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ORIGINAL ARTICLE

Bleeding and quality of life in people with Glanzmann thrombasthenia—insights from the Glanzmann's 360 study

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Abstract

Background: Glanzmann thrombasthenia (GT) is a rare platelet function disorder that results in severe bleeding. We assessed clinical symptoms and psychological parameters to identify the unmet needs associated with GT.

Objectives: Glanzmann's 360 is a mixed-methods study designed to give a contemporary snapshot of the impact of living with GT.

Methods: The study comprised a self-completion online survey complemented by interviews conducted with affected individuals and carers recruited via social media and hemophilia treatment centers.

Results: The survey was completed by 88 people with GT and 29 carers of children/young people with GT aged <16 years. The population ranged in age from <2 years to >70 years; 56% were female. Although 47% had been diagnosed with GT under the age of 2 years, 12% were diagnosed after 20 years of age. For 82%, a bleeding phenotype was apparent by the age of 5 years. Most respondents (88%) had experienced at least one bleed in the past week. Bleeding disproportionally affected women. Bleeds resulted in frequent hospital contact and considerable psychological distress: 26% of the population had scores suggestive of low self-esteem, while 30% met criteria suggestive of symptomatic depression. Exploratory analyses suggest that bleed experiences are associated with impaired health-related quality of life.

Conclusion: The Glanzmann's 360 study reveals the significant physical, psychosocial, and quality-of-life impairments that are likely to be linked to the frequent bleeds experienced by those with GT. Clinicians treating people with GT should promote access to multidisciplinary comprehensive care, including psychosocial support.

KEYWORDS
Glanzmann thrombasthenia, mixed methods, natural history, quality of life, unmet need

Essentials

- Glanzmann thrombasthenia is a rare platelet function disorder resulting in severe bleeding.
- This mixed-methods study (88 adults and 29 carers) gives a contemporary snapshot of life with Glanzmann thrombasthenia.
- Most had bled in the last week, causing distress; women were more affected than men.
- Significant physical, psychosocial, and quality-of-life impacts are linked to frequent bleeding.

1 | INTRODUCTION

Glanzmann thrombasthenia (GT) is an autosomal recessive disorder caused by absence or reduction of the glycoprotein IIb/IIIa complex on the surface of the platelet that results in a lack of platelet aggregation and a bleeding phenotype [1]. From early childhood onward, affected individuals experience bleeds including petechial hemorrhage, bruising, epistaxis, mucus membrane bleeds, joint bleeds, and gastrointestinal bleeding that may be severe and life-threatening [2,3]. The severity and frequency of bleeding episodes in GT can vary greatly among affected individuals, even within the same family. For women, heavy menstrual bleeding is common [4], and GT also increases the risk of excessive blood loss during childbirth [5,6]. Despite its impact, comprehensive data on the burden of GT and the unmet needs of those affected remain limited [7,8]. The Glanzmann's 360 study seeks to bridge this knowledge gap, offering a deeper understanding of GT's impact on people's lives beyond the clinical symptoms.

2 | METHODS

Glanzmann's 360 is a mixed-methods natural history study that combined quantitative surveys with qualitative interviews to assess the lived experiences of people with GT and their caregivers. The study was approved by the Health Research Authority and Health and Care Research Wales (22/SC/0095) and registered at ClinicalTrials.gov (NCT05315232) and the United Kingdom National Institute of Health Research (HAEM 52408). The survey was completed after obtaining online consent. All participants consented to their anonymized data being used in any presentation or publication.

2.1 | Study cohort

People aged over 16 years with GT and parents/caregivers of children with GT were eligible to participate. Recruitment was facilitated through hemophilia treatment centers (which sent out postcards to diagnosed patients containing a quick reponse code to the survey), social media campaigns on Facebook and Twitter, and relevant patient groups here; diagnosis was self-reported.

Those who completed the survey were offered the choice of being entered into a prize draw (this was not linked to survey completion) as well as the opportunity to take part in a qualitative in-depth interview. Survey data are reported here; interview data are reported in an accompanying paper. Data collection started in April 2022 and ended in October 2023.

2.2 | Study measures

We collected self-reported data on demographic characteristics, bleeds, and treatment history together with questionnaires used in other bleeding disorders or chronic disease populations to assess psychosocial well-being and health-related quality of life (HRQoL) parameters. The EuroQoL 5 Dimensions 5 Levels (EQ-5D-5L) [9] was used to measure HRQoL, adjusted to a value set specific to each participant's country of residence or nearest relevant country. The Patient Health Questionnaire (PHQ-8) [10], an established tool for identifying depression, was used to estimate symptomatic depression rates using the recommended score cut point of 10 [10]. Self-esteem was estimated using Rosenberg's self-esteem score, taking a score of 15 or less to indicate low self-esteem [11]. The Self-Efficacy to Manage Chronic Disease Scale [12] was also included, along with the Menstrual Impact Questionnaire [13]. Data on these tools are shown only for those aged over 16 years who are therefore self-reporting.

2.3 | Statistical analysis

Descriptive statistics of the sociodemographic and clinical data are presented to give an overview of the characteristics of the study population. Data are presented as number and frequency for categorical variables or mean (with SD or SE as appropriate) for continuous variables. Analyses explored associations between clinical data and psychosocial variables using standard statistical tools. *P* values were calculated from chi-squared tests for categorical variables and Kruskal–Wallis tests for continuous variables. Where categories had counts of less than 5 respondents, Fisher's exact tests were performed. Mean data were compared using the Wilcoxon rank sum test with continuity correction. For all analyses, *P* values of <.05 were taken to indicate significance.

3 | RESULTS

3.1 | Participant demographics

Our survey was completed by (or on behalf of) 117 participants. Of these, 88 were people with GT and the remainder were carers of children/young people aged <16 years with GT. Together, they comprised a GT population ranging in age from <2 years to >70 years (Table 1), of whom 56% were female, residing in 20 countries (albeit born in 27 countries) on 6 continents.

Most had been diagnosed with GT in childhood; 47% were under the age of 2 years but many experienced delayed diagnosis, with 12% only diagnosed after 20 years of age (Table 2). For most respondents (82%), a bleeding phenotype was apparent by the age of 5 years.

3.2 | Bleeding phenotypes

Most respondents (88%) had experienced at least one bleed in the past week (Figure 1); the mean value was 3 separate bleeds in the preceding week. Among respondents who reported a bleed in the past week, 34% required hospital contact and 65% reported a bleed-related hospital visit in the past 6 months. Bruising, epistaxis, and

TABLE 1 Demographic characteristics.

Characteristics	Total population (*N* = 117)	Men/boys (*n* = 51)	Women/girls (*n* = 66)
Age group			
<2 y	6 (5.1%)	4 (7.8%)	2 (3.0%)
2-5 y	11 (9.4%)	6 (11.8%)	5 (7.6%)
6-10 y	9 (7.7%)	5 (9.8%)	4 (6.1%)
11-16 y	10 (8.5%)	5 (9.8%)	5 (7.6%)
17-19 y	9 (7.7%)	7 (13.7%)	2 (3.0%)
20-29 y	28 (23.9%)	8 (15.7%)	20 (30.3%)
30-39 y	19 (16.2%)	7 (13.7%)	12 (18.2%)
40-49 y	8 (6.8%)	3 (5.9%)	5 (7.6%)
50-59 y	10 (8.5%)	5 (9.8%)	5 (7.6%)
60-69 y	2 (1.7%)	1 (2.0%)	1 (1.5%)
>70 y	5 (4.3%)	0 (0%)	5 (7.6%)
Ethnicity			
Asian	23 (19.7%)	12 (23.5%)	11 (16.7%)
Black African/Caribbean/Black British	11 (9.4%)	5 (9.8%)	6 (9.1%)
Mixed multiple ethnicity	9 (7.7%)	3 (5.9%)	6 (9.1%)
Other	6 (5.1%)	3 (5.9%)	3 (4.5%)
White	68 (58.1%)	28 (54.9%)	40 (12.1%)
Continent of residence			
Europe	75 (64.1%)	38 (74.5%)	37 (56.0%)
North America	28 (23.9%)	9 (17.6%)	19 (28.8%)
Asia	9 (8.5%)	3 (5.9%)	6 (10.6%)
Africa	1 (0.9%)	0 (0%)	1 (1.5%)
Australia	2 (1.7%)	0 (0%)	2 (3.0%)
South America	2 (0.9%)	1 (2.0%)	1 (1.5%)
Occupation			
Full-time parent/homemaker[a]	12 (10.2)	6 (11.7%)	8 (12.1%)
Employed full time[a]	47 (40.1%)	19 (37.2%)	28 (42.4%)
Employed part time[a]	11 (9.4%)	4 (7.8%)	7 (10.6%)
Student[a]	34 (29%)	13 (25.4%)	21 (31.8%)
Unemployed[a]	9 (7.6%)	5 (9.8%)	4 (6%)
Retired[a]	8 (6.8%)	0 (0%)	8 (12.1%)

Data on categorical variables are presented as frequency (percentage).

[a] Categories are not mutually exclusive.

TABLE 2 Age at diagnosis and age at which symptoms became apparent.

Age	Total population (*N* = 117)	Men/boys (*n* = 51)	Women/girls (*n* = 66)
Age at diagnosis			
<2 y	55 (47.0%)	20 (39.2%)	35 (53.0%)
2-5 y	22 (18.8%)	10 (19.6%)	12 (18.2%)
6-10 y	12 (10.3%)	7 (13.7%)	5 (7.6%)
11-19 y	13 (11.1%)	7 (13.7%)	6 (9.1%)
>20 y	15 (12.8%)	7 (13.7%)	8 (12.1%)
Age at which bleeding became apparent			
<2 y	69 (59.0%)	28 (54.9%)	41 (62.1%)
2-5 y	27 (23.1%)	17 933.3%)	10 (15.2%)
6-10 y	9 (7.7%)	1 (2.0%)	8 (12.1%)
11-19 y	6 (5.1%)	1 (2.0%)	5 (7.6%)
>20 y	6 (5.1%)	4 (6.0%)	2 (3.0%)

Data are presented as frequency (percentage).

gum/mouth bleeds were most commonly reported, both among men and women, as well as children (with carer proxy reporting), followed by bleeding after dental work or trauma (Figure 2). Muscle bleeds were also widely reported. Mean number of bleed sites reported was 5.3 (range, 1-10). Menstrual bleeding symptoms (heavy or prolonged periods) were reported by 92% of women and girls. Among women and girls who completed the Menstrual Impact Questionnaire, 32 of 54 (59%) described blood loss in their most recent menstrual period as "heavy" or "very heavy" (Figure 3).

3.3 | Treatment histories

Only 5 participants reported no history of treatment. The most widely used treatments were tranexamic acid (92/117) and recombinant factor VIIa (76/117).

3.4 | Social and psychological impact

Respondents described the social impact of bleeding (Figure 4). Most respondents (81%) had lost time from work or school because of their bleeding, while 72% (principally women/girls) had avoided engaging in sports or other physical activities because of it. Bleeding also impacted social activities and holidays for most respondents and, for a small number, affected their ability to get a job or to pursue their education (Figure 5). Inevitably, bleeding had taken a psychological and emotional toll. Over 85% of respondents reported that it had affected their mood and led to emotional problems and/or social isolation (Figure 6).

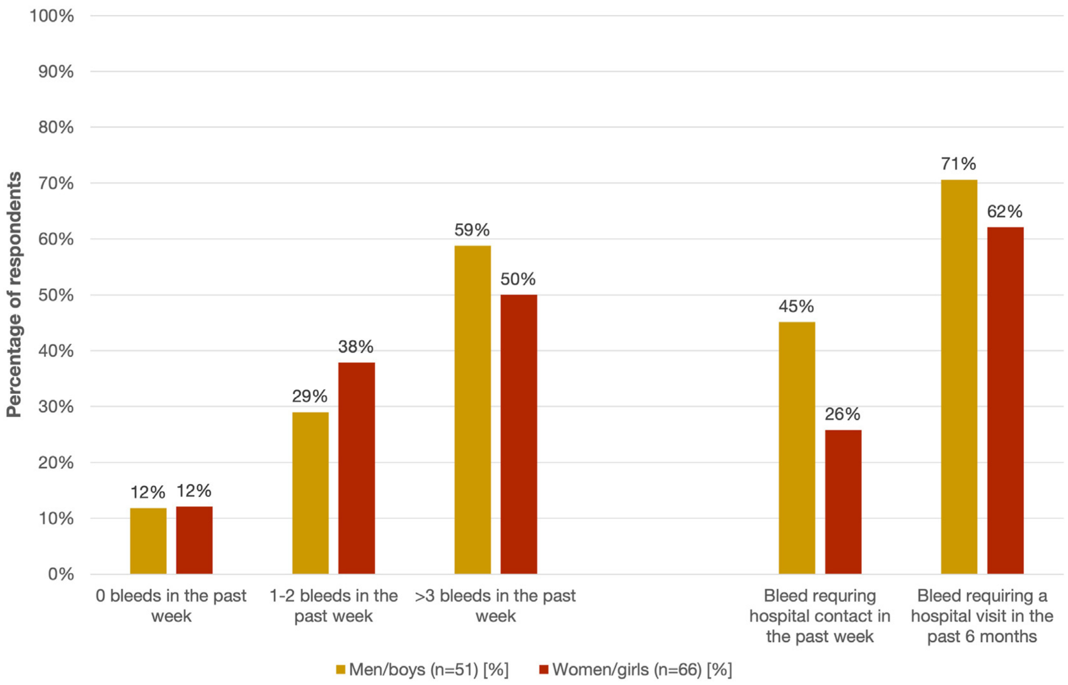

FIGURE 1 Recent bleed experiences (data are presented as frequency [percentage] for categorical variables).

3.5 | Quality-of-life impacts

EQ-5D-5L index and visual analog score (VAS) scores for the adult population are shown in Table 3, along with the results of the psychological test scores using widely accepted cut-points. These indicated that 26% of respondents had scores suggestive of low self-esteem, 24 individuals (30%) met the PHQ-8 criteria for symptomatic depression, and 4 (of 79; 5%) met criteria for severe major depression.

Exploratory subgroup analyses of participants' characteristics stratified by PHQ-8 score suggested no significant differences between those with or without symptomatic depression with respect to age, gender, educational attainment, or bleeding history (Table 4). However, those with PHQ-8 scores in the depressive range had lower self-esteem scores ($P < .001$), lower self-efficacy scores ($P < .001$), lower EQ-5D-5L index scores ($P < .001$), and lower EQ-5D-5L VAS scores ($P = .76$).

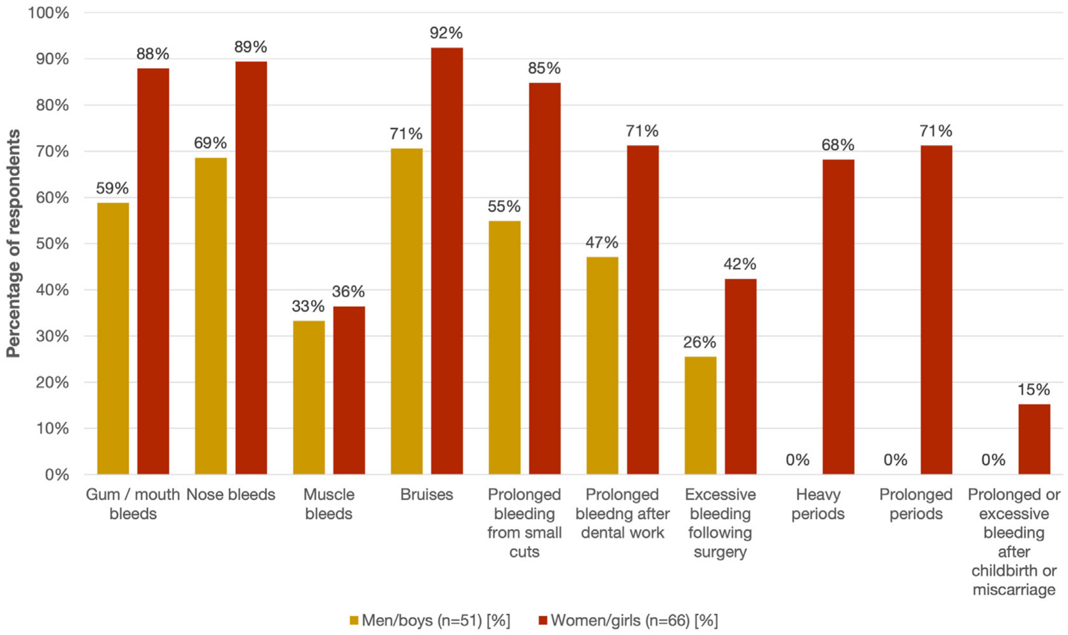

FIGURE 2 Self-reported bleed sites.

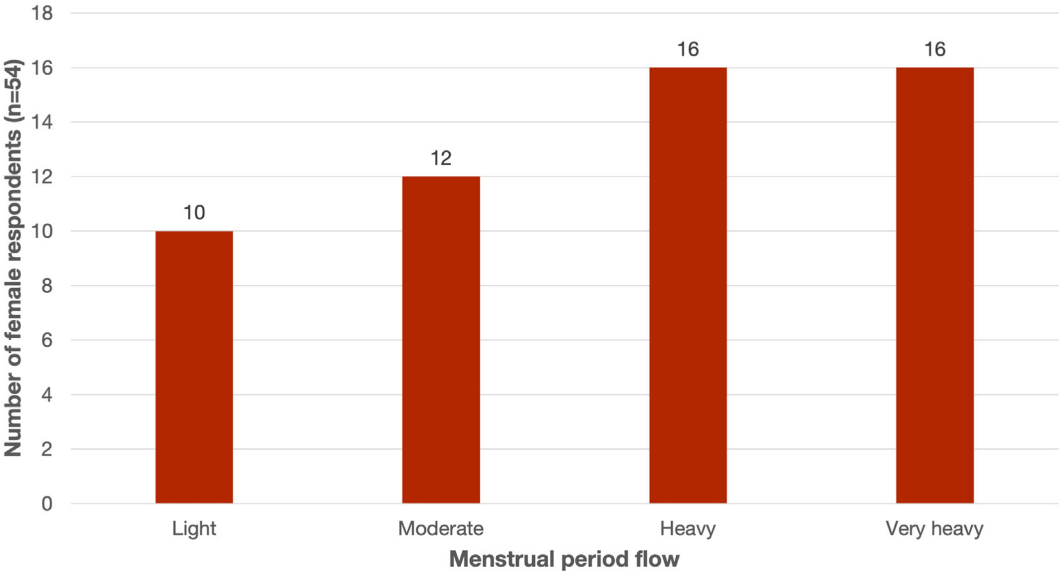

FIGURE 3 Blood loss in most recent menstrual period. Using the Menstrual Impact Questionnaire, 32 of 54 (59%) described blood loss in their most recent menstrual period as "heavy" or "very heavy".

Stratification of bleed experiences by psychological response scores (Table 5) suggested that a bleed in the past week ($P < .05$), or a hospital visit for a bleed in the past 6 months ($P < .01$) significantly impaired quality of life. However, these associations did not hold for EQ-5D-5L VAS scores. No such associations were seen with psychological scores other than the PHQ-8.

4 | DISCUSSION

The Glanzmann's 360 study underscores the substantial and multifaceted burden of GT and demonstrates not only the high prevalence of bleeding complications but also the profound psychosocial and economic consequences. Our findings show that bleeding episodes are a universal experience for those with GT, with a striking prevalence of heavy menstrual bleeding in women, a symptom that warrants urgent attention due to its impact on overall health and well-being. All survey respondents reported a bleeding history. Nearly every respondent reported bruising, nose bleeds, and gum/mouth bleeds, and almost every woman reported heavy and/or prolonged menstrual periods. Although far less common, some respondents reported gastrointestinal, cerebral, and joint bleeds; one respondent experienced an inner ear bleed after air travel.

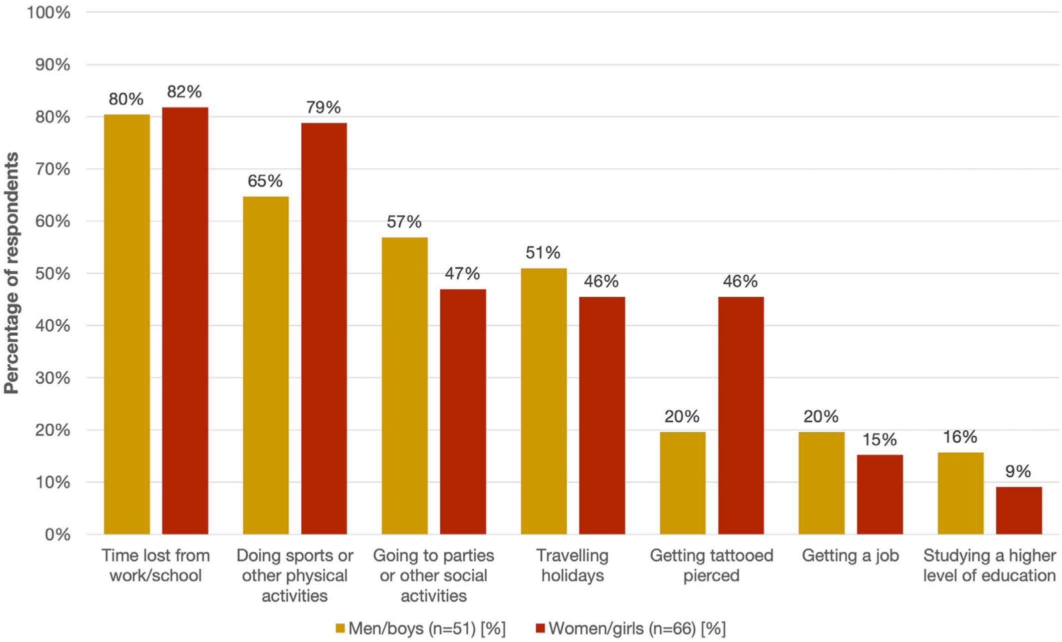

FIGURE 4 Social impact of bleeding (data are presented as frequency (percentage) for categorical variables).

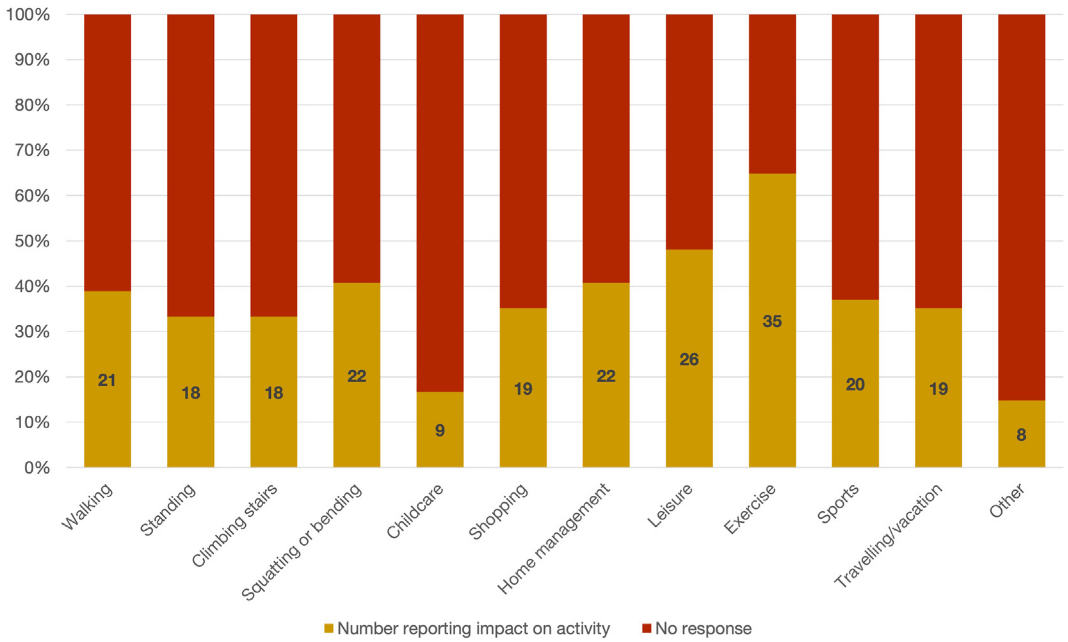

FIGURE 5 Activities impacted by menstrual blood loss as reported by women who completed the Menstrual Impact Questionnaire (*n* = 54).

Our survey asked directly about bruises, but the accompanying interview program suggested that for many people with GT, clinicians do not actively ask about bruising when discussing bleeds (thereby differentiating bruises from bleeds) and those affected do not necessarily report bruises as bleeds in, for instance, bleed diaries. The underestimation of the severity of bruising and its repercussions on the social fabric of patients' lives, particularly for young women and children, suggests a disconnect between clinical assessments currently used by clinicians and patients' lived experiences. It highlights an unmet medical need for greater awareness and proactive management strategies in clinical practice. Enhancing patient-clinician dialogue is vital not only for identifying underreported bleeding episodes in GT but also for fostering a deeper understanding of the condition' severity. This is crucial for effective disease management and treatment optimization.

Our population appeared to be well-educated with the majority receiving tertiary education (Table 4). However, there was a suggestion that for some, their GT and bleeding had impacted their ability to seek educational qualifications (12%) or work opportunities (17%), which may have led to economic impacts. Whether or not this was the

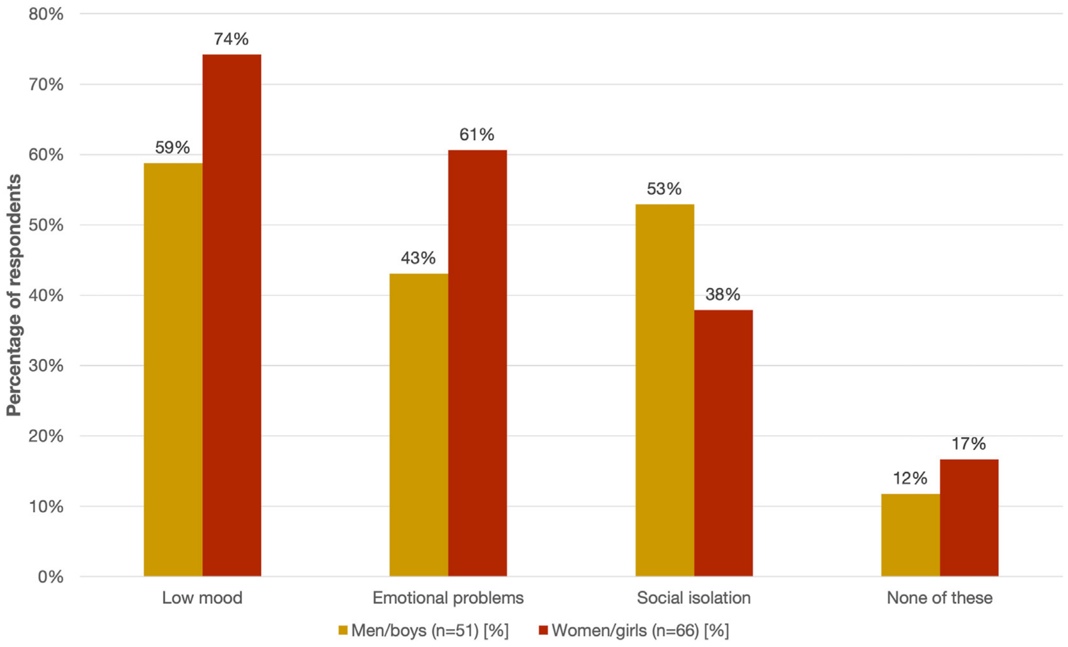

FIGURE 6 Psychological impact of bleeding (data are presented as frequency [percentage] for categorical variables).

TABLE 3 Quality-of-life and psychological test scores.

Patient reported outcome tools	Values, mean (SD)
EQ-5D-5L	
Index score (*n* = 85)	0.664 (0.311)
VAS score (*n* = 85)	62.58 (26.780)
Rosenberg self-esteem score	
All adults (*n* = 88)	19.454 (5.078)
Score 0-15 (*n* = 23)	12.913 (1.951)
Score 16-30 (*n* = 65)	21.769 (3.591)
PHQ-8 score	
All adults (*n* = 79)	8.088 (6.206)
Score 0-10 (*n* = 55)	4.6 (3.342)
Score 11-21 (*n* = 24)	16.08 (2.932)
Self-efficacy score	
All adults (*n* = 88)	6.488 (2.044)

EQ-5L-5D, EuroQoL 5 Dimensions 5 Levels; PHQ, Patient Health Questionnaire; VAS, visual analog score.

TABLE 4 Participants' characteristics stratified by depression.

Characteristics	PHQ-8 score 0-10 (*n* = 55, 69.6%)	PHQ-8 score 11-21 (*n* = 24, 30.3%)	*P* value
Age group			
16-19 y	9 (16.3%)	6 (25.0%)	.37
>20 y	46 (83.6%)	18 (75.0%)	
Gender			
Male	18 (32.7%)	10 (41.6%)	.44
Female	37 (67.2%)	14 (56.0%)	
Highest educational attainment			
Primary	12 (21.8%)	4 (16.6%)	.63
Secondary	9 (16.3)	6 (25.0%)	
Tertiary	34 (61.8%)	14 (58.3%)	
Continent of residency			
Europe	16 (29.0%)	15 (62.5%)	.005[a]
Rest of world	39 (71%)	9 (37.5%)	
Bleed in the past week			
No	10 (18.1%)	1 (4.1%)	.16
Yes	45 (81.8%)	23 (95.8%)	
Bleed requiring hospital contact in the past week			
No	44 (80.0%)	12 (50.0%)	.06
Yes	11 (20.0%)	12 (50.0%)	
Bleed requiring a hospital visit in the past 6 mo			
No	24 (43.6%)	7 (29.1%)	.23
Yes	31 (56.3%)	17 (70.8%)	
Time lost from work or education			
No	8 (14.5%)	4 (16.6%)	1
Yes	47 (85.4%)	20 (83.3%)	
Self-esteem score			
Mean (SD)	21.25 (4.448)	16.08 (3.966)	<.001
n	n = 55	n = 24	
EQ-5D-5L index score			
Mean (SD)	0.789 (0.203)	0.497 (0.321)	<.001
n	n = 55	n = 21	
EQ-5D-5L VAS			
Mean (SD)	62.36 (28.20)	60.47 (21.53)	.76
n	n = 55	n = 21	

(Continues)

result of bleeding *per se* or any particular type of bleed is an area worthy of further study.

In patients with GT, every bleed holds the potential to be severe or life-threatening, and these episodes can occur unpredictably throughout life. Bleeding was frequent among our population: most (88%) had experienced at least 1 bleed in the past week, while the whole population reported a mean 4 bleeds (including bruises) in the past week. As a result, they experienced frequent hospital contact and visits, which impacted their self-reported quality-of-life scores. Overall, EQ-5D-5L and EQ-5D-5L VAS scores were broadly similar to those that would be expected for most chronic hematologic conditions [14]. Analysis suggested the greatest decrements were in the anxiety and depression responses, followed by the pain domain.

It is no surprise that frequent bleeding has a psychological impact. Most respondents in our sample reported low mood, emotional problems, and social isolation. We explored these aspects further in the responses to several validated tools. The Rosenberg self-esteem score (which measures the sense of being capable, worthwhile, and competent) has shown mixed results in populations with bleeding disorders. A Dutch study found that young adult men (but not women) with bleeding disorders had lower self-esteem compared with peers [15]. Among our study population, 26% had scores suggestive of low self-esteem which has been previously reported [8].

The PHQ-8 questionnaire is a recognized screening tool for major depression. European data based on the PHQ-8 suggest an overall prevalence of current depressive disorder in the general population of 6.38%, with substantial variation across countries, the highest prevalence occurring in more developed countries, and in women compared with men [16]. Our data suggest that 30% of the adults who responded to the survey met the screening criteria for symptomatic depression.

TABLE 4 (Continued)

Characteristics	PHQ-8 score 0-10 (*n* = 55, 69.6%)	PHQ-8 score 11-21 (*n* = 24, 30.3%)	*P* value
PHQ-8 score			
Mean (SD)	4.6 (3.34)	16.08 (2.93)	<.001
n	n = 55	n = 24	
Self-efficacy score			
Mean (SD)	6.79 (1.98)	5.43 (2.00)	<.001
n	n = 55	n = 24	

Mean data were compared using the Kruskal–Wallis test. For categorical variables, *P* values were calculated using chi-squared tests (Fisher's exact tests where categories had counts less than 5).

EQ-5L-5D, EuroQoL 5 Dimensions 5 Levels; PHQ, Patient Health Questionnaire; VAS, visual analog score.

[a] Indicates result is significant at $P < .05$.

While this did not seem to be associated with age, gender, education, or bleeding history, there was an association with individuals' self-efficacy (a measure of the level of self-confidence in their own abilities). While our data cannot confirm a high prevalence of depression among people with GT, it does suggest a degree of psychological distress that may be linked to bleeding. As such, it echoes a recent US-based study that also used the PHQ-8 as a screener in which the rate of depression in people with von Willebrand disease was 63.6% [17]. It seems likely that this psychological distress may be linked to bleeding. This finding indicates a critical unmet need for comprehensive psychological support as a standard component of GT patient care.

Even though recent bleeding experience did not appear to affect psychological scores, stratification of participants' EQ-5D-5L responses by bleed data suggested an association. There is limited reported use of the EQ-5D-5L to assess HRQoL in those with rare bleeding disorders, however, its use in people with hemophilia shows that joint bleeds impact the domains of mobility and pain [18]. In hemophilia, pain is principally associated with joint bleeding. In our study, pain was the third most common driver of impaired EQ-5D-5L responses after anxiety and depression. Pain is known to be multifactorial; in addition to rare joint bleeding, pain in GT may be due to multiple bruising and menorrhagia. HRQoL is known to be reduced in women with heavy menstrual bleeding/menorrhagia as described by several women in our study [19] and in those with von Willebrand disease due to bleeding and treatment burden [20,21]. Our study suggests most received hospital-based care, indicating a significant burden.

The Glanzmann's 360 study provides a contemporary snapshot of living with GT. With a large age range of participants from a diverse range of countries, it represents the largest cohort in the literature to date. The study findings demonstrate the frequency and early presentation of bleeds and their impact on the lives of affected individuals. However, it has limitations such that the findings may not be representative of the wider GT community. Participants were recruited through specialist bleeding centers and may represent those with the worst bleeding experience and outcomes; others were recruited via social media and the Internet, which may have introduced a participation bias in favor of those actively seeking information about their condition. Our cohort appears to have been particularly well-educated. Our analyses were entirely exploratory and are based on relatively small sample sizes. Nevertheless, they

TABLE 5 Participants' psychological responses stratified by bleed data responses.

Patient reported outcome tool	Bleeds in past week		Bleed requiring hospital contact in the past week		Bleed requiring a hospital visit in the past 6 mo	
	0	>1	0	>1	0	>1
EQ-5D-5L index score, mean (SD)	0.833 (0.217) n = 11 $P < .05$	0.672 (0.282) n = 74	0.730 (0.254) n = 59 $P < .05$	0.514 (0.377) n = 26	0.793 (0.212) n = 33 $P < .01$	0.582 (0.338) n = 52
EQ-5D-5L VAS, mean (SD)	74 (25.03) n = 11 ns	60.89 (26.43) n = 74	65.49 (24.73) n = 59 ns	56 (30.41) n = 26	68.72 (20.72) n = 33 ns	58.69 (29.52) n = 52
Self-esteem score, mean (SD)	21.9 (5.74) n = 11 ns	19.1 (4.84) n = 74	20.11 (5.20) n = 60 ns	18.03 (4.56) n = 28	20.5 (5.45) n = 34 ns	18.79 (0.64) n = 54
PHQ-8 score, mean (SD)	6.54 (5.39) n = 11 ns	8.67 (6.11) n = 77	6.78 (5.51) n = 56 $P < .01$	11.26 (6.75) n = 23	6.22 (1.08) n = 31 $P < .05$	9.29 (6.08) n = 48
Self-efficacy score, mean (SD)	7.83 (1.43) n = 11 ns	6.67 (2.08) n = 77	6.67 (1.97) n = 60 ns	6.08 (2.17) n = 28	7.11 (1.87) n = 34 ns	6.09 (2.06) n = 54

Mean data were compared using the Wilcoxon rank sum test with continuity correction.

EQ-5L-5D, EuroQoL 5 Dimensions 5 Levels; ns, not significant; PHQ, Patient Health Questionnaire; VAS, visual analog score.

suggest there are considerable physical, psychological, social, and economic impacts associated with GT and highlight the need for further research in order to satisfy unmet needs for psychological and physical treatment needs.

5 | CONCLUSION

The Glanzmann's 360 study has shed light on the hidden impacts of GT, revealing significant physical, psychosocial, and quality-of-life impairments that are likely to be linked to frequent bleeding. Clinicians treating people with GT should be aware of these hidden impacts and promote access to multidisciplinary comprehensive care, including psychosocial support. This could be provided by the treatment center or through referral to specialist services as appropriate.

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AUTHOR CONTRIBUTIONS

Study design – K.K. and M.H. Ethical approval –; S.F. and K.K. Data analysis – K.K., M.B., and M.H. Manuscript writing, amendment, and approval – K.K., S.F., M.B., and M.H.

RELATIONSHIP DISCLOSURE

All authors are employees of Haemnet Ltd.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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