

# Identification of Factors Associated with Medication Adherence in Renal Transplant Patients: An Integrative Literature Review

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## ABSTRACT

**Objective:** To identify factors associated with medication adherence in kidney transplant patients, showing the factors that contribute to increased and decreased adherence. **Methods:** A literature review was performed, searching the Medline Complete, Academic Search Premier, Embase and CINAHL databases. Rayyan was used for job management. **Results:** Of the 1,859 works initially identified, 36 articles were included in this research. All studies involved adult patients, usually with a mean age between 40 and 50 years. Men were the majority of patients in virtually every study. Most transplant patients had been transplanted for more than one year. Adherence was measured in most studies using validated and widely used instruments, such as The Basel Assessment of Adherence to Immunosuppressive Medication Scale (Baasis) and the Adherence to Immunosuppressive Therapy Scale (ITAS). Other scales used for other diseases were also adopted, such as the Morisky instrument, used in versions with four or eight questions. Adherence values were quite distinct, ranging from very low values such as 10.8 and 16.9%, to very high values such as 90.8 or 94.5%. Among the factors that increase adherence are higher life satisfaction rate; better perception of medications; support from doctors; social support; longer waiting time on the transplant list; and better kidney function results. Among the factors that reduce medication adherence are: having a work contract; daytime sleepiness; palliative type of coping; less autonomy; financial problems; have stress; change of routine; less knowledge and literacy in health; adverse events to immunosuppressants; beliefs and concerns about immunosuppressants; lower belief in self-efficacy; and intrinsic religiosity. In addition, there were factors in which there is divergence in the literature regarding the influence on adherence, such as gender, age, income and time since transplantation. **Conclusion:** This study demonstrated that several modifiable and non-modifiable factors contribute to medication adherence, which demonstrates the importance of these findings for the care of kidney transplant patients.

Descriptors: Kidney Transplantation; Medication Adherence; Immunosuppressive Agents.

## *Identificação dos fatores associados com a adesão à medicação em pacientes transplantados renais: Uma revisão da literatura integrativa*

### RESUMO

**Objetivo:** O objetivo do trabalho foi identificar os fatores associados com a adesão à medicação em pacientes transplantados renais, mostrando os fatores que contribuem para o aumento e a diminuição da adesão. **Métodos:** Para tanto, foi realizada uma revisão integrativa da literatura, buscando nas bases de dados Medline Complete, Academic Search Premier, Embase e CINAHL. Foi usado o programa Rayyan para gestão dos trabalhos. **Resultados:** Identificaram-se inicialmente 1.859 trabalhos e foram incluídos 36 artigos. Todos os estudos envolviam pacientes adultos, geralmente com média de idade entre 40 e 50 anos. Os homens foram a maioria dos pacientes em praticamente todos os estudos. A maior parte dos pacientes transplantados possuía mais de um ano de transplante. A adesão foi aferida na maior parte dos estudos por instrumentos validados e amplamente usados, como o caso do *The Basel Assessment of Adherence to Immunosuppressive Medication Scale* (Baasis) e a Escala de Adesão à Terapia Imunossupressora (ITAS). Outras escalas usadas para outras doenças também foram adotadas, como o instrumento de Morisky, usado nas versões

de quatro ou oito questões. Os valores de adesão foram bastante distintos variando de valores muito baixos como 10,8 e 16,9%, até valores muito altos como 90,8 ou 94,5%. Entre os fatores que aumentam a adesão estão: maior índice de satisfação com a vida; melhor percepção dos medicamentos; apoio dos médicos; suporte social; maior tempo de espera em lista de transplante; e melhores resultados de função renal. Entre os fatores que diminuem a adesão à medicação cita-se: possuir vínculo de trabalho; sonolência diurna; enfrentamento tipo paliativo; menor autonomia; problemas financeiros; possuir estresse; mudança de rotina; menor conhecimento e literacidade em saúde; eventos adversos aos imunossuppressores; crenças e preocupações com os imunossuppressores; menor crença na autoeficácia; e religiosidade intrínseca. Além disso, houve fatores em que existe, na literatura, divergência quanto à influência na adesão como sexo, idade, renda e tempo de transplante. **Conclusão:** Este estudo demonstrou que diversos fatores modificáveis e não modificáveis contribuem para a adesão à medicação o que demonstra a importância destes achados para o cuidado de pacientes transplantados renais.

Descritores: Transplante de Rim; Adesão à Medicação; Imunossuppressores.

## INTRODUCTION

Kidney transplantation is considered a form of treatment for patients with kidney failure, and is a complex procedure in which the patient needs to undergo surgery, and the graft can be from a living or deceased donor. For the donation to be from a person deceased in Brazil, even if the donor has informed their intention during life, the family or guardians must consent to the donation after brain death has been confirmed. It is worth pointing out that transplantation is only one form of therapy, and the transplanted patient should follow a treatment that consists of lifestyle changes and the use of immunosuppressive treatment.<sup>1</sup>

Included in this treatment are drugs divided into the classes of antimetabolites, inhibitors of mammalian target of rapamycin (mTOR), corticosteroids, and calcineurin inhibitors.<sup>2</sup> These drugs are used post-transplant, to prevent rejection or even graft loss.<sup>3</sup>

Medication adherence is the act of the patient using medications and following the treatment as directed by the health care professionals who accompany the patient. Some factors hinder medication adherence in kidney transplant recipients, among them are the number of medications and adverse events.<sup>5</sup> The measurement of adherence can be accomplished in several ways; one of the most common is to check how often and how many doses the patient has used. There are also specific instruments for assessing adherence to immunosuppressants such as The Basel Assessment of Adherence to Immunosuppressive Medication Scale (Baasis) and the Immunosuppressive Therapy Adherence Scale (ITAS), in addition to scales used for other diseases such as the Morisky tool. However, because they are indirect ways of measuring adherence, they usually bring overestimated results. In addition, Baasis requires a website registration and Morisky, depending on the version adopted, requires payment for its use. Furthermore, it should be noted that direct methods, such as dosing the immunosuppressant dose into the blood, are not always associated with adherence, because there is an important influence of drug and food interactions, as well as different types of metabolizers.<sup>4</sup>

It is worth mentioning that the drugs used after transplantation are not only immunosuppressive ones, because, depending on the protocol, antimicrobials are used, because of susceptibility to infections in addition to other drugs, such as antiulcer drugs. There are also cases of patients who already have chronic diseases, such as diabetes and hypertension,<sup>6</sup> and will use medications for these or other health problems. Thus, the polypharmacy observed in these situations predisposes to drug interactions and adverse events, which can hinder drug adherence by making therapy more complex.<sup>7</sup>

In this sense, this work aimed to identify the factors associated with medication adherence in kidney transplant patients.

## METHODS

An integrative literature review was conducted to identify factors associated with adherence to immunosuppressive medication in kidney transplant patients. To this end, the questions “What is the frequency of immunosuppressant medication adherence in kidney transplant patients?” and “What factors are associated with immunosuppressant medication adherence in kidney transplant patients?” were formulated.

The Medical Subject Headings (MeSH) descriptors adopted in this review are the terms: “Kidney Transplantation” AND “Medication Adherence”.

The databases used were MEDLINE Complete, Academic Search Premier, Embase, and CINAHL. No time frame was defined and the analyzed papers were in Portuguese, English, and Spanish.

The inclusion criteria adopted were papers that addressed adherence to immunosuppressive medication in adult renal transplant patients. As exclusion criteria, papers that did not present the frequency of adherence or did not identify the factors significantly associated with this behavior were chosen.

After searching the databases for the papers, the Rayyan program was adopted to assist in the organization. All steps were performed by two researchers simultaneously. Initially, repeated papers were excluded. Subsequently, analysis of titles and abstracts was performed, and then of the full articles.

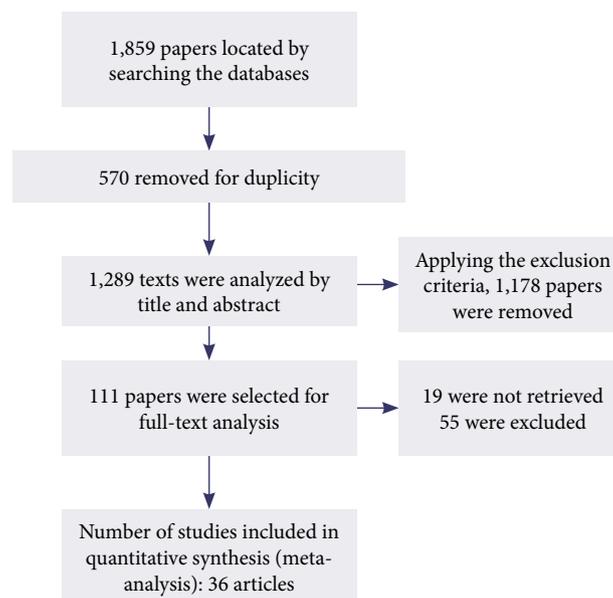
The selected papers would have the information extracted, being of characterization of the papers: year of publication, authors, location of the study (country/countries), objective of the study, type of study, sample size, age and gender of patients, time of transplantation; and of characterization of adherence: method of measuring adherence, observed outcome of adherence and the associated factors identified. Associated factors were those that, by means of univariate or multivariate statistical tests, demonstrated a significant association ( $p < 0.05$ ).

Subsequently, these factors were organized and classified as to whether they could be modified. Adopted as modifiable factors were those that, by consensus of the proponents of the study, were considered possible to be changed by intervention of the care team or not. Nonmodifiable factors were those that could not be changed (e.g., age, gender, exposure prior to transplantation to hemodialysis).

This work was not submitted to a research ethics committee since it is a literature review, as provided for in Resolution 510/2016 of the Brazilian National Health Council.

## RESULTS

Figure 1 presents the flow chart of paper selection for this review. Initially, 1,859 articles were identified and, in the end, 36 articles were selected. The first step in the identification of the articles was the removal of 570 articles for duplicity, leaving 1,289 articles for analysis by title and abstract. After applying the exclusion criteria, 1,178 articles were removed by title and abstract analysis. For full-text analysis 111 articles were selected, 19 of which were not located in their complete form in the CAPES Portal of Scientific Journals to perform this analysis. A total of 55 articles were excluded using the exclusion criteria.



**Figure 1.** Flowchart of the review on factors associated with adherence to immunosuppressant medication in kidney transplant patients.

Table 1 presents the characterization of the studies included in this work. All of the studies identified were observational, most were developed in the last decade, and had the most common goal of determining adherence and the factors associated with it. In addition, most of the studies were small, involving less than or a few hundred patients; only two studies involved larger numbers of patients, the largest being almost 54,000 patients. All studies involved adult patients, usually with an average age between 40 and 50 years. Men were the majority of patients in virtually all studies. Most of the transplant patients had more than one year of transplantation. Figure 2 presents a map with the geographical distribution of the studies.

**Table 1.** Characterization of participants from selected studies in the review on factors associated with adherence to immunosuppressive medication in kidney transplant patients.

Reference/ Country	Purpose of the study	Type of study	Sample size	Patients' age (years)	Patients' gender	Transplantation period
Brahm et al. <sup>8</sup> / Brazil	To present the preliminary results of a prevalence study and determine the risk factors for nonadherence	Cross-sectional	288	Mean 48.6 (11.6)	Men (61.5%)	Mean 7.41 (5.66) years
Brito et al. <sup>9</sup> / Brazil	To compare the coping strategies and stress in adherent and nonadherent renal transplant patients receiving immunosuppression	Comparative, Cross-sectional and Observational	50	Mean 44.1 (12.8)	Men (62%)	Mean 71.8 (12-230) months
Burkhalter et al. <sup>10</sup> / Switzerland	To determine the prevalence of nonadherence in kidney transplant patients and to determine the degree of association of depressive symptoms and daytime sleepiness on nonadherence	Cross-sectional	926	Median 59.7 (IQ 25-75: 50.26 – 67.77)	Men (63%)	Median 9.42 (IQ 4.93 – 15.85)
Burns et al. <sup>11</sup> / USA	To examine the factors that influence nonadherence in kidney transplant patients	Cross-sectional	512	Mean 52.37 (10.74)	Men (60.3%)	Mean 109 (89.2) months
Burns et al. <sup>12</sup> / USA	To examine the relationship between adherence to immunosuppressants and social support	Cross-sectional	70	Mean 51.6 (12.5)	Men (58.6%)	Mean 8.03 (5.96) years
Burns et al. <sup>13</sup> / USA	To determine the prevalence of nonadherence in kidney transplant patients and assess the relationship with various factors	Cross-sectional	61	Mean 48.85 (11.44)	Men (47.5%)	Mean 87.34 (56.2) months
Burns et al. <sup>14</sup> / USA	Use a national database of kidney transplant patients to assess the impact of adherence on health outcomes	Retrospective cohort	137	Mean 52.52 (14.02)	Men (64%)	ND
Constantiner; Cukor15 / USA	To investigate the barriers of immunosuppressive adherence in transplant patients	Cross-sectional	94	Mean 44.1 (12.1)	Men (60%)	Mean 42.0 (57.8) months
Cossart et al. <sup>16</sup> / Australia	To investigate the prevalence and reasons for nonadherence to immunosuppressants in a group of kidney transplant patients	Cohort	161	Mean age of adherents: 58.8 (± 12.6) Nonadherents: 53.5 (± 13.2)	Men (62.1%)	Adherents: 9.8 (8.3) years Nonadherents > 10.2 (7.9) years
Costa- Requena et al. <sup>17</sup> / Spain	To evaluate the percentages of adherence to immunosuppressive treatment in kidney transplant recipients for two years	Retrospective, longitudinal and descriptive	57	Mean 55.0 (13.3)	Men (71.1%)	Average 28.1 (20.4) months
Couzi et al. <sup>18</sup> / France	To evaluate the frequency and factors associated with nonadherence	Cohort	312	Mean 49.5 (13.2)	Men (68.3%)	ND
Cukor et al. <sup>19</sup> / USA	To identify nonadherence to immunosuppressants in kidney transplant patients suffering from depression	Cross-sectional	99	Mean 44.0 (12.0)	Men (59%)	Average 42 (12-312) months
Demian et al. <sup>20</sup> / Canada	To examine the relationship between literacy and health and the relationship with medication adherence	Cross-sectional observational	96	Mean 52.77 (12.56)	Men (56.2%)	Average 8.81 (7.00) years
Ganjali et al. <sup>21</sup> / Iran	To estimate the prevalence of nonadherence and associated factors	Cross-sectional observational	244	Average 39.6 (12.0)	Men (56.6%)	ND
Goldfarb-Rumyantzev et al. <sup>22</sup> / USA	To identify the factors associated with low adherence to immunosuppressive medications	Cross-sectional	199	Mean 43.0 8 14.2	Men (67%)	ND
Gremigni et al. <sup>23</sup> / Italy	To assess the impact of the patient's way of coping on medication use	Cross-sectional	34	Mean 49 (12)	Men (61.7%)	Mean 5.5 (4.0) years
Griva et al. <sup>24</sup> / Singapore	To compare and determine the factors associated with intentional and unintentional nonadherence	Cross-sectional	152	Mean 49.45 (11.44)	Men (50.7%)	ND
Kobayashi et al. <sup>25</sup> / Japan	To determine the prevalence and factors associated with nonadherence in transplant patients in Japan	Cross-sectional	219	Mean 48.3 (9.5) ranging from 29 to 74	Men (57.5%)	Average 79.1 (79.2) months
Kung et al. <sup>26</sup> / Taiwan	Understanding the influence of personal factors and beliefs about the health situation on treatment adherence	Cross-sectional	122	Mean 51.73 (1.76)	Men (57.4%)	Mean 6.78 (4.41) years

Continue...

Table 1. Continuation.

Reference/ Country	Purpose of the study	Type of study	Sample size	Patients' age (years)	Patients' gender	Transplantation period
Lalić et al. <sup>27</sup> / Serbia	To determine the degree of adherence to immunosuppressants in kidney transplant patients	Cross-sectional	60	Mean 44.45 (11.37) ranging from 21–69	Men (63.3%)	Mean 5.34 (3.84) years (ranging from 1-17).
Lee et al. <sup>28</sup> / South Korea	To investigate the relationship between immunosuppressant experience and medication adherence in kidney transplant patients	Cross-sectional	239	Mean 46.8 (10.8)	Men (59.4%)	< 1 year (19.2) 1-3 years (23.4) 3-5 years (16.7) 5-10 years (17.6) > 10 years (23.0)
Liu et al. <sup>29</sup> / China	To assess medication adherence and associated factors in kidney transplant patients	Cross-sectional	209	Mean 41.7 (10.3)	Men (63.2%)	3 to 6 months (23.4) 6 months to 1 year (24.9) 1 to 5 years (30.1) 5 to 10 years (13.4) > 10 years (8.1)
Marsicano et al. <sup>30</sup> / Brazil	To analyze the factors associated with nonadherence in kidney transplant patients	Cross-sectional	100	Mean 45.0 (13.5)	Men (65%)	Mean 72.3 (44.4) months
Pabst et al. <sup>31</sup> / Germany	To determine the prevalence of nonadherence and associated factors in kidney transplant recipients	Cross-sectional	238	Mean 53.15 years (18–78 years)	Men (65%)	Mean 7.2 (1–33) years
Pinsky et al. <sup>32</sup> / USA	To identify the characteristics and other clinical factors associated with adherence in kidney transplant patients	Retrospective cohort	15,525	0-18 years: 1.6% 19-24 years: 4.5% 24-44 years: 39.5% 45-60 years: 34.7% + 61 years: 19.7%	Men (59.7%)	ND
Rocha et al. <sup>33</sup> / Brazil	To evaluate the characteristics and risk factors related to adherence to immunosuppressive treatment in kidney transplant patients through the self-report method using the instrument Basel Assessment of Adherence Scale for Immunosuppressives (BAASIS).	Prospective cohort	59	Mean 45.8 (13.1) (Median 47.0) years	Men (57.6%)	Mean 207.1 (90.5) Median (191.0) months
Russell et al. <sup>34</sup> / USA	To identify the potential predictors and outcomes of medication adherence to immunosuppressive agents in kidney transplant patients	Longitudinal, descriptive, correlational study	121	Mean 51.1 (12.4); ranging from 22–75 years.	Men (63%)	Average 4.7 years (5.6; ranging from 0.1–20.1).
Schmid-Mohler et al. <sup>35</sup> / Switzerland	To investigate the prevalence of nonadherence to immunosuppressants	Cross-sectional	114	Mean 53.6 (11.9) years	Men (64.9%)	Median 2.6 years (IQ 25-75%: 1.7-3.8)
Silva et al. <sup>5</sup> / Brazil	To investigate how beliefs in high efficacy, locus control in health and religiosity are associated with adherence to immunosuppressants in kidney transplant patients	Cross-sectional	88	Mean 47.2 (12.9)	Men (63.6%)	Mean 108.7 (43.9) months
Teng et al. <sup>36</sup> / China	To evaluate the experience of immunosuppressant-associated symptoms in kidney transplant patients and its association with medication adherence	Cross-sectional	231	Mean 44.9 (10.7)	Men (60.6%)	ND
Vankova et al. <sup>37</sup> / Czech Republic	To determine the adherence to immunosuppressive agents in kidney transplant patients in the Czech Republic	Cohort	211	Mean 55.0 (12.4)	Men (58.3%)	Mean 6.6 (5.9) years
Vasquez et al. <sup>38</sup> / USA	To identify the factors that may affect medication nonadherence in kidney transplant patients	Cross-sectional	95	Mean between 44.4 and 47.6 years	Men (58.9%)	ND
Villeneuve et al. <sup>39</sup> / France	Assess adherence in kidney transplant patients three years after transplant	Prospective cohort	345	Mean 51.1 (13.1)	Men (63.5%)	ND
Weng et al. <sup>40</sup> / Taiwan	To determine the factors associated with immunosuppressant adherence in kidney transplant patients in Taiwan	Cross-sectional	145	Mean 45.5 (11.8); ranging from 18 to 71	Men (45.5%)	mean 7.4 (4.6) years
Xia et al. <sup>41</sup> / China	To examine the belief in immunosuppressants and the adherence to these medications by Chinese patients	Cross-sectional	208	Mean 43.7 ranging from 18 to 71	Men (63.5%)	Mean of 4.7 years; ranging from 1 to 19 years

ND: Not determined.



**Figure 2.** Geographical distribution of studies included in the review on factors associated with adherence to immunosuppressive medication in kidney transplant patients.

Data available in Repositório Institucional da UnB describe the methods of measuring adherence, the observed adherence outcomes, and the associated factors identified. Adherence was measured in most studies by validated and widely used instruments, such as the Baasis and the ITAS. Other scales used for other diseases have also been adopted, such as the Morisky instrument, used in various versions of 4 or 8 questions. The adhesion values were quite distinct ranging from very low values like 10.8 and 16.9%, to very high values like 90.8 and 94.5%. The tests used to gauge the associations involved both univariate and multivariate tests.

The associated factors were quite diverse and have been systematized in Table 2.

**Table 2.** Factors associated with adherence to immunosuppressants according to the literature review, 2021.

Factors that increase adherence	
Modifiable	Nonmodifiable
Higher life satisfaction index	
Better perception with medicines	
Increased perception of the risk of infections	
Type of immunosuppressant used (use of cyclosporine instead of tacrolimus; use of corticosteroids)	
Physicians' support	
Access to health care	
Being married	Hemodialysis period before transplant
Having social support	Longer waiting time on list
No increase in creatinine rate	
Appropriate concentration of immunosuppressants	
Better mental health	
Less perception of the seriousness of the use of immunosuppressants	
Less perception of barriers	
Intrinsic religiosity	
Factors that decrease adherence	
Employed person active in the labor market	
Use of tacrolimus	
Presence of stress	
Palliative-type confrontation	
Daytime sleepiness	
Greater difficulty in using medications	
Presence of barriers	
Financial problems	
Less knowledge or literacy in health	Not being white
Low medication knowledge	Living donor
Less understanding of graft loss	Autoimmune nephritis
Less autonomy	Having more than two transplants
Active coping form/locus of control	Not be a native of the country
Poor satisfaction with immunosuppressants	
Forgetfulness and change of routine	
Beliefs and concerns about immunosuppressants	
Low income	
Use of mycophenolate	
Adverse events to immunosuppressants	
Adverse events of the gastrointestinal tract	
Factors where there is no consensus in the literature about the influence on adherence	
Glomerular filtration rate value	Gender
Presence of depression	Age
Self-efficacy	Transplantation period
	Comorbidity index

There are associated factors that show a discrepancy, such as age, gender, and income. Some immunosuppressants have a relationship with adherence, which may be related to cost or adverse events. Many factors associated with adherence are related to the relationship with the care team, health literacy and coping, and autonomy. It was observed that factors such as social support increases the chance of adherence. Emotional issues such as stress and depression are negatively associated with adherence.

With the identification of the associated factors, it can be observed that some factors are quite persistent in contributing to nonadherence to medication, and we can mention the low knowledge or lack of credibility in immunosuppressants also contribute to nonadherence to medication.

## DISCUSSION

The results show that the articles included in this review were recent and originated mainly in North American and European countries. This is due to the fact that it is in these places where the largest number of teams and kidney transplants in the world are concentrated.<sup>42</sup> However, even though Brazil is a country with a large number of kidney transplants,<sup>1</sup> only five studies were observed among all those included.

As chronic kidney disease affects mainly adult and male people, a similar patient profile was identified in the selected articles. Corroborating these data, ABTO<sup>1</sup> describes that adult men are the most frequent renal transplant patients.

Adherence was measured in most studies by validated and widely used instruments, such as the Baasis and ITAS (data available in data repository). On the other hand, the Morisky instrument was also used in versions of four or eight questions. This instrument was initially developed for the assessment of adherence in hypertensive patients. According to Pasquali,<sup>43</sup> some authors develop their own instruments and use databases. Even though all these instruments aim to measure the same behavior, the comparison between the results is not always possible, due to the complexity of the phenomenon being evaluated and the differences in its constructs.

The presented adhesion values were diverse, ranging from very high values (close to 100%) to very low values (around 10%). These findings may be related to several factors such as patient profile, method used for adherence, observation time, the drugs used, duration of disease, among others.<sup>44</sup> Next, we will discuss the main factors related to adherence to immunosuppressants identified in the different studies.

Some demographic variables were described for association with adherence. Age and gender are pointed out as factors that can either increase or decrease adherence, and therefore should be observed with caution in the management of transplant patients<sup>21</sup>. Skin color (nonwhite) was also identified as a factor that decreases medication compliance, but because it was identified in only one study, it should not be considered in patient care. On the other hand, the fact that the patient is not a native of the country is associated with low adherence to medication must be related to barriers, such as not understanding the language of the country and difficulty interpreting their treatment.<sup>31</sup>

In a different way, it was observed that the fact that the patient is married was pointed out as a factor that increases adherence, which may be associated with the fact that the partner contributes to the patient following pharmacotherapy correctly, contributing positively to medication adherence,<sup>41</sup> that is, it would be a form of social support. Corroborating this finding, it was shown in the results that social support contributes to increased adherence, showing the importance of the patient's support network, be it material or financial help, because many patients have a slow recovery, taking time to return to their work activities. Emotional support is also important for the patient such as understanding and affectionate care and support.<sup>16</sup>

In this sense, financial problems (patients with low income) are pointed out as factors that become barriers to adherence, because the patient does not have the resources to go to the consultations or to buy the drugs at the dispensing units, making it difficult to continue the treatment.<sup>16</sup>

Also related to the patients is the higher rate of comorbidities, i.e., the parameter that informs the amount of other existing health problems and their complexity was pointed out in the results as a factor that decreases adherence to medication. This can occur either by increasing the complexity of pharmacotherapy, or by interactions between drugs.<sup>6,28</sup>

On the other hand, several qualitative factors have been described as associated with adherence. One of them was the perception about life control that concerns personal beliefs about one's own ability to control events and threats. In this sense, this factor was associated with decreased adherence, because the patient does not have autonomy in their own decisions and has no incentive to follow the treatment with the drugs because they think that their attitudes are not useful.<sup>48</sup>

Similar to this is self-efficacy, which is the individual's perception of his capabilities in performing a certain activity. This factor was positively associated with increased adherence due to the fact that the patient seeks to overcome the proposed challenges,

including those related to their treatment.<sup>49</sup> Another factor that increases adherence is intrinsic religiosity, in which the patient seeks to harmonize their interests and their needs according to their beliefs, striving to follow them, thus adhering to medication.<sup>5</sup>

Corroborating these findings, it was also observed that the patient's life satisfaction index is associated with increased medication compliance, classified as a modifiable factor that is associated with transplantation and kidney function.<sup>47</sup> Similarly, the presence of emotional factors such as stress and depression decrease medication compliance. This occurs because, many times, the patient's emotional state does not allow the patient to maintain the treatment.<sup>9</sup> In this case, the identification of these problems by the team is important to guarantee the success of the transplant.

Low literacy in health, on the other hand, was noted in the results as a factor that decreases adherence. This may occur because patients do not understand the care they need with their health after transplantation, starting with the importance of the use of immunosuppressants and the continuity of follow-up with the healthcare team.<sup>20</sup> Corroborating this finding, it was observed that low knowledge about pharmacological treatment contributes to a decrease in adherence. This may occur because immunosuppressive pharmacotherapy is not widely used by the population, which can generate insecurity and lack of knowledge about the real need for treatment in the prevention of rejection.<sup>17</sup> On the other hand, the positive perception about immunosuppressive drugs is also a factor that increases adherence, in this case, the understanding of pharmacotherapy and the belief in its effectiveness are factors that improve this behavior.<sup>24,26</sup>

In addition to these factors, other situations such as changes in routine were associated as a factor that decreases compliance, because patients end up forgetting to take their medication at the correct times. This scenario ends up being more common on weekends.<sup>35</sup> Similarly, excessive daytime sleepiness, characterized as the inability of the person to stay awake during the daytime waking period, was also associated with decreased adherence to medication,<sup>10</sup> this possibly occurs due to missed schedules or even omission of medication doses, as also occurs in routine changes.

Also in this context, work activities were associated with decreased medication adherence. It is known that kidney transplant patients return to work gradually and slowly after the procedure.<sup>1</sup> With the return to work, the patient changes the routine and, depending on the schedule of the medications, there may be forgetfulness or delay of doses causing nonadherence,<sup>35</sup> moreover, work can interfere with access to health services (routine consultations) or to medications due to incompatibility of schedules to access the medications.

Similarly, when there is ease of access to the health service and to the medical team, greater adherence to medication was observed, which may demonstrate that the transplanted patient needs to be monitored.<sup>25</sup>

Regarding kidney disease, its treatment, and the type of donor, it was observed that the time of hemodialysis performed before the transplant was pointed out as a factor that contributes to the increase of adherence. Patients who undergo hemodialysis on some days of the week need to go to the hospital for the procedure to be performed, having to adjust their routine and modify it in order to continue with the treatment.<sup>45</sup> In light of this, the value given to the transplant is higher and therefore serves as a factor that encourages careful behavior with the medications. In addition, studies<sup>18,33</sup> point out that the fact that patients stay for a long time on the transplant waiting list, hoping for the improvement of their clinical condition, influences the higher adherence at the beginning of transplantation.

Having a living donor, on the other hand, has been shown to be a factor that decreases adherence. Patients who receive living donation spend less time in the waiting line and often have preemptive transplantation (before starting dialysis). In this case, the waiting and surgery time is shorter, and may result in less value to the treatment.<sup>22</sup> Patients who have had more than one transplant were also mentioned as a factor that decreases compliance, as they may have the perception that if they have had one procedure, they are likely to have another one.<sup>25</sup>

Transplant time was a factor associated with adherence. The shorter this time, the higher the observed adherence, and vice versa. This may be related to some factors, one of which is that right after the transplant, the patient is better followed by the team, has more fear of rejection, and values more the fact that he or she does not need dialysis.<sup>46</sup> Also, it is also related to persistence in treatment, that is, remaining adherent over time.

In addition, data related to the function of the graft, such as not having an increased creatinine rate and having a higher glomerular filtration rate, were associated as factors that increase compliance, since the patient sees the benefit of the transplant in their clinical outcomes.<sup>13,27</sup>

Regarding the immunosuppressants used, it was observed that the use of some immunosuppressants that have a chance of developing adverse events can reduce the adherence and consequently the survival of kidney transplant patients.<sup>7,50</sup> An example is the use of mycophenolate that causes gastric disorders, such as diarrhea, which interfere significantly in the patient's routine.<sup>18,51</sup>

The use of tacrolimus was associated as a factor that decreases adherence. This may also be related to adverse events, because it is a drug with a narrow therapeutic window, which can cause tremors, hyperglycemia, which increases the chance of diabetes mellitus, and renal toxicity.<sup>50</sup>

Regarding possible post-transplant complications, the perception of the risk of infections was associated as a factor that increases medication compliance leading to a decrease in infection episodes and their consequences to the patient after kidney transplantation.<sup>52</sup>

A limitation of this study is that papers from the gray literature were not included; furthermore, there was a loss of papers that, even if previously selected for full-text reading, could not be retrieved. Also, even though the reviews were excluded, they did not have their references analyzed, so some papers on the topic may not have been identified. The quality of the papers included was not evaluated, nor was the research protocol registered on review sites.

## CONCLUSION

With the results obtained, the medication compliance profile of kidney transplant patients is diverse, and a set of actions and factors to stimulate this behavior.

In general, patients who understand the importance of transplantation and the use of immunosuppressants tend to be more adherent because they see benefits to the quality of life of this procedure and, therefore, use immunosuppressants. It was also identified that patients who have support, either from family or even religion and belief, have a greater chance of adherence. Mental health was also pointed out as a protective factor for nonadherence.

On the other hand, factors related to adverse events of immunosuppressants or issues that may generate barriers, such as work, financial difficulties, and language may negatively influence adherence.

It is important to know the patient and the factors that can positively and negatively influence medication use behavior, as this can be used as a strategy by the healthcare team for managing patients.

As a perspective of this work, there is the possibility of developing strategies in the care process in order to reduce possible barriers and encourage behaviors that increase adherence, as previously discussed.

## CONFLICT OF INTEREST

Nothing to declare.

## AUTHORS' CONTRIBUTION

**Substantive scientific and intellectual contributions to the study:** Costa LM and Galato D; **Conception and design:** Costa LM and Galato D; **Data analysis and interpretation:** Costa LM and Galato D; **Article writing:** Costa LM and Galato D; **Critical review:** Galato D; **Final approval:** Costa LM and Galato D.

## DATA CONFIDENTIALITY

Not applicable.

## AVAILABILITY OF RESEARCH DATA

Data are available in Repositório Institucional da UnB.

[<https://repositorio.unb.br/handle/10482/45722>]

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