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ORIGINAL ARTICLE

Multilevel factors are associated with immunosuppressant nonadherence in heart transplant recipients: The international BRIGHT study

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Factors at the level of family/healthcare worker, organization, and system are neglected in medication nonadherence research in heart transplantation (HTx). The 4-continent, 11-country cross-sectional Building Research Initiative Group: Chronic Illness Management and Adherence in Transplantation (BRIGHT) study used multistaged sampling to examine 36 HTx centers, including 36 HTx directors, 100 clinicians, and 1397 patients. Nonadherence to immunosuppressants—defined as any deviation in taking or timing adherence and/or dose reduction—was assessed using the Basel Assessment of Adherence to Immunosuppressive Medications Scale© (BAASIS©) interview. Guided by the Integrative Model of Behavioral Prediction and Bronfenbrenner's ecological model, we analyzed factors at these multiple levels using sequential logistic regression analysis (6 blocks). The nonadherence prevalence was 34.1%. Six multilevel factors were associated independently (either positively or negatively) with nonadherence: *patient level*: barriers to taking immunosuppressants (odds ratio [OR]: 11.48); smoking (OR: 2.19); *family/healthcare provider level:* frequency of having someone to help patients read health-related materials (OR: 0.85); *organization level*: clinicians reporting nonadherent patients were targeted with adherence interventions (OR: 0.66); pickup of medications at physician's office (OR: 2.31); and *policy level*: monthly out-of-pocket costs for medication (OR: 1.16). Factors associated with nonadherence are evident at multiple levels. Improving medication nonadherence requires addressing not only the patient, but also family/healthcare provider, organization, and policy levels.

KEYWORDS
clinical decision-making, clinical research/practice, compliance/adherence, heart transplantation/cardiology, immunosuppression/immune modulation, social sciences

Abbreviations: BAASIS©:, Basel Assessment of Adherence to Immunosuppressive Medications Scale©; CI, Confidence Interval; HTx, Heart Transplantation; OR, Odds Ratio; SD, Standard Deviation; Tx, Transplantation; EBV, Epstein–Barr virus.

Kris Denhaerynck and Lut Berben joint first authorship.

The BRIGHT Study team members are listed in Appendix 1.

1 | INTRODUCTION

Immunosuppressant nonadherence entails serious risks in solid organ transplantation (Tx), including heart transplantation (HTx).[1,2] Based on the ABC taxonomy, medication adherence has 3 phases: initiation, implementation, and discontinuation, and is defined as "the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen."[3] Nonadherence is linked to poor posttransplant outcomes including late acute rejection and graft loss.[2,4,5]

Knowledge of immunosuppressive nonadherence factors aids identification of at-risk patients while exposing leverage points for interventions.[6] To date, in addition to patient-related variables, confirmed factors relate to sociodemographics, therapies, or conditions,[1,7,8] with some evidence indicating links to healthcare teams and providers.[9-12] However, the focus has been primarily on patient-level factors.[1,8,13,14] In fact, most patient-level factors are only weakly associated with medication nonadherence, suggesting that other-level variables also play roles.[6,11,15] In addition, few studies exploit theoretical models that guide selection of factors for investigation.[16-18]

Therefore, we favor an ecological perspective (eg Bronfenbrenner's model[6,19,20]) that positions the transplant patient within the healthcare system's micro (family/healthcare provider), meso (transplant center), and macro (healthcare system) levels (Figure 1).[6,21–32] Reflecting this perspective, a multilevel approach to medication nonadherence is novel,[15,33] as multilevel medication nonadherence factors have received little attention in transplantation.[6,11,13,14,34] Should this new perspective reveal independent multilevel immunosuppressant nonadherence correlates, addressing such correlates would demand interventional approaches targeting not only patients but healthcare workers/family, organizations, and policymakers.[6,21,24]

With this in mind, the main hypothesis of the multicontinental "Building Research Initiative Group: Chronic Illness Management and Adherence in Transplantation (BRIGHT)" study was that multilevel factors are associated with implementation phase immunosuppressant nonadherence in adult HTx recipients.

2 | MATERIALS AND METHODS

2.1 | Design, sample, and setting

The BRIGHT cross-sectional study used a convenience sample drawn from 4 continents, 11 counties, and 36 HTx centers (minimum 2 per country), using multistage sampling to recruit centers, patients, and clinicians.[34] Eligible centers had at least 50 heart transplants performed during the past 12 to 60 months, were located in Europe, North America, South America, or Australia, and were formally supported by the center's transplant director and responsible administrator. A randomized proportional sample of adult, single-organ, *HTx recipients* was included from each center based on center size. Further inclusion criteria were the following: being between 1 and 5 years posttransplant, transplanted and followed up for routine care in the transplant center, first and single transplant, able to read in the languages spoken in the country of the participating center, and providing informed consent.[34] Each center's sample included 1-5 *clinicians* working in the center for >6 months, who worked at least 50% in direct clinical practice and were familiar with the center's posttransplant outpatient care (randomly selected where >5 clinicians were eligible). Detailed information on the BRIGHT study's methods, theoretical framework, sample size, etc., is available elsewhere.[34]

Prior to data collection, ethical approval was obtained from the University Hospitals of Leuven (Belgium) ethics committee, and all participating centers' ethics committees. All participating patients provided written informed consent. Upon local Ethical Review Board request, transplant clinicians were asked to sign consent forms; otherwise, completing the questionnaire was assumed to imply consent.

2.2 | Variables and measurement

Measuring implementation phase immunosuppressant nonadherence and its selected multilevel correlates involved 5 instruments: (1) the BRIGHT patient interview questionnaire; (2) the BRIGHT patient self-report questionnaire; (3) the BRIGHT structured form for medical record information extraction; (4) the BRIGHT clinician questionnaire; and (5) the BRIGHT transplant director questionnaire.[34] Appendix S1 summarizes all studied variables, their measurement, and psychometrics (if applicable).

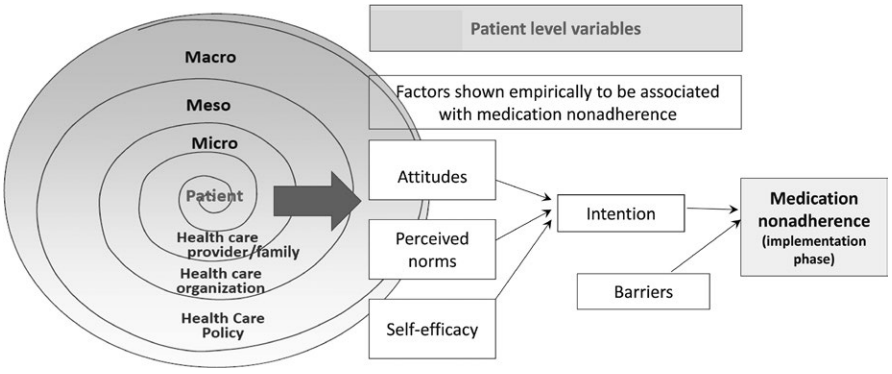

FIGURE 1 The adapted ecological model of Bronfenbrenner et al[6,19,20] (left) combined with patient-level factors derived from the Integrative Model of Behavioral Prediction[38] and empirical evidence (right)

Immunosuppressant nonadherence (implementation phase) was assessed via the Basel Assessment of Adherence to Immunosuppressive Medications Scale© (BAASIS©) (interview version).[34,35] Following the ABC taxonomy for medication adherence,[3] this measures implementation phase immunosuppressant nonadherence via 4 items, querying taking adherence, drug holidays, timing adherence, and self-initiated dose reductions. Patients scored their adherence over the past 4 weeks. Any deviation in taking, timing, or dosing was considered nonadherence.[34] The instrument's concurrent validity was demonstrated in kidney[36] and predictive validity (regarding late acute rejection incidence) in liver Tx recipients.[37]

Multilevel medication nonadherence correlates were assessed via validated instruments and investigator-developed measures (Appendix S1) (see BRIGHT methods article[34]). At the patient level, we applied the *Integrated Model of Behavioral Prediction*,[38] which posits that intention and barriers are the most proximal determinants of health behaviors (Figure 1); attitudes, perceived norms, and self-efficacy also are determinants of nonadherence. Based on empirical evidence from our research group's ongoing meta-analysis, we also added 25 literature-derived variables[8,39] (Figure 1 and Appendix S1).

Working from an ecological perspective, the model of Bronfenbrenner et al[6,19,20] (Figure 1) supported 9 micro- (interpersonal relationships, eg family, healthcare providers), 32 meso- (regarding transplant center characteristics and practice patterns), and 4 macro-level (healthcare system characteristics) variables (total: 45) (Appendix S1 and Table 1).

2.3 | Data collection

At each participating transplant center, at least 1 local BRIGHT data collector collected the data. All data collectors received formal standardized training (see BRIGHT methods article[34]). Questionnaires were sent to the centers, which distributed them to the randomly selected patients, clinicians, and to the director. Completed questionnaires were returned to the local data collector, who forwarded them to the BRIGHT study team, who checked data completeness, and contacted local data collectors regarding omissions. Data were entered into the data set by scanning the questionnaires. BRIGHT medical chart forms were entered manually. Quality checks were performed on data subsamples and corrections were made as needed.

2.4 | Data analysis

Descriptive data analysis included appropriate measures of central tendency and dispersion. Nonadherence prevalence figures were weighted to represent test countries' HTx populations. Where appropriate, assessed meso-level variables were aggregated at the center level. To evaluate the multi-item instruments' validity and reliability, psychometric analyses were performed (Appendix S1). The dimensionality of instruments was checked using (un)rotated principal component analyses and Cronbach's α (Appendix S1).

To identify multilevel correlates of medication adherence, we first predicted nonadherence via simple logistic regression analyses, invoking generalized estimating equations to account for possible within-center subject correlations.[40] Variables whose odds ratios (ORs) suggested associations (ie confidence intervals [CIs] not including 1.00) were subjected to multiple logistic regression analysis. Constructing this model required a sequential approach including blockwise entry of variable groups at each level, starting with the Integrative Model of Behavioral prediction. *Block 1* included barriers and intention, the factors most proximal to behavior; *Block 2* included attitudes, perceived norms, and self-efficacy, which directly impact intention (Figure 1). *Block 3* included patient-level variables derived from the transplant literature. *Block 4* contained micro-, *Block 5* meso-, and *Block 6* macro-level factors. Within each sequence, variables contributing independently to medication nonadherence (with OR CIs not including 1) were included in the subsequent step. We calculated a marginal R^2 statistic for each step.[41] For the final model, 4 additional R^2s we calculated per level (patient, meso, micro, and macro) by only keeping variables allocated to a respective level in the equation.

We tested our results' robustness first by disentangling "taking" and "timing"—the two main nonadherence aspects—and running 2 models using the 2 BAASIS© items assessing these dimensions. Second, multiple imputation was used to refit the final model and exclude possible bias resulting from missing data. Missingness in variables was rare at the center (median: 0%; interquartile range [IQR]: 0-0%; range: 0-6%) and clinician (median: 0%; IQR: 0-3%; range: 0-18%) levels, and 1% at the patient level (IQR: 1-2%; range: 0-12%). All analyses were performed in SAS version 9.4 (SAS Institute, Cary, NC) and R version 3.2.0 (https://cran.r-project.org/; using the MICE package for multiple imputation; http://stefvanbuuren.github.io/mice/).

3 | RESULTS

3.1 | Demographic information

Table 1 and Figure 2 show demographic information for the 36 participating centers. The majority (n = 19, 52.8%) were large centers.[34,42] They handled 2523 eligible patients. We invited 1677 patients (random selection; see Materials and Methods) to participate, of whom 244 declined and 36 died before completing the questionnaire, leaving 1397 patient participants who completed questionnaires (Figure 3) (participation rate: 83.3%; mean age: 53.6 years (standard deviation [SD] 13.2); 72.7% male; average years posttransplant: 3.4 [SD 1.4] [Table 1]).

All invited clinicians (n = 100; response rate: 100%) participated (mean clinicians per center: 2.78 [SD 1.59]; range: 1-5); mean age: 46.2 years (SD 10.2); 87% female. On average, participating clinicians had worked 10.0 years (SD 7.5) at their HTx centers, with 63% working full-time in HTx care. All 36 HTx directors also participated (response rate: 100%).

3.2 | Prevalence of nonadherence to immunosuppressants (implementation phase)

The overall prevalence of implementation phase immunosuppressant nonadherence was 34.1%. Taking nonadherence (ie missing doses)

TABLE 1 Descriptive statistics of the multilevel variables (overall sample and adherers/nonadherers [implementation phase]) and results of bivariate analysis (odds ratios [95% CI])

Variables	Values/scoring	Total sample N; mean ± SD N (%)[a]	Adherers N; mean ± SD N (%)[b]	Nonadherers N; mean ± SD N (%)[b]	Bivariate analysis Odds ratio (95% CI)
Block 1: Patient level: proximal variables based on Integrative Model of Behavioral Prediction					
Barriers to take immunosuppressants as prescribed[d]	1 (never) to 5 (always)	1382; 1.20 ± 0.31	868; 1.12 ± 0.22	514; 1.32 ± 0.38	12.33 (7.08-21.09)[c]
Intention to adhere to the immunosuppressants regimen[d]	1 (strongly disagree) to 5 (strongly agree)	1377; 4.69 ± 0.53	865; 4.75 ± 0.49	512; 4.59 ± 0.59	0.58 (0.44-0.77)[c]
Block 2: Patient level: other variables based on Integrative Model of Behavioral Prediction					
Attitudes towards taking immunosuppressants[d] (dimension positive aspects/looking towards the future)	1 (strongly disagree) to 5 (strongly agree)	1381; 4.46 ± 0.46	867; 4.48 ± 0.45	514; 4.42 ± 0.45	0.75 (0.56-1.00)[c]
Attitudes towards taking immunosuppressants (dimension worries)[d]	1 (strongly disagree) to 5 (strongly agree)	1381; 1.91 ± 0.58	868; 1.90 ± 0.60	513; 1.94 ± 0.56	1.15 (0.96-1.38)
Perceived norms related to immunosuppressants[d]	1 (strongly disagree) to 5 (strongly agree)	1374; 1.31 ± 0.60	863; 1.32 ± 0.63	511; 1.28 ± 0.54	0.89 (0.72-1.09)
Self-efficacy with taking immunosuppressants[d]	1 (not at all confident) to 5 (completely confident)	1378; 4.34 ± 0.48	865; 4.43 ± 0.84	513; 4.19 ± 0.83	0.72 (0.64-0.81)[c]
Block 3: Patient level: variables derived from empirical evidence (sociodemographic, clinical, treatment-, condition, and patient-related factors)					
Sociodemographic factors					
Gender[d]	Male	1011 (72.73%)	638 (73.17%)	373 (72.01%)	0.94 (0.72-3.57)
Age[d]	Years	1363; 53.64 ± 13.20	856; 54.81 ± 12.50	507; 51.65 ± 14.11	0.98 (0.97-0.99)[c]
Educational level[d]	1 < secondary school 2 secondary school 3 further education 4 college/university	367 (26.50%) 328 (23.68%) 382 (27.58%) 308 (22.24%)	268 (30.91%) 215 (24.80%) 211 (24.34%) 173 (19.95%)	99 (19.11%) 113 (21.81%) 171 (33.01%) 135 (26.06%)	1.31 (1.16-1.47)[c]
Employment[d]	1 (Self-)employed 2 Looking for a job 3 (Temp.) unable 4 Retired 5 Other answer options	365 (26.24%) 40 (2.88%) 304 (29.04%) 466 (33.50%) 116 (8.34%)	189 (21.70%) 22 (2.53%) 247 (28.36%) 336 (38.58%) 77 (8.84%)	176 (33.85%) 18 (3.46%) 157 (30.19%) 130 (25.00%) 39 (7.50%)	Reference 0.88 (0.40-1.91) 0.68 (0.49-0.96)[c] 0.42 (0.29-0.60)[c] 0.54 (0.35-0.85)[c]
Race[d]	White	1186 (85.88%)	755 (86.99%)	431 (84.02%)	0.79 (0.54-1.15)
Living alone[d]	Yes	265 (19.18%)	156 (18.01%)	109 (21.12%)	1.22 (0.93-1.59)
Marital status[d]	1 Single 2 Divorced/separated 3 Widowed 4 Married/living together	242 (17.45%) 149 (10.74%) 41 (2.96%) 955 (68.85%)	132 (15.17%) 87 (10.00%) 23 (2.64%) 628 (72.18%)	110 (21.28%) 62 (11.99%) 18 (3.48%) 327 (63.25%)	1.60 (1.21-2.12)[c] 1.37 (0.92-2.03) 1.50 (0.94-2.40) Reference
Clinical factors					
Cause of heart failure[d]	1 Ischemic 2 Valvular 3 Congenital 4 Idiopathic 5 Other	444 (32.70%) 40 (2.95%) 45 (3.31%) 697 (51.33%) 132 (9.72%)	284 (33.14%) 28 (3.27%) 26 (3.03%) 436 (50.88%) 83 (9.68%)	160 (31.94%) 12 (2.40%) 19 (3.79%) 261 (52.10%) 49 (9.78%)	0.94 (0.69-1.28) 0.72 (0.43-1.21) 1.22 (0.73-2.04) Reference 0.98 (0.64-1.53)
Charlson comorbidity index posttransplant[d]	Min 0; max 37	1395; 1.02 ± 1.39	877; 0.99 ± 1.39	518; 0.91 ± 1.32	0.95 (0.86-1.03)
Number of treated rejections per year in follow-up[d]	N rejections per year in follow-up	1370; 0.37 ± 0.74	860; 0.38 ± 0.74	510; 0.37 ± 0.74	0.98 (0.84-1.14)
Treatment-related factors					
Number of daily doses of immunosuppressants[d]	N dosing times/d	1384; 2.04 ± 0.25	869; 2.04 ± 0.24	515; 2.05 ± 0.26	1.26 (0.78-2.03)
Time since transplantation[d]	Years	1380; 3.36 ± 1.38	867; 3.33 ± 1.39	513; 3.41 ± 1.37	1.04 (0.98-1.11)

(Continues)

TABLE 1 (Continued)

Variables	Values/scoring	Total sample N; mean ± SD N (%)[a]	Adherers N; mean ± SD N (%)[b]	Nonadherers N; mean ± SD N (%)[b]	Bivariate analysis Odds ratio (95% CI)
Condition-related factors					
Depressive symptoms[d]	Sum score 0 to 56	1340; 1.37 ± 0.60	829; 1.35 ± 0.62	511; 1.39 ± 0.55	1.01 (0.99-1.01)
History of diabetes pretransplant[d]	Yes	366 (26.24%)	231 (26.34%)	135 (26.06%)	0.99 (0.78-1.24)
Posttransplant BMI at time of enrollment[d]	kg/m^2	1373; 27.06 ± 5.65	861; 26.85 ± 5.19	512; 27.41 ± 6.35	1.02 (0.99-1.04)
Patient-related factors					
Stages of change[d]	1 Precontemplation 2 Contemplation 3 Action/maintenance	68 (5.26%) 25 (1.93%) 1199 (92.80%)	41 (5.04%) 9 (1.11%) 763 (93.85%)	27 (5.64%) 16 (3.34%) 436 (91.02%)	0.86 (0.49-1.49)
Sleep quality[d]	0 (very poor) to 10 (very good)	1368; 6.82 ± 2.39	859; 6.95 ± 2.39	509; 6.62 ± 2.37	0.94 (0.90-0.99)[c]
Daytime sleepiness[d]	0 (not at all sleepy) to 10 (very sleepy)	1369; 3.90 ± 2.76	860; 3.75 ± 2.83	509; 4.15 ± 2.63	1.05 (1.01-1.09)[c]
Nonadherence to appointment keeping[d]	No. of last 5 appointments missed	1376; 1.08 ± 0.41	863; 1.07 ± 0.43	513; 1.09 ± 0.39	1.13 (0.89-1.43)
Currently smoking or stopped <1 y ago[d]	Yes	90 (6.57%)	41 (4.77%)	49 (9.61%)	2.12 (1.46-3.08)[c]
Health literacy: confidence filling out medical forms by oneself[d]	Adequate literacy	912 (66.86%)	560 (65.04%)	352 (69.98%)	1.25 (0.97-1.62)
Nonadherence to physical activity recommendations[d]	Sufficiently active	633 (46.24%)	420 (48.89%)	213 (41.76%)	0.75 (0.55-1.02)
Level of alcohol consumption[d]	0 No or low level drinking 1 Moderate level 2 Heavy drinking level	1356 (97.07%) 23 (1.65%) 18 (1.29%)	824 (97.17%) 16 (1.82%) 8 (0.91%)	503 (96.73%) 7 (1.35%) 10 (1.92%)	1.25 (0.86-1.83)
Adherence to sun protection measures[d]	0 (never) to 5 (always)	1377 (3.67 ± 0.81)	867 (3.71 ± 0.80)	510 (3.59 ± 0.82)	0.83 (0.72-0.96)[c]
Nonadherence to dietary guidelines[d]	Adherent	232 (16.61%)	69 (13.27%)	163 (18.59%)	1.49 (1.06-2.10)[c]
Block 4: Micro level (family/healthcare provider)					
Social support (practical support dimension)[d]	1 (never) to 5 (all the time)	1378; 1.78 ± 0.99	864; 1.73 ± 0.98	514; 1.84 ± 1.00	1.12 (0.99-1.26)
Social support (emotional dimension)[d]	1 (never) to 5 (all the time)	1380; 3.58 ± 1.24	866; 3.61 ± 1.25	514; 3.51 ± 1.22	0.94 (0.85-1.03)
Patient is a member of a patient organization[d]	Yes	329 (24.17%)	216 (25.29%)	113 (22.29%)	0.85 (0.62-1.16)
Person responsible for preparing immunosuppressants[d]	Patient alone vs partner/family or in collaboration with partner/family	1140 (83.27%)	705 (81.98%)	437 (85.46%)	1.30 (0.92-1.81)
Frequency of having someone helping them to read health-related materials[d]	1 (none of the time) to 5 (all of the time)	1370; 1.81 ± 1.22	860; 1.88 ± 1.28	510; 1.70 ± 1.11	0.88 (0.80-0.97)[c]
Fluency with language spoken at the transplant center[d]	0 (not fluent at all) to 10 (very fluent)	1386; 9.85 ± 0.76	869; 9.85 ± 0.69	517; 9.86 ± 0.87	1.01 (0.83-1.24)
Transplant team communicates in mother tongue or a language patient masters fluently[d]	Yes	1368 (98.49%)	859 (98.62%)	509 (98.26%)	0.79 (0.35-1.79)
Trust in the healthcare team[d]	1 (very low trust) to 5 (very high trust)	1378; 4.59 ± 0.49	867; 4.62 ± 0.46	511; 4.55 ± 0.54	0.75 (0.60-0.94)[c]

(Continues)

TABLE 1 (Continued)

Variables	Values/scoring	Total sample N; mean ± SD N (%)[a]	Adherers N; mean ± SD N (%)[b]	Nonadherers N; mean ± SD N (%)[b]	Bivariate analysis Odds ratio (95% CI)
Patient satisfaction with the transplant team[d]	1 (very dissatisfied) to 5 (very satisfied)	1379; 4.65 ± 0.72	866; 4.66 ± 0.76	513; 4.63 ± 0.67	0.95 (0.79-1.15)
Block 5: Meso level: transplant center (characteristics and practice patterns in view of chronic illness management)		Measured among:[a] [e]centers n = 36 [f]clinicians n = 100 [d]patients n = 1397	patient n = 877[a]	patient n = 520[a]	
Type of transplant center[e]	University teaching	30 (83.33%)	739 (84.26%)	414 (79.62%)	0.73 (0.48-1.10)
Location of the transplant program[e]	Urban	32 (88.89%)	786 (89.62%)	449 (86.35%)	0.73 (0.42-1.27)
Years since start of the transplant program[e]		34; 27.56 ± 6.51	825; 27.93 ± 5.97	505; 28.51 ± 6.27	1.02 (0.98-1.05)
Number of patients at least 1y post-Tx followed up regularly in HTx center[e,g]		34; 3.71 ± 2.74	796; 4.25 ± 2.74	481; 4.27 ± 3.13	1.00 (0.99-1.01)
Center size (based on the number of transplants in the past 5y)[e]	Small (< 75) Medium (75-100) Large (>100)	9 (25.00%) 8 (22.22%) 19 (52.78%)	114 (13.00%) 151 (17.22%) 612 (69.78%)	86 (16.54%) 96 (18.46%) 338 (65.00%)	0.86 (0.69-1.07)
Length of hospital stay after HTx surgery in the transplant program[e]	Days	35; 20.29 ± 6.97	864; 20.82 ± 6.82	510; 20.19 ± 7.44	0.99 (0.97-1.01)
Total number of yearly visits for patients who are at least 1y post-Tx[e]		35; 9.64 ± 4.81	861; 10.45 ± 4.82	513; 9.71 ± 4.49	0.97 (0.93-1.00)
Mean total time clinicians meet each patient at the outpatient clinic (patient's perspective)[d]	<10 min 11-20 min 21-30 min >30 min	76 (5.53%) 382 (27.80%) 388 (28.24%) 528 (38.43%)	42 (4.86%) 224 (25.96%) 243 (28.16%) 354 (41.02%)	34 (6.65%) 158 (30.92%) 145 (28.38%) 174 (34.05%)	0.84 (0.75-0.95)[c]
Mean average total time clinician sees patient at the outpatient heart transplant clinic (clinician's perspective)[f,g]	Hours	82; 0.63 ± 0.91	827; 0.62 ± 0.55	491; 0.58 ± 0.51	0.89 (0.69-1.06)
Patients routinely receive a formal mental health or psychological evaluation before Tx[e]	Yes	29 (80.56%)	726 (82.78%)	427 (81.12%)	0.95 (0.55-1.64)
Patients routinely undergo a formal financial-social evaluation before Tx[e]	Yes	26 (72.22%)	607 (69.21%)	357 (68.65%)	0.97 (0.68-1.39)
Adherence to immunosuppressants is routinely assessed as part of posttransplant follow-up care[f]	Yes	94 (96.91%)	877; 0.982 ± 0.07	520; 0.981 ± 0.07	0.78 (0.20-3.08)
The transplant team discussed the intake of immunosuppressants in daily life[d]	Yes	1295 (94.66%)	788 (94.83%)	483 (94.34%)	0.86 (0.57 -1.30)
Clinicians reporting that nonadherent patients are targeted with adherence interventions[f]	1 (never) to 4 (always)	95; 3.00 ± 0.68	846; 2.99 ± 0.45	500; 2.89 ± 0.44	0.59 (0.42-0.81)[c]
Are patients followed up by the same healthcare worker when they visit the outpatient clinic[e]	1 Yes 2 Some of the time 3 Rarely or never	29 (80.56%) 7 (19.44%) 0 (0.0%)	700 (79.82%) 117 (20.19%) 0 (0.0%)	390 (75.00%) 130 (25.00) 0 (0.0%)	0.76 (0.51-1.13)
The initial contact for talking to patients in case of after-hours questions or emergencies is an Advanced Practice Nurse[e]	Yes	2 (5.56%)	63 (7.18%)	27 (5.19%)	0.71 (0.30-1.67)

(Continues)

TABLE 1 (Continued)

Variables	Values/scoring	Total sample N; mean ± SD N (%)[a]	Adherers N; mean ± SD N (%)[b]	Nonadherers N; mean ± SD N (%)[b]	Bivariate analysis Odds ratio (95% CI)
The initial contact for talking to patients in case of after-hours questions or emergencies is a registered nurse[e]	Yes	7 (19.44%)	135 (15.39%)	95 (18.27%)	1.23 (0.88-1.69)
Multidisciplinary team[e]	Yes	29 (80.56%)	731 (83.35%)	419 (80.58%)	0.83 (0.54-1.26)
The Advanced Practice Nurse on the team has a certificate or other advanced specialization in transplantation[f]	Yes	34 (58.62%)	499; 0.48 ± 0.44	364; 0.46 ± 0.43	0.90 (0.56-1.46)
The clinic has someone with the title of care coordinator[f]	Yes	49 (49.00%)	877; 0.49 ± 0.41	520; 0.54 ± 0.40	1.40 (0.89-2.19)
Patient's perspective of chronic illness management implemented in HTx program (PACIC)[d]	Scoring from 11 to 55	1378; 38.48 ± 10.86	864; 38.96 ± 10.87	514; 37.65 ± 10.80	0.99 (0.98-1.00)
Healthcare worker's perspective of chronic illness management implemented in HTx program (CIMI-Bright)[f]	1 (strongly disagree) to 5 (strongly agree)	36; 2.96 ± 0.37	877; 2.92 ± 0.27	520; 2.93 ± 0.27	1.27 (0.61-2.60)
Competencies of Tx team in view of chronic illness management[f]	1 (strongly disagree) to 5 (strongly agree)	100; 3.39 ± 0.42	877; 3.33 ± 0.32	520; 3.37 ± 0.30	1.52 (0.86-2.69)
Level of preparedness of healthcare workers[f]	1 (strongly disagree) to 5 (strongly agree)	100; 3.39 ± 0.43	877; 3.37 ± 0.38	520; 3.39 ± 0.34	1.14 (0.69-1.87)
Opportunities exist in the transplant program for pretransplant patients to meet or interact with posttransplant recipients[f]	Yes	97 (97.00%)	877; 0.96 ± 0.12	520; 0.97 ± 0.11	2.32 (0.87-6.18)
Self-management support interventions are provided during long-term followup[f]	Yes	67 (67.00%)	877; 0.59 ± 0.39	522; 0.64 ± 0.37	1.73 (0.87-6.18)
Refill of immunosuppressants: pick-up at local pharmacy[d]	Yes	1117 (81.53%)	716 (83.16%)	401 (78.78%)	0.75 (0.51-1.10)
Refill of immunosuppressants: hospital pharmacy[d]	Yes	305 (22.36%)	184 (21.50%)	121 (23.82%)	1.14 (0.82-1.60)
Refill of immunosuppressants: physician's office[d]	Yes	31 (2.28%)	12 (1.40%)	19 (3.78%)	2.76 (1.57-4.85)[c]
Refill of immunosuppressants: online order[d]	Yes	114 (8.43%)	66 (7.74%)	48 (9.60%)	1.27 (0.86-1.87)
Refill of immunosuppressants: telephone order[d]	Yes	262 (19.42%)	156 (18.37%)	106 (21.20%)	1.20 (0.81-1.76)
Refill of immunosuppressants: other[d]	Yes	23 (2.12)	14 (2.02)	9 (2.29)	1.16 (0.76-1.78)
Block 6: Healthcare system level					
Health insurance covers costs of immunosuppressants[d]	1 yes fully 2 yes partly 3 no	811 (59.07%) 537 (39.11%) 25 (1.82%)	531 (61.60%) 314 (36.43%) 17 (1.97%)	280 (54.79%) 223 (43.64%) 8 (1.57%)	1.25 (0.91-1.72)
Monthly out-of-pocket expenses for immunosuppressants[d]	1 0-20$ 2 20.01-60$ 3 60.01-110$ 4 > 110$	850 (62.82%) 241 (17.81%) 129 (9.53%) 133 (9.83%)	560 (65.88%) 151 (17.76%) 75 (8.82%) 64 (7.53%)	290 (57.65%) 90 (17.89%) 54 (10.74%) 69 (13.72%)	1.25 (1.09-1.43)[c]

(Continues)

TABLE 1 (Continued)

Variables	Values/scoring	Total sample N; mean ± SD N (%)[a]	Adherers N; mean ± SD N (%)[b]	Nonadherers N; mean ± SD N (%)[b]	Bivariate analysis Odds ratio (95% CI)
Patient finds it hard to take their immunosuppressants because they cannot afford them[d]	1 (never) to 5 (always)	1372; 1.06 ± 0.33	861; 1.05 ± 0.31	511; 1.08 ± 0.38	1.28 (0.99-1.66)
Patient feel they enough money to pay for their immunosuppressants[d]	1 not enough 2 mostly enough 3 enough 4 more than enough	243 (18.37%) 244 (18.44%) 615 (46.49%) 221 (16.70%)	151 (18.11%) 154 (18.47%) 383 (45.92%) 146 (17.51%)	92 (18.81%) 90 (18.40%) 232 (47.44%) 75 (15.34%)	0.96 (0.86-1.07)

CI, confidence interval; HTx, heart transplantation; SD, standard deviation; Tx, solid organ transplantation.
[a]Within the total sample column, N's reflect sample sizes at respective levels (patients max n = 1397; centers max n = 36, and clinicians max n = 100).
[b]Within the subgroup columns, N's reflect sample sizes at the patient level (max n = 1397), implying that variables at higher levels were linked to their respective patients at center level, hence differences in sample size presentation compared to the total sample column (a) are possible.
[c]This variable was entered into the multiple model (variables also highlighted in gray tone).
[d]Asked at the patient level.
[e]Variable measured at center level (transplant director report).
[f]Variables measured at clinician level. In order to make the distinction between "adherent" and "nonadherent" groups, these variables were first aggregated at the center level, and then linked to patients from their center. For dichotomous variables expressed in percentages (yes/no), results in the "adherent" and "nonadherent" columns reflect the average percentage of clinicians who responded positively ("yes") to this particular question.
[g]Odds ratios for these variables are to be interpreted in increments of 10 units in their value.

was reported by 14.7% and timing nonadherence (>2 hours deviation from dosing schedule) by 26.5% of patients.

3.3 | Multilevel factors of immunosuppressant nonadherence

Table 1 provides descriptive statistics for all multilevel factors, both for the entire group and for adherent and nonadherent groups separately. It also reports ORs and CIs for each multilevel factor that resulted from simple logistic regression analyses predicting nonadherence.

Factors surpassing the inclusion threshold (Table 1) were entered in the multiple sequential regression model using 6 blocks (Table 2). From Block 1, *barriers* and *intention* were both initially retained; but *intention* was explained/replaced by self-efficacy (Block 2), which then lost significance with the inclusion of the Block 3 factors. Block 3 (literature-derived patient-level variables) added *smoking* and *employment*, which was later eliminated by *out-of-pocket expenses* (Block 6). From Block 4 (micro-level variables) *frequency of having someone to help read health-related materials* (a protective factor), was retained, along with 3 of Block 5's meso-level variables (*medication pick-up at the physician office; clinicians reporting targeting nonadherent patients with adherence interventions*). Finally, in Block 6's macro-level factors, we noted some collinearity between *employment* and *out-of-pocket expenses*. As only 8% of *employment*'s variability was explained by country differences, compared to 24% for *out-of-pocket expenses*, we included only *out-of-pocket expenses*. This left 6 factors associated with immunosuppressant nonadherence. Of these, 4 were independently positively associated with nonadherence (barriers to taking immunosuppressants as prescribed [OR = 11.48; 95% CI, 6.66-21.05]; currently smoking or having stopped less than a year ago [OR: 2.19; 95% CI, 1.35-3.56]; medication pick-up at physician's office [OR = 2.31; 95% CI, 1.24-4.31]; and monthly out-of-pocket immunosuppressant expenses [OR = 1.16; 95% CI, 1.02-1.33]); and 2 were negatively associated, ie protective factors (frequency of having someone to help read health-related materials [OR = 0.85; 95% CI, 0.76-0.95] and clinicians reporting targeting nonadherent patients with adherence interventions [OR = 0.66; 95% CI, 0.48-0.91]). The final model explained 21.7% of the variability in nonadherence (Table 2). If only patient-level variables were left, explained variability remained at 13.0%. Likewise, leaving in only micro-, meso-, and macro-level variables resulted in 2.4%, 8.1%, and 4.3% of explained variability, respectively.

Our sensitivity analyses confirmed all of the included variables' relationships to nonadherence. However, barriers to taking immunosuppressants as prescribed, smoking, and monthly out-of-pocket expenses for immunosuppressants were associated with its taking aspect; barriers, frequency of help reading health-related materials, medication pick-up at physician's office, and clinicians reporting that nonadherent patients were targeted with adherence interventions, were associated with its timing aspect (data not shown). Imputation of missing data did not affect the results.

4 | DISCUSSION

This multicontinental study is the first in transplantation and one of the first in chronically ill patient populations[6,15,33] to simultaneously investigate patient-, healthcare provider/family-, healthcare organization- and healthcare system-related factors' associations with medication nonadherence. Its main strengths are its large geographical coverage (11 countries) as well as its use of theory to select potential multilevel correlates.[6,19,20,38]

We confirmed previous evidence that the magnitude of implementation phase nonadherence to immunosuppressants is substantial in

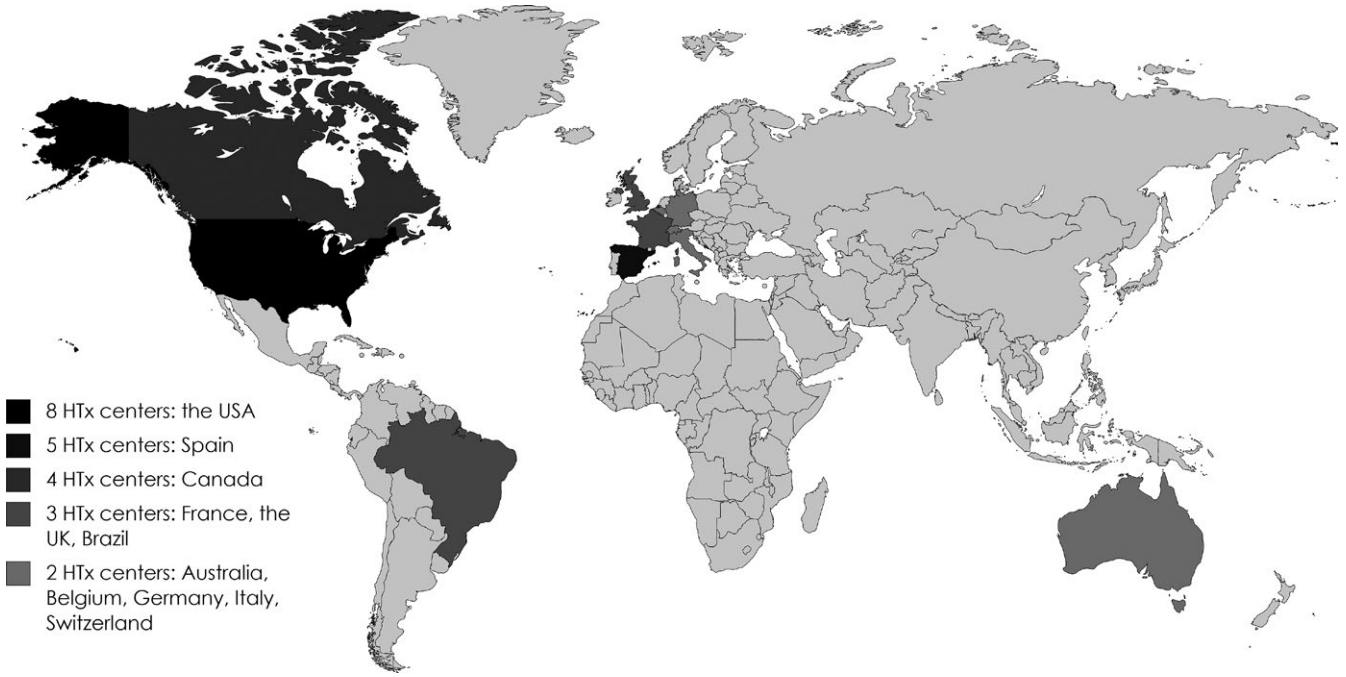

FIGURE 2 Geographical location of participating BRIGHT centers and number of centers per country (N = 36). BRIGHT, Building Research Initiative Group: Chronic Illness Management and Adherence in Transplantation; HTx, heart transplant

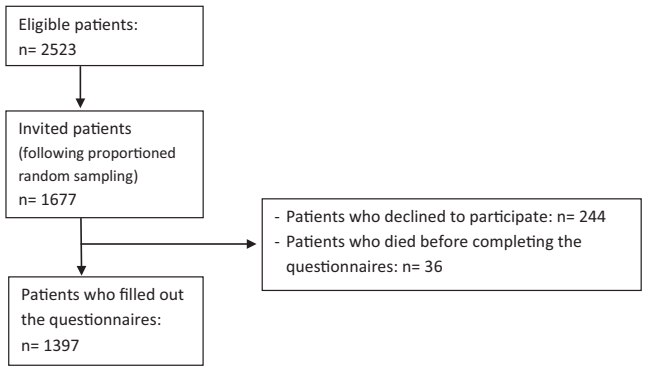

FIGURE 3 Flowchart of heart transplant patient sample

HTx[1] (overall prevalence: 34.1%). Our findings support our hypothesis that multilevel factors are associated with immunosuppressant nonadherence. Our model explained 21.7% of all variability. Congruent with a previous multilevel factor study,[15] much of this could be attributed to patient-level variables; however, higher-level variables still explained a significant amount of nonadherence. This indicates that the currently prevailing perspective—which assigns patients all responsibility for nonadherence—is incorrect.

In fact, only 2 factors were retained at the *patient level:* smoking and adherence barriers, the latter of which was our model's strongest predictor of nonadherence (OR 11.48; CI, 6.66-21.05). Given theoretical models' common treatment of barriers as proximal determinants of health behavior,[38] and the findings of other transplant studies,[17,18] this is no surprise. Assessment of barriers can guide tailored interventions.[43] Still, our final model excluded another determinant of health behavior [38] normally correlated proximally to immunosuppressant nonadherence in transplantation,[16,18] ie intention. In contrast to adherence's initiation phase, the implementation phase is subject more to nonintentional drivers than to rational ones. Self-efficacy, a factor previously associated negatively with immunosuppressant nonadherence,[4,13,44] was also excluded from the final model: Self-efficacy partly overlaps with barriers in terms of the variance levels the 2 explain, and is excluded if barriers remain.

One novel finding was smoking's independent correlation with nonadherence. We know of no studies in the transplant literature that have reported this association.[45] Both smoking and medication nonadherence are important known risk factors for poor clinical outcomes following HTx.[2,46]

At the *micro level*, we identified 1 protective factor (ie frequency of having someone help read health-related materials). This indicates a very specific aspect of social support linked closely with health literacy or the lack thereof. Congruent with previous evidence in solid organ transplantation,[11,47-49] practical, emotional, and overall social support correlate with better adherence.[50] Although positively linked with adherence in other chronically ill populations,[51] health literacy *per se* was not a significant factor in our analysis, suggesting that patients typically need support in processing health-related information.

Three *meso-level* factors correlated independently with nonadherence. Medication pick-up at the physician's office vs at a pharmacy was associated with higher levels of nonadherence. We can interpret this result from 2 perspectives. First, patients picking up their medication from a pharmacy might receive extra adherence-enhancing interventions compared to those receiving them at the physician's office. Pharmacies are increasingly augmenting their services with adherence support, an intervention proven effective in kidney transplant patients.[52,53] Alternatively, receiving medication at a physician's office,

TABLE 2 Independent predictors of medication nonadherence (implementation phase) (sequential multiple logistic regression analysis [Block 1 → 6])

Variable	Odds ratio (95%CI)	*P*-value
Block 1: Patient level: Integrative Model of Behavioral Prediction (IMBP) (n = 1377; R^2 = 12.3%)		
Barriers to take immunosuppressants as prescribed	11.90 (7.02-20.20)	<.0001
Intention to take the immunosuppressants	0.81 (0.66-0.99)	.04
+ Block 2: Patient level: Integrative Model of Behavioral Prediction (IMBP) (n = 1378; R^2 = 11.6%)		
Barriers to medication taking	9.83 (5.76-16.79)	<.0001
Self-efficacy with medication taking	*0.90 (0.82-0.99)*	*.04*
+ Block 3: Literature derived patient-level variables (n = 1363; R^2 = 14.7%)		
Barriers to take immunosuppressants as prescribed	11.60 (6.70-20.01)	<.0001
Currently smoking or stopped <1 y ago	*2.00 (1.26-3.18)*	*.003*
Employment: Looking for a job vs (Self-)employed	*0.85 (0.38-1.91)*	*.69*
Employment: Disability vs (Self-)employed	*0.67 (0.47-0.96)*	*.03*
Employment: Retired vs (Self-)employed	*0.49 (0.33-0.72)*	*.0003*
Employment: Other vs (Self-)employed	*0.53 (0.34-0.86)*	*.01*
+ Block 4: Micro-level variables: interpersonal relationships family/healthcare provider (n = 1352; R^2 = 15.9%)		
Barriers to take immunosuppressants as prescribed	12.05 (6.96-20.85)	<.0001
Currently smoking or stopped <1 y ago	2.03 (1.26-3.27)	.004
Employment: Looking for a job vs (Self-)employed	0.84 (0.39-1.85)	.67
Employment: Disability vs (Self-)employed	0.70 (0.49-0.99)	.05
Employment: Retired vs (Self-)employed	0.50 (0.34-0.74)	.0004
Employment: Other vs (Self-)employed	0.54 (0.33-0.89)	.02
Frequency of having someone helping to read health-related materials	*0.85 (0.77-0.95)*	*.004*
+ Block 5: Meso-level: healthcare organization / transplant center (n = 1283; R^2 = 21.2%)		
Barriers to take immunosuppressants as prescribed	10.92 (6.34-18.80)	<.0001
Currently smoking or stopped <1 y ago	2.11 (1.27-3.48)	.004
Employment: Looking for a job vs (Self-)employed	0.83 (0.35-1.95)	.67
Employment: Disability vs (Self-)employed	0.66 (0.46-0.94)	.02
Employment: Retired vs (Self-)employed	0.49 (0.33-0.72)	.0003
Employment: Other vs (Self-)employed	0.52 (0.31-0.85)	.009
Frequency of having someone helping to read health-related materials	0.86 (0.77-0.96)	.006
Medication pick-up at physician's office	*2.37 (1.23-4.57)*	*.01*
Clinicians reporting that non-adherent patients were targeted with adherence interventions	*0.64 (0.48-0.87)*	*.004*
FINAL MODEL: + Block 6: + macro level variables: health-care system (n = 1262; R^2 = 21.7%)		
Barriers to take immunosuppressants as prescribed	11.48 (6.66-21.05)	<.0001
Currently smoking or stopped <1 y ago	2.19 (1.35-3.56)	.002
Frequency of having someone helping to read health-related materials	0.85 (0.76-0.95)	.004
Medication pick-up at physician's office	2.31 (1.24-4.31)	.008
Clinicians reporting that non-adherent patients were targeted with adherence interventions	0.66 (0.48-0.91)	.01
Monthly out of pocket expenses for immunosuppressants	*1.16 (1.02-1.33)*	*.03*

This table presents the odds ratio's predicting nonadherence.
Odds ratios >1 indicate *a risk factor* for medication nonadherence.
Odds ratio <1 indicate *a protective factor* for medication nonadherence.
Variables were added sequentially (block 1 until 5) and significant variables retained for next step (see italic and gray highlight).

which allows especially close follow-up, might reflect the physician's perception of a higher nonadherence risk.

As expected, we found that the meso-level "clinicians reporting that patients known to be nonadherent were targeted with adherence interventions" factor was associated with lower nonadherence. Supporting patient self-management[54,55] is effective in improving outcomes.[56-58] This also includes adherence monitoring as a standard practice.[43]

Finally, at the *macro level*, congruent with previous evidence in chronic illness, monthly out-of-pocket expenses for immunosuppressants were a risk factor for nonadherence.[59,60] A recent international survey showed that out-of-pocket expenses are especially problematic in the United States, but also in Canada and Australia. Furthermore, difficulty paying medical bills is an increasing issue in a number of countries.[61] Responding to a survey, 70% of kidney transplant programs in the United States reported that patients had difficulties paying for their medication.[62] As health insurance status was not retained in our analysis, previous evidence from US studies correlating insurance status inversely with nonadherence was not confirmed.[9,11]

Given that multilevel factors were associated with nonadherence to immunosuppressants—a major risk factor for poor clinical outcomes in transplantation[2]—a multilevel intervention approach targeting not only the patient, but also micro-, meso-, and macro-level factors is necessary. Miller et al, followed by other reports and reviews, previously highlighted the importance of such action at the various levels of the healthcare system.[7,21,24,43,63]

The evidence base for multilevel medication adherence interventions is more limited than at the patient level.[14,24,63-65] High-quality studies included in the latest Cochrane review of medication adherence interventions[65] highlight the value of complex multicomponent interventions featuring support by both family members and healthcare workers (including pharmacists). However, despite addressing adherence barriers via tailored education, counseling, or daily treatment support, they have shown no significant improvements in adherence or clinical outcomes.[65] The systematic review by Viswanathan et al indicates that reducing out-of-pocket expenses and case management together with patient education and behavioral support are effective interventions.[24] At the macro level, policy interventions to decrease transplant patients' financial burden,[52] including full medication coverage, have been proven effective at enhancing adherence.[66]

Limitations of this study include the cross-sectional design, which precludes causal inferences. Second, the use of self-report to assess adherence may be questioned.[67] We carefully considered alternative adherence measures. Electronic monitoring was not feasible, as this would have increased the complexity of data collection, requiring a substantially higher research budget and more logistical support, thus potentially jeopardizing the willingness of centers, clinicians, and patients to participate in the study. While assay is in standard use for immunosuppressant monitoring, a recent study demonstrated the validity of the Medication Level Variability Index to assess nonadherence to tacrolimus in liver transplant groups.[68] We decided not to use assay for several reasons. First, transplant centers differed regarding the types of immunosuppressive regimens prescribed (ie, 63% tacrolimus based, 32% cyclosporine based), and no similar validated formula exists for adherence detection in cyclosporine-based regimens. Moreover, unavailability of electronic medical records in about one fourth of the participating centers complicated retrieval of assay values. Pharmacy refill records were not uniformly available in all centers. We therefore used a validated interview to document adherence. Another limitation of this study is that, although we included a large set of multilevel factors, more work is needed to identify relevant factors, not only at the patient level, but especially at the micro, meso, and macro levels. Future studies will need to build upon new theoretical or empirical insights.

5 | CONCLUSION

Six multilevel factors (adherence barriers, smoking, support reading health-related materials, targeting of nonadherent patients for adherence interventions, medication pick-up at the physician's office, and monthly out-of-pocket costs) were associated with immunosuppressant nonadherence. Medication adherence–enhancing interventions require a multilevel approach combining patient-, healthcare provider/family-, organization-, and policy-level strategies.

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DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation.*

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APPENDIX 1

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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