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Assessing Risk Factors and Posttransplant Outcomes of Nonadherence Among Kidney Transplant Recipients

Kateryna Maksyutynska, HBSc,[1] Benedict Batoy, HBSc,[1] Xinyu Wei, HBSc,[1] Oswa Shafei, HBSc,[1] Yanhong Li, MSc,[1] Olusegun Famure, dipHSM, MPH, MEd, CHE,[1] and S. Joseph Kim, MD, PhD, MHS, MBA, FRCPC[1,2,3]

Background. Adherence of kidney transplant recipients (KTRs) to prescribed regimens is vital for long-term graft function. This study aimed to identify adherence rates using objective and composite measures, risk factors for nonadherence, and the latter's impact on posttransplant outcomes. **Methods.** A retrospective single-center cohort study was conducted among KTR transplanted from January 1, 2003, to December 31, 2017. Overall nonadherence was defined as 1 or more of the following in the first-year posttransplant: (1) at least 1 missed clinic visit, (2) >30% missed laboratory visits, and (3) >40% coefficient of variation of calcineurin inhibitor levels. Logistic and Cox proportional hazards models were fitted to identify adherence risk factors and outcomes, respectively. **Results.** Among the included 1803 KTR, overall nonadherence was identified in 34.9%; 11.2% were nonadherent to clinic visits, 5.4% to laboratory tests, and 25.2% to medications. Recipient history of psychiatric disorders (odds artio [OR], 1.57; 95% confidence interval [CI], 1.22-2.02) or pretransplant nonadherence (OR, 1.82; 95% CI, 1.31–2.54), and private drug coverage (OR, 0.62; 95% CI, 0.48-0.80) were associated with posttransplant nonadherence. Any episode of nonadherence over the first year after transplant was associated with an increased risk of total graft failure (hazard ratio [HR], 1.52; 95% CI, 1.20-1.91), death with graft function (HR, 1.51; 95% CI, 1.11-2.05), and biopsy-proven acute rejection (HR, 2.35; 95% CI, 1.38-3.99). **Conclusions.** Adherence among KTR is influenced by both psychosocial and socioeconomic determinants which impact posttransplant outcomes. Our results emphasize feasible methods to monitor adherence and identify high-risk KTR.

(Transplantation Direct 2025;11: e1799; doi: 10.1097/TXD.0000000000001799.)

Kidney transplantation is the gold standard treatment for kidney failure. As the field of transplantation is rapidly evolving, improvements to immunosuppression therapies, surgical techniques, biomarker identification, and organ allocation have optimized kidney transplant recipient (KTR) posttransplant outcomes.[1-3] The adherence of transplant recipients is an important factor that complements the efficacy of treatments to improve patient outcomes.

Patient adherence is a broad term encompassing several domains within and beyond the field of transplantation. This includes adherence to medications (dosage and schedules), clinic visits, and scheduled laboratory tests, both pre- and posttransplantation. Among medications, immunosuppressants are of particular relevance to reduce the risk of allograft rejection.[4] In solid organ transplantation, calcineurin inhibitors (CNIs) such as cyclosporine and tacrolimus are

commonly used. These drugs have a narrow therapeutic index,[5] such that changes in exposure over time can have a significant impact on patient health.[6] However, because of varying pharmacokinetic parameters,[7,8] regular monitoring and modulating drug levels is of great importance to ensure long-term graft function.

Patient adherence is most commonly measured in relation to medication dose and schedule compliance. This is achieved through objective and subjective measurements such as therapeutic drug monitoring to ascertain medication trough levels, self-reported questionnaires, in-person interviews, electronic pill bottle opening counts, intake diaries, and prescription fill dates.[9-13] Additional measures of adherence include following laboratory testing schedules and attending clinical appointments with the nephrologist and care team.[14]

Because of differing nonadherence definitions and thresholds, the rates are highly variable among populations.[15] Although there are various available methods, currently no standardized method to assess nonadherence in the transplant population exists.[16,17] Moreover, risk factors predisposing KTR to nonadherence have yet to be systematically assessed or validated in larger study populations. Additionally, few studies have examined nonadherence as a composite factor made up of multiple discrete measures.

The diverse objectives of this study were to (1) study adherence rates in KTR defined using objective and composite criteria, (2) determine risk factors associated with KTR nonadherence in the first-year posttransplant, and (3) identify the subsequent impact of nonadherence on posttransplant outcomes beyond 1 y after transplant.

METHODS

Guidelines

This work complies with the Declaration of Helsinki and the Declaration of Istanbul. The study protocol was approved by the University Health Network Research Ethics Boards (19-5182.4).

Study Design and Population

A retrospective single-center cohort study was conducted among adult (>18 y of age) KTR who received a transplant at the University Health Network from January 1, 2003, to December 31, 2017. Patients were excluded from this study if they (1) had prior multiorgan transplants, (2) had prior kidney transplants, (3) received a transplant at another center, or (4) experienced primary graft nonfunction. Patient data were retrieved from our transplant center's electronic health record, the Organ Transplant Tracking Record, and our research database, the Comprehensive Renal Transplant Research Information System.[18]

Definitions of Nonadherence

Overall nonadherence was defined as 1 or more of the following in the first-year posttransplant: (1) at least 1 missed clinic visit, (2) >30% missed laboratory visits, and (3) >40% coefficient of variation (CV) of CNI levels. To measure clinic visit nonadherence, only appointments marked as "no-show" were evaluated as missed; rescheduled or canceled appointments were not considered missed clinic visits.[19] The following schedule is the expected frequency of patients' clinic appointments within the first year following transplant: (1) weekly during the first month (2–4 visits depending on the date of discharge), (2) biweekly during the second and third months (4 visits), (3) monthly between the fourth and sixth months (3 visits), and (4) bimonthly between the seventh and twelfth months (3 visits).

Scheduled laboratory visit nonadherence was defined by the following standard institutional laboratory schedule (and the permissible time range to complete laboratory testing from the scheduled date) within the first year following transplant: (1) twice a week (±1 d) during the first month, (2) weekly (±3 d) during the second and third months, (3) biweekly (±1 wk) between the fourth and sixth months, and (4) monthly between the seventh and twelfth months (±2 wk).

CNI trough-level variability was used as an indicator of medication nonadherence. The variability was determined by the CV of CNI blood levels within our population using the following equation:

$$ CV = \frac{\sqrt{\Sigma\ (CNI_i - \mu\ )^2/N}}{\mu} \times 100 $$

CNI_i represents individual CNI trough levels for 1 patient, μ is the mean CNI trough level for the whole population, and N is the number of trough levels collected for 1 patient. These measurements were all performed over the first-year posttransplant. When applied to our population, the 75th percentile (third quartile) CV was 40% and was used as the threshold for nonadherence. The use of the 75th percentile as the cutoff has been previously used in the literature.[20,21]

Risk Factors and Outcomes

Recipient and donor risk factors were collected at baseline to assess their relationship with KTR nonadherence during the first year posttransplant. Recipient risk factors included age, sex, cause of end-stage renal disease (ESRD), history of smoking before transplant, history of diabetes mellitus, history of psychiatric disorders, history of pretransplant nonadherence, travel distance from recipient's home to hospital (in kilometers), marital status, and drug coverage. Donor risk factors included living or deceased kidney donation. Pretransplant nonadherence was assessed using social work notes taken during detailed patient interviews at the transplant evaluation stage, with mention of any current or historic behavior of missed appointments or laboratory tests, missed or shortened dialysis sessions, inconsistent diabetes management, irregular medication intake, and other clinical domains.[22] Similarly, social work notes were utilized to define a history of psychiatric disorders, which compiled information collected from patient self-reports, relatives, medical documentation, letters from psychiatrists, and referring physicians and centers.[22] Thus, this variable was not based on a formal psychiatric assessment/diagnosis but summarizes any records of mental health concerns.

The outcomes of this study were the effect of nonadherence on posttransplant outcomes beyond 1-y posttransplant. The 1-y landmark allows the nonadherence exposure variable to accrue over the first year posttransplant. Posttransplant outcomes included death-censored graft failure (ie, return to chronic dialysis or need for preemptive retransplantation), death with graft function (ie, death prior graft loss), total graft failure (composite of the prior 2 outcomes), and biopsy-proven acute rejection after the origin of 1-y posttransplant.

Statistical Analysis

Descriptive statistics were used to assess baseline recipient and donor characteristics. Quantitative variables were expressed as a mean value with a SD or a median value with an interquartile range. Logistic regression models were fitted to evaluate the impact of risk factors on overall nonadherence and were reported as odds ratios (ORs) with 95% confidence intervals (CIs). The multivariable model was adjusted for all baseline risk factors. The Kaplan-Meier product limit method was used to graphically depict the time from cohort entry (ie, 1-y posttransplant) to the main study outcomes >10 y based on overall and domain-specific nonadherence groups. Differences in survival functions were evaluated using the log-rank test.

Cox proportional hazards models were fitted to study the effect of nonadherence on posttransplant outcomes and were reported as hazard ratios (HRs) with 95% CI. The model included overall nonadherence along with adjustment for recipient variables (age, sex, race, body mass index at transplant, history of diabetes mellitus, time on dialysis before transplant, peak panel-reactive antibody), donor variables (age, body mass index at donation, donor type), and transplant variables (cold ischemic time, type of induction, CNI at transplant discharge, delayed graft failure, transplant era). A two-tailed P value <0.05 was considered statistically significant, and all analyses were performed using Stata version 16 (StataCorp, College Station, TX).

RESULTS

Population Characteristics

Of the 2714 patients who were transplanted within the study period, 425 had a prior multiorgan transplant, 212 had a prior kidney transplant, 248 received a transplant from another center, and 26 experienced primary graft nonfunction transplants, resulting in 1803 patients being included in the study cohort (Figure 1). During 9011.5 person-years of follow-up, 327 total graft failures (136 death-censored graft failures and 191 deaths with graft function) were observed. Moreover, 55 biopsy-proven acute rejections were ascertained >8833.2 person-years of follow-up.

Among patients included in the study cohort, the mean recipient age was 51.7 (±13.4) y, and 60.7% were men

(Table 1). The main cause of ESRD was glomerulonephritis in 34.4%. The majority of recipients had no prior history of smoking (55.6%), diabetes mellitus (67.4%), psychiatric disorders (81.9%), or pretransplant nonadherence (84.9%). Deceased donation was slightly more common (54.5%) when compared with living donation (45.5%), and drug coverage was almost equally distributed between private (50.5%) and public (49.5%) payers.

Assessing Risk Factors of Nonadherence

Overall nonadherence was identified in 630 (34.9%) patients; 202 (11.2%) patients were nonadherent to clinic visits, 98 (5.4%) to laboratory visits, and 454 (25.2%) to medication (**Table S1, SDC**, https://links.lww.com/TXD/A761). Univariable analysis showed that patients with diabetes mellitus in comparison with glomerulonephritis as their cause of ESRD were at a greater risk of overall nonadherence (OR, 1.32; 95% CI, 1.02-1.70; Table 2). Similarly, recipient history of diabetes mellitus (OR, 1.30; 95% CI, 1.06-1.59), psychiatric disorder (OR, 1.69; 95% CI, 1.32-2.16), and pretransplant nonadherence (OR, 1.92; 95% CI, 1.42-2.60) were risk factors associated with overall nonadherence. In a multivariable analysis, only recipient history of psychiatric disorders (OR, 1.57; 95% CI, 1.22-2.02) and pretransplant nonadherence (OR, 1.82; 95% CI, 1.31-2.54) were independent risk factors for overall nonadherence (Table 2). Furthermore, possessing private drug coverage showed a reduced risk for overall nonadherence (OR, 0.62; 95% CI, 0.48-0.80).

Exploring Nonadherence as a Risk Factor for Posttransplant Outcomes

The cumulative probability of total graft failure was significantly greater in the overall nonadherent population in comparison with the adherent population ($P < 0.001$), driven primarily by medication nonadherence ($P < 0.001$; Figure 2). Nonadherence in any 1 of the 3 domains over the first year after transplant was associated with an increased risk of total graft failure (HR, 1.52; 95% CI, 1.20–1.91), death with graft function (HR, 1.51; 95% CI, 1.11-2.05), and biopsy-proven acute rejection (HR, 2.35; 95% CI, 1.38-3.99; Table 3). A trend toward an increased risk of death-censored graft failure was also observed (HR, 1.39; 95% CI, 0.96-2.01). CNI CV was consistently associated with an increased risk of graft, patient, and rejection outcomes, whereas biopsy-proven acute rejection was predicted by overall and domain-specific adherence measures (**Table S2, SDC**, https://links.lww.com/TXD/A761).

DISCUSSION

Patient adherence is a topic that spans many medical fields and is especially pertinent to the transplant population because of its significant impact on graft and patient outcomes.[23] To investigate this further, our study adopted a novel approach to measure adherence in KTR, using a composite of readily accessible data from the hospital's electronic record. Specifically, we used a 3-variable measure of nonadherence composed of clinic visit attendance, laboratory visit attendance, and CNI trough level variability with a priori thresholds. This was done to capture >1 dimension of adherence, unlike other approaches that rely on single, self-reported measures such as pill counts or patient-administered surveys.

Inclusion: All kidney transplants from January 1, 2003 to December 31, 2017 (n = 2,714)

Exclusions (n = 911):
- Prior multi-organ transplants (n = 425)
- Prior kidney transplants (n = 212)
- Transplant at another centre (n = 248)
- Primary graft non-function (n = 26)
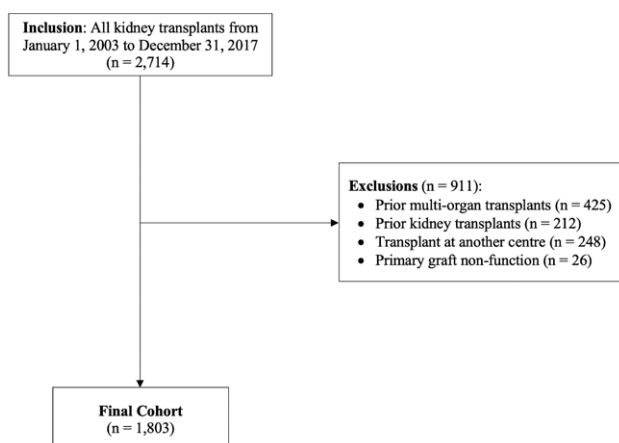
Final Cohort (n = 1,803)

FIGURE 1. Study flow diagram.

TABLE 1.

Baseline characteristics and adherence within the first-year posttransplant

Baseline characteristics	No. of patients (N = 1803)	Total cohort	Adherence (n = 1173)	Nonadherence (n = 630)
Mean recipient age (y)	1803	51.7 (±13.4)	51.5 (±13.0)	51.9 (±14.2)
Recipient sex				
Male	1,095	60.7%	726 (61.9%)	369 (58.6%)
Female	708	39.3%	447 (38.1%)	261 (41.4%)
Cause of end-stage renal disease				
Glomerulonephritis	619	34.4%	414 (35.4%)	205 (32.6%)
Diabetes mellitus	452	25.1%	273 (23.3%)	179 (28.5%)
Polycystic kidney disease	238	13.2%	165 (14.1%)	73 (11.6%)
Other	490	27.2%	318 (27.2%)	172 (27.3%)
Recipient history of smoking before transplant				
No	993	55.6%	647 (55.8%)	346 (55.1%)
Yes	794	44.4%	512 (44.2%)	282 (44.9%)
Recipient history of diabetes mellitus				
No	1216	67.4%	815 (69.5%)	401 (63.7%)
Yes	587	32.6%	358 (30.5%)	229 (36.4%)
Recipient history of psychiatric disorder				
No	1477	81.9%	994 (84.7%)	483 (76.7%)
Yes	326	18.1%	179 (15.3%)	147 (23.3%)
Recipient history of pretransplant nonadherence				
No	1154	84.9%	774 (88.1%)	381 (79.4%)
Yes	205	15.1%	105 (12.0%)	99 (20.6%)
Donor type				
Deceased	982	54.5%	621 (52.9%)	361 (57.3%)
Living	821	45.5%	552 (47.1%)	269 (42.7%)
Median travel distance from recipient's home to hospital (km)	1367	29.9 (11.2, 53.5)	29.9 (11.4, 55.8)	29.4 (10.3, 47.8)
Marital status				
Single	256	18.7%	169 (19.1%)	87 (17.9%)
Married	920	67.1%	602 (68.0%)	318 (65.4%)
Divorced/separated/widowed	196	14.3%	115 (13.0%)	81 (16.7%)
Drug coverage				
Private	695	50.5%	490 (55.1%)	205 (42.1%)
Public	682	49.5%	400 (44.9%)	282 (57.9%)

Rather, we conducted analyses using objective criteria and systematic thresholds to eliminate recall bias. Through this approach, we found overall nonadherence in our population to be 34.9% and align closely with the 30% observed in the heart transplant population.[16] However, because of varying methodologies in measuring nonadherence, this percentage is highly variable among studies.[15] To compare nonadherence rates among populations, and subsequently share strategies to improve them, a standardized and validated threshold must be developed. Our proposed adherence metric addresses several challenges associated with studying this outcome. It could be used for patient- and program-level monitoring, and incorporated into quality dashboards. Furthermore, local targets can also be set which may guide decision-making among healthcare providers.

The individual thresholds used for nonadherence in our analysis align with those used in the literature. For medication nonadherence in the literature, CV values ranging from 24.6% to 43% were associated with poor kidney graft function.[12,24,25] This range corresponds to our study's medication nonadherence threshold of CV >40%. The use of a higher cutoff considers the influence of pharmacokinetics which makes this measure variable among patients. In other transplant studies, nonadherence thresholds for clinic appointments ranged between 12% and 20%.[19,26,27] This range is marginally

higher than the cutoff value used in our analysis because we emphasized the importance of clinic visits within the first-year posttransplant. In this period, patients are most sensitive to complications of inadequate and overimmunosuppression, warranting timely dose adjustments.[28] Clinic appointments are used to monitor and intervene in patient and graft health.[29] Prior studies have employed a cutoff of 20% missed laboratory appointments, with a respective grace period, to define laboratory nonadherence.[30] Their grace period allowed for 3 d of variance from the scheduled laboratory date in the first month and 7 d from the second to sixth months in the first-year posttransplant.[30] However, in our analysis, the acceptable time range was shorter, growing to 1 wk starting at only the fourth month posttransplant, which accounts for our use of a greater nonadherence cutoff. Although not directly assessed in our study, an association between individual measures of nonadherence has been previously established, supporting the use of a composite overall nonadherence measure.[19,30]

Overall nonadherence was influenced by both psychosocial and socioeconomic determinants. In accordance with our findings, there is consensus that history of psychiatric disorders, history of nonadherence, and no supplemental private health coverage increase the risk for posttransplant nonadherence.[15,31] This may be attributed to the high cost associated with medications required for comorbid conditions or

TABLE 2.

Logistic regression for the effect of recipient and donor factors on at least 1 episode of nonadherence within the first-year posttransplant

Risk factors	Univariable analysis		Multivariable analysis	
	Odd ratio (95% CI)	*P*	Odd ratio (95% CI)	*P*
Recipient age (every 1 y increase)	1.00 (0.99-1.01)	0.59	1.00 (0.99-1.01)	0.89
Recipient sex (female vs male)	1.15 (0.94-1.40)	0.17	1.17 (0.95-1.44)	0.15
Cause of end-stage renal disease				
Diabetes mellitus vs glomerulonephritis	1.32 (1.02-1.70)	0.03	1.05 (0.68-1.60)	0.84
Polycystic kidney disease vs glomerulonephritis	0.89 (0.65-1.23)	0.50	0.97 (0.69-1.36)	0.84
Other vs glomerulonephritis	1.09 (0.85-1.40)	0.49	1.05 (0.81-1.36)	0.71
Recipient history of smoking before transplant (yes vs no)	1.03 (0.85-1.26)	0.75	0.98 (0.79-1.20)	0.83
Recipient history of diabetes mellitus (yes vs no)	1.30 (1.06-1.59)	0.01	1.20 (0.81-1.77)	0.36
Recipient history of psychiatric disorder (yes vs no)	1.69 (1.32-2.16)	<0.001	1.57 (1.22-2.02)	0.001
Recipient history of nonadherence (yes vs no)	1.92 (1.42-2.60)	<0.001	1.82 (1.31-2.54)	<0.001
Donor type (living vs deceased)	0.84 (0.69-1.02)	0.08	0.95 (0.76-1.19)	0.67
Travel distance from recipient's home to hospital (every 10-km increase)	1.00 (0.99-1.00)	0.30	1.00 (0.99-1.00)	0.47
Marital status				
Single vs married	1.04 (0.78-1.39)	0.80	0.87 (0.60-1.24)	0.43
Divorced/separated/widowed vs married	1.29 (0.94-1.77)	0.12	1.01 (0.73-1.41)	0.94
Drug coverage (private vs public)	0.60 (0.48-0.75)	<0.001	0.62 (0.48-0.80)	<0.001

difficulty incorporating additional medications into an existing schedule. More in-depth consideration of these factors during the evaluation process may help identify patients at greater risk for poor graft function after transplant.

In our analysis, significant increases in the risks for total graft failure and death with graft function were driven by medication nonadherence, potentially because of their narrow therapeutic window. As expected, the risk of total graft failure increased >10 y for both adherent and nonadherent KTR but was significantly higher in the nonadherent population. Additionally, the risk for biopsy-proven acute rejection starting 1 y after transplant increased 2-fold for nonadherent individuals. The negative effects of nonadherence on graft survival correspond to previous study findings.[19] This finding highlights the importance and responsibility of KTR in managing their health with their care team.
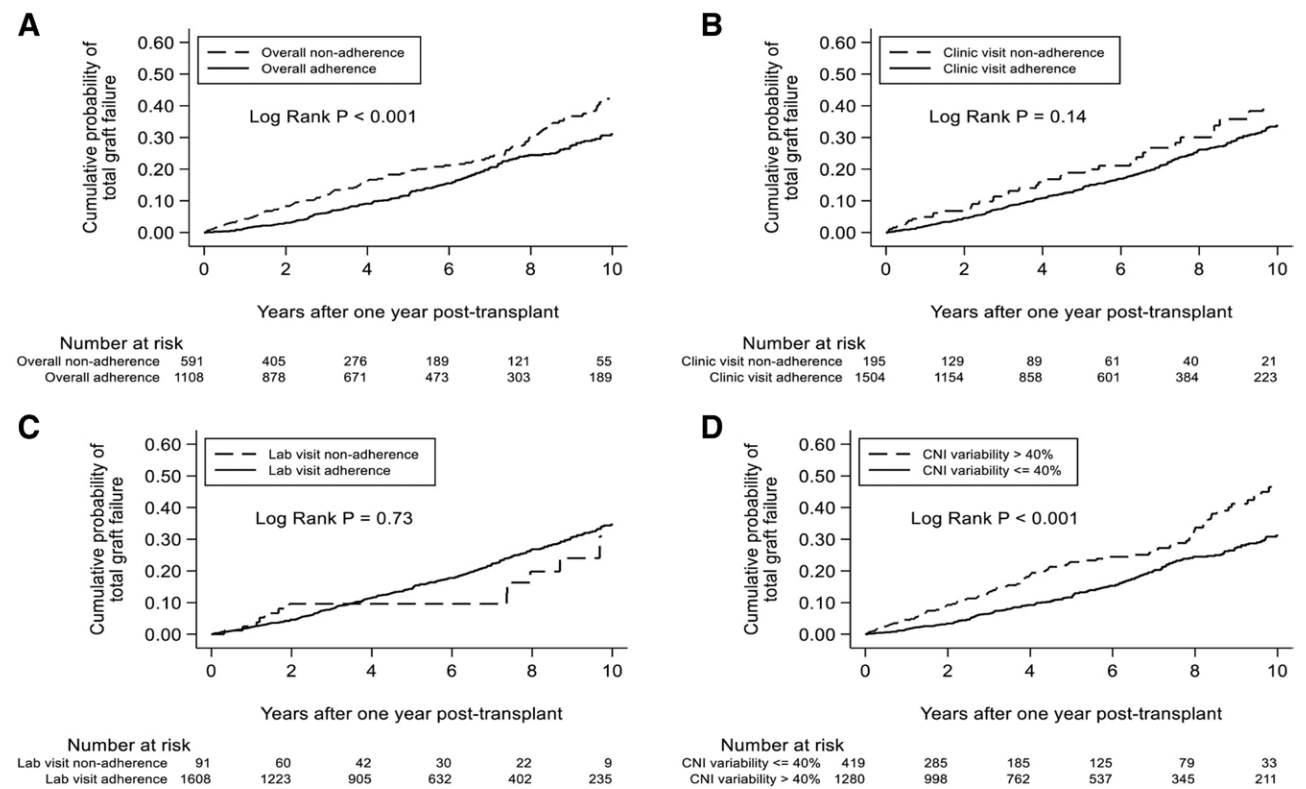

FIGURE 2. Total graft failure over 10 y starting at 1-y posttransplant, categorized by nonadherence exposure: overall nonadherence (A), clinic visit nonadherence (B), laboratory visit nonadherence (C), and CNI variability (D).

TABLE 3.

Cox proportional hazards model for the effect of overall nonadherence on transplant outcomes starting 1-y posttransplant

Outcome	Hazard ratio (95% CI)	P
Total graft failure after origin	1.52 (1.20-1.91)	<0.001
Death-censored graft failure after origin	1.39 (0.96-2.01)	0.08
Death with graft function after origin	1.51 (1.11-2.05)	0.01
Biopsy-proven acute rejection after origin	2.35 (1.38-3.99)	0.002

Education is the most commonly used intervention to address adherence; however, it is not considered the most effective.[32,33] At our center, mandatory pharmacist-led educational sessions are held to inform patients of their medications. More personalized interventions have also been explored in the literature and have been found to have positive impacts on adherence. These interventions include motivational interviewing and behavioral contracts that allow for reflection and intention-making, emphasizing the responsibility of the patient.[34,35] Specifically, incorporating quality improvements at a personal level, through linking them to daily routines, environmental cues, and supportive people, was found to improve medication adherence in KTR.[36] Furthermore, the use of health information technology, such as mobile apps to set reminders for medication, has been shown to improve adherence rates.[9,37] Therefore, multidisciplinary approaches, combining education with additional interventions are recommended.[9,38] However, further investigation of such integrative targeted interventions is required to ascertain their role in improving graft and patient outcomes and address limitations to existing studies with low methodological quality, small sample sizes, and heterogeneity in measurements.[39,40] Furthermore, future research also warrants the consideration of the scalability, cost, and pragmatism of these interventions.[41,42]

Despite our study's large and diverse population, it is limited to a single, adult cohort of KTR transplanted at a single center. Additional investigation is needed to determine whether our results are generalizable to other populations such as adolescents and young adults. Moreover, measuring nonadherence as a binary, compared with a continuous, variable may be identified as a loss of information.[43] The binary approach allows for more distinct identification of patients that would require additional interventions and is easier to adapt to a clinical setting. As previously mentioned, the nonadherence thresholds are well-defined, within a range of those used in the literature, and have been validated in previous studies. The data collected were predominantly related to the transplant recipient, with donor data limited to deceased versus living. The tendency to adhere is unlikely related to other donor characteristics, so confounding by the latter is probably small. Furthermore, there may have been some variability in posttransplant follow-up practices among transplant physicians. However, the expected clinic and laboratory test schedules used in our study reflect those applicable to the majority of our population. Finally, observational studies are always at risk of residual confounding. The consistency of the overall and domain-specific results, as well as the efforts to account for numerous potential confounders in multivariable models, should help to mitigate the risk of significant bias.

In conclusion, our study offers a novel, feasible, and objective approach to study adherence in KTR. It further emphasizes that suboptimal adherence, as measured by the domains that were captured in this analysis, is strongly associated with adverse graft and patient outcomes. These trends can be readily measured and observed because transplant centers can capture adherence using the electronic health records of KTR and use them to flag high-risk patients for appropriate interventions. Whether the use of such a monitoring strategy will improve outcomes would best be evaluated in a clinical trial.

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