, C5-Pharmacokinetics, and C6-ALK. The venation diagram revealed several clear and continuous evolution trends, such as Non-small Cell Lung Cancer venation, Chronic Myeloid Leukemia venation, Renal Cell Carcinoma venation, Chronic Lymphocytic Leukemia venation, etc. In the strategic diagram, C1-Non-small Cell Lung Cancer was the core direction located in the first quadrant, C2-Targeted Therapy was exactly at the junction of the first and fourth quadrants that meant C2 was developing, and C3-Chronic Myeloid Leukemia, C4-HER2, and C5-Pharmacokinetics were all immature that all located in the third quadrant.

### **Conclusions**

Using co-word analysis and literature visualization, we revealed the hotspots, knowledge structure, and trends of evolution of TKIs research during 2016-2020. TKIs research mainly focused on targeted therapies against varied tumors, particularly against NSCLC. The attention on CML and pharmacokinetics was gradually decreasing, but the heat of HER2 and ALK was rapidly increasing. TKIs research had shown a clear development path: TKIs research was disease-focused and revolved around "gene targets/targeted drugs/resistance mechanisms". Our outcomes will provide sound and effective support to researchers, funders, policymakers, and clinicians.

**Keywords:** TKIs, co-word analysis, literature visualization, NSCLC, targeted therapy, CML, topics distribution, HER2, pharmacokinetics,

## 1. Introduction

Tyrosine kinases (TKs) are a collective term for dozens of kinases encoded by multiple genes, which can phosphorylate tyrosine residues in cells<sup>1</sup>. Based on varied cellular localizations, the TKs family is divided into receptor tyrosine kinases (RTKs)<sup>2</sup> and non-receptor tyrosine kinases (non-RTKs)<sup>3</sup>. RTKs consist of 20 subfamilies (e.g., epidermal growth factor receptor (EGFR)<sup>4</sup>, vascular endothelial growth factor receptor (VEGFR)<sup>5</sup>), whereas non-RTKs include 10 subfamilies such as ABL, SRC, and CSK<sup>6</sup>. TKs have the common activity to catalyze the transfer of  $\gamma$ -phosphate groups on adenosine triphosphate (ATP) to the tyrosine residues of a variety of target proteins<sup>1, 3-7</sup>, and this process plays a key role in signal transduction in the cell. Abnormal activities of TKs are closely associated with proliferation, invasion, metastasis, apoptosis, and tumor angiogenesis in non-small cell lung cancer (NSCLC)<sup>8</sup>, chronic myeloid leukemia (CML)<sup>2, 9</sup>, and many other tumors. Therefore, TKs have become excellent targets for tumor therapy.

Tyrosine kinase inhibitors (TKIs) are referred to as a class of small-molecule compounds that can specifically inhibit TKs. They can penetrate through the cell membrane and block the signaling pathway of tumor proliferation, and some TKIs can also inhibit angiogenesis<sup>1, 10</sup>. TKIs have revolutionized the treatment of a variety of tumors<sup>10-12</sup>, for example, imatinib has been a typical pioneer in successfully translating oncogene research into molecular targeted therapy. Now, TKIs have developed to the fourth generation, which aims to overcome drug resistance due to mutations of T790M and C797S<sup>13</sup>. More than 30 small-molecule TKIs have been approved for marketing by the U.S. Food and Drug Administration (FDA), and hundreds of drug candidates are in various stages of clinical trials<sup>13-15</sup>. Therefore, this article aims to understand the development process of TKIs research, identify the main research directions, and analyze the potential research hotspots.

Co-word analysis is a content analysis method to study the knowledge structure and evolutionary patterns of various fields. It can facilitate researchers to identify hotspots, composition, paradigms, and evolution of a field by calculating the word pairs and co-occurrence of noun phrases in the literature<sup>16-18</sup>. This method has been used widely in medical bibliometric analysis, such as precision medicine<sup>16</sup>, neonatal ischemic-hypoxic encephalopathy<sup>19</sup>, stem cell research<sup>20</sup>, neural stem cells<sup>17</sup>, tumor immunotherapy<sup>18</sup>, disaster medicine<sup>21</sup>, medical big data<sup>22</sup>, surgical robotics<sup>23</sup>, epilepsy genetics<sup>24</sup>, etc. We propose to use the co-word analysis to explore the knowledge structure, evolution trends, and associations among sub-topics of TKIs research, aiming to help clinicians and scholars have a better understanding of TKIs and to give suggestions for research and usage of TKs.

## 2. Literature review

### 2.1 Background

In recent years, targeted therapies have become a hotspot in the development of anti-tumor drugs with their advantages of high selectivity and low side effects<sup>25, 26</sup>. TKIs are revolutionary targeted drugs that inhibit tumor proliferation by interfering with or inhibiting specific proteins within cancer cells, thus exerting prominent anti-tumor effects<sup>1-3</sup>. Among them, imatinib was the first targeted antitumor drug<sup>27</sup>, which was first approved in 2001 for the treatment of BCR-ABL-positive and Philadelphia chromosome-positive CML<sup>3, 6</sup>. And then, the first, second, and third-generation TKIs, represented by gefitinib, dasatinib, and osimertinib, have been validated in hundreds of clinical trials and approved for marketing<sup>10-12, 28, 29</sup>.

Genetic testing has been developed rapidly. Next-generation sequencing (NGS) allows for the sequencing genome and exome within days and makes it possible to identify patients with druggable mutations quickly and precisely<sup>30</sup>. Meanwhile, multidisciplinary collaboration between pharmacology and clinical science has brought a leap forward in basic research and clinical applications of TKIs. First, tumor-targeted therapies are the most established area for TKIs, especially in the treatment of lung cancer<sup>12, 15, 31, 32</sup>, and leukemia<sup>10, 11, 28, 29</sup>. It's demonstrated that TKIs improved the quality of life and extend survival in patients with advanced NSCLC<sup>33</sup>. Imatinib and gefitinib have become first-line drugs due to their outstanding clinical efficacy in patients with BCR-ABL-positive CML<sup>10, 11, 28, 29</sup>. Second, clinical trials of various drugs targeting HER2 and ALK (e.g.,

trastuzumab<sup>34, 35</sup>, patolizumab<sup>36</sup>, ceritinib<sup>37</sup>) have manifested excellent effects. Third, pharmacokinetics is another focus of TKIs research. Optimization and selectivity study is an important direction for continuing clinical trials after the launch of many TKIs. And individualized blood concentration monitoring is also important for patients with poor efficacy or severe side effects<sup>38</sup>.

## 2.2 Previous efforts

In recent years, TKIs have been widely used for tumor-targeted therapies. Numerous research efforts helped clinicians and scholars better understand TKIs and facilitated the clinical translation of study outcomes.

Based on recent reviews, the current status of TKIs research is summarized as follows: First, TKIs resistance is becoming increasingly prominent, of which genetic mutations (e.g., T790M<sup>39, 40</sup>, C797S<sup>13</sup>, D761Y<sup>41</sup>, L747S<sup>42</sup>) are the main cause. It has become a key direction to find new molecular mechanisms of TKIs resistance and to establish individualized dosing regimens. Second, the application of drugs such as Erlotinib<sup>43</sup>, Osimertinib<sup>15, 33</sup>, and Gefitinib<sup>44</sup> has gradually matured and occupied an important position in the treatment of various tumors such as NSCLC<sup>11, 12</sup>. Third, drugs targeting HER2 and ALK continue to emerge, which offers new hope for solving the plague of drug resistance<sup>45, 46</sup>. To date, hundreds of new TKIs candidates are in various stages of clinical research<sup>47</sup>.

## 2.3 The rationale for the study

Research on TKIs continues to grow to benefit more patients. However, there is still a lot of uncharted territories to explore in TKIs research. How to discover new biomarkers of TKIs? How to select TKIs with better clinical effects and fewer side effects for targeted therapy? How to overcome multidrug resistance in patients with tumors? All these questions need scientific bibliometric analysis based on the results of TKIs research. The purpose of our study is to address the following questions:

- (1) What is the overall knowledge structure of TKIs research?
- (2) What are the sub-directions of TKIs research and how do they interact with each other?
- (3) What are the evolutionary status and development trends of TKIs research in the temporal dimension?

## 3. Methods

### 3.1 Data collection and processing

It is well known that Web of Science Core Collection (WOSCC) is the most extensive and comprehensive academic literature database, so we used subjects (including "Tyrosine kinase inhibitor, Tyrosine kinase inhibitors, TKI, TKIs, Tyrosine kinases inhibitors, Tyrosine kinases inhibitors") in WOSCC to precisely search all literature about TKIs by limiting the period to 2016-2020 and the literature types to journal papers, reviews and conference papers. The specific search formula is "(TS= ("Tyrosine kinase inhibitor" OR "Tyrosine kinase inhibitors" OR "TKI" OR "TKIs" OR "Tyrosine kinases inhibitors" OR "Tyrosine kinases inhibitor")) AND LANGUAGE: (English) Refined by: DOCUMENT TYPES: ( ARTICLE OR REVIEW OR PROCEEDINGS PAPER ) Timespan: 2016-2020. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI, CCR-EXPANDED, IC".

A total of 13,895 documents were retrieved and exported in Tab-delimited (Win) format. Next, the records containing search terms in the titles or keywords were retained, while the records without keywords and the records with search terms appearing only in the abstracts were excluded<sup>48, 49</sup>. Finally, 5,584 records were obtained for the subsequent co-word network analysis. (Figure 1)

Since there are irregularities and inconsistencies in the writing of keywords submitted by the authors themselves in WOS, it is necessary to pre-process them. First, this paper aims to depict the research status of TKIs by using other terms associated with TKIs, so TKI itself, the synonyms, and

hypernyms of TKI were removed. Keywords whose meaning is broad (e.g., review, development, problem, etc.) were also removed. Secondly, the co-word analysis generally targets high-frequency keywords and their relationships, while keywords with very low frequencies cannot reflect the main direction of the current research. Therefore, this paper firstly generated a list of keywords by frequency descending order and then defined the threshold of high-frequency keywords according to the cumulative percentage of frequencies in the list<sup>50</sup>. Third, keywords with frequencies below the threshold were merged into the words with the closest meanings, and words with the same meaning and different forms were also merged, such as “BCR-ABL TKI” to “BCR-ABL” and “Epidermal Growth Factor Receptor” to “EGFR”. Fourth, after de-duplicating the merged keywords, a new list of keyword frequencies was generated.

**Figure 1.** Search procedure for documents in TKIs research. DE: descriptor; TI: title; WOSCC: Web of Science Core Collection.

### 3.2 Network construction and analysis

The keywords in a paper are an accurate description of its main content, so mining keywords and their relationships can help reveal the hidden connotation of a research field<sup>51</sup>. If two words co-occur in the same connotation unit (e.g., keywords in a paper), they are related or similar in connotation and have consistency in connotation expression. Their co-occurrence frequency is equal to the number of papers that contain them at the same time, and the greater the frequency, the stronger the semantic association between them<sup>52</sup>. By constructing co-word networks and performing structural analysis and visualization, co-word analysis can effectively reveal the underlying connotations, research structures, and even evolutionary trends of a research field<sup>53</sup>.

In this paper, the above pre-processed data were imported into SCI2<sup>54</sup> for frequency statistics and co-word network generation (.net format). Then, the .net file was imported into the network analysis tool Pajek<sup>55</sup> to calculate network indicators, including centralization (centrality)<sup>56</sup>, density<sup>57</sup>, and the clustering coefficient<sup>58</sup>, and to perform community segmentation to identify major sub-directions. The centralization refers to the centripetal or consistency of the co-word network as a whole, while centrality reflects the keywords' position in the network and its ability to influence and control the network<sup>56</sup>; The density represents the degree of association of the network as a whole, and the stronger the association, the more mature the research field; the clustering coefficient reflects the possibility that words will cluster into classes depending on the association and its strength, and the possibility that the network will be distinctly divided into several sub-networks or sub-classes. Combined with the community segmentation algorithm (Louvain)<sup>59</sup>, the co-word network will be divided into distinctive communities, each of which represents a sub-direction. with strong ties within the communities and loose ties between the communities, reflecting a greater concentration or consistency in the connotative associations of words within the community. Keywords are tightly linked within communities and loosely linked between communities, reflecting that keywords possess more focused or consistent connotations within communities.

### 3.3 Mapping and Visualization

To show the structure and characteristics of the TKIs research more intuitively and clearly, we visualized the topology, evolutionary venations, and development trend of the co-word network.

First, the visualization of the network topology. In this paper, Vosviewer<sup>60</sup> was used for the multi-level presentation of co-word networks and communities, including the inter-community and intra-community association network graphs. In the network graphs, nodes represent keywords or communities, and edges represent co-occurrence relationships between words or communities. The size of nodes and the thickness of lines are proportional to the frequency of keywords and the scale of communities, respectively, and the nodes and lines belonging to different communities are distinguished by different colors. These network diagrams visualize the importance and association relationships of keywords or communities in TKIs and help to analyze the distribution and structural

characteristics of TKIs research.

Second, the visualization of evolutionary venations. In this paper, we divided each year's records into several communities. Then we used Cortext<sup>61</sup> to calculate the overlapping relationships between communities in adjacent years and connected them through "tubes". In the tube diagram, bars of different colors and sizes represent communities of different sizes, and the tubes connected by several bars represent the continuation of the research theme, which can be considered as evolutionary venations. The evolutionary trends of TKIs research over time are visualized by graphically characterizing the continuity, convergence, and divergence of communities.

Third, the visualization of the developmental degree of the sub-directions of TKIs research. These research communities can be considered as sub-directions of TKIs research, and each community or sub direction exhibits specific development status depending on the density and centrality. So, we drew a two-dimensional strategic diagram based on the calculation of the density and centrality of each community. The strategic diagram took centrality, which represented the core degree of research directions in TKIs, as the horizontal axis, and density, which represented the developmental maturity of research directions, as the vertical axis, and the mean of community density and centrality as the origin. Ultimately, communities were mapped into 4 quadrants to visualize the degree of centrality and maturity of different research directions in TKIs.

Fourth, the visualization of burst words. The changes in keyword frequency fluctuate significantly, with some of the words appearing in sudden bursts, reflecting the existence of distinct epochal characteristics of TKIs research. Therefore, we detected keyword bursts and combined their burst weights and durations to reveal changes in the focus of TKIs research<sup>62</sup>.

#### 4. Results

##### 4.1 Themes involved in TKIs research

We extracted 10,956 unique keywords from the 5,584 available paper titles, and their total frequency was 28,743 (Figure 2). After pre-processing, 6,782 unique words with a total frequency of 26,175 were left. After several rounds of testing and discussion, the threshold value of high-frequency words was taken as 10 in this paper. So after merging the keywords with frequencies lower than 10 into their superordinate words, we finally obtained 296 keywords for the subsequent co-word analysis (Table 1). These 296 keywords whose total frequency accounted for 65.41% (17,120/26,175), can represent the mainstream of TKIs research in the past 5 years and can also reflect a strong concentration trend of TKIs research.

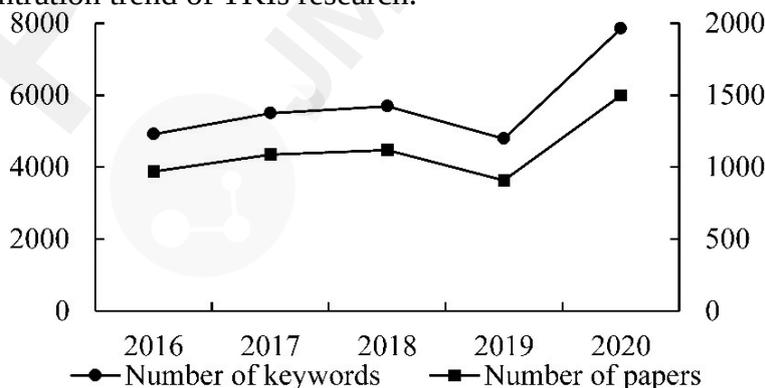


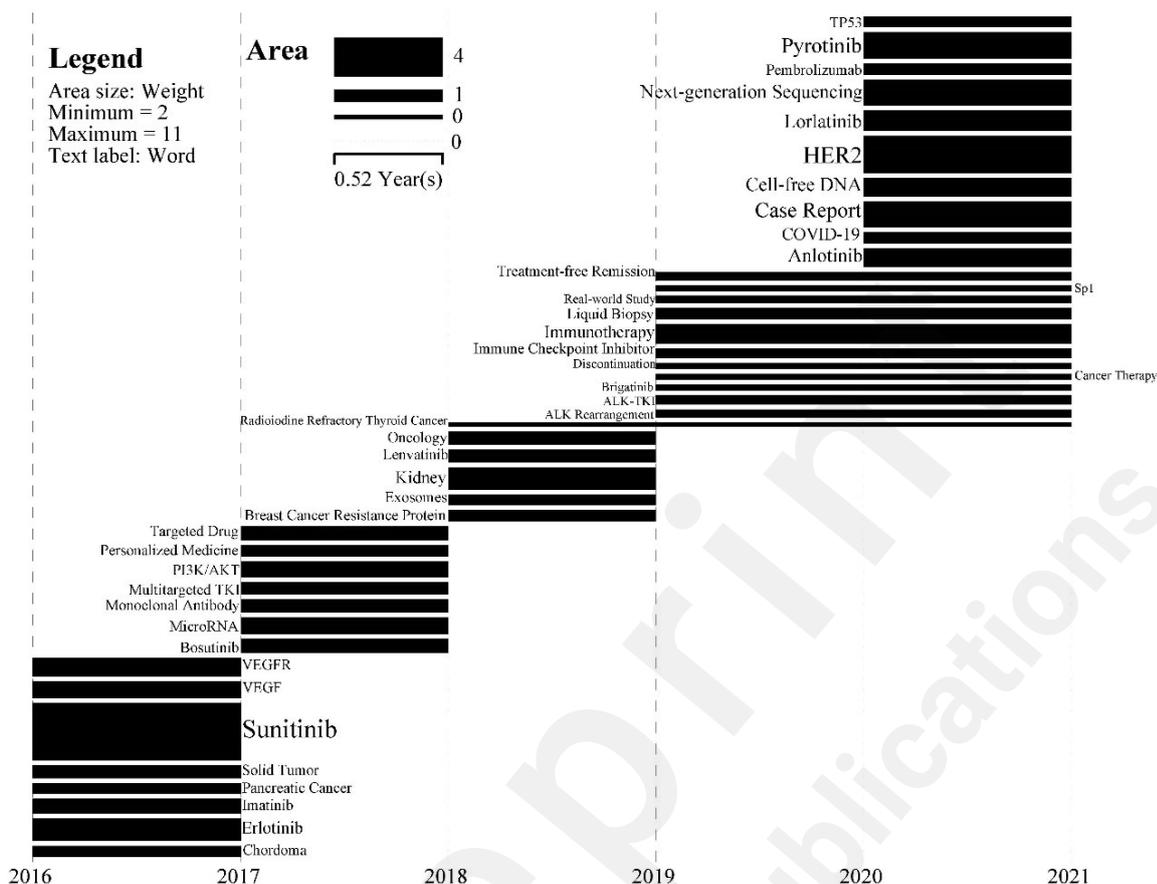
Figure 2. Yearly number of papers and words related to TKIs research (2016-2020)

Table 1. Top 100 keywords in papers related to TKIs research

Ranking	Words	Frequency	Ranking	Words	Frequency
1	Non-small Cell Lung Cancer	1344	51	Metabolism	76
2	EGFR	916	52	Angiogenesis	73
3	Chronic Myeloid Leukemia	586	53	Overall Survival	72

4	EGFR-TKI	506	54	Adenocarcinoma	72
5	EGFR Mutation	404	55	T790M Mutation	71
6	Lung Cancer	370	56	Met	70
7	Erlotinib	299	57	Lapatinib	68
8	Imatinib	283	58	Adverse Event	68
9	Osimertinib	261	59	Molecular Docking	67
10	Gefitinib	257	60	Carcinoma	66
11	Targeted Therapy	256	61	Meta-analysis	64
12	Renal Cell Carcinoma	227	62	Circulating Tumor DNA	60
13	Sunitinib	219	63	Autophagy	59
14	Lung Adenocarcinoma	207	64	Sarcoma	58
15	Mutation	201	65	Combination Therapy	58
16	Resistance	192	66	Acute Myeloid Leukemia	58
17	Afatinib	186	67	Icotinib	58
18	Chemotherapy	183	68	Leukemia	55
19	Cancer	175	69	VEGFR2	55
20	Dasatinib	162	70	Oncology	53
21	Drug Resistance	159	71	Cabozantinib	52
22	T790M	156	72	Molecular Response	52
23	ALK	156	73	Ponatinib	52
24	Brain Metastasis	136	74	Liquid Biopsy	51
25	Tumor	134	75	Renal Cancer	51
26	BCR-ABL	128	76	Acute Lymphoblastic Leukemia	50
27	Nilotinib	121	77	Plasma	48
28	Crizotinib	120	78	Epithelial-mesenchymal Transition	48
29	HER2	119	79	VEGFR-TKI	48
30	Apoptosis	113	80	Drug-drug Interaction	47
31	Metastasis	111	81	PD-L1	47
32	Acquired Resistance	111	82	VEGFR	47
33	Sorafenib	109	83	Clinical Trial	47
34	Prognosis	107	84	EGFR-TKI Resistance	46
35	Breast Cancer	107	85	Axitinib	46
36	Pharmacokinetics	107	86	Philadelphia Chromosome	45
37	Pazopanib	106	87	P-glycoprotein	45
38	Next-generation Sequencing	96	88	TKI Resistance	44
39	Hepatocellular Carcinoma	92	89	Therapeutic Drug Monitoring	44
40	Gastrointestinal Stromal Tumor	92	90	Sequencing	43
41	Lenvatinib	92	91	Neratinib	43
42	Apatinib	91	92	Receptor Tyrosine Kinase	43
43	Immunotherapy	91	93	Brutons Tyrosine Kinase	43
44	Toxicity	89	94	Immune Checkpoint Inhibitor	43
45	Metastatic Renal Cell Carcinoma	80	95	Small Cell Lung Cancer	42
46	Radiotherapy	80	96	Molecular Targeted Therapy	41
47	VEGF	78	97	Thyroid Cancer	41
48	Ibrutinib	78	98	Case Report	41
49	Progression-free Survival	77	99	ROS1	40
50	Biomarker	76	100	c-Met	39
			100	FGFR	39

100	Bevacizumab	39
100	BTK Inhibitor	39



**Figure 3.** Burst disciplines of TKIs research from 2016 to 2021

Burst keywords can represent important changes in TKIs research. Figure 3 showed a varying number of burst words in TKIs research each year, whose duration expressed in terms of the length of the horizontal bar and weight in terms of the area. As can be seen from figure 3, a variable number of emergent terms have appeared in TKIs research every year since 2016, especially in 2019 and 2020, indicating the emergence of new research themes in this field every year. And the greater weight of burst words in 2020-2021 (e.g., HER2, Pyrotinib, Next-generation Sequencing, COVID-19, Immunotherapy, ALK-TKI, ALK Rearrangement, Cell-free DNA, Liquid Biopsy, Personalized Medicine), suggests that these words in TKIs research were extensively explored by researchers in 2020.

**4.2. Correlation structure of keywords in TKIs research**

Our analysis revealed that the co-word network consisting of the above 296 keywords was exactly the maximal connected subgraph, i.e., none of the high-frequency words in TKIs research is isolated, and all of them have paths associated with others, indicating that the research topics in this field form a whole that is interrelated and interact with each other.

**4.2.1 Indicators of the correlation network**

The overall indicators of the co-word network are shown in Table 2. The average degree of the network is 49.58, which means that a keyword in TKIs research is directly associated with 49.58 other keywords on average. These 49.58 keywords represent 16.75% of the entire network, which is a relatively small percentage, indicating that the range of inter-topic associations in TKIs research is not extensive. The high degree centralization of the network indicates a strong tendency to be

centripetal or concentrated; the high closeness centralization and low betweenness centralization indicates that keywords are most directly related to each other rather than indirectly related; the high clustering coefficient indicates that keywords are likely to cluster into communities with certain words as the core. Collectively, TKIs research has clustered in certain specific sub-directions in recent years, between which the distinction is obvious. However, the density of the current co-word network is not high, i.e., the keywords are not closely related to each other, which indicates that TKIs research is more seriously fragmented and does not form a unified and mature research identity. We further divided the TKIs co-word network into six communities and calculated the module degree<sup>63</sup> to ensure a good division.

**Table 2.** The whole network indicators

Indicators	Value
Number of nodes	296
Number of lines	7338
Average degree	49.5811
Network All Degree Centralization	0.5953
Network All Closeness Centralization	0.5265
Network Betweenness Centralization	0.0525
Network Clustering Coefficient	0.4702
Density	0.1681
Number of Communities	6 (Modularity: 0.3062)

The network indicators of the keywords reflected their position and role in the TKIs co-word network (Table 3). Non-small Cell Lung Cancer, EGFR, Targeted Therapy, Lung Cancer, EGFR-TKI, Erlotinib, Chemotherapy, Cancer, Sunitinib, and Resistance all appear in the top 10 list of degree centralization and closeness centralization. The research topics associated with these words play an important role and have a strong influence on the whole field, while other words are likely to be clustered into a community with the above words as the core, forming a distinctive research sub-direction. In addition to Resistance, the above words also appear in the top 10 list of betweenness centralization, which serves as "bridges" in TKIs research, suggesting that more collaborations or synergies between TKIs research need to pass through these terms.

**Table 3.** Top-10 keywords in terms of degree, betweenness, and closeness centrality

Ranking	Words	Degree	Words	Closeness	Words	Betweenness
1	Non-small Cell Lung Cancer	224	Non-small Cell Lung Cancer	0.8060	Non-small Cell Lung Cancer	0.0552
2	EGFR	204	EGFR	0.7642	EGFR	0.0397
3	Targeted Therapy	180	Targeted Therapy	0.7195	Targeted Therapy	0.0346
4	Lung Cancer	179	Lung Cancer	0.7178	Chemotherapy	0.0320
5	EGFR-TKI	166	EGFR-TKI	0.6958	Lung Cancer	0.0291
6	Erlotinib	164	Erlotinib	0.6925	EGFR-TKI	0.0251
7	Chemotherapy	161	Chemotherapy	0.6876	Erlotinib	0.0216
8	Cancer	153	Cancer	0.6751	Sunitinib	0.0214
9	Sunitinib	151	Sunitinib	0.6720	Imatinib	0.0211
10	Resistance	142	Resistance	0.6585	Cancer	0.0206

#### 4.2.2 Analysis of thematic communities

Depending on the association between keywords, TKIs are divided into six clusters or communities with certain important terms at their core. They are C1-Non-small Cell Lung Cancer, C2-Targeted Therapy, C3-Chronic Myeloid Leukemia, C4-HER2, C5-Pharmacokinetics, and C6-ALK (Table 4). These six communities represent the sub-directions of TKIs research in 2016-2020.

They are each closely associated within but loosely associated with each other.

In terms of size, the sub-directions of TKIs research can be divided into 3 echelons (Table 5). The first echelon includes C1-Non-small Cell Lung Cancer, which contains EGFR, EGFR-TKI, EGFR Mutation, Lung Cancer, Erlotinib, etc., and C2-Targeted Therapy, which contains Renal Cell Carcinoma, Sunitinib, Chemotherapy, Cancer, Tumor, etc. These two major sub-directions contain the largest number of keywords and the largest sum of frequencies, which are the main sub-directions of TKIs research. The second echelon includes C3-Chronic Myeloid Leukemia, which contains Imatinib, Dasatinib, BCR-ABL, Nilotinib, Gastrointestinal Stromal Tumor, etc., C4-HER2, which contains Apoptosis, Breast Cancer, Lapatinib, Autophagy, Combination Therapy, etc. and C5-Pharmacokinetics, which contains Ibrutinib, Metabolism, Molecular Docking, Plasma, Drug-drug Interaction, etc. These three communities are involved in research topics that are also important for TKIs research. Keywords from these three communities are also important themes in TKIs research. The third echelon only contains C6-ALK, including Crizotinib, Met, Receptor Tyrosine Kinase, ROS1, and ALK-TKI. C6 is still in its infancy, which occupies only a little weight in TKI research.

The varying centrality and density of each community further illustrate that there are sharply differentiated sub-directions in TKIs research (Table 5). For example, C1-Non-small Cell Lung Cancer and C2-Targeted Therapy have the highest centrality, which are the core sub-directions in TKIs research. And C1-Non-small Cell Lung Cancer and C2-Targeted Therapy also have the highest density and are the most developed sub-directions in TKI research. Furthermore, the internal density of each community is higher than the density of the whole TKIs co-word network, which also indicates that each sub-direction is tightly connected internally but loosely connected to each other. The centrality and density of C6-ALK do not have comparative value due to its small size.

**Table 4.** Topic communities related to TKIs research

Community	Words
C1-64	Non-small Cell Lung Cancer; EGFR; EGFR-TKI; EGFR Mutation; Lung Cancer; Erlotinib; Osimertinib; Gefitinib; Lung Adenocarcinoma; Mutation; Resistance; Afatinib; Drug Resistance; T790M; Brain Metastasis; Acquired Resistance; Next-generation Sequencing; Adenocarcinoma; T790M Mutation; Circulating Tumor DNA; Icotinib; Liquid Biopsy; Epithelial-mesenchymal Transition; EGFR-TKI Resistance; Sequencing; Small Cell Lung Cancer; Case Report; Bevacizumab; Gefitinib Resistance; Pemetrexed; Squamous Cell Carcinoma; KRAS; Epidermal Growth Factor; Real-world Study; Leptomeningeal Metastasis; Advanced NSCLC; Cost-effectiveness; Rebiopsy; Dacomitinib; IGF-1R; STAT3; Droplet Digital PCR; Whole-brain Radiotherapy; Pleural Effusion; BIM; Uncommon Mutation; Polymorphism; Met Amplification; First-line Treatment; EGFR Exon 20; Computed Tomography; Cell-free DNA; TP53; Radiosurgery; Cisplatin; Docetaxel; Leptomeningeal Carcinomatosis; Skin Rash; Exosomes; Cerebrospinal Fluid; Exon 19 Deletion; Exon 19; Cetuximab; Metformin

- C2-97 Targeted Therapy; Renal Cell Carcinoma; Sunitinib; Chemotherapy; Cancer; Tumor; Metastasis; Sorafenib; Prognosis; Pazopanib; Hepatocellular Carcinoma; Lenvatinib; Apatinib; Immunotherapy; Toxicity; Metastatic Renal Cell Carcinoma; Radiotherapy; VEGF; Progression-free Survival; Biomarker; Angiogenesis; Overall Survival; Adverse Event; Carcinoma; Meta-analysis; Sarcoma; VEGFR2; Oncology; Cabozantinib; Renal Cancer; VEGFR-TKI; PD-L1; VEGFR; Clinical Trial; Axitinib; Immune Checkpoint Inhibitor; Molecular Targeted Therapy; Thyroid Cancer; FGFR; PDGFR; Phase I Clinical Trial; Cardiotoxicity; Vandetanib; Regorafenib; Angiogenesis Inhibitor; PD-1; Ovarian Cancer; Colorectal Cancer; Hypertension; Anlotinib; Bone Metastasis; MicroRNA; Recurrence; Soft Tissue Sarcoma; mTOR; Hypoxia; Anti-angiogenesis; Nivolumab; Prognostic Factor; AXL; RET; Phase II Clinical Trial; Everolimus; Melanoma; Anaplastic Thyroid Cancer; Differentiated Thyroid Cancer; Receptor TKI; Clear Cell Renal Cell Carcinoma; Medullary Thyroid Cancer; Cancer Therapy; mTOR Inhibitor; Kidney; Adjuvant; Tumor Microenvironment; Solid Tumor; Treatment Response; Multitargeted TKI; Neutrophil-lymphocyte Ratio; Toceranib; Multikinase Inhibitor; Antiangiogenic Therapy; Monoclonal Antibody; Sequential Treatment; Osteosarcoma; Neoplasm Metastasis; Tolerability; Esophageal Cancer; Hypothyroidism; Circulating Tumor Cell; Neoadjuvant Therapy; Met TKI; PDGF; Paclitaxel; Neuroblastoma; Oligoprogression; Cervical Cancer; Pembrolizumab
- C3-46 Chronic Myeloid Leukemia; Imatinib; Dasatinib; BCR-ABL; Nilotinib; Gastrointestinal Stromal Tumor; Acute Myeloid Leukemia; Leukemia; Molecular Response; Ponatinib; Acute Lymphoblastic Leukemia; Philadelphia Chromosome; TKI Resistance; FLT3; Kit; Quality Of Life; Adherence; Head And Neck Squamous Cell Carcinoma; Imatinib Resistance; Stem Cell Transplantation; Leukemia Stem Cell; Bosutinib; Stem Cell; Ph<sup>+</sup>ALL; Treatment-free Remission; Protein Kinase Inhibitor; Pulmonary Arterial Hypertension; Minimal Residual Disease; PDGFRA; Discontinuation; T315I; Adverse Drug Reaction; Chronic Phase; Cytokine; Interferon; c-Kit; Midostaurin; Single Nucleotide Polymorphism; Ruxolitinib; BCR-ABL Mutation; Kit Mutation; Treatment Discontinuation; Rechallenge; Src Tyrosine Kinase; BCR-ABL TKI; Patient-reported Outcome
- C4-38 HER2; Apoptosis; Breast Cancer; Lapatinib; Autophagy; Combination Therapy; Neratinib; c-Met; Gastric Cancer; Glioblastoma; AKT; Proliferation; Nanoparticles; ERK; Pancreatic Cancer; Reactive Oxygen Species; Cancer Stem Cell; Chemoresistance; Src; Hepatotoxicity; Oxidative Stress; Cell Cycle; Pyrotinib; Radiation; PI3K; Mitochondria; Trastuzumab; Migration; NF-kappa B; Gemcitabine; Drug Delivery; Glioma; Triple-negative Breast Cancer; Diarrhea; Adjuvant Therapy; Metastatic Breast Cancer; PI3K/AKT; Invasion
- C5-37 Pharmacokinetics; Ibrutinib; Metabolism; Molecular Docking; Plasma; Drug-drug Interaction; P-glycoprotein; Therapeutic Drug Monitoring; Brutons Tyrosine Kinase; BTK Inhibitor; Nintedanib; Chronic Lymphocytic Leukemia; Positron Emission Tomography; LC-MS/MS; Personalized Medicine; Anticancer; Lymphoma; Breast Cancer Resistance Protein; Interstitial Lung Disease; Spleen Tyrosine Kinase; Multidrug Resistance; Molecular Dynamics; Antitumor; Lung; Inflammation; Diabetes; Anticancer Drug; BCL-2; Bioavailability; Synthesis; Human Plasma; Mantle Cell Lymphoma; Idiopathic Pulmonary Fibrosis; Virtual Screening; UPLC-MS/MS; Pulmonary Fibrosis; Blood-brain Barrier
- C6-14 ALK; Crizotinib; Met; Receptor Tyrosine Kinase; ROS1; ALK-TKI; Alectinib; ALK Rearrangement; Immunohistochemistry; Lorlatinib; BRAF; Ceritinib; Resistance Mutation; Brigatinib

\*Note: Keywords in each community are listed in descending order of frequency.

**Table 5.** Indicators of 6 theme communities in TKIs research.

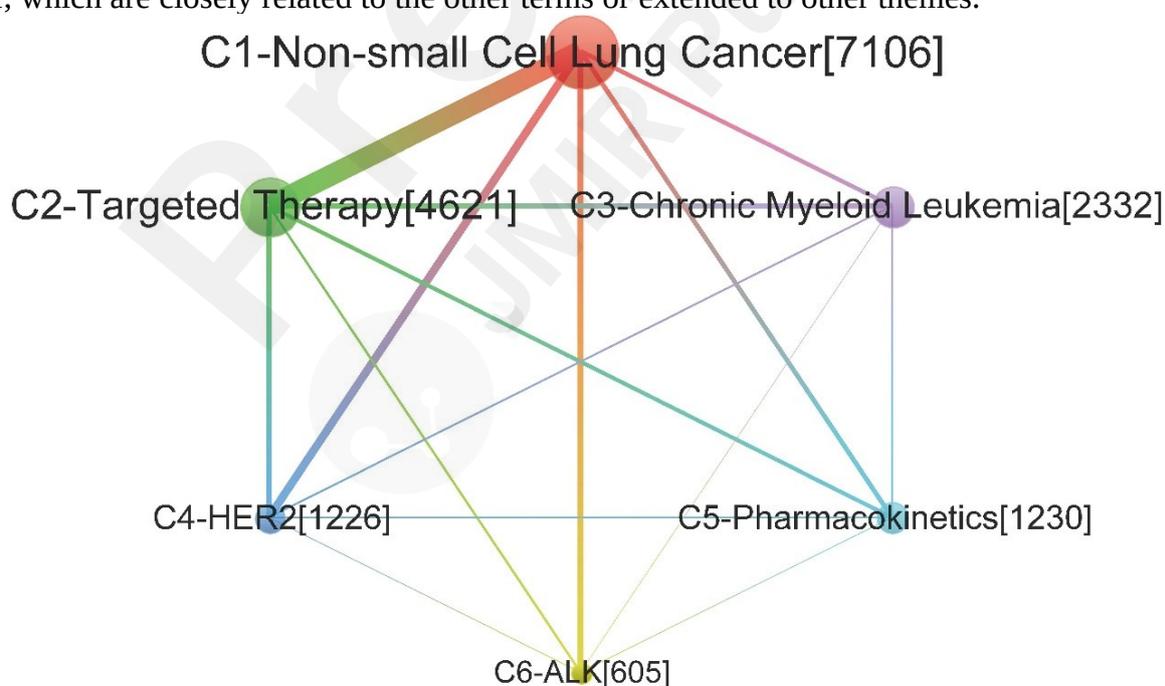
Community	Number of nodes	Number of lines	Total frequency	Average degree	Density
C1-Non-small Cell Lung Cancer	64	817	7106	61.8438	0.3989

C2-Targeted Therapy	97	1386	4621	54.9588	0.2946
C3-Chronic Myeloid Leukemia	46	297	2332	36.3696	0.2807
C4-HER2	38	203	1226	44.1579	0.2812
C5-Pharmacokinetics	37	161	1230	35.8649	0.2352
C6-ALK	14	59	605	50.6429	0.6020

### 4.2.3 Visualization of the correlation network

The diverse correlation structure within and between each sub-direction of the TKIs research is visualized in Figure 4 and Figure 5. Figure 4 shows that there are differences in the influence of varied sub-directions and that the association between these sub-directions is uneven. C1-Non-small Cell Lung Cancer and C2-Targeted Therapy have the strongest associations with the other sub-directions, which reflect the strong influence of these two directions in TKIs research. The other four sub-directions are oriented to C1 and C2, or depend on them to varying degrees. The association between C1 and C2 is significantly stronger than that between other sub-directions, so C1 and C2 are the mainstream of current TKIs research. In particular, C1 is the most central and influential sub-direction in the whole TKIs research, and the associations between C1 and other directions are generally strong. Isolated C6-ALK is not strongly associated with any other sub-direction except for a closer association with C1.

Figure 5 further shows the correlation structure within each sub-direction, where each term has a different location, function, and role. Each sub-direction has a clear hierarchy, with the most influential terms at the core, which are important research themes, and the more distant from the core of the community, the less important the terms are. For example, EGFR, EGFR-TKI, EGFR Mutation, Lung Cancer, and Erlotinib are important research themes in C1-Non-small Cell Lung Cancer, which are closely related to the other terms or extended to other themes.



**Figure 4.** Correlation structure of sub-directions in TKIs research

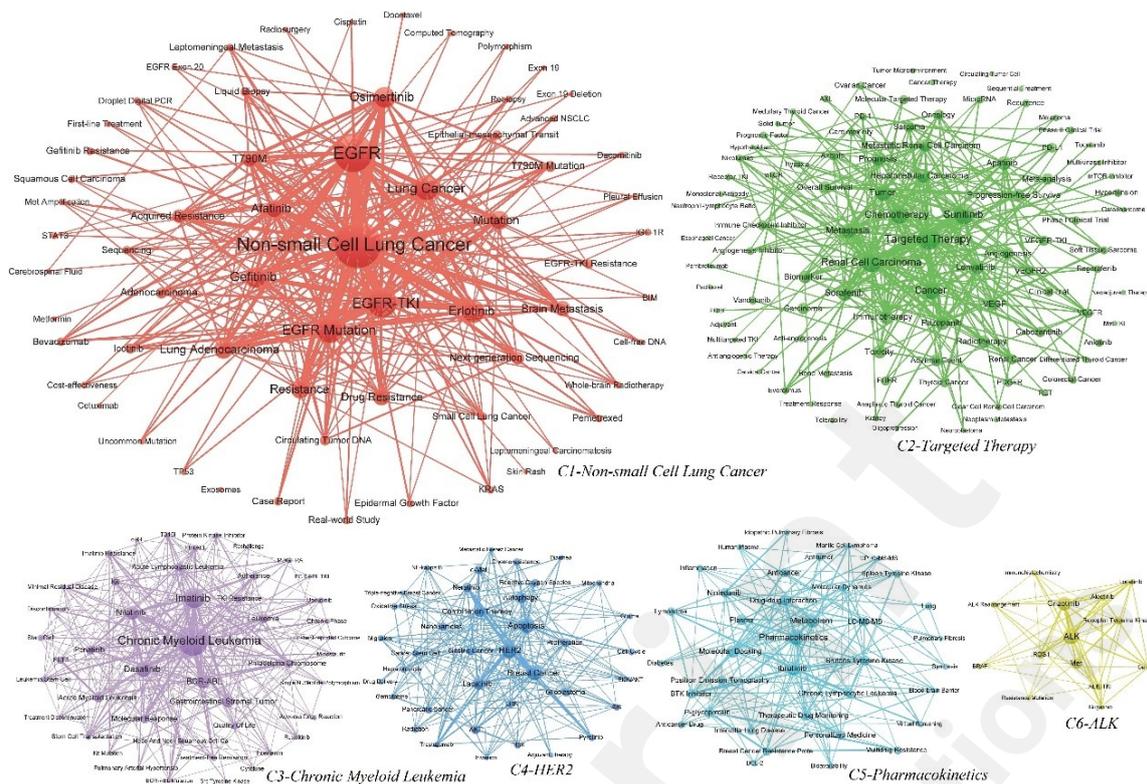


Figure 5. The internal correlation network structure of each sub-directions in TKIs research

### 4.3 Evolution patterns of and trends in TKIs research

#### 4.3.1 The evolutionary venations of research themes

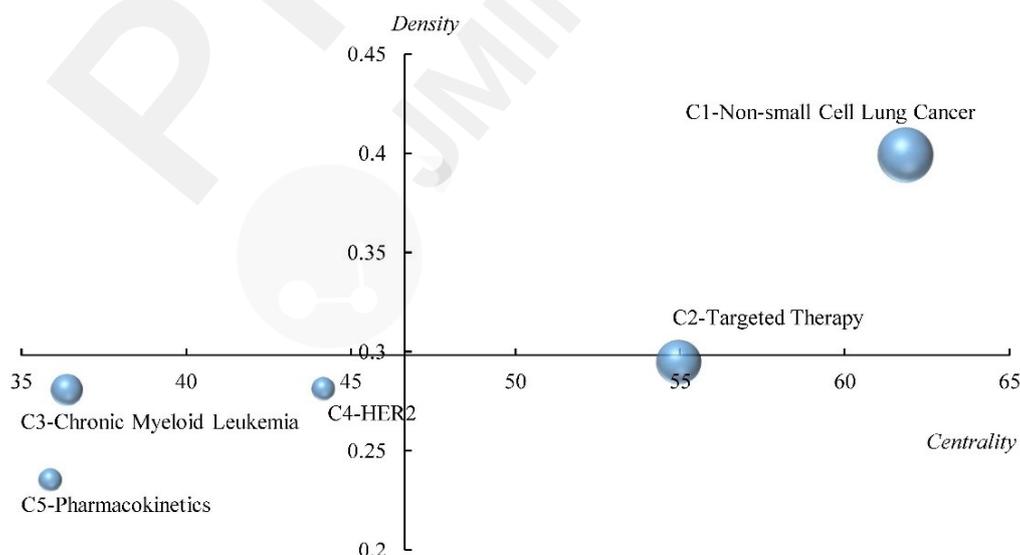
Figure 6 illustrates the historical evolution of TKIs research themes, which includes both the scale and the clear evolutionary venation of TKIs research themes. Overall, there are clear sub-directions and good continuity of TKIs research from 2016 to 2020, but their size and distribution are uneven. In descending order of size, several major evolutionary venations are the Non-small Cell Lung Cancer venation (involving Apoptosis, Gefitinib, Osimertinib, EGFR-TKI, T790M Mutation, etc.), the Chronic Myeloid Leukemia venation (involving BCR-ABL, Dasatinib, Nilotinib, etc.), the Renal Cell Carcinoma venation (involving Sunitinib, Angiogenesis, Sorafenib, Regorafenib, Pazopanib, Immunotherapy, etc.), the Chronic Lymphocytic Leukemia venation (involving Lymphoma, Brutons Tyrosine Kinase, Ibrutinib, BTK Inhibitor, etc.), and the Lapatinib venation (involving Breast Cancer, Next-generation Sequencing, ALK Rearrangement, ALK, Alectinib, etc.). There are also isolated, intermittent research themes, such as Crizotinib & ALK in 2016, apoptosis & PI3K/AKT in 2017, Molecular Docking & Anticancer in 2019, and Cabozantinib & AXL in 2020 for the first time as a sub-direction.



**Figure 6.** The evolution of themes of TKIs research over time (2016-2020).

### 4.3.2 The developmental degree of the sub-directions of TKIs research

Based on Table 5, we draw a strategic diagram (Figure 7) to visualize the developmental trends of the sub-directions in TKIs research. The C6 community wasn't drawn in the strategy diagram due to its small size and non-comparable network indicators. As shown in Figure 7, we plotted the nodes of different sizes to represent the total frequencies of the varied sub-directions of TKIs research and distributed them in four quadrants according to their density and centrality. C1-Non-small Cell Lung Cancer is in the first quadrant due to its high density and centrality, again indicating that this community is the core direction and most developed in TKIs research. C2-Targeted Therapy is located exactly at the junction of the first and fourth quadrants, which means that C2 is also the core direction of TKIs research, but is in the process of maturing. C3-Chronic Myeloid Leukemia, C4-HER2, and C5-Pharmacokinetics are all in the third quadrant, with relatively low centrality and density, which indicates that they are at the margins of TKIs research and are immature.



**Figure 7.** The relative development status and trends of 5 sub-directions in the strategic diagram.

## 5. Discussion

With the continuous progress of medicine, the targeted drugs TKIs have made great development

in basic research and have been widely used for clinical applications. Based on the results of the co-word analysis, we have a better understanding of the main research directions of TKIs and accurately assess their maturity, centrality, and interactions. First, in general, TKIs research is unbalanced. Since the first TKIs were introduced, researchers have focused on some hot terms such as NSCLC, EGFR, CML, EGFR-TKI, EGFR Mutation, Erlotinib, Imatinib, Osimertinib, Gefitinib, Targeted Therapy, Renal Cell Carcinoma, Resistance, etc. The above terms can be broadly classified into the following categories: clinical applications (e.g., NSCLC, CML, Renal Cell Carcinoma, Lung Adenocarcinoma), genetic studies (e.g., EGFR, EGFR Mutation, BCR-ABL), typical drugs (e.g., Erlotinib, Imatinib, Gefitinib, Sunitinib, Afatinib, Dasatinib, Osimertinib, Nilotinib), and chemotherapy and drug resistance (e.g., Targeted Therapy, Resistance, Chemotherapy, Drug Resistance). These terms not only reflect the areas of interest of researchers but also indicate the trends of TKIs research.

Based on the visualized co-word network, we found that the research topics tend to be clustered around a few keywords, eventually forming a hierarchical and relatively balanced thematic community. The thematic communities of the TKIs consist of C1-Non-small Cell Lung Cancer, C2-Targeted Therapy, C3-Chronic Myeloid Leukemia, C4-HER2, C5-Pharmacokinetics, and C6-ALK. First, the C1 and C2 communities are the main areas of TKIs research because of their high centrality and frequency. Among them, C1-NSCLC, the largest thematic community, has received a lot of attention from scholars. From gene targets (e.g., KRAS, EGFR, TP53, BIM) to signaling pathways (e.g., IGF-1R, STAT3), from conventional chemotherapy (e.g., Cisplatin, Docetaxel, Pemetrexed) to targeted drugs (e.g., Erlotinib, Osimertinib, Gefitinib), scholars have studied NSCLC more and more deeply. C2-Targeted Therapy indicates that TKIs are widely used in targeted therapies, and the application of TKIs has been extended to lung cancer<sup>12, 31, 32</sup>, breast cancer<sup>64</sup>, renal cancer<sup>65, 66</sup>, liver cancer<sup>67</sup>, ovarian cancer<sup>68</sup>, colorectal cancer<sup>69</sup>, leukemia<sup>11, 28, 29</sup>, thyroid cancer<sup>70, 71</sup>, cervical cancer<sup>72</sup> and many other tumors. Chemotherapy regimens containing TKIs were effective in reducing tumor metastasis and recurrence and improving the OS of patients<sup>12, 31</sup>. The use of TKIs will be further expanded to more tumor types as more clinical trials are conducted.

Second, C3 and C5 communities have declined during the development of TKIs, both of which are in a marginal position in the strategic diagram. Among C3-Chronic Myeloid Leukemia, Imatinib is the first targeted anti-tumor drug that was first approved by the FDA in 2001 for patients with BCR-ABL positive CML<sup>10, 11, 28, 29, 73</sup>. With the emergence of drug resistance, Dasatinib<sup>74</sup>, which targets the SRC, and nilotinib<sup>75</sup>, which targets BCR-ABL, have been applied to resistant patients. Research on CML has been conducted for a long time and this field is now mature, so the application of TKIs has gradually expanded from CML to other diseases, which is leading to the gradual marginalization of the C3 community. C5-Pharmacokinetics is an important interdisciplinary discipline related to TKIs, which is widely involved in the development process of TKIs<sup>76, 77</sup>. However, as small molecule drugs, the absorption, transport, distribution, and transformation of most TKIs in vivo have been clearly studied. Meanwhile, several new technologies in molecular biology (e.g., molecular docking<sup>78</sup> and virtual high-throughput screening<sup>79</sup>) are used more and more, so C5-Pharmacokinetics is gradually fading.

Despite the gradual decline of the C3 and C5 communities, new research areas such as C4-HER and C6-ALK have flourished in recent years. The overexpression, amplification, and mutations of HER2 have been found in a variety of tumors including breast cancer and NSCLC<sup>45</sup>, and targeting HER2 has achieved excellent efficacy in breast cancer<sup>64</sup>. Although several early drugs targeting HER2 had poor efficacy in NSCLC<sup>34, 36, 45</sup>, the advent of newer generation HER2-targeting drugs such as poziotinib<sup>80</sup>, pyrotinib<sup>81, 82</sup> exhibited good anti-tumor effects in clinical trials. Scholars are increasingly interested in targeting HER2 in NSCLC, while research on HER2 for breast cancer is relatively well established. Therefore, C4 may evolve in different directions in the future respectively. The C6-ALK community is small but promising. ALK mutations, especially rearrangements, exhibit strong translational activity in NSCLC<sup>83</sup>. ALK-targeted agents such as

alectinib<sup>84</sup> and brigatinib<sup>85</sup> have shown extraordinary efficacy in ALK-positive NSCLC and have become the first-line therapies<sup>86</sup>. Lorlatinib, an ALK inhibitor<sup>87</sup>, appears as a burst word in 2020, and ALK-TKI and ALK Rearrangement have a high weight in Figure 3 from 2019 to 2020, both of which indicate the rapidly rising heat of ALK. In addition, there are still several ALK-targeted drugs in development, so more literature on ALK will be published in the future and the C6 community will grow further.

We found several evolutionary venations, by analyzing the evolution of themes of TKIs research over time. These highly concentrated evolutionary venations indicate scholars' continuous and steady focus on Non-small Cell Lung Cancer, Chronic Myeloid Leukemia, Renal Cell carcinoma, Chronic Lymphocytic Leukemia, etc. These different evolutionary lines show a clear development path: TKIs research is disease-focused and revolved around "gene targets/targeted drugs/resistance mechanisms". For example, in the Chronic Myeloid Leukemia venation, investigators focused on the BCR-ABL in 2016 and focused on dasatinib and nilotinib in 2017-2020, which could both target BCR-ABL and overcome imatinib resistance<sup>74, 75</sup>. In the Non-small Cell Lung Cancer venation, investigators focused on EGFR genes in 2016, on EGFR-TKIs represented by osimertinib in 2017-2019, and on resistance mechanisms represented by T790M in 2020. In the Renal Cell carcinoma venation, investigators continued to focus on various TKIs such as sunitinib, sorafenib, regorafenib, and pazopanib, and investigators also paid attention to gene targets such as PDGFR, FGFR, c-Kit, and VEGF, and multidrug resistance. In the Chronic Lymphocytic Leukemia venation, investigators focused on B-cell-derived CLL and lymphoma in 2016, on the aberrant Bruton tyrosine kinase (BTK) from B cells in 2017, and on BTK inhibitors such as ibrutinib that can treat CLL and lymphoma in 2018-2020. Moreover, Lapatinib, a dual EGFR/HER2 TKI<sup>88</sup>, showed good efficacy in breast cancer, which made it an independent evolutionary venation in 2017 with continues heat to now.

In addition to the main few evolutionary venations, we identified some isolated themes that depict the current state of TKIs research. Crizotinib gained attention as an ALK inhibitor in 2016, but Crizotinib's declined rapidly due to its poor efficacy and the emergence of second-generation ALK inhibitors, making Crizotinib & ALK an isolated topic. Circulating Tumor DNA (ctDNA) is important for the efficacy assessment and prognosis analysis of tumors. And it's the future trend in TKIs research to use NGS or liquid biopsy technology to precisely analyze ctDNA in cell-free DNA. The PI3K/AKT pathway plays an important role in cell growth, proliferation, migration, and angiogenesis, which can be activated by RTKs. So as one of the mechanisms of TKIs, the apoptosis & PI3K/AKT venation was noticed in 2017-2018. Cabozantinib is a multi-target TKIs that can target 9 genes (e.g., AXL, Met)<sup>89</sup>, and Cabozantinib & AXL appeared as a separate topic in 2020. Furthermore, the burst words pyrotinib and anlotinib, which accounted for a relatively large weight in 2020, are also multi-target inhibitors<sup>81, 82, 90</sup>. This suggests that multi-target drugs may become an important direction for the development of TKIs and will likely receive more attention in the future. Immune checkpoint inhibitors and TKIs are important drugs for tumors. It's discovered that the combination of PD-L1 inhibitors (e.g., Pembrolizumab) and TKIs (e.g., Lenvatinib) in patients with malignant tumors was more effective than single drug<sup>91</sup>, suggesting that the combination therapy was an important development direction for future tumor therapy. For well-known reasons, many patients being treated with TKIs were co-infected with SARS-COV-2 in 2020<sup>92</sup>, and it was also suggested that some TKIs such as BTKs may have therapeutic effects on COVID-19<sup>93</sup>, which made COVID-19 a burst word in TKIs research. As the global epidemic of COVID-19 in 2021, investigators' interest in TKIs for patients infected with SARS-COV-2 would further increase.

## 6. Conclusions

In conclusion, we revealed the hotspots, knowledge structure, and trends of evolution of TKIs research during 2016-2020 utilizing co-word analysis and literature visualization. Based on the above results, we speculate that the general status of TKIs research is as follows: (1) NSCLC and CML are the most important clinical application areas for TKIs; (2) EGFR is the most common

target gene for TKIs, and EGFR-TKIs are the most commonly used molecular-targeted TKIs, among which Erlotinib, Osimertinib, and Gefitinib have gradually matured; (3) TKIs have become a mature field for targeted therapeutic applications, and drugs targeting HER2 and ALK has further expanded the application of TKIs; (4) drug resistance remains a major challenge for TKIs. Of course, our study also has some limitations: first, our search included only English literature from 2016 to 2020, while non-English literature was excluded; second, the co-word analysis didn't take the quality, influence, and rigor of the literature into account, which was a common shortcoming of such papers<sup>94-96</sup>. In a nutshell, our work remains valuable in revealing the knowledge structure and evolutionary trends of TKIs research.

### **Acknowledgments**

This study was supported by grants from *Natural Science Foundation of Hubei Province (Grant No. 2020CFB611)*.

### **Authors' Contributions**

Designed this research: Jiming Hu Miao Liu, and Zhiwei Wang;

Developed the search strategy and screened the literature: Miao Liu and Jiming Hu;

Screened and processed the keywords: Kai Xing, Miao Liu, and Jiming Hu;

Participated in the data visualization: Jiming Hu and Yan Zhang;

Made the images and tables: Jiming Hu and Yan Zhang;

Wrote the manuscript: Miao Liu, Jiming Hu, and Kai Xing;

Translated the manuscript: Kai Xing;

Reviewed and revised the manuscript: Miao Liu and Zhiwei Wang

Jiming Hu, Kai Xing, and Yan Zhang are common first authors. Miao Liu and Zhiwei Wang are common communication authors.

### **Conflicts of Interest**

The authors declare that there are no competing economic or commercial interests in this manuscript.

### **Abbreviations**

TKs: tyrosine kinases

TKIs: tyrosinase inhibitors

RTKs: receptor tyrosine kinases

non-RTKs: non-receptor tyrosine kinases

EGFR: epidermal growth factor receptor

VEGFR: vascular endothelial growth factor receptor

ATP: adenosine triphosphate

NSCLC: non-small cell lung cancer

CML: chronic myeloid leukemia

NGS: Next-generation sequencing

WOSCC: Web of Science Core Collection

BTK: Bruton tyrosine kinase

ctDNA: Circulating Tumor DNA

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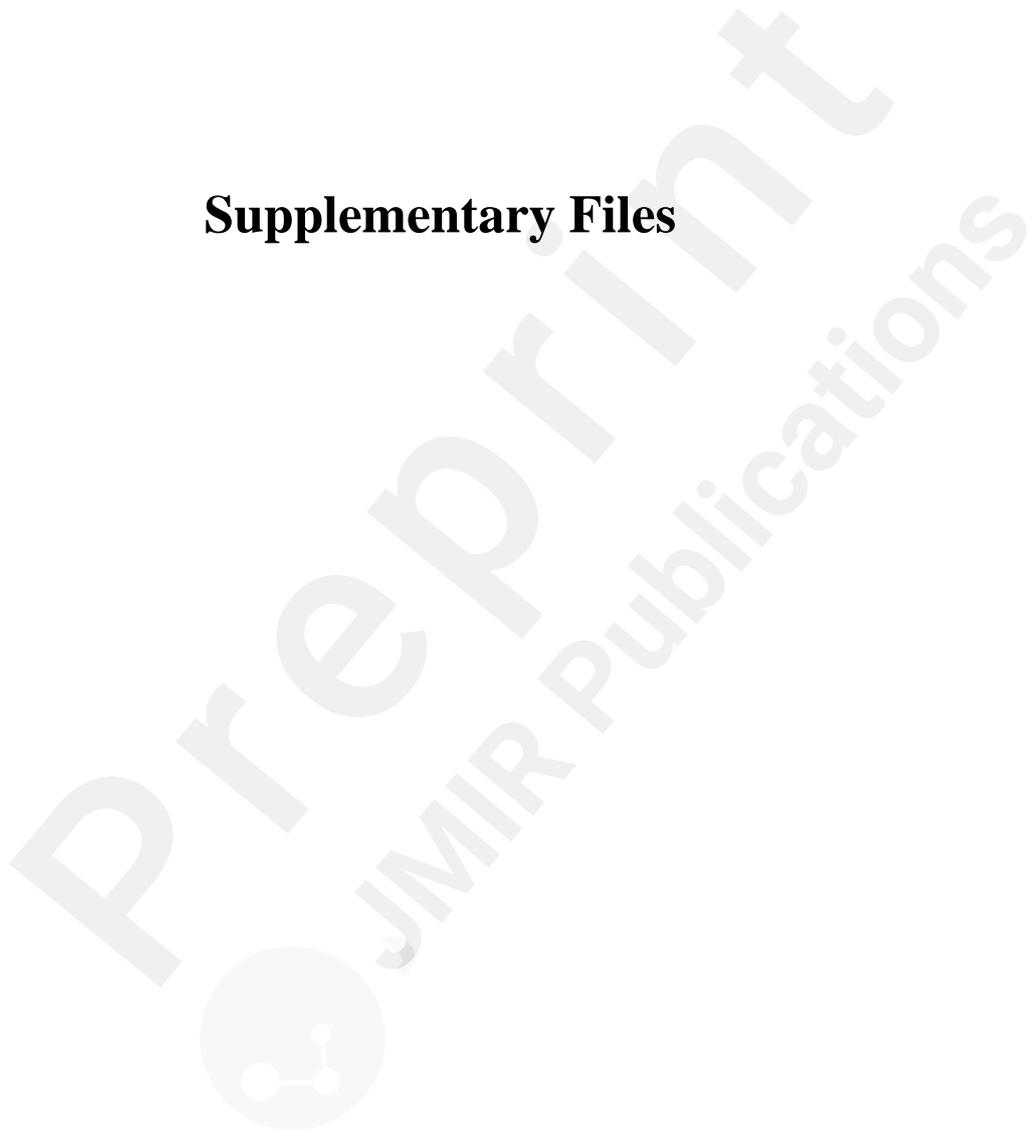
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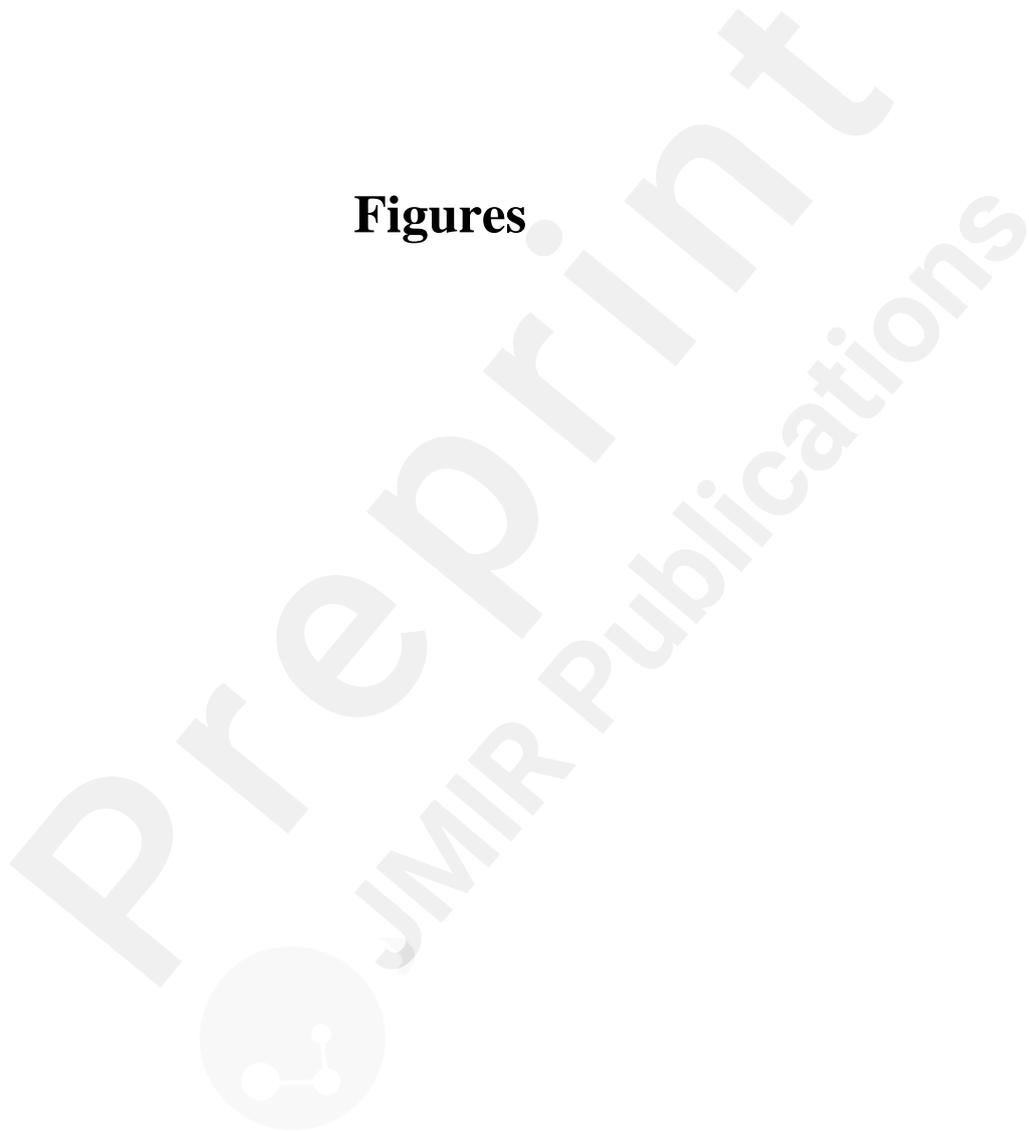
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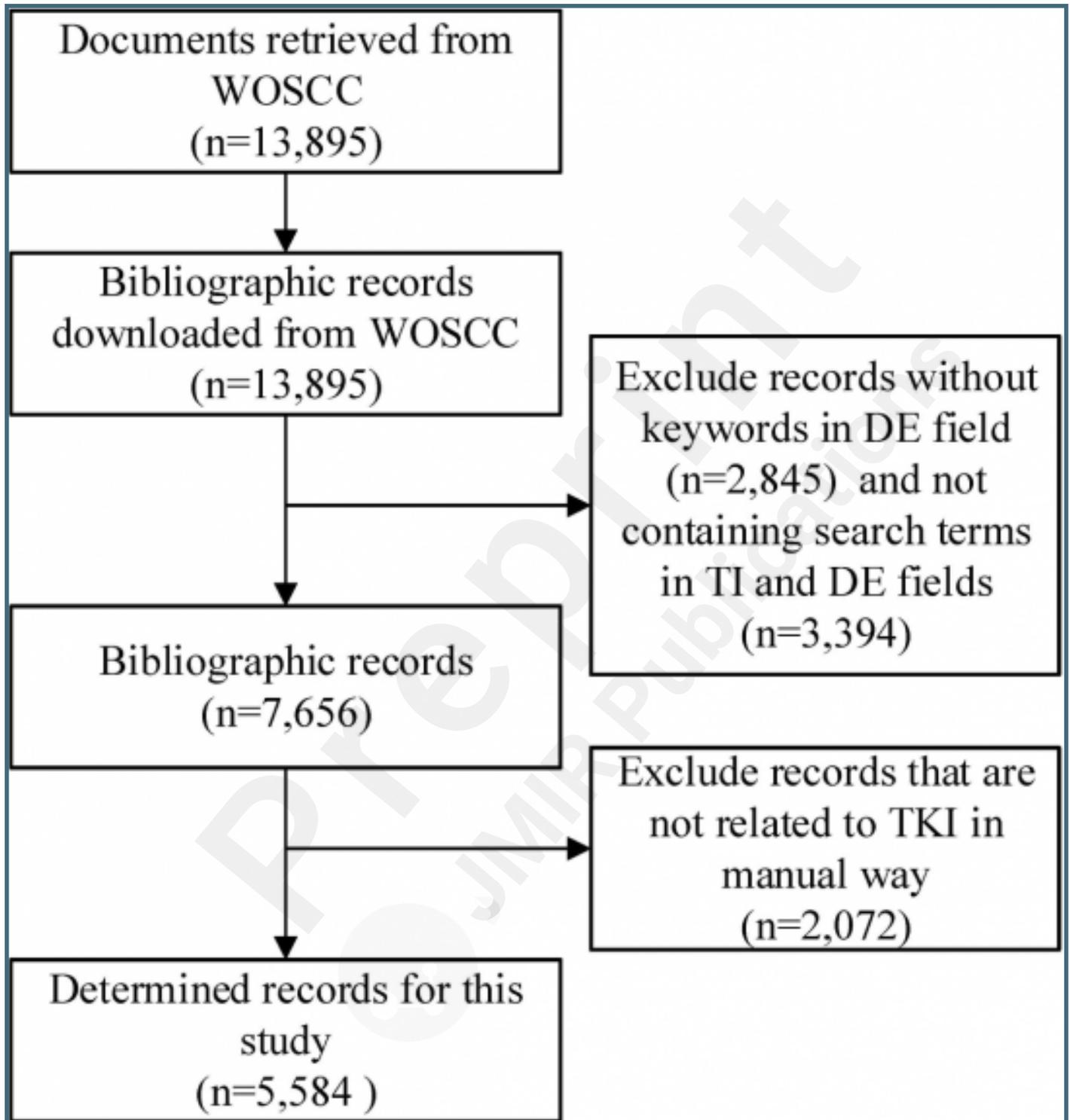
## Supplementary Files



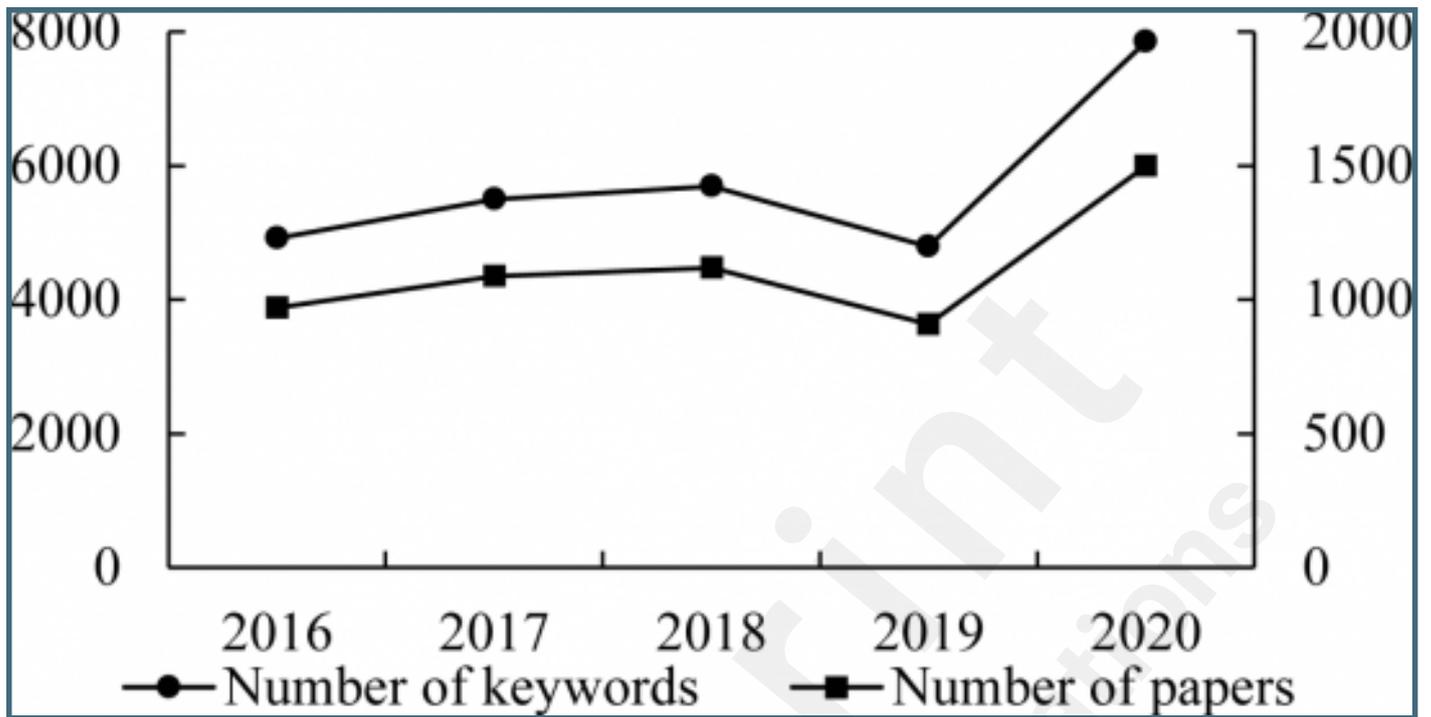
## Figures



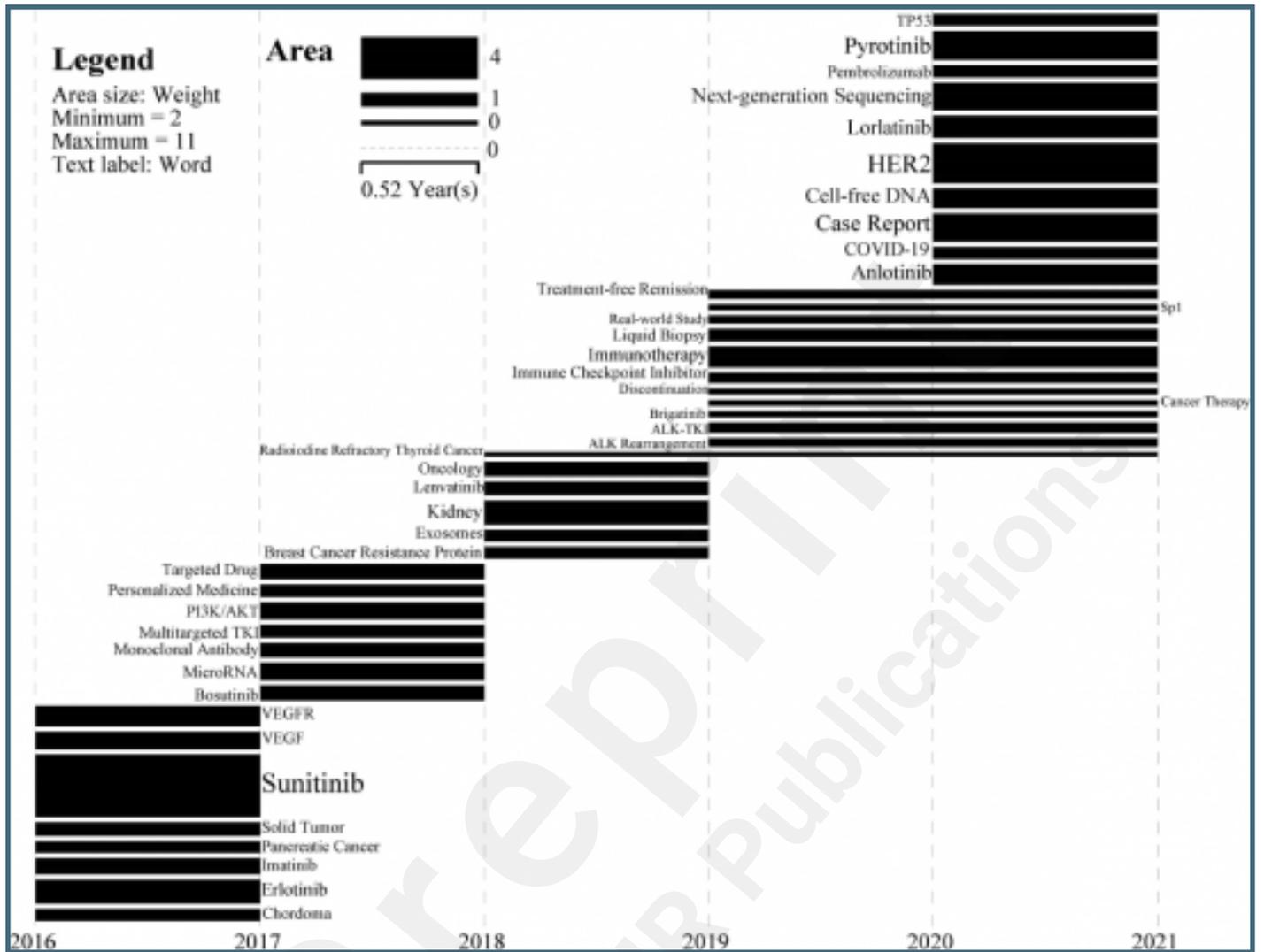
Search procedure for documents in TKIs research. DE descriptor; TI title; WOSCC Web of Science Core Collection.



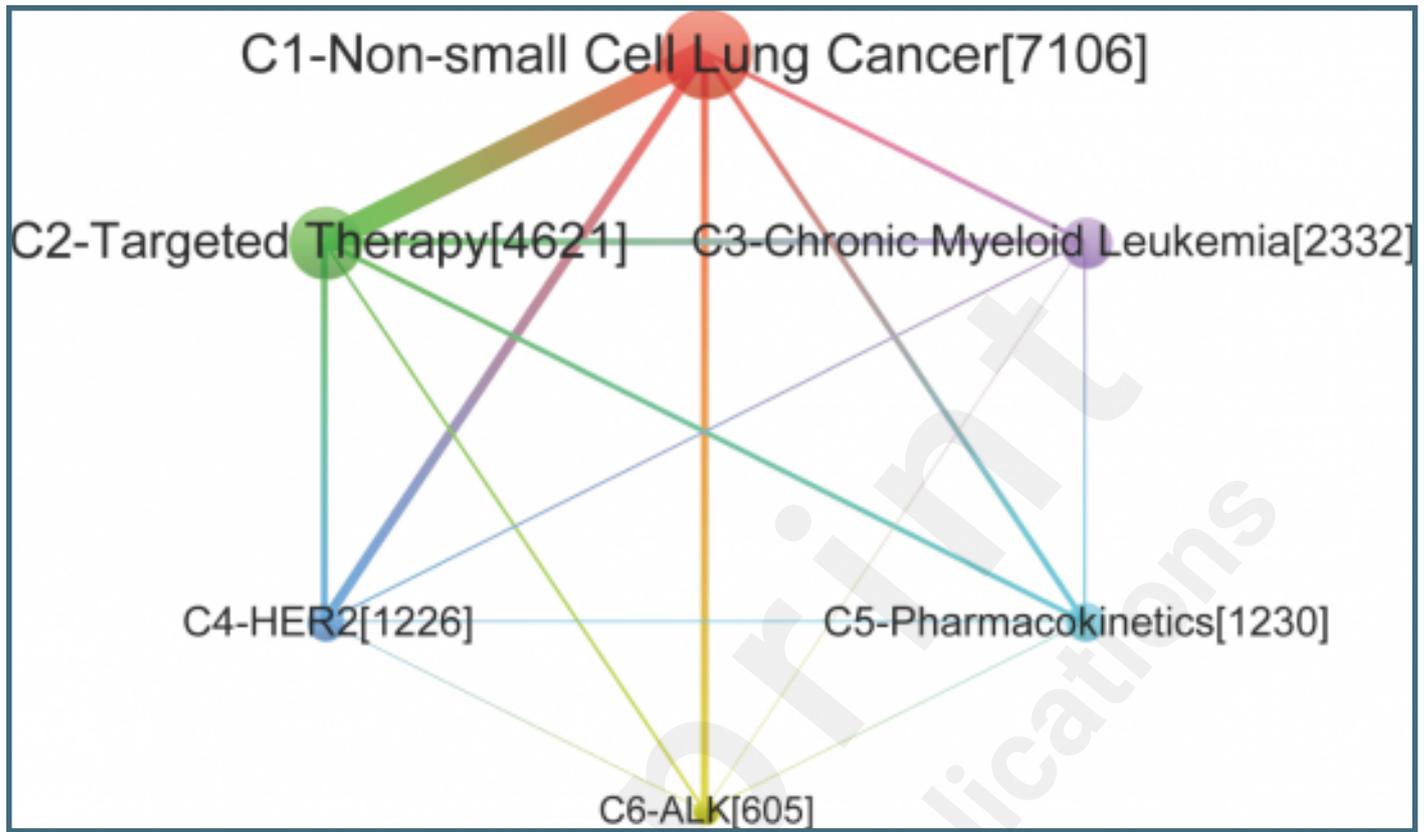
Yearly number of papers and words related to TKIs research (2016-2020).



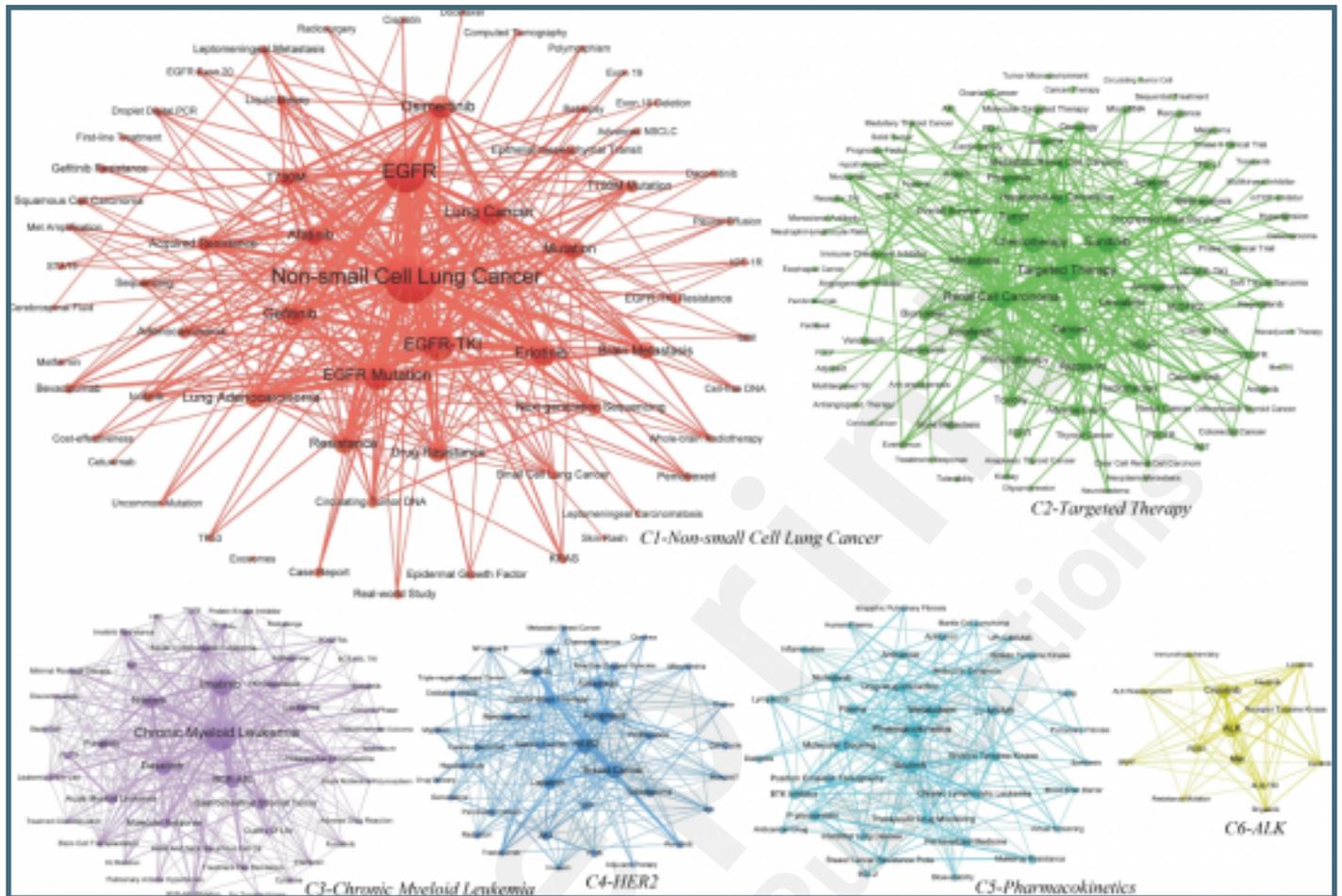
Burst disciplines of TKIs research from 2016 to 2021.



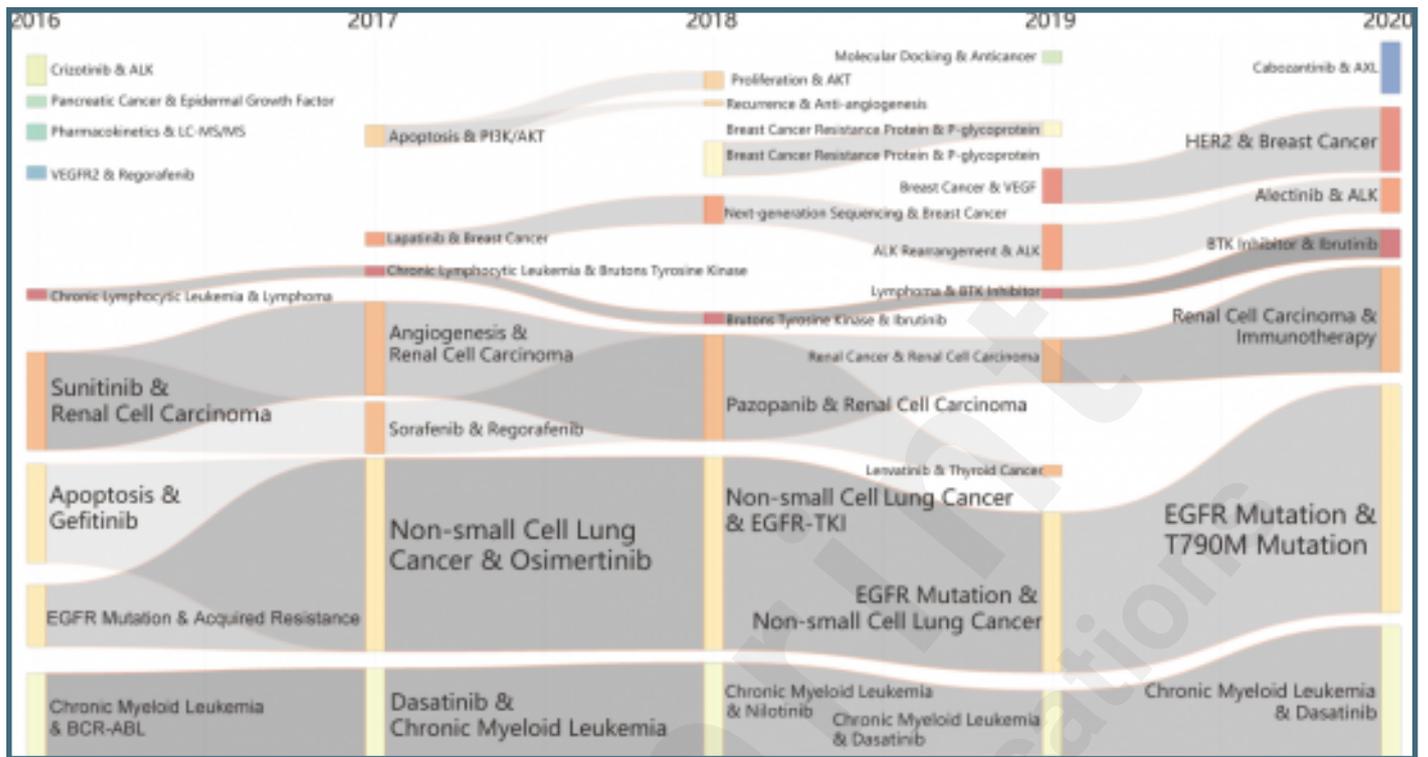
Correlation structure of sub-directions in TKIs research.



The internal correlation network structure of each sub-directions in TKIs research.



The evolution of themes of TKIs research over time (2016-2020).



The relative development status and trends of 5 sub-directions in the strategic diagram.

