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**Hematology**

# Assesment of the Risk Factors and Frequency of Iron Deficiency Based on the Severity of Hemophilla-A

Dr. Md. Adnan Hasan Masud[1*], Dr. Khan Anisul Islam[2], Dr. Atiar Rahman[3], Dr. Md. Khairul Islam[4], Dr. Farah Anjum Sonia[5], Dr. Zia Uddin Ahmed[6], Dr. Shahanaj Parveen[7]

[1]Assistant Professor, Dept. of Hematology, BSMMU, Dhaka, Bangladesh
[2]Assistant Professor, Dept. of Transfusion Medicine, BSMMU, Dhaka, Bangladesh
[3]Associate Professor, Dept. of Transfusion Medicine, BSMMU, Dhaka, Bangladesh
[4]Assistant Professor, Dept. of Transfusion Medicine, NITOR, Dhaka, Bangladesh
[5]Assistant Professor, Dept. of Transfusion Medicine, BSMMU, Dhaka, Bangladesh
[6]Associate Consultant, Dept. of Transfusion Medicine, BRB Hospital Ltd., Dhaka, Bangladesh
[7]Junior Consultant, Dept. of Transfusion Medicine, BSMMU, Dhaka, Bangladesh

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***Corresponding author:** Dr. Md. Adnan Hasan Masud
Assistant Professor, Dept. of Hematology, BSMMU, Dhaka, Bangladesh

**Abstract** **Original Research Article**

***Background:*** Hemophilia is a rare inherited X-linked recessive disorder characterized by deficiency of Factor VIII or Factor IX coagulant activity required for generation of Thrombin in the Intrinsic pathway of coagulation. Prevalence of hemophilia in Bangladesh in unknown. With increase in severity of the disease, patients experience increased frequency of spontaneous bleed. Iron deficiency is expected in these vulnerable population due either to presence of occult blood loss in urine/stool or deposition of iron in synovial membrane during repeated bleeding episodes. ***Objective:*** To find out frequency and relative risk of iron deficiency according to severity of hemophilla-A. ***Methods:*** This cross-secitonal study was conducted in the Department of Transfusion Medicine, BSMMU, Dhaka from 1-03-2021 to 1-03-2022. Within this period, a total of 56 hemophilia patients who visited the Department of Transfusion Medicine of BSMMU were included in this study. All patients were thoroughly evaluated by history and clinical examination. Baseline characteristics including age, sex, height, weight, smoking status will be recorded, relevant other information like pulse, blood pressure, temperature, anemia, hypertension, diabetes, CBC, hemoglobin, ferritin, bleeding time, clotting time, prothrombin time were recorded in a preformed data collection sheet. The results were expressed as frequency & percentage (categorical data) and mean ± SD (numerical data). Unpaired t-tests and Chi-Square tests will be performed as applicable using SPSS for windows version 22.0 and $p<0.05$ will be considered as the level of significant. Ethical clearance will be obtained from the Institutional Review Board (IRB) of BSMMU. ***Results:*** Prevalence of iron deficiency was 29 (51.8%) among the patients with hemophilia A. Mean age of hemophilia patients was 18.39 ± 8.43 years and maximum of them were in age group 11-20 years. Most common bleeding sites were knee joint (41.1%), ankle joint (19.6%), hip joint (17.9%) and elbow joint (12.5%). MCV, MCH MCHC and serum ferritin were found significantly lower in hemophilia A patients with iron deficient than iron replete. ***Conclusion:*** Iron deficiency is very common among patients with hemophilia A, the frequency and relative risk of which is higher among patents with severe disease. Therefore, the disease severity is a risk factor for iron deficiency in hemophila-A. Patients with hemophila-A should be screened regularly for iron deficiency to initiate early treatment and prevent the adverse impact of iron deficiency on wound healing, the immunity and the mental development of haemophilia patients.

**Keywords**: Hemophilia, Spontaneous bleed, Iron deficiency, pulse, blood pressure, temperature, anemia, hypertension.



## INTRODUCTION

Hemophilia is a group of hereditary X-linked recessive disorder characterized by deficiency of factor VIII or IX coagulant activity [1]. It is the most common congenital bleeding encountered in clinical practice affecting men, whereas females are usually carriers [2]. It is also known as the royal disease because Queen Victoria of the UK was a carrier of hemophilia and passed the gene to her daughters (carriers) and her son Leopold (hemophilia) [3]. Persons with hemophilia (PWH) lack sufficient amounts of or functional clotting factors VIII or IX in their blood resulting in an increased bleeding tendency. Clotting factors VIII and IX deficiencies are known as hemophilia A (HA) and

hemophilia B (HB), respectively. HA is more common and occurs 1:5,000 live male births. However, HB occurs 1:1,500-25,000 male births [4]. Till date, 1,748 Hemophilia patients have been identified in Bangladesh. However, to go by the prevalence rate, there could be 11,000 hemophilia patients and people with other inherited bleeding disorders in the country [5].

Inadequate FVIII levels result in the insufficient generation of thrombin by the FIXa and FVIIIa complex in the intrinsic pathway[6]. The severity of the Hemophilia A disease is largely determined by the extent to which different mutations abolish functional FVIII production. Severe disease is typically associated with null mutations including inversions, insertions, deletions and nonsense and mis-sense mutations, whereas milder disease is usually caused by non-null mutations such as mis-sense, single-nucleotide deletions and splicing error mutations [6]. The clinical severity of the Hemophilia A is correlated with residual FVIII levels, which is classified as severe (FVIII level<1%), moderate (FVIII level 1-5%) or mild (FVIII level 6- 40%). Hemophilia A is a lifelong bleeding disorder, the clinical course of which is dominated by both overt and covert blood loss. Frequent external blood loss from orifices, the skin and epithelial injuries would be expected to eventually cause iron deficiency in HA. Patients with.

HA, especially in severe cases, also suffer from frequent internal blood loss within the joints, resulting in the deposition of iron in the synovium [7].

Bleeding can occur anywhere from the body. The common sites are into joints and muscles and from the gastrointestinal tract. Approximately 80% of haemorrhage occurs in the joints; the ankles are most commonly affected in children, and the knees, elbows, and ankles in adolescents and adult. Spontaneous hemarthroses are characteristic of severe disease. Depending on their CF level at diagnosis, hemophilia is classified as mild, moderate or severe. Those with the severe hemophilia may bleed spontaneously and into their joints starting in the early years of life. They have the highest bleeding tendency and are highly depending on replacement therapy to live a normal life. Before replacement therapy become available, Person with severe hemophilia could hardly survive to their third decade of life. Persons with moderate hemophilia usually bleed due to trauma but could also experience spontaneous bleeding. Finally, those with mild hemophilia mostly bleed due to trauma. They are usually diagnosed as a result of family investigation or prolonged bleeding following trauma or surgery. Molecular severity may not reflect on the clinical severity meaning that people with similar CF level may have different bleeding tendencies [8]. In addition, the CF levels may rise over age resulting in changes in the severity of hemophilia [9]. Rise of CF level reduces the need for treatment and has implications for tailoring treatment among adults.

Iron deficiency might add on to the morbidity in Hemophiliacs. The iron deficiency can be due to the presence of occult blood loss in the urine and stools or due to the deposition of iron in the synovial membrane during repeated bleeding episodes [10]. Also, concurrent parasitic infestation, which is a common entity, may contribute to the iron deficiency.

Increased synovial iron stores in haemophiliac patients cannot possibly compensate for the iron deficiency resulting from external blood loss and the depletion of normal storage compartments such as the liver and the bone marrow. It can thus be reasonably predicted that HA would be causally related to iron deficiency, a condition that could potentially have an adverse impact on the clinical status of the haemophilic patient. Nonetheless, iron deficiency has not been studied adequately in haemophilia, and there is a dearth of information on this subject matter in the literature. A solitary study on the iron status of haemophiliac patients conducted on a cohort of only seven patients revealed that marrow iron stores were decreased in all and absent in four patients despite increased iron deposits in the synovium. There is therefore the need for more studies on iron deficiency in haemophilia. We predict that HA would be strongly associated with iron deficiency, and that there will be a clear correlation between the frequency of iron deficiency and the disease severity among patients with HA. If our prediction is correct, the frequency and the relative risk (RR) of iron deficiency will be higher in patients with severe HA in comparison with those having nonsevere HA. To test our prediction, we prospective evaluated the levels of haemoglobin concentrations, red cell indices and serum ferritin with respect to the disease severity in this study (Ahmed *et al.*, 2015).

**Objectives:**

**General Objectives:**

To find out frequency and risk factor of iron deficiency according to severity ofhemophilla-A.

**Specific Objectives:**

- To correlate of iron deficiency anaemia with hemophilia-A.
- To correlate serum iron profile with hemophilia-A.
- To correlate red cell indices with hemophilia-A.

## METHODOLOGY

**Types of Study:** It was a cross-sectional study.

**Study Period:** It was conducted from 1-03-2021 to 1-03-2022.

**Place of Study:** This study was carried out in the Department of Transfusion Medicine at BSMMU, Shahbag, Dhaka

**Study Population:** Hemophilia A patients.

**Sample Size:** Due to lack of resources and time constrain 56 samples are included in this study.

**Selection Criteria:**
Study subjects will be selected according to following inclusion and exclusion criteria.

**Inclusion Criteria:**

- Patients presented with bleeding diathesis.
- Patients who are not taking iron supplements.

**Exclusion Criteria:**

- Bleeding disorders other than hemophilia-A.
- Patients with fever or any evidence of infection.
- Patients with whole blood transfusion or red cell concentrate in the last 3 months

**Variables:**

- Age
- Anaemia
- Haemoglobin concentration
- Red cell indices
- Serum ferritin,
- Site of bleeding

**Study Procedure:**

Patients with hemophilia A attending at the Department of Transfusion Medicine at BSMMU were selected on the basis of the inclusion and exclusion criteria. Baseline characteristics including age, sex, height, weight will be recorded, relevant other information like pulse, blood pressure, temperature, anemia, COPD, hypertension, diabetes, CBC, hemoglobin, ferritin level, bleeding time and clotting time will be recorded in a preformed data collection sheet. All the data were compiled and sorted properly.

**Data Collection:**

Data will be collected in a pre-designed questionnaire.

**Data Processing and Analysis:**

Data were analyzed by using Statistical Package for Social Science version 22 (SPSS-22). The results were expressed as frequency with percentage (categorical data) and mean with standard deviation (numerical data) and $p<0.05$ will be considered as the level of significant. Unpaired t-tests was done for numerical data and Chi-Square tests was done for categorical data.

# RESULT

This cross-sectional observational study was conducted in the Department of Transfusion Medicine, Bangabandhu Sheikh Mujib Medical University to find out frequency of iron deficiency among patients with hemophilia A. The results are as follows:

**Table1: Frequency of iron deficiency among the patients with Hemophilia A (N=56)**

| Iron deficiency | Frequency (n) | Percentage (%) |
|---|---|---|
| Yes | 29 | 51.8 |
| No | 27 | 48.2 |

Table 1 shows frequency of iron deficiency among the patients with hemophilia. Prevalence of iron deficiency was 29 (51.8%) among the patients with hemophilia A.

**Table 2: Iron deficiency in different age group of the patients with Hemophilia A (N=56)**

| Age (years) | All patients | Iron deficient | Iron replete | p-value |
|---|---|---|---|---|
| 2-10 | 7 (12.5) | 5 (17.2) | 2 (7.4) | |
| 11-20 | 32 (57.1) | 20 (69.0) | 12 (44.4) | |
| 21-30 | 11 (19.6) | 4 (13.8) | 7 (25.9) | |
| 31-40 | 6 (10.7) | 0 (0.0) | 6 (22.2) | |
| Mean ± SD | 18.39±8.4 | 14.97±6.58 | 22.07 ± 8.75 | 0.001 |

Uniqued t test was done

Table 2 shows Iron deficiency in different age group of the patients with hemophilia A. Iron deficient was prevalent among the young. There was significant association of Iron deficiency with age of the patients with hemophilia A. Mean age of hemophilia patients was 18.39 ± 8.43 years and maximum of them were in age group 11-20 years.

**Table 3: Iron deficiency in different occupation of the patients with hemophilia A (N=56)**

| | All patients | Iron deficient | Iron replete | p-value |
|---|---|---|---|---|
| Severe | 10 (17.9) | 2 (6.9) | 8 (29.6) | 0.002 |
| Student | 37 (66.1) | 23 (79.3) | 14 (51.9) | |
| Businessmen | 5 (8.9) | 0 (0.0) | 5 (18.5) | |

| | | | | |
|---|---|---|---|---|
| Children | 4 (7.1) | 4 (13.8) | 0 (0.0) | |

Chi-Square test was done

Table 3 shows Iron deficiency in different occupation of the patients with hemophilia. Iron deficient was found significantly higher among the student with hemophilia A.

**Table 4: Bleeding site of the patients with Hemophilia A according to Iron deficiency (N=56)**

| Bleeding site | All patients | Iron deficient | Iron replete | p-value |
|---|---|---|---|---|
| Knee Joint | 23 (41.1) | 10 (34.5) | 13 (48.1) | 0.246 |
| Gum bleeding | 3 (5.4) | 3 (10.3) | 0 (0.0) | |
| Ankle Joint | 11 (19.6) | 7 (24.1) | 4 (14.8) | |
| Elbow Joint | 7 (12.5) | 4 (13.8) | 3 (11.1) | |
| Knee & elbow joint | 1 (1.8) | 1 (3.4) | 0 (0.0) | |
| Hip Join | 10 (17.9) | 3 (10.3) | 7 (25.9) | |
| Ankle & Knee Joint | 1 (1.8) | 1 (3.4) | 0 (0.0) | |

Chi-Square test was done

Table 4 shows bleeding site of the patients with hemophilia according to Iron deficiency. Most common bleeding sites were knee joint (41.1%), ankle joint (19.6%), hip joint (17.9%) and elbow joint (12.5%).

**Table 5: Biochemical parameters of the patients with Hemophilia A according to severity of hemophilia A (N=56)**

| Serum ferritin (ng/ml) | | | | |
|---|---|---|---|---|
| | Severe | Moderate | Mild | p-value |
| Hemophilia (g/dl) | 9.98±2.56 | 12.63±0.83 | 14.99±2.08 | <0.001 |
| MCV (1) | 74.80±10.41 | 82.24±5.31 | 82.99±4.42 | 0.008 |
| MCH (pg) | 23.97±3.90 | 25.53 ±2.24 | 26.19±1.71 | 0.143 |
| MCHC (gm/dl) | 31.16 ± 1.70 | 30.98±1.31 | 32.47±1.68 | 0.106 |
| Serum ferritin (ng/ml) | 82.24 ±5.31 | 110.00±37.14 | 189.69±34.64 | 0.001 |

ANOVA test was done

Table 5 shows biochemical parameters according to severity of Hemophilia A. According to the severity of Hemophilia A, hemoglobin, MCV and serum ferritin were reduced. Serum ferritin was 88.09 ± 58.14 ng/ml in severe hemophilia patients, 110.00 ± 37.14 ng/ml in moderate hemophilia patients and 189.69 + 34.64 ng/ml in mild hemophilia patients.

**Table 6: Association of severity of Hemophilia A with Iron deficiency (N=56)**

| Severity of hemophilia | All patients | Iron deficient | Iron replete | p-value |
|---|---|---|---|---|
| Severe | 33 (58.9) | 27 (81.8) | 6 (18.2) | <0.001 |
| Moderate | 16 (28.6) | 1 (6.3) | 15 (93.8) | |
| Mild | 7 (12.5) | 1 (14.3) | 6 (85.7) | |

Chi-Square test was done

Table 6 shows severity of hemophilia according to Iron deficiency. Severity of hemophilia had a strong association with iron deficiency. Severe hemophilia was 33 (58.9%), moderate hemophilia was 16 (28.6%) and mild hemophilia was 7 (12.5%).

## DISCUSSION

This study population comprised of 56 hemophilia A patients. All of the patients had mild to severe hemophilia in this study. Iron deficiency was found in 51.8% hemophilia A patients. Iron deficiency was found 48.7% hemophilia A patient in a study conducted in Nigeria. Among 50 hemophilia patients 36(72%) had haemoglobin<13 mg/dl [12]. Haptoglobin was low in 44% of patients, 31% had igb less than the 3rd percentile, 46% below the 10th percentile, and 83% below the mean value [13]. Iron deficiency was occurred in 28.3% and Iron deficiency was developed in 58.3% of hemophilia patients.

Higher results of iron deficiency are resulting from recurrent bleeding episodes either as external bleeding from orifices (as epistaxis, the skin, epithelial tissues and occult blood from both gastrointestinal and genitourinary system) or from frequent internal bleeding most commonly inside the joint and infrequently from internal organs like abdomen or brain [11].

In this study, most common bleeding sites were knee joint (41.1%), ankle joint (19.6%), hip joint (17.9%) and elbow joint (12.5%). In the study most common presentation of bleeding was joint bleeding 64.96%, followed by muscle 19.68% & gum bleeding 7.08%, petechiae 3.54%, and epistaxis 4.46%. While

Uddin (2006) reported wound bleeding (52%) & bleeding after tooth extraction (38%), Karim *et al.*, (2013) reported gum bleeding (38%) & bleed during surgical procedure such as circumcision & tooth extraction (28%) other rare presentations were hematemesis, malena, epistaxis (2%) while mucosal bleeding (15%) was reported by Hazewinkel *et al.*, (2003) [15,16].

In this study, iron deficiency was prevalent in 11-20 years age group (59.1%). There was a significant association of Iron deficiency with age of the patients.

In this study 51.8% hemophilia A patients had iron deficiency. In the study of Ahmed *et al.*, (2015), haemoglobin levels showed that all patients had moderate to severe anaemia due to active haemorrhage at the time of diagnosis [11]. Moreover, patients with iron deficiency, irrespective of the disease severity. had lower haemoglobin levels with reduced red cell indices due to the additional effect of iron deficiency. In their study about one half of their patients with HA had iron deficiency. In comparison with nonsevere HA, patients with severe HA had a significantly higher frequency of iron deficiency with an RR of 2.6. Their data suggest that patients with severe HA were about two and a half times more likely to develop iron deficiency than their counterparts with nonsevere HA.

Clinical implications of iron deficiency in HA go beyond anaemia. Iron deficiency has several adverse implications on wound healing, immunity and mental development that may affect the well-being of patients with HA. Experimental models have demonstrated that a number of bleeding disorders including FXIII deficiency, FIX deficiency and dysfibrinogenaemias adversely affect wound healing, suggesting that efficient haemostasis and adequate fibrin deposition are essential for initiating the healing process (Rodriguez-Merchan, 2012) [17]. Although there was no specific study on the effect of wound healing on HA, an experimental study on haemophilia-B (which is clinicopathologically closely related to HA), revealed evidence of impaired wound healing [18]. Therefore, by implication, HA would also be associated with poor wound healing. Iron deficiency impairs wound healing through a number of mechanisms, which include deregulation of hypoxia-inducible factor expression, decreased lactoferrin-mediated cell proliferation and attenuation of collagen synthesis [19].

In this study, Severe hemophilia was 33 (58.9%), moderate hemophilia was 16 (28.6%) and mild hemophilia was 7 (12.5%). In the study of Poongavanam *et al.*, (2017), Severe hemophilia was 70.0%, moderate hemophilia was 10.0% and mild hemophilia was 12.0% [12]. Researcher found mild disease in 25.19% of hemophilia A, moderate disease in 38.84% in hemophilia A, severe disease in 33.93% in hemophilia A, while Uddin *et al.*, (2006) reported 45%, 42.5% & 12.5% as mild, moderate & severe respectively [15]. Karim (2013) reported 52.5% as mild disease in Hemophilia A and moderate-47.5% in Hemophilia Hazewinkel (2003) found 22%, 29% & 43% in mild, moderate & severe respectively [16, 20]. These variations may be due to difference in population studied, health care facilities available & social paradigms.

In this study, serum ferritin was 88.09 58.14 ng/ml in severe hemophilia patients, 110.00 ± 37.14 ng/ml in moderate hemophilia patients and 189.69 ± 34.64 ng/ml in mild hemophilia patients. In the study of Poongavanam *et al.*, (2017), serum ferritin was comparatively low compare to this study [16]. They found serum ferritin 51.09 ± 19.13 ng/ml in severe hemophilia patients, 48.20 ± 11.41 ng/ml in moderate hemophilia patients and 54.10 ± 14.89 ng/ml in mild hemophilia patients. In developing countries where due to poor sanitary conditions there is high incidence of intestinal infestation, occult blood loss through gastrointestinal tract could also be an important contributing factor to iron deficiency. Even though Bangladesh is a developing country, its sanitation system is comparatively better than other neighboring developing countries. This study shows mean ferritin level within normal limits. Other serum iron studies might be helpful to aid in the diagnosis of Iron deficiency. A study done in Haemophilia A patients in Northern Nigeria found that higher frequency of.

## CONCLUSION

Iron deficiency is very common among patients with hemophila-A in Bangladesh. The frequency of iron deficiency was higher among patients with severe hemophila-A. Therefore, the disease severity is a risk factor for iron deficiency in hemophila-A. Patients with hemophila-A should be screened regularly for iron deficiency to initiate early treatment and prevent the adverse impact of iron deficiency on wound healing, the immunity and the mental development of hemophilia patients.

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