Health-Related Quality of Life 3 Months After Kidney Transplantation as a Predictor of Survival Over 10 Years: A Longitudinal Study

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Aim. This study explores the association between kidney function, side effects of immunosuppressive treatment, coping self-efficacy, and physical and mental HRQoL at 3 months (baseline) after kidney transplantation (KT) and their impact on patient and graft survival for up to 10 years (follow-up).

Methods. A group of 151 patients provided at baseline their socioeconomic and medical (CKD-EPI) data and completed the End-Stage Renal Disease Symptom Checklist (perceived side effects), the coping self-efficacy scale, and the SF-36. At follow-up, patients' health status was noted. Univariate GLM exploring the main effects of the independent variables on physical and mental HRQoL was performed; furthermore, Cox regression analyses were performed to determine whether the early posttransplantation factors predicted patient and graft survival.

Results. Less severe side effects of immunosuppressive treatment and higher efficacy in stopping unpleasant emotions were associated with both higher physical and mental HRQoL at baseline. Younger age was associated with higher physical HRQoL and older age, and lower efficacy in getting support from family and friend were associated with higher mental HRQoL. Patients reporting higher physical and mental HRQoL at 3 months and with higher age and better kidney function had higher odds of surviving with a functioning graft.

Conclusion. Older age, higher kidney function, and higher physical and mental HRQoL at baseline significantly improved the odds of graft and patient survival over 10 years. These results show the importance of close monitoring of early posttransplantation HRQoL along with kidney function and reported side effects because of their effect on long-term patient outcomes.

Keywords: Coping, Health-related quality of life, Kidney, Transplantation, Survival, Side effects.

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With the advances in kidney transplantation (KT) and immunosuppression, along with survival and clinical outcomes, health-related quality of life (HRQoL) is becoming an increasingly important indicator of treatment effectiveness and outcomes (*1–4*). Yet, to our knowledge, thus far, only a few studies of cross-sectional cohorts of KT recipients have examined HRQoL as a determinant of long-term clinical outcomes(*5–8*), all of them have linking lower physical HRQoL with mortality. A study exploring the effects of early post-KT HRQoL and relevant factors on long-term outcome is still missing.

The first 3 months after transplantation are considered as the most problematic period, as they are connected to dramatic changes and with increased morbidity and mortality (*4*). In solid-organ transplant recipients, HRQoL improved most significantly over the first year after transplantation and remained relatively stable afterward (*3, 9, 10*).

Immunosuppression plays an essential role in the process of preventing graft rejection and improving long-term survival. However, its side effects can compromise the HRQoL of KT recipients (*3, 11*). Although De Geest and Moons (2000) argued for side effects assessments to become an essential

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component in the evaluation of HRQoL (*12*), studies with a longitudinal design considering the impact of side effects on HRQoL or graft/patient survival are still lacking.

Kidney function is another vital indicator of the proficiency of KT and immunosuppressive treatment. Loss of kidney function was found to be associated with deteriorated HRQoL and poorer allograft survival (*13–15*).

The post-KT period presents patients with new and ongoing challenges, such as a new medication regimen or side effects (*16*). The use of effective coping strategies in the face of these challenges, has a positive effect on HRQoL (*17–19*) and, consequently, on psychological distress (*20*).

Although a number of studies have explored the determinants of HRQoL and their associations with long-term patient outcomes, to our knowledge, no study has yet investigated the association of early posttransplantation clinical and psychosocial factors with HRQoL and long-term patient survival. The aim of this study was to explore the association between post-KT factors such as kidney function, side effects of immunosuppressive treatment, and coping self-efficacy at baseline and physical and mental HRQoL, also at baseline, 3 months after KT. Furthermore, we explored the impact of these factors and HRQoL at baseline on patient and graft survival for up to 10 years.

RESULTS

The basic characteristics of the sample are shown in Table 1.

Tests for multicollinearity indicated that a low level of multicollinearity was present among the independent factors. Accordingly, to the order in which the factors were entered during GLM analysis, age was entered first, and the remaining variables are listed in order (eGFR: VIF=1.12, perceived side effects: VIF=1.18, problem-focused coping (CSE): VIF=2.99, stop unpleasant emotions (CSE): VIF=3.14, get support from family and friends (CSE): VIF=1.99).

Health-Related Quality of Life

Higher MCS at baseline was associated with older age, less severe side effects of immunosuppressive treatment, and

TABLE 1. Characteristics of the sample

Sociodemographic variables (T1)	N(%) or AM±SD
Sex	
Men/women	85 (56.3%)/66 (42.7%)
Age	47.09±13.2
Education	
Primary/secondary/university	29 (19.2%)/68 (45%)/57 (35.8%)
Income	
Low (≤1.5×min. wage)/average (1.5−2×min. wage)/high (≥2×min. wage)	85 (56.3%)/26 (17.2%)/40 (26.5%)
Family status	
Living alone/cohabitating	47 (31.1%)/104 (68.9%)
Medical variables	
Kidney function (estimated glomerular filtration rate (mL/min/1.73 m^2))	51.16±15.6
No. acute rejection episodes	0.42±0.58
Organ donor	
Deceased/living	141 (93.4%)/10 (6.6%)
Duration of dialysis (yr)	3.6±2.96
Primary kidney disease	
Glomerulonephritis/tubointersticial nephritis/polycystic kidneys	57 (37.8%)/28 (18.5%)/10 (6.6%)
Diabetes mellitus/other or unknown causes	16 (10.6%)/40 (26.5%)
Current immunosuppressive protocol (T1)	
Pred+CsA+MMF[4]/Pred+MMF+Tac[5]/CsA+MMF/Other	102 (67.6%)/37 (24.5%)/5 (3.3%)/7 (4.6%)
Side effects, coping, and health-related quality of life	
Perceived side effects of immunosuppressive treatment (ESRD-SCL TM) (T1)	1.02±0.58
Coping self-efficacy (CSE) (T1)	
Use problem-focused coping/stop unpleasant emotions/get support from family and friends	6.44±1.65/6.69±1.75/6.88±1.79
Physical and mental health-related quality of life (SF-36) (T2)	
Physical component summary (PCS)/mental component summary (MCS)	40.02±7.93/48.77±8.99
Patient and graft survival	
Average follow-up (yr)	7.11±2.22
Patient and graft survival/patient mortality/graft loss	118 (78.2%)/23 (15.2%)/10 (6.6%)

Pred, prednisone; CsA, cyclosporin A; MMF, mycophenolate mofetil; Tac, tacrolimus; ESRD-SCL TM, End-Stage Renal Disease Symptom Checklist–Transplantation Module; CSE, coping self-efficacy scale; SF-36, Short Form (36) Health Survey.

TABLE 2. Factors associated with higher physical (PCS) and mental (MCS) health-related quality of life

	PCS			MCS		
	B	F	% of explained variance–partial H^2	B	F	% of explained variance–partial H^2
Age	**–0.22**	**19.48*** **	**14.2%**	**0.12**	**5.43***	**4.4%**
Sex	–0.2	0.03 ^{ns}	0%	–1.07	0.65 ^{ns}	0.5%
Family status	v1.83	1.68 ^{ns}	1.4%	0.11	0.01 ^{ns}	0%
Education[a]		0.04 ^{ns}	0.1%		1.51 ^{ns}	2.5%
Primary	0.4			–2.82		
Secondary	0.3			–0.03		
Kidney function	–0.07	3.2 ^{ns}	2.6%	0.02	0.14 ^{ns}	0.1%
Perceived side effects of immunosuppressive treatment	**–1.87**	**22*** **	**15.7%**	**–4.77**	**20.07*** **	**14.5%**
Coping self-efficacy (CSE)						
Problem-focused coping	–0.31	0.1 ^{ns}	0.1%	0.43	0.19 ^{ns}	0.2%
Stop unpleasant emotions	**2.05**	**4.2***	**3.4%**	**3.63**	**12.54*** **	**9.6%**
Get support from family and friends	–0.81	2.36 ^{ns}	2%	–1.53	7.95**	6.3%
R^2/Adjusted R^2		42.3/37.4%			53.2/49.2%	

[a] Reference category: university education; ^{ns} not significant; * $P \leq 0.05$; ** $P \leq 0.01$; *** $P \leq 0.001$; R^2: Total variance explained by the model.

higher efficacy in stopping unpleasant emotions and lower efficacy in getting support from family and friends. The model explained 49.2% of the variance of MCS (Table 2).

Patient and Graft Survival

Information on patient and graft survival was collected 4 to 10 years after the first data collection at 3 months after transplantation, with an average follow-up period of 7.1±2.2 years.

The Cox regression χ^2 for patient and graft survival was 23.44 ($P \leq 0.05$) with a model consisting of the following significant factors: age (HR 1.03, $P \leq 0.01$), kidney function (HR 1.02, $P \leq 0.05$), PCS (HR 1.04, $P \leq 0.05$), and MCS (HR 1.06, $P \leq 0.001$). The chances of survival increase by 3% for each year of age, by 2% per each increase in kidney function by 1 mL/min/1.73 m^2, by 4% for each point in the PCS (SF-36), and by 6% for each point in the MCS (SF-36) at 3 months after KT (Table 3).

DISCUSSION

Health-related quality of life is no longer considered only as an important outcome measure in posttransplantation

TABLE 3. Cox regression models containing predictors of patient and graft survival

	Model for patient and graft survival (N=118)		
	Score		
	2Log likelihood 784.3		χ^2 23.44*
	Wald	HR	95%CI for HR
Age	**6.28****	**1.03**	**1.01–1.05**
Sex	1.05 ^{ns}	0.78	0.49–1.25
Family status	0.63 ^{ns}	1.24	0.73–2.1
Education[a]	1.18 ^{ns}		
Primary	1.17 ^{ns}	0.69	0.35–1.35
Secondary	0.22 ^{ns}	0.9	0.57–1.42
Kidney function	**4.46***	**1.02**	**1–1.03**
Perceived side effects of immunosuppressive treatment	0.39 ^{ns}	1.17	0.72–1.88
Coping self-efficacy (CSE)			
Problem-focused coping	0.81 ^{ns}	0.84	0.57–1.23
Stop unpleasant emotions	0.26 ^{ns}	0.89	0.58–1.38
Get support from family and friends	1.07 ^{ns}	1.11	0.91–1.37
Physical health-related quality of life	**4.72***	**1.04**	**1–1.07**
Mental health-related quality of life	**10.95*****	**1.06**	**1.03–1.1**

[a] Reference Category: University education; ^{ns} not significant; * $P \leq 0.05$; ** $P \leq 0.01$; *** $P \leq 0.001$.

patients but also as an effective assessment of treatment effectiveness and a predictor of adverse outcomes. Therefore, this study explored the association between early post-KT factors and physical and mental HRQoL (PCS and MCS, respectively) at baseline, 3 months after KT. Higher PCS was associated with younger age, less severe perceived side effects of immunosuppressive treatment, and with higher efficacy in stopping unpleasant emotions. Higher MCS, on the other hand, was associated with older age, less severe perceived side effects of immunosuppressive treatment, and higher efficacy in stopping unpleasant emotions and lower efficacy in getting support from family and friends. Furthermore, we explored the impact of these early factors and HRQoL at baseline on patient and graft survival for up to 10 years. We found that older age, higher kidney function, and both higher PCS and MCS at baseline significantly improved the odds of graft and patient survival over a period of 10 years.

Age was found to be associated with both PCS and MCS and survival; its role varied, however. Younger patients reported higher PCS, whereas older patients reported higher MCS. Interestingly, older age increased the likelihood of survival with a functioning kidney. A previous study shows that higher age does not have an impact on 5-year graft survival (*7*), and as Valderrabano (2001) suggests, it might be possible that the impact of end-stage renal disease on HRQoL, and thereby on mortality, is lower in elderly patients (*1*).

Surprisingly, kidney function at baseline was not significantly associated with either PCS or MCS at baseline. Previously, loss of renal function was found to be indirectly associated with deterioration of HRQoL (*13*); however, it is not clear at what level this deterioration begins (*1*). However, better kidney function at baseline was a significant predictor of long-term survival, in line with previous research (*14*).

Coping self-efficacy was another significant factor associated with higher HRQoL at baseline. Patients who were confident in their ability to stop unpleasant emotions reported a higher PCS and MCS. On the other hand, patients who scored higher on questions such as the "ability to make new friends" or the "ability to get emotional support from community organisations" reported lower MCS. White (2010) found in her sample of KT patients that a good overall quality of life was associated with the use of problem-solving coping strategies (*17*), whereas Mikula et al. (2013) found that in cases of a chronic disease, coping focused on stopping unpleasant emotions and thoughts explained most of the variance in mental HRQoL (*21*). It is possible that patients who rely more on their own resources rather than on those of their environment tend to also evaluate their HRQoL as higher. It is also possible that confidence in one's ability to use a certain coping strategy does not necessarily imply its use or availing of this type of support.

Mental component summary and PCS at baseline were significant predictors of long-term graft and patient survival. Previous studies have confirmed the association of a higher PCS with a decreased risk of mortality in both dialysis and posttransplantation patients (*1, 8, 22*). Although the levels of perceived side effects of immunosuppressive treatment did not directly predict long-term survival, they did explain the most variance in both PCS and MCS, and it is possible that they thereby had an indirect effect on survival. Higher levels of perceived side effects were previously linked with lower perceived HRQoL (*12*) as well as with poor adherence, one of the most crucial factors in sustaining good outcomes after KT (*23, 24*). It is important to note that regardless of the burden of immunosuppressive treatment, the best early posttransplantation indicators of long-term survival are higher age and better kidney function along with mental and physical HRQoL. This shows that the relationships between HRQoL, side effects of immunosuppressive treatment, adherence, and long-term outcome may be more intricate than expected and should be closely examined. It is possible that HRQoL can influence health behaviors and thereby also clinical results. Similarly, our results show the importance of monitoring HRQoL as early as 3 months after KT because of its impact on future patient and graft outcome.

Strengths and Limitations

The main strength of this study is the combination of sociodemographic, medical, and psychosocial variables in a prospective follow-up for an average of 7.11 years. All patients were assessed at a uniform posttransplantation time. The Louis Pasteur University Hospital Transplantation center in Kosice, Slovakia, where during the observation period, the average number of patients undergoing kidney transplant was 31.4 per year—about one quarter or all kidney transplantations carried out in Slovakia. Therefore, our cohort explained a relevant number of national transplanted recipients, and for this study, all consecutive patients fitting the inclusion criteria were asked to participate to prevent selection bias. However, this may also be considered as one of the limitations of the study—all of our patients were enrolled from a single center, and the sample consisted of rather younger and predominantly white patients; therefore, our findings cannot be generalized without further consideration. Similarly, we have limited information on patients who dropped out before the start of this study because of graft loss or mortality. Finally, as this was an experimental observational study, causal associations between predictors and outcomes cannot be definitely confirmed.

Implications

Patients reporting higher physical and mental HRQoL at 3 months and with better kidney function had higher odds of surviving with a functioning graft. These results show the importance of close monitoring of early posttransplantation HRQoL along with kidney function and reported side effects, because of their effect on long-term patient outcomes.

Although some of these effects may not seem as severe, they can cause a high level of distress in the patient and lead to decreased HRQoL and to breaking the immunosuppressive regimen. However, to confirm this relationship, pathways between perceived side effects, HRQoL, and adherence should be examined. Furthermore, the effect of improvement/deterioration of posttransplantation HRQoL on long-term patient outcomes should be explored.

Aside from close monitoring of kidney function and side effects of immunosuppressive treatment, a multidisciplinary team at a transplantation unit could assist their patients in improving their future HRQoL by providing intervention programs focused on dealing with depression and anxiety by providing patients with alternative coping strategies and with

peer support from other patients experiencing similar situation as they are.

In conclusion, we found that higher PCS at baseline was associated with younger age, less severe perceived side effects of immunosuppressive treatment and higher efficacy in stopping unpleasant emotions. Higher MCS was associated with older age, less severe perceived side effects of immunosuppressive treatment, and higher efficacy in stopping unpleasant emotions and lower efficacy in getting support from family and friends. Patients reporting higher PCS and MCS at 3 months and with better kidney function had higher odds of surviving with a functioning graft. Our findings show the importance of closely monitoring not only kidney function but also of PCS and MCS at baseline. To further unravel these relationships, pathways between perceived side effects, HRQoL, and adherence should be examined.

MATERIALS AND METHODS

Sample

All consecutive patients from the Louis Pasteur University Hospital Transplantation center in Kosice, Slovakia (catchment area: about 1.5 million inhabitants), who underwent a kidney transplant in the years 2003–2009 and met the inclusion criteria were asked to participate. To be included in the study, patients had to fulfill the following criteria: to be 3 months after KT; to be in a relatively stable condition, such as not being hospitalized or treated for rejection at the time of interview; to have a functioning graft; and to have no psychiatric diseases, including severe dementia and mental retardation, listed in their medical records. If the patient was hospitalized or unstable at 3 months post-KT, their assessment was deferred by 1 month. If they were still unstable at this point, they were excluded from the study because of not meeting the inclusion criteria. Because currently, there are no non–heart-beating donors in Slovakia, all patients who received a kidney graft from a deceased donor, received one from a brain-dead donor. At follow-up in 2013, data on patient status (patient and graft survival) were collected.

Of the total number of patients visiting the transplantation center in Kosice, 182 met the inclusion criteria and were asked to participate. Of these, 18 patients refused to participate (9.9%), and an additional 13 returned incomplete data (7.1%), resulting in 151 patients (response rate, 83%) who provided their data at baseline (Fig. 1). The Mann-Whitney *U* test and chi-square analyses did not indicate any significant differences between respondents and nonrespondents regarding age and sex. Each patient provided a signed informed consent form before the study. The local ethics committee approved the study.

Measures

Sociodemographic Data

The sociodemographic variables—age, sex, education, average income, and marital status—were obtained in a structured interview conducted by a trained interviewer. Educational background was categorized into three groups: primary, secondary, and university education, depending on the level of education completed. Average income was first evaluated by dividing the household budget by the number of persons in the household and then categorizing based on the legal minimum wage in the Slovak Republic as follows: low (<1.5 times the minimum wage); average (1.5 times to 2 times the minimum wage), and high (higher than 2 times the minimum wage). Family status was represented by two options: living alone (single, divorced, or widowed) and cohabitating (married/living in a cohabitating relationship). All of the sociodemographic variables were used for group comparison; however, only sex, education, and marital status were used in the analysis.

Medical Data

Information about kidney function was taken from the patients' medical records. The estimated glomerular filtration rate (eGFR) to assess kidney function at baseline was calculated using the CKD-EPI formula (mL/min/1.73 m2) (*25, 26*).

Patient and Graft Survival

At follow-up information about each patient's status was taken from medical records and was cross-checked with the hospital's transplantation statistical report. A patient's status was categorized as either "patient and graft survival" or "other" (all-cause graft loss or all-cause mortality). No patients were retransplanted during the follow-up period.

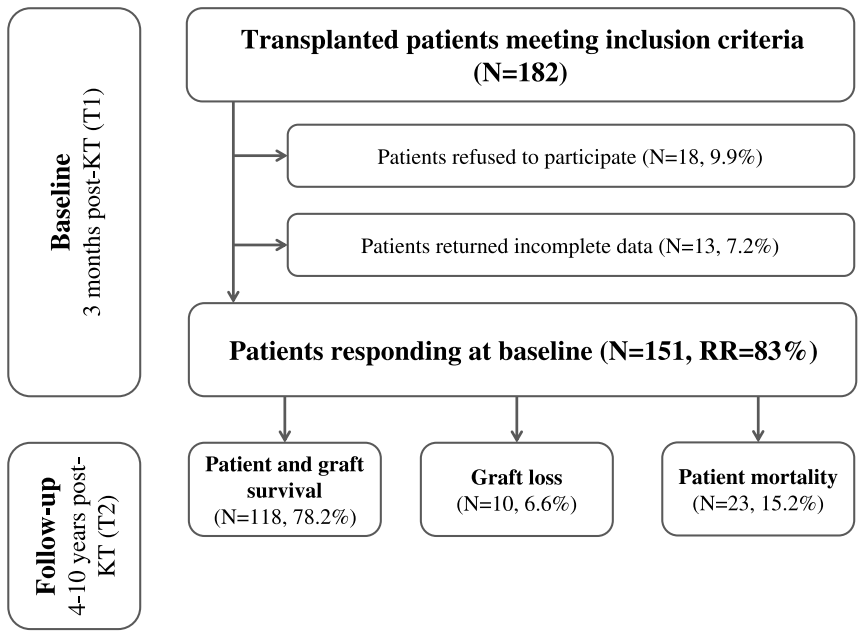

FIGURE 1. Flow-chart diagram of the data collection.

Side Effects

To assess the perceived side effects of immunosuppressive treatment at baseline, patients completed the End-Stage Renal Disease Symptom Checklist–Transplantation Module (ESRD SCL-TM) (*27*). This questionnaire was developed to assess disease-specific distress and consists of six subscales: limited physical capacity, limited cognitive capacity, cardiac and renal dysfunction, side effects of corticosteroids, increased growth of gum and hair, and transplantation-associated psychological distress. The number of items for each subscale varied from 5 to 10, and for each item, patients estimated the severity of the symptom on a scale from 0 (not at all) to 5 (extremely). Afterward, an index for each symptom or the whole scale was computed by dividing the severity index score by the number of items in the subscales (*27*). For the purpose of the analysis, only the total score indicating overall severity and distress of perceived side effects of immunosuppressive treatment was used. In our sample, Cronbach α for the total scale was 0.96.

Coping Self-Efficacy

Patients also completed the coping self-efficacy scale (CSE), a measure of self-efficacy when coping with a challenge or a threat (*28*). The scale consists of 26 items and comprises three subscales: the use of problem-focused behavior (12 items), the ability to stop unpleasant emotions (9 items), and the ability to get support from family and friends (5 items) (*28*). For each item, the patients were asked to express on an 11-point scale the extent to which they believe they could perform the described coping behavior, with a higher score indicating better coping self-efficacy. The total score for each subscale is then divided by the number of items. In our sample, Cronbach α ranged from 0.79 to 0.90.

Health-Related Quality of Life

Short Form Health Survey (SF-36) was used to assess the physical and mental HRQoL and contains 36 items on eight scales covering the physical and mental domains of HRQoL. The physical component summary (PCS) comprises four subscales: physical functioning, role limitation attributable to physical problems, bodily pain, and perception of general health, and the mental component summary (MCS) comprises the remaining four subscales: social functioning, vitality, role limitation attributable to emotional problems, and mental health (*29*). The component summary scores are normalized to a general population mean of 50 and a standard deviation of 10, where higher scores indicate better health status (*30*). The validity and reliability of the SF-36 have been confirmed in patients after KT (*31, 32*). Cronbach α for PCS and MCS was 0.90 and 0.91, respectively.

Statistics

Frequencies, means, and standard deviations were calculated for the sample description. The Mann-Whitney *U* test and chi-square test were used to examine the differences between respondents and nonrespondents. Multicollinearity analysis of the independent variables was performed. Next, a univariate general linear model (GLM) exploring the main effects of the independent variables was performed to find their associations with physical and mental HRQoL. The PCS and MCS scores (SF-36) were entered as the dependent variables for the whole sample. Sex, education, and family status were entered as fixed factors, with female sex, university education, and cohabitating as the reference group. Age, eGFR, perceived side effects of immunosuppressive treatment (ESRD-SCL-TM), the use of problem-focused behavior (CES), the ability to stop unpleasant emotions (CES), and the ability to get support from family and friends (CES) were entered as covariants.

Finally, Cox regression analyses were performed to determine whether the posttransplantation factors at baseline—3 months post-KT (age, sex, family status, education, eGFR, perceived side effects of immunosuppressive treatment [ESRD-SCL-TM]. and all three types of coping efficacy [CES]) predicted patient and graft survival, censored for all-cause graft-loss and mortality at follow-up when controlled for PCS and MCS at baseline. IBM SPSS 20 for Windows was used to analyze the data (IBM Company, Chicago, IL).

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