Self-rated health and mortality after kidney transplantation

Majerníková, Mária

Part I

General introduction

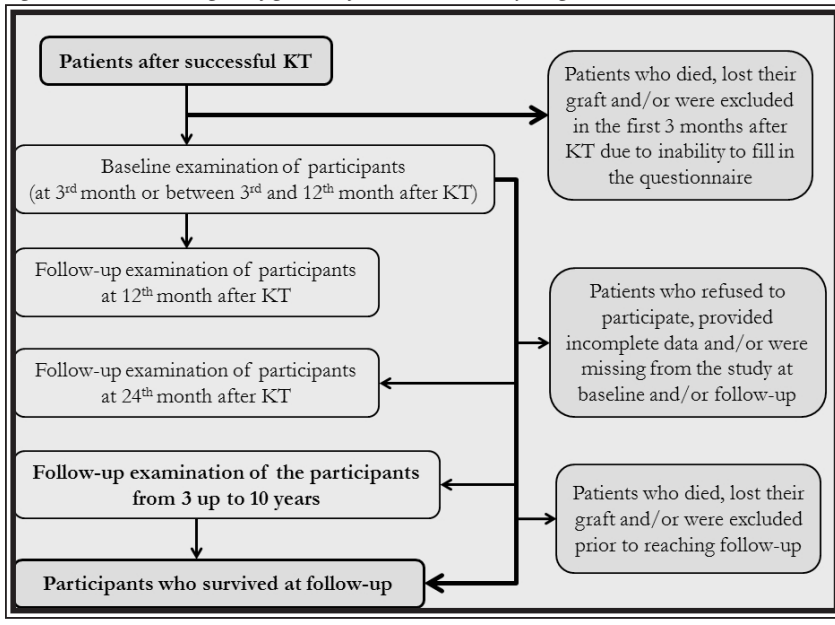
Chapter 2

Data source, measures and statistical analyses

2.1 Sample and procedure

This study is a continuation of an earlier research project performed between 2001 and 2006 by Rosenberger.[1] Both studies were carried out in the framework of cooperation between Louis Pasteur University Hospital Kosice, Safarik University Kosice, Fresenius Medical Care – Dialysis Services Slovakia in Slovakia and the University Medical Centre Groningen, University of Groningen in the Netherlands. The previous study focused on an observational cross-sectional design regarding perceived health status and its determinants after kidney transplantation (KT).[1] In line with the previous study, the main aims of the currents study focused on self-rated health and on mortality as health outcomes in kidney transplant recipients in a prospective cohort study. For general information about the study design (included recruitment, baseline and follow-up examinations), see Figure 2.1.

Figure 2.1 Flow-chart diagram of general information in the study design



Between 2001 and 2011 a total of 362 consecutive patients underwent KT at the Transplant Centre of Kosice in the eastern region of Slovakia. All were considered for participation in the study. The only inclusion criterion was graft survival at the 3rd month after KT, because the first 3 months after KT are usually considered to be the most problematic period connected to dramatic changes, increased morbidity, even mortality and some clinical aspects, such as anemia, delayed graft function, and so on during a period shorter than 3 months after transplantation depending on the pre- and peri-transplantation period.[2] In the case of any severe medical problem (infection, rejection, surgery, etc.) data collection was postponed until one month after overall clinical stabilization. Thus, the recruitment at baseline examination started at the 3rd month after successful KT, with the

aim of avoiding the collection of unreliable data. Furthermore, an improvement in SRH most often occurs at 6 months after KT and might remain unchanged for up to 2 years after KT.[3] We therefore conducted the baseline examination at the 3rd month (Chapter 3 and partially in Chapter 4) or the baseline occurred between the 3rd and 12th month after a successful KT (partially in Chapter 4 and Chapters 5-7). During the whole period of the data collection, 9 (2.5%) patients dropped out prior to reaching the 3rd month after KT: 3 (0.8%) died and 6 (1.7%) lost their transplanted kidney. The remaining patients (N=353, response rate 97.5%) were then enrolled in the study. The exclusion criterion was a lower ability or inability to answer questions during the interview due to stroke, severe dementia or mental retardation listed in the medical record. Therefore, a total of 3 (0.9%) other patients were additionally excluded. As a result, the total number of the participants decreased from 353 to 350 (a decrease in response rate from 97.5 to 96.7%).

The minimum follow-up duration was up to 1 year after successful KT; on the other hand, the maximum observed period was up to 10 years follow-up. Patients who were excluded, refused to participate, provided incomplete data and/or were missed at the baseline and/or follow-up examination, are respectively displayed in the Methods section of Chapters 3 through 7. They are shown in the flow-chart diagrams of participants in these chapters as well. Data collection was an ongoing process, and as most studies required follow-up data on every patient, we only used the latest and most current data. Thus far, no data was re-analyzed two or more times for the same dependent factor, just when compared with a differently stratified cohort. For more detailed information about the total number of participants in the whole study, see Table 2.1. For further detailed information about participants who participated in the separate parts of this study, we added detailed information regarding baseline and follow-up examinations as well as regarding response rates in the section Methods, Sample and procedure of the Chapters 3 to 7.

Table 2.1 Total number of participants enrolled in the study at baseline and at follow-up

		Time since successful kidney transplantation (in months)							**Total number (in months)**	
		3	4-12	12	24	36	48	60-120	3-12	12-120
Participants	at baseline	208	145	0	0	0	0	0	353	0
	at follow-up	0	0	89	73	64	53	71	0	350

Patients filled in the questionnaires (see 2.2.2). All participants were interviewed during regular outpatient clinical visits by trained personnel independent from the transplant team. Medical data were retrieved from medical records at the same time as sociodemographic data and data on questionnaires. Only patients who signed informed consent prior to the study were included. The local Ethics Committee in Kosice approved the study.

2.2 Measures

2.2.1 Sociodemographic data

These included age, gender, education, occupation, family status and living status. Age was treated as a continual variable. Education was categorized into elementary (primary

school, completed or not), apprenticeship (completed, or not-completed secondary school), secondary (completed, or not-completed university) and university (completed).

2.2.2 Questionnaire data

Self-rated health (SRH) was measured using the first question of the Short Form Health Survey (SF-36).[4] The SF-36 questionnaire consists of eight subscales: physical functioning, physical role limitations, bodily pain, vitality, general health perception, social functioning, emotional role limitations, and mental health.[4,5] All of these eight subscales are coded and transformed into a scale from 0 (poor health) to 100 (excellent health) in which they are presented as a standard SF-36 scores between 0 and 100, with higher scores indicating better health status.[4,5] SRH can also be determined in this way from a single item in the SF-36.[6] The SRH answer options 1 (poor), 2 (fair), 3 (good), 4 (very good) and 5 (excellent) were transformed into a standard scale from 0 (poor health) to 100 (excellent health) in which higher scores indicate better subjective well-being in health status as well.[4] The validity and reliability of the first item of the SF-36 has been confirmed in the Slovak Republic[7,8] as well as in patients with renal disease, including those after KT.[5,9,10] In Chapter 7, this scale was categorized into tertiles: scores 0 to 30 (fair and poor) were categorized as 'poor health', 31 to 60 (good) as 'average health', and 61 to 100 (excellent and very good) as 'excellent health'.[11]

Side-effects of immunosuppressive treatment were assessed using the End-Stage Renal Disease Symptom Checklist – Transplantation Module (ESRD SCL–TM), which consists of six subscales: limited physical capacity (10 items), limited cognitive capacity (8 items), cardiac and renal dysfunction (7 items), side effects of corticosteroids (5 items), increased growth of gum and hair (5 items) and transplantation-associated psychological distress (8 items).[12] This questionnaire can be used to measure the side-effects of immunosuppressive treatment as well as its disease-specific distress.[12] For each item the patient can rate the severity of the symptom on a subscale from 0 (not at all) to 5 (extremely). The scores for the subscales are transformed into a scale score by dividing the severity index score by the number of items in the subscales.[12] Higher scores indicate a higher level of side-effects from immunosuppressive treatment. In our research (Chapter 4) Cronbach's α was 0.89 for limited physical capacity, 0.87 for limited cognitive capacity, 0.85 for cardiac and renal dysfunction, 0.81 for side effects of corticosteroids, 0.85 for increased growth of gum and hair and 0.84 for transplantation-associated psychological distress.

2.2.3 Clinical data

Medical determinants were retrieved from medical files. These included primary kidney diagnosis, previous duration of dialysis (in years), source of transplanted kidney, function immediately after KT, weight, serum creatinine (laboratory methods by Scheffe), serum hemoglobin (Hb) (in grams per deciliters), therapy for anemia, uroinfection (these included pyelonephritis of the graft), acute rejection episodes (these included early and late), type of rejection treatment, chronic renal allograft dysfunction, current immunosuppressive treatment at the time of interview, comorbidity and diagnosis of graft loss and mortality.

The estimated glomerular filtration rate (eGFR) (in milliliters per minute) was calculated using the Cockroft-Gault formula[13] (Chapters 3 and 4) and the CKD-EPI formula (Chapters 5-7).[14] Chronic kidney disease (CKD) stages from 1 to 5 were determined as

recommended by guidelines:[15,16] Kidney damage with normal or higher eGFR is CKD stage 1 (eGFR≥90ml/min); kidney damage with mild reduction of eGFR is CKD stage 2 (60ml/min≤eGFR<90ml/min); kidney damage with moderate reduction of eGFR is CKD stages 3a (45ml/min≤eGFR<60ml/min) and 3b (30ml/min≤eGFR<45ml/min); kidney damage with severe reduction of eGFR is CKD stage 4 (15ml/min≤eGFR<30ml/min); and kidney failure (eGFR<15ml/min or dialysis) is CKD stage 5.[15,16]

Based on the hemoglobin value, post-transplant anemia was divided into 3 categories: severe PTA (Hb<10 g/l), mild PTA (10≤Hb<12 g/l) and no PTA (Hb≥12 g/dl).[17,18] Acute rejection episodes (early and late) as well as chronic renal allograft dysfunction were diagnosed from a biopsy according to the Banff 2009 update of diagnostic categories for renal allograft biopsies.[19] An early acute rejection episode was defined as an acute rejection episode occurring within 3 months; a late acute rejection episode was defined as an last acute rejection episode occurring after 3 months independently of a previous early acute rejection episode.[20,21] Patients received their immunosuppressive medication independently from this study solely based on the decision of their transplant nephrologists; the current practice in the transplant centre is in line with standard recommendations issued by KDIGO Clinical Practice Guideline for the care of kidney transplant recipients.[16]

Mortality data were obtained from our database of medical reports and completed with data from the "Health care surveillance authority of Slovak Republic" up to 10 years after KT (Chapters 6 and 7).

2.3 Statistical analyses

First, frequencies, means, minimum, maximum and standard deviations were calculated for the sample description. Second, the Mann-Whitney U-test and χ^2 test were used to check the differences between participants and non-participants as well as between the dependent variables (SRH at follow-up in Chapters 3-5, graft loss in Chapter 7, and mortality in Chapters 6 and 7) and the other variables at baseline. Third, stepwise linear regression was performed in order to identify predictors of SRH at follow-up (Chapter 3) and SRH at follow-up stratified due to period since transplantation (Chapter 4). Fourth, we performed Generalized Linear Models – Generalized Estimating Equations (GEE) to enable us to perform semi-parametric regressions. Furthermore, GEE are standardly used to estimate the parameters of a generalized linear model with a potential unknown correlation between studying outcomes[22,23] in SRH at follow-up (Chapter 5). Fifth, Harrell's C-statistic and Somers' D were calculated in models for mortality and graft loss (Chapter 7). Finally, Cox regression was performed in order to identify the predictors of mortality (censored for graft loss; Chapters 6 and 7) and graft loss (Chapter 7). The Statistical Package for the Social Science (IBM SPSS Inc. Chicago, IL, USA) version 16.0 (Chapters 3 and 4), version 18.0.3 (Chapter 7) and version 20 (Chapters 5 and 6) was used for these statistical analyses as well as STATA/SE 11.1 (Chapter 7).

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