

Prevalence and Modifiable Factors for Holistic Non-Adherence in Renal Transplant Patients: A Cross-Sectional Study

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Introduction: In renal transplant recipients, compliance with medical therapy is vital. Non-adherence is considered a risk factor for worst outcomes in kidney recipients, with attributed outcomes of 64% for graft loss and 80% for late acute rejection. Most literature defines adherence as self-based immunosuppression compliance but does not consider other relevant factors such as consult and procedure compliance. Therefore, this study aims to describe adherence prevalence in kidney transplant recipients and the factors related to non-adherence.

Methods: This cross-sectional study included 1030 renal transplant patients followed by Colombiana de Trasplantes between January 2019 and July 2021. Sociodemographic and clinical variables were obtained based on clinical records. The mental-health group diagnosed holistic adherence in a semi-structured interview. The diagnosis considered medication intake failure, frequency and number of failures to medical controls or other procedures, suspicious non-adherence behaviors, and serum levels of immunosuppressants. A bivariate followed a descriptive analysis, and a forward logistic regression was performed for non-adherence.

Results: Patients had a median of 47 years, and 58.1% were male. Non-adherence was presented in 30.7% of patients. The non-adherence patients were younger, with a higher prevalence of males, single, divided transplant care, had a longer time after transplantation, psychopathological diagnosis, and more reinforcement education by only nursing. Older age and multidisciplinary reinforcement education were protective factors. On the other hand, poor social support, psychopathology diagnosis, and longer time after transplant presented as non-adherence risk factors.

Conclusion: Holistic non-adherence was diagnosed in approximately one-third of renal transplant recipients. Its definition included more than just medication non-compliance and could identify more non-adherent patients. Notably, there is a need to consider the related factors in the health follow-up and encourage future research in modifiable factor interventions aiming to increase adherence and achieve better outcomes for renal transplant patients.

Keywords: treatment adherence and compliance, kidney transplantation, patient compliance, social support, patient education, mental health, psychopathology

Introduction

Kidney transplantation has been considered the best treatment for chronic kidney disease stage 4 or 5.^{1,2} In 2021, Colombia contributed with 606 (0.55%)³ of the 109,215 kidney transplants that were performed worldwide.^{3,4} In the Colombian population, at the fifth year posttransplant, approximately 11.6% of kidney transplant recipients will have a graft loss,⁵ and it is well-described worldwide that medium- and long-term outcomes are vastly influenced by adherence to treatment.^{6,7} Attributed outcomes for non-adherence have been described as high as 64% for graft loss⁸ and 80% for late acute rejection, according to global literature.⁹ Consequently, it is essential to understand and describe non-adherence in renal transplant recipients in order to improve their outcomes.

The World Health Organization considers adherence goes beyond taking prescribed pharmaceuticals and defines it as

The extent to which a person's behavior – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider.¹⁰

Meichenbaum and Turk also considered adherence as the set of specific behaviors of the patient in relation to all aspects of his treatment and not only the correct taking of his medication.¹¹ But this wide definition is poorly used in kidney transplant recipients, defined mainly as compliance with the immunosuppression therapy and leaving behind other patient behaviors. Therefore, immunosuppression non-adherence in renal transplant recipients presents between 2 and 67% upon its definition and measurement.⁶

Many factors have been related to immunosuppression non-adherence, such as younger age, poor social support, cognitive impairment, and intrinsic religiosity.^{12–15} Moreover, previous research has found modifiable risk factors associated with immunosuppression adherence, such as health beliefs, self-beliefs, and self-efficacy.^{16,17} However, these factors are limited to immunosuppression non-adherence, not with a complete understanding of adherence. Also, these results are based on relatively small samples. Therefore, we estimated non-adherence prevalence and associated factors from a wide approach, including a large sample of Colombiana de Trasplantes and its network center patients. These results may enable us to improve our population's adherence and outcomes for kidney transplant recipients.

Materials and Methods

An analytical, cross-sectional study was conducted, including all kidney transplant recipients followed by Colombiana de Trasplantes (network of 4 centers: Bogotá, Barranquilla, Rionegro, and Armenia) between January 2019 and July 2021. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology statement.¹⁸

Population and Sample

A non-randomized convenience sample was performed without prior sample size calculation by considering the inclusion of all patients who met the selection criteria. We included all patients in follow-up by Colombiana de Trasplantes after a renal transplant who continue being followed for at least one year after their evaluation. No patients were excluded. A power of 98% was estimated in R studio with the “pwr” package for the sample included ($n = 1030$) with a 95% confidence and a size effect of 0.39.¹⁹ The size effect was calculated with the Cohen formula considering a 50% expected prevalence described by Alba M²⁰ and the obtained prevalence.

Data Collection

Data were collected from the clinical history and a semi-structured interview to determine adherence. A mental health team member conducted this interview with transplant patients (two psychiatrists and one psychologist) physically or virtually. In addition, the same team interviewed all patients in the four centers. This interview explored sociodemographic characteristics, events in the immediate post-transplant period (less than three months), and events related to their behavior in the late post-transplant period (more than three months). At the end of the interview, the mental health professional diagnosed the patient's behavior as adherent or non-adherent.

Main Outcome

The diagnosis of adherence or non-adherence was a clinical holistic impression by a mental health team member that considered aspects such as pharmaceutical intake failure and its frequency, number of failures to medical controls, failure to other procedures (hospitalization, biopsies, laboratories), presence of suspicious non-adherence behaviors and serum levels of immunosuppressants. Table 1 elaborates on the postulated definitions of adherence, and Appendix 1 presents the semi-structured interview.

Table I Definitions of Adherence, Non-Adherence, and Subtypes

Name	Definition
Adherence	It is the behavioral pattern that is indicative of the patient's motivation and empowerment in relation to their treatment, oriented to the compliance of the therapeutic regimen. It differs from simple therapeutic compliance because the patient assumes an active and responsible role in relation to the post-transplant instructions and recommendations, as part of a positive patient-physician alliance.
Non-adherence	It is the modification or non-compliance with the therapeutic regimen that endangers the graft's survival or functionality, made by the patient consciously or unconsciously, openly or secretly, intentionally or unintentionally. Operationally, a non-adherent patient fails to attend monthly check-ups, omits or modifies the doses of his medications, or persistently disobeys medical orders regarding taking biopsies, hospitalization, laboratory tests, and/or careful behavior (smoking, diet).
Non-adherence subtypes	
Incidental non-adherence	This is accidental non-adherence, resulting from the patient's ignorance of the high importance of perfect discipline in the schedule and calendar of their medication intake, medical controls, laboratory tests, and other procedures ordered by their physician. It is more frequent in the first post-transplantation weeks. It seems to be more frequent in people with low educational backgrounds and/or coming from rural areas, who find it difficult to understand and adapt to medical technology.
Apathetic non- adherence	It is non-adherence resulting from the patient's psychological compromise. These are patients with clinically significant psychological pathology (depressed, distressed or psychotic) who are not interested in their treatment commitments as a result of this pathology.
Invulnerable non- adherence	It is the irresponsible behavior that characterizes many adolescents, dedicated workers, and in general, patients who evolve so successfully post-transplant that they dedicate themselves to their "normal" life and forget about the importance of the treatment. They miss one or several doses, delay the schedule for taking immunosuppressors, come back on time (or definitely late) and act as if nothing is going to happen because of these "small" oversights.
Disguised non- adherence	It is the non-adherent behavior of non-competent patients (children, intellectual disability, and patients with cognitive deficits). In this case, non-adherence is an irresponsible behavior (involuntary or deliberate) of the person empowered to administer their treatment, such as their caregiver.
Opposition non- adherence	It is the deliberate behavior of purposely oppose to the treatment. This is the case of a patient who refuses the therapeutic measures his transplant imposes on him—for example, a patient who is trying to avoid the appearance of a certain side effect that is unwilling to tolerate.
Non-specific non- adherence	When the interviewer considers that they cannot classify the patient in any of the five previous groups, a good example is the case of non-adherence (or suspected non-adherence) due to administrative reasons from the insurer.
Other definitions	
Immunosuppression non-adherence Suboptimal immunosuppressor levels	Any failure in immunosuppression compliance. Understand by having missed one or more doses of immunosuppressive medication in the previous four weeks. Immunosuppressor levels are requested for dose adjustment and regarding the patient's clinical condition. The main reasons are renal function worsening, acute rejection, clinical or paraclinical findings of toxicity, recurrent infection, secondary or adverse events, and pharmaceutical modifications that affect immunosuppressor metabolism. The suboptimal levels are defined as: <ul style="list-style-type: none"> • Tacrolimus <5 ng/mL. • Sirolimus <4 ng/mL. • Everolimus <4 ng/mL. • Cyclosporine <100 ng/mL.

Note: The required levels of immunosuppression can change depending clinical status of the patients.

Variables

Sociodemographic and clinical variables were included to characterize the patients and explore associated factors to non-adherence. The sociodemographic variables considered were gender, age, and marital status. Clinical aspects related to the transplant procedure included transplant care, number of transplants, and type of donor. Factors related to transplant follow-up were reinforcement education in the first months, early anxiogenic events, and after-transplant follow-up time. Variable definitions are presented in [Appendix 2](#).

Statistical Analysis

A descriptive analysis of the variables was performed according to their nature and distribution. Comparison of the adherence and non-adherence groups was evaluated using the chi-square test between categorical variables and Student's *t*-test or Mann–Whitney *U*-test between quantitative variables according to their distribution. Results were considered statistically significant when the *p*-value was less than 0.05. A logistic regression was performed to determine associated factors to non-adherence. We calculated crude and adjusted odds ratios (OR) with 95% confidence intervals (CI) to identify independent risk factors. For the multivariate analysis, we identified the variables with significant differences in the bivariate analysis and those clinically relevant. Variable selection was performed using a forward method. The inclusion of each variable was determined by statistical significance in ANOVA (analysis of variance) and chi-square tests compared to the previous model; once all variables were included, we sought the most parsimonious model. Any variable that changes the estimates by 10% was considered a cofounder and was controlled by its inclusion in the logistic regression.^{21,22} A complete or full model was also made, including all bivariate significant and clinically relevant variables. The final or reduced model was assessed with the Hosmer–Lemeshow test and Nagelkerke's R^2 (Pseudo-R-square).^{23,24} Multicollinearity was evaluated using the Variance Inflation Factor (VIF). Any variable with a VIF greater than five was considered highly correlated and excluded from the model.²⁵ A sub-analysis by transplant group was conducted because patients transplanted by other groups did not receive the same adherence training and reinforcement as the kidney recipients of Colombiana de Trasplantes, particularly during the pre-transplant and early post-transplant periods. Analyses were performed using R software version 4.2.2.²⁶

Ethical Statement

This study complied with International Ethical Guidelines by the Council for International Organizations of Medical Sciences (CIOMS) and the World Health Organization (WHO),²⁷ the Declaration of Helsinki,²⁸ and national ethical guidelines. All the kidneys were donated voluntarily with written informed consent in accordance with the Declaration of Istanbul.²⁹ The Ethics Committee waived the research informed consent as the study was classified as with-out-risk by Colombian Resolution 8430.³⁰ The analysis and presented results were anonymized, ensuring patient data confidentiality. The study only began after approval of the Ethics Committee.

Results

A total of 1030 patients were attended by Colombiana de Trasplantes during the study period. They had a median age of 47 years (IQR 36–58), 58.5% (*n* = 603) were men, 56.4% (*n* = 581) had a stable marital union and 30.9% (*n* = 319) were single. On the other hand, more than a third of patients had a diagnosis of psychopathology, in which affective, personality and adaptive disorders prevailed ([Table 2](#)).

Our surgical team transplanted and followed 68.1% (*n* = 701) of patients; the remaining patients were operated by other transplant groups and referred to our center (divided transplant care). Most of them of a deceased donor (69.1%) and only few patients (2.7%) were retransplanted (second or more transplant). In the first three post-transplant follow-up months, the majority of patients had a functional social support (86.3%), less than a half had an education reinforcement by psychology and nursing (45.7%), and 42.3% presented early anxiogenic events.

The holistic non-adherence was diagnosed in 30.8% (*n* = 317) and immunosuppression non-adherence in 25.9% (*n* = 267) kidney recipients.

Table 2 Characterization of Adherent and Non-Adherent Patients. Definitions for Each Variable are in [Appendix 2](#)

Variables	Total (N=1030)	Non-Adherent (n=317)	Adherent (n=713)	P-value	Non-Adjusted OR for Non-Adherence (CI 95%)
Age in years, median [IQR]	47 [36–58]	44 [34–56]	48 [37–59]	0.002 ^a	0.98 (0.97–0.99)
Sex, n(%)				0.174 ^b	
Feminine	427 (41.5)	121 (38.2)	306 (42.9)		reference
Masculine	603 (58.5)	196 (61.8)	407 (57.1)		1.21 (0.92–1.59)
Marital status, n(%)				0.001 ^a	
Single	319 (31)	117 (36.9)	202 (28.3)		reference
Stable marital union	581 (56.4)	152 (47.9)	429 (60.2)		0.61 (0.45–0.82)
Dissolved marital union	58 (5.6)	17 (5.4)	41 (5.8)		0.71 (0.38–1.29)
Underage	17 (1.7)	9 (2.8)	8 (1.1)		1.94 (0.72–5.30)
Other	55 (5.3)	22 (6.9)	33 (4.6)		1.15 (0.63–2.05)
Transplant care, n(%)				<0.001 ^a	
Single center transplant care by our group	701 (68.1)	173 (54.6)	528 (74.1)		reference
Divided transplant care	329 (31.9)	144 (45.4)	185 (25.9)		2.37 (1.80–3.13)
Time after transplant, n(%)				<0.001 ^a	
Between 0 and 12 months	134 (13.0)	22 (6.9)	112 (15.7)		reference
Between 13 and 60 months	419 (40.7)	112 (35.3)	307 (43.1)		1.83 (1.12–3.10)
61 months or more	477 (46.3)	183 (57.7)	294 (41.2)		3.14 (1.95–5.25)
Number of transplants, n(%)				0.379 ^b	
First	1002 (97.3)	311 (98.1)	691 (96.9)		reference
Second or more	28 (2.7)	6 (1.9)	22 (3.1)		0.60 (0.22–1.42)
Donor type, n(%)				0.170 ^b	
Cadaveric	712 (69.1)	229 (72.2)	483 (67.7)		reference
Living	318 (30.9)	88 (27.8)	230 (32.3)		0.80 (0.60–1.07)
Anxiogenic events[†], n(%)				0.555 ^b	
No	594 (57.7)	178 (56.2)	416 (58.3)		reference
Yes	436 (42.3)	139 (43.8)	297 (41.7)		1.09 (0.83–1.42)
Social support[†], n(%)				0.010 ^a	
Functional	889 (86.3)	259 (81.7)	630 (88.4)		reference
Poor	103 (10.0)	40 (12.6)	63 (8.8)		1.54 (1.00–2.34)
Inadequate	38 (3.7)	18 (5.7)	20 (2.8)		2.18 (1.12–4.21)
Education reinforcement[†], n(%)				<0.001 ^a	
Nursing	559 (54.3)	220 (69.4)	339 (47.5)		reference
Nursing and psychology	471 (45.7)	97 (30.6)	374 (52.5)		0.40 (0.30–0.53)
Psychopathology, n(%)				<0.001 ^a	
No	652 (63.3)	123 (38.8)	529 (74.2)		reference
Yes	378 (36.7)	194 (61.2)	184 (25.8)		4.53 (3.42–6.02)
Psychopathological diagnosis, n(%)				<0.001 ^a	
Affective Disorder	115 (11.2)	54 (17.0)	61 (8.6)		3.80 (2.51–5.77)
Personality disorder	70 (6.8)	50 (15.8)	20 (2.8)		10.75 (6.26–19.09)
Adaptive disorder	43 (4.2)	8 (2.5)	35 (4.9)		0.98 (0.41–2.06)
Intellectual disability and other developmental disorders	32 (3.1)	20 (6.3)	12 (1.7)		7.16 (3.45–15.47)
Dementia and organic disorders	15 (1.5)	13 (4.1)	2 (0.3)		27.95 (7.59–180.27)
Other	103 (10.0)	49 (15.5)	54 (7.6)		3.90 (2.52–6.02)
No psychopathological diagnosis	652 (63.3)	123 (38.8)	529 (74.2)		reference

Notes: ^aComparison by Mann-Whitney *U*-test. ^bComparison by chi-square test. *Statistically significant result $p < 0.05$. [†]First 3 months post-transplant follow-up.

Comparison Between Adherent and Non-Adherent Patients

Non-adherent patients were younger (44 vs 48 years, $p = 0.002$), with a higher proportion of single and underage patients ($p = 0.001$), and with more psychopathological diagnoses (61.2% vs 25.8%, $p < 0.001$). Non-adherents were more commonly transplanted by other transplant groups (45.4% vs 25.9%, $p < 0.001$). In the first months after transplantation, non-adherent patients had higher rates of poor and inadequate social support ($p = 0.009$), and reinforcement education was primarily given by nursing (69.4% vs 47.5%, $p < 0.001$) (Table 2). Non-adherent patients were grouped by subtype and compared by sex in Figure 1. The most common

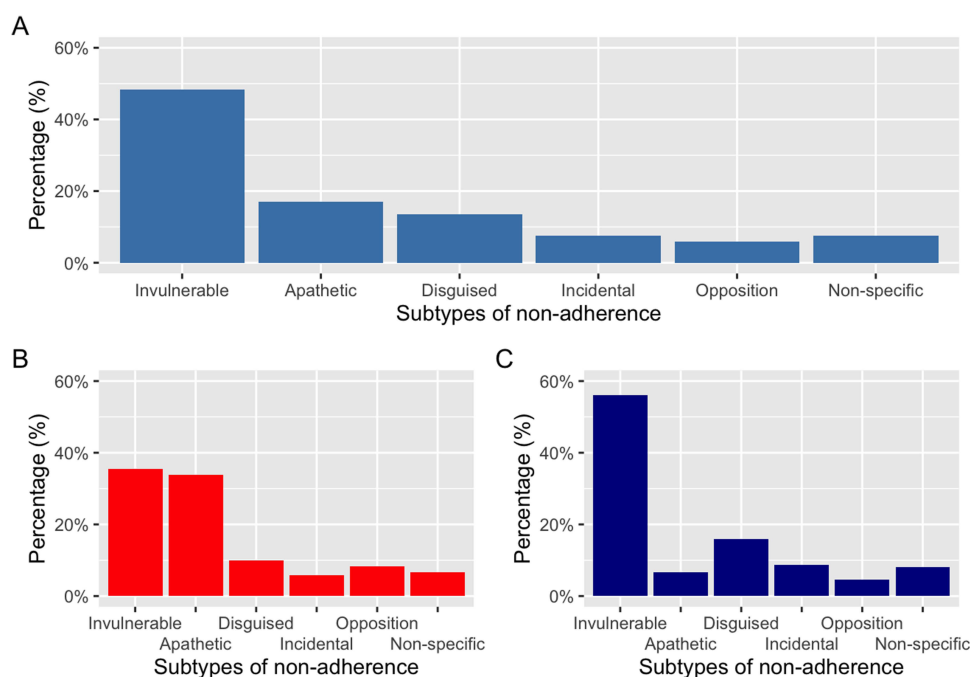


Figure 1 Graphic representation of non-adherence subtypes by sex. **(A)** Non-adherence subtypes in total population. **(B)** Non-adherence subtypes in women. **(C)** Non-adherence subtypes in men.

subtype was invulnerable (48.3%) and apathetic (17%). The comparison between subtypes is presented in [Table S1 \(Appendix 3\)](#). Definitions for each non-adherence subtype are presented in [Table 1](#) and deepened in [Appendix 2](#).

Crude Model

We found that older age performed as a protector factor with 0.98 OR (CI 0.97–0.99). Being male increased 21% the risk of non-adherence (OR 1.21, CI 0.92–1.59), and stable marital union decreased by 39% compared to being single (OR 0.61, CI 0.45–0.82). When we analyzed the marital status by sex, we found that in women there was no significant change between being single or in a marital union, but for men being in a marital union decreased 49% the risk for non-adherence (OR 0.51, CI 0.35–0.76). Patients transplanted by other transplant groups had twice the risk for non-adherence (OR 2.37, CI 1.80–3.13). On the other hand, being retransplanted or transplanted from a living donor did not have an association with adherence or non-adherence. The remaining un-adjusted ORs are presented in [Table 2](#).

Table 3 The Multivariate Model with the Results of the Factors Associated with Non-Adherence. *Statistically Significant $p < 0.05$ **Very Statistically Significant $p < 0.005$ †First 3 months post-transplant follow-up.

Variables	Adjusted OR for Non-Adherence Full Model		Adjusted OR for Non-Adherence Reduced Model	
	OR (CI 95%)	p-value	OR (CI 95%)	p-value
Age (years)	0.97 (0.96–0.98)	<0.001**	0.97 (0.96–0.98)	<0.001**
Sex (Reference feminine)				
Masculine	1.39 (1.00–1.94)	0.046*	–	–
Transplant care (Reference Single center transplant care by our group)				
Divided transplant care	1.41 (0.95–2.10)	0.088	–	–
Education reinforcement † (Reference only nursing)				
Nursing and psychology	0.42 (0.27–0.64)	<0.001**	0.36 (0.25–0.51)	<0.001**

(Continued)

Table 3 (Continued).

Variables	Adjusted OR for Non-Adherence Full Model		Adjusted OR for Non-Adherence Reduced Model	
	OR (CI 95%)	p-value	OR (CI 95%)	p-value
Anxiogenic events[†] (Reference no)				
Yes	1.04 (0.75–1.43)	0.798	–	–
Social support[†] (Reference functional)				
Poor	2.03 (1.22–3.36)	0.005*	2.09 (1.26–3.46)	0.003*
Inadequate	2.31 (1.06–4.99)	0.032*	2.31 (1.07–4.99)	0.031*
Psychopathological diagnosis (Reference no psychopathological diagnosis)				
Affective Disorder	4.18 (2.63–6.66)	<0.001**	3.71 (2.39–5.77)	<0.001**
Personality disorder	11.26 (6.26–20.97)	<0.001**	11.56 (6.45–21.45)	<0.001**
Adaptive disorder	1.26 (0.50–2.84)	0.585	1.07 (0.43–2.37)	0.866
Intellectual disability and other developmental disorders	5.24 (2.38–11.95)	<0.001**	5.50 (2.52–12.44)	<0.001**
Dementia and organic disorders	44.46 (11.10–300.66)	<0.001**	49.53 (12.52–332.7)	<0.001**
Other	3.54 (2.22–5.63)	<0.001**	3.64 (2.29–5.78)	<0.001**
Time after transplant (Reference between 0 and 12 months)				
Between 13 and 60 months	1.50 (0.85–2.73)	0.163	1.51 (0.87–2.72)	0.152
61 months or more	2.21 (1.23–4.11)	0.009*	2.38 (1.35–4.36)	0.003*

Adjusted Model

For the multivariate model, the results of the full and reduced logistic regression model are presented in Table 3. In the reduced model, age evidenced a 3% reduction in the risk of non-adherence for each year increase (OR 0.97, CI 0.96–0.98). In the first three months after transplantation, having inadequate social support increased two times the risk of non-adherence (OR 2.31, CI 1.07–4.99), and poor social support also increased the risk (OR 2.09, CI 1.26–3.46) both compared to functional social support. Joint reinforcement education by psychology and nursing behaved as a protective factor reducing the probability of non-adherence by 64% (OR 0.36, CI 0.25–0.51). Psychopathology was a risk factor for non-adherence, especially dementia, personality disorder, and developmental disorders or intellectual disability, with ORs of 49.53, 11.56 and 5.50, respectively. Finally, a post-transplant follow-up time greater than five years presented an OR of 2.38 (CI 1.35–4.36), behaving as a risk factor for non-adherence compared to less than 12 months.

According to Bagley SC standards on logistic regression documentation,³¹ our reduced model had sufficient events per variable (63:1), there was no multicollinearity, Hosmer and Lemeshow test supported the model goodness of fit (p 0.13), and Nagelkerke R² was 0.294.

Sub-Analysis by Transplant Group

Non-adherence was found in 24.7% of kidney recipients who received single-center transplant care in Colombiana de Trasplantes and 43.8% in patients who received divided transplant care transplanted by other groups (P < 0.001) (Figure 2). In addition, patients that received divided transplant care were older (46 vs 49 years, p 0.003), with a higher proportion of stable marital union and other civil status patients (p 0.03), greater time after transplant (32% vs 76.9% of more than five years, p < 0.001), less living donor transplants (7.9% vs 15.8%, p < 0.001).

The multivariate model in patients transplanted by our group showed that age and education reinforcement by nursing and psychology were protective factors for non-adherence, male sex, psychopathology, five years or more after transplant, and poor and inadequate social support were risk factors for non-adherence. On the other hand, the

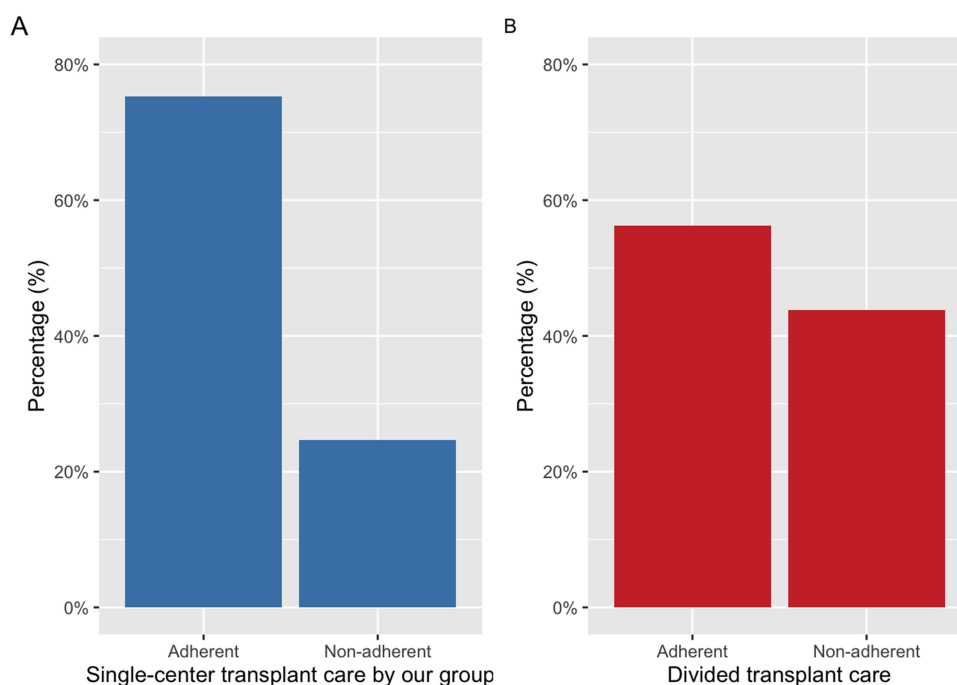


Figure 2 Relative frequencies of adherence and non-adherence in (A) patients transplanted and followed by a single center (Colombiana de trasplantes) and (B) patients transplanted by another group and followed by our center.

multivariate model for divided transplant care patients evidenced age and psychopathology as the only associated factors to non-adherence. Further details are presented in [Appendix 3 \(Tables S2–7\)](#).

Discussion

Adherence is a key factor for kidney transplant outcomes.^{6,7} Therefore, multiple studies have measured it, with a prevalence between 1.6 and 58.7% depending on their highly variable definitions.³² The most widely used definition is immunosuppression compliance, but even in its measuring methods there are essential differences. Data collection involves diverse methods such as electronic monitoring, self-report, pill count, patient interview, physician estimates, and immunosuppression blood levels.^{32,33} On the other hand, on a literature review of Denhaerynck et al,⁶ we can acknowledge different immunosuppression non-adherence definitions such as 20% missed of prescribed doses in six months, three or more missed doses in the last month, one or more missed doses in the previous week, taking less than 90% of prescribed doses, less than 80% of a prescribed medication refill, among others. In our study, we evidenced a non-adherence prevalence of 30.8%, self-reported immunosuppression non-compliance of 25.9%, and low immunosuppression blood levels in 15.7% of patients. Considering that non-adherent patients have a higher risk of worse outcomes and may benefit from early intervention, a broader definition of adherence, such as the one used in this study, allows higher non-adherence diagnosis compared to a definition based on self-report immunosuppression compliance and immunosuppression blood levels.

As previously discussed, numerous studies have explored non-adherence-related factors, hoping this understanding may increase adherence and provide better outcomes for renal transplant patients. In our study, age was significantly associated with non-adherence, adherent patients were older than non-adherent, and age presented an OR of 0.97, suggesting that each year of life led to less non-adherence risk. These findings are consistent with Belaiche S systematic review,³² in which recipients under 50 years were considered more non-adherent than those older. Also, Zachcial et al¹³ reported an age OR of 0.96 (CI 0.94–0.99) for non-adherence, implying fewer problems implementing recommendations with older age. Some authors consider that this adherence deterioration may be caused by increased independence and responsibility to the young person over their medication and management.³⁴ A path to overcome this is establishing a support person outside the medical team who encourages continuous self-care and supervises treatment adherence.³⁴

Another related factor was social support. Non-adherent patients presented higher rates of poor and inadequate social support. Furthermore, in the multivariate analysis, poor and inadequate social support approximately increased twice the non-adherence risk compared to functional support. Our results are consistent with previous evidence that stated that social support is associated with adherence.^{17,35,36} In fact, Chisholm-Burns M. and collaborators³⁶ described that not only good social support was related to better adherence but that affectionate support was especially associated with increased adherence. It has been theorized that social support acts as a buffer that prevents or alleviates the impact of stressful events.^{36,37} Therefore, Vyavaharkar and Chisholm-Burns^{36,38} suggest that greater social support allows better management of stress and more favorable outcomes. These results may be significant by the fact that there is evidence that social support is a modifiable factor,^{39,40} and its improvement may provide better adherence and outcomes for renal transplant recipients.

We evidenced significant differences between marital status in adherent and non-adherent patients, with a non-adjusted odds ratio as a protective risk factor in a stable marital union compared to being single. These results are comparable to those presented by Zachcial et al,¹³ who described that being in a relationship is a non-significant protective factor against non-adherence, and Couzi et al⁴¹ who reported that being single behaves as a significant risk factor for non-adherence. Conversely, another study found higher rates of non-adherence in those in a relationship (married or cohabiting), but a small sample may have limited these results.⁴²

On the other hand, a further analysis by sex and marital status of our data found that a stable marital union was a protective factor in men but not for women. This evidence is similar to the results of Neubert et al,⁴³ which described the recipient's social support and relationship quality as a predictor of adherence in male transplant, contrary to women's results, in which only mental quality of life and education level influenced adherence. Scholz et al also established that women's support for their partners was positively related to adherence intention, but men's support was slight negatively related.⁴⁴ This pattern is also described in other pathologies, such as an HIV prospective study that reported being married or in a stable union is a risk factor for non-adherence in females.⁴⁵ Potential explanations are that women are more empathetic and understand better how to support their male partners.⁴⁶ Another elucidation may be that the problem is not in the skill to provide support but in their responsiveness to their partner's changing needs. In stressful experiences, women are better at adapting to their partner's needs, and men tend to have more negative reactions.⁴⁷

Our results suggest that reinforcement education by a multidisciplinary team composed of psychology and nursing behaves as a protective factor against non-adherence. Previous research has associated limited health literacy with adverse outcomes and in chronic kidney disease with higher mortality and lower access to transplantation.^{48,49} Therefore, education is considered an essential aspect of renal transplant treatment. Furthermore, even some authors have described the importance of updated and effective education programs for improving health literacy as a well-known barrier.^{49–51} Consequently, this multidisciplinary education reinforcement may be a key strategy to improve health literacy and adherence in renal transplant recipients.

A diagnosis of psychopathology was presented in more than a third of the kidney recipients. Likewise, results of the German cohort KTx360 reported that almost 27.5% of kidney transplant patients had a current and a 49.2% a lifetime mental disorder.⁵² A Korean cohort reported a depression incidence of 18.8 per 1000 person-years.⁵³ It is well described the higher prevalence of significant depression and anxiety in transplant recipients, which could be up to 63% in the first year posttransplant.^{54–56} This prevalence of psychopathology is even higher than in chronic kidney disease patients (CKD). This was reported in Palmer et al systematic review and meta-analysis that estimated a depression prevalence of 21.4% in CKD and in 25.7% in kidney recipients.⁵⁷ It has been established that surgery and transplantation can produce great stress and strong emotions in kidney transplant recipients, which can affect personal integrity and identity, allowing psychopathology onset and problems.^{58–60} Various studies have described the psychological results after kidney transplants, reporting anxiety and depression as the most commonly presented disorders.^{59,60} However, these studies have also found interpersonal relationship disturbances, emotional coarctation, and cognitive impairment.^{60–62}

In our study, not only psychopathological diagnosis was prevalent but also one of our study's most significant associations with non-adherence. The non-adjusted odds ratio indicated 4.5 times the risk of non-adherence compared to patients without the diagnosis. In the final logistic regression revealed that dementia, intellectual disability or development disorders, affective and personality disorders behave as risk factors for non-adherence. Only the adaptive disorder

did not present an association with non-adherence. Similar to our study, Gelb et al⁶³ reported that adherence can be affected by the psychopathology of the renal recipients.⁶³ Therefore, pre- and post-transplant psychological assessment may be beneficial to screen and treat any psychopathological disturbances, aiming to enhance adherence and patient outcomes.

Time after transplant was also a determinant factor for adherence. Our study suggested that patients with five or more years of post-transplant follow-up presented twice the risk for non-adherence than those with less than a year after transplant. A systematic review reported 11 studies that found time after transplant as a related factor to non-adherence. The systematic review also highlighted the different and not well-established threshold time that increases the risk of non-adherence.³² Moreover, Burkhalter et al⁶⁴ reported an increase of 20% in the odds for taking non-adherence and 16% in the overall non-adherence for each additional five years since the transplant. These results can be explained by less supervision of the health team and lack of continuous education reinforcement with time.^{13,65} Also, it could be interpreted as patients that get used to medications over time have a better feeling and less need for treatment perception.^{13,65,66}

The non-adherence of the patients that received divided transplant care versus single-center transplant care by our group was significantly more. Consistently, the non-adjusted OR for divided transplant care was 2.3 times the risk versus single-center transplant care of our group. These findings may have multiple explanations. On one side, it is well described that good relationships with healthcare professionals are facilitators to adherence^{67–69}, and receiving the complete transplant process in the same center may enhance better relations. On the other hand, our institution assessed and reinforced adherence actively in the pretransplant, early posttransplant, and late posttransplant period; likewise, several authors evidenced that adherence programs enhance adherence prevalence and outcomes.^{70,71}

Notably, this study supports the relevance of social support, educational reinforcement, and psychopathology as adherence-modifiable factors in renal transplant recipients.^{72,73} Similar associated factors have been found in non-adherent CKD patients in pre-dialysis and hemodialysis, including age, social support, depressive symptoms, and marital status.^{72,73} For this population, there is evidence of the benefits of education and psycho-social interventions in adherence.^{74,75} In kidney recipients, a meta-analysis from Zhu et al⁷⁶ confirmed that patients that received adherence interventions had a higher rate of adherence (OR 2.36, CI 95% 1.22–4.57) than those who did not received them. Some interventions include education, behavioral interventions, pharmacist care, and smartphone reminders. Furthermore, another systematic review conducted by Low et al⁷⁷ described the increased effectiveness of multidimensional interventions rather than unidimensional, but declared that adherence is a poorly managed problem. Therefore, institutions such as the American Society of Transplantation gave practical recommendations to improve adherence, including educational interventions, cognitive behavioral interventions, and health information technology.⁷⁸

There are important limitations to disclose. First, the cross-sectional design could limit the quality and quantity of the recollected data. Besides, since the study design, we do not have information on the adherence change across time as a multifactorial process. Second, the definition of adherence may appear widely subjective and could restrain the reproducibility of our methodology in other populations. Also, adherence was obtained mostly from self-reported information, which, on the one hand, is reported to capture more non-adherent patients than other assessment methods,⁷⁹ but on the other hand, it has the potential to lose precision on recall bias.⁷⁸ Third, the recollection was mainly in the covid 19 pandemic, which can influence the adherence process. Finally, the generalization of the results may be restricted by the convenience sample methodology. Therefore, there is a need for more extensive studies with heterogenic populations to assess these related factors to adherence. Studies that evaluate interventions are based on the associated factors to non-adherence evidence, in order to find new strategies that could improve adherence and outcomes in renal transplant recipients.

Conclusion

This study suggests that a wide definition of non-adherence, including more than immunosuppression compliance, can capture more patients that may benefit from an early diagnosis and treatment. That approximately one-third of kidney transplant recipients are non-adherent. Age, education reinforcement, social support, and psychopathological diagnoses are associated with renal transplant recipient's adherence. Therefore, these factors should be considered in the health

team follow-up and even in prediction tools to target non-adherence risk. Also, to screen and treat psychopathological disorders as a prevalent factor in non-adherent patients. Finally, there is a need for future research to study novel interventions to modifiable factors, such as educational reinforcement and social support, that could improve adherence and outcomes in renal transplant patients.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that there are no conflicts of interest in this work.

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