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Deficiency of F-VIII, F-IX and VWF are the Most Prevalent Clotting Factors in Nineveh Province

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Abstract
***Background*:** Hemophilia is a recessive mutation in X-linked chromosome. Hemophilia A is characterized by a deficiency of clotting factor F-VIII. Hemophilia B is characterized by a deficiency of clotting factor F-IX. Fibrin Stabilizer is a deficiency of F-XIII. Alexander's disease is a deficiency of clotting factor F-VII. Von Willebrand disease is a deficiency of clotting factor VWF. Afibrinogenemia is a deficiency of clotting factor F-I.
Aim: This study amid to find out prevalence of deficiency clotting factors in Nineveh province.
***Methods*:** This research was conducted at Ibn-Sina Teaching Hospital. Staco special kits were used to determine factors under the study.
Results: 365 out of 829 total patients have been detected deficiency in one or more of different types of factors. The most prevalence of deficiency factors in Nineveh are F-VIII, FIX and VWF. Infected males are more than females. The ages between 1-20 years and blood groups (A^+, B^+, and O^+) are most prevalent.
Conclusions: It is necessary to monitor patients during the initial disease, follow it up, and use effective treatment methods to limit the increased number of cases. Moreover, it is necessary to follow up on the family's genetic history to avoid new infections.
Keywords: Hemophilia, F-VIII, F-VII, F-IX, F-XIII, VWD.

Introduction:

The word (Hemophilia) is derived from two Greek words, Haima: means blood, and Philia means friend. It is a hereditary disease in which the patient lacks types of proteins called clotting factors that work with platelets to stop bleeding at the site of infection [1-3].

There are two main types of hemophilia. Hemophilia A is characterized by a deficiency of clotting factor F-VIII, and it accounts for about 90% of cases of hemophilia. 70% of cases of hemophilia A are considered to be of serious degree. Hemophilia B is characterized by a deficiency of clotting factor F-IX. Hemophilia is a very rare disorder, with approximately 1 in 1,000 people developing hemophilia A compared to 1 in 5,000 having hemophilia B [4, 5].

The third type of hemophilia is called acquired hemophilia. This disease is caused by the autoimmune antibodies of types F-VIII and F-IX of clotting factors. There are several predisposing factors, such as age, pregnancy, autoimmune disease, or cancer [6, 7].

Most cases of hemophilia are hereditary as a result of a defect in one of the genes for clotting factors carried on the X chromosome. On this basis, the number of infected males is more than females, because of the possibility infected females should be mutated both of X chromosomes [8].

The symptoms of hemophilia are characterized by severe bleeding and easy bruising. The severity of symptoms varies according to the deficiency in clotting factors. Bleeding can occur externally or internally. Signs of external bleeding include bleeding in the mouth from a wound, bruising, loss of teeth, or severe nosebleeds from any minor wound. Internal bleeding occurs, blood in the urine or stool, deep bruising, and deep joint or muscle bleeding. A person with hemophilia may experience internal bleeding in the brain as a result of exposure to trauma or exposure to a more serious injury. Symptoms of brain bleeding include headache, vomiting, lethargy, behavioral changes, and vision disturbances [9, 10].

Hemophilia is diagnosed through clinical signs, complete blood tests, clotting time, and clotting factor levels. Titrations of coagulation factors F-VIII and F-IX are performed to confirm diagnosis and determination of disease severity, as well as titration of coagulation time (partial prothrombin time PPT), prothrombin time – PT, partial thromboplastin time PTT and international normalized ratio INR [11-13].

The first treatment is by providing replacement therapy, which is the administration of or replacement of clotting factors that are usually low or missing. Treatment can also be given by transferring fresh plasma to the patient and sometimes by giving the seventh activated factor [14-16].

Factor F-XIII Deficiency (Fibrin Stabilizer): was first reported in 1960. It is the rarest factor deficiency, occurring in 1 out of 5 million births. It is inherited in an autosomal recessive manner, which means that both parents must carry

the gene to pass it on to their children. It affects men and women equally [17, 18].

Up to 30% of patients experience spontaneous intracranial hemorrhage, which is a brain hemorrhage leading cause of death. Other symptoms of F-XIII deficiency include bruising, nose and mouth bleeding, muscle bleeding, and delayed bleeding after surgery [19, 20].

Factor F-VII deficiency (Labile or Proconvertin, Alexander's disease): was first recognized in 1951. It is the most common rare bleeding disorder with an incidence estimated at 1 in 300,000-500,000. It is inherited in an autosomal recessive gene. F-VII is a protein that when it binds to a tissue factor, starts the coagulation cascade, which leads to the formation of a blood clot [21].

Babies are often diagnosed with F-VII deficiency during the first six months of their lives, after experiencing bleeding in the central nervous system, such as an intracranial or gastrointestinal hemorrhage. Bleeding can also occur in the skin, mouth, nose, and genitourinary system. Women often experience severe menorrhagia and heavy periods [22-24].

Von Willebrand disease (VWD): is an inherited disorder caused by a deficiency of clotting protein (VWF). VWF binds to factor F-VIII, and platelets in the walls of blood vessels, helping to form a platelet plug during the coagulation process. People with VWD experience continual nosebleeds, easy bruising, and extremist bleeding during and after invasive procedures, such as tooth extractions and surgery. Women often experience profuse menstrual bleeding and postpartum bleeding [25, 26].

Afibrinogenemia (congenital hemophilia): is an inherited blood disorder which the blood does not clot normally. It occurs in a deficiency of fibrinogen (factor F-I), which is necessary for blood to clot. Affected individuals may be prone to severe bleeding episodes, especially during infancy and childhood. Afibrinogenemia is assumed to be transmitted as an autosomal recessive mutation.

In the current study, we aimed to find out the number of patients with deficiency factors whether in F-I, F-VII, F-VIII, F-IX, F-XIII, and VWD in Nineveh province and estimate the significant correlation between factors and patients in age, gender, and the blood group. This study is carried out from September 2014 to November 2019 [27-29].

Materials and methods:

This research was conducted at Ibn-Sina Teaching Hospital. Blood samples were collected from patients who were subjected to initial clinical examinations. Tests were carried out to confirm hemophilia. Staco special kits were used for each factor. The tests were performed using Stago STart Hemostasis Analyzer Labx -Canada. The test is based on the coagulation method in which all the coagulation factors are present, except for the factor to measure, which is brought by the tested dilute plasma, and the coagulation is triggered with cephalin, activator (aPTT reagent), and calcium. The measurement factor is the determining factor and the coagulation time is inversely proportional to the concentration of the agent to be measured. There is an inverse linear relationship seen on a logarithmic graph paper, between the concentration measurement factor and the corresponding coagulation time. The number of patients participating in this study is 829 patients. They were clinically examined as deficient in one or more types of clotting factors. The patient's age is divided into 4 groups: (1-20y, 21-40y, 41-60y, and 61-80y).

According to the report of the specialist doctor, an examination of the deficiency of the factor was conducted according to the established data and the medical history of the patient in addition to determining whether there was a previous case of hemophilia in the patient's family. The statistical analysis was carried out using SPSS version 25. Comparison between variables and factors and significant values were conducted using one-way ANOVA.

Results:

365 out of 829 total patients have been detected deficiency in one or more of different types of factors. The number of patients for each detected factor were: F-I= 3, F-VII= 6, F-VIII= 301, F-IX=22, F-XIII= 10 and VWF= 30. Some patients had a deficiency in more than one factor. The mean, standard deviation, and standard error for variables and factors are illustrated in the table (1).

Table 1: Mean, standard deviation and standard error for variables and factors.

Parameter	No. Statistic	Mean	Std. Error	Std. Deviation
Gender	365	1.21	±0.021	0.410
Age	365	1.51	±0.032	0.605
Blood group	365	3.67	±0.118	2.255
F-XIII	10	3.100	±0.2879	0.9104
F-VIII	301	8.201	±1.1940	20.7149
F-IX	22	53.377	±8.5233	39.9780
F-VII	6	18.2667	±14.10548	34.55123
F-I	3	15.3333	±14.83333	25.69209
VWF	30	32.6120	±5.72275	31.34478

According to the genders with the deficient factors, all statistical parameters are shown in table (2). As a general, the number of infected males is more than females based on the type of factor, figure (1). The significant correlation between genders and factors with Pearson 2-detailed program is shown in table (2).

Table 2: Descriptive analysis and significant value of genders with all parameters. ↓↓: Correlation is significant at the 0.01 level.

Factor	Gender	N	Mean	Std. Deviation	Std. Error	Sig.
F-XIII	Male	9	3.067	0.9592	0.3197	
	Female	1	3.400	.	.	
	Total	10	3.100	0.9104	0.2879	0.116
F-VIII	Male	247	8.058	18.9928	1.2085	
	Female	54	8.854	27.4602	3.7369	
	Total	301	8.201	20.7149	1.1940	0.015
F-IX	Male	14	51.179	29.1198	7.7826	
	Female	8	57.225	56.5097	19.9792	
	Total	22	53.377	39.9780	8.5233	0.074
F-VII	Male	4	27.0100	41.03488	20.51744	
	Female	2	0.7800	0.02828	0.02000	
	Total	6	18.2667	34.55123	14.10548	-0.392
F-I	Male	2	0.5000	0.00000	0.00000	
	Female	1	45.0000	.	.	
	Total	3	15.3333	25.69209	14.83333	1.000↓↓
VWF	Male	12	41.8517	31.87316	9.20099	
	Female	18	26.4522	30.30245	7.14236	
	Total	30	32.6120	31.34478	5.72275	-0.245

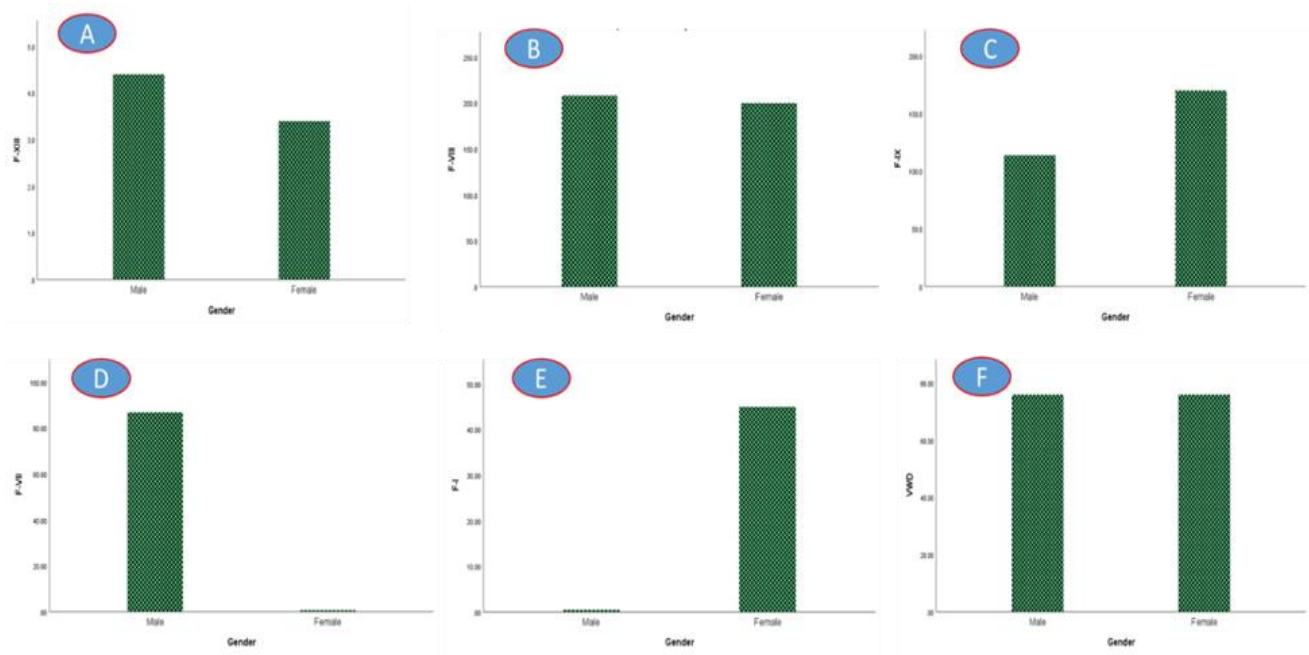

Fig. 1: Gender VS factors. A: F-XIII, B: F-VIII, C: F-IX, D: F-I, E: F-VII, F: VWD (VWF).

In the current study, most ages affected by hemophilia fall within the range of 1-40 years rather than other groups. The descriptive data was recorded between age groups and deficient factors are illustrated in the table (3). The significant value for variables is lucid in figure (2).

Table 3: Descriptive analysis and significant value of age groups with all parameters.

Factor	Age	N	Mean	Std. Deviation	Std. Error	Sig.
F-XIII	1-20y	5	2.840	1.0455	0.4675	
	21-40y	5	3.360	0.7765	0.3473	
	41-60y	0	.	.	.	
	61-80y	0	.	.	.	
	Total	10	3.100	0.9104	0.2879	0.301
F-VIII	1-20y	157	7.654	15.9601	1.2738	
	21-40y	128	9.349	26.3705	2.3308	
	41-60y	15	4.360	4.0410	1.0434	
	61-80y	1	4.600	.	.	
	Total	301	8.201	20.7149	1.1940	0.006
F-IX	1-20y	17	54.535	40.9823	9.9397	
	21-40y	5	49.440	40.5890	18.1520	
	41-60y	0	.	.	.	
	61-80y	0	.	.	.	
	Total	22	53.377	39.9780	8.5233	-0.055
F-VII	1-20y	3	29.3333	49.94170	28.83385	
	21-40y	2	10.4200	13.54817	9.58000	
	41-60y	0	.	.	.	
	61-80y	1	.7600	.	.	
	Total	6	18.2667	34.55123	14.10548	-.338
VWF	1-20y	23	31.8826	31.39236	6.54576	
	21-40y	7	35.0086	33.56424	12.68609	
	41-60y	0	.	.	.	
	61-80y	0	.	.	.	
	Total	30	32.6120	31.34478	5.72275	0.43

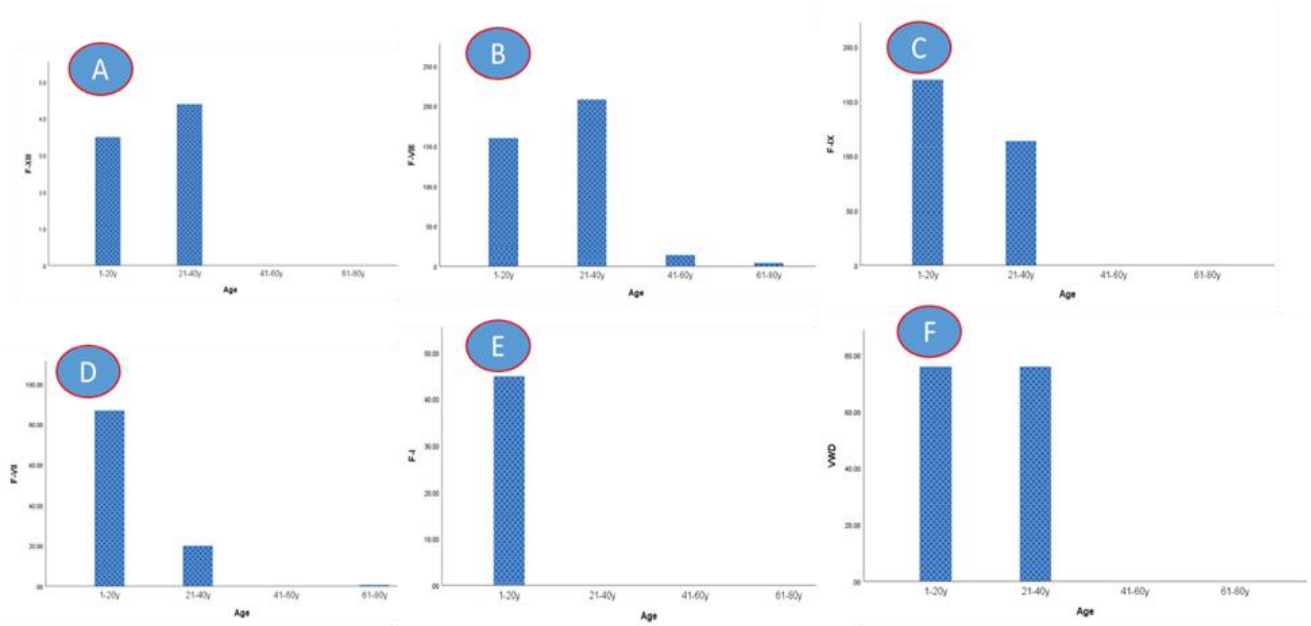

Fig. 2: Age groups VS factors. A: F-XIII, B: F-VIII, C: F-IX, D: F-I, E: F-VII, F: VWD (VWF).

Through the analysis of the initial results, it is generally clear that most of the blood groups exposed to hemophilia are A^+, B^+, and O^+. The metadata was recorded between blood groups, and the missing factors were explained in Table (4). The significant value of the variables is evident in figure (3).

Table 4: Descriptive analysis and significant value of blood groups with all parameters.

Factor	B.group	N	Mean	Std. Deviation	Std. Error	Sig.
F-XIII	A+	4	3.250	.2887	.1443	
	A-	0	.	.	.	
	B+	2	2.950	.9192	.6500	
	B-	0	.	.	.	
	AB+	3	3.700	.6083	.3512	
	O+	1	1.000	.	.	
	O-	0	.	.	.	
	Total	10	3.100	.9104	.2879	-.0.333
F-VIII	A+	79	10.806	29.6523	3.3361	
	A-	12	4.033	2.1343	0.6161	
	B+	95	8.229	21.6551	2.2218	
	B-	6	4.950	5.1189	2.0898	
	AB+	39	7.949	13.8950	2.2250	
	O+	63	6.790	10.9053	1.3739	
	O-	7	2.429	1.2107	0.4576	
	Total	301	8.201	20.7149	1.1940	0.068
F-IX	A+	8	57.375	50.2405	17.7627	
	A-	0	.	.	.	
	B+	6	51.050	48.4983	19.7994	
	B-	0	.	.	.	
	AB+	3	40.000	5.1962	3.0000	
	O+	5	57.800	28.6566	12.8156	
	O-	0	.	.	.	
	Total	22	53.377	39.9780	8.5233	-0.28
F-VII	A+	2	43.8800	60.98089	43.12000	
	A-	0	.	.	.	
	B+	2	0.8200	0.02828	0.0200	
	B-	0	.	.	.	
	AB+	0	.	.	.	
	O+	2	10.1000	14.00071	9.90000	
	O-	0	.	.	.	
	Total	6	18.2667	34.55123	14.10548	-0,355
VWF	A+	5	40.7100	36.45779	16.30442	
	A-	0	.	.	.	
	B+	13	31.9954	31.06120	8.61483	
	B-	2	66.0000	14.14214	10.00000	
	AB+	4	26.1350	29.51887	14.75943	
	O+	5	24.3060	34.26698	15.32466	
	O-	1	0.8000	.	.	
	Total	30	32.6120	31.34478	5.72275	-0.210

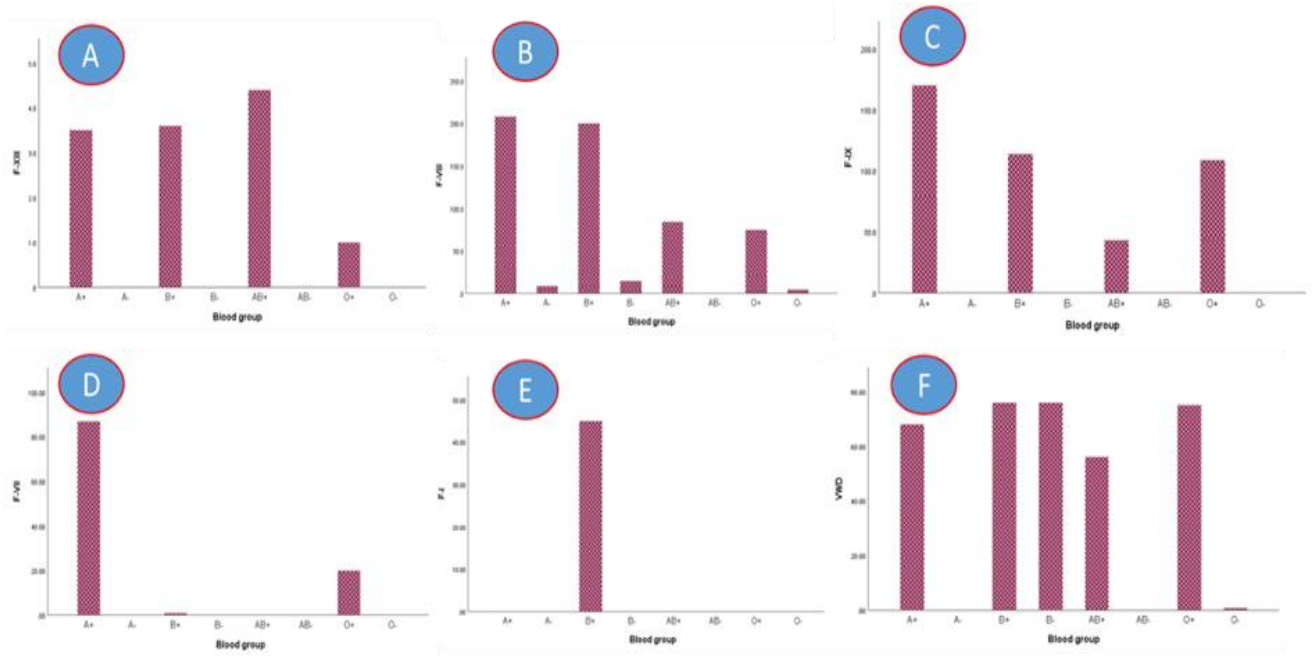

Fig. 3: Blood group VS factors. A: F-XIII, B: F-VIII, C: F-IX, D: F-I, E: F-VII, F: VWD (VWF).

Through the statistical analysis of the results, we found that the most prevalent factors in the Nineveh governorate are the F-VIII, F-IX, and VWF. A comparison was made between the two factors according to the main characteristics of the study, figure (4).

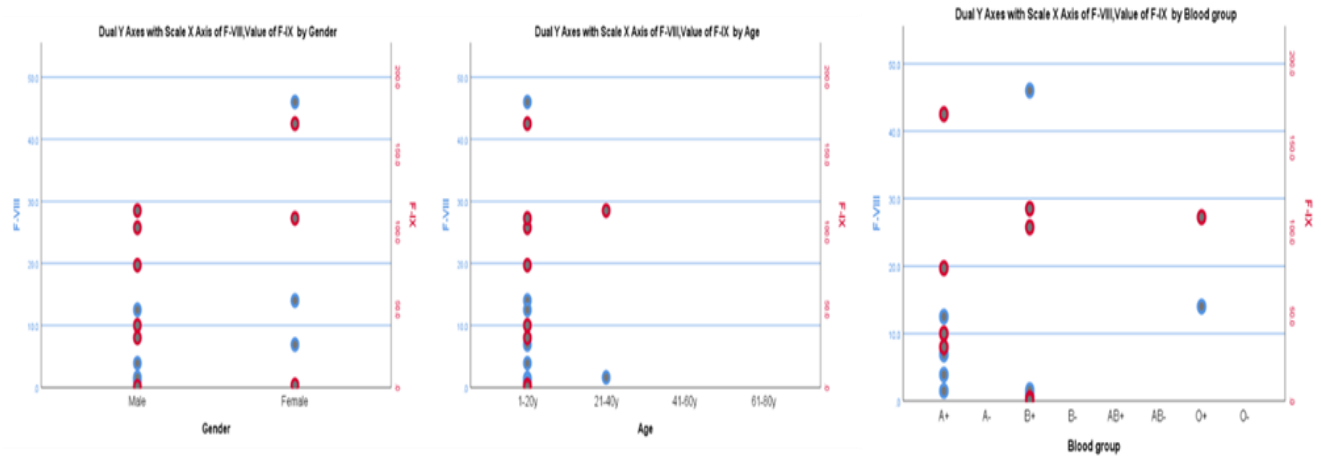

Fig. 4: Comparison between F-VIII and F-IX with gender, age, and blood groups. Blue circle: F-VIII. Red circle: F-IX.

Discussion:

Hemophilia is considered one of the common diseases worldwide. Hemophilia appears as a result of a deficiency of one or more of the proteins called clotting factors in platelets which are responsible for the clotting of the blood. The Deficiency of any clotting factor may lead to bleeding in certain parts during wounds or even internal bleeding of the body's organs [30].

There are three main challenges facing doctors who care for patients with hemophilia type A today: improving results by increasing use for prevention of F-VIII. Prevention and elimination of Inhibitors of F-VIII. Expanding access to F-VIII concentrates on developing countries [31].

Through the preliminary analysis of the study results, it has clear that the highest number of the deficiency factor was F-VIII, and this is not surprising because most studies confirmed that deficiency of F-VIII is the most common. The number of patients reached 301 out of 365, with a rate of 82.4%. This result is agreed upon with the done studies [32]. The deficiency in VWF reached 30 patients with a rate of 8.2%. Then, the deficiency of F-IX in 22 patients with a rate of 6%. Since hemophilia is linked to the X chromosome. It is plausible that males will have more infected than females for all factors except for VWF where females were affected more than males. Our data recorded a correlation coefficient between genders and F-I with $P < 0.01$. There is a significant value between genders and all

other factors under study. The concentration of F-IX and F-I was more in females than males and equal between the genders for the VWF.

It has been recorded that the most vulnerable age groups are between 1- 40 years old, and this is what is realistically recorded in most studies [33]. There is no significant relationship observed between the age groups and the factors under study. Most hemophiliacs are confined to A^+, B^+, and O^+ blood groups except VWF were recorded high numbers with B^- and AB^+ blood groups. There is no significant relationship between blood groups and factors.

By observing the measurement of the concentration of the factors, it becomes clear that the F-VIII is the highest concentrations compared to the F-IX. The most age group in which an increase in the number of injuries was shown between 1-20 years old for the main factors. On the other hand, the number of injured persons for blood type A is the major group compared to other blood types for F-VIII and F-IX. The number of cases was observed approximately equal between F-IX and VWF due to that the F-IX is usually considered relating to VWF [34].

Hemophilia can be treated safely and effectively by infusion of clotting factor concentrates that are currently available. Joint weakness can be prevented by regular administration of these concentrates. In cases of emergency shock, it is necessary to administer clotting factor concentrates immediately. All potential carriers should be identified to optimize genetic counseling and hemostasis at the time of delivery. This may prevent excessive bleeding in the mother and any newborns with hemophilia. Because hemophilia is a rare disease that needs a multidisciplinary approach, patients should be cared for in comprehensive care hemophilia treatment centers.

Conclusion:

Although hemophilia is a rare disease, there are monitored numbers in Nineveh governorate that cannot be underestimated. Through this study, it is clear that deficiency of factors (F-VIII, F-IX, and VWF) are the most prevalent. The age group at highest risk is between 1-20 years. The study recorded that the most susceptible blood types are: A^+, B^+, and O^+. It is necessary to monitor patients during the initial disease, follow it up, and use effective treatment methods to limit the increased number of cases. Moreover, it is necessary to follow up on the family's genetic history to avoid new infections.

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