Abstract. — OBJECTIVE: In the last 20 years, the field of myeloproliferative neoplasm (MPN) has changed dramatically. This study aims to provide new ideas for the scientific research of MPN by systematically combing the literature.

MATERIALS AND METHODS: CiteSpace and VOSviewer were used to carry out a bibliometric analysis of MPN papers to visualize the development process, research hotspots, and cutting-edge trends in clinical practice, mechanisms, and management strategies related to MPN.

RESULTS: 1,099 authors from 736 institutions in 113 countries/regions published 11,922 papers in 1,807 academic journals. The United States and Italy were in the leading positions in this research field. Mayo Clinic is the institution with the largest number of publications. Only a few countries and institutions have shown active cooperation. Ayalew Tefferi and Ruben A. Mesa are outstanding contributors to the field. Blood and Leukemia are considered influential journals based on publications and citations. In this field, the research of MPN mainly focuses on the occurrence and progress mechanism of MPN, the clinical significance of non-driving gene mutation, optimization of primary and secondary thromboprophylaxis, clinical research of long-acting interferon and JAK2 inhibitors, and exploration of better therapies for myelofibrosis (primary and secondary) and post-MPN acute myeloid leukemia (AML).

CONCLUSIONS: The research is in a stage of rapid development. The collaboration between different institutions or countries (regions) still has room to grow. The hotspot analysis shows that the research of MPN mainly focuses on gene mutation, thrombosis, new drug applications, disease progression, etc.

Key Words: Myeloproliferative neoplasm, Essential thrombocytopenia, Polycythemia vera, Myelofibrosis, Bibliometrics.

Introduction

Myeloproliferative neoplasms (MPN) are a group of malignant clonal disorders of hematopoietic stem cell origin, characterized by excessive proliferation of one or more lines of mature myeloid cells. The classic Philadelphia chromosome (Ph)-negative MPN in the 2016 World Health Organization (WHO) classification and diagnostic criteria for MPN includes polycythemia vera (PV), essential thrombocytopenia (ET), pre-fibrotic/early primary myelofibrosis (pre-PMF), and overt PMF. Over the past two decades, with the dis-covery of driver mutations such as JAK2, MPL, CALR, and a series of non-driver mutations, as well as the standardization of the morphological analysis of bone marrow pathology and the introduction of the MPN-10 symptom load assessment scale for MPN patients, the diagnostic model of MPN has transitioned from a “clinical-pathological” to a “clinical-pathological-molecular” diagnostic model. Therapeutically, the use of novel drugs such as JAK2 inhibitors, which may alter the natural course of MPN patients, has led to significant advances in the treatment of MPN.

As research increases year by year, the medical field generates a huge pile of information. How to distinguish important information in a certain medical field, such as revolutionary progress and research hotspots, is a key problem we face. Bibliometrics is the discipline that applies mathematical and statistical methods to the study of a wide range of communication media. In 1969, Pritchard proposed to use bibliometrics instead of literature statistics to evaluate the literature research trend qualitatively and quantitatively. After entering the 21st century, bibliometrics has gradually integrated computer science, information...
Current status and hotspots evolution in myeloproliferative neoplasm

Science, statistics, and so on. Different from traditional reviews, bibliometrics provides a more objective description of disciplinary progress. Applying bibliometrics to the MPN field can excavate and analyze large-scale MPN-related information, which can help scholars quickly grasp the distribution of countries/regions, authors, journals and research hotspots in this research field for future research. The purpose of this study is to explore the research hotspots and development trends of MPN in the recent 20 years, and to provide new ideas for basic research and clinical prevention and treatment.

Materials and Methods

The data were extracted from Web of Science Core Collection and downloaded within one day on September 3, 2022. The search terms were as follows: “myeloproliferative neoplasm”, “essential thrombocythemia”, “polycythemia vera”, “primary myelofibrosis”. The search date was from January 1, 2001, to January 1, 2022. The retrieved literatures were exported in the form of all records and references, saved as plain text files, and stored in download_txt format. All valid data were collected on the Web of Science Core Collection. Microsoft Excel 2019 was used to analyze the trend of the number of articles published in the year, and the countries/regions and institutional distribution, author contributions, core journals, keywords and timeline viewers were all visually analyzed by CiteSpace (available at: http://cluster.cis.drexel.edu/~cchen/citespace/) and VOSviewer (available at: https://www.vosviewer.com/).

CiteSpace and VOSviewer are two analytical software with scientific methods, powerful functions and complementary, which are widely used in bibliometrics. CiteSpace software is a visualization software based on co-citation analysis theory, pathfinder network algorithm and other methods to measure documents in specific fields. The main functions include co-citation and coupling analysis of documents, cooperation analysis of scientific research networks, contribution analysis of fields, etc. VOSviewer software is based on the principles of co-citation data or co-occurrence data to construct and present bibliometric maps with differences in distance, size and density between nodes. Nodes of the same color are used as a cluster, and different colors distinguish different clusters. The distance between nodes indicates the closeness and similarity between subject words, and the size of nodes represents the frequency of occurrence. The higher the density, the closer the connection and the stronger the correlation. To display the data more accurately, Scimago Graphica (available at: https://www.graphica.app/) and GraphPad Prism 8 (San Diego, CA, USA) were also used to visually analyze the literature.

Results

Analysis of Annual Publications Distribution

A total of 11,922 pieces of literature were included, the language was limited to English, and the article type was limited to articles or reviews. As shown in Figure 1, the number of articles related to MPN increased year by year. From 2001 to 2004, the output of publications during this period was extremely low and the research remained stagnant. The amount of literature increased steadily from 2004 to 2015 and stabilized from 2015 to 2019. From 2019 to 2021, the number of published articles surged again, indicating that MPNs have become a topic of increasing interest.

We performed a visual analysis of published journals using VOSviewer software. We found that 11,922 articles related to MPN were published in 1,807 academic journals. The journal Blood (677, 6.16%) had the highest volume of output, followed by Leukemia (321, 2.92%). Among the top 10 academic journals, the highest impact factor (IF) is Blood (25.476). In addition, 50% of the journals belong to Q1. The impact of journals depends on the number of times they are co-cited, reflecting whether the journal has a significant impact in a specific research field. Of the top 10 co-cited academic journals, all have been cited more than 5,000 times. As shown in Table 1, the most-cited journal was Blood (82,387, 18.34%), followed by Leuke-mia (24,173, 5.38%). According to the 2021 Journal citation reports (JCR), almost all the co-cited journals in the top 10 journals, except the Journal of Biological Chemistry, were in Q1.

Analysis of the Cooperative Relationship

A total of 11,922 articles were published from 113 different countries and 736 institutions. As can be seen from Figure 2, the largest number of publications are from the United States (4,265,
Figure 1. Trends of MPN publications over the past 21 years.

28.26%), Italy (1,374, 9.10%) and Germany (1,058, 7.01%), with the United States in particular being well over three times higher than the other countries. Figure 3 shows that the research institution with the largest number of publications was Mayo Clinic (618, 4.73%). Of the top 10 institutions, 50% belong to the United States. Some countries and institutions showed active cooperation, such as the Netherlands, Belgium, Poland, Hungary, Austria, Ireland and Scotland, Stanford University, Icahn School of Medicine at Mount Sinai and University of Milan. But overall, the cooperation is localized.

In total, 1,099 authors participated in the publication of literature on MPN. Figure 4A shows

Table I. Top 10 journals and co-cited journals with the highest number of publications.

<table>
<thead>
<tr>
<th>Rank</th>
<th>Journal</th>
<th>Count (%)</th>
<th>IF(^1) (2021)</th>
<th>JCR(^2)</th>
<th>Co-cited Journal</th>
<th>Citation (%)</th>
<th>IF(^1) (2021)</th>
<th>JCR(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Blood</td>
<td>677 (6.16%)</td>
<td>25.476 Q1</td>
<td>Blood</td>
<td>82,387 (18.34%)</td>
<td>25.476 Q1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Leukemia</td>
<td>321 (2.92%)</td>
<td>12.883 Q1</td>
<td>Leukemia</td>
<td>24,173 (5.38%)</td>
<td>12.883 Q1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>British Journal of Hematology</td>
<td>292 (2.65%)</td>
<td>8.615 Q1</td>
<td>New England Journal of Medicine</td>
<td>19,659 (4.38%)</td>
<td>176.079 Q1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>American Journal of Haematology</td>
<td>262 (2.38%)</td>
<td>13.265 Q1</td>
<td>British Journal of Haematology</td>
<td>18,978 (4.22%)</td>
<td>8.615 Q1</td>
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<tr>
<td>5</td>
<td>Leukemia Research</td>
<td>232 (2.11%)</td>
<td>3.715 Q3</td>
<td>Journal of Clinical Oncology</td>
<td>10,102 (2.25%)</td>
<td>50.717 Q1</td>
<td></td>
<td></td>
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<tr>
<td>6</td>
<td>Leukemia &amp; Lymphoma</td>
<td>207 (1.88%)</td>
<td>2.996 Q3</td>
<td>American Journal of Haematology</td>
<td>9,027 (2.01%)</td>
<td>13.265 Q1</td>
<td></td>
<td></td>
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<tr>
<td>7</td>
<td>Annals of Hematology of Haematology</td>
<td>203 (1.85%)</td>
<td>4.030 Q2</td>
<td>Nature</td>
<td>9,007 (2.01%)</td>
<td>69.504 Q1</td>
<td></td>
<td></td>
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<tr>
<td>8</td>
<td>European Journal of Haematology</td>
<td>193 (1.75%)</td>
<td>3.674 Q3</td>
<td>Haematologica</td>
<td>7,753 (1.73%)</td>
<td>11.047 Q1</td>
<td></td>
<td></td>
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<tr>
<td>9</td>
<td>International Journal of Hematology</td>
<td>168 (1.53%)</td>
<td>2.319 Q4</td>
<td>Proceedings of the National Academy of Sciences of the United States of America</td>
<td>7,540 (1.68%)</td>
<td>12.779 Q1</td>
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<tr>
<td>10</td>
<td>Haematologica</td>
<td>150 (1.36%)</td>
<td>11.047 Q1</td>
<td>Journal of Biological Chemistry</td>
<td>5,790 (1.29%)</td>
<td>5.486 Q2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^1\text{IF, impact factor; JCR, Journal Citation Reports.}\)
Figure 2. A, Country collaboration network; (B) The top 10 countries in the field of MPN (2001-2022).

Figure 3. A, Affiliation collaboration network; (B) The top 10 affiliations in the field of MPN (2001-2022).

Figure 4. A, Author collaboration network; (B) The top 10 authors in the field of MPN (2001-2022).
that there are fewer isolated circles, indicating that there is no lack of academic collaboration between authors in the field, such as Srdan Vertovsek, Ayalew Tefferi, Francesco Passamonti, Jeanjacques Kiladjian, Ross L. Levine, Tiziano Barbui, Paola Guglielmelli, Claire N. Harrison, Heinz Gisslinger, Juergen Thiele and Francisco Cervantes. Centricity is an index that measures the importance of nodes in the network. Generally, nodes not less than 0.1 are regarded as relatively important nodes. As shown in Figure 4B, Ayalew Tefferi had the most published papers (423, 3.95%). Among the top 10 authors, Ayalew Tefferi and Ruben A. Mesa had a high (≥0.10) centrality, which indicated the strong influence of these two authors on each other’s work as well as on the work of other groups. Each circle represents an author, the lines between the circles represent the connections among authors, and the connection networks of different colors indicate the cooperative clusters among different authors. Co-cited authors refer to two or more authors who are simultaneously cited by another or more papers, and these two or more authors constitute the co-cited relationship. Of the 1,788 co-cited authors, 8 have been cited more than 1,500 times. Ayalew Tefferi (4,407, 3.36%) was the most frequently cited author, followed by Robert Kralovics (2,112, 1.61%).

**Highly Cited Papers Analysis**

The dual-map overlay of journals showed the distribution of relationships between journals, with cited journals on the left and cited journals on the right, and colored paths between them demonstrating the cited relationships. The orange path in Figure 5 indicates that literature published in Molecular/Biology/Genetics and Health/Nursing/Medicine journals are frequently cited by Molecular/Biology/Immunology journals. The green path demonstrates that documents published in Molecular/Biology/Genetics and Health/Nursing/Medicine journals are frequently cited in Medicine/Medical/Clinical journals.

Co-citation, as a research method to measure the degree of relationship between articles, means that two or more articles are cited by one or more articles at the same time, and the two articles are considered as a co-citation relationship. Among the 2,224 co-cited references retrieved, Table II shows the ten most frequently cited references, which represented the milestone of MPN. The co-cited references in 2005, 2008, 2012, 2013 and 2016 have been frequently cited, which means that there are some significant studies related to MPN in these years. Specifically, the JAK2 driver gene mutation was discovered in 2005, the WHO guidelines made significant changes to the diagnosis and treatment of MPN in 2008, the JAK inhibitor ruxolitinib was introduced in 2012, the CALR driver gene mutation was discovered in 2013, and the WHO guidelines made significant changes again to MPN in 2016. The 10 references published in 2020 and most frequently cited in 2021 can reflect the current research hotspots from the side. Clinical trials of new drugs such as ropeginterferon alfa-2b, ruxolitinib, and the new JAK inhibitor fedratinib are actively underway. Next-generation sequencing and the prognostic role of non-driver genes such as SF3B1, SRSF2, U2AF1, etc. in MPN have been
paid attention to. In terms of basic research, the application of single-cell analysis in MF have revealed some important pathogenesis21-30.

**The Analysis of Hotspots and Frontiers**

By analyzing keywords, we can summarize the research themes to explore the hotspots and research directions. The minimum number of occurrences of keywords was set to 50. Of the 20,678 keywords, 261 met the threshold. The frequently used keywords in this study were related to the classification, diagnosis, treatment, and prognosis of the diseases. The diagnostic aspect highlighted the important role played by genetic mutations, in particular JAK2 mutations. Regarding the actual therapy of MPN, there were more studies on JAK2 inhibitor with ruxolitinib as a representative. As for prognosis, the main concerns were thrombotic events and survival.

We used VOSviewer software to cluster keywords in the literature to reflect the basic knowledge structure of this research field. The circles and labels form a unit, with different colored units forming different clusters. As shown in Figure 6A, we can see clusters of red, purple, blue, yellow and green, which represent the five different directions of study. The keywords of the red cluster are expression, activation, stem-cells, thrombopoietin and proliferation. The keywords represented by purple clusters mainly include activating mutation, JAK2, CALR and MPL. The keywords of the blue cluster include polycythemia vera, essential thrombocythemia, hydroxyurea, interferon and thrombosis. The keywords of the yellow cluster mainly in-clude myelofibrosis, myeloid metaplasia, JAK2 inhibitor, ruxolitinib, and survival. The main keywords of the green cluster are acute myeloid-leukemia, leukemia, myelodysplastic syndromes, transient myeloproliferative disorder, and somatic mutations. As shown in Figure 6B, except for the four disease names (MPN, PV, ET, PMF) related to MPN, the top 10 keywords reflect people’s concerns: gene mutation, thrombosis, treatment, and prognosis. This is consistent with the hot spots reflected in Figure 6A.

**Discussion**

This study used CiteSpace and VOSviewer to describe and visually present annual publications, countries, institutions, influential authors, and highly cited papers in the MPN field over the last 20 years to understand the research hotspots, frontiers, and trends in the field.

The analysis of countries/regions shows that the country with the highest number of publications is the United States (618), followed by Italy (431) and Germany (286), together accounting for 10.22% of the total. Among the top five countries, one belongs to the North American region and four to the European region. This suggests that the United States and Europe are the leading regions for research into MPNs. Among the top 10 countries, Canada has the highest centrality (0.22), which means that it plays a key role as a bridge in the global network of country collaboration. Among the top 10 research institutions, Mayo Clinic (618) from the United States has the highest number of publications. However, as can be seen from Figure 2, Italy and Germany have more foreign cooperation, although most of the cooperation are limited to the West. There is a lack of close cooperation between the research-leading
Occident and the populous Asia. Considering the rarity of MPN\textsuperscript{31}, this situation is not conducive to the development of this research field. Therefore, it is necessary to strengthen cooperation and exchanges between different countries and institutions in the future, especially between the Occident and the Asia.

In terms of authors and co-cited authors, Ayalew Tefferi is the author with the highest number of publications (423) and co-citations (4407). Notably, Ayalew Tefferi (0.1) and Ruben A. Mesa (0.1) have the greatest publication impact and make the most outstanding contributions in the field of MPN. They made significant contributions to the diagnosis, treatment and participation in the revisions of international guidelines for MPN\textsuperscript{28,32-35}. Based on the journals and co-cited journals, the journal Blood had the highest published volume (677) and cited volume (82,387), followed by Leukemia. Given the high impact factor of these two journals, it is clear that the research of MPN is very important.

The most cited reference in recent years is ‘Acquired Mutation of The Tyrosine Kinase JAK2 In Human Myeloproliferative Disorders’\textsuperscript{12}. It indicates that the discovery of driver genes, especially JAK2, has promoted the diagnosis and treatment of MPN. Conventional therapy has limited benefit for patients with myelofibrosis, and 2 clinical studies\textsuperscript{17,18} of ruxolitinib for myelofibrosis have shown that sustained ruxolitinib treatment results in significant and durable reductions in splenomegaly and disease-related symptoms, improvement in quality of life and moderate toxicity. The other two are the revisions of the WHO classification\textsuperscript{1,16} of myeloid neoplasms and acute leukemia in 2008 and 2016. These two revisions made significant changes to the diagnosis and treatment. By analyzing the top 10 references published in 2020 and frequently cited in 2021, current research hotspots mainly focus on long-acting interferons, JAK inhibitors, next-generation sequencing, non-driver genes, single-cell analysis, etc\textsuperscript{21-30}.

Based on keyword co-occurrence analysis, we can know the distribution and development of different re-search hotspots in a field. Cluster analysis of keywords was performed, resulting in five color clusters. The red and purple clusters mainly represent the pathogenesis and progression mechanism of MPN, the blue cluster represents the treatment of PV and ET, the yellow cluster represents the treatment of MF, and the green cluster represents the prognosis of MPN. According to the results of cluster analysis, the top 10 key-words, the original literature were read, and the research hotspots and development frontiers of MPN were determined. The main points are as follows: study the pathogenesis and progression mechanism of MPN, clarify the role of different types of genes in diagnosis and prognosis, optimize thrombosis prevention strategies, evaluate the efficacy of new therapies such as long-acting interferons and JAK2 inhibitors, etc.
inhibitors for the treatment of MPN, improve the prognosis of MPN patients, and explore personalized programs of PMF and post-MPN acute myeloid leukemia (AML).

Conclusions

The research is in a stage of rapid development. Globally, the United States and Italy are the leading countries for this study. Among the research institutions, Mayo Clin is the one with the highest impact on the results. The collaboration between different institutions or countries still has room to grow. Ayalew Tefferi and Ruben A. Mesa are outstanding contributors in this field. Blood and Leukemia are considered influential journals based on publications and citations. The hotspot analysis shows that the research of MPN mainly focuses on gene mutation, thrombosis, new drug applications, disease progression, etc.

Conflict of Interest

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

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Authors’ Contribution

All authors contributed to ideation, manuscript drafting and review.

Informed Consent

Not applicable.

Ethics Approval

Not applicable.

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