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TITLE: GENERALIZED AND SPECIFIC ANXIETY IN ADOLESCENTS FOLLOWING HEART TRANSPLANT

Short Running Title: Anxiety in Adolescents After Heart Transplant

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Abbreviations:

Extracorporeal membrane oxygenation (ECMO)

Generalized Anxiety Disorder 7 Scale (GAD-7)

Pediatric Quality of Life Inventory (PedsQL)

Post Heart Transplant Fears Questionnaire (PHTF)

Ventricular assist device (VAD)

Abstract

Background: Mental health concerns are associated with worse outcomes after adult heart transplant. Illness-specific anxiety is associated with worsened psychological well-being after other solid organ transplants but has never been characterized after pediatric heart transplant.

Methods: This single-center cross-sectional study aimed to evaluate illness-specific and generalized anxiety after heart transplantation in adolescents. A novel 12-item “Post Heart Transplant Fears” questionnaire (PHTF), the Generalized Anxiety Disorder-7 (GAD-7) and the Pediatric Quality of Life Inventory (PedsQL) were administered. Univariate associations of demographics, clinical features, and medication adherence as measured by immunosuppression standard deviation with the PHTF and GAD-7 scores were evaluated. Internal consistency and validity of the PHTF were examined.

Results: In total, 30 patients participated. The most common illness-specific fears were retransplantation, rejection, and more generally post-transplant complications. The PHTF had good internal consistency (Cronbach $\alpha = 0.88$). Construct validity was demonstrated between PHTF and GAD-7 ($r = 0.62$) and PedsQL ($r = -0.54$ to -0.62). 23% endorsed moderate to severe generalized anxiety symptoms. More severe symptoms were associated with older age at survey ($p = 0.03$), older age at listing ($p = 0.01$) and having post-transplant complications ($p = 0.004$). Patients with moderate or severe symptoms were more likely to report late immunosuppression doses ($p = 0.004$).

Conclusions: Illness-specific and generalized anxiety may be prevalent after pediatric heart transplant. Screening for anxiety in adolescents post-transplant may identify those at risk for adverse outcomes including nonadherence. The PHTF is a brief, valid and reliable instrument identifying illness-specific anxiety in this population.

Keywords: Pediatric Heart Transplant; Generalized Anxiety; Illness-specific Anxiety; Adolescents

Introduction

Despite advancements in medical and surgical management, heart transplantation is the only life-prolonging option for some pediatric patients with end stage heart disease. According to data from the Pediatric Heart Transplant Study, the numbers of both listed and transplanted pediatric patients are slowly increasing, with improving post-transplant survival [1]. However, the risk of morbidity and death remain. For many pediatric patients and their caregivers, life post heart transplantation results in improved physical functioning, but also involves the management of a new chronic condition and the potential for complications such as infection, rejection, renal failure, and malignancy [1]. In addition, transplant recipients face the inevitable risk of coronary allograft vasculopathy which increases with time [2], resulting ultimately in reoccurrence of heart failure symptoms and potential for retransplantation.

Transplantation also seeks to improve the health related quality of life for pediatric patients with end stage heart disease, however, a subset remains at risk for impaired psychological well-being following transplant [3], as well as impaired health related quality of life, neuropsychological outcomes, and family function as compared to non-transplant recipients [4]. While mental health disorders are well studied in adult patients after heart transplantation [5-7], less is known about the long-term mental health of pediatric heart transplant recipients [8-10].

Limited studies suggest that pediatric heart transplant patients may have increased risk of psychological disorders when compared to the general population. One study found that a quarter or greater of pediatric heart transplant recipients are at risk for emotional adjustment issues immediately following transplant [11]. Previous research suggests that approximately a third of patients continue to experience significant psychosocial distress in the years following heart transplantation [12], including symptoms of post-traumatic stress disorder [13] and emotional and behavioral disorders [14]. It is possible that mental health concerns are worse in patients with a more complicated clinical course, given prior studies in adult heart transplant patients associating anxiety and depression and hospital length of stay [7], although this association has not been explored in the pediatric population.

The causes of impaired psychological well-being after heart transplant are not well understood. It is possible that illness-specific anxiety about post-transplant complications contributes to worse health related quality of life post-transplant. Fear of rejection following solid organ transplants has been identified in an adult population [15, 16], and intrusive thoughts about graft rejection have been shown to contribute to poor psychological well-being after lung transplantation [17]. Across other chronic illness populations, there is growing evidence for the presence of illness-specific anxiety and fears related to disease progression or recurrence [18-20], distinct from generalized anxiety disorder [21]. Importantly, illness-specific anxiety has been associated with generalized anxiety, depression, and increased health care utilization in other adult chronic illness populations [22].

In adult transplant patients, mental health concerns such as generalized anxiety and depression are also associated with increased risk of graft loss and death [23]. One factor contributing to poor outcomes in adult recipients may be the association between poor mental health and nonadherence to medication regimen [24, 25]. Mental health concerns in pediatric transplant patients may similarly contribute to non-adherence, which in turn increases morbidity and mortality [26]. Illness-specific anxiety as a possible contributor has yet to be studied in pediatric transplant recipients. Adult transplant and other chronic illness literatures underscore the importance of examining illness-specific anxiety in pediatric transplant recipients as it may contribute to poorer mental health, and subsequent risk of adverse health outcomes.

The aims of the current study were (1) to develop and validate a novel measure to assess illness-specific anxiety in adolescents after heart transplantation (2) to characterize the prevalence and scope of illness-specific anxiety and generalized anxiety in adolescents after heart transplant, and (3) to evaluate for association between illness-specific anxiety and generalized anxiety symptoms following heart transplant with health experiences prior to and after transplantation. It was hypothesized that illness-specific and generalized anxiety are both prevalent among adolescent patients post heart transplantation. It was also hypothesized that illness-specific and generalized anxiety are associated with complications in clinical course both before and after transplantation and worse medication adherence.

Methods

Procedures and Recruitment

This single-center cross-sectional study included all patients with a history of heart transplantation greater than 12 years of age followed within a pediatric heart transplant program who gave written informed consent or written informed assent with parent or guardian written informed consent if less than 18 years of age. Patients were excluded if they were non-English speaking or unable to complete the questionnaires due to cognitive/developmental impairment. Two patients were excluded as they were assessed to be nearing end of life by the clinical team, and thus likely to be inappropriate for the present study.

The study was approved by the Institutional Review Board. Heart transplant recipients were approached by the principal investigator or the research coordinator at the time of a routine outpatient follow-up visit and enrolled patients independently completed all measures detailed below. Demographic characteristics and information on clinical course were obtained by review of the electronic health record.

Adherence

Immunosuppression troughs were recorded and a standard deviation of trough levels was calculated as a surrogate for medication adherence [27,28]. Additionally, patients' self-report of adherence was obtained by review of clinic notes on the day of the surveys. Specifically, patients were asked "how many missed or late immunosuppression doses have you had in the last week?".

Existing Measures

The Generalized Anxiety Disorder 7 (GAD-7) is a self-report instrument designed for adults consisting of seven items measuring generalized anxiety. Items have four response options increasing in frequency, and scores are summed with higher scores reflecting higher severity of symptoms [29]. The GAD-7 has been validated for detection of anxiety symptoms in adolescents with generalized anxiety disorder [30] and adult heart transplant recipients [31].

The Pediatric Quality of Life Inventory (PedsQL) 4.0 Generic Core Scale is a 23-item instrument that assesses physical, emotional, social, and school functioning. The PedsQL 3.0 Cardiac Module is a 27-item instrument that assesses symptom burdens, perceived physical

appearance, treatment anxiety, cognitive problems, and communication. All items are scored on a 5-point Likert scale. Items are reverse-scored and linearly transformed to a 100-point scale such that higher scores indicate a better health related quality of life. The PedsQL Generic Core Scale is used to create a psychosocial health summary score, computed as the sum of the items divided by the number of items in the emotional, social, and school functioning scales [32]. Both the PedsQL 4.0 Generic Core Scales and PedsQL 3.0 Cardiac Module have been utilized in pediatric heart transplant recipients [3].

Statistical Analyses

Data are reported as means \pm standard deviations or median with interquartile range (IQR) for continuous variables and frequencies with percentages for categorical variables. Total GAD-7 scores were considered as both continuous and binary variables with patients dichotomized into two groups, those reporting moderate or severe anxiety symptoms (GAD-7 score ≥ 10) and those reporting minimal or mild anxiety symptoms (GAD-7 score 0-9). Associations of patient demographics, pre-transplant course, transplant characteristics, and post-transplant course with GAD-7 scores (both continuous and binary variables) were assessed using Fisher's exact test, Spearman correlation coefficient, Wilcoxon rank sum test, or Kruskal-Wallis test, as appropriate. Total Post Heart Transplant Fears (PHTF, see below) scores and individual PHTF item score were examined as a 5-point Likert scale, as well as linearly transformed a 100-point scale such that higher scores indicating more anxiety. Associations between PHTF scores and patient demographics, pre-transplant course, transplant characteristics, and post-transplant course were assessed using a two-sample *t*-test or analysis of variance for categorical variables, and Spearman correlation coefficient for continuous variables. All analyses were performed using SAS Version 9.4 (SAS Institute Inc, Cary, NC), with statistical significance set at a *p*-value less than 0.05 using a two-sided test.

Post Heart Transplant Fears (PHTF): Measure Development and Validation

Measure Development

The novel Post Heart Transplant Fears (PHTF) questionnaire was developed after discussion with an experienced survey researcher. Validated measures of illness-specific anxiety in other chronic disease states were reviewed [16-20, 33]. Items from published measures that

were applicable to the post-heart transplant experience were selected or adapted as appropriate, and 9-items were selected with responses on a 5-point Likert scale ranging from “never” (1) to “always” (5). An additional 3-items were included inquiring about understanding of complications of heart transplantation and discussing worries about complications with loved ones and health care team members with responses on a 5-point Likert scale ranging from “strongly disagree” (1) to “strongly agree” (5). All metric items were discussed with experts in medical management of pediatric heart transplantation as well as psychological care post pediatric heart transplantation. The PHTF was reviewed by two adolescent heart transplant patients for comprehension and context prior to conducting the study. The PHTF questionnaire items are included in Table 3.

Psychometric Properties of PHTF

The psychometric properties of the PHTF were examined. Scale internal consistency reliability was determined by Cronbach’s coefficient alpha (α). To establish construct validity, intercorrelations between the PHTF scores and total GAD-7 score, PedsQL 4.0 Generic Core Scale Psychosocial summary score, and PedsQL Cardiac Module Treatment Anxiety subscale score were performed using Pearson or Spearman correlation coefficient.

The internal consistency of the PHTF was good (Cronbach $\alpha = 0.88$). Construct validity was also demonstrated with medium to high r values between PHTF total score, GAD-7 total score ($r = 0.62$) and the PedsQL Psychosocial summary score ($r = -0.54$) and Cardiac Module Treatment Anxiety subscale score ($r = -0.62$) (Table 1).

Results

Patient Characteristics

Table 2 summarizes patient demographic and clinical characteristics. Of 31 eligible patients, only one patient declined participation in the study yielding a participation rate of 97%. Most patients were male (73.3%) and Caucasian (80%) with a median age of 17.5 years. There was about equal representation of pre-transplant diagnosis of congenital heart disease and cardiomyopathy. Median time from transplant at the time of survey was 8.0 years. Thirty percent of patients had experienced a pre-transplant complication including cardiac arrest, stroke, need

for extracorporeal membrane oxygenation (ECMO) and/or need for ventricular assist device (VAD). Thirty percent of patients experienced a post-transplant clinical complication including cardiac arrest, stroke, need for ECMO and/or need for dialysis. Thirty percent of patients had coronary vasculopathy, 33% had at least one episode of graft rejection.

Adherence

Most patients were on tacrolimus (93.3%) with a median immunosuppression standard deviation of 1.56 (43% ≥ 2). Twenty percent of patients reported at least one late dose of immunosuppression in the last week.

Illness-specific Anxiety

There was a significant association between greater PHTF score and greater GAD-7 score or more severe generalized anxiety ($r = 0.62, p = 0.0003$). There also was a significant association between greater PHTF score with a lower PedsQL total score ($r = -0.56, p = 0.001$) and PedsQL Psychosocial subscale score ($r = -0.54, p = 0.002$), indicating worse health related quality of life and psychological well-being.

There were three items within the PHTF that a notable percentage of patients reported worrying about “often” or “always” (Table 3). These included worrying about rejection while waiting for biopsy results (26.7%), worrying about needing another transplant (20%), and serious post-transplant complications (20%). When specifically asked about their worries, a notable percentage of patients reported that they were not discussing fears about long-term complications with their family or providers. About a quarter of patients chose that they “disagree” or “strongly disagree” with the statement that they discuss their worries about long-term complications of heart transplantation with their loved ones (23.3%) and healthcare team (13.3%), and 10% disagreed that they had a good understanding of the complications of heart transplant.

Higher overall illness-specific anxiety was associated with female gender (mean PHTF score 46.2 ± 14.0 vs. 23.8 ± 22.7 in male, $p = 0.01$). Individual PHTF item analysis revealed a significant association between immunosuppression standard deviation ≥ 2 and increased patient worry about rejection while waiting for biopsy results (mean 61.5 ± 32.1 vs. 41.7 ± 25.7 SD < 2 , $p = 0.04$). There were no other associations of demographic or clinical features with PHTF total

score, including age at survey ($r = 0.28, p = 0.13$) and post-transplant complications including cardiac arrest, stroke, ECMO, or dialysis (mean 38.6 ± 21.6 vs. 24.8 ± 22.7 without complications, $p = 0.14$).

Generalized Anxiety

Nearly a quarter of the patients (23.3%) reported moderate to severe anxiety symptoms (GAD-7 score ≥ 10), Table 4). Of the individual items in the GAD-7, patients were most likely to report “becoming annoyed or irritable” (43.3%), “feeling afraid as if something awful might happen” (30%), “feeling nervous, anxious, or on edge” (26.7%), and “worrying too much about different things” (26.7%) over half the days or nearly every day.

Higher GAD-7 scores or more severe generalized anxiety symptoms were significantly associated with older age at the time of the survey ($r = 0.41, p = 0.03$), older age at transplant listing ($r = 0.46, p = 0.01$), and any post-transplant complication (cardiac arrest, stroke, need for ECMO and/or need for dialysis) (median GAD-7 score 10 vs. 1.5 without complication, $p = 0.004$). Each post-transplant complication was evaluated individually, and both stroke (median 15 vs. 3.5, $p = 0.03$) and need for ECMO (median 10 vs. 2.5, $p = 0.01$) were significantly associated with more severe generalized anxiety symptoms. There were no significant associations with any other patient demographic criteria, pre-transplant complications, history of rejection, history of coronary vasculopathy, ED visits or hospitalizations, or immunosuppression trough standard deviation.

Notably, moderate or severe generalized anxiety symptoms were significantly associated with patients reporting late (> 2 hours after dose time) or missed immunosuppression doses within the past two weeks (57.1% vs. 8.7%, $p = 0.004$) during clinical interview, compared to those that expressed minimal or mild generalized anxiety symptoms.

Discussion

To our knowledge, this is the first study to evaluate illness-specific anxiety in pediatric patients after heart transplantation. In addition, the study may provide further insight into the prevalence of generalized anxiety in this population. Our results suggest that illness-specific

anxiety, as well as generalized anxiety, may be prevalent in adolescent and young adult patients after heart transplant.

Nearly a quarter of patients in the study reported moderate to severe generalized anxiety symptoms, which is almost five times the prevalence of generalized anxiety in the healthy adolescent population [34]. Chronic illness in adolescents is a risk factor for anxiety disorders [35] which may explain the higher prevalence in the post-transplant population. Additionally, older patient age at the time of study and at listing was associated with more severe generalized anxiety symptoms. As such, it may be important to target this older population of pediatric heart transplant recipients for screening, as they may be more likely to require additional mental health intervention. Interestingly, generalized anxiety symptoms were not significantly associated with patient gender in the current study, whereas generalized anxiety is more prevalent in females in the general population [36]. It may be that adolescent patients after heart transplant are disproportionately affected by generalized anxiety symptoms, regardless of gender effects. Alternatively, gender effects may not have been observed due to the study's 73% male predominance.

In addition to generalized anxiety, illness-specific anxiety was prevalent among the study sample across all ages with 20-30% of patients endorsing fears related to need for retransplantation, graft rejection, or complications. Furthermore, unlike with generalized anxiety, illness-specific anxiety was associated with female gender, which may identify female patients as a population at increased need for screening. Notably, illness-specific anxiety was not associated with any pre- or post-heart transplant complications. Thus, it would seem that a notable percentage of adolescents with heart transplants will have worries about complications regardless of their clinical course. Finally, results suggested that adolescents may not be discussing their fears with their families or their loved ones, further underscoring the importance of screening.

Findings also suggested that the presence of generalized anxiety symptoms is associated with late immunosuppression doses per patient report during clinical interview. This is consistent with previous studies that have shown that mental health disorders are associated with nonadherence in the adolescent population [26]. Similarly, a study of adolescent liver transplant recipients found that patients with greater immunosuppression standard deviation reported worse

mental health than those with less variation of immunosuppressant trough levels [37]. Additionally, patients in the current study who had more variability in their immunosuppression trough levels were more likely to endorse illness-specific worries about graft rejection. Another study in adolescent transplant patients associated nonadherence with both symptoms of depression and worries related to their illness [38]. Whether having anxiety drives nonadherence or nonadherence contributes to further anxiety is currently unclear, however it is fair to conclude that adolescent patients identified with generalized or illness-specific anxiety may require more support to ensure medication adherence and improve their long-term health outcomes.

Like many pediatric transplant studies, this single-center sample size is small. The study population also only focused on adolescent aged pediatric transplant patients. Development of more simplistic metrics of illness-specific anxiety will be needed for studies with younger patients. Larger, multi-center studies would also be valuable for evaluating the prevalence of anxiety across the entire pediatric heart transplant population as well as examining associations with longitudinal health outcomes including morbidity and mortality. Additionally, the PHTF is a novel measure, and not validated for transplant-specific anxiety outside of this study. The current study did not evaluate the presence of other mental health disorders, such as depression. Although anxiety and depression often overlap, prevalence and impact on outcomes may differ. The current study was also limited by the lack of reliable strategies for evaluating nonadherence. While immunosuppression standard deviation has been used in prior studies, this is a surrogate measure of adherence which may be impacted by additional factors such as drug absorption or medication interactions [27, 28]. Furthermore, self-reported medication adherence may not always be reliable, especially in the adolescent population.

Despite these limitations, this study suggests that adolescent heart transplant patients are likely to benefit from screening for illness-specific and generalized anxiety symptoms with brief, validated instruments. Identification of patients with illness-specific anxiety and generalized anxiety may identify those at risk for medication nonadherence and adverse health outcomes. While there are no formal recommendations for psychosocial care in the pediatric heart transplant population, the 2010 International Society for Heart and Lung Transplantation Guidelines for care of heart transplant recipients recommends that each heart transplant team have a psychologist and that patients be regularly screened for depression [39]. Many pediatric

centers do not have psychological support readily available [12], particularly in outpatient clinic settings. The GAD-7 and PHTF are short and easy to use tools which can be used by multidisciplinary healthcare providers to screen and to identify transplant recipients in need of evaluation and formal psychological treatment.

References

1. Dipchand, A.I., et al., *Ten yr of pediatric heart transplantation: a report from the Pediatric Heart Transplant Study*. *Pediatr Transplant*, 2013. **17**(2): p. 99-111.
2. Dipchand, A.I., et al., *The registry of the International Society for Heart and Lung Transplantation: seventeenth official pediatric heart transplantation report--2014; focus theme: retransplantation*. *J Heart Lung Transplant*, 2014. **33**(10): p. 985-95.
3. Uzark, K., et al., *Quality of life in pediatric heart transplant recipients: a comparison with children with and without heart disease*. *J Heart Lung Transplant*, 2012. **31**(6): p. 571-8.
4. Fredericks, E.M., et al., *Post-transplant adjustment--the later years*. *Pediatr Transplant*, 2014. **18**(7): p. 675-88.
5. Pudlo, R., et al., *The Occurrence of Mood and Anxiety Disorders in Heart Transplant Recipients*. *Transplantation Proceedings*, 2009. **41**(8): p. 3214-3218.
6. Dew, M.A. and A.F. DiMartini, *Psychological disorders and distress after adult cardiothoracic transplantation*. *J Cardiovasc Nurs*, 2005. **20**(5 Suppl): p. S51-66.
7. Dew, M.A., et al., *Prevalence and risk of depression and anxiety-related disorders during the first three years after heart transplantation*. *Psychosomatics*, 2001. **42**(4): p. 300-13.
8. Wray, J. and R. Radley-Smith, *Depression in pediatric patients before and 1 year after heart or heart-lung transplantation*. *The Journal of Heart and Lung Transplantation*, 2004. **23**(9): p. 1103-1110.
9. Wray, J. and R. Radley-Smith, *Longitudinal assessment of psychological functioning in children after heart or heart-lung transplantation*. *J Heart Lung Transplant*, 2006. **25**(3): p. 345-52.
10. Wray, J. and R. Radley-Smith, *Prospective psychological evaluation of pediatric heart and heart-lung recipients*. *J Pediatr Psychol*, 2007. **32**(2): p. 217-22.
11. Demaso, D.R., et al., *The longitudinal impact of psychological functioning, medical severity, and family functioning in pediatric heart transplantation*. *The Journal of Heart and Lung Transplantation*, 2004. **23**(4): p. 473-480.
12. Cousino, M.K., et al., *Psychosocial functioning in pediatric heart transplant recipients and their families*. *Pediatric Transplantation*, 2018. **22**(2): p. e13110.

13. Farley, L.M., et al., *Parenting stress and parental post-traumatic stress disorder in families after pediatric heart transplantation*. J Heart Lung Transplant, 2007. **26**(2): p. 120-6.
14. Todaro, J.F., et al., *Review: cognitive and psychological outcomes in pediatric heart transplantation*. J Pediatr Psychol, 2000. **25**(8): p. 567-76.
15. Jamieson, N.J., et al., *Motivations, Challenges, and Attitudes to Self-management in Kidney Transplant Recipients: A Systematic Review of Qualitative Studies*. Am J Kidney Dis, 2016. **67**(3): p. 461-78.
16. Nilsson, M., et al., *The perceived threat of the risk for graft rejection and health-related quality of life among organ transplant recipients*. J Clin Nurs, 2011. **20**(1-2): p. 274-82.
17. Forsberg, A., et al., *Fear of graft rejection 1-5 years after lung transplantation-A nationwide cohort study*. Nurs Open, 2018. **5**(4): p. 484-490.
18. Lee-Jones, C., et al., *Fear of cancer recurrence--a literature review and proposed cognitive formulation to explain exacerbation of recurrence fears*. Psychooncology, 1997. **6**(2): p. 95-105.
19. Herschbach, P., et al., *Fear of progression in chronic diseases: psychometric properties of the Fear of Progression Questionnaire*. J Psychosom Res, 2005. **58**(6): p. 505-11.
20. Thewes, B., et al., *Fear of cancer recurrence: a systematic literature review of self-report measures*. Psychooncology, 2012. **21**(6): p. 571-87.
21. Dinkel, A., et al., *Comorbidity of fear of progression and anxiety disorders in cancer patients*. Gen Hosp Psychiatry, 2014. **36**(6): p. 613-9.
22. Lebel, S., et al., *Does fear of cancer recurrence predict cancer survivors' health care use?* Support Care Cancer, 2013. **21**(3): p. 901-6.
23. Dew, M.A., et al., *Depression and Anxiety as Risk Factors for Morbidity and Mortality After Organ Transplantation: A Systematic Review and Meta-Analysis*. Transplantation, 2015. **100**(5): p. 988-1003.
24. Dew, M., et al., *Medical compliance and its predictors in the first year after heart-transplantation*. J Heart Lung Transplant, 1996. **15**(6): p. 631-645.
25. Dew, M., et al., *Early post-transplant medical compliance and mental health predict physical morbidity and mortality one to three years after heart transplantation*. J Heart Lung Transplant, 1999. **18**(6): p. 549-562.
26. Dobbels, F., et al., *Growing pains: non-adherence with the immunosuppressive regimen in adolescent transplant recipients*. Pediatr Transplant, 2005. **9**(3): p. 381-90.
27. Christina, S., et al., *Medication level variability index predicts rejection, possibly due to nonadherence, in adult liver transplant recipients*. Liver Transplantation, 2014. **20**(10): p. 1168-1177.

28. Shemesh, E., et al., *The Medication Level Variability Index (MLVI) Predicts Poor Liver Transplant Outcomes: A Prospective Multi-Site Study*. American Journal of Transplantation, 2017.
29. Spitzer, R.L., et al., *A Brief Measure for Assessing Generalized Anxiety Disorder*. Archives of Internal Medicine, 2006. **166**(10): p. 1092.
30. Mossman, S.A., et al., *The Generalized Anxiety Disorder 7-item scale in adolescents with generalized anxiety disorder: Signal detection and validation*. Ann Clin Psychiatry, 2017. **29**(4): p. 227-234A.
31. Conway, A., et al., *Accuracy of anxiety and depression screening tools in heart transplant recipients*. Applied Nursing Research, 2016. **32**: p. 177-181.
32. Uzark, K., et al., *Quality of Life in Children With Heart Disease as Perceived by Children and Parents*. PEDIATRICS, 2008. **121**(5): p. e1060-e1067.
33. Simard, S., et al., *Fear of cancer recurrence in adult cancer survivors: a systematic review of quantitative studies*. J Cancer Surviv, 2013. **7**(3): p. 300-22.
34. Burstein, M., et al., *Threshold and subthreshold generalized anxiety disorder among US adolescents: prevalence, sociodemographic, and clinical characteristics*. Psychol Med, 2014. **44**(11): p. 2351-62.
35. Pao, M. and A. Bosk, *Anxiety in medically ill children/adolescents*. Depress Anxiety, 2011. **28**(1): p. 40-9.
36. Vesga-Lopez, O., et al., *Gender differences in generalized anxiety disorder: results from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)*. J Clin Psychiatry, 2008. **69**(10): p. 1606-16.
37. Fredericks, E.M., et al., *Adherence and health-related quality of life in adolescent liver transplant recipients*. Pediatr Transplant, 2008. **12**(3): p. 289-99.
38. Wray, J., et al., *Adherence in adolescents and young adults following heart or heart-lung transplantation*. Pediatr Transplant, 2006. **10**(6): p. 694-700.
39. Costanzo, M.R., et al., *The International Society of Heart and Lung Transplantation Guidelines for the care of heart transplant recipients*. J Heart Lung Transplant, 2010. **29**(8): p. 914-56.

Table 1. PHTF validation: correlation between overall anxiety score from PHTF questionnaires and other validated measures (GAD-7, PedsQL)

	<i>r</i>	<i>p</i>
GAD-7 Total score	0.62	0.0003
PedsQL Generic Core Total score	-0.56	0.001
Physical functioning subscale	-0.48	0.01
Psychosocial Summary subscale	-0.54	0.002
Emotional functioning subscale	-0.71	<.0001
Social functioning subscale	-0.32	0.09
School functioning subscale	-0.18	0.36
PedsQL Cardiac Module		
Heart Problems and Treatment subscale	-0.44	0.02
Treatment II subscale (if taking medications)	-0.49	0.01
Perceived Physical Appearance subscale	-0.71	<.0001
Treatment Anxiety subscale	-0.62	0.0003
Cognitive Problems subscale	-0.28	0.13
Communication subscale	-0.67	<.0001

† Data are presented as *r*, Pearson or Spearman correlation coefficient (p-value).

Table 2. Patient demographic, transplant, and post-transplant characteristics (N=30)

	N (%) or Median (interquartile range)
Male gender	22 (73.3)
Age at survey, years	17.5 (15.6-19.2)
Time from transplant to survey, years	8.0 (4.0-14.6)
Caucasian race	24 (80.0)
Diagnosis	
Cardiomyopathy	15 (50.0)
Congenital heart disease	14 (46.7)
Other (Familial hyperlipidemia)	1 (3.3)
Pre-Transplant	9 (30.0)
History of cardiac arrest	3 (10.0)
History of stroke	1 (3.3)
Need for ECMO	5 (16.7)
Need for VAD	2 (6.7)
Pre-transplant ICD	1 (3.3)
Transplant Listing/Operation	

Age at listing, years	(N=28)	7.6 (3.3-13.4)
Listing status		
1A		15 (50.0)
1B		3 (10.0)
2		11 (36.7)
Unknown		1 (3.3)
Waiting time, days	(N=28)	55 (22.5-188)
Age at Transplant, years		8.3 (3.1-14.3)
NYHA class		
I		1 (3.3)
II		10 (33.3)
III		14 (46.7)
IV		4 (13.3)
Unknown		1 (3.3)
Hospital length of stay since Transplant, days		14 (12-22)
(N=29)		
Post-Transplant		
Post-transplant complication		9 (30.0)
Cardiac arrest		2 (6.7)
Stroke		3 (10.0)
Need for ECMO		5 (16.7)

Need for Dialysis	4 (13.3)
Coronary vasculopathy	9 (30.0)
Post-transplant Lymphoproliferative Disorder (PTLD)	4 (13.3)
Antibody Mediated Rejection (AMR)	3 (10.0)
Rejection episodes	10 (33.3)
Unplanned hospitalization in the past year	7 (23.3)

Table 3. Post Heart Transplant Fears (PHTF) questionnaires N=30

	Never	Rarely	Sometimes	Often	Always	Not reported
How often do the following statements apply to you						
I worry about needing another transplant	8 (26.7)	7 (23.3)	9 (30.0)	2 (6.7)	4 (13.3)	---
I am nervous prior to doctor's appointments	15 (50.0)	7 (23.3)	4 (13.3)	2 (6.7)	2 (6.7)	---
I worry about rejection of my heart waiting for results from my biopsies	9 (30.0)	7 (23.3)	6 (20.0)	4 (13.3)	4 (13.3)	---

I worry about rejection of my heart waiting for results of my blood work	10 (33.3)	7 (23.3)	5 (16.7)	3 (10.0)	5 (16.7)	---
I worry about missing school or work due to complications of my heart transplant	14 (46.7)	7 (23.3)	3 (10.0)	5 (16.7)	0 (0.0)	1 (3.3)
I worry about serious post-transplant complications	10 (33.3)	9 (30.0)	5 (16.7)	3 (10.0)	3 (10.0)	---
I worry that if I develop complications from my heart transplant, it may hurt my friendships and relationships	15 (50.0)	4 (13.3)	7 (23.3)	3 (10.0)	1 (3.3)	---
When I take my medications, I think about rejection of my transplanted heart	13 (43.3)	8 (26.7)	6 (20.0)	1 (3.3)	2 (6.7)	---
I don't enjoy life because I am worried about complications from my heart transplant	18 (60.0)	4 (13.3)	7 (23.3)	0 (0.0)	1 (3.3)	---
How much do you agree with the following statements	Strongly disagree	Disagree	Neutral	Agree	Strongly agree	
I have a good understanding of the long-term complications of heart transplantation	0 (0.0)	3 (10.0)	7 (23.3)	7 (23.3)	13 (43.3)	---
I discuss my worries about long-	5 (16.7)	2 (6.7)	6 (20.0)	8	9	---

term complications of heart transplantation with my loved ones				(26.7)	(30.0)	
I discuss my worries about long-term complications of my heart transplantation with my doctors and healthcare team	1 (3.3)	3 (10.0)	9 (30.0)	10 (33.3)	7 (23.3)	---
† Data are presented as N (%)						

Table 4 Generalized Anxiety Disorder 7-items (GAD-7) Scale (N=30)

	Not at all sure	Several days	Over half the days	Nearly every day
Over the last 2 weeks, how often have you been bothered by the following problems				
Feeling nervous, anxious, or on edge	17 (56.7)	5 (16.7)	3 (10.0)	5 (16.7)
Not being able to stop or control worrying	20 (66.7)	4 (13.3)	3 (10.0)	3 (10.0)
Worrying too much about different things	15 (50.0)	7 (23.3)	2 (6.7)	6 (20.0)
Trouble relaxing	18 (60.0)	8 (26.7)	2 (6.7)	2 (6.7)
Being so restless that it's hard to sit still	19 (63.3)	6 (20.0)	3 (10.0)	2 (6.7)
Becoming easily annoyed or irritable	12 (40.0)	5 (16.7)	6 (20.0)	7 (23.3)
Feeling afraid as if something awful might happen	15 (50.0)	6 (20.0)	4 (13.3)	5 (16.7)
Total score, Median (IQR)				
5 (0-9)				
Minimal (score 0-4)				
15 (50.0)				
Mild (score 5-9)				

8 (26.7)

Moderate (score 10-14)

4 (13.3)

Severe (score 15 and higher)

3 (10.0)

		Not difficult at all	Somew hat difficult	Very difficult	Extremely difficult
If you checked off any problems, how difficult have these made it for you to do your work, take care of things at home, or get along with other people	N = 20	3/20 (15.0)	14/20 (70.0)	2/20 (10.0)	0/20 (0.0)

† Data are presented as N (%) unless otherwise indicated.