



The Portuguese Version of the Immunosuppressant Therapy Adherence Scale (ITAS) among Liver Transplant Recipient Patients: Translation and Psychometric Properties

Ana Paula Jesus-Nunes,* Mychelle Morais-de-Jesus,* Adriana Dantas-Duarte,* Tayne Miranda Moreira,† Felipe Coelho Argolo,‡ Alessandra de Oliveira Castro,§ Maria Auxiliadora Evangelista,§ Liana Codes,§ Paulo Lisboa Bittencourt,§ Lucas C. Quarantini||

* Programa de Pós-graduação em Medicina e Saúde, Faculdade de Medicina da Universidade Federal da Bahia, Salvador, Bahia, Brazil.

† Faculdade de Medicina da Universidade Federal da Bahia, Salvador, BA, Brazil.

‡ Serviço de Psiquiatria, Com-HUPES, Universidade Federal da Bahia, Salvador, Brazil.

§ Hospital Universitário da Universidade Federal da Bahia, Salvador, Bahia, Brazil.

|| Programa de Pós-graduação em Medicina e Saúde, Faculdade de Medicina da Universidade Federal da Bahia, Salvador, Bahia, Brazil;
Hospital Universitário da Universidade Federal da Bahia, Salvador, Bahia, Brazil.

ABSTRACT

Introduction and aim. Transplant recipients are chronically ill patients who rely on medical treatment throughout life to achieve positive results. Despite that, medication nonadherence after liver transplantation is extremely common. The self-report, one of several methods for measuring adherence, is easy to apply and low cost. Thus, this study aims to translate and validate the Immunosuppressant Therapy Adherence Instrument (ITAS) in Brazilian Portuguese for liver transplant recipients. **Material and methods.** A total of 139 liver transplant recipients were selected from a general hospital, who were assessed by using the Portuguese version of ITAS. The scale was translated based on the model proposed by Wild, *et al.* and its psychometric properties were assessed. **Results.** The average Cronbach's α coefficient was 0.830. ITAS and Basel Assessment of Adherence with Immunosuppressive Medications Scale (BAASIS) presented significant correlation, with a Spearman's ρ coefficient = 0.300 ($S = 309,580$; $p < 0.001$). The area under the receiver operating characteristics (ROC) curve was 0.638 (95% CI: 0.557 - 0.715). Factor analysis results indicated that the carelessness factor model was the optimal model, and the factor "feeling worse" was the lowest. **Conclusion.** The Portuguese version of ITAS has adequate psychometric properties to measure adherence to immunosuppressant therapy.

Key words. Adherence. Liver Transplantation. Immunosuppression. Psychometrics.

INTRODUCTION

Adherence to a medical regimen is defined as the extent to which the patient's behavior coincides with the clinical prescriptions.¹ Among the greatest challenges to the success of transplants is to ensure regular adherence of immunosuppressive drugs. This is essential for the proper functioning of the graft.²

Immunosuppressant therapy nonadherence after liver transplantation is reported in 72.9% subjects who took less than 100% of the prescribed doses, tracked with electronic

monitoring.³ Therefore, almost half of transplant recipients have some non-adherent behavior, such as not using the medication regularly, nor taking the correct dose, nor the required timescales.^{4,5} Despite the clinician's efforts to inform patients about the importance of immunosuppression to the maintenance of the graft, to avoid its rejection and other clinical outcomes negative, such consequences often occur.⁶ In addition, nonadherence generates significant socioeconomic impacts on the health systems.⁷

There are several methods for measuring adherence. One of them, the self-report can measure adherence easily

and with very low cost, that being the most employed method in the clinical setting and research of medication nonadherence.^{8,9} A validated self-report instrument is recommended for investigation of adherence behavior and can predict clinical outcomes. There is no gold standard to measuring adherence to immunosuppressive drugs,¹⁰ so other objective methods and clinical outcomes can be used for correlation.¹¹ Adherence should be evaluated in the long term and strengthened through therapeutic strategies such as systematic education that may contribute to the adherence of medications.¹²

Brazil is the second country in the world in terms of numbers of liver transplantations.¹³ Despite this fact there is no validated specific instrument to measure immunosuppressant therapy adherence for liver transplantations in Brazil. The aim of this study was to translate and assess the validation of the Immuno-suppressant Therapy Adherence Instrument (ITAS) to Brazilian Portuguese for patients submitted to liver transplantations.

MATERIAL AND METHODS

Design, sample and setting

This psychometric study was conducted in a general hospital (Hospital Português da Bahia) and in a Teaching Hospital (Universidade Federal da Bahia). Patients were recruited between September 01, 2014 and June 20, 2015. The assessments were applied to the participants who agreed to sign an informed consent form. The general sociodemographic survey was administered to all participants (n = 139). Patients were included in the study if

they met the following criteria: received a liver transplant, able to understand the Portuguese language, and 18 years or older at the time of the study. Patients unable to read (illiteracy) and those who were submitted to retransplantation were excluded from the sample.

Demographic characteristics

Age, gender, marital status, and time post-transplant were assessed.

Variables and measurement

The ITAS is a self-report measure of immunosuppressant therapy adherence targeted to solid-organ transplant recipients, developed to be a reliable measure of adherence to immunosuppressant therapy in the three months prior to when research is conducted. The four items assess the behaviors of forgetfulness, carelessness, neglect and cessation due to feeling worse. Responses are designed for the patient to choose each behavior's frequency, in order to minimize patients' providing a positive adherence response of "yes". Response option levels are: 0 % of the time, 1-20 %, 21-50% and greater than 50%. Raw scores can range from 0 (greater than 50% for all items), indicating very poor adherence, to 12 (0% for all items), indicating perfect adherence. Scores below 80% indicate poor adherence.¹⁴

A psychometric re-evaluation of the ITAS was performed and two theoretically linked psychosocial constructs were selected to design the construct validity analysis: social support and resilience. The results demon-

Table 1. The final version of the ITAS scale in Brazilian Portuguese.

ESCALA DE ADESÃO À TERAPIA IMUNOSSUPRESSORA (ITAS). Circule a letra da resposta que melhor estima a porcentagem de tempo descrita em cada uma das 4 questões.				
	0% (nenhuma)	1-20%	21-50%	Mais de 50% (Muito frequentemente)
1. Nos últimos 3 meses, com que frequência você esqueceu de tomar seu(s) medicamento(s) imunossupressor(es)?	A	B	C	D
2. Nos últimos 3 meses, com que frequência você foi descuidado ao tomar seu(s) medicamento(s) imunossupressor(es)?	A	B	C	D
3. Nos últimos 3 meses, com que frequência você parou de tomar seu(s) medicamento(s) imunossupressor(es) porque se sentiu pior?	A	B	C	D
4. Nos últimos 3 meses, com que frequência você deixou de tomar seu(s) medicamento(s) imunossupressor(es) por qualquer razão?	A	B	C	D

Legenda: 3 para "0% (nenhuma frequência) do tempo"; 2 para "1%-20% do tempo"; 1 para "21-50% do tempo"; 0 para "mais de 50% do tempo". Pontuação: Alta - baixa; sendo 0 baixa e 12 alta.

strated the ITAS statistical relationships with these constructs and confirmation that the ITAS is a valid and reliable measure of IST adherence.¹⁵

The Brazilian Portuguese version of the Basel Assessment of Adherence with Immunosuppressive Medications Scale (BAASIS), validated in kidney transplant patients was used as a standard for comparison. The BAASIS is a self-report instrument for measuring nonadherence (NA) in transplantations, that measures: taking adherence, drug holidays, timing adherence, and dose reduction in a four-week period. Responses are given a six-point scale: Never (0), once per month (1), every second week (2), every week (3), more than once per week (4), and every day (5).¹⁶

Translation

The ITAS was translated as according to the method proposed by Wild, *et al.*¹⁷ The original questionnaire was translated independently by two fluent English speakers. This process resulted in two preliminary versions. A consensus among both translators resulted in a reconciled version. Next, a reverse translation from Portuguese to English was conducted.

The final version (Table 1) was applied to 30 liver transplant patients, who were asked about their understanding of the instrument.

Statistical analysis

Items were coded as 0, 1, 2, and 3 according to the Likert scale responses of “greater than 50%”, “21-50%”, “1-20%”, and “0%”, respectively.¹⁴ Since ITAS and BAASIS present opposite punctuation directions, BAASIS raw score was inverted before analysis.

Cronbach's α based on a polychoric correlation matrix was calculated to assess internal validity. Polychoric based α is considered to be more reliable in ordinal structured data.¹⁸

Convergent validity was assessed with Spearman's ρ correlation coefficient between ITAS and BAASIS (previously validated). ITAS accuracy considering BAASIS classification as a gold standard was evaluated by logistic regression. Individuals were labeled non-adherent if BAASIS items presented any answer different from “never”.^{19,20}

The Area Under the Receiver Operating Characteristic (AUROC) curve was calculated with respective confidence intervals estimated using bootstrap resampling. An optimal cut-point was determined using Youden criterion and used to determine accuracy, sensitivity, specificity, positive and negative predictive values.

Maximum-likelihood exploratory factor analysis with Varimax rotation was performed to analyze the optimal

number of latent factors and to investigate factor loadings related to each item.

Analysis was performed using R programming language and environment.²¹

Ethic

This study was approved by the local Institutional Review Board (MCO-UFBA - process number 14/2002) and was carried out in accordance to Declaration of Helsinki (version dated 2013). The researchers ensured that the documents would be kept confidential.

RESULTS

Sample characteristics

Visual inspection (histogram) and normality tests (Shapiro-Wilk; $p < 0.001$) suggested non-normality of the data. Descriptive analysis on the overall sample ($n = 139$) revealed that the majority of the participants were male (77%). The median age was 55.00 (Interquartile range [IQR]: 46.00-61.00). The participants were predominantly married (67.4%). The average time between transplant and collection was approximately 56.7 months IQR 30,00-79,00) (Table 2).

Psychometric properties

Internal consistency

Internal consistency measured by polychoric Cronbach's alpha coefficient value was high ($\alpha = 0.830$; Standardized $\alpha = 0.800$).

Table 2. Socio-demographic characteristics of liver transplant recipients who were assessed by using the Portuguese version of ITAS.

Variable	Patients (n = 139)
Male gender (%)	108 (77.7)
Age (1st Qu. / Median / 3rd Qu.)	48.00 / 57.00 / 64.00
Education (years)	< 9 years 34 (24.5%) > 9 years 105 (75.5%)
Marital Status (%)	
Married	93 (67.4)
Single	24 (17.4)
Divorced	15 (10.9)
Widower	6 (4.3)
Post-transplant (mean, months)	56.7

ITAS: Immunosuppressant Therapy Adherence Instrument. SD: Standard deviation.

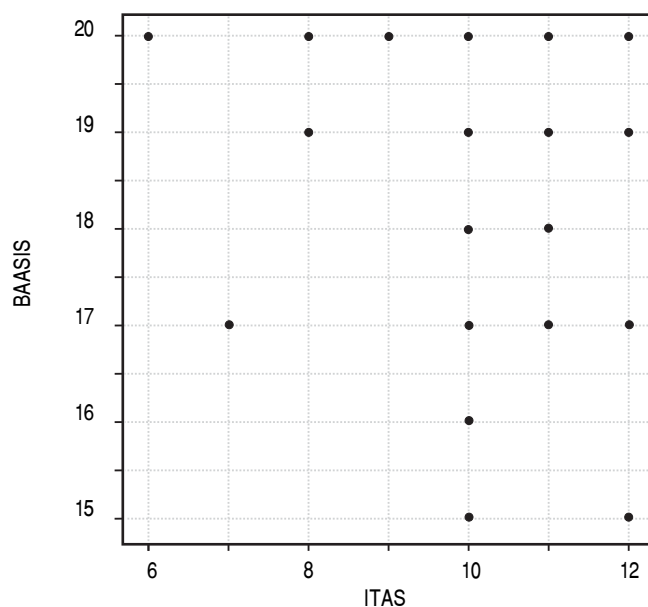


Figure 1. Correlation plot. Opacity indicates frequency of overlaid points of the ITAS and BAASIS.

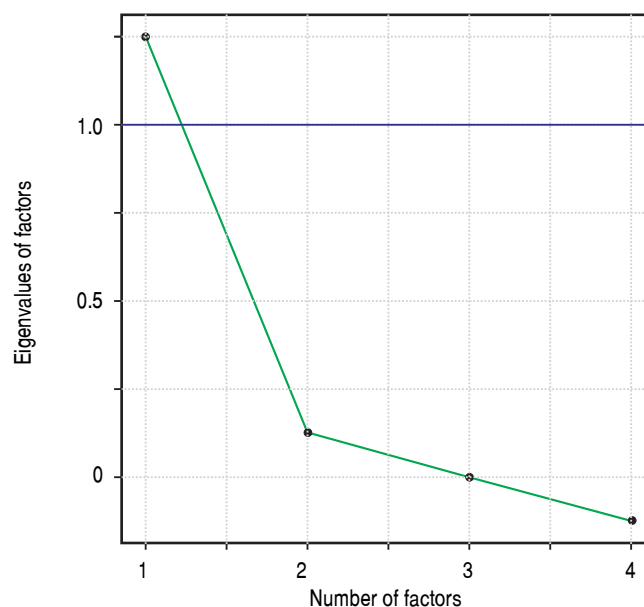


Figure 3. Scree plot of the ITAS.

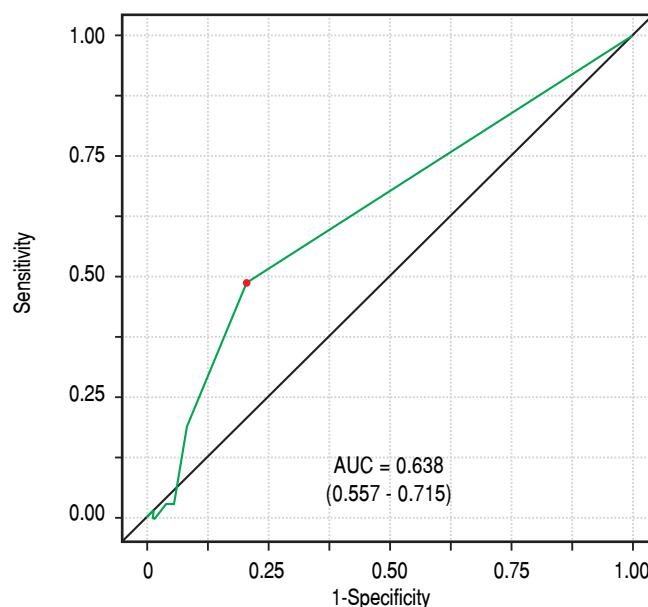


Figure 2. Area Under ROC curve. Red point indicates optimal cut-point value.

Table 3. Factor analysis of the ITAS, load values (Loading) for the first factor and sum of the squared factor loadings (Communalities).

Questions	Loading (F1)	Communalities
Forgetfulness	0.362	0.131
Carelessness	0.997	0.995
Feeling worse	-0.050	0.002
Neglect	0.358	0.128

Convergent validity

ITAS and BAASIS (inverted) presented significant correlation, with a Spearman's coefficient = 0.302 ($S = 312.500$; $p < 0.001$) (Figure 1).

Classificatory performance and accuracy measures

ITAS discriminatory performance considering BAASIS classification as the outcome can be seen in figure 2 (AU-ROC = 0.638; 95% CI: 0.557 - 0.715). Reporting at least one negative response was the optimal cut-point (accuracy = 0.647; sensitivity = 0.492; specificity = 0.792; positive predictive value = 0.688; negative predictive value = 0.626).

Factor analysis

A single factor model was adequate to ITAS test data ($\chi^2 = 2.77$; $df = 2$; $p = 0.250$). Carelessness presented higher loading (0.997), followed by Forgetfulness (0.362) and Neglect (0.358), in table 3. Factor analysis data is shown in table 4 and the scree plot with eigenvalues for different number of factors is displayed in figure 3.

DISCUSSION

The ITAS contributes as a valid instrument for immunosuppressant medication adherence in solid organ transplants²² and several studies use the ITAS as an adherence

Table 4. Polychoric correlation matrix of the ITAS.

	Forgetfulness	Carelessness	Feeling worse	Neglect
Forgetfulness	1,000	*	*	*
Carelessness	0,554	1,000	*	*
Feeling worse	0,449	0,512	1,000	*
Neglect	0,451	0,634	0,655	1,000

* $X_{ij} = X_{ji}$.

measure.²²⁻²⁵ The aim of this study was to translate the ITAS to Brazilian Portuguese and to evaluate its psychometric properties in adult liver transplant recipients. The version of the ITAS - scale Brazilian Portuguese facilitates the measurement of immunosuppressant adherence in transplant patients, and reduces negative outcomes for example graft loss and death.

The ITAS is an instrument easy to apply that takes no longer than 5-10 min to complete. It is relatively inexpensive, simple, and can be conducted rapidly when compared with other methods of adherence assessment. In this study, we included patients from various parts of Brazil who had their transplants in the state of Bahia, therefore our study sample reflects a wider scale in Brazil. The answers (in percentage ranges) of this version were maintained to preserve continuity, but may present difficulties to patients presenting cognitive deficits, poor educational levels and low social support.²²

Internal consistency provides an estimate of the equivalence of items from the same scale, and values between 0.70 and 0.95 are considered to be acceptable.^{26,27} Our Brazilian Portuguese version of the scale presented good internal consistency and was similar to previously published studies - Cronbach's alpha = 0.81.¹⁵ Items within the scale were correlated as expected.

Factor analysis solution with a single factor was adequate, indicating higher loading values for Carelessness (0.997), Forgetfulness (0.362), and Neglect (0.358). Feeling Worse (item 3) factor loading was close to zero (-0.050), since almost all patients included in the sample (98.6%) answered this item with option A: 0% (none). This behavior was not observed in the original ITAS validating studies¹⁴ and might be due to regional differences. This hypothesis can be verified in further studies replicating the experiments in other regions.

Concerning convergent validity, our findings indicate that the translated ITAS correlates well with the translation of the BAASIS scale, an instrument validated in Brazil.¹⁶ AUROC value of 0.5 should be considered a minimum.²⁸ Therefore, our results (AUROC = 0.638) indicate satisfactory discrimination for adherence.

The result of the psychometric properties analysis suggest that the Portuguese translated version of ITAS in Brazil

is a psychometric scale internally consistent, with good convergent validity with BAASIS^a. These findings need to be replicated in further studies. Altogether, these results require confirmation in larger samples with regional variance.

This study has some limitations. The sample may be subject to a bias recruitment due to convenience sampling, because the participants included in the study were those who attended routine consultations. Non-adherent patients may be more prone to miss consultations and, therefore, to not be included in the survey. Our sample covers only liver transplant patients and the results cannot be generalized to other types of transplants.

In conclusion, the ITAS instrument was successfully translated and an analysis of the data confirmed its consistency and convergent validity with a validated tool. The translation and validation of the ITAS instrument contributes to the applicability and relevance of the instrument for the Brazilian population.

ABBREVIATIONS

- **AUROC:** Area Under the Receiver Operating Characteristic.
- **BAASIS:** Basel Assessment of Adherence with Immunosuppressive Medications Scale.
- **ITAS:** Immunosuppressant Therapy Adherence Instrument.

SUPPORT

This project was partially supported by the National Council of Technological and Scientific Development (CNPq): 462014/2014-2 - Edital Universal MCT/CNPQ 2014. Another part of the funding (totaling 100% with the funding above) was supported by the scholarships from the Coordination for the Improvement of Higher Level Personnel (CAPES). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGEMENTS

The authors thank all the patients who agreed to be included in this study for their cooperation. We are also grateful to Raquel Roberts for proofreading, José Edson Oliveira Filho, Carolina Arruda and Maria Isabel Teles.

REFERENCES

- WHO. Adherence to Long-term Therapies. Evidence for Action Switzerland: World Health Organization. 2003.
- Burra P, Germani G, Gnoato F, Lazzaro S, Russo FP, Cillo U, Senzolo M. Adherence in liver transplant recipients. *Liver Transplantation* 2011; 17:760-70
- Stilley CS, DiMartini AF, de Vera ME, Flynn WB, King J, Sereika S, Tarter RE, et al. Individual and environmental correlates and predictors of early adherence and outcomes after liver transplantation. *Progress in transplantation* 2010; 20: 58-67.
- Laederach-Hofmann K, Bunzel B. Noncompliance in organ transplant recipients: a literature review. *General Hospital Psychiatr* 2000; 22: 412-24.
- Germani G, Lazzaro S, Gnoato F, Senzolo M, Borella V, Rupolo G, Cillio U, et al. Nonadherent behaviors after solid organ transplantation. *Transplantation Proceedings* 2011; 43: 318-23.
- Serper M, Patzer RE, Reese PP, Przytula K, Koval R, Ladner DP, Levitsky J, et al. Medication misuse, nonadherence, and clinical outcomes among liver transplant recipients. *Liver transplantation* 2015; 21(1): 22-8.
- De Oliveira PC, Mucci S, Silva ESV, Leite RF, Paglione HB, Erbs JL, Araujo CAS, et al. Assessment of Factors Related to Adherence to Treatment in Liver Transplantation Candidates. *Transplantation proceedings* 2016; 48: 2361-5.
- Dew MA, DiMartini AF, De Vito Dabbs A, Myaskovsky L, Steel J, Unruh M, Switzer GE, et al. Rates and risk factors for nonadherence to the medical regimen after adult solid organ transplantation. *Transplantation* 2007; 15; 83: 858-73.
- Osterberg L, Blaschke T. *Adherence to Medication*. *N Eng J Med* 2005; 353: 487-97.
- Stirratt MJ, Dunbar-Jacob J, Crane HM, Simoni JM, Czajkowski S, Hilliard ME, Aikens JE, et al. Self-report measures of medication adherence behavior: recommendations on optimal use. *Translational Behavioral Medicine* 2015; 5: 470-82.
- Leven EA, Annunziato R, Helcer J, Lieber SR, Knight CS, Wlodarkiewicz C, Soriano RP, et al. Medication adherence and rejection rates in older vs younger adult liver transplant recipients. *Clinical transplantation* 2017.
- Asavakarn S, Sirivatanauksorn Y, Promraj R, Ruenrom A, Limsrichamrern S, Kositamongkol P, Mahawithitwong P, et al. Systematic Pharmaceutical Educational Approach to Enhance Drug Adherence in Liver Transplant Recipients. *Transplantation proceedings* 2016; 48: 1202-7.
- Pacheco L. Liver transplantation in Brazil. *Revista do Colégio Brasileiro de Cirurgiões* 2016; 43: 223-4.
- Chisholm MA, Lance CE, Williamson GM, Mulloy LL. Development and validation of the immunosuppressant therapy adherence instrument (ITAS). *Patient Education and Counseling* 2005; 59: 13-20.
- Wilks SE, Spivey CA, Chisholm-Burns MA. Psychometric re-evaluation of the immunosuppressant therapy adherence scale among solid-organ transplant recipients. *J Evaluation in Clinical Practice* 2010; 16: 64-8.
- Marsicano E de O, Fernandes Nda S, Colugnati F, Grincenkov FR, Fernandes NM, De Geest S, Sanders-Pinheiro H. Transcultural adaptation and initial validation of Brazilian-Portuguese version of the Basel assessment of adherence to immunosuppressive medications scale (BAASIS) in kidney transplants. *BMC Nephrology* 2013; 14: 108.
- Wild D, Grove A, Martin M, Eremenco S, McElroy S, Verjee-Lorenz A, Erikson P, et al. 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.
- Gadermann AM, Guhn M, Zumbo BD. Estimating Ordinal Reliability for Likert-Type and Ordinal Item Response Data: A Conceptual, Empirical, and Practical Guide. *Practical Assessment, Research & Evaluation* 2012; 17: 1-13.
- Marsicano EO, Fernandes NS, Colugnati FA, Fernandes NM, De Geest S, Sanders-Pinheiro H. 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.
- Tielen M, Van Exel J. Attitudes to medication after kidney transplantation and their association with medication adherence and graft survival: a 2-year follow-up study. *J Transplant* 2014; 2014: 675301.
- R Development Core Team R. R: A Language and Environment for Statistical Computing. Vienna, Austria; 2011.
- Chisholm MA, Lance CE, Mulloy LL. Patient factors associated with adherence to immunosuppressant therapy in renal transplant recipients. *AJHP* 2005; 62: 1775-81.
- Promraj R, Dumronggittigule W, Sirivatanauksorn Y, Ruenrom A, Tovikkai C, Limsrichamrern S, Kositamongkol P, et al. Immunosuppressive Medication Adherence in Liver Transplant Recipients. *Transplantation Proceeding* 2016; 48: 1198-201
- Tsapepas D, Langone A, Chan L, Wiland A, McCague K, Chisholm-Burns M. A longitudinal assessment of adherence with immunosuppressive therapy following kidney transplantation from the Mycophenolic Acid Observational RENal Transplant (MORE) study. *Ann Transplant* 2014; 19: 174-81.
- Sankaranarayanan J, Collier D, Furasek A, Reardon T, Smith LM, McCartan M, Langnas AN. Rurality and other factors associated with adherence to immunosuppressant medications in community-dwelling solid-organ transplant recipients. *Research in Social and Administrative Pharmacy* 2012; 8: 228-39.
- Kimberlin CL, Winterstein AG. Validity and reliability of measurement instruments used in research. *Am J Health System Pharmacy* 2008; 65: 2276-84.
- Tavakol M, Dennick R. Making sense of Cronbach's alpha. *Int J Medical Education* 2011; 2: 53-5.
- Hajian-Tilaki K. Receiver Operating Characteristic (ROC) Curve Analysis for Medical Diagnostic Test Evaluation. *Caspian J Internal Medicine* 2013; 4: 627-35.

Correspondence and reprint request:

Lucas C. Quarantini, M.D.
Universidade Federal da Bahia, Hospital Universitário
Professor Edgard Santos-Serviço de Psiquiatria.
Rua Augusto Viana, s/n 3 andar Serv. Psiquiatria, Canela,
40110909 - Salvador, BA - Brazil.
Tel.: (71) 30234111. Fax: (71) 30234111
E-mail: lcq@ufba.br