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Reliability and Validity of the Japanese Version of the Basel Assessment of Adherence to Immunosuppressive Medications Scale in Kidney Transplant Recipients

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Background. A valid and reliable instrument that can measure adherence is needed to identify nonadherent patients and to improve adherence. However, there is no validated Japanese self-report instrument to evaluate adherence to immunosuppressive medications for transplant patients. The purpose of this study was to determine the reliability and validity of the Japanese version of the Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS).
Methods. We translated the BAASIS into Japanese and developed the Japanese version of the BAASIS (J-BAASIS) according to the International Society of Pharmacoeconomics and Outcomes Research task force guidelines. We analyzed the reliability (test–retest reliability and measurement error) and validity of the J-BAASIS (concurrent validity with the medication event monitoring system and the 12-item Medication Adherence Scale) referring to the COSMIN Risk of Bias checklist.
Results. A total of 106 kidney transplant recipients were included in this study. In the analysis of test–retest reliability, Cohen's kappa coefficient was found to be 0.62. In the analysis of measurement error, the positive and negative agreement were 0.78 and 0.84, respectively. In the analysis of concurrent validity with the medication event monitoring system, sensitivity and specificity were 0.84 and 0.90, respectively. In the analysis of concurrent validity with the 12-item Medication Adherence Scale, the point-biserial correlation coefficient for the "medication compliance" subscale was 0.38 ($P<0.001$).
Conclusions. The J-BAASIS was determined to have good reliability and validity. Using the J-BAASIS to evaluate adherence can help clinicians to identify medication nonadherence and institute appropriate corrective measures to improve transplant outcomes.(Transplantation Direct 2023;9: e1457; doi: 10.1097/TXD.0000000000001457.)

Kidney transplantation is the optimal renal replacement therapy for improving survival and quality of life for patients with end-stage kidney disease.[1-3] Significant advances in immunosuppression therapy, surgical techniques, and postoperative management over the past few decades have led to a dramatic improvement in short-term renal allograft survival. However, the long-term renal allograft survival in kidney transplantation has not substantially changed.[4,5] One of the major barriers to long-term renal allograft survival is antibody-mediated rejection (AMR).[6,7] Medication nonadherence (MNA) is a risk factor for de novo donor-specific antibody development leading to AMR and graft loss in kidney

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transplant recipients (KTRs).[8,9] Nearly half of KTRs with AMR-associated renal allograft failure have been identified as MNA.[7] The prevalence of MNA in KTRs has been reported as 36%, the highest reported rate among kidney, heart, liver, pancreas/kidney–pancreas, and lung/heart–lung transplant recipients.[10] MNA is a modifiable risk factor to minimize the risk of graft failure in KTRs.

Identifying nonadherent patients is the first step in minimizing the risk of complications of MNA. Assessment measures of medication adherence include observation of medication intake, self-reporting, healthcare provider or family member assessment, electronic monitoring, pharmacy refill records, pill counts, and therapeutic drug monitoring. Each method of measurement has advantages and disadvantages. Self-reporting is the most common method for assessing medication adherence because it is simple, inexpensive, and relatively noninvasive despite its limitations, including recall bias and social desirability bias. The Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS) was developed by the Leuven-Basel Research Group, following the ABC taxonomy, which defined adherence as "the process by which patients take their medication as prescribed."[11,12] The ABC taxonomy indicated that adherence has 3 quantitative measurable components: "initiation," "implementation," and "persistence."[12] The BAASIS was translated into Portuguese, and the reliability and validity were demonstrated for KTRs.[13] The BAASIS was revised in 2020, and the "initiation" item was added. The new BAASIS thus consists of a 5-item questionnaire measuring adherence to immunosuppressive medications: implementation in the past 4 wk (items 1A, "Taking adherence"; item 1B, "Drug holiday"; item 2, "Timing adherence", and item 3, "Dosing adherence"), persistence in the past year (item 4), and initiation in the past year (item 5). Patients with any deviation from these questions are considered as MNA. The BAASIS has been recommended by the Transplant360 Task Force to evaluate the incidence of medication adherence in transplant recipients.[14]

To date, there is no validated Japanese self-reporting tool to evaluate adherence to immunosuppressive medications in transplant recipients. The purpose of this study was to determine the reliability and validity of the Japanese version of the BAASIS (J-BAASIS).

MATERIALS AND METHODS

Study Design and Participants

We conducted a single-center cross-sectional study at the Osaka Metropolitan University Hospital. The inclusion criteria were KTRs aged 18 to 80 y at least 1 y posttransplant, whereas the exclusion criteria were (1) refusal to participate in this study, (2) inability to complete the Japanese questionnaires on their own (eg, inability to read, understand, write Japanese), (3) inability to take medication on their own, and (4) retransplantation. This study was approved by the Ethics Committee of Osaka Metropolitan University Graduate School of Medicine (No. 2021-089). All participants provided written informed consent for participation in the study, and all the procedures were in accordance with the Declaration of Helsinki.

Eight eligible KTRs with diverse backgrounds, including age, gender, and education levels, hospitalized between June and July 2021, were recruited for participation in cognitive debriefing interviews. A total of 120 eligible KTRs who visited our hospital between October and December 2021 were recruited for the examination of the reliability and validity of the J-BAASIS. We offered no incentives to participate in or complete the surveys.

Our Management of Adherence

Before performing a kidney transplant, we first explain to the KTRs and their families that taking immunosuppressive medications in the correct doses every day at the same time is critical to improve graft and patient survival. In the immediate posttransplant period during hospitalization, the nurses bring immunosuppressive medications to the KTRs and count the number of empty pill wrappings after taking immunosuppressants. The stability of the patient's adherence as well as the patient's condition are monitored, and the management of medication is eventually left up to the patient. At the first discharge after surgery, the pharmacists explain the importance and side effects of the immunosuppressants to the KTRs.

When the KTRs are readmitted, we confirm whether they are adhering to their regimens. If adherence is determined to be poor, the nurse intervenes in the management of medication, by bringing immunosuppressive medications or counting the number of empty pill wrappings. However, the assessment of their adherence in ambulatory practice is only by measuring the blood concentrations of calcineurin inhibitors.

Translation and Cultural Adaptation

The authors of the BAASIS gave us permission to develop the J-BAASIS. They provided us with the Japanese translation of the BAASIS, which had not been validated, and they recommended that we produce a Japanese translation according to the International Society of Pharmacoeconomics and Outcomes Research task force guidelines.[15] We first asked a translator who is a native speaker of Japanese, fluent in English, and residing in Japan to translate the BAASIS into Japanese. Our research team, consisting of 3 transplant surgeons, a transplant coordinator, and a researcher of transplant nursing, compared and combined this Japanese translation with the Japanese translation provided by the authors of the BAASIS and made the first draft of the J-BAASIS. We next asked a translation company that was experienced in back translation and had no prior knowledge of the original BAASIS to translate the first draft of the J-BAASIS into English. The back translation was reviewed by the authors of the BAASIS. We revised the first revision of the J-BAASIS based on the back translation review and produced the second draft of the J-BAASIS. We conducted cognitive debriefing interviews on the recruited 8 KTRs who had diverse backgrounds, including age, gender, and education levels during their hospitalization. At the cognitive debriefing interview, each KTR was individually interviewed after filling out the second draft of the J-BAASIS. We inquired whether there were any words or expressions that they did not understand or found unacceptable, and they were asked to repeat all the questions in their own words. Our research team revised and made the third (final) draft of the J-BAASIS based on the results of the cognitive debriefing interviews. The final draft of the J-BAASIS was again translated into English by the translation company, and the back translation version was verified by the authors of the BAASIS. The J-BAASIS was finalized after the completion of all the steps described above. There are 2 versions of

the BAASIS (the written self-report version and interview version). We produced these 2 versions of the J-BAASIS, but we used the written self-report version of the J-BAASIS in this study.

Medication Event Monitoring System

The medication event monitoring system (MEMS; eCAP; Information Mediary Corp., Ottawa, Canada) is an electronic monitoring device embedded with a microprocessor in the lid of the medication container. The MEMS cap records the date and time of each removal of the cap from the medication bottle. We chose methylprednisolone to use in this system for 3 reasons. First, almost all KTRs took methylprednisolone at our institution. Second, methylprednisolone is a small-sized tablet and packaged individually, not in pharmaceutical blister packs, so that each tablet can be separated and placed in a bottle without causing any problems with tablet stability or hygiene. Third, methylprednisolone is administered as a single tablet regimen once a day for almost all patients, and it can be managed in a portable bottle, which reduces the patient burden and bias associated with bottle management. Timing adherence was defined as the percentage of doses taken within a 4-h interval (±2 h) consistent with the standard intake time of the patient. The patient was determined as MNA when timing adherence was <98%.[16,17]

The 12-Item Medication Adherence Scale

The World Health Organization (WHO) defined adherence as "the extent to which a person's behavior, taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider."[18] The 12-item Medication Adherence Scale was developed by Ueno et al to evaluate adherence in patients with chronic disease in reference to the adherence concept of the WHO, and its reliability and validity were demonstrated.[18,19] This scale consists of 12 items and is categorized into 4 subscales (3 items for each subscale): (1) medication compliance, (2) collaboration with healthcare providers, (3) willingness to access and use information about medication, and (4) acceptance to take medication and how taking medication fits the patient's lifestyle. A 5-point Likert scale is used to rate each item from 1 (never) to 5 (always). The 12-item Medication Adherence Scale score is calculated after summing the scores for each item. A higher score indicates higher adherence.

The Self-Assessment for Adherence of Immunosuppressive Medication

The Self-Assessment for Adherence of Immunosuppressive Medication is an adherence scale originally developed for this study, which asks patients to answer the question, "Please tell us your self-assessment of immunosuppressant medication use in the past 4 wk," using an 11-point scale (0 point: never to 10 points: always).

Social Desirability

Social desirability is the tendency for people to present themselves in ways that they feel are more appropriate or socially acceptable to others. The Japanese version of the Balanced Inventory of Desirable Responding (BIDR-J), which consists of 24 items of the 2-factor subscales (12 items, "Impression Management" and 12 items, "Self-Deception"), was developed by Tani et al.[20,21] A 7-point Likert scale was used to rate each item from 1 (strongly disagree) to 7 (strongly agree). The BIDR-J score was calculated after summing the scores for each item. A higher score indicated higher social desirability.

Study Procedure

The eligible and willing participants were randomly assigned to 2 groups, the J-BAASIS group and the J-BAASIS + MEMS group, with random numbers generated by computer. All participants filled out a background questionnaire, the Self-Assessment for Adherence of Immunosuppressive Medication, and the J-BAASIS (the first survey). They answered the Self-Assessment for Adherence of Immunosuppressive Medication, J-BAASIS, 12-item Medication Adherence Scale, and BIDR-J in similar conditions during their following outpatient visit 4 to 6 wk later (the second survey). The participants in the J-BAASIS + MEMS group were briefed on how to use the MEMS by a physician (H.M.), who filled the bottles with individually packed tablets of methylprednisolone at the first survey. The patients took the methylprednisolone tablets daily using the MEMS until the second survey.

Statistical Analysis

Data are presented as number (percentage) for categorical data and median (interquartile ranges [IQRs]) for continuous data. Pearson's chi-square test was used to compare the categorical data of 2 independent groups, whereas the Mann-Whitney *U* test was used to compare the continuous data of 2 independent groups when performing a univariate analysis. To examine the influence associated with using the MEMS on adherence, the Wilcoxon rank-sum test was used to test the difference between the first and second surveys in the Self-Assessment for Adherence of Immunosuppressive Medication scores between the J-BAASIS and J-BAASIS + MEMS groups. A 2-sided $P < 0.05$ was considered to be significant. All analyses were performed using R 4.1.1 (The R Project for Statistical Computing).

We analyzed the reliability and validity of the J-BAASIS referring to the COSMIN Risk of Bias checklist.[22] Test–retest reliability and measurement error were investigated to determine the reliability of the J-BAASIS. To stratify participants who had stable adherence status, our Self-Assessment for Adherence of Immunosuppressive Medication was used as the anchor scale. Participants whose scores remained unchanged between the first and second surveys were included in the analysis of test–retest reliability and measurement error. Test–retest reliability was assessed by Cohen's kappa coefficient.[23] Measurement error was assessed by the observed, positive, and negative agreements.[24] Concurrent validity was investigated to determine the validity of the J-BAASIS. Concurrent validity of the J-BAASIS at the second survey using the MEMS was assessed by sensitivity and specificity. Concurrent validity of the J-BAASIS at the second survey with the "medication compliance" subscale (3 items) and overall scale (12 items) of the 12-item Medication Adherence Scale was assessed by the point-biserial correlation coefficient.

RESULTS

We recruited 120 eligible KTRs, of whom 110 KTRs who agreed to participate in this study were randomly assigned to the 2 groups. Excluding 4 participants who withdrew or

did not complete the questionnaires, the complete data sets of 106 KTRs from both surveys (valid response rate was 96.4%) were included in this analysis. A participant was switched from the J-BAASIS + MEMS group to the J-BAASIS group after randomization because the participant did not take methylprednisolone every day. The patient characteristics are shown in Table 1. The median age of the participants was 52 (IQR, 43–62) y, and 61% were male. Most participants (94%) received kidney transplantation from living donors, and the median transplant vintage was 55 (IQR, 21–108) mo. MNA for each item and for the J-BAASIS as a whole at the first survey is shown in Table 2.

Reliability

The number of participants whose scores of the Self-Assessment for Adherence of Immunosuppressive Medication in the second survey improved, remained unchanged, and worsened compared with the first survey was 21 (20%), 59 (56%), and 26 (25%), respectively. We included the 59 participants whose scale scores remained unchanged in the analysis of test–retest reliability and measurement error. In the analysis of test–retest reliability, Cohen's kappa coefficient was 0.62, indicating substantial agreement based on a guideline proposed by Landis and Koch.[25] In the analysis of measurement error, the observed agreement, positive agreement, and negative agreement were 0.81, 0.78, and 0.84, respectively.

TABLE 1.

Patient characteristics

	All	J-BAASIS	J-BAASIS+MEMS	
	N = 106	N = 56	N = 50	*P*
Age, y	52 (43–62)	52 (44–58)	53 (42–62)	0.70
Gender				0.64
Female	41 (39%)	20 (36%)	21 (42%)	
Male	65 (61%)	36 (64%)	29 (58%)	
Donor type				0.78
Deceased donor	6 (5.7%)	4 (7.1%)	2 (4.0%)	
Living donor	100 (94%)	52 (93%)	48 (96%)	
Transplant vintage, mo	55 (21–108)	63 (34–107)	40 (15–109)	0.14
Medication number	9.0 (7.0–12)	10 (7.0–12)	9.0 (7.3–11)	0.64
Serum creatinine, mg/dL	1.50 (1.12–1.78)	1.51 (1.09–1.90)	1.48 (1.17–1.72)	0.99
Education level				0.53
Junior high school	14 (13%)	5 (8.9%)	9 (18%)	
High school	42 (40%)	22 (39%)	20 (40%)	
Junior college/technical school	23 (22%)	13 (23%)	10 (20%)	
University	27 (26%)	16 (29%)	11 (22%)	
Employment status				0.68
Full-time	53 (50%)	28 (50%)	25 (50%)	
Part-time	12 (11%)	5 (8.9%)	7 (14%)	
Unemployed	41 (39%)	23 (41%)	18 (36%)	
Household income, million JPY				0.33
<2	13 (13%)	11 (20%)	2 (4.2%)	
2–4	30 (29%)	15 (28%)	15 (31%)	
4–6	25 (25%)	13 (24%)	12 (25%)	
6–8	15 (15%)	6 (11%)	9 (19%)	
8–10	6 (5.9%)	2 (3.7%)	4 (8.3%)	
10–12	7 (6.9%)	4 (7.4%)	3 (6.2%)	
12–14	3 (2.9%)	2 (3.7%)	1 (2.1%)	
>14	3 (2.9%)	1 (1.9%)	2 (4.2%)	
No. of household members				0.091
1	14 (13%)	11 (20%)	3 (6.0%)	
2	40 (38%)	17 (30%)	23 (46%)	
3	25 (24%)	14 (25%)	11 (22%)	
4	11 (10%)	7 (13%)	4 (8.0%)	
5	14 (13%)	5 (8.9%)	9 (18%)	
6	2 (1.9%)	2 (3.6%)	0 (0.0%)	
Medication management				0.92
Oneself	103 (97%)	55 (98%)	48 (96%)	
Family/caregiver	3 (2.8%)	1 (1.8%)	2 (4.0%)	
Pill box/reminder use				1.00
Yes	64 (60%)	34 (61%)	30 (60%)	
No	42 (40%)	22 (39%)	20 (40%)	

Categorical variables were expressed as count (percentage) and continuous variables were expressed as median (IQRs). Categorical variables were compared using the chi-square test and continuous variables were compared using the Mann-Whitney *U* test.

IQR, interquartile range; J-BAASIS, Japanese version of the Basel Assessment of Adherence to Immunosuppressive Medications Scale; J PY, Japanese yen; MEMS, medication event monitoring system.

TABLE 2.

MNA using the J-BAASIS

		Nonadherent
	Mean ± standard deviation	Number (percentage)
Implementation in the past 4 wk		
Taking adherence (item 1A)	0.12 ± 0.33	13 (12%)
Drug holiday (item 1B)	0.019 ± 0.14	2 (1.9%)
Timing adherence (item 2)	0.50 ± 0.50	53 (50%)
Dosing adherence (item 3)	0.019 ± 0.14	2 (1.9%)
Persistence in the past year (item 4)	0.00 ± 0.00	0 (0.0%)
Initiation in the past year (item 5)	0.00 ± 0.00	0 (0.0%)
J-BAASIS	0.55 ± 0.50	58 (55%)

J-BAASIS, the Japanese version of the Basel Assessment of Adherence to Immunosuppressive Medications Scale; MNA, medication nonadherence.

Validity

We included the 50 participants of the J-BAASIS + MEMS group in the analysis of concurrent validity between the J-BAASIS and MEMS. In the second survey, 28 (56%) and 31 (62%) participants were classified as MNA by the J-BAASIS and MEMS, respectively. In the analysis of concurrent validity, sensitivity and specificity were 0.84 and 0.90, respectively.

We included all 106 participants in the analysis of concurrent validity between the J-BAASIS and 12-item Medication Adherence Scale. In the second survey, 59 participants (56%) were classified as MNA by the J-BAASIS. In the analysis of concurrent validity, the point-biserial correlation coefficients for the "medication compliance" subscale and the overall scale of the 12-item Medication Adherence Scale were 0.38 ($P < 0.001$), indicating low correlation based on Guilford's Rule of Thumb, and 0.12 ($P = 0.23$), indicating negligible correlation, respectively.[26] Moreover, there was no significant difference between the nonadherent and adherent groups by the overall scale ($P = 0.36$), whereas the nonadherent group had a higher score than the adherent group by the "medication compliance" subscale ($P < 0.001$; Table 3).

Bias

In the first survey, there was no significant difference in patient characteristics (Table 1), the score of the Self-Assessment for Adherence of Immunosuppressive Medication (J-BAASIS group, 10 [IQR, 9.0–10] versus J-BAASIS + MEMS group, 10 [IQR, 9.0–10], $P = 0.97$), and the prevalence of MNA using the J-BAASIS (J-BAASIS group, 28/56 versus J-BAASIS + MEMS group, 29/50, $P = 0.53$). Moreover, the J-BAASIS + MEMS group did not differ significantly from the J-BAASIS group in the differences in the Self-Assessment for Adherence of Immunosuppressive Medication scores between the first and second surveys (Wilcoxon signed-rank test, $P = 0.57$).

In the J-BAASIS + MEMS group, 5 participants (10%) were classified as nonadherent by the MEMS while adherent by the J-BAASIS in the second survey. These mismatched participants (n = 5) did not differ significantly from the other participants (n = 45) in the total BIDR-J score (104 [IQR, 103–126] versus 105 [IQR, 98–114], $P = 0.48$), "Impression Management" subscale (52 [IQR, 49–65] versus 56 [IQR, 48–60], $P = 0.94$), and "Self-Deception" subscale (57 [IQR, 54–57] versus 51 [IQR, 43–55], $P = 0.16$).

TABLE 3.

Scores for subscales of the 12-item Medication Adherence Scale

	J-BAASIS		
	Adherent group (N = 47)	Nonadherent group (N = 59)	*P*
"Medication compliance" subscale (3 items)	15 (15–15)	14 (13–15)	<0.001
"Collaboration with healthcare providers" subscale (3 items)	11 (9.0–12)	11 (9.0–13)	0.83
"Willingness to access and use information about medication" subscale (3 items)	10 (9.0–12)	10 (8.0–11)	0.40
"Acceptance to take medication and how taking medication fits the patient's lifestyle" subscale (3 items)	13 (12–14)	13 (12–14)	0.70
Overall (12 items)	48 (44–53)	47 (43–52)	0.36

The scores were expressed as median (IQRs) and compared using the Mann-Whitney *U* test.
IQR, interquartile range; J-BAASIS, the Japanese version of the Basel Assessment of Adherence to Immunosuppressive Medications Scale.

Risk Factors for MNA

Gender, donor type, transplant vintage, serum creatinine, education level, employment status, number of household members, medication management, and pill box/reminder use had no significant relationship with MNA. However, age ($P = 0.015$), medication number ($P = 0.001$), and household income ($P = 0.034$) were significantly different between adherent and nonadherent participants based on J-BAASIS (Table 4).

DISCUSSION

A valid and reliable instrument that can measure adherence is needed to identify nonadherent patients and intervene to minimize risk of poor clinical outcomes. Thus, we translated the BAASIS, which is recommended as a validated self-report instrument to assess adherence to immunosuppressants in organ transplant recipients, into Japanese with attention to cultural adaptation. The J-BAASIS was determined to have good reliability (test–retest reliability and measurement error) and validity (concurrent validity with the MEMS). Following the COSMIN Risk of Bias checklist, demonstrating the concurrent validity with the MEMS, regarded as the gold standard to measure adherence, and examining the biases potentially occurring during this study were the key strengths of our study. This validation study provides further evidence to support the psychometric properties of BAASIS.

By the J-BAASIS and MEMS, 58 of 106 (55%) and 31 of 50 (62%) participants were classified as MNA in the present study, respectively. A previous systematic review of 37 studies on MNA in KTRs demonstrated that the prevalence of MNA was 1.6% to 96%.[27] This wide range can be attributed to several reasons, such as different methods in evaluating MNA as well as different definitions in diagnosing MNA and the lack of similarities among these studies regarding their population, methodology, and risk factors of MNA. The prevalence of MNA using the BAASIS in KTRs was previously reported to be 34% to 66% and that of the present study was within this range.[13,28-34] This prevalence range of MNA using the BAASIS

was relatively >36% reported by a previous meta-analysis.[10] This is probably because the BAASIS uses an intentionally strict scoring method and includes timing adherence as a criterion. The BAASIS assesses the "initiation," "implementation," and "persistence" phases of adherence in the ABC taxonomy, whereas the MEMS assesses the "implementation" phase. In the present study, 1 item of the J-BAASIS criteria, timing of nonadherence, accounted for half of the participants.[12] On the other hand, no participant indicated either "persistence in the past year" or "initiation in the past year." Both of these items and "drug holiday" and "dosing adherence" had floor effects, similar to previous studies.[28-30,35] Because the BAASIS is not based on a reflective model but on a formative model, we did not validate it on structural validity and internal consistency of the J-BAASIS according to the COSMIN Risk of Bias checklist,[22,36] unlike a previous report of BAASIS validation.[13]

Reliability

The quality of the J-BAASIS was satisfactory in terms of test–retest reliability, but it presented lower performance than in a previous study (Cohen's kappa coefficient, 0.62 versus 0.88).[13] This may be because of the difference in the time interval between the 2 surveys. Marsicano et al[13] performed 2 questionnaire surveys at an interval of 7 d, whereas we conducted the surveys at an interval of 4 to 6 wk. Our interval had been expected to be too long because items 1A, 1B, 2, and 3 of the BAASIS were questions about implementation of immunosuppressive medications in the past 4 wk. Thus, we selected participants who had temporal stability of adherence status using our original Self-Assessment for Adherence of Immunosuppressive Medication as an anchor scale and conducted the test–retest reliability analysis.

On the other hand, in the analysis of measurement error, we calculated the positive and negative agreement according to the COSMIN Risk of Bias checklist,[22] because the outcome obtained by BAASIS is dichotomous. The positive agreement and negative agreement were 0.78 and 0.84, respectively. This could be confirmed as a good measurement error. As with the test–retest reliability, stratification of patients might have been appropriate, but the time interval between the 2 surveys might have been too long and inadequate.

Validity

The present study demonstrated that the J-BAASIS had good concurrent validity with the MEMS. The MEMS is highly accurate in measuring adherence in theory; therefore, it has been used in a wide range of studies as the gold standard to measure adherence.[37] A previous study reported that the MEMS had accuracy and robustness.[17] However, the disadvantages of the MEMS include the inability to confirm how many pills were removed from the bottles or if the pills were actually ingested. Additionally, there is the possibility of mechanical failure or the patient's refusal to use it because of user burden. In fact, it was reported that 42% of the participants did not use the MEMS as instructed during the 1-y follow-up period despite being trained and supported.[38] In the J-BAASIS + MEMS group, 2 patients telephoned to ask how to open the lid, but all patients were able to use the MEMS as instructed. Another previous study was unable to use this method because of its considerable cost in concurrent validity analysis.[13] For solid organ transplant recipients, high sensitivity for the detection of timing adherence of immunosuppressive medication intake is needed in assessment measures of adherence because small deviations from prescribed immunosuppressive medication schedules may lead to a poor transplant outcome.[39-41] Therefore, good concurrent validity of the J-BAASIS with the MEMS, which our study determined, takes on a major significance for the BAASIS.

The present study demonstrated that the J-BAASIS had no concurrent validity with the overall 12-item Medication

TABLE 4.

Comparison of risk factors for MNA between nonadherent and adherent participants based on the J-BAASIS

	J-BAASIS		
	Adherent (N = 48)	Nonadherent (N = 58)	*P*
Age, y	55 (47–70)	50 (40–59)	0.015
Gender			0.67
Female	17 (35%)	24 (41%)	
Male	31 (65%)	34 (59%)	
Donor type			0.86
Deceased donor	2 (4.2%)	4 (6.9%)	
Living donor	46 (96%)	54 (93%)	
Transplant vintage, mo	55 (24–94)	55 (19–110)	0.84
Medication number	10 (9–13)	8.5 (7.0–11)	0.001
Serum creatinine, mg/dL	1.47 (1.10–1.83)	1.50 (1.17–1.72)	0.89
Education level			0.33
Junior high school	8 (17%)	6 (10%)	
High school	22 (45.8)	20 (35%)	
Junior college/technical school	8 (17%)	15 (26%)	
University	10 (21%)	17 (29%)	
Employment status			0.12
Full-time	22 (46%)	31 (53%)	
Part-time	3 (6.2%)	9 (16%)	
Unemployed	23 (48%)	18 (31%)	
Household income, million JPY			0.034
<2	8 (18%)	5 (8.8%)	
2–4	17 (38%)	13 (23%)	
4–6	11 (24%)	14 (25%)	
6–8	1 (2.2%)	14 (25%)	
8–10	3 (6.7%)	3 (5.3%)	
10–12	4 (8.9%)	3 (5.3%)	
12–14	0 (0.0%)	3 (5.3%)	
>14	1 (2.2%)	2 (3.5%)	
No. household members			0.18
1	7 (15%)	7 (12%)	
2	21 (44%)	19 (33%)	
3	9 (19%)	16 (28%)	
4	2 (4.2%)	9 (16%)	
5	7 (15%)	7 (12%)	
6	2 (4.2%)	0 (0.0%)	
Medication management			
Oneself	45 (94%)	58 (100%)	0.18
Family/caregiver	3 (6.2%)	0 (0.0%)	
Pill box/reminder use			0.32
Yes	32 (67%)	32 (55%)	
No	16 (33%)	26 (45%)	

Categorical variables were expressed as count (percentage) and continuous variables were expressed as median (IQRs). Categorical variables were compared using the chi-square test, and continuous variables were compared using the Mann-Whitney *U* test.
IQR, interquartile range; J-BAASIS, the Japanese version of the Basel Assessment of Adherence to Immunosuppressive Medications Scale; JPY, Japanese yen; MNA, medication nonadherence.

Adherence Scale, although there was a slight concurrent validity with the "medication compliance" subscale. The internal consistency (Cronbach's alpha 0.78) and structural validity (Confirmatory factor analysis χ^2/df = 2.6, CFI = 0.94, and RMSEA = 0.069) of the 12-item Medication Adherence Scale have been determined.[19] However, its concurrent validity has not been investigated.[19] One reason is that there is no Japanese adherence scale in which reliability and validity have been investigated. The 12-item Medication Adherence Scale includes some underlying principles, recommended by the WHO, of not only medication compliance but also psychosocial factors related to medication behavior, particularly provider–patient collaboration and relationship as well as patient lifestyle. The poor concurrent validity might be attributed to the difference between the concept of the 12-item Medication Adherence Scale and that of the BAASIS.

Bias

It was pointed out that the MEMS has some disadvantages; it records not the true intake dose but removal of the cap and has a possibility to negatively impact established adherence routines or conversely improve normal adherence through an intervention effect (Hawthorne effect). We tried to reduce the participant burden associated with using the MEMS and have them routinely take their medications as much as possible. In this study, the change in adherence between the 2 surveys in the J-BAASIS + MEMS group did not differ significantly from that in the J-BAASIS group. This result indicated that the use of the MEMS had little influence on adherence. Additionally, to reduce selection bias, we recruited all eligible KTRs who visited our hospital during the recruitment period and used the random assignment of participants. As expected, there was no significant difference in patient characteristics and adherence between the J-BAASIS and J-BAASIS + MEMS groups.

Furthermore, self-report adherence measurements are prone to social desirability bias and tend to underestimate MNA.[42] The social desirability bias is usually attributed to the responders' wanting to provide appropriate and acceptable responses to current social norms, whether consciously or unconsciously. Pearson et al[43] reported that self-reported adherence did not correlate with social desirability. On the other hand, Nieuwkerk et al[44] found that self-reported adherence was related to viral load for low social desirability patients but not for high social desirability patients. In this study, we demonstrated that the score of social desirability was not associated with the mismatch in the diagnosis of MNA between the MEMS and J-BAASIS. Among the 5 participants who were nonadherent by the MEMS but adherent by the J-BAASIS, 1 participant was determined as MNA by the MEMS because the participant 1 d missed taking his medication within the designated time range (±2 h) by 1 h. The remaining 4 participants several times took methylprednisolone with one of their twice-daily medications and failed to take it at their daily designated times. The reason for this difference between the MEMS and J-BAASIS may be that the participants were unaware they had mistakenly taken their medication or that there may have been recall bias or social desirability bias.

The impact of the social desirability bias on underestimating MNA might have been limited because participants in the J-BAASIS + MEMS group answered the J-BAASIS after monitoring their adherence by the MEMS. Both versions (the written self-report version and interview version) of the BAASIS consist of the same items, although they are worded slightly differently. In this study, we used the written self-report version of the J-BAASIS. This was because adherence measurement through a face-to-face interview has the potential to decrease accuracy by increasing biases caused by social desirability, interviewer characteristics, and questionnaire structure, and avoiding a face-to-face interview in favor of using a computer or paper-based questionnaire to measure adherence is recommended to help address social desirability concerns.[45] Additionally, we used the written version this time because we plan to conduct future intervention studies using mobile apps, which are increasingly being used in recent years.[46]

Risk Factors for MNA

The WHO defined 5 main domains of risk factors which can influence adherence behavior: patient-related, therapy-related, condition-related, health system/healthcare team-related, and socioeconomic-related.[18] We compared the patient-related factors (age and gender), therapy-related factors (medication number), condition-related factors (donor type, transplant vintage, and serum creatinine), and socioeconomic-related factors (education level, employment status, household income, number of household members, medication management, and pill box/reminder use) between adherent and nonadherent participants based on J-BAASIS.

Nonadherent KTRs had higher household income than adherent KTRs in this study, which was conducted in Osaka, Japan. Marsicano et al[33] speculated that the characteristics of the healthcare system where the patient lives, including access to care and healthcare cost coverage, could influence the association between MNA and income. Studies conducted in Juiz de Fora, Brazil, and Pittsburgh, United States, reported that higher income was associated with MNA, whereas a study conducted in New York, United States, reported that lower income was associated with MNA.[33,47,48] In the United States, 70% of KTRs reported serious problems with paying for their medications, and 68% of KTRs reported deaths or graft losses as a result of cost-related MNA.[49] By contrast, in Japan, patients have free access to any healthcare provider, from small clinics to large hospitals with the latest facilities, and the self-pay burden of KTRs is minimized to only 0 to 20 000 yen according to income level by the country's Medical Payment for Services and Supports for Persons with Disabilities. Therefore, there is no differentiation by family income in access to care and healthcare cost coverage, and KTRs have few economic obstacles in procuring medications.

Additionally, nonadherent participants were younger in age than adherent participants in this study. Age has been reported as an MNA risk factor. A systematic review showed that younger KTRs (<50 y) were considered as more nonadherent in 13 studies, in contrast to older KTRs (>50–65 y) in 3 studies.[27] MNA in younger patients is related to factors such as lifestyle disruptions, active social life, and high empowerment (health locus of control and self-efficacy), whereas MNA in older patients is related to factors such as forgetfulness, need for care, complexity of medication regimen, and side effects.[50]

Furthermore, adherent KTRs took a greater number of medications than nonadherent KTRs in this study. In general, taking more medications is associated with other therapy-related factors for MNA, including complexity of medication

regimen, frequent changes in medication regimen, side effects, and more comorbidity.[27] However, a previous study also reported that the number of medications negatively correlated with MNA in Japanese KTRs.[51] The background of this result might be the patients' psychological factors (belief in the need for medications, empowerment, fear of graft loss, and indebtedness to the donor) or the use of a pillbox or reminder.[52]

Risk factors for MNA can be divided into modifiable and nonmodifiable ones.[53] The J-BAASIS could be used to identify risk factors for MNA in Japanese transplant recipients and to develop effective adherence-improving interventions in future studies.

The present study has several limitations. First, the study had a limited sample size and possible selection bias as a result of the choice of recruitment location. Osaka Metropolitan University Hospital is an urban university hospital, and we recruited KTRs who had visited our hospital for their scheduled checkups and therefore more likely to be adherent to their medication. Second, only the once-daily regimen of methylprednisolone was interred by the MEMS for the J-BAASIS+MEMS group, and we could not measure MNA of immunosuppressive medications taken twice daily. However, a previous study showed that there was no significant difference in MNA using the MEMS between once- and twice-daily dose schedules.[54] Finally, we determined the reliability and validity of the J-BAASIS but not the validity of other psychometric properties, such as responsiveness and interpretability. Further longitudinal studies are required to validate these other psychometric properties.

In conclusion, the J-BAASIS demonstrated good reliability and validity. Using the J-BAASIS to evaluate adherence can help clinicians to identify MNA and institute appropriate corrective measures to improve transplant outcomes.

REFERENCES

1. Port FK, Wolfe RA, Mauger EA, et al. Comparison of survival probabilities for dialysis patients vs cadaveric renal transplant recipients. *JAMA.* 1993;270:1339–1343.
2. Laupacis A, Keown P, Pus N, et al. A study of the quality of life and cost-utility of renal transplantation. *Kidney Int.* 1996;50:235–242.
3. Wolfe RA, Ashby VB, Milford EL, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. *N Engl J Med.* 1999;341:1725–1730.
4. Lamb KE, Lodhi S, Meier-Kriesche HU. Long-term renal allograft survival in the United States: a critical reappraisal. *Am J Transplant.* 2011;11:450–462.
5. Lodhi SA, Lamb KE, Meier-Kriesche HU. Solid organ allograft survival improvement in the United States: the long-term does not mirror the dramatic short-term success. *Am J Transplant.* 2011;11:1226–1235.
6. Gaston RS, Cecka JM, Kasiske BL, et al. Evidence for antibody-mediated injury as a major determinant of late kidney allograft failure. *Transplantation.* 2010;90:68–74.
7. Sellares J, de Freitas DG, Mengel M, et al. Understanding the causes of kidney transplant failure: the dominant role of antibody-mediated rejection and nonadherence. *Am J Transplant.* 2012;12:388–399.
8. Wiebe C, Gibson IW, Blydt-Hansen TD, et al. Evolution and clinical pathologic correlations of de novo donor-specific HLA antibody post kidney transplant. *Am J Transplant.* 2012;12:1157–1167.
9. Wiebe C, Gibson IW, Blydt-Hansen TD, et al. Rates and determinants of progression to graft failure in kidney allograft recipients with de novo donor-specific antibody. *Am J Transplant.* 2015;15:2921–2930.
10. Dew MA, DiMartini AF, De Vito Dabbs A, et al. Rates and risk factors for nonadherence to the medical regimen after adult solid organ transplantation. *Transplantation.* 2007;83:858–873.
11. De Geest S. The Basel Assessment of Adherence to Immunosuppressive Medication Scale (BAASIS©). 2022. Available at https://baasis.nursing.unibas.ch. Accessed August 1, 2022.
12. Vrijens B, De Geest S, Hughes DA, et al.; ABC Project Team. A new taxonomy for describing and defining adherence to medications. *Br J Clin Pharmacol.* 2012;73:691–705.
13. Marsicano Ede O, Fernandes Nda S, Colugnati F, et al. Transcultural adaptation and initial validation of Brazilian-Portuguese version of the Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS) in kidney transplants. *BMC Nephrol.* 2013;14:108.
14. Dobbels F, Berben L, De Geest S, et al.; Transplant360 Task Force. The psychometric properties and practicability of self-report instruments to identify medication nonadherence in adult transplant patients: a systematic review. *Transplantation.* 2010;90:205–219.
15. Wild D, Grove A, Martin M, et al.; ISPOR Task Force for Translation and Cultural Adaptation. Principles of good practice for the translation and cultural adaptation process for Patient-Reported Outcomes (PRO) measures: report of the ISPOR Task Force for Translation and Cultural Adaptation. *Value Health.* 2005;8:94–104.
16. Takemoto SK, Pinsky BW, Schnitzler MA, et al. A retrospective analysis of immunosuppression compliance, dose reduction and discontinuation in kidney transplant recipients. *Am J Transplant.* 2007;7:2704–2711.
17. Schafer-Keller P, Steiger J, Bock A, et al. Diagnostic accuracy of measurement methods to assess non-adherence to immunosuppressive drugs in kidney transplant recipients. *Am J Transplant.* 2008;8:616–626.
18. World Health Organization. Adherence to long-term therapies: evidence for action. 2003. Available at https://apps.who.int/iris/handle/10665/42682. Accessed August 1, 2022.
19. Ueno H, Yamazaki Y, Yonekura Y, et al. Reliability and validity of a 12-item medication adherence scale for patients with chronic disease in Japan. *BMC Health Serv Res.* 2018;18:592.
20. Paulhus DL. Two-component models of socially desirable responding. *J Pers Soc Psychol.* 1984;46:598–609.
21. Tani I. Development of Japanese version of Balanced Inventory of Desirable Responding (BIDR-J). *Jpn J Pers*. 2008;17:18–28.
22. Mokkink LB, de Vet HCW, Prinsen CAC, et al. COSMIN Risk of Bias checklist for systematic reviews of Patient-Reported Outcome Measures. *Qual Life Res.* 2018;27:1171–1179.
23. Cohen J. A coefficient of agreement for nominal scales. *Educ Psychol Meas*. 1960;20:37–46.
24. Cicchetti DV, Feinstein AR. High agreement but low kappa: II. Resolving the paradoxes. *J Clin Epidemiol.* 1990;43:551–558.
25. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics.* 1977;33:159–174.
26. Fischer JE, Bachmann LM, Jaeschke R. A readers' guide to the interpretation of diagnostic test properties: clinical example of sepsis. *Intensive Care Med.* 2003;29:1043–1051.
27. Belaiche S, Décaudin B, Dharancy S, et al. Factors relevant to medication non-adherence in kidney transplant: a systematic review. *Int J Clin Pharm.* 2017;39:582–593.
28. Massey EK, Tielen M, Laging M, et al. Discrepancies between beliefs and behavior: a prospective study into immunosuppressive medication adherence after kidney transplantation. *Transplantation.* 2015;99:375–380.
29. Cossart AR, Staatz CE, Campbell SB, et al. Investigating barriers to immunosuppressant medication adherence in renal transplant patients. *Nephrology (Carlton).* 2019;24:102–110.
30. Kobayashi S, Tsutsui J, Okabe S, et al. Medication nonadherence after kidney transplantation: an internet-based survey in Japan. *Psychol Health Med.* 2020;25:91–101.
31. Zhang P, Zhu X, Yan J, et al. Identification of immunosuppressive medication nonadherence factors through a combined theory model in renal transplant recipients: 6-12. *Front Pharmacol.* 2021;12:655836.
32. Silva AN, Moratelli L, Tavares PL, et al. Self-efficacy beliefs, locus of control, religiosity and non-adherence to immunosuppressive medications in kidney transplant patients. *Nephrology (Carlton).* 2016;21:938–943.
33. Marsicano EO, Fernandes NS, Colugnati FA, et al. Multilevel correlates of non-adherence in kidney transplant patients benefitting from full cost coverage for immunosuppressives: a cross-sectional study. *PLoS One.* 2015;10:e0138869.
34. Moradi O, Karimzadeh I, Davani-Davari D, et al. Pattern and associated factors of adherence to immunosuppressive medications in

kidney transplant recipients at a referral center in Iran. *Patient Prefer Adherence.* 2019;13:729–738.
35. De Bleser L, Dobbels F, Berben L, et al. The spectrum of nonadherence with medication in heart, liver, and lung transplant patients assessed in various ways. *Transpl Int.* 2011;24:882–891.
36. Bollen KA, Diamantopoulos A. In defense of causal-formative indicators: a minority report. *Psychol Methods.* 2017;22:581–596.
37. Nerini E, Bruno F, Citterio F, et al. Nonadherence to immunosuppressive therapy in kidney transplant recipients: can technology help?. *J Nephrol.* 2016;29:627–636.
38. Low JK, Manias E, Crawford K, et al. Improving medication adherence in adult kidney transplantation (IMAKT): a pilot randomised controlled trial. *Sci Rep.* 2019;9:7734.
39. De Geest S, Abraham I, Moons P, et al. Late acute rejection and subclinical noncompliance with cyclosporine therapy in heart transplant recipients. *J Heart Lung Transplant.* 1998;17:854–863.
40. Abbott K. Medication compliance in transplantation. *Am J Transplant.* 2007;7:2647–2649.
41. Nevins TE, Thomas W. Quantitative patterns of azathioprine adherence after renal transplantation. *Transplantation.* 2009;87:711–718.
42. Gokoel SRM, Gombert-Handoko KB, Zwart TC, et al. Medication non-adherence after kidney transplantation: a critical appraisal and systematic review. *Transplant Rev (Orlando).* 2020;34:100511.
43. Pearson CR, Simoni JM, Hoff P, et al. Assessing antiretroviral adherence via electronic drug monitoring and self-report: an examination of key methodological issues. *AIDS Behav.* 2007;11:161–173.
44. Nieuwkerk PT, de Boer-van der Kolk IM, Prins JM, et al. Self-reported adherence is more predictive of virological treatment response among patients with a lower tendency towards socially desirable responding. *Antivir Ther.* 2010;15:913–916.
45. Stirratt MJ, Dunbar-Jacob J, Crane HM, et al. Self-report measures of medication adherence behavior: recommendations on optimal use. *Transl Behav Med.* 2015;5:470–482.
46. Pérez-Jover V, Sala-González M, Guilabert M, et al. Mobile apps for increasing treatment adherence: systematic review. *J Med Internet Res.* 2019;21:e12505.
47. Constantiner M, Rosenthal-Asher D, Tedla F, et al. Differences in attitudes toward immunosuppressant therapy in a multi-ethnic sample of kidney transplant recipients. *J Clin Psychol Med Settings.* 2018;25:11–19.
48. Ng YH, Litvinovich I, Leyva Y, et al. Medication, healthcare follow-up, and lifestyle nonadherence: do they share the same risk factors?. *Transplant Direct.* 2022;8:e1256.
49. Axelrod DA, Millman D, Abecassis MM. US health care reform and transplantation, part II: impact on the public sector and novel health care delivery systems. *Am J Transplant.* 2010;10:2203–2207.
50. Gandolfini I, Palmisano A, Fiaccadori E, et al. Detecting, preventing and treating non-adherence to immunosuppression after kidney transplantation. *Clin Kidney J.* 2022;15:1253–1274.
51. Obi Y, Ichimaru N, Kato T, et al. A single daily dose enhances the adherence to immunosuppressive treatment in kidney transplant recipients: a cross-sectional study. *Clin Exp Nephrol.* 2013;17:310–315.
52. Nevins TE, Nickerson PW, Dew MA. Understanding medication nonadherence after kidney transplant. *J Am Soc Nephrol.* 2017;28:2290–2301.
53. Russell CL, Ashbaugh C, Peace L, et al. Time-in-a-bottle (TIAB): a longitudinal, correlational study of patterns, potential predictors, and outcomes of immunosuppressive medication adherence in adult kidney transplant recipients. *Clin Transplant.* 2013;27:E580–E590.
54. Nevins TE, Robiner WN, Thomas W. Predictive patterns of early medication adherence in renal transplantation. *Transplantation.* 2014;98:878–884.