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Prevalence and Correlates of Cost-Related Medication Nonadherence to Immunosuppressive Drugs After Heart Transplantation

The International Multicenter Cross-sectional Bright Study

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Background: Cost-related medication nonadherence (CRMNA) refers to not taking medications as prescribed because of difficulties paying for them. **Objectives:** The aims of this study were (1) to assess the prevalence of CRMNA to immunosuppressants in heart transplant recipients internationally and (2) to determine multilevel correlates (patient, center, and healthcare system levels) of CRMNA. **Methods:** Using data from the cross-sectional international BRIGHT study, applying multistaged sampling, CRMNA was assessed via 3 self-report items in 1365 patients from 36 heart transplant centers in 11 countries. Cost-related medication nonadherence was defined as any positive answer on any of the 3 items. Healthcare system–level (ie, insurance coverage, out-of-pocket expenditures) and patient-level (ie, intention, perceived financial burden, cost as a barrier, a health belief regarding medication benefits, cost-related self-efficacy, and demographic factors) CRMNA correlates were assessed. Correlates were examined using mixed

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logistic regression analysis. **Results:** Across all study countries, CRMNA had an average prevalence of 2.6% (range, 0% [Switzerland/Brazil] to 9.8% [Australia]) and was positively related to being single (odds ratio, 2.29; 95% confidence interval, 1.17–4.47), perceived financial burden (odds ratio, 2.15; 95% confidence interval, 1.55–2.99), and cost as a barrier (odds ratio, 2.60; 95% confidence interval, 1.66–4.07). Four protective factors were identified: white ethnicity (odds ratio, 0.37; 95% confidence interval, 0.19–0.74), intention to adhere (odds ratio, 0.44; 95% confidence interval, 0.31–0.63), self-efficacy (odds ratio, 0.54; 95% confidence interval, 0.43–0.67), and belief about medication benefit (odds ratio, 0.70; 95% confidence interval, 0.57–0.87). Regarding variability, 81.3% was explained at the patient level; 13.8%, at the center level; and 4.8%, at the country level. **Conclusion:** In heart transplant recipients, the CRMNA prevalence varies across countries but is lower than in other chronically ill populations. Identified patient-level correlates are novel (ie, intention to adhere, cost-related barriers, and cost-related self-efficacy) and indicate patient-perceived medication cost burden.

KEY WORDS: healthcare costs, heart transplantation, medication adherence, multilevel correlates

Heart transplant recipients depend on lifelong immunosuppressive (IS) and co-medication regimens[1,2]; however, nonadherence is common. Occurring in 14.5 cases per 100 persons per year,[3] it is associated with poor clinical and economic outcomes.[4–7] One likely factor is medication cost, which patients' health insurance may cover fully, partially, or not at all.[8]

Cost-related medication nonadherence (CRMNA) consists of 3 behaviors, namely, not filling a prescription and skipping or reducing doses because of their cost,[9] and is a distinct concept from medication nonadherence as defined by the ABC taxonomy[10] (the prevalence and determinants of the latter have previously been reported as part of the BRIGHT study).[11,12] The 2014 Commonwealth Fund International Health Policy Survey of Older Adults assessed CRMNA, defined as either not filling a prescription or skipping doses within the last 12 months because of out-of-pocket (OOP) costs.[13] The lowest nonadherence rates occurred in France, Norway, Sweden, Switzerland, and the United Kingdom (<3%); the highest were observed in the United States (16.8%), Canada (8.3%), and Australia (6.8%).[13,14] Nonadherence correlates with cost; for example, 41% of chronically ill patients in the United States have monthly OOP medication expenses exceeding 1000 USD, and only 2% of those in Sweden do.[14]

In transplantation, CRMNA issues focus primarily on the United States,[15–18] which has both the lowest proportion of health-insured patients and the highest OOP medication burden of all developed nations.[14,15,18] In a survey of 254 US adult and pediatric transplant programs regarding IS-related cost issues,[17] 83% of the transplant programs reported that patients frequently contacted them with concerns about their medication costs. More than 70% of surveyed centers indicated that at least every fifth patient had difficulties affording ISs,[17] and more than two-thirds (68%) attributed deaths and graft losses to CRMNA.[17] However, CRMNA prevalence in heart transplantation and overall transplant populations in international (including US) samples remains unexplored.

For patients with cardiovascular disease (N = 1849; >40 years old), CRMNA's relevance was shown in a 2016 study conducted in Western Canada. With roughly 80% of the sample reporting OOP spending on medication, the CRMNA rate was 4.1% (95% confidence interval, 2.6–6.3). Almost 5% of the sample spent at least 5% of their household income OOP for medications. These patients were significantly more likely to report CRMNA than were those spending less than 5%.[19]

Understanding CRMNA and identifying at-risk patients require a clearer knowledge of its determinants and/or correlates. Findings in chronically ill and transplant populations show that sociodemographic risk factors include younger age,[20–22] female gender,[20,22,23] not being married,[24] a lower education level,[24] unemployment,[21] and being black or Hispanic.[22,24–26] Patient-level factors linked with CRMNA include patient-perceived medication regimen-related financial burden,[27] perceived financial stress,[28] financial insecurity regarding healthcare,[28] food insecurity,[25,28] health beliefs,[22,29] and private health insurance coverage.[30] Linked to insurance coverage, OOP medication expenditure[14] is intrinsically linked to a country's healthcare system and its medication coverage (eg, the presence of a third-party copayment system).

To capture all modifiable factors that provide leverage points for CRMNA-preventive or CRMNA-remedial interventions, a theoretical perspective considering risk factors occurring not only in patients[31] but also at other healthcare system levels (eg, transplant centers, healthcare systems)[32] is desired. Therefore, we selected a theoretical framework combining an ecological perspective[32] with that of the Integrative Model of Behavioral Prediction[31] (Figure). On the basis of this model, both patient-level factors and healthcare system characteristics influence CRMNA. The relative contributions of multilevel factors to CRMNA variability remain unknown.

This study had 3 aims: aim 1, to assess the prevalence of CRMNA to immunosuppressants in heart transplant recipients internationally; aim 2, to identify

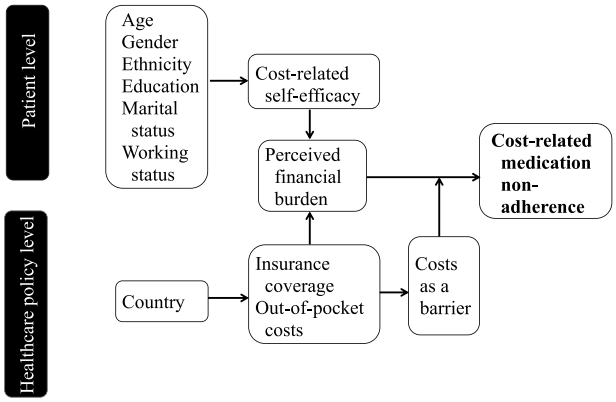

FIGURE. *Theoretical framework (adapted).*[31,32]

correlates of CRMNA; and aim 3, to determine the proportions of CRMNA variability attributable to patient-, center-, and healthcare system–level factors.

Methods

Design, Sample, and Setting

This study was a secondary analysis of data collected for the international cross-sectional multicenter BRIGHT (**B**uilding **R**esearch **I**nitiative **G**roup: Chronic Illness Management and Ad**h**erence in **T**ransplantation[33,34]) study. The methods and procedures of the BRIGHT study have been described in detail elsewhere[11,34] (see also Clinicaltrials.gov ID: NCT01608477). The authors of the BRIGHT study used a multistage sampling approach and included 11 countries, 36 heart transplant centers, and 1365 patients. Inclusion criteria for heart transplant centers were as follows: (1) being located in Europe, North America, South America, or Australia and (2) having performed a minimum of 50 heart transplants for the previous 12 to 60 months. Using a stratified random sampling approach based on center size,[34] patients were included if they fulfilled the following criteria: (1) heart transplant recipient; (2) 18 years or older at the time of inclusion; (3) transplanted and followed up for routine care in one of the participating transplant centers; (4) first transplant; (5) single-organ transplant; (6) 1 to 5 years post transplant; (7) no professional support in medication taking, that is, a nurse or nursing aide or other health personnel (excluding family members) in supporting a heart transplant patient at home in preparing and/or taking medication; (8) capacity to read, understand, and sign written informed consent; and (9) provision of written informed consent. Participants were excluded from the analysis if they omitted information from any of the 3 items assessing CRMNA (see section hereinafter). The study was approved centrally by the ethics committee of KU Leuven in Belgium and by each participating center's institutional review board. Before data collection, the study was explained to each patient and written informed consent was obtained.[34]

Variables and Measurement

Data used in this analysis were collected using 2 survey instruments,[34] one completed by the participating heart transplant centers' transplant directors and the other completed by their patients. The transplant director questionnaire collected data on each center's structural characteristics and practice patterns; the patient questionnaires assessed CRMNA, health behaviors, psychosocial factors, and perceptions of care provided. Variables were assessed using instruments specifically developed for the BRIGHT study, as described hereinafter.[34]

Cost-Related Medication Nonadherence

Cost-related medication nonadherence was assessed at patient level using 3 questions adapted from a previous study by Wilson et al.[9] Three cost-related behaviors were measured: First, patients were asked how often over the preceding 12 months they had not filled their prescription for immunosuppressants because they were too expensive (options: never, once, twice, 3–4 times, 5–6 times, 7 or more times). Second, they were asked whether, over the past 12 months, they had ever skipped a dose of their immunosuppressants to make their prescription last longer because of lack of money (options: no, never; yes, sometimes; yes, often). Third, patients indicated whether, over the past 12 months, because of lack of money, they had reduced their dose of immunosuppressants (eg, by cutting pills in half) so that the prescribed supply would last longer (options: no, never; yes, sometimes; yes, often). The responses were operationalized dichotomously as "no" (0) if patients answered "never" on all 3 items and "yes" (1) if positive on any of the three.

Multilevel Correlates of CRMNA

We assessed insurance coverage and OOP costs at the country level and formal pretransplant financial-social factors at the center level as healthcare system characteristics. Assessing insurance coverage involved asking patients whether their health insurance covered the costs of immunosuppressants fully (options: yes, full coverage; yes, partial coverage; or no coverage). The OOP immunosuppressant cost assessment was derived from a study that asked chronically ill patients their monthly OOP medication expenses (0–20, 20.01–60, 60.01–110, and >110 USD [adapted to match the respondents' national currencies]).[35] Pretransplant financial-social evaluation was assessed by asking the transplant directors whether their patients routinely underwent formal financial-social evaluations (yes/no).

At the patient level, 5 correlates of CRMNA were included: intention to adhere, an adherence barrier, a health belief, cost-related self-efficacy, and perceived financial

burden (derived from the Integrative Model of Behavioral Prediction).[31] Intention, that is, the cognitive representation of a person's readiness to adhere, was assessed as the average score for 3 items (Likert-type scale; range, 1–5 ["strongly disagree" to "strongly agree"]). The items were as follows: (1) "My planning is to strictly follow the prescription of my immunosuppressive medication," (2) "I will make sure that I never omit any intake of my immunosuppressive medications," and (3) "I always intend to take my immunosuppressive medications on time." The Cronbach α across these 3 items was 0.81. Cost as a barrier to adherence was assessed by a single item asking patients how often they found it difficult to take their IS medication because of the expense (Likert-type scale; range, 1–5 ["never" to "always"]). To assess cost-related self-efficacy, patients were asked how confident they were that they would take their immunosuppressants exactly as prescribed despite their expense (single item; 5-point Likert-style scale; range, 1–5 ["not at all confident" to "completely confident"]). One health belief was assessed: the belief in the benefits of a heart transplant compared with adverse effects caused by ISs (single item; Likert-type scale; range, 1–5 ["strongly disagree" to "strongly agree"]). This belief was selected based on previous research linking income to increased worries and experiences of adverse effects.[29] To assess patients' perceived financial burden regarding their IS regimens, they were asked whether they felt they had enough money to pay for their ISs (1 item; Likert-style scale; range, 1–4 ["more than enough" to "not enough"]). We took this item from the Supporting Medication Adherence in Renal Transplantation questionnaire.[36]

Furthermore, our CRMNA model included 6 sociodemographic factors (Figure): age in years, gender, marital status (single, married/living with partner, divorced/separated, widowed), ethnicity (white or other), educational level (primary/grade or no school, completed high/secondary school, completed further education/training, completed college/university), and employment ([self-]employed, looking for a job, on disability, retired, other [eg, student, volunteer]).

Data Analysis

To address aim 1, variables were summarized by country and for the entire sample using descriptive statistics including frequencies, percentages, and measures of central tendency (means, medians) and dispersion (standard deviations, interquartile ranges), depending on measurement levels and distribution of the variables. To produce estimates that reflected the country-specific transplant population sizes, CRMNA prevalence was weighted for heart transplant population sizes at the national level.

Aim 2 (to determine CRMNA correlates) was addressed via simple logistic regression analyses testing the selected variables' association with CRMNA. We accounted for the cluster sampling via a random intercept at the transplantation center level. To adjust for multiple testing, we adapted probability values via the false discovery rate method and reported these as q values.[37]

Achieving aim 3 meant disentangling the proportions of CRMNA variability explainable at the patient, center, and country levels. To do so, we added random intercepts for country and (nested within that) center to a logistic regression analysis, thereby allowing calculation of the intracluster correlations for these levels.[38] Although the "insurance coverage" and "OOP costs" were measured at the patient level, a substantial part of their variability likely results from country-level policy decisions; therefore, we explored the magnitude of these 2 healthcare system factors' variability at the country level via 2 similar linear random-intercept regression analyses.

SAS 9.4 (SAS Institute Inc, Cary, North Carolina) software was used for data analysis. The level of significance was set at $P < .05$, with a false discovery rate threshold of 5% (expressed as q values).[37]

Results

Sample Characteristics

In the 36 participating centers in 11 countries, 2523 patients were eligible for inclusion. Of these, we randomly invited 1677 to participate; 1397 responded by returning questionnaires; and of this number, 1365 (81.4% of invitees) answered all 3 CRMNA questions. The number of participants is distributed as follows: 753 European, 472 North American, 49 Australian, and 40 Brazilian participants. The dropout is due to refusals (n = 250), death (n = 36), and missing data (n = 51). This group's data were the basis of our analysis.

Of the 36 participating centers, 30 (83.3%) were university hospitals and 32 (88.89%) were situated in urban environments. On average, participating transplant programs had existed for 27.6 ± 6.5 years. The mean number of heart transplants performed for the past 5 years was 125.5 ± 75.5.

Table 1 summarizes the patient sample characteristics. Almost three-quarters of patients were male (n = 986, 72.6%); the mean age was 53.6 ± 13.2 years (range, 18–82 years); on average, posttransplantation time was 3.35 ± 1.38 years. More than two-thirds were married or living with a partner (n = 938). Approximately one-quarter (26.3%) were employed (n = 357), and most were white (n = 1162, 88.1%). Full insurance coverage for IS drugs was available to 59%, and 62.5% (n = 838) reported monthly OOP costs of less than 20 USD.

International Prevalence and Variability of Cost-Related Nonadherence to Immunosuppressants

The overall weighted CRMNA prevalence was 2.6% (n = 36; Table 2), ranging from 0% in Switzerland and

TABLE 1 Characteristics of the Total Sample and Patients With and Without Cost-Related Medication Nonadherence, and Univariable Analyses of Correlates of Cost-Related Medication Nonadherence

	Total Sample	CRMNA n (%)	No CRMNA n (%)	OR (95% CI)	P[a]	Q[b]
Patient level factors						
Age (n = 1365), mean (SD), y	53.6 (13.2)	50.8 (13.3)	53.7 (13.4)	0.98 (0.96–0.99)	.04	0.10
Gender (n = 1359): male, n (%)	986 (72.6)	33 (68.8)	953 (72.7)	0.89 (0.47–1.69)	.73	0.85
Ethnicity (n = 1355): white (vs other ethnicities), n (%)	1162 (88.1)	33 (68.8)	1129 (86.7)	0.37 (0.19–0.74)	.005	0.02
Educational status (n = 1355),[c] n (%)				0.80 (0.58–1.08)	.15	0.25
Less than high/secondary school	356 (26.3)	11 (22.9)	345 (26.4)	–	–	–
Completed high/secondary school	321 (23.7)	13 (27.1)	308 (23.6)	–	–	–
Completed further education/training	377 (27.8)	16 (33.3)	361 (27.6)	–	–	–
Completed college/university	301 (22.2)	8 (16.7)	293 (22.4)	–	–	–
Marital status (n = 1356), n (%)						
Single	234 (17.3)	15 (31.3)	219 (16.7)	2.29 (1.17–4.47)	.016	0.05
Married/living with partner[d]	938 (69.2)	28 (58.3)	910 (69.6)	Reference	–	–
Divorced/separated	144 (10.6)	4 (8.3)	140 (10.7)	0.96 (0.33–2.85)	.95	0.95
Widowed	40 (2.9)	1 (2.1)	39 (3.0)	0.61 (0.08–4.73)	.63	0.77
Employment status (n = 1360), n (%)	404 (29.7)	14 (29.2)	390 (29.7)			
Working	357 (26.3)	12 (3.4)	345 (96.6)	Reference	–	–
Looking for a job[d]	39 (2.9)	1 (2.6)	38 (97.4)	0.91 (0.11–7.50)	.93	0.95
Disability	343 (25.2)	21 (6.1)	322 (93.9)	1.81 (0.84–3.90)	.13	0.24
Retired	458 (33.7)	8 (1.8)	450 (98.3)	0.52 (0.20–1.32)	.17	0.27
Other (student, volunteer, …)	163 (12.0)	6 (3.7)	157 (96.3)	1.10 (0.40–3.06)	.86	0.95
Intention to adhere (n = 1360),[c] mean (SD)	4.7 (0.5)	4.3 (0.8)	4.7 (0.5)	0.44 (0.31–0.63)	<.0001	<.0001
Perceived financial burden (n = 1317),[c] mean (SD)	2.4 (1.0)	3.0 (1.1)	2.4 (1.0)	2.15 (1.55–2.99)	<.0001	<.0001
Cost as a barrier (n = 1356),[c] mean (SD)	1.1 (0.3)	1.3 (0.7)	1.1 (0.3)	2.60 (1.66–4.07)	<.0001	0.0002
Cost-related self-efficacy (n = 1350),[c] mean (SD)	4.4 (1.0)	3.5 (1.4)	4.4 (1.0)	0.54 (0.43–0.67)	<.0001	<.0001
Belief in benefits of HTx compared with adverse effects caused by taking immunosuppressives (n = 1350),[c] mean (SD)	4.6 (1.0)	4.1 (1.3)	4.6 (0.9)	0.70 (0.57–0.87)	.002	0.009
Healthcare system factors						
Insurance coverage (n = 1357), n (%)[c]				1.44 (0.88–2.36)	.08	0.16
Yes, fully	811 (59.1)	21 (43.8)	774 (59.1)			
Yes, partly	537 (39.1)	24 (50.0)	513 (39.2)			
No	25 (1.8)	3 (6.2)	22 (1.7)			
Monthly out-of-pocket costs (n = 1340), n (%)[c]				1.18 (0.88–1.58)	.25	0.34
0–20 USD	838 (62.5)	23 (50.0)	815 (63.0)	–	–	–
20.01–60 USD	241 (18.0)	10 (21.7)	231 (17.9)	–	–	–
60.01–110 USD	129 (9.6)	5 (10.9)	124 (9.6)	–	–	–
>110.01 USD	132 (9.9)	8 (17.4)	124 (9.6)	–	–	–
Formal pretransplant financial-social evaluation, n (%)	948 (69.5)	39 (81.3)	909 (69.1)	1.88 (0.68–5.10)	.23	0.34

Values in bold indicate significance ($P < .05$).
Abbreviations: CRMNA, cost-related medication nonadherence; CI, confidence interval; HTx, heart transplantation; OR, odds ratio; USD, US dollar.
[a]Level of significance: $P < .05$.
[b]False discovery rate–corrected P value.
[c]Entered into the model as a continuous variable (without a particular reference category).
[d]Reference category.

TABLE 2 Prevalence of Cost-Related Nonadherence (Per Item/Combined Items) and Description of Patient and Healthcare System Factors for Total Sample and Per Country

	Overall	Belgium	Spain	France	Canada	United States	Australia	Italy	United Kingdom	Germany	Switzerland	Brazil
N (patients/centers)	1365/40	74/2	223/5	151/3	117/5	336/9	51/2	108/3	96/3	64/2	46/2	98/4
Overall CRMNA	36 (2.6)[a] 48 (3.5)[b]	2 (2.7)	6 (2.7)	3 (2.0)	8 (6.8)	19 (5.6)	5 (9.8)	1 (0.9)	3 (3.1)	1 (1.6)	0 (0.0)	0 (0.0)
Item 1: not filling prescription due to costs, n (%)	17 (1.3)[a] 20 (1.5)[b]	0 (0.0)	1 (0.5)	1 (0.7)	5 (4.3)	7 (2.1)	3 (5.9)	1 (0.9)	1 (1.0)	1 (1.6)	0 (0.0)	0 (0.0)
Item 2: skipping of doses due to costs, n (%)	18 (1.3)[a] 29 (2.1)[b]	0 (0.0)	5 (2.2)	2 (1.3)	2 (1.7)	15 (4.5)	3 (5.9)	0 (0.0)	2 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Item 3: dose reduction due to costs, n (%)	14 (1.0)[a] 21 (1.5)[b]	2 (2.7)	2 (0.9)	2 (1.3)	3 (2.6)	10 (3.0)	1 (2.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Patient-level factors												
Age, mean (SD), y	53.6 (13.2)	53.2 (12.6)	56.2 (11.9)	50.4 (12.8)	54.7 (13.4)	56.1 (12.8)	50.6 (13.6)	57.2 (12.7)	49.2 (14.6)	54.9 (10.5)	50.2 (14.8)	46.6 (13.2)
Gender: male, n (%)	986 (72.6)	50 (67.6)	170 (76.2)	113 (74.8)	84 (72.4)	228 (68.3)	31 (60.8)	90 (83.3)	74 (77.9)	48 (76.2)	32 (69.6)	66 (67.4)
Ethnicity: white	1162 (88.1)	73 (95.7)	201 (91.4)	135 (90.0)	103 (89.6)	250 (75.1)	33 (70.2)	107 (99.1)	91 (94.8)	63 (100.0)	42 (91.3)	64 (65.3)
Education												
Less than high/ secondary school	356 (26.3)	25 (34.3)	132 (59.7)	32 (21.5)	12 (10.4)	24 (7.1)	6 (12.0)	61 (56.5)	10 (10.4)	10 (15.9)	4 (8.7)	40 (40.8)
Completed high/ secondary school	321 (23.7)	23 (31.5)	32 (14.5)	34 (22.8)	31 (27.0)	78 (23.3)	7 (14.0)	26 (24.1)	43 (44.8)	4 (6.4)	5 (10.9)	38 (38.8)
Completed further education/training	377 (27.8)	15 (20.6)	29 (13.1)	58 (38.9)	19 (16.2)	119 (35.4)	19 (38.0)	16 (14.8)	21 (21.9)	40 (63.5)	33 (71.4)	8 (8.2)
Completed college/ university	301 (22.2)	10 (13.7)	28 (12.7)	25 (16.8)	53 (46.1)	115 (34.2)	18 (36.0)	5 (4.6)	22 (22.9)	9 (14.3)	4 (8.7)	12 (12.2)
Marital status												
Single	234 (17.3)	8 (10.8)	26 (11.7)	32 (21.3)	19 (16.4)	58 (17.4)	13 (25.5)	14 (13.1)	26 (27.7)	6 (9.5)	8 (17.4)	24 (24.5)
Married/living with partner	938 (69.2)	56 (75.7)	155 (69.5)	99 (66.0)	79 (68.1)	234 (70.1)	34 (66.7)	81 (75.7)	57 (60.6)	49 (77.8)	31 (67.4)	63 (64.3)
Divorced/separated	144 (10.6)	8 (10.8)	32 (14.4)	19 (12.7)	10 (8.6)	29 (8.6)	4 (7.8)	10 (9.4)	9 (9.6)	6 (9.5)	6 (13.0)	11 (11.2)
Widowed	40 (2.9)	2 (2.7)	10 (4.5)	0 (0.0)	8 (6.9)	13 (6.9)	0 (0.0)	2 (1.9)	2 (2.1)	2 (3.2)	1 (2.2)	0 (0.0)
Employment												
Working	357 (26.3)	17 (23.0)	19 (8.6)	52 (34.4)	32 (27.8)	105 (31.3)	22 (43.1)	29 (26.9)	35 (36.5)	13 (20.6)	15 (32.6)	18 (18.4)
Looking for a job	39 (2.9)	1 (1.4)	8 (3.6)	8 (5.3)	0 (0.0)	6 (1.8)	2 (3.9)	1 (0.9)	5 (5.2)	1 (1.6)	2 (4.4)	5 (5.1)
Disability	343 (25.2)	22 (29.7)	75 (33.8)	26 (17.2)	38 (33.0)	97 (28.9)	8 (15.7)	25 (23.2)	17 (17.7)	10 (15.9)	12 (26.1)	13 (13.3)
Retired	458 (33.7)	21 (28.4)	100 (45.1)	36 (23.8)	36 (31.3)	98 (29.2)	5 (9.8)	46 (42.6)	26 (27.1)	38 (60.3)	7 (15.2)	45 (45.9)
Other (student, volunteer, etc)	163 (12.0)	13 (17.6)	20 (9.0)	29 (19.2)	9 (7.8)	30 (8.9)	14 (27.5)	7 (6.5)	13 (13.5)	1 (1.6)	10 (21.7)	17 (17.4)
Intention to adhere, mean (SD)	4.7 (0.5)	4.7 (0.4)	4.8 (0.4)	4.7 (0.6)	4.6 (0.6)	4.6 (0.7)	4.5 (0.6)	4.9 (0.3)	4.7 (0.5)	4.6 (0.5)	4.7 (0.4)	4.8 (0.4)

(continues)

TABLE 2 Prevalence of Cost-Related Nonadherence (Per Item/Combined Items) and Description of Patient and Healthcare System Factors for Total Sample and Per Country, Continued

	Overall	Belgium	Spain	France	Canada	United States	Australia	Italy	United Kingdom	Germany	Switzerland	Brazil
Perceived financial burden, mean (SD)	2.4 (1.0)	1.9 (0.8)	2.6 (0.9)	2.4 (1.1)	2.5 (1.0)	2.3 (0.8)	2.3 (0.8)	2.8 (1.2)	2.3 (1.1)	2.9 (0.9)	2.1 (0.9)	2.1 (0.3)
Cost as a barrier, mean (SD)	1.1 (0.3)	1.0 (0.2)	1.1 (0.4)	1.0 (0.2)	1.0 (0.2)	1.1 (0.4)	1.1 (0.4)	1.0 (0)	1.0 (0.2)	1.0 (0.1)	1.0 (0.1)	1.1 (0.6)
Cost-related self-efficacy, mean (SD)	4.4 (1.0)	4.2 (1.0)	4.5 (1.0)	4.4 (0.9)	4.3 (1.0)	4.4 (1.0)	4.5 (0.7)	4.4 (1.1)	4.6 (0.8)	4.2 (1.1)	4.1 (1.2)	4.1 (1.3)
Belief in benefits of Htx compared with taking adverse effects caused by immunosuppressives, mean (SD)	4.6 (1.0)	4.5 (1.0)	4.7 (0.8)	4.5 (1.0)	4.6 (0.9)	4.5 (1.1)	4.7 (0.8)	4.6 (0.9)	4.6 (1.0)	4.4 (1.1)	4.5 (0.9)	4.7 (0.8)
Healthcare system factors												
Insurance coverage												
Yes, fully	811 (59.1)	65 (87.8)	49 (22.1)	146 (97.3)	71 (60.7)	105 (31.2)	7 (14.0)	99 (91.7)	86 (92.9)	43 (67.2)	28 (60.9)	98 (100.0)
Yes, partly	537 (39.1)	9 (12.2)	167 (75.2)	4 (2.7)	42 (35.9)	220 (65.3)	43 (86.0)	9 (8.3)	7 (7.7)	19 (29.7)	17 (37.0)	0 (0.0)
No	25 (1.8)	0 (0.0)	6 (2.7)	0 (0.0)	4 (3.4)	12 (3.6)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.1)	1 (2.2)	0 (0.0)
Monthly out-of-pocket costs												
0–20 USD	838 (62.5)	60 (81.1)	113 (50.9)	127 (87.6)	73 (62.9)	127 (38.0)	11 (22.4)	101 (95.3)	74 (84.1)	31 (49.2)	24 (53.3)	97 (99.0)
20.01–60 USD	241 (18.0)	11 (14.9)	86 (38.7)	2 (1.4)	8 (6.9)	80 (24.0)	8 (16.3)	5 (4.7)	9 (10.2)	25 (39.7)	7 (15.6)	0 (0.0)
60.01–110 USD	129 (9.6)	1 (1.4)	16 (7.2)	0 (0.0)	17 (14.7)	66 (19.8)	14 (28.6)	0 (0.0)	2 (2.3)	6 (9.5)	6 (13.3)	1 (1.0)
>110.01 USD	132 (9.9)	2 (2.7)	7 (3.2)	16 (11.0)	18 (15.5)	61 (18.2)	16 (32.7)	0 (0.0)	3 (3.4)	1 (1.6)	8 (17.8)	0 (0.0)
Formal pretransplant financial-social evaluation	948 (69.5)	23 (31.1)	152 (68.2)	0 (0.0)	117 (100.0)	337 (100.0)	51 (100.0)	60 (55.6)	23 (24.0)	41 (64.1)	46 (100.0)	98 (100.0)

Abbreviation: CRMNA, cost-related medication nonadherence (defined as not taking medications as prescribed because of difficulties associated with the patients' ability in paying for them and operationalized as any indication of CRMNA by any of 3 items assessed); HTx, heart transplantation; USD, US dollar.

[a]Weighted for country-specific transplant population sizes.

[b]Unweighted prevalence.

Brazil to 9.8% in Australia. Examining our 3 studied CRMNA aspects, we found that, overall, 1.5% reported unfilled prescriptions (highest weighted rates: Australia, 5.8%; and Canada, 4.3%), 2.1% skipped doses (highest weighted rates: Australia, 5.9%; and United States, 4.5%), and 1.5% reduced doses because of cost (highest weighted rates: United States, 3%; and Canada, 2.6%) (Table 2). Furthermore, we observed that 35.4% of patients with CRMNA (ie, in the United States, Australia, France, Spain, Canada, and the United Kingdom) exhibited at least 2 of the 3 cost-related adherence behaviors, with 8.3% of patients exhibiting all 3 (ie, in the United States and Canada).

Multilevel Correlates of CRMNA

Table 2 lists healthcare system– and patient-level factors overall and by country. Regarding healthcare system factors, except for Brazil, countries whose centers performed formal pretransplant financial-social evaluations, namely, Canada, the United States, Australia, and Switzerland, were those where patients reported the highest OOP costs. At least 15% of these 4 countries' patients reported monthly OOP costs of more than 110 USD, and between 39.2% (Switzerland) and 86% (Australia) of patients paid part or all of their IS costs.

Table 1 shows the results of our univariable analyses on potential CRMNA correlates. Three risk factors emerged as significant: higher perceived financial burden (odds ratio, 2.15; 95% confidence interval, 1.55–2.99; $q < 0.0001$), cost as a barrier to medication adherence (odds ratio, 2.60; 95% confidence interval, 1.66–4.07; $q = 0.0002$), and being single (compared with being married or living with a partner) (odds ratio, 2.29; 95% confidence interval, 1.17–4.47; $q = 0.05$). Three factors were protective: higher intention to adhere to immunosuppressants (odds ratio, 0.44; 95% confidence interval, 0.31–0.63; $q < 0.0001$), higher cost-related self-efficacy (odds ratio, 0.54; 95% confidence interval, 0.43–0.67; $q < 0.0001$), and higher belief in the benefits of heart transplantation compared with the adverse effects of immunosuppressants (odds ratio, 0.70; 95% confidence interval, 0.57–0.87; $q = 0.009$). Lower CRMNA was also found in whites compared with other racial groups (odds ratio, 0.37; 95% confidence interval, 0.19–0.74; $q = 0.02$). Regarding interaction effects, we found higher probabilities of CRMNA in cases where high OOP expenses accompanied higher perceived financial burden ($P = .03$, $q = 0.08$).

Cost-Related Medication Nonadherence Variability Explained by Factors at the Various Healthcare System Levels

The percentage of CRMNA variability explainable at the country level was 4.8% ($P = .31$, $q = 0.40$), with the center level accounting for 13.8% ($P = .08$, $q = 0.16$). This implies that most variability (81.4%) was at the patient level.

The percentages of "insurance coverage" and "OOP cost" variability attributable to country-level differences were, respectively, 60.1% and 24.1%.

Discussion

To our knowledge, this is the first study to investigate prevalence and multilevel correlates of CRMNA in an adult heart transplant population. It adds to the insights obtained from the 2013 and 2014 Commonwealth Fund International Health Policy Surveys[13,14] and from country-specific reports on CRMNA in chronically ill populations[39] in the United States, Canada, and Brazil.[13,19,30,40–42] The BRIGHT study focuses on medication adherence and CRMNA, whereas this substudy is focused on CRMNA only, a part of medication adherence.

This study's strengths include the use of a theoretical framework including both patient[31] and healthcare system[32] factors. Compared with the 12.5% prevalence of CRMNA found by Schoen et al,[14,40] who used 2 of our 3 items in a large international sample of chronically ill patients, our heart transplant sample indicated surprisingly little CRMNA (2.6%). However, our sample's intercountry variability was similar to what the Commonwealth surveys indicated.[13,14] Factors linked to CRMNA were intention to adhere, perceived financial burden, cost as a barrier to medication adherence, cost-related self-efficacy, the tested health belief, marital status (single), and race—all of which were situated at the patient level of our model.

Our sample's CRMNA was considerably lower than those of other chronically ill samples,[14] possibly because heart transplant recipients prioritize adherence to immunosuppressants higher than to other medications. Although CRMNA represents only a small part of overall nonadherence, the transplant literature consistently shows lower nonadherence to immunosuppressants than to other medications.[1,2,43] In addition, more financial support is available for immunosuppressants in transplant recipients (eg, drug vouchers), and because IS nonadherence is a known risk factor concerning solid organ transplantation outcomes,[7] care teams work particularly hard to help patients adhere to those regimens.[44] Some centers in the United States offer patients financial support programs to address the financial hurdle of drug prescription.[45,46]

Concerning international CRMNA variability, we found the highest rates in Australia (9.8%), Canada (6.8%), and the United States (5.6%). The 2013[14] and 2014[13] Commonwealth surveys reported, respectively, 29% and 16.8% CRMNA prevalence in chronically ill patients and older chronically ill adults in the United States, 14% and 6.8% in Australia, and 13% and 8.3% in Canada.[13,14] The United States typically has the highest nonadherence rates not only for medication[40] but also for other health behaviors[25,47]; however, it ranked only third in our study. We only can hypothesize whether this observation might be due to patients with better socioeconomic or insurance status

having more favorable chances for selection for transplantation, as has been shown in renal transplant recipients. Admittedly, once transplanted, many transplant programs have financial assistance programs to support patients to pay for their transplant and immunosuppressants.[48,49]

In our theoretical model, patient-level factors were significantly associated with CRMNA. In line with an earlier finding that being married is a protective factor, we found that being single was a risk factor for CRMNA.[24] The fact that divorced/separated or widowed persons did not show any tendency for increased CRMNA may suggest the latter groups are not at the same financial disadvantage of singles and may have sources of income or savings singles do not have. Race was also significantly associated with CRMNA. The literature, however, only partially supports this link.[22,24,26] Conversely, our findings did not corroborate sociodemographic factors reported elsewhere, for example, younger age,[20–22] female gender,[20,21,23,27] lower educational level,[24] and unemployment.[21] Overall, however, this study confirmed the importance of patient-level variables derived from the Integrative Model of Behavioral Prediction.[31] More specifically, we found significant correlations between CRMNA and intention to adhere, cost-related self-efficacy, cost-related barriers, and health belief. To our knowledge, of these factors, only the CRMNA–health belief link has previously been tested in chronically ill samples.[22,29] Perceived financial burden, another significant correlate in our study, has previously been associated with CRMNA in chronically ill groups.[27] Indeed, previous evidence also linked CRMNA to other potential influences on patients' perceived ability to finance their medication regimens, including perceived financial stress,[19,28] financial insecurity regarding healthcare,[28] and food insecurity.[28]

Although most CRMNA variability was explained by patient-level factors, several (nonsignificant) results also suggested center- and country-level connections. The center-level suggestions might reflect pretransplantation financial evaluation practice patterns or underimplementation of financial support programs for medication in settings with high OOP[8,50] expenses (not assessed here). The country level encompasses all healthcare policy measures and practices concerning medication coverage. Our lack of significant correlations between CRMNA and any of the studied healthcare system factors contrasts with earlier findings relating it to OOP[14] expenses and insurance coverage.[8,30] However, we did note that these factors' relevance increased alongside perceived financial burden.

In Australia, Canada, and the United States, substantial numbers of patients reported only partial coverage of IS medications, leading to comparatively high OOP costs. Our country-level estimations of these expenses varied similarly to those observed by Schoen et al.[14] Among the 5 countries with the highest OOP costs and high median per capita income (ie, Switzerland, Norway, the United States, Australia, and Canada),[14,51] however, only Australia, the United States, and Canada showed high CRMNA rates. This discrepancy has been explained, at least between Switzerland and the United States, by the fact that, whereas Switzerland's insurance system is transparent regarding deductibles and cost-sharing, that of the United States is dauntingly complex: insurance disputes are commonplace, and continuity of insurance is not guaranteed.[40] Similar complications (eg, payment denials or lower-than-expected coverage) have been reported in Australia, which may explain Australians' high CRMNA prevalence.[40]

As for the practical implications of our results, despite CRMNA's low overall prevalence, it should certainly be on every transplant clinician's radar, and in Australia, Canada, and the United States, its high prevalence warrants corrective action. From 2010 to 2013, Commonwealth surveys of all 3 countries showed increases regarding both CRMNA prevalence and monthly OOP expenses (per capita spending > 1000 USD) in chronically ill adults, with each year's highest CRMNA prevalence (21%) occurring in the United States.[14]

Overall, in addition to overall medication adherence, the fifth vital sign in transplant follow-up care,[52] CRMNA must be monitored as a serious health concern. The 3 questions we used to assess CRMNA serve this purpose well. In the United States, center-specific programs (eg, at Kaiser Permanente or Virginia Commonwealth University)[45,46] can provide guidance as well as specific financial support programs where high OOP medication costs apply.[8,50] In addition, Patel et al[28] correlated asking one's doctor for less costly medication with a lower probability of CRMNA, and a 2011 randomized controlled trial demonstrated the clinical and financial effects of full insurance coverage for preventive medication after myocardial infarction.[53] This latter study is relevant in all contexts, but particularly in those with high OOP costs.[14]

Although CRMNA affects all chronically ill groups,[19] the high specificity of IS treatment and the heart transplant population of the BRIGHT study limit direct application of our findings to other cardiovascular populations. Further research using the BRIGHT methodology could increase CMRNA-related knowledge on a range of cardiovascular populations internationally. For now, though, particularly in areas with high OOP medication expenses, all cardiovascular nurses and other healthcare professionals should be vigilant regarding CRMNA. Determining whether patients' resources cover their medication regimen could be guided by the questions used here. Moreover, the same nurses should familiarize themselves with and refer CRMNA patients to financial support programs for medication.[8,50]

Various limitations affect the current study. We assessed CRMNA in view of immunosuppressants but

What's New and Important

- Cost-related medication nonadherence referring to not taking medications as prescribed because of difficulties paying for them is lower in heart transplant recipients than CRMNA in chronically ill patients.
- Cost-related medication nonadherence among heart transplantation recipients varies among countries.
- Significant CRMNA-related factors in this study were intention to adhere, perceived financial burden, cost as a barrier to medication adherence, cost-related self-efficacy, health belief regarding medication benefits, marital status (single), and ethnicity.

not to other medications. As heart transplant recipients' medication regimens include treatments for both pretransplant comorbidities and those that develop post heart transplantation, this population has a heavy treatment burden[1]; therefore, authors of further research should focus on other aspects of their medication regimens beyond immunosuppressants. The focus of the BRIGHT study was on the posttransplant period, which provides only limited information. Authors of future research could focus on pretransplant or repeated assessment of CRMNA post transplant. In addition, our cross-sectional study design precludes causal inferences, the use of self-reporting to assess CRMNA as well as covariates might have introduced measurement error, and the low proportion of patients with CRMNA left us with insufficient statistical power to perform multivariable analyses.

Conclusion

The authors of this study found that heart transplant recipients' overall CRMNA prevalence (2.6%) is lower than chronically ill patients' CRMNA prevalence. We observed considerable intercountry variability in CRMNA. Our analyses identified similar CRMNA-related, patient-related factors (ie, intention to adhere, perceived financial burden, cost as a barrier to medication adherence, cost-related self-efficacy, health belief regarding medication benefits, marital status [single], and ethnicity [ie, not being white]) than those reported in the CMRNA literature studying other chronically ill populations.

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