**Original article**

**Title : Natural history and quality of life in patients with Glanzmann thrombasthenia and Bernard Soulier syndrome: an observational study from India**

**Short running title**: Natural history of GT and BSS

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**Natural history and quality of life (QoL) in patients with Glanzmann thrombasthenia and Bernard Soulier syndrome: an observational study from India**

**Abstract**

***Background and Objectives***: Inherited platelet function disorders (IPFDs) are not well studied as compared to haemophilia and other bleeding disorders. Present study is aimed to understand the natural history and quality-of-life (QoL) in the two well studied IPFDs i.e. Glanzmann thrombasthenia (GT) and Bernard Soulier syndrome (BSS).

***Methods***: This is an ambispective, observational study. Demographics, medical data, mortality due to bleeding, comorbidities and treatment products were recorded; Health related quality of life (HRQoL) was captured using EuroQol five-dimensional questionnaire (EQ-5D), 36-Item Short Form Health Survey (SF-36) and Functional Assessment of Chronic Illness Therapy (FACIT) scales. The severity of bleeding was assessed by annual bleed rate (ABR) and International Society on Thrombosis and Haemostasis – Bleeding assessment tool (ISTH-BAT) score.

***Results***: The mean and median ages of 76 patients (64 GT, 12 BSS) were 18 and 14 years respectively. Epistaxis, Ecchymosis, gingival bleed, gastrointestinal (GI) bleed and soft tissue bleed were the commonest clinical manifestations. Menorrhagia was seen in all females in the reproductive age group. There was a statistically significant difference in the mean ISTH-BAT scores between GT and BSS (P= 0.016). Platelet transfusion was the main mode of treatment; none of the patients in the present series were on activated recombinant factor VII (rFVIIa) therapy. Between 2000 and 2025, there were 13 deaths reported due to bleeding mainly due to inaccessibility to treatment or treatment products. However, the relationship between quality of life (QoL) scores and ISTH-BAT score was weak.

***Interpretation and Conclusion***: The need for optimal treatment strategies to improve QoL and providing timely access to specific treatment products to prevent mortality is underscored.

**Introduction**

Inherited platelet function disorders (IPFDs) are heterogeneous disorders encompassing a wide spectrum of bleeding manifestations; severity varies among different types and even in patients with the same disorder. The relatively milder IPFDs often escape the conventional laboratory tests and specific tests required for their diagnosis are not available in majority of the laboratories. The ISTH-BAT is an useful tool in picking up mild IPFD cases through relevant laboratory investigations.

The two commonest inherited platelet function disorders, Glanzmann
thrombasthenia (GT) and Bernard Soulier syndrome (BSS)
occur with a general incidence of 1 per million, but they are much more prevalent in regions of high consanguinity [1-2]. Both GT and BSS are autosomal recessive disorders, though a few BSS patients are reported with autosomal dominant inheritance [3]. GT is caused due to a quantitative or qualitative deficiency in GP IIb-IIIa receptors on platelets resulting in absent/reduced platelet aggregation, whereas BSS is caused due to defective GP 1b-IX-V receptors help in the adhesion of platelets to subendothelium through von Willebrand factor (VWF).

The treatment protocols for GT and BSS are not uniform and they depend on the type and extent of bleed or response to a particular treatment product. Prophylaxis is generally not advocated for GT and BSS. The conventional treatment products are topical hemostatic sealants, antifibrinolytics, platelets and recombinant activated factor VII (rFVIIa), while stem cell transplantation and gene therapy are the corrective therapies [4-5].

 Most of the published reports across the world are on haemophilia and other bleeding disorders. Despite being common in some endogamous areas in India, there is no information on the natural history of these bleeding disorders. The real-world evidence on the type of bleeding, optimised treatment strategies and utilization of treatment products in India is limited. Present report provides baseline information on the demographic data, clinical course of the disease, treatment products used, mortality and QoL in Indian patients with GT and BSS.

**Material and Methods**

***Design and eligibility***: This is an ambispective observational cohort study, which adhered toStrengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. The study was conducted between November 2023 and April 2025 and the data was collected retrospectively from registered patients and also from new patients registered prospectively in the Hospital Registry. The eligibility criteria for enrolment were confirmed laboratory diagnosis of GT or BSS by both platelet aggregometry and flow cytometry. The study included both pediatric and adult patients. Overall, 76 patients (64 GT, 12 BSS) were included in the present analysis. An informed consent was taken from all patients or their guardians. The study was approved by the Institutional Ethics Committee.

***Data collection and statistical analysis***: The study team developed a case record form specifically designed for the study, which included demographics, bleed history, treatment. In addition, mortality due to bleeding and the cause of death were also taken. Bleed data included events 24 months prior to data collection. The ABR was calculated as sum total of bleed events during the previous 24 months divided by 2. Since it is a qualitative study, no statistical formula was applied to calculate the sample size in the present analysis. Descriptive statistics was used to summarize demographic variables and bleeding characteristics. Continuous variables were reported as mean ± standard deviation (SD) or median (range), while categorical variables were presented as frequencies and percentages. Group comparisons between GT and BSS were performed using unpaired t-test for continuous variables (e.g., ABR and ISTH-BAT scores). Normality of data was assumed based on clinical distribution patterns, and significance testing was done accordingly. Correlation between ISTH-BAT scores and QoL parameters (EQ-5D, SF-36, and FACIT) was assessed using **Pearson’s correlation coefficient**, assuming linear relationships and normal distribution of variables.  A **p-value < 0.05** was considered statistically significant in all analyses. All analyses were performed using Microsoft Excel and GraphPad Prism version 9.0 (GraphPad Software Inc., San Diego, USA).  ***EQ-5D***: The questions are mainly based to assess 5 parameters: mobility, physical activity, self-care, pain, and depression in five different scales (0-5). There are different versions of EQ 5D based on different age groups; EQ-5D-5L *Self-given* for 16 + years of age, EQ-5D-5L *Proxy* for 0-8 years, and EQ-5D-Y *Youth* for 8-16 years of age [6].

***SF-36:*** TheShort-form (SF) health survey consists of 36-items covering various parameters vitality, physical activity, pain, general health, mental health and social activities. The mean score is calculated from a score ranging between 0 and 100; lower score indicates poor QoL, and higher score indicates excellent QoL [7].

***FACIT***: The FACIT-F is a 13-item questionnaire, mainly on fatigue and its effect on the routine activities. The score ranges between 0 and 52 ; higher score is suggests less fatigue  [8]. **Results**

Demographic profile of the patients are shown in Table 1. There were 41 males and 35 females in the study group. Mean and median ages of the study group were 17.99 (12.14) and 14.25 years respectively. The mean and median ages of BSS patients were higher than those of GT patients (Table 1). Among 76 cases, 54 (71.05%) had parental consanguinity and 32 had another affected family member (42.1%). Seventeen patients (22.37%) were diagnosed at birth and 22 patients (28.95%) were diagnosed before the age of 5 years. The annual income in majority of the patients in the present series was < 3 lakhs INR.

***Bleeding manifestations****:* The mean ABR in this study cohort over the preceding 24 months was 11.85 while in BSS it was much lower i.e. 1.85. Only one GT patient, who was 6 year old, did not have any bleeding episode at the time of enrolment. The mean ISTH - BS was 10.5 in GT and 6 in BSS cases. The unpaired t-test showed statistically significant differences both in ABR (P=0.0152) and ISTH-BAT scores (P=0.0059) between BSS and GT patients (Figures 1 & 2). Majority of the patients had the three classical platelet related clinical manifestations i.e. epistaxis, ecchymosis and gum bleed followed by soft tissue bleed and GI bleed. Menorrhagia and postpartum bleed were the common clinical manifestations in all women in the reproductive age group in both BSS and GT (Table 2).

***Treatment products****:* Only 33 patients (43.4%) were treated with platelet concentrate for bleeding episodes and none of the patients had taken rFVIIa for their bleeding. Eighteen patients (23.7%) had used antifibrinolytics with or without platelet concentrate. Alternate medicine (Homeopathy and Ayurvedic medication) was being used by 13 (17.1%) GT patients; 17 patients (22.4%) had taken whole blood and 22 patients (28.9%) had taken fresh frozen plasma (FFP) during different bleeding episodes both as hemostatic therapy and as a supportive care for anaemia. But majority of these transfusions were done before their final laboratory diagnosis was done in an advanced laboratory. All 19 females in the reproductive age had menorrhagia as the major clinical manifestation and 7 were on oral contraceptive pills. Majority of the patients with gum bleeding and epistaxis were successfully managed by using antifibrinolytics. All females with menorrhagia were given oral iron supplementation indefinitely for chronic anaemia. Post-partal bleed and bleeding after circumcision was observed in 3 and 10 patients respectively. Intracranial haemorrhage was reported in two cases, one of which required a surgery to excise the hematoma (Table 3)

***Mortality***: Thirteen GT patients died between 2000 and 2025 in 64 families interrogated during this analysis. In 12 of these patients, the cause of death was non-availability/non-accessibility of treatment products. No mortality was reported in BSS families (Table 4)

***QoL***: [Table](https://bmjopen.bmj.com/content/14/11/e088538.long#F2) 5 shows the scores of the EQ-5D-5L for both GT and BSS patients as per the EQ-5D-5L questionnaire.  Majority of patients (>90%) reported no mobility problem, self-care and other routine activities, while more than 50% of the cases had no discomfort or anxiety/depression.The ISTH-BAT score in comparison with all the three QoL scores showed weak negative correlation. The correlation matrix representing the data is shown in Figure 3.

**Discussion**

There is paucity of data on the natural history of GT and BSS not only in the world literature but even in countries like India where there is a higher prevalence of these disorders due to the prevalence of high endogamy. The present study is an observational study on the natural history of 76 participants with GT and BSS. The study was undertaken to understand the extent and severity of bleeding manifestations, type of treatment and overall QoL in patients with GT and BSS in India.

Both GT and BSS are generally associated with mild to severe mucocutaneous bleeding. They make approximately 4-5 % of all bleeding disorders diagnosed in any of the comprehensive coagulation laboratories in the country [9-10]. However, this may not be the actual prevalence of these disorders, since many of the mild cases do not even report to the hospital. Moreover, since the confirmation of diagnosis requires both platelet aggregometry and flow cytometry which are available only in few select diagnostic centres, GT and BSS patients with mild clinical manifestations are hardly diagnosed. Third, “mild” bleeding in general is considered as “normal” bleeding and they never report to the hospital. Thus, substantial number of patients with IPFDs including GT and BSS remains undiagnosed, which in few cases require specialized phenotypic investigations and molecular tools like nextgen sequencing [11].

There is no reported data on the type of bleed, treatment products QoL or mortality in patients with the two commonest IPFDs in India. Present analysis for the first time provides a first- hand information on a sizeable number of patients with GT and BSS. The ISTH-BAT score was first validated in patients with von Willebrand disease (VWD), but subsequently, it is being validated in different types of bleeding disorders including GT and BSS [12]. It is still debated whether it is the most appropriate tool for assessing the bleeding symptoms in patients with GT and BSS. Despite its limitations, the ISTH‐BAT is considered as the best means of assessing bleeding severity as it takes both frequency and severity into consideration. Both ABR and ISTH-BAT score have been applied in this analysis. Previous studies from India have shown that menorrhagia is an important clinical indicator for women with underlying bleeding disorders [13-14]. In addition, postpartum bleeding in women with GT and BSS is equally challenging, requiring highly specialized multi-disciplinary medical management [15-16] .Unlike haemophilia, intracranial bleeding is rare in patients with GT and BSS. There are only isolated case reports on either intracranial or spinal cord bleeds in patients with GT [17-18]. There were 2 GT cases who gave a history of IC bleed in this series. The bleeding severity was milder in BSS as compared to GT patients, which is in line with earlier reports [19].

Patients with GT and BSS do not need routine prophylaxis; so the treatment strategies generally should aim at pre-surgery prophylaxis or during severe life-threatening bleeding. Platelet concentrates are always considered as the first line treatment for severe bleeding in inherited platelet function defects like GT and BSS. However one of the major concerns with platelet transfusion is the development of platelet antibodies due to alloimmunization which is reported in as high as 25-70% of the patients [20-21]. Though there are protocols for use of leukocyte depleted and human leukocyte antigen (HLA) matched platelets, this is not feasible in most of the clinical settings in India. Though rFVIIa was approved for use in GT patients in 2004, and has been the standard of care for GT patients, none of our patients were treated with this product till date. This is mainly because most of the patients in this series belonged to lower economic strata of the society and could not have afforded the exorbitant cost of the product. Isolated case reports are published on use of rFVIIa in BSS patients [22-23], but it is not licensed to for use in BSS patients. As per the United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) and British Society of Haematology (BSH) guidelines, for mild bleeding manifestations, tranexamic acid or other anti-fibrinolytics may be used, while rFVIIa is the preferred treatment for severe, non- life threatening bleeding and unselected platelet transfusion is advised only in severe life threatening bleeding. Use of herbal medicines like Ankaferd blood stopper have also shown promising results when used both as topical hemostatic agent as well as systemically in refractory GT cases [24-25]. Thirteen patients were on alternate medicine (ayurvedic or homeopathy) in the present series; however the details of these medications could not be obtained.

Mortality in GT and BSS patients is hardly reported but the prognosis of the diseases are generally reported to be good. Thirteen cases of death were reported due to bleeding and seven of which were solely due to non-availability of treatment products. Though platelet concentrates are available in most of the blood banks, their ready availability in remote parts is uncertain and majority of the patients in this series may not afford rFVIIa for any acute bleeding episode.

It is always debated whether the ISTH‐BAT is an appropriate measure of the severity of bleeding due to domain saturation. However, this is the only tool available currently for the quantitative measurement of bleeds. The HRQoL is influenced by patient perception of illness [26]. In our study, we did not find a significant association of ISTH-BAT score with any of the QoL scores. A similar report of negative association of QoL data with ISTH-BAT score has been published by another group [27].

The strength of our study is the inclusion of a large number of patients with GT and BSS. To the best of our knowledge, this is to first study from India assessing the bleeding phenotype, treatment products used and QoL in a large cohort of patients with GT and BSS. Insight into the natural history of these two disorders can have far reaching implications in terms of patient counselling about the prognosis and therapeutic strategies to reduce bleeding related mortality. Limitations of the study include its retrospective nature and heterogeneity of patient population. Nonetheless, given the rarity of the condition, this was the most practical approach which enabled us to present this highly valuable data.

In conclusion, the present analysis provides a baseline data on the natural history of two rare platelet function disorders. The study is a step in understanding the clinical features of the diseases and the type of treatment. Superficial bleed like epistaxis, GI bleed and echhymoses were the commonest clinical manifestations; the BS in BSS patients was much lower than that of GT. Menorrhagia and post-partal bleed were seen in majority of the women in the reproductive age group. Majority of our patients were treated with either platelet concentrates and/or anti-fibrinolytic agents and none were on rFVIIa. Mortality was reported only in GT patients and it was mainly due to inaccessibility to treatment products on time. Overall, this study sets a reference for future clinical trials or for drawing attention of relevant agencies to make treatment products easily available for these two rare disorders similar to haemophilia.

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**Legends for Tables and Figures**

**Table 1: Demographic data of patients**

The mean and median ages of patients in the current series were low i.e. approximately 18 years and 14 years respectively for GT and BSS; except one BSS patient, all were below the age of 50 years. Around 71% of the patients had parental consanguinity.

**Table 2:** **Bleeding symptoms and severity in patients with GT and BSS**

Mucosal bleed was the commonest clinical manifestation in both GT and BSS; Menorrhagia and post-partal bleed were important clinical indicators in women in the reproductive age group

**Table 3: Treatment products used by patients with GT and BSS**

Platelet concentrate and/or antifibrinolytics were the commonest treatment products used by patients; none of the patients had used rFVIIa

**Table 4. Mortality in patients with GT and BSS**

Between 2000 and 2025, 13 deaths were reported in 64 GT families; the mortality was mainly attributed to inaccessibility to treatment products

**Table 5: Table 5. EQ-5D-5L in patients with GT and BSS**

Except mild pain, anxiety and discomfort in around half of the patients, most of the patients did not report any major problem in their routine activities.

**Figure 1: Annualized bleeding rate (ABR) in GT and BSS patients**

The unpaired t-test Box plot shows significantly higher ABR in GT as compared to BSS patients (*p*<0.05).

**Figure 2: ISTH-BAT scores in GT and BSS patients**

The unpaired t-test shows significant differences in ISTH-BAT scores between GT and BSS (*p*<0.05).

**Figure 3. Correlation matrix showing association between ISTH-BAT score and QoL parameters (EQ-5D, SF-36 and FACIT) in GT and BSS cases**

A weak negative correlation was seen between ISTH BAT and all three QoL (EQ-5D, SF-36 and FACIT) scores

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| **Table 1. Demographic data of patients** |
|  |  |  |  |
|  **Parameter** | **GT****(n=64)** | **BSS****(n=12)** | **Total****(n=76)** |
| Males | 34 | 7 | 41 |
| Females | 30 | 5 | 35 |
| Present Age (years) |  |  |  |
| <1 | 0 | 0 | 0 |
| 1-12 | 37 | 4 | 41 |
| 13-18 | 13 | 4 | 17 |
| 19-50 | 14 | 3 | 17 |
| >50 | 0 | 1 | 1 |
| Age at diagnosis (years) |  |  |  |
| At birth | 17 | 2 | 19 |
| <5 | 28 | 1 | 29 |
| 5-10 | 12 | 5 | 17 |
| >10 | 7 | 4 | 14 |
| Mean + SD (years) | 13.98+9.14 | 22+15.13 | 17.99+12.14 |
| Median | 12 | 16.5 | 14.25 |
| Range | 1-38 | 12-65 | 1-65 |
| Positive family history |  |  |  |
| Yes | 25 | 7 | 32 |
| No | 39 | 5 | 44 |
| Parental consanguinity |  |  |  |
| Yes | 47 | 7 | 54 |
| No | 17 | 5 | 22 |
| Annual Income (INR) |  |  |  |
| <50000 | 3 | 4 | 7 |
| 50000-3 lacs | 52 | 8 | 60 |
| >3 lacs | 9 | 0 | 9 |

The mean and median ages of patients in the current series were low i.e. approximately 18 years and 14 years respectively; except one BSS patient, all were below the age of 50 years. Around 71% of the patients had parental consanguinity

**Table 2. Bleeding data of 76 patients with GT and BSS**

|  |  |  |  |
| --- | --- | --- | --- |
| **Type of bleed** | **GT****(Number/%)** | **BSS****(Number/%)** | **Total****(Number/%)** |
| Epistaxis | 45 (70.3) | 7 (58.3) | 52 (64.3) |
| Ecchymosis | 44 (68.8) | 7 (58.3) | 51 (63.5) |
| Gum bleed | 37 (57.8) | 6 (50) | 43 (53.9) |
| Haematuria | 7 (10.9) | 0 (0) | 7 (5.5) |
| GI bleed | 19 (29.7) | 4 (33.3) | 23 (31.5) |
| IC bleed | 2 (3.1) | 0 (0) | 2 (1.5\6) |
| Soft tissue bleed | 26 (40.6) | 2 (16.7) | 28 (28.7) |
| Joint bleed | 2 (3.1) | 0 (0) | 2 (1.6) |
| Menorrhagia | 15 (88.2) | 4 (100)\* | 19 (94.1) |
| Post-partum bleed | 2 (40) | 1 (25)\* | 3 (32.5) |
| No bleed | 1 (1.6) | 0 (0) | 1 (1.6) |
| Circumcision | 10 (29.4) | 0 (0) | 10 (29.4) |
| Other bleed | 17 (26.6) | 0 (0) | 17 (26.6) |

\*The denominator in these cases is the total number of women in the reproductive age group or those who went through post-partal period

Mucosal bleed was the commonest clinical manifestation in both GT and BSS; Menorrhagia and post-partal bleed are important clinical indicators in women in reproductive age group

**Table 3. Treatment products used by patients with GT and BSS**

|  |  |  |  |
| --- | --- | --- | --- |
| **Product** | **GT****(No/%)** | **BSS****(No/%)** | **Total****(No/%)** |
| Whole Blood | 17 (26.6) | 0 (0) | 17 (22.4) |
| FFP | 21 (32.8) | 1 (8.3) | 22 (28.9) |
| Platelet concentrate | 26 (40.6) | 7 (58.3) | 33 (43.4) |
| rFVIIa | 0 (0) | 0 (0) | 0 (0) |
| Anti-fibrinolytics | 14 (21.9) | 4 (33.3) | 18 (23.7) |
| Hormonal therapy | 7 (10.9) | 0 (0) | 7 (9.2) |
| Alternate medicine | 13 (30.3) | 0 (0) | 13 (17.1) |

Platelet concentrate and/or anti-fibrinolytics were the commonest treatment products used by patients; none of the patients had used rFVIIa.

**Table 4. Mortality in patients with GT and BSS**

|  |  |  |
| --- | --- | --- |
|  | **GT****(N=64)** | **Total****(N=76)** |
| Total no. of deaths due to bleeding | 13 | 13 |
| No. of deaths due to non-availability of treatment products | 12 | 12 |
| Other causes | 13 | 13 |

Between 2000 and 2025, 13 deaths were reported in 64 GT families; the mortality was mainly attributed to inaccessibility to treatment products

**Table 5. EQ-5D-5L in patients with GT and BSS**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Mobility | Self-Care | Unusual Activity | Pain/ Discomfort | Anxiety/ Depression |
| No Problem (%) | 89.5 | 98.7 | 85.5 | 52.6 | 61.8 |
| Slight Problem (%) | 10.5 | 1.3 | 11.8 | 42.1 | 31.6 |
| Moderate Problem (%) | 0 | 0 | 2.6 | 5.3 | 6.6 |
| Severe problem (%) | 0 | 0 | 0 | 0 | 0 |
| Unable to do (%) | 0 | 0 | 0 | 0 | 0 |

Except mild pain, anxiety and discomfort in around half of the patients, most of the patients did not report any problem in their routine activities

**Figure 1: Annualized bleeding rate (ABR) in GT and BSS patients**

**Annual Bleed Rate (ABR)**

The unpaired t-test Box plot shows significantly higher ABR in GT as compared to BSS patients (*p*<0.05)

**Figure 2: ISTH-BAT scores in GT and BSS patients**

**ISTH-BAT Score**

The unpaired t-test shows significant differences in ISTH-BAT scores between GT and BSS (*p*<0.05)

**Figure 3. Correlation matrix showing association between ISTH-BAT score and QoL parameters (EQ-5D, SF-36 and FACIT) in GT and BSS cases**

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A weak negative correlation was seen between ISTH BAT and all three QoL (EQ-5D, SF-36 and FACIT) score