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Assessment of health-related quality of life in pediatric hematopoietic stem cell transplant recipients: progress, challenges and future directions

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Abstract

This article provides an overview of health-related quality of life (HRQoL) assessments in pediatric hematopoietic stem cell transplants, focusing on the relationship between child and parent proxy ratings of the child's HRQoL and how measurement of HRQoL may be incorporated into clinical decision-making. Parent and child ratings of the child's health may be affected differently by unequal access to and incongruent understanding of available information, as well as the effect of age difference on interpretation. In particular, parents and children may experience the impact of clinical events on HRQoL very differently. The recent US Federal emphasis on 'patient-centeredness' has helped fuel the development and application of more clinically functional and low-burden HRQoL measures. Future work in pediatric hematopoietic stem cell transplants must seek to capture the experiences and perceptions of all those involved.

Keywords

Child Health Ratings Inventories; health-related quality of life; hematopoietic stem cell transplant; parent-child difference; Patient-Reported Outcomes Measurement Information System™

For more than 20 years, researchers have grappled with the impact of hematopoietic stem cell transplantation (HSCT) on recipients' health-related quality of life (HRQoL). HRQoL in this context refers to a multidimensional construct, incorporating the individual's subjective appraisal of his/her functioning and well-being. The 'health-relatedness' refers to those aspects of overall quality of life that are influenced by the individual's health and are within the purview or influence of the healthcare sector [1].

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HSCT provides a compelling context within which to consider HRQoL, given its toll on the physical and emotional health of the recipient. The gravity of the underlying condition, the intensity of the treatment, and the potential for early and delayed sequelae all can adversely alter HRQoL. Specifically, HSCT offers potentially life-saving treatment for advanced malignancies and otherwise incurable diseases of hematologic, immunologic or metabolic origin. The treatment itself, however, beginning with a multi-day, and often multimodal, preparative regimen is intense, putting the recipient at risk for end organ toxicity, infection and bleeding. Following the initial transplant period, patients remain vulnerable to infection and, for recipients of allogeneic HSCT, to emergence or re-emergence of acute or chronic graft-versus-host disease (GVHD). In the several months following HSCT, patients are kept in protective isolation, which further taxes their ability to participate in typical social and role activities, such as school.

In this article, the authors will review the evolving field of HRQoL in pediatric HSCT with particular focus on two broad areas: the impact of child versus parent rater of the child's HRQoL, and the future directions with regard to assessment and incorporation into clinical decision-making. In 2012, the authors summarized the state of science of HRQoL after pediatric HSCT with the added focus of functional and neurocognitive outcomes, provided by distinguished colleagues [2]. The reader is directed to that review for general descriptions of the HRQoL trajectory over the first 1–2 years post-transplant.

Barriers to early research on HRQoL in children/ adolescents

Research about pediatric HRQoL in general has lagged behind that in adults in two important ways. First, prior to the early 1990s, there were very few pediatric instruments that addressed the full range of HRQoL as a multidimensional construct. Instead, earlier instruments focused largely on a single aspect of functioning, such as psychosocial or physical functioning. Secondly, it was widely believed that children, particularly those of school age (i.e., latency), lacked the capacity to reflect on their own HRQoL. Historically, parents or other proxies (e.g., providers and teachers) were preferred raters.

Approaches to measurement of HRQoL

Over the past 15 years, there has been a burgeoning of pediatric HRQoL instruments, which have been used in clinical sub-populations, healthy children and epidemiologic surveys [3,4], and an increasing appreciation for the capacity of child raters to report on their own HRQoL.

Within the pediatric HSCT population, several studies have addressed the impact of HSCT on HRQoL. As recently reported [2], many of the initial studies employed generic HRQoL measures, such as the Pediatric Quality of Life (PedsQL™) 4.0 General Core Scales [5], the Child Health Questionnaire (CHQ) [6], the Child Health Ratings Inventories (CHRIs)-General Health Module (CHRIs-General) [7–9] and the Health Utilities Index 2/3 [10]. With the exception of the CHRIs-General, which was developed for use with children with chronic disease, the other instruments have been used successfully in healthy children as well as those with chronic conditions. Most of these generic measures are health profile measures, generating summary scores for each of the domains (or dimensions) of HRQoL,

including physical, emotional and role functioning. Some of the measures, notably the PedsQL and the CHQ, also provide scores for physical and psychosocial subscales; the PedsQL generates a total score of all 23 items. Scores are scaled from 0 to 100, in which higher scores reflect better HRQoL. In contrast, the Health Utilities Index 2/3 is a preference-based measure, generating utility weights that can be used in quality-adjusted survival or cost-effectiveness analyses. All of the instruments have rater-specific versions for child/adolescent self-report as well as a parent-proxy report. The PedsQL and the CHRIs-General also offer age-specific versions for younger children (5–12 years) and adolescents (13 years of age and over). The CHQ has a single self-report measure for children 8–18 years.

As the field of HRQoL was evolving, early studies of HRQoL were cross-sectional in design; more recently, longitudinal studies have been conducted to describe the HRQoL trajectory over the first 1–2 years following HSCT [11]. All of the measures listed above have demonstrated adequate measurement properties in either kind of study – cross-sectional or longitudinal – including responsiveness to change over time, a required characteristic of measures used in longitudinal analyses. In addition to our 2012 review, which was prepared as part of the NCI, NHLBI, Pediatric Blood and Marrow Transplant Consortium First International Conference on Late Effects after Pediatric Hematopoietic Cell Transplantation, this literature and descriptions of the measures are summarized in the 2008 systematic review by Clarke *et al.* [12] and the 2005 critical review of the literature by Tsimicalis *et al.* [13].

In addition to validated generic instruments, two other tools have been validated for use in the pediatric HSCT populations: the Behavioral, Affective and Somatic Experiences Scale, designed to assess aspects of HRQoL in patients undergoing active, intensive therapy (such as HSCT) [14–16], and the CHRIs-HSCT, the only HSCT-specific HRQoL instrument for children. The CHRIs-HSCT is a 10-item measure, yielding three domain scores (i.e., hassles, body image and worry/distress). The questions themselves ('item content') address specific aspects of the HSCT experience, as summarized in Table 1. The CHRIs-HSCT can be used with a generic, multidimensional HRQoL core measure, as a 'plug-in' module. The preliminary psychometric properties of the CHRIs-General and CHRIs-HSCT were described in a cross-sectional sample of 122 pediatric HSCT recipients aged 5–18 years and their parents [8], and then subsequently in three separate longitudinal evaluations [9,17].

The principal HSCT-specific instrument for adults to capture the acute HSCT experience is the Functional Assessment of Cancer Therapy–Bone Marrow Transplant (FACT–BMT) [18]. Huang *et al.* adapted the FACT–BMT for adult survivors of HSCT, which is referred to as the FACT–BMT Survivor scale [19]. Studies are underway to evaluate the performance of this instrument in survivors of pediatric HSCT.

While the availability of several generic and HSCT-specific measures has allowed researchers to overcome previous barriers to HRQoL investigation, in some sense, this proliferation of measures has hampered direct comparisons between studies.

The use of standardized measures can overcome this limitation. In this context, standardization refers to the use of the same measure across studies within the same population. Standardization within the population is best illustrated by the 2004 NIH Consensus Conference, which was convened to establish standardized criteria to advance clinical trials in chronic GVHD [20]. Chronic GVHD, a devastating complication of HSCT, has been found to be associated with altered HRQoL and physical performance, particularly among adults [21,22], as well as long-term survivors of HSCT [23], and pediatric recipients [24,25]. In addition to end organ evaluation metrics, the NIH criteria included recommendations for standardized HRQoL assessment tools for adults and children, calling for the use of both generic and transplant-specific measures [26]. The panel selected the ShortForm (SF)-36 [27] and FACT-BMT [18] for the adult population and the CHRIs (General and HSCT) and the Activity Scale for Kids [28], the latter of which assesses physical disability in children.

In the absence of standard measures across studies, the use of standardized scores (e.g., mean: 50 [standard deviation: 10]) and/or the use of a cutoff value (i.e., at risk cutoff) [4] facilitate interpretation of study findings. The 2011 report by Brice *et al.* [29] is an excellent example of the second approach (see accompanying editorial by Kline [30]). The 2012 study by Oberg *et al.*, reporting on the 2-year trajectory of HRQoL of 80 children cared for in a US-based transplant center, leveraged the availability of normative data from the PedsQL to compare HRQoL scores of HSCT recipients with age-based norms [31].

Inter-rater comparisons

The availability of instruments for both child and parent raters with parallel content has allowed researchers to explore levels of agreement between self and proxy ratings across a wide range of health states and age groups. Previous research on inter-rater comparisons was limited by the inclusion of different items for each rater, complicating the interpretation of the often limited to modest agreement observed between raters. In a 2008 review article by Upton *et al.*, the authors noted that there was limited information in published studies about the variables contributing to levels of parent-child (P-C) agreement [32], which represented an important gap in our current knowledge base. The authors provided a cogent summary of methodological reporting of inter-rater agreement to be used in future studies, including information about the reliability of the instrument in the sample, details about mode of administration for each rater and the setting of data collection and analyses of inter-rater concordance at both the individual and the group level [32].

Several factors inform rater selection and influence their reports. While the data suggest that many children are capable of providing self-report, there are subgroups that may not be capable, such as children who are too sick, too young or those who have a cognitive impairment as a result of the underlying disease and/or treatment. Proxy ratings are likely to be more informative than the data being missing altogether.

The perceptions of a proxy rater may differ from those of the child about him/herself in two distinct ways. First, the proxy rater may not have the same access to the information that the child might. For example, the parent proxy does not typically see the child engage in school

activities and forms his/her perceptions of the child's school functioning from various sources of information (e.g., discussions with teachers, the child's daily reports and periodic grade reports) that may be different from the information the child relies on to make his/her determination of school functioning. This is called information variance. One of the unique aspects of the acute HSCT period, stemming from the initial hospitalization and early recovery period, is that children are generally in protective isolation, not attending school or participating in age-appropriate activities with peers. Consequently, children and parents are thrust together, sharing the same routine and daily reality, much more than they would normally be if the child were in school.

In the clinical setting, however, information variance may also be manifested by differential access to and/or understanding of clinical events. Children may be less aware of the implications of a change in clinical status, particularly if that change is not associated with discrete symptoms or altered functioning.

The child and parent may weigh the available information differently. Parents may compare current functioning to prior functioning or anticipated future functioning, or compare one child's functioning with that of another sibling or friend. This is referred to as criterion variance. In a fascinating report by Davis *et al.*, 15 parent versus child pairs underwent cognitive interviewing, using the 'think aloud' technique as they completed a generic HRQoL instrument [33]. The qualitative analysis of these interviews, performed individually with each rater, revealed that the P-C discordance may be the result of different reasoning and response styles, rather than divergence in the interpretation of the individual items [33]. Both of these forms of variance may explain why reports from parents and children are not the same.

Several studies have explored P-C comparisons in ratings of the child's HRQoL, principally utilizing methods to characterize the extent of agreement, such as Pearson or inter-class correlations, percentage agreement or Bland-Altman plots [34]. Levels of agreement vary by study sample from poor to strong and appear to be affected by factors including health status (healthy versus ill population), severity of disease, child age, level of emotional distress of parent and/or child/adolescent, the particular aspect of HRQoL and, possibly, the instrument(s) used [32].

Establishing the link between the HSCT clinical course & HRQoL

Several authors have explored demographic and family factors associated with HRQoL scores, such as child age, race/ethnicity and family factors, including parental emotional functioning (EF) and family cohesion. Barrera *et al.* highlighted the importance of pretransplant family cohesion on subsequent HRQoL [35]. The role of parental EF and adjustment on children's HRQoL over time has also been described [9,35,36]. In contrast, few studies have identified the impact of baseline clinical characteristics on HRQoL or definitively established the link between the well-characterized clinical outcomes of HSCT, including organ toxicity, risk of infection and potential for acute and/or chronic GVHD, and HRQoL. This may be explained, at least in part, by the relative infrequency of clinical events, particularly in their more severe form (e.g., extensive chronic GVHD) in children.

Our group initially evaluated the association between physician-rated clinical severity and children's self-reported HRQoL in a cross-sectional study of 82 children [37], finding that HRQoL was lower for children with increased clinical severity. The authors later explored the relationship between discrete clinical outcomes and each of the domains of general and HSCT-specific HRQoL in a longitudinal evaluation of 160 parent-proxy raters of children's HRQoL [9], relying on pattern-mixture models to account for nonignorable missing data. Overall, the authors found stronger association between clinical events and HSCT-specific domains. Specifically, chronic GVHD was significantly associated with the 'hassles' domain (β : 27.5 [3.3]; $p < 0.001$) and the body image domain (β : 23.2 [6.2]; $p < 0.001$), but not significantly associated with generic HRQoL domains of physical, emotional or role functioning.

Subsequently, in a longitudinal study of 165 P-C pairs (children's age: 5–18 years), the authors found that parents' ratings of their children's physical functioning were more sensitive to grade of infection [38], as measured by trained research staff, using the Common Toxicity Criteria of Adverse Events version 3.0 [101]. Infections were categorized as absent, localized or systemic. Children's physical functioning scores were essentially identical for those in the absent or localized group, whereas those in the systemic infection group had physical functioning scores of approximately ten points lower than the others. In contrast, parent rating of the children's physical functioning was approximately 12 points lower for each successive severity level. The interaction of rater and infection grade was statistically significant ($p = 0.003$) (Figure 1). The authors do not know if parents and children were told different things about the clinical significance of localized infection in the setting of an immunocompromised state, or if they assigned a different meaning to that state on their own.

Based on our observation of rater-grade interaction, the authors then explored clinical factors that may explain differences between parent and child reports [36]. The authors created models to explain parent-minus-child differences for each domain of generic HRQoL (i.e., physical, emotional and role functioning) using the CHRIs-General, which was collected prior to transplant at day 45 and at 3, 6 and 12 months following HSCT. In addition to an overall model that took into account the full 12-month trajectory, the authors also created separate models for clinical variables, pertaining to specific time points or populations (e.g., acute GVHD in recipients of allogeneic transplant only over 3 months). The authors again utilized pattern mixture models to account for nonignorable missing data, this time creating strata based on the reason for a missed assessment [39].

The results were striking. Overall, parents rated children's HRQoL lower than children did. In each of the models, child age and parent EF at baseline were associated with P-C differences. Duration of illness was significantly associated with rater differences in role and physical functioning, but not in children's EF. Higher baseline child age was associated with a better agreement (as the difference in P-C gets closer to zero). Similarly, higher baseline parent EF was associated with more agreement between parent and child. Emotional and physical functioning move from greater disagreement to greater agreement over time; this pattern is attenuated with role functioning (Figure 2).

However, in separate models by clinical events, the differences between P–C reports was even more pronounced. Clinical complications had greater impact on parental ratings than child ratings across all domains, increasing adjusted P–C differences. To illustrate this, for each clinical complication, parental EF was set at the mean baseline value, child age was set at the mean value of 10.5 years and log duration of illness was set at 1 year. Among children with severe (i.e., grade 3 or 4) acute GVHD, P–C differences in physical functioning were 22 points further apart (95% CI: –39 to –4; $p = 0.015$) further apart when compared with children without acute GVHD. Similarly, P–C differences in EF were eight points further apart (95% CI: –15 to –1; $p = 0.034$) further apart when the child had extensive chronic GVHD (Figure 3) as compared with limited chronic GVHD or none. Similarly, for role functioning, systemic infection and end-organ toxicity produced differences of 14 (95% CI: –22 to –6; $p = 0.001$) and 21 points (95% CI: –40 to –1; $p = 0.037$), respectively. One might imagine that divergence of P–C perceptions about the child’s HRQoL could be an additional source of stress for both raters, particularly in the setting of severe clinical complications.

These results highlight the complexity of P–C ratings. They suggest, as Upton proposed, that qualitative methods be employed to understand more fully “the processes through which parents and children make decisions when rating child HRQoL” [32].

Clinical applications of HRQoL information

HRQoL information has many applications in the clinical setting. It can help the patient and provider monitor the effects of the underlying disease and its treatment, and spur a discussion that may help divulge areas of importance to the individual patient and guide clinical decision-making.

Although routine HRQoL assessment has been used in adult-based care far more often than pediatric-based care, the overt benefit of this assessment in changing outcomes has been mixed. Studies have shown that while HRQoL assessment may facilitate communication between patients and providers [40,41], it has not been shown to result in significant changes in clinical management, improvement in patient satisfaction or changes in HRQoL [40–42].

Providers often report not understanding what the HRQoL scores mean or what to do with the information. Several studies have pointed to the need for management suggestions to accompany HRQoL information in the clinical setting. Moreover, formal evaluation of presentation formats is needed to determine ease and accuracy of interpretation. Several Internet-based HRQoL assessment systems now include brief reports for patients and providers.

The other fear providers raise about the incorporation of HRQoL assessments in clinical practice is increased encounter time. Engelen *et al.* recently reported the results of a sequential cohort study of 193 children, who were enrolled shortly after the completion of treatment for cancer (or status post-HSCT) [43]. The study was designed to evaluate the impact of giving patient HRQoL scores to providers on patient–provider communication about HRQoL domains and the identification of HRQoL problems. Strikingly, the

intervention did result in increased discussion of EF and psychosocial functioning, while not increasing the duration of the visit. However, the intervention did not result in increased referrals, change satisfaction levels or lead to an overall improvement in HRQoL [43]. This is one of the first formal intervention studies in pediatric oncology/ transplantation. Future studies, conducted during the treatment phase, are needed to evaluate if availability of HRQoL scores can alter outcomes during active treatment.

Expert commentary & five-year view

It is exciting to consider what will unfold over the next 5 years in the field of HRQoL assessment for pediatric HSCT recipients. The availability of validated instruments, the use of electronic data capture systems and the gradual incorporation of HRQoL scores into clinical assessment all bode well for the future.

Several additional factors will undoubtedly shape the future of HRQoL assessment. The first is the emerging emphasis in the USA on ‘patient-centeredness,’ as evidenced by the 2010 creation of the Patient-Centered Outcomes Institute, a nonprofit corporation via Public Law 111–148. With increased patient-centeredness, the dialog could be expanded to include what is important to the patient (and his/her family), including those aspect of HRQoL threatened by disease and/or treatment, and the identification of issues that need to be addressed to enhance recovery and optimize functioning. In the arena of HRQoL assessment, one might envision expanding the standard assessment to a more individualized assessment, as proposed by Frick *et al.* with the Schedule for the Evaluation of Individual Quality of Life [44]. In this measurement approach, previously used with adults prior to autologous transplant, the individual nominates the five most important domains of quality of life without direct cueing to health or treatment. This information would elucidate for providers what is really important to the individual patient and may enhance adjustment and, ultimately, recovery.

Another potential ‘game changer’ is the Patient-Reported Outcomes Measurement Information System (PROMIS[®]), a trans-NIH initiative established in 2004, which has resulted in the creation of rich item banks in multiple areas of HRQoL for both adults and children [102]. Item banks can be administered in short forms (4–10 items) or through computer adaptive testing (with 3–7 items), which are available for parent-proxy report or child self-report. In addition to domains of physical, mental and social well-being, PROMIS instruments are also available to assess domains such as pain (and pain interference), fatigue and sexuality, all of which are commonly altered during or following cancer treatment. A 10-item global health scale has been created to assess adult quality of life, which has successfully been mapped to the EuroQoL-5 Dimension, a preference-based instrument, yielding utility weights that can be used in comparative–effectiveness studies [45,46]. A version of this scale is currently under development for pediatric use [Tucker C, Pers. Comm.]. The brevity, yet comprehensiveness, of the global scales may allow for more frequent assessment with minimal responder burden and the ability to target further measurement based on scoring patterns on global items. This, too, will reduce burden for people who do not need further assessment, but will ensure that among those who do, more in-depth probing is undertaken.

While clinical validation studies of PROMIS scales in HSCT populations are still underway, the public availability of PROMIS scales, common metrics and multiple modes of administration address many of the measurement gaps in the field of HRQoL assessment. PROMIS tools can be used alone or in combination with HRQoL legacy tools to expand existing constructs. The availability of PROMIS scales will facilitate the inclusion of HRQoL end points into clinical trials through groups such as the Children's Oncology Group and the Pediatric Blood and Marrow Transplant Consortium [47].

Despite the opportunities, the field of pediatric HRQoL assessment also faces several challenges that will need to be addressed over the next 5 years. First, we must strive to expand the capture of family members that we routinely assess to include fathers as well as mothers, languages other than English or Spanish, various education levels and different racial, ethnic and disease groups; the latter is reflective of the expanding indications for HSCT. Second, further research is needed to understand the impact of emerging trends in care (e.g., progenitor sources, reduced intensity conditioning regimens, approach to acute GVHD prevention) on HRQoL. In addressing both of these challenges, we must ensure that the studies are adequately statistically powered to evaluate the HRQoL of each of these personal and clinical factors. Third, we must also expand the time trajectory beyond the first year to understand the long-term HRQoL implications of HSCT on survivors, not restricting this inquiry to the subset that might continue to receive HSCT care in the HSCT center. Remote data capture, using Internet-based scales will facilitate this enormously. Related topics include understanding the extent to which the first year is clinical and HRQoL course is predictive of later functioning and identifying the factors that influence longer term HRQoL. Fourth, further research is needed to guide researchers and clinicians about how to approach HRQoL measurement as children 'grow out' of pediatric instruments to adult-based scales. Finally, we need to address the best way to capture the full experience of survivorship within a medical focus and within a 'life' focus, using qualitative approaches, as needed, to supplement the information gleaned from questionnaires.

HRQoL assessment after pediatric HSCT, like HSCT itself, has undergone considerable changes over the past 20 years. We have moved from fledgling instrumentation and small cross-sectional studies to robust measurement with validated instruments and large multicenter studies. Researchers have called for standardization of reporting studies to facilitate comparisons across them, as well as the use of appropriate statistical methods to handle thorny topics, such as nonignorable missing data, multiple outcomes, dual raters and myriad clinical complications.

In closing, clarity of purpose is needed in future HRQoL research. Over the past two decades, we have demonstrated that we can measure HRQoL following HSCT – often from children and adolescents themselves. Going forward, we must ask ourselves, what are we trying to understand about this complex phenomenon? What aspects must be obtained through patient (or proxy report) and what can be answered elsewhere? How can we best communicate HRQoL results so that they accurately reflect the experience of the patient (and family) receiving care and the providers who deliver it?

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Key issues

- Pediatric health-related quality of life (HRQoL) assessment has greatly increased in the past 15 years in a variety of populations, including children undergoing hematopoietic stem cell transplant (HSCT).
- Few studies report on the relationship between the well-characterized clinical outcomes of HSCT and parent or child ratings of pediatric HRQoL in general and HSCT-specific domains.
- Inter-rater comparisons reveal differences in the perceptions of child and parent proxy raters that may affect their evaluation of pediatric HRQoL.
- Research has demonstrated that parent/child agreement is influenced by child age, time post-transplant, parent emotional functioning and the presence of clinical complications.
- Clinical complications resulting from pediatric HSCT have a much greater influence on parent-proxy ratings of the child's HRQoL than the child's ratings, reflecting potential variability in access to and understanding of clinical information.
- Although HRQoL assessment may strengthen the patient-provider relationship, it has not been definitively shown to promote significant improvement in clinical management, patient satisfaction or patient HRQoL. Furthermore, providers report not understanding what to do with HRQoL scores and increased encounter time to administer measures as barriers.
- The current 'patient-centered' climate has increased emphasis on the importance of collecting and utilizing HRQoL assessments, highlighted by efforts to provide individualized assessments and create standardized, lower-burden measurement tools.
- Many challenges still need to be addressed in pediatric HRQoL assessment, particularly the longitudinal interplay between changing trends in clinical care and HRQoL ratings of children and parent proxies.

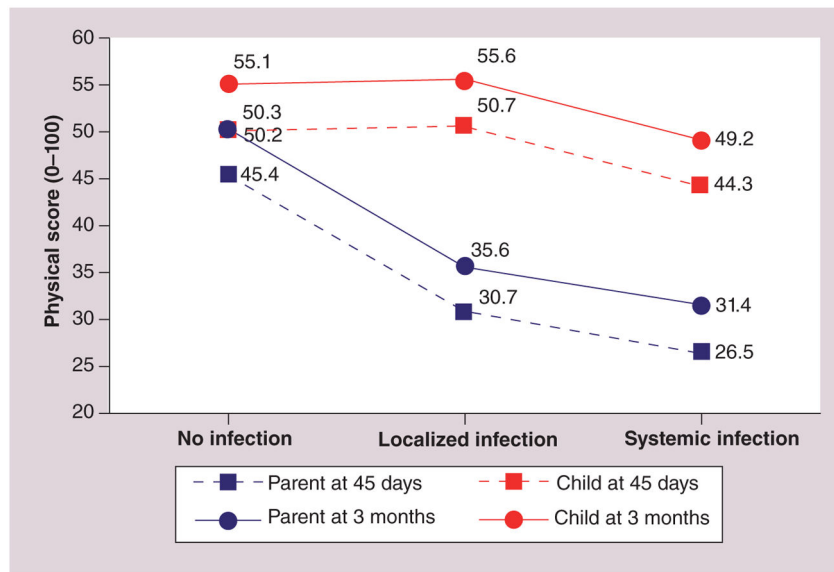


Figure 1. Child Health Ratings Inventories physical functioning scores for child and parent rater by degree of infection severity.

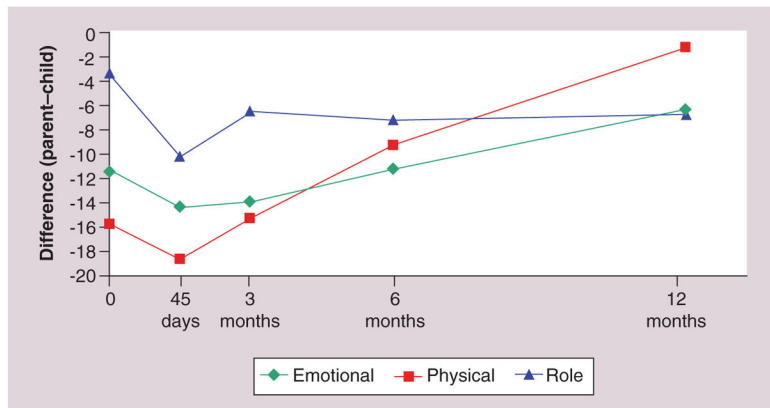


Figure 2.
Parent-child differences across health-related quality of life domains and time.

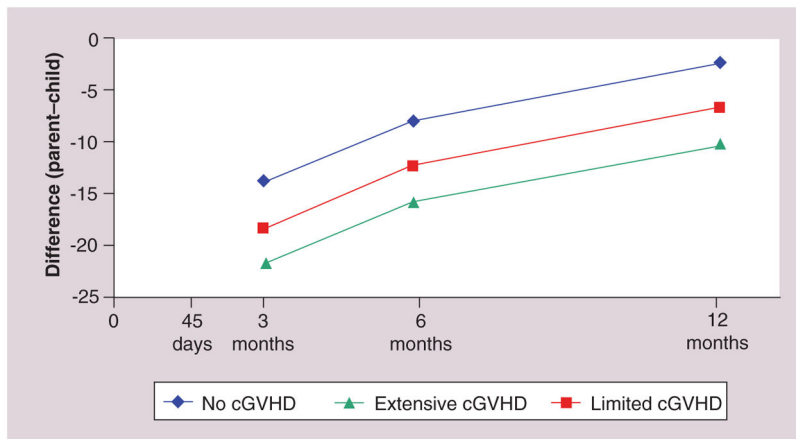


Figure 3. Parent-child differences in emotional functioning by degree of chronic graft-versus-host disease
cGVHD: Chronic graft-versus-host disease.

Table 1

Item content of Child Health Ratings Inventories-hematopoietic stem cell transplantation module.

Domain	Item concept
Body image	Having puffy cheeks and a puffy body because of medicines taken Having lost hair
Hassles	Having to wear a mask in public Avoiding foods that should not be eaten because of the transplant Taking medicine the way it is supposed to be taken Explaining the transplant to friends
Distress	Worrying about having to go back to the hospital Worrying about getting an infection Worrying about the disease coming back Time spent thinking about the transplant