ORIGINAL ARTICLE

Congenital platelet disorders and health status–related quality of life

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Abstract
Background: Patients with congenital blood platelet disorders (CPDs) demonstrate a predominantly mucocutaneous bleeding tendency. Repeated bleeds throughout life can have a significant impact on health status–related quality of life (HR-QoL), but few studies have investigated HR-QoL in patients with CPDs.

Objectives: To determine HR-QoL in patients with suspected or confirmed CPDs as compared with the general Dutch population and to assess the association between bleeding phenotype and HR-QoL.

Methods: Data were derived from the Thrombocytopathy in the Netherlands (TiN) study, a cross-sectional study of individuals suspected for a congenital platelet defect. TiN patients with an increased ISTH Bleeding Assessment Tool (ISTH-BAT) score (>3 in men and > 5 in women) were included for analysis. HR-QoL was assessed with the Short Form (SF)-36 survey. Bleeding symptoms were evaluated with the ISTH-BAT, resulting in a bleeding score.

Results: One hundred fifty-six patients were analyzed, of whom 126 (81%) were women. Sixty-two patients (40%) had a confirmed CPD. Compared to the general Dutch population, patients with a suspected or confirmed CPD reported decreased physical functioning, limitations in daily activities due to physical health problems, limitations in social activities, decreased energy levels and fatigue, pain, and lower general health status. HR-QoL was not correlated with the ISTH-BAT score and was similar in patients with a confirmed CPD and those in whom a CPD could not be diagnosed.

Conclusion: A bleeding tendency in patients with a suspected or confirmed CPD significantly impacts HR-QoL, independent of a confirmed explanatory diagnosis.

KEYWORDS
bleeding tendency, congenital blood platelet disorders, health status, quality of life, SF-36
1 | INTRODUCTION

Congenital blood platelet disorders (CPDs) are disorders of primary hemostasis and can be due to defects in the adhesion, activation, secretion, or aggregation of platelets.\(^1\) Patients typically present with mucocutaneous bleeds or persistent bleeding following a hemostatic challenge such as dental extraction, invasive procedures, or childbirth.\(^2\) Although a study on the overall prevalence of CPDs has never been undertaken, it is suggested that it is similar to that of von Willebrand disease (VWD).\(^3\)

Repeated bleeds throughout life can have a significant impact on quality of life, since it can hinder activities of daily living, social functioning, and educational achievements. Health status–related quality of life (HR-QoL) is a multidimensional concept for evaluating the physical, mental, emotional, and social health of an individual.\(^6\) Assessment of HR-QoL has become increasingly important in patient-centered care, since it provides valuable information on the impact of the disease on daily activities and can guide clinical decision making.\(^5\) In contrast to hemophilia and VWD,\(^6-9\) information on HR-QoL in patients with CPDs is lacking.

The aim of the present study was to assess HR-QoL in adult patients with suspected or confirmed CPDs as compared with the general Dutch population and to study the association between HR-QoL and bleeding phenotype. To our knowledge, this is the first study on HR-QoL in patients with CPDs.

2 | METHODS

2.1 | Thrombocytopenia in the Netherlands study

Data were derived from the Thrombocytopenia in the Netherlands (TiN) study. The TiN study is a nationwide cross-sectional study to collect data on clinical characteristics, functional assays, and genetics in a real-life population of patients with suspected or confirmed congenital platelet disorders. Inclusion and exclusion criteria of the TiN study can be found in Appendix S1. In all included patients, laboratory tests were performed for platelet count, aggregation to 4 agonists (ADP, arachidonic acid, collagen, ristocetin), platelet ADP and ATP content, mepacrine staining, surface receptor expression with flow cytometry, and genetic analysis with a selected primary hemostasis gene panel. Platelet morphology, gray platelets, and leukocyte inclusion bodies were assessed in a peripheral blood smear.

2.2 | Participant selection

For the current study, we evaluated data from TiN patients with a bleeding tendency defined as an increased ISTH Bleeding Assessment Tool (ISTH-BAT) score (>3 in men and >5 in women).\(^10\) We included new patients suspected for a CPD, as well as patients with a previously confirmed CPD. These patients are referred to as “study group patients.” We excluded patients diagnosed with an acquired platelet defect.

2.3 | ISTH bleeding assessment tool

The bleeding phenotype was assessed with the ISTH-BAT, administered by experienced physicians. The ISTH-BAT systematically evaluates 14 different bleeding symptoms, scored on a scale ranging from 0 to 4 points, and results in an ISTH-BAT bleeding score (BS).\(^11\) Higher scores indicate a more severe bleeding phenotype.

2.4 | Short Form-36

HR-QoL was assessed with the Dutch version of the Short Form (SF)-36 survey. The SF-36 is a generic measure assessing 8 physical and mental health domains: physical and social functioning, role limitations due to physical or emotional problems, general health, mental health, bodily pain, and vitality (Table S1).\(^12,13\) For each domain, scores are converted to a 0-100 scale, with higher values reflecting a better quality of life. Control data from the general Dutch population were obtained from a nationwide health status survey.\(^14\)

2.5 | Brief Illness Perception Questionnaire

The Dutch language version of the Brief Illness Perception Questionnaire (B-IPQ) was used to assess the cognitive and emotional representations of illness. The 9 dimensions of the B-IPQ include consequences, timeline, personal control, treatment control, identity, concern, understanding, emotional response, and causal factors (Table S2). All of the dimensions except causal factors are rated on a linear scale from 0 to 10. Higher scores reflect a more negative (unfavorable) illness perception, except for the dimensions personal control, treatment control, and understanding, where a higher score indicates a more positive (favorable) illness perception.
perception.\textsuperscript{15} Control data from the general Dutch population were not available.

## 2.6 | Definitions

The term \textit{study group patients} refers to all patients included in the current study, that is, new patients suspected for a CPD where a diagnosis could not be confirmed, as well as patients with a confirmed CPD. In the TiN study, a confirmed CPD was diagnosed when abnormal platelet function was found on at least 2 occasions, of which one was in our diagnostic laboratory. These patients are referred to as \textit{confirmed CPD patients}. A bleeding tendency was defined as an increased ISTH-BAT score (>3 in adult men and >5 in adult women).\textsuperscript{10} Comorbidity was defined as the presence of one or more conditions with a duration of at least 6 months in the last year\textsuperscript{16} and was self-reported.

## 2.7 | Statistical analyses

Statistical analyses were performed with IBM SPSS Statistics 25 and RStudio version 0.99. Descriptive results were presented as medians (interquartile ranges [IQRs]) for continuous data and frequencies (percentages) for categorical data. Differences in SF-36 scores between study group patients and the general Dutch population were evaluated with linear regression analyses adjusted for age, sex, and comorbidity as other determinants of HR-QoL. For each SF-36 domain, a linear regression was performed, with the SF-36 domain as outcome and group (general population or study group patient) as determinant. A significance level of $P \leq 0.01$ was used to correct for multiple comparisons. Correlations between SF-36 domains and the ISTH-BAT score (as a proxy for bleeding phenotype), between B-IPQ dimensions and the ISTH-BAT score and between B-IPQ dimensions and the SF-36 domain general health perception were calculated with nonparametric Spearman’s rank correlation. Correlation coefficients ($\rho$) of 0.20 to 0.39 were considered weak, 0.40 to 0.59 moderate, 0.60 to 0.79 strong and >0.8 very strong.\textsuperscript{17} Only moderate or stronger correlations were considered relevant.

## 3 | RESULTS

### 3.1 | Patient characteristics

A total of 200 patients were included in the TiN cohort, of whom 31 did not have an objective bleeding tendency and 6 were diagnosed with an acquired platelet defect. Thus, 163 patients with a suspected or confirmed CPD and an objective bleeding tendency were included for the current analysis, of whom 156 patients completed the questionnaire and were included in the study group. Patient characteristics are shown in Table 1. The majority of patients were women (81%). The median age was 44 years for women (IQR, 31-55) and 45 years for men (IQR, 31-61). The median BS was 11 for women (IQR, 9-14) and 10 for men (IQR, 7-13). A CPD was confirmed in 62 of 156 patients (40%). The most commonly observed comorbidities were hypertension (17%), type 2 diabetes mellitus (6%), and endometriosis (4%).

### 3.2 | Health-related quality of life

Compared to the general Dutch population, study group patients reported decreased physical functioning and limitations in the type or amount of regular daily activities due to physical health problems. They also reported limitations in social activities, decreased energy levels and fatigue, pain, and lower general health status (Figure 1 and Table S3). HR-QoL was similar in patients with a confirmed CPD and those in whom a CPD could not be diagnosed (Table S4). Women reported significantly more pain than men. The other domain scores were not significantly different between men and women.

### 3.3 | Association between HR-QoL and bleeding phenotype

The ISTH-BAT score, as a proxy for bleeding phenotype, was not correlated with any of the SF-36 domains (Table S5) nor with any of the B-IPQ dimensions (Table S6).

## TABLE 1 Patient characteristics

|                          | General Dutch population\textsuperscript{a} n = 1742 | Study group\textsuperscript{b} patients n = 156 | Confirmed CPD patients\textsuperscript{c} n = 62 |
|--------------------------|--------------------------------------------------|-----------------------------------------------|-------------------------------------------------|
| Sex                      | Women, n (%)                                      | 761 (44)                                      | 126 (81)                                        | 41 (66)                                          |
|                          | Men, median (IQR)                                 | 49 (36-63)                                    | 45 (31-61)                                     | 53 (32-63)                                      |
| Age                      | Men, median (IQR)                                 | 41 (30-60)                                    | 44 (31-55)                                     | 45 (32-57)                                      |
|                          | Women, median (IQR)                               | NA                                            | 10 (7-13)                                      | 10 (6-14)                                       |
| Bleeding score           | Men, median (IQR)                                 | NA                                            | 11 (9-14)                                      | 11 (9-17)                                       |
|                          | Women, median (IQR)                               | NA                                            |                                                 |                                                 |
| Comorbidity              | Yes, n (%)                                        | 856 (49)                                      | 92 (59)                                        | 34 (55)                                          |

Abbreviations: CPD, congenital blood platelet disorder; IQR, interquartile range; NA, not available.

\textsuperscript{a}See Aaronson et al.\textsuperscript{14}  
\textsuperscript{b}Patients included in the study with a suspected or confirmed CPD.  
\textsuperscript{c}Study group patients in whom a CPD was confirmed.
3.4 | Brief illness perception questionnaire

Perceiving more consequences of bleeds, perceiving more physical complaints due to bleeds, perceiving more concerns about bleeds, and perceiving a more extreme emotional response to bleeds were associated with lower general health perception (Table 2).

4 | DISCUSSION

To our knowledge, this is the first study on HR-QoL in a large cohort of patients with suspected or confirmed CPDs. Our patients reported decreased physical functioning, limitations in the type or amount of regular daily activities due to physical health problems, limitations in social activities, decreased energy levels and fatigue, pain, and lower general health status as compared with the general Dutch population. HR-QoL was similar in patients with a confirmed CPD and those in whom a CPD could not be diagnosed and was not associated with the ISTH-BAT score. More negative illness perceptions were related to lower general health perceptions.

The domain general health reflects the perception of general health status. Patients with a suspected or confirmed CPD may believe their health is poor and likely to get worse due to recurrent bleeds and hospital visits. This might especially be true for patients without a definitive diagnosis, due to insecurity about their current and future health status. Also, patients perceiving more consequences of bleeds, more physical complaints due to bleeds, more concerns about bleeds, or a more extreme emotional response to bleeds experienced lower general health status. The domain vitality measures energy levels and fatigue. Especially women with CPDs might experience fatigue due to the development of iron-deficient anemia as a consequence of menorrhagia. The decrease in energy levels could also account for lower levels of social activity. The lower scores in the domains physical functioning, role limitations due to physical problems, and bodily pain are more difficult to explain, as in general, mucocutaneous bleeds do not induce physical impairment or pain. It could not be explained by the bleeding phenotype, since there was no correlation between the SF-36 domain scores and the ISTH-BAT score. Possibly, HR-QoL scores were influenced by illness perception. It is generally understood that HR-QoL and illness perception are related, and we found negative correlations between the SF-36 domain general health perception and the B-IPQ domains consequences, identity, concern, and emotional response.
Possibly, patients were anxious to exercise because they feared bleeds and therefore felt physically impaired.

Previous studies on HR-QoL in patients with bleeding disorders mostly focused on patients with von Willebrand disease and hemophilia or on women with menstrual disorders.21–24 Only a few studies included a limited number of patients with CPDs.25,26 These studies used questionnaires other than the SF-36 to assess HR-QoL and are therefore not comparable. Patients with VWD, another primary hemostasis defect with similar clinical characteristics, reported a reduced HR-QoL for the domains general health and vitality.9 HR-QoL in patients with VWD was mainly affected by acute bleeds. This is in contrast to haemophilia, where HR-QoL depends on long-term effects, such as orthopedic status, comorbidities and hepatitis C infection27,28 and where the domains physical functioning and general health were most affected.7

There was a risk for selection bias. There is no database or registry for congenital platelet disorders in the Netherlands. Patients included in the study were mainly patients who recently visited a hemophilia treatment center. Besides that, patients with a more severe bleeding phenotype were perhaps more willing to participate in the study. Therefore, milder types of CPDs are likely underrepresented in our study population. This could explain the lower HR-QoL in our patients as compared to the general population. However, in our analysis, HR-QoL was not correlated with the bleeding phenotype.

We reported no correlation between the ISTH-BAT score and domains of the SF-36. A possible explanation for this finding is that the ISTH-BAT score and HR-QoL capture different time frames: the ISTH-BAT score reflects symptoms throughout one’s entire life, regardless of the symptoms still being present, while the SF-36 measures one’s health status in the preceding weeks to months. A patient with a high ISTH-BAT score due to severe bleeding problems in the past can have a relatively good quality of life due to the absence of bleeds in the past year. Another possible explanation is that only patients with an increased ISTH-BAT score were included and, as mentioned before, milder types of CPDs with lower ISTH-BAT scores were likely underrepresented in our study population. As a result, the calculated correlation coefficient might not reflect the true correlation between ISTH-BAT score and HR-QoL, since certain data are missing.

A major challenge of HR-QoL evaluation is the interpretation of the observed differences. A difference of 3 to 5 points has been considered clinically relevant.29 However, although scores for the SF-36 domains range from 0 to 100, for some domains the score range is limited due to dichotomous answers, and therefore it does not seem defensible to use this 3- to 5-point difference for all domains.

Evaluating HR-QoL has become increasingly important in patient-centered care because it will help to comprehend the patient’s perspective on the disease. Our patients showed an impaired HR-QoL independent of a confirmed CPD, indicating that a bleeding tendency is a considerable health problem on its own. Even after extensive laboratory testing, as advised by the ISTH,30 many patients remain without a definitive diagnosis due to the complexity of platelet function testing. Accurately informing patients about their condition and treatment options and creating awareness among other physicians might improve the HR-QoL of patients with a bleeding disorder, even those without a definitive diagnosis. In addition, proper counseling of patients may modify the patient’s perception of illness, which could improve their HR-QoL.

For future studies, it could be interesting to assess changes in HR-QoL from time of initial diagnosis, to explore whether education on the disease will benefit these patients. Since different populations may vary in their perception of health and associated comorbidities, it will be useful to conduct similar studies in other populations.

In conclusion, our study showed that a bleeding tendency in patients with a suspected or confirmed CPD significantly impacts HR-QoL, independent of a confirmed explanatory diagnosis and that this patient group is one to care for.

RELATIONSHIP DISCLOSURES
The authors report nothing to disclose.

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AUTHOR CONTRIBUTIONS
RS and RU designed the study. MB collected and analyzed the data and drafted the article. MB, MK, EB, MC, JE, KvG, RT, RU, and RS contributed to the final version of the manuscript.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

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