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Psychosocial and medical determinants of long-term patient outcomes

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Chapter 2

DATA SOURCES

This chapter provides a general overview of the origin of the data (2.1), the study design, population and data collection (2.2) as well as the measures (2.3) and statistical procedures (2.4) used.

2.1   ORIGIN OF THE DATA

This study was carried out in a framework of cooperation between Safarik University; the Louis Pasteur University Hospital Kosice; Fresenius Medical Care – Dialysis services Slovakia in Slovakia; the Irish Haemophilia Society, Ireland; and the University Medical Centre Groningen, University of Groningen, the Netherlands, as a part of a larger Chronic Disease Research Programme within the Graduate School Kosice Institute for Society and Health (KISH). The aim of this programme is to explore factors that prevent the development or exacerbation of chronic diseases, such as coronary heart disease, multiple sclerosis, Parkinson's disease, end-stage renal disease or rheumatoid arthritis, as well as factors that help eliminate health disparities caused by chronic diseases and that promote health, well-being and quality of life.

Part I of this study is a continuation of an earlier research project performed by Rosenberger between 2001 and 2006, and later Majernikova (2007 – 2013), both of which were focused on perceived health status in patients with end-stage renal disease.[1, 2] In line with their studies, the main aims of this current study included health-related quality of life, impact of treatment and patient outcomes in patients after kidney transplantation.

During the course of this study an opportunity arose to extend the study also to patients affected by haemophilia in cooperation with the Irish Haemophilia Society. This study therefore forms Part II of this thesis.

2.2   STUDY DESIGN, POPULATION AND DATA COLLECTION

The design of the study was set as a combination of cross-sectional and longitudinal. For general information about the study design, study population and data collection, please refer to Figure 2.1.

2.2.1   KIDNEY TRANSPLANT RECIPIENTS

All kidney transplant (KT) patients were interviewed either at their hospital appointment at 3 months or on the anniversary of their successful transplantation and during follow-up up to 12 years later. Patients who underwent KT were all recruited through the Louis Pasteur University Hospital Transplantation centre in Kosice, located in the eastern region of Slovakia. Between 2001 and 2009 a total of 394 patients underwent KT in this transplantation center. At the time additional 139 patients who were transplanted prior to this period were attending the Transplantation centre.

All consecutive patients who met the inclusion criteria were asked to participate. To be included in the study at baseline patients had to fulfil the following criteria: to be a minimum of 3 months

and a maximum of 7 years after KT; to be in a relatively stable condition, such as not being hospitalised 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 patients were hospitalised or unstable at the scheduled interview time, their assessment was deferred by one month. If they were still unstable at this point, they were excluded from the study due to not meeting the inclusion criteria. Patients received their immunosuppressive medication independently from this study, based solely on the decision of their transplant nephrologists; in line with standard recommendations issued by the 'Kidney Disease Improving Global Outcomes' (KDIGO) Clinical Practice Guideline for the care of kidney transplant recipients.[3]

The time of the baseline interview was scheduled for the 3rd month after KT, since the first 3 months after transplantation are considered as the most problematic period connected to dramatic changes and increased morbidity and mortality.[4]

Out of the total of 533 patients, 10 (1.9%) patients dropped out prior to reaching the 3rd month after KT: 3 (0.6%) died and 7 (1.3%) lost their transplanted kidney; an additional 82 (15.4%) underwent their transplantation more than 7 years ago. A further 3 (0.6%) patients were excluded due to a history of stroke. Thus, the total number of patients who were considered for the study was 438 (82.2%). The minimum follow-up duration was 3 year after successful KT; on the other hand, the maximum observed period was up to 12 years of follow-up. Patients who were excluded, declined 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 6. For more detailed information about the total number of the participants in the whole study, see Table 2.1.

All KT 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 the data on questionnaires. All participants were provided with information about the study and signed an informed consent statement prior to the study. Participation in the study was fully voluntary and anonymous, with no incentives provided for participation.

2.2.2   PATIENTS WITH HAEMOPHILIA

In order to obtain information on patients with haemophilia, the National Member Organisations (NMO) of the World Federation of Haemophilia (WFH) from a number of countries in the European and North American region played an important role. The NMOs completed surveys on access to treatment and patient services provided in their country as well as recruited all patients who participated in the study. The majority of the NMOs completed two surveys 3 years apart; however, since not all organisations provided information both times, the information was analysed as cross-sectional, with some longitudinal comparisons.

When recruiting individual haemophilia patients, the NMOs were asked to randomly select 20 young male adults with severe haemophilia, with FVIII/IX (levels <1 IU dL-1) and to ask them to complete a survey. The patients had to fulfil the following inclusion criteria: severe haemophilia, with FVIII/IX, minimum age 18, maximum age 35, disclosed previous history of inhibitors. The minimum age was chosen because at the age of 18 patients usually choose to continue on prophylaxis or change their regimen. The maximum age of 35 years was defined by the time when the first country (Sweden) initiated prophylactic treatment. All patients with haemophilia invited to participate in the study completed a one-off survey. Patients and NMOs which were excluded, declined to participate and/or provided incomplete data, are respectively displayed in the Methods section of Chapters 7 through 10. For more detailed information about the total number of the participants in the whole study, see Table 2.2.

In haemophilia patients, the data collection was performed by e-mail or phone by the local NMO representative. All participants were provided with information about the study and signed an informed consent statement prior to the study. Participation in the study was fully voluntary and anonymous, with no incentives provided for participation.

Figure 2.1 Flow-chart of the study design and data collection
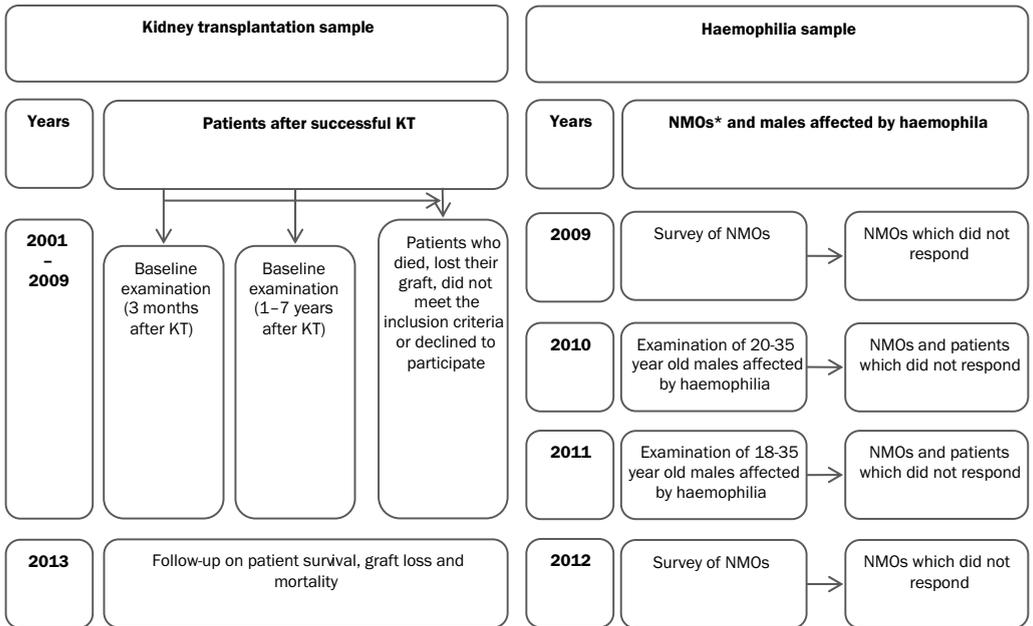
*National Member Organisations

Table 2.1 Description of the samples used in this study:

Patients after successful kidney transplantation

Chapter		3	4	5	6
Sample size		177	151	297	331
Design		Cross-sectional	Longitudinal	Cross-sectional Longitudinal	Cross-sectional Longitudinal
Time since successful transplantation at baseline		3 months – 7 years	3 months	3 months – 1 year	3 months – 6 years
Data collection	Baseline	Interview	Interview	Interview	Interview
	Follow-up	–	Medical records /NCOT*	Medical records /NCOT*	Medical records /NCOT*
Time period	Baseline	2001–2006	2003–2009	2002–2009	2002–2009
	Follow-up	–	2013	2013	2013
Response rate		78%	83%	91%	76%
Age	Mean	48.4	47.1	48.1	49.6
	SD	12.1	13.2	12.8	12
Sex	Male	107 (60.5%)	85 (56.3%)	183 (61.6%)	187 (56.5%)
	Female	70 (39.5%)	66 (42.7%)	114 (38.4%)	144 (43.5%)

* NCOT – National Center for Organ Transplantation, Slovak Republic

Table 2.2 Description of the samples used in this study:

Haemophilia patients and National Member Organisations

Chapter		7	8	9	10
Sample type		NMOs*	NMOs*	Patients	Patients
Sample size		19	35	124	58
Design		Survey	Survey	Cross-sectional	Cross-sectional
Time period		2009	2012	2011	2010
Response rate		44.2%	81.4%	77.5%	72.5%
Age	Mean	–	–	27.0	27.5
	SD	–	–	4.6	4.7

*National Member Organisation

2.3   MEASURES

2.3.1   *SOCIODEMOGRAPHIC DATA*

In patients after KT, sociodemographic data included age, sex, education, occupation, number of hours worked per week, average income and family status. Educational background was categorised into 3 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 categorised based on the legal minimum wage in the Slovak Republic as follows: low (lower than 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). Minimum wage is an indicator of the financial situation that is adjusted for the income of all family members according to the Slovak Ministry of Social Affairs.5 Family status was represented by 2 options: living alone (single, divorced, widowed) and cohabitating (married/living in a cohabitating relationship).

In patients with haemophilia, information on age, sex, occupation, and the number of hours worked per week were collected.

2.3.2   *MEDICAL DATA*

In patients after KT, information about kidney function, serum albumin, number of acute rejection episodes, number of comorbidities and adherence was taken from patient medical records or recorded during the interview.

The estimated glomerular filtration rate (eGFR) to assess kidney function at baseline was calculated using the Cockcroft-Gault equation[6] and later the CKD-EPI formula (ml/min/1.73m^2).[7, 8]

Comorbidity was assessed as a total sum of comorbid diseases (Chapter 3) and by the Charlson Comorbidity Index (CCI)[9], which uses a simple weighted scoring system based on the presence or absence of 19 comorbid conditions (Chapter 6). Each comorbid condition is assigned a score ranging from 1 to 6 depending on the risk of dying associated with it. Scores are then summed to provide a total score. The CCI has been validated as a predictor of survival and health status in numerous patient groups, including the chronic kidney disease population.[10]

Perceived side-effects of immunosuppressive treatment were assessed by the End-Stage Renal Disease Symptom Checklist – Transplantation Module (ESRD SCL-TM).[11] This questionnaire was developed to assess disease-specific distress and consists of 6 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 symp-

tom on a scale from 0 (not at all) to 5 (extremely). Afterwards, a severity index for each symptom and the whole scale was computed by dividing the severity index score by the number of items in the subscales, where a higher index indicated a higher burden of perceived side-effects.[11]

Adherence evaluation was based on collateral reports – a combination of the self-evaluation of adherence by the patient and an estimate of the patient's adherence by his/her nephrologist based on regular check-ups and clinical results.[12-15] In a confidential interview patients were asked: "Over the last month, how often did you skip a dose, delay taking a dose by more than 2 hours or change the timing of a dose?" They were instructed to rate their adherence on a scale from 1 to 5, where excellent adherence was represented by 1 (the patient did not break the prescribed regimen over the past month), 2 (once over the past month), 3 (2–3 times over the past month), 4 (once per week over the past month), and 5 represented very poor adherence (more than 2 times a week). Subsequently, the nephrologist was interviewed about each patient's adherence with the immunosuppression therapy using the same scale while taking into consideration his/her opinion on immunosuppressant level variations or knowledge about prescribed and used immunosuppressants. Patients were considered to be adherent only if they declared their adherence by themselves as excellent, in agreement with their physician's opinion.

Graft loss and *mortality data* was taken from medical records, cross-checking it with the transplantation statistical report of the hospital. A patient's status was categorised as either patient and graft survival, all-cause graft loss or all-cause mortality. No patients were re-transplanted during the follow-up period.

Medical data in patients with haemophilia included the type of haemophilia, severity, treatment regime (prophylaxis vs. on-demand, length of time on each regimen, dose of each infusion and number of infusions per week), current regimen, history of inhibitors, bleeding episodes per year, target joints, serious bleeding episodes, mobility, recurring bleeding episodes, surgery, pain and use of pain medication, and days missed from work due to haemophilia as total number of days missed from work per year. Primary prophylaxis was defined as having a preventive aim with infusion regularly several times a week during the whole year to prevent bleeding episodes from occurring. The respondents were asked to report the number of times per week prophylactic treatment was administered. On-demand was defined as administering treatment when needed to treat a bleed. A target joint was defined as three or more bleeding episodes into the same joint in a consecutive 3-month period. Annual factor consumption was calculated on self-reported use.

Access to medical services was assessed by a questionnaire developed on the document outlining the European principles of haemophilia care[16] to examine the extent to which the European principles of care reflect the reality of haemophilia care in participating countries. The questionnaire comprised 31 questions covering aspects of the 10 basic requirements for haemophilia care.

2.3.3   PSYCHOSOCIAL FACTORS

In patients after KT, in order to further analyse personal and social factors associated with HRQoL and patient outcomes, additional questionnaires were added to the questionnaires used in baseline assessment. Those especially include questionnaires on well-being, social support, coping efficacy and social participation. Brief information about the psychosocial measures and a short description used in this study are provided in Table 2.3. A detailed description of the measures is addressed in individual chapters of this thesis.

2.3.4   HEALTH-RELATED QUALITY OF LIFE

In KT patients, health-related quality of life was evaluated using the Short Form Health Survey (SF-36), which consists of 8 sub-scales: Physical functioning (PF), Role limitation attributable to physical problems (RP), Bodily pain (BP), Perception of general health (GH), Social functioning (SF), Vitality (VIT), Role limitation attributable to emotional problems (RE) and Mental health (MH). The first four subscales (PF, RP, BP, GH) comprise the Physical component summary (PCS), and the other four subscales (SF, VIT, RE, MH) comprise the Mental component summary (MCS).[17] 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.[24] The validity and reliability of the SF-36 have been confirmed in patients after KT.[25, 26]

   In haemophilia patients, quality of life was assessed using the EQ-5D questionnaire, a generic health-related utility value measure which has been previously used in haemophilia patients.[27] It is used to determine a utility value based on five dimensions of quality of life: Mobility, Self-care, Usual activities, Pain/discomfort and Anxiety.[18] The validity and reliability of the EQ-5D have been confirmed in patients with haemophilia.[28]

Table 2.3 Brief information about the psychosocial measures and a short description used in this study

Construct	Measure	Type of variables (Chapters)	Short description
Health-related quality of life	Short Form Health Survey (SF-36)[17]	Dependent (Chapter 3,4) Independent (Chapter 3,4,6)	Generic measure of self-reported physical and mental HRQoL (PCS and MCS)
Health-related quality of life	EuroQOL five dimensions questionnaire (EQ-5D)[18]	Dependent (Chapter 9,10)	Generic health-related utility value measure
Personality	Eysenck Personality Questionnaire Revised – Abbreviated (EPQR-A)[19]	Independent (Chapter 3)	Personality questionnaire comprising two factors: extroversion and neuroticism
Psychological distress	General Health Questionnaire-12 (GHQ-12)[20]	Independent (Chapter 3)	Screening instrument used to detect psychological distress/strain
Side-effects of immunosuppressive treatment	End-Stage Renal Disease Symptom Checklist – Transplantation Module (ESRD-SCL-TM)[11]	Dependent (Chapter 4,5,6)	Questionnaire assessing disease-specific distress, severity of perceived side-effects of the immunosuppressive treatment
Coping self-efficacy	Coping Self-Efficacy Scale (CSE)21	Dependent (Chapter 4)	Measure of self-efficacy when coping with a challenge or threat
Adherence	Collateral reports[14]	Independent (Chapter 5) Dependent (Chapter 5)	Combination of self-evaluation of adherence by the patient and an estimate of patient's adherence by his/her nephrologist
Perceived social support	Multidimensional Scale of Perceived Social Support (MSPSS)[22]	Independent (Chapter 5)	Scale assessing perceived availability and satisfaction with support perceived from family, friends or "significant other"
Social Participation	Participation Scale[23]	Independent (Chapter 6) Dependent (Chapter 6)	Scale based on the International Classification of Functioning, Disability and Health assessing perceived restrictions in social participation

2.4 STATISTICAL PROCEDURES

Several statistical methods were used in this study to analyse data and all of them were performed using the statistical software package IBM SPSS for Windows, versions 16.0, 18.0 and 20.0 (IBM company, Chicago, Illinois, USA). A detailed description of the statistical analyses used to explore the research questions are addressed in the individual chapters of this thesis.

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Part I

QUALITY OF LIFE AND PATIENT OUTCOMES IN KIDNEY TRANSPLANT RECIPIENTS

Several medical factors that have been previously linked with HRQoL have been explored in Part I of this thesis. We focused predominantly on the role of kidney function, comorbidity or perceived side-effects of immunosuppressive treatment; we explored their associations with HRQoL and long-term patient outcomes while controlling them for relevant sociodemographic and psycho-social factors.