Rare Inherited Bleeding Disorders and rare Inherited Platelet Function Disorders in children -A Single Center Experience

By:

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Abstract

Background and Objectives:

An accurate assessment of the degree of bleeding is essential for the prompt identification and suitable treatment of hereditary bleeding and platelet abnormalities so we aim in our study to assess the prevalence, clinical pattern and the degree of bleeding using two different bleeding scores in different types of rare inherited bleeding disorders in our institute

Methods:

This is A cross sectional study to identify children with rare inherited bleeding and platelet disorders, involving 102 children with rare bleeding disorders was conducted. A thorough history, general examination, and laboratory tests were performed over a period of one-years including all patients diagnosed with inherited platelet's function abnormalities and different types of rare bleeding disorders admitted to our hematology unit, pediatric department, sohag university during this period. Complete blood count, activated partial thromboplastin time, prothrombin time and specific factor assay. In response, additional tests were done including flow cytometry analysis and platelet function assays.

Results: From 102 patients included in our study, 58 patients (56.9%) had inherited platelet function abnormalities (IPFDs) of them 43 patients (74.1%) had Glanzmann thrombasthenia. The remaining 44 patients (43.1%) had different types of rare bleeding disorders. About 80% of the study group reported having a favorable consanguinity history.

Conclusion: Glanzman thrombasthenia was the commonest IPFDs in our study and factor 1 deficiency was the commonest rare bleeding disorder.

Keywords: ISTH-BAT, SMOG, rare bleeding disorders, rare inherited platelet function disorder

Introduction:

Bleeding disorders are a heterogeneous group of rare genetic abnormalities that, due to various mechanisms of action, result in bleeding diathesis. The Hemophilia (H) A and B and von Willebrand disease (VWD) are the most prevalent coagulation disorders. Rare bleeding disorders (RBDs) are the classification given to certain coagulation anomalies (Palla et al., 2015).

IPFDs, or inherited platelet function disorders, are rare bleeding diseases. Hereditary microthrombocytopenias, macrothrombocytopenias, and diseases of these problems can be defined as abnormalities of platelet granules, platelet membranes, and defective platelet coagulant action (Al-Huniti and Kahr, 2020).

The link between IPFDs and clinical effects varies widely, even within the same kind, ranging from nearly negligible to potentially lethal. Because of this, it has long been understood that patients need close medical supervision as well as an accurate diagnosis made as soon as possible. It has been established that roughly 60 different types of IPD are caused by molecular anomalies in about 75 different genes. It is uncertain how common the milder issues are. This is because many people go untreated for years or perhaps their whole lives (Palma-Barqueros et al., 2021). Clinically severe bleeding and blood loss in trauma and surgical intervention patients can occur rapidly and without regard to platelet count. Despite many attempts to identify and characterize IPDs as well as the regular and frequent discovery of "new disorders," there are still few therapeutic alternatives for the prevention and treatment of bleeding caused by IPDs (Bargehr et al., 2023).

Accurate assessment of bleeding severity is necessary for timely identification and appropriate management of inherited bleeding disorders. The International Society of Thrombosis and Haemostasias (ISTH) had established a Bleeding Assessment Tool (BAT) score in order to attain a dependable and consistent assessment of bleeding severity (Rodeghiero et al., 2010).

The international Society on Thrombosis and hemostasis- bleeding assessment tool is a questionnaire established to evaluate the degree of bleeding in both adults and children so it becomes simpler to distinguish between healthy and pathological bleeding tendencies. The ISTH-BAT score includes 14 parts depend on analysis of the past bleeding difficulties. Studies have indicated that people with high bleeding scores often have inherited bleeding issues (Adelaja et al., 2023). The

International Working Group (IWG) has developed a consensus-based immune thrombocytopenia (ITP) bleeding assessment tool (ITP-BAT) with criteria and terminology consistent with other bleeding illnesses. The three primary domains of bleeding symptoms were skin (S), visible mucosae (M), and organs (O) using a severity grading system (SMOG). When the patient is examined, each bleeding symptom is assessed (Rodeghiero et al., 2013).

Aim of the study

We aim in our study to assess the prevalence, sits of bleeding and the degree of bleeding using two different bleeding scores (ISHT-BAT) and (SMOG) in different types of inherited platelets functions abnormalities and types of rare inherited bleeding disorders in pediatric department sohag university.

Patients and Methods

. **Ethical consideration**

1- A verbal informed consent was obtained from mothers before the study.

2- The approval of the local ethical committee was obtained before the study. (Approval Number: Soh- Med-22-05-14; dated May

3- Confidentiality and personal privacy were maintained throughout all stages of the research**.**

Competing Interests

The authors declare no competing interests.

There was no fund.

Sample size calculation:

The sample size was calculated according to the equation: $N=z^2 p (1- p) / d^2$ (Pourhoseingholi et al., 2013) where:
N= the desired sample size, Z= the statistic corresponding to level of confidence (1.96), P= Expected prevalence or proportion (0.064) (Terrell et al., 2010), d = precision. (d is considered 0.05 to produce good precision and smaller error of estimate)

$N = 1.96^2 \times 0.064 (1-0.064) / 0.05^2 = 92$ cases, we increased the sample size to 102 cases to avoid non-responsiveness rate.

Inclusion criteria: we include in our study 102 children (0–18 years) with inherited platelets function abnormalities and rare bleeding disorder who were admitted and followed up at the Pediatric Hematology Unit at Sohag University Hospitals between the first of June 2022 and to the end of end of May 2023.

Funding

Exclusion criteria: we excluded patients with common bleeding disorders like hemophilia A and B, acute ITP and Von Willbrand factor deficiency.

Study procedure:

all of our patients subjected to:

Complete history includes the current age, gender and bleeding site and pattern with focusing on family history of bleeding tendency and any drug usage. The ISTH-BAT and SMOG score questionnaires were then applied to each subject to determine the severity of bleeding.

ISTH-BAT score include 14 variables are Epistaxis, cutaneous bruising, bleeding from minor wound, oral cavity bleeding, GIT bleeding, hematuria, bleeding after tooth extraction, bleeding after surgery, menorrhagia, post-partum hemorrhage, muscle hematoma, hemarthrosis, CNS bleeding and other bleeding problems. All 14 criteria are given a score between 0 and 4, except for CNS hemorrhage, which is rated 0, 3, or 4. The total of these scores is the final score. Maximum score 56 points. in children below 18 years score below 2 bleeding disorders are unlikely while if score 3 or above abnormal bleeding disorders are considered (Rodeghiero et al., 2010).

Skin, visible mucosae, and organs are the three categories into which bleeding symptoms in SMOG are divided, each with varying degrees of severity. Every bleeding problem is looked with each visit. If there is any deadly bleeding, the grade is 5. The severity is evaluated from 0 to 3 or 4. The SMOG system's description is accurate and consistent of the bleeding phenotype in ITP, and the IWG strongly supports the implementation and validation of this idea in future clinical research (Roşu et al., 2022).

Physical examinations : including: Anthropometric measurements, vital sign and examination of the bleeding sites.

Laboratory procedures: including complete blood count (CBC), Prothrombin time (PT), activated partial thromboplastin time (aPTT), thrombin time (TT), bleeding time, fibrinogen level and other coagulation factors levels assay according to each case. When IPFDs were suspected, a platelet function evaluation was recommended. Platelet function tests by Light transmission aggregometry (LTA) using a range of platelet agonists such as collagen, adrenaline, arachidonic acid (AA), and ristocetin are mixed with platelet-rich plasma to assess the platelets' function (Pacheco et al., 2023). Flow cytometry assessment: Antibodies against GPIIb

(CD41), GPIIIa (CD61), GPIb (CD42b), and GPIX (CD42a) used to assess platelet glycoprotein (GP) expression. Glycoprotein expression abnormalities may be a sign of clearly defined IPFDS (Gresele et al., 2015)

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Six milliliters of aseptic venous blood were drawn for each participant in our study; two milliliters were added to a marked 3.2% citrated bottle for the clotting profile analysis (to maintain a standard 9:1 blood to anticoagulant ratio), and two milliliters were collected into an ethylene diamine tetra-acetic acid (EDTA) (K2-EDTA) (1.2 mg/mL) for proper mixing of the samples collected in both tubes.

1- CBC automated cell counter, was performed on EDTA samples XN-1000 (Sysmex, Japan). with examination of Leishman-stained PB smears for differential leucocytes count and examination of platelets size.

2-Comprehensive coagulation factors analysis using chemicals purchased from Sysmex, an automatic blood coagulation analyzer, to assess coagulation profile individual factor assay using aCS-1600 System analyzer (Sysmex corporation, Kobe, Japan).

3- Bleeding time using modified Ivy method (Andrews and Berndt, 2013)

4- Platelet aggregation **test** using light transmittance aggregometry. The method of aggregation. Citrated whole blood was centrifuged for ten minutes at 1000 rpm to create a supernatant known as platelet-rich plasma (PRP). In order to concentrate platelets, the PRP was spun for 10 minutes at 2000 rpm after that. A platelet count on PRP was performed using XN-1000 (Sysmex, Japan), and counts were corrected by dilution with autologous PPP between 200 and 400 × 109/L. Platelet aggregation was measured using the turbidimetric method in a 2-channel aggregometer (Chrono-Log 450 Model; Chrono-Log, Havertown, Pennsylvania). According to the manufacturer, light transmission was adjusted to 100% with PPP and 0% with PRP for each measurement, which is equivalent to 100% absorption. The measurement of platelet aggregation was done two hours after blood collection. A variety of agonists are used at varying doses in the suggested baseline panel, which includes the agonists collagen, ADP, epinephrine, arachidonic acid, ristocetin, and thrombin receptor-activating peptide (TRAP). Using protocol (Saultier et al., 2017).

5- Flow cytometric analysis of platelet glycoproteins, standard 4-color flow cytometry of the whole glycoprotein IIb/IIIa complex (GPIIb-IIIa) on the surface of the platelets was used to evaluate the surface expression of platelet glycoproteins. 100 μL of platelet-derived pulp (PRP)

were treated with 10 μL of phycoerythrin conjugated (PE) anti-CD41 and fluorescein isothiocyanate (FITC) conjugated anti-CD41 for 20 minutes at room temperature.

CD61 binds to the GPIIb and GPIIIa . The flowcytometric analysis was performed using FACS Caliber flow cytometry and Cell Quest software (BD Biosciences, USA). An isotype-matched negative control made up of anti-human IgG was used for each sample. A forward and side scatter histogram was used to determine the platelet population. Next, the platelet population's CD41 and CD61 were assessed using the Cell Quest software program.

Statistical analysis:

The data were examined using SPSS version 25, a statistical analysis program. Quantitative data were expressed using means ± standard deviation, range, and interquartile range. To represent qualitative data, percentages and numbers were utilized. proportions. A significance threshold of 5% was established for each statistical test used in the study. We used a t-test to assess differences across numerical variables; however, we used a Mann-Whitney U test for non-parameter

Results

Our results will be demonstrated in the following tables and figures:

TABLE (1): Distribution of studied population according to their diagnosis

Diagnosis	No of patients	%
Factor I ↓	**16**	**15.7%**
Factor II ↓	**1**	**1.0%**
Factor V↓	**2**	**2.0%**
Factor VII ↓	**9**	**8.8%**
Factor X ↓	**10**	**9.8%**
Factor XIII↓	**4**	**3.9%**
Bernard Soiler syndrome	**14**	**13.7%**
Glnzzmann thrombathenia	**43**	**42.2%**
hereditary vitamin k ↓	**1**	**1.0%**
factor VII ↓, factor II, factor X	**1**	**1.0%**
un classified platelet function disorders	**1**	**1.0%**

Table 1 **shows that** Glanzmann thrombasthenias was the most common IPFD in 43 cases (42.2%), followed by factor I (fibrinogen) deficiency in 16 cases (15.7%), Bernard Souter syndrome in 14 cases (13.7%), factor X in 10 cases (9.8%), factor VII in 9 cases (8.8%), while,hereditary vitamin K, factor VII, factor II, factor X, and unknown anomalies in platelet function were the least prevalent RBDs

TABLE (2): Demographic data according to diagnosis

	Age (year)		Female		Male		Weight/kg		Positive family history		Positive consanguinity	
			N	%	N	%			N	%	N	%
Bernard Soiler Syndrome	8.39	±2.86	5	10.2%	9	17.0%	28.9	±9.6	13	15.9%	13	15.9%
Factor X↓	6.54	±4.69	6	12.2%	4	7.5%	21.5	±11.9	7	8.5%	7	8.5%
Factor I↓	10.28	±5.48	7	14.3%	9	17.0%	31.8	±16.7	16	19.5%	16	19.5%
Factor II↓	18.0	±0.0	1	2.0%	0	0.0%	70.0	±0.0	1	1.2%	1	1.2%
Factor V↓	12.0	±5.66	1	2.0%	1	1.9%	32.5	17.7	1	1.2%	1	1.2%
Factor Vii ↓	9.59	±4.20	3	6.1%	6	11.3%	29.6	±9.4	2	2.4%	2	2.4%
Factor Vii ↓, Factor II,Factor X	1.5	±0.0	0	0.0%	1	1.9%	11.0	±0.0	1	1.2%	1	1.2%
Factor XIII↓	7.0	±4.08	2	4.1%	2	3.8%	21.0	±9.8	4	4.9%	4	4.9%
Glanzmann thrombathenia	8.81	±5.54	22	44.9%	21	39.6%	27.5	±14.9	35	42.7%	35	42.7%
Hereditary vit k ↓	2.0	±0.0	1	2.0%	0	0.0%	12.0	±0.0	1	1.2%	1	1.2%
Un classified platelet function disorders	17.0	±0.0	1	2.0%	0	0.0%	80.0	±0.0	1	1.2%	1	1.2%

Table 2 shows that the mean age for patients with factor I deficiency was 18 years which was the highest age group, while the mean age for patients with combined factor II, factor VII and factor X was 1.5 year which was the lowest age group.

44.9% of Glanzmann thrombocytopenia patients were female while 17% of Bernard Soiler Syndrome patients were male compared to 10.2% female. Higher rates of positive

consanguinity and positive family history were observed in Glanzmann thrombasthenia (42.7%), Factor I deficiency (19.5%), and Bernard Soiler Syndrome (15.9%) .

TABLE (3): Sites of bleeding according to diagnosis

Ecchymosis		Epistaxis		Gum		Site of operation		Melena		Rectum		Umbilical		Bleeding by trauma only	
No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Bernard Soiler Syndrome															
0	0%	13	22.%	1	5.9%	1	25.0%	0	0%	0	0%	0	0.0%	0	0%
Factor X↓															
6	11.3%	1	1.7%	2	11.8%	1	25.0%	1	25%	0	0%	0	0.0%	0	0%
Factor I↓															
13	24.5%	5	8.6%	5	29.4%	1	25%	0	0%	0	0%	4	44.4%	9	42.9%
Factor II↓															
1	1.9%	0	0%	0	0%	0	0%	0	0%	0	0%	1	11.1%	0	0%
Factor V↓															
1	1.9%	1	1.7%	1	5.9%	0	0%	0	0%	0	0%	0	0%	2	9.5%
Factor Vii ↓															
6	11.3%	2	3.4%	1	5.9%	1	25%	1	25%	0	0%	0	0%	0	0%
Factor Vii ↓, Factor II,Factor X															

1	1.9 %	0	0%	0	0%	0	0%	0	0%	0	0 %	0	0%	0	0 %
Factor XIII↓															
3	5.7 %	0	0%	1	5.9 %	0	0%	0	0%	0	0 %	3	33. 3%	1	4. 8 %
Glanzmann thrombathenia															
1	39.6 %	35	60. 3%	6	35. 3%	0	0%	1	25 %	1	10 0 %	1	11. 1%	9	4 2. 9 %
Hereditary vit k ↓															
0	0%	0	0%	0	0%	0	0%	1	25 %	0	0 %	0	0%	0	0 %
Un classified platelet function disorders															
1	1.9 %	1	1.7 %	0	0%	0	0%	0	0%	0	0 %	0	0%	0	0 %

Table (3) shows that epistaxis was the most common bleeding disorder in both Bernard Soiler (22.4%) and Glanzmann thrombasthenia (60.3%). Ecchymosis was common in both factor I (24.5%) and factor X (11.3%)

Table (4): Bleeding scores according to diagnosis

		Mean ± SD	**Median**	**Percentile 25**	**Percentile 75**	**p-value**
ISTH BAT Score	**Bernard Soiler Syndrome**	6.36 ± 1.82	6.0	5.0	7.0	**0.038 (S)**
	Factor X↓	9.00 ± 1.7	9.0	8.0	10.0	
	Factor I↓	8.38 ± 1.71	9.0	7.0	9.5	
	Factor II↓	14 ± 0	14.0	14.0	14.0	

	Factor V↓	10 ± 0	10.0	10.0	10.0	
	Factor Vii ↓	7.44 ± 2.07	7.0	6.0	8.0	
	Factor Vii ↓, Factor II, Factor X	7 ± 0	7.0	7.0	7.0	
	Factor XIII↓	10.25 ± 1.26	10.0	9.5	11.0	
	Glanzmann thrombathenia	8.12 ± 3.12	7.0	6.0	10.0	
	Hereditary vit k ↓	7.00 ± 0	7.0	7.0	7.0	
	Un classified platelet function disorders	10 ± 0	10.0	10.0	10.0	
SMOG	**Bernard Soiler Syndrome**	3.21 ± 0.43	3.0	3.0	3.0	**0.010 (HS)**
	Factor X↓	3 ± 0	3.0	3.0	3.0	
	Factor I↓	3.25 ± 0.45	3.0	3.0	3.5	
	Factor II↓	4 ± 0	4.0	4.0	4.0	
	Factor V↓	3.5 ± 0.71	3.5	3.0	4.0	
	Factor Vii ↓	3 ± 0	3.0	3.0	3.0	
	FactorVii ↓, Factor II, Factor X	3 ± 0	3.0	3.0	3.0	
	Factor XIII↓	3 ± 0	3.0	3.0	3.0	
	Glanzmann thrombathenia	3.51 ± 0.59	4.0	3.0	4.0	
	Hereditary vit k ↓	3 ± 0	3.0	3.0	3.0	
	Un classified platelet function disorders	4 ± 0	4.0	4.0	4.0	

*T test was used.

Table (4) showed that patients with Bernard Soiler syndrome had the lowest mean ISTH BAT score while patient with factor II deficiency had the highest bleeding score with significant p value < 0.05. The mean SMOG score was highest in patients had factor II deficiency and unclassified platelets dysfunction while lowest mean SMOG score was in

patients had factor VII , factor X , combined factor II, VII, X , factor XIII and hereditary vit K deficiency with high significant P value <0.05.

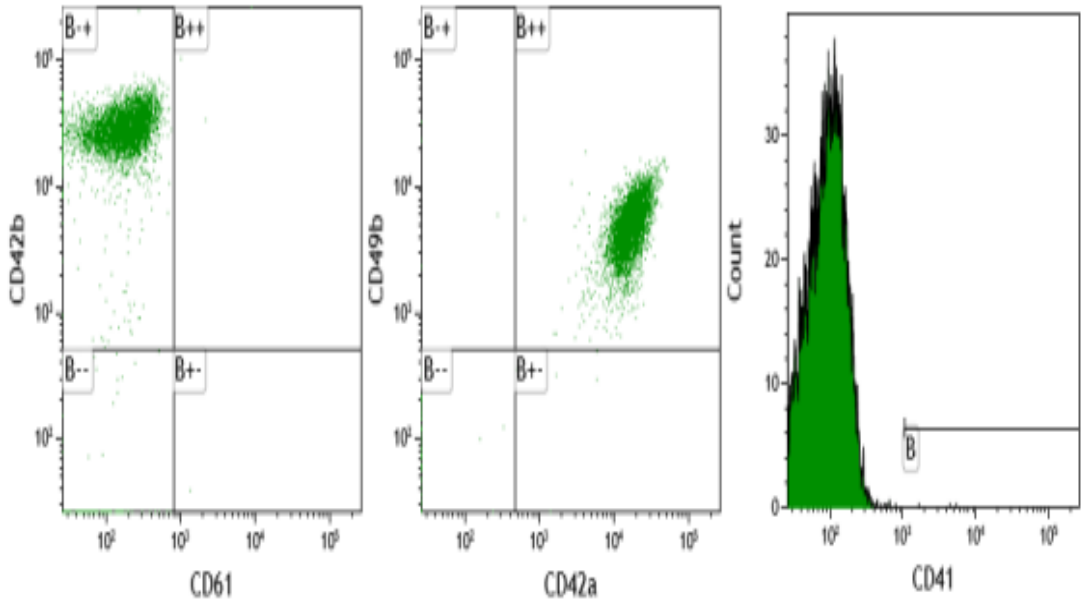

Fig (1): Flow cytometry assay of platelets surface glycoproteins: CD41 (GPIIb): 0.05% CD61(GpIIIa): 0.05%. CD42a (GPIX): 98.7% CD42b (GPIb-alpha): 99.0% CD49b (GPIa): 98.9%. Deficient CD61 (GpIIIa) and CD41 (GPIIb) expression consistent with Glanzmann Thrombasthenia

Fig (2)

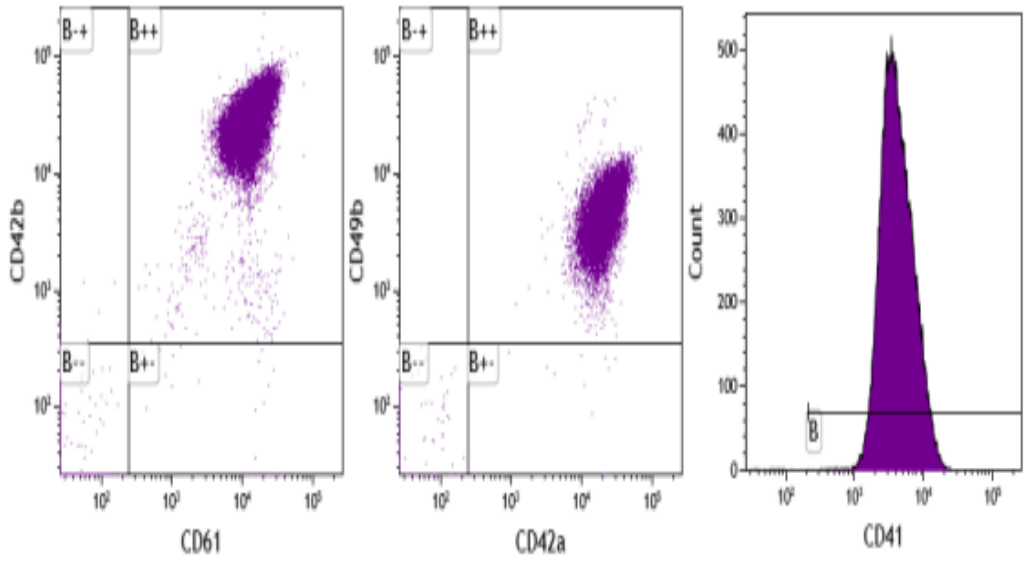

Fig (2): Flow cytometry assay of platelets surface glycoproteins: CD41 (GPIIb): 97.7% CD42a (GPIX): 98.0% CD42b (GPIb-alpha): 97.5% CD49b (GPIa): 96.5% CD61(GpIIIa): 98.3% Normal Range: >70% Normal Result

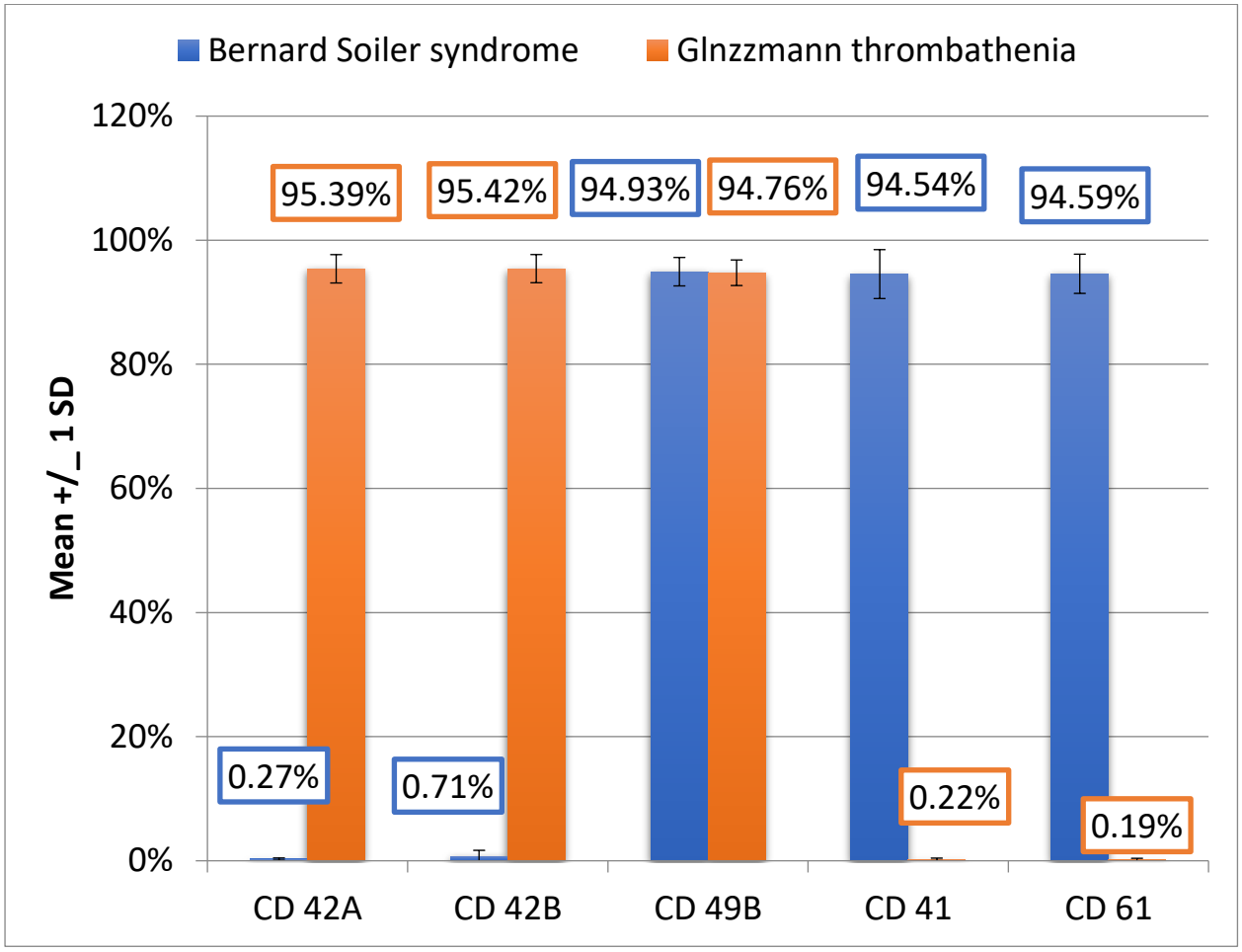

Fig (3): Comparison between Bernard Soiler syndrome and Glanzmann Thrombasthenia as regard CD markers

Fig (3) CD 42A and CD 42B: For Bernard Soiler syndrome, absent expression (0.27% and 0.71%) For Glanzmann thrombasthenia, the mean values normal (95.4% and 95.42%). The p-values are both < 0.002, indicating a statistically significant difference between the two conditions for these CD markers.CD 49B: The mean values are very similar between the two conditions (94.93% vs 94.76%) and the p-value is 0.7, indicating no statistically significant difference. CD 41 and CD 61: For Bernard Soiler syndrome, normal expression (94.54% and 94.59%). For Glanzmann thrombasthenia, the mean values are very low (0.22% and 0.19%) absent expression.

Discussion:

A wide range of conditions are included in the clinical symptoms and prevalence of inherited bleeding disorders. These comprise von Willebrand disease (VWD), uncommon bleeding disorders, hemophilia A and B, and inherited platelet function disorders (IPFDs). VWD, hemophilia A, and hemophilia B are the three inherited bleeding disorders that are most common. Autosomal recessive inheritance is typically responsible for rare hereditary bleeding disorders, such as those involving deficits in fibrinogen, FII, FV, FV + FVIII, FVII, FX, FXI, and FXIII (Pacheco et al., 2023).

Among the most common heritable bleeding disorders are IPFDs. These disorders can be classified into three categories: platelet adhesion disorders, such as Bernard-Soulier syndrome; platelet aggregation disorders, such as Glanzmann thrombosthenia; platelet receptor disorders; and a group of disorders collectively known as storage pool disease, which is brought on by a lack of platelet granules or their contents (Elshinawy, 2021).

The purpose of the study was to assess the prevalence, clinical pattern and the degree of bleeding using two different bleeding scores (ISHT -BAT and SMOG) in different types of IPFDS and rare inherited bleeding disorders in hematology unit pediatric department sohag university. 102 children with IPFDs and RBDs were included in our study. Of them, 58 patients (56.9%) had IPFDs, 43 cases (74.1%) had Glanzmann thrombasthenia. 44 cases (43.1%) had additional rare bleeding disorders with Factor I deficiency was present in 16 cases (36.3%) of the total RBDs, making it the most frequent RBDs. The findings of our results were consistent with a study conducted by Gupta et al., which found that IPFDs are the most common bleeding disorders following hemophilia. Of the 872 Indian bleeders Their age at presentation ranged from 2 to 47 years, 312 (or 35.8%) had inherited issues related to platelet function (Gupta et al., 2007). In contrast to our findings, FXIII deficiency was reported by Adel et al. to be the most frequent condition (Adel et al., 2021). The average age of the study group was 8.35 years. This is consistent with the results of Mahmood et al. who found that the 165 patients had an average age of 9 years and 3 months (Mahmood et al., 2020). In our patient population, the ratio of male to female has been 1:1; male sex is more common (41.5%) in rare bleeding illnesses, whereas female sex is more common (57.1%) in IPFD. Furthermore, a 1:1 male-to-female ratio was found in the patients of Kamal et al. with a higher incidence of male sex (66.7%) in unusual bleeding diseases (Kamal et al., 2022). Conversely, IPFD distributions for both genders were similar.

According to our research, men had a 41.5% higher risk than women of having rare bleeding diseases which go with the result of Islam SIA, Quadri MI (Islam and Quadri, 1999). It was found by Abdelwahab and Khaddah that 80 percent of men have unusual bleeding problems (Abdelwahab and Khaddah, 2012). There was a notable incidence of hereditary bleeding problems in the study group since more than 80% of the participants had a history of positive consanguinity. Our findings indicate that epistaxis is the most common bleeding problem among individuals with Bernard Soiler and Glanzmann's disease based on the diagnosis. thrombasthenia, as well as in individuals with inadequate levels of Factor X and Factor I. The most frequent site of bleeding in patients with Factor VII insufficiency was ecchymosis, followed by bleeding per gum. Epistaxis was the bleeding site that happened the least frequently. When Mahmood et al. examined the nature of the condition and its symptoms in the Pakistani population, they discovered that the most common complaint in patients with Factor V, Factor I, and Factor VII deficiency was mucocutaneous hemorrhage (Mahmood et al., 2020). In terms of bleeding scores based on diagnosis, our findings indicate that the F II deficiency had the greatest score, 14±0, while Bernard Soiler syndrome had the lowest mean ISTH BAT score, 6.36±1.82. Vitamin K deficiency inherited was assessed at 7±0. Conversely, Saes et al. used real data from the RBiN experiment to evaluate the extent of bleeding in patients with uncommon bleeding disorders demonstrates that patients with deficits in Factor V and FXIII had the highest median scores (Saes et al., 2020). Similarly, therapy revealed that the study by Peyvandi et al which was published 25 years ago, had the lowest mean ISTH BAT score of 5.36±1.82 for Bernard Soiler syndrome (Peyvandi et al., 2009). The study was titled Rare Bleeding Disorders: General Characteristics of Clinical Symptoms, Diagnosis, and Treatment. A mean SMOG of 3.21±0.43, 3.25±0.45 for Factor X deficiency, 4±0 for Factor II deficiency, 3.5±0.71 for Factor V deficiency, 3±0 for Factor VII deficiency, 3±0 for Factor VII deficiency + Factor II+ Factor X deficiency, 3±0 for Factor XIII deficiency, 3.51±0.59 for Glanzmann thrombasthenia, 3±0 for hereditary vitamin K deficiency, and 4±0 for unclassified platelet function disorders were linked to Bernard Soiler syndrome patients. On the other hand, the mean SMOG for Bernard Soiler syndrome was 3.21±0.43 and for Glanzmann thrombasthenia it was 3±0.59. These

findings were reported by Palla et al. in their study on the development of a bleeding score as a diagnostic tool for patients with uncommon bleeding disorder (Palla et al., 2015).

Conclusion: Glanzman thrombasthenia was the commonest IPFDs in our study and factor 1 deficiency was the commonest rare bleeding disorder. BS syndrome patients had the lowest bleeding severity while factor II deficiency had the highest bleeding severity according to ISTH-BAT score.

Limitation of the study: short duration of the study and being single center study.

Recommendation: Increase the duration of the study and increase awareness about IPFDs and RBDs in our institute with high rate of consanguinity which lead to high prevalence of IPFDs and different types of RBDs in our study.

Acknowledgment : The authors would like to thank each and every patient who participated in this study.

Data availability the authors confirm that all data supporting the findings of this study are available within the article, its supplementary material, and upon reasonable request. All supporting data are available within the article.

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