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Clinical Profile of Bleeding Patterns Among Hemophilia A Patients in East Java, Indonesia

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ABSTRACT

Background: Hemophilia often presents with recurrent and spontaneous hemorrhages, which may involve deep muscles, leading to hematoma formation and hemarthrosis. There is a paucity of evidence regarding bleeding patterns in hemophilia, especially in low- and middle-income countries. This study aimed to describe the bleeding patterns among patients with Hemophilia A.

Methods: A cross-sectional study was conducted by collecting data from children with Hemophilia A registered at the Indonesian Hemophilia Society (IHS) in East Java between January 2019 and May 2024. The bleeding patterns analyzed included annualized bleeding rate (ABR) and bleeding types.

Results: A total of 71 pediatric patients with Hemophilia A were enrolled: mild (n=19, 27%), moderate (n=50, 70%), and severe (n=2, 3%). The mean patient age was 10 years, and the mean age at diagnosis was 4 years. Hematoma was the initial complaint in approximately 39% of patients. The bleeding types among mild versus moderate hemophilia included gum bleeding (77% vs. 23%), epistaxis (33% vs. 66%), hemarthrosis (50% vs. 50%), intracranial hemorrhage (66% vs. 33%), hematuria (66% vs. 33%), and post-traumatic bleeding (50% vs. 50%). The most frequently affected joints were the knee (75%), ankle (68%), and elbow (66%) across the severity classifications. In patients with mild hemophilia, ABR values were: 12/year (n=9, 47%), 13–24/year (n=5, 26%), and >24/year (n=5, 26%). In moderate hemophilia: 12/year (n=24, 48%), 13–24/year (n=17, 34%), and >24/year (n=9, 18%). In severe hemophilia, ABR was >24/year in both patients (100%).

Conclusion: Moderate hemophilia A was more prevalent than mild or severe. Surprisingly, severe bleeding events such as intracranial hemorrhage were more common in the mild group. The ABR was highest among patients with the severe hemophilia A.

Keywords: *Annual bleeding rate, Bleeding, Haemophilia A, Haemorrhage, Severity*

1. INTRODUCTION

Hemophilia, commonly referred to as the 'royal disease,' is an uncommon X-linked recessive genetic bleeding ailment. Hemophilia A is associated with a deficiency of clotting factor VIII, while deficiencies of clotting factors IX and XI result in hemophilia B and C, respectively [(1)]. Hemophilia A is acknowledged globally, with a prevalence of 6 per 100,000 individuals and an incidence rate of 1:5,000. The incidence of hemophilia A is around 6.6 per 100,000 males in low-income countries and 12.8 per 100,000 males in high-income countries. Hemophilia primarily affects men because it is an X-linked, recessive disorder [(2)]. Patients with hemophilia are more likely to bleed or develop clots because they do not have enough clotting factors VIII and IX, which are essential for blood coagulation.

The activity level of the coagulation factor classifies this condition into three degrees of severity: mild, moderate, and severe. Severe hemorrhagic episodes can occur in different locations, such as the genitourinary system, gums, mucosal membranes, and particularly the joints, with the knee joints being the most vulnerable. Furthermore, significant hemorrhaging in vital areas, including as the brain, gastrointestinal system, and the neck, has been recorded, each representing a serious risk for

patient life [3]. Individuals with severe hemophilia may encounter spontaneous hemorrhaging, but those with moderate types typically sustain bleeding following mild to moderate trauma. Patients with mild hemophilia may remain undiagnosed for years and exhibit hemorrhage just following surgical procedures or significant trauma [4]. Hemarthrosis is the hallmark of a severe form of hemophilia and is the most common outcome. It occurs either spontaneously or following trauma. In Bangladesh, nearly eighty percent of children with hemophilia displayed joint symptoms, with knee joint arthropathy being the most common. Nonetheless, certain European investigations identified primarily ankle joint involvement. Muscular hemorrhage transpires in 10–25% of hemorrhagic incidents associated with severe hemophilia and is considered a significant contributor to impairment in this condition. Approximately seventy-five percent of individuals with severe hemophilia have muscular bleeding at some point in their lives [5]. CNS hemorrhage is an additional cause of morbidity and mortality in hemophilia. Gastrointestinal hemorrhage occasionally manifests in hemophilia. It may arise spontaneously or as a consequence of prevalent causes of gastrointestinal hemorrhage. Hematuria is a concerning symptom of hemophilia that may exacerbate hydronephrosis or ureteral blockage in specific people. Investigating the prevalence and sites of hemorrhage in individuals with hemophilia might enable the prediction and prompt recognition of the condition in previously undetected cases. Consequently, it facilitates the implementation of prompt safeguards. The annualized bleeding rate (ABR) is recognized as an effectiveness metric for prophylactic replacement therapy, complementing evaluations of FVIII or FIX trough levels. Nonetheless, modern clinical studies progressively employ ABRs as primary and comparative outcome measures. This study aimed to investigate the bleeding patterns, including episodes and kinds, in patients with hemophilia A in East Java.

2. MATERIALS AND METHODS

This research employed a cross-sectional design utilizing comparative analytical techniques. The Indonesian Hemophilia Society supplied a roster of hemophilia A patients in East Java from January 2019 to May 2024. Data on bleeding episodes experienced by patients in the past year was gathered through direct interviews during their hospital visits for check-ups. Parents of children with hemophilia who withheld consent were excluded from the study. Informed consent from parents was acquired. Demographic and clinical information, including age, age at diagnosis, severity, bleeding presentation, and joint involvement, was recorded. Data was evaluated via SPSS software following filtration in Excel. The bleeding patterns encompassed are the annualized bleeding rate (ABR) and forms of bleeding. The Ethics Committee of Dr. Soetomo General Academic Hospital Surabaya has sanctioned the study.

3. RESULTS

A total of 71 patients with hemophilia A were recorded in the East Java Indonesian Hemophilia Society. Hemophilia is categorized into three different groups based on factor activity: mild (n=19, 27%), moderate (n=50, 70%), and severe (n=2, 3%). The average age of the patients in this study was 10 years. The average age upon diagnosis was 4 years. The study solely comprised male individuals, with no instances of hemophilia among females detected in our sample. Hematoma was the initial complaint in around 39% of pediatric cases. The bleeding types in mild vs. moderate hemophilia were gum bleeding (77% vs. 23%), epistaxis (34% vs. 66%), hemarthrosis (50% vs. 50%), intracranial hemorrhage (66% vs. 34%), hematuria (66% vs. 34%), and post-traumatic bleeding (43% vs. 43%). The most frequently affected hemarthrosis (bleeding in the joints) were knee (75%), shoulder (40%), and ankle joints (7%) in mild, moderate, and severe classifications of hemophilia A (Table 1).

Table 1. Clinical characteristic of Hemophilia A

Variables	Hemophillia severity, n (%)		
	Mild	Moderate	Severe
Clinical manifestations			
Hemarthrosis	6 (50%)	6 (50%)	0 (0%)
Epistaxis	2 (34%)	4 (66%)	0 (0%)
Hematuria	2 (66%)	1 (34%)	0 (0%)
Intracranial hemorrhage	2 (66%)	1 (34%)	0 (0%)
Post traumatic bleeding	7 (43%)	7 (43%)	2 (14%)
Gum bleed	17 (77%)	5 (23%)	0 (0%)
Joint affected hemarthrosis			

Ankle	22 (68%)	8 (25%)	2 (7%)
Shoulder	3 (60%)	2 (40%)	0 (0%)
Knee	30 (75%)	10 (25%)	0 (0%)
Wrist	7 (70%)	3 (30%)	0 (0%)
Elbow	16 (66%)	7 (30%)	1 (4%)
Target Joint			
None	5 (55%)	4 (45%)	0 (0%)
1 joint	7 (22%)	24 (75%)	1 (3%)
>1 joint	7 (23%)	22 (73%)	1 (4%)

The annualized bleeding rate was determined by dividing the number of clinically relevant episodes occurring one year prior to the initial evaluation by history and emergency department records. In patients with mild hemophilia, the annualized bleeding rate (ABR) was 12/year (n=9, 48%), 13-24/year (n=5, 26%), >24/year (n=5, 26%). However, in patients with moderate hemophilia, the ABR was 12/year (n=24, 48%), 13-24/year (n=17, 34%), >24 (n=9, 18%). In patients with severe hemophilia, the ABR was >24/year (n=2, 100%).

Table 2. Annual bleeding rate (ABR) of Hemophilia A

Variables	Hemophillia severity, n (%)		
	Mild	Moderate	Severe
Annual bleeding rate			
12/year	9 (48%)	24 (48%)	0 (0%)
13-24/year	5 (26%)	17 (34%)	0 (0%)
>24/year	5 (26%)	9 (18%)	2 (100%)

4. DISCUSSION

Hemophilia A arises from abnormalities in the FVIII gene located on the X chromosome. Generally, females have two X chromosomes, whereas males possess one X and one Y chromosome. This genetic structure heightens males' vulnerability to X-linked disorders like hemophilia A, as they possess a single X chromosome, unlike females who have two and can sometimes compensate for a deficient gene [6]. Females frequently act as asymptomatic carriers, with the incidence of the disease among them being exceptionally rare. This tendency was apparent in our group, which consisted only of male patients. The present study comprised solely male participants. X-linked hereditary coagulation disorders, such as hemophilia A and B, primarily impact males, whereas females serve as carriers. The worldwide frequency of hemophilia A is roughly 1 case per 5,000 males. Hemophilia A is more frequent than hemophilia B. Hemophilia A constituted almost 80% of all hemophilia cases in most studies. Researchers established that the prevalence of Hemophilia A in the Pakistani population was moderate, at 65% [7].

This investigation identified 71 cases of hemophilia A. These results align with prior investigations [8]. 50% of hemophilia patients exhibit moderate hemophilia, followed by mild hemophilia at 19% and severe hemophilia at 2%. Research conducted in Western nations revealed a higher proportion of mild cases relative to moderate and severe hemophilia. This conclusion contrasts with a research conducted by Larsson in the Swedish population, which identified moderate hemophilia as the most prevalent kind, occurring in 54% of cases. This study investigates blood loss patterns, including episodes and kinds, among individuals with hemophilia A in East Java. The hemorrhagic symptoms of hemophilia significantly influence the treatment approach. In a separate investigation, the average age was 11.99 ± 2.49. The median age at the initial bleeding episode was 5 years, and the mean frequency of spontaneous bleeding in the preceding year was 13.5 [9]. A total of 58 individuals (64.5%) were diagnosed in the 0–1 age cohort, whereas 20 patients (22.2%) were diagnosed in the 1–2 age cohort. The median age of patients at the time of diagnosis was 1 year. Karim et al. demonstrated that 64% of the hemophiliacs in their study suffered their initial bleeding episode before to one year of age [1]. An independent investigation by Raina et al. indicated that the

majority of patients presented within the 1–5 year age range (52.86%), followed by those under 1 year (27.14%), which differs from the current study. As a hereditary disorder, most patients experience their initial bleeding episode at a young age; however, they frequently receive a delayed diagnosis. In a distinct study, the median age of initial hemorrhage was 3.5 years, while the median age at diagnosis was 5 years. John and colleagues recorded a similar observation, indicating a median age of initial bleeding at 1.5 years and a median age of diagnosis at 3 years. In most studies, hemophilia A accounted for almost 80% of all hemophilia cases.

Researchers identified a low prevalence of hemophilia A in the Pakistani population, at 65% [10]. The Indiana Hemophilia & Thrombosis Center's analysis indicates that roughly 25% of persons with hemophilia present a mild version, 15% display moderate manifestations, and a substantial 60% suffer from severe manifestations. Conversely, our research indicated that the incidence of severe hemophilia was marginally elevated compared to prior studies. Hemophilia is divided into mild, moderate, and severe categories based on severity, with severe being the most common, comprising 43% to 55.7% of cases. In the current study, severe hemophilia exhibited the highest prevalence at 44.64%, whereas moderate hemophilia had the lowest prevalence at 19.64%. In Bangladesh, the mild variety was identified as the most widespread. This markedly differs from the findings of Mishra et al., who indicated a prevalence of severe disease at 80.5%, while mild to moderate cases constituted less than 20% of their research population (3). Nigam et al. found no significant variance in disease severity within categories, with patient distribution almost equal at 32.28% mild, 37.4% moderate, and 30.32% severe.

The primary site of hemorrhage is contingent upon local variables. In regions where circumcision is routinely performed, postcircumcision hemorrhage has been identified as the most prevalent initial bleeding event, occurring in 51.4-62% of instances [11]. Excluding this, posttraumatic hemorrhage has been identified as the most prevalent early sign of hemophilia; our study also saw it in 43% of cases. Gum bleeding is identified as the most prevalent presenting symptom (77%), followed by joint bleeding (hemarthrosis) at 50%. In the current investigation, cutaneous bleeding and hemarthrosis were the predominant clinical symptoms, with the former occurring in 80% of cases, surpassing the latter at 73%. Joint bleeding or hemarthrosis frequently represents the initial manifestation, as seen by John and associates, with the knee being the most usually affected joint, as recorded by Singh et al. and Payel and colleagues. The thigh is the most prevalent location for natural muscle bleeding due to its substantial muscle mass and exposure to repetitive activities. Gum bleeding was observed in fifty percent of the subjects and was more common among those with severe hemophilia (median episodes 4 versus 1 in cases with moderate hemophilia). A substantial percentage of people encountered genitourinary bleeding, including 36.4% of the total. Alternative forms of hemorrhaging were rare but remained apparent. Our investigation identified cerebral bleeding, associated with significant mortality and morbidity risks, in 3 patients of hemophilia. In a multicenter research, symptomatic intracranial hemorrhage (ICH) occurred in 4% of 744 patients, with 40% of cases manifesting within the first week of life, predominantly attributed to trauma as the primary triggering factor [2].

The World Federation of Hemophilia indicates that the knees are the most frequently affected joints (45%), succeeded by elbows (30%), ankles (15%), shoulders (3%), and wrists (2%). The knee is the most often afflicted joint, occurring in 75% of cases, followed by the elbow and ankle joints [12]. In our study, the knee joint was the most prevalent at 75%, although the ankle joint was more common at 68% than the elbow joint at 66%. A study conducted in Bangladesh similarly revealed increased involvement of the ankle joint. These findings align with the research conducted by Mishra et al., which similarly revealed knee joint involvement in around 57.1% of cases. Hemarthrosis was predominantly observed in the severe group (84.4%), with the knee joint (75.6%) being the most commonly damaged area, followed by the elbow joint (11.1%). The ankle joint was affected at a rate of 3.3%, while the hip joint was involved at a rate of 1.1%. A comparable study on hemophiliacs in Jodhpur, India, revealed that hemarthrosis was the primary clinical manifestation (80.35%), with the knee joint (68%) being the most frequently afflicted, followed by the ankle joint (52%) and the elbow joint (36%). In our analysis, in which the ankle joint was the second most often afflicted joint. In the present study, 87.3 % of participants indicated experiencing at least one occurrence of joint swelling, with one, two, or more knee joints being the most common. According to Sajid et al., the knee joint is the most often affected joint, occurring in 48% of cases, whereas multiple joint involvement is observed in 36% of instances. [13]

Individuals with severe hemophilia experience an annual average of 20 to 30 bouts spontaneous or severe hemorrhaging subsequent to minor trauma. Joints are the traditional sources of hemorrhage in individuals with severe hemophilia. Furthermore, spontaneous bleeding is rare in mild instances, but repeated joint bleeding may occur in up to 25% of intermediate cases, resulting in delayed suspicion [4]. The annualized bleeding rate (ABR) has been recognized as a measure of success for preventative replacement therapy, complementing evaluations of FVIII or FIX trough levels. In contemporary therapeutic studies, ABRs are progressively employed as both comparative and primary outcome metrics. ABR estimate is susceptible to subjective evaluation, as both patients and treating physicians must delineate each hemorrhage [14]. A study utilizing musculoskeletal ultrasound shown that sensations of pain, edema, and warmth are unreliable indications for identifying bleeding, resulting in several false positive and negative outcomes. During the investigated period, there was a significant reduction in the total incidence of synovial bleeding events among patients receiving preventative treatment compared to those on on-demand medicine. The overall ABR in patients with severe hemophilia A decreased by a factor of 6.9 during the follow-up period, whereas the AJBR fell by up to 8.7-fold. Miesbach et al. asserted that prophylaxis

significantly reduced bleeding in patients across all age groups, including those with severe, moderate, and mild hemophilia A (median annualized bleeding rate of 22.1 in patients with severe hemophilia receiving on-demand treatment versus a median of 1.5 in those receiving prophylactic therapy). In patients with severe hemophilia A who shifted from on-demand medication to prophylaxis, the total annualized bleeding rate (ABR) decreased from 38 to 1.1. The most significant impact of prophylaxis was shown in the initial three years, during which medicine was accessible solely to those with a high frequency of bleeding events [15]. The median annualized bleeding rate (ABR) for individuals undergoing prophylaxis ranged from 1.0 to 4.0 in severe hemophilia A, whereas the median ABRs for those receiving on-demand treatment varied from 4.5 to 18.0. The average ABR in the prophylaxis cohort of the other study was 0.16 for moderate hemophilia and 0.3 for severe hemophilia, in contrast to 1.32 in the ESPRIT investigation. In the episodic therapy cohort, the annual bleeding rate (ABR) was 3.0, 3.5, and 5.3 for mild, moderate, and severe hemophilia, respectively, in contrast to 5.76 reported in the ESPRIT research.

5. CONCLUSIONS

In conclusion, individuals with hemophilia A may exhibit a wide array of clinical symptoms and may require continuous care. Hemophilias are globally dispersed and exhibit a varied presentation based on the severity of the condition. The moderate hemophilia A is more prevalent than the mild and severe. Severe hemorrhaging, including cerebral hemorrhage, is more prevalent in mild hemophilia A. The ABR is more severe than both mild and moderate hemophilia A.

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