Self-rated health and mortality after kidney transplantation

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Part I

General introduction

Chapter 1

Introduction

1.1 General introduction

This study focuses on self-rated health (SRH), morbidity and mortality in kidney transplant (KT) recipients and will try to add to and improve existing knowledge based on these domains after KT. It is important to further understand the role of SRH in improving patients' well-being, decreasing morbidity and increasing survival of KT recipients.

This first chapter mainly introduces the existing knowledge about KT, describes differences between the incidence and prevalence of chronic kidney disease (CKD) across Europe as well as in the Slovak Republic and shows the possibilities for SRH as a potential indicator of health status in transplant recipients. In line with this, the section on the research questions regarding SRH presents the reasons, such as medical factors, why SRH might be a valid indicator of worsening health in general and moreover, why SRH might be an independent predictor of mortality and graft loss in the transplant population. The section also presents the structure of this thesis.

1.2 Chronic kidney disease

Kidney transplantation

Due to its superior results in mortality, morbidity and cost utilization in comparison with dialysis, KT is the treatment method of a choice among the renal replacement therapies (RRT), such as dialysis modalities (hemodialysis - HD and peritoneal dialysis - PD) and transplantation for chronic kidney disease (CKD) in its last stage (kidney failure).[1-3] Consequently, patients are independent from any elimination method after a successful surgical procedure, though lifelong use of immunosuppressive medication is necessary to prevent immunological rejection of the transplanted graft.[4,5]

On the other hand, a transplanted kidney can fail to function after some time depending on known and/or unknown factors, which for a patient means a return to the dialysis category. Medical factors influencing the failure of a transplanted graft and/or factors connected to this failure are well known.[4-6] Graft failure after a successful surgical procedure might be defined as a decrease in the estimated glomerular filtration rate due to acute (early and late) rejection episodes, chronic renal allograft dysfunction, pyelonephritis, as well as vascular and other diseases originating from the kidney.[4,5] Furthermore, systemic comorbidities, such as cardiovascular disease, including stroke; metabolic illness, including diabetes mellitus; hypertension, liver disease and others, also help indirectly to stimulate kidney failure.[4,5] Additional complications and adverse effects of treatment, such as a calcineurin inhibitor toxicity, can be mentioned as well.[4,5]

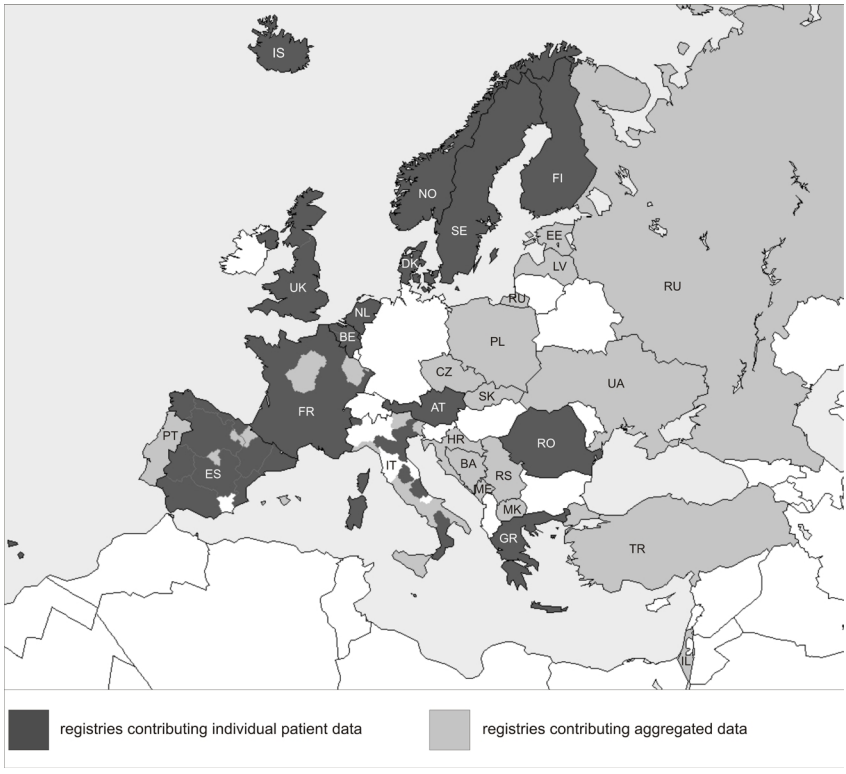
When graft failure progresses, post-transplant anemia, which is a known marker of kidney failure, is increased,[5-7] and the risk of patient mortality and morbidity becomes higher, too; the risk of graft loss might also increase. At the same time, a patient's quality of life and well-being, including SRH, decrease.

Epidemiology of chronic kidney disease

According to the European Renal Association–European Dialysis and Transplant Association (ERA–EDTA) Registry, the incidence and prevalence of CKD and its treatment modalities for the last stage (kidney failure) are known across Europe.[8-10] The process of collecting,

processing and publishing the latest annual data via national and regional renal registries takes approximately more than two years, because such data must be derived from 52 data sets from national or regional renal registries in 29 countries (Figure 1.1). Therefore, in this thesis we show the European results of RRT statistics for 2010.[8,9] The 2011 Annual Report of the Slovak Republic on CKD is also available.[11]

Figure 1.1 National and regional renal registries that contributed data to the ERA-EDTA Annual Report for 2010[8]



Data on the monitoring of pre-dialyzed patients in regard to the different stages of CKD (between CKD stages 1 and 4, including CKD stage 5 as a pre-dialyzed period) is still lacking according to the ERA–EDTA Registry; data from Slovak Registries is, however, known: as of 31 December 2010 this was 2,672.4 per hundred thousand inhabitants,[11,12] and by 31 December 2011 the overall number had increased to 2,903.8.[11,12] These data show that, while the incidence of dialysis between these two years is approximately the same, the number of patients with dialysis in the pre-dialyzed CKD stages has increased at the nephrology clinics in Slovakia.

In 2010, the overall incidence rate of RRT (including dialysis and transplant modalities) among all registries reporting to the ERA–EDTA Registry was 123 per million population (pmp) (n = 91,798), and the overall prevalence of RRT was 741 pmp (n = 551,005).[9] In contrast, the Slovak Republic Registries have no data based on the overall incidence rate of RRT and no data based on the overall prevalence rate of RRT, because these official data include dialysis patients

only. Therefore, we analyzed dialysis (HD and PD) treatment modality data and data from performed transplantations from the ERA-EDTA Annual Report and compared them with data from the Slovak Registries.

In 2010 the incidence rate of dialysis at 91 days among all registries reporting to the ERA–EDTA Registry was 82.8 pmp (n = 61,816),[8,9] while in the Slovak Annual Registries at 90 days it was 52.8 pmp (n=287) in 2010[13,14] and 52.7 pmp (n=285) in 2011.[11,12] The prevalence of dialysis among all registries reporting to the ERA–EDTA Registry was 476.0 pmp (n=355,954),[8,9] while in Slovakia this was 736 pmp (n=4001) in 2010[13,14] and increased to 749.8 pmp (n=4052) in 2011.[11,12]

The overall number of KT performed in 2010 among all registries reporting to the ERA–EDTA Registry was 29.2 pmp (n = 21,740),[8] and in Slovakia this was 28.7 pmp (n=156).[13,14] Unfortunately, this number decreased in Slovakia to 21.6 pmp (n=117) in 2011.[11,12] The number of recipients on the waiting list also decreased from 90.7 pmp (n=493) in 2010[13,14] to 88 pmp (n=478) in 2011, because of the use of more strict criteria for putting patients on the waiting list.[11,12]

Upon comparison of the most recent data among European[8] (Annual Report 2010) and Slovak[12,13] (Annual Report 2010) Registries, a nearly similar result was found regarding the overall prevalence of RRT among all registries reporting to the ERA–EDTA Registry and the dialysis prevalence evidenced by the Slovak Annual Report. Previously, the comparison was based only on the dialysis modality between the ERA-EDTA Annual Report and the Slovak Registry, with the latter showing a higher prevalence in Slovakia. On the other hand, a lower incidence was found in Slovakia. This correlates with the possible higher number of pre-emptive KT across Europe and the lower number in Slovakia, together with the number of patients on the waiting list and the overall number of KT performed in Slovakia as well. As explained earlier the Slovak Annual reports do not show evidence by the overall incidence and prevalence and total RRT.[11-14] Table 1.1 provides more detailed information on the comparison of European and Slovakia data on dialysis modality and KT in 2010.

Table 1.1 Annual data comparison (recalculated per million population) between the European and Slovakia Registry in 2010

	Dialysis Therapy		**Kidney Transplantation**	
	incidence*	prevalence	performed	waiting list
Europe	82.8	476	29.2	n.a.
Slovakia	52.8	736	28.7	90.7

**incidence at 91 days among all registries reporting to the ERA–EDTA Registry and at 90 days in the Slovak Republic*
n.a. – not available

Thus far, the results from the Slovak Registry have shown that the prevalence of pre-dialyzed and dialyzed patients increased in 2011 compared with 2010. On the other hand, the prevalence of patients on the waiting list decreased during the same period. This might be explained, for example, by the higher incidence of comorbidities in this sample together with a lower chance for a successful kidney surgical procedure due to longer time on waiting list, because 59% of such patients are, unfortunately, dialyzed longer than 2-3 years. This might be one reason why the number of transplanted recipients in 2010 was higher than in 2011, and the number of the patients on the waiting list was lower in 2011 than in 2010 upon further exclusion of these recipients from the waiting list.

1.3 Self-rated health

SRH is an umbrella term which encompasses the correlations between the understanding of physical, psychological and social domains.[15] This individual well-being has been defined in different ways over the years,[16,17] but not surprisingly, one important and unchanged element based on improving SRH together with decreasing morbidity and mortality[18,19] has remained part of it. Skills and knowledge based on the physical, psychological and social fields might improve life satisfaction in general.[16,19] These abilities should also reduce acute and/or chronic diseases, their perceptions, incidence and prevalence.[20] The question "In general, would you say your health is: a) excellent, b) very good, c) good, d) fair, e) poor." best represents the concept of SRH.[21]

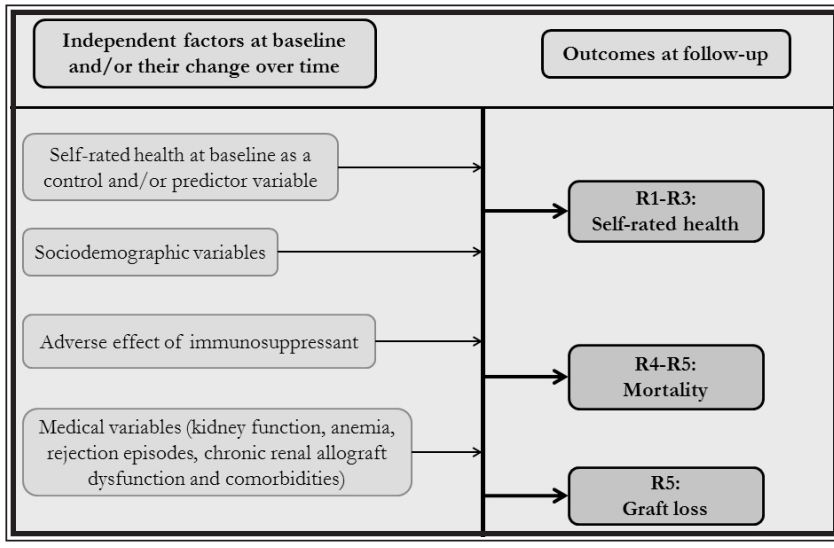
Several meta-analyses and systematic reviews in the general population have shown SRH to be an important outcome criterion alongside traditional biomarkers[22] and a predictor of future health status.[23,24] Persons with poor SRH have a higher mortality risk compared with those having excellent SRH even after controlling for a range of demographic and clinical variables.[23,25,26]

These findings have also been studied in CKD patients, including dialyzed patients[25] and transplanted recipients.[26,27] Surprisingly, the mentioned outcomes in a dialyzed population were only shown by Thong et al.[25] in 2008 when this study was already ongoing. Only one study regarding pre-transplant physical functioning as an indicator of a patient's risk for post-transplantation death had been described, by Kutner et al.[27] in 2006. No previous findings had been shown before the mentioned studies. This was the main reason why our research was oriented on SRH and tried to fill the gap between the general predictors of increased risk of mortality in the transplant population, because in the general population SRH had already been shown to be an independent predictor of mortality. Thus, SRH might be used for patients' risk stratification in adverse outcomes, because those reporting poor well-being have a significantly higher chance of mortality or being more in need of health care provisions compared with their peers.[28]

1.4 Primary aim of the study and research questions

The primary aim of this thesis is to explore the potential of self-rated health (SRH) as a general predictor of patients' and graft survival in kidney transplant recipients, because we were not aware of any other study showing that SRH was a general predictor of mortality and graft loss in the transplant population and moreover that SRH at baseline affected long-term outcomes in this population. As a first step, this study will focus on changes over time in medical and psychological factors after transplantation, and the impact of these changes on SRH at follow-up. The next part of the primary aim of this study will explore medical determinants and SRH as predictors of mortality. We will study: 1) the associations between sociodemographic, psychological and medical factors and SRH; 2) medical factors, namely anemia as predictors of mortality independent of kidney function; and 3) SRH as a predictor of graft loss and mortality in patients after KT. The basic model for SRH, graft loss and mortality prediction examined within this thesis is presented in Figure 1.2. The five research questions listed below are formulated based on the previous model.

Figure 1.2 Figure describing relationship between SRH, graft loss and mortality prediction according to the research questions (R1-R5)



Research question 1 will explore the relationship between graft function and self-rated health in patients after kidney transplantation. We will study the association of the absolute level of glomerular function and SRH at follow-up and also the impact of the change in glomerular function over time on SRH at follow-up (Chapter 3).

Research question 2 will explore changes over time in the medical and non-medical factors associated with SRH and compare their associations with SRH by time since transplantation (Chapter 4).

Anemia is recognized as an important comorbidity accompanying CKD. Therefore, **research question 3** will explore whether a change in anemia after kidney transplantation over time independently predicts self-rated health at up to 8-years follow-up according to CKD stages stratification (Chapter 5).

Research question 4 will explore whether anemia shortly after kidney transplantation predicts mortality at up to 10 years follow-up in kidney transplant recipients due to stratification of CKD stages (Chapter 6).

Research question 5 will explore whether SRH in an early period after KT predicts mortality and graft loss at up to 10 years follow-up (Chapter 7).

1.5 The structure of the thesis

This thesis is divided into 4 parts and consists of 8 chapters: Part I – General introduction (Chapters 1 and 2), Part II – Self-rated health as a health outcome (Chapters 3-5), Part III – Patient and graft mortality as a health outcome (Chapters 6-7) and Part IV – Discussion of the study findings (Chapter 8).

Chapter 1 *"Introduction"* provides information about self-rated health and chronic kidney disease with the main focus on kidney transplantation. Furthermore, a model and

5 research questions regarding self-rated health and mortality prediction are formulated.

Chapter 2 *"Data source, measures and statistical analyses"* provides information about the sample, data source, measures and statistical analyses used in chapters 3-7.

Chapter 3 *"Self-rated health after kidney transplantation and the change in graft function"* focuses on the use of change over time regarding glomerular filtration rate instead of the baseline absolute level of kidney function as a significant predictor of SRH one year after kidney transplantation, because we expect a more precise prediction of the change over time on SRH at follow-up during the observation period.

Chapter 4 *"Factors associated with self-rated health after kidney transplantation – a prospective study"* explores changes over time in medical and non-medical factors associated with SRH and compares their associations with SRH according to time since transplantation: an early (baseline at the third month and follow-up at twelfth month after transplantation) versus a late (baseline at one and follow-up at two years after transplantation) cohort. Furthermore, this chapter also evaluates and discusses the differences between outcomes in a varying period since transplantation and their significant relationship to SRH.

Chapter 5 *"Anemia has an independent negative impact on self-rated health in kidney transplant recipients with well-functioning grafts: findings from an 8-year follow-up study"* explores whether a change in hemoglobin value over time, like the known impact on anemia of renal origin, is a predictor of self-rated health at up to 8 years follow-up in patients with chronic kidney disease controlled for CKD stages.

Chapter 6 *"Anemia is an independent predictor of mortality in kidney transplant recipients: results from a 10-year follow-up study"* is also based on a stratification of the sample according to CKD stages. This study explores whether post-transplant anemia is a predictor of mortality independently of kidney function.

Chapter 7 *"Self-rated health predicts mortality and graft loss after kidney transplantation: a 10-year follow-up study"* explores whether self-rated health in an early period after transplantation is a general predictor of mortality and graft loss at up to 10 years follow-up in kidney transplanted recipients.

Chapter 8 *"Discussion"* presents the condensed outcomes of this study, discusses them in the framework of existing knowledge, argues their strengths and weakness, goes into their implications for practice and offers new possibilities for further research.

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