



# A bibliometric analysis of the research on hematological tumor microenvironment

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**Background:** In recent years, the incidence of hematological tumors has increased. The tumor microenvironment (TME) is the local biological environment in the process of tumor occurrence and development and is closely related to hematological malignancies, including lymphoma and leukemia. This study aims to conduct a bibliometric analysis of the research on the hematological TME, reflect the general situation of the research in this field, and remind the focus of future research.

**Methods:** Search the Science Citation Index Expanded (SCI-E) database on the Web of Science Core Collection (WOSCC). Use subject terms to search tumor microenvironment; the limited search subject is Hematology, and the time range is from 1990 to July 18, 2021. Use CiteSpace software to analyze the number of annual papers published, the number of citations, the distribution of disciplines, the distribution of countries/institutions, the distribution of authors, the distribution of journals, and the frequency of use of keywords and its trend of change.

**Results:** There were 1,992 related research articles cited 77,213 times. The top 5 countries with the number of published papers in this field are: the United States, Italy, China, Germany, and the United Kingdom; the top 5 centrally ranked countries are the United States, Italy, Spain, France, and Japan. Literature and cooperation are mainly from the United States. The top three researchers with several published papers are Anderson KC, Ansell SM, and Gascoyne RD. Their centrality scores are all low, with only 5 researchers reaching above 0.01, and there is less collaboration between the authors. High-quality papers are from *Blood*, *Cancer Res*, *P Natl Acad Sci USA*, and *Nature*. Keyword analysis shows that immunotherapy is the current focus of research in this field.

**Conclusions:** The research on the microenvironment of hematological malignancies is rapidly developing. At present, the main research focus is on targeted immunotherapy.

**Keywords:** Hematological malignancies; tumor microenvironment (TME); bibliometrics; immunotherapy

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## Introduction

In recent years, the incidence of hematological tumors has increased. Statistics show that the number of new cases of non-Hodgkin's lymphoma, Hodgkin's lymphoma, and leukemia in 2002 were 300,571, 62,329, and 300,522, respectively. In 2018, they were 758,314, 106,157, and 746,039, respectively. Almost all have doubled, and the number of deaths has also increased significantly (1,2). Analysis of the reasons is mainly related to the pollution of the living environment and the advancement of diagnostic technology (3,4). With the deepening of research, people have a richer understanding of the pathogenesis of hematological malignancies. Ioannides and Whiteside first proposed the tumor microenvironment (TME). It is defined as the local biological environment in the process of tumorigenesis and development, which can provide a scaffold and barrier for the growth of tumor cells and generate immune exempt areas, providing tumors with a "culture base" (5). With the deepening of research on TME, the oncology community is paying increased attention to the role of TME in tumorigenesis and development (6,7). TME mainly plays an important role in three aspects: the most direct role is to provide a growth environment for tumors; certain components in TME can weaken the therapeutic effect of anti-tumor drugs; the local immune response is immunosuppressive, helping tumor cells escape immune surveillance (6,8). Studies have shown that TME is closely related to hematological malignancies, including lymphoma and leukemia (9,10). Generally, hematological TME consists of cells including tumor-associated macrophages, follicular dendritic cells, fibroblastic reticular cells and endothelial cells (11). Bibliometrics is a method of indirect research on developing a certain field that has emerged in recent years. Compared with reviews, by analyzing most literatures on some theme, it can reflect the annual development and change trend of research in the field and the current research focus, especially to sort out important research and research institutions and researchers in this field (12,13). The research results of bibliometrics help researchers grasp this field's development direction and avoid repeated research (14). A previous bibliometric analysis of TME in oral cancer provided an overview of the research status in oral oncology (15). This study conducts a bibliometric analysis of the research on the hematological TME, reflects the general situation of the research in hematology, and reminds the focus of future research.

## Methods

### *Search objects*

We searched the Science Citation Index Expanded (SCI-E) database on the Web of Science Core Collection (WOSCC). The database is the primary data source for bibliometrics research, which can provide subject retrieval and limit the research field, minimize invalid retrievals and make retrieval results more accurate (16).

### *Retrieval steps*

First, use subject terms to search, the search term is tumor microenvironment; then, the search subject is limited to Hematology; the time range is from the earliest document time of the database to the last retrieval time of this research (July 18, 2021); finally, the search results are obtained.

### *Statistical and bibliometrics analysis*

Export all records of the search results and cited references in plain text format, and use CiteSpace software to analyze the number of annual papers published, the number of citations, the distribution of disciplines, the distribution of countries/institutions, the distribution of authors, the distribution of journals, the frequency of use of keywords, and the trend of change is analyzed to reflect the research on the microenvironment of hematological malignancies. In this descriptive study, variables were expressed as numbers and percentages. No comparison was conducted; therefore, no P value was set.

## Results

### *Retrieval results*

There are 1,992 related research documents, including 1,211 original articles, 500 reviews, 240 meeting abstracts, 40 proceedings papers, 22 editorial materials, 19 book chapters, and 19 early access, 14 letters, 3 corrections, and 2 notes (Tables 1,2, Figure 1). The citation frequency is 77,213 times, the h-index count is 130, and the average number of citations per paper is 38.76 (Figure 2).

### *Distribution of countries and institutions*

We use CiteSpace V software to analyze data and generate national visualization maps (Figure 3) and institutional

**Table 1** Document type analysis

Literatures	Records	% of 1,992
Original articles	1,211	60.8
Reviews	500	25.1
Meeting abstracts	240	12.0
Proceedings papers	40	2.0
Editorial materials	22	1.1
Book chapters	19	1.0
Early access	19	1.0
Letters	14	0.7
Corrections	3	0.2
Notes	2	0.1

**Table 2** Annual distribution of the number of papers in the past 20 years

Years	Records	% of 1,992
2021	44	2.2
2020	200	10.0
2019	183	9.2
2018	156	7.8
2017	181	9.1
2016	145	7.3
2015	123	6.2
2014	115	5.8
2013	100	5.0
2012	91	4.6
2011	113	5.7
2010	86	4.3
2009	80	4.0
2008	65	3.3
2007	48	2.4
2006	37	1.9
2005	38	1.9
2004	32	1.6
2003	25	1.3
2002	17	0.9

visualization maps (*Figure 4*). The results show the top 5 countries for the number of papers published in this field are the United States, Italy, China, Germany, and the United Kingdom; the top 5 centrally ranked countries are the United States, Italy, Germany, Spain, and France (*Tables 3,4*). The results suggest that the United States is in a leading position in research in this field. The institutional analysis also shows that institutions that have published many papers and those with more collaborations are also mainly from the United States (*Tables 5,6, Figure 4*).

### Authors

The top three researchers with the number of papers published in this field are Anderson KC, Ansell SM, and Gascoyne RD. However, the centrality scores are all low, and only 5 researchers who reach over 0.01 are: Gascoyne RD, Anderson KC, Gribben JG, Steidl C, and Wilcox RA indicate that although some authors have published more papers, there is less collaboration among authors (*Tables 7,8, Figure 5*). In terms of paper citations, the top three authors of citations are Burger JA, Hideshima T, and Steidl C, but the top three co-cited centralities (the third had two authors) are Anderson KC, Simmons PJ, Gabrilovich DI, and Bataille R (*Tables 9,10*), and most of these authors are from the United States. The author's co-cited visualization map (*Figure 6*) shows that the authors have more intensive mutual citations, reflecting that the main research results in this field are concentrated on these authors.

### Journals distribution

Of the 1,992 articles from 184 journals, 22 journals have published over 20 articles, accounting for 1,676 articles, 84.1% of the total literature (*Table 11*). Regarding the number of published papers, related papers are concentrated in hematology professional journals (*Table 11*). However, in terms of the number of citations or centrality (*Tables 12,13*), high-quality papers are still concentrated in authoritative journals, including *Blood*, *Cancer Res*, *P Natl Acad Sci USA*, and *Nature* (*Table 12*).

### Keywords analysis

We used CiteSpace V software to generate a keyword

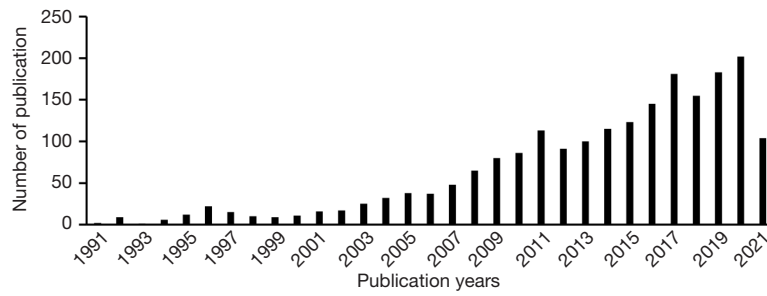


Figure 1 Annual changes in the number of papers published.

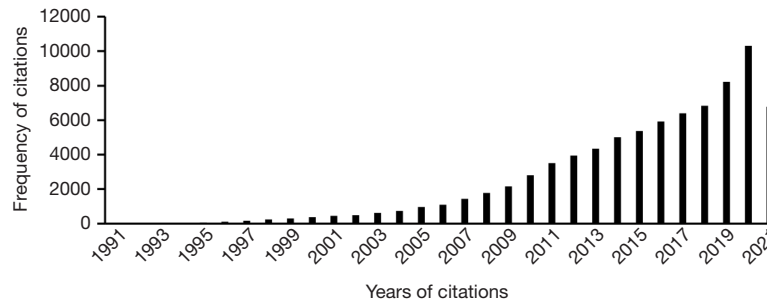


Figure 2 Annual changes of the citation frequency.

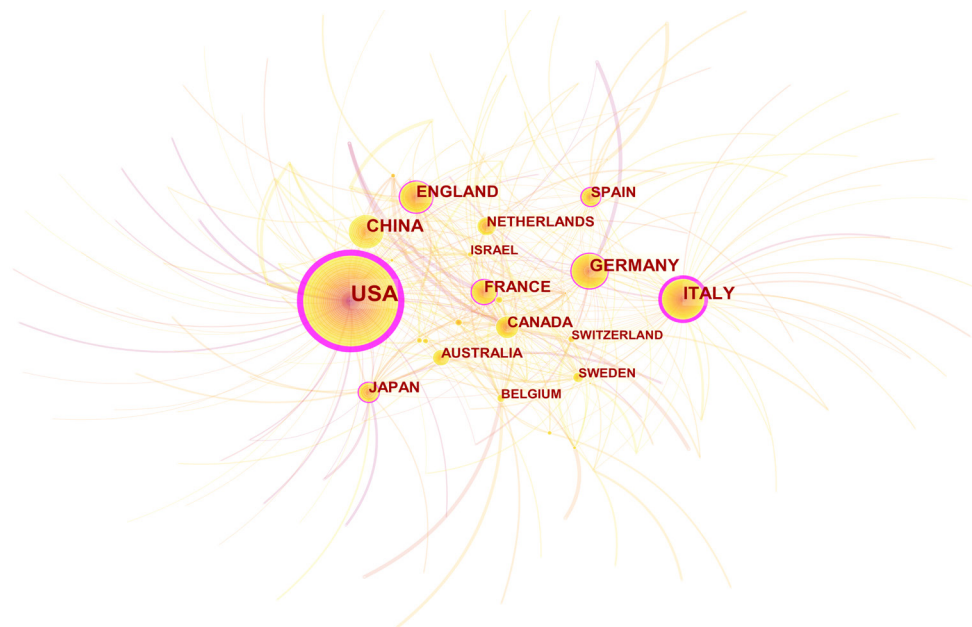


Figure 3 A visual map of countries.

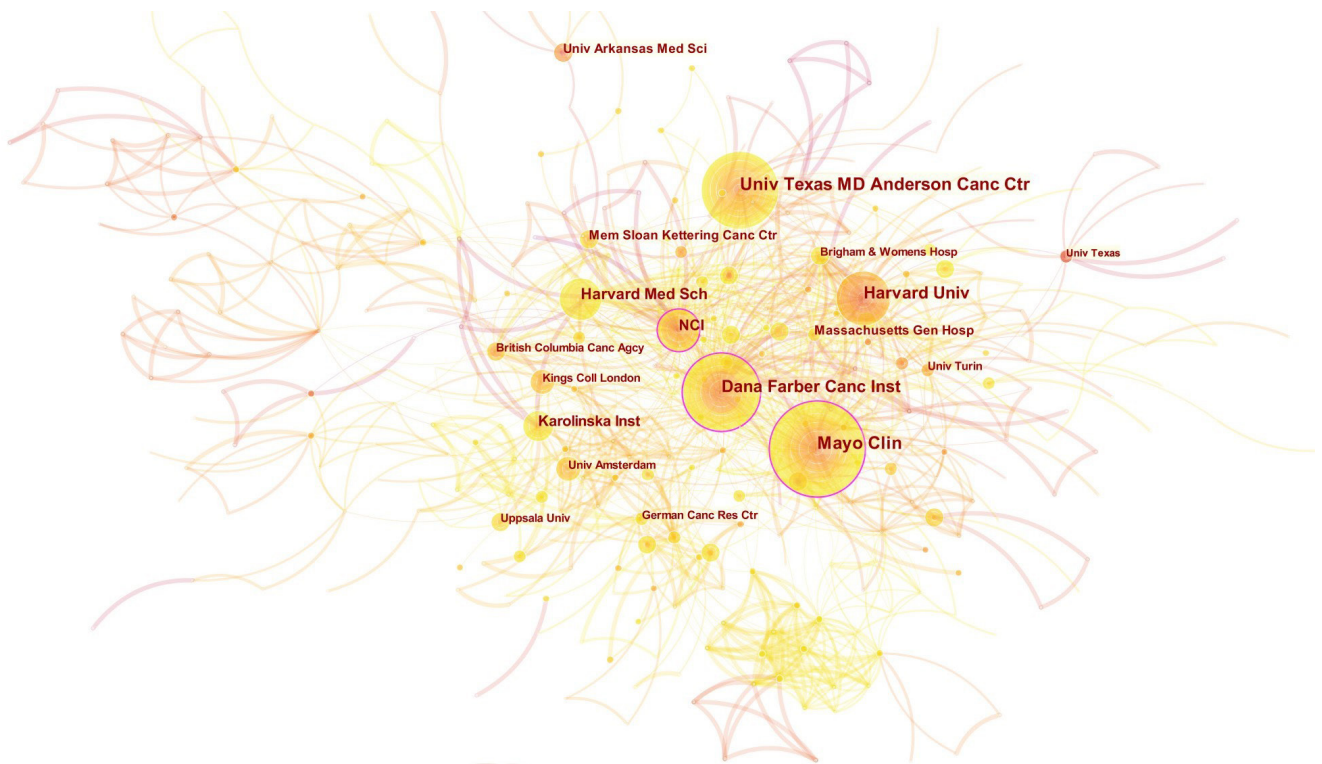


Figure 4 Visualization map of institutions.

Table 3 Top 10 countries in terms of publication

Rank	Countries	Records
1	USA	864
2	Italy	221
3	China	185
4	Germany	175
5	England	140
6	France	123
7	Canada	98
8	Japan	92
9	Spain	75
10	Australia	61

Table 4 Top 10 countries in terms of centrality

Rank	Countries	Centrality
1	USA	0.82
2	Italy	0.39
3	Germany	0.15
4	Spain	0.14
5	France	0.13
6	Japan	0.10
7	Australia	0.10
8	England	0.09
9	Canada	0.07
10	Netherlands	0.05

**Table 5** Top 10 institutions in terms of number of papers published

Rank	Institutions	Records
1	Mayo Clin	70
2	Dana Farber Canc Inst	69
3	Univ Texas MD Anderson Canc Ctr	67
4	Harvard Univ	62
5	Harvard Med Sch	36
6	NCI	34
7	Karolinska Inst	31
8	Massachusetts Gen Hosp	16
9	Mem Sloan Kettering Canc Ctr	15
10	British Columbia Canc Agency	15

**Table 6** Top 10 institutions in terms of centrality

Rank	Institutions	Centrality
1	Dana Farber Canc Inst	0.16
2	Mayo Clin	0.14
3	NCI	0.11
4	Univ Texas MD Anderson Canc Ctr	0.07
5	Harvard Univ	0.05
6	Harvard Med Sch	0.05
7	German Canc Res Ctr	0.04
8	Columbia Univ	0.04
9	Karolinska Inst	0.03
10	British Columbia Canc Agency	0.03

**Table 7** Top 5 authors in the number of papers published

Rank	Authors	Records
1	Anderson KC	34
2	Ansell SM	25
3	Gascoyne RD	16
4	Steidl C	15
5	Richardson PG	15

co-occurrence map (*Figure 7*). The top 10 keywords in terms of frequency of use and centrality are listed in *Tables 14* and *15*. For keywords with high frequency, we

**Table 8** Top 5 authors of centrality

Rank	Authors	Centrality
1	Gascoyne RD	0.02
2	Anderson KC	0.01
3	Gribben JG	0.01
4	Steidl C	0.01
5	Wilcox RA	0.01

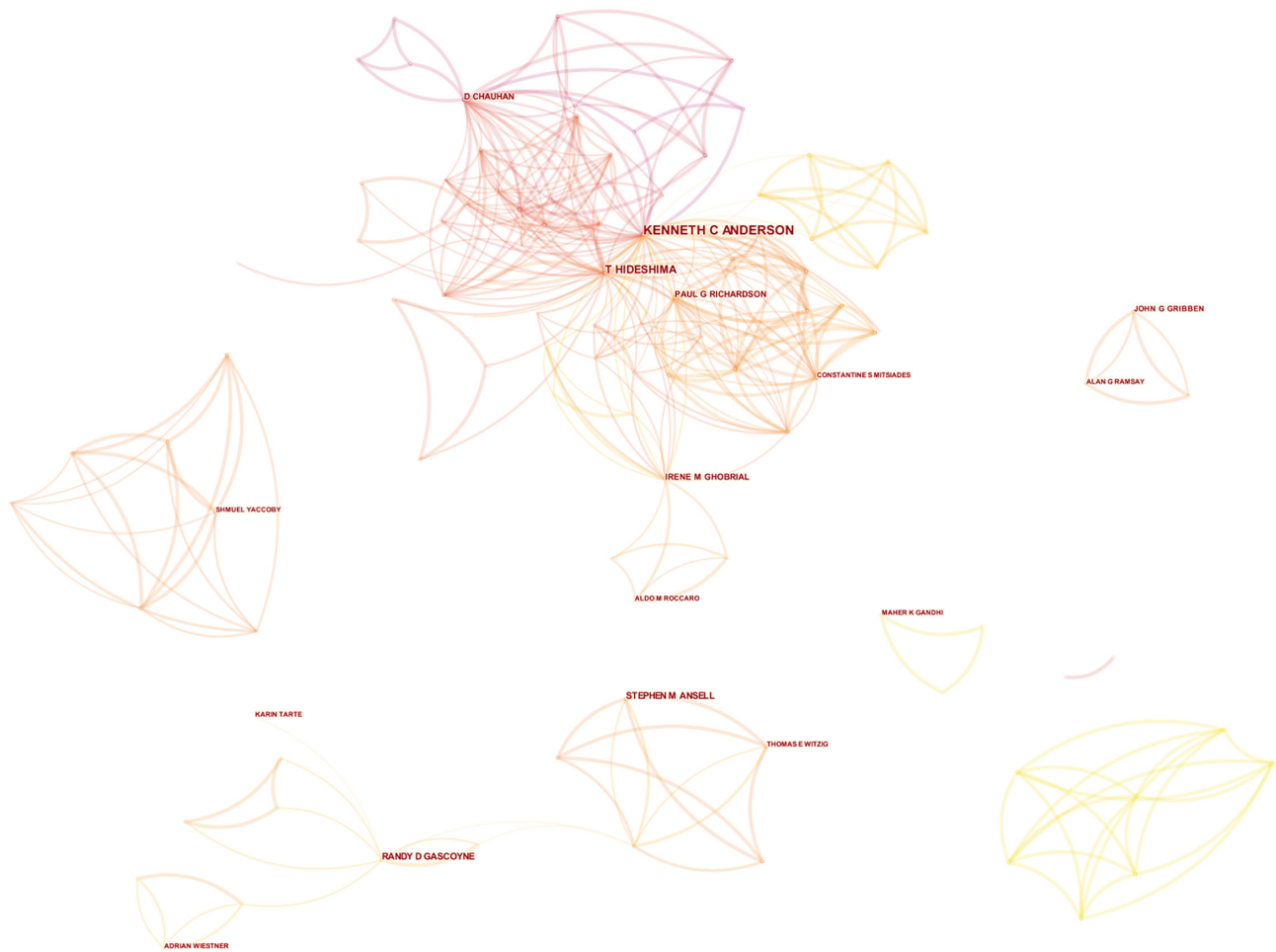
use CiteSpace to perform burst detection on keywords (*Figure 8*). We can observe the transformation of colony stimulus factors, growth factors, cytokines, tumor necrosis factors at the beginning into currently commonly used drugs, immunotherapy. This reflects the gradual transformation of research in this field, from the initial analysis of microenvironmental components to immunotherapy. It is also a typical process of medical research, the evolution from potential mechanism research to clinical intervention.

## Discussion

This study analyzed the microenvironmental research literature related to hematological malignancies and found that the research in this field is concentrated in several large medical research institutions in the United States. Although researchers often quote documents from each other, the cooperation between them is few. Most papers are published in professional journals on the blood system, and high-level research is published in authoritative, comprehensive journals. Keyword analysis shows that current research focuses on tumor immunotherapy. Taken together these findings, we provided an overview of studies on hematological TME.

Many molecular therapeutic targets for hematological malignancies have been discovered with the deepening of molecular biology research and technological advancement (9,17-20). The drugs developed in this way delay the progression of the disease to a significant extent and significantly improve the patient's disease-free survival (DFS) and quality of life (21-23). However, some authors believe it has not helped complete the eradication of tumors (9). However, several recent studies have shown that targeted therapy based on the TME can significantly improve DFS (23,24). This study shows that the research in this field has experienced a typical process, from primary





**Figure 5** The author's co-authored visualization map.

to clinical. Initially, it was mainly experimental research to deeply analyze the expression characteristics and mechanism of various factors in the microenvironment of tumor cells (25), changes in matrix composition in the bone marrow and other tissues (26). It gradually shifts to the relationship between the specific tumor and the microenvironment (27) until the vital research of immunotherapy in recent years (28). Of course, researchers are still deeply studying the relationship between numerous factors and cells in the TME and lymphoma, leukemia, and myeloma. Related research results are also published continuously, but these studies have been accumulated for a long time in the early stage. Further exploration based on work also explains why most research is concentrated on a few medical research institutions in the United States.

The real rapid development of TME research was in the

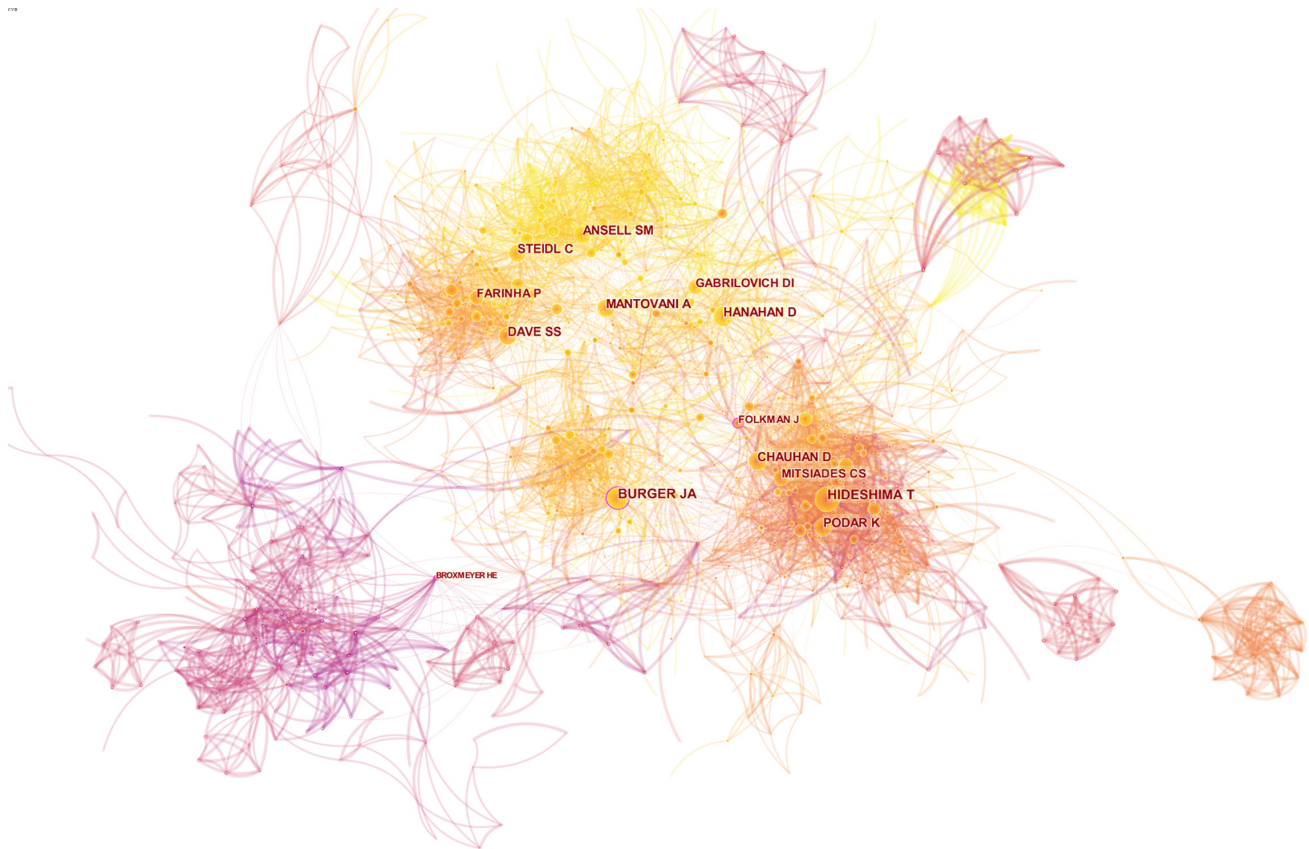
1970s. New biomedical research technologies continued to appear, which technically solved the research difficulties. For example, Folkman *et al.* discovered factors closely related to tumor angiogenesis (29). Researchers have gradually realized that inhibiting angiogenesis can effectively treat cancer, and subsequently, the vascular endothelial growth factor has gradually become an effective target for cancer treatment (30). Based on this, related drugs have been developed and used clinically (31,32). Therefore, more and more studies have confirmed that cell composition, various factors, and local physical properties in the TME all play a direct role in the efficacy of anti-tumor therapy (33). After over 50 years of continuous efforts, many research results of the TME have been continuously transformed into clinical treatment of tumors, and a large number of satisfactory results have been achieved (8).

**Table 9** The top 10 most cited authors

Rank	Authors	Citations
1	Burger JA	139
2	Hideshima T	123
3	Steidl C	122
4	Hanahan D	119
5	Ansell SM	109
6	Dave SS	101
7	Swerdlow SH	88
8	Mantovani A	84
9	Green MR	79
10	Chauhan D	76

**Table 10** Top 10 authors of centrality in co-citation

Rank	Authors	Centrality
1	Anderson KC	0.29
2	Simmons PJ	0.26
3	Gabrilovich DI	0.21
4	Bataille R	0.21
5	Abboud SL	0.20
6	Hideshima T	0.12
7	Steidl C	0.12
8	Ribatti D	0.12
9	Broxmeyer HE	0.12
10	Liesveld JL	0.12



**Figure 6** The author's co-cited visualization map.



**Table 11** Top 22 journals by publications

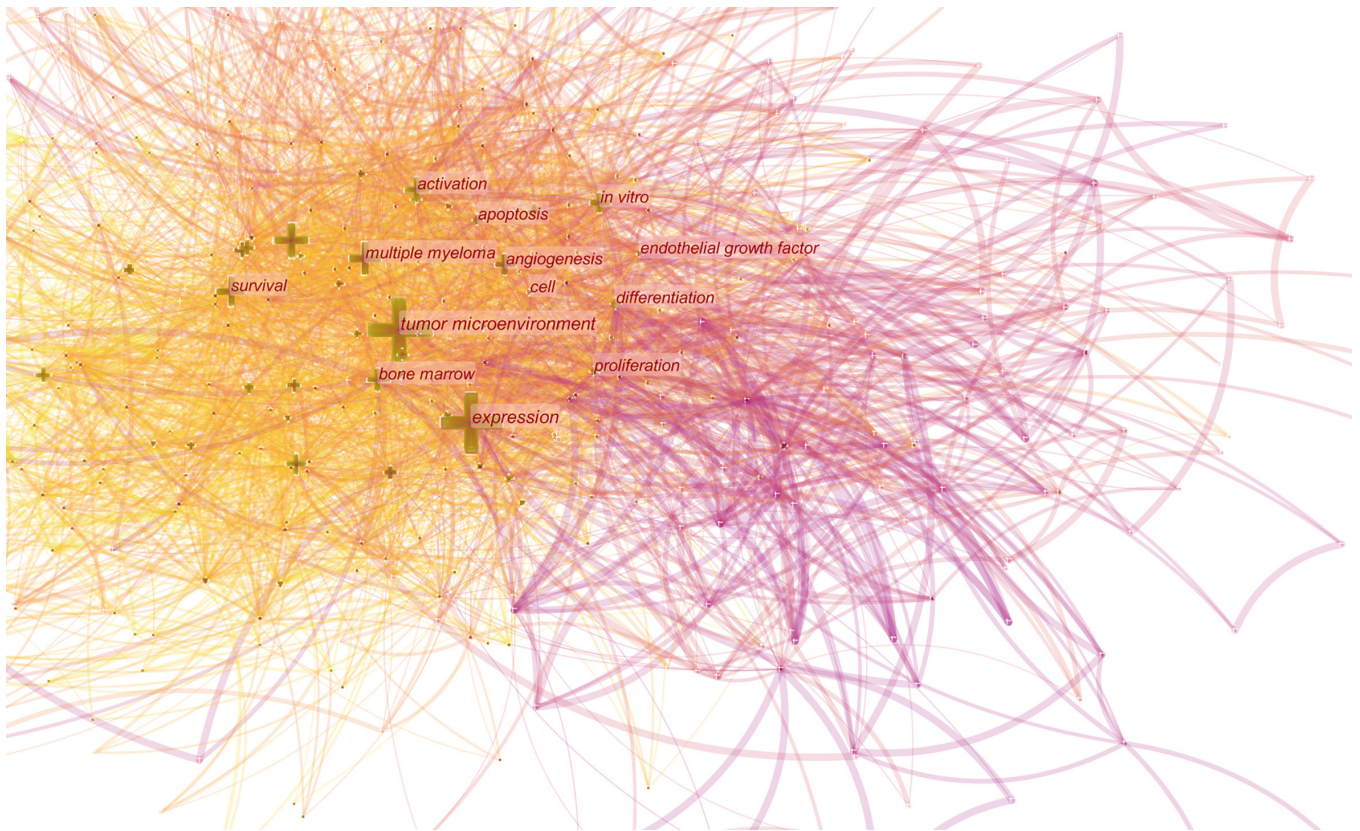
Rank	Journals	Papers	Percentage
1	<i>Blood</i>	457	22.9
2	<i>Leukemia</i>	133	6.7
3	<i>Leukemia Lymphoma</i>	125	6.3
4	<i>Journal of Leukocyte Biology</i>	116	5.8
5	<i>Journal of Hematology Oncology</i>	107	5.4
6	<i>British Journal of Haematology</i>	103	5.2
7	<i>Haematologica</i>	94	4.7
8	<i>Stem Cells</i>	89	4.5
9	<i>Critical Reviews in Oncology Hematology</i>	81	4.1
10	<i>Experimental Hematology</i>	41	2.1
11	<i>Clinical Lymphoma Myeloma Leukemia</i>	40	2.0
12	<i>Leukemia Research</i>	39	2.0
13	<i>Blood Advances</i>	31	1.6
14	<i>Stem Cells and Development</i>	31	1.6
15	<i>Pediatric Blood Cancer</i>	30	1.5
16	<i>Blood Cancer Journal</i>	27	1.4
17	<i>Cytotherapy</i>	24	1.2
18	<i>International Journal of Hematology</i>	24	1.2
19	<i>Annals of Hematology</i>	22	1.1
20	<i>American Journal of Hematology</i>	21	1.1
21	<i>Current Opinion in Hematology</i>	21	1.1
22	<i>Hematological Oncology</i>	20	1.0

**Table 12** Top 10 journals cited

Rank	Journals	Citations
1	<i>Blood</i>	1,510
2	<i>Cancer Res</i>	1,176
3	<i>P Natl Acad Sci USA</i>	1,092
4	<i>Nature</i>	1,011
5	<i>Clin Cancer Res</i>	970
6	<i>New Engl J Med</i>	913
7	<i>J Immunol</i>	882
8	<i>Leukemia</i>	874
9	<i>J Clin Invest</i>	856
10	<i>J Clin Oncol</i>	842

**Table 13** Top 10 journals of centrality in citation

Rank	Journals	Centrality
1	<i>Biochem Bioph Res Co</i>	0.08
2	<i>Brit J Cancer</i>	0.07
3	<i>J Cell Physiol</i>	0.07
4	<i>Int J Cancer</i>	0.06
5	<i>Carcinogenesis</i>	0.06
6	<i>J Clin Invest</i>	0.05
7	<i>Embo J</i>	0.05
8	<i>Nat Cell Biol</i>	0.05
9	<i>J Cell Biol</i>	0.05
10	<i>J Immunother</i>	0.05



**Figure 7** Keyword co-occurrence map. Identified in the figure are keywords that often appear together.

**Table 14** Top 10 most used keywords

Rank	Keywords	Frequency
1	expression	383
2	microenvironment	325
3	cancer	245
4	tumor microenvironment	216
5	multiple myeloma	203
6	survival	192
7	bone marrow	159
8	t cell	153
9	activation	153
10	<i>in vitro</i>	134

**Table 15** Top 10 keywords for centrality

Rank	Keywords	Centrality
1	microenvironment	0.17
2	expression	0.16
3	bone marrow	0.12
4	cell	0.09
5	cytokine	0.09
6	cancer	0.08
7	colony stimulating factor	0.07
8	survival	0.06
9	<i>in vitro</i>	0.06
10	apoptosis	0.06

Top 25 Keywords with the Strongest Citation Bursts

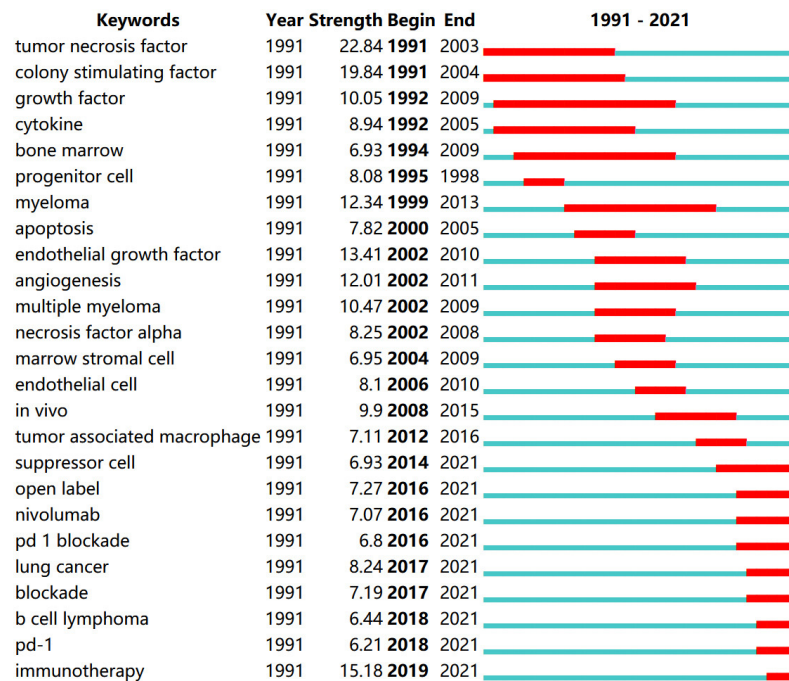


Figure 8 Top 25 keywords with the strongest citation bursts.

Compared with other TME studies, the microenvironment research of hematological malignancies has been carried out a little later. However, according to our analysis results, it can be seen that in this field, the process of transformation from basic to clinical is faster. However, as mentioned earlier, related research is concentrated on the United States, and there is little cooperation. This makes it necessary to be more cautious in promoting related research results to various people. Future research can appropriately observe different regions and races (34). Besides, we suggest more research to be carried out on the effect of PD-1/L1 inhibitor or CAR-T therapy on TME.

### The limitations of this study

The search literature of this study is limited to “hematology”, and a small amount of related literature may be missed. However, this study only discusses hematological malignancies. Therefore, for the mechanism studies that may be missed in this part, researchers can search for related papers by other methods to further understand.

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### Footnote

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <https://dx.doi.org/10.21037/atm-21-3924>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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