

# A bibliometric analysis of publications on venous thromboembolism in children from 1988 to 2019

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## Abstract

**Introduction:** Venous thromboembolism (VTE) in children not only imposes a heavy burden on the medical resources and economy of the society, but also seriously affects the growth and development of children, even threaten children's lives. A large number of publications have been performed in this field in recent years. In this bibliometric analysis, publications on VTE in children were examined and analyzed to explain the present research hotspots.

**Methods:** Articles related to VTE in children published in the PubMed database from 1988 to June 18, 2019 were selected as the research sample. BICOMB software was used to retrieve the annual publications, journals, journal source countries and the high-frequency major medical subject headings (MeSH) terms on the articles. Then, the co-word matrix was constructed by BICOMB using the selected high-frequency MeSH terms. Next, gCLUTO software was used to analyze the matrix by double clustering and visual analysis in a strategy of hotspot identification. In addition, CiteSpace software was used to perform the knowledge map of co-authors to explore the core authors.

**Results:** One thousand seven hundred seventy-nine articles on VTE in children were obtained. Seven hundred ninety academic journals distributed in 58 countries have published articles on VTE in children, and the developed countries and the United States were the major force in the journal source countries. Nowak-Göttl U occupied an important position in this field. We constructed a co-word matrix composing of 37 high-frequency MeSH terms, generated visual matrix and visual hill, and classified the hot-spots into 5 aspects based on 8 categories.

**Conclusion:** The results show that the research trend of children's VTE has been increasing gradually, and the sound achievement has been obtained in these hotspots in relation to the area of inherited thrombophilia, prevention and control, treatment, diagnosis, prevalence, risk factors, and complication study. However, there is a lack of communication and cooperation in this field, and the gap of national and regional research results is huge. To sum up, this study provides evidence and guidance for researchers, clinicians, and educators.

**Abbreviations:** ACCP = American College of Chest Physicians, BICOMB = Bibliographic Item Co-Occurrence Matrix Builder, CVAD = central venous access device, CVC = central venous catheter, DVT = deep venous thrombosis, ICU = Intensive Care Unit, IF = impact factor, IPC = intermittent pneumatic compression, IT = inherited thrombophilia, LMWH = low molecular weight Heparin, LOS = length of stay, MeSH = major medical subject headings, MJI = Manco Johnson Instrument, MRV = magnetic resonance Venography, MV score = modified Villalta score, PE = pulmonary embolism, PTS = post-thrombotic syndrome, RAM = risk assessment model, VTE = venous thromboembolism.

**Keywords:** bibliometric analysis, children, venous thromboembolic diseases, VTE

Editor: Vasile Valeriu Lupu.

This study was supported by the Hospital Management Research Fund of Xiangya Hospital, Central South University (No. 2016GL08), the Xiangya clinical big data system construction project of Central South University (No. 2013096) and Chinese Nursing Association (No. ZHKY201606).

The authors have no conflicts of interest to disclose.

Ethics approval and consent to participate: Not applicable.

Data availability statement: Data will be made available on request.

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How to cite this article: Tian L, Zhang Y, Zeng J, Wang L, Gao H, Su Y, Li Y. A bibliometric analysis of publications on venous thromboembolism in children from 1988 to 2019. *Medicine* 2020;99:20(e20114).

Received: 6 September 2019 / Received in final form: 25 January 2020 / Accepted: 3 April 2020

<http://dx.doi.org/10.1097/MD.00000000000020114>

## 1. Introduction

Venous thromboembolism (VTE), including pulmonary embolism (PE) and deep vein thrombosis (DVT), has been increased significantly over the past 20 years in children.<sup>[1]</sup> A multicenter study conducted in the United States from 2001 to 2007 showed that the diagnostic rate of VTE in children increased by 70%, that is, 58 out of 10,000 hospitalized children (0.58%) had VTE.<sup>[2]</sup> This increase may be due to the advance in VTE diagnosis, successful medical or surgical interventions in childhood diseases such as premature infants, malignant neoplasms and congenital heart disease and the increasing use of central venous access device (CVAD).<sup>[3–5]</sup>

VTE in pediatric patients has a serious impact in terms of economic burden and disease progression. A child's VTE can cost nearly \$30,000, increase the average length of hospital stay by about 8 days, and increase the number of outpatient follow-up visits.<sup>[6–8]</sup> At the same time, 50% of children with VTE had no thrombus subsidence, the recurrence rate of VTE was 8%, and more than one third of children with VTE had the complication of post-thrombotic syndrome (PTS). The mortality rate of VTE in children was 2%, and even in pediatric patients with PE, the mortality rate increased to 9%.<sup>[9–14]</sup> Therefore, more and more medical personnel and scientific researchers have participated in the frontier of VTE in children with sound research results, including prevalence, etiology and pathogenesis, diagnosis, prevention and control, drug treatment, thrombolytic therapy, and complications on VTE in children. These studies have made important contributions and provided meaningful guidance for the clinical decision-making of VTE in children.

Bibliometrics is a set of special research methods that quantify documents, words, authors, citations, and co-citations through mathematical and statistical techniques.<sup>[15,16]</sup> In this study, co-word analysis was used to estimate the co-occurrence, frequency of two words in the same article, then cluster analysis was carried out to reflect the relationship between the words, and then the structure and changes of the subjects or themes represented by these words were analyzed.<sup>[17]</sup> In this way, the information related to the authors, journals, journal source countries, and the major medical subject headings (MeSH) terms was traced in these articles, and the content, characteristics, internal relations and scientific structure of children's VTE publications were summarized. This study aimed to analyze the literature published in the PubMed database on VTE in children and provided evidence and guidance in this field for researchers, clinicians, and educators.

## 2. Materials and methods

### 2.1. Search strategy

This study retrieved the literature from PubMed. Data retrieval strategy included the following contents: #1 “Pulmonary Embolism” [Majr] OR “Venous Thromboembolism” [Majr] OR VTE [Text Word] OR DVT [Text Word] OR PTE [Text Word] OR PE [Text Word] OR Venous Thromboembolism [Title/Abstract] OR Pulmonary Embolism [Title/Abstract] OR deep vein thrombosis [Title/Abstract] OR Venous thrombosis [Title/Abstract] and #2 (“Child” [Majr] OR “Adolescent” [Majr] OR “Infant, Newborn” [Majr] OR “Pediatrics” [Majr] OR Child [Title/Abstract] OR Adolescent [Title/Abstract] OR Infant [Title/Abstract] OR neonatal [Title/Abstract] OR youth [Title/Abstract] OR Pediatrics [Title/Abstract] OR children [Title/Abstract], and #3 “1988/01/01” [Date-Publication]: “2019/06/18” [Date-Publication]. The scope of literature selection was limited to the

clinical trial, review, meta-analysis, observational study, randomized controlled trial, systematic reviews, case reports, clinical study, and multicenter study. In addition, there was no language restriction in this study.

### 2.2. Data and analysis

In this study, Bibliographic Item Co-Occurrence Matrix Builder (BICOMB) developed by the department of information management and information systems (medical science) of China Medical University was used to analyze the year of publication, journal, journal source country, and the MeSH terms.<sup>[18]</sup> Due to the length of the article, only the high-frequency MeSH terms with frequency ( $\geq 15$ ) were selected in this study.

The co-word matrix was constructed by BICOMB using the selected high-frequency MeSH terms, and the co-word matrix was imported into gCLUTO 1.0 software, a graphical cluster toolkit developed by Rasmussen and Karypis at the University of Minnesota.<sup>[19]</sup> Graph clustering method was used to perform the double clustering analysis on the co-word matrix, in which cosine was taken as similarity function and I2 as standard function. In order to determine the optimal number of clusters, the different number of clusters was selected to repeat graph clustering analysis.<sup>[20]</sup> The minimum average similarity between classes (ESim) and the maximum average similarity within classes (ISim) were used as optimization results. Then, the double aggregation was further visualized to generate the visual matrix and the visual hill.

CiteSpace (5.5.R2,64 bit) software was used to perform the knowledge map of co-authors to explore the core authors. In the knowledge map, the node represents the author. The size of the node reflects the number of publications, and the larger the node, the higher the number of publications. The lines between nodes represent the co-occurrence relationship between authors, and their thickness indicates the strength of co-occurrence. In addition, the centrality is an index to measure the importance of nodes in the network. If value of centrality is  $> 0.1$ , there is an important position of the node in the network. The purple circle is the key marker in the knowledge map. If there is a purple circle, it means that the centrality of the node is not  $< 0.1$ .<sup>[21]</sup> These indexes were used to measure and identify the importance of co-authors in this field.

## 3. Results

### 3.1. Analysis of annual publications

A total of 1779 articles on VTE in children were obtained. Table 1 and Figure 1 showed the publication trend in the past 31 years from 1988 to 2019. In general, the publication trend has increased from 1988 to 2018. There were 14 publications in 1988, and the number of publications reached 149 in 2018. In this study, PubMed was only retrieved before June in 2019, and the number of papers has reached 57 in the first half of 2019. From 1988 to 2002, no more than 36 papers were published each year, showing a slow increase generally. From 2003 to 2009, the annual publication trend continued to grow, but the number of papers was no more than 66 per year. However, from 2013 to 2018, the annual number of papers increased significantly, reaching to 149 in 2018.

### 3.2. Analysis of journals and journal source countries

In total, 790 academic journals have published articles on VTE in children. Among the top 11 journals (Table 2), the journal of

**Table 1**  
**Distribution of annual publications related to VTE in children during 1988 to 2019.**

Rank	Year	Publications	Percent	Cumulative percent
1	1991	10	0.56	0.56
2	1988	14	0.79	1.35
3	1990	17	1.00	2.35
4	1992	18	1.01	3.36
5	1995	20	1.12	4.48
6	1989	23	1.29	5.77
7	1997	23	1.29	7.06
8	1996	24	1.35	8.41
9	1993	25	1.41	9.82
10	1999	28	1.57	11.39
11	2000	28	1.57	12.96
12	1994	28	1.57	14.53
13	1998	29	1.63	16.16
14	2002	36	2.02	18.18
15	2001	36	2.02	20.20
16	2004	39	2.19	22.39
17	2005	45	2.53	24.92
18	2003	53	2.98	27.90
19	2007	56	3.15	31.05
20	2019	57	3.20	34.25
21	2008	62	3.49	37.74
22	2006	65	3.65	41.39
23	2009	66	3.71	45.10
24	2010	71	3.99	49.09
25	2011	74	4.16	53.25
26	2012	93	5.23	58.48
27	2013	105	5.90	64.38
28	2014	105	5.90	70.28
29	2015	123	6.91	77.19
30	2016	127	7.14	84.33
31	2017	130	7.31	91.64
32	2018	149	8.38	100.00

thrombosis research (impact factor [IF] 2018,3.27;Q2 [journal partition based on Clarivate Analytics journal citation report]) contributed to the largest number of publications (34 publications, 1.91%), followed by Pediatric emergency care

(IF2018,1.12,Q3; 26 publications, 1.46%). Archives de pediatrie: organe officiel de la Societe francaise de pediatrie (IF2018,0.36,Q4; 24 publications, 1.35%), and seminars in thrombosis and hemostasis (IF2018,1.29,Q2; 23 publications, 1.29%).

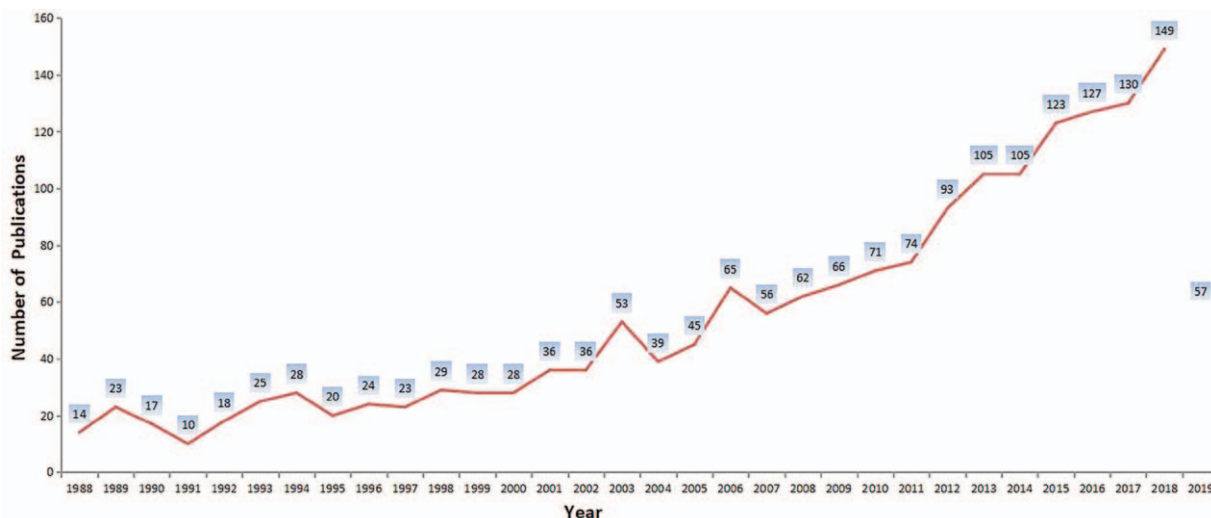
A total of 58 journal source countries have published articles on VTE in children. Among the top 15 countries (Table 3), the United States contributed to the largest number of publications (736 publications, 41.37%), followed by England (362 publications, 20.35%), and Germany (129 publications, 7.25%).

**3.3. Analysis of co-authors**

Table 4 and Figure 2 showed the top 10 co-authors based on the value of centrality involving VTE in children. There were 215 nodes and 510 links in the co-author map generated by CiteSpace software (Fig. 2), and Nowak-Göttl U ranked the first, followed by Goldenberg NA, Male C and Mitchell L based on the value of centrality (Table 4) and the co-author knowledge map based on the centrality (Fig. 2). None of the co-author’s centrality value is >0.1 (Table 4), and none of the nodes representing the co-authors in the co-author knowledge map is marked with a purple circle (Fig. 2). The larger the node (representing the co-author), the larger the publication. Therefore, Nowak-Göttl U and Goldenberg NA published more articles in the field of children’s VTE due to the larger nodes.

**3.4. Analysis of co-word matrix and double clustering of MeSH terms**

In this study, some synonyms were combined to obtain 3099 effective MeSH terms, in which 37 MeSH terms have appeared for no <15 times (Table 5). The results of double clustering of high-frequency MeSH terms were visualized to obtain the visual matrix (Fig. 3) and the visual hill (Fig. 4). In the visual matrix, the black horizontal lines separated these MeSH terms into eight categories. The figures in Table 6 were cluster number, such as 1 represented cluster 1. Combining with the results of Table 6, the similarity of Cluster 1 was the highest (ISim=0.704, ESim=0.112), indicating that the consistency of high MeSH terms was



**Figure 1.** Distribution of annual publications related to VTE in children during 1988 to 2019. Fifty-seven represents the number of articles published in PubMed database from January 1, 2019 to June 18, 2019.

**Table 2****Top 11 journals according to the number of publications related to VTE in children.**

Rank	Journal	Country	Publications	Percent	IF 2018	JCR partition
1	Thrombosis research	England	34	1.91	3.27	Q2
2	Pediatric emergency care	USA	26	1.46	1.12	Q3
3	Archives de pediatrie: organe officiel de la Societe francaise de pediatrie	France	24	1.35	0.36	Q4
4	Seminars in thrombosis and hemostasis	USA	23	1.29	3.40	Q2
5	The Journal of pediatrics	USA	22	1.23	3.74	Q1
6	Pediatric blood and cancer	USA	22	1.23	2.49	Q1
7	Journal of pediatric surgery	USA	19	1.07	2.09	Q2
8	Blood	USA	18	1.01	16.56	Q1
9	Pediatric nephrology	Germany	18	1.01	2.82	Q1
10	Journal of thrombosis and haemostasis: JTH	USA	18	1.01	4.66	Q1
11	Journal of pediatric hematology/oncology	England	18	1.01	8.73	Q1

the highest. Followed by cluster 3 (ISim=0.623, ESIm=0.097), cluster 5 (ISim=0.617, ESIm=0.024) and cluster 0 (ISim=0.616, ESIm=0.104). In the visual hill, the shape of each hill was a gauss curve, which represented a rough estimate of the data distribution within each category. The volume was proportional to the number of objects and the height of the hill was proportional to the similarity within the category. The visual hill also showed that the research on the children's VTE in this study was divided into eight categories. Moreover, the peak of cluster 1 in the visual hill had the highest density, suggesting the highest internal similarity, the minimum standard deviation within the class, the best clustering effect and the high degree of concentration. According to the visual matrix, the clustering results of MeSH terms were analyzed in Table 6.

#### 4. Discussion

According to our study, it is found that the research on VTE in children correlates with the number of annual publication, increasing from 14 articles in 1988 to 149 articles in 2018. There were two key points for the increasing number of children's VTE papers. From 1995 to 2011, the annual circulation increased gradually, from 20 in 1995 to 74 in 2011. From 2012 to 2018, annual circulation continued to rise, reaching to 149 in 2018. This may be due to the first and latest publication of the American

College of Chest Physicians (ACCP) guidelines on children's VTE treatment in 1995 and 2012,<sup>[22]</sup> which stimulated the increase of papers in the field of VTE in children to some extent. Besides, American Society of Hematology 2018 Guidelines for management of VTE: treatment of pediatric VTE<sup>[23]</sup> has been issued, which may further stimulate the in-depth and extensive research in the field of VTE in children in the future. In addition, an increase in the number of indexed journals in the PubMed database may also lead to an increase in the number of publications. Although the annual research volume of children's VTE is increasing, it should be noted that the overall research progress in this field is still slow.<sup>[22]</sup>

According to the top 11 journals, the journals with IF >3.00 contributed to 7.46% (IF >10.00, 1.01%; 10.00 ≥ IF > 5.00, 1.01%; 5.00 ≥ IF > 3.00, 5.44%) of the total number of publications. Through journal partition based on Clarivate Analytics journal citation report, it is found that except 2 journals are in Q3 and Q4, the other 9 journals are in and above Q2. At present, some journals published in articles on children's VTE are of relatively high quality, which is not difficult to find. However, publishing studies related to VTE in children in journals with high IF, such as >10, is really challenging.

The top 15 journal source countries who engaged in the field of VTE in children, contributed to 1647 publications, accounting for 92.57% of the total publications. Among them, the number of publications issued by 2 developing countries including India and China is 47 (2.64%), and except for the above 2 countries, the rest of 1600 publications are issued by developed countries, accounting for 89.93%. It indicates that the developed countries are far more involved than the developing countries in the study field of VTE in children, and there is a big gap between them. In

**Table 3****Top 15 journal source countries according to the number of publications related to VTE in children.**

Rank	Country	Publications	Percent	Cumulative percent
1	United States	736	41.37	41.37
2	England	362	20.35	61.72
3	Germany	129	7.25	68.97
4	France	92	5.17	74.14
5	Switzerland	70	3.93	78.07
6	Netherlands	61	3.43	81.50
7	Italy	33	1.86	83.36
8	India	32	1.80	85.16
9	Australia	28	1.57	86.73
10	Spain	24	1.35	88.08
11	Japan	21	1.18	89.26
12	Denmark	18	1.01	90.27
13	China	15	0.84	91.11
14	New Zealand	14	0.79	91.90
15	Ireland	12	0.67	92.57

**Table 4****Top 10 co-authors according to centrality related to VTE in children.**

Rank	Co-authors	Centrality	Country
1	Nowak-Göttl U	0.04	Germany
2	Goldenberg NA	0.03	USA
3	Male C	0.03	Germany
4	Mitchell L	0.03	Canada
5	Kenet G	0.02	Israel
6	Andrew M	0.02	Canada
7	Marzinotto V	0.02	Canada
8	van Ommen CH	0.01	Netherlands
9	Warren P	0.01	USA
10	Tarango C	0.01	USA

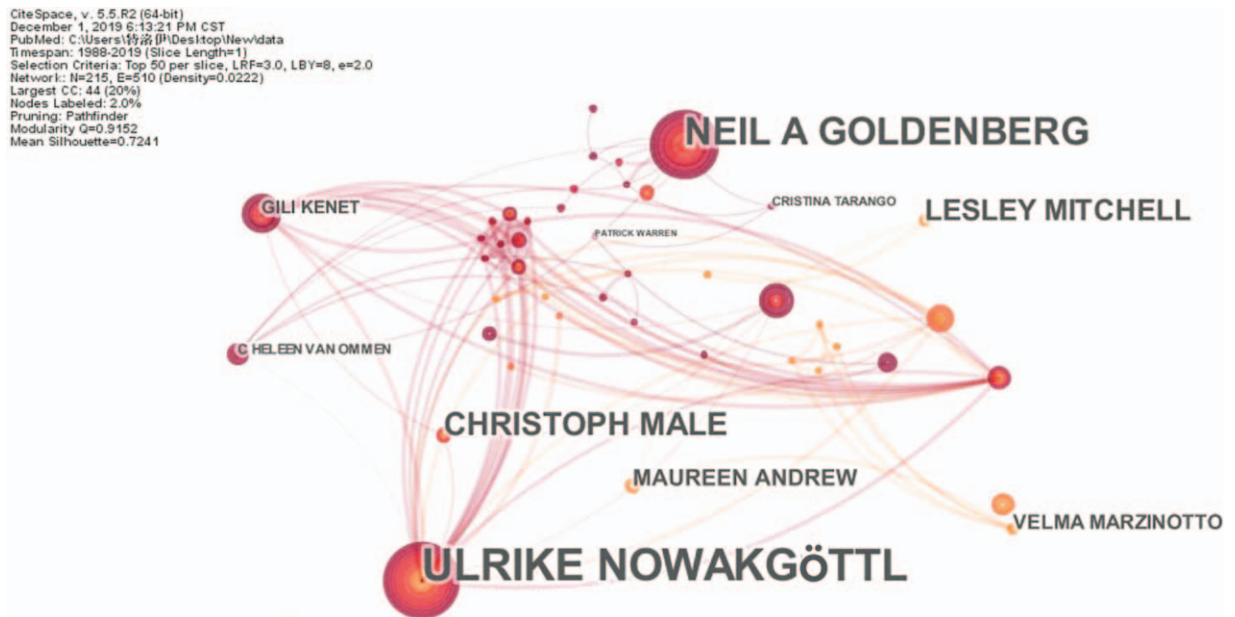


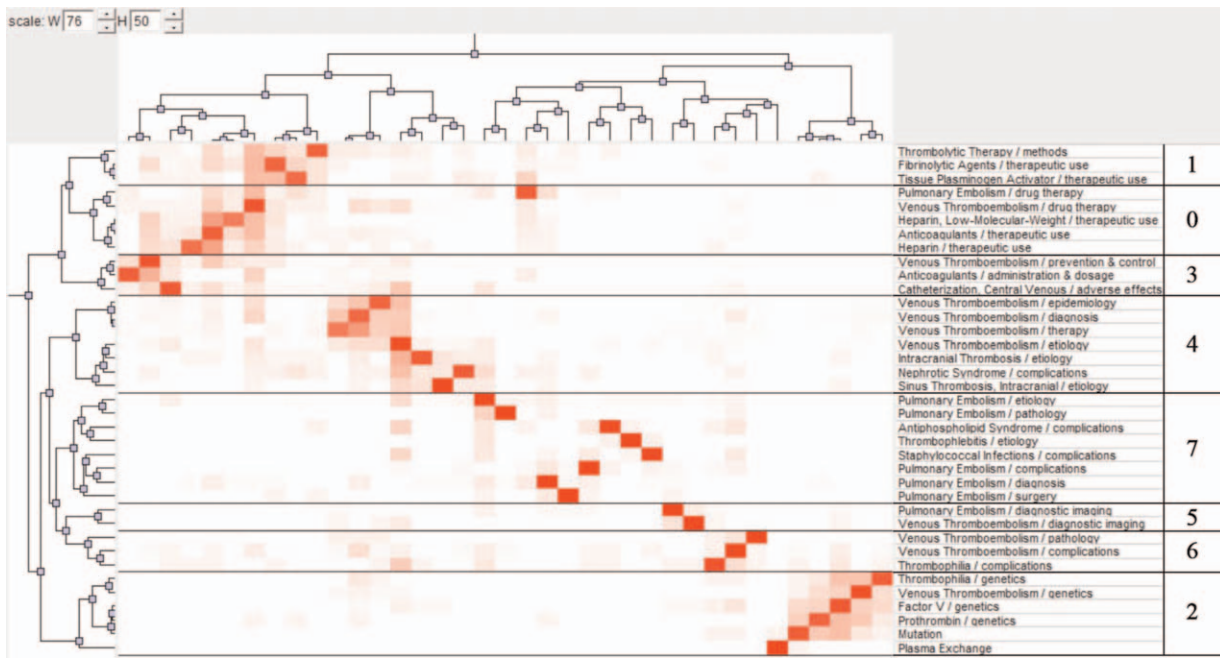
Figure 2. Map of co-authors performing studies related to VTE in children.

Table 5

High frequency (n ≥ 15) MeSH terms related to VTE in children.

Rank	Major MeSH terms	Frequency	Percent	Cumulative percent
1	Venous thromboembolism/etiology	149	2.42	2.42
2	Venous thromboembolism/drug therapy	110	1.78	4.20
3	Venous thromboembolism/diagnosis	79	1.28	5.48
4	Anticoagulants/therapeutic use	75	1.22	6.70
5	Pulmonary embolism/etiology	73	1.18	7.88
6	Venous thromboembolism/epidemiology	68	1.10	8.98
7	Venous thromboembolism/prevention and control	59	0.96	9.94
8	Pulmonary embolism/diagnosis	51	0.83	10.77
9	Venous thromboembolism/complications	49	0.79	11.56
10	Venous Thromboembolism / therapy	41	0.66	12.22
11	Catheterization, central venous/adverse effects	38	0.62	12.84
12	Pulmonary embolism/complications	34	0.55	13.39
13	Venous thromboembolism/genetics	33	0.53	13.92
14	Pulmonary embolism/diagnostic imaging	32	0.52	14.44
15	Fibrinolytic agents/therapeutic use	31	0.50	14.94
16	Factor V/genetics	29	0.47	15.41
17	Pulmonary embolism/drug therapy	28	0.45	15.86
18	Heparin, low-molecular-weight/therapeutic use	22	0.36	16.22
19	Anticoagulants/administration and dosage	22	0.36	16.58
20	Intracranial thrombosis/etiology	21	0.34	16.92
21	Venous thromboembolism/diagnostic imaging	21	0.34	17.26
22	Sinus thrombosis, intracranial/etiology	20	0.32	17.58
23	Thrombolytic therapy/methods	19	0.31	17.89
24	Staphylococcal infections/complications	19	0.31	18.20
25	Pulmonary embolism/surgery	18	0.29	18.49
26	Plasma exchange	18	0.29	18.78
27	Tissue plasminogen Activator / therapeutic use	18	0.29	19.07
28	Thrombophilia/complications	17	0.28	19.35
29	Antiphospholipid syndrome/complications	17	0.28	19.63
30	Prothrombin/genetics	17	0.28	19.91
31	Heparin/therapeutic use	17	0.28	20.19
32	Pulmonary embolism/pathology	17	0.28	20.47
33	Thrombophlebitis/etiology	16	0.26	20.73
34	Thrombophilia/genetics	16	0.26	20.99
35	Nephrotic syndrome/complications	15	0.24	21.23
36	Venous thromboembolism/pathology	15	0.24	21.47
37	Mutation	15	0.24	21.71

MeSH= major medical subject headings.



**Figure 3.** Visualized matrix of biclustering of highly frequent major MeSH terms on VTE in children. The number in the figure represents the cluster group, for example, 0 represents cluster 0.

the future, developing countries need to increase their research efforts to facilitate the international research exchanges in order to enhance its international influence in the field of children VTE. Moreover, the number of publications issued by 3 Asian countries including China, India, and Japan is 68 (3.88%); the number of publications issued by 9 Europe countries including England, Germany, France, Switzerland, Netherlands, Italy, Spain, Denmark, and Ireland is 585 (46.82%); the number of publications issued by 2 Oceania countries including Australia and New Zealand is 42 (2.36%) and by 1 North America country, namely the United States, is 736 (41.37%). It has been reported that DVT and PE are considered rare in Asian population compared with Caucasians.<sup>[24]</sup> The above results illustrate that the United States, which accounts for almost one-half of the total publications, has proved to be a major force in

this field. To sum up, there are two reasons for the research gap of VTE incidence in children:

1. the difference of regional incidence of VTE; and
2. the higher the level of national scientific research, the more the related journals with the more international influence.

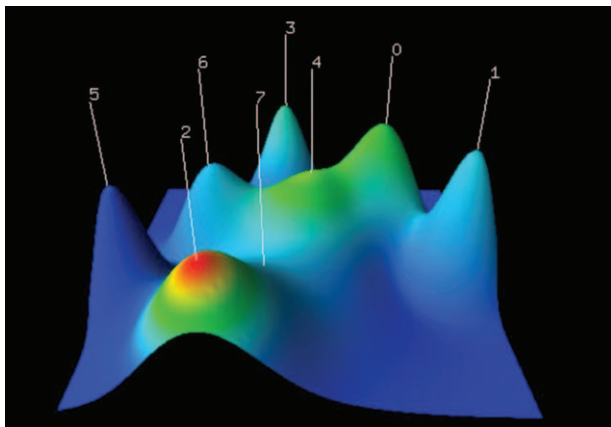
Therefore, more academic resources should be promoted for developed countries and the United States to do relevant research in the field of VTE in children, and more opportunities should be established to publish and display these research results.

Through knowledge map, information about potential collaborators was obtained to seek cooperation with other researchers. As a co-author, Nowak-Göttl U who is from Germany and mainly engaged in the research of incidence, influencing factors, prevention and treatment, etiology on VTE in children, ranked the first with the centrality value of 0.04. Even though her centrality result is <0.1, it is still believed that she is an active and professional researcher in this field, owing to the close cooperation between research teams centered on her. In other words, she is the core member of influential research teams. In addition, it is found that none of the centrality value >0.1, indicating that many authors did not collaborate closely in this field. The lack of communication and cooperation is not conducive to promoting researchers' mutual learning and progress in the field of VTE in children.

In this study, eight clusters were obtained by means of double clustering analysis of co-word matrix of high-frequency MeSH terms (≥15). Based on the clustering results, the following research hotspots were summarized in this field:

#### 4.1. Inherited thrombophilia study of VTE in children based on cluster 2.

Inherited thrombophilia (IT) refers to the tendency of VTE in the case of hypercoagulability caused by genetic traits, such as



**Figure 4.** Visualized hill of biclustering of highly frequent major MeSH terms on VTE in children. The number in the figure represents the cluster group, for example, 0 represents cluster 0.

**Table 6****Data results of double cluster analysis of highly frequent major MeSH terms on VTE in children.**

Cluster	Clustering results of MeSH terms	Size	ISim	ISdev	ESim	ESdev
0	Pulmonary embolism/drug therapy, venous thromboembolism/drug therapy, heparin, low-molecular-weight/therapeutic use, anticoagulants/therapeutic use, heparin/therapeutic use	5	0.616	0.072	0.104	0.027
1	Thrombolytic therapy/methods, fibrinolytic agents/therapeutic use, tissue plasminogen activator/therapeutic use	3	0.704	0.033	0.112	0.011
2	Thrombophilia/genetics, venous thromboembolism/genetics, factor V / genetics, prothrombin/genetics, mutation, plasma exchange	6	0.453	0.133	0.021	0.014
3	Venous thromboembolism/prevention and control, anticoagulants/administration and dosage, catheterization, central venous/adverse effects	3	0.623	0.047	0.097	0.033
4	Venous thromboembolism/epidemiology, venous thromboembolism/diagnosis, venous thromboembolism/therapy, venous thromboembolism/etiology, intracranial thrombosis/etiology, nephrotic syndrome/complications, sinus thrombosis, intracranial/etiology	7	0.445	0.081	0.085	0.025
5	Pulmonary embolism/diagnostic imaging, venous thromboembolism/diagnostic imaging	2	0.617	0.000	0.024	0.005
6	Venous thromboembolism/pathology, venous thromboembolism/complications, thrombophilia/complications	3	0.462	0.020	0.069	0.045
7	Pulmonary embolism/etiology, pulmonary embolism/pathology, antiphospholipid syndrome/complications, thrombophlebitis/etiology, staphylococcal infections/complications, pulmonary embolism/complications, pulmonary embolism/diagnosis, pulmonary embolism/surgery	8	0.205	0.026	0.037	0.026

ESdev=standard deviation of similarity between classes, ESim=average similarity between classes, ISdev=standard deviation of average similarity within classes, ISim=average similarity within classes, MeSH=major medical subject headings.

mutations of factor 2 (F2: rs1799963) and factor 5 (F5: rs6025), and the deficiency of antithrombin, protein S, and protein C.<sup>[25,26]</sup> The studies mainly concentrated on the following two points: the impact of IT on the formation of VTE in children; can children with VTE or offspring of thrombophilic families benefit from IT testing? Studies have shown that IT plays an important role in VTE in children. With the occurrence of more than two genetic traits, the risk of VTE is further increased; however, the extent of this effect may be affected by specific pediatric subgroups (e.g., first episode and recurrent VTE, induced and non-induced VTE), in which other risk factors may play a more important role, such as the presence of central venous catheter (CVC) or potential medical conditions.<sup>[27–29]</sup> Study have shown that IT test should be performed in patients with non-induced VTE, recurrent VTE, and those with a strong family history of VTE. However, the benefits of IT test are less clear for other pediatric patients.<sup>[28]</sup>

#### 4.2. Prevention and control study of VTE in children based on cluster 3

Studies have shown that early activity,<sup>[30]</sup> mechanical prevention including intermittent pneumatic compression (IPC) and graduated compression stockings, and pharmacologic prophylaxis are the main prevention strategies for VTE in children.<sup>[9]</sup> For the pharmacologic prophylaxis, even recommendations for therapeutic ranges are low molecular weight heparin (LMWH) anti-Xa 0.1 to 0.3 U/mL or warfarin INR1.3 to 1.9 from the 2012 Chest guidelines.<sup>[31]</sup> There are still limited studies on the efficacy and safety of anticoagulants in preventing VTE in pediatric patients. Preventive LMWH is reported to have a risk of bleeding of 0.8% in massive bleeding and 3% in minor bleeding.<sup>[32]</sup> Therefore, in order to effectively balance the risks and benefits of

preventive measures, the risk assessment model (RAM) is suggested to be used to stratify VTE risks.<sup>[33]</sup>

#### 4.3. Treatment study of VTE in children based on clusters 0 and 1

Early identification and diagnosis of VTE can ensure timely treatment and adequate anticoagulation to reduce the harms associated with VTE. The purpose of anticoagulation is to prevent clot proliferation and embolism, maintain vascular access, and prevent bacteremia.<sup>[34]</sup> The most commonly used treatment for DVT in children is LMWH, which provides several potential benefits, including fewer changes by other concurrent drugs, predictable pharmacokinetics and minimal monitoring comparing with heparin and warfarin.<sup>[31,35]</sup> Thrombolysis which is given systemically or via a catheter-directed approach is a more aggressive treatment for the management of DVT.<sup>[36]</sup> High- and low-dose systemic thrombolytic regimens have been established in children, usually with anticoagulation and close monitoring of bleeding at the same time.<sup>[37,38]</sup> Tissue plasminogen activator (alteplase) is a major thrombolytic agent for thrombolysis, and study have showed that thrombolysis is more effective in preventing PTS than in anticoagulation.<sup>[39]</sup>

#### 4.4. Diagnosis study of VTE in children based on clusters 4 and 5

It mainly involves laboratory and imaging diagnosis research. In laboratory diagnosis, a lot of researches have been performed on d-dimer, and study have indicated that d-dimer has not been proven to diagnose VTE in pediatric clinical trials, but a recurrence risk.<sup>[40]</sup> When VTE is suspected, the imaging method is chosen depending on the location of the thrombosis.

Historically, venography has been the gold standard, which is very useful in assessing limbs or thoracoabdominal areas. Recently, magnetic resonance venography (MRV) and computed tomography venography have replaced traditional venography as the main imaging tool for abdomen and chest. In addition, MRV is the preferred method for the diagnosis of cerebral sinus venous thrombosis.<sup>[36]</sup>

#### 4.5. Prevalence, risk factors, and complication study of VTE in children based on clusters 3, 4, 6, and 7

At present, although many studies around the world have reported the incidence of children's VTE, there is still no consensus on the prevalence of children's VTE. The results of children's VTE incidence vary greatly from 0.00% to 77.78%,<sup>[41,42]</sup> owing to the different research subjects, design, sample size, and data collection time in each study. Risk factors for VTE in children include multiple genetic and acquired factors. Acquired factors mainly include certain diseases, their corresponding treatments and individual risk factors. Risk factors associated with the disease include premature delivery, inflammatory diseases, trauma (especially severe trauma of lower limb or pelvic fractures), cancer diagnosis, dehydration, poor perfusion, decreased mobility, and severe infection.<sup>[33]</sup> Treatment-related risk factors include CVAD (which is considered as the most important risk factor), intensive care unit (ICU) admission, surgery, parenteral nutrition, chemotherapy (such as steroid or asparaginase use), length of stay (LOS), blood transfusion, intubation, mechanical ventilation, estrogen-containing hormone therapy (such as oral contraceptives), and inotropic support.<sup>[3,11,43]</sup> Individual risk factors include age and obesity.<sup>[11]</sup> PTS is the most common complication of VTE. At present, the reported results of the incidence of children's PTS are quite different.<sup>[44,45]</sup> The incidence of children's PTS varies from 10% to 60%, mainly depending on the different tools for the incidence assessment of PTS.<sup>[46]</sup> The modified Villalta (MV) score and the Manco Johnson Instrument (MJI) are the two most commonly used tools.<sup>[47]</sup> It should be noted that the differences of scores given by different tools are mainly attributed to subjective symptoms rather than objective signs.<sup>[22]</sup>

However, our study still has some limitations. First, PubMed was chosen as the only data source in this study, and there may be limitations in the research results. Therefore, in the follow-up research, retrieval method should be adopted in multi-database to avoid the data limitation. Moreover, the inclusion and exclusion criteria of literature are not strictly given in this study. If bibliometrics and co-word analysis include reviews and clinical trial articles, these materials may contain repetitive studies. If reviewing articles are excluded and clinical trials are only included, some research hotspots may be lost. These limitations need to be addressed and improved in future studies.

## 5. Conclusion

In this study, the development trend of children's VTE in recent 31 years is summarized and analyzed to illustrate the research hotspots of this field. It is found that the research trend of children's VTE has been increasing gradually, indicating that the problem of VTE in children has aroused the concern. The research results in these hotspots were obtained regarding the area of IT, prevention and control, treatment, diagnosis, prevalence, risk factors, and complication study of VTE in

children. However, communication and cooperation in this field is lacked with the huge gap of national and regional research.

## Author contributions

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