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A bibliometric analysis for relapsed/refractory Non-Hodgkin lymphoma

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Abstract. – OBJECTIVE: This study aimed to analyze the current research status and trends of publications on relapsed/refractory Non-Hodgkin lymphoma (r/r NHL) using CiteSpace software and to know which centers and authors we should follow in the first place while doing research on r/r NHL.

MATERIALS AND METHODS: The publications were retrieved from the Web of Science Core collection database, and CiteSpace (5.5.R5) software was used to analyze the authors, institutions, countries, and keywords.

RESULTS: A total of 567 publications from 2009 to 2021 were retrieved, and the most fertile authors, institutions, nationalities and keywords in the field of r/r NHL were identified. Pier Luigi Zinzani team, Kensei Tobinai team, Andre Goy team, and Julie M. Vose team are recognized the main research teams in this field. USA makes the greatest contribution having research funds for r/r NHL. Key cluster areas of research include mantle cell lymphoma, pathway, lymphoma, relapse, pixantrone, Non-Hodgkin lymphoma, romidepsin, relapsed, T-cell lymphoma, and activated T cells. According to the keywords' timeline, the research trends of r/r NHL changed from bone marrow transplantation, radioimmunotherapy, chemotherapy to novel target drugs (like ibritumomab tiuxetan, inhibitor) and criteria EBM.

CONCLUSIONS: The bibliometric study provides insights into hotspots and trends in the field of r/r NHL in the past 12 years. It serves us to extract useful information from complex data and provide information for clinicians and researchers.

Key Words:
Bibliometric analysis, Relapsed/Refractory Non-Hodgkin lymphoma, CiteSpace.

Abbreviations

ASCT, autologous stem cell transplant; CAR, chimeric antigen receptor; HL, Hodgkin Lymphoma; HDC, high-dose chemotherapy; IC, Index Chemicus; MM, Master of Medicine; PhD, Doctor of Philosophy; PD-1, programmed death-1; r/r NHL, relapsed/refractory Non-Hodgkin lymphoma; WHO, World Health Organization; WOS, Web of Science.

Introduction

Lymphoma is the most frequent solid tumor of hematological malignancies that originates from lymph nodes and lymphoid tissues. It can be categorized into Hodgkin Lymphoma (HL) and Non-Hodgkin lymphoma (NHL) (accounting for approximately 90% of all lymphomas) based on histopathology[1]. According to the GLOBOCAN cancer statistics based on the World Health Organization (WHO) for the year 2020, there were an estimated 19.3 million malignant tumor cases newly diagnosed worldwide. HL and NHL (2.8%) accounted for 3.2% of new cases[2]. Despite the overall better outcomes of NHL, approximately one-third of patients develop relapsed/refractory disease, and the cure rate is below 30%.

Current therapy options for relapsed/refractory NHL include high-dose chemotherapy (HDC) with autologous stem cell transplant (ASCT), salvage chemotherapy, immunotherapy, radioimmunotherapy, and chimeric antigen receptor (CAR) T-cell therapy[3,4]. However, no standard treatment strategies have been established for R/R NHL except for ASCT. Therefore, our research is meaningful.

Compared HDC with ASCT in the treatment of R/R NHL to conventional chemotherapy, nearly half of the patients without cancer survived five years or more while only 10% of the patients treated with conventional chemotherapy have five years or more survival[5]. This clinical trial estab-

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lished the foundation for HDC with ASCT for the treatment of R/R NHL. However, elderly patients with poor performance or a history of chemotherapeutic resistance require other effective salvage regimens.

Research hotspots and trends in R/R NHL point out effective research directions, which will help clinicians make better therapeutic decisions for patients.

Bibliometric analysis is conducted by computational and visual analytic approaches, is a statistical and quantitative method to analyze the academic information and scientific outcomes of the literature[6]. Bibliometric analyses have been widely applied by researchers in a variety of medical specialties including breast cancer research[7], surgery[8], acute myeloid leukemia[9], health care[10], PD-1 and PD-L1 fields[11]. But bibliometric analysis on R/R NHL has not been published.

This study aims to comprehensively analyze research trends in R/R NHL based on the Web of Science (WOS). We conducted the bibliometric analysis to reveal research trends associated with R/R NHL and to predict possible future hotspots. The objects of the analysis are authorship status of papers, institutions and countries of origin, titles, journals of publication, abstracts, keywords, references and categories.

Materials and Methods

This research focused on previously published literature, and there is no ethics statement needed to be approved.

Data Source and Search Strategy

We searched the Web of Science Core Collection databases and retrieved data from Science Citation Index Expanded (SCI-Expanded) and Index Chemicus (IC) from 1985 to 2021. The recent update of WOS is 31 March 2021. Given the sensitivity and accuracy of the literature, we used Chemicus. Then, we set the search strategy as follows.

Languages: English

Document types: Article and Review
#1 TI = (refractory OR relapsed OR recurrent OR resistant)
#2 AB = (refractory OR relapsed OR recurrent OR resistant)
#3 #1 OR #2
#4 TI = (Lymphoma, Non-Hodgkin*)
#5 AB = (Lymphoma, Non-Hodgkin*)
#6 #4 OR #5
#7 #3 AND #6

A total of 567 articles were retrieved and exported into a txt format document, including full records and cited references.

Analysis Tool

CiteSpace (V5.7 R5, invented by Chen Meichao of Drexel University) is a web-based Java application for data analysis and visualization. The main procedural steps of visualization bibliometric tools include time slicing, thresholding, modeling, and mapping[12]. This study outlines the research hotspots and trends based on CiteSpace's document visualization analysis.

The parameters of CiteSpace were as follows: time slicing from to 1985-2021 (1), term source (all selection), node type (choose one at a time), selection criteria (30), pruning (pathfinder, pruning sliced networks, pruning the merged network), and visualization (cluster view-static, show merged network)[13].

Microsoft Excel 2010 software was used to record data and demonstrate visualization with the spreadsheet[14]. We used a general Microsoft Excel 2010 spreadsheet for data manipulation and supplementary visualization of CiteSpace (**Supplementary Table I**).

Results

Analysis of Publication Literatures Output

Although the search range was set from 1985 to 2021, no published articles met the inclusion criteria until 2009. Between 2009 and 2021, 567 research publications were identified on the topic of r/r NHL. The literature search process is shown in Figure 1. The publications consisted of 511 articles and 56 reviews. As shown in Figure 2, between 2017 and 2021, the annual publications showed a rapid increase with 208 findings published within four years, accounting for 36.7% of the total publications. The number of publications (n=70) peaked in 2020.

Distribution of Authors and Co-Authors

According to Price's law[15], the number of productive authors who have written half of the articles is equal to the square root of the total number of authors, half of the reviews must be published

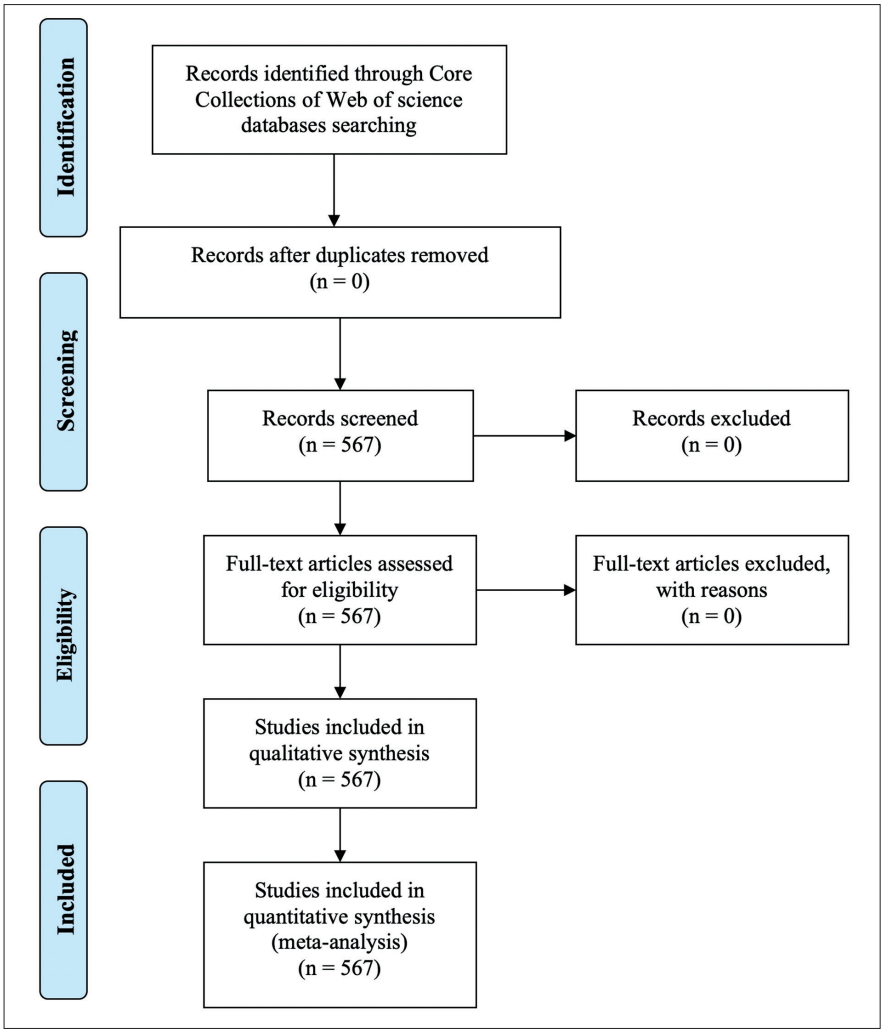

Figure 1. The search process and the screening of the articles for identifying the eligible studies.

by the core authors, the minimum number of published articles of core authors was N (N= $0.749\times\mu_{max}^{1/2}$), and μ_{max} is the number of papers published by the most productive authors. In this study, μ_{max}=16, therefore, N takes integer 3. From 2009 to 2021, the total number of authors who have published six articles is 304, which accounts for over half of the authors. The analysis indicates that a stable core research group has been formed in the field of relapsed/refractory Non-Hodgkin lymphoma.

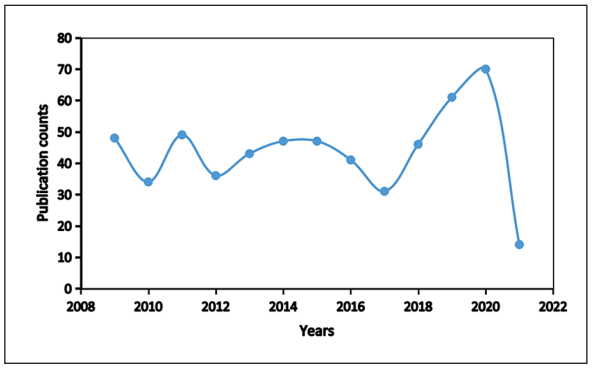

Figure 2. Trends in the number of publications on patients with Relapsed /Refractory non Hodgkin lymphoma between 2009 and 2021. The horizontal coordinates represent the year of publication, and the vertical coordinates represent the number of publications.

As shown in the co-authorship network map of authors in Table I and Figure 3, among the top 20 authors based on the number of papers published, studies with centrality >0.1 only accounts for 5%. These findings demonstrate that researchers in r/r NHL are less cooperative among different institutions. Pier Luigi Zinzani, who came from the Institution Hematolology & Medical Oncology "L. e A. Seràgnoli" University of Bologna in Italy, has established a relatively stable research team and occupies a research area[16], and has the greatest number of publications (16) and closeness centrality (0.22).

Table I. The top 20 authors who published the highest number of literature on Relapsed/Refractory Non-Hodgkin Lymphoma from 2009 to 2021.

Ranking	Author	Centrality	Year	Counts
1	Pier Luigi Zinzani	0.22	2011	16
2	Kensei Tobinai	0.04	2010	13
3	Andre Goy	0.19	2011	11
4	Julie M Vose	0.05	2009	10
5	Gilles Salles	0.11	2016	9
6	Bruce D Cheson	0.07	2010	9
7	Ian W Flinn	0.06	2014	9
8	Laurie H Sehn	0.1	2012	8
9	Michinori Ogura	0.07	2010	8
10	Mehdi Hamadani	0.06	2009	8
11	Masafumi Taniwaki	0.01	2010	8
12	Kristie A Blum	0.09	2009	7
13	Anas Younes	0.03	2012	7
14	Thomas E Witzig	0.02	2011	7
15	Ajay K Gopal	0.11	2014	6
16	Thomas M Habermann	0.06	2009	6
17	Wojciech Jurczak	0.06	2015	6
18	Barbara Pro	0.04	2011	6
19	Vincent Ribrag	0.02	2018	6
20	Won Seog Kim	0	2017	6

Analysis of Countries and Institution Distribution

According to the collaboration networks of research institutions (Figures 4 and 5) and the top 10 institutions based on closeness degree centrality (Table II) in the relapsed/refractory Non-Hodgkin lymphoma study field, the institution with the highest degree centrality (0.16) was University Bologna, Italy, and the institutions with the most publications (30) were University of Texas MD Anderson Cancer Center (USA); other research institutions with more than 13 articles including Mayo Clinic (USA), Memorial Sloan Kettering Cancer Center (USA), National Cancer Center (Japan), Washington University

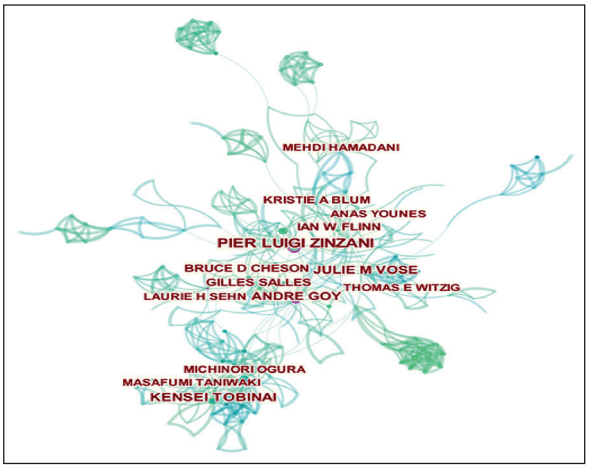

Figure 3. Co-authorship Map of authors.

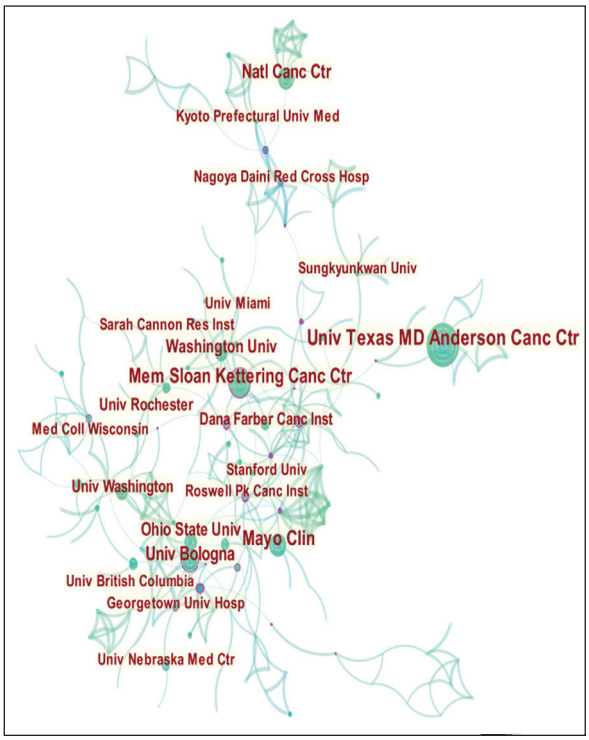

Figure 4. Visual analysis of research institutions and relationship with each other. Circle size represents the contribution to publications, and purple circle represents the high citation.

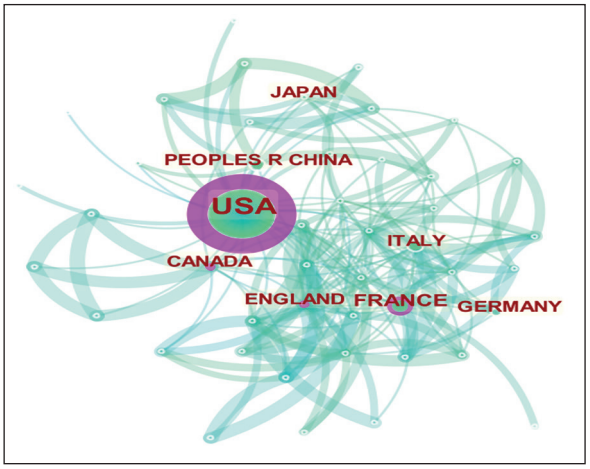

Figure 5. Published country map.

(USA), Ohio State University (USA), Dana-Farber Cancer Institute (USA), University of Nebraska Medical Center (USA), Sarah Cannon (England). In sum, evaluated from publication quantities and degree centrality, Mayo Clin in the USA was the leading position of research in relapsed/refractory Non-Hodgkin lymphoma study fields.

Analysis of Keywords Co-Occurrence

Research field hotspots and their evolution can be found by keyword co-occurrence and clustering[17]. As shown in Figure 6, excluded unrelated terms, such as 'trail', 'therapy', 'phase ii', 'cancer', and added synonymous keywords like 'Non-Hodgkin lymphoma', 'Non-Hodgkin lymphoma', unified 'Non-Hodgkin lymphoma', top 10 frequent keywords contained 'rituximab', 'chemotherapy', 'Non-Hodgkin lymphoma', 'trial' ,'bone marrow transplantation' ,'survival' ,'expression', 'radioimmunotherapy', 'regimen', 'cyclosphamide'. The keyword with degree centrality ≥ 0.1 is 'bone marrow transplantation'. The trend visualization (Figure 6) shows that 'bone marrow transplantation' has a downward trend.

Analysis of Keywords Categories and Cluster

The developmental trends in the research field can be revealed through keyword cluster analysis. The modularity (Q-value) and mean silhouette values were calculated when cluster analysis was performed. The cluster was identified as significant while Q>0 s. If the mean silhouette value is > 0.5, the clusters obtained are seen as reasonable. If the average silhouette value is > 0.7, the clusters obtained were considered credible[18]. The cluster analysis focuses on the structural features, highlighting key nodes and important links, while the timeline focuses on delineating the relationship between the clusters and the time span of the cluster. The smaller the cluster number, the larger is the cluster.

It can be seen from the cluster view and information table (Figure 7, Table III) that the research of r/r NHL is divided into 10 clustered categories. The cluster modularity value is 0.4391 (>0.3), while the mean silhouette value is 0.7104 (>0.5, >0.7), which means that cluster is reasonable and credible.

Analysis of Keywords Timeline View

According to the timeline view of Relapsed/Refractory Non-Hodgkin lymphoma (Figure 8), from cluster timeline progression, 'mantle cell lymphoma' covered all time span of data collected, 'relapse', 'lymphoma', and 'Non-Hodgkin lymphoma' were the most dominant categories in accordance with our research area of bibliometric analysis. In addition to the aforementioned cluster of keywords, research areas with a large time span include 'pathway'. Observed by keywords in

Table II. The top 10 active institutions which contributed to research of Relapsed/Refractory Non-Hodgkin Lymphoma.

Ranking	Counts	Centrality	Year	Institution	Country
1	30	0.06	2009	Univ Texas MD Anderson Canc Ctr	USA
2	25	0.14	2009	Mayo Clin	USA
3	21	0.06	2012	Mem Sloan Kettering Canc Ctr	USA
4	21	0.1	2009	Natl Canc Ctr	Japan
5	20	0.16	2011	Univ Bologna	Italy
6	17	0.15	2014	Washington Univ	USA
7	15	0.03	2009	Ohio State Univ	USA
8	14	0.09	2013	Dana Farber Canc Inst	USA
9	13	0.03	2011	Univ Nebraska Med Ctr	USA
10	13	0.04	2014	Sarah Cannon Res Inst	England

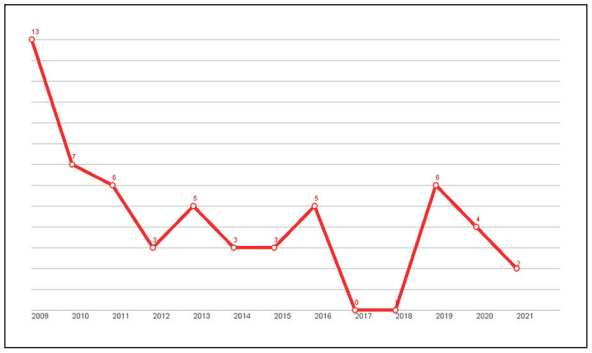

Figure 6. Map of keyword trend 'bone marrow transplantation.

the distribution of timeline, including 'anti-cd19 chimeric antigen receptor t cell', 'biomarker', 'radiation therapy', 'cytokine release syndrome', 'anti-cd45', 'cd22', 'anti body-radionuclide conjugate' appeared after year 2020. This indicates that these keywords articles were the key literatures for the current research, and also indicates that the research of r/r DLBCL in recent years is dominated by novel strategies and drugs.

Analysis of Keywords Burst

According to keywords burst view of r/r NHL (Figure 9), observed from keywords burst evolvement, in the early period (2009-2014), the frequency of the following keywords arose rapidly: 'bone marrow transplantation', 'combination', 'blood', 'I 131 tositumomab', 'low grade', 'large cell lymphoma', 'leukemia', 'chop', 'activation', 'radioimmunotherapy', 'chemotherapy plus rituximab', 'ibritumomab tiuxetan'. In the middle period (2015-2018), the frequency of following keywords increased expectedly: 'refractory', 'inhibitor', 'open label', 'risk', 'Non-Hodgkin lymphoma'. In recent years (2019-2021), the frequency of the following keywords appeared abruptly: 'multicenter', 'ibrutinib', 'idelalisib', 'outcm', 'immunotherapy', 'salvage chemotherapy', 'safety', 'criteria'. Excluding insignificant keywords, the main research field in the early period was with regard to various therapeutic interventions, including bone marrow transplantation, chemotherapy, target therapy and immunotherapy. In the middle period, the research direction turned to discussion of inhibitors, and in the last few years, the publications are more relevant to immunotherapy.

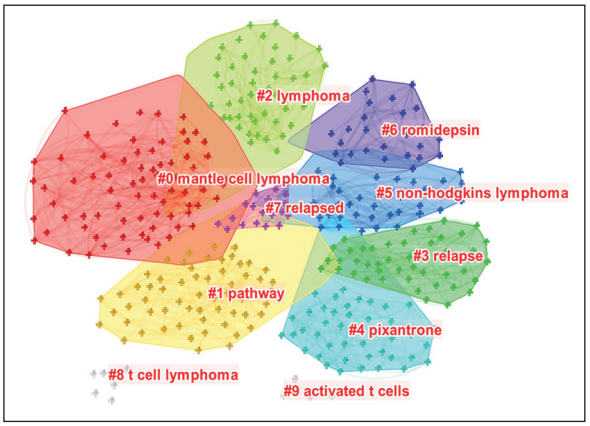

Figure 7. Clustering map of keywords based on CiteSpace.

Discussion

During the past 30 years, many studies on r/r NHL have been conducted, but we found there is no in depth Scientometric analysis literatures are published. In this study, articles on relapsed/refractory Non-Hodgkin lymphoma in the Core Collections of Web of Science database from 2009 to 2021 were bibliometrically analyzed by Citespace V (http://cluster.cis.drexel.edu/~cchen/citespace/).

According to the above bibliometric analysis, the output of publications fluctuated from 2009 to 2017, and it is worth noting that publications have substantially increased since 2017, which means that r/r NHL has received increasing attention.

Based on the above observation, we sorted out the core authors, and then, identified main research teams in this field, such as the Pier Luigi Zinzani, Kensei Tobinai, Andre Goy, and Julie M. Vose. The significance of this discovery is an indispensable process for studying r/r NHL. For example, Pier Luigi Zinzani, as the author of 16 publications, has committed to the clinical research of r/r NHL, which includes relapsed/refractory T-cell lymphomas, relapsed/refractory primary mediastinal large B-cell lymphoma, and relapsed/refractory mantle cell lymphoma and treatment regimens involving lenalidomide, rituximab, bortezomib, and nivolumab[16,19-22].

Visualization revealed cooperation among institutions and countries in the field of r/r NHL. The USA makes greatest contribution, having research funding for the r/r NHL. The most influential institutions are the University Texas MD Anderson Cancer Center, Mayo Clinical, Memorial Sloan Kettering Cancer Center, National Cancer Center, and University Bologna, among

Table III. Keywords cluster character.

Cluster number	Silhouette	Middle year	Name of cluster	The top three keywords based on Loglikelihood ratio, p-level algorithm	Keywords (High frequency, high centrality)
0	0.589	2012	Mantle cell lymphoma	Mantle cell lymphoma (32.08, 1.0E-4); follicular lymphoma (21.62, 1.0E-4); cyclophosphamide (13.83, 0.001)	Follicular lymphoma (65,0.06); b cell (18,0.11)
1	0.655	2013	Pathway	Pathway (17.31, 1.0E-4); idelalisib (16.9, 1.0E-4); diagnosis (16.49, 1.0E-4)	Cancer (38,0.12); Apoptosis (19,0.09)
2	0.764	2012	Lymphoma	Lymphoma (19.11, 1.0E-4); autologous (11.46, 0.001); f 18 fluorodeoxyglucose (7.63, 0.01)	Non hodgkins lymphoma (21,0.05); Lymphoma (67,0.09)
3	0.68	2013	Relapse	Relapse (14.46, 0.001); remission (10.36, 0.005); international prognostic index (8.75, 0.005)	Non hodgkins lymphoma (41,0.03); Relapse (37,0.1)
4	0.7	2014	Pixantrone	Pixantrone (19.91, 1.0E-4); diffuse large b-cell lymphoma (16.88, 1.0E-4); daratumumab (12.67, 0.001)	Non-hodgkin lymphoma (77,0.08);
5	0.816	2014	Non-hodgkins lymphoma	Non-hodgkins lymphoma (16.77, 1.0E-4); chemotherapy (10.49, 0.005); central nervous system (10.44, 0.005)	Rituximab (134,0.06); Combination (27,0.1); Chemotherapy (110,0.1)
6	0.791	2013	Romidepsin	Romidepsin (12.93, 0.001); cutaneous t-cell lymphoma (12.93, 0.001); conditioning regimen (7.55, 0.01)	Disease (18,0.03); Prognostic factor (8,0.04)
7	0.853	2012	Relapsed	Relapsed (16.4, 1.0E-4); radioimmunotherapy (15.78, 1.0E-4); bendamustine (13.45, 0.001)	Therapy (109,0.05); Bendamustine (17,0.05)
8	0.994	2009	t cell lymphoma	t cell lymphoma (11.01, 0.001); folate analog (11.01, 0.001); 10 propargyl 10 deazaaminopterin (11.01, 0.001)	Model (2,0.05)
9	0.978	2014	Activated t cells	Activated t cells (13.01, 0.001); bispecific antibody (8.52, 0.005); autologous stem cell transplantation (6.16, 0.05)	Anti cd20 antibody (3,0.02)

which have close cooperative relationships. In addition, it was found that the majority of the organizations belonged to the USA with a high cooperative frequency. As shown in Figure 4, the USA, Italy, France, Germany, People's Republic China, and Japan are the top six countries. China is the sole developing country from Asia in the top six productive countries, while the USA, as a core source of published studies, have the strongest collaboration with other countries to promote the clinical research development of this field.

The keyword co-occurrence network map demonstrates that over the years, the focus of research of patients on r/r NHL is to find novel therapies, including next-generation monoclonal antibodies, such as anti-CD40 monoclonal antibody[23], anti-CTLA-4 monoclonal antibody[24], novel cellular therapy, such as fludarabine, bortezomib, and rituximab[25], and therapies directed against new targets[26,27]. However, high-dose chemotherapy followed by stem cell transplantation is also the standard therapy scenario, as reported by the PARMA trial[5]. However, the prerequisite

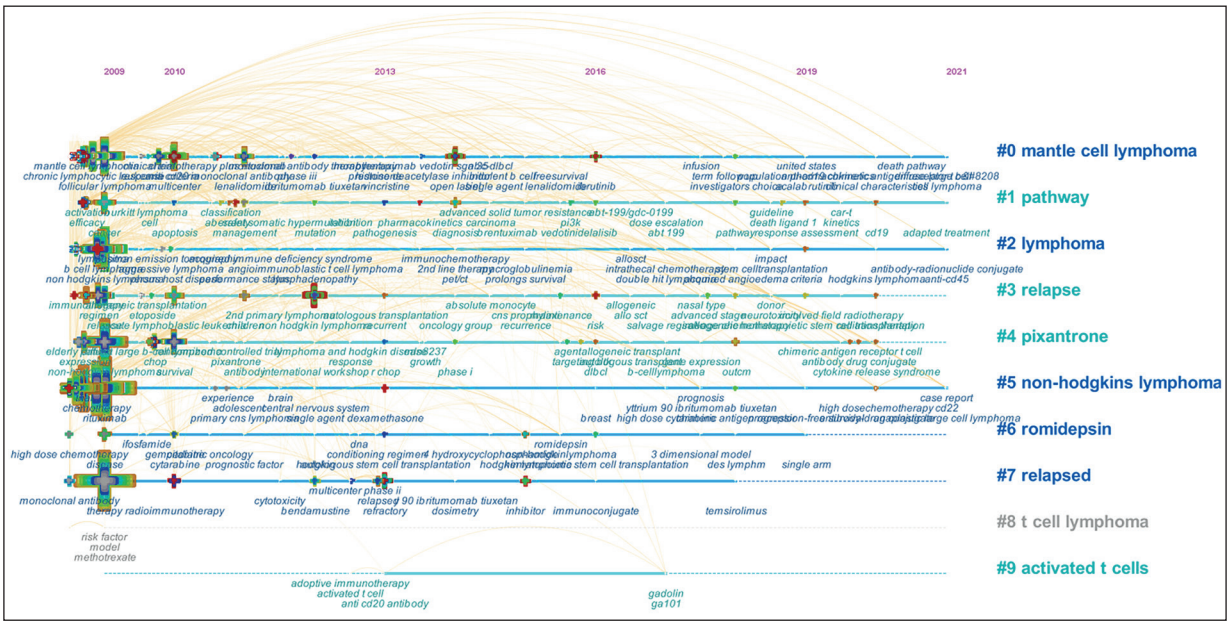

Figure 8. Map of keywords timeline. Cross size represent contribution to the published.

is vital to chemotherapy, and approximately 50% of patients with relapsed/refractory Non-Hodgkin lymphoma are not eligible for ASCT[28]; therefore, 'bone marrow transplantation' has lost its advantage as a treatment.

Figure 5 indicates that cluster regions #1, 5 and 7 play important roles in the research on relapsed/refractory Non-Hodgkin lymphoma. #1 reflects a clinical trial based on pathogenesis of relapsed/refractory Non-Hodgkin lymphoma, including pathway[29], apoptosis[30-32], etc.; #5 and #7 reflect common chemotherapy, such as rituximab, and combination therapy[33,34].

Top 25 Keywords with the Strongest Citation Bursts

Keywords	Year	Strength	Begin	End	2009 - 2021
bone marrow transplantation	2009	5	2009	2010	
combination	2009	3.41	2009	2010	
blood	2009	3.35	2009	2012	
i 131 tositumomab	2009	3.22	2009	2010	
low grade	2009	3.21	2009	2011	
large cell lymphoma	2009	3.1	2009	2011	
leukemia	2009	2.93	2009	2011	
chop	2009	2.77	2010	2011	
activation	2009	2.76	2010	2014	
radioimmunotherapy	2009	5.81	2011	2014	
chemotherapy plus rituximab	2009	3.76	2011	2013	
ibritumomab tiuxetan	2009	3.33	2012	2014	
refractory	2009	3.78	2013	2018	
inhibitor	2009	3.93	2015	2019	
multicenter	2009	2.76	2015	2021	
open label	2009	5.04	2016	2019	
ibrutinib	2009	4.49	2016	2019	
idelalisib	2009	3.17	2016	2021	
risk	2009	2.88	2016	2017	
non hodgkin lymphoma	2009	5.99	2017	2019	
outcm	2009	5.92	2018	2021	
immunotherapy	2009	4.01	2018	2021	
salvage chemotherapy	2009	2.75	2018	2021	
safety	2009	3.42	2019	2021	
criteria	2009	3.27	2019	2021	

Figure 9. Keywords with the strongest citation burst.

According to the keyword's timeline, the main diseases of r/r NHL are aggressive lymphomas, such as 'mantle cell lymphoma', 'follicular lymphoma', 'b cell lymphoma', 'diffuse large b cell lymphoma', and 'chemotherapy', 'rituximab', 'therapy radioimmunotherapy' are also the most studied areas in the early years. The studies of monoclonal antibodies against cell surface antigens are always research hotspots, such as 'anti-CD45'[35], 'CD38'[36], and 'CD37'[37]. 'CAR-T'[38] and 'checkpoint blockade'[39] have been studied in different areas and different eras.

With the development of Evidence Based Medicine (EBM) in recent years, EBM is proposed to focus on the design of clinical studies, and scientific community has embraced EBM-related initiative to develop clinical guidance[40], researches of r/r NHL also focus on EBM, with keywords like 'multicenter' 'outcm' 'salvage chemotherapy' 'safety' 'criteria' etc. Thus, the research trends of relapsed/refractory Non-Hodgkin lymphoma have been transferred from bone marrow transplantation, radioimmunotherapy, chemotherapy to novel target drugs (such as ibritumomab tiuxetan, inhibitor) and criteria EBM.

This study has some limitations that should be considered in future studies. We only retrieved data from the database of SSCI and SCIE in the WOS core collection which may not be comprehensive. The existing potential biases related to bibliometric analysis, include language bias, institutional bias, and influential researcher bias. Thus, we will include other databases, such as Scope, Google Scholar and PubMed to conduct a more comprehensive analysis and implement a complete annual bibliometric analysis in future studies.

Conclusions

Based on CiteSpace, we conducted a relatively extensive analysis of the literature for studies of relapsed/refractory non-Hodgkin to discover publication characteristics and trends. With the exception of high-dose chemotherapy followed by autologous hematopoietic stem cell transplantation, there are no universally acknowledged treatment approaches worldwide, which results in a diversity of treatment options for R/R NHL. Through this analysis, we not only gain insights into the current state of research on R/R NHL from the commonalities of study authors, institutions, countries, keywords, and cluster plot analysis, but also identified research hotspots and trends in this field. It serves us to extract useful information from complex data and provide more information for clinicians and researchers.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Authors' Contribution

Conceptualization: Zhang Fupeng; Zhou Yongming; Data curation: Liu Likun; Project administration: Zhou Yongming; Resources: Zhou Jing; Software: Zhang Fupeng; Supervision: Zhou Yongming ; Visualization: Bao Jizhang; Writing-original draft: Zhang Fupeng; Writing-reviews & editing: Zhao Xiaoyan.

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Data Availability Statement

The datasets generated during the current study are available from the corresponding author on reasonable request. All data generated or analysed during this study are included in this published article.

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