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Bibliometric Analysis of Original Articles on CAR-T Cell Therapy

Wei Li[1, 2], Li Wan[1, 2, *]

[1]Department of Pharmacy, Maternal and Child Health Hospital of Hubei Province, Wuhan, China
[2]Women and Children's Hospital of Hubei Province, Wuhan, China

Email address:
liwei1988hust@126.com (Wei Li), 1027949621@qq.com (Li Wan)
[*]Corresponding author

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Abstract: *Background*: Chimeric antigen receptors (CARs)-engineered T cells (CAR-T cells) therapy is a promising immunotherapy for leukemia. Encouraged by the world's first adult patient who underwent the clinical trial of CAR-T cells therapy achieved great success, more and more institutions and pharmaceutical companies devoted to the CAR-T R&D. This study aimed at exploring the status and trends of current researches on CAR-T cell therapy through bibliometric analysis. *Methods*: Original publications on CAR-T cell therapy were collected from the Web of Science Core Collection between 2007 and 2019.11.14. Data were analyzed in terms of publication outputs, journals, countries, institutions, authors, co-authorship, co-citation, research hotspots and evolution trends through VOSviewer and CiteSpace. *Results*: A total of 961 publications were identified in the period of 2007 to 2019. *Molecular Therapy* published the highest number of publications, followed by followed by *Blood*, *Clinical Cancer Research* and *Cancer Immunology Research*. The USA, which devoted the largest number of articles and the most extensive cooperation with other countries, was the most leading country in this field. The University of Pennsylvania published the largest number of articles were the most influential institution. June CH was the most productive authors in this field. Maude SL had the most cited article published on *New Engl J Med* in 2014. The hotspots of CAR-T cell therapy research were "CAR", "immunotherapy", "lymphocyte", "antitumor activity" and "leukemia, whereas the major frontier was chronic lymphocytic leukemia. *Conclusion*: This study gives investigators the landscape of CAR-T cell therapy research from the perspective of bibliometrics.

Keywords: CAR-T, Immunotherapy, Bibliometric Analysis, VOSviewer, CiteSpace

1. Introduction

Leukemia is a malignant proliferative disease of hematopoietic stem cells, which will cause more than 0.4 million new cases and 0.3 million related deaths worldwide, estimated by the global cancer statistics 2018 [1, 2]. Currently, chemotherapy [3], radiotherapy [4], targeted therapy [5], differentiation therapy [6], stem cell transplantation [7] and immunotherapy [8] were the major therapeutic methods for this disease. Chimeric antigen receptors (CARs)-engineered T cells (CAR-T cells) therapy, is a promising immunotherapy for leukemia [9]. This novel immunotherapy uses autologous or allogeneic T cells to attack malignant cells [10, 11]. In the past few years, clinical trials from several centers to assess CAR- CAR-T cell therapy for lymphoma have demonstrated encouraging outcomes by targeting CD19, CD20 or CD30 [12-14]. Leukemia patients receiving effective CAR-T cells therapy have more valuable opportunities for subsequent transplantation and finally everlasting remission [15]. Though much progress has been made in this field, the safety of this therapy still remains to be a prime consideration. The occurrence of servere adverse event when using CAR-T cells therapy was reported [16]. To broaden the application of CAR-T cell therapy in the near future, researcher should focus on the overcoming antigen loss relapse and enhancing efficacy and safety [10].

Since the initial development of CARs in 1989, CAR-T cells have evolved into the fourth generation [17]. Existing publications mainly summarized the application of CAR-T cells therapy in preclinical and clinical studies and technologies in CARs design. However, there is no bibliometric analysis on researches in this area. To fill in this research gap, a bibliometric method was used to analyze the original articles on CAR-T cells therapy, hoping to have a comprehensive understanding of current status and trend of this field.

2. Methods

2.1. Data Collection

Data were retrieved from the Web of Science Core Collection (WoSCC) on November 15, 2019 (database updated to November 14, 2019). The search query terms were as follows: TS=(CAR-T cell therapy OR CAR-T therapy OR CAR-T cell immunotherapy) AND Language: (English) AND Document Types: (Article). Time span was set to between 1900 and November 15, 2019.

2.2. Data Extraction

The query retrieved 961 bibliographic records between 2007 and 2019 on November 15, 2019. Chose the full record and cited references option, when downloading data from WoSCC. Tab-delimited file format is recommended for VOSviewer, while plain text file format is for CiteSpace. The bibliographic records, including title, abstract, authors, journals, institutions, countries, keywords, references, WoSCC categories, quartile in category and impact factor (IF) of the journal were extracted.

2.3. Data Analysis

VOSviewer 1.6.13 was used to analyze the journal citation, co-authorship and co-citation network. CiteSpace 5.4 was performed to analyze the co-citation keywords. OriginPro 9.1 was applied to make histograms and line charts. In network visualization, each node represented an item (journal, institution, keyword, etc.), and the size of nodes represented the frequency of occurrence. The distance between two nodes represented the relevance of two items. Nodes adopting different colors in network represented different clusters.

3. Results

3.1. Publication Outputs

961 articles related to CAR-T cell therapy were published between 2007 and 2019. Since the first article was appeared in 2007, the CAR-T related study obtained very slow increase in the following three years. Until 2010, the world's first adult patient who underwent the clinical trial of CAR-T cells therapy achieved great success [18]. Since then, more and more scientists and intensive cooperation started to engage in this field. This led to the first acceleration in the number of publications. The second acceleration appeared in 2018 (Figure 1).

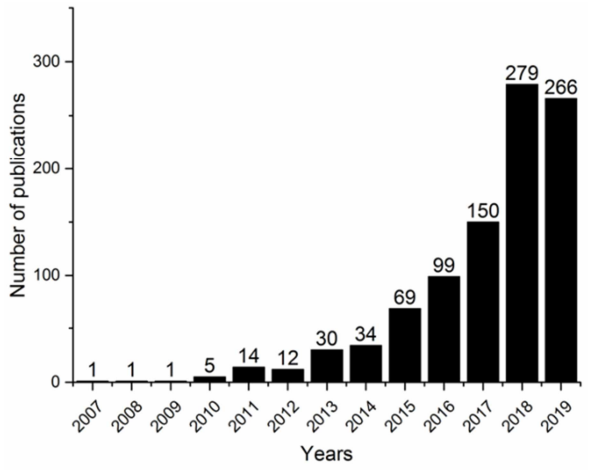

Figure 1. *Annual publications on CAR-T cell therapy research. The annual number of publications continually increased over time.*

3.2. Journal Analysis

The 961 articles in CAR-T research were published in 263 academic journals and 25 categories, including oncology, research experimental medicine, hematology and immunology. Additionally, 142 (53.40%) journals had no more than 2 articles. The top 15 active journals published 365 articles, accounting for 37.98% of the total publications (Table 1), which indicated that study on CAR-T had formed a systematic hierarchy. *Molecular Therapy* published the largest number of articles (IF2018, 8.402; 52 articles, 5.41%), followed by *Blood* (IF2018, 16.562; 40 articles, 4.16%), *Clinical Cancer Research* (IF2018, 8.911; 32 articles, 3.32%) and *Cancer Immunology Research* (IF2018, 8.619; 28 articles, 2.91%). The quartile in category was distributed in Q1 and IF of the journals ranged from 2.776 to 17.161 (excluding *Oncotarget*).

Table 1. *Top 15 active journals on CAR-T related study.*

Rank	Journal	Country	Counts	Percentage (%)	Citescore	IF2018
1	*Molecular Therapy*	USA	*52*	5.41	Q1	8.402
2	*Blood*	USA	*40*	4.16	Q1	16.562
3	*Clinical Cancer Research*	USA	*32*	3.32	Q1	8.911
4	*Cancer Immunology Research*	USA	*28*	2.91	Q1	8.619
5	*Cytotherapy*	Norway	*26*	2.70	Q1	4.297
6	*Oncoimmunology*	USA	*25*	2.60	Q1	5.333
7	*Cancer Research*	USA	*23*	2.39	Q1	8.378
8	*Journal of Hematology & Oncology*	UK	*21*	2.18	Q1	8.731
9	*PLoS One*	USA	*18*	1.87	Q1	2.776

Rank	Journal	Country	Counts	Percentage (%)	Citescore	IF2018
10a	*Frontiers in Immunology*	Switzerland	*17*	1.77	Q1	4.716
10b	*Human Gene Therapy*	USA	*17*	1.77	Q1	3.855
10c	*Journal for Immunotherapy of Cancer*	USA	*17*	1.77	Q1	8.676
10d	*Oncotarget*	USA	*17*	1.77	-	-
10e	*Science Translational Medicine*	*USA*	*17*	*1.77*	*Q1*	*17.161*
11	*Leukemia*	UK	*15*	1.56	Q1	9.944

3.3. Country and Institution Analysis

The 961 articles were contributed by investigators from 50 countries, mainly from the USA, China, Germany, UK, Italy and Japan. The top 10 countries (5 European countries, 2 American countries, 2 Asian countries and 1 Oceania countries) published most of the articles, were influential countries in CAR-T related research. Of the top ten countries, the USA published the highest number of articles and established extensive cooperation with other countries, suggesting its core status in this area (Figure 2 and Table 2). As the only developing country in the top 10 list, China (204 articles) had made noticeably progress in this field. However, the average citations (avg. citations) of China is 10.88 compared to that of the USA (42.93), indicating the quality of publications has yet to be improved.

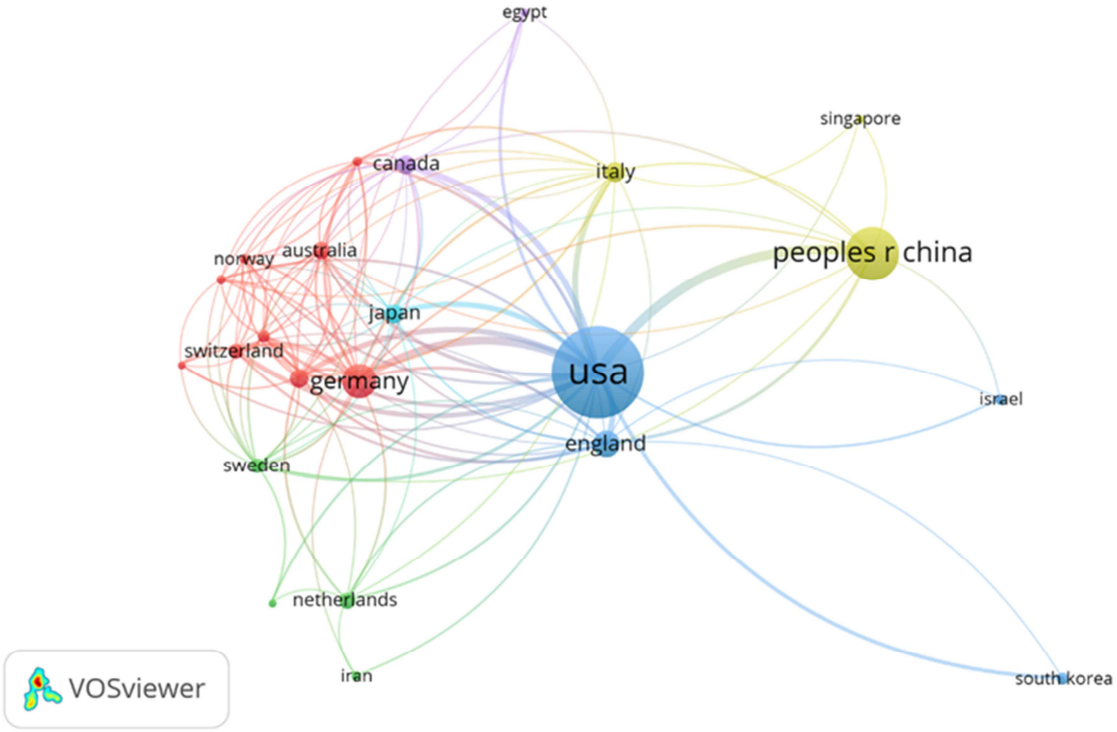

Figure 2. *Country co-authorship network map. The knowledge mapping with the countries as the network node is shown. The size of each circle nodes represents the number of articles published by the country. The link between two nodes represents the relevance of two countries.*

1,096 institutions were engaged in CAR-T related study. The top 10 institutions published 470 of the 961 publications, accounting for 48.91%. University of Pennsylvania (94 articles, USA) ranked the first, followed by Memorial Sloan-Kettering Cancer Center (55 articles, USA) and National Cancer Institute (52 articles, USA) (Table 2). What's more, the top 10 institutions were all from USA, once again proving its leading position in this field.

Table 2. *Ten leading countries and institutions.*

Rank	Country	Frequency	Avg. Citations	Institution (Country)	Frequency	Avg. Citations
1	USA	612	42.93	University of Pennsylvania (USA)	94	76.44
2	China	204	10.88	Memorial Sloan-Kettering Cancer Center (USA)	55	60.73
3	Germany	87	44.59	National Cancer Institute (USA)	52	79.31
4	UK	55	19.78	University of Washington (USA)	50	59.52
5	Italy	30	53.7	University of Texas MD Anderson Cancer Center (USA)	50	88.62
6	Japan	28	35.68	Baylor College of Medicine (USA)	46	60.46
7	France	26	38.81	Fred Hutchinson Cancer Research Center (USA)	39	68.31
8	Canada	25	75.48	Texas Children's Hospital (USA)	37	59.05
9	Australia	24	57.88	Harvard Medical School (USA)	24	12.21
10	Netherlands	19	32.32	Children's Hospital of Philadelphia (USA)	23	113.65

3.4. Author Analysis

These 961 articles were written by 5,842 authors and the average number of co-authors per article was 6.08. The top 20 productive authors ranked by publications were exhibited in Table 3. June CH (USA, 43 articles) took the lead, followed by Dotti G (USA, 30 articles), Cooper LJN (USA, 27 articles) and Jensen MC (USA, 22 articles). June CH, world-renowned expert and pioneer in CAR-T cell therapy, who led his team to design the world's first FDA-approved cell therapy product, Kymriah [19]. The top 20 prolific authors devoted 384 articles (39.96% of the total) to CAR-T research. Of the 20 high-yielding authors, 19 authors were from the USA. Mackall CL (13 articles, 1,877 citations) ranked first with an avg. citations of 144.38, followed by Grupp SA (126.71), June CH (122.12) and Fry TJ (120.80), manifesting their important role in this research direction. June CH (University of Pennsylvania, USA) cooperates with Grupp SA (USA), Cooper LJN (USA), Frey NV (USA) and Zhao YB (USA). Jensen MC (USA), Dotti G (USA), Grupp SA (USA) and Sadelain M (USA) have many collaborators. Overall, the author's partnership is mainly restricted to national authors and the international cooperation remains to be strengthened (see in Figure 3).

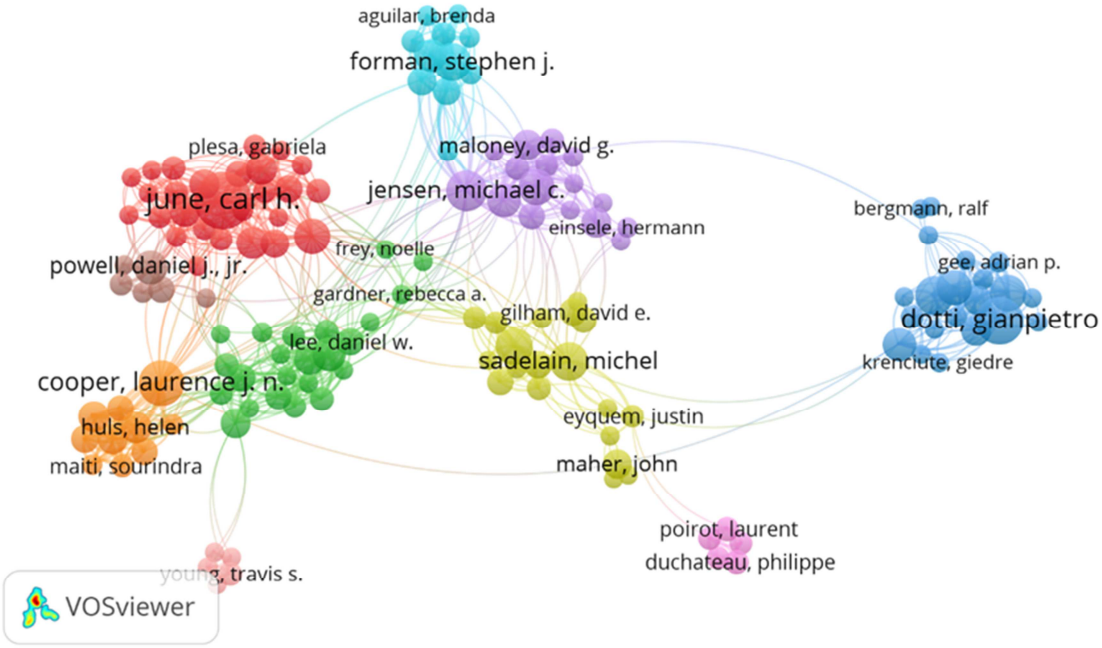

Figure 3. *Author co-authorship network map. The size of each circle node represents the number of articles published by the author. The link between two nodes represents the relevance of two authors. Nodes in different colors represent different clusters.*

Table 3. *Top 20 prolific authors ranked by publication number.*

Rank	Author	Frequency (citation)	Avg. citation	Affiliation	Country
1	June CH	43 (5,251)	122.12	University of Pennsylvania	USA
2	Dotti G	30 (2,193)	73.10	University of North Carolina at Chapel Hill	USA
3	Cooper LJN	27 (1,247)	46.19	University of Texas MD Anderson Cancer Center	USA
4	Jensen MC	22 (1,997)	90.77	University of Washington	USA
5a	Brenner MK	20 (1,874)	93.70	Houston Methodist Hospital	USA
5b	Forman SJ	20 (822)	41.10	Beckman Research Institute at City of Hope National Medical Center	USA
5c	Sadelain M	20 (1,575)	78.75	Memorial Sloan-Kettering Cancer Center	USA
6	Brentjens RJ	18 (1,043)	57.94	Memorial Sloan-Kettering Cancer Center	USA
7a	Grupp SA	17 (2,154)	126.71	Children's Hospital of Philadelphia	USA
7b	Riddell SR	17 (1,989)	117.00	Fred Hutchinson Cancer Research Center	USA
7c	Savoldo B	17 (1,722)	101.29	University of North Carolina at Chapel Hill	USA
8a	Abken H	16 (462)	28.88	University of Regensburg	Germany
8b	Rooney CM	16 (1,660)	103.75	Texas Children's Hospital	USA
9a	Fry TJ	15 (1,812)	120.80	Children's Hospital Colorado	USA
9b	Gottschalk S	15 (383)	25.53	Jude Children's Research Hospital	USA
9c	Powell DJ Jr	15 (998)	66.53	University of Pennsylvania	USA
9d	Turtle CJ	15 (1,491)	99.40	Fred Hutchinson Cancer Research Center	USA
10a	Brown CE	14 (770)	55.00	Beckman Research Institute of City of Hope	USA
10b	Maus MV	14 (754)	53.86	Massachusetts General Hospital	USA
11	Mackall CL	13 (1,877)	144.38	Stanford University School of Medicine	USA

3.5. Cited Authors and References Co-citation Analysis

Co-citation analysis was effective in uncovering the relationship and structure of journals, authors and articles in academic community [20]. As shown in Figure 4, the top 237 authors were presented in the cited authors co-citation network. Kochenderfer JN (725 citations) ranked the first, followed by Maude SL (607 citations), Brentjens RJ (495 citations), Lee DW (421 citations), Porter DL (429), Turtle CJ (335), Grupp SA (331), Davila ML (326), Morgan RA (255), Kalos M (251), Sadelain M (228), Neelapu SS (202), Rosenberg SA (177), Brudno JN (161), Gattinoni L (149), Savoldo B (149), Park JH (143), Lamers CHJ (143), Kershaw MH (142) and Long AH (140). The largest node in the co-citation network was Kochenderfer JN, revealing his bellwether role in CAR-T research (Figure 4). Kochenderfer JN, came from National Cancer Institute, first reported that donor-derived allogeneic anti-CD19-CAR T cells could cause regressions of relapsed malignancies after allogeneic transplantation in 2013 [11]. Furthermore, Rosenberg SA (red cluster), chief of surgery at the National Cancer Institute, provided key technologies in the research of the second FDA-approved CAR-T product named Yescarta. In Figure 4, authors who focused on a similar field and had close collaboration with other partners were assigned into one of the four colored clusters.

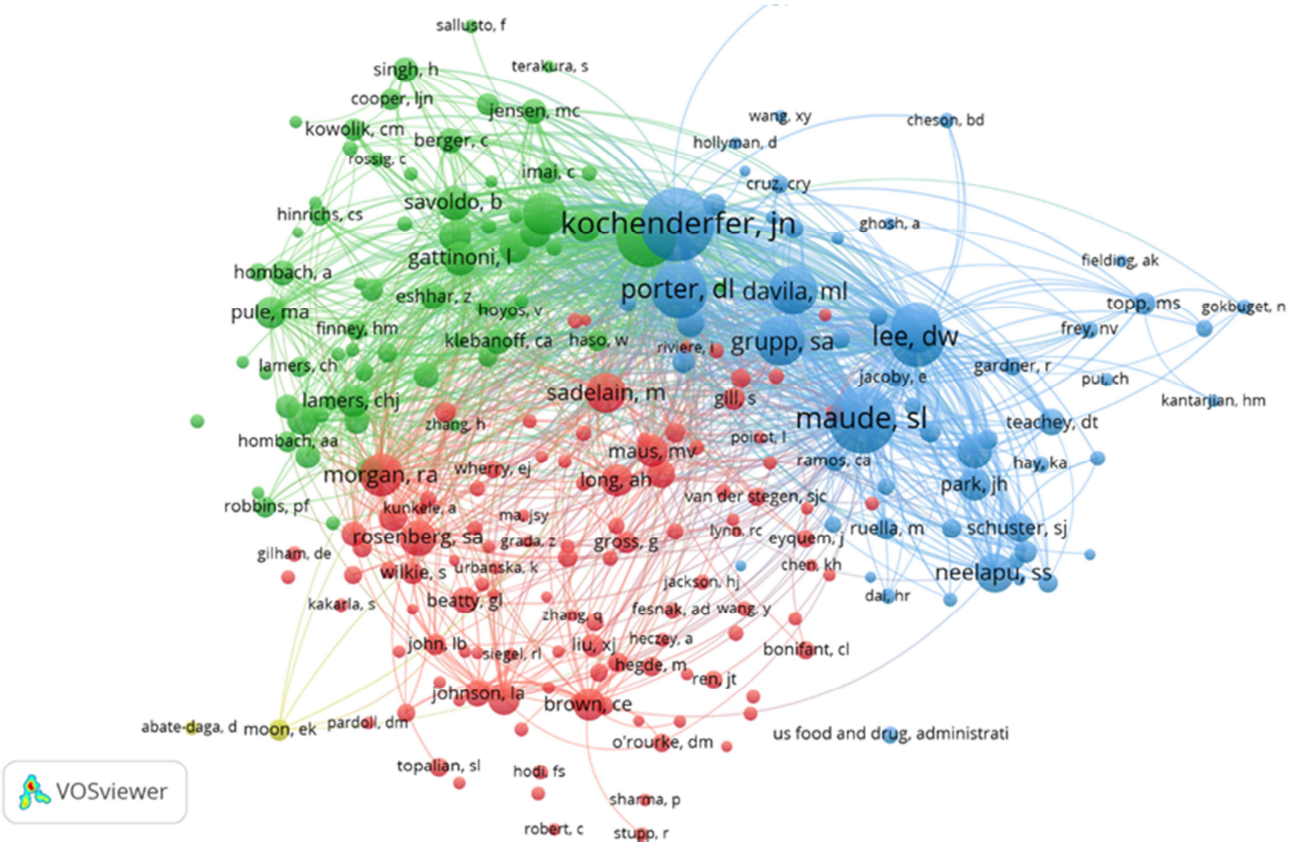

Figure 4. *Cited author co-citation network map. The size of each circle node represents the number of articles published by the cited author. The link between two nodes represents the relevance of two cited authors. Nodes in different colors represent different clusters.*

Cited references co-citation analysis is an important method to explore the structure and evolution path of a specific field [21]. The cited references co-citation knowledge map was composed of 21,539 publications with 224 nodes and 19,142 connection lines (Figure 5). The biggest blue node is Maude SL, who comes from Children's Hospital of Philadelphia. Her article titled "Chimeric Antigen Receptor T Cells for Sustained Remissions in Leukemia" published in *New Engl J Med* proposed that autologous anti-CD19-CAR T cells were effective in treating refractory and relapsed acute lymphoblastic leukemia (ALL) [22]. This article was cited 366 times all together in these 961 CAR-T related literature and was cited 1,773 times in WoSCC. These top 20 cited references covering clinic trials for treatment of leukemia, CAR-T technologies, case report and safety and effectiveness evaluation, were the intellectual bases in CAR-T research (Table 4 and Figure 5).

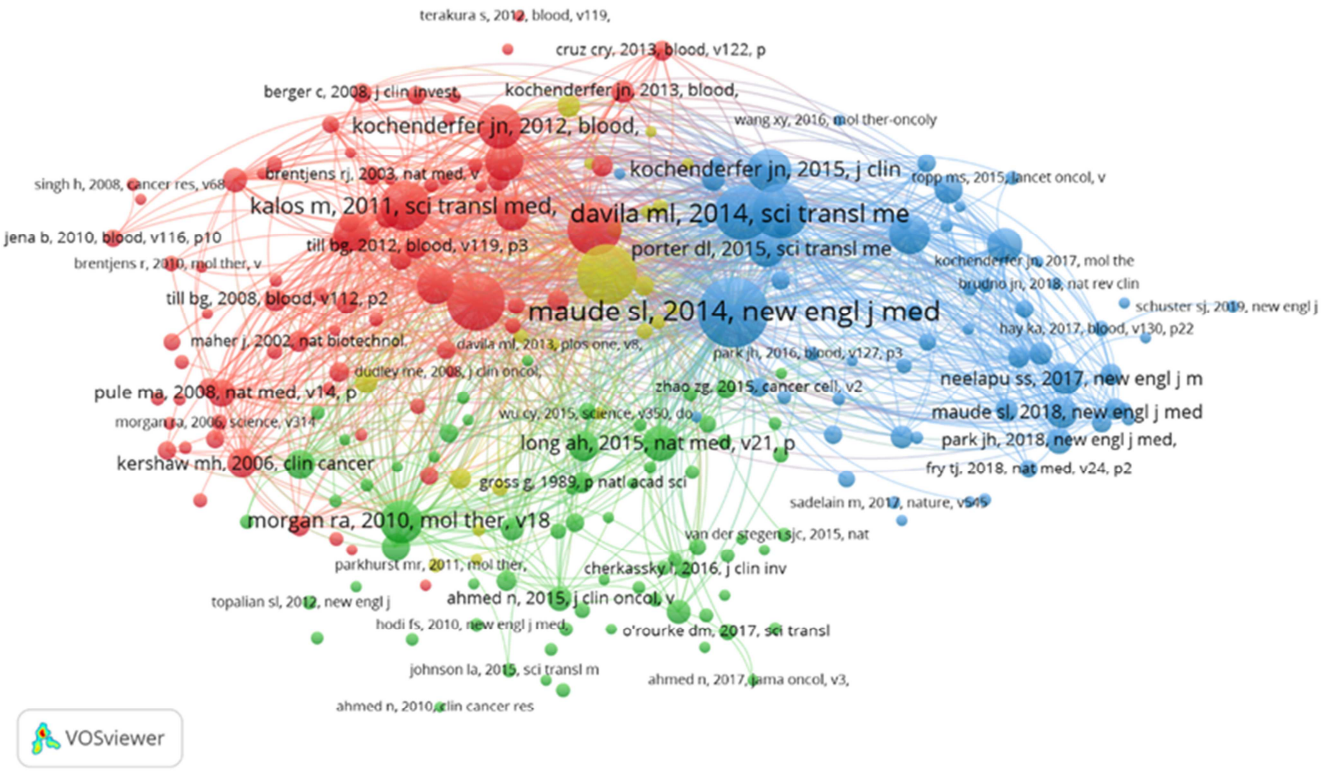

Figure 5. *Cited reference co-citation network map. The link between two nodes represents the relevance of two cited reference. Nodes in different colors represent different clusters.*

Table 4. *Top 20 cited references in CAR-T research.*

Rank	Cited references	Citations	Citations in WoSCC
1	Maude SL, 2014, *New Engl J Med*, V371, P1507, DOI: 10.1056/nejmoa1407222	366	1,773
2	Grupp SA, 2013, *New Engl J Med*, V368, P1509, DOI: 10.1056/nejmoa1215134	283	1,576
3	Porter DL, 2011, *New Engl J Med*, V365, P725, DOI: 10.1056/nejmoa1103849	273	1,799
4	Davila ML, 2014, *Sci Transl Med*, V6, DOI: 10.1126/scitranslmed.3008226	253	998
5	Lee DW, 2015, *Lancet*, V385, P517, DOI: 10.1016/s0140-6736(14)61403-3	253	1,033
6	Brentjens RJ, 2013, *Sci Transl Med*, V5, DOI: 10.1126/scitranslmed.3005930	243	1,004
7	Kalos M, 2011, *Sci Transl Med*, V3, DOI: 10.1126/scitranslmed.3002842	207	1,123
8	Kochenderfer JN, 2012, *Blood*, V119, P2709, DOI: 10.1182/blood-2011-10-384388	176	792
9	Kochenderfer JN, 2015, *J Clin Oncol*, V33, P540, DOI: 10.1200/jco.2014.56.2025	173	701
10	Morgan RA, 2010, *Mol Ther*, V18, P843, DOI: 10.1038/mt.2010.24	162	1,034
11	Turtle CJ, 2016, *J Clin Invest*, V126, P2123, DOI: 10.1172/Jci85309	154	481
12	Brentjens RJ, 2011, *Blood*, V118, P4817, DOI: 10.1182/blood-2011-04-348540	139	665
13	Savoldo B, 2011, *J Clin Invest*, V121, P1822, DOI: 10.1172/jci46110	131	541
14	Milone MC, 2009, *Mol Ther*, V17, P1453, DOI: 10.1038/mt.2009.83	131	500
15	Porter DL, 2015, *Sci Transl Med*, V7, DOI: 10.1126/scitranslmed.aac5415	125	536
16	Long AH, 2015, *Nat Med*, V21, P581, DOI: 10.1038/nm.3838	125	338
17	Lee DW, 2014, *Blood*, V124, P188, DOI: 10.1182/blood-2014-05-552729	122	573
18	Kochenderfer JN, 2010, *Blood*, V116, P4099, DOI: 10.1182/blood-2010-04-281931	117	638
19	Neelapu SS, 2017, *New Engl J Med*, V377, P2531, DOI: 10.1056/nejmoa1707447	109	496
20	Maude SL, 2018, *New Engl J Med*, V378, P439, DOI: 10.1056/nejmoa1709866	102	476

3.6. Keywords Co-occurrence Analysis and New Research Frontiers

Keywords with high frequency and centrality represent research hotspots during a period of time, whereas burst keywords reveal new research frontiers [23]. The higher frequency and stronger centrality value of keywords reflected the more important of its role in the field [24]. Among the 2,981 keywords extracted from the 961 publications, the top 5 high-frequency keywords were “chimeric antigen receptor”, “immunotherapy”, “lymphocyte”, “antitumor activity” and “leukemia” (Table 5). The top 10 keywords with the strongest citation burst represent new research frontiers were exhibited in Table 6. The burst keywords were relatively concentrated in

the 2010-2015 interval, which witnessed the booming development of studies in CAR-T cells therapy. Of the 10 strongest citation burst keywords, the keyword "chronic lymphocytic leukemia (CLL)", with a longest burst duration of six years, was the major frontier in this field.

Table 5. *The top 20 co-occurrence keywords.*

Rank	Keyword	Counts	Centrality	Rank	Keyword	Counts	Centrality
1	chimeric antigen receptor	287	0.16	11	in vivo	95	0.06
2	immunotherapy	286	0.14	12	T cell	88	0.14
3	therapy	250	0.17	13	remission	86	0.04
4	expression	163	0.08	14	acute lymphoblastic leukemia	86	0.12
5	cancer	155	0.12	15	lymphoma	85	0.06
6	lymphocyte	151	0.14	16	leukemia	81	0.14
7	adoptive immunotherapy	131	0.09	17	persistence	78	0.11
8	antitumor activity	129	0.17	18	CD19	72	0.06
9	B cell	115	0.04	19	CAR-T cell	71	0.05
10	activation	103	0.06	20	receptor	71	0.01

Table 6. *Top 10 keywords with the strongest citation bursts.*

Keyword	Year	Strength	Begin	End	2007-2019
adoptive immunotherapy	2007	11.77	2010	2014	
lymphocyte	2007	4.77	2010	2012	
growth	2007	2.86	2010	2014	
chronic lymphocytic leukemia	2007	5.53	2011	2016	
cancer regression	2007	4.85	2011	2015	
metastatic melanoma	2007	3.88	2011	2015	
CD28 costimulation	2007	3.63	2011	2013	
adverse event	2007	5.91	2012	2014	
persistence	2007	5.71	2012	2015	
ovarian cancer	2007	4.83	2012	2015	

4. Discussion

Immunotherapy is another revolutionary breakthrough after surgery, chemoradiotherapy and targeted therapy. 2017 is a great year of global immunotherapy, and also a CAR-T year, which has witnessed the approval of two CAR-T cancer immunotherapy drugs [19, 25]. Behind its success is the continuous investment of research and development funds, technology and researchers. Those successful cases light up the hope for CAR-T immunotherapy. All those above might account for the second rapid publication growth in 2018.

Among the top 15 journals, 9 (60%) journals, including *Science Translational Medicine* (IF2018, 17.161), *Blood* (IF2018, 16.562) and *Leukemia* (IF2018, 9.944) had an IF greater than 8.000. Those journals with an IF more than 8.000 focus their research areas on hematology and oncology. And they were core journals in the research field of CAR-T cells therapy.

The top 10 countries (5 European countries, 2 American countries, 2 Asian countries and 1 Oceania countries) published most of the articles. The USA contributed to 612 publications (63.68% of the total), reflecting its leading role in CAR-T cells therapy area. There were many reasons account for this phenomenon. Firstly, the USA is the world's most advanced economy with numerous world-leading scientific research institutes, researchers and pharmaceutical companies. Secondly, the higher incidence of leukemia in Europe and USA forced researchers to pay more attention to this field [26]. Data showed that, up to Nov 30, 2019, a total of 439 clinical trials were testing CAR-T cells (clinicaltrials.gov, search term "chimeric antigen receptor"). China with a total number of 201 clinical trials is now the most active area of clinical research for CAR T cells. The USA and Europe occupies the second and third position with a trial number of 189 and 35, respectively. The number of clinical trials, to some degree, is the reflection of scientific prowess in CAR-T cell therapy.

Five of the top 20 prolific authors were included in the top 20 cited author list, with regard to the co-citation counts. Puzzlingly, June CH, who led the initial development of CAR-T treatment, was not in the top cited authors list in this analysis. This probably because research in this field was still in the initial stage.

Keywords are the author's generalization and refinement of the article content. Keywords with higher centrality and frequency were "chimeric antigen receptor", "immunotherapy", "lymphocyte", "antitumor activity" and "leukemia", suggesting that hotspots represented by these keywords are at the core of CAR-T cell therapy research. To date, a large number of chimeric antigen receptors targeting CD19, CD20, CD22 [15], CD30, GPC3 [27] and BCMA [28] were designed and entered in clinical trials. CAR-T cell therapy has made promising progress in hematological oncology. However, this success has yet to be applied to solid tumors, and the reasons for this are being widely investigated. Firstly, solid tumors present barriers that are absent in

hematologic cancers. CAR T cells have to surmount difficulties to traffic successfully from blood into solid tumor site. Secondly, how to smoothly infiltrate the stromal elements of solid tumors is another challenge [29]. Thirdly, immunosuppressive tumor microenvironment is also a challenge and much work remains to be done [30]. Lastly, the potential immunogenicity and toxicity of CAR T cells cannot be ignored. Given those challenges, the following direction of CAR-T cell therapy is to solve those confusing puzzles.

5. Conclusion

From 2007 to 2019, the number of CAR-T cell therapy related publications increased year by year. *Molecular Therapy* published the highest number of publications, followed by followed by *Blood*, *Clinical Cancer Research* and *Cancer Immunology Research*. The USA, which devoted the largest number of articles and the most extensive cooperation with other countries, was the most leading country in this field. The University of Pennsylvania published the largest number of articles were the most influential institution. June CH was the most productive authors, who led his team to design the world's first FDA-approved cell therapy product. Maude SL had the most cited article published on *New Engl J Med* in 2014. The hotspots of CAR-T cell therapy research were “CAR”, “immunotherapy”, “lymphocyte”, “antitumor activity” and “leukemia, whereas the major frontier was CLL. In summary, this study gives investigators the landscape of CAR-T cell therapy research from the perspective of bibliometrics.

Conflict of Interest Statement

The authors declare that they have no competing interests.

Author’s Contribution

Wei Li collected the data and analyzed, written the initial draft and revised it. Li Wan was the project leadership and designed the work.

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References

[1] F. Bray, J. Ferlay, I. Soerjomataram et al., "Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries," *CA Cancer J Clin*, vol. 68, no. 6, pp. 394-424, 2018.

[2] M. Greaves, "Leukaemia 'firsts' in cancer research and treatment," *Nature Reviews Cancer*, vol. 16, no. 3, pp. 163-172, 2016.

[3] C. Saygin and H. E. Carraway, "Emerging therapies for acute myeloid leukemia," *Journal of Hematology & Oncology*, vol. 10, no. 1, pp. 93, 2017.

[4] C. N. Simone, J. C. Morris, D. M. Stewart et al., "Radiation therapy for the management of patients with HTLV-1-associated adult T-cell leukemia/lymphoma," *Blood*, vol. 120, no. 9, pp. 1816-1819, 2012.

[5] B. J. Druker, "Perspectives on the development of imatinib and the future of cancer research," *Nature Medicine*, vol. 15, no. 10, pp. 1149-1152, 2009.

[6] Z. Y. Wang and Z. Chen, "Acute promyelocytic leukemia: from highly fatal to highly curable," *Blood*, vol. 111, no. 5, pp. 2505-2515, 2008.

[7] J. J. Cornelissen and D. Blaise, "Hematopoietic stem cell transplantation for patients with AML in first complete remission," *Blood*, vol. 127, no. 1, pp. 62-70, 2016.

[8] D. O. Acheampong, C. K. Adokoh, D. B. Asante et al., "Immunotherapy for acute myeloid leukemia (AML): a potent alternative therapy," *Biomedicine & Pharmacotherapy*, vol. 97, pp. 225-232, 2018.

[9] R. A. Gardner, O. Finney, C. Annesley et al., "Intent-to-treat leukemia remission by CD19 CAR T cells of defined formulation and dose in children and young adults," *Blood*, vol. 129, no. 25, pp. 3322-3331, 2017.

[10] Z. Wang, Z. Wu, Y. Liu, W. Han, "New development in CAR-T cell therapy," *Journal of Hematology & Oncology*, vol. 10, no. 1, pp. 53, 2017.

[11] J. N. Kochenderfer, M. E. Dudley, R. O. Carpenter et al., "Donor-derived CD19-targeted T cells cause regression of malignancy persisting after allogeneic hematopoietic stem cell transplantation," *Blood*, vol. 122, no. 25, pp. 4129-4139, 2013.

[12] B. Cai, M. Guo, Y. Wang et al., "Co-infusion of haplo-identical CD19-chimeric antigen receptor T cells and stem cells achieved full donor engraftment in refractory acute lymphoblastic leukemia," *Journal of Hematology & Oncology*, vol. 9, no. 1, pp. 131, 2016.

[13] W. Y. Zhang, Y. Wang, Y. L. Guo et al., "Treatment of CD20-directed chimeric antigen receptor-modified t cells in patients with relapsed or refractory B-cell non-hodgkin lymphoma: an early phase IIa trial report," *Signal Transduct Target Ther*, vol. 1, pp. 16002, 2016.

[14] C. M. Wang, Z. Q. Wu, Y. Wang et al., "Autologous T cells expressing CD30 chimeric antigen receptors for relapsed or refractory hodgkin lymphoma: an open-label phase I trial," *Clinical Cancer Research*, vol. 23, no. 5, pp. 1156-1166, 2017.

[15] J. Pan, Q. Niu, B. Deng et al., "CD22 CAR T-cell therapy in refractory or relapsed B acute lymphoblastic leukemia," Leukemia, vol. 33, no. 12, pp. 2854-2866, 2019.

[16] R. A. Morgan, J. C. Yang, M. Kitano et al., "Case report of a serious adverse event following the administration of T cells transduced with a chimeric antigen receptor recognizing ERBB2," *Molecular Therapy*, vol. 18, no. 4, pp. 843-851, 2010.

[17] G. Gross, T. Waks, Z. Eshhar, "Expression of immunoglobulin-T-cell receptor chimeric molecules as functional receptors with antibody-type specificity," *Proc Natl Acad Sci U S A*, vol. 86, no. 24, pp. 10024-10028, 1989.

[18] D. L. Porter, B. L. Levine, M. Kalos et al., "Chimeric antigen receptor- modified T cells in chronic lymphoid leukemia," *N Engl J Med*, vol. 365, no. 8, pp. 725-733, 2011.

[19] V. Prasad, "Immunotherapy: Tisagenlecleucel - the first approved CAR-T-cell therapy: implications for payers and policy makers," *Nature Reviews Clinical Oncology*, vol. 15, no. 1, pp. 11-12, 2018.

[20] H. Small, "Co-citation in the scientific literature: a new measure of the relationship between two documents," *J Am Soc Inf Sci*, vol. 24, pp. 265-269, 1973.

[21] H. Liao, M. Tang, L. Luo, C. Li, F. Chiclana, X. Zeng, "A Bibliometric Analysis and Visualization of Medical Big Data Research," Sustainability, vol. 10, no. 2, pp. 166, 2018.

[22] S. L. Maude, N. Frey, P. A. Shaw et al., "Chimeric antigen receptor t cells for sustained remissions in leukemia," *N Engl J Med*, vol. 371, no. 16, pp. 1507-1517, 2014.

[23] C. Chen, "CiteSpace II: detecting and visualizing emerging trends and transient patterns in scientific literature," *J Am Soc Inf Sci Technol*, vol. 57, no. 3, pp. 359-377, 2006.

[24] Y. Hong, Q. Yao, Y. Yang et al., "Knowledge structure and theme trends analysis on general practitioner research: a co-word perspective," *BMC Family Practice*, vol. 17, pp. 10, 2016.

[25] S. S. Neelapu, F. L. Locke, N. L. Bartlett et al., "Axicabtagene ciloleucel CAR T- cell therapy in refractory large B- cell lymphoma," *N Engl J Med*, vol. 377, no. 26, pp. 2531-2544, 2017.

[26] S. Yang, J. Li, R. P. Gale, X. Huang, "The mystery of chronic lymphocytic leukemia (CLL): why is it absent in Asians and what does this tell us about etiology, pathogenesis and biology," *Blood Reviews*, vol. 29, no. 3, pp. 205-213, 2015.

[27] Z. Jiang, X. Jiang, S. Chen et al., "Anti-GPC3-CAR T cells suppress the growth of tumor cells in patient-derived xenografts of hepatocellular carcinoma," *Frontiers in Immunology*, vol. 7, pp. 690, 2016.

[28] X. Yao, S. Zhu, J. Huang et al., "Developing a novel anti-bcma CAR-T for relapsed or refractory multiple myeloma," *Blood*, vol. 134, no. supplement_1, pp. 50, 2019.

[29] U. Anurathapan, A. M. Leen, M. K. Brenner, J. F. Vera, "Engineered T cells for cancer treatment," *Cytotherapy*, vol. 16, no. 6, pp. 713-733, 2014.

[30] K. Newick, S. O'Brien, E. Moon, S. M. Albelda, "CAR T cell therapy for solid tumors," *Annual Review of Medicine*, vol. 68, no. 1, pp. 139-152, 2017.