Characteristics of the study of pharmacological interventions for the management of type A hemophilia A in pediatrics: bibliometric analysis

Características del estudio de intervenciones farmacológicas para el manejo de la hemofilia tipo A en pediatría: análisis bibliométrico

DOI: https://dx.doi.org/10.17981/ingecuc.21.2.2025.01
Artículo de Investigación Científica. Fecha de Recepción: 17/01/2025, Fecha de Aceptación: 06/06/2025.

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To cite this paper
L. Manrique-Rubio, A. Unigarro-Sánchez, D. Echeverry-Guerrero, L. Roa-Hernández, A. García-Divantoque, K. Celis-Canelón, R. Maya-Acevedo, H. Rodriguez-Cruz & J. Orozco-Chinome "Characteristics of the study of pharmacological interventions for the management of type A hemophilia A in pediatrics: bibliometric analysis," INGE CUC, vol. 21, no. 2, 2025. DOI: https://dx.doi.org/10.17981/ingecuc.21.2.2025.01

Abstract

Introduction: Hemophilia A in pediatrics is a topic of interest due to the catastrophic, out-of-pocket, and health costs it generates, in addition to the disease burden it causes. Recently, the need to identify novel therapies has been emphasized.
Objective: To evaluate the characteristics of research on pharmacological interventions for the management of hemophilia A in pediatrics.
Method: Bibliometric study. A semi-structured search was conducted in the Scopus database.
Results: A total of 363 articles were included. The first publication was in 1964. Predominantly, the scientific output consisted of original articles (87.32%; n=317), followed by reviews (6.1%; n=22). International collaboration was 7.98%. The University Medical Center Utrecht (Netherlands) was the most prolific and impactful institution, while the United States was the most prolific and impactful country. The most frequently used keywords were blood coagulation factor 8, intravenous drug administration, and hemarthrosis. The co-occurrence network revealed three research niches related to therapy, age groups, and specific outcomes.
Conclusions: A modest growth in research on pharmacological interventions for the management of hemophilia A in pediatrics was identified. The research has been based on primary data, led by Dutch institutions and in Japan, despite the United States being the most prolific country. The most frequently studied topics are related to pathophysiology, coagulation factor VIII, complications, and hemarthrosis.

Keyword: Hemophilia A, Therapeutics, Pediatrics, Biomedical Research, Bibliometrics.

Resumen

Introducción: La hemofilia tipo A en pediatría es un tema de interés, debido al costo de bolsillo, catastrófico y de salud que genera, además de la carga de enfermedad que ocasiona. En tiempos recientes, se ha impulsado la necesidad de identificar terapias novedosas.
Objetivo: Valorar las características de la investigación sobre intervenciones farmacológicas para el manejo de la hemofilia tipo A en pediatría.
Método: Estudio bibliométrico. Se realizó una búsqueda semi-estructurada en la base de datos Scopus.
Resultados: Se incluyeron 363 artículos. La primera publicación fue realizada en 1964. Predominantemente, la producción científica estuvo compuesta por artículos originales (87,32%; n=317), seguido de revisiones (6,1%; n=22). La colaboración internacional fue del 7,98%. El Centro Médico Universitario de Utrecht (Países Bajos) se posicionó como la institución más prolífica y con mayor impacto, mientras que Estados Unidos fue el país más prolífico y con mayor impacto. El factor de coagulación sanguínea 8, administración de drogas intravenosas, y hemartrosis, han sido las palabras claves más usadas. La red de coocurrencia, reveló tres nichos de investigación, relacionados a terapia, grupos etarios y desenlaces específicos.
Conclusión: Se identificó un crecimiento modesto de la investigación sobre intervenciones farmacológicas para el manejo de la hemofilia tipo A en pediatría. La investigación ha sido a expensas de datos primarios, siendo liderada por instituciones holandesas y en Japón, a pesar de ser Estados Unidos el país más prolífico. Los temas estudiados con mayor frecuencia, están relacionados a la fisiopatología, el factor VIII de la coagulación, complicaciones, y la hemartrosis.

Palabras clave: Hemofilia A, Terapéutica, Pediatría, Investigación Biomédica, Bibliometría.

INTRODUCTION

Hemophilia A is an acquired hematological disorder resulting from the loss of immune tolerance to autologous factor VIII [1]. This condition is often associated with a significant number of complications or states of systemic hyperactivity, including malignancies, autoimmunity, pregnancy, infections, or even reactions to certain medications [1]. It is recognized as a condition that imposes a substantial disease burden, particularly in children [2,3]. This is due to its profound impact on family functionality, as affected children become highly dependent, leading to catastrophic out-of-pocket expenses and elevated healthcare costs [2].

Establishing an effective therapeutic regimen for hemophilia A is complex, requiring the evaluation of numerous factors. First-line therapy typically involves the use of immunosuppressants and bypassing agents [4,5]. However, the high cost of these treatments often limits timely access, resulting in exacerbations and complications that may necessitate hospitalization [6]. Currently, various scientific organizations and research groups have prioritized basic and clinical research into hemophilia A, aiming to identify novel therapeutic targets with higher efficacy [4, 5, 6].

Despite these efforts, the global analysis and characterization of research on hemophilia A in pediatric populations remain underexplored. This gap hinders the identification of research priorities and the assessment of the relevance of ongoing medical investigations. To address this need, the objective of this study was to describe the characteristics of research on pharmacological interventions for the management of hemophilia A in pediatric patients.

METHODS

This cross-sectional bibliometric study used Scopus as the data source. Scopus was chosen because it serves both as an indexing database for peer-reviewed literature and as a citation index, making it a reliable tool for this type of research, as demonstrated in previous studies [7,8].

To identify the relevant evidence, a search strategy was developed using keywords derived from the Health Sciences Descriptors (DeCS) and their synonyms in both English and Spanish. These keywords were related to “Pharmacological Intervention,” “Hemophilia A,” and “Pediatrics.” Inclusion criteria required the selection of any article available in full text, provided its objective was directly related to pharmacological interventions for hemophilia A in pediatric populations. Errata and conference abstracts were excluded. Following a pilot test, the following search query was finalized: TITLE-ABS-KEY(“Hemophilia A”) OR TITLE-ABS-KEY(“Hemophilia As”) OR TITLE-ABS-KEY(“Hemophilia”) OR TITLE-ABS-KEY(“Congenital Hemophilia A”) OR TITLE-ABS-KEY(“Congenital Hemophilia As”) OR TITLE-ABS-KEY(“Classic Hemophilia”) OR TITLE-ABS-KEY(“Classic Hemophilias”) OR TITLE-ABS-KEY(“Haemophilia”) OR TITLE-ABS-KEY(“Autosomal Hemophilia A”) OR TITLE-ABS-KEY(“Autosomal Hemophilia As”) OR TITLE-ABS-KEY(“Factor VIII Deficiency”) OR TITLE-ABS-KEY(“Congenital Factor 8 Deficiency”) OR TITLE-ABS-KEY(“Congenital Factor VIII Deficiency”) AND TITLE-ABS-KEY(“Drug Therapy”) OR TITLE-ABS-KEY(“Drug Therapies”) OR TITLE-ABS-KEY(Chemotherapy) OR TITLE-ABS-KEY(Chemotherapies) OR TITLE-ABS-KEY(Pharmacotherapy) OR TITLE-ABS-KEY(Pharmacotherapies) AND TITLE-ABS-KEY(Infant) OR TITLE-ABS-KEY(“Preschool Child”) OR TITLE-ABS-KEY(“Preschool Children”) OR TITLE-ABS-KEY(Child) OR TITLE-ABS-KEY(Adolescent) OR TITLE-ABS-KEY(Adolescents) OR TITLE-ABS-KEY(Adolescence) OR TITLE-ABS-KEY(Teens) OR TITLE-ABS-KEY(Teen) OR TITLE-ABS-KEY(Teenagers) OR TITLE-ABS-KEY(Teenager) OR TITLE-ABS-KEY(Youth) OR TITLE-ABS-KEY(Youths).

Once the results were obtained, the metadata was exported in .csv format for a manual review of titles and abstracts by the authors. This step ensured that the results were directly related to the study topic and allowed for the standardization of synonyms. Subsequently, the scientific production was characterized, and maps and graphs were constructed to visualize research trends and patterns. The search was conducted on June 10, 2024.

The analysis was performed using the bibliometrix package in R (version 4.3.1) [9]. Frequency and percentage calculations were carried out using Microsoft Office Excel 2020.

Ethical statements

This study did not require ethical committee approval, as it did not involve research on humans, biological models, or the use of medical records.

RESULTS

A total of 363 articles were included after applying the inclusion and exclusion criteria. The first publication dates back to 1964, establishing a 60-year analysis window up to 2024. The scientific output predominantly consisted of original articles (87.32%; n=317), followed by review articles (6.1%; n=22). International collaboration accounted for 7.98% (Table 1). Since the first publication in the 1960s, a modest number of publications were observed until 1984, when a marked growth occurred, followed by a sustained decline in recent years (Figure 1). Citation trends mirrored this pattern, showing fluctuations but generally remaining low (Figure 1).

TABLE 1. GENERAL CHARACTERISTICS OF SCIENTIFIC PRODUCTION ON THE MANAGEMENT OF HEMOPHILIA A IN PEDIATRICS (N=363)

	n	%
Authors		
Authorships	1412	-
Authors of single-authored documents (N=1412)	54	3.82
Article Typology		
Original Articles	317	87.32
Reviews	22	6.1
Books	1	0.27
Editorials	3	0.82
Short Papers	1	0.27
Letters	19	5.22
Collaboration		
Single-authored articles	54	-
Co-authorships per article (average)	4.56	-
International co-authorships	-	7.98
Average Citations per Document	19.52	-
Keywords	413	-
Scientific Sources	206	-

When exploring leading affiliations, the University Medical Center Utrecht (Netherlands) emerged as the most prolific and impactful institution, with 10 published articles and an h-index of 8. It was followed by Nara Medical University (Japan), with 8 articles and an h-index of 7. In terms of countries, the United States was the most prolific and impactful, with 93 documents and an h-index of 27, followed by Germany and Italy, with 35 and 29 articles, respectively. Italy ranked second in research impact, with an h-index of 13.

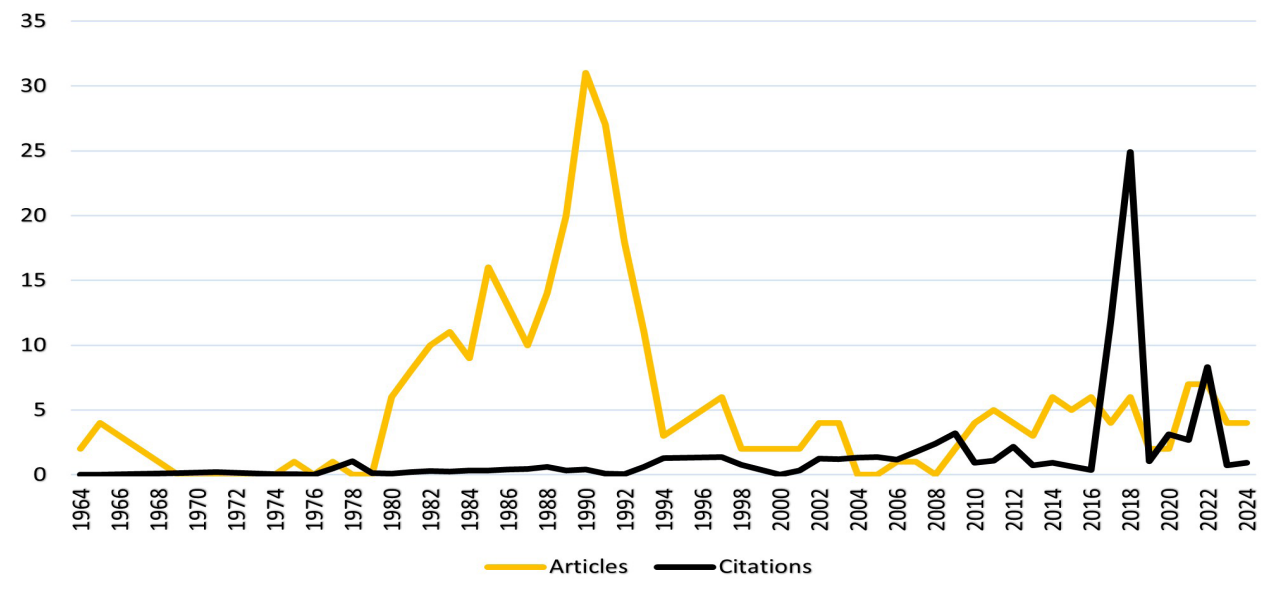

Figure 1. Scientific growth of research on pharmacological interventions for the management of type A hemophilia A in pediatrics.

Haemophilia (n=35) was the journal with the highest number of publications related to the topic of interest (Figure 2-A). However, the New England Journal of Medicine had the highest number of cumulative citations (n=1,333) (Figure 2-B). Despite this, Haemophilia exhibited the greatest impact based on h-index (Figure 2-C), g-index (Figure 2-D), and m-index (Figure 2-E). Notably, Haemophilia experienced significant growth in publications starting in 2001, with a marked increase in recent years (Figure 2-F).

Regarding collaboration networks, the United States demonstrated the highest number of collaborations, particularly with European countries such as Germany and Italy, and in Asia with Japan (Figure 3-A). The University Medical Center Utrecht emerged as one of the most prominent international reference centers, followed by Nara Medical University and Nagoya University Hospital (Japan) (Figure 3-B).

In terms of research patterns and thematic trends, a word cloud of the most frequently used keywords highlighted “factor VIII,” “therapeutics,” “intravenous drug administration,” and “hemarthrosis” as the most common terms (Figure 4-A). During the first 30 years of research, studies focused primarily on coagulation factors, particularly in men, children, and adults (Figure 4-B). Between 1995 and 2024, the most prominent topics included disseminated intravascular coagulation, pathophysiology, and studies involving women (Figure 4-C). A co-occurrence network analysis revealed three primary research niches: therapy types, age groups, and specific outcomes (Figure 4-D).

DISCUSSION

This study is the first to explore the characteristics and research patterns of pharmacological interventions for managing hemophilia A in pediatric populations. Interestingly, there are very few bibliometric analyses in the global literature that have examined the scientific evolution and trends in hematological disorders, particularly hemophilia [10,11].

One such study that may help identify regional research trends was conducted by Aldossary et al. [12], who assessed the state of global research on von Willebrand disease. Using the Web of Science database, they identified over 3,000 documents, revealing Italy as home to the most prolific institution, while the United States stood out as the most productive country. Their findings highlighted key research topics, such as bleeding time during pregnancy and desmopressin [12]. When compared to the present analysis, similar patterns emerge regarding the leading countries and institutions, which are predominantly high-income nations with robust science and technology infrastructures. This can likely be attributed to the presence of well-established research groups dedicated to the study of hematological disorders.

Another analysis, focusing on primary immune thrombocytopenia, an autoimmune hematological disorder, also utilized the Web of Science database. It identified slightly over 2,000 published studies, with China emerging as the most prolific country [13]. By contrast, research on hemophilia A remains relatively modest when compared to studies on sickle cell anemia. Mussa et al. [14] identified approximately 12,000 studies published between 1990 and 2020, exposing a significant gap in pluralism and relevance in research. This gap persists despite hemophilia A being a critical clinical condition, even if less prevalent than sickle cell anemia [14]. Such disparities align with the annual publication frequency, which remains low, even compared to earlier years.

However, it is noteworthy that approximately 90% of the publications consist of primary data articles, highlighting the strong interest among researchers in generating new knowledge on pharmacological interventions [15]. A key question to explore is whether the frequency and impact of research on hemophilia A in pediatrics correlate with the countries reporting the highest relevance or those with the greatest demand for healthcare services and unmet needs.

These findings are crucial for assessing the relevance, pertinence, and gaps in research, as well as for establishing mission-oriented policies and roadmaps [16, 17, 18,19]. Hemophilia A appears to be an undervalued and under-researched condition in many regions of the world. This study may be the first bibliometric analysis to examine global research on hemophilia A, as no prior studies with similar objectives were identified.

In an era of overwhelming scientific production, meta-science and scientometrics have become essential tools to make sense of the biomedical research landscape. By systematically

evaluating patterns, gaps, and inconsistencies in the existing literature, these approaches help uncover areas where evidence remains weak, contradictory, or absent [20, 21, 22, 23]. This is not just an academic exercise; it directly impacts the quality and validity of the evidence base that informs clinical decisions and health policies [24,25]. Identifying research gaps through quantitative analyses enables a more intentional and efficient allocation of resources toward studies that truly matter, ultimately fostering a more reliable, equitable, and patient-centered biomedical science [26,27].

Limitations:

Given the study design, it is impossible to determine causality to explain the observed patterns and trends. Additionally, the reliance on a single database may exclude evidence from other sources.

CONCLUSIONS

A modest growth in research on pharmacological interventions for the management of hemophilia A in pediatric populations was identified, particularly when compared to other topics in biomedicine. The majority of this research has relied on primary data and has been led by institutions in the Netherlands and Japan, despite the United States being the most prolific country with the highest overall impact. It was found that international collaboration occurs in only approximately 1 in 10 studies. The most frequently studied topics are related to pathophysiology, coagulation factor VIII, complications such as disseminated intravascular coagulation, and hemarthrosis.

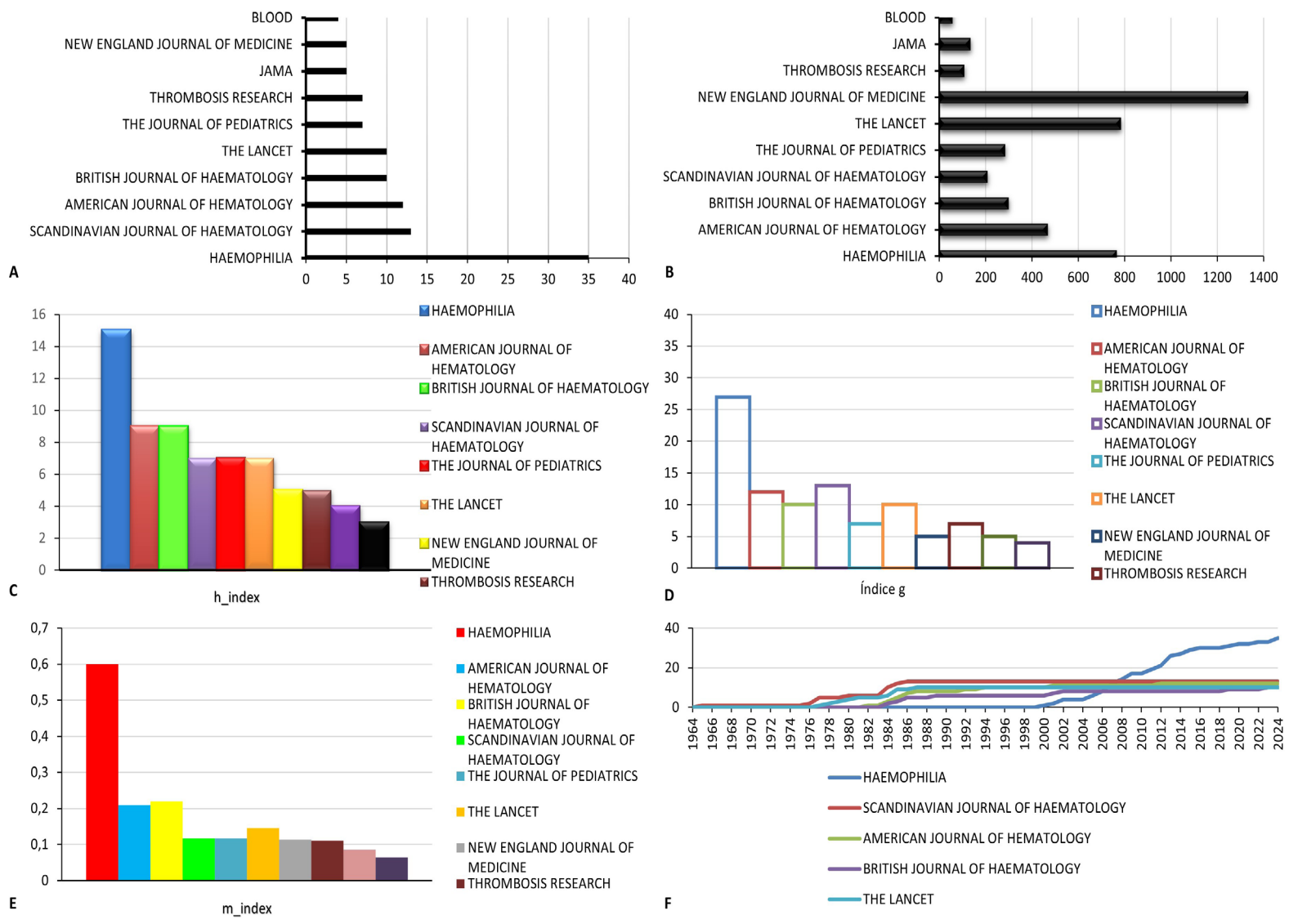

Figure 2. Journals with publications on hemophilia A therapeutics in pediatrics. A. Frequency of published articles. B. Total citations obtained. C. H-index obtained. D. G-index obtained. E. M-index obtained. F. Cumulative frequency of articles published over time.

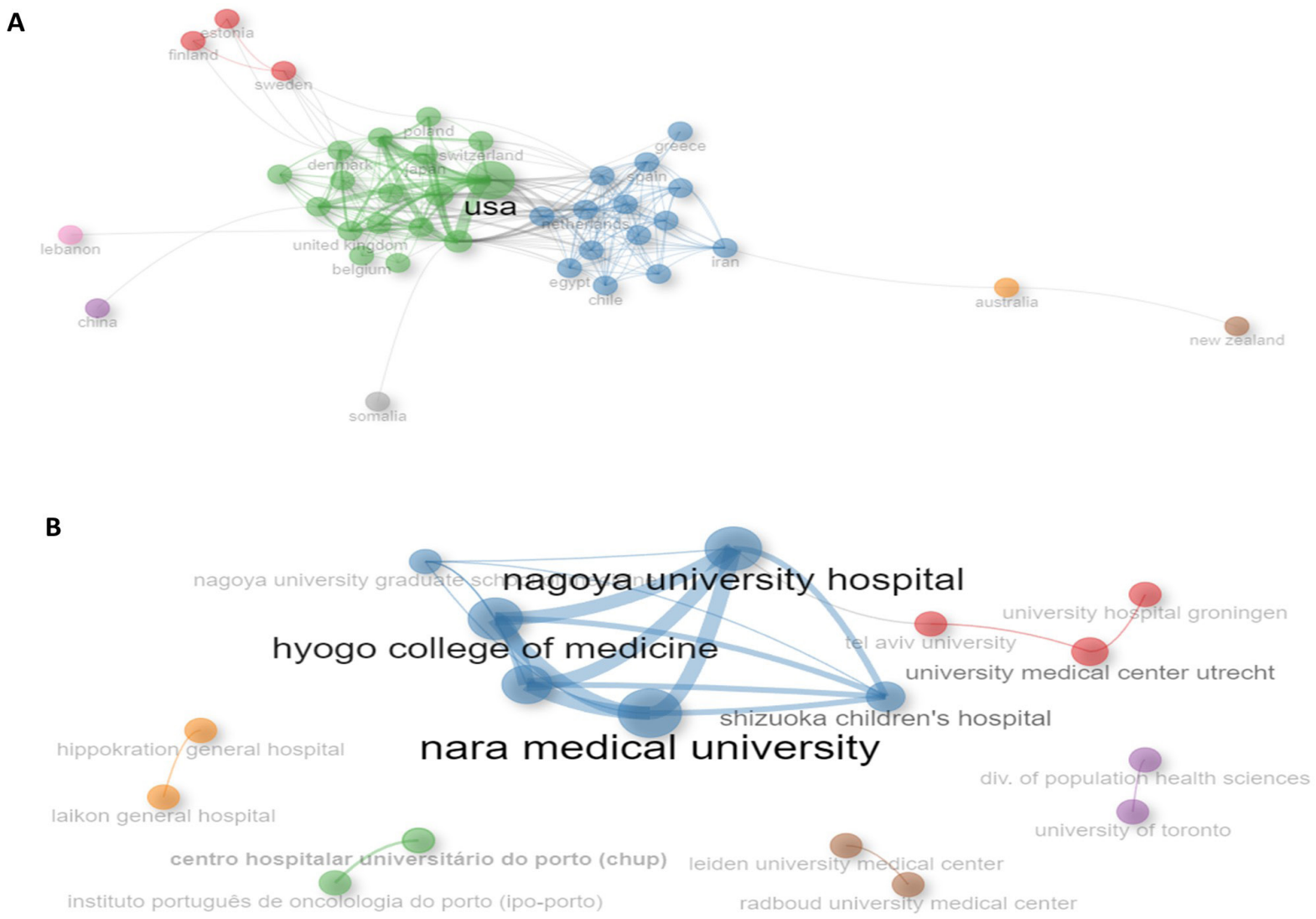

Figure 3. Collaborative research networks on hemophilia A therapeutics in pediatrics. A. Collaboration between countries. B. Collaboration between institutions.

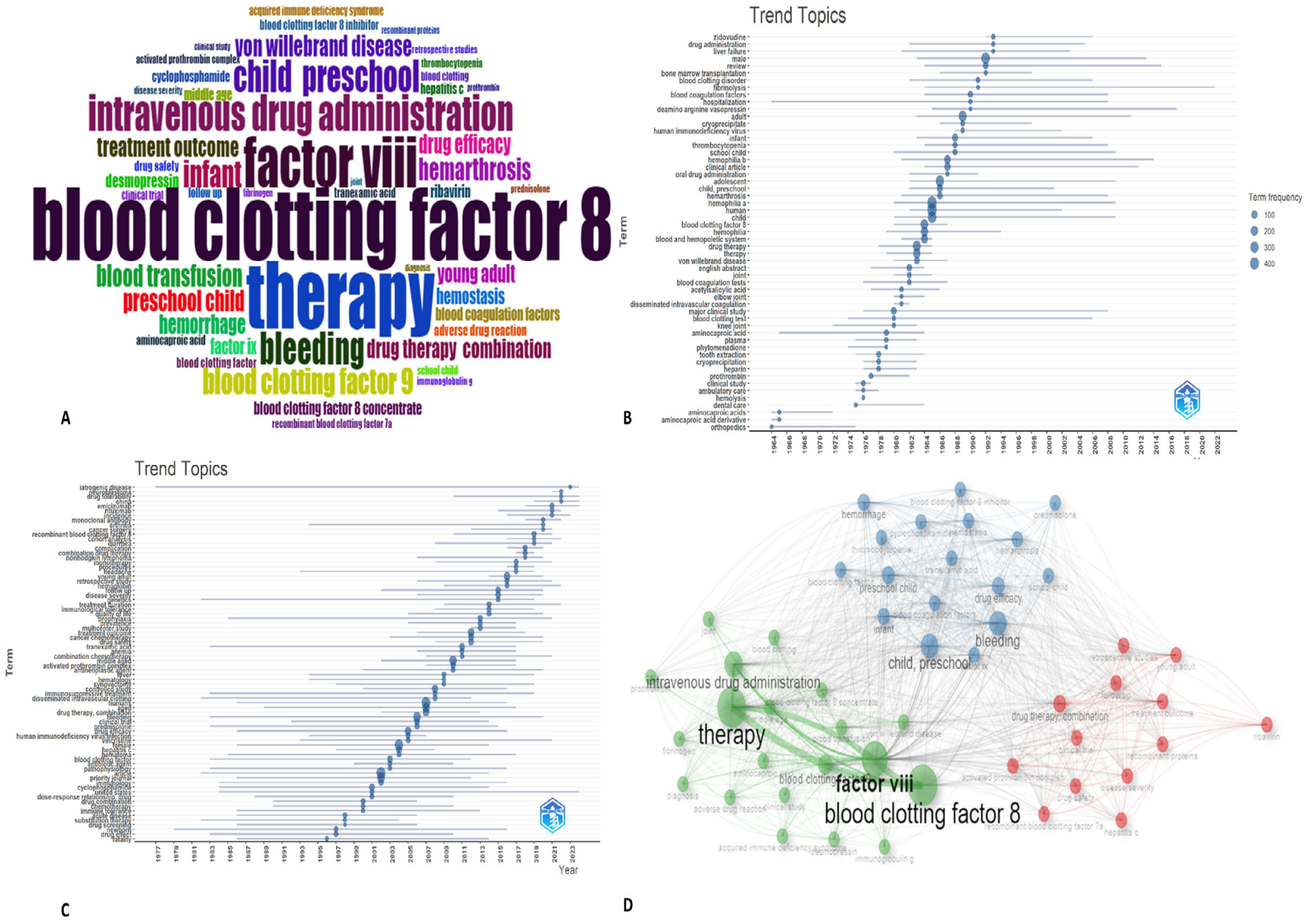

Figure 4. Trends and co-occurrence of topics on therapeutics in hemophilia A in pediatrics. A. Cloud of most frequent keywords. B. Most frequently studied topics before 1994 C. Most frequently studied topics after 1994. D. Co-occurrence network of most relevant terms.

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L. Manrique-Rubio: conceptualization, research, methodology, writing-original draft, writing-revision and editing. **A. Unigarro-Sánchez:** conceptualization, research, methodology, writing-original draft, writing-revision and editing. **D. Echeverry-Guerrero:** conceptualization, research, methodology, writing-original draft, writing-revision and editing. **L. Roa-Hernández:** research, methodology, data analysis, writing-original draft, writing-revision and editing. **A. García-Divantoque:** conceptualization, research, methodology, writing-original draft, writing-revision and editing. **K. Celis-Canelón:** conceptualization, research, methodology, writing-original draft, writing-revision and editing. R. Maya-Acevedo: conceptualization, research, methodology, writing-original draft, writing-revision and editing. H. Rodriguez-Cruz: conceptualization, research, methodology, writing-original draft, writing-revision and editing. J. Orozco-Chi**nome:** conceptualization, research, methodology, writing-original draft, writing-revision and editing.

FUNDING

This study was funded by the authors.

ACKNOWLEDGMENTS

None

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