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REVIEW ARTICLE

Knowledge gaps in health-related quality of life research performed in children with bleeding disorders – A scoping review

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Abstract

Introduction: Bleeding disorders (BDs) may influence health-related quality of life (HRQoL) in children and caregivers. Measuring HRQoL gives insight into domains requiring support and provides an opportunity to evaluate the effects of novel therapies.

Aim: To gain insight in the current body of literature on HRQoL in children with BDs in order to identify knowledge gaps for research and further development of this field.

Methods: Scoping review.

Results: We included 53 articles, describing studies mainly performed in Europe and North–America (60.4%) and mostly within the last ten years. Only 32% studies included children <4 years. Almost all studies (47/53, 88.7%) were performed in boys with haemophilia, pooling haemophilia A and B ($n = 21$) and different disease severities ($n = 20$). Thirteen different generic and five disease-specific HRQoL-questionnaires were applied; all questionnaires were validated for haemophilia specifically. Six (11,3%) combined generic and disease-specific questionnaires. Self-reports were most frequently applied (40/53, 75.5%), sometimes combined with proxy and/or parent-reports (17/53, 32.1%). Eleven studies used a reference group (20.8%). Statistical analyses mostly consisted of mean and SD (77.4%).

Conclusion: HRQoL-research is mainly performed in school-aged boys with haemophilia, treated in developed countries. Pitfalls encountered are the pooling of various BDs, subtypes and severities, as well as the application of multiple generic questionnaires prohibiting comparison of results. More attention is needed for broader study populations including other BDs, young children, feminine such as young children, feminine bleeding issues and platelet disorders, as well as the use of HRQoL as an effect-measurement tool for medical interventions, and more thorough statistical analysis.

KEYWORDS
blood coagulation disorders [MESH], child [MESH], haemophilia [MESH], quality of life [MESH], research design [MESH], review [MESH]

1 | INTRODUCTION

Bleeding disorders (BDs) lead to an increased bleeding tendency due to a quantitative or qualitative defect in either platelets or coagulation factors. Due to heterogeneity in pathophysiology and severity, inter-individual bleeding phenotype varies greatly between affected individuals. Typical bleeding manifestations of BDs affecting the primary haemostasis are extensive bruising and mucosal bleeding such as epistaxis, heavy menstrual bleeding and surgical bleeding.[1] When the secondary haemostasis is affected, bleeding also presents as muscle and joint bleeds. Severe bleeding such as intracranial or gastrointestinal bleeding is less frequently encountered but devastating.[2] Children with BDs also endure life style interventions, medical appointments, venipunctures and treatment. This may cause anxiety, depression, atypical behaviour or isolation due to less participation in social and physical activities.[3] When the level of individual disease control, societal participation and general life expectations is affected by the BD, it may negatively influence quality of life.[4]

Quality of life (QoL) is defined by the World Health Organization as *an individual's perception of their position in life* in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns'.[5,6] Health-Related QoL (HRQoL) specifically focusses on the effects of health, illness and treatment on an individual's life and excludes all non-health-related aspects of QoL.[6,7] Over the past years, HRQoL-assessment is increasingly acknowledged as a marker of health outcome in children with chronic diseases as it visualizes disease burden.[8] It provides insights in the need for treatment or interventions, in return, giving physicians patient-tailored goals to improve medical care.[9] To measure HRQoL, two categories of questionnaires are used: generic and disease-specific questionnaires. Generic questionnaires are broadly applicable and facilitate comparisons between groups with different (chronic) diseases or healthy children from a general population sample. Disease-specific questionnaires focus on the influence of the specific symptoms and characteristics of a certain disease on the patients, being validated for this specific condition.[8] In children, both the child and the caregiver rate the impact of the disease on the HRQoL of the child. These different points of view are relevant and could be assessed simultaneously. For this, three subcategories of HRQoL measurement questionnaires are distinguished: firstly age-appropriate self-reports measuring the child's HRQoL as reported by the child itself. Secondly proxy-reports, evaluating the child's HRQoL as reported by the parents or caregivers. Thirdly parent-reports, measuring how the child's disease impacts parenthood and family-life.[10,11] The aim of this study was to gain insight in the steadily increasing body of literature on HRQoL in children with all types of BDs in order to identify knowledge gaps for research and further development of this field. For that purpose, we performed a systematic review of current literature, and details of published studies were summarized. Subsequently, the unmet needs observed were addressed and presented as a scope for future research.

2 | MATERIAL AND METHODS

2.1 | Study selection

We used the methodological framework for scoping reviews as described by Arksey and O'Malley[12] and recommendations by Levac et al.[13] and Pham et al.[14] The following stages were followed: 1: identify the research question, 2: identify relevant articles, 3: select articles, 4: chart the data and 5: collate, summarize and report the results. Not applicable was stage 6 (consult of consumers and stakeholders).[12–14]

2.2 | Eligibility criteria

Articles were eligible if HRQoL-results were published of children (<18 years old) with a BD, defined as either an inherited platelet disorder (IPD) or deficiency or abnormal function of coagulation factors. When results of children and adults were combined, articles were solely included if the results for the paediatric population were presented and analysed separately. Articles had to be written in Dutch or English. Exclusion criteria were: no HRQoL-questionnaire results available, no full text available, conference abstracts, methodology of validation or cross-cultural adaptation of HRQoL-questionnaires, acquired BDs and articles presenting only aggregated results from children and adults.

2.3 | Search strategy

We performed a systematic search in the following electronic databases: EMBASE, MEDLINE Ovid and Cochrane CENTRAL on 29 April of 2019 and updated 1 June 2021 with the help of an experienced biomedical librarian and Cochrane information specialist (WB). A search for grey literature was not conducted. The search-query consisted of a broad range of key words related to BDs, (HR)QoL and children (Supplement 1). The query was adjusted to the requirements of specific databases. No publication date limitations were applied. All records were imported into an EndNote library for bibliographic management and duplicates were removed. Records were screened on title and abstract by two independent researchers (C.M./E.H.). Only articles meeting the inclusion criteria were included after reading the full text. Of the included articles, references were checked for missed articles.

2.4 | Data collection

A preset data format was developed prior to extracting data of the final set of included articles in an Excel (Microsoft 2016) spreadsheet, including author(s); year of publication; journal of publication; country of origin; type of BD; disease severity and whether the HRQoL-results were reported separately or pooled according to severity, age-appropriate and validated; number of included patients and caregivers; age; application of a reference group; type of generic and/or disease-specific HRQoL-questionnaire, and lastly the used descriptive statistics for the HRQoL-results. Tables were made in Word (Microsoft 2018) and illustrations were designed using Pages (Apple Inc, 2007).

3 | RESULTS

The search yielded 718 records and using references two additional articles were found. After removal of duplicates, 508 records were screened on title/abstract. After the first screening, 99 articles were reviewed in full text independently, after oral discussion and agreement by two independent reviewers on incongruent articles, 53 articles were included in this scoping review.[15–65] These final articles were subdivided into two different subgroups: 21 articles described studies that measured the effect of an intervention, such as treatment and/or sporting activities,[47–54,57,58,60,61,65–68] and 32 articles described studies that measured HRQoL at a single time point.[15,16,20–22,24–29,31–37,39,40,69] An overview of the search and screening process for this scoping review is illustrated in a PRISMA Flow Diagram (Figure 1).

TABLE 1 Characteristics of included publications.

General characteristics	Number ($n = 53$)	Percentage (%)
Subgroups		
QoL at single time point	32	60,4
QoL before and after intervention	21	39,6
Publication year		
2000–2004[a]	4	7,5
2005–2009	3	5,7
2010–2014	16	30,2
2015–2019	21	39,6
2020–2021	9	17,0
Country		
Europe	19	35,8
Northern America	13	24,5
Asia	10	18,9
Middle East	4	7,5
Oceania	2	3,8
Mixed	5	9,4

Abbreviation: QoL, quality of life.

[a]We found no articles published before the year 2000 that met our inclusion criteria.

3.1 | General characteristics of included articles

General characteristics of the included articles are demonstrated in Table 1. All articles were published after the year 2000 with the majority published after 2010 (86.8%). In summary, HRQoL-research in children with BDs has been performed in a variety of countries around the world, but the majority of studies were performed in Europe (21/53, 39.6%) and Northern America (11/53; 21%). The others were performed in Asia (10/53, 18.9%), the Middle–East (4/53, 7.5%) and Australia (2/53, 3.8%, details in Supplement 2). Five papers described the results of HRQoL-studies performed by an international cooperation. HRQoL was measured at a single time-point in 32 articles (32/52, 61.9%). In 19 articles (17/53, 32.1%) the change in HRQoL was analysed in children with haemophilia by measuring a within-patient change as a measurement for the impact of interventions such as education,[49,51,57,67] sports or yoga,[48,50,52,59,60,66] or around the introduction of novel factor replacement therapies.[54,56,59,61,62,64] In 4 articles (4/21, 19.0%), an inter-patient difference was investigated, comparing HRQoL in a group with and without an intracranial or frequent bleedings with HRQoL in on demand treatment versus prophylaxis groups.[47,53,58,68] In two articles (2/21, 9.5%), non-haemophilia patients were pooled with haemophilia patients in the final analysis (details in Supplement 2).[50,60]

3.2 | General characteristics of included patients

An overview of the general patient characteristics is presented in Table 2. Importantly, study populations ranged from 13 to 339 children, but most included a maximum of 149 children (44/53, 86.3%). Fifty articles mentioned the minimal age of the included children (50/53, 94.3%). Sixteen included children <4 years of age (16/50, 32.0%), with five articles including children from the age of <1 year (5/16, 31.3%). The other 34 articles included patients ≥4 years of age (34/50, 68.0%). The vast majority of included articles studied HRQoL in children with haemophilia (47/53, 88.7%), of which 36 pooled haemophilia A and B patients (36/47, 76.6). When children with haemophilia A and B were reported separately, 16 articles addressed haemophilia A (16/21, 76.2%) and 5 haemophilia B (5/21, 23.8). Articles that published data of children with other BDs than haemophilia, were sparse (3/53, 5.7%): one article reported on children with Von Willebrand Disease (VWD),[21] and one on children with IPD.[37] Three articles included patients with various BDs other than haemophilia and one article pooled haemophilia with VWD.[32,35,50,60] These four articles pooled the results in single analysis. For a visualization of the main body of research see Figure 2, details in Supplement 2.

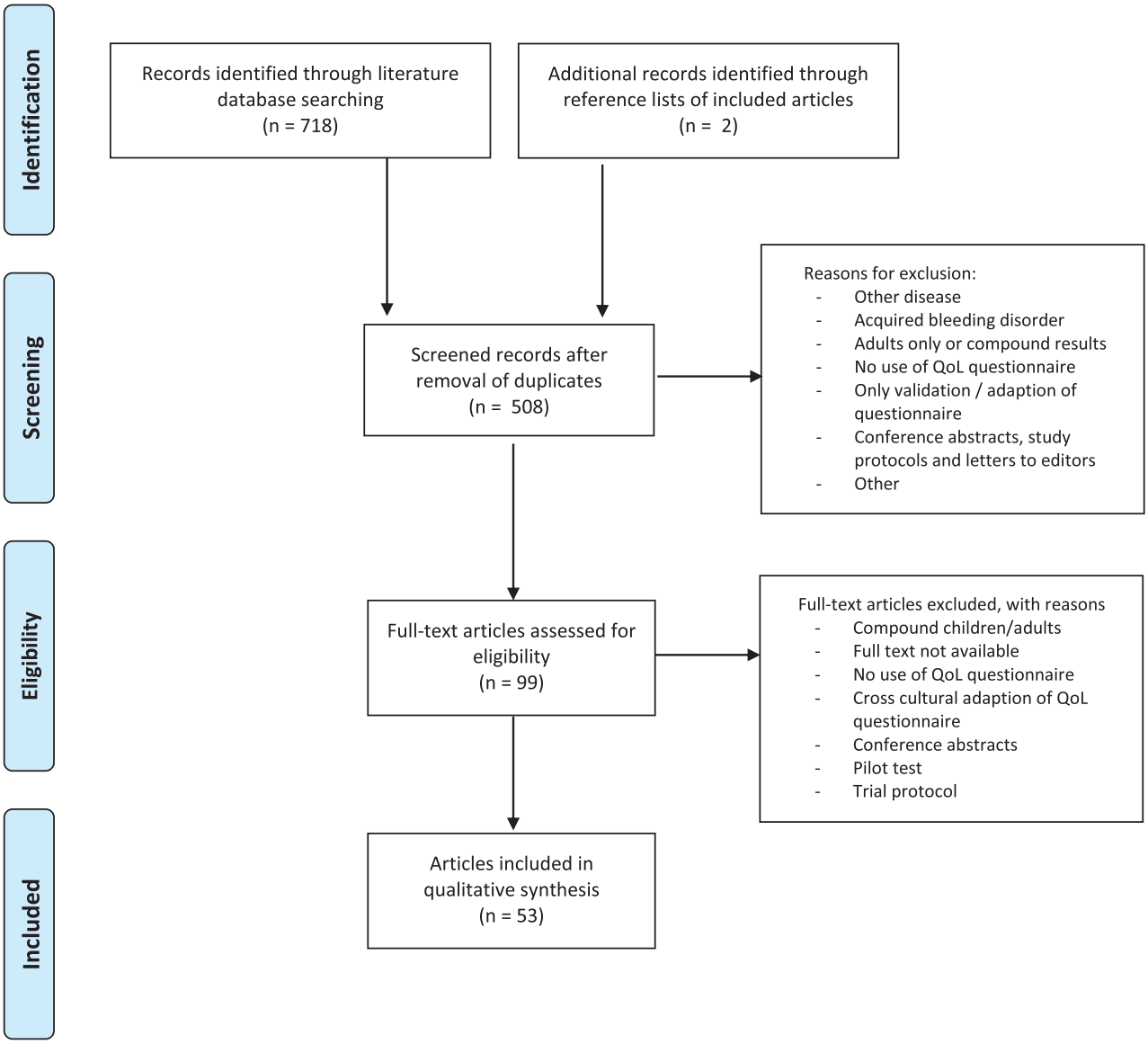

FIGURE 1 PRISMA Flow Diagram.

3.3 | Severity of bleeding in relation to HRQoL-research

Besides the fact that different BDs may influence HRQoL differently, the severity of disease will of course affect HRQoL as well. For example, haemophilia is divided into mild, moderate and severe haemophilia, based on the lowest documented FVIII or FIX activity level.[70] VWD is subdivided into type 1, type 2 and type 3. Type 1 and 3 are defined as quantitative defects and type 2 is defined as a qualitative defect.[71] Other BDs are either heterogeneous or homogenous, with the residual activity of the specific coagulation factor sometimes associated with bleeding phenotype. Inherited platelet disorders are divided into multiple subgroups based on platelet number, receptor defects, flowcytometric results or are clustered by results of DNA-analysis.[72] In the context of disease severity, we found that 44 articles specifically mentioned the severity of BDs. In 14/44 (31.8%) articles a patient with similar disease severity were included. In the other 30 articles various disease severities were pooled at inclusion (68.2%), but in 10/30 (33.3%) results were depicted per severity. This made it possible to correlate HRQoL-results with a specific disease and/or disease severity in 24/44 (54.5%); details in Supplement 2).

3.4 | HRQoL-questionnaires

Twenty-seven studies used 13 different generic questionnaires due to requirement of age-appropriate questionnaires, but also to the large variation on generic questionnaires. Use of multiple questionnaires was observed in one study. The generic questionnaires PedsQoL and KINDL, and the utility measurement tool EQ-5D were most often used (17/27, 63.0%; Table 3). Thirty-five studies used a disease-

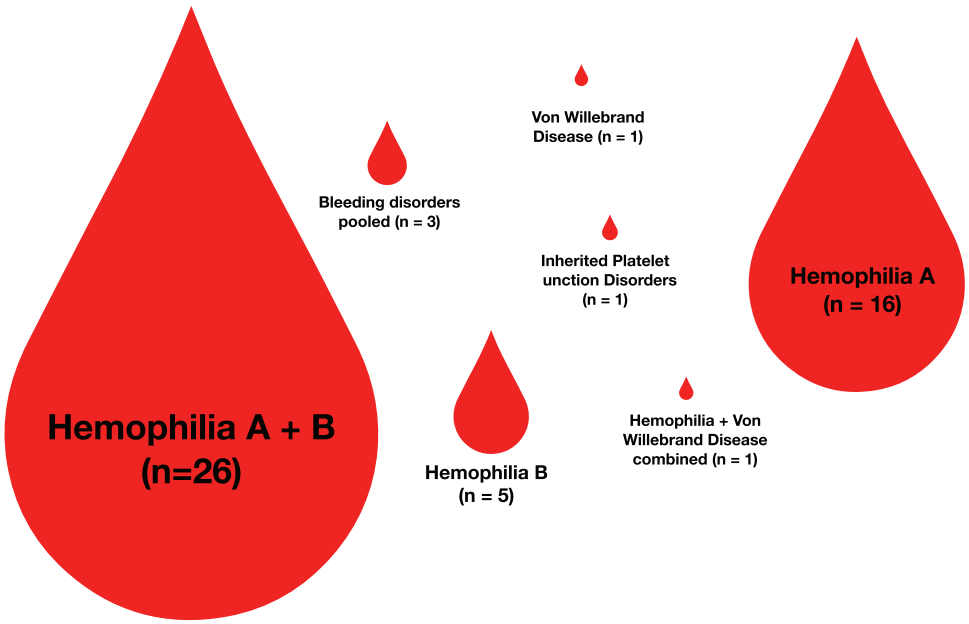

FIGURE 2 Visualisation of the main body of research that has been performed in the field of QoL in pediatric patients with different bleeding disorders. Figure to scale. QoL, quality of life.

specific questionnaire, all developed for haemophilia (n = 35). Five different disease-specific questionnaires were used in patients with haemophilia. The HaemoQoL (26/35, 74.3%) and CHO-KLAT (5/35, 14.3%) were used most often, followed by the Adapted InhibQoL (2/35, 5.7%), QUAL-HEMO (1/35, 2.9%) and Hemo-Sat (1/35, 2.9%). These haemophilia-questionnaires were also used once in VWD patients (n = 1)[50] and once in a pooled patients group with rare BDs (n = 1).[35] In one article HRQoL was assessed in children with IPDs by a disease-specific questionnaire developed for acquired immune thrombocytopenia (ITP).[37] (Table 3). All HRQoL questionnaires were age-appropriate for the included patients (Table 4).

Six studies combined a generic and disease-specific questionnaire (11.3%).[16,33,46,52,56,68] To compare HRQoL results, 11 studies used a reference group (20.8%), of which 10 studies compared with a healthy reference group,[21,26,31–33,42,47,50,60,66] and three (also) compared the results with HRQoL obtained in children with another chronic disease.[16,31,32] Two HRQoL studies in children with haemophilia used a control group that also suffered from haemophilia but did not experience an intracranial haemorrhage or was not on prophylaxis.[47,58]

Lastly, most questionnaires standardly consist of different versions: a self-report, proxy-report and/or parent-report. All possible combinations were found in the included studies (Figure 3). Five studies analysed the child's HRQoL by surveying the child, the parents view on the child (proxy) and the parental HRQoL.[16,21,48,62,73] The majority (23/53, 43.4%) solely evaluated the HRQoL by the answers given by the child itself. Twelve studies added a proxy-report (12/53, 22.6%).[23,24,30,34,39,40,54,58–60,67,68] Three studies assessed only the impact of the child's disorder on the parental HRQoL by using a parent-report (17.0%),[28,57,69] One study did not mention which versions were used.[47]

3.5 | Descriptive statistics

The mean and standard deviation (SD) were the descriptive statistics that were used most often. They were used in 88.7% and 77.4% respectively of the included articles. Thereafter, a range (24.5%), median (24.5%) and interquartile range (IQR, 13.2%) were frequently used as descriptive statistics. The effect size was used in five articles (9.4%), followed by the difference from baseline and p-values (both 7.5%), the minimal clinically important difference (MCID) or documentation of the outliers (both 5.7%), standard error (3.8%; Supplement 2).

4 | DISCUSSION

4.1 | Summary of knowledge gaps

From the body of evidence summarized in our scoping review, we have extracted the following knowledge gaps:

1. Future HRQoL-research should focus on all types of BDs, both sexes, all ages and continents.

   There is hardly any research on the effect of treatment in patients with BDs other than haemophilia. Although more rare, prophylaxis with factor concentrates is also give in patients with other factor deficiencies than haemophilia, as well as on demand treatment using blood product transfusions or desmopressin.[74,75] And only in children with haemophilia HRQoL-research has been done by measuring a within-patient change around the introduction of novel interventions or therapies. The benefit of currently used (on-demand) treatment options, transfusions and desmopressin in

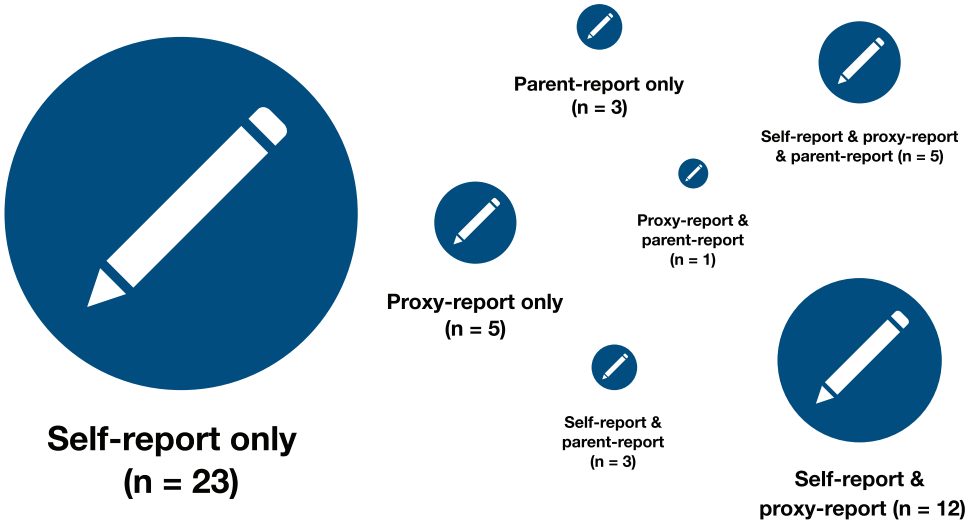

FIGURE 3 Visual impression of the distribution of used QoL questionnaire versions in 52/53 included articles of the scoping review. Figure to scale. QoL, quality of life.

all BDs is missing. Especially, HRQoL-research in children with VWD, IPDs and rare factor deficiencies is missing. As bleeding patterns differ between various BDs, HRQoL-questionnaires for use in VWD and IPDs should focus on skin, mucosal and perioperative bleeding and the addition of a symptom checklist to quantify the impact of skin or feminine bleeding issues is advisable.[76,77] This is even more relevant, because girls are grossly underrepresented in studies as is the result of the high volume of haemophilia studies which is an X-linked disease. Also, only a minority of HRQoL-research included children <4 years of age. This results in a knowledge gap on the child's gross motor development, vaccinations and initiation of prophylaxis in severe haemophilia,[11] as well as the effect of BDs on the bidirectional influence between infants and caregivers and early disease acceptance.[78] For this purpose, we advise to use a generic questionnaire that is, designed to measure HRQoL in young children between 0—4 years old, such as ITQOL.[79] Finally, the distribution of countries shows that children from Africa and South America, and to a lesser extent Asia, are underrepresented. This matters, because children in developing countries may report a reduced HRQoL in other domains than children in developed countries due to differences in (parental) education, socio-economic state and medical health care systems. We advise to use validated existing questionnaires after translation, taking different cross-cultural perspectives into account.[78,80–82]

2. Strive for homogenous study groups or present results separately.

   Disease severity influences bleeding frequency and bleeding complications. Therefore, studies should aim to present results per severity type. Final outcomes will otherwise be negatively influenced. For example, mean HRQoL may be overestimated for the severely affected children when children with a severe phenotype are underrepresented. Homogeneity also accounts for the use of prophylaxis in haemophilia and other rare coagulation factor deficiencies, as well as the fact if the patient has formed inhibitors.

3. Focus on follow-up in time, using the proper questionnaire and report-form for the desired outcome.

   Instead of measuring HRQOL at a single time point, evaluation during follow-up provides clinicians with continuous information.[83] In this light, it is important to strive for a patients perspective as early as possible. In young children a proxy-report remains essential, but parallel evaluation of the caregivers perspective on HRQoL at an older age may still give more insight in the system around the child.[84] To value the results not only within the patient group, a healthy age-adapted reference group is relevant when generic tools are used. The choice of measurement tool also depends on the desired outcome: is it evaluation of 'health profile' or generation of 'utility scores' for the purpose of economic evaluations such as Quality Adjusted Life Years (QALYs). To guide this choice, it is important to realize that there are two types of generic HRQoL questionnaires: 'profile measurement tools' such as the PedsQoL and CHQ generating health profiles. Of these, our study shows that the PedsQoL was most often used for children (6/27, 22%). The 'utility measurement tools' generate utility as HRQoL-based outcome. Our review show that the EQ-5D is most often used for utility outcomes (6/27, 22%). For the disease specific questionnaires, we conclude that for haemophilia HaemoQoL is most used often (26/35, 74%) both the long (77 items) and the short version (16 or 35 items) which support comparisons of outcomes. CHO-KLAT was used less frequently (5/35, 14%), but it has been validated against the PedsQoL and is therefore also valuable. For other BDs no disease specific outcome measurement tools are available.

4. Tools are needed to compare or meta-analyse results obtained from various questionnaires.

   In line with the former, the large number of generic and disease-specific questionnaires used in HRQoL-research is striking. As there is no universal tool to compare the various questionnaires, comparison of differences in SDs of comparable domains should be made possible as an alternative to meta-analysis data.[85,86] The recently

TABLE 2 Characteristics of included patients.

Patient characteristics	Number (*n*)	Percentage (%)
Number of patients in included publications[a]	(*n* = 51)	
<50	23	45,1
50–99	13	25,5
100–149[b]	8	15,7
150–199[b]	4	7,8
200–299	1	2,0
300–399[b]	2	3,9
Youngest age of included children	(*n* = 50)[c]	
<4 years	16	32,0
≥4 years	34	68,0
Type of bleeding disorder	(*n* = 53)	
Haemophilia A + B pooled	26	49,1
Haemophilia A only	16	30.2
Haemophilia B only	5	9,4
Bleeding disorders pooled	3	5,7
Inherited Platelet Disorders	1	1,9
Von Willebrand Disease (VWD)	1	1,9
Haemophilia A + B and VWD pooled	1	1,9
Severity of bleeding disorder stated	(*n* = 44)	(83,0)
Multiple severity types pooled	30	68,2
Results pooled¶	20	
Results separated	10	
Severely affected patients only	14	31,8
Severity of bleeding disorder omitted	(*n* = 9)	(17,0)

Note: All articles that included different grades of disease severity but pooled the QoL results.

Abbreviation: QoL, quality of life; RBDs, rare bleedings disorders; VWD, Von Willebrand disease.

[a]Number of included patients that filled in the QoL questionnaire.

[b]Three articles reported the number of children on behalf of which caregivers had filled in the questionnaire.

[c]Three articles did not mention the minimal age of the included children.

developed 'Item Response Theory' (IRT) may however be key to overcome these issues. IRT scales items and persons on a single metric, comparing the results between the groups longitudinally in time.[87] In paediatric care, this is even more relevant as longitudinal follow-up of a child into adulthood is of advisable and otherwise requires various age-adjusted tools.

5. HRQoL research should provide detailed descriptive statistics.

Many studies solely used the mean and SD, or median and IQR as the single descriptive statistics for HRQoL-results. By doing so, data only gives insight in the average well-being but neglects the possible coping strengths of the upper outliers or the need for extra supporting strategies for the lower outliers. We therefore advise

TABLE 3 Overview of HRQoL-questionnaires in inherited bleeding disorders.

Characteristics of questionnaires	Number (*n*)	Percentage (%)
Generic QoL questionnaires	(*n* = 27)	
EQ-5D, subtypes VAS, Y-3 and 5L	6	22,2
PedsQL	6	22,2
KINDL	5	18,5
CHQ	3	11,1
SF-36	3	11,1
CarerQoL	1	3,7
CHIP-CE	1	3,7
GAD-7	1	3,7
ITQOL	1	3,7
KIDSCREEN	1	3,7
PHQ-9	1	3,7
Quality of My Life questionnaire	1	3,7
TAPQOL	1	3,7
Disease-specific questionnaires—Haemophillia[a]	(*n* = 35)	
Haemo-QoL	26	74,3
CHO-KLAT	5	14,3
Adapted Inhib QoL	2	5,7
QUAL-HEMO	1	2,9
Hemo-Sat	1	2,9
Disease-specific questionnaires—IPD	(*n* = 1)	
Kids ITP Tool[b]	1	
Reference group	(*n* = 53)	
No reference group	42	79,2
Healthy reference only	8	15,1
Healthy reference + other disease reference	2	3,8
Other disease reference only	1	1,9

Abbreviations: Adapted Inhib QoL = adapted inhibitors quality of life; CarerQoL, care related quality of life; CHIP-CE, child health and illness profile—child edition; CHO-KLAT, Canadian hemophilia outcome-Kids Life Assessment Tool; CHQ, Child Health Questionnaire; D, domains; EQ, Euro quality of life; GAD, generalized anxiety disorder; Haemo-QoL, haemophilia quality of life; Hemo-Sat, health-related quality of life and satisfaction; ITQOL, infant and toddler quality of life; Kids ITP Tools, kids immune mediated thrombocytopenia tool; L, levels; PedsQL, pediatric quality of life inventory; PHQ, Patient Health Questionnaire; QoL, quality of life; QUAL-HEMO, hemophilia age group-specific quality of life questionnaire; SF, short form health survey; TAPQOL, TNO-AZL preschool children quality of life; VAS, visual analogous scale; Y, Young.

[a]Disease specific questionnaire validated in haemophilia patients.

[b]This disease specific questionnaire is validated in children with immune mediated thrombocytopenia (ITP) but in the publication by Khair, K. et al. (2018) it is used in children with inherited platelet defects.

TABLE 4 Overview of used HRQoL questionnaires per age group.

Brand Name	Full name	Age groups	Report version
CarerQoL	Care Related Quality of Life	Parents only (proxy)	Proxy
CHIP-CE	Child Health and Illness Profile—Child Edition	6 till 11 years	Proxy
CHO-KLAT	Canadian haemophilia outcome-Kids Life Assessment Tool	4 till 18years	Proxy and patient
CHQ	Child Health Questionnaire	5 till 18 years	Proxy and patient
EQ-5D	EuroQoL 5 Domains	≥18 years	Patient
EQ-5D VAS	Visual Analogue Scale	Not specified	n.a.
EQ-5D 3L	5 Domains 3 Levels	≥18 years + parents	Proxy and patient
EQ-5D 5L	5 Domains 5 Levels	≥18 years + parents	Proxy and patient
EQ-5D-Y	5 Domains—Young	I: 4 till 7, II: 8 till 18 years	Proxy and patient
GAD-7	Generalized Anxiety Disorder-7	>8 years	Patient
Haemo-QoL	Haemophilia Quality of Life	I: 4 till 7 years, II: 8 till 12 years, III: 13–16 years	Proxy and patient
Hemo-Sat	Health-related quality of life and satisfaction	<17 years	Proxy and patient
ITQOL	Infant and Toddler Quality of Life	≥2 months till < 6 years	Proxy
Kids ITP Tools	Kids immune mediated thrombocytopenia tool	2 till 18 years	Proxy and patient
PedsQL	Pediatric Quality of Life Inventory	2 till 18 years	Proxy and patient
PHQ-9	Patient Health Questionnaire-9	≥11 years	Patient
QUAL-HEMO	Haemophilia age group-specific quality of life questionnaire	Child, adolescent and parents, ages n.o.s.	Proxy and patient
SF-36	36-item Short Form Health Survey	≥14 years	Patient
TAPQOL	TNO-AZL Preschool Children Quality of Life	≥9 months till < 6 years	Proxy

to provide a SD/IQR and a range as well as the outliers, especially in studies pooling multiple disease severities. Finally, the minimal clinically important difference (MCID) was rarely used, but MCID is of value in studies evaluating novel or various treatment options. As it overcomes the gap that statistically significant effects are not always of clinical importance to a patient. Likewise, the effect size can quantify the effectiveness of a specific intervention.[88]

4.2 | Strengths and limitations

The search query for this scoping review consisted of a broad range of key-words and did not set limitations on publication date and study type, creating an overview on HRQoL in all children with a BD. Limitations are the language restrictions to English and Dutch. In addition, other bibliographic databases than PubMed, Cochrane and Embase may have yielded additional articles. Also, sometimes the parental questionnaire was added as a subpart of the proxy-questionnaire. We could only identify this if this intervention was described in the methods section of included articles. If not, the parental questionnaire was not scored.

5 | CONCLUSIONS AND FUTURE PERSPECTIVES

In this scoping review, we provide an overview of the available research on HRQoL in children with all types and severities of BDs. We demonstrate that HRQoL-research in children with BDs is an upcoming research field with still important knowledge gaps which should be addressed. But we also demonstrated that certain areas have been studied more than others. So far, studies have been mainly performed in school-aged boys with haemophilia treated in developed countries. As a result, we used the identified knowledge gaps to suggest five recommendations for future research. Focus should be on performing HRQoL-research worldwide in other BDs than haemophilia, with attention to female gender-related bleeding problems and the utilization of more sophisticated statistical parameters to identify not only the risk groups but also the groups with better coping strategies.

AUTHOR CONTRIBUTIONS

Elise J. Huisman and Caroline Mussert performed the systematic review and distracted articles. Elise J. Huisman wrote the paper. Elise J. Huisman and Caroline Mussert analyzed the data, Caroline Mussert designed the illustrations, Guannan Bai, Hein Raat, Caroline Mussert

and Marjon H. Cnossen critically revised the manuscript. Guannan Bai, Hein Raat, Caroline Mussert and Marjon H. Cnossen approved the submitted and final version.

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CONFLICT OF INTEREST STATEMENT

The authors state that they have no interests which might be perceived as posing a conflict or bias.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request. Data remains available in the Erasmus MC and guarded for access on demand for 15 years according to national regulations.

ETHICS STATEMENT

Research ethics committee (REC) approval was given for the preparation of this manuscript. The authorship for this manuscript conforms to the international committee of medical journal editors (ICMJE) guidelines. For reviews IRB-approval is waivered in the Erasmus University Medical Center.

PATIENT CONSENT STATEMENT

Not applicable.

CLINICAL TRIAL REGISTRATION

Not applicable.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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