Received: 8 August 2019 | Revised: 27 November 2019 | Accepted: 5 December 2019

DOI: 10.1111/petr.13642

ORIGINAL ARTICLE

WILEY

The impact of caregiver post-traumatic stress and depressive symptoms on pediatric transplant outcomes

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Funding information
This project was funded by the National Institutes of Health #R01 DK080740.

Abstract

PTSS as well as symptoms of depression have been reported in children who experience a serious medical adversity as well as their caretakers. The adverse effects of PTSS, when experienced by the patients, on medical outcomes have been clearly documented. However, the impact of those symptoms, if any, when experienced by the caretakers on child outcomes has not been investigated prospectively. We evaluated whether caregiver PTSS and depression symptoms predict adherence to medications and medical outcomes in a prospective multisite study. Four hundred children participated in MALT. Caretaker PTSS were assessed by the IES and depressive symptoms by CES-D. During 2 years of follow-up, the MLVI was used to determine adherence. Centrally read, biopsy-confirmed organ rejection was the primary medical outcome. IES scores were not associated with either adherence or rejection outcomes. In contrast, there were significant correlations between CES-D (depression) scores and lower adherence, $r = .13$, $P < .001$, and a trend toward higher scores on the CES-D among those whose children had experienced rejection, 12.4 (SD = 10.9) versus 9.1 (SD = 8.6), $P = .077$. Caregivers' PTSS were not a risk factor for poor child outcomes in this cohort, whereas depression symptoms were associated with non-adherence and possibly increased rates of rejection. Further study can validate if caregivers' depression as opposed to PTSS confers greater risk and should be a focus during the clinical care of medically ill children.

KEYWORDS

adherence, depression, medication level variability index, post-traumatic stress symptoms, transplant

1 | INTRODUCTION

Solid organ transplantation is often a life-saving treatment for chronic and serious health conditions. However, it is not so much an end-point as it is a transition into another lifelong condition: one of living with and caring for a transplanted organ.[1,2] In addition, even in long-term survivors, there is still the threat of death as well as other potential adverse effects, such as medical

Abbreviations: CES-D, The Center for Epidemiologic Studies Depression Scale; IES, Impact of Events Scale; MALT, Medication Adherence in Children Who Had a Liver Transplant; MLVI, Medication Level Variability Index; PMBS, Parent Medication Barriers Scale; PTSD, Post-traumatic stress disorder; PTSS, Post-traumatic stress symptoms.

Trial Registration: ClinicalTrials.gov: NCT-01154075

complications, transplant rejection or loss, and infection.[3,4] Such experiences have been conceptualized by some researchers as potentially emotionally traumatic,[5] leading to PTSS. PTSS are based on the features of PTSD including re-experiencing of the trauma, avoidance of its reminders, negative cognitions and mood, and alterations in physiological arousal.[6] These symptoms rarely become prominent enough to merit the full-blown diagnosis of PTSD. While PTSD, when diagnosed, should be treated, it is not yet clear whether PTSS should be treated in the medical setting, and if so, how.

PTSS have been reported in survivors of a wide range of medical diseases, including in transplant recipients.[7] The association between post-traumatic stress and non-adherence to medical recommendations has been consistently observed among cardiovascular patients.[8] The presence of avoidance symptoms (ie, staying away from painful reminders of their experience) is thought to be the reason for this connection, as patients may strive to avoid situations that spark reminders, such as taking medications or doctor's visits.[9]

Caretakers, and especially parents, may suffer from PTSS related to the child's illness.[10] A study of caregivers for pediatric liver transplant recipients found a high level of PTSS, with 50.6% of parents endorsing at least moderately severe symptoms of PTSD and 27.1% meeting full diagnostic criteria for PTSD.[2] Among caregivers of transplant recipients, PTSS have been found to be correlated with depression as well[2]; this too can harm a parent's ability to orchestrate the demands of their child's illness.[11,12] Although PTSS have been more widely demonstrated among caregivers of transplant recipients, it is important to examine the impacts of these symptoms and depression in tandem.

PTSS in caregivers of pediatric transplant recipients are prevalent and can be quite severe,[13] and although the presence of those symptoms does not necessarily constitute a disorder, it may still warrant treatment to improve parent quality of life.[14] But when it comes to child (the patient's) outcomes, some distress in the parents could also, potentially, serve an adaptive function. For example, some concerns about the child's illness may lead to more, not less, attention to the child's care. The MALT prospective multisite study (described elsewhere; 15) offered an opportunity to look at the degree to which the presence of PTSS or depression in parents of children who had a liver transplant is associated with non-adherence to medications and rejection outcomes. We hypothesized that both PTSS and depressive symptoms in the caregivers will be associated with poor child outcomes. In addition to looking at total PTSS score, we evaluated the specific symptom clusters of avoidance and intrusion, hypothesizing that avoidance in particular would be more likely to be associated with poor outcomes. Because of the extensive data collected on patients in the MALT study and the large sample size, we were also able to consider covariates associated with PTSS, depression, and also non-adherence, as well as if findings varied by patient age groupings.

2 | METHODS

2.1 | Participants

Participants were enrolled in the MALT cohort.[15] The timeframe for data collection was August 2010-June 2015, which included 2 years of follow-up for each patient. This multisite prospective trial achieved its recruitment goal of enrolling 400 children or adolescents aged 1-17 and their families from five pediatric liver transplant centers in the United States (Cincinnati Children's Hospital Medical Center; Mattel Children's Hospital, UCLA; Lurie Children's Hospital, Chicago; Children's Hospital of Pittsburgh of UPMC; and Mount Sinai Medical Center). Inclusion/exclusion criteria have been described elsewhere[15] and are summarized below:

1. Age 1-17 years old at enrollment,
2. Receipt of a liver transplant at least 1 year prior to enrollment (we excluded recipients in the first year since transplant since variability in levels in this period is more likely to be affected by graft dysfunction and by variable prescription practices, not by patient adherence),
3. Tacrolimus is prescribed,
4. Participants had to be seen at the enrolling center at least once in the 2 years prior to enrollment, to ensure completeness of data.

Exclusion criteria were as follows:

1. More than one transplant (including bone marrow replacement),
2. Biopsy-proven rejection within the past 6 months from enrollment (to ensure that pre-existing rejection is not the immediate reason for fluctuation in medication levels),
3. Hepatitis C (as hepatitis C infection in transplant recipients might affect tacrolimus prescription practices),
4. Instructed by a physician not to obtain tacrolimus levels for at least 1 year,
5. Participants who were seen only for consultation (with most or all of the child's routine care is provided at another center), to ensure that follow-up is occurring at the center of record,
6. Medically unstable/hospitalized at the time of enrollment (because of concerns about inability to provide informed consent/assent),
7. Participants or guardians who were actively psychotic or severely disoriented due to any cause, including hepatic encephalopathy (temporary exclusion), or had been diagnosed with moderate or severe mental retardation as defined in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV).

In the event that more than one caregiver attended the enrollment visit, families were asked to choose one respondent.

2.2 | Procedures

This prospective multisite study was approved by the respective Institutional Review Boards of all participating institutions and involved caregiver consent and child assent in accordance with each institution's policies. At their enrollment visit, caregivers and patients were asked to complete a brief questionnaire packet assessing possible predictors of non-adherence (described below). In addition, patient medical variables and outcomes were followed for a 2-year period. Data were sent via a secure web-based interface to a data-coordinating center (The EMMES Corporation).

2.3 | Measures

2.3.1 | Impact of events scale (IES)

The IES is a widely used measure of distress in the face of a stressful event.[16] Both the IES and the newer IES-R measure intrusion and avoidance, while the IES-R also measures hyperarousal. Hyperarousal is the least specific of the dimensions as it highly overlaps with general anxiety and distress.[17] In evaluating PTSS symptoms in parents of transplant recipients, who are expected to be more distressed than the general population at baseline, we chose not to tap into the hyperarousal dimension as it could artificially increase the score and make our results less specific to PTSD.

As per IES guidelines, items can be keyed to a specific event. The patient's caregiver was asked to complete the IES in response to their child's illness and treatment. This validated 15-item instrument is scored on a four-point scale ranging from 0 (Not at all) to 5 (Often). The IES yields a total score as well as Avoidance and Intrusion subscales. The Avoidance scale consists of 8 items that assess symptoms such as numbing of responsiveness, and avoidance of feelings, situations, and ideas, while the 7 items of the Intrusion scale capture the experience of intrusive thoughts, nightmares, and intrusive feelings and imagery. Respondents rate how often they experienced each of the symptoms during the last 7-day period. The IES, and its structure, has demonstrated strong reliability and validity.[16,18] In the present study, Cronbach's α was 0.90 for the total score, 0.83 for the Avoidance scale, and 0.86 for the Intrusion scale. The total score, ranging from 0 to 75, is obtained by totaling the scores of each item. In our previous study of 447 caretakers of children with food allergy—a life-threatening illness—the mean IES score was 14.4.[19] The average IES score of caretakers who sought mental health consultation was above 14, whereas the average IES score for those who did not seek such help was <11. We therefore predefined a cutoff value of >14 to denote above-average distress that is likely to lead to substantial discomfort (as exemplified by seeking mental health support).

2.3.2 | The center for epidemiologic studies depression scale (CES-D)

The CES-D is one of the most frequently used depression scales for adult populations, with published psychometric data for both medically well and medically ill adults.[20] It was used to evaluate depression symptoms in the primary caregiver of the child participant in MALT. The CES-D is a 20-item scale, asking about depression symptoms in the past week. Items are scored on a scale from 1 (rarely) to 4 (most of the time). Cronbach's α in the present study was 0.89.

2.3.3 | Parent medication barriers scale (PMBS)

The PMBS is a scale designed to assess parent-/patient-perceived barriers to child medication adherence[21]; this measure was included as a possible covariate of non-adherence. The parent version consists of 16 items. Each item is rated on a Likert-like scale from 1 (strongly disagree) to 5 (strongly agree). Reliability and validity have been established including factor analyses supporting the composition of items.[21] The PMBS was administered to caregivers of children aged 11 and older; Cronbach's α was 0.89.

2.4 | Electronic chart review

2.4.1 | The medication level variability index (MLVI)

The MLVI is defined as the degree of variation in blood levels of tacrolimus, the primary immunosuppressive medication used to prevent allograft rejection in liver transplant recipients.[22] It was shown to be a good representation of patient adherence and is not substantially affected by metabolic or absorption issues.[15] The MLVI is calculated as the standard deviation of at least three consecutive tacrolimus trough blood levels for each patient. Measurement of trough blood levels of tacrolimus was standard practice in participating centers and was obtained approximately once every 3 months. A higher MLVI denotes more fluctuation in levels and is interpreted as erratic adherence. MLVI can also be treated as a clinically meaningful dichotomous variable, in which a value >2 units is considered to denote clinically significant non-adherence, based on previous data.[15] A higher MLVI has been found to be a significant predictor of future rejection in MALT and other cohorts.[15,23]

2.4.2 | Central pathologist-diagnosed rejection

The primary outcome measure in the MALT study was biopsy-defined rejection, as determined based on two independent readings in a central pathology laboratory; if the pathologists disagreed, the case was adjudicated by the senior study pathologist.[15] For each

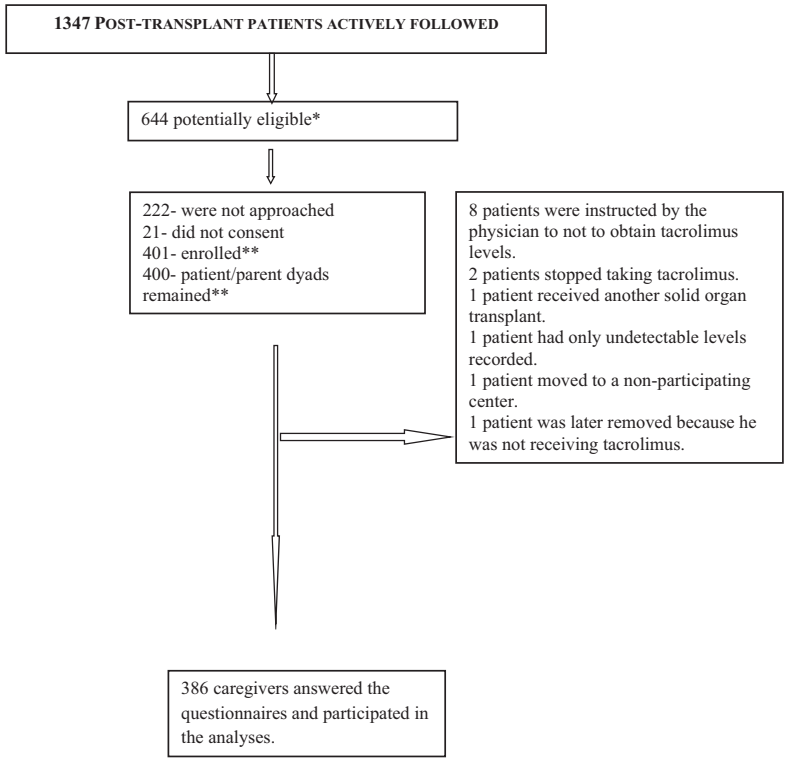

FIGURE 1 Consort Diagram. *Potentially eligible = may have been eligible for the primary analysis, based on preliminary chart review data. The primary analysis cohort was slightly different as presented elsewhere.[17] **One patient turned out to be ineligible because he had a previously undocumented transplant; this patient was not included in analyses

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participant, if there was at least one biopsy-proven episode of rejection during the study period, it was entered as a positive value (positive rejection). Thus, even if a participant had more than one rejection episode, it was counted as one event for the primary analysis (yes/no rejection occurring during the follow-up period, regardless of the number of rejection episodes).

2.5 | Statistical analyses

Statistical analyses were performed using the SAS System for Windows 9.3 (SAS Institute Inc). As predefined in the MALT statistical analysis plan, missing data were not imputed in this study. We correctly predicted that missing data will be very rare, and we were concerned that missing data may not be missing at random but that we will not know in advance what pattern to invoke in imputation strategies. The fact that the sample's primary analysis population was representative of the 44-center population enrolled in the SPLIT (Studies of Pediatric Liver Transplantation) national cohort [15] suggests that our data were representative and generalizable.

Preliminary analyses were used to determine covariates of the study measures. Pearson's correlation coefficients were used to test correlations between numeric scores. Chi-square tests were performed to test differences in distribution for categorical variables. Non-parametric Kruskal-Wallis tests were conducted to compare numeric values between groups. Multiple linear regression and logistical regression models were then conducted to test the relationship between the measure scores at baseline and MLVI over the 2-year follow-up period, measured as a level and a threshold, with relevant covariates included. We ran these analyses for the overall cohort and also examined whether there were any differences in findings depending on patient age-group (children aged 12 and under, N = 290 vs adolescents, N = 110).

3 | RESULTS

The MALT study enrolled 400 patients, and of these, 386 (97%) caregivers completed the IES and CES-D. Children of these caregivers were at a mean age of 2.9 (SD = 3.4), and 202 (52.3%) were female primary caregivers. Figure 1 displays a CONSORT diagram for the present analyses. The mean score on the IES was 13.3 (SD = 13.3) representing an average value just below the cutoff of 14. Forty percent of the sample scored above this threshold, which was significantly greater than the percentage of caregivers who scored above the clinical cutoffs for depression (23%), $\chi^2 = 33.3$, $P < .001$.

TABLE 1 Significant demographic associations with IES avoidance, N = 386

	IES avoidance score, Mean (SD)	Overall *P* value
Participant race		
Asian (reference group)	9.4 (8.8)	.038
Black/African American	6.3 (6.8)	
White	5.1 (6.3)	
Other	6.7 (8.1)	
Caregiver education		
Some high school or less	8.2 (8.1)	.015
High school degree/GED	6.1 (6.9)	
Vocational school/some college	5.6 (6.1)	
College degree (reference group)	4.2 (5.8)	
Professional/graduate degree	4.9 (6.1)	
ESL		
Yes	8.1 (8.9)	.039
No	5.2 (6.3)	
Partner status		
Single	6.9 (7.0)	.014
Married/partnered	5.2 (6.4)	

TABLE 2 Linear regressions of caregiver baseline measure scores on MLVI

Age at baseline	Measure	*P* value	*R* square
Overall	[a]Total IES score	.65	.1627
	[b]Avoidance subscale	.50	.1648
	[c]Intrusion subscale	.73	.159
	[d]Total CES-D score	.27	.1615
1-12 y	Total IES score	.77	.1631
	Avoidance subscale	.68	.1649
	Intrusion subscale	.77	.1583
	Total CES-D score	.48	.1613
>12 y	Total IES score	.66	.2265
	Avoidance subscale	.48	.2306
	Intrusion subscale	.85	.2246
	Total CES-D score	.59	.2197

[a]Correlates for Total IES score include time since transplant, race, caregiver education, insurance type, caregiver partner status, and the PMBS.

[b]Correlates for Intrusion subscale include time since transplant, race, caregiver education, insurance type, and the PMBS.

[c]Covariates for Avoidance subscale include time since transplant, race, caregiver education level, insurance type, caregiver partner status, English as second language, and the PMBS.

[d]Correlates for Total CES-D score include time since transplant, race, caregiver education, insurance type, caregiver partner status, and the PMBS.

3.1 | Covariate analyses

To examine demographic and medical correlates of caregiver PTSS and depression, Kruskal-Wallis comparisons first were conducted between possible correlates and IES total score/CES-D score, respectively. No significant associations were found between IES total score and patient gender, patient race or ethnicity (Hispanic/Latino or non-Hispanic/Latino), insurance, caregiver education level, or donor type (living versus deceased). There was a significant negative correlation between time since transplant and IES score, $r = -.11$, $P = .033$. PTSS levels also differed by caregiver partner status. Caregivers who reported being single had higher scores than those who were partnered, 15.8 (SD = 14.5) versus 12.5 (SD = 12.5), $H = 6.4$, $P = .040$.

When examining the IES subscales, there were no significant associations for the Intrusion subscale, with the exception of time since transplant, $r = -.13$, $P < .001$. However, there were significant findings for Avoidance. Table 1 depicts the mean scores within each of these categories. Avoidance score differed by patient race, $H = 8.4$, $P = .038$, as well as caregiver education level, $H = 11.3$, $P = .015$, English as a second language, $H = 4.3$, $P = .039$, and partner status, $H = 4.8$, $P = .014$. For the CES-D, there were significant associations with partner status, $H = 11.3$, $P = <.001$, also with single caregivers scoring higher, and insurance, $H = 11.3$, $P = <.001$, with publically insured caregivers scoring higher.

Preliminary analyses were also run to examine covariates of MLVI. MLVI (continuous) was significantly associated with patient race, $H = 24.78$, $P = <.001$, caregiver education, $H = 17.23$, $P = <.001$, and insurance type, $H = 6.87$, $P = .032$. When MLVI was treated as a categorical variable, it was significantly associated with patient race, $\chi^2 = 12.66$, $P = <.001$, caregiver education, $\chi^2 = 15.54$, $P = <.001$, ethnicity, $\chi^2 = 5.64$, $P = .018$, and partner status, $\chi^2 = 3.96$, $P = .047$. MLVI was also significantly associated with parent-reported barriers to adherence (as measured by the PMBS), $r = .12$, $P = .024$, and trended toward significance, $H = 3.40$, $P = .065$, when MLVI was measured categorically.

3.2 | IES and CES-D as predictors of MLVI and central pathologist-diagnosed rejection

Next, we examined whether IES and CES-D scores were associated with MLVI. The correlation between MLVI and IES total score was not significant, $r = .07$, $P = .16$. Similarly, when MLVI was measured categorically, Kruskal-Wallis tests revealed that this relationship was non-significant, $P = .74$. The IES subscale scores and MLVI were also not significantly associated. However, CES-D, treated as either

TABLE 3 Logistic regressions of caregiver baseline measures scores on MLVI threshold

Age at baseline	Measure	Odds ratio	Confidence interval	*P* value	*R* square
Overall	Total IES score	1.000	(0.98, 1.02)	.99	.0807
	Avoidance subscale	1.000	(0.96, 1.04)	1.00	.0808
	Intrusion subscale	1.000	(0.97, 1.03)	.98	.0807
	Total CES-D score	1.016	(0.99, 1.05)	.28	.0829
1-12 y	Total IES score	1.000	(0.98, 1.02)	.99	.0807
	Avoidance subscale	1.000	(0.96, 1.04)	1.00	.0808
	Intrusion subscale	1.000	(0.97, 1.03)	.98	.0807
	Total CES-D score	1.016	(0.99, 1.05)	.28	.0829
>12 y	Total IES score	1.000	(0.98, 1.02)	.99	.0807
	Avoidance subscale	1.000	(0.96, 1.04)	1.00	.0808
	Intrusion subscale	1.000	(0.97, 1.03)	.98	.0807
	Total CES-D score	1.016	(0.99, 1.05)	.28	.0829

Note: Correlates for all models include time since transplant, race, caregiver education, insurance type, caregiver partner status, ethnicity, and the PMBS.

a continuous or a categorical variable, was significantly associated with MLVI (r = .13, P < .001, and χ^2 = 6.2, P = .001, respectively).

Given the prospective design, we conducted a series of multiple linear and multivariate logistic regression on IES total score, its subscales, and CES-D score to examine psychosocial predictors of MLVI score controlling for the significant correlates identified in earlier analyses. Tables 2 and 3 depict these non-significant findings for the entire cohort and when considering different age-groups. As shown, we took a conservative approach to inclusion of covariates.

We also examined whether IES scores or CES-D score was associated with central pathologist-diagnosed rejection. There were no significant differences in scores on the IES and its subscales for patients who had versus had not experienced a rejection episode. For the CES-D, a non-significant trend was detected when examining score differences; parent mean score for those whose child had experienced rejection was 12.4 (SD = 10.9) versus 9.1 (SD = 8.6), P = .077, for those who did not.

Finally, as a secondary analysis, we looked at whether an above cutoff score on the CES-D was associated with MLVI or rejection. The results were non-significant when looking at MLVI continuously or categorically. Consistently, the proportion of patients experiencing rejection according to a CES-D above threshold classification (25.6% versus 15.4%) did trend toward significance, P = .089.

4 | DISCUSSION

In this prospective multisite trial, we found that parental PTSS were not associated with (later) worse child adherence to medications and/or with later rejection of the transplanted organ. Parental depression was significantly associated with worse adherence but with small effect sizes. Our hypothesis that these symptoms would impact outcomes relevant to pediatric transplant was largely unsupported. This may reflect the relative weight of the broad range of covariates that we were able to consider as well. Interestingly too, findings did not vary depending on whether patients were younger children or adolescents.

It could be the case that these PTSS-related findings are constrained by the limitations of the version of the IES utilized, which only assesses the PTSD symptoms of avoidance and intrusion. Although speculative, the inclusion of other cluster symptoms such as "negative alterations in cognitions and mood" and "alterations in arousal and reactivity" may have led to different findings. We did not look at the patient's own symptoms in this study. In previous studies, patient PTSS have been conclusively shown to be associated with poor outcomes.[10,22]

Nevertheless, our data demonstrate that parental depression may be a worthwhile target for assessment and intervention given the frequency of symptoms that were reported. Parental depression is well-established as a risk factor for parenting difficulties. One possible explanation for this is that mood disorders are often uniquely accompanied by avolition which may well be a factor when oversight of healthcare management is disrupted.[24,25] Similarly, parent-perceived barriers to adherence were associated with MLVI, although again weakly so. It may be fruitful to consider parent depression and barriers to adherence concurrently; an interesting area for future study would be to determine whether a mechanism behind how depression impacts child outcomes is increased by perception of barriers to adherence by caregivers and/or families.

Finally, to some extent we were able to take a closer look at PTSS as the IES includes items that can be grouped into "avoidance" vs. "intrusion" clusters. It is notable that the avoidance cluster, but not the intrusion cluster, was associated with demographic variables that usually confer increased risk, such as race, lower educational status, English as second language (rather than primary language), and single parents. Avoidance cluster symptoms may be the more likely presentation of traumatic stress in certain ethnic

or socio-economic groups. Importantly, those symptoms were not associated with poorer outcomes, suggesting that prominent avoidance symptoms in parents should not be regarded as indicating increased risk, but rather as a specific manifestation of the distress phenomenology. However, clinicians perhaps should be mindful of the possible manifestation of avoidance. For example, although not measured here, attendance at appointments may be compromised.[26]

In addition to those limitations described above, our study did not examine the effect of full-fledged diagnosed PTSD or major depression. In addition, the population studied was very specific and our results may not be fully generalizable across parents of pediatric patients. However, transplant populations offer a unique opportunity to capture relationships with adherence because there is an objective outcome measure available.

In conclusion, PTSS have been previously reported in caregivers of children with medical illnesses.[27] Those symptoms were sometimes thought to be associated with worse child outcomes.[28] Our findings, on the one hand, are consistent with others' observations about the prevalence of PTSS in parents of children with chronic health conditions. On the other hand, the findings of this study challenge the thought that those symptoms are necessarily associated with poorer child outcomes. To our knowledge, this is the largest prospective study to date that looked at the development of robustly defined medical and behavioral outcomes in children whose parents have varying levels of PTSS at baseline.

Our results echo others' observation that parents of children with chronic illness may be quite resilient even if somewhat distressed.[29] Although we did not evaluate this construct in our study, an important future direction may be to explore post-traumatic growth,[30] a positive attribute of post-traumatic experiences that may lead to better coping in some parents. In a medical setting in which resources are scarce, it would appear that the detection of depression in a parent should carry a higher level of concern about the child's well-being than the realization that the parent is distressed about their child's illness. Certainly, parents meeting criteria for PTSD require mental health services, but when it comes to understanding correlates of non-adherence for pediatric patients from a wide age range, the present study has helped to start isolating other caregiver contributors and to reconsider others.

CONFLICT OF INTEREST

There are no conflicts of interest.

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How to cite this article: Annunziato RA, Stuber ML, Supelana CJ, et al. The impact of caregiver post-traumatic stress and depressive symptoms on pediatric transplant outcomes. *Pediatr Transplant*. 2020;24:e13642. https://doi.org/10.1111/petr.13642