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Can Pre-Transplant Quality of Life Scores Predict Post-Transplant Mortality in Adolescents with Cystic Fibrosis?

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CAN PRE-TRANSPLANT QUALITY OF LIFE SCORES PREDICT POST-TRANSPLANT MORTALITY IN ADOLESCENTS WITH CYSTIC FIBROSIS?

By

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Can Pre-Transplant Quality of Life Scores
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Introduction: Cystic fibrosis (CF) is the most common indication for pediatric lung transplantation and ranks number three for adults. However, using the current criteria for selection and timing of a transplant, the survival benefit of this procedure in pediatric patients is controversial (Liou & Cahill, 2008). Modification of the current selection criteria has the potential to reduce mortality rates both for those on the waitlist and those who receive a transplant. Use of the Cystic Fibrosis Questionnaire-Revised (CFQ-R; Quittner et al., 2012), a well-validated, disease-specific quality of life measure may improve pre-transplant decision-making and thus, reduce mortality.

Methods: This multi-center study evaluated whether specific domains on the CFQ-R (i.e., Physical Functioning, Respiratory Symptoms) and parent proxy reports on the CFQ-R (i.e., Health Perceptions, Vitality, Role/School Functioning) predicted mortality 4 years post-transplant for the Transplant group (n=28) and 2 years post-evaluation for the Waitlist group (n=35). These analyses controlled for physical predictors (i.e., age, CF-related Diabetes (CFRD), FEV_1 % predicted), to assess whether the CFQ-R added additional and unique variance. Cox Regressions were used to measure the overall impact of the CFQ-R scales and Receiver Operating Characteristic (ROC) curves were used to assess the sensitivity and specificity of optimal cut-points of significant CFQ-R domains.

Results: The CFQ-R scales explained *additional* and *unique* variance in mortality for both the Transplant and Waitlist groups. The Respiratory Symptoms scale was a significant predictor of mortality for the Transplant group. The Respiratory Symptoms and Physical Functioning scales were both significant predictors of mortality for the Waitlist group. ROC curves indicated that the Respiratory Symptoms scale was a strong measure of survival for the Transplant group (AUC = 0.86) and both scales were good measures of survival for the Waitlist group (both with an AUC = 0.71). Optimal cut-points were: 1) 47.20 for the Respiratory Symptoms scale for the Transplant group, 2) 37.50 for the Respiratory Symptoms scale for the Waitlist group, and 3) 28.48 for the Physical Functioning scale for the Waitlist group.

Conclusions: This study suggested that including patient-reported outcomes could aid pre-transplant decision making. More accurate pre-transplant decisions could reduce post-transplant mortality in adolescents with CF. Including the patient's perceptions of functioning in the transplant decision-making process was shown to be effective and importantly, utilized a patient-centered approach. Respiratory Symptoms scores can indicate when to prioritize and move adolescents forward to transplant when they are approaching the identified cut-point. In addition, Respiratory Symptoms and Physical Functioning scores can be used to identify those adolescents who should be put on the waitlist. Future directions include development of a weighting algorithm to improve accuracy and the possible addition of a lie scale to ensure the validity of the scores. Although this study laid the foundation for use of the CFQ-R in transplant decision-making, to adequately test these relationships, a multi-center study using the LAS in conjunction with the CFQ-R is needed.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

Chapter 1

Introduction

Cystic Fibrosis (CF) is an autosomal, recessive genetic disorder that affects the lungs, pancreas, sinuses, reproductive organs, and sweat glands, and is the most frequent reason for pediatric lung transplantation (Braun & Merlo, 2011; Liou & Cahill, 2008; Ratjen et al., 2015). However, a large pediatric transplant study found no survival benefit of lung transplantation for pediatric patients with CF using the current criteria for selection and timing (Liou et al., 2007). In addition, a substantial number of patients typically die on the waitlist prior to receiving a lung transplant (UNOS, 2015), which suggests that the current selection criteria could benefit from modification.

Pre-transplant decisions using the Lung Allocation Score (LAS) are based on a prediction of post-transplant length of survival in comparison to survival without a transplant (UNOS, 2015). Identification of critical factors that affect when to list, as well as when to transplant, may improve outcomes in this patient population. In particular, patient-reported outcomes (PROs; symptoms and daily functioning), which are not currently utilized in the evaluation process, have shown promise for improving both the timing of transplant listing and the critical window for transplantation for adults with CF (Sole et al., 2016). To date, this has not been examined in pediatric CF patients awaiting lung transplantation. The purpose of this study was to evaluate the use of a well-validated health-related quality of life measure for CF to predict pediatric post-transplant length of survival (Cystic Fibrosis Questionnaire-Revised; CFQ-R, Quittner et al., 2005; Quittner et al., 2012).

Transplantation in Cystic Fibrosis

Survival for CF patients has improved substantially in the past 30 years as a result of earlier diagnosis via newborn screening and new medications that treat inflammation and infection. Recently the first disease-modifying drug was approved for those with the G551D mutation (Ramsey et al., 2011). Current predicted median age of survival is 41.1 years in the US and this year, half of the population is over 18 years of age (CF Foundation, 2013). Despite this increase in survival, many individuals with CF will need a lung transplant at some point in their lives (CF Foundation, 2013) and individuals with CF comprise the third largest group requiring lung transplantation in adulthood (Thabut et al., 2013). Data from the UNOS database indicates that, on average, 150-200 transplants per year were performed in individuals with CF over the past 5 years (i.e., average of 22 pediatric patients). However, this rate is increasing and data from 2013 documented 245 transplants in CF (i.e., 32 pediatric patients). Of these, more than 80% in 2013 survived the first year post-transplant (UNOS, 2015). However, these data do not reflect the number of patients who died on the waitlist or the length of long-term survival; adult survival at five years post-transplant is approximately sixty percent (Yusen et al., 2014). This study examined how the use of a well-established PRO for CF, completed by patients on the waitlist, improves the accuracy of timing for this procedure and related rates of mortality.

Selection of Candidates for Transplant

Improving post-transplant survival is predicated on improving pre-transplant decision-making. Prior to 2006, length of time on the waitlist was the primary criterion for when patients would receive a transplant, leading to a high mortality rate on the

waitlist (Rosenblatt, 2009). Many individuals were listed much earlier than necessary to accrue time on the waitlist as an "insurance policy" (Kozower et al., 2008), which concealed the needs of those with worse disease severity and thus, greater need.

Beginning in 2006, the LAS score was implemented and included several physical markers of disease severity, disease type, and co-morbid conditions (LAS; Egan et al., 2006). The LAS compiled those factors, each uniquely weighted, to create a comparison between the predicted length of survival with versus without a transplant (UNOS, 2015). Benefits of this revised criteria included fewer patients dying on the waiting list and increased survival/benefit post-transplant. In addition, the LAS aimed to make the organ allocation system more efficient and give pediatric and adolescent patients greater access to transplantation.

Following introduction of the LAS, the number of patients on the waitlist decreased dramatically because it identified those with greater need. One study evaluating the length of survival post-transplant using only the LAS as the predictor reported the following survival rates: 96.5% survived 3 months; 93.3% survived 6 months; 88.4% survived 12 months; and 67.8% survived 3 years (Thabut, et al., 2013). However, application of the LAS score to pediatrics led to higher rates of mortality (Rosenblatt, 2009). To address this limitation of the LAS score for pediatric populations, those under 12 are currently evaluated based on waiting time alone, and patients 12 to 17 years are listed based on the LAS score, but are given preference over younger pediatric patients (Rosenblatt, 2009).

The shortcomings of the LAS and the challenges of using it in pediatric populations, has led to the need for the inclusion of new markers that predict survival in

this young age group. This study evaluated the use of a PRO, not currently included in the listing process, to improve post-transplant survival. Inclusion of PRO data, which measures self-reported respiratory symptoms and physical functioning, may lead to earlier listing of children with CF (Sole et al., 2016).

Transplant Benefits for Pediatric Patients with CF

The success of transplantation for pediatric patients with CF is, at best, controversial. Studies evaluating median length of survival post-transplant have found inconsistent results, ranging from 4.7 to 7.3 years (Liou & Cahill, 2008; Oshrine, McGrath & Goldfarb, 2014). Liou and Cahill (2008) found minimal benefit for lung transplantation when compared to those not transplanted. Clear survival benefits were found for only 5 out of 514 patients. However, as they mentioned in their discussion, transplantation may not improve the amount of time a patient lives, but may improve the quality of that time, as measured by a health-related quality of life (HRQoL) measure.

To answer this question, the Cystic Fibrosis Questionnaire-Revised (CFQ-R), the most widely used measure of HRQoL in CF, was given to adolescents listed for transplant at each clinic visit leading up to and following transplant (Quittner, Barker, Blackwell, Romero & Woo, 2009; Quittner et al., 2012). Quality of life improved significantly for approximately two years following transplant but then began to decline. This improvement was seen in several domains of the CFQ-R: Respiratory Symptoms, Physical Functioning, Health Perceptions, Social Functioning, Eating Problems, and Treatment Burden. These results illustrated both the sensitivity of this measure to predict pre and post-transplant outcomes and the impact of transplant on several domains of daily functioning. Thus, the addition of this measure could aid in the process of selecting

candidates for transplant and decisions related to when to transplant. This study evaluated the use of the CFQ-R, given prior to transplantation, to predict post-transplant survival.

Patient-reported Outcomes (PROs)

The CFQ-R is one example of a patient-reported outcome (PRO) that provides a more complete picture of the patient's functioning. It measures the patient's perspective on respiratory symptoms and daily physical, emotional, and social functioning. It can provide information, in addition to the standard physical indicators for transplant, which may be helpful in decisions related to both listing and moving forward to transplant (Bernstein, Kleinman, Barker, Revicki & Green, 2002; Sole et al., 2016).

Recently, the Federal Drug Administration (FDA), approved the use of PROs as primary or secondary endpoints for clinical trials, including drug registration studies (FDA, 2009). The CFQ-R was recently used as the primary endpoint for approval of a new inhaled antibiotic for CF and thus, has met the FDA PRO criteria (Retsch-Bogart et al., 2009; Ramsey et al., 2011). Despite their clinical utility, PROs are not currently used to evaluate readiness for transplant, and have only recently been used to evaluate the efficacy of new medications. A PRO used in the transplant process may provide unique information about the patient's daily functioning, and as such, represents the patient's voice in what is a highly risky and life-changing procedure. Utilizing this information may prove to be critical in this decision-making process. This major aim of this study was to evaluate use of the CFQ-R scores to predict post-transplant survival.

Utilizing the CFQ-R for Transplant Decision-Making

Recently, the CFQ-R was used to predict mortality on the waitlist, as well as death, following transplantation in adults with CF in Spain (Quittner & Sole, 2015; Sole

et al., 2016). This study found an association between the CFQ-R Physical Functioning and Treatment Burden scores and death *prior to* transplant. In this prospective study, the transplant team was blinded to the CFQ-R results, enabling them to make decisions using the traditional physical markers of disease severity. Results indicated that the addition of the CFQ-R data would have altered pre-transplant decisions, with a potential impact of decreased waitlist mortality (e.g., appropriately transplanting sooner; Sole et al., 2016). This study offered significant support for using the CFQ-R as a predictor of waitlist survival, however, this has not been tested in pediatric patients.

Transplantation in pediatric patients with CF differs in terms of their care prior to and post-transplant. Caregivers, often parents, take major responsibility for their child's care and are a significant source of support. Therefore, many predictors of transplant success relate to the caregiver's characteristics (i.e., financial stability, social support, adherence to current CF treatments, expectations for success), which are taken into account along with the patient's health status. Thus, this study examined the caregiver's perspective of the adolescent's HRQoL (parent proxy). In sum, the purpose of this study was to evaluate the relationship between specific CFQ-R scales and post-transplant and waitlist survival in a pediatric sample. The following were the aims of the study.

Chapter 2

Aims

Aim 1: To determine whether specific domains on the CFQ-R, chosen a priori, (i.e., Physical Functioning, Respiratory Symptoms) predict mortality 4 years post-transplant and 2 years on the waitlist, after controlling for physical parameters (i.e., age, CF-related Diabetes (CFRD), FEV_1 % predicted).

Hypothesis 1: Pre-transplant CFQ-R scores on the two selected domains will be significantly related to waitlist and post-transplant mortality, after controlling physical indicators.

Aim 2: To determine whether specific domains on the caregiver version of the CFQ-R, chosen a priori, (i.e., Vitality, Health Perceptions, School Functioning) predict survival 4 years post-transplant and 2 years on the waitlist, after controlling for physical parameters (i.e., age of child, CFRD, FEV_1 % predicted). Given that the caregiver version of the CFQ-R has not been tested before, domains were selected because of their similarity to contraindications for transplant.

Hypothesis 2: Pre-transplant CFQ-R scores on these domains will be significantly related to post-transplant survival, after controlling for physical indicators.

Aim 3: To determine which CFQ-R scores (identified in Aims 1 and 2) predict the probability of mortality at greater than 50% 4 years post-transplant and 2 years on the waitlist.

Hypothesis 3: This is an exploratory aim and thus, specific cut-offs on the CFQ-R scores are not specified, but will be determined as part of this analysis.

Chapter 3

Methods

Participants

This study analyzed data retrospectively from a larger, multi-center investigation that examined differences in HRQoL before and after lung transplant in pediatric patients with CF (Quittner et al., 2009). Participants were recruited from 10 hospitals affiliated with the International Pediatric Lung Transplant Collaborative: Children's Hospital Los Angeles, Children's Hospital of Wisconsin, Duke University Medical Center, Hospital for Children (London), The Hospital for Sick Children (Toronto), St. Louis Children's Hospital, Children's Hospital of Pittsburgh, The Johns Hopkins Hospital, University of Florida Hospital at Gainesville, and Stanford Medical Center.

Inclusion criteria for the study were: 1) diagnosis of CF, 2) age over 5 years, 3) referred for lung transplantation at one of the above named transplant centers, 4) ability to communicate/read English or Spanish, and 5) ability to perform pulmonary function tests. All participants/parents gave written consent or assent for participation. IRB approval was obtained at all sites and IRB approval for retrospective analyses conducted at the University of Miami was also obtained. Primary analyses for the larger study have been published (Quittner et al., 2009).

For this study, only participants who were recruited prior to receiving a transplant were included in the analyses. Participants were separated into "transplant" and "waitlist" groups. Participants from the larger study who had already received a transplant were not included.

Procedures

Participants were enrolled between June 30, 2003 and August 7, 2008. Transplants were performed between July 7, 2003 and August 26, 2008. Each participant was followed for five years or until death. Due to missing data at 5 years post-transplant, the analyses for the Transplant group focused on post-data through 4 years. The current median length of post-transplant survival for the 12-17 age group, as noted previously, is 4.7 years. Thus, the 4-year post-transplant time-point marked long-term survival for the Transplant group. However, the analyses for the Waitlist group focused on post-data through 2 years. While exact data is not available for those who are removed from the waitlist due to becoming too sick for transplant, most patients are transplanted within 2 years of registration on the waitlist (UNOS, 2015). Thus, analyses focused on mortality at or before the 2-year time-point for the Waitlist group.

Participants were given the CFQ-R at every clinic visit prior to transplant. These measures (child and proxy versions) were completed before any physiological measures were obtained to avoid biasing their responses. Participants were enrolled in the study when they presented for transplant evaluation. The participants who received a transplant during the study period made up the "transplant" group, and those who did not receive a transplant made up the "waitlist" group. The CFQ-R completed immediately prior to transplant, and the first CFQ-R completed after study entry for the waitlist group, will be used for the analyses. Survival was determined using medical chart records, death records, or a publicly posted obituary.

Measures

Survival

Survival was determined based on medical chart review, presence of assessment data in later waves of the parent project, and publicly posted obituaries or death records. Individuals were only listed as "dead" or "alive" if this information was confirmed. An individual could be confirmed "alive" if they had participated in the study at a later time-point or had any later medical data, such as from a clinic visit, hospital admission, or rejection episode (demonstrated by chart review). At each time point, survival was coded as a dichotomous variable.

Cystic Fibrosis Questionnaire-Revised (CFQ-R)

HRQoL was measured using the CFQ-R, a disease specific measure (Quittner et al., 2012). There are 3 versions of the CFQ-R: 1) Child: ages 6-13 with 46 items; 2) Teen/Adult: ages 14-60, with 60 items; and 3) Parent: proxy measure for children ages 6 to 13, with 43 items. Participants rated the items on a 4-point Likert scale assessing frequency or difficulty. The CFQ-R has demonstrated strong internal consistency (Child Cronbach's α= 0.88; Teen/Adult Cronbach's α= 0.72, and Parent Cronbach's α= 0.81), strong convergent validity with physical health outcomes, good test-retest reliability, and is the most widely used measure of HRQoL for CF (Sawicki et al., 2011; Quittner, Buu, Messer, Modi & Watrous, 2005; Quittner et al., 2012). Responses yield domain scores (8 Child domains, 12 Teen/Adult domains, and 11 Parent domains) that are standardized onto a 0-100 scale, with higher scores indicating better HRQoL. The CFQ-R has been translated into 38 languages (Goss & Quittner, 2007).

Disease Severity

FEV_1% predicted and CFRD status were collected via chart review as indicators of disease severity. Both are part of the LAS score and are related to probability of dying (UNOS, 2015).

FEV_1% Predicted. FEV_1% predicted is a measure of lung function representing forced expiratory volume in 1 second, with norm values calculated using gender, height, and age (CF Foundation, 2014). It is the most commonly used indicator of disease severity and progression. Lung function has been used to predict length of survival in individuals with CF, regardless of transplant. FEV_1% predicted <30% has been correlated with 50% mortality at two years. However, more recent studies have determined that the median length of survival for an individual with an FEV_1% predicted score <30% (prior to transplant) is now approximately 3.9 years, due to advances in available treatments for CF (Faro & Sweet, 2014). To move forward to transplantation, an FEV_1% predicted <30% is commonly used (Rosenblatt, 2009; UNOS, 2015).

Cystic Fibrosis-Related Diabetes (CFRD). A diagnosis of CFRD prior to transplantation indicates greater disease severity. It also complicates post-transplant care because of the long-term insulin requirements post-transplant. CFRD also increases risks of complication and death in the early postoperative period (Moran et al., 2010). CFRD status was gathered through medical chart review and was coded as a dichotomous predictor.

Statistical Analyses

Missing Data. Little's MCAR test was performed followed by separate variance t-tests to examine whether missingness was associated with available variables including

survival outcome. Missing data were then handled using multiple imputation (MI) using 10 imputations using IBM SPSS Statistics (version 22; Graham, Olchowski & Gilreath, 2007). All variables included in the analyses were included in the MI model, allowing for all available disease severity, HRQOL, and survival data, to contribute to the MI model.

Cox Proportional Hazards Regression. To test Aim 1, which hypothesized that the CFQ-R Physical Functioning and Respiratory Symptoms scales would significantly predict mortality at 4 years post-transplant and 2 years on the waitlist, Cox proportional hazards regressions were performed. A Cox proportional hazards regression is a class of regression analyses used to model survival at a given time point relative to a set of predictors. Statistical significance was determined by the *p* value of each predictor ($p < 0.05$), examined separately. The effect size (e.g., that variable's contribution to prediction of survival) was determined by the hazard ratio for each predictor (i.e., the increase in the risk of the event (death) occurring as the predictor increases by one standard deviation unit; Cox, 1972). For Aim 2, which hypothesized that the CFQ-R parent Vitality, Health Perceptions and School Functioning scales would significantly predict mortality at 4 years post-transplant and 2 years on the waitlist, a second Cox Proportional Hazards regression was performed.

ROC Curves. For Aim 3, significant domains of the CFQ-R were evaluated using Receiver Operating Characteristic (ROC) curves (DeLong, DeLong & Clarke-Pearson, 1988). The optimal cut-point was determined by evaluating the resulting ROC curve generated cut-points using Youden's Information Criterion (YIC) indices. The YIC indices compare the balance of the sensitivity (i.e., identification of true positives) and specificity (i.e., identification of true negatives) of each cut-point, to determine best fit.

This process allowed us to determine the cut-point that optimizes both sensitivity and specificity. In this project, sensitivity represents the CFQ-R score that correctly predict survival, while specificity represents the CFQ-R score that correctly predicts mortality. Thus, for the transplant group, sensitivity would indicate that transplant may not be likely to extend life span. For the waitlist group, sensitivity would indicate that moving forward to transplant is urgent. Analyses were performed using IBM SPSS Statistics (version 22).

Chapter 4

Results

Demographics

Demographic and health variables were compared in the transplant (n=28) and waitlist groups (n=34), and few statistically significant differences were found (see Table 1). Participants in both were similar in age, gender, race and ethnicity. Importantly, both groups had similar levels of lung function (*M* transplant = 27.88% predicted; *M* waitlist = 31.67%). In addition, caregivers in both groups reported similar demographic characteristics. In contrast, prevalence of CFRD differed in the two groups (transplant group 32%; waitlist group =47%; F (2, 56) = 74.448, $p < 0.001$).

Survival analyses were collected at one, two, four, and five years post-transplant for the transplant group and at similar intervals for the waitlist group. For this study, only survival analyses four years post-transplant or two years post-evaluation were used. Data on mortality for both groups is included in Table 1. By four years post-transplant, 10 patients had died and an additional five died the following year. In the waitlist group, 11 patients had died within two years with four additional deaths by the fourth year. In total, a little less than half of the Waitlist group died during the study period, however it is important to note that survival data was missing for a significant portion of the waitlist group (see Table 2).

Missing Data

The number of missing data points differed by variable (See Table 2). Results of Little's MCAR test indicated that the data were not missing completely at random (χ^2 (28) = 41.89, $p = 0.04$). To follow up, separate variance t-tests were used to compare individual variables. A significant difference was found for FEV_1% predicted and

Caregiver CFQ-R Vitality, such that those individuals with lower FEV_1% predicted (M = 44.0) were more likely to be missing their Caregiver CFQ-R Vitality. A significant difference was also found for CFRD and CFQ-R Physical Functioning and CFQ-R Vitality. Those individuals with higher Physical Functioning (M = 59.33) and those with lower Caregiver CFQ-R Vitality (M = 46.67) were more likely to be missing CFRD status. In terms of the outcome variable, only age was significantly different for both two and four-year mortality. Younger individuals were more likely to be missing outcome data for both two (M = 13.27) and four-year mortality (M = 12.95).

Based on these results, it was assumed data were missing at random, and related to these specific variables. Thus, missing data was addressed using multiple imputation, with 10 imputations. All variables related to missingness were included in the imputation model analyses (i.e., FEV_1% predicted, age, CFRD status, CFQ-R scale scores, and mortality), as well as group membership (Transplant or Waitlist group, entered as a dichotomous, categorical indicator). Analyses were run on each imputed dataset separately. Results were then pooled after analyses were completed.

Cox Regression

Transplant group full model. For Aim 1, it was hypothesized that the Physical Functioning and Respiratory Symptoms on the CFQ-R would predict survival 4 years post-transplant, after accounting for the variance attributable to physical indicators (age, CFRD, FEV_1 % predicted). This hypothesis received strong support. The overall model using only the physical parameters was not significant. After including the two CFQ-R domain scores, the overall model was significant at the $p = 0.05$ level (χ^2 (5) = 13.29, p = 0.04). Importantly, including the CFQ-R scores accounted for additional and unique

variance, leading to a statistically significant Chi Square change ($\chi^2 \Delta = 8.40$, $p = 0.03$). See Table 4 for these results.

Transplant group individual predictors. In examining the individual predictors for Aim1, which evaluated physical indicators, age, lung function, and CFRD status were not significant. In the second model, which included the CFQ-R Physical Functioning and Respiratory Symptoms scales, only the CFQ-R Respiratory Symptoms scale predicted survival 4 years post-transplant, after controlling for age, CFRD status, FEV_1 % predicted, and CFQ-R Physical Functioning (B = -0.08, SE = 0.04, Wald = 5.95, p = 0.04, Exp(B) = 0.92, 95% CI = 0.85-0.99). Note that the standardized beta and odds ratio for this analysis indicated that the effect sizes were small. See Table 5 for these results.

Waitlist group full model. Next, it was hypothesized that the CFQ-R Physical Functioning and Respiratory Symptoms scores would predict survival 2 years on the waitlist, after controlling for physical indicators (age, CFRD, FEV_1 % predicted). This hypothesis was not supported. The overall model using only the physical parameters was not significant. After including the two CFQ-R domain scores, the overall model was, again, not significant at the $p = 0.05$ level using (χ^2 (5) = 4.65, $p = 0.48$). See Table 6 for these results.

Waitlist group individual predictors. In examining the individual physical indicators, none were significant. In the second model, which included the CFQ-R Respiratory Symptoms scale (B = -0.02, SE = 0.01, p = 0.22, Exp(B) = 0.98) and the CFQ-R Physical Functioning scale (B = -0.001, SE = 0.01, p = 0.92, Exp(B) = 1.00) were not significant predictors. See Table 7 for these results.

Transplant group caregivers full model & individual predictors. For Aim 2, it was hypothesized that the Vitality, Health Perceptions, and School Functioning domains of the CFQ-R Parent version would predict survival 4 years post-transplant, after accounting for the physical parameters (age, CFRD, FEV_1 % predicted). This hypothesis was not supported. The overall model, using only physical indicators was not significant (See statistics above, pg. 15; See Tables 4 and 5). The second step of the model, which included the CFQ-R Parent domains, was not significant (χ^2 (6) = 11.74, p = 0.12).

Waitlist group caregivers full model & individual predictors. The first model using only the physical parameters for the Waitlist group was also not significant (χ^2 (3) = 2.20, p = 0.53) and furthermore, no significant individual predictors emerged. The second model, which included the CFQ-R Parent domains, was also not significant (χ^2 (6) = 5.69, p = 0.46) and had no significant individual predictors. See Tables 6 and 7 for these results.

ROC Curves

For Aim 4, ROC curves were used to determine the optimal cut-point for the two CFQ-R domains that predicted survival. This was an exploratory aim and thus, no specific cut-point was hypothesized. The area under the curve (AUC) was used to evaluate the ability of the measure to accurately distinguish between the two groups (alive or dead). The Youden's Information Criterion (YIC) was used to compare the cut-points, with a larger YIC value considered a better balance of sensitivity and specificity.

Respiratory symptoms scale for transplant group. The AUC (AUC = 0.82, 95% CI = 0.66-0.97) indicated that the Respiratory Symptoms scale was a strong measure of survival (See Figure 1). Thirteen cut-points were examined in the Transplant group

(See Tables 8 and 9 for cut-points and full results). The Respiratory Symptoms cut-point of *47.20* had the largest YIC value (YIC = 0.55). This was identified as the "optimal" cut-point, yielding an 74% sensitivity and an 81% specificity (See Figure 2). Thus, using a cut-point of 47.20, 74% of those who score above the cut-point, if transplanted, were alive four years later and 81% of those who score below the cut-point, if transplanted, were dead four years later.

Chapter 5

Discussion

Previous research has demonstrated that physical parameters are not sufficient for predicting waitlist or post-transplant mortality (Rosenblatt, 2009). Identifying accurate predictors of when to list and when to prioritize an adolescent for transplant is vital for improving pre-transplant decision making. Thus, this study aimed to evaluate the CFQ-R's ability to predict waitlist and post-transplant mortality for adolescents with CF. Overall, the results of this study indicated that the inclusion of the CFQ-R could improve pre-transplant decision-making, leading to reduced post-transplant mortality. Furthermore, the inclusion of this measure adds the patient's assessment of their daily functioning into the transplant evaluation process, which is not currently reflected in the measures of disease severity current utilized (e.g., lung function, O_2 saturation). In addition, use of the CFQ-R is cost-efficient (i.e., free) and adds minimal time (e.g., 8 minutes) and burden to the patient's evaluation time.

The initial aim of this study was to evaluate whether the Respiratory Symptoms and Physical Functioning scales would explain *additional* and *unique* variance in the Transplant and Waitlist groups of adolescents with CF. This aim received moderate support. The addition of the Respiratory Symptoms scale explained unique variance in post-transplant mortality. For the Transplant group, the Respiratory Symptoms scale was a significant predictor of mortality, after accounting for traditional physical parameters (e.g., age, CFRD, FEV_1% pred). For the Waitlist group, no significant predictors of mortality emerged, after controlling for the physical parameters. These results are the

first to identify a patient-reported outcome as a significant predictor of post-transplant mortality in adolescents with CF.

Importantly, lung function was *not* a significant predictor of mortality in either the Transplant or Waitlist group in this study. These findings suggest that lung function is not adequate for identifying individuals who should be listed and prioritized for transplant. Notably, there was not a significant difference in lung function between the Transplant and Waitlist groups, suggesting that lung function is not sensitive enough to differentiate those who should be listed or prioritized for transplant. The measurement of lung function has several limitations. First, it is effort-dependent and patients may underperform on this test because of lack of motivation or fatigue. Second, FEV_1 % predicted represents lung function at one point in time and does not capture a larger window of functioning. In contrast, the CFQ-R has a 2-week recall period and captures a broader, more comprehensive sampling of symptoms and physical performance. The limitations of lung function measurements also apply to other physical parameters used for pre-transplant decision-making, such as oxygen saturation, 6-minute walk. Thus, adding patient-reported outcomes, such as the CFQ-R may substantially improve transplant decision-making.

The second aim, which evaluated the caregiver's responses on the CFQ-R did not explain additional and unique variance for either the Transplant or Waitlist group. One possible reason these scales did not predict mortality in our study is that they were completed by parents of teens who were 14 years and older, which is contrary to its development and validation. The parent version of the CFQ-R should only be completed by parents of children up to age 13. Thus, more than half of these data were obtained

from parents whose adolescents were older than 13, possibly reducing the accuracy of their report.

The final aim was to identify optimal cut-points for the Respiratory Symptoms scale to improve decisions about when to prioritize an adolescent for lung transplantation. The Respiratory Symptoms scale served as an important, early indicator of disease severity and the need to be prioritized for transplant. It discriminated between those who will live or die after transplant and when used in conjunction with other markers of disease severity, it will likely improve the accuracy and utility of pre-transplant decisions.

For those already on the transplant list, the Respiratory Symptoms scale appeared to serve as an alarm bell that signals when to prioritize an adolescent for transplant. This scale would function best when used to identify a declining trajectory of respiratory symptoms, prior to reaching the threshold (i.e., 47). Thus, this scale could be used to indicate when an adolescent on the waitlist should be transplanted. Importantly, adding the CFQ-R to the transplant evaluation process would add minimal burden in terms of both time and cost for the patients and providers.

Limitations

This study has several limitations. First, the sample size for both the waitlist and transplant group was small and the analyses were under-powered. We had 28 adolescents in the transplant group and 35 in the waitlist group. Currently, approximately 22 pediatric patients are transplanted in the US each year, thus, obtaining a sufficient sample size would require a larger number of sites and additional funds. Further, our effects sizes were small and may have been related to the small sample size and missing data. Importantly, an individual predictor may have a small effect size but can translate into

increased survival for an adolescent. Despite this limitation, our results are similar to those recently published on use of the CFQ-R in a waitlist adult sample in Spain (Sole et al., 2016).

Another limitation was the use of the *parent* version of the CFQ-R to assess Health Perceptions, Treatment Burden and School Functioning, even in adolescents who were 14 years and older. As mentioned previously, the parent version of the CFQ-R should be given to caregivers of children 6 to 13 years of age, but half of our parents were completing it on children much older. The most important and relevant information comes from the patient, him or herself, and this should be considered in future studies.

This study had an additional limitation of a large amount of missing data. Importantly, the survival variable had high rates of missing data. A disruption during data collection in the original study contributed significantly to the missing data. Some of the degree of missing data in a variable was related to another variable, indicating that the data was not missing completely at random. Those who had worse lung function were more likely to be missing their Caregiver CFQ-R Vitality. Those individuals with higher Physical Functioning (M = 59.33) and those with lower Caregiver CFQ-R Vitality (M = 46.67) were more likely to be missing CFRD status. Importantly, younger individuals were also more likely to be missing outcome data for both two and four-year mortality. Multiple imputation was used to account for the bias created by the missing data. However, it is possible that additional bias remained in the data, suggesting a need for replication in another sample with complete data.

In addition, this study was conducted during the implementation of the LAS score for transplantation and thus, we did could not evaluate the CFQ-R scales in conjunction

with the LAS. We did use similar physical parameters to test our aims, but these should be retested using the LAS. This would enhance the clinical utility of our approach.

Clinical Implications and Future Directions

This the first study to demonstrate that use of a patient-reported outcome could reduce post-transplant mortality in adolescents with CF. Adding this instrument, completed by the patients themselves, is highly innovative and provides a systematic way to include the patient's voice. Furthermore, completion of these scales takes less than five minutes and the CFQ-R is available for free. Thus, inclusion of these CFQ-R scales is clinically relevant and cost-effective.

Future research should evaluate the CFQ-R in relation to the LAS as a tool to predict waitlist and post-transplant mortality in a multi-center, prospective design. This would provide a rigorous test of this evaluation method in a nationally representative sample. This study identified the Respiratory Symptoms scale as a significant predictor of mortality, but in a larger sample, it may be possible that other CFQ-R scales would also be informative. In the adult transplant study in Spain, Sole and colleagues (2016) identified the Health Perceptions, Vitality, and Role Functioning scales as predictors of when to list and patient mortality.

The CFQ-R scale could be modified for use in the transplant context. One approach might be to test the individual items on the CFQ-R in conjunction with the LAS, and develop a weighting system to improve prediction. One question that has arisen is the possibility that, if the CFQ-R scale was added to the LAS, patients would "fake bad" in order to move forward to transplant more quickly. Although there is no evidence,

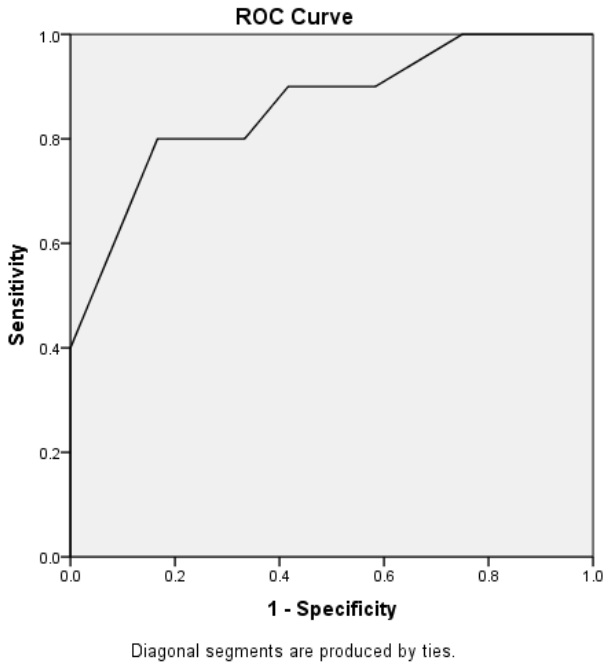
to date, that patients manipulate or inflate their responses on the CFQ-R, it might useful to explore the addition of a "lie" scale to this measure.

This study was the first to evaluate the use of a PRO to improve pre-transplant decision making for adolescents with CF. Improvements in this process are critical due to the high post-transplant mortality that has been observed using current selection criteria. The addition of the specific CFQ-R scale, identified in this study, could reduce post-transplant mortality. An optimal cut-point was also identified for this scale, which would allow clinicians to improve their prediction of survival post-transplant. More accurate prediction of survival could significantly improve the decision of when to transplant, and would incorporate the patient's perception of daily functioning. This study provided a foundation for the inclusion of the CFQ-R Respiratory Symptoms scale in the transplant evaluation process. Future multi-center studies will be needed to confirm these findings in conjunction with the LAS.

FIGURES

Figure 1

Transplant Group – Respiratory Symptoms ROC curve



TABLES

Table 1

Demographic and Medical Characteristics of Participants

Characteristic	Transplant Group (n = 28)	Waitlist Group (n = 34)
Age at study entry (years) (*SD*)	14.79 (3.30)	13.83 (3.5)
FEV_1 % predicted (*SD*)	27.88 (8.39)	31.67 (10.18)
CFRD diagnosed	32%	47%
Gender %		
Male	21%	33%
Female	79%	67%
Race		
White	96%	100%
Other	4%	0%
Ethnicity %		
Hispanic	32%	24%
Non-Hispanic	68%	76%
Parental Education %		
<High school	11%	21%
High school graduate	18%	9%
College	64%	50%
Family Income %		
$10 - 24,999	18%	18%
$25 - 49,999	14%	15%
$50 - 74,999	21%	9%
$75 +	14%	18%
Parental Marital Status		
Single/Never married	11%	3%
Married	68%	62%
Divorced/Separated/ Widowed	18%	33%
Deceased at Outcome (n)	10	11

Table 2
Missing Data

Variable	Transplant Group % Missing	Waitlist Group % Missing
Age	0	0
Gender	0	0
FEV_1 % predicted	10.71	5.88
CFRD diagnosed	10.71	2.94
Race	7.14	26.47
Ethnicity	0	0
Parental Education	7.14	20.59
Family Income	35.71	14.71
Parental Marital Status	3.57	2.94
CFQ-R Respiratory Symptoms Scale	0	29.41
CFQ-R Physical Functioning Scale	0	29.41
CFQ-R Caregiver Vitality Scale	14.29	0
CFQ-R Caregiver Health Perceptions Scale	3.57	0
CFQ-R Caregiver School Functioning Scale	3.57	0
Four-Year Survival	21.43	----
Two-Year Survival	-----	48.57

Table 3
CFQ-R Scale Scores

	Full Sample		Transplant Group		Waitlist Group	
	Mean	Std. Deviation	Mean	Std. Deviation	Mean	Std. Deviation
Physical Functioning	40.8	26.93	35.91	26.36	44.71	27.12
Respiratory Symptoms	52.58	20.63	56.05	20.93	49.80	20.24
Vitality	52.38	16.41	51.33	16.19	53.22	16.74
Health Perceptions	37.43	23.88	31.83	18.54	41.90	26.83
School/Role Functioning	57.42	22.53	58.15	20.67	56.83	24.18

Table 4
Cox Regression Model Results – Transplant Group

	-2 Log Likelihood	**Chi-Square**	**df**	***p***	**Chi-Square Change**	**df**	***p***
Participant CFQ-R Model 1 (Aim 1)	49.93	5.72	3	0.23			
Participant CFQ-R Model 2 (Aim 1)	41.52	13.29	5	0.04	8.40	2	0.03
Caregiver CFQ-R Model 1 (Aim 2)	49.93	5.72	3	0.23			
Caregiver CFQ-R Model 2 (Aim 2)	43.61	11.74	6	0.12	6.31	3	0.14

Table 5
Cox Regression Individual Predictors – Transplant Group

	Variable	B	SE	Wald	*p*	Exp(B)
Participant CFQ-R Model 1	Age	0.11	0.13	1.06	0.34	1.12
	CFRD	-0.21	0.69	0.28	0.76	0.81
	FEV_1 % predicted	0.09	0.06	4.44	0.10	1.10
Participant CFQ-R Model 2 (Aim 1)	Age	0.12	0.15	0.82	0.43	1.12
	CFRD	0.88	0.98	1.46	0.37	2.41
	FEV_1 % predicted	0.11	0.07	4.11	0.09	1.12
	Respiratory Symptoms	-0.08	0.04	5.95	0.04	0.92
	Physical Functioning	0.00	0.02	0.24	0.94	1.00
Caregiver CFQ-R Model 2 (Aim 2)	Age	0.14	0.21	1.14	0.51	1.15
	CFRD	0.24	0.98	0.28	0.81	1.27
	FEV_1 % predicted	0.12	0.08	3.73	0.16	1.13
	Vitality	0.02	0.06	1.94	0.80	1.02
	Health Perceptions	-0.04	0.05	1.92	0.45	0.97
	Role Functioning	-0.03	0.04	1.34	0.47	0.97

Table 6
Cox Regression Model Results – Waitlist Group

	-2 Log Likelihood	**Chi-Square**	**df**	***p***	**Chi-Square Change**	**df**	***p***
Participant CFQ-R Model 1 (Aim 1)	98.59	2.36	3	0.54			
Participant CFQ-R Model 2 (Aim 1)	96.35	4.65	5	0.48	2.24	2	0.36
Caregiver CFQ-R Model 1 (Aim 2)	98.59	2.36	3	0.54			
Caregiver CFQ-R Model 2 (Aim 2)	95.19	5.78	6	0.49	3.41	3	0.37

Table 7
Cox Regression Individual Predictors – Waitlist Group

	Variable	B	SE	Wald	*p*	Exp(B)
Participant CFQ-R Model 1	Age	-0.04	0.07	0.85	0.62	0.96
	CFRD	-0.09	0.63	0.18	0.88	0.91
	FEV_1 % predicted	0.01	0.03	1.35	0.79	1.01
Participant CFQ-R Model 2 (Aim 1)	Age	-0.05	0.07	1.25	0.46	0.95
	CFRD	0.08	0.77	0.34	0.92	1.08
	FEV_1 % predicted	0.01	0.03	0.96	0.82	1.01
	Respiratory Symptoms	-0.02	0.01	1.84	0.22	0.98
	Physical Functioning	-0.00	0.01	0.33	0.92	0.10
Caregiver CFQ-R Model 2 (Aim 2)	Age	-0.03	0.08	0.56	0.73	0.97
	CFRD	0.13	0.69	0.25	0.86	1.13
	FEV_1 % predicted	0.02	0.04	2.23	0.59	1.02
	Vitality	0.02	0.03	1.19	0.48	1.02
	Health Perceptions	-0.02	0.02	1.25	0.44	0.98
	Role Functioning	-0.01	0.02	0.64	0.65	0.99

Table 8
ROC Curves – Transplant Group - Respiratory Symptoms Scale

Cutpoint	Sensitivity	Specificity	Youden
7.30	0.00	1.00	0.00
15.25	0.08	1.00	0.08
30.55	0.17	1.00	0.17
40.30	0.25	1.00	0.25
43.05	0.41	0.94	0.35
47.20	0.74	0.81	0.55
52.80	0.77	0.64	0.42
56.95	0.85	0.58	0.43
62.50	0.85	0.52	0.37
69.45	0.88	0.41	0.28
77.75	0.96	0.28	0.24
80.55	1.00	0.19	0.19
91.65	1.00	0.13	0.13

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