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ORIGINAL ARTICLE

Impact of prophylaxis on health-related quality of life of boys with hemophilia: An analysis of pooled data from 9 countries

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Abstract

Background: Prophylaxis reduces the frequency of bleeds in boys with severe hemophilia and is the standard care for their management in resource-abundant countries. The effect of prophylaxis on Health-Related Quality of Life (HRQoL) has not been established, because the sample sizes of most studies are too small to explore the relationship of multiple factors that influence HRQoL.

Methods: The aim of this study was to assess the impact of hemophilia severity and treatment regimen on HRQoL and to establish the minimum important difference (MID) using the international level of score distributions. HRQoL data were pooled from 7 studies across 9 countries. HRQoL was measured using the Canadian Hemophilia Outcomes–Kids' Life Assessment Tool (CHO-KLAT). A mixed-effect linear regression analysis was employed to assess the impact of prophylaxis on the CHO-KLAT score.

Results: Data from 401 boys with hemophilia were analyzed (57.6% severe hemophilia and 57.6% receiving prophylaxis). The model revealed that receiving prophylaxis was significantly associated with higher HRQoL (regression coefficient 8.5, 95% confidence interval [CI] 3.9-13.1). Boys with severe hemophilia had a significantly lower HRQoL as compared to boys with moderate and mild hemophilia whose CHO-KLAT scores were 7.0 and 6.6 points higher, respectively. There was a significant interaction between treatment and disease severity ($P = 0.023$), indicating prophylaxis has the most significant impact in boys with severe hemophilia. Based on these pooled data, the MID of the CHO-KLAT was established at 6.5.

Conclusions: This study confirms the positive effect of prophylaxis on HRQoL in boys with hemophilia in a real-world setting and provides initial benchmarks for interpreting HRQoL scores based on use of the CHO-KLAT instrument.

KEYWORDS
health-related quality of life, hemophilia A, hemophilia B, outcome measures, pediatrics

Essentials

- Effect of prophylaxis on Health-Related Quality of Life (HRQoL) in boys with hemophilia has not been established.
- Pooled real-world data from 7 studies (9 countries) was analyzed to assess this effect.
- Prophylaxis has a significant positive impact on HRQoL in boys with severe hemophilia.
- Effect of prophylaxis was consistent across countries.

1 | INTRODUCTION

Prophylaxis, defined as the regular infusion of clotting factor concentrates (CFCs) in anticipation of and in order to prevent bleeding, has proven superior to on-demand treatment (ie, treatment at the time of bleeding) in reducing bleed rates in boys with hemophilia.[1,2] Efficacy of long-term prophylaxis has been documented based on improvement in joint function scores and imaging studies of index joints (ankles, knees, and elbows) that assess the extent and severity of hemophilic arthropathy, annualized total bleeding rates/index joint bleeding rates and the assessment of physical activity. Existing evidence has consistently shown that prophylaxis, even at low doses, improves these outcomes.[2–5] Therefore, primary prophylaxis is considered standard of care to prevent joint bleeding in very young boys with severe hemophilia.

There remain barriers to initiation of and adherence with prophylaxis.[6,7] From the family's perspective, a major barrier is the need for regular intravenous infusions of CFCs that require reliable venous access. From a payer perspective, long-term prophylaxis is expensive, as >90% of the costs are due to CFCs.[8] Accordingly, access to prophylaxis as well as the type of prophylaxis regimen (high, intermediate, or low dose) is largely dependent on a country's resources. For the purposes of this study, we refer to countries as resource abundant versus resource constrained based on the availability of, and access to, CFCs.

Patient-reported outcomes, such as Health-Related Quality of Life (HRQoL), are of value when assessing the impact of various

management strategies in persons with hemophilia. HRQoL is a multidimensional construct that represents the net impact of health on a person's well-being and functioning, in the context of one's expectations. As such, it brings the patient's perspectives to bear. Over the past decade, the introduction of HRQoL measures demonstrated the positive impact of prophylaxis treatment on the quality of life of adults with hemophilia.[9] Of note, evidence of a positive impact of long-term prophylaxis on HRQoL in boys with hemophilia is lacking.[10] The reasons for this are likely multifactorial. One possible explanation is that because both the severity of hemophilia and availability of CFCs influence the decision to prescribe prophylaxis,[11] a large sample size is required to evaluate the impact of treatment, in order to control the confounding relationship between treatment and clinical condition. To date, this has not been possible, as most of the published studies are observational with small sample sizes. In addition, the use of generic HRQoL measures are often not sensitive to hemophilia-specific issues.

The Canadian Hemophilia Outcomes–Kids Life Assessment Tool (CHO-KLAT) is a disease-specific HRQoL instrument validated for use in boys 4-18 years of age. It has been used in a number of clinical studies[5,12–20] and was found to be sensitive to clinically important changes in the setting of the use of factor (F) VIII/FIX concentrates for the management of boys with hemophilia.[17] Pooled CHO-KLAT data from clinical studies in 9 countries provided a sample size large enough to allow evaluation of the impact of treatment on HRQoL while controlling for confounding relationships.

The primary aim of this analysis was to estimate the incremental impact of prophylaxis on HRQoL in boys with hemophilia, after adjusting for key demographic and clinical factors. The secondary aim was to establish the minimum important difference (MID) of the CHO-KLAT.

2 | METHODS

This is a secondary analysis of pooled data, using comparable variables, from 7 studies in 9 countries that measured HRQoL using the CHO-KLAT.[12,13,16–20] The countries, representing cultural and economic diversity, included Brazil, Canada, China, France, Germany, Jamaica, the Netherlands, Spain, and the United Kingdom. Convenience sampling of boys with hemophilia was used with the exception of 1 study that used a random representative sample.[12] This secondary data analysis of pooled data was approved by the Research Ethics Board at the Hospital for Sick Children, Canada.

2.1 | Variables

We sought to estimate the relative impact of a variety of demographic and clinical variables on HRQoL. However, as a secondary analysis, it is important to note that the variables included were limited to those collected in each of the contributing studies.

2.1.1 | Outcome variable

The CHO-KLAT is a 35-item questionnaire that can be administered to children with hemophilia between ages of 7 and 18 years. The measure is scored on a 0-100 scale, with 100 being the optimum score, indicating best HRQoL.[17,21] Study participants independently completed the questionnaire by self-report. Help with reading was provided if required, but all boys were encouraged to select the answers on their own. This procedure was consistent in all of the 7 studies. Only the child self-report score was used for the analysis in this study.

2.1.2 | Demographic and clinical variables

Demographics and clinical variables including treatment regimen (on-demand or prophylaxis), level of severity (mild, moderate, or severe), and age were extracted from the data collected and stored. The regimens of prophylaxis (ie, dosages and frequencies) varied across the 7 studies, but for the purpose of this secondary analysis, prophylaxis was defined as regularly scheduled infusions of FVIII/IX at least once weekly for a minimum of 3 months. Hemophilia severity was defined according to the participant's baseline FVIII or FIX levels, in the absence of treatment, at the time of study entry, using the International Society on Thrombosis and Haemostasis definitions (ie, severe, <1% factor activity; moderate, 1%-5% factor activity; and mild, >5% factor activity).[22]

2.2 | Analyses

Descriptive statistics were performed by country and to summarize the distribution of the CHO-KLAT scores. To assess differences in HRQoL associated with treatment and severity of disease, the pooled sample was divided into 6 groups, based on 3 levels of severity (mild, moderate, and severe) and 2 levels of treatments (on-demand or prophylaxis).

To evaluate the impact of prophylaxis on HRQoL, multilevel modeling was employed. Multilevel modeling is an extension of ordinary least squares regression in which the data have a hierarchical/clustered/nested structure. Traditional methods, such as multiple linear regression analysis, assume that the subjects' scores are independent. If this assumption is not met, the results from the model are unreliable and may be misleading. In this pooled data analysis, the data included individuals nested within countries in which treatment strategies were different, and therefore the effect of severity of disease on HRQoL may differ. Thus, multilevel modeling was selected to avoid presenting spurious results.

A 2-level mixed-effect linear regression analysis (a random-intercept and slope model) of boys with hemophilia (level 1) nested within countries (level 2) was employed in this study. Including random variation on level 2 (country) allowed for possible similarities of boys living in the same country, and therefore, receiving similar treatment within the same health care system. The outcome variable was the CHO-KLAT score, and the explanatory variables were

treatment (on-demand or prophylaxis), severity of hemophilia (mild, moderate or severe), type of hemophilia (A or B), and age. As the treatment regimen is often highly associated with the severity of the disease (eg, boys with severe hemophilia in resource-abundant countries are likely to receive long-term prophylaxis), the interaction term between treatment and severity was also included in the model. The modeled variances (R^2) for each level were calculated using the method proposed by Snijders and Bosker.[23]

Minimum important difference was estimated using a distribution-based method, described by Norman et al,[24] where the value of 0.5 standard deviation (SD) corresponds to the MID across various studies. Thus, in this study, the MID was defined as one half of an SD of the CHO-KLAT score from pooled data. Given the broad range of boys included in this study, this was expected to be an extremely conservative estimate.

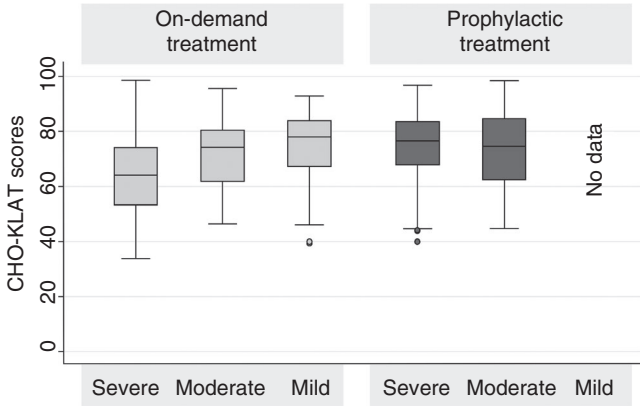

FIGURE 1 Distributions of Canadian Hemophilia Outcomes–Kids' Life Assessment Tool (CHO-KLAT) scores by severity and treatment

3 | RESULTS

Self-reported data were available from 407 boys with hemophilia who participated in 7 studies. Of these, 6 cases were excluded: 1 boy due to a missing CHO-KLAT score and 5 because their prophylaxis was short-term (<3 months). Thus, data from 401 boys were available for analysis.

Table 1 summarizes the characteristics of the participants and the CHO-KLAT scores by country. The mean age of the entire cohort was 12.2 years (SD 3.1). In total, 84.5% (339 of 401) had hemophilia A, and 57.6% (231 of 401) were receiving prophylaxis. The majority of boys with severe hemophilia received prophylaxis in most of the countries, with the exception of China and Jamaica, where very few boys were receiving prophylaxis. Of the 401 boys, 57.6% (231 of 401) had severe disease, 26.9% (108 of 401) had moderate, and 15.5% (62 of 401) had mild disease. None of the boys with mild hemophilia received prophylaxis.

When the data were pooled to examine the univariate impact of treatment, we found that boys with mild hemophilia receiving on-demand therapy had the highest (best) CHO-KLAT scores (mean 74.8, SD 12.8), followed by those with severe hemophilia receiving prophylaxis (mean 74.7, SD 12.4), those with moderate hemophilia receiving prophylaxis (mean 73.5, SD 14.2), those with moderate hemophilia receiving on-demand therapy (mean 72.2, SD 11.6), and finally those with severe hemophilia receiving on-demand therapy (mean 64.9, SD 14.5). The CHO-KLAT score distributions by severity and treatment are illustrated in Figure 1. A comparison between boys receiving prophylaxis and on-demand therapy is shown in Table 2.

The results of the multilevel regression model, with country as a random effect, shown in Table 3, indicates that age, type of treatment, and severity of hemophilia were significant predictors of CHO-KLAT scores. The fixed part of the model indicates that boys with moderate or severe hemophilia who received prophylaxis had CHO-KLAT scores that were 8.5 points higher than those receiving on-demand therapy ($P < 0.001$). Boys with mild

TABLE 1 Sample description by country

Country	Year of data collection	n	Mean age (SD)	Severe (%)	Prophylaxis (%)	Prophylaxis in severe hemophilia (%)	Prophylaxis in nonsevere hemophilia (%)	Hemophilia A (%)	Mean CHO-KLAT score (SD)
Brazil[12]	2011-2013	46	12.9 (3.0)	69.6	71.7	90.6	28.6	76.1	72.0 (10.5)
Canada[12]	2004, 2010-2013	168	11.9 (3.1)	63.1	62.5	87.7	19.4	82.7	75.0 (13.0)
China[16]	2011-2012	60	12.4 (3.0)	36.7	30	36.4	26.3	93.3	63.7 (10.6)
France[13]	2010	31	11.5 (3.6)	54.8	54.8	88.2	14.3	74.2	77.1 (10.0)
Germany[13]	2010	27	11.6 (2.7)	59.3	63	100	9.1	88.9	70.8 (14.1)
Jamaica[20]	2015	8	13.6 (3.1)	25	0	0	0	87.5	57.1 (12.6)
Netherlands[13]	2010	31	12.4 (3.0)	64.5	67.7	100	9.1	90.3	82.5 (8.6)
Spain[13]	2010	22	13.0 (3.2)	68.2	68.2	100	0	90.9	78.9 (11.1)
United Kingdom[13]	2010	8	12.9 (2.2)	12.5	62.5	100	57.1	87.5	77.1 (9.7)
Total	—	401	12.2 (3.1)	57.6	57.6	85.3	20.0	84.5	73.3 (12.9)

CHO-KLAT, Canadian Hemophilia Outcomes–Kids Life Assessment Tool; SD, standard deviation.

TABLE 2 Subject characteristics

	On-demand	Prophylaxis	Total
Sample size, n (%)	170 (42.4)	231 (57.6)	401
Age, mean (SD)	12.4 (3.0)	12.0 (3.1)	12.2 (3.1)
Severity, n (%)			
Mild	62 (100)	0 (0.0)	62 (15.5)
Moderate	74 (68.5)	34 (31.5)	108 (26.9)
Severe	34 (14.7)	197 (85.3)	231 (57.6)
Type, n (%)			
Hemophilia A	144 (84.7)	195 (84.4)	339 (84.5)
Hemophilia B	26 (41.9)	36 (58.1)	62 (15.5)
CHO-KLAT Score, mean (SD)	71.7 (13.1)	74.5 (12.7)	73.3 (12.9)

CHO-KLAT, Canadian Hemophilia Outcomes–Kids Life Assessment Tool; SD, standard deviation.

and moderate hemophilia had scores that were 6.6 and 7.0 points higher than those with severe disease, respectively ($P = 0.045$ and $P = 0.007$). The interaction between treatment regimen and severity was also significant ($P = 0.023$), confirming our a priori clinical hypothesis that prophylaxis is of greatest benefit for boys with severe hemophilia. As an example, according to this model, a 12-year-old boy with severe hemophilia A would have a CHO-KLAT score of 65.3 if treated with on-demand therapy, and a score of 73.8 if treated with prophylaxis.

Based on our model, in general, the association between mild or moderate severity and higher HRQoL score was stronger in the resource-abundant countries (European countries and Canada), while it was weaker in the resource-constrained countries (China and Jamaica), with Brazil intermediate (estimated variance of random effect coefficients of severity 9.73). The variance of random effect on treatment among countries was relatively small (estimated variance of random effect coefficients of treatment 4.26), with the highest positive treatment effect in the Netherlands (Data S1). To aid in characterizing the access to the CFCs for each country, Table S1 also includes the information of factor concentrate use per capita. The CFC use per capita in European countries and Canada were above 4 International Units (IU) per capita at the time of data collection, while it was lower in Brazil, at 1.73 IU per capita, and very low in Jamaica, at 0.26 IU per capita.[25–28] Although it was not reported in the WFH Global Survey, the Netherlands' value is assumed to be close to the other European countries, and China's value is close to the Jamaican value.

The proportion of the variance explained (ie, R^2) by the first level (individual level) was 0.06 and the second level (country level) was 0.07, indicating 6% and 7% of the total variance in the CHO-KLAT scores, respectively, were explained in the model.

Finally, the MID, defined as half of an SD, was determined. As shown in Table 2, the SD of the CHO-KLAT score was 12.9 in the pooled sample, with slight variance of SDs ranging from 12.7 to 13.1 depending on severity and treatment. Thus, the MID is determined to be 12.9/2 = 6.45.

TABLE 3 Multilevel linear regression results

Fixed effect	Coefficient	SE	95% CI
Constant	56.7	3.3	50.3 to 63.1
Age, per year	0.7	0.2	0.4 to 1.1
Treatment (reference: on-demand)			
Prophylaxis	8.5	2.3	3.9 to 13.1
Severity (reference: severe)			
Moderate	7.0	2.6	2.0 to 12.1
Mild	6.6	3.3	0.2 to 13.1
Treatment × Severity			
Prophylaxis × Moderate	−7.4	3.3	−13.8 to −1.0
Prophylaxis × Mild	NA		
Type (reference: hemophilia A)			
Hemophilia B	1.5	1.6	−1.7 to 4.7
Random effect	**Coefficient**	**SE**	**95% CI**
Level 2 (country)			
Treatment variance	4.3	6.5	0.2 to 83.8
Severity variance	9.7	5.7	3.1 to 30.4
Constant variance	<0.001	<0.001	<0.001 to 0.2
Level 1 (individuals)			
Residual variance	128.7	9.3	111.7 to 148.3

CI, confidence interval; SE, standard error.

4 | DISCUSSION

These pooled data from 7 studies across 9 countries enables the description of the impact of prophylaxis, after adjusting for the severity of disease, on the HRQoL in boys with hemophilia using a well-validated HRQoL instrument, the CHO-KLAT.[29] The results indicate that the HRQoL scores in boys with severe hemophilia receiving prophylaxis are similar to the HRQoL scores for boys with mild hemophilia receiving on-demand therapy. Thus, prophylaxis has a positive impact on HRQoL. The results of this study have also generated the first estimate of MID for the CHO-KLAT, which provides important information for interpretation of CHO-KLAT scores.

The results of this analysis confirms the positive effect of prophylaxis on HRQoL in boys with hemophilia. In our study, the boys with severe hemophilia receiving prophylaxis had CHO-KLAT scores that were, on average, an estimated 8.5 points higher than boys of the same severity who received on-demand therapy, and this effect of prophylaxis was consistent across countries. The magnitude of the effect of the prophylaxis was slightly larger than the effect of the severity, indicating that prophylaxis may be capable of canceling out the incremental burden of severe hemophilia relative to moderate hemophilia. This study further demonstrates that prophylaxis has the greatest positive effect on HRQoL in boys with severe hemophilia.

The prophylaxis regimens varied among the countries; however, the variance of the treatment effect was not large. These results underscore the importance of prophylaxis per se, specifically that any prophylaxis regimen has a positive impact on the HRQoL in boys with severe hemophilia. Indeed, benefit from the low-dose prophylaxis regimens in reducing the frequency of bleeds has been reported.[5,30] On the contrary, the variance of severity effect among countries (level 2) was twice as large as the one for treatment, and stronger negative effects of having severe disease was found consistently in the resource-constrained countries compared to those in the resource-abundant countries. There may be several reasons for this relationship, but we believe that this is most likely due to the inequality in access to CFCs. In resource-abundant countries where prophylaxis is the standard of care for management of boys with severe hemophilia, there is both access to prophylaxis started early in life as well as access to CFCs for those who do not require prophylaxis. Consequently, these boys experience lower bleeding rates, less bleed-related arthropathy and better activity levels, compared to those in resource-constrained countries where CFCs are less accessible.[12] Thus, even within the same hemophilia severity group, health status differs widely among countries, which results in a large variance of the clinical impact of hemophilia between countries. These data may be used in advocacy programs to governments/funding agencies requesting support for some form of prophylaxis for young boys with severe hemophilia.

One of the strengths of HRQoL measures is their ability to detect disease effects that are not evident on physical examination but are reportedly the most salient to patients. However, the interpretability of the HRQoL score is a challenge. Thus, the establishment of the MID for the CHO-KLAT is important for the measure. We are of the opinion that the MID reported in this communication is valid because our calculations are based on the largest HRQoL study in boys with hemophilia using data for a well-validated HRQoL instrument, the CHO-KLAT, derived from multiple observational studies. The estimated MID from this study will be of value for the interpretation of treatment/intervention effects related to HRQoL as measured by the CHO-KLAT in boys with hemophilia. In the current era of novel factor and nonfactor hemostatic therapies, it remains to be determined whether existing tools will be sensitive to detect change in HRQoL associated with use of these therapies. Nevertheless, whether new tools or modifications to existing tools are used, the MID estimate is paramount in interpreting the effects of different therapeutic strategies. This will contribute important information regarding the relative benefits of the very expensive but highly effective novel factor and nonfactor hemostatic therapies. Patient-reported outcomes, such as are reported by the CHO-KLAT, are increasingly required by regulatory and funding agencies as they consider requests for approval and purchase of novel hemostatic therapies in the hemophilia population.

There are some limitations to this study. First, although this study used pooled data from multiple clinical studies to obtain an adequate sample size to control for confounding factors, some important confounders, specifically, joint scores, activities level, and inhibitor status, were not included, as the source data sets did not include these data from a sufficient number of cases to permit such analyses. Similarly, dose, frequency, and starting age of prophylaxis were not consistently collected in the original studies, and thus we could not include those variables in the statistical model. Although prophylaxis regimens differed between countries included in the pooled data analysis, treatment standards were, in general, similar within countries, and therefore we expect that differences in the latter are included in the random effect of the model. Second, in this study, the countries were not randomly selected. Although resource-constrained countries were included, the majority of participating centers were from resource-abundant countries. Multilevel regression is able to estimate the coefficient for each country; however, it is skewed toward mean values. Thus, the coefficients in the model could be over/underestimated. Finally, the MID was established using the distribution method. As HRQoL is a subjective measure, only patients are in a position to ultimately judge whether a difference is important. The anchor-based method, which compares changes in HRQoL scores to an external measure of change (such as a self-reported global rating of change), is generally preferred to establish the MID. Although we believe the MID established in this study is robust becaude it is based on a large sample size, the use of cross-sectional data has limitations.

5 | CONCLUSION

This real-world study provides empirical evidence supporting the positive effect of prophylaxis on HRQoL in boys with hemophilia.

The effects of prophylaxis on HRQoL are similar across countries, indicating the importance of prophylaxis per se. This study provides an estimate of the aggregated impact of hemophilia and its treatment, and also delivers initial benchmarks for interpreting HRQoL scores based on use of the CHO-KLAT instrument. Future prospective studies are necessary to systematically assess the impact of specific treatment regimens, age at start of prophylaxis, intensity of prophylaxis, adherence, inhibitor status, and activity profiles of boys with hemophilia and other important confounders.

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RELATIONSHIP DISCLOSURE

None of the authors have any disclosures relevant to this paper.

AUTHOR CONTRIBUTIONS

KU and VEP contributed equally to this work. KU, VEP, VSB, and NLY conceived and designed the study. VEP, AA, CA, LBD, JDAC, BF, KF, JG, SH, KHL, SM, MO, LT, SV, PV, CW, GW, RW, and NLY participated in the conduct of the studies and data collection. KU organized data collaboration. KU, VEP, VSB, and NLY participated in analyses and wrote the manuscript. All authors reviewed the final version of the manuscript and support this publication.

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SUPPORTING INFORMATION

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

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