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ORIGINAL ARTICLE

Therapeutic education as a tool to improve patient-reported and clinical outcomes after renal transplantation: results of the EPHEGREN multicenter retrospective cohort study

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SUMMARY

Patients are not always aware of the inconveniences associated with renal transplantation, which they compare with a « rebirth », and from which they expect complete recovery. Therapeutic education is proposed to prepare patients for their life after transplantation. This study evaluated the impact of pretransplant therapeutic education on patient-reported outcomes and rejection-free survival over the first year. We collected data from 383 renal transplant patients followed-up in seven centers. Patients who benefited from therapeutic education before transplantation ($N = 182$) were compared with patients who did not ($N = 139$) for quality-of-life, adherence and adverse events using the Pearson's chi-square test, one-way ANOVA or t-test. The association between therapeutic education and time to acute rejection was investigated using Cox models. The patients who benefited from therapeutic education reported adverse events less frequently (*e.g.*, tremor: 9% vs. 32.4%, $P = 0.01$) and better quality-of-life (MCS-QOL: 50.7 ± 8.1 vs. 47.7 ± 9.5, $P = 0.02$; PCS-QOL: 49.1 ± 7.1 vs. 46.0 ± 9.2, $P = 0.013$). No difference was found on adherence. Rejection-free survival was slightly better in the therapeutic education group (HR = 0.44, 95% CI = [0.19–1.01]). This multicenter retrospective cohort study suggests that integrating therapeutic education to care pathways entails clinical benefit, in terms of quality-of-life, self-reported adverse events and rejection-free survival. Randomized clinical trials are necessary to confirm this.

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Key words
graft rejection, immunosuppressants adverse effects, kidney transplantation, patient education, quality-of-life, therapeutic education

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Introduction

Kidney transplantation is considered the best renal replacement therapy for patients with end-stage kidney disease, as it improves patient survival and quality-of-life, and allows healthcare cost savings [1,2]. In fact, patients and their families often think that transplantation will be a rebirth. Yet, 30 to 40% of the patients do not report a better health-related quality-of-life (HR-QOL) after kidney transplantation compared with dialysis [3–5]. One possible explanation could be that transplantation does not meet their expectations. Indeed, it is associated with inconveniences and constraints, some of which may not have been anticipated by the patients, such as the numerous follow-up visits and new medications, together with their rigorous dosing schedule and possible adverse effects. Kidney transplantation can therefore be particularly challenging, especially for patients expecting complete recovery from their initial disease and a "back-to-normal" life [6].

In order to maximize the chances of success, transplant recipients need to acquire new skills and knowledge about their transplantation, follow-up and medications, and to realize the benefits of an adapted diet and physical activity [7]. Urtsad *et al* invited healthcare professionals to include holistic educational approaches in their interventions. Therapeutic education programs focus on patient perceptions and facilitate exchanges between patients and their healthcare team [8], allowing the detection of barriers to adherence and the initiation of further interventions targeted among others on adherence, immunosuppressants and their potential adverse effects. As reported by several authors, the information must be repeated, patient-individualized and progressive [6,9,10]. One goal of therapeutic education is to enhance patients self-management and help them not to be so dependent on their illness, using an empowerment approach before and after transplantation, in order to teach them not to succumb to resignation but to regain power over the illness with an informed choice. In this context, therapeutic education programs considering therapeutic objectives and patient needs, expectations and preferences, have been part of patient care in France since 2009 [11]. These programs are centered on patients' daily life, social, psychological and environmental factors and are permanently adapted to disease evolution and patient lifestyle. Collective and individual therapeutic education sessions on a series of themes (including understanding transplantation and follow-up, physical activity, diet, medications, psychological support) are set up between patients and interdisciplinary teams composed of physicians, psychologists, nurses, physiotherapists, dieticians and pharmacists trained in therapeutic education. The organization of therapeutic education programs may slightly differ between centers, depending on the resources allocated and priorities fixed by the healthcare team, in relation with the environment (centers located in big cities vs. countryside for instance). In some centers, long-term transplant patients participate in therapeutic education sessions and share their experience with future or newly transplanted patients. Still, no matter the exact content or modalities of organization of the therapeutic education programs, they are expected to increase patients' autonomy outside the medical environment, improve their adherence and reduce their level of discomfort induced by immunosuppressive drug-related adverse effects, by enhancing their knowledge and self-management, adaptation and security skills on their health status and care.

The ultimate objective of therapeutic education programs is to improve patient quality-of-life and, ideally, long-term graft survival. According to Urstad *et al.* in 2013, there was limited evidence in favor of the effectiveness of therapeutic education in renal transplant recipients [7]. Eight years later, evidence is still scarce. Only a few published studies have explored the relationship between therapeutic education and what Osborne *et al.* defined as "proximal" or "intermediate outcomes" in their program logic model [7,12], *i.e.*, patient adherence, immunosuppressive drug concentrations or HR-QOL [13]. Two randomized clinical trials have reported significant effects of therapeutic education on compliance [14,15]. Up until now, no study has demonstrated

Transplant International 2021; 34: 2341–2352

the efficacy of therapeutic education in terms of distal outcomes, *i.e.*, rejection-free or patient survival.

The main objectives of our study were to evaluate the impact of therapeutic education performed prior to transplantation on: patient-reported health-related quality-of-life; adherence; adverse events; rejection-free survival in kidney transplant patients over the first year.

Materials and methods

Study population and data collection

This study was performed on follow-up data of adult kidney graft recipients transplanted between 2013 and 2017 and enrolled in the EPHEGREN multicenter prospective pharmacological cohort study [16]. The EPHEGREN study was sponsored by the University Hospital of Limoges and complied with the legal requirements of the Declaration of Helsinki and received approval from the regional Ethics Committee (nr. 130-2013-30, 11/20/2013) and authorization from the National Committee for Informatics and Liberties (912242 ACT, 2012).

All patients followed-up in seven French transplantation centers (University Hospitals of Amiens, Bordeaux, Limoges, Poitiers, Rouen, Toulouse and Tours) were eligible to participate in the cohort, except patients who either did not understand the protocol or were not able to read in French. All patients gave their informed consent on a written, signed and dated consent form. They were enrolled during the first month after transplantation, and EPHEGREN study visits were defined at months 1 (M1), M3, M6, M12, M18, M24 and M36 after transplantation. Clinical and biological data were collected from medical records in a clinical research form. Calcineurin inhibitors trough concentrations (C_0) were registered exhaustively in the database. Patient-reported adherence, health-related quality-of-life and adverse events were collected at each study visit using self-administered questionnaires.

Adherence was evaluated using the Morisky–Levine–Green 4-Item Medication Adherence Scale (MMAS-4) [17], which has been validated in the French language, and is widely used in transplant patients. While the MMAS-4 was initially constructed and validated by Morisky *et al.* in hypertension with a moderate Cronbach's α (0.61) [17], its properties were similar in our transplantation cohort (Cronbach's $\alpha = 0.68$). The sensitivity and specificity of the scale in terms of identification of nonadherent patients have been previously assessed in a subgroup of patients of the EPIGREN cohort, by confronting MMAS-4 scores to face-to-face interviews with a trained pharmacologist [18]. High estimates of sensitivity (98.7%) and specificity (80.0%) were obtained from 389 interviews with 172 patients.

HR-QOL was evaluated using the 36-Item Short-Form Health Survey (SF-36), which displays a good internal reliability [19] and allows the calculation of two composite scores, one for the mental (MCS-QOL) and one for the physical (PCS-QOL) dimensions, based on its eight dimensions [20].

Adverse events, including psychological disorders, were reported by the patients on a specific form [18,21–23]. Briefly, the adverse events form is composed of a list of 27 symptoms derived from the immunosuppressive drugs-induced adverse effects considered by the French Biomedicine Agency and was previously validated through patient interviews by clinical pharmacologists [18]. This form displayed a better sensitivity for the detection of AEs (79%) than medical records (29%).

Participation in therapeutic education programs

Participation or not in therapeutic education sessions was recorded retrospectively after the end of the EPHEGREN cohort study, because the recording of this information was not initially planned. When a therapeutic education program was available at the date of the patients' inclusion and when considered eligible by the transplant team, patients were invited to participate in therapeutic education sessions as part of their routine care. Patients could benefit from therapeutic education prior to and/or within the first year after transplantation.

When programs are on-going, pretransplant therapeutic education is proposed to patients when they are registered on the transplant waiting list. It consists of individual or collective sessions conducted by multidisciplinary teams in order to provide the patients with individualized information on the transplantation, treatments, nutrition and physical activity adapted to their individual context, motivation and beliefs, and propose them psychological support. Post-transplant therapeutic education sessions occur at variable time-points, usually around the sixth month, actually from as early as one month up to the end of the first year post-transplantation. Patients of the cohort who benefited from therapeutic education sessions only post-transplantation were not considered in this study because time between the therapeutic education intervention and outcomes was not recorded and potentially highly variable. Therefore, the patients included in the "therapeutic education" group were only those who participated in therapeutic education sessions prior to transplantation, and the "control group" was comprised

of patients who did not benefit from any therapeutic education session, either because they were not proposed or they refused to participate.

Statistical analysis

Statistical analysis was performed using R version 3.6. (R Project for Statistical Computing: http://www.r-project.org). Categorical data were reported as frequencies and percentages, and continuous data as their mean ± standard deviation (SD) when their distribution was Gaussian or as their median and interquartile range (IQR) when it was not.

The groups were compared for proportions using the Pearson's chi-square or the Fisher's exact tests for categorical data, and the Student t-test or one-way ANOVA for continuous variables. Bonferroni risk correction was applied in case of multiple comparisons. Individual CNI underexposure was investigated through the proportion of C_0 values below the lowest bound of the therapeutic window (cyclosporine: 150 ng/ml; tacrolimus: 5 ng/ml), as a potential confounding risk factor for acute rejection. The relationships between therapeutic education and patient-reported outcomes were explored at one year post-transplantation. A Cox model including the potential confounding factors (transplantation from living donor, cold ischemia time, delayed graft function and retransplantation) was built for rejection-free survival, first using univariate analyses and then including variables characterized by a p-value <0.2 in an intermediate model. The final model was built by backward stepwise selection of the covariates, based on the Bayesian information criterion. The robustness of the results was planned to be assessed by 1000 bootstraps followed by 1000 backward stepwise selections based on the same process. The hazard ratios (HR) and 95% confidence intervals (95%CI) derived from the final model and the percentage of selection of each covariate in the bootstrap procedure were calculated [24]. Time to rejection was estimated using Kaplan–Meier analysis and the therapeutic education and control groups were compared using the log-rank test. The proportionality of risks in the final models was evaluated using the Schoenfeld residuals. Two-sided *P*-values < 0.05 were considered to be statistically significant.

Results

Description of the population

Three hundred and eighty-three patients of the EPHEGREN cohort between were initially considered for this study: 182 patients participated in therapeutic education sessions prior to transplantation and 139 did not, while 62 patients were not included as they benefited from therapeutic education after transplantation only (Fig. 1). Of note, 57 patients of the therapeutic education group benefited from therapeutic education both prior to and after transplantation. Their main socio-demographic and clinical characteristics are summarized in Table 1.

There were more frequent living-donor transplantation procedures, shorter cold ischemia time and still more frequent delayed graft function in the therapeutic education group, and immunosuppressive strategies at one month post-transplantation (M1) were different between the two groups (Table 1). The most prescribed strategy was the association of mycophenolate mofetil and tacrolimus in both groups (77.5% in the therapeutic education group and 59.4% in the control group). The other immunosuppressive strategies were based on a CNI alone or combined with everolimus (14.3% in the education group and 1.4% in the control group), or on cyclosporine and mycophenolate (8.2% in the education group and 39.1% in the control group).

Relationships between therapeutic education and outcomes

Overall, the patients of the therapeutic education group reported significantly better mental and physical HR-QOL at the end of the first year (MCS-QOL =50.7 ± 8.1 vs. 47.7 ± 9.5, $P = 0.02$; PCS-QOL = 49.1± 7.1 vs. 46.0 ± 9.2, $P = 0.013$) post-transplantation. Similar results were obtained when patients who benefited from therapeutic education both prior to and after transplantation were excluded from the intervention group dataset (MCS-QOL = 51.0 ± 8.8, $P = 0.02$ and PCS-QOL = 48.9 ± 7.7, $P = 0.03$).

Nonadherence at one year post-transplantation was declared by, respectively, 6.3% and 5.9% of the patients in the therapeutic education and in the control group ($P = 0.908$). Patient-reported adverse events are presented in Fig. 2. At the end of the first year, patients of the therapeutic education group declared overall significantly fewer tremors (12.9% vs. 32.4%, $P < 0.001$), weight gain (11.0% vs 22.9%, $P = 0.016$), shortness of breath (7.7% vs. 23.8%, $P = 0.001$), joint pain (7.1% vs 21.0%, $P = 0.002$), overall pain (7.7% vs. 19.0%, $P = 0.011$), edema of the lower extremities (7.7% vs. 31.4%, $P < 0.001$), cramps (8.4% vs. 20.0%, $P = 0.011$), increased skin sensitivity (6.5% vs. 19.0%, $P = 0.003$) and hair growth (7.1% vs. 31.4%, $P < 0.001$). Similar results were obtained when patients who benefited from

Transplant International 2021; 34: 2341–2352

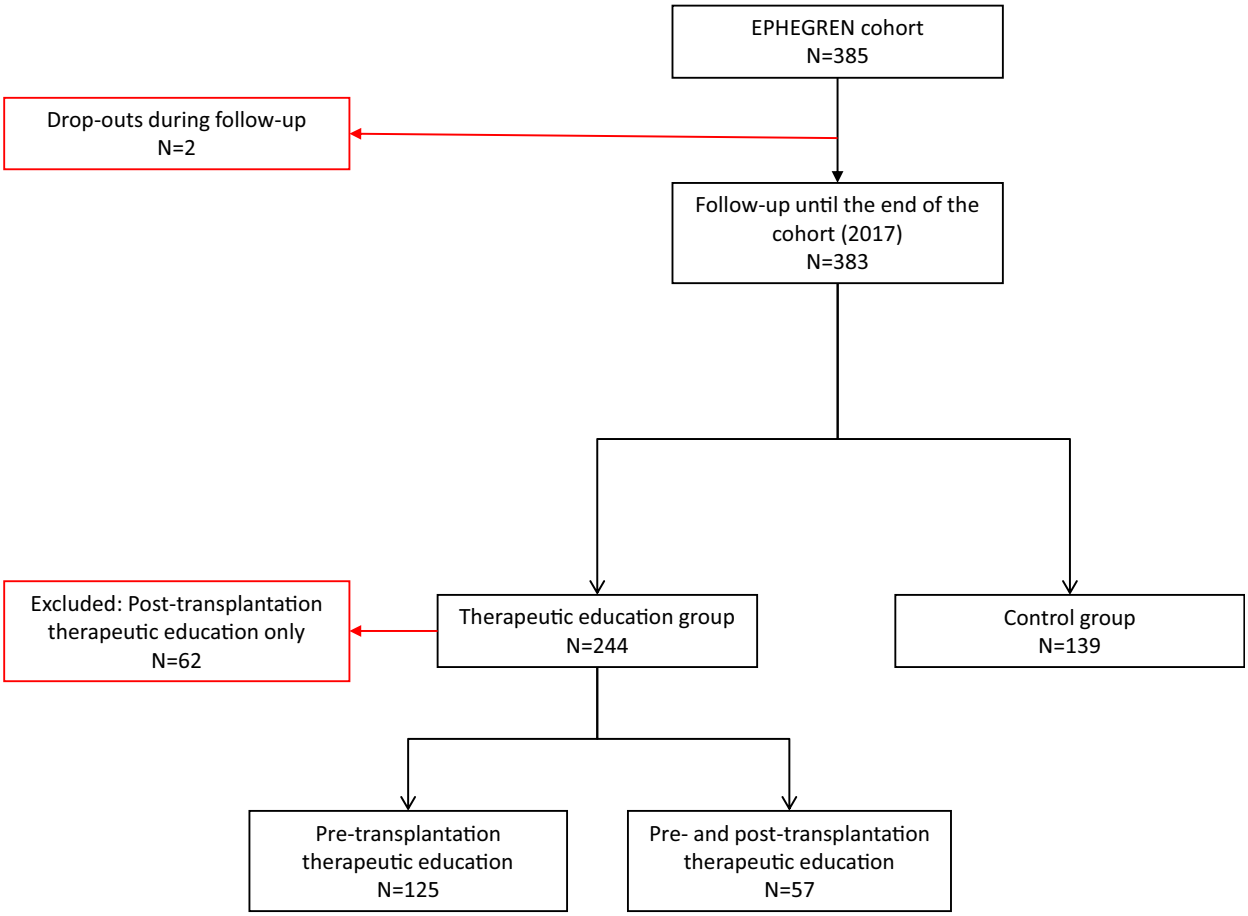

Figure 1 Flowchart of patients included in the study (STROBE).

therapeutic education both prior to and after transplantation were not considered in the analysis. Interestingly, the effect was observed as soon as 6 months post-transplantation (Fig. 3), and the proportion of patients reporting adverse events was significantly lower in the therapeutic education group whatever the CNI they received.

The proportion of C_0 below the target differed neither between therapeutic education and control groups ($P = 0.104$), nor between patients who experienced rejection and those who did not ($P = 0.934$).

No statistically significant difference was found between groups on graft loss (4.4% in the therapeutic education group vs. 7.2% in the control group, $P = 0.404$). Patients who experienced graft loss were compared with patients without graft loss on their adherence class, without evidencing any difference ($P = 0.527$).

The relationship between therapeutic education and rejection-free survival over the first year post-transplantation was explored in 319 patients out of the total of 321, because of missing data about rejection in two patients. The results of the univariate and multivariate analyses of potential covariates are presented in Table 2. The transplant center, rank of kidney transplantation, cold ischemia time, CMV mismatch, immunosuppressive strategy and participation in therapeutic education sessions were selected in the intermediate model, but multivariate analysis found no significant variable associated with rejection-free survival. Consequently, no bootstrap analysis was done (Table 2). Participation in therapeutic education sessions tended to decrease the risk of acute rejection over the first year post-transplantation (HR = 0.44, 95% CI = [0.19–1.01] (Fig. 4)).

Discussion

This retrospective study suggests that therapeutic education is beneficial for health-related quality-of-life, self-reported adverse events and rejection-free survival over the first year post-transplantation. To the best of our

Table 1. Characteristics of the patients included in the study (N = 321).

	Control group	Therapeutic education group	*P*
n	139	182	
Transplantation center, *n* (%)			<0.001
Amiens	101 (72.7)	0 (0.0)	
Bordeaux	16 (11.5)	65 (35.7)	
Limoges	4 (2.9)	17 (9.3)	
Poitiers	1 (0.7)	0 (0.0)	
Rouen	0 (0.0)	100 (54.9)	
Tours	17 (12.2)	0 (0.0)	
Gender: male, n (%)	91 (65.5)	125 (68.7)	0.626
Age (years), mean (SD)	55.9 (12.4)	55.2 (14.75)	0.842
Occupational status, *n* (%)			0.575
Active	69 (49.6)	100 (54.9)	
Retired or without professional activity	56 (40.3)	68 (37.4)	
Unknown	14 (10.1)	14 (7.7)	
Immunosuppressive strategy at M1, *n* (%)			<0.001
Tacrolimus/MMF	82 (59.0)	141 (77.5)	
Cyclosporine/MMF	54 (38.8)	15 (8.2)	
Other*	3 (2.2)	26 (14.3)	
Primary kidney disease, *n* (%)			0.729
Diabetic nephropathy	9 (6.5)	10 (5.5)	
Genetic disease	36 (25.9)	42 (23.1)	
Glomerulonephritis	40 (28.8)	57 (31.3)	
Interstitial nephritis	10 (7.2)	15 (8.2)	
Vascular nephropathy	10 (7.2)	37 (20.3)	
Others	34 (24.5)	21 (11.5)	
Hypertension before transplantation, *n* (%)	131 (94.2)	175 (96.2)	0.592
Diabetes before transplantation, *n* (%)	24 (17.3)	29 (15.9)	0.868
Rank of kidney transplantation > 1, *n* (%)	24 (17.3)	18 (9.9)	0.076
Donor's age (years), mean (SD)	55.0 (13.5)	56.3 (16.30)	0.459
Cold ischemia time (min), mean (SD)	903 (366)	735 (384)	<0.001
Living donor, n (%)	6 (4.3)	36 (19.8)	<0.001
Delayed graft function: yes, *n* (%)	1 (0.7)	42 (23.1)	<0.001
CMV mismatch, *n* (%)			0.117
D−/R−	36 (25.9)	50 (27.5)	
D−/R+	34 (24.5)	38 (20.9)	
D+/R−	27 (19.4)	54 (29.7)	
D+/R+	42 (30.2)	40 (22.0)	
EBV mismatch, *n* (%)			0.518
D−/R−	1 (0.7)	3 (1.6)	
D−/R+	2 (1.4)	7 (3.8)	
D+/R−	3 (2.2)	4 (2.2)	
D+/R+	133 (95.7)	168 (92.3)	
Duration of follow-up (months), mean (SD)	803 (304)	828 (364)	0.504
Presence of DSA before transplantation, *n* (%)	4 (2.9)	3 (1.7)	0.718
Apparition of *de novo* DSA, *n* (%)	18 (12.9)	9 (4.9)	0.273
Proportion of patients with C_0 < target, *n* (%)	110 (80.3)	156 (87.6)	0.104
Number of mismatch HLA	4.7 (1.60)	4.7 (1.84)	0.781

IQR, interquartile range.

*"others" stands for the following strategies: cyclosporine alone, cyclosporine/everolimus, tacrolimus alone, tacrolimus/everolimus, tacrolimus/MMF/everolimus, tacrolimus/MMF/sirolimus, MMF alone.

Transplant International 2021; 34: 2341–2352

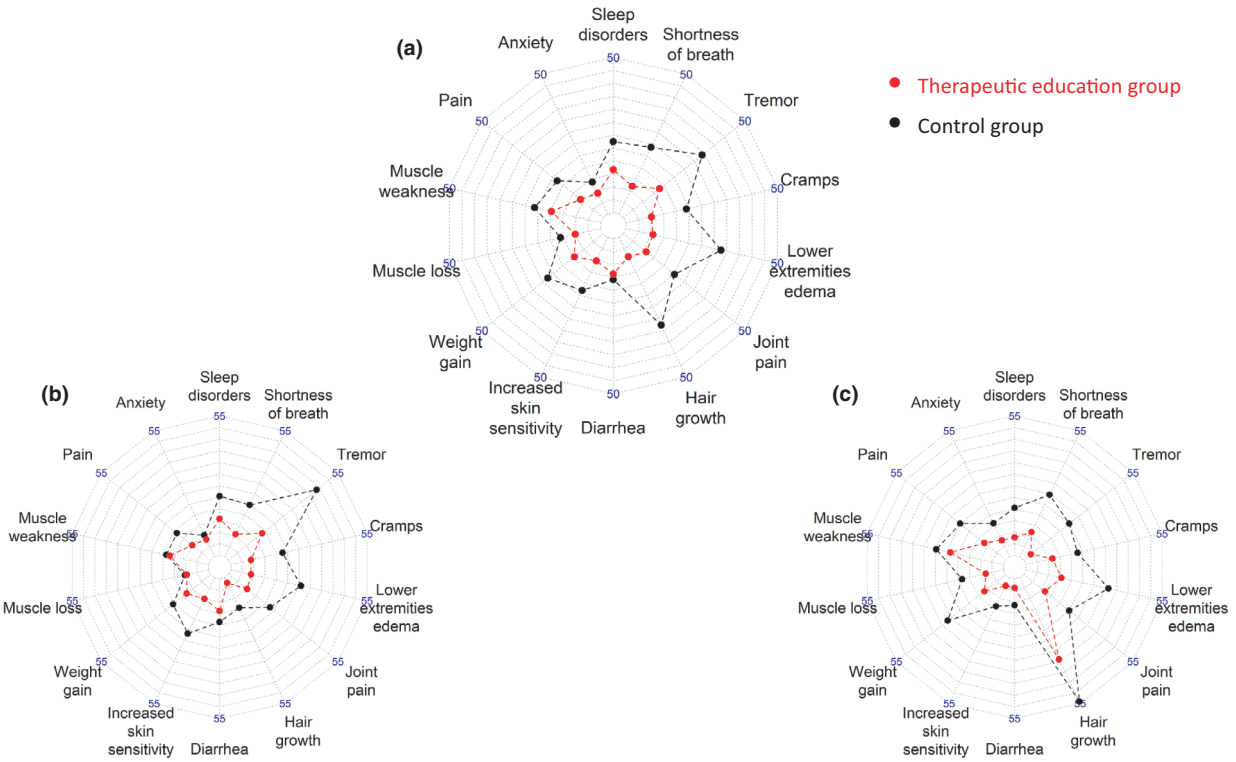

Figure 2 Adverse events reported by the patients (in % patients) at M12 in the therapeutic education and control groups (a) In patients on tacrolimus only (b) In patients on cyclosporine only (c).

knowledge, this is the first study of its kind: literature on the impact of therapeutic education on transplant patient outcomes is scarce, and most of the previous studies focused on proximal or intermediate outcomes, such as patients' knowledge, compliance, behavior and perception [7,12]. One of the strengths of our study is that it explores the relationships with outcomes on all levels: proximal (patients' adherence), intermediate (health-related quality-of-life and adverse events) and distal (rejection-free survival). Although patient participation in therapeutic education sessions was collected retrospectively, this study was based on a prospective, unselected cohort of renal transplant patients who reported HR-QOL, adherence and adverse events on standardized questionnaires at regular intervals over time. Interestingly, although not standardized, the therapeutic education programs of the different investigation centers displayed comparable theoretical therapeutic objectives, listed in a so-called "skills referential for kidney transplantation" which is included in all therapeutic education programs authorized by health authorities. Therapeutic education could be proposed either before or after transplantation, or both, depending on the centers. As the dates of the therapeutic education interventions were not recorded, the delays between interventions and outcomes could not be estimated, preventing from conducting survival analysis according to the participation in therapeutic education sessions after transplantation. The small number of patients who only benefited from therapeutic education after being transplanted were excluded from the study in order to minimize bias and avoid fallacious interpretation, and only patients who benefited from interventions before transplantation were included in this study.

Because of its retrospective design, potential selection biases could not be excluded, representing a weakness in this study. However, the following potential confounding factors were taken into consideration: retransplantation, transplantation from living donors, cold ischemia time, delayed graft function, center effect, immunosuppressive strategy. First, a similar number of patients benefited from retransplantation in the therapeutic education and in the control groups, suggesting that it did not influence the results. Moreover, retransplantation, transplantation from living donors, cold ischemia time and delayed graft function were included as covariates in the survival analysis and were not significant in the cox model. These results suggest that the analyses were not biased by the

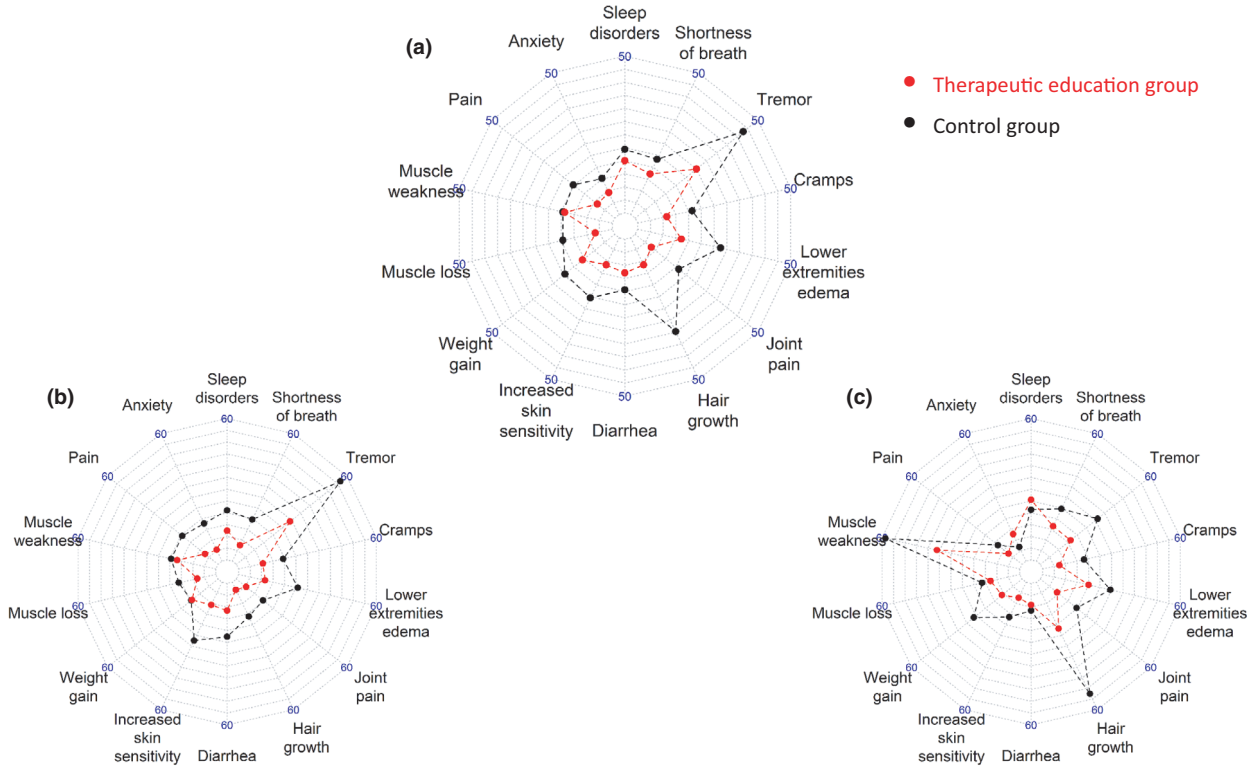

Figure 3 Adverse events reported by the patients (in % patients) at M6 in the therapeutic education and control groups (a) In patients on tacrolimus only (b) In patients on cyclosporine only (c).

inclusion of retransplant patients or patients who benefited from transplantation from living donors. In addition, the variable proportion of patients who benefited from therapeutic education in the different centers (from 0% to 100%) could be questioned. Therapeutic education programs have been progressively launched since 2009, while the inclusions of patients in the EPHEGREN cohort had started 2 years before. Therefore, some centers only proposed to a few patients, or none at all, to participate in their therapeutic education programs as these were not available at the time of their inclusions. The potential center effect was excluded because it was not a significant covariate of the explored outcomes. Finally, even though the immunosuppressive strategies differed between groups, they were also not associated with either of the explored outcomes, excluding an "immunosuppressive strategy" effect. Therefore, although the two groups were not perfectly comparable as could be the case in a randomized controlled study, the results of this study may still have a fairly good predictive value, as they are based on the exploration of diverse "real-life" therapeutic education practices.

In contrast with our findings, the only study exploring the relationship between some kind of therapeutic education (psychoeducational interventions) and allograft survival, also by a French group [25], found no significant improvement over ten years. However, despite its RCT design, this study presented flaws which might have thwarted the differences between groups. First, the patients enrolled were transplanted in 2002 and 2003, long before therapeutic education in its modern form became mandatory in France [11]. The aim of psychoeducational interventions at that time was mainly to improve patient adherence, considering that it would lead to better survival. The relationship between adherence and long-term graft survival has actually been demonstrated [16,26,27], but there are multiple other determinants of graft survival, including patient capacity to identify at-risk situations and make appropriate decisions. Interventions aimed at improving adherence do not cover these aspects, contrary to therapeutic education, which aims to improve patient self-efficacy. Secondly, this study was not initially planned for long-term evaluation and was probably not powered to demonstrate a significant influence on long-term graft survival [28]. The present study included a larger number of patients ($N = 321$) followed-up between 2013 and 2017, *i.e.*, after therapeutic education programs had been

Table 2. Univariate and multivariate analyses of the association of rejection-free survival and potential risk factors over the first years post-transplantation.

	Univariate analyses			Multivariate analyses			
Covariate	HR	95% CI	*P*	HR	95% CI	*P*	% Bootstrap selection
Transplantation center (vs. Amiens)							
Bordeaux	**0.36**	**[0.10–1.32]**	**0.124**				
Limoges	2.11	[0.66–6.72]	0.208				
Poitiers	0.00	[0.00–inf]	0.997				
Rouen	**0.46**	**[0.16–1.35]**	**0.157**				
Tours	0.96	[0.12–7.50]	0.969				
Living donor	0.00	[0.00–inf]	0.997				
Donor age	1.01	[0.98–1.03]	0.710				
Recipient age at time of transplantation	0.99	[0.96–1.02]	0.452				
Recipient gender (M vs. F)	1.39	[0.55–3.53]	0.488				
Occupational status (retired vs. active)	1.18	[0.52–2.69]	0.692				
Primary kidney disease (vs. diabetic nephropathy)							
Genetic disease	0.92	[0.10–8.27]	0.944				
Glomerulonephritis	2.08	[0.27–21.09]	0.484				
Interstitial nephritis	0.00	[0.00–inf]	0.997				
Others	0.79	[0.08–7.63]	0.842				
Vascular nephropathy	2.37	[0.26–21.18]	0.441				
Pretransplant hypertension (recipient)	1.09	[0.15–8.09]	0.933				
Pretransplant diabetes (recipient)	1.87	[0.44–7.98]	0.397				
Rank of kidney transplantation (>1 vs. 1)	**1.93**	**[0.72–5.20]**	**0.194**				
CMV mismatch (vs. D−/R−)							
D−/R+	2.43	[0.61–9.71]	0.210				
D+/R-	**2.99**	**[0.79–11.27]**	**0.106**				
D+/R+	2.19	[0.55–8.74]	0.269				
Presence of DSA before transplantation	1.86	[0.25–13.81]	0.545				
Apparition of *de novo* DSA	0.77	[0.17–3.46]	0.735				
Proportion of patients with C_0 < target	1.05	[0.31–3.56]	0.934				
HLA mismatch	1.09	[0.85–1.38]	0.505				
Cold ischemia time	**1.00**	**[1.00–1.00]**	**0.056**				
Delayed graft function	0.58	[0.14–2.48]	0.465				
Immunosuppressive strategy at M1 (vs. cyclosporine/MMF)							
Tacrolimus/MMF	**0.43**	**[0.18–1.00]**	**0.050**				
Others*	**0.25**	**[0.03–1.98]**	**0.189**				
Participation in therapeutic education	**0.44**	**[0.19–1.01]**	**0.054**				

*"others" stands for the following strategies: cyclosporine alone, cyclosporine/everolimus, tacrolimus alone, tacrolimus/everolimus, tacrolimus/MMF/everolimus, tacrolimus/MMF/sirolimus, MMF alone. Bold is used for covariates selected (p<0.2 in the univariate cox model) and integrated in the multivariate cox model.

recommended by health authorities in France. These programs have been set up and proposed to patients progressively since 2009, explaining why not all patients participated in therapeutic education sessions before transplantation. Moreover, patients are free to decline the proposal to participate in therapeutic education programs. This may have an impact on the evaluated outcomes, as one may argue that the choice to not participate or the fact of not being able to participate in therapeutic education sessions (because of convictions, language or reading barriers) may constitute a confusion bias. Still, the results obtained in this study suggest that therapeutic education is beneficial for patients, and a strategy targeting specifically these categories of patients with adapted therapeutic education interventions should probably be explored. Finally, the therapeutic education sessions proposed to the patients not only had the aim of improving adherence, but also of providing them with individualized tools in order to gain autonomy, become proactive and make relevant decisions for the management of their condition, graft and care in the context of their personal life.

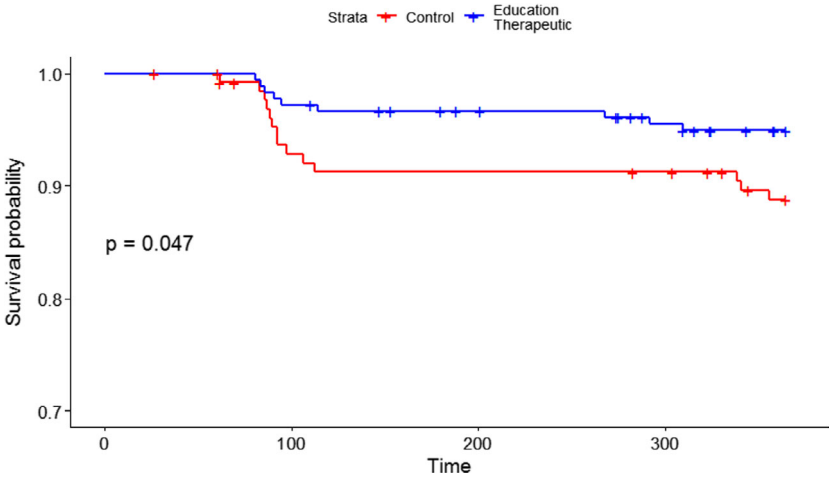

Figure 4 Kaplan–Meier curves of rejection-free survival in renal transplant patients who participated in pretransplant therapeutic education vs. those who did not.

To the best of our knowledge, this study is the first one to report a positive impact of therapeutic education on transplant patients' health-related quality-of-life. HR-QOL is a major outcome from the patient's standpoint and is increasingly acknowledged as such by healthcare providers [29]. The mean mental and physical HR-QOL scores at one year were overall higher in patients in the therapeutic education group. In a previous work, we found that patients at risk of poor HR-QOL over time could be identified as early as one month post-transplantation [5]. Therefore, early evaluation of HR-QOL may help to target those patients who may benefit most from therapeutic education and individual management.

In this study, adverse events were recorded using a validated form. Even though it has not been published (Table S1), it is shorter but close to the 59R-MTSOSD published in 2008 by Dobbels *et al* and provides reliable results. The results of our study suggest that therapeutic education sessions provided by multidisciplinary teams have a positive impact on patient-reported adverse events. The aim of these sessions is to prepare patients for transplantation in its acute phase and cope with their status of transplant patients in the long term, by improving their knowledge about their illness, drugs and their potential adverse effects, as well as about adapted physical activities and diet. The positive impact of therapeutic education on patient-reported adverse events may result from two mechanisms: first, being aware of the potential adverse effects may help patients cope with them better. For instance, knowing about the risk of tremor with calcineurin inhibitors may help patients accept this discomfort and lead to a decrease in tremor reporting, rather than a real decrease in the frequency of this adverse effect. Interestingly, the profiles of adverse effects declared by the patients were characteristic of the calcineurin inhibitors, and the benefic effect of therapeutic education on the perception of adverse effects was observed for patients on either cyclosporine or tacrolimus. Secondly, educative interventions may encourage patients to take appropriate actions to prevent or manage adverse events. This could be the case for weight gain, through the more frequent adoption of adequate diet and physical activity in patients who participated in therapeutic education sessions [13,30–33]. This has also been reported for an educational intervention about skin protection in the prevention of skin cancer that led to significantly less sun damage [34].

We found no significant influence of therapeutic education on patient-reported adherence. This might be because of the small proportion of patients reporting nonadherence (approx. 6% at one year) and low statistical power. The difference on adherence between groups, if any, may therefore need a much larger population to be evidenced. Another hypothesis could also be that therapeutic education favors a trustworthy relationship between patients and healthcare providers and encourages patients to declare nonadherence episodes, while patients who do not participate in therapeutic education sessions might under-declare nonadherence episodes. Moreover, therapeutic education programs teach patients how to handle missed or delayed drug doses. When declared, nonadherence episodes can be managed and corrective actions taken (including patient-initiated actions). Many studies have evaluated the impact of therapeutic education on adherence, with contradictory results [15,25,28,32,35]. This may be because of the fact that, despite a consensual definition of adherence, there is still no gold standard measurement, leading to discrepant results [36,37].

Multivariate analysis evidenced no association between the occurrence of acute graft rejection and the

Transplant International 2021; 34: 2341–2352

covariates tested. Rejection-free survival in the therapeutic education group was 46%-better, and the difference between groups was close to significance. This tight difference might be related to the differences between groups in demographic or clinical characteristics, although none of the potential confounding factors tested was significant. Unfortunately, the paucity of pre-transplantation data prevented us from testing other potential risk factors. Moreover, the impact of immunosuppression strategies on QOL and graft outcome could not be evaluated in this study as strategies largely changed over time and many patients switched from one immunosuppressant to another.

In conclusion, despite limitations because of potential biases, confounding factors and missing data this cohort study allowed evaluating real-life patient care, gathering data on events along time and examining multiple outcomes for therapeutic education. This study is the first of its kind to assess the effects of therapeutic education in a prospective cohort of kidney transplant patients, suggesting benefits on distal (rejection-free survival) outcomes and showing clear benefits on intermediate (quality-of-life, adverse events) outcomes. Large-scale randomized controlled trials should now be conducted to confirm current findings and improve the level of evidence of the benefits of therapeutic education on outcomes of all levels.

Authorship

CV: participated in data analysis and manuscript writing. CM: participated in the coordination of the EPHEGREN cohort, in data analysis and manuscript writing. PM: participated in research design, coordinated the EPHEGREN cohort and participated in manuscript writing. JPR, LC, NK, IE, PFW, MB, LE and AT: participated in the performance of the research.

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Conflict of interest

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 The adverse events form composed of a list of 27 symptoms derived from the immunosuppressive drugs-induced adverse effects, presented as the original French version and a English version

REFERENCES

1. Heldal K, Midtvedt K, Lonning K, *et al*. Kidney transplantation: an attractive and cost-effective alternative for older patients? A cost-utility Study. *Clin Kidney J* 2019; **12**: 888.
2. Howard K, Salkeld G, White S, *et al*. The cost-effectiveness of increasing kidney transplantation and home-based dialysis. *Nephrology* 2009; **14**: 123.
3. Goetzmann L, Ruegg L, Stamm M, *et al*. Psychosocial profiles after transplantation: a 24-month follow-up of heart, lung, liver, kidney and allogeneic bone-marrow patients. *Transplantation* 2008; **86**: 662.
4. Griva K, Davenport A, Newman SP. Health-related quality of life and long-term survival and graft failure in kidney transplantation: a 12-year follow-up study. *Transplantation* 2013; **95**: 740.
5. Villeneuve C, Laroche ML, Essig M, *et al*. Evolution and determinants of health-related quality-of-life in kidney transplant patients over the first 3 years after transplantation. *Transplantation* 2015; **100**: 640.
6. Crawford K, Low JK, Manias E, Williams A. Healthcare professionals can assist patients with managing post-kidney transplant expectations. *Res Social Adm Pharm* 2017; **13**: 1204.
7. Urstad KH, Wahl AK, Andersen MH, Oyen O, Hagen KB. Limited evidence for the effectiveness of educational interventions for renal transplant recipients. Results from a systematic review of controlled clinical trials. *Patient Educ Couns* 2013; **90**: 147.
8. Birkhauer J, Gaab J, Kossowsky J, *et al*. Trust in the health care professional and health outcome: a meta-analysis. *PLoS One* 2017; **12**: e0170988.
9. Kim HS, So HS. A prediction model development on quality of life in kidney transplant recipients. *J Korean Acad Nurs* 2009; **39**: 518.
10. Ladin K, Smith AK. Active medical management for patients with advanced kidney disease. *JAMA Intern Med* 2019; **179**: 313.
11. French_law. *French law on public health (loi Hôpital Patients Santé et Territoires)*. Available from: https://

www.legifrance.gouv.fr/eli/loi/2009/7/21/2009-879/jo/texte. 2009.
12. Osborne RH, Elsworth GR, Whitfield K. The Health Education Impact Questionnaire (heiQ): an outcomes and evaluation measure for patient education and self-management interventions for people with chronic conditions. *Patient Educ Couns* 2007; **66**: 192.
13. De Bleser L, Matteson M, Dobbels F, Russell C, De Geest S. Interventions to improve medication-adherence after transplantation: a systematic review. *Transpl Int* 2009; **22**: 780.
14. Chisholm MA, Mulloy LL, Jagadeesan M, DiPiro JT. Impact of clinical pharmacy services on renal transplant patients' compliance with immunosuppressive medications. *Clin Transplant* 2001; **15**: 330.
15. Giacoma T, Ingersoll GL, Williams M. Teaching video effect on renal transplant patient outcomes. *ANNA J* 1999; **26**: 29, 81.
16. Villeneuve C, Rousseau A, Rerolle JP, *et al.* Adherence profiles in kidney transplant patients: causes and consequences. *Patient Educ Couns* 2020; **103**: 189.
17. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. *Med Care* 1986; **24**: 67.
18. Marquet P, Merville P, Kamar N, *et al.* Pharmacoepidemiological study in renal transplantation: comparison of different tools for the collection of data on treatments, side effects and compliance. *Clin Pharmacol Therapeut* 2011; **87**(Issue Supplement S1): S9.
19. Perneger TV, Leplege A, Etter JF, Rougemont A. Validation of a French-language version of the MOS 36-Item Short Form Health Survey (SF-36) in young healthy adults. *J Clin Epidemiol* 1995; **48**: 1051.
20. Leplege A, Ecosse E, Verdier A, Perneger TV. The French SF-36 Health Survey: translation, cultural adaptation and preliminary psychometric evaluation. *J Clin Epidemiol* 1998; **51**: 1013.
21. Boini S, Bloch J, Briançon S, Gentile S, Germain L, Jouve E. Surveillance de la qualité de vie des sujets atteints d'insuffisance rénale chronique terminale. *Néphrologie Thérapeutique* 2009; **5**: S177.
22. Boini S, Bloch J, Briancon S. [Monitoring the quality of life of end-stage renal disease patients. Quality of life report - REIN - Dialysis 2005]. *Nephrol Ther* 2009; **5** (Suppl 3): S177.
23. Agency AdlBB. Rapport de l'Agence de la Biomédecine 2012 - Greffe rénale. 2013 [Report of the Biomedicine Agency 2012 - Kidney transplant. 2013] [cited 2013 Aug 11] .Available from: http://www.agence-biomedecine.fr/annexes/bilan2012/donnees/organes/06-rein/synthese.htm.
24. Sauerbrei W, Schumacher M. A bootstrap resampling procedure for model building: application to the Cox regression model. *Stat Med* 1992; **11**: 2093.
25. Breu-Dejean N, Driot D, Dupouy J, Lapeyre-Mestre M, Rostaing L. Efficacy of psychoeducational intervention on allograft function in kidney transplant patients: 10-year results of a prospective randomized study. *Exp Clin Transplant* 2016; **14**: 38.
26. Denhaerynck K, Dobbels F, Cleemput I, *et al.* Prevalence, consequences, and determinants of nonadherence in adult renal transplant patients: a literature review. *Transpl Int* 2005; **18**: 1121.
27. Tielen M, van Exel J, Laging M, *et al.* Attitudes to medication after kidney transplantation and their association with medication adherence and graft survival: a 2-year follow-up study. *J Transplant* 2014; **2014**: 675301.
28. Dobbels F, De Bleser L, Berben L, *et al.* Efficacy of a medication adherence enhancing intervention in transplantation: the MAESTRO-Tx trial. *J Heart Lung Transplant* 2017; **36**: 499.
29. Wang Y, Snoep JD, Hemmelder MH, *et al.* Outcomes after kidney transplantation, let's focus on the patients' perspectives. *Clin Kidney J* 2021; **14**: 1504.
30. Klaassen G, Zelle DM, Navis GJ, *et al.* Lifestyle intervention to improve quality of life and prevent weight gain after renal transplantation: Design of the Active Care after Transplantation (ACT) randomized controlled trial. *BMC Nephrol* 2017; **18**: 296.
31. Schmid-Mohler G, Zala P, Graf N, *et al.* Comparison of a behavioral versus an educational weight management intervention after renal transplantation: a randomized controlled trial. *Transplant Direct* 2019; **5**: e507.
32. Alikari V, Tsironi M, Matziou V, *et al.* The impact of education on knowledge, adherence and quality of life among patients on haemodialysis. *Qual Life Res* 2019; **28**: 73.
33. Balducci S, D'Errico V, Haxhi J, *et al.* Effect of a behavioral intervention strategy on sustained change in physical activity and sedentary behavior in patients with type 2 diabetes: the IDES_2 randomized clinical trial. *JAMA* 2019; **321**: 880.
34. Robinson JK, Guevara Y, Gaber R, *et al.* Efficacy of a sun protection workbook for kidney transplant recipients: a randomized controlled trial of a culturally sensitive educational intervention. *Am J Transplant* 2014; **14**: 2821.
35. Beck DE, Fennell RS, Yost RL, Robinson JD, Geary D, Richards GA. Evaluation of an educational program on compliance with medication regimens in pediatric patients with renal transplants. *J Pediatr* 1980; **96**: 1094.
36. Farmer KC. Methods for measuring and monitoring medication regimen adherence in clinical trials and clinical practice. *Clin Ther* 1999; **21**: 1074. Discussion 3.
37. Gokoel SRM, Gombert-Handoko KB, Zwart TC, van der Boog PJM, Moes D, de Fijter JW. Medication non-adherence after kidney transplantation: a critical appraisal and systematic review. *Transplant Rev (Orlando)* 2020; **34**: 100511.