Spectrum Of Clinical and Psychosocial Profile of Haemophilia Carriers

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Abstract—**Background: Haemophilia is an X-linked recessive disorder caused by deficiencies in clotting factor VIII (hemophilia A) or IX (hemophilia B), predominantly affects males. However, female carriers often overlooked can experience significant bleeding due to skewed X-chromosome inactivation and variable factor levels. The clinical and psychosocial challenges faced by these carriers remain underrecognized and insufficiently studied. Therefore, this study aims to evaluate the clinical severity among hemophilia carriers in relation to their factor levels and to establish a correlation between clinical manifestations and psychosocial outcomes.**

Aims and Objectives: This study aims to assess the clinical and psychological profile of hemophilia carriers, explore the correlation between bleeding severity and emotional distress, and categorize carriers using updated nomenclature and standardized tools.

Materials and Methods: A one-year cross-sectional study was conducted at the Hemophilia Day Care Centre, Maulana Azad Medical College and Lok Nayak Hospital, New Delhi. Fifty obligate hemophilia A carriers aged over 12 years were enrolled following informed consent. Clinical data were recorded using a structured proforma. Bleeding severity was assessed via the ISTH-Bleeding Assessment Tool (BATS), while psychological health was evaluated using the Depression, Anxiety, and Stress Scale (DASS-21). Statistical analysis was performed to determine correlations between bleeding scores and psychological distress.

Results: Participants had a mean age of 28.46 ± 8.04 years, with 76% in the reproductive age group. Pubertal menorrhagia (46%) emerged as the most frequent initial symptom. Notably, 24% of carriers were asymptomatic with normal factor levels (>40 IU/mL), yet 40% experienced bleeding despite similar levels, underscoring clinical heterogeneity. A significant positive correlation ($p < 0.001$) was found between BATS and DASS-21 scores, indicating that increased bleeding severity is associated with heightened emotional distress. Mild carriers (BATS 6–9) reported moderate psychological impact (mean DASS ≈ 20), while those with severe bleeding (BATS 8) exhibited the highest distress levels (mean DASS ≈ 27).

Conclusion: Haemophilia carriers often face symptomatic bleeding and psychological challenges even with normal factor levels. The strong link between bleeding severity and emotional distress emphasizes the need for comprehensive care, including early diagnosis, patient education, and integrated clinical-psychological support. Addressing these hidden burdens is essential to enhance the quality of life for hemophilia carriers.

I. INTRODUCTION

Haemophilia is a rare genetic bleeding disorder caused by a deficiency or dysfunction of clotting factor VIII (hemophilia A) or factor IX (hemophilia B). Inherited in an X-linked recessive manner, it primarily affects males, while females typically act as carriers of the defective gene. Globally, hemophilia A affects approximately one in every 5,000 live male births, and hemophilia B about one in 30,000, with hemophilia A comprising nearly 80–85% of all cases. For every male with hemophilia, an estimated 1.6 females carry the mutation. Although traditionally considered asymptomatic, many carriers exhibit bleeding symptoms due to random X-chromosome inactivation (lyonization), which can reduce the expression of the functional clotting factor gene.

In the context of hemophilia, female carriers are classified into two distinct groups: obligatory carriers and possible carriers. Obligatory carriers are those who must carry the affected X chromosome by virtue of their family history. This category includes all daughters of men with hemophilia; mothers of a single son with hemophilia who also have another affected male relative such as a brother, maternal grandfather, uncle, nephew, or cousin; mothers of a son with hemophilia who additionally have a female relative confirmed to be a carrier, such as their own mother,

sister, maternal grandmother, aunt, niece, or cousin; and mothers of two or more sons with hemophilia. In contrast, possible carriers are women who may harbor the haemophilia gene but without definitive proof. This group encompasses all daughters of known carriers; mothers of one son with hemophilia who lack other affected or carrier relatives; and female relatives of carriers, including sisters, mothers, maternal grandmothers, aunts, nieces, and cousins.

The ISTH Scientific and Standardization Committee has proposed a revised nomenclature for hemophilia carriers to better reflect the wide clinical and laboratory spectrum observed in women and girls with hemophilia-associated mutations. This classification acknowledges that plasma factor VIII or IX levels in carriers can vary widely due to lyonization, ranging from severely reduced to completely normal, and that bleeding phenotype does not always correlate with factor levels alone. Accordingly, women and girls are classified as having severe hemophilia when factor levels are <0.01 IU/mL, moderate hemophilia at 0.01–0.05 IU/mL, and mild hemophilia at >0.05 to <0.40 IU/mL, mirroring the traditional severity definitions used in males. Importantly, carriers with factor levels within the normal range (≥0.40 IU/mL) may still experience abnormal bleeding and are therefore designated as symptomatic carriers, while those with normal levels and no bleeding tendency are termed asymptomatic carriers.

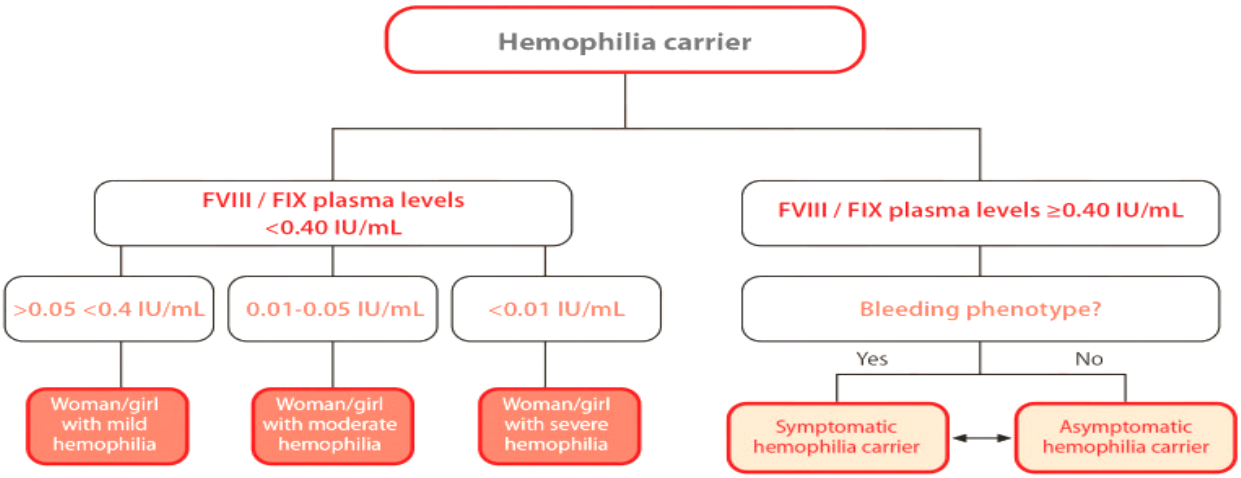


Fig. A new haemophilia carrier nomenclature to define hemophilia in women and girls

Haemophilia carriers show age-related clinical and psychosocial variation. Childhood symptoms are often mild and underrecognized, delaying diagnosis. Reproductive years are marked by heavy menstrual bleeding, anemia, and obstetric risks, while later life may involve chronic pain, joint damage, and reduced quality of life.

Psychosocial burden aligns more with bleeding severity than factor levels: severe deficiency has the highest distress, moderate causes persistent stress, and mild leads to intermittent anxiety. Even carriers with normal levels may experience distress due to underrecognition, whereas asymptomatic carriers have minimal impact. Integrated clinical and psychosocial care is essential.

Recent progress in genetic diagnostics, bleeding assessment tools, and non-invasive prenatal testing has improved early detection and risk stratification among carriers. Evidence-based therapies such as antifibrinolytics, factor replacement, and multidisciplinary counseling have enhanced clinical outcomes and reproductive decision-making. This study seeks to bridge that gap by evaluating both the bleeding manifestations and psychological profile of hemophilia carriers, thereby contributing to more informed and empathetic care for this often-overlooked population.

II. AIMS AND OBJECTIVES

- To evaluate the clinical and psychosocial characteristics of hemophilia carriers using standardized tools.
- To classify carriers based on updated nomenclature and analyse the link between bleeding severity and psychological impact.

Sample size and calculations

The sample size was calculated according to the formula:

Prevalence(P)=0.26

Q=1-P, d=margin of error, error=5%, confidence interval=95%.

sample size N =

$$\frac{Z \times alpha2\ XP\ X(1-P)}{d2}$$

Based on the formula and values given above:

Sample size required N =

[0.95 x 0.05x0.05x0.26 (1-0.26)] / 0.05^2= 182

Based on the formula and values given above:

Sample size required N = Thus, 95% confidence interval, the proposed sample size for the study is 182

We are enrolling a sample size of convenience- 50 patients in our study.

Descriptive statistics were used to summarize data, with continuous variables expressed as mean ± standard deviation (e.g., mean age 28.46 ± 8.04 years) and categorical variables reported as frequencies and percentages. A statistically significant correlation ($p < 0.001$) was found between bleeding severity (BATS score) and psychological distress (DASS score), with results stratified by clinical categories such as asymptomatic, symptomatic, and mild to severe carriers.

III. ETHICAL CONSIDERATIONS

All participants were provided with a consent form and informed about the study's objectives, including their right to withdraw at any point without explanation. Confidentiality of personal data was strictly maintained throughout. For individuals aged above 12 years, assent was obtained alongside parental or guardian consent. The study protocol received formal approval from the Institutional Ethical Committee (IEC) prior to initiation.

Ethical clearance

Ethical clearance has been obtained from the institutional ethics committee F.1/MAMC/MD/MS (108/01/2024/No.136.

IV. RESULTS

This study included 50 obligate female carriers of hemophilia A, all aged ≥12 years. The mean age of participants was 28.46 ± 8.04 years, with ages ranging from 13 to 42 years. The cohort was predominantly composed of young adults aged 20–35 years, reflecting increased clinical detection during the reproductive years. Fewer participants were identified during early adolescence (13–18 years), largely through family screening, while representation declined in women older than 35 years.

Diagnosis ranged from 7–20 years, with most cases identified during adolescence (12–16 years) when bleeding symptoms become evident; early childhood diagnosis was less common, and delayed diagnosis (≥18 years) was rare, indicating gaps in early recognition.

There was a modest urban predominance (58% vs 42% rural). Most carriers had secondary or senior secondary education, and the majority were married. Socioeconomically, most belonged to the lower-middle class, suggesting financial and access-related barriers to care.

Clinically, menstrual-related bleeding was the most common presentation (52%), followed by epistaxis (16%) and joint bleeding (4%), while 28% were asymptomatic. Bleeding occurred in 73% of months, with a mean frequency of 0.73, reflecting a significant ongoing clinical burden

Mild or asymptomatic carriers had little to no bleeding, while moderate–severe cases showed recurrent mucocutaneous and joint bleeds. Life-threatening bleeding occurred in 10%, mainly in severe cases, where over half were affected. Family history was noted in 20%, more often in severe disease, suggesting underrecognition in milder cases. Complications (24%), especially hemarthrosis, were concentrated in moderate–severe carriers.

Treatment needs increased with severity: desmopressin was used in 28% (mainly for gynecological/obstetric bleeding), 16% required regular factor replacement (mostly moderate–severe), and transfusions (14%) were more common in severe cases. Joint bleeding (30%) also closely correlated with higher disease severity

Factor VIII levels varied widely: 12% had severe deficiency (<1%), 16% moderate (1–10%), and most

were mild or near-normal, with some supranormal due to therapy. Factor IX levels were largely normal.

By ISTH-SSC classification, asymptomatic carriers were the largest group, followed by symptomatic and mild hemophilia; severe, moderate, and mild cases comprised ~12%, 16%, and 20%, respectively.

Only 36% received prenatal genetic counseling and 24% had planned tertiary-center deliveries. Peripartum needs included factor replacement (28%) and transfusions (20%), highlighting care gaps. Ongoing issues included musculoskeletal morbidity (40%), recurrent bleeding (24%), psychosocial distress (16%), and barriers to treatment access.

Bleeding severity was assessed using the ISTH Bleeding Assessment Tool (ISTH-BAT), which enabled categorization of participants as asymptomatic, mild, moderate, or severe. This evaluation demonstrated that a considerable proportion of carriers with factor levels within the conventionally normal range nevertheless experienced clinically significant bleeding, underscoring the limitations of relying solely on laboratory values and highlighting the importance of thorough clinical assessment. Psychological evaluation using the Depression, Anxiety, and Stress Scale (DASS-21) revealed a strong positive correlation between bleeding severity and emotional distress ($p < 0.001$), with progressively higher distress scores observed alongside increasing ISTH-BAT scores, indicating a clear association between bleeding burden and psychosocial impact.

The study also applied the updated ISTH Scientific and Standardization Committee (SSC) nomenclature, which integrates factor activity levels with bleeding phenotype to classify carriers into five clinically meaningful categories: women with mild, moderate, or severe hemophilia, symptomatic carriers with normal factor levels, and asymptomatic carriers. Data analysis employed descriptive and inferential statistical methods, with continuous variables summarized as means with standard deviations and categorical variables expressed as frequencies and percentages. Results were presented using tables and graphical formats to illustrate key demographic, clinical, and laboratory characteristics in accordance with international standards.

Table: Bleeding Severity and Psychological Distress Among Hemophilia Carriers

Carrier Category	Factor Level (IU/mL)	BATS Score Range	Mean DASS-21 score
Asymptomatic	> 40	0–3	< 10
Symptomatic (Normal Level)	> 40	4–6	15–20
Mild Carrier	5–40	6–9	≈ 20
Moderate Carrier	1–5	7–10	≈ 24
Severe Carrier	< 1	≥ 8	≈ 27

Table 20: Association of BATS score with DASS score in haemophilia carriers (n=50)

BATS Score	Phenotype	DASS range maximum value
5	Asymptomatic (n=12)	13
6–7	Symptomatic (n=20)	20
6, 8, 9	Mild (n=7)	20
7–8	Moderate (n=8)	27
8	Severe (n=3)	27

V. DISCUSSION

This study underscores the underrecognized clinical and psychosocial burden of hemophilia A carriers, often mislabeled as asymptomatic. Among 50 obligate carriers (mean age 28.46 years), 62% were diagnosed at 11–15 years (mean 13.9), aligning with menarche and early bleeding symptoms. In contrast, other studies report diagnosis around 30 years, highlighting delays and the need for early screening. Adolescence and reproductive years emerge as key periods for timely diagnosis, counseling, and support.

A slight urban predominance (58% vs 42% rural) reflects better access to care and awareness, while rural carriers face significant healthcare barriers, emphasizing the need for equitable outreach. Educational levels were relatively high, with most completing secondary or higher education, suggesting that education improves awareness, healthcare utilization, and informed reproductive choices

The cohort highlights how sociodemographic and clinical factors shape care in hemophilia A carriers.

The predominance of married women emphasizes the need for reproductive counseling and family-centred support, while lower middle-class status points to barriers such as financial constraints and limited health literacy. Clinically, frequent pubertal menorrhagia and bleeding symptoms identify adolescence as a key period for early detection, though asymptomatic carriers remain a diagnostic challenge, supporting proactive screening and multidisciplinary care.

Using ISTH classification, marked variability was observed: 24% had normal factor VIII (>40%), yet 40% reported bleeding; 14% were mild, 16% moderate, and 6% severe. Overall, 56% were symptomatic despite normal levels, challenging the "asymptomatic carrier" concept. Severe cases presented before age 10, while mild–moderate cases appeared by adolescence. Rural residence and lower socioeconomic status were linked to greater severity and delayed diagnosis, whereas urban carriers benefited from earlier detection, underscoring disparities in access to care.

Factor VIII levels alone do not predict bleeding risk due to lyonization and individual variability, as symptoms may occur even with normal levels—supporting individualized assessment and early screening. In this cohort, no major bleeds occurred in mild cases, while one moderate carrier required hospitalization, indicating risk at intermediate levels. BATS scores (5–9) effectively stratified severity, from 5 in asymptomatic carriers to 8 in severe cases. Antifibrinolytic use increased with severity, required in most symptomatic and all mild–severe carriers.

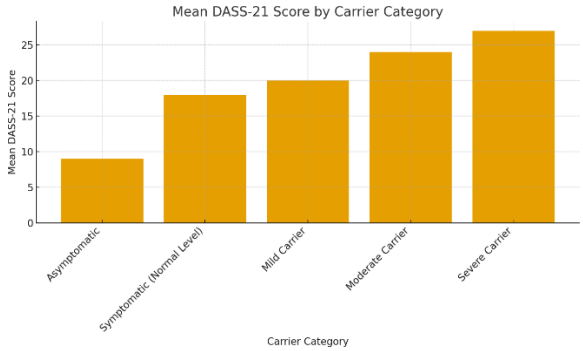
Heavy menstrual bleeding was the main indication for antifibrinolytics, rising with severity, while epistaxis and joint bleeding were less common and severity-specific. Factor replacement was unnecessary in asymptomatic and mild carriers but needed in some moderate and all severe cases. Transfusion needs also increased with severity. Overall, management burden escalates progressively, emphasizing tailored, resource-sensitive care

Among 50 hemophilia A carriers, anemia severity increased with clinical severity: mild carriers showed mixed anemia, moderate carriers had moderate–severe anemia, and all severe carriers had Hb <8 g/dL. Prenatal counseling was received by ~50–57% of asymptomatic/symptomatic carriers, with universal uptake in defined severity groups. Delivery outcomes reflected risk—uneventful in asymptomatic carriers but hemorrhagic complications in all mild, moderate, and severe cases—highlighting rising obstetric risk with severity.

In 24 deliveries, intervention needs escalated with severity: none in asymptomatic women, minimal in symptomatic cases, varied therapy in mild carriers, and universal transfusion in moderate/severe groups. DASS-21 findings showed parallel increases in psychological distress, progressing from minimal in asymptomatic carriers to universal severe depression in severe cases, with a strong association between clinical severity, obstetric risk, and emotional burden ($P < 0.001$).

Analysis of 50 hemophilia carriers shows a clear severity-dependent increase in psychological burden. Anxiety rose from minimal in asymptomatic carriers to moderate in most mild cases, severe in the majority of moderate carriers, and universal severe anxiety in severe carriers. Stress followed a similar gradient ($P < 0.001$), progressing from minimal in asymptomatic individuals to predominantly severe in moderate and severe groups.

Bleeding severity (BATS) strongly correlated with psychological distress ($P < 0.001$): low scores in asymptomatic carriers aligned with minimal impact, intermediate scores with mild–moderate burden, and high scores (20–27) in mild–moderate and severe carriers corresponded to the greatest distress. Overall, increasing phenotypic severity closely parallels rising emotional burden, emphasizing the need for integrated, patient-centered care addressing both clinical and psychosocial aspects



Graph: Correlation Between BATS Score and DASS-21 Score

The graph shows a steady rise in mean DASS-21 scores from asymptomatic to severe hemophilia carriers. Asymptomatic carriers have the lowest

psychological distress, while severe carriers exhibit the highest scores. The trend indicates that worsening clinical severity is associated with greater emotional and psychological burden. This visual representation reinforces the statistical finding that bleeding severity is directly associated with psychological distress. It also supports the argument for routine mental health screening in hemophilia carriers, especially those with moderate to severe bleeding symptoms. The emotional burden of living with a chronic, unpredictable condition can be profound, and addressing it is essential for holistic care.

This study provides a compelling case for rethinking how hemophilia carriers are identified, classified, and managed. By combining clinical evaluation, standardized bleeding scores, and psychological assessment, it offers a more complete picture of the challenges faced by carriers. The findings advocate for a multidisciplinary approach that includes haematologists, gynecologists, genetic counselors, and mental health professionals. Such collaboration is vital to improving outcomes and quality of life for hemophilia carriers, particularly in resource-limited settings, where awareness and access to care remain limited.

VI. LIMITATIONS

This study had several limitations. Many hemophilia carriers exhibit factor VIII or IX levels within the low-normal range, making laboratory diagnosis difficult, as normal levels do not necessarily rule out carrier status. Additionally, skewed X-chromosome inactivation can result in significantly reduced factor levels and clinical symptoms, which may not be captured by standard testing. The von Willebrand factor (VWF) antigen test, which could have provided further diagnostic clarity, was not performed. The study was also constrained by a relatively small sample size and included only obligate carriers of hemophilia A, which may limit the generalizability of the findings.

VII. CONCLUSION

This study identified a significant proportion of phenotypically symptomatic hemophilia carriers with normal factor VIII levels, underscoring that bleeding manifestations may occur independent of laboratory values. A strong correlation between BATS and DASS scores revealed that greater bleeding severity is associated with heightened psychological distress and reduced quality of life. Once considered clinically silent, hemophilia carriers are now recognized to experience a broad spectrum of bleeding and psychosocial challenges that are frequently overlooked, resulting in delayed diagnosis and inconsistent management. Effective care requires early identification, standardized evaluation, and individualized treatment planning. Addressing both the clinical and emotional aspects through multidisciplinary collaboration, patient education, and community awareness is crucial to achieving holistic, patient-centred management for hemophilia carriers