Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jptcp.v31i3.4819

A CROSS-SECTIONAL STUDY ON THE PREVALENCE OF HEMOPHILIA IN DISTRICT LARKANA SINDH PAKISTAN

Khalida Unar[1*], Aiman Amur[2*], Majeeda Ruk[3], Ayaz Ali Unar[4]

[1*]Institute of Microbiology Shah Abdul Latif University Khairpur, Sindh, Pakistan
[2*]Department of Zoology, Government College University Hyderabad, Sindh, Pakistan
[3]Department of Zoology Shah Abdul Latif University Khairpur, Sindh, Pakistan
[4]Institute of Pharmacy, Shaheed Mohtarma Benazir Bhutto Medical university, Sindh, Pakistan

***Corresponding Author:** Khalida Unar[1*], Aiman Amur[2*]
E-Mail:Amuraiman@Gmail.Com[2], Khalida.Unar@Salu.Edu.Pk[1]

Abstract
An inherited bleeding problem is hemophilia. Recombinant clotting factor VIII or factor IX and immunosuppressive drugs are used to treat hemophilia A or B to stop the development of alloantibodies and inhibitors. Treatment of hemophilia is a problem due to the formation of inhibitors to these factors. Patients with inhibitors are treated with activated recombinant factor VII and plasmaderived activated prothrombin complex concentrate. Treatment differs depending on the circumstance since bleeding is more likely to occur in cases of pregnancy, surgery, and cancer. The major topic of this study was to assess healthy persons' awareness of hemophilia and their familiarity with this condition from birth. 30 people from rural Sindh participated in a cross-sectional, random study. All participants were asked regular questions about their awareness of the illness, and SPSS software was used to analyze the data. There is currently no long-term or permanent treatment for hemophilia. Hemophilia may be temporarily cured by factor replacement. The direction of gene therapy or stem cell treatment, both of which are under development, may lead to a permanent cure. Previous research has shown that gene therapy seldom succeeds in curing patients for many months without the requirement for recombinant factor replenishment. To obtain a long-lasting and permanent cure for hemophilia, more adjustments to the treatment plan are necessary.

Keywords: Hemophilia, genetics, Pakistan. Treatments, causes.

Introduction

Hemophilia is a hereditary blood illness in which there is insufficient clotting factor in the blood, which prevents the blood from clotting when it drains. The key genetic and hereditary disease-causing factor, including hemophilia and the lack of blood clotting factor, is the presence of X-chromosomes (Miller, 2021). The lack of blood clotting factors and disorders like hemophilia are both linked to Xchromosomes, which are the primary source of genetic and hereditary diseases. Any person with this condition has blood that cannot stop the flow of blood in the event of any damage. Hemophilia A

is caused by a shortage of VIII factors in the blood, while Hemophilia B is brought on by a shortage of IX factors (Obeagu, 2022). These are only two examples of the several types of hemophilia. Hemophilic A is more prevalent than Hemophilic B, although both varieties are very rare. For example, hemophilic A is identified in one out of every 5,000 newborns, but hemophilic B is extremely uncommon and impossible to locate in everyday conditions (Peyvandi et al., 2019). Aside from all of these risk factors, a few more instances of hemophilia have been documented, including hemophilia C and parahemophilia, which are characterized by intrinsic factor XI and V deficits, respectively. Both genetic alterations and any kind of damage (acquired) may result in parahemophilia. There are thought to be 4 lakh individuals worldwide who have different types of hemophilia, according to estimates. A physician by the name of Dr. John Conrad Otto enlarged the history of this uncommon illness in 1803 since it was thought that affected families with hemophilia were known as "Bleeders." The very first occurrence of this disease was documented approximately ten centuries ago during the time of Abacaxis (Ram Prakash, 2019).

The life of a hemophiliac patient entirely relies on the use of medicine; without it, they may not live healthily and risk dying before reaching maturity. It was formerly thought that persons with hemophilia maybe 10 years younger than healthy individuals (De la Corte-Rodriguez, RodriguezMerchan, Alvarez-Roman, & Jiménez-Yuste, 2021). Due to a variety of factors, 30% of hemophilia patients did not need any treatment to control their bleeding, and 8% of these individuals had fatal bleeding, such as GIT, intracranial, and retroperitoneal hemorrhage. Because of the change in bleeding time, it might be clinically classified as anything from a mild sickness to a life-threatening condition (Hall, Carter, Bradbury, Barfield, & O'Neill, 2021). Patients with AHA (Acquired Hemophilia A) shared almost all of the same comorbidities and received nearly identical treatment as that given to patients with antiplatelets, thus from a clinical standpoint, it would appear that they would need specialized care. Numerous studies on hemophilia have shown that specific hemostasis along with blood coagulation may regulate or affect this hereditary illness (Jankowska, Sauna, & Atreya, 2020). Although there isn't a particular treatment for AHA, it may be managed with the use of Porcine VIII factor and Recombinant VII-a factor. Supplemental medication was provided to them in order to spare them from life-threatening problems. A rough estimate of this illness would be that over 18,000 people with hemophilia were recorded in Pakistan, however only 8–10% of those patients received medication, and the remainder had improper diagnosis and treatment (Sandilands, Williams, & Rylands, 2022). The main goal of this study was to evaluate public perceptions of hemophilia; hence a cross-sectional survey was carried out to gather information.

The emergence of autoantibodies against the clotting factors may potentially result in the acquisition of hemophilia (Yousphi, Bakhtiar, Cheema, Nasim, & Ullah, 2019). The frequency of acquired hemophilia is one in a million, which is very unusual. 1-3 Internal or external bleeding that may be spontaneous or associated with insignificant trauma occurs in hemophilia. It may result in consequences such as compartment syndrome, hemarthrosis, cerebral bleeding, and persistent anaemia. To stop the emergence of these issues, early identification and treatment are necessary. In unique circumstances including pregnancy, major operations, and cancer, the treatment changes. This review seeks to give the latest suggestions for the management of certain disorders or procedures in hemophiliacs as well as new developments in the diagnosis and treatment of hemophilia (Coppola et al., 2022; Srivastava et al., 2020).

Causes of hemophilia

When a blood artery is injured, platelets are activated at the site of the lesion, which triggers the clotting factors and causes a fibrin blood clot to form through the "Intrinsic route" (Afshari, 2022). In order to activate factor X, which in turn activates prothrombin activator and transforms prothrombin to thrombin, factor VIII and factor IX are necessary. The conversion of fibrinogen to fibrin, which traps platelets and creates clots, is aided by thrombin. Factor IX cannot be activated without factor XI. 5 Genetic transmission of factors VIII, IX, or XI to the progeny occurs via the X chromosome (F8

and F9) and chromosome 4 (F11) (Sanchez-Lara, Nathanson, & Valentino, 2022). Any flaw in these genes results in the lack or diminished synthesis of these components. Occasionally, 'inhibitor' antibodies to these factors may form. Inhibitors may emerge idiopathically in healthy individuals without any genetic defects or as a reaction to treatment with clotting factors in hemophiliacs. Prothrombin time (PT) and activated partial thromboplastin time (apt) are extended in these individuals even after clotting factor treatment (Kato et al., 2021).

Genetic Factors

In men and homozygous females (only conceivable in the children of a carrier female and a hemophilic male), hemophilia A is inherited as an X-linked recessive trait (Cattaneo, 2019). It is advised that levels of factor VIII and IX be evaluated in all known possible carriers before surgery and in the case of clinically severe bleeding since moderate hemophilia A is known to develop in heterozygous females owing to X-inactivation. The factor IX gene for hemophilia B is found on the X chromosome (Xq27.1-q27-2). Similar to hemophilia A, it is an X-linked recessive disease, which explains why often only men are afflicted. A rare and unusual form of hemophilia B called hemophilia B Leyden, in which sufferers experience episodes of excessive bleeding in childhood but have few bleeding issues after puberty, was discovered by George Brownlee and Merlin Crossley in 1990. They demonstrated that two sets of genetic mutations were preventing two key proteins from attaching to the DNA of these individuals. This absence of protein attachment to the DNA resulted in the gene that makes clotting factor IX, which stops excessive bleeding, being turned off (Berntorp et al., 2021; Perrin, Herzog, & Markusic, 2019).

Associated Disorders

Both hemophilia A and hemophilia B are linked to illnesses that entail additional coagulation cascade abnormalities. Von Willebrand disease, acquired hemophilia, other clotting factor deficits (factor VII, V, X, or XI), or platelet abnormalities should also be taken into account in patients with bleeding issues. Important prognostic and therapy implications result from the discovery of these additional diseases (Bulut, Sapru, & Roach, 2020).

Symptoms and Signs

Typically, patients with the severe type of hemophilia are identified very early in life. Large cephalhematomas or excessive bleeding after circumcision are symptoms of the illness. Patients with milder illness types often show up later in life. Pain and swelling in a weight-bearing joint, such as a knee, hip, or ankle, are the primary symptoms (Möller et al., 2019). Hemarthrosis, or bleeding into the joint area, is what is to blame for the swelling and agony. Repeated bouts of hemarthrosis result in degradation of the articular cartilage, fibrosis, joint ankylosis, and muscle atrophy. Hemarthrosis irritates and inflames the synovium. Following a trauma, bleeding may happen in any joint Iannucci and Luddenham (2001). While hemophilia-related bleeding may happen everywhere in the body, the central nervous system is where it can have the most severe effects.

Hemophilia and its complications

Serious and moderate hemophilia sufferers are substantially more likely to have severe consequences. Both the illness and its treatment have the potential to cause complications. Frequently occurring issues include:

- Deep internal bleeding, such as deep muscle bleeding, may cause a limb to enlarge or become numb or painful.
- Hemarthrosis (hemophilic arthropathy) may cause joint injury that might result in excruciating pain, deformity, or even joint destruction as well as the onset of crippling arthritis.
- Blood transfusions used in medical therapy may spread infections.

- adverse effects of clotting factor therapy, such as the emergence of immunological inhibitors that reduce the efficacy of factor replacement.
- A major medical emergency known as intracranial bleeding is brought on by pressure within the skull. It may result in death, nausea, unconsciousness, confusion, and brain damage (Franjić).

The loss of cartilage and persistent proliferative synovitis are two features of hemophilia arthropathy. If an intra-articular hemorrhage is not stopped right once, it might lead to chondrocyte death and disrupt the production of proteoglycans (Wilkins, 2021). Hemarthrosissynovitis-hemarthrosis is a cycle of excessive bleeding that may occur when the frail and hypertrophied synovial lining tries to expel the blood. Iron buildup in the synovium may also cause an inflammatory reaction that activates the immune system and stimulates angiogenesis, causing the loss of cartilage and bone (Jain & Ravikumar, 2020). A mild type of hemophilia known as hemophilia C, plasma thromboplastin antecedent (PTA) deficiency, or Rosenthal syndrome. People with hemophilia C do not spontaneously bleed, unlike those with hemophilia A, which is one of its indications and symptoms. Hemorrhages often occur in these situations after severe surgery or an accident. However, individuals with hemophilia C may have symptoms that are strikingly similar to those of other types of the disorder, such as oral bleeding, nosebleeds, and blood in the urine.

Treatment For Hemophilia

In order for the blood to clot correctly, replacing the missing blood clotting factor is the best strategy to treat hemophilia. Clotting factor concentrates, which are used as therapeutic items, are often injected into the patient's vein.

Specialists including orthopaedic surgeons, physiotherapists, and dentists collaborated with s pecialised hemophilia centers to design programs of comprehensive care.Elective surgery, in particular orthopaedic procedures, became safe and feasible, and it helped to reduce or cure t he musculoskeletal abnormalities that had arisen as a result of bleeding episodes into joints an d muscles that had gone undiagnosed or insufficiently treated (Srivastava et al., 2020).

Factor Replacement Therapies:

Also known as "factor," these treatments use a molecule that is either recombinant (which is c omparable to the human factor found in nature) or a real human molecule (plasma derived.) These procedures raise the body's levels of a factor that promotes better clotting and consequ ently less bleeding.An injection into a vein is used to administer the medication intravenously

. Another name for this procedure is "infusion" (Garraud et al., 2022)

The best technique to treat hemophilia so that the blood can clot correctly is to replace deficient clotting factors. Coagulation factor concentrates, which are often used as therapeutic items, are injected directly into the vein of the patient to accomplish this. Typically, medical professionals will prescribe preventative and episodic therapy items. Prophylactic care is used to halt bleeding episodes before they start, whereas episodic care is used to treat bleeding episodes as they happen.

Treatment Centers

The best approach to treat hemophilia, a complicated illness, is at hemophilia treatment facilities (HTC). An HTC gives patients the support and training they need to handle any disorder-related concerns. The team is made up of nurses, physiotherapists, hematologists, and other experts in the field of blood.

Treatment Medications.

Clotting factor concentrations come in two primary varieties:

Plasma-derived Factor Concentrates.

Blood proteins including albumin, clotting factors, and antibodies are found in plasma. Human blood plasma is used to create a variety of factor concentrate products, during which the plasma is put through a number of steps and the clotting factors are isolated. These goods are ultimately dried and frozen before packing (Ghetmiri, Cohen, & Menezes, 2021).

Recombinant factor concentrates.

Recombinant antihemophilic factor concentrate, which is not derived from human plasma, was given FDA approval in 1992. Using DNA technology, this has been genetically altered to eliminate or inactivate bloodborne viruses.

Materials And Methods Study Area

The study was carried out in rural Sindh, and the analysis utilized a generally healthy population. Data on all hemophilic cases ever recorded in the Larkana area were gathered for this purpose.

Collecting data

A single form was then created using the information gathered from the questionnaire. They were organised according to the kind of inquiries and the answers that were given.

Some of the instances were left with blanks because there was insufficient data on inheritance and if someone in the patient's family had hemophilia.

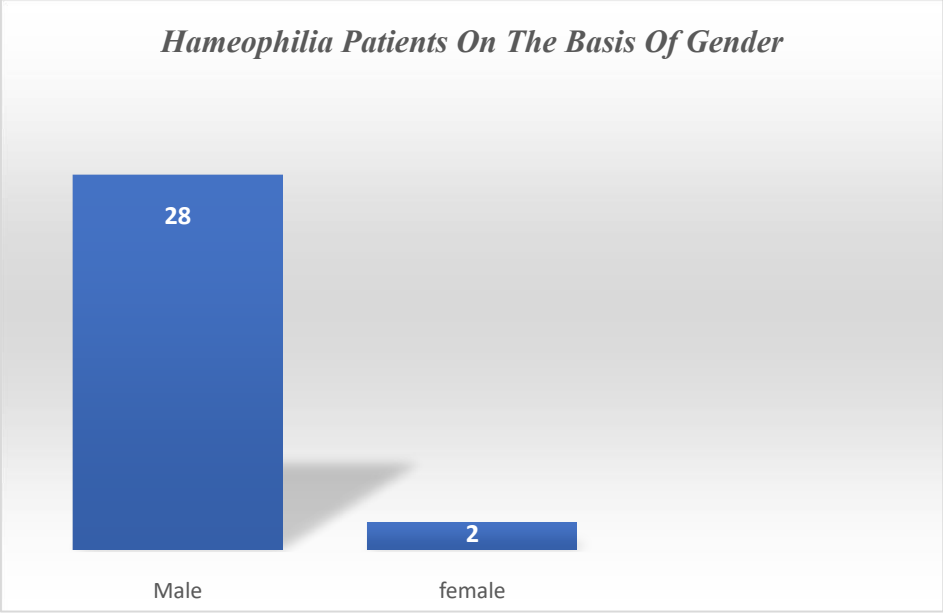
Participants

A cross-sectional survey was undertaken to see how well people understood about hemophilia; apart from data, each person had a different degree of education.

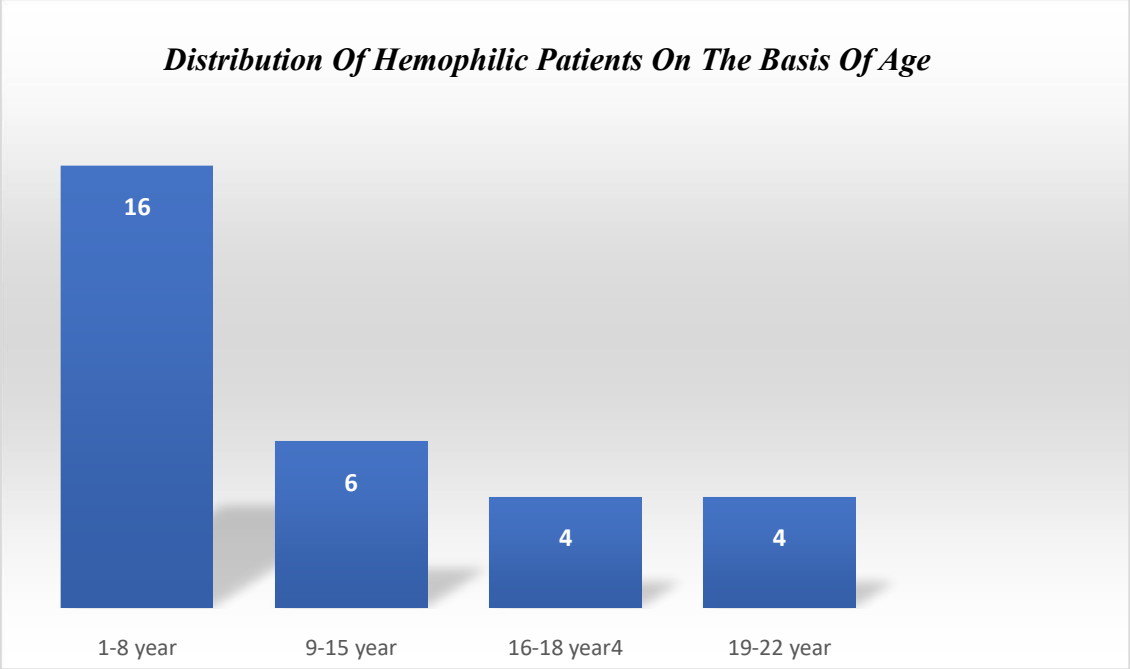
Questionnaire

The questionnaire was divided into three sections, each of which included demographic information such as gender, age, and if an inherited condition existed. ***Results***

Data on all hemophilic cases ever recorded in the Larkana area were gathered for this purpose. We had also created and administered a survey. To collect information from the area, this questionnaire was sent to Larkana's registered hemophilia groups. This research has 30 patients in total. The graph 1 depicts the proportion of Hameophila patients according on their gender. According to the statistics, out of 30,28 patients with this disease, 28 are male.



The age distribution of patients with hemophilia is shown in Graph 2. The majority of patients are between the ages of 1 and 18 with a frequency of 16. The frequency of the 9-15 age group is six, while the frequency of the 19-22 age group is just four.



The third test result is presented in tabular format. This frequency finding pertains to the inheritance of people with hemophilia. The majority of sufferers have inherited the disease.

S.#	Gender	Age	Inheritance
1	Male	14 Years	-
2	Female	4 Years	-
3	Male	14 Years	Yes
4	Female	5 Years	Yes
5	Male	19 Years	Yes
6	Male	5 Years	-
7	Male	1 Years	-
8	Male	18 Years	Yes
9	Male	10 Years	-
10	Male	5 Years	-
11	Male	2 Years	No
12	Male	11 Months	-
13	Male	17 Years	Yes
14	Male	6 Years	-
15	Male	19 Years	-
16	Male	7 Years	Yes
17	Male	7 Years	-
18	Male	11 Years	No
19	Male	8 Years	No
20	Male	5 Years	No

21	Male	2	Years	No
22	Male	22	Years	Yes
23	Male	5	Years	Yes
24	Male	7	Years	Yes
25	Male	16	Years	-
26	Male	20	Years	Yes
27	Male	15	Years	Yes
28	Male	18	Years	Yes
29	Male	8	Years	Yes
30	Male	5	Years	Yes

Discussion

This blood illness is uncommon compared to other disorders that affect the population, yet sufferers experience more suffering due to financial strain and physical strain. Due to the very low number of hemophilia patients, no significant research on the illness and its consequences was conducted in the ancient world. It was found that people with hemophilia were allowed to die since the disorder's pathophysiology was not well understood owing to a lack of research in the field. The achievement of this milestone dates back to the previous two decades, when advancements in medicine helped lower mortality rates and it was discovered that males were more likely than women to have hemophilia owing to the existence of excessive X chromosomal inheritance. According to a survey done in Pakistan, there is a very small population of people with hemophilia registered with the Hemophilic Society. As a result, it is the primary responsibility of the family members of those affected by the disease to register their patients with the society in order to eradicate the disease so that the number of patients and their responsibility with regard to this fatal disease can be managed appropriately.

Conclsion

The majority of patients with this deadly illness are still unaware of the pathogenesis and therapy of hemophilia, a highly rare genetic disorder-related condition. Patients with hemophilia have extremely high disease rates, which may lead to bleeding and joint injury. The main goal of this illness was to assess the general population's degree of awareness about hemophilia in rural Sindh, and it was quickly realized that most people knew very little about the illness' symptoms and course of treatment. It was noted that a seminar should be held by health care professionals (HCPs) to raise awareness about hemophilia among Sindh's rural population.

Future Directions

Life expectancy varies with disease severity and access to effective treatment, like most elements of the condition. People with severe hemophilia who don't get enough current therapy have much shorter lives and often never reach adulthood. Life expectancy was barely 11 years on average until the 1960s, when effective treatments became accessible. The life expectancy of the typical hemophilia patient getting adequate care was 50 to 60 years by the 1980s. With the right care, hemophiliac men today may have quite normal lives with an average lifetime that is around 10 years less than that of a man without the condition. Since the 1980s, HIV/AIDS acquired via treatment with tainted blood supplies has replaced bleeding as the top cause of mortality in persons with severe hemophilia.

Intracranial hemorrhage, which now causes one-third of all hemophilia fatalities, is the second most common cause of mortality associated with severe hemophilia complications. Hepatitis infections that result in cirrhosis and restriction of air or blood flow as a result of soft tissue bleeding are two additional leading causes of mortality.

Informed Consent Statement:

All study participants provided their consent after receiving all necessary information.

Acknowledgments:

We appreciate the cooperation of the participants.

Conflicts of Interest:

The authors argue that they are not parties with conflicting interests.

References

[1] Afshari, M. (2022). The impact of compounds from cigarette smoke on blood coagulation in vitro.

[2] Berntorp, E., Fischer, K., Hart, D. P., Mancuso, M. E., Stephensen, D., Shapiro, A. D., & Blanchette, V. (2021). Hemophilia. *Nature Reviews Disease Primers, 7*(1), 1-19.

[3] Bulut, Y., Sapru, A., & Roach, G. D. (2020). Hemostatic balance in pediatric acute liver failure: epidemiology of bleeding and thrombosis, physiology, and current strategies. *Frontiers in Pediatrics, 8*, 618119.

[4] Cattaneo, M. (2019). Inherited disorders of platelet function. In *Platelets* (pp. 877-904): Elsevier.

[5] Coppola, A., Franchini, M., Tripodi, A., Santoro, R. C., Castaman, G., Marino, R., . . . Contino, L. (2022). Acquired hemophilia A: Italian Consensus Recommendations on diagnosis, general management and treatment of bleeding. *Blood Transfusion, 20*(3), 245.

[6] De la Corte-Rodriguez, H., Rodriguez-Merchan, E. C., Alvarez-Roman, M. T., & JiménezYuste, V. (2021). Applying World Health Organization 2020 guidelines on physical activity and sedentary behavior to people with hemophilia. *Expert Review of Hematology, 14*(5), 429436.

[7] Franjić, S. Intracerebral Hemorrhage.

[8] Garraud, O., Hamzeh-Cognasse, H., Chalayer, E., Duchez, A., Tardy, B., Oriol, P., . . . Cognasse, F. (2022). Platelet transfusion in adults: an update. *Transfusion Clinique et Biologique*.

[9] Ghetmiri, D. E., Cohen, M. J., & Menezes, A. A. (2021). Personalized modulation of coagulation factors using a thrombin dynamics model to treat trauma-induced coagulopathy. *NPJ systems biology and applications, 7*(1), 1-17.

[10] Hall, E. J., Carter, A. J., Bradbury, J., Barfield, D., & O'Neill, D. G. (2021). Proposing the VetCompass clinical grading tool for heat-related illness in dogs. *Scientific Reports, 11*(1), 111.

[11] Jain, K., & Ravikumar, P. (2020). Recent advances in treatments of cartilage regeneration for knee osteoarthritis. *Journal of Drug Delivery Science and Technology, 60*, 102014.

[12] Jankowska, K. I., Sauna, Z. E., & Atreya, C. D. (2020). Role of microRNAs in Hemophilia and Thrombosis in Humans. *International Journal of Molecular Sciences, 21*(10), 3598.

[13] Kato, T., Hanawa, T., Asou, M., Asakawa, T., Sakamaki, H., & Araki, M. (2021). Autoimmune factor V deficiency that took 16 years to diagnose due to pseudodeficiency of multiple coagulation factors. *Case reports in medicine, 2021*.

[14] Miller, C. H. (2021). The Clinical Genetics of Hemophilia B (Factor IX Deficiency). *The Application of Clinical Genetics, 14*, 445.

[15] Möller, K. Ä., Klein, S., Seeliger, F., Finn, A., Stenfors, C., & Svensson, C. I. (2019). Monosodium iodoacetate-induced monoarthritis develops differently in knee versus ankle joint in rats. *Neurobiology of Pain, 6*, 100036.

[16] Obeagu, E. I. (2022). Hemophilia B: A Review. *Int. J. Curr. Res. Chem. Pharm. Sci, 9*(1), 14-20.

[17] Perrin, G. Q., Herzog, R. W., & Markusic, D. M. (2019). Update on clinical gene therapy for hemophilia. *Blood, The Journal of the American Society of Hematology, 133*(5), 407-414.

[18] Peyvandi, F., Tavakkoli, F., Frame, D., Quinn, J., Kim, B., Lawal, A., . . . Wong, W. Y. (2019). Burden of mild hemophilia A: systematic literature review. *Hemophilia, 25*(5), 755-763.

[19] Ram Prakash, S. (2019). *Clinical Profile of Hemophilia Patients and Assessment of their Quality of Life.* Coimbatore Medical College, Coimbatore,
[20] Sanchez-Lara, P. A., Nathanson, J., & Valentino, L. A. (2022). Gene Therapy in Hemophilia: Latest Developments. In *Advances in Hemophilia Treatment* (pp. 155165): Springer.
[21] Sandilands, K., Williams, A., & Rylands, A. J. (2022). Carer burden in rare inherited diseases: a literature review and conceptual model. *Orphanet Journal of Rare Diseases, 17*(1), 1-20.
[22] Srivastava, A., Santagostino, E., Dougall, A., Kitchen, S., Sutherland, M., Pipe, S. W., . . . Windyga, J. (2020). WFH guidelines for the management of hemophilia. *Hemophilia, 26*, 1158.
[23] Wilkins, R. A. (2021). *Haemarthrosis of the ankle in hemophilia A and B: prevalence, impact and intervention.* University of Leeds,
[24] Yousphi, A. S., Bakhtiar, A., Cheema, M. A., Nasim, S., & Ullah, W. (2019). Acquired hemophilia A: a rare but potentially fatal bleeding disorder. *Cureus, 11*(8).