PRE- TO-POST-TRANSPLANTATION PSYCHOSOCIAL FUNCTIONING, HEALTH-RELATED QUALITY OF LIFE, AND NONADHERENCE IN PEDIATRIC PATIENTS

by

CYD KUMIKO EATON

(Under the Direction of Ronald L. Blount)

ABSTRACT

The goal of this study was to investigate differences in psychosocial functioning that occurred from pre-to-post transplantation and to identify pre-transplant psychosocial predictors of post-transplant health-related quality of life (HRQOL) and medication nonadherence in a sample of pediatric patients (ages 0-21 years) awaiting and eventually receiving a solid organ transplant. Patient, parent, and family factors were evaluated prior to transplantation at baseline (Time 1). Approximately 6 months after patients received a solid organ transplant, study measures were re-administered (Time 2). The final sample included 55 parents who completed data collection at both time points. Data were analyzed to 1) examine pre-to-post-transplant differences in patient health-related quality of life (HRQOL) and patient, parent, and family psychosocial functioning; and 2) identify pre-transplant psychosocial predictors of post-transplant HRQOL and medication nonadherence. Due to the large patient age range and the significant, inverse relationships between patients' ages at Time 1 and HRQOL at Time 2, a post-hoc investigation was conducted to further analyze how patients' ages potentially influenced HRQOL after transplantation. Results indicated that patients' HRQOL improved and parents' psychological distress decreased from pre-to-post-transplantation. Pre-transplant

HRQOL emerged as the best predictor of post-transplant HRQOL for patients, with higher pre-transplant HRQOL predicting higher post-transplant HRQOL. Measurement issues prevented the valid assessment and analysis of medication nonadherence. The post-hoc investigation suggested that patients' ages at the time of the pre-transplant evaluation related to post-transplant HRQOL in several different ways. Results offer information that providers may use as psychoeducation for families during the pre-transplant evaluation. Results further suggest that there is clinical utility in evaluating patients' HRQOL at the pre-transplant evaluation to identify areas of psychosocial functioning that may benefit from targeted intervention to support better post-transplant HRQOL and adjustment. Lastly, patients' ages at the time of the pre-transplant evaluation may differentially influence post-transplant levels of HRQOL.

INDEX WORDS: Pediatric, transplant, health-related quality of life, psychosocial functioning, nonadherence, patients, parents, families

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by

CYD KUMIKO EATON

BS, University of Florida, 2008

MS, University of Georgia, 2014

A Dissertation Submitted to the Graduate Faculty of The University of Georgia in Partial Fulfillment of the Requirements for the Degree

DOCTOR OF PHILOSOPHY

ATHENS, GEORGIA

2017

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CYD KUMIKO EATON

Major Professor:	Ronald L. Blount
Committee:	Cynthia Suveg
	Anne Shaffer

Electronic Version Approved:

Suzanne Barbour
Dean of the Graduate School
The University of Georgia
August 2017

DEDICATION

My dissertation is dedicated to the families who generously volunteered their time to participate in my investigation. I am grateful for their investment in supporting scholarly work that has the long-term goal of improving quality of life for future children and families going through the transplant process. My dissertation is also dedicated to my mother, Doreen Yamamoto, and my brother, Sam Eaton, for their unwavering support and encouragement as I made my way through graduate school.

ACKNOWLEDGEMENTS

My investigation and dissertation would not have happened without the mentorship of my research advisor, Ronald L. Blount, Ph.D. With Dr. Blount's guidance and support, I have exceeded the expectations I set for myself when I began graduate school in 2011 and grown as a clinical scientist and an individual. I also want to thank the graduate and undergraduate members, past and present, of the Pediatric Psychology Lab who contributed to my investigation.

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CHAPTER 1

INTRODUCTION

In the United States, approximately 1,880 pediatric patients are currently wait-listed for solid organ transplantation (United Network for Organ Sharing, 2015). The majority of patients referred for transplantation have a congenital disorder or suffered an acute illness that resulted in end-stage organ disease. In the case of end-stage organ disease, transplantation is often considered the optimal treatment for enhancing patients' physical health and overall health-related quality of life (HRQOL), which encompasses physical, emotional, social, and academic functioning. Post-transplantation outcomes have improved over the years due to medical advances that have led to increased organ graft survival rates for pediatric patients (Organ Procurement and Transplantation Network and Scientific Registry of Transplant Recipients, 2012). Many pediatric patients survive into adolescence and young adulthood with better HRQOL (LaRosa, Baluarte, & Meyers, 2011). Transplantation is considered a trade from having a life threatening disease to having a life-long chronic health condition, which requires patients to take daily medications to maintain healthy organ function. There are significant challenges that patients and families may face during the transplantation process, such as adjusting to a new medication regimen, attending frequent medical appointments, and potentially missing academic, social, and professional activities. Facilitating a smooth transition from pre- to post-transplantation may help patients and their families cope with these challenges and enhance the benefits of transplantation.

Before transplantation occurs, patients and their families typically undergo a pre-transplant evaluation, which involves meeting with multidisciplinary healthcare providers, including psychologists, at a transplant center. The goal of the psychological evaluation is to provide families with more information about the psychosocial and behavioral aspects of transplantation and assess and identify stressors and barriers to successful transplantation (Shellmer, Brosig, & Wray, 2014). Because little longitudinal research has been conducted to follow pediatric patients from before to after transplantation, there is a lack of empirical data to guide pre-transplant evaluations of psychological factors that relate to important post-transplant, psychosocial outcomes, including HRQOL and nonadherence. There is a need to identify modifiable risk factors present in patients and families (e.g., emotional stress, barriers to adherence) that are associated with these post-transplant outcomes. If these factors are identified in the pre-transplant period, providers will be able to recommend early intervention to begin addressing these issues before moving into the post-transplant period. Earlier identification of risk factors would help support the transition into the post-transplant phase and, ideally, enhance post-transplant, psychosocial outcomes for patients and families. Prior research has been conducted to evaluate a standard, pre-transplant evaluation tool used to identify potential risk factors in pediatric transplant candidates (Fisher et al., 2011; Fung & Shaw, 2007). To date, no data have been published relating this tool to actual pre- or post-transplant outcomes.

A biopsychosocial model provides an appropriate framework to conceptualize how psychosocial risk and protective factors in the pre-transplant phase will relate to and predict outcomes in the post-transplant phase. The biopsychosocial model is grounded in developmental theory of child psychopathology (e.g., Dodge & Pettit, 2003) positing that biological, socioemotional, and environmental factors reciprocally influence the development of

maladaptive outcomes over time. Adaptations of the biopsychosocial model have been applied to pediatric psychology research with different pediatric medical populations to determine how these factors relate to issues specific to children with health needs (e.g., feeding problems, diabetes self-care, early onset asthma; Berlin, Davies, Lobato, & Silverman, 2009; Berz et al., 2007; Holmes et al., 2006). For patients and families awaiting solid organ transplantation, biopsychosocial variables present before transplantation (e.g., socioemotional functioning, time since diagnosis) may be related to HRQOL and nonadherence after transplantation. To identify risk and protective factors associated with these important post-transplant outcomes in pediatric transplant recipients, the current study's primary goal was to isolate pre-transplant psychological, social, medical, and environmental factors that relate to post-transplant HRQOL and nonadherence. To meet this goal, prior research from the pre- and post-transplant periods will be reviewed. Findings from the literature review will guide the identification of potential risk and protective factors related to the primary outcomes of interest for patients and families going through the transplantation process.

Socioemotional Functioning

The pre-transplant period can be emotionally stressful for patients and families. Emotional stress may be related to the decision to move forward with transplantation and potential disruption to the family unit (Shellmer et al., 2014), in addition to patients' declining physical health while awaiting transplantation (Aldridge, 2008). Pediatric patients, specifically, appear to have lower psychological functioning before, compared to after, transplantation (DeMaso, Kelley, Bastardi, O'Brien, & Blume, 2004; Wray & Radley-Smith, 2004; Wray & Radley-Smith, 2007). Pediatric patients awaiting transplantation have also demonstrated higher depression symptoms compared to other children with chronic illnesses (Wray & Radley-Smith,

2004). These findings suggest that the pre-transplant period is an emotionally stressful time for pediatric patients.

Similar to patients, parents of children awaiting transplantation have also endorsed higher levels of psychological distress compared to parents of healthy children (Wray & Radley-Smith, 2007). Results from qualitative studies suggest that parents experience significant emotional distress, anxiety, and depression in the pre-transplant period (Aldridge, 2008). For mothers and fathers of children awaiting kidney transplantation, higher levels of depressive symptoms or parenting stress were related to greater difficulty coping effectively with stress (Zelikovsky, Schast, & Jean-Francois, 2007). Consistent with patient findings, parents appear to experience significantly more emotional stress before transplantation, which may be related to poor abilities to cope with these feelings. Data from the pre-transplant period on pediatric patients' psychological functioning and that of their parents are limited by single organ group representation and use of unstandardized measures.

Post-transplant research tends to suggest that pediatric solid organ transplant recipients and parents continue to experience increased psychosocial distress, including high levels of post-traumatic stress (Farley et al., 2007; Mintzer et al., 2005; Young et al., 2003), anxiety, depression, and psychological distress symptoms (e.g., Berney-Martinet et al., 2009; Fredericks, Lopez, Magee, Shieck, & Opipari-Arrigan, 2007; Gritti et al., 2005; Penkower et al., 2003). One study contrarily indicated no differences in psychosocial adjustment compared to norms (Qvist et al., 2004), though variability in results may be due to differences in sample sizes, organ groups represented, or child age. In light of post-transplant findings that pediatric transplant recipients and their parents continue to experience greater psychological distress, psychoeducation and training on use of healthy coping skills may support improvements in patient and parent

emotional functioning during the waiting period and after transplantation. Information on how these variables change from pre- to post-transplant in a large, diverse sample is needed to inform these clinical recommendations.

The impact of the stress and uncertainty associated with transplantation on family functioning is another factor to consider as patients move from the pre-to-post-transplantation phase. Overall, family functioning seems to improve within a year of pediatric liver transplantation (Taylor, Franck, Gibson, & Dhawan, 2005). Despite these improvements, families of children with liver, kidney, heart, or bone marrow transplants continued to endorse a significant impact of the child's health condition on the family that actually increases 1- and 6-months after transplantation (Rodrigue et al., 1997). By four years post-transplantation, parents of pediatric liver transplant recipients reported significantly less impact of the illness on the family compared to the normative sample of parents with chronically ill children (DeBolt, Stewart, Kennard, Petrik, & Andrews, 1995). By two years post-transplantation, families of pediatric liver transplant recipients demonstrated levels of family dysfunction (e.g., issues with problem-solving, communicating, regulating emotions and behaviors) that were below the established threshold for family dysfunction (i.e., the sample of families of pediatric liver transplant recipients were not demonstrating family dysfunction; Alonso et al., 2008). Overall, the literature suggests that family functioning is affected by the transplantation process, particularly before and immediately after transplantation. Over time, the impact of transplantation on family functioning seems to decrease. The post-transplant period may signify an eventual return to relative normalcy after significant uncertainty and stress related to the child's health, resulting in better family functioning. Additional, updated data with larger sample sizes is needed to clarify how family functioning changes during the transplantation process.

HRQOL

As expected for seriously ill individuals, pediatric patients with end-stage organ disease have significantly lower HRQOL compared to healthy and chronically ill norms (Varni, Limbers, & Burwinkle, 2007) and transplanted patients (Goldstein et al., 2009) across domains of HRQOL (i.e., physical, school, social, emotional). Lower physical HRQOL indicates difficulty participating in physical activities (e.g., running) and activities of daily living (e.g., doing chores) at similar levels to peers, which is typical for children with chronic illness (Pinquart & Teubert, 2011). Lower HRQOL related to school is likely related to a combination of missing school due to illness (Weil, Rodgers, & Rubovits, 2006) and risk for lower cognitive functioning and academic skills observed in patients awaiting transplantation (Reed-Knight, Lee, Cousins, & Mee, 2015). Consistent with the tendency for pediatric patients with end-stage organ disease to miss school due to illness, this population also may miss opportunities to socialize with same-aged peers, resulting in impaired social HRQOL (e.g., unable to keep up when playing with other children; Annunziato, Jerson, Seidel, & Glenwick, 2012). Lower emotional HRQOL (e.g., feeling sad, scared, or angry) is likely related to patients experiencing significant psychological distress while awaiting transplantation (e.g., DeMaso et al., 2004).

Younger age at the time of transplantation appears to be associated with better post-transplant physical HRQOL (Taylor, Franck, Gibson, Donaldson, & Dhawan, 2009). In children awaiting transplantation, higher levels of patient and parent anxiety and depression symptoms related to better physical, psychosocial, and overall HRQOL (Eaton et al., 2015), highlighting the potential importance of assessing these factors across the family unit. The limited data from the pre-transplant phase suggest that patient demographic factors or patient and parent psychological

functioning variables may serve as risk or protective factors related to patient HRQOL in the pre- and possibly post-transplant phases.

Although HRQOL is generally thought to improve after transplantation (e.g., Barrera, Boyd Pringle, Sumbler, Saunders, 2000; Cole et al., 2004; Dew et al., 1997), pediatric transplant recipients continue to experience lower HRQOL (Anthony, BarZiv, & Ng, 2010; Fredericks et al., 2008; Limbers et al., 2011; Qvist et al., 2004), even up to 10 years after transplantation (Ng et al., 2012). Despite the benefits of transplantation, post-transplantation risk for poorer psychosocial, academic, and physical functioning remains for some patients (Anthony et al., 2010). Additionally, post-transplant HRQOL appears to remain stable over an 18-month period of time for adolescent transplant recipients (Devine, Reed-Knight, Simons, Mee, & Blount, 2010), suggesting that deficits in HRQOL will continue without targeted intervention.

Post-transplant investigations have identified possible demographic, medical, and psychosocial factors related to lower HRQOL in pediatric transplant recipients. In adolescent transplant recipients, for example, higher baseline HRQOL, parental income, and medication adherence, lower rates of rescheduled clinic appointments and family conflict, and presence of a rejection episode were identified as factors predicting HRQOL over 18-months (Devine et al., 2011). Also for adolescent transplant recipients, greater parental perceived need for mental health services was inversely correlated with patient HRQOL on several domains related to patient, parent, and family functioning (Reed-Knight et al., 2013). In pediatric liver transplant recipients, a number of demographic and medical factors (e.g., age, race, number of hospitalizations, parental education level) were related to better HRQOL (Bucuvalas et al., 2003). Overall, pre- and post-transplant findings suggest potential factors that, if measured in the pre-transplant phase, may predict patient HRQOL after transplantation.

Medication Nonadherence

Identifying risk and protective factors related to nonadherence is of particular interest for pediatric patients awaiting and eventually receiving solid organ transplants. Transplant recipients must take daily medications and attend regular clinic visits to ensure the continued health of the transplanted organ, and ultimately, the recipient's physical wellbeing. Most, though not all, pediatric patients with end-stage organ disease have taken daily medications for an extended period of time. Before receiving a solid organ transplant, medication regimens tend to be less strict with regard to timing of administration. In contrast, immediately after receiving a transplant, patients must begin taking anti-rejection medications exactly 12 hour apart every day. This medication regimen will continue for the rest of patients' lives to prevent organ rejection.

Although providers stress the importance of this post-transplant adjustment to how patients take medications, approximately 43% of pediatric transplant recipients are nonadherent to their medication regimens (Dobbels et al., 2010). Nonadherence is a leading cause of poor post-transplant medical outcomes, including organ rejection, hospitalization, and death, for pediatric transplant recipients (Fredericks et al., 2007). In adolescent transplant recipients, medication adherence demonstrated stability over an 18-month period of time when measured via multiple methods (i.e., self-report, serum immunosuppressant levels, categorization system; Loiselle et al., 2015), suggesting that, in the absence of intervention, nonadherence behavior and related medical consequences will continue.

Isolating psychosocial risk and protective factors present before transplantation would help detect patients at risk for post-transplant nonadherence. Identified risk and protective factors in the pre-transplant period could guide efforts to address individual factors that would likely be amenable to intervention to curtail high nonadherence rates in the post-transplant period. For

example, results from a study of adult transplant recipients demonstrated that pre-transplant medication nonadherence, lower social support, higher educational level, and lower conscientiousness predicted greater post-transplant nonadherence (Dobbels et al., 2009). Another study of pre-to-post-transplant outcomes in adult renal transplant recipients found that a pre-transplant history of nonadherence was related to more post-transplant nonadherence (Douglas, Blixen, & Bartucci, 1996). In adult heart transplant recipients, individuals with greater pre-transplant psychological impairment and lower pre-transplant emotional, family, or social support demonstrated significantly higher post-transplant mortality, primarily associated with medical noncompliance (Favaloro et al., 1999). Another study similarly demonstrated that adult heart transplant recipients with a history of substance abuse and greater psychosocial risk had increased risk of post-transplant medical nonadherence and mortality (Shapiro et al., 1995).

Although adult literature suggests pre-transplant nonadherence and psychosocial problems are risk factors for post-transplant nonadherence to medications and subsequent mortality, little pediatric research has been conducted to replicate these findings or examine other potential predictors. Results of a study of pediatric heart transplant recipients suggested that greater pre-transplant "parental psychosocial risk," as determined by an unstandardized evaluation by a psychiatrist and social worker, was associated with greater risk of sub-therapeutic immunosuppressant trough levels and rejection episodes, which may reflect medication nonadherence behavior (Stone et al., 2006). These results are limited by use of an unstandardized categorization method used to determine "parental psychosocial risk," which further emphasizes the need for more rigorous investigations of pre-transplant factors related to post-transplant nonadherence in pediatric transplant recipients.

Pediatric research conducted in the post-transplant period has identified malleable psychological variables related to nonadherence. These findings may guide researchers in identifying pre-transplant variables that predict poorer nonadherence in the post-transplant period. For example, post-transplant research suggests that higher levels of adolescent internalizing symptoms and behavior problems, parent stress, and dysfunctional parent-child interactions, and lower levels of family cohesion relate to greater nonadherence (Fredericks et al., 2007; Gerson, Furth, Neu, & Fivush, 2004; Maikranz, Steele, Dreyer, Stratman, & Bovaird, 2007; McCormick King et al., 2014). Greater levels of nonadherence have also been shown to relate to lower levels of HRQOL (Fredericks et al., 2007), suggesting a potentially bidirectional relationship between these two important aspects of functioning for pediatric transplant recipients.

Barriers to adherence have also been shown to predict medication nonadherence, organ rejection, infections, and death (Eaton et al., 2015; Simons, McCormick, Devine, & Blount, 2010). Barriers to adherence also represent a potential mechanism in the relationship between patient emotional functioning (e.g., depression, anxiety, post-traumatic stress symptoms) and medication nonadherence (McCormick King et al., 2014). Since post-transplant barriers have been shown to be stable over an 18-month period of time in adolescent transplant recipients (Lee et al., 2014; Simons et al., 2010), inverse relationships between barriers and nonadherence will likely continue without targeted intervention. An investigation of how pre-transplant barriers to adherence relate to post-transplant medication nonadherence may inform efforts to problem-solve around patients' obstacles before moving into the post-transplant phase.

The Current Study

Research conducted in the pre- and post-transplantation phases has been informative about relationships between psychosocial functioning, nonadherence and HRQOL. However, most pediatric research investigations have been limited to examining these factors in either the pre- or the post-transplantation phase rather than determining potential differences from before to after transplantation. Fundamental questions remain about relationships between the pre- and post-transplant phases, including: 1) What differences in patient HRQOL and patient or parent psychosocial functioning occur between the two phases?; and 2) What pre-transplantation variables predict post-transplantation HRQOL and nonadherence for patients?

The current study was developed to answer these questions. The overall goals of the study were to quantify pre-to-post-transplant differences in patient HRQOL and patient, parent, and family psychosocial functioning and to determine pre-transplant risk and protective factors to guide assessment and intervention efforts to support better post-transplant outcomes for pediatric patients and their families. The primary post-transplant outcomes of interest were patient HRQOL and medication nonadherence. Given evidence of relationships with HRQOL and nonadherence, the following variables were also examined: patient and parent psychological functioning, parental barriers to adherence, and the impact of the patient's health condition on their family.

Based on the literature review, the following hypotheses were made regarding pre- to post-transplant changes: 1) patient HRQOL will improve; 2) patient and parent psychological distress will decrease; and 3) the impact of the patient's health condition on the family will increase. For predicting post-transplant outcomes, it was hypothesized that greater psychological distress, barriers to adherence, and impact of the patient's health condition on the family at Time

1 would predict greater nonadherence and poorer HRQOL at Time 2. Baseline HRQOL and medication nonadherence were hypothesized to be positively related to post-transplant HRQOL and nonadherence, respectively.

CHAPTER 2

Method

Participants

Participants included parents/legal guardians of any pediatric patient under 21 years of age who presented for their child's pre-transplant evaluation (Time 1) at Children's Healthcare of Atlanta, Egleston. The patient must have subsequently received a solid organ transplant to be eligible for follow-up data collection at 6 months post-transplantation (Time 2). Figure 1 presents a consort diagram of current patients who progressed from Time 1 to Time 2, with attrition data. There were 123 parents approached to enroll in the study at their child's pre-transplant evaluation. Of these parents, eight declined to enroll (see Comparison of parents who enrolled versus declined section). There were 115 parents enrolled in the study at Time 1. Of these families, six were excluded due to not returning measures, for a total of 109 complete datasets at Time 1. The average age of patients at Time 1 was 8.61 (*SD* = 6.37; range = 0-20.44). Of these patients, 47 patients were evaluated for a kidney transplant, 33 for a liver transplant, and 29 for a heart transplant. The average number of medications taken by patients at Time 1 was 6.72 (*SD* = 3.54; range = 1-18). See Table 1 for more details on enrolled participants at Time 1.

For patients who progressed to 6-months post-transplantation (Time 2), 55 parents completed data collection. Of patients who progressed to Time 2, one family declined to complete any measures because of lack of interest in spending time completing measures, two families did not complete measures due to loss of contact, and one patient died following transplantation. The average age of patients at Time 2 was 9.67 (*SD* = 6.29; range = .69-21.44).

Of these patients, 24 received a kidney transplant, 16 received a heart transplant, and 15 received a liver transplant. The average number of medications taken by patients in the 6-month post-transplant phase was 7.74 (*SD* = 2.94; range = 3-15). Patients in the final sample waited an average of 6.22 months (*SD* = 5.37) after their initial evaluation until they received their transplant. After transplantation, an average of 6.17 months (*SD* = .68) passed until parents completed the Time 2 measures. See Table 2 for demographic details on patients whose parents completed data collection at Time 2.

Comparison of parents who enrolled versus declined. At baseline recruitment, eight families declined to participate due to lack of interest in being part of the study. These eight families were compared to the 109 families who completed data collection at Time 1 on the patient's age, gender, race, and organ evaluation type, parental education level, and annual family income. There were significantly higher numbers of non-Caucasian children in the refusal group compared to the enrolled group at Time 1 ($\chi^2 = 4.72$, $p = .03$). There were no other significant differences between families who chose to participate in the study versus those who declined at baseline. The eight families who refused to participate were also compared to the 55 families who completed Time 2 data collection. There continued to be a significantly higher number of non-Caucasian children in the refusal group compared to the enrolled group at Time 2 ($\chi^2 = 6.43$, $p = .01$). No other demographic differences were found between these groups.

Procedures

This study was part of a larger investigation that has full Institutional Review Board approval from both participating institutions. All participants were recruited from a pediatric transplant center in the Southeastern United States. Although children and adolescents ages 8

years and older were invited to participate, only parent data were considered in the current study. Exclusion criteria for parents included being non-English speaking.

Pre-transplantation (Time 1). Prior to enrollment, trained research assistants approached families in the clinic room while attending the patient's pre-transplant evaluation. The research assistant introduced the study, answered any questions the parent had, and invited the parent to enroll. Parents were explicitly told that participating in the study was completely voluntary and confidential and did not impact the evaluation outcome in any way. Before completing any measures, parents provided written informed consent and Health Insurance Portability and Accountability Act (HIPAA) release. After consent and HIPAA release were obtained, parents completed Time 1 measures. Upon completing all Time 1 measures, participants were each given a $10 retail gift card as compensation for their time.

Post-transplantation (Time 2). After the pre-transplant evaluation was completed, a trained research assistant monitored the patient's transplantation status to determine if and when the patient was listed for a transplant. Once listed, the research assistant monitored the medical record to determine when the patient was actually transplanted. Once transplanted, a research assistant followed up with the parent approximately 6 months from the date of transplantation to complete the Time 2 measures. Parents were typically approached in the clinic room during the patient's outpatient appointment to complete Time 2 measures. If families were not scheduled for an appointment within the 6-month post-transplant time frame, they were contacted via telephone and invited to complete measures via mail. When Time 2 measures were completed and received, participants were each given a $10 retail gift card as compensation for their time.

Measures

See Appendix for a schedule of which measures are administered at Time 1 and Time 2.

Demographic information. Parents provided demographic information about the patient and themselves (e.g., age, race, income) using a standard questionnaire.

Medical chart review. Medical information (e.g., number of current medications, time since diagnosis that led to the need for transplantation, date of transplantation) was collected from the patient's electronic medical record. Serum immunosuppressant level data for rapamycin and tacrolimus was collected from the medical chart after transplantation (see Medication Nonadherence section for more information on how these data were extracted and calculated).

Patient HRQOL. Parents of children 3 years and older completed the Pediatric Quality of Life Inventory Parent Report, Generic Core Scales (PedsQL; Varni, Seid, & Kurtin, 2001), a proxy-report of children's HRQOL. Parents completed appropriate forms for their child's age (e.g., toddler form). The PedsQL is comprised of five domains: Physical, Emotional, Social, and School HRQOL. For patients not enrolled in school, parents have a "not applicable" option when responding to these items. The Total HRQOL score is comprised of all four domains. The Psychosocial Health Summary Score (Psychosocial HRQOL) is comprised of the Emotional, Social, and School HRQOL domains. The Physical Health Summary Score (Physical HRQOL) is comprised of the Physical domain.

For each item, parents reported on how much of a problem a specific task was for their child to complete in the past month (e.g., "Walking," "Playing with other children"). Responses were provided using a 5-point Likert-scale ranging from "Never" to "Almost Always." Before calculating domain scores, PedsQL items were reverse scored and transformed to a 0-100 point scale (Varni, 2012). The PedsQL has demonstrated validity and reliability in large investigations of healthy, chronically ill, and acutely ill pediatric patient populations (Varni et al., 2001; Varni et al., 2007). At Time 1, internal consistency was excellent for Total ($\alpha = .95$), Psychosocial ($\alpha =$

.90), and Physical (α = .92) HRQOL; good for School (α = .87) HRQOL; and acceptable for Emotional (α = .71) and Social (α = .73) HRQOL. At Time 2, internal consistency was excellent for Total (α = .90) HRQOL; good for Psychosocial (α = .83) and Physical (α = .81) HRQOL; acceptable for Emotional (α = .74) and Social (α = .72) HRQOL; and questionable for School (α = .68) HRQOL.

Medication nonadherence. Information on patients' medication nonadherence was obtained via proxy-reports from all enrolled parents and serum immunosuppressant levels (Time 2 only). These data provided both subjective and objective impressions of patients' medication nonadherence.

Parent proxy-report. The Medication Adherence Measure (MAM; Zelikovsky & Schast, 2008) was administered to all parents. The MAM asks participants to provide nonadherence data for medications taken by the patient. To determine a patient's level of medication nonadherence, the respondent reports on how many dosages were completely missed or taken late by the patient in the past 7 days. "Late" dosages are defined as those taken more than 1 hour later than prescribed. Late dosing is of particular interest for transplant patients because antirejection medication dosages must be taken 12 hours apart to ensure consistent immunosuppressant levels in the body and prevent organ rejection (Shemesh et al., 2004; Zelikovsky & Schast, 2008). To calculate nonadherence data, the total number of missed or late medication doses were divided by the total number of prescribed doses for all medications taken in the past week and multiplied by 100 (e.g., [number of missed medication doses / total number of prescribed doses for all medications] x 100 = % nonadherence for missed medications). Medications taken on an "as needed" basis were not included in adherence calculations. An overall "nonadherence" value was also calculated by averaging the percentage of missed and late medications for each patient. In

previous research, the MAM has demonstrated positive correlations adherence data obtained via electronic monitoring, which supports the measures convergent validity (Zelikovsky, Schast, Palmer, & Meyers, 2008).

Serum immunosuppressant levels. Serum immunosuppressant level for rapamycin and tacrolimus were collected from patients' medical records after transplantation (Time 2). Cyclosporine serum levels were not collected given the nonlinear relationship with this medication's blood levels after intake (Cakaloglu, Tredger, Devlin, & Williams, 1994). Post-transplantation, there was one patient who was prescribed cyclosporine and was omitted from all analyses involving serum immunosuppressant levels. The remaining patients in the Time 2 sample were prescribed tacrolimus.

To obtain an index of the patient's medication-taking behavior after transplantation, all available laboratory values were collected from the patient's medical chart, omitting values obtained during inpatient hospitalizations. Values collected during inpatient hospitalizations were omitted because medical providers, rather than the patient or their family members, were responsible for administering medications as scheduled during these extended hospital stays. Prior research has demonstrated that serum immunosuppressant levels that have greater standard deviation values or coefficient of variation values are related to higher incidences of rejection episodes in patients with liver or kidney transplants (Eid, Tuchman, & Moudgil, 2014; Hsiau, Fernandez, Gjertson, Ettenger, & Tsai, 2011; Shemesh et al., 2004). Thus, higher standard deviation and coefficient of variation (CoV%) values are considered to be reflective of more erratic, less consistent medication-taking behavior that suggests medication nonadherence. The CoV% values were calculated for all available laboratory values collected immediately after transplant and up to 12-months post-transplant. The 6-12 month post-transplant time frame was

examined as a subset of the serum levels since laboratory values collected between the 0-6-month post-transplant time period are considered less valid due to patients often experiencing medical instability and frequent medication adjustments, which could bias the CoV% values (Shemesh et al., 2008). Additionally, there is evidence that serum levels collected between 6-12 months post-transplantation are more variable in pediatric patients who experience rejection episodes compared to patients who did not experience rejection episodes (Pollock-BarZiv et al., 2010).

Patient emotional and behavioral functioning. Parents completed proxy-reports of the patient's emotional and behavioral functioning.

Behavioral Assessment for Children-2nd Edition Parent Rating Scales (BASC-2-PRS; Reynolds & Kamphaus, 2004). Parents of children 3 years and older completed the BASC-2-PRS, a proxy-report of children's behavioral and emotional functioning. For the purposes of this investigation, parents completed the Anxiety, Depression, Aggression, Attention Problems, and Hyperactivity subscales of the BASC-2-PRS. For each item, parents responded to how frequently their child felt a certain way in the past month (e.g., "Is nervous," "Cries easily") using a 4-point Likert-scale ranging from "Never" to "Almost Always." For each subscale, raw scores are converted to *T*-scores for the purpose of comparing the sample to norms. *T*-scores between 60-69 are considered "at risk" and *T*-scores greater than or equal to 70 are considered "clinically significant" (Reynolds & Kamphaus, 2004). At Time 1, internal reliability was good for the Anxiety subscale ($\alpha = .82$); acceptable for the Hyperactivity ($\alpha = .73$) and Aggression ($\alpha = .74$) subscales; questionable for the Depression subscale ($\alpha = .66$); and unacceptable for the Attention Problems subscale ($\alpha = .14$). At Time 2, internal reliability was good for the Depression ($\alpha = .83$)

and Anxiety (α = .88) subscales; acceptable for the Hyperactivity (α = .74) and Aggression (α = .75) subscales; and unacceptable for the Attention Problems subscale (α = .23).

Parent psychological functioning. Parents completed self-reports of their own emotional distress and functioning.

Brief Symptom Inventory-18 (BSI-18; Derogatis, 2001). Parents completed the BSI-18, a self-report measure of adult psychological distress. The BSI-18 yields three subscales (Depression, Anxiety, and Somatization) and the Global Symptom Inventory (GSI), which is a composite of the three subscale scores. Parents reported on how much they were bothered by a particular symptom (e.g., "Feeling tense or keyed up," "Feeling no interest in things") in the past 7 days using a Likert-scale ranging from "Not at all" to "Extremely often." Raw scores were converted to *T*-scores for the purposes of comparing the sample to norms. GSI scores above 63 are indicative of clinically significant psychological distress (Derogatis, 2001). As evidence for its validity, the BSI-18 demonstrated strong, positive correlations with the Symptom Checklist-90-Revised, the scale upon which the BSI-18 was derived (Recklitis & Rodriguez, 2007). At Time 1, internal consistency was acceptable for the Anxiety scale (α = .78); good for the Depression (α = .81) and Somatization (α = .86) scales; and excellent for the GSI (α = .92) scale. At Time 2, internal consistency was good for the Depression (α = .84) and Anxiety (α = .87) scales and excellent for the Somatization (α = .91) and GSI (α = .94) scales.

Impact of Event Scale-Revised (IES-R; Creamer, Bell, & Failla, 2003). The IES-R is self-report measure of adult PTSD symptoms related to a specific event identified in the instructions. Items map onto the PTSD criteria in the DSM-IV-TR (APA, 2000) and yields Intrusion, Avoidance, and Hyperarousal subscales. At Time 1, parents responded to "how distressing" each item has been in the past 7 days, specific to their child's medical condition. At

Time 2, parents responded to the same items but with respect to their child's transplant. Parents respond to each item using a 5-point Likert-scale ranging from "Not at all" to "Extremely." The IES-R has demonstrated strong internal consistency when used with parents of pediatric cancer survivors (Barakat, Alderfer, & Kazak, 2005; Kazak et al., 2004) and children with current cancer diagnoses (Jurbergs, Long, Ticona, & Phipps, 2009). At Time 1, internal consistency was acceptable for the hyperarousal scale (α = .71); good for the intrusion (α = .84) and avoidance (α = .88) scales; and excellent for the total scale (α = .92). At Time 2, internal consistency was good for the hyperarousal (α = .85), intrusion (α = .84), and avoidance (α = .82) scales; and excellent for the total scale (α = .92).

Impact on the Family Scale-Revised (IOF-R; Stein & Jessop, 2003). The IOF-R is a parent -report measure of the degree to which parents perceive that having a child with a serious medical condition affects their family (e.g., "We see family and friends less because of my child"). Parents responded to each item using a 4-point Likert scale ranging from "Strongly agree" to "Strongly disagree." The original scale includes four subscales. This study only included the Familial/social (9 items) and Personal Strain (6 items) subscales. The Familial/Social subscale assesses how a child's health condition potentially disrupts family social interactions and the Personal Strain subscale assesses parental psychological impact of having a child with a health condition. Prior research indicates that the IOF-R is associated with more maternal psychiatric symptoms, poorer child health, and poorer child psychological functioning (Stein & Jessop, 2003). At Time 1, internal consistency was good for the Familial/social (α = .84) and Personal Strain (α = .82) subscales and excellent for the Total scale (α = .91). At Time 2, internal consistency was good for the Familial/social (α = .86) and Personal Strain (α = .85) subscales and excellent for the Total scale (α = .92).

Barriers to Pediatric Adherence for Parents (BPAP; Loiselle et al., 2014). The BPAP is a self-report of parents' own barriers to helping their child take medications as prescribed (e.g., "Sometimes I forget to make sure my child takes his/her medicine"). Items are based on behavioral or cognitive domains that have demonstrated strong correlations with pediatric adherence. Parents responded to how much they agreed with a particular statement using a 5-point Likert-scale ranging from "Strongly disagree" to "Strongly agree." Higher total scores suggest more barriers. Data regarding the validity and reliability of the BPAP, along with results from a factor analysis, are in progress, though preliminary evidence demonstrates strong, positive correlations between the BPAP total score and parent anxiety, depression, and post-traumatic stress symptoms, as well as impact of the child's health condition on the family (Loiselle et al., 2014). Internal consistency was excellent for the BPAP at Time 1 ($\alpha = .95$) and Time 2 ($\alpha = .90$).

Statistical Analyses

Statistical analyses were conducted using IBM SPSS Statistics Version 22. For analyses involving hypothesis testing, results yielding *p*-values of $< .05$ were accepted as statistically significant. Data were inspected prior to analyses to assess the shape and distribution and determine whether transformation procedures or nonparametric analytic approaches were needed (e.g., square root transformation). Descriptive analyses (e.g., mean, standard deviation, range) were conducted for all study variables. To assess between time point differences in HRQOL and psychosocial variables (i.e., BSI-18, BASC-2-PRS, IOF-R, IES-R), 2-tailed paired-samples *t*-tests were conducted. For measures that had *T*-scores or published norms (i.e., the PedsQL, BASC-2-PRS, BSI-18, IES-R), 2-tailed, one-sample *t*-test analyses were used to compare the

current sample to normative data. Cohen's *d* (Cohen, 1988; Cohen, 1992) was calculated as the effect size for all *t*-test results.

To identify Time 1 psychosocial factors and demographic variables (e.g., patient age at Time 1, family income, parent education level) associated with medication nonadherence and HRQOL at Time 2, bivariate correlations were calculated (Pearson product-moment for continuous variables, Spearman's rank order for ordinal variables, point biserial for dichotomous variables). Demographic variables that were not continuous or ordinal were dichotomized prior to conducting bivariate correlational analyses. If there were any demographic or medical variables that were significantly correlated with the Time 2 outcomes (HRQOL and nonadherence), partial correlations were conducted to control for the effects of these variables. Correlations between demographic or medical variables and study variables were reported in the Preliminary Analyses section, as these factors were considered as potential covariates.

To determine pre-transplant factors that predicted Time 2 Total HRQOL, hierarchical multiple regression analyses were conducted. Entry of variables in regression analyses were guided by results of bivariate correlations. Demographic or medical variables associated with Total HRQOL at Time 2 were entered as covariates in Step 1 followed by Time 1 HRQOL in Step 2. Time 1 psychosocial variables demonstrating statistically significant correlations with HRQOL at Time 2 were entered in subsequent steps of the regression. For predicting Time 2 medication nonadherence, demographic or medical variables that were statistically associated with nonadherence at Time 2 were entered as covariates in Step 1 followed by Time 1 nonadherence at Step 2. Time 1 psychosocial variables demonstrating statistically significant correlations with nonadherence were entered in subsequent steps of the regression. Given power constraints, if multiple psychosocial variables beyond Time 1 Total HRQOL or nonadherence

emerged as significantly correlated with the outcome variables, predictor variables were entered in the final step individually to determine if they accounted for significant additional variance beyond baseline HRQOL or nonadherence. If not, these variables were omitted from the final models.

Power analysis

Sample sizes needed to detect medium effect sizes (Cohen, 1992) were determined a priori for all planned analyses using G*Power (Faul, Erdfelder, Lang, & Buchner, 2009). For 2-tailed, paired-samples *t*-test analyses examining differences in mean levels of variables from Time 1 to Time 2, 34 participants were required to detect effects (power = .80, α = .05, and effect size = .50). For 2-tailed, one-sample *t*-tests examining the difference from a constant (comparison of sample mean to norms), 34 participants were required to detect effects (power = .80, α = .05, and effect size = .50). For Pearson product-moment correlation analyses, 84 participants were needed to achieve adequate power (power = .80, α = .05, and effect size = .30). For hierarchical multiple regression analyses with two to five predictors entered, a sample size of 33 to 92 participants was needed to achieve adequate power (power = .80, α = .05, and effect size = .15-.30).

CHAPTER 3

Preliminary Analyses

Descriptive Analyses and Transformations

Descriptive data for study variables that were assessed for pre-to-post-transplant differences, including means, standard deviations, and ranges, are presented in Tables 3-4. These study variables, as well as parental barriers to adherence (Time 1 *M* = 62.38, *SD* = 22.05, range = 2 to 149; Time 2 *M* = 57.31, *SD* = 14.46, range = 39 to 99), were normally distributed, with the exception of parent-reported percentages of missed (Time 1 *M* = 3.09, *SD* = 7.44, range = 0 to 32.94; Time 2 *M* = .43, *SD* = 2.31, range = 0 to 16.67) and late (*M* = 1.07, *SD* = 2.68, range = 0 to 9.52; Time 2 *M* = 1.00, *SD* = 2.31, range = 0 to 20.69) medications and overall nonadherence (Time 1 *M* = 2.08, *SD* = 3.79, range = 0 to 16.47; Time 2 *M* = .71, *SD* = 2.26, range = 0 to 10.34) at Time 2. The parent-reported nonadherence variables had an overrepresentation of 0% nonadherence, resulting in positively skewed data (kurtosis = 11.75 – 48.61, skewness = 3.54 – 6.84). Because the distribution of the data violated the assumptions needed to conduct Pearson product-moment correlational analyses, the data were transformed using a square root transformation. Even with this transformation, the data remained positively skewed and non-normally distributed (kurtosis = 6.89 – 27.46, skewness = 2.77 – 4.97). Because of this issue, correlations between Time 1 psychosocial variables and Time 2 parent-reported nonadherence variables were examined using Pearson product-moment correlations with the transformed nonadherence data and Spearman's rho with the non-transformed nonadherence data to account for skewed distribution. Spearman's rho is recommended when data is skewed and does not meet

the normality requirement for Pearson product-moment correlations (Hauke & Kossowski, 2011). Due to limitations of both correlation types (Hauke & Kossowski, 2011), correlations with the parent-reported nonadherence data were interpreted with caution. The decision was made to not conduct planned regression analyses due to the extreme non-normality of the parent-reported nonadherence measures.

Demographic and Medical Covariates

Prior to conducting further analyses, correlations between study variables and demographic (patient age, race, and sex, parent race, sex, education level, and marital status, and annual family income) and medical variables (time since diagnosis that led to the need for transplantation, number of medications prescribed to patient) were conducted to identify potential covariates. Patient age at Time 1 was significantly correlated with Total HRQOL at Time 2, with younger patients demonstrating better HRQOL (r = -.34, p = .02). Thus, patient age at Time 1 was used as a covariate in subsequent correlational analyses involving Total HRQOL at Time 2.

Parent marital status was significantly correlated with the percentage of late medications at Time 2 when parent-reported nonadherence data were analyzed using Spearman's rho coefficient (ρ = -.29, p = .04). Single parents reported more late medications for their children than their married counterparts. No other demographic or medical variables were associated with HRQOL or nonadherence at Time 2.

CHAPTER 4

Pre-to-Post Transplant Differences and Comparison to Norms

Pre-to-Post-Transplant Differences in HRQOL and Psychosocial Functioning

Differences in patients' functioning. Mean differences between patient HRQOL and psychological functioning variables at Time 1 and Time 2 were examined using paired samples *t*-test analyses. Detailed results are presented in Table 3. For HRQOL, patients demonstrated significant improvements on Physical, Social, Psychosocial, and Total HRQOL between Times 1 and 2, with medium to large effect sizes. There were no significant differences between time points for Emotional or School HRQOL. There were no significant differences in patient psychological functioning (e.g., symptoms of depression, anxiety, aggression, attention problems, hyperactivity) between Times 1 and 2, though decreases in depressive symptoms from Time 1 to Time 2 approached statistical significance and a medium effect size.

Differences in parental and family functioning. Mean differences between parent and family psychological functioning variables at Time 1 and Time 2 were examined using paired samples *t*-test analyses. Detailed results are presented in Table 4. There were significant reductions in parental symptoms of depression, anxiety, somatization, and overall emotional distress between Times 1 and 2, with medium effect sizes. There were significant reductions from Times 1 and 2 in total PTSD symptoms and PTSD symptoms related to avoidance of thoughts about their child's transplant, with medium effect sizes. There were no significant reductions between time points on PTSD symptoms related to intrusive thoughts or physiological

arousal. There were no significant differences between time points on the impact of the patient's health condition on the family.

Comparison of Patient and Parent Psychosocial Functioning to Norms

Patient psychosocial functioning. Patient HRQOL domains at Time 1 and Time 2 were compared to healthy and chronically ill norms (Varni et al., 2001). When compared to healthy norms, patients had significantly lower HRQOL across all domains at both Times 1 and 2 with large effect sizes. Of note, effect sizes for the magnitude of difference between HRQOL at Time 2 and the normative data were smaller than their Time 1 counterparts. See Table 5 for detailed results.

When Time 1 HRQOL data were compared to chronically ill norms, Physical, School, Psychosocial, and Total HRQOL were significantly lower with medium to large effect sizes. Emotional and Social HRQOL were similar to chronically ill norms at Time 1. At Time 2, only School HRQOL was significantly lower than chronically ill norms, with a medium effect size. All other HRQOL domain levels at Time 2 were similar to those of chronically ill norms. See Table 6 for detailed results.

At Time 1, patients had significantly lower symptoms of aggression (M = 45.98, SD = 7.32, t = -3.61, p = .001) compared to norms (Reynolds & Kamphaus, 2004). The effect size was medium (d = .46). There were no other significant differences compared to norms on patient psychological or behavioral symptoms (i.e., symptoms of depression, anxiety, hyperactivity, attention problems) at Time 1. At Time 2, patients demonstrated significantly lower symptoms of aggression (M = 45.69, SD = 9.21, t = -3.14, p = .003, d = .44) and anxiety (M = 46.31, SD = 11.45, t = -2.16, p = .04, d = .34) compared to norms. Effect sizes were medium. There were no

other significant differences compared to norms on patient psychological or behavioral symptoms at Time 2.

Parent psychosocial functioning. Parent psychosocial variables at Time 1 and Time 2 were compared to norms when available (i.e., BSI-18 and IES-R only; there were no appropriate norms available for the IOF-R scale). At Time 1, there were no significant differences between parental symptoms of depression, anxiety, somatization, or overall emotional distress (i.e., BSI-18 GSI) and norms (Derogatis, 2001). At Time 2, parents reported significantly lower symptoms of depression (M = 46.63, SD = 8.58, t = -2.83, p = .007, d = .36), somatization (M = 45.92, SD = 9.54, t = -3.08, p = .003, d = .42), and overall emotional distress (M = 43.83, SD = 12.09, t = -3.69, p = .001, d = .56) compared to norms. Effect sizes ranged from medium to large. Parental anxiety symptoms were similar to norms at Time 2.

Detailed results for how parental symptoms of PTSD compared to norms are presented in Table 7. PTSD symptoms at Time 1 were compared to published norms of mothers whose children were in treatment for cancer and PTSD symptoms at Time 2 were compared to mothers whose children survived cancer treatment (Kazak et al., 2004). At Times 1 and 2, parents reported significantly lower levels of PTSD symptoms compared to these norms across all domains, with large effect sizes.

CHAPTER 5

Using Time 1 Psychosocial Variables to Predict Patients' Levels of HRQOL at Time 2

Correlations Between Time 1 Psychosocial Variables and Time 2 HRQOL

Associations among patient, parent, and family predictor variables at Time 1 and patients' Total HRQOL levels at Time 2 were examined. Partial correlations were used when examining correlations with Total HRQOL at Time 2 to control for patient age at Time 1. All other correlations among variables were examined using Pearson product-moment correlations. Detailed results are presented in Table 8. Patient HRQOL at Time 2 was significantly and positively correlated with patient HRQOL at Time 1. Patient HRQOL at Time 2 was significantly and negatively correlated with patient symptoms of aggression, hyperactivity, depression, and anxiety, and the overall impact of the patient's health condition on the family at Time 1. Patients who had better Total HRQOL, fewer symptoms of aggression, hyperactivity, depression, or anxiety, or less impact of their health condition on the family at Time 1 had better Total HRQOL at Time 2.

Predicting HRQOL at Time 2

Multiple Time 1 variables emerged as being significantly correlated with patient HRQOL at Time 2, including patient symptoms of aggression, hyperactivity, depression, and anxiety, and the impact of the patient's health condition on the family. To enhance the parsimony and statistical power of the final regression model used to predict Total HRQOL at Time 2, preliminary analyses were used to determine if correlated Time 1 variables added significant

variance beyond that of patient age (Step 1) and Total HRQOL (Step 2) at Time 1 by inserting single variables in the Step 3 of the model.

Results of preliminary regression analyses. When patient age and Total HRQOL at Time 1 were entered in the first two steps of the model, the two variables accounted for 46.7% of the variance (F = 16.22, p < .001). When patient aggression was added at Step 3, aggression did not account for significant additional variance (ΔR^2 = .01, p = .38) and was not a significant predictor of HRQOL at Time 2 (β = -.12, p = .38). When patient hyperactivity was added at Step 3, hyperactivity did not account for significant additional variance (ΔR^2 = .05, p = .052) and was not a significant predictor of HRQOL at Time 2 (β = -.26, p = .052). When patient depression was added at Step 3, depression did not account for significant additional variance (ΔR^2 = .04, p = .09) and was not a significant predictor of HRQOL at Time 2 (β = -.24, p = .09). When patient anxiety was added at Step 3, anxiety did not account for significant additional variance (ΔR^2 = .04, p = .10) and was not a significant predictor of HRQOL at Time 2 (β = -.24, p = .10). When the impact of the patient's health condition on the family was added at Step 3, this variable did not account for significant additional variance (ΔR^2 = .05, p = .07) and was not a significant predictor of HRQOL at Time 2 (β = -.25, p = .07). Because no variables tested at Step 3 added significant additional variance beyond that of patient age and Total HRQOL at Time 1 in the prediction of Total HRQOL at Time 2, the final model did not include a Step 3.

Final prediction model. The final regression model used to predict Total HRQOL at Time 2 included patient age at Time 1 in Step 1 and Total HRQOL at Time 1 in Step 2. At Step 1, patient age at Time 1 did not account for significant variance (R^2 = .06, F = 2.52, p = .12). At Step 2, Total HRQOL at Time 1 accounted for significant additional variance (ΔR^2 = .41, p < .001). The final model accounted for 46.7% of the variance (F = 16.22, p < .001) and Total

HRQOL at Time 1 was the only significant predictor of Total HRQOL at Time 2 ($\beta = .64$, $p < .001$). In the final model, patient age at Time 1 was not a significant predictor of HRQOL at Time 2 ($\beta = -.17$, $p = .16$). Patients who had better Total HRQOL at Time 1 were predicted to have significantly better HRQOL at Time 2.

CHAPTER 6

Post-hoc Investigation of How Patient Age at Time 1 Relates to Patient HRQOL at Time 2

Due to the significant association between patient age at Time 1 and Total HRQOL at Time 2 and the large age range represented in the current sample, the decision was made to further explore the association between patient age and HRQOL from pre-to-post-transplantation. The goal of this post-hoc investigation was to better understand how patients' ages before transplantation potentially influenced their levels of HRQOL at 6-months post-transplantation. Preliminary analyses indicated that patient age at Time 1 was significantly correlated with patient Total HRQOL at Time 2, with patients who were younger at the time of their pre-transplant evaluation demonstrating better HRQOL at Time 2 (r = -.34, p = .02).

To further investigate the role of patients' ages on their level of HRQOL post-transplantation, the sample was dichotomized into "child" (i.e., < 12 years of age) and "adolescent/young adult" (AYA; i.e., ≥12 years of age) age groups based on the age split used by the Center for Disease Control and Prevention (2016). There were 25 patients in the child group (12 females, 13 males) and 20 patients in the AYA group (10 females, 10 males). The child group had 15 patients with kidney transplants, 6 with heart transplants, and 4 with liver transplants. The AYA group had 8 patients with kidney transplants, 5 with heart transplants, and 7 with liver transplants. The child group (M = 5.11 years, SD = 3.22, range = 1.30 to 11.13 years) was significantly younger than the AYA group (M = 15.31 years, SD = 2.40, range = 12.03 to 20.44; t = -11.79, p < .001) at Time 1. The child group (M = 3.62 years, SD = 3.54) had significantly shorter lengths of time between the diagnosis that led to transplantation and Time 1

than the AYA group (M = 9.02, SD = 6.80; t = -3.44, p = .001). The child group was more likely than the AYA group to have public health insurance (χ^2 = 4.38, p = .04). There were no other significant differences between the child and AYA groups on demographic or medical factors.

Post-hoc analyses goals and plan. The first goal of this investigation was to examine between age group mean differences on the six domains of HRQOL at Time 2. It was hypothesized that the child group would have significantly better HRQOL compared to the AYA group. Independent samples *t*-tests were used to address the first goal. The second goal was to examine differences in mean levels of HRQOL from Time 1 to Time 2 within the child group and within the AYA group. It was hypothesized that both age groups would demonstrate significant improvements in HRQOL between time points but demonstrate variability in the magnitude of post-transplant gains, with children potentially making larger improvements than AYAs. Paired samples *t*-test analyses were used to address the second goal. The third goal was to compare HRQOL at Time 2 in child group and AYA group to healthy and chronically ill norms (Varni et al., 2001). It was hypothesized that the child group would have smaller differences in HRQOL compared to healthy and chronically ill norms than the AYA group (i.e., the child group would have HRQOL levels that were closer to those of norms than the AYA group). One-sample *t*-tests were used to address the third goal. The final goal was to examine correlations between Time 1 study variables and Total HRQOL at Time 2 within the child group and within the AYA group. These final analyses were exploratory and, hence, no hypotheses were made. Pearson product-moment correlations were used to address the final goal. For these analyses, results yielding *p*-values of $< .05$ were accepted as statistically significant. Cohen's *d* was calculated as the effect size for *t*-test analyses.

Are there between age group differences on mean levels of HRQOL at Time 2? Patients in the child group had significantly higher Emotional HRQOL at Time 2 compared to AYAs, with a large effect size. There were no other significant differences between age groups on the other domains of HRQOL at Time 2. Mean HRQOL levels in the child group were consistently higher than those of AYAs at Time 2, with the exception of School HRQOL. The magnitude of differences between the child and AYA groups on Physical, Psychosocial, and Total HRQOL were in the range of medium effect sizes. Results are presented in detail in Table 9.

What differences in HRQOL occur from Times 1 to 2 within the child and AYA groups? Detailed results are presented in Table 10. Within the child group, Total HRQOL increased significantly from Time 1 to Time 2 with a medium effect size. Differences in Emotional and Physical HRQOL approached statistical significance and effect sizes were medium and large, respectively. Social, School, and Psychosocial HRQOL levels did not demonstrate significant differences from Time 1 to Time 2.

Within the AYA group, Physical, School, Psychosocial, and Total HRQOL increased significantly from Time 1 to Time 2, with large effect sizes. Differences in Social HRQOL approach statistical significance, with a medium effect size. Emotional HRQOL did not differ significantly from Time 1 to Time 2.

How do HRQOL levels at Time 2 compare to norms within the child and AYA groups? Patients' levels of HRQOL at Time 2 were first compared to healthy norms within the child and AYA groups. Results are presented in detail in Table 11. Within the child group, patients had significantly lower Physical, Social, School, Psychosocial, and Total HRQOL compared to healthy norms, with large effect sizes. Emotional HRQOL within the child group was similar to

healthy norms. Within the AYA group, patients had significantly lower HRQOL across all domains compared to healthy norms, with large effect sizes.

Next, patients' levels of HRQOL at Time 2 were compared to chronically ill norms within the child and AYA groups. Results are presented in Table 12. Within the child group, Emotional, Social, School, Psychosocial, and Total HRQOL were not significantly different from chronically ill norms, with small to medium effect sizes. With the exception of School HRQOL, these domains trended towards being better than norms. The child group's Physical HRQOL was significantly better than that of chronically ill norms, with a medium effect size. Within the AYA group, all domains of HRQOL were not significantly different from chronically ill norms, with small to medium effect sizes. Emotional HRQOL trended towards being significantly worse than that of chronically ill norms.

How do Time 1 psychosocial variables correlate with Total HRQOL at Time 2 within the child and AYA groups? Within the child group, patient HRQOL and hyperactivity symptoms at Time 1 were significantly correlated with patient HRQOL at Time 2. Children with better Total HRQOL or lower hyperactivity symptoms at Time 1 had significantly better Total HRQOL at Time 2. There were no other significant correlations between patient or parent variables at Time 1 and patient HRQOL at Time 2 within the child group. See Table 13 for detailed results.

Within the AYA group, patient HRQOL and depression and anxiety symptoms at Time 1 were significantly correlated with patient HRQOL at Time 2. The impact of the patient's health condition on the family at Time 1 was also significantly correlated with patient HRQOL at Time 2. AYAs who had better Total HRQOL, lower symptoms of depression and anxiety, or less impact of their health condition on the family at Time 1 had significantly better Total HRQOL at

Time 2. There were no other significant correlations between patient or parent variables at Time 1 and patient HRQOL at Time 2 within the AYA group. See Table 14 for detailed results.

CHAPTER 7

Using Time 1 Psychosocial Variables to Predict Patients' Nonadherence at Time 2

Time 1 Correlations with Nonadherence at Time 2

Associations among predictor variables at Time 1 and patients' levels of medication nonadherence at Time 2 (parent-reported percentages of missed medications, late medications, and the average of the two [overall nonadherence], and CoV% values) were examined. Associations with the parent-reported nonadherence variables were examined using the square root transformed versions of those variables and Pearson product-moment correlations. These results are presented in detail in Table 15. The percentage of missed medications at Time 2 was significantly and positively correlated with patient symptoms of aggression and hyperactivity, the impact of the patient's health condition on the family, and parental barriers to adherence. The percentage of late medications at Time 2 was significantly and negatively correlated with the impact of the patient's health condition on the family at Time 1. There were no other significant correlations between Time 1 predictors and Time 2 parent-reported nonadherence outcomes.

Associations with the parent-reported nonadherence variables were also examined using Spearman's rho correlations to account for the non-normal distribution of the parent-reported nonadherence data. Results are presented in detail in Table 16. The impact of the patient's health condition at Time 1 was significantly and negatively correlated with the percentage of medications taken late at Time 2. There were no other significant correlations between Time 1 predictor variables and parent-reported nonadherence at Time 2 when the data were examined using Spearman's rho.

Associations with patients' CoV% values were also examined using serum immunosuppressant values that were collected immediately after transplantation (CoV% all lab values) and values collected between 6- and 12-months post-transplantation. Results are presented in detail in Table 17. There were no significant correlations between Time 1 predictors and CoV% values. Given the lack of significant correlations between CoV% values and Time 1 predictors, no hierarchical regression models were examined.

CHAPTER 8

Discussion

The current study provides initial answers to questions about differences that occur in pediatric transplant recipients' levels of HRQOL, as well as patient and parent psychosocial functioning, from the time of the pre-transplant evaluation to 6-months after transplantation. Results also identify psychosocial factors present in the pre-transplant phase that relate to patients' levels of overall HRQOL and medication nonadherence in the early post-transplant phase. There is little empirical research in pediatric transplantation that has longitudinally examined pre- and post-transplantation changes in or predictors of these variables (e.g., Cole et al., 2004; Rodrigue et al., 1997; Wray & Radley-Smith, 2004), highlighting the novelty and practical significance of the knowledge generated from this study. Additionally, a post-hoc investigation of HRQOL at Time 2 provides insight into how pediatric transplant candidates' age at the time of the pre-transplant evaluation may differentially relate to their physical and psychosocial functioning after transplantation. An interpretation of findings and recommendations for future research directions and clinical application are provided.

Pre-to-Post-Transplant Differences in Patients' Psychosocial Functioning and Comparison to Norms

The first hypothesis, that patient HRQOL would improve from Time 1 to Time 2, was partially supported. Patients demonstrated significant improvements from Time 1 to Time 2 on all HRQOL domains except Emotional and School, with medium to large effect sizes. These results are consistent with prior research demonstrating that HRQOL improves from pre-to-post-

transplantation in adult transplant recipients (Dew et al., 1997) and pediatric bone marrow transplant recipients (Barrera et al., 2000). One prior study has shown significant improvements in HRQOL levels from the time of listing for transplantation to 12-months post-transplantation for children who received a liver transplant at age 5 or younger (Cole et al., 2004). The current study is the first study to demonstrate significant improvements in HRQOL from the pre-transplant evaluation to 6-months after transplantation in a sample of children, adolescents, and young adults with kidney, liver, and heart transplants. These findings provide encouraging information for families of pediatric patients going through the pre-transplant evaluation process, as patients may expect to see significant improvements in their physical functioning (e.g., ability to walk, run, engage in self-care), social functioning (e.g., make friends with same-aged peers), and overall HRQOL within a relatively short amount of time after transplantation.

The lack of improvement in School or Emotional HRQOL after transplantation was unexpected. However, many children have not fully reintegrated back to school early in the post-transplantation phase (Brosig et al., 2014). Patients may still miss significant amounts of school due medical complications, needing to attend frequent medical appointments, or not feeling well, physically, resulting in less improvement on the School HRQOL scale. Further, prior research suggests that pediatric patients continue to be at risk for lower academic functioning in the post-transplant phase (Anthony et al., 2010), suggesting that pre-to-post-transplant differences in School HRQOL may be smaller than what is observed in other areas of functioning, such as Physical or Social HRQOL. Improving School HRQOL after transplantation may also require more time compared to other areas of HRQOL or the implementation of academic accommodations to facilitate progress after missing significant amounts of schooling. The lack of pre-to-post transplant improvements in Emotional HRQOL may reflect the continued

uncertainty of how successful transplantation will be for patients and adjustment to new treatment regimens introduced in the early post-transplant phase (Lerret et al., 2014). These stressors may result in patients continuing to feel scared, nervous, or sad within the first 6-months after transplantation. Our research would benefit from continuing to follow this cohort of patients into the 12-month post-transplantation phase to determine whether significant improvements in School and Emotional HRQOL occur after patients are more likely to be considered medically stable.

Patients' HRQOL levels were compared to healthy and chronically ill norms (Varni et al., 2001) at Times 1 and 2 to further contextualize the differences that occurred between time points. At Time 1, patient HRQOL was significantly lower across all domains when compared to healthy norms, with large effect sizes. At Time 2, patient HRQOL continued to significantly lower across all domains when compared to healthy norms, but effect sizes, though still large, were smaller compared to their Time 1 counterparts. These results complement the findings that patient HRQOL generally improves from Time 1 to Time 2 by providing further support that HRQOL increased after transplantation and moved closer to that of a healthy child.

When patient HRQOL was compared to chronically ill norms at Time 1, all domains except Emotional and Social HRQOL were significantly lower than norms, with large effect sizes. Encouragingly, when patient HRQOL was compared to chronically ill norms (i.e., norms collected from children presenting at orthopedics, cardiology, rheumatology, or diabetes clinics; Varni et al., 2001) at Time 2, all domains except for School HRQOL were similar to norms. As with the lack of pre-to-post-transplant mean difference in patients' levels of School HRQOL, the lower score on this domain may also reflect that many patients are still not fully integrated back into school within the first 6-months after being transplanted. This finding highlights the

importance of forming collaborative partnerships between medical providers and schools to ensure that pediatric transplant recipients have a smooth re-entrance into school (Weil et al., 2006). It is promising that, by 6-months post-transplantation, pediatric patients' HRQOL levels had generally improved and were comparable to those of other children with chronic medical conditions that were not considered immediately life-threatening (e.g., diabetes, juvenile rheumatoid arthritis; Varni et al., 2001).

As pediatric transplant recipients often experience HRQOL deficits years after transplantation (e.g., Ng et al., 2012), it remains unclear how much more improvement in HRQOL patients can expect after the first 6-months post-transplantation. The prior study that followed a cohort of patients under the age of 5 years from the time of listing for a liver transplant to 12-months post-transplant found slight improvements in HRQOL from 6-to-12-months post-transplantation (Cole et al., 2004). Further investigation of these changes across time is needed with larger samples with representation of older children and adolescents. Prior research has shown that adolescent transplant recipients' HRQOL does not change over an 18-month period of time (Devine et al., 2010), suggesting that, at some point, post-transplant improvements in HRQOL cease. There may be clinical utility in identifying a time point at which HRQOL typically stabilizes to maximize the benefit of intervention efforts to improve patients' physical and psychosocial functioning following transplantation.

The next hypothesis, that patients' psychological distress would decrease between Time 1 and Time 2, was not supported, as there were no mean differences in patients' symptoms of depression, anxiety, aggression, attention problems, or hyperactivity from pre-to-post-transplantation. Additionally, the comparison of the current sample to norms (Reynolds & Kamphaus, 2004) showed that patients in this study had similar or significantly lower symptoms

of emotional and behavioral problems at both Time 1 and Time 2. The current study's findings are inconsistent with the small body of research examining pre-to-post-transplantation differences in children's psychological functioning. These prior studies suggest that patients' emotional distress levels decrease after transplantation and that children present with significantly higher pre-transplant symptoms of depression compared to healthy children and other pediatric patients with chronic illnesses (DeMaso et al., 2004; Wray & Radley-Smith, 2004; Wray & Radley-Smith, 2007).

Differences between the current findings and those reported in previous studies may be related to the population sampled and the measures used to assess children's psychological functioning. One of the prior longitudinal studies only examined heart transplant recipients and used the Children's Global Assessment Scale (CGAS) to assess psychological functioning (DeMaso et al., 2004), which relied on the researchers' clinical judgments to assess children's levels of psychological impairment. Though CGAS scores were generated by one researcher who was blinded to the patients' pre-existing cardiac condition, this assessment approach is notably different from how children's psychological functioning was assessed in the current study (i.e., parent proxy-report using a validated, standardized measure). The other prior longitudinal studies used validated measures (i.e., Child Behavior Checklist, Mood and Feelings Questionnaire; Achenbach & Rescoria, 2001; Angold & Costello, 1987) but contained very small samples of children who received heart and heart-lung transplants (Wray & Radley-Smith, 2004; Wray & Radley-Smith, 2007). Thus, there are methodological differences between the current study and previous investigations that may have contributed to differences in results. For research conducted in the post-transplant phase, there is greater variability in findings with patients demonstrating both worse and similar psychological functioning compared to norms (e.g.,

Fredericks et al., 2007; Qvist et al., 2004). These equivocal findings may also reflect the methodological variability present in many studies within pediatric transplantation (i.e., heterogeneity in administered measures, patient ages, organ groups) and the tendency to include smaller samples collected from single sites that may not represent the broader population of pediatric transplant recipients.

Overall, the similarity of psychological functioning between this study's sample and normative data may provide hope for families going through the transplant process. These findings suggest that pediatric patients with end-stage organ disease are emotionally resilient and able to cope well with the stress and uncertainty of transplantation. At the same time, patients demonstrated significantly lower Emotional HRQOL compared to healthy norms, suggesting that some children may experience sub-clinical emotional adjustment issues during the transplant process. These adjustment issues may be mild or specific to the transplant process rather than manifesting as clinically significant emotional or behavioral problems. Future investigators may consider measuring patients' adjustment to transplantation, emotional resilience, or other potentially protective constructs (e.g., social support) to identify factors that facilitate better coping in the pre- and post-transplant phases.

Pre-to-Post-Transplant Differences in Parents' Psychological Functioning and Comparison to Norms

The hypothesis that parental psychological distress would decrease from Time 1 to Time 2 was partially supported. Parents endorsed significantly lower symptoms of depression, anxiety, somatization, and overall distress at 6-months post-transplantation compared to baseline levels. At this time point, parents also reported significantly lower symptoms of PTSD and, specifically, avoidance symptoms related to thinking about their child's transplant. The current study is the

first to examine how parental PTSD symptoms differ from pre-to-post-transplantation. These findings are consistent with the limited existing data on differences that occur in parental psychological functioning from before to after their child receives a transplant, which suggest that the pre-transplantation phase is a more stressful time for parents than after transplantation (Wray & Radley-Smith, 2007; Aldridge, 2008). Similar to patient findings, the reduction in parental psychological distress between the two time points highlights parents' resilience and abilities to cope with stress during an uncertain time. At the pre-transplant evaluation, parents who report experiencing increased stress related to their child's medical condition may benefit from learning that their feelings of distress will likely decrease after transplantation, even without intervention.

Interestingly, although parental psychological distress generally decreased from Time 1 to Time 2, comparisons to norms indicated that parents were not experiencing significant distress at either time point. At Time 1, there were no significant differences between the current sample and healthy adult norms (Derogatis, 2001) on symptoms of depression, anxiety, somatization, or overall distress. After transplantation at Time 2, parents endorsed similar or significantly lower symptoms of psychological distress compared to norms. Similar results were found for PTSD symptoms, with parents in the current sample reporting significantly lower symptoms compared to parents of children undergoing cancer treatment (Kazak et al., 2005). As with patients' results, the current study's findings on parental psychological functioning during the transplantation process highlight the resilience of many families going through the transplantation process. Although the pre- and early post-transplant phases are marked by uncertainty and changes in family routines, parents seem to be coping well, psychologically.

Alternatively, it is possible that the measures used in the current did not adequately capture the form of distress experienced by parents of children with end-stage organ disease who eventually received a solid organ transplant. Future researchers should consider including alternate methods of assessing parents' experiences of distress, such as physiological measures (e.g., cortisol levels, heart rate variability) or assessments of HRQOL and disruption of daily routines (e.g., missing work, difficulty with child care, difficulty adjusting to child's new medical treatment). Utilizing novel assessments of stress may provide richer and more accurate information about the challenges faced by parents of children evaluated for and receiving solid organ transplants.

Pre-to-Post-Transplant Differences in the Impact of the Patient's Health Condition on the Family

The hypothesis that the impact of the patient's health condition on the family would increase from Time 1 to Time 2 was not supported. There were no significant mean differences on the IOF-R scales and effect sizes were very small. These findings were inconsistent with a previous study that used an older version of the IOF-R to measure the impact on the family in a pediatric transplant sample before, 1 month after, and 6 months after transplantation (Rodrigue et al., 1997). This prior study showed that the impact on the family increased after transplantation, with these increases persisting 6-months later.

Because there were no available normative data for the IOF-R, it was not possible to compare the current sample to a chronic illness or healthy sample to determine whether families going through the transplant process experienced significantly greater family impact. It is possible that families were significantly more impacted by their child's health condition in the pre-transplant phase compared to families of children with other health conditions and that this

level of impact continued into the post-transplant phase. Future researchers may consider collecting a comparison sample of children with another medical condition to assess this hypothesis that families going through the transplantation process experience consistently higher levels of family impact compared to families of children with other health conditions.

Alternatively, it is possible that examining mean differences from the time of the pre-transplant evaluation to 6-months after transplantation was premature for detecting significant differences. Prior research has shown that families of pediatric liver transplant recipients demonstrate significantly lower impact of the patient's health condition on the family and lower levels of family dysfunction compared to norms and published thresholds at 2-4 years after transplantation (Alonso et al., 2008; DeBolt et al., 1995). Continued assessment of this construct at later post-transplant time points and collection of a comparison sample would help determine how families are impacted by their child's evolving health condition over time. Potential comparison samples include families of children who are newly diagnosed with a life-long chronic illness that requires continuous medical intervention (e.g., inflammatory bowel disease [IBD]) or going through similarly stressful and invasive treatments for a serious illness (e.g., cancer treatment).

Predicting Patient HRQOL at Time 2 from Psychosocial Variables at Time 1

The hypothesis that greater psychological distress, parental barriers to adherence, and impact of the patient's health condition on the family at Time 1 would predict poorer Total HRQOL at Time 2 was partially supported. Preliminary analyses identified patient age at Time 1 as a demographic covariate related to Total HRQOL at Time 2. The directionality of the relationship was consistent with prior research identifying younger age at the time of transplantation as relating to better post-transplant physical HRQOL in pediatric liver transplant

recipients (Bucuvalas et al., 2003; Taylor et al., 2009). Partial correlations between Time 1 variables and Total HRQOL at Time 2, controlling for patient age at Time 1, identified significant positive correlations with Total HRQOL at Time 1, as well as significant negative correlations with patient symptoms of aggression, hyperactivity, depression, and anxiety and the impact of the patient's health condition on the family at Time 1. These findings are consistent with prior results in pediatric transplant samples and other pediatric populations (i.e., heart disease, epilepsy) showing that family functioning and patient emotional dysfunction are inversely related to HRQOL (Cohen, Mansoor, Langut, & Lorber, 2007; Devine et al., 2011; Eaton et al., 2015; Simons et al., 2008; Stevanovic, Jancic, & Lakic, 2011).

Using results from the bivariate correlations, a parsimonious hierarchical regression model was developed to predict Total HRQOL at Time 2. After accounting for patient age and Total HRQOL at Time 1 in the first two steps of the model, patient emotional and behavioral problems and the impact of the patient's health condition on the family did not account for significant additional variance when entered as single variables at Step 3. The final model predicting Total HRQOL at Time 2 only contained patient age and Total HRQOL at Time 1, with Total HRQOL at Time 1 accounting for the majority of variance and emerging as the only significant predictor. The current findings are consistent with those reported in a study of adolescent transplant recipients in which baseline HRQOL explained the most variance in HRQOL measured 18-months later, though other predictors were also identified in this study (e.g., family income, family conflict, adherence; Devine et al., 2011). Given that some of the correlations between Time 1 variables and Time 2 HRQOL were in the large effect size range (e.g., patient symptoms of hyperactivity, depression, and anxiety), the nonsignificant results may have been related to the smaller sample size or heterogeneity of the samples' HRQOL levels

based on patients' ages. Alternatively, many of the patients' psychological variables were captured on the HRQOL assessment, suggesting that the measures overlapped considerably and were not measuring distinct constructs.

Patients' levels of pre-transplant HRQOL appear to be the best predictors of post-transplant HRQOL, with lower pre-transplant HRQOL acting as a risk factor for lower post-transplant HRQOL. Total HRQOL captures aspects of patient anxiety, depression, and behavior problems, suggesting that, although the BASC-2-PRS subscales did not add significant additional variance to the regression model, emotional and behavioral factors were contributing and relating to post-transplant HRQOL. While Physical HRQOL is unlikely to change in the pre-transplant phase, Emotional and Social HRQOL may be amenable to behavioral intervention to improve patients' abilities to cope with negative emotions and to develop and maintain quality social relationships with same-aged peers. School HRQOL may also be a target of intervention via collaboration with hospital-based schoolteachers to facilitate home- or hospital-bound instruction for patients who are medically able while they await transplantation. Plans for transitioning back to school after transplantation may also be developed in the pre-transplant phase (Weil et al., 2006). Ideally, if patients' psychosocial difficulties are targeted and result in better overall HRQOL in the pre-transplant phase, patients may enjoy better HRQOL after transplantation. If patients have enhanced post-transplant emotional, social, and academic functioning, they may adjust more easily to having a new medical condition (i.e., transplant) and implementing new treatments.

Post-hoc Investigation of Patient Age at Time 1 as it Related to HRQOL at Time 2

Given the significant, negative relationship between patient age at Time 1 and Total HRQOL at Time 2, the decision was made to further investigate these relationships. This post-

hoc investigation was pursued because of the large age range represented in the current sample, which gave rise to questions about how developmental differences between older and younger patients may have influenced results, particularly for the examination of pre-to-post-transplant differences in HRQOL and how HRQOL compared to normative data. Results of this investigation indicated that patients' ages at Time 1 were related to HRQOL at Time 2 in ways that were not fully captured when the sample was analyzed as a whole (i.e., without accounting for patients' ages at Time 1 beyond entering this variable as a covariate in correlational analyses).

The first hypothesis, that the children would demonstrate significantly better HRQOL at Time 2 compared to the AYAs was partially supported. Children had significantly higher Emotional HRQOL at Time 2 compared to the AYAs, with a large effect size. These results suggested that patients who were younger at the time of the pre-transplant evaluation experienced less fear, sadness, anger, or nervousness after transplantation than older patients. This finding is inconsistent with prior pediatric transplant literature indicating no effect of child age on symptoms of emotional distress before and after transplantation (DeMaso et al., 2004; Wray & Radley-Smith, 2004). Although mean differences did not reach statistical significance, children had higher Physical, Psychosocial, and Total HRQOL than the AYAs with medium effect sizes, indicating that, in general, being younger at the time of the transplant evaluation was associated with better post-transplant quality of life in multiple domains. These results are consistent with prior research showing that younger age at the time of transplantation is associated with better HRQOL after transplantation (Bucuvalas et al., 2003; Taylor et al., 2009). Conversely, evidence from post-transplant and other chronic illness samples has indicated that pre-adolescents and younger children experience more and less deficits in HRQOL than older

children (Gerson et al., 2010; Haavisto et al., 2013; Varni et al., 2007). The contrast in findings between prior studies and the current investigation may be related to differences in patients' medical conditions represented in the sample or the length of time since patients were transplanted.

The lack of mean differences and small effect sizes associated with School HRQOL indicate that children and AYAs experiences similar deficits in their academic functioning after transplantation. This finding likely relates to both children and AYAs missing significant amounts of school before and early after transplantation to manage transplant-related medical needs. For younger children, their end-stage organ disease may have been so severe that they have never consistently attended school prior to transplantation. Older children may be more likely to fall behind peers due to increased academic expectations and rigor at school. Social HRQOL was also similar between age groups, indicating that age at the time of transplantation likely has less influence on the ability to get along with same-aged peers after transplantation or that transplantation influences Social HRQOL similarly across the pediatric age span. Given the equivocal findings in prior literature compared to the current findings, results should be replicated with a larger sample size to further evaluate their validity.

Results partially supported the next hypothesis, that both age groups would demonstrate significant improvements in HRQOL between time points but demonstrate variability in the magnitude of these differences, with children potentially showing greater improvement than AYAs. The AYAs demonstrated significant improvements on all domains of HRQOL except for Emotional, which was slightly lower at Time 2 compared to Time 1. The children only showed significant improvements on Total HRQOL, though Physical and Emotional HRQOL increased after transplantation with large effect sizes. This is the first study to investigate pre-to-post-

transplantation differences in HRQOL based on patients' ages at the time of the pre-transplant evaluation.

The most novel finding from this portion of the analyses was that, while AYAs had lower HRQOL across domains after transplantation compared to children, AYAs made larger improvements in HRQOL between time points than children. This finding was inconsistent with the portion of the hypothesis stating that children would make the largest post-transplant improvements in HRQOL. These results provide hope for AYAs going through the transplantation process who may feel discouraged that they are experiencing significant deficits in physical, social, emotional, and academic functioning related to their medical condition. Providers may inform AYA patients that their Physical and Psychosocial HRQOL is expected to improve on most domains after receiving a transplant without significant intervention beyond receiving medical treatment for their new transplant. Because Emotional HRQOL did not differ from Times 1 to 2, particular attention may be focused on assessing AYAs' emotional functioning and coping in the early months after transplantation. Although post-transplant results did not indicate that patients were experiencing clinically significant levels of psychological distress, there may be issues related to adjusting to a new medical condition that mildly affect mood and could benefit from brief intervention.

The hypothesis that children would have smaller differences in HRQOL compared to healthy and chronically ill norms than the AYAs was partially supported. Compared to healthy norms, children and AYAs had significantly worse HRQOL at Time 2 with the exception of the children's Emotional HRQOL, which was similar to that of healthy children. Patients who are younger children at the time of transplantation may be less aware of the process or gravity of their medical condition that led to transplantation and experience less emotional distress as a

result. In contrast, AYAs may be highly aware of the transplant process and potential negative outcomes of transplantation and, in turn, respond with heightened emotional distress.

AYAs' lower levels of Emotional HRQOL compared to children's is consistent with a prior study showing that AYA cancer survivors who underwent treatment at older ages experienced significantly more post-treatment emotional distress than patients who were treated at younger ages (Kazak et al., 2010). In our transplant sample, it may be useful to consider these findings in the context of living with chronic stress in the form of a life-threatening medical condition. AYAs had been diagnosed with a serious medical condition for significantly longer than the children, suggesting that they and their families had been under chronic stress related to the diagnoses for longer as well. Given evidence of relationships between chronic stress, mood dysregulation, and physical dysfunction (Shonkoff et al., 2012), the longer amount of time that AYAs spent living with a chronic, life-threatening, and physically-debilitating health condition may have explained this age groups' lower levels of Emotional HRQOL. In contrast, the children had been chronically ill and, thus, chronically stressed, for shorter amounts of time resulting in less disruption to their emotional functioning during and after the transplant process. Alternatively, because AYAs had been living with a medical condition for longer than children, their parent who completed the measure of HRQOL may have had a more stable view of the patient's identity as being a child with physical and psychosocial deficits. Parents of children who had been sick for less time may have more easily adapted to their child's changing health status or been more perceptive of changes in HRQOL.

Compared to chronically ill norms, children and AYAs were similar across most domains of HRQOL. Transplantation is considered a trade from having a life-threatening disease to a chronic medical condition (Lerret et al., 2014), thus it is encouraging that patients in both age

groups achieved this level of HRQOL within just 6-months of receiving a transplant. For children, the Physical HRQOL domain was actually significantly better than that of chronically ill norms. Although research conducted in the post-transplant phase indicates that pediatric patients continue to experience significant deficits in HRQOL up to 10 years after transplantation (Ng et al., 2012), it remains possible that some patients may continue to see improvements in HRQOL in the post-transplant phase and eventually achieve levels that are close to those of healthy children and AYAs. At this point, it is unknown if patients' HRQOL continues to improve after 1-year post-transplantation (Cole et al., 2004) or if HRQOL levels begin to stabilize. It is also unknown if AYAs continue to show the largest increases in post- compared to pre-transplant HRQOL or children may demonstrate a slower but steadier rate of improvement. Continued follow-up of patient cohorts representing a wide age range would help answer these remaining questions.

The final, exploratory set of post-hoc analyses showed that there were differences in correlations between Time 1 psychosocial variables and Total HRQOL at Time 2 that emerged between age groups. Baseline HRQOL was associated with post-transplant HRQOL in both ages groups. However, for children, only hyperactivity symptoms at Time 1 were significantly and positively related to HRQOL at Time 2. These data are consistent with prior research showing that symptoms of attention deficit/hyperactivity disorder (ADHD) are related to lower HRQOL in children with epilepsy (Sherman, Slick, Connelly, & Eyrl, 2007). Children with ADHD, in general, demonstrate significantly impaired psychosocial HRQOL (Klassen, Miller, & Fine, 2004) in comparison to healthy children and children with asthma (Escobar et al., 2005). Children with ADHD have demonstrated severely impaired psychosocial HRQOL that is comparable to that of children with newly diagnosed cancer and cerebral palsy (Varni &

Burwinkle, 2006). These findings are consistent with the social, emotional, and academic issues that arise from the ADHD symptom constellation. For children presenting with higher hyperactivity symptoms and a chronic medical condition, such as solid organ transplant, the impact on Psychosocial HRQOL may be even more significant. Further, younger children may, developmentally, be more likely than AYAs to present with behavioral problems (Bongers, Koot, van der Ende, & Verhulst, 2004), such as those captured on the Hyperactivity scale of the BASC-2-PRS. The lack of relationship between Total HRQOL and symptoms of attention problems may be explained by the poor internal reliability of the Attention Problems subscale in the current sample.

In contrast to children, AYAs demonstrated significant correlations between depression and anxiety symptoms and the impact of the patient's health condition on the family at Time 1 with Total HRQOL at Time 2. These findings are consistent with those reported in a study of adolescents with IBD demonstrating that parental distress, which is captured on the IOF-R scale used in the current study, and adolescent depressive symptoms both related to adolescents' HRQOL, even after controlling for disease severity and demographic factors (Herzer, Denson, Baldassano, & Hommel, 2011). Other research has demonstrated significant inverse relationships between patient symptoms of anxiety and HRQOL in pediatric patients with other medical conditions (e.g., epilepsy, chronic pain; Johnson, Jones, Seidenberg, & Hermann, 2004; Mahrer, Montano, Gold, 2012; Stevanovic, Jancic, & Lakic, 2011). In adolescent samples, the dual influence of patients' feelings of sadness, nervousness, and worry and families' experience of stress related to the patient's medical condition may be more disruptive to daily physical and psychosocial functioning than in child samples. Feelings of depression and anxiety may also be more prevalent in AYA versus child samples (Costello, Mustillo, Erkanli, Keeler, & Angold,

2003) and, hence, more relevant to their overall HRQOL. Replication of these results in larger samples with greater representation of the pediatric age span is needed to validate findings.

Predicting Patient Nonadherence at Time 2 from Psychosocial Variables at Time 1

The hypothesis that greater psychological distress, parental barriers to adherence, impact of the patient's health condition on the family, and nonadherence at Time 1 would predict patient nonadherence at Time 2 was not well supported. Unfortunately, the parent proxy-report nonadherence data had an extremely non-normal distribution due to an overrepresentation of parents reporting no missed or late medications for their child in the past week. To alleviate this issue, a square root transformation was used to correct the non-normal distribution of the parent proxy-report data. Even with this transformation procedure, the data remained highly skewed. When these transformed data were analyzed using Pearson product-moment correlations, significant, positive relationships were found between patient symptoms of aggression and hyperactivity, the impact of the patient's health condition on the family, and parental barriers to adherence at Time 1 and the percentage of missed medications at Time 2.

These correlations make intuitive sense: patients with more behavioral problems, families who are more negatively affected by the child's health condition, and parents with more barriers to adherence prior to transplantation would likely be expected to have children who miss more medications after transplantation. Beyond the intuitive nature of these findings, the current results are consistent with prior literature from both pediatric transplantation and other chronic illnesses showing that greater child behavioral problems, family dysfunction, and barriers to adherence relate to higher levels of medication nonadherence (Eaton et al., 2015; Fredericks et al., 2007; Reed-Knight et al., 2013; Simons et al., 2010). However, the violation of the normality assumption for Pearson product-moment correlations rendered these results untrustworthy and

possibly invalid. The parent proxy-report data were also analyzed using Spearman's rho correlations to account for the non-normal distribution. The impact of the patient's health condition on the family at Time 1 was significantly and negatively correlated with the percentage of late medications taken at Time 2. Parents who identified as experiencing less family impact and stress from their child's health condition may have felt more relaxed about administering medications in a timely manner, potentially resulting in more medications being taken late. Because of the distribution concerns with the data, these results should also be interpreted cautiously.

The extreme skewness of the parent proxy-report data highlights issues with using self-report measures to assess patients' medication nonadherence. Specifically, self-report measures often underestimate nonadherence due to social desirability concerns (Stirrat et al., 2015), resulting in data, such as those in the current study, that may be invalid or not representative of true medication-taking behavior. Despite this limitation, self-report measures of nonadherence are the most cost-effect method for routinely monitoring medication-taking behaviors. However, if these instruments are not sensitive to detecting true cases of nonadherence, there could be serious clinical consequences for failing to identify nonadherent patients, including organ rejection or death (Fredericks et al., 2007). Further, data collection and research quality suffers by not accurately capturing patients' behavior and potentially influencing results. The development of more sensitive and valid self-report assessments of nonadherence is needed to address these significant limitations. Stirrat and colleagues (2015) recently reviewed pediatric self-reports for measuring nonadherence and developed specific recommendations for how to improve future measures (e.g., estimate overall nonadherence within a longer time interval, such

as the past 30 days, to reduce ceiling effects). These recommendations may guide future endeavors to develop sensitive, valid, and reliable instruments for measuring nonadherence.

Objective measures of nonadherence have been recommended, particularly for transplant recipients (Stuber et al., 2008), as a complementary method to self-reports for assessing nonadherence (Quittner et al., 2008). Consistent with this recommendation, the current study included an objective measure of nonadherence: CoV% for immunosuppressant laboratory values collected after patients were transplanted. These data were normally distributed but no significant correlations with psychosocial predictor variables at Time 1 emerged. Prior literature has shown that psychosocial variables, such as parental emotional functioning related to their child's medical status and patient social and school HRQOL, are related to variation in laboratory values in pediatric transplant recipients (Fredericks et al., 2007; Fredericks et al., 2008). The lack of relationships observed in this sample may have related to the relatively short time frame during which these values were collected (i.e., immediately post-transplantation and up to 12-months later). Immunosuppressant values are often not stable until 6-months after transplantation due to potential medical complications or medication adjustments (Pollock-BarZiv et al., 2010; Shemesh et al., 2008). Additionally, it was not possible to assess the validity of CoV% values collected for the current sample due to the normality issues with the parent-reported nonadherence data. Future researchers should re-examine how CoV% values relate to the Time 1 psychosocial predictors included in this study when patients' medical statuses become more stable (i.e., at 12-months post-transplantation or later). Furthermore, alternative methods for assessing medication nonadherence should be explored (e.g., the MEMSCap™ electronic monitoring system), particularly in light of the issues encountered with the parent proxy-report measure utilized in the current study. The inclusion of multiple methods of

measuring nonadherence would provide greater opportunities to reliably assess the validity of these instruments.

Limitations

Although the current study adds new and novel information to the pediatric transplantation literature, it was not without limitations. There were significant differences between the eight families who refused to participate (7%) versus those who completed measures for the study at Time 1, specifically on patients' races. Thus, the current sample may not be fully representative of all families who present for solid organ transplant evaluations. Of note, there were no census data available on the racial breakdown of children who present for solid organ transplants. The full Time 1 sample was nearly 50% non-Caucasian and the Time 2 sample was nearly 40% non-Caucasian, which is consistent with racial demographics in the United States and actually an overrepresentation of non-Caucasian individuals than in the state where these data were collected (United States Census Bureau, 2014).

The sample size was small, which reduced statistical power for correlational and post-hoc analyses. The sample was also comprised of patients representing a large age range (0-21 years). Post-hoc analyses of HRQOL at Time 2 based on patients' ages at Time 1 were included to address this limitation and strengthen findings by providing preliminary data on how results may vary based on patient age. Because it was not possible to control when patients were transplanted or what type of transplant was needed for a given patient, there was variability in the amount of time that passed between time points and unequal representation of the three organ groups that were included in the study.

Parents were the sole respondents to study measures though multiple reporters are commonly used to assess child psychosocial functioning to address potential informant

discrepancies (Mash & Hunsley, 2005). Additionally, the self- and proxy-report measures of psychological dysfunction utilized in the current study may not have adequately captured the stress experienced by patients and families going through the transplantation process. There may be utility in gathering alternative measures of participants' distress, such as physiological indices of patient and parent stress (e.g., measuring salivary or blood cortisol levels, heart rate, blood pressure; Miller, Chen, & Zhou, 2007; Taylor, Repetti, & Seeman, 1997).

Only one post-transplant follow-up time point was included for data collection. However, patient and parent functioning may continue to change as patients move further away from their date of transplantation. It will be important to continue following patients beyond the early post-transplant phase to increase our understanding of patients' long-term psychosocial outcomes and pre-transplant variables that may predict these outcomes.

Clinical Implications

Results of the current study extend our understanding of how pediatric patients with end-stage organ disease and their families change, psychosocially, from the pre-to-post-transplantation phase and identify factors present before transplantation that relate to post-transplant HRQOL. These preliminary findings serve as a starting point for providing psychoeducation to families of children undergoing evaluation for a solid organ transplant on how aspects of patients' HRQOL and parents' psychological functioning may improve from pre-to-post-transplantation. Most significantly, the current findings help guide pre-transplant evaluation practices by identifying pre-transplant patient HRQOL as the best predictor of post-transplant patient HRQOL. These results suggest that lower pre-transplant HRQOL is a risk factor for lower post-transplant HRQOL. These results provide preliminary empirical evidence for the utility of routinely assessing this construct using the PedsQL (Varni et al., 2001) at the

pre-transplant evaluation and after transplantation to obtain standardized information about patients' physical, emotional, social, and academic functioning. The PedsQL is efficiently administered (i.e., takes less than 10 minutes to complete), which would enable providers to obtain comprehensive information without disrupting clinic flow. Patients who present with low HRQOL prior to transplantation may benefit from intervention to address psychosocial deficits related to academic, social, or emotional functioning. If these aspects of HRQOL can be addressed before transplantation, patients may have a smoother transition, psychosocially, into the post-transplantation phase.

The issues that arose with measuring nonadherence in the current study raise concerns about the validity of using self-report assessments of nonadherence, both in clinical and research settings, and emphasize the need to develop more sensitive and accurate evaluation procedures. The current results highlight the necessity of including multiple measures of nonadherence whenever possible. Additionally, the problems with the self-report measure used in the current study suggest that alternative self-report instruments need to be developed to address issues with ceiling/floor effects and social desirability that likely bias data gathered with these assessments. Given the clinical utility of being able to assess nonadherence efficiently and inexpensively using self-report measures, future researchers should consider large-scale development and testing of such instruments.

Lastly, the post-hoc investigation of differences in HRQOL based on patients' ages at the time of the pre-transplant evaluation may help providers consider what differences in HRQOL occur after transplantation for individual patients. Younger children may experience better HRQOL after transplantation that is closer to that of healthy norms. Conversely, AYAs may have lower HRQOL at the pre-transplant evaluation but make larger post-transplant

improvements than younger children. Encouragingly, patients appear to make significant gains in multiple domains of HRQOL, regardless of their age and without intervention beyond medical treatment required for maintaining the solid organ transplant. Further investigation of how HRQOL is related to patients' ages or developmental statuses is warranted to guide individualized and tailored pre-transplant assessment and intervention efforts to support the adjustment and coping of patients and families throughout the transplantation process.

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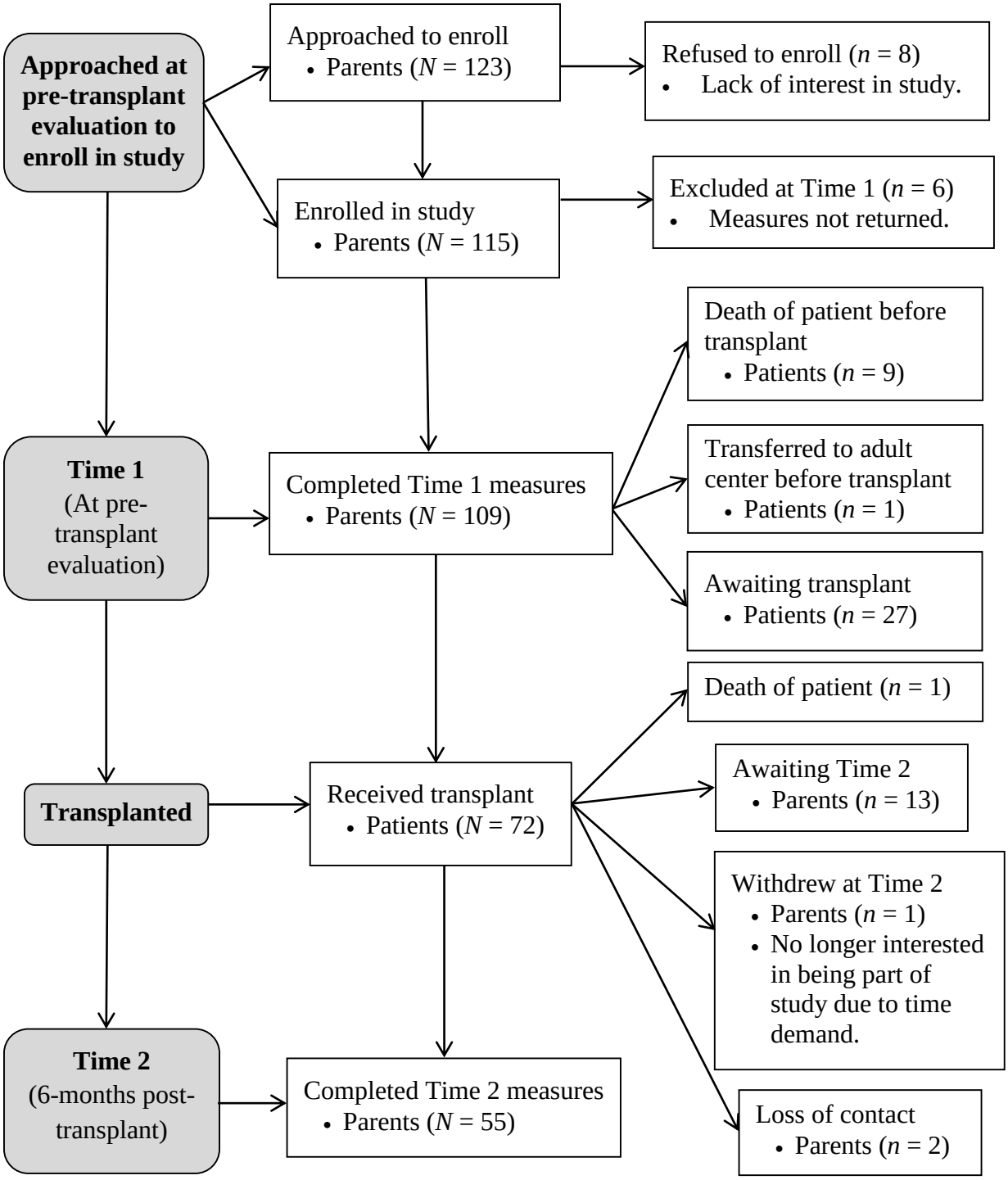

Figure 1: Flow of Participants from the Time of Study Enrollment to Time 2

Note. This figure illustrates the number of participants at both Time 1 and 2 and the number of participants excluded at Time 1 or lost to follow-up at Time 2.

Table 1. *Demographic Information for Families Enrolled in the Study at Time 1*

Factor	Patients		Parents	
	Frequency	%	Frequency	%
Sex				
Male	59	54.1	12	11
Female	50	45.9	97	89
Race				
Caucasian/White	57	52.3	60	55
African American/Black	40	36.7	41	37.6
Hispanic	4	3.7	7	6.4
Asian	1	.9	1	.9
Multiracial	7	6.4	--	--
Insurance type				
Medicare	51	46.8	--	--
Private	45	41.3	--	--
Medicare and private	13	11.9	--	--
Family income				
Less than $10,000	--	--	12	11
$10,000-24,999	--	--	17	15.6
$25,000-49,999	--	--	20	18.3
$50,000-74,999	--	--	30	27.5
$75,000-99,999	--	--	12	11
$100,000+	--	--	13	11.9
Prefer not to report	--	--	5	4.6
Parent marital status	--	--		
Married	--	--	80	73.4
Single, never married	--	--	18	16.5
Divorced or separated	--	--	11	10.1
Parent education level				
High school diploma/GED or less	--	--	25	22.9
Some college	--	--	33	30.3
Associate’s degree	--	--	10	9.2
Bachelor’s degree	--	--	27	24.8
Graduate degree	--	--	14	12.8

Note. $N = 109$.

Table 2. *Demographic Information for Families with Completed Time 2 Questionnaires*

Factor	Patients		Parents	
	Frequency	%	Frequency	%
Sex				
Male	26	47.3	7	12.7
Female	29	52.7	48	87.3
Race				
Caucasian/White	33	60.0	34	61.8
African American/Black	16	29.1	16	29.1
Hispanic	2	3.6	5	9.1
Multiracial	4	7.3	--	--
Insurance type				
Medicare	21	38.2	--	--
Private	27	49.1	--	--
Medicare and private	7	12.7	--	--
Family income				
Less than $10,000	--	--	5	9.1
$10,000-24,999	--	--	6	10.9
$25,000-49,999	--	--	8	14.5
$50,000-74,999	--	--	13	23.6
$75,000-99,999	--	--	8	14.5
$100,000+	--	--	10	18.2
Prefer not to report	--	--	5	9.1
Parent marital status	--	--		
Married	--	--	45	81.8
Single, never married	--	--	7	12.7
Divorced or separated	--	--	3	5.5
Parent education level				
High school diploma/GED or less	--	--	12	21.8
Some college	--	--	18	32.7
Associate's degree	--	--	4	7.3
Bachelor's degree	--	--	13	23.6
Graduate degree	--	--	8	14.5

Note. $N = 55$.

Table 3. *Descriptive Data for Paired Patient Variables and Differences from Time 1 to Time 2*

Variable	Time 1		Time 2					
HRQOL	*M* (*SD*)	Range	*M* (*SD*)	Range	*t*	*df*	*p*	*d*
Physical	60.27 (27.84)	9.38 – 100	73.98 (22.89)	0 – 100	-3.09	39	.004	-.54
Emotional	68.63 (20.85)	5 – 100	71.04 (19.38)	15 – 100	-.81	39	.42	-.11
Social	74.47 (20.03)	30 – 100	80.75 (19.17)	41 – 100	-2.34	39	.02	-.32
School	56.58 (28.44)	0 – 100	62.10 (21.70)	20 – 100	-1.59	34	.12	-.22
Psychosocial	64.89 (18.71)	30 – 100	72.30 (17.59)	28.33 – 100	-3.38	39	.002	-.41
Total	64.77 (20.65)	21.87 – 100	74.07 (18.14)	19.57 – 100	-3.65	39	.001	-.48
Psychological Functioning	*M* (*SD*)	Range	*M* (*SD*)	Range	*t*	*df*	*p*	*d*
Depression	51.33 (10.39)	32 – 73	48.38 (10.58)	30 – 78	1.96	39	.06	.28
Anxiety	48.28 (11.31)	30 – 70	46.50 (11.82)	29 – 79	1.25	39	.22	.15
Aggression	46.05 (7.52)	34 – 67	45.55 (9.30)	34 – 73	.53	39	.60	.06
Attention problems	49.08 (10.26)	29 – 76	50.85(10.59)	33 – 73	-1.65	39	.11	-.17
Hyperactivity	47.43 (8.20)	34 – 99	47.30 (11.37)	28 – 77	.09	39	.93	.01

Note. There were five patients not attending school at the time of data collection, which accounts for the different degrees of freedom for this domain of HRQOL.

Table 4. *Descriptive Data for Paired Parent Variables and Differences from Time 1 to Time 2*

Variable	Time 1		Time 2					
Psychological Stress	*M* (*SD*)	Range	*M* (*SD*)	Range	*t*	*df*	*p*	*d*
Depression	50.09 (9.52)	40 – 71	46.70 (8.51)	40 – 67	6.30	52	.02	.38
Anxiety	50.79 (10.60)	30 – 71	47.23 (11.06)	38 – 78	6.93	52	.04	.33
Somatization	48.98 (9.77)	41 – 73	46.25 (9.73)	39 – 76	5.45	52	.04	.28
Global Stress Index	49.64 (11.44)	33 – 75	44.11 (12.16)	33 – 74	8.96	52	.002	.47
PTSD symptoms	*M* (*SD*)	Range	*M* (*SD*)	Range	*t*	*df*	*p*	*d*
Avoidance	6.74 (6.37)	0 – 30	4.45 (4.64)	0 – 21	2.49	52	.02	.41
Intrusion	8.47 (5.38)	0 – 20	6.91 (5.35)	0 – 24	1.76	52	.09	.29
Hyperarousal	4.83 (3.90)	0 – 16	3.66 (4.57)	0 – 19	1.74	52	.09	.28
Total PTSD	20.04 (13.29)	0 – 48	15.02 (13.01)	0 – 63	2.33	52	.02	.38
Impact on the family	*M* (*SD*)	Range	*M* (*SD*)	Range	*t*	*df*	*p*	*d*
Familial/social	18.24 (5.33)	9 – 36	18.23 (5.49)	9 – 34	1.15	51	.88	.002
Personal strain	13.44 (3.80)	6 – 24	13.42 (4.43)	5 – 24	1.04	51	.97	.005
Total impact	31.58 (8.63)	15 – 60	31.65 (9.47)	15 – 58	-.08	51	.94	-.008

Table 5. *Comparison of Patient HRQOL to Healthy Norms at Each Time Point*

Variable	Norms	Time 1				Time 2			
HRQOL	*M* (*SD*)	*M* (*SD*)	*t*	*p*	*d*	*M* (*SD*)	*t*	*p*	*d*
Physical	89.32 (16.35)	59.77 (28.31)	-6.84	<.001	1.28	76.04 (22.55)	-3.95	<.001	.67
Emotional	82.62 (17.54)	69.77 (20.91)	-4.04	<.001	.67	72.70 (19.43)	-3.43	.001	.54
Social	91.56 (14.20)	73.92 (20.52)	-5.64	<.001	1.00	81.44 (18.79)	-3.61	.001	.61
School	85.47 (17.61)	56.72 (27.66)	-6.49	<.001	1.24	63.63 (22.33)	-6.11	<.001	1.09
Psychosocial	86.58 (12.79)	64.65 (18.52)	-7.76	<.001	1.28	73.79 (17.50)	-4.90	<.001	.84
Total	87.61 (12.33)	64.60 (20.81)	-7.25	<.001	1.35	75.67 (17.89)	-4.48	<.001	.78

Note. Patient HRQOL at Time 1 and Time 2 was compared to published healthy norms (Varni et al., 2001). There were 43 patients at Time 1 and 45 patients at Time 2. There were four patients and Time 1 and six patients at Time 2 who were not attending school and were omitted from analyses.

Table 6. *Comparison of Patient HRQOL to Chronically Ill Norms at Each Time Point*

Variable	Norms	Time 1				Time 2			
HRQOL	*M* (*SD*)	*M* (*SD*)	*t*	*p*	*d*	*M* (*SD*)	*t*	*p*	*d*
Physical	73.28 (27.02)	59.77 (28.31)	-3.13	.003	.49	76.04 (22.55)	.82	.42	-.12
Emotional	73.05 (23.27)	69.77 (20.91)	-1.03	.31	.15	72.70 (19.43)	-.12	.91	.02
Social	79.77 (21.91)	73.92 (20.52)	-1.87	.07	.28	81.44 (18.79)	.60	.55	-.08
School	71.08 (23.99)	56.72 (27.66)	-3.24	.002	.55	63.63 (22.33)	-2.08	.04	.32
Psychosocial	74.80 (18.16)	64.65 (18.52)	-3.59	.001	.55	73.79 (17.50)	-.39	.70	.02
Total	74.22 (18.40)	64.60 (20.81)	-3.03	.004	.49	75.67 (17.89)	.54	.59	-.08

Note. Patient HRQOL at Time 1 and Time 2 was compared to published chronically ill norms (Varni et al., 2001). There were 43 patients at Time 1 and 45 patients at Time 2. There were four patients and Time 1 and six patients at Time 2 who were not attending school and were omitted from analyses.

Table 7. *Comparison of Parent Variables to Norms at Each Time Point*

Variable	Norms	Time 1			Norms	Time 2		
PTSD symptoms	*M* (*SD*)	*M* (*SD*)	*t*	*d*	*M* (*SD*	*M* (*SD*)	*t*	*d*
Avoidance	13.10 (14.00)	6.73 (6.37)	-7.42*	.59	9.40 (9.40)	4.45 (4.64)	-7.77*	.67
Intrusion	19.30 (9.80)	8.35 (5.41)	-15.02*	1.27	12.10 (9.70)	6.91 (5.35)	-7.07*	.66
Hyperarousal	11.20 (10.00)	4.89 (4.04)	-11.58*	.83	6.70 (7.30)	3.66 (4.57)	-4.85*	.50
Total PTSD	43.60 (14.00)	19.96 (13.50)	-12.98*	1.72	28.20 (24.50)	15.02 (13.01)	-7.37*	.67

Note. Parental PTSD symptoms were compared to published norms of mothers whose children were in treatment for cancer at Time 1 and mothers whose children survived cancer treatment at Time 2 (Kazak et al., 2005). There were 55 parents at Time 1 and 54 parents at Time 2 for the PTSD symptoms.

*$p<.001$

Table 8. *Correlations Between Psychosocial Predictor Variables at Time 1 and Patient HRQOL at Time 2*

Variables	**1**	2	3	4	5	6	7	8	9	10	11
Outcome											
1. HRQOL at T2	--										
Patient variables at T1											
2. HRQOL	**.66*****	--									
3. Aggression	**-.34***	-.35*	--								
4. Attention problems	**-.16**	-.16	.13	--							
5. Hyperactivity	**-.50****	-.43**	.68***	.54***	--						
6. Depression	**-.53*****	-.52***	.66***	.01	.47**	--					
7. Anxiety	**-.53*****	-.55***	.32*	.01	.29	.59***	--				
Parent variables at T1											
8. PTSD symptoms	**-.25**	-.41**	.02	.30	.33*	.07	.16	--			
9. Global Stress Index	**-.31**	-.53***	.06	.24	.26	.19	.18	.69***	--		
10. Impact on family	**-.52****	-.49**	.52***	.36*	.51***	.60***	.39*	.29*	.45**	--	
11. Adherence barriers	**-.25**	-.32*	.25	.33*	.26	.29	.12	.14	.22	.57***	--

Note. Correlations with HRQOL at Time 2 are partial correlations that controlled for patient age at Time 1. All other correlations are Pearson product-moment correlations.

$^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$

Table 9. *Comparison of Patient HRQOL at Time 2 Between Age Groups*

Variable	Child	AYA			
HRQOL	*M* (*SD*)	*M* (*SD*)	*t*	*p*	*d*
Physical	80.50 (17.34)	70.47 (27.20)	1.50	.14	.44
Emotional	78.60 (18.17)	65.33 (18.81)	2.40	.02	.72
Social	81.60 (17.06)	81.25 (21.21)	.06	.95	.02
School	63.50 (26.01)	63.77 (18.41)	-.04	.97	-.01
Psychosocial	76.62 (17.31)	70.27 (17.52)	1.22	.23	.36
Total	78.25 (15.61)	72.44 (20.34)	1.09	.28	.32

Note. There were 25 patients in the Child group and 20 patients in the AYA group. There were five children and one AYA who were not attending school at the time of data collection and were omitted from analyses involving the School HRQOL domain.

Table 10. *Differences in HRQOL from Time 1 to Time 2 within the Child and AYA Groups*

Variable	Time 1	Time 2				
Child HRQOL	*M* (*SD*)	*M* (*SD*)	*t*	*df*	*p*	*d*
Physical	63.95 (29.72)	77.50 (17.61)	-2.01	19	.06	-.55
Emotional	68.25 (16.72)	76.75 (18.66)	-1.94	19	.07	-.48
Social	75.44 (16.72)	80.25 (17.43)	-1.36	19	.19	-.28
School	60.42 (35.82)	60.10 (25.55)	.06	15	.96	.01
Psychosocial	69.10 (18.14)	74.34 (17.87)	-1.74	19	.10	-.29
Total	67.27 (20.78)	75.70 (16.01)	-2.25	19	.04	-.45
AYA HRQOL	*M* (*SD*)	*M* (*SD*)	*t*	*df*	*p*	*d*
Physical	56.58 (26.06)	70.47 (27.20)	-2.33	19	.03	-.61
Emotional	69.00 (24.74)	65.33 (18.81)	1.02	19	.32	.17
Social	73.50 (23.29)	81.25 (21.21)	-1.90	19	.07	-.35
School	53.36 (20.85)	63.77 (18.41)	-2.48	18	.02	-.53
Psychosocial	60.67 (18.77)	70.27 (17.52)	-3.00	19	.007	-.53
Total	62.26 (20.73)	72.44 (20.34)	-2.87	19	.01	-.50

Note. There were 20 matched pairs in the Child and AYA groups. There were four children and one AYA who were not attending school at one of the two time points and, therefore, were omitted from analyses.

Table 11. *Comparison of the HRQOL at Time 2 to Healthy Norms in the Child and AYA Age Groups*

Variable	Norms	Time 2				
Child HRQOL	*M* (*SD*)	*M* (*SD*)	*t*	*df*	*p*	*d*
Physical	89.32 (16.35)	80.50 (17.34)	-2.54	24	.02	.52
Emotional	82.62 (17.54)	78.60 (18.17)	-1.11	24	.28	.23
Social	91.56 (14.20)	81.60 (17.06)	-2.92	24	.008	.63
School	85.47 (17.61)	63.50 (26.01)	-3.78	19	.001	.99
Psychosocial	86.58 (12.79)	76.62 (17.31)	-2.88	24	.008	.65
Total	87.61 (12.33)	78.25 (15.61)	-3.00	24	.006	.67
AYA HRQOL	*M* (*SD*)	*M* (*SD*)	*t*	*df*	*p*	*d*
Physical	89.32 (16.35)	70.47 (27.20)	-3.10	19	.006	.84
Emotional	82.62 (17.54)	65.33 (18.81)	-4.11	19	.001	.95
Social	91.56 (14.20)	81.25 (21.21)	-2.17	19	.04	.57
School	85.47 (17.61)	63.77 (18.41)	-5.14	18	<.001	1.20
Psychosocial	86.58 (12.79	70.27 (17.52)	-4.16	19	.001	1.06
Total	87.61 (12.33)	72.44 (20.34)	-3.33	19	.003	.90

Table 12. *Comparison of the HRQOL at Time 2 to Chronically Ill Norms in the Child and AYA Age Groups*

Variable	Norms	Time 2				
Child HRQOL	*M* (*SD*)	*M* (*SD*)	*t*	*df*	*p*	*d*
Physical	73.28 (27.02)	80.50 (17.34)	2.10	24	.04	-.32
Emotional	73.05 (23.27)	78.60 (18.17)	1.53	24	.14	-.27
Social	79.77 (21.91)	81.60 (17.06)	.54	24	.60	-.09
School	71.08 (23.99)	63.50 (26.01)	-1.30	19	.21	.30
Psychosocial	74.80 (18.16)	76.62 (17.31)	.52	24	.61	-.10
Total	74.22 (18.40)	78.25 (15.61)	1.30	24	.21	-.24
AYA HRQOL	*M* (*SD*)	*M* (*SD*)	*t*	*df*	*p*	*d*
Physical	73.28 (27.02)	70.47 (27.20)	-.46	19	.65	.10
Emotional	73.05 (23.27)	65.33 (18.81)	-1.83	19	.08	.36
Social	79.77 (21.91)	81.25 (21.21)	.31	19	.76	.07
School	71.08 (23.99)	63.77 (18.41)	-1.73	18	.10	.34
Psychosocial	74.80 (18.16)	70.27 (17.52)	-1.16	19	.26	.25
Total	74.22 (18.40)	72.44 (20.34)	-.39	19	.70	.09

Table 13. *Correlations Between Psychosocial Predictor Variables at Time 1 and Patient HRQOL at Time 2 Within the Child Group*

Variables	**1**	2	3	4	5	6	7	8	9	10	11
Outcome											
1. HRQOL at T2	--										
Patient variables at T1											
2. HRQOL	**.61****	--									
3. Aggression	**-.32**	-.34	--								
4. Attention problems	**-.35**	-.31	.08	--							
5. Hyperactivity	**-.54***	-.50*	.61**	.73***	--						
6. Depression	**-.19**	-.41	.66**	-.03	.34	--					
7. Anxiety	**-.36**	-.42	.25	.16	.31	.43	--				
Parent variables at T1											
8. PTSD symptoms	**.13**	-.36	-.18	.42	.30	-.15	-.12	--			
9. Global Stress Index	**-.21**	-.64**	-.01	.42	.43	.24	.03	.60**	--		
10. Impact on family	**-.21**	-.53*	.40	.45*	.68**	.48*	.42	.22	.63**	--	
11. Adherence barriers	**-.31**	-.60**	.14	.42	.38	.25	.18	.37	.45*	.50*	--

$^{*}p < .05, ^{**}p < .01, ^{***}p < .001$

Table 14. *Correlations Between Psychosocial Predictor Variables at Time 1 and Patient HRQOL at Time 2 Within the AYA group*

Variables	**1**	2	3	4	5	6	7	8	9	10	11
Outcome											
1. HRQOL at T2	--										
Patient variables at T1											
2. HRQOL	**.70****	--									
3. Aggression	**-.29**	-.37	--								
4. Attention problems	**.05**	.06	.21	--							
5. Hyperactivity	**-.43**	-.36	.75***	.33	--						
6. Depression	**-.76*****	-.69**	.66**	.08	.59**	--					
7. Anxiety	**-.67****	-.68**	.37	-.18	.26	.75***	--				
Parent variables at T1											
8. PTSD symptoms	**-.42**	-.35	.14	.08	.18	.31	.51*	--			
9. Global Stress Index	**-.28**	-.32	.08	-.17	.07	.14	.44	.34**	--		
10. Impact on family	**-.59****	-.47*	.66**	.28	.65**	.73***	.39	.23	.10	--	
11. Adherence barriers	**-.21**	-.11	.42	.29	.33	.36	.08	.13	.09	.73***	--

$^{*}p < .05, ^{**}p < .01, ^{***}p < .001$

Table 15. *Pearson Product-Moment Correlations Between Psychosocial Predictor Variables at Time 1 and Medication Nonadherence at Time 2*

Variables	**1**	**2**	**3**	4	5	6
Outcomes at T2						
1. % missed meds	--					
2. % late meds	**-.04**	--				
3. % nonadherence	**.52*****	**.83*****	--			
Patient variables at T1						
4. % missed meds	**.01**	**.03**	**.02**	--		
5.% late meds	**-.01**	**-.14**	**-.11**	-.11	--	
6. % nonadherence	**.02**	**-.05**	**-.07**	.84***	.44**	--
7. HRQOL	**-.22**	**.02**	**-.10**	-.11	-.08	-.18
8. Aggression	**.42****	**-.18**	**.09**	-.05	.08	.02
9. Attention problems	**.21**	**.06**	**.18**	.08	.24	-.22
10. Hyperactivity	**.32***	**-.10**	**.10**	-.08	.08	-.01
11. Depression	**.29**	**-.21**	**-.02**	.10	.17	.20
12. Anxiety	**.15**	**-.11**	**-.02**	.29	.13	.35*
Parent variables at T1						
13. PTSD symptoms	**.05**	**-.06**	**-.01**	.01	.23	.14
14. Global Stress Index	**-.02**	**-.008**	**.004**	-.10	.33*	.09
15. Impact on family	**.41****	**-.33***	**-.04**	-.07	-.01	-.06
16. Adherence barriers	**.51*****	**-.12**	**.19**	-.08	.28	.08

Note. Correlations between patient variables and parent variables at T1 appear in Table 14. MAM data was transformed using a square root transformation due to the skewed distribution of the data.
$^{*}p<.05$, $^{**}p<.01$, $^{***}p<.001$

Table 16. *Spearman's Correlations Between Psychosocial Predictor Variables at Time 1 and Medication Nonadherence at Time 2*

Variables	**1**	**2**	**3**	4	5	6
Outcomes at T2						
1. % missed meds	--					
2. % late meds	**.10**	--				
3. % nonadherence	**.60*****	**.81*****	--			
Patient variables at T1						
4. % missed meds	**.01**	**.22**	**-.07**	--		
5.% late meds	**.03**	**-.18**	**-.10**	-.08	--	
6. % nonadherence	**.07**	**.09**	**.01**	.75***	.53***	--
7. HRQOL	**-.25**	**-.09**	**-.20**	-.10	-.03	-.18
8. Aggression	**.29**	**-.07**	**.11**	.05	.12	.15
9. Attention problems	**.16**	**-.02**	**.15**	.09	.07	.15
10. Hyperactivity	**.14**	**-.05**	**.09**	-.11	.04	-.03
11. Depression	**.19**	**-.12**	**-.002**	.19	.18	.27
12. Anxiety	**.20**	**.01**	**.07**	.30	.14	.37*
Parent variables at T1						
13. PTSD symptoms	**.02**	**-.05**	**.04**	-.03	.21	.13
14. Global Stress Index	**.002**	**.01**	**.07**	-.04	.28	.16
15. Impact on family	**.17**	**-.31***	**-.11**	-.04	.02	-.01
16. Adherence barriers	**.25**	**-.13**	**.04**	-.03	.39**	.24

Note. Correlations between patient variables and parent variables at T1 appear in Table 14. Spearman's rho correlations were used to examine correlations with MAM due to violation of the normal distribution assumption required to conduct Pearson product-moment correlations.

$^{*}p<.05$, $^{**}p<.01$, $^{***}p<.001$

Table 17. *Correlations Between Psychosocial Predictor Variables at Time 1 and CoV% for Tacrolimus Levels at Time 2*

Variables	**1**	**2**
Outcomes at T2		
1. CoV% all values	**--**	
2. CoV% 6-12 month values	**.49*****	**--**
Patient variables at T1		
3. % missed meds	**-.01**	**-.23**
4.% late meds	**.02**	**.11**
5. % nonadherence	**-.001**	**.16**
6. HRQOL	**-.15**	**.12**
7. Aggression	**.20**	**.09**
8. Attention problems	**-.22**	**-.21**
9. Hyperactivity	**-.01**	**.07**
10. Depression	**.09**	**.11**
11. Anxiety	**-.21**	**-.23**
Parent variables at T1		
12. PTSD symptoms	**.11**	**-.11**
13. Global Stress Index	**.17**	**-.04**
14. Impact on family	**-.05**	**-.09**
15. Adherence barriers	**-.03**	**-.01**

Note. Correlations between patient variables and parent variables at T1 appear in Table 14. CoV% values are all for tacrolimus.
$^{*}p<.05, ^{**}p<.01, ^{***}p<.001$

Appendix

Schedule of Measures Administered at Each Time Point

Parent measures	Pre-transplant	6 months post-transplant
Medication Adherence Measure – *Patient's medication adherence*	x	x
Pediatric Quality of Life Inventory (PedsQL) – *Parent's report of child's HRQOL*	x	x
Impact of Event Scale-Revised – *Parent's PTSD symptoms*	x	x
Brief Symptom Inventory-18 – *Parent's psychological distress*	x	x
Impact on the Family Scale-Revised – *Impact of child's health condition on family*	x	x
Barriers to Pediatric Adherence for Parents – *Parent's barriers to adherence*	x	x
Behavior Assessment System for Children-2-PRS – *Child's internalizing and externalizing symptoms*	x	x
Demographic Questionnaire	x	