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Multilevel correlates of immunosuppressive nonadherence in kidney transplant patients – the multicenter ADHERE BRAZIL study --Manuscript Draft--

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In submitting this form as corresponding author, I confirm that each author agrees with the points checked above and has participated sufficiently in the intellectual content, the analysis of data, if applicable, and the writing of the manuscript to take public responsibility for it. Each author has	Yes

reviewed the manuscript, believes it represents valid work, and approves it for submission. Moreover, should the Editors request the data upon which the manuscript is based, the authors shall produce it.	
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Indicate which figures should be published in color: as follow-up to "Do you have color illustrations? "	Figure 2
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Reporting of all human and animal studies conforms to the following:	Declaration of Helsinki http://www.wma.net/en/30publications/10policies/b3/ ; Declaration of Istanbul http://www.declarationofistanbul.org ; Institutional Review Board
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Abstract:	Background : Immunosuppressive nonadherence is a risk factor for worse outcomes after kidney transplantation (KT). Brazil, having the world's largest public, fully covered transplantation system and the second highest KT volume worldwide, provides a unique setting for studying multilevel correlates of nonadherence (patient, health care provider, transplant center, and health care system levels) independent of patients' financial burden. Methods : By applying a multistage sampling approach, we included 1,105 patients from 20 KT centers. Nonadherence to immunosuppressives (implementation phase) was defined as any deviation in taking or timing adherence and/or dose reduction assessed by the BAASIS © . Based on Bronfenbrenner's ecological model, we assessed multilevel factors using established instruments and measures specifically developed for this study and analyzed their independent	

contribution to nonadherence by performing sequential logistic regression analysis. Results : The nonadherence prevalence rate was 39.7%. The following factors were independently associated with nonadherence: Patient level - having a stable partner (OR:0.75; CI:0.58–0.97), nonadherence to appointments (OR:2.98; IC:2.03–4.39), and nonadherence to physical activity recommendations (OR:1.84; CI:1.38–2.46); and T ransplant center level - satisfaction with the waiting room structure (OR:0.54;CI:0.42–0.71), consultation >30 minutes (OR:1.60; CI:1.19–2.14), adequacy of the consultation frequency (OR:0.62; CI:0.43–0.90), and centers with >500 beds (OR:0.58; CI:0.46–0.73). Conclusions : As the first multicenter study assessing multilevel correlates of nonadherence in KT, our findings point to the need for multilevel interventions beyond the patient level, targeting transplant center practice patterns as an approach to tackle nonadherence.

Juiz de Fora, 25 January 2020

Subject: Revision of MS: TPA-2019-1053 Manuscript, Transplantation.

Dear Editors,

Thank you for your helpful comments and suggestions for improving the quality of our manuscript. We carefully reviewed each comment raised and subsequent questions asked. Below, we provide our point-by-point responses (presented in italics). We include the revised manuscript and a copy in which the changes are indicated in red. We hope that our revisions and responses are acceptable and that the manuscript currently conforms to the standards of *Transplantation Journal*.

Yours sincerely,

Helady Sanders-Pinheiro

On behalf of my co-authors

To the editors

Editor 1

The authors present on a very compelling topic and have generated a large amount of data. However, my major concern is eloquently summarized by Reviewer 2 in the discussion of the application of statistical analysis to the available data. I feel that a revision of the statistical approach might be necessary to drive home the points of this manuscript.

We appreciate the opportunity to address the comments raised by the reviewers. We revised the methodology of the statistical analysis and answered all questions posed. As results of the revision, a new figure was added (Figure 4) and the following files were changed (4): main body, Tables 1 and 2, supplemental digital content, Materials and Methods.

Stats Review

1. The ecologic model utilized is not in the strictest sense a statistical or probabilistic construct and thus does not obviate the need to be cautious in the construction of the model as well as interpretation.

We appreciate this comment and thank the reviewer. Given the wide range of variables collected and their complex dependence structure, the ecologic model was used more as a strategy for multiple modelling rather than a statistical/probabilistic construct, than a statistical/probabilistic construct, as the model talks per se, given that this is not the purpose of GEEs.

In our new approach, variables of the patient and meso levels, which are the two most extensively studied, were divided into blocks, and the proximity of the variable to the analysis unit, i.e., the patient, was used to order the blocks. The patient and micro level variables were analyzed in the following two blocks: individual non-modifiable variables (Block 1) were adjusted first, followed by modifiable patient and micro level variables (behaviors and medication taken) (Block 2). The next block included the opinions and perceptions of the patients regarding the center and aspects of clinical practice from the meso level (Block 3). The last block included variables related to the center infrastructure from meso level and characteristics of the health care system from macro level (Block 4). This last block included center and health system variables

that did not vary among patients recruited from the same center. This approach is commonly used in epidemiologic studies, and disseminated by Victora et al. (Victora CG, Huttly SR, Fuchs SC, et al. The role of conceptual frameworks in epidemiological analysis: A hierarchical approach. *Int J Epidemiol.* 1997;26(1):224-227).

We described this new approach in the Materials and Methods on page 13, lines 7-11 as follows:

“Following the ecological model, a hierarchical approach was used for the analysis of multilevel correlates.⁴⁹ This approach adopted a forward-driven variable selection method grouped in blocks considering the proximity of the variable levels to the patient in a causal theoretic framework and the potential of modifiability by clinical practice.”

Additional revisions were applied in the Materials and Methods on page 13, lines 18-22 and page 14, lines 1-10 as follows:

“For variable selection, we followed recent recommendations regarding statistical significance evaluation and used a mixed approach considering 95% confidence intervals, p-values, and effect sizes.^{51,52} However, for multiple model variable selection, given the large number of variables and probability of increased false discovery rate (FDR), we adopted this approach to correct p-values, so-called q-values,⁵³ using Bonferroni correction.

The modeling scheme sequentially included a blockwise entry of a group of variables. We started with variables related to the patient level, including non-modifiable (Block 1) and modifiable variables at patient-level plus micro level variables (Block 2). In Block 3, we included opinions/perceptions of patients regarding the center and aspects of clinical practice from meso level. The final block, Block 4, included variables of center infrastructure from meso level and characteristics of health care system from macro level (Tables 1 and 2). Variables showing OR with 95% confidence interval (CI) not including 1.00 and variables with a CI including 1 but a q-value smaller than 0.10 and an effect of 25% or more (for increased or decreased chance) were included in each block analysis.^{51,54} The same criteria were used to maintain the variables each time a new block was adjusted, this turn using p-value, by hand made selection.”

The reviewers bring up excellent points that need to be addressed:

1. Given 64 variables and four spaces, was a P value based selection of variables appropriate? Given the above was any need for correction for false discovery utilized?

The set of potential variables were reviewed, 11 were excluded, and 53 variables were retained for bivariate analysis (Table 1, Supplemental Digital Content, Materials and Methods). The variable choice for modelling was not exclusively based on the p-value. In fact, it involved a combination of thresholds for p-values/q-values (explained below), effect sizes, being Odds Ratio adopted. The same criteria were applied after each block adjustment, but this time, the selection was based on the p-value of the adjusted model.

This strategy is consistent with the new statement of the American Statistician Society for testing associations and was recently noted as a truly adequate approach for model selection for testing associations as stated by Goodman et al. (Goodman WM, Spruill SE, Komaroff E. A Proposed Hybrid Effect Size Plus p -Value Criterion: Empirical Evidence Supporting its Use, The American Statistician.2019;73:sup1, 168-185, DOI: 10.1080/00031305.2018.1564697) and the previous literature concerning statistics and epidemiology. Although the original analysis of this manuscript was performed before Goodman's article, this approach is regularly used by our research group given its use in epidemiological studies as described by Victora et al. (Victora CG, Huttly SR, Fuchs SC, et al. The role of conceptual frameworks in epidemiological analysis: A hierarchical approach. Int J Epidemiol. 1997;26(1):224-227) and the ASA 2016 statement regarding the misuse of the p-value (Wasserstein RL & Lazar NA. The ASA Statement on p-Values: Context, Process, and Purpose, The American Statistician.2016;70:2, 129-133, DOI: 10.1080/00031305.2016.1154108).

Additionally, this adjustment was manually performed rather than automatically performed by an algorithm. Following each block variable adjustment, eligibility to withdraw variables from the model considered the association/collinearity among the variables, the conceptual model, and analyzing changes in the Odds Ratio and p-values on models with and without a given variable. This approach is also used for mediation variables assessment as stated by VanderWeele et al. (VanderWeele TJ, Vansteelandt S. Odds ratios for mediation analysis for a dichotomous outcome. Am. J. Epidemiol. 2010;172:1339-48).

However, the reviewers raised an important point regarding the false discovery rate (FDR), and after consulting the biostatistician, a q-value approach was adopted for the bivariate analysis and, consequently, for the variable selection for the multivariate analysis. The q-value is an “adjusted p-value” for multiple comparison tests introduced by Smyth and the R Core Team (Smyth, G., and the R Core Team. 2010. p. adjust. Part of the R package stats. <http://www.r-project.org/>) implemented in R and Stata (Newson RB. Frequentist q-values for multiple-test procedures. *The Stata Journal*.(2010;10(4):568–584). We used the Bonferroni correction.

Q-values were generated for each block of variables and the whole set. The selection criteria using q-values were <0.05 (95% CI not including 1.00) or <0.10 AND Odds ratio (OR) ≥ 1.25 or $OR \leq 0.75$ and handmade consideration of potential associations/collinearity as previously explained.

The description of the variable criteria was revised, and the option of using the q-value was included in the text as stated above.

Materials and Methods on page 13, lines 18-22 and page 14, lines 1-10:

“For variable selection, we followed recent recommendations regarding statistical significance evaluation and used a mixed approach considering 95% confidence intervals, p-values, and effect sizes.^{51,52} However, for multiple model variable selection, given the large number of variables and probability of increased false discovery rate (FDR), we adopted this approach to correct p-values, so-called q-values,⁵³ using Bonferroni correction.

The modeling scheme sequentially included a blockwise entry of a group of variables. We started with variables related to the patient level, including non-modifiable (Block 1) and modifiable variables at patient-level plus micro level variables (Block 2). In Block 3, we included opinions/perceptions of patients regarding the center and aspects of clinical practice from meso level. The final block, Block 4, included variables of center infrastructure from meso level and characteristics of health care system from macro level (Tables 1 and 2). Variables showing OR with 95% confidence interval (CI) not including 1.00 and variables with a CI including 1 but a q-value smaller than 0.10 and an effect of 25% or more (for increased or decreased chance) were included in each block analysis.^{51,54} The same criteria were used to

maintain the variables each time a new block was adjusted, this turn using p-value, by hand made selection.”

2. Given large center differences, were same factors found in each center? If so, why the difference and given wide disparity does the mean have relevance?

This study was not designed to provide valid estimates of the nonadherence prevalence in each center. The broad range of nonadherence percentages observed must not be interpreted as prevalence rates, and this information was removed from the text (Abstract and Results) and substituted with the 95% CI of the overall prevalence. Thus, we cannot assume this presented range as actual differences in the outcome.

Results, page 15, lines 14-15. “Overall implementation immunosuppressive nonadherence was 39.7%, 95% CI (36.8-42.6).”

The differences among centers and their impact on nonadherence prevalence were the subject matter of this study. The sampling strategy aimed to obtain a sample that is as representative of the country as possible; thus, the number of patients included from each center was based on a combination of the geographical localization and center activity.

The GEE approach was adopted to attempt to determine a possible intra-cluster correlation, and in case this observable or non-observable differences actually impacts, a moderate to strong correlation structure would be estimated. However, using an exchangeable structure approaches for the correlation matrix for the adjusted models, the coefficients varies between 0.01 to 0.02, and the estimates of the standard errors of the model coefficients did not differ from the independent structure.

3. It is unclear what 64 variables were initially chosen? How were they chosen?

As stated above, we determined the variables to be studied based on the ecological model and previously published studies (all cited as references). As stated above, after your suggestion, the decision criteria for including a variable in the multivariate analysis using q-values were $q < 0.05$ (95% CI not including 1.00) or < 0.10 AND $OR \geq 1.25$ or $OR \leq 0.75$ and handmade consideration of potential associations/collinearity.

The description of the variable criteria was revised, and the option of using the q-value was included in the text.

Materials and Methods on page 13, lines 18-22 and page 14, lines 1-10:

“For variable selection, we followed recent recommendations regarding statistical significance evaluation and used a mixed approach considering 95% confidence intervals, p-values, and effect sizes.^{51,52} However, for multiple model variable selection, given the large number of variables and probability of increased false discovery rate (FDR), we adopted this approach to correct p-values, so-called q-values,⁵³ using Bonferroni correction.

The modeling scheme sequentially included a blockwise entry of a group of variables. We started with variables related to the patient level, including non-modifiable (Block 1) and modifiable variables at patient-level plus micro level variables (Block 2). In Block 3, we included opinions/perceptions of patients regarding the center and aspects of clinical practice from meso level. The final block, Block 4, included variables of center infrastructure from meso level and characteristics of health care system from macro level (Tables 1 and 2). Variables showing OR with 95% confidence interval (CI) not including 1.00 and variables with a CI including 1 but a q-value smaller than 0.10 and an effect of 25% or more (for increased or decreased chance) were included in each block analysis.^{51,54} The same criteria were used to maintain the variables each time a new block was adjusted, this turn using p-value, by hand made selection.”

4. Were the confounders validated in an external set? or even between centers in a formal way?

We believe that this comment is based on the previous interpretation of the modelling as a machine learning approach. We hope that we clarified this misunderstanding.

5. It would be beneficial to describe the ecologic construct and separate it out from the statistical analysis as much as possible. The different spaces still each require a formal statistical analysis and the ecologic model is more a framework of multilevel factors (originally in Psychology) that each influence behavior.

As stated above, given the wide range of variables collected and their complex dependence structure, the ecologic model was used more as a strategy for multiple modelling rather than a statistical/probabilistic construct as the model talks per se, given that this is not the purpose of GEEs, a population average estimation.

Concerning the comments from **Referee 1**:

We thank you for your comments and suggestions for strengthening our paper.

This is an interesting study regarding correlates of immunosuppressive non-adherence in renal transplant recipients in Brazil; we appreciate your submission to Transplantation. A few additional comments:

1. In the introduction, would encourage the authors to describe detrimental effects of nonadherence - rejection and its related morbidity/mortality and cost to the federally funded system. The brief literature review in the introduction is nice, but should probably be reserved for the discussion section. In the introduction would instead focus on the magnitude of the problem and potential impact of a solution versus describing what already has been done. The last two paragraphs are nice.

We believe that the innovative aspect of our study is the proposed framework of the multilevel variables associated with nonadherence, i.e., the ecological model. We think that it is important to introduce this concept and the limited evidence already available to explain why we chose this methodology. Indeed, we fully agree regarding the detrimental effect of nonadherence on graft survival and increased costs. We changed the first paragraph and included more information as you suggested.

Introduction, page 8, lines 2-6. *“Nonadherence to immunosuppressive therapy is a major risk factor for poor clinical and economic outcomes following kidney transplantation (KT). Fifteen to 60% of late acute rejections, 35-45% of graft loss, and, thus, increased costs occur as a consequence of nonadherence. Therefore, decreasing nonadherence is a potential avenue to improve these unfavorable results.¹⁻⁵”*

2. - Interesting that the consent came from the center's director - was there any bias

in which centers chose versus chose not to participate? Did centers invited to participate but did not participate have poorer outcomes?

The centers were chosen by convenience, but we aimed to obtain a sample as representative as possible of the country regions and size of centers. We invited 21 centers, and only one center refused to participate. The survival individual rates are not available in Brazil for such an analysis.

3. Unclear of term- 'adult attending' KT recipients.

Only patients who attended office visit were randomly chosen. We used this term to clarify how the selection was performed. We provided more detail in the Materials and Methods, page 12, lines 16-17.

“Patients scheduled for a regular outpatient clinic appointment in the KT center were randomly selected.”

We also cited this type of patient selection as a limitation in the Discussion on page 21, lines 20-22; page 22, lines 1-6, as follows: *“Second, we randomly selected patients scheduled for routine visits and further included only attendees. This strategy was used to effectively collect data. However, patients visit KT centers every six months at most, and the average data collection time was 6.5 months (data not shown), allowing for all followed patients to be randomly selected. Approximately half of the included patients underwent a transplantation over five years ago, which allowed us to evaluate both patients recently living with a KT and surviving patients who adapted to all aspects of immunosuppressive treatment.”*

4. Information of second to last paragraph in 2.1 Design section about Brazil's emerging economy, etc is redundant to what is stated in the introduction.

We opted to provide more detailed information regarding the health system where the study was conducted because it is a recommendation of the EMERGE guidelines (De Geest S, Zullig LL, Dunbar-Jacob J, et al. ESPACOMP Medication Adherence Reporting Guideline (EMERGE). Ann Intern Med. 2018;169(1):30–35. doi:10.7326/M18-0543). This recently published guideline for a best reporting practices aims to enhance and harmonize

research reporting adherence and consequently advance research and patient outcomes.

5. Bronfenbrenner's model is an interesting concept and the authors should explain more about this framework for the general audience; there are many variables - almost a shot gun approach (64 variables!) and a devil's advocate would argue that of course a few variables reached significance in the model.

Our objective was to explore variables at different levels that could be associated with nonadherence. For the first time, variables related to clinical practice were studied. However, the model is still not ideal. This concern is already reported as a limitation indicating that this field needs further exploration.

Discussion, page 22, lines 13-16. “Notably, another very relevant point is the variable corollary included in our multilevel analysis, in which the assessment of behavioral factors, such as health literacy, barriers and beliefs, and aspects of the chronic illness care model were limited. Research in this field has only recently begun, and we further need to explore what is indeed relevant.”

We also critically reviewed the variables and reduced to 53 variables distributed across the four levels. We first conducted a bivariate analysis of each variable and then chose the variables to include in the multivariable analysis; only variables presenting association, quoted by a 95% confidence interval (CI) not including 1.00 ($q < 0.05$) or q -value < 0.10 and an effect of 25% ($OR \geq 1.25$ or ≤ 0.75) were included. Eleven variables (Block 1 – 02, Block 2 – 02, Block 3 – 05, and Block 4 – 02) met the association criteria to compose the analysis of our final model (Tables 1 and 2, Figure 4). The multivariate analysis was performed in 4 blocks based on the levels of the ecological model and the variable's potential to be modifiable. This method was better described in the Materials and Methods on page 13, lines 18-22 and page 14, lines 1-10 and Table 2.

“For variable selection, we followed recent recommendations regarding statistical significance evaluation and used a mixed approach considering 95% confidence intervals, p-values, and effect sizes.^{51,52} However, for multiple model variable selection, given the large number of variables and probability of increased

false discovery rate (FDR), we adopted this approach to correct p-values, so-called q-values,⁵³ using Bonferroni correction.

The modeling scheme sequentially included a blockwise entry of a group of variables. We started with variables related to the patient level, including non-modifiable (Block 1) and modifiable variables at patient-level plus micro level variables (Block 2). In Block 3, we included opinions/perceptions of patients regarding the center and aspects of clinical practice from meso level. The final block, Block 4, included variables of center infrastructure from meso level and characteristics of health care system from macro level (Tables 1 and 2). Variables showing OR with 95% confidence interval (CI) not including 1.00 and variables with a CI including 1 but a q-value smaller than 0.10 and an effect of 25% or more (for increased or decreased chance) were included in each block analysis.^{51,54} The same criteria were used to maintain the variables each time a new block was adjusted, this turn using p-value, by hand made selection.”

6. Previous research has demonstrated that health literacy plays a critical role in medical adherence; were the authors able to measure a variable that may have served as a proxy for health literacy?

Unfortunately, we did not evaluate health literacy. Some variables at the patient level were not studied. We included health literacy in the corollary of the variables not included as a limitation of the study. Discussion, page 22, lines 13-16. “Notably, another very relevant point is the variable corollary included in our multilevel analysis, in which the assessment of behavioral factors, such as health literacy, barriers and beliefs, and aspects of the chronic illness care model were limited. Research in this field has only recently begun, and we further need to explore what is indeed relevant.”

7. What was the setting of administration of surveys? Were surveys administered by staff who may have 'pressured' respondents to provide favorable comments?

The patient surveys were administered during regular outpatient clinic appointments by a trained local coordinator. Misinformation is a limitation of using surveys as a data collection method. In 65% of the centers, the coordinator was a part of the care team. However, in 75% of the cases, the coordinators were nurses or pharmacists, i.e.,

professionals who patients usually feel more comfortable to inform. We included this information accordingly. Materials and Methods section, page 12, line 18-21. “The BAASIS^{28,34} and other instruments were applied by an interview by trained local research coordinators (65% part of the care team; 75% nurses/pharmacists), who also extracted clinical data from patient medical files using structured forms.”

8. An important finding to emphasize is that patient factors only explained 10% of variability - the authors should further offer solutions nonadherence for centers and the system.

Even after the new statistical analysis, the patient-related factors only explained 8.4% of the variability. In this type of study exploring behaviors, this is a common feature as reported in the BRIGHT study. We already included a paragraph in the Discussion about how our findings suggest strategies to decrease nonadherence. We changed this text to enhance clarity.

Discussion, page 18, lines 15-21.

“Our final model explained 16.5% of the variability of nonadherence, and meso level factors contributed significantly. The extent to which the final model explains the variability, albeit leaving room for further optimization,^{1,60} is similar to that reported in the BRIGHT study.⁸ Further enhancement of the explanatory power of the models is needed, and more focus on non-patient related factors is warranted in future research as multi-level factors also explain some of the variance not previously studied.”

Discussion, page 21, lines 1-19.

“Since multilevel factors are associated with nonadherence in KT and nonadherence is a risk factor for poor graft outcomes, strategies to reduce nonadherence should include actions at the patient, micro, meso, and macro levels. Interventions at all levels of healthcare have been previously proposed to be relevant.^{7,60} Limited evidence has shown that measures effective in reducing nonadherence in KT involve complex multiple dimensions actions. Benefits include tailored patient education (patient level), coordinated actions to increase social support (micro level) and self-care management by improved nursing care or additional pharmaceutical attention (meso level).^{7,11,60} Similar to some other chronic

diseases, financial help or advice regarding easier access to immunosuppressives (macro level) have been proven to be effective.^{7,11,78} However, high-quality studies call attention to the need for interventions that could be integrated into daily care and aim to improve clinical outcomes beyond adherence to treatment.^{7,10,78} Considering our results, we can speculate how centers should change their care to decrease nonadherence. The finding that having a steady partner is negatively associated with nonadherence provides a clue for the identification of patients at risk and support measures to improve social support, such as educative groups. The association with missing appointments and being physically inactive direct measures to improve self-monitoring and self-efficacy, such as multidisciplinary care involving psychologists and physical educators. Finally, the patients' perception of the adequacy of the proposed routine care schedule points out to develop individualized care."

9. This reviewer enjoyed the multi-level conceptual model to assess nonadherence - congratulations to the authors. For the discussion, would move away from only describing the results of the study versus using them as an impetus for change at the policy level. Can the authors offer potential solutions? How can the negative predictors be better tied together to explain nonadherence in general? For (extreme) examples, should we only transplant patients if they have stable partners? Should all centers improve their waiting rooms?

As stated above, we already changed the paragraph according to you suggestion.

Discussion, page 21, lines 1-19.

"Since multilevel factors are associated with nonadherence in KT and nonadherence is a risk factor for poor graft outcomes, strategies to reduce nonadherence should include actions at the patient, micro, meso, and macro levels. Interventions at all levels of healthcare have been previously proposed to be relevant.^{7,60} Limited evidence has shown that measures effective in reducing nonadherence in KT involve complex multiple dimensions actions. Benefits include tailored patient education (patient level), coordinated actions to increase social support (micro level) and self-care management by improved nursing care or additional pharmaceutical attention (meso level).^{7,11,60} Similar to some other chronic

diseases, financial help or advice regarding easier access to immunosuppressives (macro level) have been proven to be effective.^{7,11,78} However, high-quality studies call attention to the need for interventions that could be integrated into daily care and aim to improve clinical outcomes beyond adherence to treatment.^{7,10,78} Considering our results, we can speculate how centers should change their care to decrease nonadherence. The finding that having a steady partner is negatively associated with nonadherence provides a clue for the identification of patients at risk and support measures to improve social support, such as educative groups. The association with missing appointments and being physically inactive direct measures to improve self-monitoring and self-efficacy, such as multidisciplinary care involving psychologists and physical educators. Finally, the patients' perception of the adequacy of the proposed routine care schedule points out to develop individualized care."

Concerning the comments by **Referee 2**:

We thank you for your comments and suggestions for strengthening our paper.

OVERVIEW:

Nonadherence to immunosuppression medication is a modifiable risk factor for graft loss and poor graft outcomes. However, most studies have investigated patient-level and socio-demographic-related factors. The authors investigated a multilevel correlates of nonadherence (patient, health care provider, transplant center, and health care system levels) independent of the patient-level financial burdens. The article provides some insight on the multilevel factors associated with medication nonadherence. However, the authors appear to use a form of machine learning and machine-driven model selection to determine which factors remained in the final model and do not provide sufficient details as to why other factors were eliminated. While machine learning and machine-driven model building is a unique technique for large databases, the method can yield 'weird' associations that do not have any clinical significance and may not be modifiable. The authors should revise the model selection methodology and provide more details on why some factors were considered and others excluded for consideration in the final model. Additionally, while the reviewers

appreciate that the previous work of the authors, this article is still missing some information that, even if stated in previous articles, should be reported, succinctly, as well. More details on this and other minor comments below.

ABSTRACT

The abstract is well written, succinct, and details in each section are sufficient.

We thank you for your comment.

INTRODUCTION

Minor

1. The authors need to rephrase the research aim and hypothesis to clarify that this study was conducted among kidney transplant recipients.

The information is included as suggested.

Introduction, page 10, lines 3-7.

“Therefore, the aim of the ADHERE BRAZIL study is to assess the prevalence and multilevel correlates of nonadherence to immunosuppressives (implementation phase) in kidney transplanted patients in a full-coverage health care system. We hypothesize that multilevel factors, at patient, healthcare provider, healthcare service, and health policy levels, correlate to nonadherence to immunosuppressives in this population.”

METHODS

Major

3. As mentioned above, the modelling strategy described by the authors seems to be computer-generated based on the variance-covariance matrix, instead of using factors determined ad hoc. It is unclear from the text or Table 1 which factors were considered for model building and the reasoning to include/exclude certain factors (such as excluding 'acute rejection' or 'tips for remembering to take immunosuppressives'). Additionally, it is unclear why micro and macro blocks (levels) were excluded from the model building because there seem to be sufficient variation and sample within some (maybe not all) of the variables.

The set of potential variables was reviewed, 11 were excluded, and 53 variables were retained for the bivariate analysis ([Table 1, Supplemental Digital Content, Materials and Methods](#)). The variable choice for the modelling was not exclusively based on the p-value and included a combination of thresholds for p-values/q-values (explained below), effect sizes, and Odds Ratio. The same criteria were applied after each block adjustment, and this time, the selection was based the on p-value from the adjusted model.

*This strategy is consistent with the new statement of the American Statistician Society for testing associations and was recently noted as a truly adequate approach for model selection for testing associations as stated by Goodman et al. (Goodman WM, Spruill SE, Komaroff E. A Proposed Hybrid Effect Size Plus p -Value Criterion: Empirical Evidence Supporting its Use, *The American Statistician*.2019;73:sup1, 168-185, DOI: 10.1080/00031305.2018.1564697) and the previous literature concerning statistics and epidemiology. Although the original analysis of this manuscript was performed before Goodman’s article, this approach is regularly used by our research group given its use in epidemiological studies as described by Victora et al. (Victora CG, Huttly SR, Fuchs SC, et al. The role of conceptual frameworks in epidemiological analysis: A hierarchical approach. *Int J Epidemiol*. 1997;26(1):224-227) and the ASA 2016 statement regarding the misuse of the p-value (Wasserstein RL & Lazar NA. The ASA Statement on p-Values: Context, Process, and Purpose, *The American Statistician*.2016;70:2, 129-133, DOI: 10.1080/00031305.2016.1154108).*

*Additionally, this adjustment was manually performed rather than automatically performed by an algorithm. Following each block variable adjustment, eligibility to withdraw variables from the model considered the association/collinearity among the variables, the conceptual model, and analyzing changes in the Odds Ratio and p-values on models with and without a given variable. This approach is also used for mediation variables assessment as stated by VanderWeele et al. (VanderWeele TJ, Vansteelandt S. Odds ratios for mediation analysis for a dichotomous outcome. *Am. J. Epidemiol*. 2010;172:1339–48).*

However, the reviewers raised an important point regarding the false discovery rate (FDR), and after consulting the biostatistician, a q-value approach was adopted for the bivariate analysis and, consequently, for the variable selection for the multivariate analysis. The q-value is an “adjusted p-value” for multiple comparison tests introduced by Smyth and the R Core Team (Smyth, G., and the R Core Team. 2010. p. adjust. Part of the R

package stats. <http://www.r-project.org/>) implemented in R and Stata (Newson RB. Frequentist q-values for multiple-test procedures. *The Stata Journal*.(2010;10(4):568–584). We used the Bonferroni correction.

Q-values were generated for each block of variables and the whole set. The selection criteria using q-values were <0.05 (95% CI not including 1.00) or <0.10 AND Odds ratio (OR) ≥ 1.25 or $OR \leq 0.75$ and handmade consideration of potential associations/collinearity as previously explained.

In summary, we first performed a bivariate analysis of each variable and then selected only variables which presented association, quoted by 95% confidence interval (CI) not including 1.00 ($q < 0.05$) or q-value < 0.10 and an effect of 25% ($OR \geq 1.25$ or ≤ 0.75) for inclusion in the multivariable analysis. Eleven variables reached the association criteria and were included in the analysis of our final model. The multivariate analysis was performed in blocks based on the levels of the ecological model and its potential to be modifiable. This methodology was better described in the Materials and Methods on page 13, lines 18-22 and page 14, lines 1-10 and Table 2.

“For variable selection, we followed recent recommendations regarding statistical significance evaluation and used a mixed approach considering 95% confidence intervals, p-values, and effect sizes.^{51,52} However, for multiple model variable selection, given the large number of variables and probability of increased false discovery rate (FDR), we adopted this approach to correct p-values, so-called q-values,⁵³ using Bonferroni correction.

The modeling scheme sequentially included a blockwise entry of a group of variables. We started with variables related to the patient level, including non-modifiable (Block 1) and modifiable variables at patient-level plus micro level variables (Block 2). In Block 3, we included opinions/perceptions of patients regarding the center and aspects of clinical practice from meso level. The final block, Block 4, included variables of center infrastructure from meso level and characteristics of health care system from macro level (Tables 1 and 2). Variables showing OR with 95% confidence interval (CI) not including 1.00 and variables with a CI including 1 but a q-value smaller than 0.10 and an effect of 25% or more (for increased or decreased chance) were included in each block analysis.^{51,54} The same criteria were used to

maintain the variables each time a new block was adjusted, this turn using p-value, by hand made selection.”

4. The authors seem to have knowledge, or ability to determine, time since transplant but did not consider this variable for the descriptive statistics or in the model. Please explain why this variable was not reported and considered for the model. If the authors choose to not include this variable, they should list the exclusion of this variable in the limitations.

This variable was evaluated; this information is reported in Table 1 and Supplemental Digital Content, Materials and Methods. One inclusion criterion for the patients was having >1-year post-transplant because we wanted to evaluate patients living longer with their grafts, who experienced the benefits of reduced morbidity of end stage chronic kidney disease and were supposedly adapted to this new life. We categorized this variable as until or more than 5 years post transplantation.

Materials and Methods, page 10, lines 21-22. “Inclusion criteria for the patients were as follows: >1 year post-transplant, ability to understand the objectives of the study, and written informed consent.³³”

The randomly selected sample consisted of approximately half of the studied patients in each category. This information was not included in the multivariate analysis because it did not present the level of association for selection. We stated this aspect as a limitation.

Discussion, page 22, lines 2-5.

“Approximately half of the included patients underwent a transplantation over five years ago, which allowed us to evaluate both patients recently living with a KT and surviving patients who adapted to all aspects of immunosuppressive treatment.”

5. The authors should provide more details on the collection of center-level data that describes how the transplant center representative was selected, what their role was, and when the center-level data collection took place.

We thank you for this comment. The requested information was added.

Materials and Methods, page 12, lines 21-22; page 13, lines 1-2. “Regarding center-level data, a nominated representative of the transplant center (45% nephrologists, 45% transplant nurses, and 10% pharmacists) completed the structured questionnaire using the RedCap system during the same period of patient data collection.³³”.

6. Was there any correlation test performed between variables at different levels? For example, there may be a significant correlation between education, familiar income, and the center's number of beds (possibly a larger center is in a more affluent neighborhood) and the inclusion of correlated factors would skew the analysis.

We thank you for this relevant comment. The strategy adopted for the model selection, handmade, allowed us to address this issue by modifications of the estimates when the variables were adjusted together given their association or even small frequency effects, which in general overestimate point estimates, but provide wide range 95% CI. This approach is also used for mediation variable assessments as stated by VanderWeele et al. (VanderWeele TJ, Vansteelandt S. Odds ratios for mediation analysis for a dichotomous outcome. Am. J. Epidemiol. 2010;172:1339–48).

7. For missing data at the patient-level, which variables were missing? The current statement on missing data is insufficient and needs further explanation on how missing data was handled. If multiple imputation was not used, then the statistical software defaulted to using complete case analysis, which should be stated in the statistical analysis.

We had a few missing data points (only 8/1105, 0.07%). Because missing data were rare, we performed a complete case analysis. This information was included.

Materials and Methods, page 14, lines 17-20. “We found no missingness in center-level variables, and we rarely observed missingness at patient level (median 0%, range: 0-1.8%; IQR: 0.18%; 99.7% of variables: <1%). Based on these findings, we decided to not proceed with imputation, and then complete case analysis was applied.”

Minor

8. Page 11, line 10-20: This paragraph can be removed because it is redundant to the Introduction.

We opted to provide more detailed information regarding the health system where the study was conducted because it is a recommendation of the EMERGE guidelines (De Geest S, Zullig LL, Dunbar-Jacob J, et al. ESPACOMP Medication Adherence Reporting Guideline (EMERGE). Ann Intern Med. 2018;169(1):30–35. doi:10.7326/M18-0543). This recently published guideline for best reporting practices aims to enhance and harmonize research reporting adherence and, consequently, advance research and patient outcomes.

9. What are the 'operational issues' that precluded participant interviews from being conducted?

Only patients who attended office visits were randomly chosen. Local, trained health professionals who volunteered to participate in the study conducted the data collection. Occasionally, the patient interview took too much time, precluding the opportunity to randomly selected other patients to be interviewed. We arbitrarily chose to name such issues operational issues.

RESULTS

Major

10. The authors report that nonadherence ranged from 11-65.2% which is a large range. I would strongly encourage the authors to report a comparison table of centers (possibly stratified by nonadherence quartiles) to show how similar or different a center with 11% nonadherence is from a center with 65.2% nonadherence.

This study was not designed to provide valid estimates of the nonadherence prevalence at each center. The differences among the centers and their impact on the nonadherence prevalence were the subject matter of the study. Furthermore, the adopted sampling strategy aimed to represent the country and was based on geographic region and center transplant activity. The broad range of nonadherence

percentages observed must not be interpreted as prevalence, and this information was removed the text and substituted by the 95% CI of the overall prevalence.

Results, page 15, lines 14-15. **“Overall implementation immunosuppressive nonadherence was 39.7%, 95% CI (36.8-42.6).”**

The adopted GEE approach attempted to capture possible intra-cluster correlations among the centers. In case this observable or non-observable differences actually have an impact, a moderate to strong correlation structure would be estimated by the method. However, using an exchangeable structure approach for the correlation matrix for the adjusted models, the coefficients slightly varied, and the estimates of the standard errors of the model coefficients did not significantly differ from the independent structure. Thus, heterogeneity exists among the centers, but its magnitude did not play a very strong role in the nonadherence prevalence; thus, these data do not support the suggested analysis.

Minor

11. Please list out the three meso factors kept in the model.

We thank you for your comment. After applying the new statistical approach suggested by the reviewers, four meso level factors remained in the final model. We changed the text accordingly. This information is also listed in Table 2.

Results, page 15, line 22; page16, lines 1-17. **“The two variables included in Block 1 (patient level, non-modifiable), age and having stable partner, were retained in the analysis. After the inclusion of variables of Block 2 (patient level – modifiable and micro level), nonadherence to appointment keeping and nonadherence to physical activity recommendations remained. From Block 3 (Meso level, patients’ perceptions of care) three new variables were selected: patient’s satisfaction with waiting room structure, consultation frequency and time of consultation. From Block 4, only the hospital size was retained. Thus, our final model, derived from 53 variables, included seven independent correlates of implementation immunosuppressive nonadherence. Three factors, namely, nonadherence to appointment keeping (OR 2.98; 95% CI:2.03–4.39); nonadherence to physical activity recommendations (OR 1.84; 95% CI:1.38–2.46), and a longer office visit duration (30 minutes) (OR 1.58; 95% CI:1.15–2.17), were positively associated with immunosuppressive**

nonadherence. Four factors were negatively associated: having a stable partner (OR 0.75; 95% CI:0.58–0.97), satisfaction with the waiting room structure (OR 0.54; 95% CI:0.42–0.71), the patients’ perceived adequacy of the consultation frequency (OR 0.62; 95% CI:0.43–0.90), and the number of beds in the transplant center hospital (>500 beds) (OR 0.58; 95% CI:0.46–0.73) (Table 2, Figure 4). This final model explained 16.5% of the variability of immunosuppressive nonadherence. Patient-related factors explained only 8.4% of the variability (Table 2).”

DISCUSSION

12. The authors need to discuss the major limitation of survival bias in their study. The authors need to discuss that the patients that were possible the most nonadherent were the patients that were not alive post-transplant to be surveyed. This limitation is common to cross-sectional studies. Although the sample includes surviving patients, inferences between the main outcome (nonadherence) and graft survival should be made with caution.

This aspect of the sample was stated in a paragraph discussing the limitations. Discussion, page 21, line 20.

“As limitations, a cross-sectional study design did not allow causal inferences.”

Discussion, page 22, lines 2-5.

“Approximately half of the included patients underwent a transplantation over five years ago, which allowed us to evaluate both patients recently living with a KT and surviving patients who adapted to all aspects of immunosuppressive treatment.”

TABLES/FIGURES

Minor

13. Table 1 should be reformatted to include headers for the patient- and center-level reported variables. The current format using (*) and (#) are confusing and hard to read.

Table 1 was changed as suggested.

**Multilevel correlates of immunosuppressive nonadherence in kidney transplant patients –
the multicenter ADHERE BRAZIL study**

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Clinical trial notation: ClinicalTrials.gov on 10/10/2013, NCT02066935.

Authorship

All authors participated in the research design, revision process, and final approval of the manuscript.

H.S. participated in the writing of the first version of the paper.

H.S. and E.O.M. participated in the performance of the research.

F.A.B.C. and K.D. participated in the data analysis.

Disclosure

The authors of this manuscript have no conflicts of interest to disclose.

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Abbreviations

BAASIS®, The Basel Assessment of Adherence to Immunosuppressive Medications Scale

BRIGHT, Building Research Initiative Group: Chronic Illness Management and Adherence in Transplantation study

CI, Confidence interval

ERB, Ethics research board

GEE, Generalized estimating equations

KT, Kidney transplant

OR, Odds ratio

RedCap, Research Electronic Data Capture

SD, Standard deviation

Abstract

Background: Immunosuppressive nonadherence is a risk factor for worse outcomes after kidney transplantation (KT). Brazil, having the world's largest public, fully covered transplantation system and the second highest KT volume worldwide, provides a unique setting for studying multilevel correlates of nonadherence (patient, health care provider, transplant center, and health care system levels) independent of patients' financial burden. **Methods:** By applying a multistage sampling approach, we included 1,105 patients from 20 KT centers. Nonadherence to immunosuppressives (implementation phase) was defined as any deviation in taking or timing adherence and/or dose reduction assessed by the BAASIS[®]. Based on Bronfenbrenner's ecological model, we assessed multilevel factors using established instruments and measures specifically developed for this study and analyzed their independent contribution to nonadherence by performing sequential logistic regression analysis. **Results:** The nonadherence prevalence rate was 39.7%. The following factors were independently associated with nonadherence: *Patient level* - having a stable partner (OR:0.75; CI:0.58–0.97), nonadherence to appointments (OR:2.98; IC:2.03–4.39), and nonadherence to physical activity recommendations (OR:1.84; CI:1.38–2.46); and *Transplant center level* - satisfaction with the waiting room structure (OR:0.54; CI:0.42–0.71), consultation >30 minutes (OR:1.60; CI:1.19–2.14), adequacy of the consultation frequency (OR:0.62; CI:0.43–0.90), and centers with >500 beds (OR:0.58; CI:0.46–0.73). **Conclusions:** As the first multicenter study assessing multilevel correlates of nonadherence in KT, our findings point to the need for multilevel interventions beyond the patient level, targeting transplant center practice patterns as an approach to tackle nonadherence.

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7 **Keywords:** clinical decision-making, clinical research/practice, medication nonadherence,
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9 kidney transplantation/nephrology, immunosuppression/immune modulation, multilevel
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11 analysis
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1 Introduction

Nonadherence to immunosuppressive therapy is a major risk factor for poor clinical and economic outcomes following kidney transplantation (KT). Fifteen to 60% of late acute rejections, 35-45% of graft loss, and, thus, increased costs occur as a consequence of nonadherence. Therefore, decreasing nonadherence is a potential avenue to improve these unfavorable results.¹⁻⁵ Medication adherence refers to the process by which patients take their medication as prescribed and three measurable phases: initiation, implementation, and persistence.⁶ Understanding the multilevel, modifiable correlates and risk factors of medication nonadherence is crucial for intervention development.^{3-5,7,8}

Although there is a growing awareness that factors beyond the patient level are also related to medication adherence, most studies investigating immunosuppressive nonadherence in transplantation have primarily evaluated socio demographic-, patient-, disease- and treatment-related factors^{1,3,9} while largely ignoring higher system-level factors (e.g., organization of transplant follow-up care and financial burden of immunosuppressives).^{1,7,10,11}

An exception is the BRIGHT (Building Research Initiative Group: Chronic Illness Management and Adherence in Transplantation) study,^{8,12} which evaluated 1,397 heart transplant patients in 36 centers across 11 countries and 4 continents. For the first time, this study identified several multilevel correlates of immunosuppressive nonadherence following heart transplantation and noted their importance for risk assessment and multilevel intervention development.^{7,10,11,13-15}

In KT, only one study attempted to explore the multilevel factors associated with nonadherence. Unfortunately, its single center design did not allow for a full exploration of

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4 micro, meso, and macro level variables (clinical practice patterns).^{15,16} Thus, broader data to
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7 guide strategic adherence interventions in KT are lacking.
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10 The study of multilevel factors related to immunosuppressive nonadherence can be
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12 guided by Bronfenbrenner's ecological model, which posits that individual behavior is a result of
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14 multilevel determinants with the patient in the center (patient level), followed by the influence
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16 of their health care provider/family (micro level), the healthcare organization (meso level) and
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18 the health care system and related policies (macro level)^{15,17} (Figure 1). In addition to studies
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20 focusing on patient-level variables, such as demographic characteristics, practice patterns
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22 (meso and macro levels) applying better principles of chronic illness management resulted in
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24 favorable clinical and health care utilization outcomes in chronically ill populations,¹⁸ including
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26 KT patients.^{13,14}
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33 Brazil, which ranks second worldwide in the absolute number of KT, provides a relevant
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35 setting for understanding multilevel factors related to nonadherence in KT.¹⁹ As an emerging
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37 economy thus overall less resourceful than the USA and Europe, Brazil has the largest public
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39 and fully covered transplantation system.¹⁹ Patients can have a transplant independent of their
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41 income and insurance status, and patients' financial burden, which is a major driver of
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43 nonadherence to immunosuppressives in the US, the highest KT volume worldwide, is a less
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45 prominent factor in nonadherence.^{9,20,21} Variations in transplant care provision exist among
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47 centers and regions in Brazil²²⁻²⁴, congruent with other countries/regions.^{1,8} A few
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49 nonrepresentative Brazilian studies showed a prevalence of nonadherence to
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51 immunosuppressives among KT patients ranging from 16-70%, depending on the case findings,
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measurement methods applied and operational definitions. Additionally, information regarding the correlates of nonadherence in emerging economies, such as Brazil, is limited.^{16,25-32}

Therefore, the aim of the ADHERE BRAZIL study is to assess the prevalence and multilevel correlates of nonadherence to immunosuppressives (implementation phase) in kidney transplanted patients in a full-coverage health care system. We hypothesize that multilevel factors, at patient, healthcare provider, healthcare service, and health policy levels, correlate to nonadherence to immunosuppressives in this population.

2 Materials and methods

2.1 Design, sampling, and setting

The ADHERE BRAZIL study is a cross-sectional study using a multistage sampling approach. A stratified sample of 20 Brazilian KT centers (Figure 2), a randomized proportional sample of 1,105 KT patients based on the center's activity and region, and a representative of the transplant service were included. The methodology of the ADHERE BRAZIL study has been previously reported in detail (sample size, sample strata, theoretical framework, etc.)³³ and was adapted from the BRIGHT study.^{8,12} In brief, inclusion criteria for the centers were ≥10 KTs performed per year over the 5-year period preceding the start of the study (2010-2014) and written consent for participation by the transplant center's director. A randomized proportional sample of adult attending KT recipients was recruited from the centers based on the center's KT activity and the Brazilian region. Inclusion criteria for the patients were as follows: >1 year post-transplant, ability to understand the objectives of the study, and written informed consent.³³

The Brazilian universal and public health care system provides full access to and coverage of the transplant surgery, immunosuppressives, laboratory examinations, and post-transplant follow-up care.¹⁹ Brazil is an emerging economy characterized by social and economic diversity throughout the country. Variations exist in the health care infrastructure, access to health care and patterns of clinical practice at the transplant center level.²²⁻²⁴

Ethical approval was provided by the Ethics Research Board (ERB) of the University Hospital of Federal University of Juiz de Fora (CAAE 27972914.1.1001.5133, approval number 691.120), and each participating center received approval from their local ERBs.

2.2 Variables and measurements

Adherence to immunosuppressives

To assess the implementation phase of adherence⁶ to immunosuppressives, we used the validated interview version of the Basel Assessment of Adherence with Immunosuppressive Medication Scale – BAASIS[®].^{28,34} Congruent with the ABC taxonomy of medication adherence, this self-report questionnaire measures the implementation phase of immunosuppressive nonadherence (implementation nonadherence) using four items (taking and timing adherence, drug holidays, and dose reduction). KT recipients who reported any deviation in any item over the past four weeks were considered nonadherent.^{28,33} The concurrent and predictive validities of the BAASIS[®] have been established.^{28,35}

Multilevel correlates of immunosuppressive nonadherence

Variable selection was guided by Bronfenbrenner's ecological perspective based on the influence of multiple levels of healthcare on the patients' behavior (Figure 1).^{15,17} Fifty-three potential multilevel correlates were assessed using data abstraction from medical records, established self-report instruments, or investigator-developed questionnaires (Supplemental Digital Content, Materials and Methods).³³ At the patient level, we studied 23 variables, which were divided into demographic, clinical, treatment-related, condition-related and behavioral factors.^{16,36-43} Regarding the upper healthcare levels, we assessed 4 variables at the micro level (interpersonal dimension of care, e.g., patient satisfaction with the transplant team),^{12,44} 22 at the meso level (KT service characteristics and clinical practice patterns, e.g., duration of office visits)^{12,13,16,45-48} and 4 at the macro level (healthcare system characteristics, e.g., local refill of immunosuppressive medications)^{12,16} (Supplemental Digital Content, Materials and Methods).

2.3 Data collection

After ERB approval, data collection began via the Research Electronic Data Capture (RedCap) system (<http://www.project-redcap.org/>).³³ Data collection ran from December 2015 to June 2017. Patients scheduled for a regular outpatient clinic appointment in the KT center were randomly selected. After arrival at the transplant center and enrollment based on the inclusion criteria, patients received information regarding the ADHERE study and provided written informed consent. The BAASIS©^{28,34} and other instruments were applied by an interview by trained local research coordinators (65% part of the care team; 75% nurses/pharmacists), who also extracted clinical data from patient medical files using structured forms. Regarding center-level data, a nominated representative of the transplant center (45% nephrologists, 45% transplant nurses, and 10% pharmacists) completed the

structured questionnaire using the RedCap system during the same period of patient data collection.³³

2.4 Statistical analysis

Data are described by measures of central tendency and dispersion as appropriate depending on the measurement level and distribution (i.e., means, medians, standard deviations, interquartile intervals and percentages). Following the ecological model, a hierarchical approach was used for the analysis of multilevel correlates.⁴⁹ This approach adopted a forward-driven variable selection method grouped in blocks considering the proximity of the variable levels to the patient in a causal theoretic framework and the potential of modifiability by clinical practice. We first considered nonadherence to immunosuppressives as a binary variable using generalized estimating equations (GEE)⁵⁰ assuming Binomial family and logit link function, providing raw Odds Ratios (OR) as associate parameter likewise univariate logistic regression. GEE account for centers intra-class correlation, modeling the variance-covariance matrix according to a predefined correlation structure that usually increases the standard error estimates of the model parameters. We used the “exchangeable” structure since is the most flexible with fewer parametric assumptions.⁵⁰

For variable selection, we followed recent recommendations regarding statistical significance evaluation and used a mixed approach considering 95% confidence intervals, p-values, and effect sizes.^{51,52} However, for multiple model variable selection, given the large number of variables and probability of increased false discovery rate (FDR), we adopted this approach to correct p-values, so-called q-values,⁵³ using Bonferroni correction.

The modeling scheme sequentially included a blockwise entry of a group of variables. We started with variables related to the patient level, including non-modifiable (Block 1) and modifiable variables at patient-level plus micro level variables (Block 2). In Block 3, we included opinions/perceptions of patients regarding the center and aspects of clinical practice from meso level. The final block, Block 4, included variables of center infrastructure from meso level and characteristics of health care system from macro level (Tables 1 and 2). Variables showing OR with 95% confidence interval (CI) not including 1.00 and variables with a CI including 1 but a q-value smaller than 0.10 and an effect of 25% or more (for increased or decreased chance) were included in each block analysis.^{51,54} The same criteria were used to maintain the variables each time a new block was adjusted, this turn using p-value, by hand made selection. Additionally, a marginal pseudo-R² statistic was calculated in each block analysis and the final model by retaining only the variables allocated to the respective level in the equation.⁵⁴ As we considered acute rejection an outcome, it was not included in analysis. None of the variables at the micro and macro levels presented sufficient robustness (OR) for inclusion in the sequential model.

We checked the robustness of our results by rerunning the analysis of the “taking” and “timing” dimensions of the BAASIS[®] separately. We found no missingness in center-level variables, and we rarely observed missingness at patient level (median 0%, range: 0-1.8%; IQR: 0.18%; 99.7% of variables: <1%). Based on these findings, we decided to not proceed with imputation, and then complete case analysis was applied. All analyses were performed using STATA (version 14, StataCorp LP, College Station, TX, USA).

3 Results

3.1 Sample characteristics

Most KT centers (n=17, 85%) were low/moderate activity services, i.e., performing 50 to 150 KT per year.^{23,33} At the beginning of the study (2014), 5,785 patients were under follow-up at participating centers. As shown in Figure 3, 1,763 were randomly selected from the scheduling list of routine office visits, but only 1,647 met the inclusion criteria. Of these, 296 patients could not perform interviews due to operational issues, 143 refused to participate, and 103 did not attend their consultation. Thus, ultimately, 1,105 patients were included in the study (participation rate 67%, mean age 47.6±12.6 years, 58.5% males, years post-KT 6.20±4.81; 65.2% received grafts from deceased donors) (Figure 3, Table 1).

3.2 Prevalence of immunosuppressive nonadherence (implementation phase)

Overall implementation immunosuppressive nonadherence was 39.7%, 95% CI (36.8-42.6). Timing nonadherence (delay greater than 2 h) was the most frequent issue (30.5%), followed by taking nonadherence (forgetting), reported by 14.3%. Drug holidays (5.9%) and dose reduction were less frequently reported (5.4%).

3.3 Multilevel factors of immunosuppressive nonadherence

Descriptive and bivariate analyses of multilevel factors in the entire sample and separately by subgroups of adherers and non-adherers are shown in Table 1. Furthermore, multiple logistic regression analysis, by blockwise variable selection, took place. The two

variables included in Block 1 (patient level, non-modifiable), age and having stable partner, were retained in the analysis. After the inclusion of variables of Block 2 (patient level – modifiable and micro level), nonadherence to appointment keeping and nonadherence to physical activity recommendations remained. From Block 3 (Meso level, patients' perceptions of care) three new variables were selected: patient's satisfaction with waiting room structure, consultation frequency and time of consultation. From Block 4, only the hospital size was retained. Thus, our final model, derived from 53 variables, included seven independent correlates of implementation immunosuppressive nonadherence. Three factors, namely, nonadherence to appointment keeping (OR 2.98; 95% CI:2.03–4.39); nonadherence to physical activity recommendations (OR 1.84; 95% CI:1.38–2.46), and a longer office visit duration (30 minutes) (OR 1.58; 95% CI:1.15–2.17), were positively associated with immunosuppressive nonadherence. Four factors were negatively associated: having a stable partner (OR 0.75; 95% CI:0.58–0.97), satisfaction with the waiting room structure (OR 0.54; 95% CI:0.42–0.71), the patients' perceived adequacy of the consultation frequency (OR 0.62; 95% CI:0.43–0.90), and the number of beds in the transplant center hospital (>500 beds) (OR 0.58; 95% CI:0.46–0.73) (Table 2, Figure 4). This final model explained 16.5% of the variability of immunosuppressive nonadherence. Patient-related factors explained only 8.4% of the variability (Table 2).

Sensitivity analysis confirmed the relevance of all variables included in the final multivariate model. Considering each dimension, taking nonadherence was associated with nonadherence to appointment keeping, nonadherence to physical activity recommendations, satisfaction with the waiting room structure, and the number of beds in the transplant center hospital. Additionally, when we separately evaluated the nonadherence by the timing question,

we found all seven correlates of nonadherence by BAASIS four questions were also associated, except for having a steady partner (data not shown).

4 Discussion

This is the first multicenter study evaluating multilevel correlates of implementation immunosuppressive nonadherence in KT patients at the patient, family/healthcare provider, healthcare organization, and healthcare system levels performed in the 2nd highest volume KT country worldwide, with the largest public, fully covered transplantation system, yet being an emerging economy. The ADHERE BRAZIL study, built on the BRIGHT study methodology^{8,12}, thus, adds much-needed data to broaden the still limited scientific basis of modifiable multilevel correlates of immunosuppressive nonadherence and fuel the development of adherence-enhancing interventions in transplantation and other chronic conditions. This study is the third to analyze multilevel variables in the transplant setting^{8,12,16} and one of the few in chronic conditions.⁵⁵⁻⁵⁷ The main strengths of this study are its large sample size and demographic characteristics (age, gender, type of donor, immunosuppressive regimen), which aimed to represent the Brazilian KT population but, with the appropriated caution, also resembles world KT population, and adds data on the understudied transplantation outcomes in emerging economies. In addition, this study adopted a theoretical approach, the Bronfenbrenner's ecological model, to guide variable selection,^{15,17} which is often missing in medication adherence research.⁵⁸

We used the latest conceptualization of the three phases of medication adherence and focused on the implementation phase.⁶ The overall prevalence of implementation

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4 nonadherence was substantial (39.7%), calling for investment in implementation of adherence-
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6 enhancing interventions in transplant follow-up care.^{1,16,58,59} The prevalence of implementation
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8 nonadherence found in our study is comparable to previous self-report assessments in KT
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10 patients, which widely varied from 8-65% depending on the case findings, measurement
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12 methods and operational definitions used.^{1,3,4,9,21,60} Admittedly, our BAASIS® assessment
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14 captures the taking and timing dimensions of implementation nonadherence with timing
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16 contributing the most to nonadherence, which should be considered in the interpretation of
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18 our results.⁸
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25 Multilevel correlates were associated with immunosuppressive nonadherence in KT
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27 patients, and our study is, therefore, congruent with the recently reported BRIGHT study
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29 involving heart transplant patients,⁸ although the correlates studied are not entirely
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31 comparable. We assessed fewer patient-level factors than the BRIGHT study and focused more
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33 on meso level factors, an understudied aspect of transplant management.^{7,10,11} Data on
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35 adaptable meso level factors might provide leverage points to adapt transplant centers'
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37 practice patterns as part of multi-level medication adherence interventions.^{7,10,11} Our final
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39 model explained 16.5% of the variability of nonadherence, and meso level factors contributed
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41 significantly. The extent to which the final model explains the variability, albeit leaving room for
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43 further optimization,^{1,60} is similar to that reported in the BRIGHT study.⁸ Further enhancement
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45 of the explanatory power of the models is needed, and more focus on non-patient related
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47 factors is warranted in future research as multi-level factors also explain some of the variance
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49 not previously studied.
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4 The major finding of our study is that we need to broaden our approach to address
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6 nonadherence beyond the patient level. Multilevel interventions that include measures
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8 focusing on structural elements of transplant centers and transplant practice patterns are
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10 recommended. Embracing principles of chronic illness management, a care model that
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12 combines broad attention to preparing patients to self-manage their condition and treatment
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14 in home settings, continuity of care and optimizing delivery system design and information
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16 systems, while working with community health resources has shown improvement in
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18 medication adherence, clinical and economic outcomes in transplant care^{13,14} and other chronic
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20 conditions.¹⁸
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27 At the patient level, three factors were included in the final model. As reported by
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29 others, better social support (having a stable partner) was negatively associated with
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31 nonadherence.^{1,61-64} We found a positive relationship between nonadherence to
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33 immunosuppressives and to physical activity among KT patients, a novel finding. The rate of
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35 failure to engage in sufficient physical activity varies among post-KT patients from 35 to
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37 84%.^{1,65,66} However, unsurprisingly, both conditions share many negatively associated factors,
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39 such as low self-efficacy, drug side effects, low socioeconomic status, comorbidities,
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41 depression,^{1,21,65,66} and adverse outcomes.^{1,65,67} Few studies have investigated nonadherence
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43 to appointment keeping in KT patients.^{1,68,69} Among them, only Taber and colleagues reported
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45 the same high correlation between immunosuppressive and appointment nonadherence found
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47 here.⁶⁹ In their large longitudinal study, although they used another diagnostic method, the
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49 incidence (14.6%) was similar to ours, and nonadherence to healthcare appointments showed a
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51 synergistic effect as a risk factor for graft loss when associated with medication
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4 nonadherence.⁶⁹ Notably, immunosuppressive nonadherence and these two other health
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6 behaviors (physical activity and healthcare appointments) seem to share a clustered profile,
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8 justifying the need for further investigations.
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11 At the meso level, structural aspects of transplant centers — their size and a better
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13 physical structure — have never been described in relation to nonadherence in KT. In a large
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15 study of dyslipidemia, a chronic condition, the higher the number of followed patients at a
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17 given center, the better was the adherence to statin treatment.⁷⁰ Furthermore, among HIV
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19 patients, a higher prevalence of nonadherence was observed in smaller centers that treated
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21 less than 100 patients.⁷¹ Although information regarding the facility structure does not reveal
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23 information regarding clinical practice, we can speculate that in large centers, the greater
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25 availability of human, equipment and physical resources could promote improved healthcare,
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27 better patient self-management and, consequently, better adherence.^{3,18,72,73} An interesting
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29 finding of our study was that patient satisfaction with the frequency of scheduled visits was a
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31 protective factor against nonadherence. Greater satisfaction with the health care received is
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33 part of our framework, but this variable was reported by only one study examining KT.⁶⁴
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37 Surprisingly, longer office visits (30 vs. 15 minutes) were more frequent among nonadherent
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39 patients. This aspect has not been previously reported in KT. A possible explanation is that
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41 longer office visits do not necessarily result in better care, quoted by increased adherence.
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43 Conversely, in HIV patients, more time spent in consultation resulted in better patient-provider
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45 communication and better adherence to antiretroviral therapy.^{74,75} However, data on office
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47 visits in general primary care struggle with this information, since authors showed a better care
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49 for medication quality indicators seemed to be independent of visit duration.^{76,77}
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4 Since multilevel factors are associated with nonadherence in KT and nonadherence is a
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6 risk factor for poor graft outcomes, strategies to reduce nonadherence should include actions
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8 at the patient, micro, meso, and macro levels. Interventions at all levels of healthcare have
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10 been previously proposed to be relevant.^{7,60} Limited evidence has shown that measures
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12 effective in reducing nonadherence in KT involve complex multiple dimensions actions. Benefits
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14 include tailored patient education (patient level), coordinated actions to increase social support
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16 (micro level) and self-care management by improved nursing care or additional pharmaceutical
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18 attention (meso level).^{7,11,60} Similar to some other chronic diseases, financial help or advice
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20 regarding easier access to immunosuppressives (macro level) have been proven to be
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22 effective.^{7,11,78} However, high-quality studies call attention to the need for interventions that
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24 could be integrated into daily care and aim to improve clinical outcomes beyond adherence to
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26 treatment.^{7,10,78} Considering our results, we can speculate how centers should change their care
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28 to decrease nonadherence. The finding that having a steady partner is negatively associated
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30 with nonadherence provides a clue for the identification of patients at risk and support
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32 measures to improve social support, such as educative groups. The association with missing
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34 appointments and being physically inactive direct measures to improve self-monitoring and
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36 self-efficacy, such as multidisciplinary care involving psychologists and physical educators.
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38 Finally, the patients' perception of the adequacy of the proposed routine care schedule points
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40 out to develop individualized care.
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53 As limitations, a cross-sectional study design did not allow causal inferences. Second, we
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55 randomly selected patients scheduled for routine visits and further included only attendees.
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57 This strategy was used to effectively collect data. However, patients visit KT centers every six
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months at most, and the average data collection time was 6.5 months (data not shown), allowing for all followed patients to be randomly selected. Approximately half of the included patients underwent a transplantation over five years ago, which allowed us to evaluate both patients recently living with a KT and surviving patients who adapted to all aspects of immunosuppressive treatment. Third, we used a validated self-report instrument to assess the implementation dimension of nonadherence. Compared to electronic monitoring, this method provides more sparse sampling and is less reliable but is cheaper and more feasible.^{28,79} The Brazilian health system does not routinely record medication dispensation, rendering pharmacy refill records unavailable as a diagnostic method for immunosuppressive nonadherence. Electronic monitoring provides a better description of the implementation phase but precludes a more complex collection, analysis, and interpretation of information, thus demanding further economic resources and logistic support, which is difficult to accomplish in a multicenter study. Notably, another very relevant point is the variable corollary included in our multilevel analysis, in which the assessment of behavioral factors, such as health literacy, barriers and beliefs, and aspects of the chronic illness care model were limited. Research in this field has only recently begun, and we further need to explore what is indeed relevant. Finally, we evaluated the KT population in a single country. Following the US, Brazil has the second largest renal transplant volume worldwide,^{19,80} and studying 20 centers enables us to perform a reasonable analysis of clinical post-transplant practice.

In conclusion, this is the first multicenter study to evaluate multilevel factors associated with immunosuppressive nonadherence in KT. In our sample, which shares some epidemiologic patterns with the global KT population, implementation nonadherence was prevalent and

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4 associated with multilevel factors (patient and transplant service levels). These results suggest
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7 strategies targeting to reduce nonadherence should include measures at the level of transplant
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9 center practice instead of only those directed to patient characteristics.
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Data availability

The data supporting the findings of this study are openly available in Open Science Framework
at <https://osf.io/zg97b/> and <https://osf.io/qhmdg/>

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Figure legends

Figure 1. Bronfenbrenner's ecological model of multilevel correlates applied in this study.

Adapted from Bronfenbrenner¹⁷ and Berben et al.¹⁵ (with permission).

Figure 2. Distribution of participating centers in the ADHERE BRAZIL study across the country.

Colors indicate transplant activity as follows: red, high activity (>150 KT/year); green, moderate activity (50 to 150 KT/year); and blue, low activity (<50 KT/year).³³ KT – kidney transplantation.

Figure 3. Sample flowchart of kidney transplant patients included in the study. KT – kidney transplantation.

Figure 4. Forest plot of the final sequential logistic regression after hierarchical selection of implementation nonadherence to immunosuppressives (BAASIS, 4 questions). Three patient level variables and 4 meso level (transplant center) variables were retained. Odds ratios and 95% confidence intervals are shown.

Supplemental Digital Content

Additional supporting information is provided online in the supporting information tab for this article: Supplemental Digital Content, Materials and Methods.

Table 1. Descriptive statistics and bivariate analysis of nonadherence to immunosuppressives (implementation phase) by BAASIS®

distributed across four levels (patient, micro, meso, and macro) and grouped by adherents and nonadherents.

Variable	Values/Scoring	Total sample	Adherents	Nonadherents	Bivariate analysis
		N, Mean+/-SD N (%)	N, Mean+/-SD N (%)	N, Mean+/-SD N (%)	Odds ratio (95% CI), P value/q-value
Patient-level: variables derived from empirical evidence (sociodemographic, clinical, treatment-, condition- and patient-related factors)					
SOCIO-DEMOGRAPHIC FACTORS (Block 1)					
Age (P)	Years	1105, 47.6±12.6	666, 48.5±12.7	439, 46.1±12.3	0.986 (0.976-0.995), P=0.004/q=0.048
Sex (P)	Male	647 (58.5%)	400 (60.1%)	247 (56.3%)	0.856 (0.672-1.090), P=0.207/q>0.999
Educational level (P)	Illiterate (0-4 years)	86 (7.8%)	57 (8.6%)	29 (6.6%)	Reference
	Elementary school (4-8 years)	431 (39.0%)	268 (40.2%)	163 (37.1%)	1.147 (0.704-1.870), P=0.581/q=0.696
	High school (>8 to 11 years)	423 (38.3%)	250 (37.5%)	17 (39.4%)	1.254 (0.768-2.049), P=0.365/q=0.696
	College (<11 years)	165 (14.9%)	91 (13.6%)	74 (16.9%)	1.568 (0.910-2.700), P=0.105/q=0.696
Race (P)	Non-Caucasian	537 (48.6%)	301 (45.2%)	236 (53.8%)	1.050 (0.980-1.124), P=0.165/q=0.240
Marital status (P)	Steady partner	662 (60.0%)	421 (63.2%)	241 (55.1%)	0.721 (0.565-0.920), P=0.009/q>0.999
Working status (P)	Actively employed	257 (23.3%) ⁸	140 (21.0%)	117 (26.6%)	1.140 (1.030-1.801), P=0.373/q>0.099
Familiar income (P)	Brazilian reference wages/month				
	1. Up to 1 reference wage	281 (25.4%)	162 (24.4%)	119 (27.1%)	Reference
	2. >1 to 3 wages	582 (52.7%)	350 (52.6%)	232 (52.8%)	0.875 (0.656-1.168); P=0.367/q>0.099
	3. >3 to 5 wages	157 (14.2%)	102 (15.3%)	55 (12.5%)	0.713 (0.476-1.067); P=0.100/q>0.099
	4. More than 5 wages	84 (7.6%)	51 (7.7%)	33 (7.5%)	0.888 (0.543-1.454); P=0.639/q>0.099
CLINICAL FACTORS (Block 1)					
Chronic kidney disease etiology (P)	1. Chronic glomerulonephritis	316 (28.6%)	176 (26.4%)	140 (31.9%)	Reference
	2. Undetermined	315 (28.5%)	202 (30.3%)	113 (25.7%)	0.675 (0.486-0.937), P=0.019/q>0.099
	3. Hypertensive Nephropathy	222 (20.1%)	129 (19.4%)	93 (21.2%)	0.885 (0.625-1.255), P=0.496/q>0.099

	4. Diabetic Nephropathy	96 (8.7%)	66 (9.9%)	30 (6.8%)	0.545 (0.334-0.888), P=0.015/q>0.099
	5. Polycystic Kidney Disease	65 (5.9%)	43 (6.5%)	22 (5.0%)	0.654 (0.375-1.147), P=0.140/q>0.099
	6. Other	91 (8.2%)	50 (7.5%)	41 (9.3%)	0.969 (0.605-1.551), P=0.896/q>0.099
Time on pre-KT treatment (P)	Months	1104, 40.4±40.4	666, 41.7±39.5	438, 38.3±41.7	0.998 (0.995-1.001), P=0.247/q>0.099
Pre-KT treatment modality (P)	1. Hemodialysis	1028 (93.0%)	621 (93.2%)	407 (92.7%)	Reference
	2. Peritoneal dialysis	40 (3.7%)	21 (3.1%)	19 (4.3%)	1.466 (0.782-2.747), P=0.232/q>0.099
	3. Preemptive	37 (3.3%)	24 (3.6%)	13 (3.0%)	0.812 (0.408-1.617), P=0.554/q>0.099
Acute rejection (P)	Yes	250 (22.8%)	137 (20.8%)	113 (26.0%)	1.363 (1.027-1.810), P=0.032/Not applicable
TREATMENT-RELATED FACTORS (Block 1/2)					
Time since transplantation, categories (P)(Block 1)	1. Up to 5 years	566 (51.2%)	346 (51.9%)	220 (50.1%)	1.060 (0.834-1.348), P=0.631/q>0.099
	2. More than 5 years	539 (48.8%)	320 (48.1%)	219 (49.9%)	
Type of donor (P) (Block 1)	1. Living	384 (34.8%)	221 (33.2%)	163 (37.1%)	0.837 (0.651-1.075), P=0.164/q>0.099
	2. Deceased	721 (65.2%)	445 (66.8%)	276 (62.9%)	
Immunosuppressives (P) (Block 2)	Prednisone	1048 (94.8%)	634 (95.2%)	414 (94.3%)	0.801 (0.470-1.367), P=0.801/q>0.099
	Tacrolimus	849 (76.8%)	518 (77.8%)	331 (75.4%)	0.863 (0.650-1.144), P=0.360/q>0.099
	Sodium mycophenolate	699 (63.3%)	420 (63.1%)	279 (63.5%)	1.032 (0.805-1.323), P=0.803/q>0.099
	Azathioprine	153 (13.8%)	93 (14.0%)	60 (13.7%)	0.955 (0.673-1.354), P=0.796/q>0.099
	Cyclosporine	142 (12.8%)	84 (12.6%)	58 (13.2%)	1.074 (0.753-1.534), P=0.692/q>0.099
	Everolimus	138 (12.5%)	84 (12.6%)	54 (12.3%)	0.961 (0.667-1.384), P=0.831/q>0.099
	Mofetil mycophenolate	83 (7.5%)	50 (7.5%)	33 (7.5%)	1.044 (0.663-1.645), P=0.851/q>0.099
	Sirolimus	72 (6.5%)	39 (5.9%)	33 (7.5%)	1.267 (0.786-2.041), P=0.331/q>0.099
BEHAVIORAL FACTORS (Block 2)					
Nonadherence to appointments (P)	Missed at least 1 of the last 5 visit	140 (12.7%)	55 (8.3%)	85 (19.4%)	2.639 (1.837-3.790), P<0.001/q>0.001
Smoking (P)	Current smoker	43 (3.9%)	21 (3.1%)	22 (5.0%)	1.719 (0.938-3.151), P=0.079/q>0.099
Nonadherence to physical activity recommendations (P)	Less than 150 minutes per week	764 (69.1%)	431 (64.7%)	333 (75.8%)	1.738 (1.326-2.278), P<0.001/q>0.001
Micro level (Family/Healthcare provider) (Block 2)					

Tips for remembering to take immunosuppressives (P)	Yes	327 (29.8%)	197 (29.7%)	130 (29.9%)	0.993 (0.764-1.291), P=0.961/q>0.099
Help needed to prepare immunosuppressives (P)	Yes, from family	118 (10.7%)	75 9 (11.3%)	43 (9.8%)	0.874 (0.591-1.292), P=0.591/q>0.099
Patient satisfaction with the transplant team (P)	From 0 to 100	1104, 97.0±0.8.14 (96.5-97.5)	665, 97.0±8.33	439, 96.98±7.86	1.001 (0.986-1.016), P=0.912/q>0.099
Patient trust in the transplant team (P)*	From 0 to 100	1104, 97.87±6.10 (97.51-98.23)	665, 98.0±5.78	439, 97.66±6.56	0.992 (0.973-1.011), P=0.403/q>0.099
Meso level: transplant center (characteristics and practice patterns in view of chronic illness management)					
PATIENT’S PERCEPTION OF CENTER STRUCTURAL CHARACTERISTICS AND PRACTICE PATTERNS (Block 3)					
Not satisfied with the waiting room structure (P)	Yes	472 (42.8%)	245 (36.9%)	227 (51.7%)	1.815 (1.420-2.320), P<0.001/q>0.001
Average total time of medical consultation (C)	1. 15 minutes	348 (31.5%)	235 (35.3%)	113 (25.7%)	1.561 (1.184-2.057), P=0.002/q=0.014
	2. 30 minutes	757 (68.5%)	431 (64.7%)	326 (74.3%)	
Difficulties in scheduling appointments (P)	Yes	114 (10.4%)	55 (8.3%)	59 (13.5%)	1.705 (1.156-2.514), P=0.007/q=0.049
Adequacy of the frequency of consultation (P)	Yes	955 (86.6%)	592 (89.0%)	363 (82.9%)	0.593 (0.420-0.839), P=0.003/q=0.021
Adequacy of the consultation time (P)	Yes	1046 (95.8%)	639 (96.1%)	407 (92.9%)	0.532 (0.312-0.905), P=0.020/q=0.140
Patients followed up by the same healthcare professional (C)	Yes	610 (55.2%)	371 (55.7%)	239 (54.4%)	0.978 (0.759-1.261), P=0.865/q>0.099
Consultation schedule type (C)	1. Individual	670 (60.6%)	426 (64%)	244 (55.6%)	0.721 (0.558-0.931), P=0.012/q=0.084
	2. Groups	435 (39.4%)	240 (36%)	195 (44.4%)	
CENTER INFRASTRUCTURE AND TEAM COMPOSITION (Block 4)					
Transplant center activity (number of transplants/year in the last 5 years) (C)	1. Low (<50)	422 (38.2%)	251 (37.7%)	171 (38.9%)	Reference
	2. Moderate (50-150)	398 (36.0%)	239 (35.9%)	159 (36.2%)	0.932 (0.528-1.645), P=0.807/q>0.099
	3. High (>150)	285 (25.8%)	176 (26.4%)	109 (24.8%)	0.643 (0.307-1.351), P=0.244/q>0.099
Transplant center ADHERE region (C)	1. North/Northeast/Central West	267 (24.1%)	147 (22.1%)	120 (27.3%)	0.753 (0.564-1.008), P=0.057/q>0.099
	2. Southeast/South	838 (75.9%)	519 (77.9%)	319 (72.7%)	
Number of beds in the transplant center hospital (C)	1. Small/medium hospital: up to 150 beds	86 (7.8%)	41 (6.1%)	45 (10.2%)	Reference-
	2. Large hospital: 151 to 500 beds	592 (53.6%)	322 (48.3%)	270 (61.5%)	0.756 (0.447-1.278), P=0.297/ q=0.344
	3. Large specialized hospital: >500 beds	427 (38.6%)	303 (45.5%)	124 (28.3%)	0.354 (0.206-0.610), P<0.001/q>0.001

Health professionals on the transplant team (C)	Nurse	1059 (95.8%)	641 (96.2%)	418 (95.2%)	0.766 (0.413-1.424), P=0.400/q>0.099
	Psychologist	932 (84.3%)	56 (85.0%)	366 (83.4%)	0.913 (0.650-1.283), P=0.3601/q>0.099
	Social worker	1085 (98.2%)	658 (98.8%)	427 (97.3%)	0.452 (0.181-1.127), P=0.088/q>0.099
	Nutritionist	1021 (92.4%)	617 (92.6%)	404 (92.0%)	0.994 (0.622-1.587), P=0.980/q>0.099
	Clinical pharmacists	874 (79.1%)	541 (81.2%)	333 (75.8%)	0.755 (0.559-1.020), P=0.067/q>0.099
	Physical therapist	478 (43.3%)	264 (39.6%)	214 (48.7%)	1.409 (1.094-1.813), P=0.008/q=0.144
Multiprofessional team, Brazilian law (C)	Doctor+ nurse + nutritionist + psychologist + social worker	1105 (80.2%)	541 (81.3%)	345 (78.6%)	0.867 (0.638-1.183), P=0.372/q>0.099
CHRONIC ILLNESS MODEL PRACTICES (Block 4)					
Continuing education directed to KT team (C)	Yes	1080 (97.7%)	650 (97.6%)	430 (97.9%)	1.092 (0.475-2.505), P=0.836/q>0.099
Electronic medical records (C)	Yes	595 (53.8%)	388 (58.3%)	207 (47.5%)	0.668 (0.520-0.859), P=0.002/q=0.038
Clinical guidelines (C)	Yes	1039 (94.0%)	633 (95.0%)	406 (92.3%)	0.607 (0.296-1.245), P=0.174/q>0.099
Patient diary (incentive for self-management) (C)	Yes	829 (75.0%)	478 (71.8%)	351 (79.9%)	1.514 (1.126-2.037), P=0.006/q=0.114
Waiting room educational activities (C)	Yes	529 (47.9%)	309 (46.4%)	220 (50.1%)	1.154 (0.897-1.483), P=0.265/q>0.099
Macro level: health care system (Block 4)					
Private insurance (P)	Yes	259(23.4%)	150 (22.5%)	109 (24.8%)	1.115 (0.841-1.476), P=0.447/q>0.099
Laboratory examinations by the public health system (P)	Yes	997 (90.4%)	603 (90.8%)	394 (89.7%)	0.872 (0.581-1.307), P=0.507/q>0.099
Refill of immunosuppressives in another city (P)	Yes	506 (45.8%)	311 (46.8%)	195 (44.4%)	0.896 (0.704-1.140), P=0.371/q>0.099
Immunosuppressive refills in a distant place (P)*	Yes	596 (54.0%)	350 (52.5%)	246 (56.3%)	1.131 (0.888-1.439), P=0.317/q>0.099

KT – Kidney transplantation. P – Variable measured according to the patient's perspective. C – Variable measured according to the center's perspective (transplant center representative).

In the Total sample column, N represents the total sample size as follows: patients=maximum 1105, centers=maximum 20. In the subgroups, after the classification, adherents=maximum 666, nonadherents=maximum 439. Variable scores at the meso and macro

levels, collected by the center's perspective, were attributed to patients, according to the multistage sampling profile. Fewer observations are possible depending on data availability.

Blocks included in the statistical analysis are indicated after the column label.

Variables shown in light gray (23) were included in the multiple model (95% CI not including 1.00 or q-value<0.10 and effect $\geq$ 25%).

Table 2. Multivariate analysis of implementation nonadherence to immunosuppressives

(BAASIS©, 4 questions) by a sequential logistic regression.

Nonadherence to immunosuppressives (BAASIS 4 questions)	Odds ratio	95% Conf. interval	P>z
Block 1 Patient level: non-modifiable variables derived from empirical evidence (sociodemographic and clinic-related factors) (n=1103, R2: 2.4%)			
Age	0.99	0.98-1.00	0.008
Stable partner	0.79	0.61-1.00	0.062
Block 2: + Patient level: nonmodifiable variables and Micro level variables (n=1101, R2: 8.4%)			
Age	0.99	0.98-1.00	0.030
Stable partner	0.77	0.59-0.99	0.044
<i>Nonadherence to appointment keeping</i>	<i>2.52</i>	<i>1.74-3.63</i>	<i>< 0.001</i>
<i>Nonadherence to physical activity recommendations</i>	<i>1.83</i>	<i>1.38-2.41</i>	<i>< 0.001</i>
Block 3: + Meso level: opinions/perceptions of patients regarding the center and aspects of clinical practice variables (n=1097, R2: 14.5%)			
Stable partner	0.74	0.61-1.00	0.088
Nonadherence to appointment keeping	2.89	1.97-4.23	< 0.001
Nonadherence to physical activity recommendations	1.79	1.34-2.37	< 0.001
<i>Satisfaction with the waiting room structure</i>	<i>0.54</i>	<i>0.41-0.70</i>	<i>< 0.001</i>
<i>Average total time of medical consultation (center's perspective, longer than 30 minutes)</i>	<i>1.69</i>	<i>1.18-2.43</i>	<i>0.005</i>
<i>Adequacy of the frequency of consultation (patient's perspective)</i>	<i>0.62</i>	<i>0.43-0.90</i>	<i>0.011</i>
FINAL MODEL: + Block 4 Meso level: center infrastructure and Macro level (n=1097, R2: 16.5%)			
Stable partner	0.75	0.58-0.97	0.031
Nonadherence to appointment keeping	2.98	2.03-4.39	< 0.001
Nonadherence to physical activity recommendations	1.84	1.38-2.46	< 0.001
<i>Satisfaction with the waiting room structure</i>	<i>0.54</i>	<i>0.42-0.71</i>	<i>< 0.001</i>
<i>Average total time of medical consultation (center's perspective, longer than 30 minutes)</i>	<i>1.58</i>	<i>1.15-2.17</i>	<i>0.005</i>
<i>Adequacy of the frequency of consultation (patient's perspective)</i>	<i>0.62</i>	<i>0.43-0.90</i>	<i>0.012</i>
<i>Number of beds in the transplant center hospital (>500 beds)</i>	<i>0.58</i>	<i>0.46-0.73</i>	<i>< 0.001</i>

Sequential logistic regression was performed by adding variables potentially associated in the bivariate analysis (OR with CI not including 1.0 or q value < 0.10 and an effect $\geq$ 25% by OR) in blocks. Variables are retained in the next block analysis if they presented an OR with a CI not including 1.0 or an effect $\geq$ 25% by OR and a p value < 0.10.

* Variables included in **Block 1, Patient level, nonmodifiable** (02): SOCIODEMOGRAPHIC FACTORS: Age, Marital status (stable partner); **Block 2, Patient level (modifiable variables) and Micro level** (02): CONDITION-RELATED FACTORS: Nonadherence to appointment keeping, Smoking (Active), Nonadherence to physical activity recommendations; **Block 3, Meso level, opinions/perceptions of patients regarding the center and aspects of clinical practice** (05): STRUCTURAL CHARACTERISTICS: Satisfaction with the waiting room structure; PRACTICE PATTERNS: Average total time of medical consultation (center's perspective; 30 minutes vs. 15 minutes), Difficulties in scheduling appointments, Adequacy of the frequency of consultation; Type of consultation scheduling (individual vs. group); **Block 4, Meso level, center infrastructure and Macro level** (02): CENTER INFRASTRUCTURE: Number of beds in the transplant center hospital (large specialized hospital: >500 beds vs. smaller hospital); ASPECTS OF CHRONIC ILLNESS MODEL: Certified electronic medical record/register.

Micro- or Macro-level variables that did not reach the criteria of association and, thus, were not included.

Figure 2

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Figure 4

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