Clinical Cutoffs for Adherence Barriers in Solid Organ Transplant Recipients: How Many Is Too Many?

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Objective The current study used multiple statistical methods to determine empirically derived and clinically relevant cutoff scores on the Adolescent Medication Barriers Scale (AMBS) and Parent Medication Barriers Scale (PMBS) to detect adolescents and young adults with solid organ transplants who experienced medication nonadherence or negative medical outcomes. **Methods** Participants included 71 patients and 80 caregivers. Cutoff scores were determined via receiver operating characteristic curve analyses, *t*-test analyses, and the sensitivity and specificity of using certain cutoff scores. **Results** AMBS scores of ≥3 barriers and PMBS scores of ≥2 barriers were determined as the ideal cutoffs for identifying patients meeting criteria for the outcome variables. **Conclusions** Clinicians should consider using these recommended cutoff scores when assessing adherence barriers in adolescents and young adults with solid organ transplants and their families. Patients or caregivers endorsing barriers above the cutoffs may benefit from further assessment or intervention to address barriers, nonadherence, or related medical issues.

Key words adherence; barriers; pediatric; transplant.

Long-term survival rates after transplantation have improved considerably in the past decade, with 80% of pediatric recipients reaching adolescence and young adulthood (LaRosa, Baluarte, & Meyers, 2011). Receiving a transplant trades a life-threatening illness for a chronic medical condition, requiring daily sustained adherence to medications (Griffin & Elkin, 2001; LaRosa et al., 2011). Medication regimens after transplantation are complex, requiring a large number of different medications to be administered using schedules that change frequently (Shellmer, Dabbs, & Dew, 2011). In pediatric chronic illness populations, rates of medication adherence are approximately 50% (La Greca & Mackey, 2009). In adolescents and young adults (AYAs), a recent systematic review of the literature indicated that, on average, 43% of patients are nonadherent to their immunosuppressant medications (Dobbels et al., 2010). Adolescence and young adulthood represent times of transition into more responsible and autonomous roles across all domains of life. This transition creates opportunities for missteps, resulting in higher rates of nonadherence in this age-group and organ rejection rates that are second only to individuals over the age of 65 years (La Greca & Mackey, 2009; Smith, Ho, & McDonald, 2002).

Medication nonadherence is the leading cause of organ rejection (Shaw, Palmer, Blasey, & Sarwal, 2003), suggesting that the identification of factors influencing its occurrence is critical. Late dosing is a form of medication nonadherence that is particularly relevant to most antirejection medications (e.g., tacrolimus, cyclosporine), given the need to maintain consistent therapeutic serum immunosuppressant blood levels to prevent organ rejection (Shemesh et al., 2004; Zelikovsky & Schast, 2008). Late dosing for non-antirejection medications additionally suggests that patients have difficulty establishing and following routines related to the medication regimen, in general, and

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may indicate that the patient is experiencing barriers to complete adherence (Zelikovsky & Schast, 2008).

Barriers have been shown to be the most powerful predictor of a number of health practices in pediatric populations, including adherence (Marhefka et al., 2008; Modi & Quittner, 2006; Rapoff, 2010). Barriers can consist of nonmodifiable factors (i.e., demographics), modifiable factors (e.g., cognitive and environmental), and readiness factors (e.g., motivation and perceived benefits; Rapoff, 2010). The types of barriers associated with poor medication adherence in pediatric transplant recipients include cognitive factors (e.g., forgetting, poor planning), aversive medication properties (e.g., hard to swallow, tastes bad), and voluntary resistance to medication taking (Simons, McCormick, Mee, & Blount, 2009). Barriers have been shown to mediate the relationship between behavioral and emotional dysfunction and adherence (McCormick King et al., 2014; Reed-Knight, Lewis, & Blount, 2013), suggesting they have a unique influence on adherence. AYAs with higher levels of barriers are at greater risk for experiencing negative medical outcomes such as rejection episodes, hospitalizations, and/or death (Simons, McCormick, Devine, & Blount, 2010). Barriers have also been shown to be stable over time, suggesting that they will not resolve on their own over time without targeted intervention (Lee et al., 2014).

The Adolescent Medication Barriers Scale (AMBS) and Parent Medication Barriers Scale (PMBS) were developed to assess AYAs' barriers to medication adherence via self- and parent proxy-report (Simons & Blount, 2007). Though originally developed with solid organ transplant recipients, it has been used to assess barriers in other pediatric populations (Reed-Knight et al., 2013; Silverstein, Fletcher, & Moyan, 2014). Despite the measures' frequent use in the literature and strong psychometric properties, an established clinical cutoff score does not yet exist for either scale. Clinical cutoffs provide useful decision-making information for providers and have been recommended as requirements for evidence-based screening instruments (Mash & Hunsley, 2005). A clinical cutoff would allow the AMBS and PMBS to be used in a clinical setting to screen and identify AYAs who are experiencing a critical number of barriers that have been demonstrated to interfere with adherence and be associated with negative medical outcomes. Identifying at-risk AYAs would allow for further assessment of barriers to adherence and intervention before life-threatening consequences, such as nonadherence-related rejection episodes, graft loss, hospitalizations, retransplantation, and mortality (Falkenstein, Flynn, Kirkpatrick, Casa-Melley, & Dunn, 2004).

This study is the first to determine a statistically derived cutoff score on the AMBS and PMBS to identify AYAs with solid organ transplants who are at risk for medication nonadherence or negative medical outcomes (e.g., rejection episodes, hospitalizations, infections). The current study used a novel multimethod approach, which included receiver operating characteristic (ROC) curve analyses, to determine the criterion validity of using the AMBS and PMBS to identify patients on the outcome variables of interest and establish a standard cutoff score for each scale. ROC curve analyses were followed up with independent samples *t*-tests to determine a unique cutoff score for the AMBS and PMBS and to optimize the clinical utility of the identified cutoffs. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of suggested cutoff scores were examined to select a cutoff score that would enhance the ability for health care providers to efficiently identify patients at risk for nonadherence and poor medical outcomes in clinical settings. Given known relationships between barriers, medication nonadherence, and negative medical outcomes in AYA transplant recipients (Simons et al., 2010), it was hypothesized that AYAs with AMBS or PMBS scores above the identified cutoffs would present with more incidences of medication nonadherence and negative medical outcomes than those with scores below the cutoffs.

Method

Participants

For the purposes of the current study, ''AYA'' was defined as a patient between the age of 11 and 21 years (at the research site, patients transfer to adult-based care by the age of 21 years). Participants included 71 AYA patients, aged 11–20 years ($M = 15.86$, $SD = 2.45$), and 80 caregivers, aged 30–73 years ($M = 43.98$, $SD = 7.52$). Approximately 54.9% ($n = 39$) of patients were male and 93.8% ($n = 75$) of caregivers were female. Of the AYA patients, 57.7% ($n = 41$) received kidney transplants, 23.9% received liver transplants ($n = 17$), 16.9% received heart transplants ($n = 12$), and 1.4% had a double lung transplant ($n = 1$). The average time since transplantation was 4.86 years ($SD = 4.41$, range = 4 months to 15.42 years). See Table I for more details on the demographic composition of participants.

Measures

Adolescent Medication Barriers Scale

The AMBS is a 17-item factor-analytically–derived measure of patient-perceived barriers to taking prescribed medications (e.g., ''I don't like what the medication does to my appearance''; Simons & Blount, 2007). AYAs are instructed to respond to each item using a 5-point Likert scale (1 = *Strongly disagree* to 5 = *Strongly agree*). The AMBS

Table I. *Demographic Information*

	Patients		Caregivers	
	N = 71		*N* = 80	
Factor	*M*	*SD*	*M*	*SD*
Age (years)	15.86	2.45	43.98	7.52
Antirejection medication doses per week	25.32	7.75	28.26	6.92
Other medication doses per week	27.04	17.14	29.78	17.70
	Frequency	%	Frequency	%
Sex				
Male	39	54.9	5	6.3
Female	32	45.1	75	93.8
Ethnicity				
Caucasian	45	63.4	51	63.8
African American	20	28.2	24	30.0
Asian-East Indian	1	1.4	1	1.3
Other	5	7.0	4	5.0
Family income				
Less than $10,000	9	13.4	11	14.1
$10,000–24,999	11	16.4	13	16.7
$25,000–49,999	19	28.4	21	26.9
$50,000–74,999	9	13.4	11	14.1
$75,000–99,999	5	7.5	6	7.7
$100,000–149,999	6	9.0	7	9.0
$150,000+	8	11.9	9	11.5
Caregiver marital status				
Married	42	60.9	50	62.5
Single	9	13.0	11	13.8
Divorced	10	14.5	11	13.8
Separated	5	7.2	5	6.3
Widowed	2	2.9	2	2.5
Partnered	1	1.4	1	1.3

Notes. The average number of antirejection and other medications listed under ''Caregiver'' refers to the average number of medication doses prescribed to the caregiver's adolescent or young adult.

was developed for and validated with AYA patients (Simons & Blount, 2007). For the current study, a ''Total Endorsement'' score was used to truncate the range of possible scores to be between 0 and 17. For the purpose of determining a standard and clinically useful cutoff score to identify AYAs at risk for nonadherence or adverse medical outcomes, a smaller range of scores was preferable to the Total Score, which ranged from 17 to 85. To calculate the Total Endorsement score, items to which AYAs responded with 4 (*Agree*) or 5 (*Strongly agree*) were coded as ''1'' to denote that the barrier was endorsed. For items to which AYAs responded with 1 (*Strongly disagree*), 2 (*Disagree*), or 3 (*Not sure*), the item was coded as ''0'' to denote that the barrier was not endorsed. The Total Endorsement score was calculated by summing all recoded items for each participant. Higher total endorsement scores indicated that the AYAs perceived themselves as having more barriers to medication adherence. Before dichotomization, the internal consistency of the AMBS total score was good ($\alpha = .87$).

Parent Medication Barriers Scale

The PMBS is a 16-item factor-analytically–derived measure of caregivers' perceptions of their AYA's barriers to taking prescribed medications (e.g., ''My child finds it hard to stick to a fixed medication schedule''; Simons & Blount, 2007). Caregivers are instructed to respond to each item using a 5-point Likert scale (1 = *Strongly disagree* to 5 = *Strongly agree*). The PMBS was developed for and validated with caregivers of AYA patients (Simons & Blount, 2007). A ''Total Endorsement'' score was used to truncate the range of scores possible on the PMBS to be between 0 and 16. Similar to the AMBS, a smaller range of scores on the PMBS was preferable for determining a clinically useful cutoff to identify patients at risk for nonadherence and negative medical outcomes (the PMBS total score ranges from 16 to 80). To calculate the Total Endorsement score, items to which caregivers responded with 4 (*Agree*) or 5 (*Strongly agree*) were coded as ''1'' to denote barrier endorsement. For items to which caregivers responded with 1 (*Strongly disagree*), 2 (*Disagree*), or 3 (*Not sure*), the item was coded as ''0'' to denote that the barrier was not endorsed. The Total Endorsement score was calculated by summing each participant's recoded items. Higher total endorsement scores indicated that the caregiver perceived their AYA as having more barriers to adherence. Before dichotomization, the internal consistency of the PMBS total score was good ($\alpha = .88$).

Medication Adherence Measure

The Medication Adherence Measure (MAM) is a structured interview that assesses AYA- and caregiver-reported adherence for each individual, prescribed medication that was missed or taken late in the past week (Zelikovsky & Schast, 2008). AYA- and caregiver-reported adherence for each prescribed medication was used to determine patients' average medication nonadherence rates over the past 7 days. Medications taken on an ''as needed'' basis were not included in calculations of missed or late doses. ''Late'' medication doses included any medications taken >1 hours past the scheduled time recommended by the provider. Separate percentages of missed or late medications were calculated for ''antirejection medications'' (e.g., tacrolimus) and ''other medications'' (e.g., non-antirejection prescription medications, such as labetalol or amlodipine, or over-the-counter medications, such as

multivitamins) prescribed for the patient. Antirejection medications were reported separately due to the relationship between nonadherence to these medications and organ rejection (Shemesh et al., 2004). Data on other medications were included to further highlight general difficulties with following medication regimens as directed. The total number of antirejection or other medication doses that were missed or taken late was divided by the total number of antirejection or other medication doses prescribed and multiplied by 100 to provide a percentage of missed or late doses for each type of medication. The MAM has demonstrated positive correlations with adherence rates measured via electronic monitoring in pediatric transplant recipients, suggesting good convergent validity (Zelikovsky, Schast, Palmer, & Meyers, 2008).

Medical Outcomes

Patients' medical records were reviewed to collect data on medical outcomes in the 6 months before participation in the study, including the presence of rejection episodes, infections, and hospitalizations due to transplant-related complications. The use of retrospective medical data was supported by prior research demonstrating that specific and overall adherence barriers are longitudinally stable (Lee et al., 2014; Simons et al., 2010). The demonstrated stability of barriers identified by the AMBS and PMBS suggest that these issues likely influence medical outcomes across a wide span of time.

Procedures

The current study is part of a larger study that recruited participants from a pediatric transplant clinic in the United States. All procedures were approved by the participating institutional review boards. Participants provided informed consent, assent, and Health Information Portability and Accountability Act release before completing measures. The majority of AYAs ($n = 69$, 97.2%) and caregivers ($n = 79$, 98.8%) completed interviews over the telephone, with the remainder completing them in person. Clinical outcome data were collected via a medical chart review. Participants received $20 gift cards as compensation for their participation.

Analyses

All statistical analyses were conducted using IBM Statistical Package for the Social Sciences, Version 20. ROC curve analyses were conducted to determine cutoff scores on the AMBS and PMBS by detecting patients who met criteria for the presence of medication nonadherence and negative medical outcomes (i.e., presence of rejection episodes, infections, or hospitalizations). ROC curve analyses provide indications of a measure's diagnostic efficiency by estimating the probability that an individual will be correctly classified as meeting criteria for a dichotomized dependent variable (Youngstrom, 2014).

In the current study, the AMBS or PMBS Total Endorsement scores were entered as the test variables and dichotomized nonadherence and medical outcome variables were entered as the state variables. To dichotomize percentages of nonadherence to antirejection and other medications, individuals who reported ≥10% missed or late medications were identified as nonadherent and coded as 1 and individuals who reported <10% missed or late medications in the past week were identified as adherent and coded as 0. The decision to use a cutoff of <10% missed or late medications to dichotomize "nonadherence" was determined a priori and based on previous research validating the AMBS and PMBS with AYA transplant recipients (Simons & Blount 2007; Simons et al., 2009), and research with adult transplant recipients (Hilbrands, Hoitsma, & Koene, 1995) and other pediatric populations (Marhefka et al., 2004; Wu, Pai, Gray, Denson, & Hommel, 2013). No other cut points were examined for nonadherence variables. For nonadherence variables, the AMBS was analyzed with AYA-reported nonadherence and the PMBS was analyzed with caregiver-reported nonadherence. The three different medical outcomes (i.e., rejection episodes, infections, and hospitalizations) were dichotomized to indicate whether the patient had (coded as 1) or had not (coded as 0) experienced any of these medical incidents.

Area under the curve (AUC) values were calculated as indicators of how well the AMBS or PMBS classified individuals on the selected outcomes (Bewick, Cheek, & Ball, 2004). AUCs that had p-values of <.05 were accepted as statistically significant predictors of the outcome variables. When an ROC curve analysis yielded an AUC estimate ranging between 0.7 and 1.00 (an AUC of 1.00 suggests the test has perfect diagnostic accuracy), the AMBS or PMBS was considered to be a "well-performing" test for classifying participants on the outcome of interest (Youngstrom, 2014).

After determining that the AMBS or PMBS was a well-performing test for detecting the presence or absence of a selected outcome, Youden's index (J) was calculated in the first step toward determining a cutoff point that would accurately classify patients on the clinical criterion (e.g., presence of missing ≥10% of medications, presence of having a rejection episode) when sensitivity and specificity were of equal importance ($J = \text{sensitivity} + \text{specificity} - 1$; Bewick et al., 2004). Although useful for providing direction for determining cutoff scores, Youden's index does not

account for the clinical meaningfulness of using cutoff scores that result in greater sensitivity or specificity (Bewick et al., 2004). For AYA transplant recipients, there is long-term value in identifying patients at risk for nonadherence and negative medical outcomes, which outweighs the increased potential for false-positive screens. To this end, a more sensitive clinical cutoff score was preferable for the purposes of this study. Additionally, using Youden's index presented the possibility of finding multiple cutoff points on the AMBS and PMBS, depending on the stated variable of interest. One of the primary aims of the current study was to determine a single cutoff point on the AMBS and PMBS that would help clinicians efficiently screen and identify patients at risk for nonadherence and negative medical outcomes.

In the interest of determining a single sensitive cutoff score, planned follow-up analyses were conducted if Youden's index suggested multiple cutoff points on the AMBS and PMBS. To accomplish this goal, *t*-test analyses were used to determine whether the multiple cutoff scores suggested by Youden's index resulted in clinically meaningful and statistically significant mean differences between participants on the outcome variables. Cross-tab analyses were then used to calculate the sensitivity (i.e., proportion of true positives in the entire sample), specificity (i.e., proportion of true negatives in the entire sample), PPV (i.e., proportion of true positives out of all positive results in the sample), NPV (i.e., proportion of true negatives out of all negative results in the sample), and diagnostic accuracy (i.e., percentage of true positives and true negatives in the entire sample) of using each of the suggested cutoff scores. Higher PPV, NPV, and diagnostic accuracy values reflect a stronger diagnostic test (Akobeng, 2006). Based on the results of these follow-up analyses, the most sensitive and clinically meaningful cutoff score was selected for the AMBS and PMBS.

Results

Does the AMBS Discriminate Between Better and Worse Medical and Adherence Outcomes?

Medical Outcomes

Of the 71 AYAs who completed the AMBS, 26.8% ($n = 19$) had rejection episodes, 21.1% ($n = 15$) had infections, and 25.4% ($n = 18$) had hospitalizations. The ROC curve for the AMBS was statistically significant for rejection episodes. The AUC was 0.670 [$SE = 0.06$, $p = .022$, 95% confidence interval (CI) = 0.55–0.79]. The Youden's index of 0.396 suggested that the cutoff score for identifying true positive and true negative cases of rejection episodes when sensitivity and specificity were of equal importance was ≥4 barriers, resulting in a diagnostic accuracy rate of 71.83%. The ROC curves for the AMBS were not significant for other medical outcomes. See Table II for data on the sensitivity, specificity, PPV, and NPV of the AMBS cutoff scores determined by ROC curve analyses.

Adherence Outcomes

The ROC curve for the AMBS was statistically significant for missed antirejection medications. The AUC was 0.720 ($SE = 0.08$, $p = .045$, 95% CI = 0.56–0.88). The Youden's index of 0.40 suggested that the cutoff score for identifying true positive and true negative cases of missed antirejection medications when sensitivity and specificity were of equal importance was ≥4 barriers, resulting in a diagnostic accuracy rate of 66.18%. The ROC curve for the AMBS was statistically significant for late antirejection medications. The AUC was 0.701 ($SE = 0.06$, $p = .004$, 95% CI = 0.58–0.83). The Youden's index of 0.358 suggested that the cutoff score for identifying true positive and true negative cases of late antirejection medications was ≥3 barriers, resulting in a diagnostic accuracy rate of 67.65%.

The ROC curve for the AMBS was statistically significant for missed other medications. The AUC was 0.786 ($SE = 0.07$, $p = .016$, 95% CI = 0.66–0.91). The Youden's index of 0.535 suggested that the cutoff score for identifying true positive and true negative cases of missed other medications when sensitivity and specificity were of equal importance was ≥3 barriers, resulting in a diagnostic accuracy rate of 60%. The ROC curve for late other medications was not statistically significant. See Table II for data on the sensitivity, specificity, PPV, and NPV of the AMBS cutoff scores determined by ROC curve analyses.

Does the PMBS Discriminate Between Better and Worse Medical and Adherence Outcomes?

Medical Outcomes

Of the 80 AYAs whose caregivers completed the PMBS, 25% ($n = 20$) had rejection episodes, 20% ($n = 16$) had infections, and 27.5% ($n = 22$) had hospitalizations. The ROC curves for the PMBS were not statistically significant for any medical outcome variables.

Adherence Outcomes

The ROC curve for the PMBS was not statistically significant for missed antirejection medications. The ROC curve for the PMBS was statistically significant for late antirejection medications. The AUC was 0.717 ($SE = 0.06$, $p = .002$, 95% CI = 0.60–0.84). The Youden's index of 0.378 suggested that the cutoff score for identifying true positive and true negative cases of late antirejection

Table II. *Sensitivity and Specificity at Cutoff Points on the AMBS Derived From ROC Curve Analyses*

Variable	Presence	Absence	*n*	Sensitivity	Specificity	PPV	NPV	Accuracy %
Medical outcomes								
Rejection episodes*				0.74	0.71	0.48	0.88	71.83
<4 barriers	5	37	42					
≥4 barriers	14	15	29					
Total	19	52	71					
Adherence outcomes								
≥10% missed AR*				0.75	0.65	0.22	0.95	66.18
<4 barriers	2	39	41					
≥4 barriers	6	21	27					
Total	8	60	68					
≥10% late AR**				0.72	0.64	0.64	0.72	67.65
<3 barriers	9	23	32					
≥3 barriers	23	13	36					
Total	32	36	68					
≥10% missed other*				1.00	0.53	0.26	1.00	60.00
<3 barriers	0	23	23					
≥3 barriers	7	20	27					
Total	7	43	50					

Notes. AR = antirejection medications; other = non-antirejection medications. PPV = positive predictive value; NPV = negative predictive value. Adherence was reported by the AYA for all AMBS analyses.

*Area under the curve (AUC) was significant at $p < .05$; **AUC was significant at $p < .01$.

medications when sensitivity and specificity were of equal importance was ≥3 barriers, resulting in a diagnostic accuracy rate of 66.23%.

The ROC curve for the PMBS was not statistically significant for missed other medications. The ROC curve for the PMBS was statistically significant for late other medications. The AUC was 0.664 ($SE = 0.07$, $p = .031$, 95% CI = 0.53–0.80). The Youden's index of 0.269 suggested that the cutoff score for identifying true positive and true negative cases of late other medications when sensitivity and specificity were of equal importance was ≥2 barriers, resulting in a diagnostic accuracy rate of 60.00%. See Table III for data on the sensitivity, specificity, PPV, and NPV of the PMBS cutoff scores determined by the ROC curve analyses.

Follow-Up Analyses to Recommend Single Cutoff Scores on the AMBS and PMBS

AMBS Follow-Up Analyses

Because ROC curve analyses suggested cutoff scores of either ≥3 or ≥4 endorsed barriers on the AMBS, follow-up analyses were conducted to recommend a single standard AMBS cutoff score. *T*-test analyses indicated that when a cutoff score of ≥3 barriers was used, AYAs endorsing ≥3 barriers had significantly more rejection episodes [$M_{\geq 3} = 1.47$, $SD = 0.11$; $M_{<3} = 1.12$, $SD = 0.07$; $t(63.83) = -2.77$, $p = .007$; $d = 3.80$], missed more antirejection medications [$M_{\geq 3} = 3.66$, $SD = 5.29$; $M_{<3} = 1.19$, $SD = 3.14$; $t(57.99) = -2.37$, $p = .021$; $d = 0.57$], and missed more other medications [$M_{\geq 3} = 7.21$, $SD = 14.25$; $M_{<3} = 0.95$, $SD = 2.17$; $t(27.42) = -2.25$, $p = .032$; $d = 0.61$] than AYAs endorsing <3 barriers. Mean differences between the percentage of late antirejection medications approached significance for AYAs who endorsed ≥3 barriers versus those who endorsed <3 barriers [$M_{\geq 3} = 17.94$, $SD = 22.32$; $M_{<3} = 8.50$, $SD = 18.66$; $t(65.77) = -1.90$, $p = .062$; $d = 0.46$]. *T*-test analyses indicated that when a cutoff score of ≥4 barriers was used, AYAs endorsing greater ≥4 barriers had significantly more rejection episodes [$M_{\geq 4} = 1.48$, $SD = 0.51$; $M_{<4} = 1.19$, $SD = 0.59$; $t(65.76) = -2.22$, $p = .03$; $d = 0.53$], missed antirejection medications [$M_{\geq 4} = 4.14$, $SD = 5.42$; $M_{<4} = 1.42$, $SD = 3.56$; $t(40.73) = -2.31$, $p = .026$; $d = 0.59$], late antirejection medications [$M_{\geq 4} = 20.35$, $SD = 25.08$; $M_{<4} = 8.89$, $SD = 16.80$; $t(41.29) = -2.07$, $p = .045$; $d = 0.54$], and missed other medications [$M_{\geq 4} = 8.89$, $SD = 16.04$; $M_{<4} = 1.28$, $SD = 3.14$; $t(19.97) = -2.10$, $p = .049$; $d = 0.66$] than AYAs endorsing <4 barriers.

The Youden's index suggested a cutoff score of ≥4 barriers for identifying cases of rejection episodes and missed antirejection medications. A cutoff score of ≥3 barriers resulted in higher sensitivity and lower specificity for both rejection episodes (sensitivity = 0.84;

Table III. *Sensitivity and Specificity at Cutoff Points on the PMBS Derived From ROC Curve Analyses*

Variable	Presence	Absence	*n*	Sensitivity	Specificity	PPV	NPV	Accuracy %
Adherence outcomes								
≥10% late AR**				0.78	0.60	0.51	0.83	66.23
<3 barriers	6	30	36					
≥3 barriers	21	20	41					
Total	27	50	77					
≥10% late other*				0.84	0.43	0.51	0.79	60.00
<2 barriers	4	15	19					
≥2 barriers	21	20	41					
Total	25	35	60					

Notes. AR = antirejection medications; other = non-antirejection medications; PPV = positive predictive value; NPV = negative predictive value. Adherence was reported by the caregiver for all PMBS analyses.
*Area under the curve (AUC) was significant at $p < .05$; **AUC was significant at $p < .01$.

specificity = 0.58) and missed antirejection medications (sensitivity = 0.88; specificity = 0.52) compared with a cutoff score of ≥4 barriers. The Youden's index suggested a cutoff score of ≥3 for identifying cases of late antirejection medications and missed other medications. A cutoff score of ≥4 barriers resulted in lower sensitivity and higher specificity for both late antirejection medications (sensitivity = 0.56; specificity = 0.75) and missed other medications (sensitivity = 0.86; specificity = 0.67) compared with a cutoff score of ≥3. Both cutoff scores resulted in comparably large effect sizes when examining the magnitude of mean differences. A cutoff score of ≥3 barriers on the ABMS, however, not only yielded clinically relevant and statistically significant mean differences between groups but also resulted in higher sensitivity for identifying patients experiencing rejection episodes and medication nonadherence. Therefore, a score of ≥3 endorsed barriers was determined to be the overall optimal cutoff score for the AMBS.

PMBS Follow-Up Analyses

Because ROC curve analyses suggested cutoff scores of either ≥2 or ≥3 endorsed barriers on the PMBS, follow-up analyses were conducted to determine a single PMBS cutoff score. *T*-test analyses indicated that when a cutoff score of ≥2 barriers was used, caregivers endorsing ≥2 barriers reported significantly more late antirejection medications [$M_{\geq 2} = 11.80$, $SD = 12.89$; $M_{<2} = 4.39$, $SD = 9.15$; $t(71.36) = -2.94$, $p = .004$; $d = 0.66$] and late other medications [$M_{\geq 2} = 10.63$, $SD = 12.76$; $M_{<2} = 3.97$, $SD = 7.87$; $t(53.09) = -2.48$, $p = .016$; $d = 0.63$] than caregivers endorsing <2 barriers. *T*-test analyses indicated that when a cutoff score of ≥3 barriers was used, caregivers endorsing ≥3 barriers had significantly more late antirejection medications [$M_{\geq 3} = 11.98$, $SD = 13.04$; $M_{<3} = 5.83$, $SD = 10.26$; $t(74.15) = -2.31$, $p = .024$; $d = 0.52$] than caregivers endorsing <3 barriers. There were no statistically significant differences for the percentage of late other medications for caregivers endorsing ≥3 versus <3 barriers [$M_{\geq 3} = 10.44$, $SD = 12.16$; $M_{<3} = 5.83$, $SD = 10.93$; $t(54.90) = -1.54$, $p = .13$; $d = 0.40$].

The Youden's index suggested a cutoff score of ≥3 barriers for identifying cases of late antirejection medications. A cutoff score of ≥2 barriers resulted in higher sensitivity and lower specificity for taking antirejection medications late (sensitivity = 0.85; specificity = 0.48) compared with a cutoff score of ≥3 barriers. The Youden's index suggested a cutoff score of ≥2 barriers for identifying cases of late other medications. A cutoff score of ≥3 barriers resulted in lower sensitivity and higher specificity for taking other medications late (sensitivity = 0.72; specificity = 0.51) compared with a cutoff score of ≥2. A cutoff score of ≥2 barriers also resulted in larger effect sizes when examining the magnitude of mean differences compared with a cutoff score of ≥3 barriers. A cutoff score of ≥2 barriers on the PBMS yielded clinically relevant and statistically significant mean differences between groups and resulted in higher sensitivity for identifying patients experiencing medication nonadherence. Therefore, a score of ≥2 endorsed barriers was determined to be the overall optimal cutoff score for the PMBS.

Discussion

The current study aimed to determine a standard clinical cutoff score on the AMBS and PMBS that could be used to identify AYA patients with solid organ transplants who are at risk for experiencing medication nonadherence and

negative medical outcomes that are often related to nonadherence (e.g., rejection episodes). The AMBS and PMBS are validated measures of barriers to adherence for AYA solid organ transplant recipients, but neither scale had established cutoff scores to inform efficient screening of patients in clinical settings. Recommended cutoff scores are clinically useful for helping providers estimate the probability of experiencing specific negative outcomes (e.g., nonadherence, rejection episodes) for pediatric patients who score above the cutoff (Youngstrom, 2014). For both scales, cutoff points were determined through a novel, multimethod approach to statistical analysis and careful consideration of the clinical utility of using specific cutoffs. When this analytic approach yielded multiple potential cutoff points, the most sensitive cutoff point was accepted over the most specific, due to the clinical importance of detecting positive cases of nonadherence and negative medical outcomes in AYA solid organ transplant recipients. Given the significant consequences of experiencing the negative medical outcomes examined in this study (e.g., rejection episodes, infections, hospitalizations), a higher rate of false positive cases was viewed as a necessary cost of using a more sensitive cutoff point.

Results suggested that cutoff scores of ≥3 endorsed barriers on the AMBS and ≥2 endorsed barriers on the PMBS best achieved the goal of identifying empirically derived, clinically useful, and sensitive markers of nonadherence and negative medical outcomes. A cutoff score of ≥3 endorsed barriers on the AMBS adequately classified patients who experienced rejection episodes, ≥10% missed or late antirejection medication doses, and ≥10% missed ''other'' medication doses. A cutoff score of ≥2 endorsed barriers on the PMBS adequately classified patients who experienced ≥10% late antirejection medication doses and ≥10% late ''other'' medication doses. Consistent with hypothesized results, patients with AMBS or PMBS scores that were at or above identified cutoffs presented with more incidences of nonadherence and negative medical outcomes than those with scores below the cutoffs.

A higher cutoff score was determined for the AMBS than the PMBS. This finding was consistent with previous research indicating that pediatric patients and caregivers endorse different barriers to adherence (Lee et al., 2014) and at different rates (Modi & Quittner, 2006). Considering the emphasis in adolescence on increasing independence when preparing to transition to adult-based clinics (Gilleland, Amaral, Mee, & Blount, 2011), caregivers may not be as attuned to the number of adherence barriers experienced by the patient. Additionally, some of the items on the PMBS pertained to internal thoughts and processes (e.g., ''My child does not want other people to notice him/her taking the medicine'') about which caregivers may be unaware. Caregivers have been shown to endorse lower mean levels of barriers on the PMBS compared with AYA report on the AMBS (Reed-Knight et al., 2013; Simons et al., 2010), which likely led to determining a lower cutoff score on the PMBS.

In the current study, the AMBS discriminated between patients on three nonadherence outcomes and one medical outcome (i.e., rejection episodes), while the PMBS discriminated on two nonadherence outcomes. The only unique nonadherence outcome predicted by the PMBS, rather than the AMBS, was taking ≥10% of ''other'' medications (i.e., non-antirejection medications) late. The lack of statistical significance of the ROC analyses for the PMBS and ≥10% missed antirejection or other medications was likely due to low endorsement of missed medications by caregivers and issues related to overall statistical power. Low self-reported missed medications may have reflected social desirability concerns (Greenley et al., 2012), with caregivers feeling more comfortable reporting that medications were taken late rather than missed completely.

Results of the current study suggest that there is some clinical utility in assessing caregiver-reported barriers using the PMBS. However, because the AMBS was able to classify patients on more clinical outcomes, providers may choose to prioritize assessing AYA-reported barriers in fast-paced clinical settings. Administering and scoring the AMBS takes less than 10 min. If a more comprehensive assessment of barriers is preferred, administering the PMBS may provide greater insight into the types of barriers endorsed by the patient or the nature of patient–caregiver interactions related to taking medications (e.g., whether the caregiver needs to remind the patient to take his/her medications). Whether clinicians choose to administer both measures or prioritize the AMBS over the PMBS, results of the current study suggest that both measures are promising methods for quickly identifying patients at risk for general medication nonadherence and, for the AMBS, rejection episodes.

Despite the clinical utility of using cutoff scores, clinicians should continue to examine the specific barriers endorsed on the AMBS or PMBS. Specific barriers have been shown to be stable over time (Lee et al., 2014) and correlate with future nonadherence and adverse medical outcomes (Simons et al., 2010). Identifying individual barriers could provide useful information about adherence-related challenges to guide intervention processes (e.g., implementing a cell phone alarm reminder system to overcome barriers related to forgetting doses). Assessing individual barriers may be important for patients who fall below the recommended AMBS and PMBS

cutoff scores. Although results of the current study suggest that patients below the cutoff have lower incidences of nonadherence and rejection episodes, these patients may still benefit from intervention to address specific persistent barriers and prevent continued challenges over time.

In addition to providing clinically useful results, the current study included the application of a novel combination of statistical analyses with consideration of the clinical implications to optimize the performance of the cutoffs. The utility of using ROC curve analyses and Youden's Index to assess measure performance and determine clinical cutoffs on validated scales has been demonstrated in previous studies with pediatric patients with different chronic medical conditions (Stoppelbein, Greening, Moll, Jordan, & Suozzi, 2012; Wu et al., 2013). The current study extended this methodology by examining mean differences and effect sizes on clinical outcomes when multiple cutoff points were suggested by ROC curve and Youden's Index analyses. Lastly, the sensitivity and specificity of using the various suggested cutoff points was analyzed with regard to the clinical needs of AYAs with solid organ transplants. The most sensitive cutoff points were ultimately selected from those yielded by statistical analyses. Higher sensitivity was considered critical to the application of the AMBS and PMBS in clinical settings owing to the significant consequences of medication nonadherence for AYA solid organ transplant recipients, including rejection, hospitalizations, decreased health-related quality of life, and death (Fredericks, Lopez, Magee, Shieck, & Opipari-Arrigan, 2007).

Although the current study represented a novel application of statistical analyses to determine clinically relevant cutoff scores on two validated measures, it was not without limitations. Cutoff scores were initially determined by calculating Youden's Index, which assumed sensitivity and specificity to be of equal importance (Bewick et al., 2004). For the purposes of the current study, this approach was viewed as an unbiased method to narrow down specific cutoff scores, which could then be followed by other analyses and clinical decision making to determine a single sensitive cutoff score. However, this method is not the only available procedure and other instrument developers may prefer approaches that initially prioritize sensitivity or specificity. Future researchers should explore other methodologies and approaches to accomplish similar goals.

The current study used self-reported medication adherence as the primary adherence outcomes. Given the complexity of measuring adherence and differences in adherence rates yielded by assessment type (Quittner, Modi, Lemanek, Ievers-Landis, & Rapoff, 2008), researchers should examine how the AMBS or PMBS classify patients based on alternative measures of adherence, such as electronic monitoring. Self-report methods have been shown to underestimate nonadherence rates when compared with electronic monitoring methods, which provide in vivo measurements of nonadherence (Maikranz, Steele, Dreyer, Stratman, & Bovaird, 2007; Wu et al., 2013). These findings suggest that clinical cutoffs may have differed if other methods were used to measure nonadherence in the current study. Additionally, participants' reported adherence was dichotomized based on a $\geq$10% nonadherence split. Other adherence cut points may also have resulted in different clinical cutoff scores on the AMBS and PMBS. Lastly, the current study's sample size was relatively small compared with those of other studies that determined cutoff scores on measures for pediatric patients using ROC curve analyses (Lai et al., 2011). Compared with similar literature with pediatric transplant patients, the current sample size was relatively large (Dobbels et al., 2010). Future research on the AMBS and PMBS would benefit from replicating the current results with adherence data obtained via other methodologies (e.g., electronic monitoring) and considering different cut points for dichotomizing adherence based on report type.

The current study used novel methodology to determine clinical cutoff scores on the AMBS and PMBS that identify patients experiencing medication nonadherence and negative medical outcomes related to nonadherence. Clinicians working with AYA solid organ transplant recipients should consider using the AMBS and PMBS with the recommended cutoff scores ($\geq$3 barriers for the AMBS and $\geq$2 barriers for the PMBS) in routine practice, while continuing to examine the individual barriers endorsed by patients and caregivers. Clinical cutoff scores provide efficient means for providers to screen and identify pediatric patients at risk for having negative medical outcomes (Youngstrom, 2014). Further assessment or intervention may be implemented as needed for patients scoring at or above the clinical cutoff score. Researchers developing screening instruments for pediatric patients should consider using similar methodology presented in the current study to determine empirically derived and clinically useful cutoff points to enhance utility in fast-paced medical settings.

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