Bibliometric And Visualization Analysis of Essential Thrombocythemia Research Published Worldwide from 2001 to 2024

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Article

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Abstract: Objective: In recent years, the field of Essential Thrombocythemia (ET) research has seen a significant accumulation of scientific findings, but comprehensive bibliometric analyses remain lacking. This study aims to fill that gap by performing a thorough bibliometric analysis of ET research, identifying key contributors and collaboration networks, and mapping the development trends to provide insights for future research directions. Methods: A bibliometric analysis of ET-related publications from 2001 to 2024 was conducted using CiteSpace, VOSviewer, and R packages. Data were retrieved from the Web of Science Core Collection, with a focus on publication volume, citation analysis, co-authorship networks, co-citation relationships, and citation bursts. Results: A total of 4,297 studies published in 778 journals were included in the analysis. ET research has seen rapid growth, with researcher clusters in the United States and Europe driving progress through extensive regional and international collaborations. Leading researchers, such as Ayalew Tefferi from the Mayo Clinic and Alessandro M. Vannucchi from the University of Florence, have made significant advances in ET classification, molecular mechanisms, targeted therapies, and disease management. The discovery of driver mutations, such as JAK2, has revolutionized the diagnostic and therapeutic approaches to ET. Research focus has shifted from clinical morphological diagnosis to molecular diagnostics, with the field now entering the era of targeted therapies. However, the inherent heterogeneity of ET continues to present challenges for the widespread implementation of personalized precision treatment. Conclusion: Bibliometric analysis demonstrates significant advances in ET research, particularly in molecular pathology and targeted therapies. However, the heterogeneity of ET remains a major obstacle to personalized treatment. Future research should focus on further elucidating the pathogenesis of ET and improving stratified management approaches to achieve individualized precision therapy.

Keywords: Essential Thrombocythemia; Bibliometric Analysis; CiteSpace; Collaboration Networks; Global Research Trends

1. Introduction

Essential Thrombocythemia (ET) is a type of myeloproliferative neoplasms (MPNs) characterized by abnormal proliferation of megakaryocytes in the bone marrow, resulting in persistently elevated platelet counts in peripheral blood, and an increased risk of thrombosis [1].

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Although the pathophysiological mechanisms of ET are complex, significant milestone discoveries have been achieved through continuous research efforts. The identification of the JAK2 V617F mutation, in particular, has reshaped our understanding of the disease, significantly advancing research and clinical management of ET [2]. This discovery has shifted the diagnostic approach from a morphological to a molecular basis, facilitating the development of targeted therapies such as ruxolitinib, and ultimately contributing to the current therapeutic landscape of ET [3]. Subsequently, the driving roles of CALR and MPL mutations in ET have been confirmed, addressing the gap in molecular diagnostics for JAK2-negative patients [4]. These advances have enhanced the precision of ET diagnosis and classification, marking a steady progression towards personalized medicine.

However, despite significant advances in diagnosis and treatment, many critical issues in ET remain unresolved. The mechanisms underlying the progression of ET to myelofibrosis and acute myeloid leukemia are still unclear, and stratification in diagnosis and treatment needs further refinement to better implement personalized therapies [5]. The considerable heterogeneity among ET patients continues to pose a major challenge to precision medicine. Although ruxolitinib has demonstrated efficacy in other MPNs, its application in ET remains limited [6]. Current antiplatelet therapies are insufficient to completely mitigate the risk of thrombosis in ET and may exacerbate bleeding complications associated with the disease. While hydroxyurea can control platelet levels in peripheral blood, it has little impact on the progression of bone marrow fibrosis, and its long-term use is associated with an increased risk of secondary malignancies, limiting its survival benefits in younger patients [7]. These challenges highlight the need for further in-depth research on the molecular biology of ET, the improvement of clinical stratification systems, and the optimization of personalized precision therapies. Additionally, the development of novel drugs and treatment approaches remains crucial to addressing the unmet needs in ET management.

Bibliometrics involves the quantitative analysis of literature, combined with visualization tools, to study publications in a given field. It provides insights into the number of publications, citation relationships, and collaboration networks among authors, institutions, and regions, as well as the historical trends of research topics, the dissemination of knowledge, and the development of academic disciplines [8]. In the medical field, bibliometrics has been applied in cardiovascular diseases [9], respiratory diseases [10], neurological disorders [11], autoimmune diseases [12], and cancer [13]. By offering quantitative data, bibliometrics enables researchers to quickly and comprehensively understand the development history, research dynamics, and future trends of a particular disease, precisely identify milestone studies, and recognize key researchers and relevant institutions [14]. To our knowledge, there is currently limited bibliometric research in the field of ET. Therefore, we conducted a bibliometric analysis of ET-related literature indexed in the Web of Science database from 2001 to 2024, using bibliometric software. This analysis aims to provide researchers with a more comprehensive understanding of the evolutionary trajectory of ET research, highlighting core publications, key research findings, and emerging topics. Ultimately, this study seeks to offer valuable insights and guidance for future ET research, contributing to both clinical practice and fundamental scientific progress.

2. Materials and Methods

2.1. Search Strategy and Data Acquisition

Two researchers (DC and QJ) conducted a systematic search in the Web of Science Core Collection (WoSCC) database, covering the period from January 1, 2001, to July 30, 2024. In cases of disagreement, a third reviewer (YW) made the final decision. The search terms used were “Essential Thrombocytosis” or “Essential Thrombocythemia.” The search was restricted to the Science Citation Index Expanded (SCI-EXPANDED), and only articles and reviews published in English were included, excluding conference abstracts and editorials. The search yielded 4,394 records, of which 4,297 studies were included in the final analysis. All relevant publications were downloaded on September 20, 2024, and stored as download_results.txt files, including “full records and cited references.”

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2.2. Data Analysis

All data were imported into CiteSpace 6.4.R1 for analysis. After filtering, no duplicate entries were found. WoSCC was used to analyze publication years. The collaboration networks among authors, institutions, and countries, as well as co-citation of references and journals, and co-occurrence of keywords, were visualized. The R package "bibliometrix" was used to analyze the geographical distribution of countries. Time slicing, thresholds, and pruning techniques were applied to present results in graphical and tabular formats. The time span was set from January 2001 to July 2024, with each slice spanning 1 year. Appropriate pruning methods, such as minimum spanning tree and pathfinder, were selected based on the analysis. In the various network graphs, node size represents the frequency of co-occurrence or co-citation, and color indicates the year. Citation bursts for references and keywords were also analyzed to identify emerging topics in the ET field. Synonyms in the keyword analysis were merged, including "myeloproliferative neoplasm" and "myeloproliferative neoplasms," as well as "JAK2" and "tyrosine kinase JAK2."

3. Results

3.1. Publication and Citation Trends

A search in the Web of Science database using the topic "Essential Thrombocythemia (ET)" yielded a total of 4,394 publications. After screening for duplicates, no redundant documents were found. Two authors independently conducted eligibility assessments, excluding 65 conference abstracts, 17 preprints, 14 book chapters, and 1 retracted article. Ultimately, 4,297 publications were included for analysis, comprising 3,373 research articles (78.50%) and 924 reviews (21.50%). These studies were published in 778 journals and authored by 17,758 researchers from 4,093 institutions across 84 countries or regions.

Figure 1 illustrates the trends in the number of publications and citations related to ET from 2001 to 2024. In 2001, 65 ET-related publications were recorded, followed by a steady increase, peaking at 281 publications in 2020. Although the annual output slightly declined thereafter, there were still 239 publications in 2023. Excluding the data for 2024, the compound annual growth rate (CAGR) of ET publications from 2001 to 2023 was 6.14%. Despite some fluctuations, the overall trend indicates a growing interest in ET research over time. In terms of citations, ET-related studies have been cited 168,387 times, with an average of 39.19 citations per paper and an h-index of 173. Compared to the growth in publication volume, the increase in citations has been more rapid, rising from 27 citations in 2001 to 14,493 citations in 2023, with a CAGR of 33.07%. This indicates that ET research has gained widespread dissemination and recognition within the scientific community.

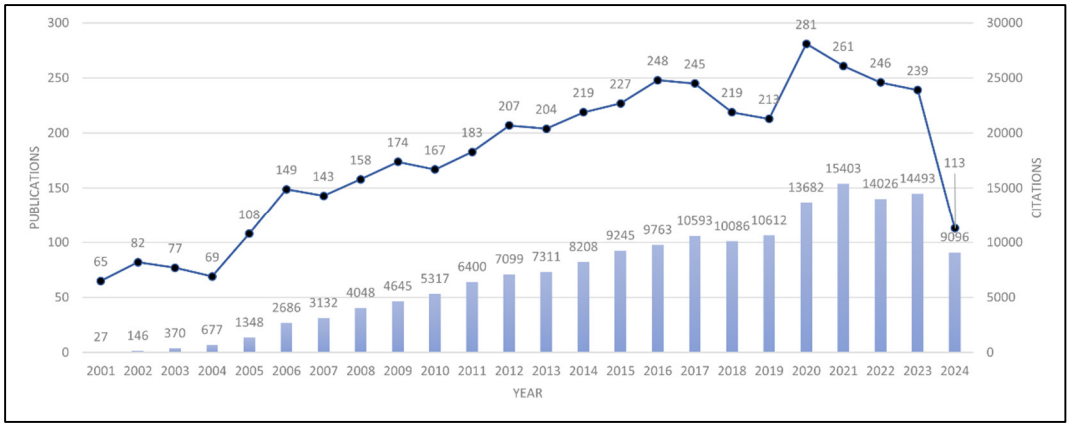

Figure 1. Annual Publications and Citations in ET Research.

3.2. Country/Region Contributions and Collaboration Networks

The analysis of publication volume and citation counts by country and region (Table 1) shows that the United States leads in both publication volume (1,299 articles, 24.23%) and total citations

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(76,507). Italy ranks second in both publication volume (636 articles, 11.86%) and total citations (52,083), followed closely by China, Germany, England, and France. Although European countries have fewer publications than the United States, they demonstrate stronger performance in average citations per article, with Italy at 81.89, Germany at 87.60, the UK at 89.81, and France at 74.64, all surpassing the US average of 58.90. This suggests that European research outputs in this field have a higher level of academic impact and dissemination. In recent years, Asian countries have shown notable progress. China ranks fifth in publication volume (291 articles, 5.43%), while Japan is seventh (219 articles, 4.09%). However, both countries display weaker performance in average citations per article, indicating that as emerging contributors, their research efforts still require further maturation and consolidation.

Table 1. Top 15 Countries/Regions with the Most Related Publications.

Rank	Country Or Region	Publications	Percentage(%)	Total citations	Averrage citations
1	USA (North America)	1299	24.23%	76507	58.90
2	Italy (Europe)	636	11.86%	52083	81.89
3	Germany (Europe)	371	6.92%	32499	87.60
4	England (Europe)	301	5.61%	27032	89.81
5	China (Asia)	291	5.43%	5644	19.40
6	France (Europe)	268	5.00%	20004	74.64
7	Japan (Asia)	219	4.09%	6059	27.67
8	Spain (Europe)	163	3.04%	15267	93.66
9	Denmark (Europe)	133	2.48%	5627	42.31
10	Austria (Europe)	128	2.39%	12808	100.06
11	Switzerland (Europe)	112	2.09%	10326	92.20
12	Turkey (Asia)	104	1.94%	935	8.99
13	Sweden (Europe)	99	1.85%	8109	81.91
14	Canada (North America)	89	1.66%	5826	65.46
15	Australia (Oceania)	80	1.49%	5733	71.66

The co-authorship analysis (Figure 2) of countries and regions reveals the collaborative relationships between nations. The United States undeniably holds a leading position, having established an extensive international collaboration network through cross-continental partnerships. The U.S. maintains close research ties with European countries, while also collaborating with countries such as China, Japan, and Canada. European nations serve as major research hubs on par with the U.S., characterized by strong regional cooperation, forming tightly-knit scientific clusters. At the same time, Europe maintains cross-continental collaborations with countries in the Americas, Asia, and Oceania. Asian countries, however, occupy a relatively peripheral position in the network, indicating significant potential for future scientific collaborations.

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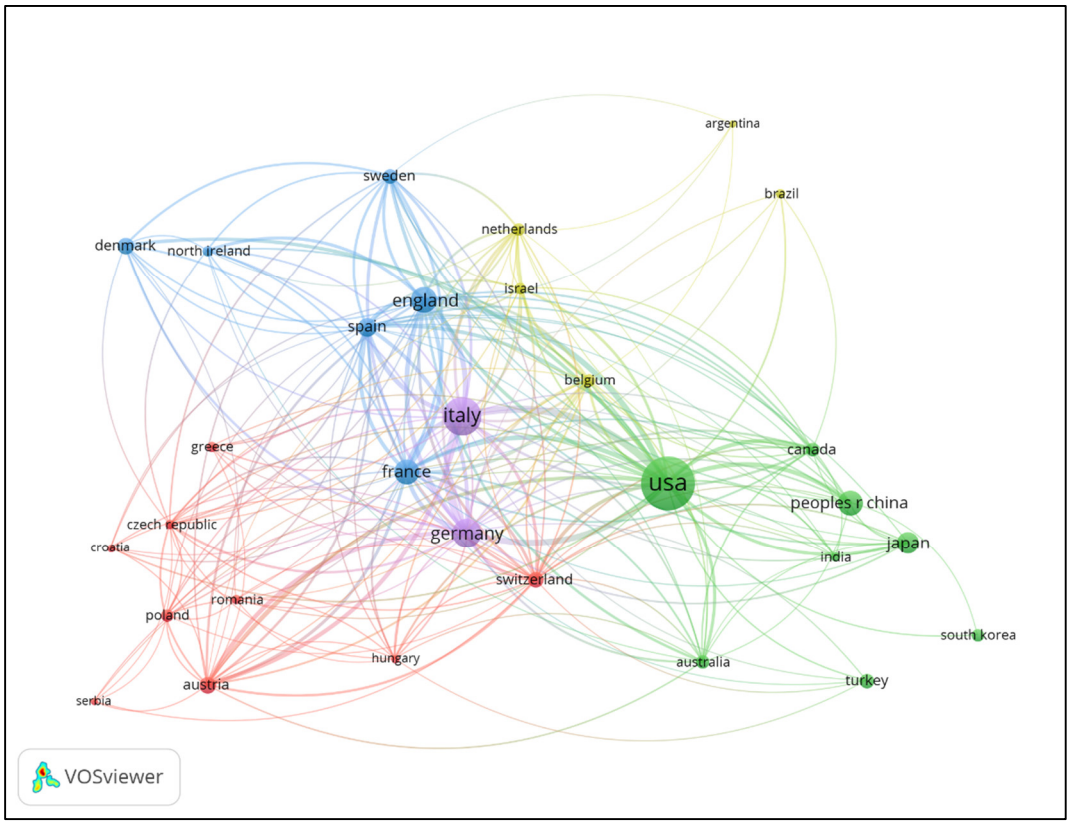

Figure 2. Visualization of Country/Region Co-Authorship Network.

By overlaying a time analysis onto the co-authorship collaboration network (Figure 3), we can clearly observe the evolving trends in scientific cooperation among countries. In the early years (2001–2010), global ET research was primarily led by the United States, along with European countries such as Italy, Germany, and the United Kingdom. International collaborations were largely concentrated between these European nations and the U.S. These countries have maintained their leadership positions, consistently producing a substantial body of research and fostering active international partnerships. However, after 2013, the scientific capabilities of Asian countries began to strengthen. Nations like China and Japan have expanded their collaborations with Western countries, significantly elevating their status within the international research network.

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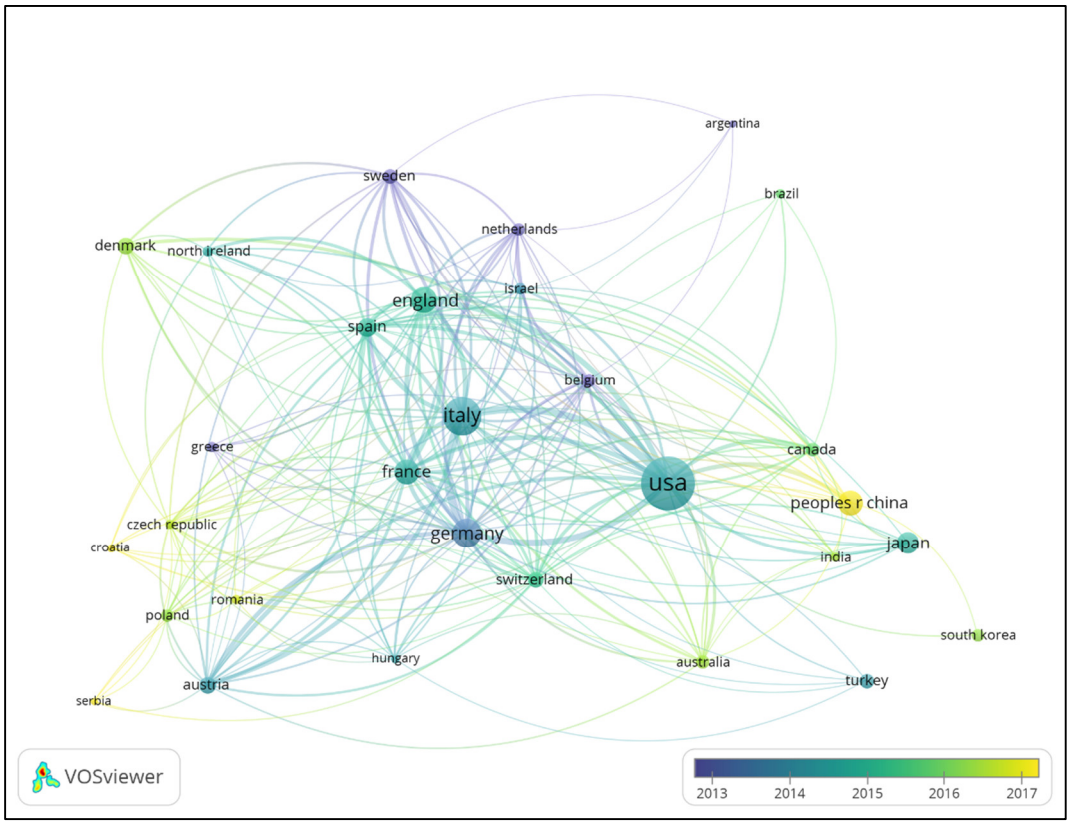

Figure 3. Time-Overlay Visualization of the Country/Region Co-Authorship Network.

In conclusion, Western countries, particularly in Europe and North America (Figure 4), have long dominated the global ET research landscape due to their sustained scientific accumulation and established collaboration networks. However, the rise of emerging powers in Asia has injected new momentum into international scientific collaboration, advancing the globalization of ET research efforts.

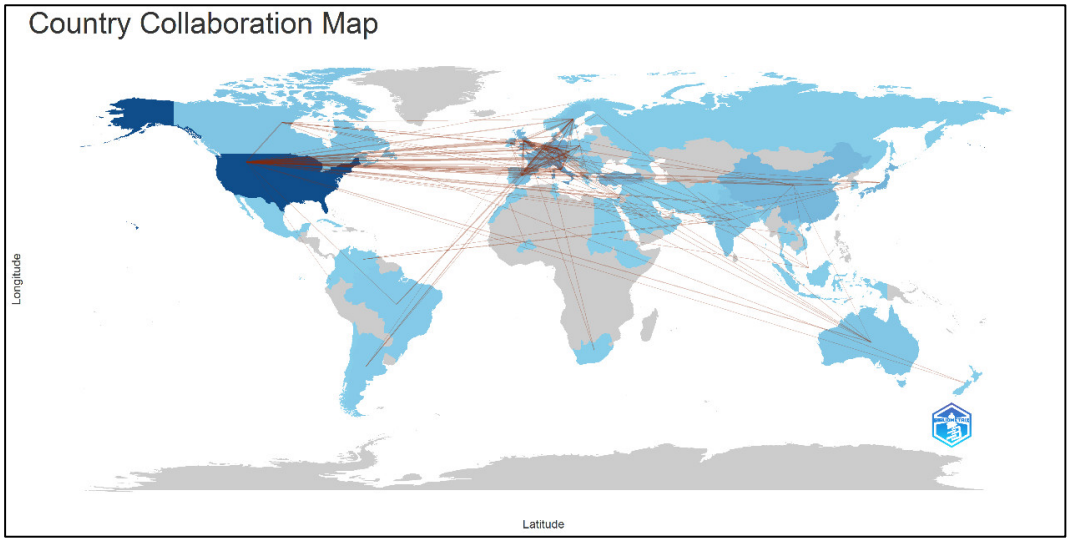

Figure 4. Global Geographical Distribution of Country/Region Collaborations.

3.3. Institutional Contributions and Collaboration Networks

As illustrated in Table 2 and Figure 5, the Mayo Clinic in the United States and the University of Florence in Italy play leading roles in the ET research collaboration network. The Mayo Clinic has produced the largest number of publications and ranks first in total citations. It also demonstrates

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strong performance in average citations per paper and total link strength. The time overlay analysis shows that from 2012 to 2020, the Mayo Clinic maintained active international collaborations with several top European and American research institutions, solidifying its position as a leading institution in the field. There is no doubt that the Mayo Clinic is one of the most academically influential institutions in ET research. Similarly, the University of Florence acts as a pivotal hub in the network, holding the highest total link strength and ranking second in terms of publication volume. It not only maintains close collaborations with other Italian research institutions, such as the University of Pavia and Ospedali Riuniti Bergamo, but also forms a dense regional collaboration cluster within Europe. Furthermore, it plays a crucial role in linking European institutions with international partners, thus contributing significantly to the globalization of ET research.

Table 2. Top 20 Institutions with the Highest Number of Publications.

Rank	Insitution	Publications	Percentage(%)	Total citations	Averrage citations	total link strength
1	Mayo Clinic (USA)	289	3.72%	25780	89.20	300
2	University of Florence (Italy)	166	2.14%	20907	125.95	325
3	MD Anderson Cancer Center (USA)	146	1.88%	9579	65.61	138
4	University of Pavia (Italy)	87	1.12%	21001	241.39	170
5	Medical University of Vienna (Austria)	82	1.05%	10612	129.41	181
6	University of Cologne (Germany)	79	1.02%	12849	162.65	140
7	Ospedali Riuniti Bergamo (Italy)	74	0.95%	8665	117.09	138
8	University of Copenhagen (Denmark)	65	0.84%	3194	49.14	77
9	University of Cambridge (UK)	63	0.81%	8401	133.35	27
10	Icahn School of Medicine at Mount Sinai (USA)	62	0.80%	1300	20.97	57
11	Memorial Sloan Kettering Cancer Center (USA)	61	0.78%	3291	53.95	86
12	Harvard Medical School (USA)	57	0.73%	1423	24.96	77
13	Harvard University (USA)	57	0.73%	11086	194.49	59
14	University of Milan (Italy)	57	0.73%	2758	48.39	59
15	Guy's & St Thomas' NHS Foundation Trust (UK)	55	0.71%	3058	55.60	72
16	Johns Hopkins University (USA)	52	0.67%	2830	54.42	30
17	University of Padua (Italy)	52	0.67%	3781	72.71	106
18	University of Barcelona (Spain)	48	0.62%	7702	160.46	86
19	Zealand University Hospital (Denmark)	48	0.62%	1235	25.73	72
20	Catholic University (Italy)	46	0.59%	2095	45.54	61

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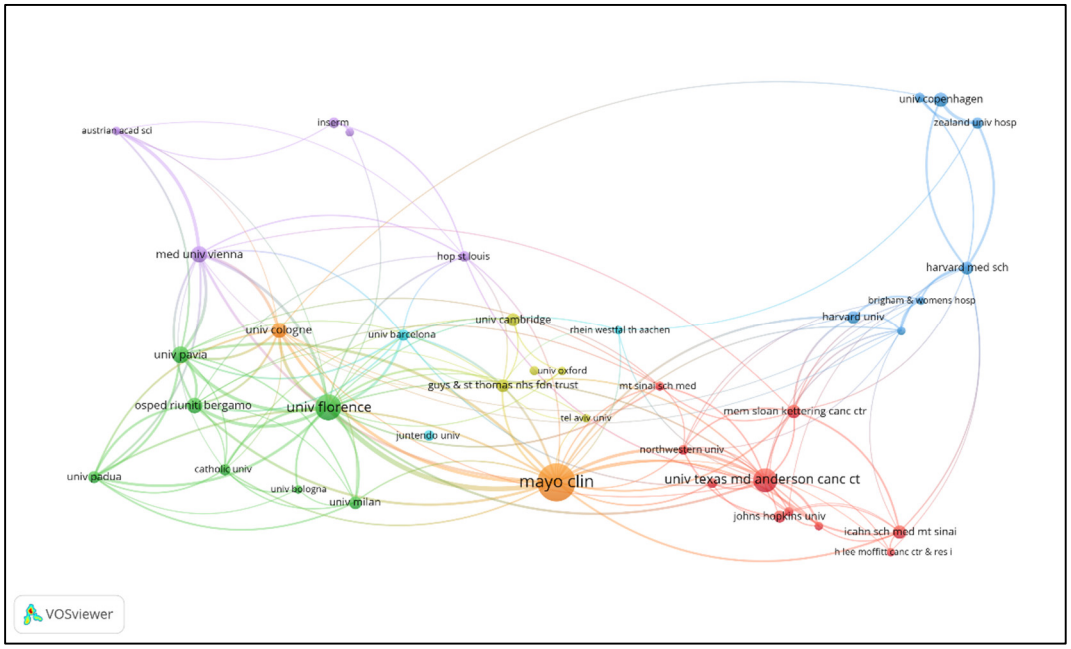

Figure 5. Visualization of Institutional Co-citation Network.

In recent years (2018 and beyond), several emerging research collaborations have gained attention (Figure 6). Institutions such as Harvard Medical School, the Icahn School of Medicine at Mount Sinai, and Zealand University Hospital have rapidly expanded their collaboration networks, showing a clear trend of growth. These institutions maintain close collaborations, particularly with core institutions in the United States and Europe. For example, the partnership between Harvard University and the University of Copenhagen has significantly contributed to advancing ET research.

Overall, the collaboration network in the field of ET research demonstrates clear characteristics of both globalization and regionalization. Core institutions, through long-standing and extensive collaborations, continue to drive scientific progress in the field, while the rise of emerging institutions further expands the scope and depth of research, ensuring its continued growth.

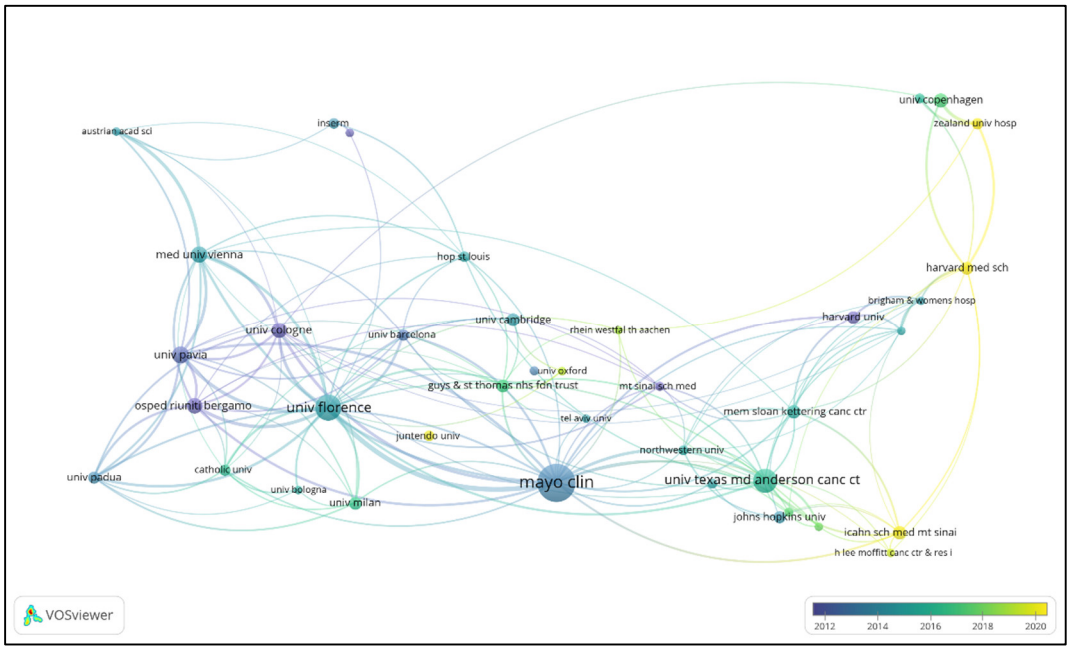

Figure 6. Time-Overlay Visualization of Institutional Co-citation Network.

3.4. Journal Contributions and Citation Networks

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Table 3 presents data on publication volume and citation counts for the 20 most influential journals in global Essential Thrombocythemia (ET) research. These journals collectively published over one-third (34.47%) of the research literature, serving as the primary platforms for disseminating ET research findings. Among these journals, Blood stands out with 290 articles and 37,349 citations, making it not only the journal with the highest number of publications but also the most cited. This dominance is further reflected in the co-citation network (**Figure 7**), where Blood occupies a central position, extensively connecting with other journals, highlighting its role as the main hub for disseminating research outcomes and cutting-edge knowledge in the ET field. Several breakthrough studies that have driven progress in the ET field—such as those on driver mutations [15,16], targeted therapies [17], stratified diagnostics [18], and complications [17]—have been published in Blood.

Table 3. Top 20 Journals with the Most Publications.

Rank	Journal	Publications	Total Ciation	Average Citations	Impact Factor (2023)	JCR
1	Blood	290	37349	128.79	21.0	Q1
2	New England Journal of Medicine	17	12818	754.00	96.2	Q1
3	Leukemia	126	9988	79.27	12.8	Q1
4	American Journal of Hematology	149	5310	35.64	11.0	Q1
5	British Journal of Haematology	107	5299	49.52	5.1	Q2
6	Journal of Clinical Oncology	25	4693	187.72	45.3	Q1
7	Haematologica	80	3396	42.45	10.3	Q1
8	Annals of Hematology	132	2475	18.75	3.0	Q3
9	Haematologica-The Hematology Journal	44	2416	54.91	10.3	Q1
10	Leukemia Research	97	1881	19.39	2.1	Q4
11	European Journal of Haematology	101	1647	16.31	4.2	Q2
12	Experimental Hematology	53	1455	27.45	3.6	Q3
13	Blood Cancer Journal	46	1374	29.87	12.9	Q1
14	Blood Advances	43	1343	31.23	7.5	Q1
15	Leukemia & Lymphoma	82	1310	15.98	2.2	Q3
16	Seminars In Thrombosis and Hemostasis	47	1306	27.79	5.4	Q2
17	Cancer	32	1128	35.25	8.3	Q1
18	International Journal of Hematology	93	1029	11.06	1.8	Q4
19	Journal of Hematology & Oncology	19	870	45.79	12.5	Q1
20	Journal of Thrombosis and Haemostasis	23	836	36.35	6.9	Q2

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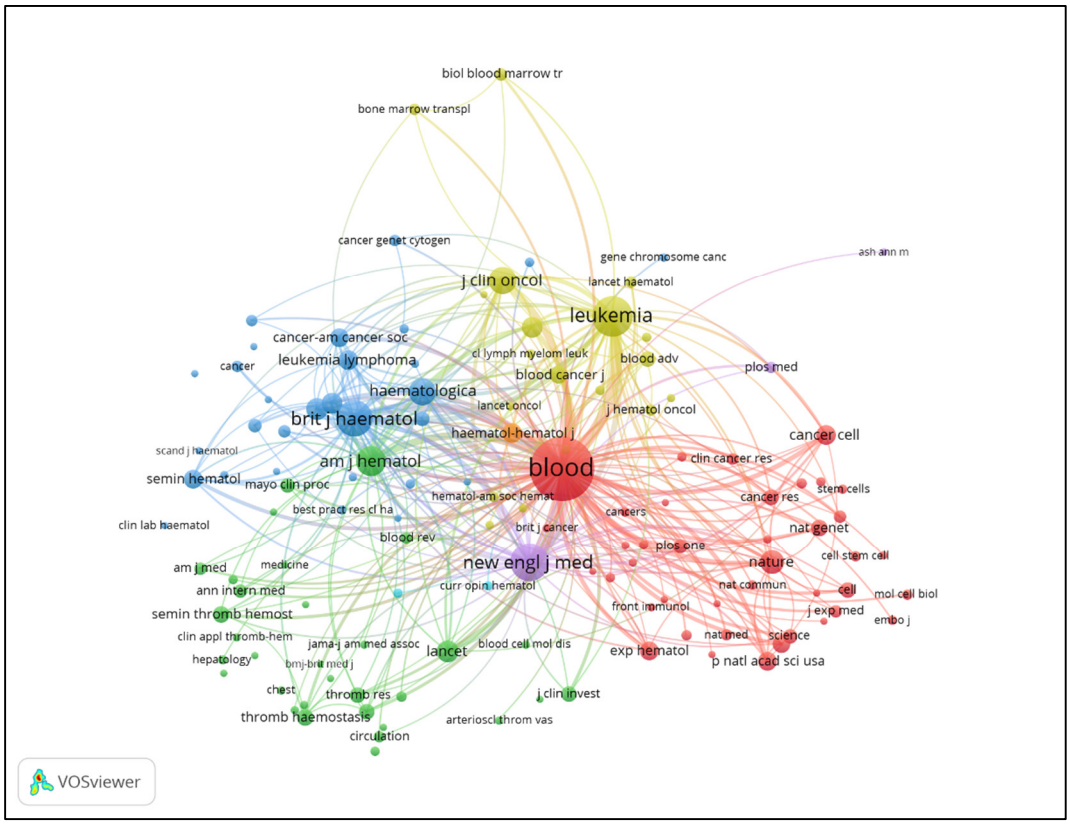

Figure 7. Visualization of Journal Co-citation Network.

Correspondingly, although the New England Journal of Medicine (NEJM) has published only 17 ET-related papers, it enjoys a prestigious reputation in the academic community due to the groundbreaking nature of these studies. In particular, NEJM has made pioneering contributions to the understanding of the JAK2 V617F mutation [19], the clinical trials of ruxolitinib [20], and the association between the JAK2 V617F mutation and thrombosis risk [21]. With these breakthrough studies, NEJM has garnered 12,818 citations, achieving the highest average citation rate of 754 citations per article. In the co-citation network, it forms another key node of influence. Additionally, journals such as Leukemia, the American Journal of Hematology, the British Journal of Haematology, and the Journal of Clinical Oncology have also demonstrated strong performance in terms of publication volume and citation counts. These journals provide critical support for scientific advancements in the ET field and have become important platforms for significant research breakthroughs.

The journal overlay map (**Figure 8**) visualizes the flow of knowledge from foundational research to the knowledge frontier, helping us understand the macro-development structure of the discipline. In the journal overlay map, the clusters of citing journals are located on the left, while the clusters of cited journals are on the right. The x-axis of the circles represents the publication volume of these journals, and the y-axis represents the number of authors. The thickness of the lines indicates the frequency of citations. It is immediately apparent that the “Molecular, Biology, Genetics” field serves as the primary knowledge base, while the “Health, Nursing, Medicine” field provides the second-largest knowledge foundation. Research outputs from these two fields, along with discoveries from other areas, flow into the “Molecular, Biology, Immunology” and “Medicine, Medical, Clinical” fields, forming the knowledge frontier. This indicates that Essential Thrombocythemia (ET) research is built on a solid foundation of molecular biology, immunology, and clinical medicine. It also establishes a clear translational pathway from basic science to clinical applications, tightly connected with cutting-edge research in molecular mechanisms and personalized therapies. This reflects the interdisciplinary integration that characterizes the knowledge structure of the ET field.

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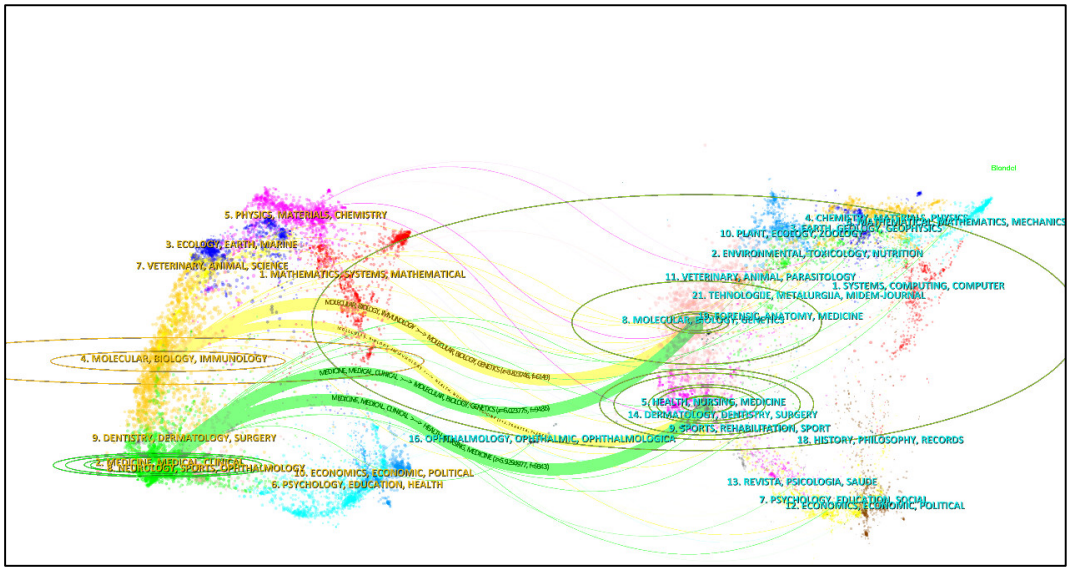

Figure 8. Dual-map Overlay of Journals. On the left side of the map are the citing journals, while the cited journals appear on the right. The length of each ellipse reflects the number of contributing authors, and its width represents the volume of publications.

3.5. Journal Contributions and Collaboration Networks

Table 4 lists the contribution information of the 15 most prolific authors in the field of ET research. Ayalew Tefferi (USA, Mayo Clinic) stands out as the most influential researcher, with 238 publications and 22,511 citations. His research spans various aspects of ET, including diagnostic and therapeutic guidelines [22], pathophysiological mechanisms [23], clinical trials of targeted therapies [24], and stratified treatment strategies [25]. In the co-citation network (**Figure 9**), Ayalew Tefferi's leading role in ET research is further confirmed. His node is both the largest and the most central in the network, and his extensive connections with other researchers indicate that he has provided a rich knowledge base for the field. He serves as both a pioneer and a foundational figure across multiple research directions.

Table 4. Top 15 Authors with the Most Publications.

Rank	Author	Country/Region	Institution	Documents	Citations	Total Link Strength	H-index
1	Ayalew Tefferi	USA	Mayo Clinic	238	22511	614	88
2	Alessandro M. Vannucchi	Italy	University of Florence	177	18735	915	78
3	Srdan Verstovsek	USA	MD Anderson Cancer Center	139	9011	306	42
4	Tiziano Barbui	Italy	Papa Giovanni XXIII Hospital	138	13955	656	69
5	Ruben Mesa	USA	UT Health San Antonio Cancer Center	123	8738	277	42

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6	Hans Carl Hasselbalch	Denmark	Zealand University Hospital	103	3462	241	35
7	Claire N. Harrison	UK	Guy's and St Thomas' Hospitals	101	9127	353	39
8	Paola Guglielmelli	Italy	University of Florence	93	6941	459	49
9	Animesh Pardanani	USA	Mayo Clinic	82	8242	304	43
10	Juergen Thiele	Germany	University of Cologne	76	5511	304	43
11	Francesco Passamonti	Italy	University of Pavia	71	9317	456	44
12	Giovanni Barosi	Italy	IRCCS Policlinico San Matteo	60	8348	327	36
13	Jean-Jacques Kiladjian	France	Saint-Louis Hospital	57	6115	256	33
14	Elisa Rumi	Italy	University of Pavia	55	5928	371	42
15	Guido Finazzi	Italy	Papa Giovanni XXIII Hospital	54	6230	358	47

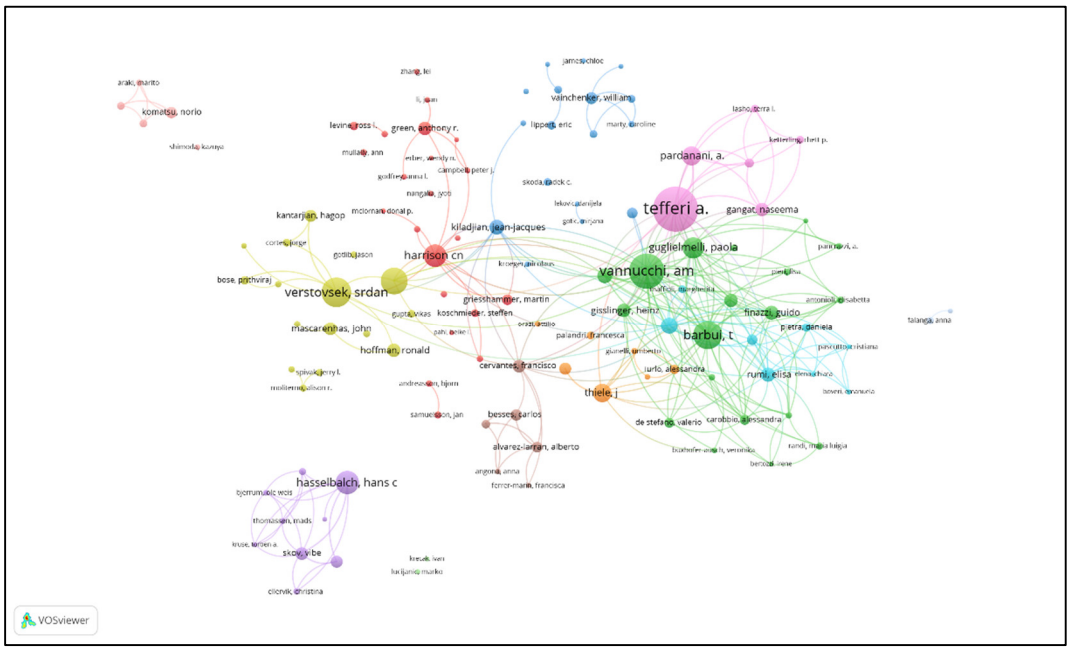

Figure 9. Visualization of Author Co-authorship Network.

Another leading researcher is Alessandro M. Vannucchi, who has made significant contributions to the molecular diagnostic criteria for ET [26], the clinical application of ruxolitinib [20], and the management of ET-related complications [27]. He has published 177 papers with 18,735 citations, and his Total Link Strength reaches 915, highlighting his central role in collaborative research across regions. In the co-citation network, Vannucchi is also a major node located at the center of the network, widely cited by researchers from various regions, indicating that his work has been extensively referenced worldwide. Other notable researchers, such as Srdan Verstovsek, Tiziano

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Barbui, and Ruben Mesa, have each published over 100 papers and received thousands of citations, making outstanding contributions to the advancement of ET research.

In the co-authorship network analysis (**Figure 10**), we can more intuitively and clearly observe the collaborative relationships between authors, visualizing the activity and influence of various research clusters. Alessandro M. Vannucchi, Tiziano Barbui, Paola Guglielmelli, Francesco Passamonti, and Guido Finazzi, all prominent Italian researchers, have formed a large and closely-knit collaboration cluster. This group also demonstrates strong collaboration with both European and North American research clusters. Ayalew Tefferi and his colleagues from the Mayo Clinic have established a relatively independent research cluster in North America, while maintaining frequent collaborations with European researchers. Srdan Verstovsek has created another relatively independent cluster in the United States, working extensively with researchers from the UK and Italy. Meanwhile, Hans Carl Hasselbalch is a distinguished researcher from Denmark who, along with his Danish colleagues, has made significant contributions to the ET field. Although his collaborations with mainstream European and North American clusters are limited, Hasselbalch's work has nonetheless established a unique influence within ET research.

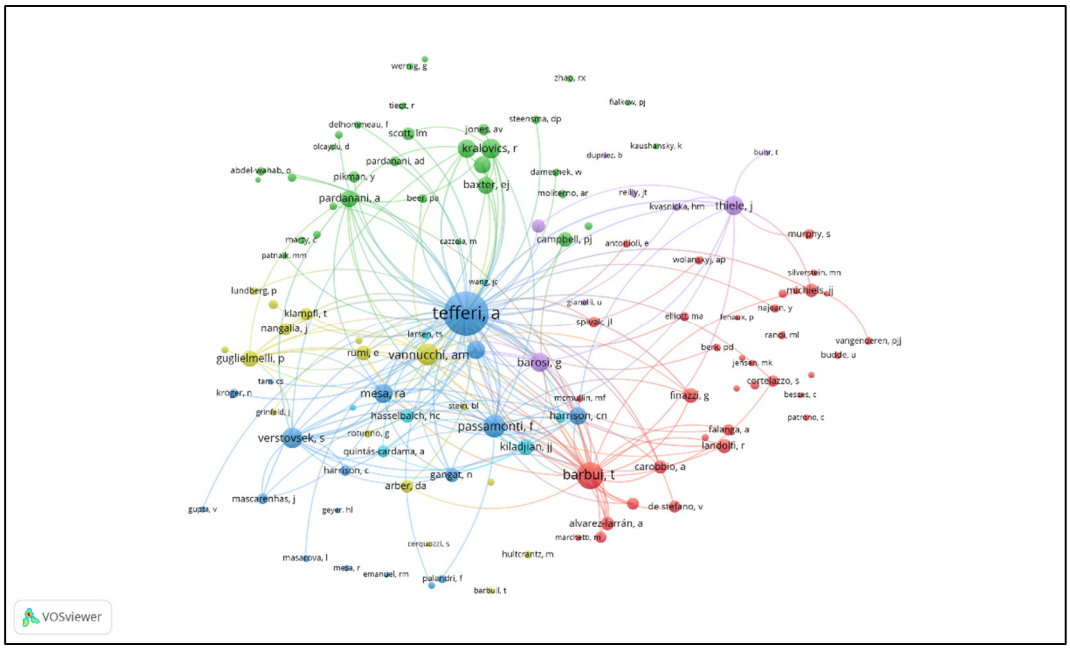

Figure 10. Visualization of Author Co-citation Network.

3.6. Document Contributions and Citation Analysis

In Essential Thrombocythemia (ET) research, several highly cited papers have established the foundational pillars of the field (**Table 5**). Arber et al. (2016), with 6,674 citations, provided a revised classification of myeloid neoplasms and acute leukemia, which has become widely referenced. This study updated the clinical diagnostic criteria for ET and has since served as a key reference in hematology and oncology globally. Simultaneously, the discoveries by Kralovics (2005) and Baxter (2005) regarding the JAK2 mutation mechanism propelled molecular pathology research in ET, offering new insights into the disease's pathogenesis. These papers have laid the groundwork for the ET research framework and continue to play a pivotal role in guiding subsequent studies.

Table 5. Top 10 Cited Documents in ET Research.

Rank	Title	Citation	First Author	Institution	Journal
1	The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia [28]	6674	Daniel A. Arber	Stanford University, USA	Blood
2	A gain-of-function mutation of JAK2 in myeloproliferative disorders [19]	2867	Robert Kralovics	University Hospital Basel, Switzerland	The New England Journal of Medicine

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3	Acquired mutation of the tyrosine kinase JAK2 in human myeloproliferative disorders [15]	2822	E. Joanna Baxter	University of Cambridge, UK	The Lancet
4	Activating mutation in the tyrosine kinase JAK2 in polycythemia vera, essential thrombocythemia, and myeloid metaplasia with myelofibrosis [23]	2376	Ross L. Levine	Harvard Medical School, USA	Cancer Cell
5	The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms [30]	1515	Joseph D. Khoury	MD Anderson Cancer Center, USA	Leukemia
6	Somatic mutations of calreticulin in myeloproliferative neoplasms [16]	1461	Thorsten Klampfl	CeMM, Vienna, Austria	The New England Journal of Medicine
7	JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis [20]	1392	Claire Harrison	Guy's Hospital, UK	The New England Journal of Medicine
8	Somatic CALR mutations in myeloproliferative neoplasms with nonmutated JAK2 [29]	1351	Jyoti Nangalia	University of Cambridge, UK	The New England Journal of Medicine
9	MPLW515L is a novel somatic activating mutation in myelofibrosis with myeloid metaplasia [31]	1099	Yana Pikman	Harvard Medical School, USA	PLoS Medicine
10	JAK2 exon 12 mutations in polycythemia vera and idiopathic erythrocytosis [21]	944	Linda M. Scott	University of Cambridge, UK	The New England Journal of Medicine

The analysis of the citation network (**Figure 11 and Figure 12**) further reveals the academic connections and influence between these core publications. In the citation network diagram, papers such as Kralovics (2005) [19] and Arber (2016) [28] occupy central positions, reflecting their foundational role in ET research. Following the release of the revised World Health Organization classification in 2016, the citations of Arber (2016) [28] surged, indicating its widespread application in clinical diagnostics. Early studies focused heavily on JAK2 mutation-related literature, which propelled research into the molecular mechanisms of ET. Over time, however, clinical diagnosis and therapeutic strategies for ET have gradually become the focal point of academic attention.

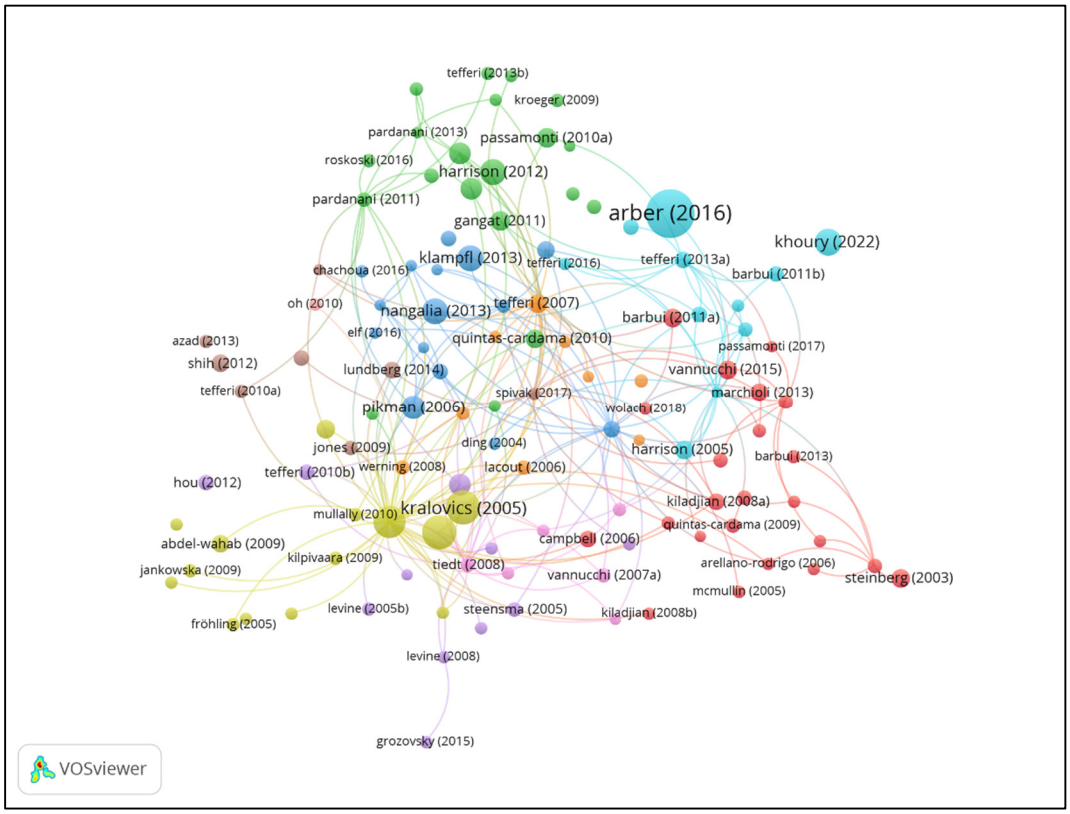

Figure 11. Visualization of Document Citation network.

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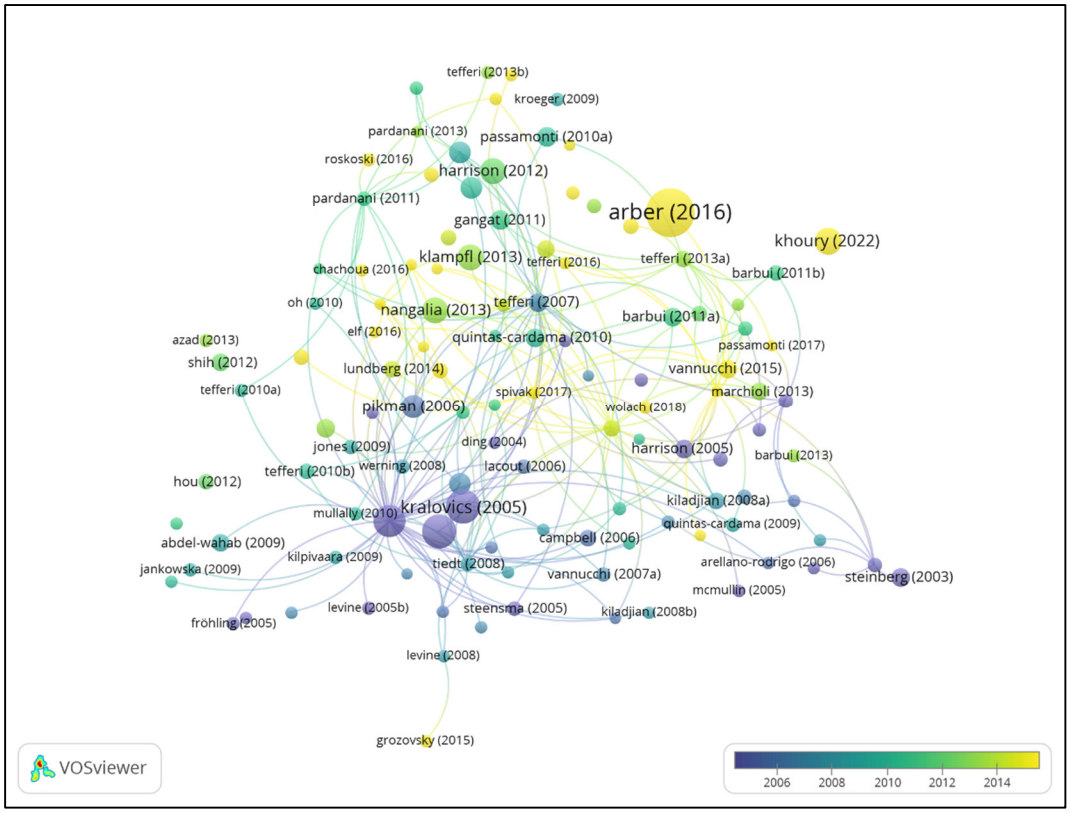

Figure 12. Time-overlay Visualization of Document Citation network.

The co-citation network (**Figure 13**) reveals the construction and evolution of the knowledge system within the ET field. Following the discovery of the JAK2 mutation, key papers such as Baxter (2005) [15], Levine (2005) [23], and Kralovics (2005) [19] formed an important academic cluster, establishing the core theoretical framework regarding the molecular mechanisms of ET. Additionally, the discovery of the CALR mutation has gradually become a new research hotspot, with Klampfl (2013) [16] and Nangalia (2013) [29] forming a new cluster, reflecting the further deepening of molecular research in ET. Arber (2016) [28]and subsequent classification revisions, along with papers such as Khoury (2022) [30], have created a diagnostic standards cluster, showcasing the close relationship between clinical applications and foundational research.

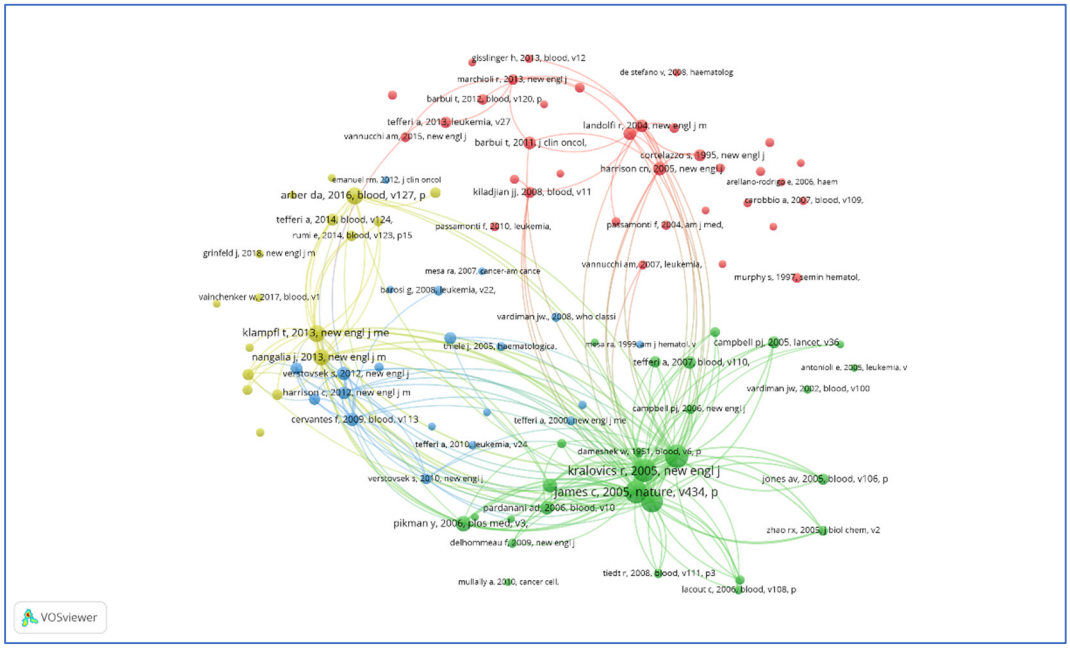

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Figure 13. Visualization of Document Co-citation network.

In summary, research in the ET field has shown a gradual shift from molecular pathology towards clinical diagnostics. The citation burst (**Figure 14**) analysis highlights the temporal dynamics of this transition: from early studies on JAK2 mutations, to the rise of CALR mutations, and finally to the widespread citation of the WHO classification revisions. This reflects the multidimensional development of ET research. These advances have not only greatly enhanced our understanding of the disease's pathogenesis but have also promoted the application of new diagnostic standards and therapeutic strategies, facilitating the adoption of personalized medicine in ET treatment. Future research will likely focus on further integrating molecular mechanisms with clinical diagnostics, driving the development of precision medicine in the ET field.

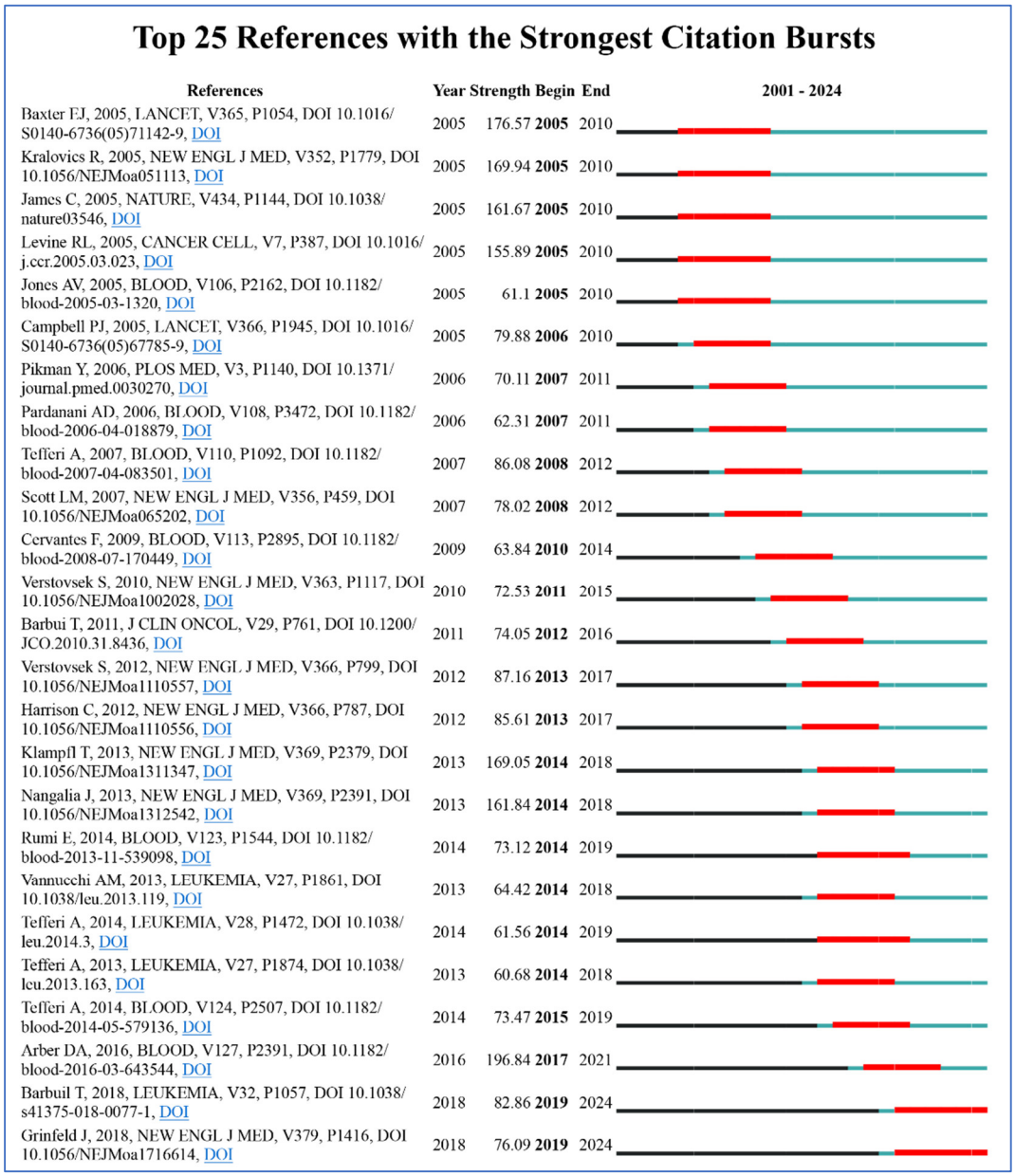

Figure 14. The top 25 references with strongest citation bursts. The red lines indicate the time span of citation bursts, with references organized chronologically in ascending order according to the year each burst began.

3.7. Keyword Contributions and Research Trend Analysis

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The bibliometric analysis of keywords helps map the knowledge structure, evolutionary pathways, and emerging trends in ET research from various perspectives. The frequency of keyword (Table 6) reflects the core concepts and themes within ET studies. As expected, "Essential Thrombocythemia" is the most frequently cited keyword. The high occurrence of terms like "Polycythemia Vera" and "Myeloproliferative Neoplasms" indicates that ET is often studied in conjunction with other myeloproliferative disorders. Other high-frequency keywords include "Tyrosine Kinase JAK2", "Prognosis and Prognostic Factors", "Mutations (Somatic and Activating)", "Myelofibrosis", "Leukemia", and "Thrombosis", highlighting that molecular and pathological mechanisms, prognosis evaluation, and the management of complications form the core of ET research.

Table 6. High occurrences keywords in ET research.

Keyword	Freq.	Total Link Strength	Keyword	Freq.	Total Link Strength
Essential Thrombocythemia	2847	14483	Therapy	233	1340
Polycythemia Vera	2346	13160	Expression	230	1089
Myeloproliferative Neoplasms	1446	8479	Classification	226	1362
Tyrosine Kinase Jak2	1399	8245	World-Health-Organization	214	1417
Prognosis And Prognostic Factors	1044	6144	Disease	207	1046
Mutations (Somatic and Activating)	1020	5994	Activation	173	772
Myelofibrosis	906	5643	Allele Burden	157	1122
Jak2 V617f Mutation	804	4817	Management	156	862
Leukemia	743	3796	Criteria	145	847
Myeloproliferative Disorders	723	3834	Cells	136	588
Thrombosis	667	3644	Available Therapy	135	897
Primary Myelofibrosis	639	4079	Neoplasms	127	721
Myeloid Metaplasia	443	2804	Diagnostic-Criteria	118	718
Calreticulin	354	2247	Bone-Marrow	117	585
Diagnosis	333	1919	Anagrelide	117	672
Hydroxyurea	323	1921	Efficacy	116	740
Survival	302	1887	Cancer	116	488
International Working Group	296	2066	Transformation	111	728
Ruxolitinib	273	1813	Stem-Cell Transplantation	107	666
Thrombopoietin Receptor	248	1288	Leukocytosis	106	725

The keyword co-occurrence network analysis further delineates the close relationships between research themes and the structural framework of knowledge. As shown in the Figure 15, the largest red cluster is composed of keywords such as "Essential Thrombocythemia", "Polycythemia Vera", "Myeloproliferative Neoplasms", "Tyrosine Kinase JAK2", "JAK2 V617F Mutation", "mutations", "Calreticulin", "MPL", and "TET2". These keywords reflect the in-depth exploration of the molecular and pathological mechanisms underlying MPNs. The green cluster includes keywords such as "prognosis and prognostic factors", "complications", "hydroxyurea", "anagrelide", "management", and "thrombosis", indicating a focus on the prevention and management of complications. The blue cluster features keywords like "myelofibrosis", "primary myelofibrosis", "allele burden", "ruxolitinib", and "leukemic transformation", highlighting research efforts aimed at controlling disease progression and the transformation of ET. Lastly, the yellow cluster comprises keywords such as "classification", "diagnostic criteria", "myeloid neoplasms", and "World Health Organization", representing studies and discussions on the classification standards and diagnostic systems for ET and related diseases.

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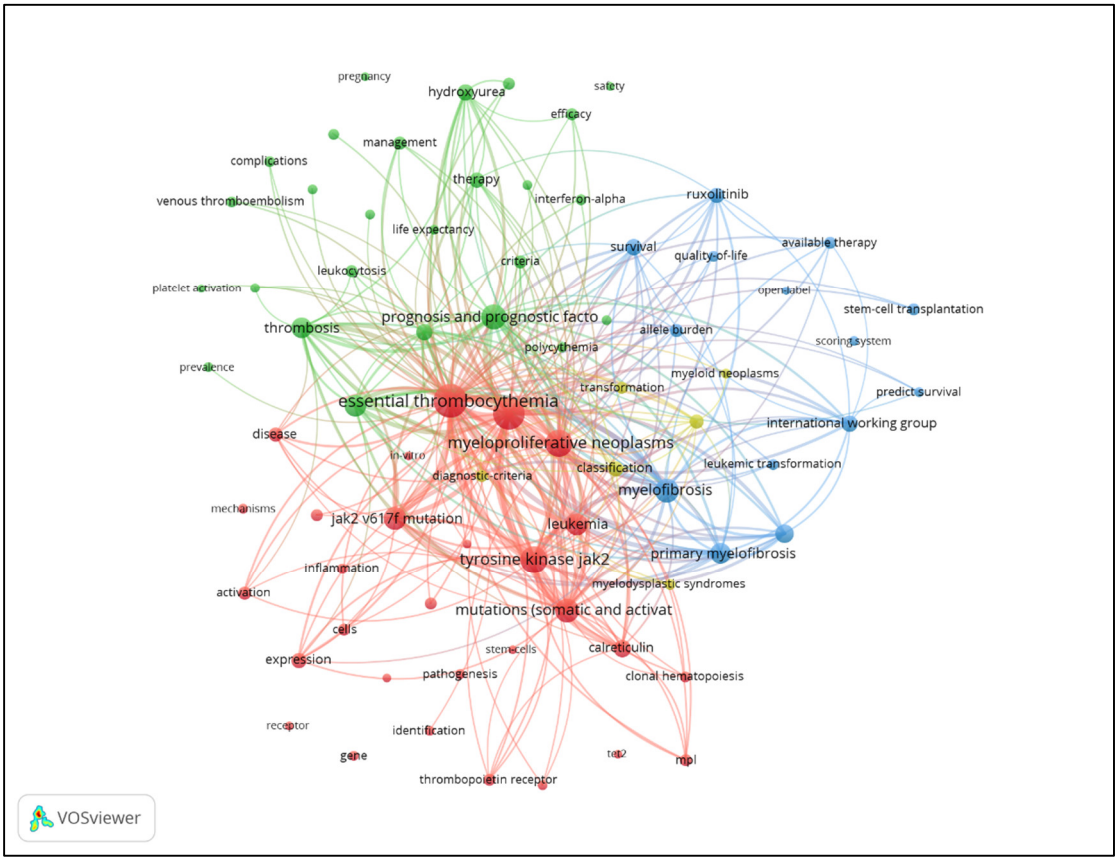

Figure 15. Visualization of Keyword Co-occurrence Network.

The keyword timeline analysis (Figure 16) and keyword burst analysis (Figure 17) clearly illustrate the historical evolution and shifting research hotspots in the field of Essential Thrombocythemia (ET). In the early 2000s, research focused on the classification, diagnostic criteria, and complications of the disease, with keywords such as "prognosis and prognostic factors", "diagnostic criteria", "myelofibrosis", and "hydroxyurea" occupying prominent positions, reflecting the emphasis on disease definition and complication management. The discovery of the JAK2 V617F mutation in 2005 dramatically reshaped the understanding of ET in hematology. This breakthrough shifted the research focus towards molecular mechanisms, driving the transition from morphological to molecular diagnostics and leading to the development and clinical application of targeted therapies such as ruxolitinib. In recent years, keywords like "next-generation sequencing", "health organization classification", "symptom burden", and "molecular responses" indicate the field's gradual movement toward precision medicine. Additionally, terms such as "inflammation", "oxidative stress", "C-reactive protein", and "endothelial cells" suggest that researchers are increasingly focused on the role of inflammation in the pathogenesis of MPNs, leading to a deeper understanding of the pathological mechanisms underlying ET.

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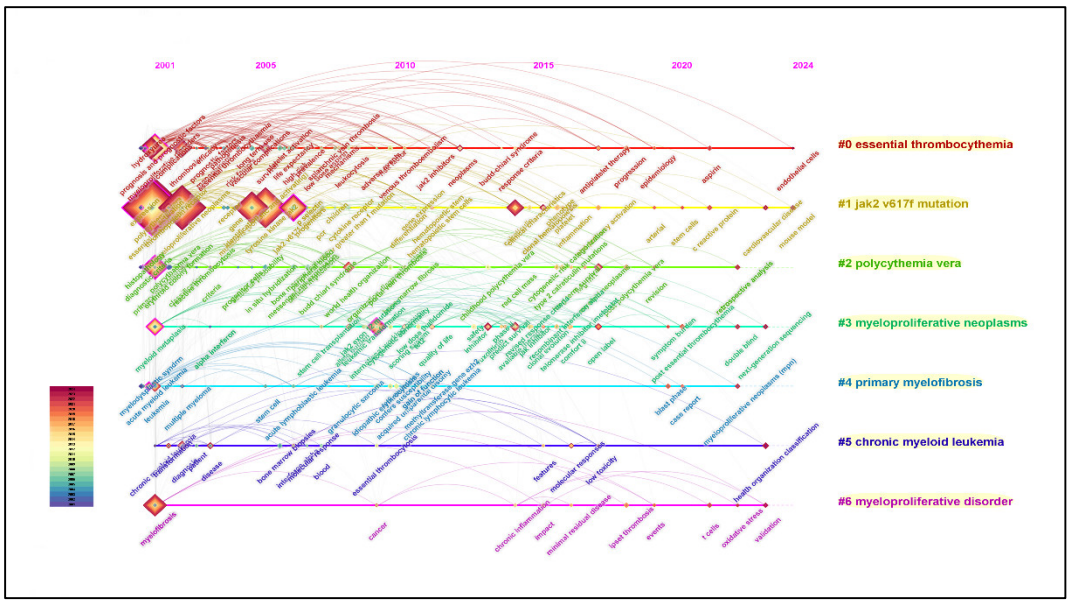

Figure 16. Timeline Visualization of High-frequency Keywords from 2001 to 2024.

Top 30 Keywords with the Strongest Citation Bursts

Keywords	Year	Strength	Begin	End	2001 - 2024
myeloproliferative disorders	2001	147.42	**2001**	2010	
myeloid metaplasia	2001	46.75	**2001**	2012	
leukemia	2001	29.82	**2001**	2008	
diagnostic criteria	2001	19.67	**2001**	2008	
hydroxyurea	2001	16.79	**2001**	2006	
vera study group	2001	16.43	**2001**	2004	
chronic myeloid leukemia	2001	12.87	**2001**	2006	
bone marrow	2001	10.73	**2001**	2006	
thrombotic complications	2001	10.62	**2001**	2009	
bone marrow transplantation	2001	10.15	**2001**	2006	
erythroid colony formation	2002	16.6	**2002**	2008	
expression	2001	17.25	**2003**	2007	
prognostic factors	2003	11.93	**2003**	2016	
identification	2004	12.65	**2004**	2014	
receptor	2004	9.71	**2004**	2005	
stem cell	2005	11.44	**2005**	2008	
jak2 v617f mutation	2006	54.28	**2007**	2011	
leukocytosis	2008	13.03	**2009**	2013	
calreticulin	2014	36.56	**2015**	2024	
inflammation	2016	10.4	**2016**	2024	
available therapy	2014	24.04	**2017**	2024	
myeloid neoplasms	2017	18.31	**2017**	2024	
transformation	2002	13.81	**2017**	2024	
low toxicity	2017	10.56	**2017**	2021	
clonal hematopoiesis	2015	22.28	**2018**	2024	
open label	2017	17.74	**2018**	2024	
post polycythemia vera	2018	13.16	**2018**	2022	
ruxolitinib	2013	22	**2020**	2024	
post essential thrombocythemia	2020	10.73	**2020**	2022	
survival	2003	15.3	**2022**	2024	

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Figure 17. Top 30 Keywords with the Strongest Citation Bursts. The red lines indicate the time span of citation bursts, with references organized chronologically in ascending order according to the year each burst began. * Tables may have a footer.

In summary, since 2005, research themes in the ET field have undergone a significant shift from clinical morphology to molecular biology, marking a profound transformation. Currently, the field is steadily advancing toward precision and personalized medicine, showcasing a clear developmental trajectory. This evolution highlights the systematic and multi-layered nature of ET research.

4. Discussion

Through bibliometric analysis, we have observed significant progress in Essential Thrombocythemia (ET) research over the past two decades, particularly in molecular mechanisms, clinical management, and international collaboration. From 2001 to 2023, ET research has shown a consistent upward trend, with the average number of annual publications exceeding 200 in the past five years. Citation counts have surged from 27 in 2001 to 14,493 in 2023, indicating the widespread dissemination and global impact of research outcomes in this field. In terms of contributions by countries and regions, the United States leads both in publication volume and citation count, demonstrating its leadership in the field. Italy follows closely, particularly excelling in average citations per paper. European countries, through close intra-regional cooperation and extensive collaborations with the U.S. and other nations, have maintained a strong influence on the direction of ET research. In contrast, although China, Japan, and other Asian countries have produced a substantial number of publications, their average citation rates are relatively lower, suggesting that research in these regions is still in the accumulation phase. Strengthening international collaboration could enhance their impact in the future. At the institutional level, Mayo Clinic and the University of Florence play pivotal roles in ET research. Mayo Clinic leads in both publication and citation metrics and holds a central position in international collaborations. The University of Florence acts as a hub in European ET research, contributing significantly to regional and international partnerships.In terms of academic influence, Blood is the most impactful journal in ET research, ranking first in both publication volume and citation count. The New England Journal of Medicine stands out for its research on JAK2 mutations and related clinical trials, with the highest average citation per article. The journal overlay map illustrates the development model of ET research, showing that the integration of the Molecular, Biology, Genetics and Health, Nursing, Medicine fields forms the knowledge foundation of ET research, driving continuous progress in the field. Regarding researcher influence, Ayalew Tefferi and Alessandro M. Vannucchi are among the most impactful scholars in this domain. Their research spans a broad range of topics, from molecular mechanisms to clinical management, and both have demonstrated unique strengths in high productivity and extensive collaboration. Several landmark studies have significantly advanced ET research. For example, Arber's (2016) revision of the WHO classification and the discoveries by Kralovics (2005) and Baxter (2005) on the JAK2 mutation mechanism have revolutionized ET research, shifting the diagnostic approach from morphological to molecular biology.

Keyword-related analyses indicate that ET research has evolved from an early focus on classification and prognosis to molecular mechanisms and targeted therapies. The discovery of the JAK2 V617F mutation marked a milestone in ET research. Subsequently, the roles of CALR and MPL mutations in ET were further elucidated, deepening the understanding of its pathological mechanisms. The JAK2 V617F mutation is present in 50–60% of ET patients, leading to sustained activation of the JAK-STAT signaling pathway, allowing hematopoietic stem cells to proliferate abnormally without dependence on hematopoietic growth factors, making this mutation a core mechanism of ET pathogenesis [32]. For JAK2-negative ET patients, CALR (calreticulin) and MPL mutations are the primary drivers. CALR mutations are the most common driver mutation in JAK2-negative ET patients, accounting for approximately 20–25% [33]. These mutations cause abnormalities in calcium regulation and protein folding, also activating the JAK-STAT pathway and

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promoting abnormal platelet production. Additionally, around 5–10% of JAK2-negative patients have MPL (myeloproliferative leukemia virus oncogene) mutations, which also result in abnormal activation of the JAK-STAT pathway [34]. These mutations share similar pathological mechanisms with JAK2 mutations, driving the abnormal proliferation of myeloid cells and disease progression [35]. Although all three driver mutations can lead to the ET disease phenotype, they exhibit significant differences in thrombosis risk and disease progression. JAK2 mutations not only cause abnormal proliferation of myeloid cells but also elevate levels of pro-inflammatory cytokines (such as IL-6), damaging vascular endothelial cells, activating platelets, and creating an inflammatory bone marrow environment, thus correlating with higher risks of thrombosis and disease progression [36]. In contrast, although CALR mutations are associated with higher platelet counts, the platelets have lower aggregation potential, and the influence on inflammatory cytokines is minimal, resulting in lower risks of thrombosis and disease progression [16]. MPL mutations, on the other hand, mainly stimulate fibroblast proliferation and collagen fiber formation, leading to a higher risk of bone marrow fibrosis [35]. In summary, the discovery of JAK2, CALR, and MPL driver mutations has established the molecular biology framework for ET pathogenesis, paving the way for more refined diagnostic classification and stratified treatment strategies; however, the high genetic heterogeneity of ET suggests that further research is still needed despite significant progress in understanding disease mechanisms. A subset of patients, known as “triple-negative ET”, lacks known driver mutations, and the underlying mechanisms remain unclear, requiring further investigation [37]. Additionally, non-driver mutations such as TET2, ASXL1, and DNMT3A significantly impact disease manifestation by regulating epigenetic control and stem cell self-renewal, commonly seen in high-risk patients, which increase the risk of disease progression and transformation into bone marrow fibrosis or acute myeloid leukemia [38]. Overall, the high genetic heterogeneity of ET determines the variability in disease progression and complication risks among patients, directly influencing prognosis and demanding a higher degree of individualized and precision medicine in treatment.

The advancement of molecular mechanism research has led to the development of JAK2 inhibitors, such as ruxolitinib, marking the beginning of a new era in targeted therapy for Essential Thrombocythemia (ET). For patients carrying the JAK2 V617F mutation, ruxolitinib effectively reduces the release of inflammatory cytokines and the abnormal proliferation of hematopoietic cells by inhibiting the JAK-STAT signaling pathway, thereby lowering platelet levels and reducing the risk of thrombosis [39]. Additionally, ruxolitinib can alleviate disease-related symptoms such as itching, fatigue, and attention deficits [40]. Due to its direct inhibition of JAK2 activity, ruxolitinib may also have the potential to slow the progression of fibrosis [41]. However, despite the breakthrough represented by JAK2 inhibitors (e.g., ruxolitinib) in targeted therapy, they have not yet replaced aspirin and hydroxyurea as the standard treatments for ET, primarily due to the genetic complexity of ET patients [6]. While the JAK2 mutation is the most common driver mutation, 25–35% of patients are driven by CALR or MPL mutations, and a portion of triple-negative ET patients still have unidentified driver mutations [42]. JAK2 inhibitors are primarily effective in JAK2-positive patients, whereas targeted therapies for CALR and MPL mutations are still in early stages of development, limiting the broader application of existing targeted therapies [43]. Moreover, the molecular mechanisms of ET differ from other MPNs. Although JAK2, CALR, and MPL mutations all activate the JAK-STAT pathway, the mutation burden in ET patients is relatively low, and disease progression is slower [44]. ET is primarily characterized by abnormal platelet production, with minimal impact on other myeloid cells and a lower risk of bone marrow fibrosis. Additionally, ET patients generally do not exhibit significant splenomegaly or severe systemic inflammatory responses, as seen in myelofibrosis or polycythemia vera, resulting in a lower dependence on targeted therapies. While JAK2 inhibitors can reduce platelet levels, they are still less effective than current antiplatelet therapies in controlling thrombotic events, and concerns remain about their long-term safety [45]. Therefore, further exploration and research are needed to develop more effective and safer therapeutic strategies for targeted treatment in ET.

Our study also shows that classification and stratified treatment of patients have long been key issues in ET research. Currently, for low-risk elderly patients, standard therapies centered on

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hydroxyurea and low-dose aspirin generally meet the needs of both patients and clinicians, achieving good symptom control when the risks are manageable [46]. However, for younger patients and those with high-risk ET, existing treatment options remain inadequate. High-risk patients exhibit significant heterogeneity compared to low-risk patients, with a more complex genetic background of hematopoietic stem cells, often accompanied by multigene mutations and other high-risk factors for thrombosis [47]. Although hydroxyurea combined with aspirin is effective in some patients, this combination is insufficient to fully control the risk of thrombosis in high-risk patients, and the long-term use of hydroxyurea is particularly concerning due to its potential to increase the risk of leukemic transformation [48]. Moreover, targeted therapies are not ideal for controlling disease progression, even in high-risk ET patients with JAK2 mutations. JAK2 inhibitors struggle to consistently and completely suppress the mutation burden, while the complex genetic background of hematopoietic stem cells in high-risk patients further limits the efficacy of single-agent targeted therapies [49]. For patients with CALR or MPL mutations, targeted therapies similar to JAK2 inhibitors are still under development, and effective treatment options are lacking. These challenges complicate the clinical management of high-risk patients. Children and young adults with ET are another group that requires special attention. For their clinical presentations are often atypical, and the JAK2 mutation rate is lower. Children and young adults with ET require special attention because their clinical presentations are often atypical and the JAK2 mutation rate is lower, with some children possibly carrying undiscovered mutations or having more complex genetic backgrounds [50]. The current ET diagnostic standards and risk stratification models are primarily based on data from adult patients and may not be fully applicable to pediatric and young adult populations. Due to insufficient research and long-term follow-up, although the disease course is longer in children and young adults, our understanding of their disease progression and the risk of transformation to myelofibrosis or acute myeloid leukemia remains inadequate. The long-term safety and efficacy of current treatments (e.g., hydroxyurea and aspirin) in children and young adults are also underexplored. In particular, the long-term use of hydroxyurea may lead to bone marrow suppression or increase the risk of malignant transformation, which could be more pronounced in pediatric and young adult patients [51], and the use of targeted therapies such as JAK2 inhibitors in this population remains highly uncertain [52]. In conclusion, the management of ET in children and young adults continues to face many challenges, primarily due to the lack of research data, long-term prognostic evaluation, and tailored treatment strategies specific to this population. Future research should focus more on this group to develop more targeted treatment and follow-up plans.

The results of keyword analysis show that the role of inflammation in the pathogenesis and progression of Essential Thrombocythemia (ET) has received increasing attention. In ET patients, driver mutations activate the JAK-STAT signaling pathway, maintaining a state of chronic inflammation [53]. The overactivation of this pathway due to the JAK2 mutation leads to the secretion of various pro-inflammatory cytokines, such as IL-6, TNF-α, and IL-1β [54]. These cytokines not only stimulate hematopoietic cells but also alter the hematopoietic microenvironment, enhancing the pro-inflammatory and pro-fibrotic properties of macrophages, endothelial cells, and fibroblasts in the bone marrow, ultimately contributing to the development of myelofibrosis [55]. Additionally, these pro-inflammatory factors damage the vascular endothelium, increasing the risk of thrombosis [56–58]. Chronic inflammation is a major driver of thrombotic complications in ET patients. Inflammation-induced activation of endothelial cells and platelet aggregation significantly increase the risk of thrombosis. For example, IL-6 and other inflammatory cytokines promote platelet production and activate platelet function, directly leading to thrombus formation [59,60].

Studies have shown a strong correlation between elevated inflammation levels in ET patients and a higher incidence of thrombotic events [61,62]. Chronic inflammation also accelerates the transformation of ET to acute leukemia through the sustained release of cytokines and oxidative stress, which promote DNA damage and the accumulation of gene mutations [63]. Inflammatory responses triggered by JAK2 V617F or CALR mutations result in the prolonged secretion of pro-inflammatory cytokines including IL-6, TNF-α, and IL-1β [64]. These cytokines not only increase DNA damage by inducing oxidative stress but also impair DNA repair mechanisms, exacerbating

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genomic instability, thereby facilitating the transformation to leukemia [65]. Pro-inflammatory cytokines can also disrupt the self-renewal and differentiation of hematopoietic stem cells, leading to their overproliferation or abnormal differentiation, which results in the formation of abnormal hematopoietic clones [66–69]. This is particularly pronounced in patients with additional mutations such as TET2, ASXL1, and others, where inflammation further drives stem cell dysfunction and the expansion of clonal hematopoiesis [70–74]. Furthermore, inflammation may contribute to immune evasion, helping abnormal hematopoietic stem cells escape immune surveillance. Chronic inflammation suppresses the function of normal immune cells, such as T cells and natural killer cells, reducing their ability to monitor the abnormal proliferation of hematopoietic cells, which may promote disease progression and transformation, particularly in high-risk ET patients [75–77]. Inflammation is also considered a key factor in the progression of ET to myelofibrosis. Pro-inflammatory cytokines (e.g., IL-6 and TNF-α) tend to accumulate in the bone marrow. Studies have shown that TGF-β and other pro-inflammatory cytokines stimulate fibroblast proliferation, leading to fibrotic tissue deposition and extracellular matrix remodeling, which eventually result in the development of myelofibrosis [78–80]. This fibrosis further exacerbates the pathological progression of ET, leading to more severe hematopoietic disorders and clinical complications.

In conclusion, our study, through bibliometric analysis, has comprehensively revealed the rapid development of ET research and, to some extent, quantified the contributions of prominent researchers and institutions. It has also illustrated the collaboration networks between countries and regions and visualized the shifts and evolution of research hotspots in the field. Over the past two decades, ET research has made significant progress, particularly in the areas of molecular mechanisms, targeted therapies, and international collaboration. However, future research must continue to focus on genetic heterogeneity and personalized treatment. There is still a substantial need for the development of new drugs and therapies to address the clinical challenges posed by this complex disease.

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