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Blood diffusion to novel therapies: A quantitative analysis of scholarly output in Haemophilia from India

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Lack of specific protein factors, such as factor VIII and factor IX, results in haemophilia, a genetic bleeding condition. Due to its genetics, haemophilia affects an individual, but we can see how it has an impact on a whole generation. The goal of this study is to determine the extent to which our Indian researchers have been able to advance this highly sought-after field. Although this study was intended to last 75 years, it had to be restricted to the years 1991 to 2021 due to a shortage of publications at the time of data mining. There was a total of 81 publications found, and after analysing them, it was found that India and the USA collaborated more frequently than France and the UK. The National Institute of Immunohaematology (NIIH), located in Mumbai, is India's most productive institution in terms of the number of publications or ongoing work. Haemophilia, factor viii, and gene therapy were the most commonly used keywords. Indian researchers still need to put in a lot of effort in this area because, according to studies from around the world, haemophilia is spreading like a fire. Continuous research and knowledge of the needs of the population are required if we are to improve not only our position in the world but also the way we are treated, which would make life better.

Keywords: Blood coagulation, Bleeding disorder, Gene therapy, Research trend, Scientometrics

Haemophilia is an inherited bleeding disorder caused by deficiency or dysfunction of the coagulation proteins[1,2].

Haemophilia is generally of two types that is haemophilia A and haemophilia B and both are congenital disorders mainly caused by the deficiency of two coagulation proteins, factor VIII for haemophilia A and factor IX for haemophilia B. These clotting factors are an integral part of blood coagulation. An individual with haemophilia may have severe, moderate, or mild forms of the disease. In earlier days the deficiency of coagulation factor XI (FXI) was considered haemophilia C however, currently, only haemophilia A and B are the only types of haemophilia, and all other clotting factors deficiencies are generally referred to as rare bleeding disorders. Haemophilia A is often known as classical haemophilia whereas haemophilia B is called Christmas disease.

The symptoms of Haemophilia A and B are quite similar, and are both characterized by bleeding, especially in large joints such as elbows, knees, and ankles(the index joints); such joint bleeding eventually results in painful and disabling haemophilic arthropathy. However, intercranial bleeding or bleeding of an internal organs rare and life-threatening may occur, regardless of the severity of the disease, but especially in the severe forms[3].

Haemophilia is a genetic disorder generally caused by a mutation in one of the genes that are found/located in the X chromosome which is responsible for blood clots, this can affect or prevent the clotting protein from working properly or be missing altogether. As males have XY chromosomes and females have XX chromosomes, males inherit an X chromosome from the mother only and females inherit one each from both the parents. There exists a huge difference in the number of genes present on X chromosomes and Y chromosomes, X chromosomes have more genes than the Y chromosome.Males have only one copy of the X chromosome whereas females have two copies and due to this condition males are vulnerable to haemophilia because if they inherit the X chromosome they are affected by the mutation in either the factor VIII or factor IX gene it can prevent the blood from clotting. In rare cases, females also inherit the affected genes. In those cases, either both of the X chromosomes are affected or one of them is affected and the other one is inactive or missing. In females, bleeding symptoms may be similar to males with haemophilia[4]. The chances of having

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haemophilia are the same for both males and females whereas males are more susceptible to this disease because only one copy of the X chromosome can cause haemophilia A or haemophilia B depending on the deficiency of the factor VIII and factor IX.

In recent decades severe haemophilia cases have improved due to the availability of safe and effective blood products. Before the availability of safe blood products, blood-transmitted viruses like the hepatitis C virus and HIV were used to infect a substantial percentage of haemophilia patients who were treated with commercially accessible pooled plasma-derived clotting factor concentrates[5].

In the 1950s and 1960s only whole blood plasma and fresh plasma were used to treat Haemophiliacs. Unfortunately, the amount of FVIII or FIX was not enough in these blood products to stop the bleeding. Thus most people with severe haemophilia used to die in childhood or early adulthood, development of haemorrhages in vital organs or after surgery or trauma was one of the most common causes of death[6].

With the development of safer blood products, the treatment paradigm of Haemophilia changed, instead of treating bleeding episodes mainly on-demand, the use of prophylactic therapy came into the picture where regular administration of factor concentrate is given to prevent the bleeding events[7]. The current approach toward the treatment of Haemophilia involves replacing the specific deficient clotting factor to promote normal haemostasis. Several groups are investigating novel nonfactor therapies to either replicate the cofactor function of the deficient factor or modify the balance of coagulation proteins toward the pro haemostatic[8].

Indian Scenario

According to the annual report 2021 shared by the World Federation for Haemophilia (WFH), from 2010 onwards cases have risen continuously and the patients of haemophilia A and Haemophilia B have made a slope in increased cases that shift from approximately 1,50,000 cases in 2010 to almost 4,00,000 cases in 2020 globally.

Similarly, Haemophilia Federation (India) in their annual report 2019, stated the total number of active haemophilic patients in India was 21824, 21101 males, and 723 females. The number of people with a deficiency of Factor VIII was very high, 17606 which results in haemophilia A followed by deficiency of Factor IX causes (haemophilia B). These statistics suggest that in India, most haemophilia patients are suffering from haemophilia A and haemophilia B. Pateints with other diseases such as Von Will brand disease (VWD), a bleeding disorder caused by the low levels of Von Will brand Factor, and some other unknown bleeding disorders were also quite high[9] (Fig. 1).

The immediate goal should be the extension of haemophilia care programs in developing countries, there are also several objectives for high-income countries, haemophilia has moved from the status of a neglected and often fatal hereditary haemorrhagic disorder to a group of a well-characterized molecular entity in the last 3 decades[10]. There is a necessity of involving a newer generation of physicians, who appear to be attracted by the more appealing thrombotic side of haemostasis so that the interest and expertise in the field of Haemophilia are maintained[11].

The quantitative study from 1992 to 2020 using web of science core collection database is not attempted by the researchers. Though Vellaichamy and Jeyshankar (2008) have made an attempt to analyse the scholarly output using the Scopus database. Given thegrowing incidences of Haemophilia it becomes very important to dedicate proper research to this, Funding agencies should formulate policies to foster the research and developments between India and other developing countries in this field[12]. This study attempts to find out the Indian contribution in terms of collaboration, publications, keywords, and other parameters toward this neglected disease.

Methodology

Data for this study were identified by using one of the popular citation database "Web of Science" a database of selective citation index of scholarly publications including journals, proceedings, books,

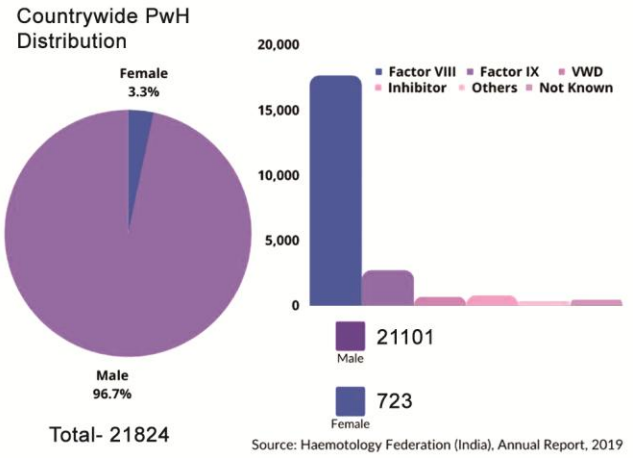

Fig. 1 — Countrywide (India) distribution of patients with Haemophilia, 2019

and data compilations[13]. The data was retrieved using the web of science core collections and the basic search strategy was used using the "All field" function. Keywords were “haemophilia”, “haemophilia in humans”, and “haemophilia in India” using the Boolean operator "OR". A total of 81 publications were found from India in the database for the year ranging from 1950 to 2021. Due to the shortage of data from 1950 to 1951, I restricted my study from 1991 to 2021 which is approximately 30 years. The document types were as follows, Articles (54), Reviews (23), Meeting Abstract (3), Proceedings paper (2), and Book chapters (1). The data was exported in excel and normal text format for further analysis. VOSVIEWER software was used to analyse keyword co-occurrences and collaboration mapping.

Results and Discussion

Publication Year

Though the search was after independence that is from 1950 but due to lack of scholarly pieces, only 1 publication in 1992 was found and after that from 2000 onwards was fluctuated, suggests the trend was not regular or there might be chances of negligence from the researchers working in this area. Most articles were published in 2016 and counted 10 papers in a single year followed by the year 2018 which counted 7 papers. But the trend is no more visible in recent years as the number of publications started decreasing and also last year in 2021, only 2 publications were found in the database (Fig. 2).

Research Areas

Most publications were found in the Haematology section that only counted 31 records also because this is a bleeding disorder and lies in the area of haematology. But the other research area which is Research Experimental Medicine was quite impressive because it also shows a good number of publications (12) (Fig. 3).

Active Organisations

Organisations play an important role in the promotion of research as it also promotes collaboration between the organisations and international collaborations. In Haematology research it is supposed that the organisations working primarily on blood-related disorders will be the prime focus. The most productive organisation was Christian Medical College Hospital, Vellore with the highest number of publications which is 22 followed by the League of European Research Universities (18), Indian Council of Medical Research, India (15), and Udice French Research Universities with 14 publications. From India, the National Institute of Immunohematology was on top of the list with 13 publications (Table 1).

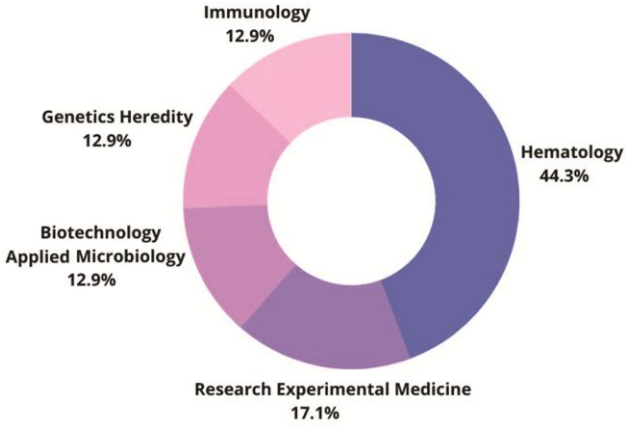

Fig. 3 — Topmost research areas

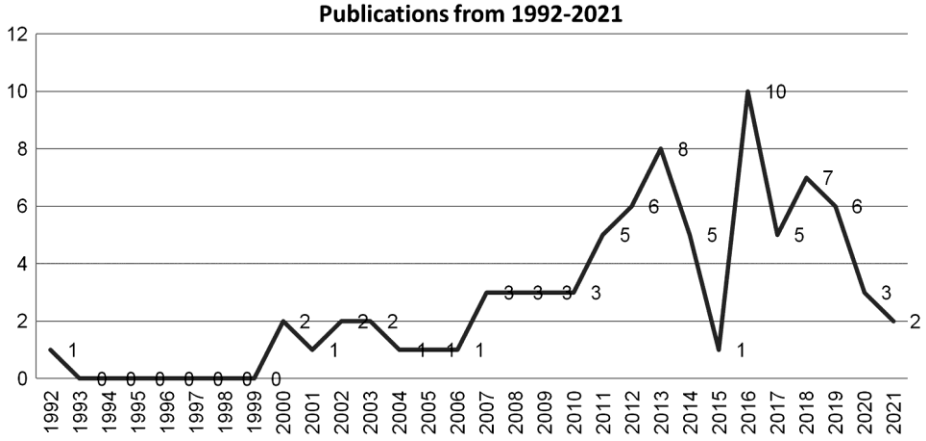

Fig. 2 — Publications over the years

Indian collaboration

Collaboration between organisations and countries is essential to create global, intergenerational networks that enable the explicit cooperation possibilities required to ensure that the advantages of global collaborative research, which is becoming more and more common in many domains, outweigh the disadvantages[14]. To enhance knowledge and encourage beneficial changes in practice, international collaborative research entails cross-country teams that share research interests, perform research, and promote research findings[15]. Figure 4 suggests that Indian authors have collaborated with almost 42 countries directly or indirectly and mapping has been done in 6 clusters. Indian authors have collaborated frequently with the authors of the USA with almost 27 publications and 698 citations followed by England, France & Italy with 10, 16 & 7 publications with more than 50 citations. Mapping also highlights that in 2012, India actively collaborated with countries including France, Japan, Belgium, *etc*. In recent years, India collaborated with countries including Bulgaria, Switzerland, Russia, *etc*.

Table 1 — Top 10 most active organisations

Organisations	Records	% of 81
Christian Medical College Hospital, Vellore	22	27.16
League Of European Research Universities, Leru	18	22.22
Indian Council of Medical Research (ICMR)	15	18.51
Udice French Research Universities	14	17.28
ICMR National Institute OfImmunohaemotology (NIIH)	13	16.04
Institut National De La Sante Et De La Recherche Medicale (INSERM)	12	14.81
Sorbonne Universite	11	13.58
Universite De Paris	11	13.58
Indian Institute Of Technology (IIT), system	7	8.64
Assistance PubliqueHopitaux, Paris	6	7.40

Keywords co-occurrence mapping

Keywords play an important role in indexing the publications as it allows researchers to find out most suitable research publications in the databases and search engines. A total of 229 keywords were found as author keywords co-occurrences and a Total of 188 keywords were screened having 18 clusters. The most used keywords were Haemophilia, Factor VIII, Gene Therapy, Haemophilia, and Coagulation with occurrences 11, 9, 7, 5, and 3 respectively (Fig. 5).

Most prolific journals

Finding the right destination for your work is very important as it also contributes to or affects the reach of your publication as well as increases the chances to communicate your finding to peers working in the same area. This analysis revealed that the most opted journal by the researchers for their work was *Haemophilia* with 8 records followed *by Journal of Thrombosis and Haemostasis* and *Cochrane Database of Systematic Reviews* with 5 and 3 records respectively (Table 2).

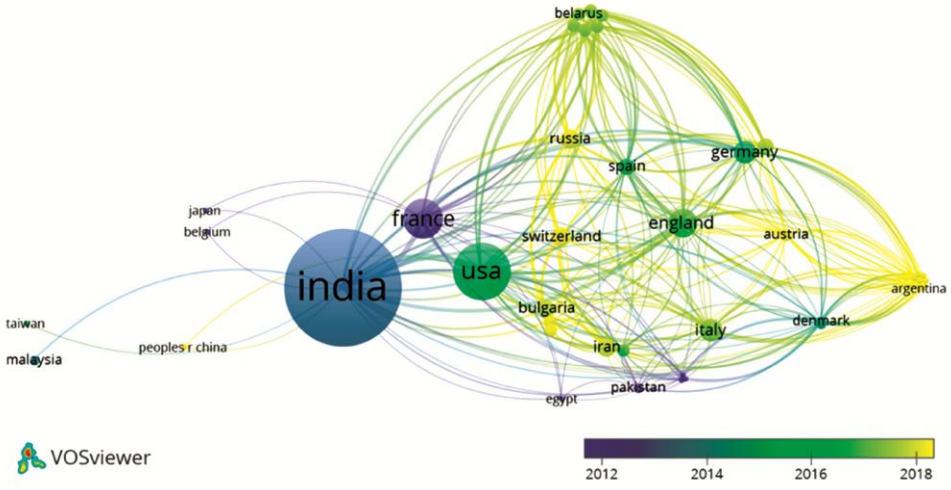

Fig. 4 — International collaboration

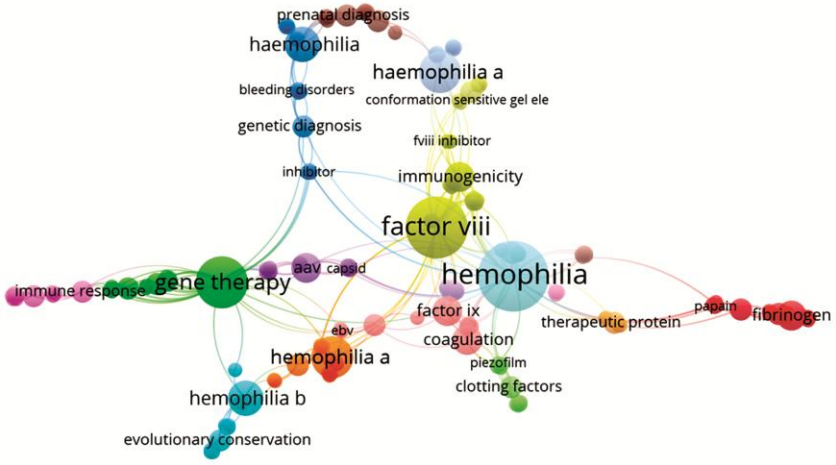

Fig. 5 — Keywords co-occurrence (author keywords)

Table 2 — Top prolific journals

Publication Titles	Record Count	% of 81
Haemophilia	8	9.877
Journal of Thrombosis And Haemostasis	5	6.173
Cochrane Database Of Systematic Reviews	3	3.704
Human Gene Therapy	3	3.704
Indian Journal of Hematology And Blood Transfusion	3	3.704
Blood	2	2.469
Transfusion	2	2.469
2008 Cairo International Biomedical Engineering Conference	1	1.235
Acta Haematologica	1	1.235
American Journal of Hematology	1	1.235

Conclusion

The number of haemophilic patients worldwide, including India, is increasing for a number of reasons. One of the potential causes could be ignorance/less knowledge of the influencing factors or a deficiency in factors IX and VII, but in terms of scholarly output, it does not demonstrate the positive trend of the outputs from Indian researchers as only discovered 81 publications were found in the web of science core collection, which is incredibly low and surprising. In this highly sought-after area of study, there is a need to provide scholarly production a major boost.

Conflict of interest

The author declares no conflict of interest.

References

1 Peyvandi F, Garagiola I & Young G, The past and future of haemophilia: diagnosis, treatments, and its complications. *Lancet*, 9 (2016) 187.

2 Mannucci PM & Tuddenham EGD, The haemophiliac - from royal genes to gene therapy. *N Engl J Med*, 344 (2001) 1773.

3 Fischer K, Ljung R, Platokouki H, Liesner R, Claeyssens S, Smink E& Van den Berg HM, Prospective observational cohort studies for studying rare diseases: the European PedNet Haemophilia Registry. *Haemophilia*, 20 (2014) e280.

4 Centre for Disease Control and Prevention, Hemophilia.

5 Morfini M, Coppola A, Franchini M & Di Minno G. Clinical use of factor VIII and factor IX concentrates. *Blood Transfus*, 11 (2013) s55.

6 Mannucci PM, Back to the future: a recent history of haemophilia treatment. *Haemophilia*, 14 (2008) 10.

7 Rocino A, Franchini M & Coppola A, Treatment and Prevention of Bleeds in Haemophilia Patients with Inhibitors to Factor VIII/IX. *J Clin Med*, 6 (2017) 46.

8 Matuk-Villazon O, Roberts JC& Corrales-Medina FF. Hemophilia: The Past, the Present, and the Future. *Pediatr Rev*, 42 (2021) 672.

9 National Heamophilia Foundation for all bleeding disorders, annual report, 2019.

10 FranchiniM & Mannucci PM, Past, present and future of hemophilia: a narrative review. *Orphanet J Rare Dis*, 7 (2012) 24.

11 Mannucci PM & Roberts HR, Uncertain times for research on haemophilia and allied disorders. *J Thromb Haemost*, 3 (2005) 423.

12 Alagarsamy V & Ramalingam J, Scientometric methods for the evaluation of hemophilia research. *Library Philosophy and Practice (e-journal*), (2018).

13 Birkle C, Pendlebury DA, Schnell J & Adams J; Web of Science as a data source for research on scientific and scholarly activity. *Quant Sci Stud*, 1 (2020) 363.

14 Dusdal J & Powell JJW, Benefits, Motivations, and Challenges of International Collaborative Research: A Sociology of Science Case Study. *Science and Public Policy*, 48 (2021) 235.

15 Yao B, International Research Collaboration: Challenges and Opportunities. *J Diagn Med Sonogr*, 37 (2021) 107.