

# Measurement of non-adherence to immunosuppressive medication in liver transplantation recipients

Mensuração da não-adesão aos medicamentos imunossupressores em receptores de transplante de fígado  
Medición de la no adhesión a los medicamentos inmunosupresores en receptores de trasplante de hígado

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## Keywords

Treatment adherence and compliance; Medication adherence; Liver transplantation; Comprehensive health care; Nursing care

## Descritores

Cooperação e adesão ao tratamento; Adesão à medicação; Transplante de fígado; Assistência integral à saúde; Cuidados de enfermagem

## Descriptores

Cumplimiento y adherencia al tratamiento; Cumplimiento de la medicación; Trasplante de hígado; Atención integral de salud; Atención de Enfermería

## Submitted

February 11, 2019

## Accepted

April 8, 2019

## Abstract

**Objective:** Assessing the level of non-adherence to immunosuppressive therapy in a sample of liver transplantation recipients using the *Basel Assessment of Adherence with Immunosuppressive Medication Scale*; correlating socio-demographic features and clinical factors to medication non-adherence.

**Methods:** This cross-sectional epidemiological study was conducted between March 2016 and March 2018 at the outpatient service for liver transplantations of the Federal University of São Paulo.

**Results:** Forty-nine patients were assessed. The level of medication non-adherence after liver transplantation was 49%. It was directly correlated to the use of mycophenolic acid ( $p=0.007$ ) and to multiple daily dosing of immunosuppressant medication ( $p=0.004$ ). No statistically significant correlations were found between non-adherence to immunosuppressive therapy, socio-demographic features, and the remaining clinical variables assessed.

**Conclusion:** This study shows that nearly half of all patients are not compliant with immunosuppressive therapy after liver transplantation. Given poor liver transplantation outcomes are intimately related to adherence failure, nurses need to assess this behavior in outpatient follow-up of liver transplantation recipients.

## Resumo

**Objetivo:** Avaliar os níveis de não-adesão à terapia imunossupressora em uma amostra de receptores de transplante de fígado utilizando a *Basel Assessment of Adherence with Immunosuppressive Medication Scale*; correlacionar as características sociodemográficas e os fatores clínicos à não-adesão medicamentosa.

**Métodos:** Estudo epidemiológico e transversal, realizado entre março 2016 e março 2018 no ambulatório de transplante de fígado da Universidade Federal de São Paulo.

**Resultados:** Foram avaliados 49 pacientes. O nível de não-adesão medicamentosa no transplante de fígado foi de 49% e esteve diretamente relacionado ao uso do ácido micofenólico ( $p=0,007$ ) e à administração de múltiplas doses de imunossupressores diariamente ( $p=0,004$ ). Não foram encontradas correlações estatisticamente significativas entre a não-adesão à terapia imunossupressora e as características sociodemográficas e demais variáveis clínicas analisadas.

**Conclusão:** Este estudo mostrou que quase a metade dos pacientes deixaram de aderir à terapia imunossupressora no pós transplante de fígado. Uma vez que os desfechos desfavoráveis no transplante estão intimamente relacionados à falhas na adesão, é importante os enfermeiros avaliarem esse comportamento durante o seguimento ambulatorial dos receptores de transplante de fígado.

## Resumen

**Objetivo:** Analizar los niveles de no adhesión a la terapia inmunosupresora en una muestra de receptores de trasplante de hígado utilizando la *Basel Assessment of Adherence with Immunosuppressive Medication Scale* y correlacionar las características sociodemográficas y los factores clínicos con la no adhesión a los medicamentos.

**Métodos:** Estudio epidemiológico y transversal realizado entre marzo de 2016 y marzo de 2018 en los consultorios externos de trasplante de hígado de la Universidad Federal de São Paulo.

**Resultados:** Fueron analizados 49 pacientes. El nivel de no adhesión a los medicamentos del trasplante de hígado fue de 49% y está directamente relacionado con el uso de ácido micofenólico ( $p=0,007$ ) y con la administración de varias dosis inmunosupresoras diariamente ( $p=0,004$ ). No se encontró correlación estadísticamente significativa entre la no adhesión a la terapia inmunosupresora y las características sociodemográficas y demás variables clínicas analizadas.

**Conclusión:** Este estudio mostró que casi la mitad de los pacientes dejó de realizar la terapia inmunosupresora en el posttrasplante de hígado. Dado que los desenlaces desfavorables del trasplante están intimamente relacionados con fallas en la adhesión, es importante que los enfermeros evalúen ese comportamiento durante el seguimiento ambulatorio de los receptores de trasplante de hígado.

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## DOI

<http://dx.doi.org/10.1590/1982-0194201900044>



## How to cite:

Oliveira PC, Paglione HB, Silva e Silva V, Schirmer J, Roza BA. Measurement of non-adherence to immunosuppressive medication in liver transplantation recipients. *Acta Paul Enferm.* 2019;32(3):319-26.

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**Conflicts of interests:** Despite being Editor in Chief and Associate Editor for *Acta Paulista de Enfermagem*, Schirmer J and Roza BA were not involved in manuscript assessment.

## Introduction

Liver transplantation (LT) is considered the standard treatment for patients with progressive liver disease, for whom no other treatments are warranted.<sup>(1)</sup> Upon indication, it is considered a successful treatment that affords long-term survival and improvement in quality of life.<sup>(2)</sup> Brazil is the country with the world's largest public transplantation system, with the public healthcare system (Unified Health System, or SUS) funding 96% of all transplantation-related procedures. Therefore, liver transplantation is a priority within national healthcare policies.<sup>(3,4)</sup> Regarding funding, all treatment steps are funded by the national administration, including dispensing immunosuppressive medication and outpatient follow-up — costs that can amount to R\$ 2.2 billion a year.<sup>(5,6)</sup>

Data from the Brazilian Registry of Transplantation show that 2,122 LT procedures were performed in 2018, which represents an increase in 2.4% from the previous year. In absolute terms, Brazil is ranked second worldwide in LT procedures, amounting to a total 10.5 transplants per million population (pmp).<sup>(7)</sup> Currently, there are 75 liver transplantation teams spread out over 15 Brazilian states; the State of São Paulo accounts for over a third (30.1%) of the total LT procedures performed. Regarding type of donor, most LT procedures (92.4%) use deceased donors.<sup>(7)</sup>

One-year survival rates for patients and grafts are 77% and 74%, respectively, and five-year survival rates are 70% and 67%, also respectively,<sup>(7)</sup> depending on patient condition for LT indication and other variables — such as related morbidity, access to a healthcare team, and ability to develop and manage self-care.<sup>(7-10)</sup>

Positive transplantation outcomes are directly related to patients regularly committing to their own treatment. Due to the inherent risk for graft rejection, patients are submitted to immunosuppressive therapy post-transplantation<sup>(10)</sup> and should be monitored for signs of rejection.<sup>(11)</sup>

Non-adherence (NA) to post-transplantation therapy is understood as any deviation from the prescribed immunosuppressive regimen that may negatively impact the expected outcome<sup>(12)</sup> — including errors in following prescribed dosing and dosing time. It is considered a multi-dimension phenomenon determined by the interaction of multiple factors, such as the patient's healthcare system, their socio-economic level, modality of provided treatment, the patient's medical condition, and underlying disease.<sup>(13)</sup> Patients are considered compliant to pharmaceutical management upon using 80% to 110% of the prescription medication.<sup>(14)</sup> In the setting of transplantation, NA is estimated to vary from 2% to 67%, with an annual average around 35.6%,<sup>(5,10)</sup> which results in graft rejection or failure, increased treatment costs, and morbimortality.<sup>(13,15,16)</sup>

Studies show different strategies to identify NA, among them counting tablets, applying self-reported questionnaires, reporting side-effects of immunosuppressive (IMS) therapy, laboratory analysis of IMS serum levels, and electronic monitoring.<sup>(13,14-18)</sup> However, self-reporting is the most common form of assessing NA, which has been shown to be useful in medical practice, easily applied, and of low cost. This method is moderately correlated to other measurement strategies and shows good capacity to predict medical outcomes. Despite its poor sensitivity, self-reporting questionnaires are highly specific and can be combined with other strategies, yielding information on the patient's medication-use behavior.<sup>(13,19,20)</sup>

In Brazil, studies of NA during post-transplantation follow-up are still in their early stages. Lack of data on this issue's actual dimensions makes implementing public policies focused on improvement of LT- and treatment-adherence-related clinical outcomes a difficult task.<sup>(20,21)</sup> Thus, this study's aim is to assess the levels of immunosuppressive therapy NA in a sample of patients submitted to the Basel Assessment of Adherence with Immunosuppressive Medication Scale (BAASIS®) while correlating the sample's socio-demographic features and clinical factors to medication NA.

## Methods

Cross-sectional epidemiological study<sup>(22)</sup> including adult liver transplantation patients, for whom consent was obtained, in follow-up at the outpatient service of the São Paulo Federal University (UNIFESP) Hospital. This study was reviewed and approved by UNIFESP's Institutional Review Board under protocol number 623.082 CAAE 1643201470005505.

Data were collected between March 2016 and March 2018 from all patients using the hospital's outpatient service over this period who met the inclusion criteria. Information were obtained during a previously scheduled visit with healthcare professionals working under UNIFESP's Multi-professional Residency in Organ Procurement and Transplantation, who were previously trained by researchers.

Patients with severe hepatic encephalopathy were excluded from the sample, as their cognitive state prevented them from answering the questionnaire used in this study. Undergoing double transplantation or having undergone more than one LT procedure were also considered an exclusion criterion, given risk of bias.

The BAASIS® scale's Portuguese version was used to assess adherence. The instrument's conceptual model for assessing medication adherence considers the difference between the number of prescribed doses and dosing times and actual patient conduct. It consists of four yes/no questions for self-reporting of immunosuppressive regimen adherence over the past four weeks of treatment. All positive responses (yes) to questionnaire items are considered NA; in the event of a positive response, other questions are asked about patient behavior.<sup>(19,20)</sup>

Patients were also asked about their referred perception of medication adherence over the past 4 weeks using a visual analogue scale varying from perfect adherence (100%) to non-adherence (0% = 0 cm).<sup>(19)</sup> Additional instruments were developed to report socio-demographic and medical variables of post-LT patients. Part of the information was obtained from patient medical records and the remaining part was obtained from patient interviews.

Collected data were compiled and stored in electronic spreadsheet format (Microsoft Excel® software) for descriptive analysis. Spreadsheets were also used for statistical analysis in SPSS®, version 20.0.

In terms of statistical methodology, initial data analysis was solely descriptive. For categorical variables, data is shown in absolute and relative frequencies; for numerical variables, data is shown in summary measures (average, quartiles, minimum, maximum, and standard deviation).

Associations between two categorical variables were verified using the chi-squared test or Fisher's exact test. Averages were compared between two groups using Student's t-test or independent-samples t-test.

Effects on NA considered to be simultaneous were adjusted for using logistic regression. Due to the large number of predictive variables in comparison to sample size, variables with a 10% significance level of association to the dependent variable in univariate analysis were selected for the initial models. Then, variables with significance level under 5% were excluded one by one, in order of significance. Additionally, the Hosmer-Lemeshow test was used to assess goodness of fit to the final model.

## Results

Fifty-seven patients were assessed. However, 8 patients were excluded on the basis of incomplete questionnaires. Thus, our final sample comprised 49 patients.

Patient age ranged from 18 to 73 years (average of 47.0, SD = 17.3 years). Out of the full sample, 57.1% were male, 55.1% white, and 51.0% married. In terms of education and income, 42.9% of patients had attended school for a period of 9 to 12 years and 22.4% for a period of 5 to 8 years. In 61.2% of cases, per capita income was under 1 minimum wage; unemployment rate was over 65% and only 22.4% of patients participated in paid work activities. Sixty-five point three percent of patients were catholic, 46.9% lived with their spouses, and 69.4% could count on a support network. In terms

of access to the outpatient center, 67.3% used buses as a means of transportation and 63.3% used only one transport modality. Most patients (71.4%) reported having no transportation issues to arrive at the outpatient center.

Patients were classified according to baseline disease, transplantation time, and IMS regimen (Table 1). Most patients (25.0%) presented with viral hepatitis, followed by malignant neoplasms of liver (14.6%), and autoimmune disease (10.4%). On average, patients were submitted to transplantation 7 years prior, and 55.1% of patients were submitted to the procedure over 6 years prior. In only two cases, transplantation was recent (under 1 year). In terms of IMS therapy, nearly all patients (98.0%) used tacrolimus, 65.3% used mycophenolic acid, and 24.5% used prednisone. Thus, 73.5% of patients used combined IMS therapy (two drugs or more) and only 26.5% of cases consisted of immunosuppressive monotherapy with two daily tacrolimus doses. In the remaining cases, patients were under a multiple dose and medication regimen.

**Table 1.** Distribution of patients per baseline disease, transplantation time, and immunosuppressive regimen

Characteristics	n(%)
Baseline disease	
Viral hepatitis	12(25.0)
Autoimmune condition	5(10.4)
Malignant neoplasm of liver	7(14.6)
Other <sup>1</sup>	24(50.0)
LT time (years)	
<1 year	2(4.1)
1-2 years	10(20.4)
2-5 years	10(20.4)
6 years or greater	27(55.1)
Immunosuppressive therapy <sup>1</sup>	
Tacrolimus	48(98.0)
Mycophenolic acid	32(65.3)
Azathioprine	1(2.0)
Everolimus	2(4.1)
Prednisone	12(24.5)
Cyclosporine	1(2.0)
# of IMS drugs	
1	13(26.5)
2	25(51.0)
3	11(22.5)

<sup>1</sup>Multiple response — Sum of percentages does not total 100%. n=49 cases

Application of the BAASIS® instrument showed that 49% of patients showed non-adherence in one of the four situations covered or more, at least once, in the past four weeks. Out of the four NA-assessing

BAASIS® questions, question 3 (“Do you recall having taken your immunosuppressive medications with more than 2 hours’ time difference from the prescribed dosing time, in the past 4 weeks?”) showed the highest percentage of positive answers (40.8% compared to a maximum of 20.4% (Table 2).

**Table 2.** Distribution of adherence to immunosuppressive medication in adult patients submitted to LT per BAASIS® item

BAASIS® items	n(%)
1. Do you recall not having taken your immunosuppressive medications some times in the past 4 weeks?	49(100.0)
No	39(76.6)
Yes	10(20.4)
1.1 Frequency of not having taken your immunosuppressive medications some times in the past 4 weeks.	48(100.0)
Never	38(79.2)
Once a month	5(10.4)
Every two weeks	4(8.3)
Every week	1(2.0)
2. Have you skipped several consecutive doses of your immunosuppressive medications in the past 4 weeks?	48(100.0)
No	46(95.8)
Yes	2(4.1)
2.1 Frequency of having skipped several consecutive doses of your immunosuppressive medications in the past 4 weeks.	49(100.0)
Never	46(93.9)
Once a month	3(6.1)
3. Do you recall having taken your immunosuppressive medications with more than 2 hours’ time difference from the prescribed dosing time, in the past 4 weeks?	49(100.0)
No	29(59.2)
Yes	20(40.8)
3.1 Frequency of having taken your immunosuppressive medications with more than 2 hours’ time difference from the prescribed dosing time, in the past 4 weeks.	49(100.0)
Never	29(59.2)
Once a month	10(20.4)
Every two weeks	5(10.2)
Every week	3(6.1)
More than once a week	1(2.0)
Every day	1(2.0)
4. Have you reduced the prescribed amount of your prescribed immunosuppressive medications during the past 4 weeks?	49(100.0)
No	49(100.0)
4.1 Frequency of having reduced the prescribed amount of your prescribed immunosuppressive medications during the past 4 weeks.	49(100.0)
Never	49(100.0)
Score	49(100.0)
45	1(2.0)
50	2(4.1)
70	2(4.1)
80	6(12.2)
90	15(30.6)
95	6(12.2)
100	17(34.7)

Distribution of post-LT adherence and NA according to socio-demographic and medical features (Table 3) showed an association between NA and the

use of mycophenolic acid ( $p=0.007$ ) and the number of immunosuppressive drugs in use ( $p=0.004$ ). Thus, patients using mycophenolic acid show a higher NA percentage (76.5%) in comparison to patients not using this medication (34.4%). Additionally, patients using only one medication (tacrolimus) show a higher adherence percentage (84.6%) in comparison to patients using a combination of two drugs (28.0%). Thus, the use of two IMS medications or more seems to favor NA. Other medical and socio-demographic features were analyzed in combination to adherence, but no statistically significant differences were seen. Only one factor revealed marginal significance, marital status. As seen in the following table, patients without a spouse (single, divorced, or widowed) showed a directly proportional association to NA ( $p=0.065$ ).

**Table 3.** Distribution of adherence in liver transplantation according to clinical and socio-demographic features

Items	Yes n(%)	No n(%)	n	P-value	Unadjusted critical region (95% CI)
<b>Patient level</b>					
<i>Socio-demographic features</i>					
Sex	24(49.0)	25(51.0)	49	0.322	
Female	12(57.1)	9(42.9)	21		1.78(0.57-5.58)
Male	12(42.9)	16(57.1)	28		-
Ethnicity	24(49.0)	25(51.0)	49	0.656	
Non-white	10(45.5)	12(54.5)	22		0.77(0.25-2.39)
White	14(51.9)	13(48.1)	27		-
Marital status	24(49.0)	25(51.0)	49	0.065 <sup>a</sup>	
Single	12(70.6)	5(29.4)	17		5.10(1.34-19.47)
Married	8(32.0)	17(68.0)	25		-
Divorced	2(50.0)	2(50.0)	4		2.12(0.25-17.93)
Widowed	2(66.7)	1(33.3)	3		4.25(0.33-54.07)
Education	24(49.0)	25(51.0)	49	0.117 <sup>a</sup>	
1-4 years	2(20.0)	8(80.0)	10		0.28(0.05-1.62)
5-8 years	8(72.7)	3(27.3)	11		2.93(0.60-14.23)
9-12 years	10(47.6)	11(52.4)	21		-
13 or greater	4(57.1)	3(42.9)	7		1.47(0.26-8.23)
Family income	24(49.0)	25(51.0)	49	0.661 <sup>a</sup>	
Up to 1 minimum wage	16(53.3)	14(46.7)	30		-
2-5 minimum wages	8(44.4)	10(55.6)	18		0.70(0.22-2.26)
>5 minimum wages	0(0.0)	1(100.0)	1		(1)
Occupation	24(49.0)	25(51.0)	49	0.422 <sup>a</sup>	
Employed/self-employed	7(63.6)	4(36.4)	11		3.06(0.68-13.79)
Unemployed/on leave	7(58.3)	5(41.7)	12		2.45(0.58-10.33)
Student/volunteer	2(50.0)	2(50.0)	4		1.75(0.21-14.93)
Retired	8(36.4)	14(63.6)	22		-
Religion	24(49.0)	25(51.0)	49	0.122 <sup>a</sup>	
Catholic	13(40.6)	19(59.4)	32		-
Spiritist	0(0.0)	1(100.0)	1		(1)
Evangelical	10(66.7)	5(33.3)	15		2.92(0.81-10.56)
None	1(100.0)	0(0.0)	1		(1)

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Continuation.

Items	Yes n(%)	No n(%)	n	P-value	Unadjusted critical region (95% CI)
<i>Disease-related features</i>					
Baseline disease	23(47.9)	25(52.1)	48	0.749 <sup>a</sup>	
Viral hepatitis	6(50.0)	6(50.0)	12		1.00(0.25-4.00)
HI (autoimmune)	3(60.0)	2(40.0)	5		1.50(0.21-10.65)
Malignant neoplasm of liver	2(28.6)	5(71.4)	7		0.40(0.06-2.48)
Other	12(50.0)	12(50.0)	24		-
LT time (years)	24(49.0)	25(51.0)	49	0.300 <sup>a</sup>	
<1 year	0(0.0)	2(100.0)	2		(1)
1-2 years	4(40.0)	6(60.0)	10		0.72(0.16-3.13)
2-5 years	7(70.0)	3(30.0)	10		2.51(0.53-11.83)
6 years or greater	13(48.1)	14(51.9)	27		-
<b>IMS</b>					
Tacrolimus	24(49.0)	25(51.0)	49	0.490 <sup>a</sup>	
No	1(100.0)	0(0.0)	1		-
Yes	23(47.9)	25(52.1)	48		(1)
Mycophenolic acid	24(49.0)	25(51.0)	49	0.007 <sup>a</sup>	
No	13(76.5)	4(23.5)	17		0.16(0.04-0.61)
Yes	11(34.4)	21(65.6)	32		
Azathioprine	24(49.0)	25(51.0)	49	1.000 <sup>a</sup>	
No	24(50.0)	24(50.0)	48		-
Yes	0(0.0)	1(100.0)	1		(1)
Everolimus	24(49.0)	25(51.0)	49	1.000 <sup>a</sup>	
No	23(48.9)	24(51.1)	47		-
Yes	1(50.0)	1(50.0)	2		1.04(0.06-17.69)
Prednisone	24(49.0)	25(51.0)	49	0.456	
No	17(45.9)	20(54.1)	37		-
Yes	7(58.3)	5(41.7)	12		1.65(0.44-6.15)
Cyclosporine	24(49.0)	25(51.0)	49	0.490 <sup>a</sup>	
No	23(47.9)	25(52.1)	48		-
Yes	1(100)	0(0.0)	1		(1)
# of IMS drugs	24(49.0)	25(51.0)	49	0.004	
1	11(84.6)	2(15.4)	13		14.14(2.48-80.68)
2	7(28.0)	18(72.0)	25		-
3	6(54.5)	5(45.5)	11		3.09(0.71-13.47)

## Discussion

In recent years, advancements in immunosuppressive therapy have afforded greater safety to transplantation patients, thereby reinforcing the benefits of transplantation. However, post-transplantation non-adherence to IMS treatment is still an issue to be overcome.

In this study, 49.0% of patients analyzed were non-adherent in one of the four situations assessed by the BASSIS questionnaire or more, for at least once in the past four weeks. This rate is superior to several other rates reported in international studies, where NA rate was between 5% and 47%.<sup>(23-26)</sup>

Out of these, only one study showed an NA rate (73%) superior to the one found in this study. However, the method adopted to measure non-ad-

herence was electronic monitoring, not a self-reporting instrument.<sup>(27)</sup> This is significant, as it makes comparison of post-transplantation adherence outcomes especially difficult, due to non-standardization of measurement methods used in different studies.<sup>(26)</sup>

In the United States, the most recent data show an improvement in graft rejection and failure in patients submitted to liver transplantation. In 2014, 6-month graft failure rate in transplantation patients was 7.8% for deceased donor grafts and 12.5% for living donor grafts, and 1-year survival rate was 10.3% and 15.1%, respectively. This global improvement in graft failure and survival rates is most likely due to several factors, including either technological and surgical technique advancements or improvement in medical management and immunosuppressive therapy — it may not be necessarily due to improved medication adherence.<sup>(28-33)</sup>

Treatment for management of grafts consists of a combination of immunosuppressive agents with different mechanisms of action. This strategy minimizes morbidity and mortality individually associated to each immunosuppressive agent class, maximizing global treatment efficacy.<sup>(34)</sup>

Standard therapy for rejection prophylaxis is calcineurin inhibitors, typically tacrolimus or cyclosporine (in cases where tacrolimus is contraindicated) alone or in combination with mycophenolate mofetil or mycophenolate sodium, everolimus, and corticosteroids.<sup>(34)</sup>

In this study, 76.5% of patients using mycophenolic acid showed failure in medication use. Mycophenolates are known for their adverse reactions and lead to IMS dose decrease or suspension in 40%-50% of cases. Gastrointestinal side effects are the main reason for dosing change or discontinuation, which usually compromises short- and long-term graft survival outcomes. Abdominal pain, diarrhea, and changes in mucous membranes, such as ulcers and submucosal inflammation are common signs of mycophenolic acid gastrointestinal toxicity.<sup>(34,35)</sup>

Our samples consisted mainly of patients submitted to LT over six years prior. Treatment adherence behavior may be affected by the presence

of other associated comorbidities and limitations, which may contradict the patient's expectations of overall medical improvement upon transplantation, thereby directly affecting adherence rates. Perception of transplantation as a modality of treatment, not a cure, may lead patients away from recognizing its positive effects and reduce patient motivation regarding treatment over the post-transplantation period,<sup>(36)</sup> which in turn contributes to the high non-adherence rate seen in this study.

It is important to note that the study transplant center has seen an abrupt decrease in the number of transplantation procedures performed over recent years; from 2012 to 2016, an average of 19 transplants were performed annually. However, in 2017, only one transplantation procedure was performed by the team.<sup>(7)</sup> This led to the study sample mainly consisting of recipients in the late post-transplantation period, thus poorly representing recent transplantations.

Results showing a correlation between fewer daily doses and protective factors for NA are in accordance with other studies. An integrative review<sup>(13)</sup> compiling risk factors for non-adherence to immunosuppressive medications in adult patients submitted to liver transplantation showed that a decrease in dosage for single daily doses is related to a lower rate of NA, due to adherence difficulties caused by concomitant use of combined medications. As an intervention proposal, we suggested a change in dosage from two daily doses to a single daily dose. This intervention showed significant decrease in NA, stabilization of drug serum levels, and absence of liver, kidney, and heart complications.<sup>(13,25-32)</sup>

Traditionally, when assessing NA in the setting of transplantation, one must correlate social and cultural factors to adherence findings. However, in this study, only one variable showed a certain level of relevance, marital status. Higher adherence scores were seen in married patients in comparison to single, widowed, or divorced patients. Despite spousal influence being considered inconclusive in a few studies, a recent study showed a correlation between being separated or divorced and NA.<sup>(33)</sup> Given the family and social setting can be characterized as a

significant support network, it is possible to suggest that related variables can directly affect an individual's life and consequently, their adherence.<sup>(36)</sup>

The consequences of IMS NA are multiple. For patients, they include some of the worst transplantation prognoses, with an increase in rejection rate, graft loss, and mortality. For the healthcare system, impact can be estimated on the basis of the costs of additional diagnoses, increases in immunosuppressive therapy for rejection, and eventually, the costs of retransplantation. Thus, immunosuppressive regimen NA can be considered a public health issue and an important bioethical issue as well, given the growing demand for transplantation as a therapeutic option and the need to ration financial resources in healthcare.<sup>(11,27,37)</sup>

This study presents some limitations, given it is a cross-sectional study with a convenience sample. Still, its results bring forth a need for incorporating adherence measurements into clinical nursing practice in the care of transplantation patients to improve quality of care and potentially develop interventions focusing on improving adherence rates.

## Conclusion

This study's results show that nearly half of all patients are not compliant with immunosuppressive therapy after liver transplantation, over the period of study. Given poor liver transplantation outcomes are intimately related to adherence failure, nurses need to assess this behavior in outpatient follow-up of liver transplantation recipients, in order to drive action for mitigating the risk of non-adherence in these patients. Further studies are warranted in this field to qualitatively assess the causes of NA and support the implementation of interventions focusing on reducing the rates of non-adherence to immunosuppressive treatment in liver transplantation.

## Acknowledgements

The authors thank the Brazilian National Council for Scientific and Technological Development (CNPq)

for funding the research project under, which the thesis for this paper was developed. The thesis was part of a project grant for studying the impact of multi-professional care on adherence in the liver transplantation setting, under CNPq's Universal Bid for Tenders. The main author also thanks CNPq for funding given by the Demanda Social program.

## Collaborations

Oliveira PC, Paglione HB, Silva e Silva V, Schirmer J, and Roza BA state their contribution to the conception of the study, the analysis and interpretation of data, drafting of the paper, relevant critical review of intellectual content, and approval of the final version for publication.

## References

1. Meirelles Júnior RF, Salvalaggio P, Rezende MB, Evangelista AS, Della Guardia B, Matiolo CE Lourenço et al. Transplante de fígado: história, resultados e perspectivas. *einstein* (São Paulo). 2015;13(1):149-52.
2. Castro-e-Silva Jr O, Sankarankutty AK, Oliveira GR, Pacheco E, Ramalho FS, Dal Sasso K. et al. Transplante de fígado: indicação e sobrevida. *Acta Cir Bras*. 2002; 17(Suppl 3):83-91.
3. Paim J, Travassos C, Almeida C, Bahia L, Macinko J. O sistema de saúde brasileiro: história, avanços e desafios. *Lancet*. (Série Brasil). 2011;11-31.
4. Brasil Ministério da Saúde. Portal da Saúde. Transplante [ O Brasil aumenta número de doadores e bate recordes em transplantes [Internet]. Brasília, DF; Ministério da Saúde; 2018. [citado em 2018 Dez 7]. Disponível em: <http://portalms.saude.gov.br/noticias/agencia-saude/44442-brasil-aumenta-doacao-de-orgaos-e-bate-recorde-em-transplantes>
5. Brasil. Ministério da Saúde. Secretaria de Atenção à Saúde. Política Nacional de Transplantes de Tecidos, Órgãos e Partes do Corpo Humano. Lei 9.434/97 regulamentada pelo Decreto 2.268/97. [Internet]. Brasília, DF: Ministério da Saúde; 1997. [citado 2018 Dec 27]. Disponível em: [http://www.planalto.gov.br/ccivil\\_03/decreto/1997/d2268.htm](http://www.planalto.gov.br/ccivil_03/decreto/1997/d2268.htm)
6. Brasil. Ministério da Saúde. Secretaria de Atenção à Saúde. Portaria Nº 712, de 13 de agosto de 2014. Aprova o Protocolo Clínico e Diretrizes Terapêuticas da Imunossupressão no Transplante Renal [Internet]. Brasília, DF, Ministério da Saúde; 2014. [citado 2018 Dez 27]. Disponível em: <http://portal.arquivos.saude.gov.br/images/pdf/2014/agosto/14/IMUNOSSUPRESSAO-TRANSPLANTE-RENAL-MINUTA-Portaria-SAS-PCDT.pdf>
7. Associação Brasileira de Transplante de Órgãos (ABTO). Registro Brasileiro de Transplantes- RBT. 2018: Jan/Dez. Dimensionamento dos Transplantes no Brasil e em cada Estado [Internet]. São Paulo: ABTO; 2018. [citado 2018 Dec 18]. Disponível em: [http://www.abto.org.br/abtov03/Upload/file/RBT/2018/Lv\\_RBT-2018.pdf](http://www.abto.org.br/abtov03/Upload/file/RBT/2018/Lv_RBT-2018.pdf)

8. Martin P, DiMartini A, Feng S, Brown Jr RS, Fallon M. Evaluation for liver transplantation in adults: 2013 Practice Guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. *Hepatology*. 2014;59(3):1144-65.
9. Xu MM, Brown RS Jr. Liver transplantation for the referring physician. *Clin Liver Dis*. 2015;19(1):135-53.
10. Morrissey PE, Flynn ML, Lin S. Medication noncompliance and its implications in transplant recipients. *Drugs*. 2007;67(10):1463-81. Review.
11. Pinsky BW, Takemoto SK, Lentine KL, Burroughs TE, Schnitzler MA, Salvalaggio PR. Transplant outcomes and economic costs associated with patient noncompliance to immunosuppression. *Am J Transplant*. 2009;9(11):2597-606.
12. Morrison A, Stauffer ME, Kaufman AS. Defining medication adherence in individual patients. *Patient Prefer Adherence*. 2015;9:893-7.
13. Oliveira RA, Turrini RNT, Poveda VB. Adherence to immunosuppressive therapy following liver transplantation: an integrative review. *Rev Lat Am. Enfermagem*. 2016; 24:e2778.
14. Correr CJ, Otuki MF, Soler O. Assistência farmacêutica integrada ao processo de cuidado em saúde: gestão clínica do medicamento. *Rev Pan-Amaz Saude*. 2011; 2(3):41-9.
15. Lamba S, Nagurka R, Desai KK, Chun SJ, Holland B, Koneru B. Self-reported non-adherence to immunosuppressant therapy in liver transplant recipients: demographic, interpersonal, and intrapersonal factors. *Clin Transplant*. 2012;26(2):328-35.
16. Dew MA, DiMartini AF, De Vito Dabbs A, Myaskovsky L, Steel J, Unruh M, et al. Rates and risk factors for nonadherence to the medical regimen after adult solid organ transplantation. *Transplantation*. 2007;83(7):858-73.
17. Su GC, Greanya ED, Partovi N, Yoshida EM, Shapiro RJ, Levy RD. Assessing medication adherence in solid-organ transplant recipients. *Exp Clin Transplant*. 2013;11(6):475-81.
18. 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(9):882-91.
19. Dobbels F, Lut B, De Geest S, Drent G, Lennerling A, Whittaker C, Kugler C. Transplant360 Task Force. The psychometric properties and practicability of self-report instruments to identify medication non-adherence in adult transplant patients to date: a systematic review. *Transplantation*. 2010;90(2):205-19.
20. Marsicano EDO, Fernandes NS, Colugnati F, Grincekov FRS, Fernandes NMS, De Geest S, 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 Nephrology*. 2013 14:108.
21. Geest S, Berben L. Editorial. *Acta Paul Enferm*. 2014; 27(3): 4-4.
22. Lima-Costa MF, Barreto SM. Tipos de estudos epidemiológicos: conceitos básicos e aplicações na área do envelhecimento. *Epidemiol Serv Saúde*. 2003; 12(4):189-201.
23. Correia DT, Barbosa A, Mega I, Barroso E, Monteiro E. Adesão nos doentes transplantados. *Acta Med Port*. 2007; 20:73-85.
24. Leite Rf, Silva AC, Oliveira PC, Silva LM, Pestana JM, Schirmer J, et al. Mensuração da adesão aos medicamentos imunossupressores em receptores de transplante renal. *Acta Paul Enferm*. 2018; 31(5):489-96.
25. Burra P, Germani G, Gnoato F, et al. Adherence in liver transplant recipients. *Liver Transpl*. 2011;17:760-70.
26. Neuberger JM, Bechstein WO, Kuypers DR, Burra P, Citterio F, De Geest S, et al. Practical recommendations for long-term management of modifiable risks in kidney and liver transplant recipients: a guidance report and clinical checklist by the Consensus on Managing Modifiable Risk in Transplantation (COMMIT) Group. *Transplantation*. 2017;101:S1-S56.
27. Stillel CS, DiMartini AF, de Vera ME, Flynn WB, King J, Sereika S, et al. Individual and environmental correlates and predictors of early adherence and outcomes after liver transplantation. *Prog Transplant*. 2010; 20:5866.
28. Whitsett M, Levitsky. J Medication adherence in liver transplantation. *Clin Liver Dis*. 2018;10(6):157-60. Review.
29. Eberlin M, Otto G, Krämer I. Increased medication compliance of liver transplant patients switched from a twice-daily to a once-daily tacrolimus-based immunosuppressive regimen. *Transplant Proc*. 2013;45(6):2314-20.
30. Dopazo C, Rodriguez R, Llado L, Calatayud D, Castells L, Ramos E, et al. Successful conversion from twicedaily to once-daily tacrolimus in liver transplantation: observational multicenter study. *Clin Transplant*. 2012;26(1):E32-7.
31. Beckebaum S, Lacob S, Sweid D, Sotiropoulos GC, Saner F, Kaiser G, et al. Efficacy, safety, and immunosuppressant adherence in stable liver transplant patients converted from a twice-daily tacrolimus-based regimen to once-daily tacrolimus extended-release formulation. *Transplant Int*. 2011;24(7):666-75.
32. Toha MR, Teoa V, Kwana YH, Raaja S, Tanc SD, Tan JZY. Association between number of doses per day, number of medications and patient's non-compliance, and frequency of readmissions in a multi-ethnic Asian population. *Prev Med Report*. 2014; 1:43-7.
33. Reber S, Morawa E, Stöbel L, Jank S, Vitinius F, Eckardt K, et al. Prevalence and Modifiable Determinants of Non-Adherence in Adult Kidney Transplant Recipients in a German Sample. *Z Psychosom Med Psychother*. 2016; 62(3):270-83.
34. Brasil. Ministério da Saúde – Secretaria de Ciência, tecnologia e Insumos Estratégicos/CONITEC – Comissão Nacional de Incorporação de Tecnologias no SUS : Protocolo clínico e diretrizes terapêuticas imunossupressão no transplantante hepático em adultos – relatório de recomendação. Agosto 2016 [Internet]. [citado 2018 Maio 8]. Disponível em: conitec.gov.br
35. Staatz CE, Tett SE. Pharmacology and toxicology of mycophenolate in organ transplant recipients: an update. *Arch Toxicol*. 2014; 88(7):1351-89.
36. Vasconcelos AG, Pessoa VL, Menezes FW, Florêncio RS, Frota MX. Repercussões no cotidiano dos pacientes pós-transplante cardíaco. *Acta Pau Enferm*. 2015; 28(6):573-9.
37. Malta DC, Silva MM, Albuquerque GM, Lima CM, Cavalcante T, Jaime PC, et al. A implementação das prioridades da Política Nacional de Promoção da Saúde, um balanço, 2006 a 2014. *Ciênc Saúde Coletiva*. 2014;19(11):4301-12.