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Quality of Life at a 10-Year Follow-Up of Children Born Preterm with Post-Hemorrhagic Ventricular Dilatation: A Cohort Study

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Keywords
Health-related quality of life · Intraventricular hemorrhage · Post-hemorrhagic ventricular dilatation

Abstract

Background: Post-haemorrhagic ventricular dilatation (PHVD) is commonly seen in extremely preterm babies, carries significant morbidity, and may cause neonatal mortality. There is a lack of literature on the subsequent health-related quality of life (HRQoL) in childhood. The aim of this work was to assess the quality of life of preterm babies after PHVD at 10 years of age using two validated questionnaires. ***Methods:*** Children with PHVD were assessed as part of the 10-year follow-up of the drainage, irrigation, and fibrinolytic therapy trial. The HRQoL outcome was measured using parent-reported EQ-5D-5L and HUI-3 questionnaires. Both questionnaires produce a summary score anchored at 1 (best health) and 0 (equivalent to death). ***Results:*** Median scores at follow-up were 0.65 (IQR 0.36–0.84; $n = 44$) for the EQ-5D-5L and 0.52 (IQR 0.22–0.87; $n = 51$) for the HUI-3. Similar proportions had a score below 0.2 (HRQoL [20%], HUI-3 [21%]), while 20% had a HRQoL score above 0.80 compared to 34% using HUI-3. The most severe problems from the EQ-5D-5L were reported in the self-care, mobility, and activity domains, while the HUI-3 reported worse problems in ambulation, cognition, and dexterity domains. Infants with worse (grade 4) intraventricular haemorrhage had poorer HRQoL than those with grade 3 bleeds. ***Conclusion:*** Children who survive to 10 years of age after PHVD have on average lower HRQoL than their peers. However, the reported range is wide, with a quarter of the children having scores above 0.87 (similar to population norms), while a fifth have very low HRQol scores. Impact was not uniform across domains, with mobility/ambulation a concern across both measures.

Plain Language Summary

What we know already: Babies born very preterm are at high risk of dying or developing brain injuries around birth, and that bleeding into the fluid spaces in the head (ventricles) is one of the most common problems. Some of these

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children go on to develop a condition known as "post-haemorrhagic ventricular dilatation (PHVD)" where the fluid spaces can get enlarged. Many of these children die, and we know that those who survive have a higher risk of developmental problems. What we do not know is how this affects their quality of life as they grow. The DRIFT trial was a study which investigated a new treatment for PHVD. As part of the study, when the surviving children reached 10 years of age, we asked their parents two sets of questions about their child's "health-related quality of life."***What we discovered:*** Children who had PHVD had a wide range of results, with around a quarter having scores similar to children in the general population, but around one-fifth having low scores, suggesting poor quality of life. They appeared to have particular problems with movement and self-care. However, while the scores were lower than some children, they maybe similar, or better, than children with autism or Down syndrome.

Introduction

Preterm births represent a large global burden, with around 15 million babies being born preterm per year, and the numbers likely increasing [1]. The leading cause of childhood mortality is complications attributed to prematurity [2], and one major complication is intraventricular haemorrhage (IVH) [3] and subsequent post-haemorrhagic ventricular dilatation (PHVD) [4].

IVH after preterm birth is a significant worldwide problem, and both IVH and PHVD are associated with significant increased mortality [5], and strongly influence decisions around limitation or withdrawal of care [6]. Reducing IVH and other perinatal brain injury is a key part of the UK National Maternity Ambition [7] and while a small number of interventions may reduce the risk [8, 9], no effective treatment is currently available [10, 11].

However, despite this substantial health burden, there is uncertainty about the long-term outcomes as the children grow, and little is known about the later health-related quality of life (HRQoL). The World Health Organisation (WHO) defines quality of life as the "individuals" 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 [12]. A number of studies have reported the health-related quality of life (HRQoL) of preterm infants, reporting impacts in emotional, social functioning, speech, and dexterity; although, overall the subjective experience of their quality of life may be similar to their peers [13–15]. However, there is little literature on quality of life in preterm children after severe IVH and PHVD despite it being a clinically important event, and a major factor assessed in neonatal care when considering withdrawal of care in these sick infants [6].

The drainage, irrigation, and fibrinolytic therapy (DRIFT) trial was a randomised controlled trial of a novel neurosurgical and medical treatment, which followed up infants with IVH or PHVD to 10 years of age [10]. While the study showed benefits of DRIFT in cognitive outcomes, overall HRQoL measures were similar across the two treatment arms [10].

Aim

The aim was to assess the quality of life in the cohort of infants with severe neonatal IVH and resultant PHVD at 10 years of age; data were obtained from the DRIFT randomised controlled trial.

Materials and Methods

DRIFT Study Design and Population

The trial recruited preterm neonates with severe (grade 3 or 4) IVH, and corresponding PHVD, in 4 clinical centres, in the UK and Poland, and randomised them to either receive DRIFT or standard non-surgical treatment. DRIFT is a therapy involving an intraventricular injection of a fibrinolytic, followed by continuous lavage for up to 72 h [16]. The standard care arm of the trial consisted of control of ventricular expansion by lumbar punctures, or by using a ventricular access device. In total, 77 babies were recruited between 2003 and 2006 [16], and the 10-year follow-up assessed a total of 52 of these children between February 2015 and April 2016 [10, 17]. Further details on the initial trial and patient flow are presented in Appendix A.

HRQoL Data (Primary Outcome)

At the 10-year follow-up, parents were asked to complete questionnaires for two, validated, generic measures of their child's HRQoL.

- The Health Utilities Index (HUI-3) [18] measures eight attributes of quality of life: vision, hearing, speech, emotion, cognition, ambulation, dexterity, and pain [19]. They are discriminated by a score of 1 (no restrictions to their HRQoL) to 5 or 6 depending on the level measured (representing poor HRQoL).
- The EQ-5D-5L [20] measures five domains: self-care, usual activities, mobility, anxiety/depression, and pain/discomfort. Each provides an ordinal scale ranging from one to five, with one being no problems experienced to five being extreme problems experienced.

Attribute/domain responses for these measures are mapped to a summary score based on general population "valuation sets" provided by the EQ-5D-5L [21] and HUI-3 developers [19]. For both the EQ-5D-5L and HUI-3, the summary HRQoL score is

Table 1. Patient characteristic, split by initial study arm

Patient Characteristic	*n*	Standard Care	DRIFT	*p* value
Sex	51			0.167
Male		14 (60.9)	22 (78.6)	
Female		9 (39.1)	6 (21.4)	
Gestational age, weeks, mean	51	28.7 (3.0)	27.6 (2.6)	0.179
<28, *n* (%)		9 (39.1)	16 (57.1)	0.200
28–37, *n* (%)		14 (60.9)	12 (42.9)	
Birthweight, mean	51	1,347 (533)	1,102 (336)	0.051
<1,000 g		7 (30.4)	12 (42.9)	0.491
1,000–1,499 g		10 (43.5)	12 (42.9)	
>1,500 g		6 (26.1)	4 (14.3)	
Maternal age, years, mean	26	28.2 (6.3)	28.5 (7.0)	0.900
<30, *n* (%)		7 (58.3)	9 (64.3)	0.756
30 and older, *n* (%)		5 (41.7)	5 (35.7)	
IVH grade	51			0.877
3		12 (52.2)	14 (50.0)	
4		11 (47.8)	14 (50.0)	
VP shunt	51			0.741
Yes		8 (34.8)	11 (39.3)	
No		15 (65.2)	17 (60.7)	

Numbers are mean (SD) or *n* (%) as appropriate. *p* values derived from χ^2 test or *t* test as appropriate.

anchored at a maximum score of 1 (best health) and 0 (often considered equivalent to death) [22]. It should be noted that scores below 0 are possible with both measurements and represent an extremely poor HRQoL.

Demographic and Other Data

Demographic and neonatal data were obtained through medical records and specific research data collection sheets and recorded in a dedicated research database. Further data included the following:

- Demographic data: sex (male or female), gestational age at birth (categorised as less than 28 weeks, 28–32, or 33 and above), birthweight (categorised as <1,000 g, 1,000–1,499 g, 1,500–2,499 g, ≥2,500 g), maternal age (categorised as <30 or 30 years and above)
- IVH characteristics: IVH graded as 3 or 4 [23].
- Treatments provided: DRIFT treatment arm (DRIFT/standard) and subsequent ventriculo-peritoneal (VP) shunt (yes/no) before discharge.

Statistical Analysis

Initially, the median response scores for each of the HRQoL questions were derived, and the final summary score calculated using published scoring algorithms [19, 21], alongside an estimate of how correlated the summary scores were. Next, we derived and compared the summary scores for the HRQoL measures, split by the demographics and clinical characteristics of the population (as categorised above). Finally, we derived a linear regression model to assess the multivariable relationships between the covariates and the overall HRQoL (derived separately for each measure). For this model, gestational age at birth, birthweight, and maternal age were included as continuous terms.

Categorical data are presented with the number percentage (*n* [%]), and continuous data are presented as median (inter-quartile range [IQR]) or mean (standard deviation or 95% CI). Univariable comparisons between groups were made using the Mann-Whitney test (or an extension of it to 3 or more groups [24]). Analysis was performed on STATA version 17.

Results

Study Population and Participant Flow

From the 77 children recruited to the DRIFT trial, 52 survivors were enrolled in the 10-year follow-up. One participant had incomplete responses on both the HUI-3 and the EQ-5D-5L, leaving 51 participants for the analysis.

The majority of infants were male (*n* = 36 [70.6%]) (Table 1). Half were extremely preterm (<28 weeks at birth) (*n* = 25 [49.0%]) and had a birthweight between 1,000 and 1,499 g (*n* = 22 [42.3%]). Half of the children had grade 3 IVH (26 [50.9%]) and half had grade 4 IVH (25 [49.0%]).

Overall HRQoL Scores

The median HRQoL score at the 10-year follow-up was 0.66 (IQR 0.35–0.87) for the ED-5D and 0.52 (0.22–0.87) for the HUI-3. The distribution of summary scores and individual domains are shown in Figures 1 and 2, and while many children had scores above 0.8,

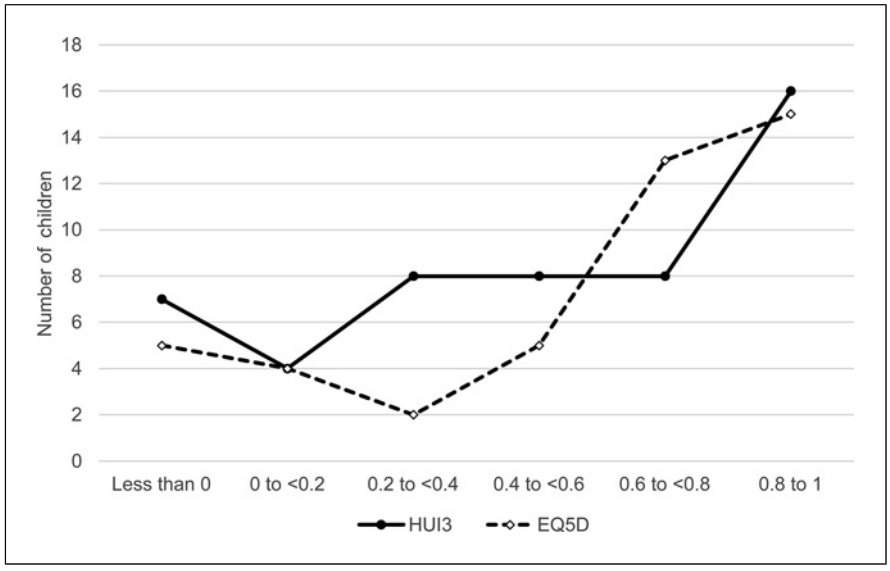

Fig. 1. Distribution of the summary HRQoL scores.

some had scores below 0. The two summary scores were highly correlated ($p < 0.001$), with an r^2 of 0.70 (Table 2).

Univariable Associations with HRQoL

There was little evidence that either HRQoL score was different by sex, maternal age, birthweight, or gestational age categories at birth (Table 3). There was some weak evidence that increasing gestational age was associated with increasing EQ-5D-5L ($p_{trend} = 0.059$) but not HUI-3 scores ($p_{trend} = 0.111$). There was stronger evidence that increasing birthweight was associated with higher EQ-5D-5L ($p_{trend} = 0.013$) and HUI-3 summary scores ($p_{trend} = 0.022$). Children with grade 4 IVH had lower EQ-5D-5L (0.45 [IQR 0.11–0.71] versus 0.82 [IQR 0.62–0.92], $p = 0.0016$ and HUI-3 scores [0.34 vs. 0.80], $p = 0.0004$) than those with grade 3. While there was only weak evidence that infants who received a VP shunt had a lower EQ-5D-5L scores (0.60 [0.13–0.72] versus 0.76 [0.45–0.90], $p = 0.0864$), there was stronger evidence for a reduction in their HUI-3 scores (0.34 [−0.04–0.61] versus 0.80 [0.43–0.93], $p = 0.0004$). Overall, children who received DRIFT treatment had similar HRQoL scores (EQ-5D, $p = 0.7919$; HUI-3, $p = 0.8696$).

Multivariable Linear Regression

In the multivariable model (Table 4), IVH grade 4 was associated with substantially lower EQ5D (−0.31 [−0.53 to −0.08], $p = 0.008$) and HUI-3 (−0.31 [−0.53 to −0.08], $p = 0.009$) scores at 10 years. Once adjusted for IVH grade, there was little evidence for any association with either HRQoL scores by sex, gestational age, birthweight, need for a VP shunt, or DRIFT treatment arm (all p values >0.1).

Discussion

The aim of this work was to evaluate, and describe, the quality of life in children who experienced IVH and PHVD. At 10 years of age, following severe IVH in the neonatal period, HRQoL measures are estimated at around 0.5–0.6, depending on the score and summary statistic used; substantially lower than the likely population mean of 0.93 (SD 0.13) [25]. Overall children scored a median of one or two in most of the domains, indicating slight or no problems, but some had very low scores, with around 10% scoring less than 0. Individual domains are difficult to assess in isolation, but a high level of disability was reported in cognition on the HUI-3 tool. Overall, children with lower birthweights or gestational ages reported lower HRQoL measures, but this association may be predominantly due to a higher risk of a more severe IVH.

The relatively small number of children providing HRQoL scores at 10 year follow-up limits the statistical power to identify small but clinically important associations between patient characteristics and subsequent quality of life. However, this cohort represents the largest to date with systematic and long-term HRQoL follow-up, which allowed us to signpost the most influential associations for future work. While the relatively small sample size may limit the generalisability of this study, the cohort

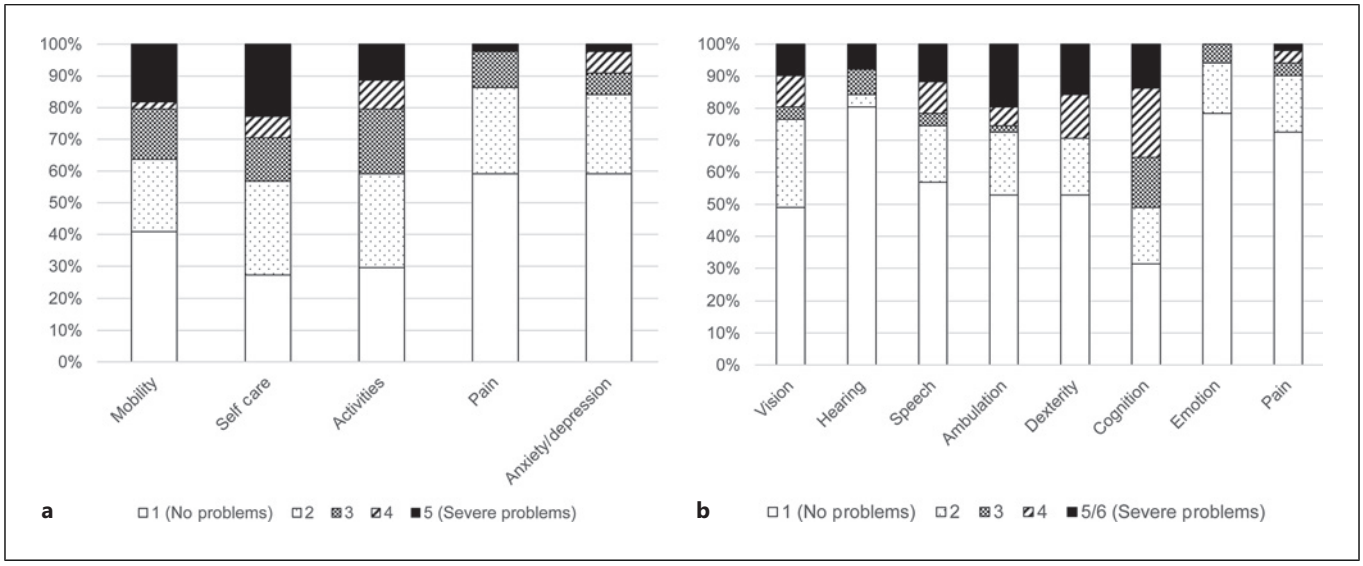

Fig. 2. Individual domain responses for the (**a**) EQ-5D-5L and (**b**) HUI-3.

Table 2. HRQoL domain and summary scores

EQ-5D-5L (n = 44)				HUI-3 (n = 51)			
domain	median (IQR)	mean (SD)	no impairment reported, %	domain	median (IQR)	mean (SD)	no impairment reported, %
Mobility	2 (1–3)	2.34 (1.49)	18 (40.9)	Vision	2 (1–2)	2.04 (1.36)	25 (49.0)
Self-care	2 (1–4)	2.68 (1.52)	12 (27.3)	Hearing	1 (1–1)	1.53 (1.24)	41 (80.4)
Usual activities	2 (1–3)	2.43 (1.32)	13 (29.6)	Speech*	1 (1–3)	2.02 (1.45)	29 (56.9)
Pain/discomfort	1 (1–2)	1.59 (0.87)	26 (59.1)	Ambulation	1 (1–4)	2.31 (1.83)	27 (52.9)
Anxiety/ depression	1 (1–2)	1.68 (1.03)	26 (59.1)	Dexterity	1 (1–4)	2.25 (1.66)	27 (52.9)
				Cognition	3 (1–4)	2.71 (1.50)	16 (31.4)
				Emotion*	1 (1–1)	1.27 (0.57)	40 (78.4)
				Pain*	1 (1–2)	1.45 (0.90)	37 (72.6)
Summary score**	0.66 (0.35–0.87)	0.58 (0.36)	-	Summary score**	0.52 (0.22–0.87)	0.50 (0.38)	–

Numbers are n (%) or mean (SD). A lower attribute/domain response indicates less impairment, while a lower summary score indicates worse HRQoL. *Domain responses are between 1 and 6, except for the specific domains of the HUI-3 (speech, emotion, and pain) which have only 5 response categories. **Summary score derived from "valuation sets" [20, 22].

was recruited from neonates gathered across the country and may represent the wider UK population with severe IVH [16]. We used parent proxy responses, and parental perceptions of HRQoL may be influenced by their own expectations, and the burden they have faced when caregiving [15, 26, 27]. Indeed, while parents may place less importance regarding psychosocial aspects such as self-esteem, cognition, and emotion than children [13, 14, 26, 28], proxy reporting was needed to ensure consistent results across the cohort [27]. Finally, to adjust for confounders, linear regression models were used assuming normally distributed residuals.

One previous study assessing HRQoL in children with PHVD at 5 years suggested a similar reduced overall HRQoL, but with impact in motor, emotional, social, and school domains [29], while other studies have noted that

Table 3. Summary HRQoL scores split by patient characteristics

Patient demographics	*n*	EQ-5D-5L summary score median (IQR)	*p* value	p_{trend}	*n*	HUI-3 summary score median (IQR)	*p* value	p_{trend}
Sex								
Male	33	0.62 (0.25–0.85)	0.194		36	0.43 (0.12–0.89)	0.322	
Female	11	0.74 (0.63–0.89)			15	0.70 (0.46–0.84)		
Gestational age, weeks								
<28	21	0.60 (0.17–0.77)	0.173	0.059	25	0.43 (0.06–0.75)	0.107	0.111
28–37	23	0.79 (0.36–0.89)			26	0.66 (0.37–0.93)		
Birthweight								
<1,000 g	17	0.60 (0.26–0.80)	0.108	0.013	19	0.46 (0.18–0.73)	0.082	0.022
1,000–1,499 g	19	0.64 (0.14–0.89)			22	0.43 (0.06–0.91)		
>1,499 g	8	0.88 (0.63–0.93)			10	0.71 (0.57–0.97)		
Maternal age, years								
<30	16	0.67 (0.35–0.86)	0.812	0.469	16	0.49 (0.35–0.91)	0.598	
30 and older	10	0.74 (0.39–0.92)			10	0.83 (0.04–0.94)		
IVH grade								
Grade 3	24	0.82 (0.62–0.2)	0.002		26	0.80 (0.43–0.93)	0.004	
Grade 4	20	0.45 (0.11–0.71)			25	0.34 (−0.04–0.61)		
DRIFT								
Yes	25	0.64 (0.32–0.85)	0.792		28	0.51 (0.35–0.83)	0.870	
No	19	0.71 (0.42–0.88)			23	0.59 (0.07–0.92)		
VP shunt								
Yes	28	0.61 (0.18–0.71)	0.066		19	0.39 (−0.03–0.63)	0.018	
No	16	0.75 (0.49–0.92)			32	0.69 (0.38–0.93)		

Numbers are *n* (%) or median (IQR). *p* values derived using Mann-Whitney U, Kruskal-Wallis, or Cuzick's test for trend as appropriate.

Table 4. Results of multivariable linear regression model for the two HRQoL summary scores

Covariate	EQ-5D-5L (*n* = 44)		HUI-3 (*n* = 51)	
	mean difference (95% CI) (*n* = 26)	*p* value	mean difference (95% CI) (*n* = 26)	*p* value
Male	−0.17 (0.41–0.72)	0.166	−0.13 (−0.34–0.09)	0.253
Gestational age, weeks	0.01 (−0.07–0.08)	0.889	−0.3 (−0.10–0.05)	0.447
Birthweight, kg	0.15 (−0.31 to −0.61)	0.502	0.30 (−0.16–0.77)	0.193
IVH grade 4 (vs. 3)	−0.31 (−0.53 to −0.08)	0.008	−0.31 (−0.53 to −0.08)	0.009
VP shunt (yes)	0.05 (−0.19–0.28)	0.693	−0.04 (−0.26–0.19)	0.755
DRIFT (yes)	0.09 (−0.13–0.31)	0.416	0.12 (−0.09–0.33)	0.243

Numbers are mean increase/difference (95% CI) for HRQoL score for each unit of the covariate (e.g., kg of birthweight).

lower HRQoL outcomes may depend on physical function [15, 28]. However, many of the parents in our study reported their children experienced no problems with pain or anxiety (EQ-5D-5L), or hearing, speech, ambulation dexterity, emotion or pain (HUI-3). Furthermore, the age of assessment may be important, with previous work suggesting improvements in HRQoL after preterm birth as the children grow [15]. In this work, mobility and corresponding activities appear to be the most commonly impacted. A higher grade of IVH was strongly associated with worse HRQoL at 10 years of age, and while DRIFT has been shown to improve cognitive outcomes in this group of infants, it is unlikely to improve motor outcomes, and so the results of this analysis are consistent with our published analysis of trial outcomes [10].

While no further studies on the efficacy of DRIFT have been published since this initial trial, the proof of principle that washing blood out of the brain reduces cognitive disability has led to alternative techniques (e.g., neuroendoscopic lavage) being more widely adopted and investigated. Of note, in our cohort, the presence of a VP shunt was not independently associated with worse HRQoL later in life despite some work suggesting to have a VP shunt is a poor prognostic outcome [30].

There remains a lot of uncertainty regarding the neonatal care of children with severe IVH, and withdrawal of care in neonatal units is commonly performed due to concerns over future HRQoL [6]. In this work, the summary scores appear substantially lower than the estimated normative means (0.93 [SD 0.13]) [25], as well as likely lower than an English population cohort of all children born extremely preterm [14]. In that work, the HUI-3 scores of 11-year-old children, born before 26 weeks of gestation in 2006, had a median score of 0.76 (IQR 0.38–0.97) compared to 0.52 (0.22–0.87) in this work.

However, interpreting what the scores may mean to the child needs to be performed in context of the clinical case and the views of the family. Comparison with other, perhaps more common disease processes suggest that the absolute metrics in this cohort (e.g., a HUI-3 median score of 0.52) appear higher to those reported for children with autism spectrum disorders (0.41) [25] or trisomy 21 (0.34) [25]. These referenced values are from sampled children using a similar methodology, and from a cohort of children with a similar demographic and age range to this work. However, data were limited to families of children with disability or severe illness who had applied for financial support, and therefore may represent a more disabled cohort than other children with their conditions. Interestingly, the results are also similar than those seen in survivors of adult stroke (measured 6 months after an ischaemic stroke; mean HUI-3 0.44 (SD 0.37) [31], another condition where novel active post-event treatment has reduced mortality [32] and increased intact survival [33].

However, it should be noted that while the median (and mean) scores reported for this cohort appears to suggest a similar HRQoL to many other childhood conditions, the range seen was often broader (e.g., the IQR for the HUI-3 was 0.22–0.87), with a substantial proportion with scores below 0, suggesting that outcome is more varied and difficult to predict in this group. Scores below zero indicate a HRQoL where physical, mental, or social functioning are likely severely compromised, alongside limitations and reduced ability to engage in daily activities.

Conclusion

Overall, around one-fifth of all children who survive PHVD have a very low HRQoL, while a quarter have scores above 0.87 (similar to population norms). However, impact was not uniform across domains. A higher (grade 4) IVH grade was the only clear factor tested that was predictive of poorer HRQoL. These parent-reported data on their children's HRQoL may be useful for professionals and parents when discussing ongoing care plans, and future work could usefully explore more predictors of better HRQoL, in survivors of neonatal PHVD.

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Statement of Ethics

Ethical approval was granted by the NHS Health Research Authority, NRES Committee South West - Central Bristol (14/SW/1078). Parents gave written informed consent. The children gave their assent for follow-up.

Conflict of Interest Statement

A.R., C.W., S.J., P.B., I.P., A.W., K.L., and D.E.O. reported no conflicts of interest.

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management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Author Contributions

A.R. participated in the study concept and design, analysis and interpretation of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. C.W., S.J., and I.P. participated in the study concept and design, analysis and interpretation of data, critical revision of the manuscript for important intellectual content, and obtaining funding. P.B. participated in interpretation of data and critical revision of the manuscript for important intellectual content, A.W. designed, obtained funding, led the original DRIFT trial, and participated in this study concept and design analysis and interpretation of data, and critical revision of the manuscript for important intellectual content. K.L. and D.E.O. participated in the study concept and design, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and obtaining funding.

Data Availability Statement

The data that support the findings of this study are not publicly available due to containing information that could compromise the privacy of research participants but maybe available from the corresponding author (D.E.O.) upon reasonable request.

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