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# Bibliometric analysis of studies about acute myeloid leukemia conducted globally from 1999 to 2018

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**Abstract**

A bibliometric study is performed to analyze publication patterns in a specific research area and to establish a landscape model that can be used to quantitatively weigh publications. This study aimed to investigate AML research networks and to conduct a trend-related keyword analysis. We analyzed 48,202 studies about AML published from 1999 to 2019 in the Web of Science Core Collection. The network analysis was conducted using the R&R studio software. The journal *Blood* had the highest number of published articles with an h-index of 410. The USA had the highest number of total publications (18,719, 38.3%) and research funded by the government, institutions, and pharmaceutical companies (5,436, 10.8%). The institute with the largest number of publications was the MD Anderson Cancer Center. Kantarjian H, Garcia-Manero G, and Ravandi F were the leading authors of publications about AML. Keyword analysis revealed that FLT 3, micro-RNA, and NK cell topics were the hotspots in the cell and gene area in all publications. The overall AML research landscape is popular in the field of translational research as it can identify molecular, cell, and gene studies conducted by different funding agencies, countries, institutions, and author networks. With active funding and support from the Chinese government, the productivity of scientific research is increasing not only in the AML field but also in the medical/health-related science field.

**Key Words** Acute myeloid leukemia, Citation, Bibliometric, Web of Science core collection

## INTRODUCTION

Acute myeloid leukemia (AML) is an allelic heterogeneous disease in which progression is caused by multiple molecular pathways [1, 2]. Malignant disorder of hematopoietic stem cells is characterized by the clonal expansion of abnormally differentiated blasts of a myeloid lineage [3, 4]. The prognosis of AML is influenced by several factors, such as age, general health status of the patient, specific complications, and abnormal clinical characteristics, including cytogenetic and molecular features [5, 6]. Based on the Surveillance, Epidemiology, and End Results cancer stat facts, AML has a poor prognosis, with a 5-year survival rate of approximately 27%, and it is fatal if left untreated [7].

The outcomes of current standard treatments are still extremely unsatisfactory. The long-term disease-free survival rate of patients aged >60 years is <10%, with a median overall survival (OS) rate of <1 year, regardless of treatment method [6-10]. In 2018, approximately 19,520 newly diagnosed AML cases were recorded in the USA, accounting for 30% of all new leukemia cases [8]. Although several research approaches are available, the treatment of AML has not significantly changed for more than 30 years. Currently, studies about the pathophysiology of AML and new treatments for the condition are conducted [11-13].

Recent developments in cytogenetics and next-generation technologies have significantly improved the understanding of the AML genome, which resulted in scientific progress in terms of patient management. Moreover, promising clinical trials have been conducted, and the use of new AML agents has been approved, thereby improving the clinical outcomes of patients with AML [14]. Over 50,000 AML studies are published in the Web of Science Core Collection

(WoSCC) (www.webofknowledge.com). The WoSCC online database includes the Science Citation Index (SCI), Science Citation Index Expanded (SCIE), and Arts & Humanities Citation Index (A&HCI) [15]. Thus far, none of these studies performed a bibliometric analysis of AML research data. This study performed a bibliometric analysis of publications related to AML, which is a field of interest that has grown quantitatively over the last two decades. A specific analysis of publications related to AML can provide insights about research opportunities and information about research areas that are developed by funding agencies.

## MATERIALS AND METHODS

Data were obtained from the WoSCC of Clarivate Analytics on February 1, 2019. To obtain data about funding agencies, countries of publication, author information, and journal keywords, we searched the WoSCC database using the terms 'acute myeloid leukemia' and '1999–2018' for the publication year. Moreover, 1,125 studies that used "Acute Myeloid Leukaemia" in British English as a research topic were included in the analysis. These terms were translated into American English for the analysis. The types of literature included original articles, reviews, meeting abstracts, proceeding papers, and letters. All publication information records were downloaded in XML format, and the relevant publication data in the XML file were parsed using an R script. In this study, we analyzed the network based using the igraph package of R, and data were visualized using the ggplot2 package and ggnetwork. The igraph is efficient in handling large networks and is productive when used as a high-level programming language. The package was used to calculate figures, including degree of betweenness [16]. The open datasets in the WoSCC were analyzed. Moreover, this was a non-interventional study. Thus, approval from the ethics committee was not required.

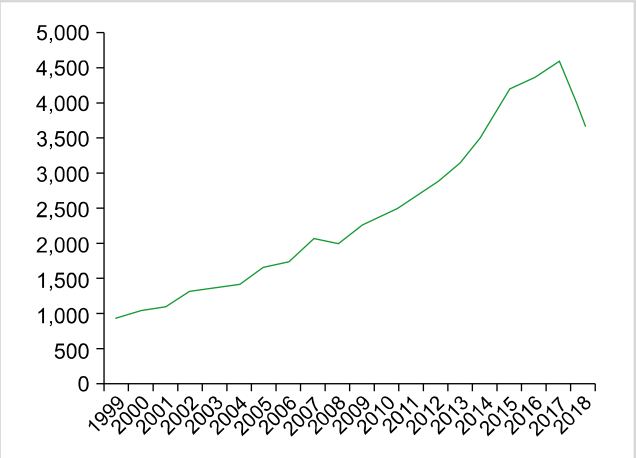


**Fig. 1.** Studies related to AML published from 1999 to 2018.

## RESULTS

### Analysis of the number of AML publications

leven different types of document were collected from a total of 48,201 studies published from 1999 to 2018. The most frequently collected items were articles (60%), conference overviews (19%), review articles (15%), and letters (4%). Most papers (98.4%) were written in English. Meanwhile, French, Spanish, and German were used in <0.3% of publications (data not shown).

The total number of publications has increased over the

**Table 1.** Publication status of research funded by various agencies from 1999 to 2008 (stage 1) and from 2009 to 2018 (stage 2).

| No. | 1999–2008 (stage 1) | | | 2009–2018 (stage 2) | | |
|---|---|---|---|---|---|---|
| | Funding institution (country) | N of publications | % | Funding institution (country) | N of publications | % |
| 1 | NCI+NIH+HHS (USA) | 1,612 | 11.1 | NIH (USA) | 1,854 | 5.5 |
| 2 | NHLBI+NIH+HHS (USA) | 230 | 1.6 | NNSF (China) | 1,434 | 4.3 |
| 3 | NIDDK+NIH+HHS (USA) | 153 | 1.1 | NCI+NIH+HHS (USA) | 759 | 2.3 |
| 4 | NIGMS+NIH+HHS (USA) | 121 | 0.8 | NCI (USA) | 812 | 2.4 |
| 5 | NIAID+NIH+HHS (USA) | 71 | 0.5 | Novartis (Switzerland)[a] | 350 | 1.0 |
| 6 | Medical Research Council (UK) | 65 | 0.5 | Celgene (USA)[a] | 345 | 1.0 |
| 7 | NCRR+NIH+HHS (USA) | 65 | 0.5 | Leukemia and Lymphoma Society (USA)[a] | 293 | 0.9 |
| 8 | NIEHS+NIH+HHS (USA) | 61 | 0.4 | Medical Research Council (UK) | 274 | 0.8 |
| 9 | INTRAMURAL+NIH+HHS (USA) | 54 | 0.4 | German Research Foundation (Germany) | 272 | 0.8 |
| 10 | PHS+HHS (USA) | 50 | 0.3 | Cancer Research (UK) | 248 | 0.7 |

[a]Based on the location of the headquarters.
Abbreviations: DFG, Deutsche Forschungsgemeinschaft (German Research foundation); HHS, Health and Human Services; IRP, Intramural Research Program; NCI, National Cancer Institute; NCRR, National Center for Research Resources; NHLBI, National Heart, Lung, and Blood Institute; NIAID, National Institute of Allergy and Infectious Diseases; NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases; NIEHS, National Institute of Environmental Health Sciences; NIGMS, National Institute of General Medical Sciences; NIH, National Institutes of Health; NNSF, National Natural Science Foundation of China; PHS, Public Health Service.

last two decades, with <1,000 publications in 1999 and more than 1,000 publications per year since 2001. Since then, the number of AML publications has constantly increased, with more than 2,000 studies published since 2009 and more than 4,000 since 2015. Thus, a right-upward linear trend was observed (Fig. 1).

An extremely slight decrease in the number of publications (−44, −0.97%) was only observed in 2008. In the same year, the World Health Organization (WHO) published the WHO Classification of Myeloid Neoplasms and Acute Leukemia: Rationale and Important Changes [17], wherein the classification and treatment guidelines for AML were revised. The guidelines included a new category of neoplasms that develop after a previous treatment. Moreover, it conducted a review of important studies about secondary malignancies that may be caused by previous treatments [17-19]. The results of these studies have a significant impact on subsequent guidelines and studies about AML treatment [20, 21]. In 2018, the number of publications recorded might not have been accurate as some of the publications in the later part of 2018 were not retrieved due to delays in the update of the WoSCC database for a few weeks [22].

The decline in the number of publications in 2018 might not be caused by a reduction in the number of publications. Rather, it may be a result of a delay in the publication of information in the WoSCC database [22].

## Analysis of AML research that was externally funded

We analyzed the network in the trends of studies about AML conducted by different external funding agencies by dividing the study period into two 10-year stages: stage 1) 1999–2008 and stage 2) 2009–2018. In the field of research, funding reflects current global challenge, industrial strategy challenge, medical and environmental challenge, government and industry research, new molecular developments, scientific public health, and health policies that determine future research priorities [23-25]. Therefore, we divided the steps of funding in some agencies and identified how they conducted the research. Data obtained in stage 1 revealed that government health agencies collaborate with funding agencies in conducting AML research (Table 1). All US health care institutions [e.g., the National Institutes of Health (NIH), National Cancer Institute (NCI), and Health and Human Services (HHS)] have been ranked based on the number of publications from the research studies funded by themselves.

In stage 2, the NIH was still the leading funding agency, followed by the National Natural Science Foundation (NNSF) of China (Table 1, Fig. 2). There were only four publications funded by the Chinese government in 2008. However, the number reached to 283 in 2018, indicating an increase in the volume by about 70%. Thus, it ranked third overall. With active funding and support from the Chinese government, the productivity of scientific research continues to increase not only in the AML field but also in the medical/health-related science field [26]. Over the last two decades, publications funded by the US government accounted for 10.2% of all publications.

In addition, there was a significant increase in the NNSF funding, as provided by the government of China, for the areas of breast and lung cancer, which have been the topic of most studies in the field of oncology in recent decades. After HHS (breast cancer, 13.2%; lung cancer, 9.2%) and NIH (breast cancer, 13.0%; lung cancer, 9.1%) in the USA, the funding support of NNSF for breast cancer (6.8%) and lung cancer (8.3%) ranked third among all oncology areas.

Less than 1% of the publications are sponsored and funded by non-US government agencies. Thus, the external agencies

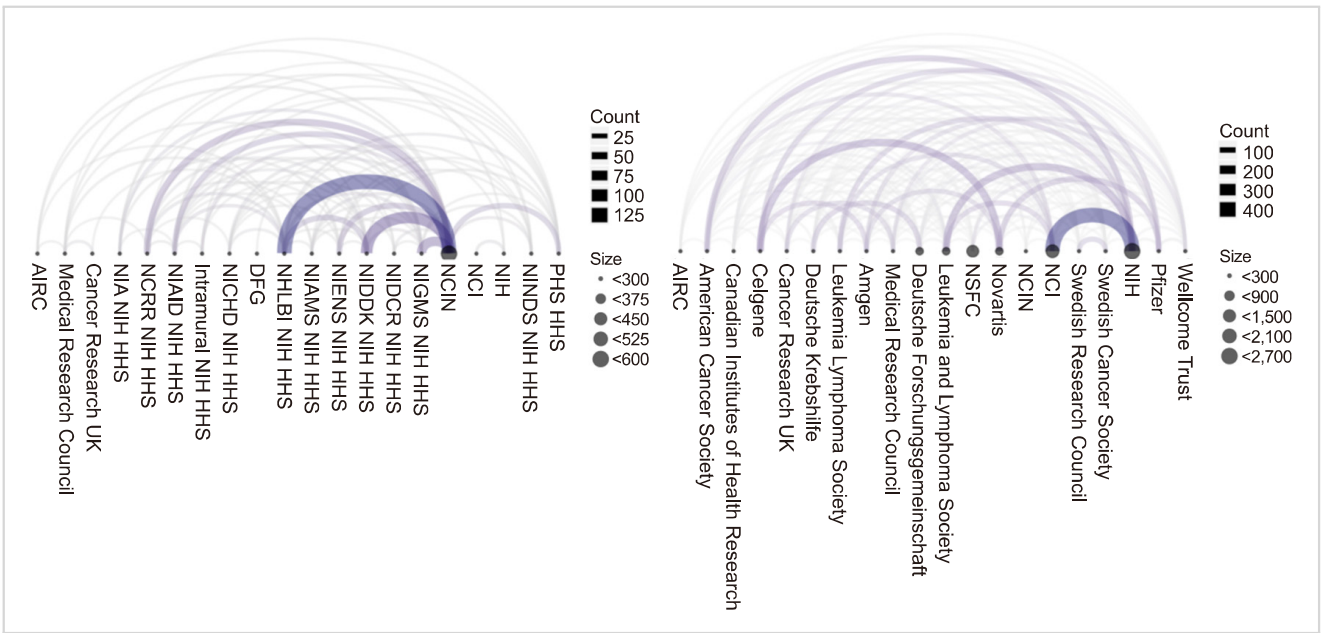


Fig. 2. Changes in network based on funding sources from 1999 to 2008 (stage 1) and from 2009 to 2018 (stage 2).

are ranked 10th in terms of the number of studies published.

## Analysis of journals based on h-index

*Blood* (14%), a journal of the American Society of Hematology, published the highest number of AML-related articles. The h-index (HI) of each journal was used to assess research productivity based on the number of publications cited by authors and the number of citations that authors have received in other publications [27, 28]. In this study, HI was used because it is a better and more accurate measurement tool for journal quality and citation power. The journal *Blood* (HI-410) had the highest citation average of AML-related articles, followed by *Leukemia* (HI-168) and *Haematologica* (HI-120). The *Journal of Clinical Oncology* (HI-482) and *Cancer Research* (HI-404) published a lower number of AML-related articles than *Blood*; however, the average HI of these journals was high (Table 2). There were 2,772 academic journals that published at least one AML-related article. However, 35% of these journals focused on the core academic journals with HI in the top 2%. The Bradford's law described the scattering and exponentially lessening reappearance when searching for references in journals, and it can be used to distinguish the core journals in a specific field [29, 30]. The Bradford's law of bibliometric analysis can be applied to the field of AML research.

**Table 2.** Top 15 journals that published papers about acute myeloid leukemia from 1999 to 2018.

| Journals | Country | Publisher | N of publications (%) | HI[a] | AML-related publications H-index | |
|---|---|---|---|---|---|---|
| | | | | | Average | ACPI[b] |
| Blood | USA | American Society of Hematology | 6,763 (14.0) | 410 | 197 | 28.78 |
| Leukemia | UK | Nature Publishing Group | 1,902 (3.9) | 168 | 113 | 37.41 |
| Haematologica | Italy | Ferrata Storti Foundation | 2,178 (4.5) | 120 | 59 | 17.1 |
| Bone Marrow Transplantation | UK | Nature Publishing Group | 836 (1.7) | 116 | 46 | 12.08 |
| Biology of Blood and Marrow Transplantation | USA | Elsevier BV | 789 (1.6) | 103 | 51 | 15.74 |
| Leukemia Research | UK | Elsevier Ltd. | 1,367 (2.8) | 78 | 50 | 13.57 |
| Leukemia Lymphoma | UK | Taylor & Francis | 1,177 (2.4) | 79 | 43 | 10.28 |
| Annals of Hematology | Germany | Springer Verlag | 691 (1.4) | 70 | 35 | 9.00 |
| Journal of Clinical Oncology | USA | American Society of Clinical Oncology | 1,034 (2.1) | 482 | 135 | 55.41 |
| Cancer Research | USA | American Association for Cancer Research | 642 (1.3) | 404 | 87 | 49.91 |

[a]HI: the h-index value was based on a list of publications ranked in descending order by the Times Cited count. The h-index indicates that there are h papers that have been cited at least h times. The H-index score from the WoSCC (1999–2018).
[b]Average citations per item (ACPI): ACPI is the average number of cited articles for all items in the resultset. It is the sum of the times cited divided by the number of results in the timespan (1999–2018) [24].

**Table 3.** Status of countries that published studies related to acute myeloid leukemia from 1999 to 2018.

| No. | 1999–2008 (stage 1) Publication status (total: 14,559) | | | 2009–2018 (stage 2) Publication status (total: 33,653) | | |
|---|---|---|---|---|---|---|
| | Country | N of publications | % of the total | Country | N of publications | % of the total |
| 1 | USA | 5,625 | 38.7 | USA | 13,094 | 38.9 |
| 2 | Germany | 2,025 | 14.1 | China | 4,044 | 12.0 |
| 3 | Italy | 130 | 8.9 | Germany | 3,872 | 11.5 |
| 4 | Japan | 1,211 | 8.3 | Italy | 2,461 | 7.3 |
| 5 | France | 906 | 6.2 | France | 2,169 | 6.4 |
| 6 | England | 867 | 6.0 | Japan | 1,899 | 5.6 |
| 7 | Netherlands | 709 | 4.9 | England | 1,827 | 5.43 |
| 8 | Canada | 627 | 4.3 | Canada | 1,504 | 4.5 |
| 9 | Spain | 419 | 2.9 | Netherlands | 1,267 | 3.8 |
| 10 | China | 408 | 2.8 | Spain | 1,152 | 3.4 |

## Analysis of the countries of publication

In two, six, and two countries in North America, Europe, and Asia, respectively, which are included in the top 10 countries, approximately 99% of AML-related articles were published within 20 years. Moreover, a total of 14,559 and 33,653 articles were published from 1998 to 2008 and from 2009 to 2018, respectively. In terms of the volume of publications, the US (38.7%) ranked first during stage 1, followed by Germany (14.1%) and Italy (8.9%). In stage 2, the USA (38.9%) remained at the top, and China ranked second (12%). Moreover, the rank of Germany changed from second to third (11.5%). Compared to stage 1, the total number of publications increased by 231% in stage 2. The rate of publication in China was faster than the overall global growth rate (Table 3). In this study, the growth scale of China was confirmed using a larger context of research output. Furthermore, the type of supplementation required for sustainable qualitative growth and how this development will affect the AML field in the future should be assessed. Thus, further studies must be conducted to identify methods that are more effective in precisely quantifying the impact. In stage 2, publications in the USA (13,094 articles) and China (4,044 articles) accounted for 50.1% of the total number of publications about AML (Table 3). In addition, a highly concentrated network was identified between the USA, England, China, and a cumulative quantity from 1999 to 2018 was noted between Germany, France, and Italy (Fig. 3).

## Network analysis of institutions and authors

In total, 48,202 articles about AML published from 1999 to 2018 were conducted by 21,476 research institutions. Articles conducted by the top 50 (0.2%) institutions accounted for approximately 40% (39.8%) of the total number of publications (Table 4). Of the 48,202 publications, 14,559 and 33,653 were published from 1999 to 2008 (stage 1) and from 2009 to 2018 (stage 2), respectively. The University of Texas MD Anderson Cancer Center had the highest number of publications, followed by Fred Hutchinson Cancer Research Center and Harvard University. The Chinese institutions were not included in the top 50. However, they ranked second in terms of the number of publications in stage 2. Furthermore, the strongest centralities were identified between the University of Texas and Harvard University (Fig. 4).

## Analysis of authors

In total, 48,202 articles about AML research published from 1999 to 2018 were written by more than 100,000 authors. Table 4 shows the top 10 authors (five each from the USA and Germany) and the number of articles they have published. Hagop M. Kantarjian (896) ranked first, followed by Guillermo Garcia-Manero (504) and Farhad Ravandi-Kashani (493), who are all from the University of Texas MD Anderson Cancer Center. Each of the top 10 active authors contributed at least 4,887 articles, accounting for 10.7% of the total number of articles about AML. Therefore, they were referred to as productive authors. The

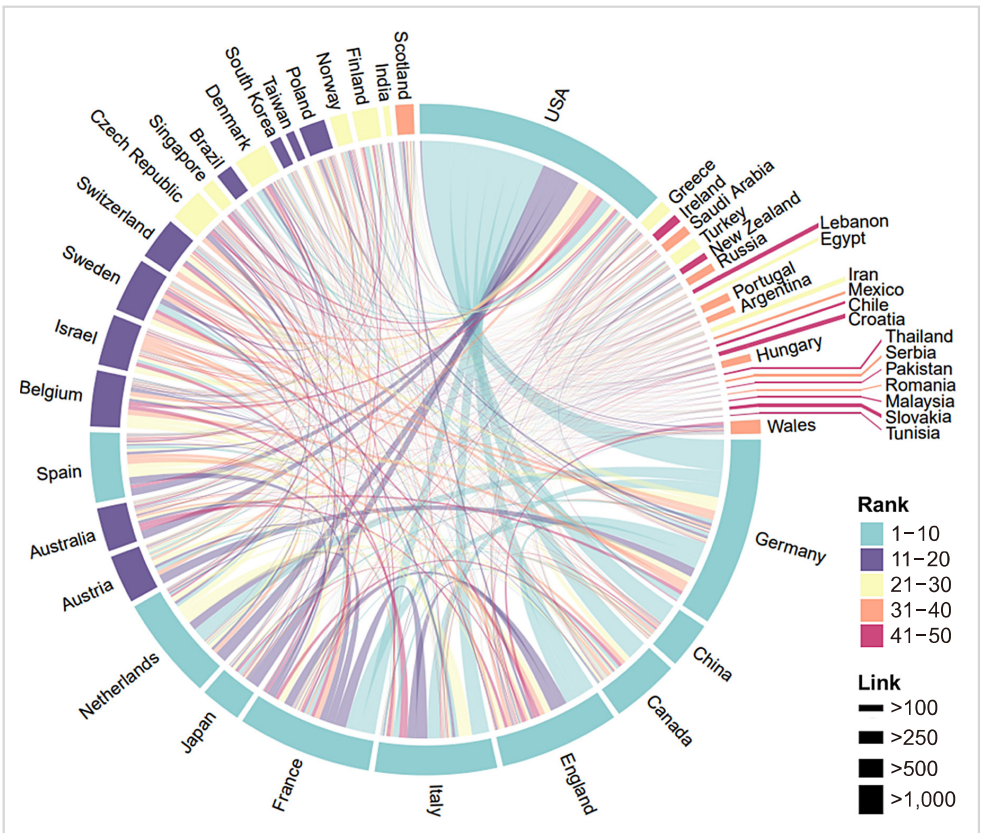


**Fig. 3.** Network of countries that copublished articles correlated to acute myeloid leukemia from 1999 to 2018. Ranking was based on the volume of publications. According to the frequency of the network, it was expressed as the thickness of the link.

**Table 4.** Top 10 active authors (affiliations) who published articles related to acute myeloid leukemia from 1999 to 2018 (centrality, eigen closeness data not shown).

| No. | Author/affiliation | N of publications | Degree[a] | Estimated betweenness[b] | H-index[c] | ACPI[d] |
|---|---|---|---|---|---|---|
| 1 | Hagop M. Kantarjian (MD Anderson Cancer Center) | 896 | 2,899 | 80.53 | 61 | 32 |
| 2 | Guillermo Garcia-Manero (MD Anderson Cancer Center) | 504 | 1,919 | 14.04 | 46 | 17 |
| 3 | Farhad Ravandi-Kashani (MD Anderson Cancer Center) | 493 | 2,119 | 14.05 | 44 | 17.6 |
| 4 | Hartmut Döhner (University of Ulm, UULM) | 426 | 777 | 46.68 | 70 | 44.14 |
| 5 | Torsten Haferlach (MLL Münchner Leukämielabor) | 410 | 821 | 50.39 | 62 | 37.53 |
| 6 | Wolfgang Hiddemann (Ludwig-Maximilians-University of Munich) | 387 | 572 | 13.82 | 60 | 34.23 |
| 7 | Gerhard Ehninger (Universitaetsklinikum Dresden) | 352 | 486 | 42.99 | 42 | 22.44 |
| 8 | Konstanze Döhner (University of Ulm, UULM) | 346 | 656 | 5.47 | 59 | 34.66 |
| 9 | Marcucci, Guido (City of Hope Comprehensive Cancer Center) | 342 | 322 | 15.33 | 67 | 43.02 |
| 10 | Andreeff, Michael (MD Anderson Cancer Center) | 331 | 829 | 3.54 | 60 | 38.39 |

[a]Degree: the degree of a vertex is its most basic structural property and the number of its adjacent edges.
[b]Estimated betweenness: the vertex and edge betweenness are (roughly) defined by the number of geodesics (shortest paths) going through a vertex or an edge [16].
[c]H-index: the h-index value is based on a list of publications ranked in descending order by the Times Cited count. An index of h indicates that there are h papers that have been cited at list h times.
[d]Average citations per item (ACPI): this is the average number of cited articles for all items in the result set. It is the sum of the times cited divided by the number of results in the timespan [22].


**Fig. 4.** Network mapping of the top 50 and 20 institutions that copublished publications related to acute myeloid leukemia from 1999 to 2018. *Government agencies (e.g., NIH, NCI, and MRC) were excluded from the analysis. The organization was unified as much as possible via machine learning.

network mapping of the top 50 authors has shown that they are not part of a single institution only as they also work together with different research groups and multinational clinical trials (Fig. 5). For the top 50 authors, the HI of each score ranged from 20 to 72. In this analysis, none of the authors ranked higher than high-quality authors who have several publications in low-ranking journals (data not shown). The Bradford's law of bibliometric is applicable to the authors of AML. As with the institutional analysis, the Chinese authors were not included in the top 50 in terms of the number of publications. This result is contrast to that of the total number of publications in China within the last 10 years. There were no distinct productive institutions and authors from China, and a high number of authors might be distributed throughout the country.

## Analysis of keywords related to cell and gene studies

Key words are the most important link to specific issues and trends that researchers or authors want to point out in their publications, particularly with regard to related research enquiries and theories. In this study, the keywords were subdivided based on their use in cellular and genetic/molecular research. The heat map method can identify the occurrence of simultaneous exposures over time (Fig. 6). Since the central keyword in this analysis was AML, we excluded all words except AML, and the words that were alternate expressions for the same scientific term (e.g., FLT3=fms related tyrosine kinase 3, MRD=minimal residual disease, and MRNA or MiRNA=MicroRNA) were refined. FLT3 was the most frequently used keyword, followed by micro-RNA, NK-cell, P-glycoprotein, and dendritic cells (Fig. 6).

For the analysis of keywords, publication impact factor

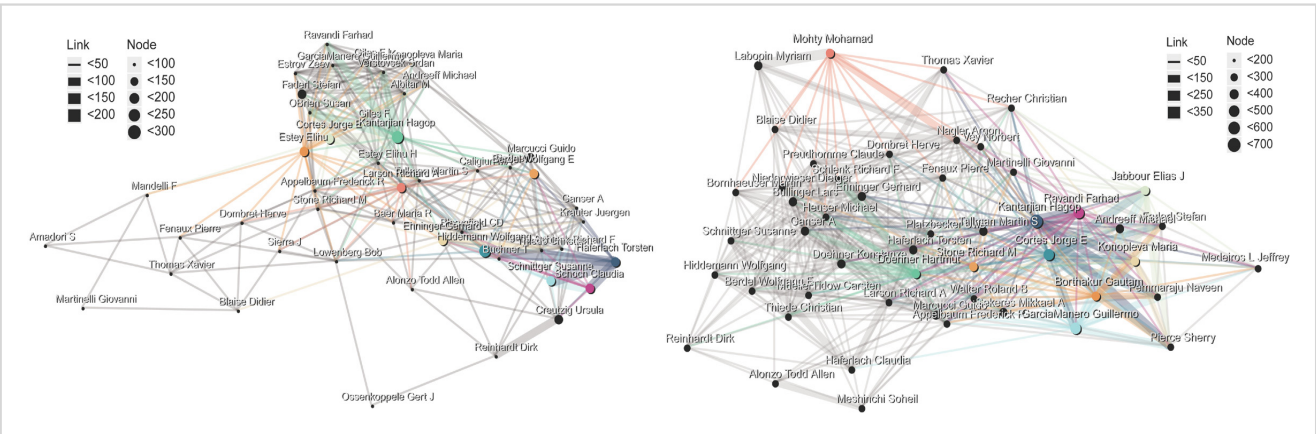


**Fig. 5.** Network mapping of the top 50 authors who published articles related to acute myeloid leukemia from 1999 to 2018. Nodes express the volume of the author's publication, and links represent the network frequency of coauthor activities.

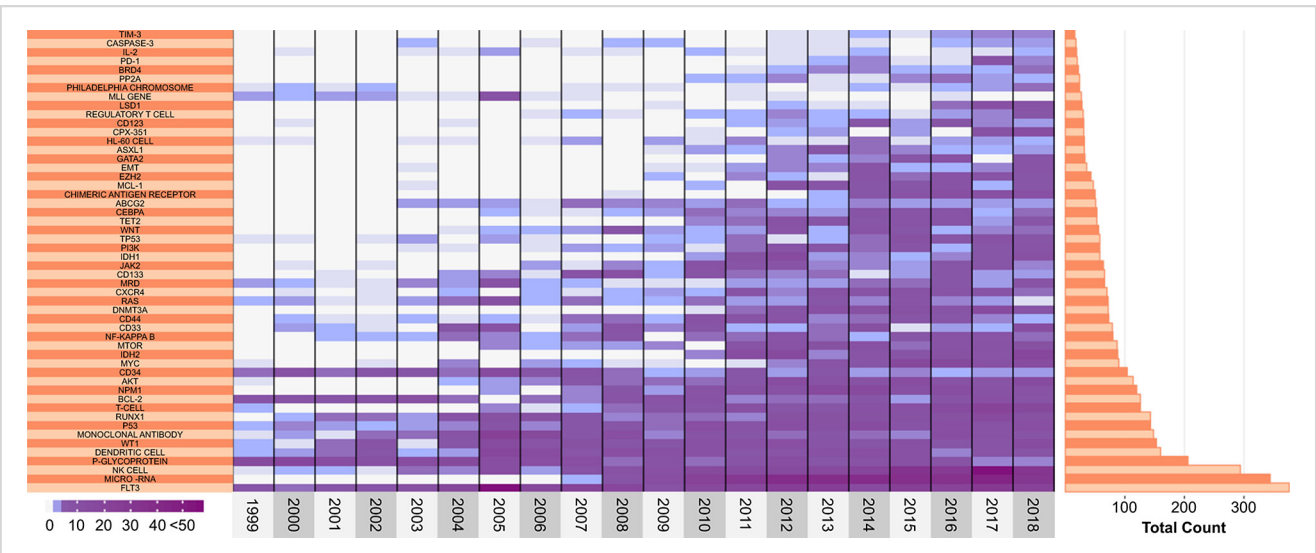


**Fig. 6.** Most commonly used keywords in articles related to cellular and molecular studies about acute myeloid leukemia from 1999 to 2018. Frequency of using a keyword is represented by bold color. The total count represents the sum of the frequencies for over 20 years.

(IF) and HI were not reflected, and only the total exposure frequency of each keyword was considered. However, in the future, the IF and HI of the publications should be considered when performing a keyword analysis.

## DISCUSSION

In this study, we analyzed the data retrieved from the WoSCC to evaluate the global scientific output of AML-related research conducted from 1999 to 2018. This analysis included countries of publication, publication journals with HI, institutions, authors, and research areas identified using keywords related to AML research. The objective was to identify the trends in AML research to obtain an overall image of the research landscape. Our findings showed that the total amount of publications about AML has been increasing since 1999. The journal *Blood* published the highest number of publications about AML, followed by *Leukemia* and *Haematologica*. Although the USA published the highest number of articles, China has a rapid increase in its research output over the last decade. However, networks among institutions were not frequently observed and must be developed in the future. Hagop M. Kantarjian (896) had the highest number of publications, followed by Guillermo Garcia-Manero (504) and Farhad Ravandi-Kashani, who are all from the University of Texas MD Anderson Cancer Center. We conducted an analysis of keywords, such as FLT3, micro-RNA, NK-cell, P-glycoprotein, and dendritic cells, which were considered the major areas of interest, and translational research was at the forefront of AML research. This bibliometric analysis of the AML research area was based on the total number of publications, not the HI or IF of each individual publication. The limitation of our research indicates that our results do not accurately reflect real-world research areas. Thus, future studies must perform a quantitative bibliographical analysis with consideration of the quality of publications.

In summary, this bibliometric analysis showed that the overall AML research landscape is popular in the field of translational research as it identifies molecular, cell, and gene studies conducted by different funding agencies, countries, institutions, and author networks. Based on this analysis model, other bioresearch fields can be developed and can help shape future research directions.

## Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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