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Psychosocial and medical determinants of long-term patient outcomes

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Chapter 11

GENERAL DISCUSSION,
IMPLICATIONS AND CONCLUSIONS

This thesis has dealt with health-related quality of life (HRQoL), medication-related factors and patient outcomes in patients after kidney transplantation (KT) and patients with bleeding disorders. The theoretical framework of this thesis included the revised conceptual model of HRQoL by Wilson and Cleary.¹ The proposed model contained several medical and psychosocial variables which may have an influence on HRQoL and patient outcomes in both patients after KT and patients with a bleeding disorder. Our findings have improved the understanding of these domains, which are associated with health perceptions after KT and in patients with haemophilia. We showed that a) HRQoL in transplanted recipients is predicted by sociodemographic, psychological and medical determinants; b) HRQoL, adherence to an immunosuppressive regimen and restrictions in social participation are associated with long-term patient outcomes such as graft loss and mortality in patients after KT; c) prophylactic vs. on-demand treatment is associated with different levels of quality of life in adults with haemophilia; and d) disparities exist across Europe regarding access to medical care in patients with haemophilia. This chapter summarizes and discusses the main findings of our study (11.1; 11.2), examines its strengths and limitations (11.3) and finally indicates implications for practice (11.4) as well as possibilities for further research (11.5) and conclusions (11.6).

11.1 MAIN FINDINGS

Research Question 1 (Chapter 3, 4)

Are psychosocial factors, such as personality traits, psychological distress and coping efficacy, associated with HRQoL in patients after KT when controlled for relevant socioeconomic and medical factors?

We explored the impact of neuroticism, extroversion and psychological distress individually on a patient's HRQoL when controlled for mutually as well as for sociodemographic and medical variables. Higher physical HRQoL was associated with younger age, higher education and income, a low number of co-morbid diseases, lower neuroticism and distress. Higher mental HRQoL was associated with higher education and income, longer time from KT, higher extroversion, lower neuroticism and distress. In both physical and mental HRQoL, actual distress was the best predictor, even when controlled for neuroticism (Chapter 3).

We also examined the association between kidney function, side-effects of immunosuppressive treatment and coping self-efficacy and physical and mental HRQoL at 3 months after KT. Higher efficacy in stopping unpleasant emotions was associated with both higher physical and mental HRQoL at 3 months post-KT. Additionally, lower efficacy in getting support from family and friends was associated with higher mental HRQoL (Chapter 4).

Research Question 2 (Chapter 4)

Is HRQoL at 3 months after KT a significant predictor of future patient and graft survival?

In addition to exploring the association between relevant medical factors, coping self-efficacy and physical and mental HRQoL at 3 months after KT, we also addressed the impact of physical and mental HRQoL at 3 months after kidney transplantation (KT) on patient and graft survival for up to 10 years. Patients reporting higher physical and mental HRQoL at 3 months had higher odds of surviving with a functioning graft over 10 years. Higher age and better kidney function also increased the odds of survival with functioning graft (Chapter 4).

Research Question 3 (Chapter 5)

Which factors are associated with adherence in patients after KT in their first year after KT? Is the level of adherence in the first year after KT a significant predictor of future graft loss and patient mortality?

We investigated the association of sociodemographic factors, medical factors (kidney function, side-effects) and social support with different levels of adherence. Female sex, higher education, higher perceived side-effects of corticosteroids, better perceived cardiac and renal function, higher perceived family social support and lower support from significant others in the first year post-transplantation were associated with full adherence to immunosuppressive treatment. The predictive value of adherence to immunosuppressive medication in the first year after KT as a determinant of graft loss and mortality up to 12 years was also explored. Poor adherence to the immunosuppressive medication in the first year after KT increased the likelihood of graft loss and death over 12 years compared with adherent patients (Chapter 5).

Research Question 4 (Chapter 6)

Is the level of social participation in patients after KT associated with their HRQoL as well as with socioeconomic and medical factors? Is social participation a significant predictor of future graft loss and patient mortality?

We explored the association between physical and mental HRQoL and relevant post-KT factors, such as kidney function, side-effects of immunosuppressive treatment, comorbidity and social participation (SP). Restrictions in SP were associated with living alone, worse kidney function, more severe side-effects of immunosuppressive treatment and lower physical HRQoL. Furthermore, we explored the impact of SP when controlled for relevant sociodemo-

graphic and medical factors at baseline on future graft loss and mortality for up to 10 years. Restrictions in SP at baseline were associated with increased risk of graft loss or mortality at follow-up, along with lower education, worse kidney function and a higher number of comorbidities (Chapter 6).

Research Question 5 (Chapters 7, 8)

What is the level of access to patient care and services outlined in the European principles of haemophilia care in Europe?

We surveyed 19 national haemophilia patient organisations in Europe about the organisation of haemophilia care and treatment modalities available at the national level. The responses received highlighted differences in the level of care. There was a wide range in factor VIII consumption, and in some Eastern European countries cryoprecipitate is still used (Chapter 7).

Additionally, we conducted a survey of 35 national haemophilia patient organisations in Europe about the level of access to patient care and services at the national level as outlined in the European principles of haemophilia care in Europe. Again, the responses received highlighted major differences in the availability of treatment and care. There was a wide range in factor VIII consumption, with usage ranging from 0.20 IU/capita in Armenia to 8.56 IU/capita in Sweden (median: 3.59 IU/capita). The decrease in health budgets in many countries was not matched by decreases in the use of FVIII per capita. In the 19 countries which responded to the previous survey, there was a significant improvement in access to prophylaxis and home treatment (Chapter 8).

Research Question 6 (Chapters 9, 10)

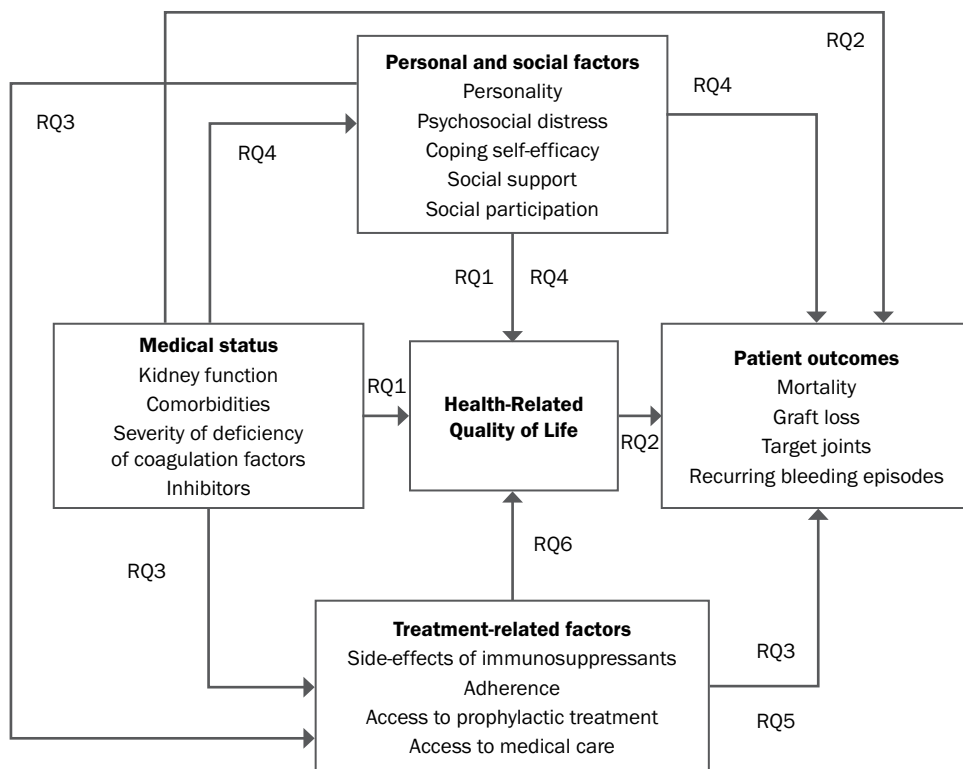
Do differences in medical outcomes and quality of life exist in adult haemophilia patients depending on their level of access to prophylactic treatment throughout childhood?

We analysed among four and six countries the long-term effects of prophylaxis and the continuing benefit of this treatment into adulthood as opposed to the change to on-demand once adult or lifelong on-demand protocol. Long-term prophylaxis was associated with a lower the presence of target joints, the occurrence of serious bleeding episodes, recurring bleeding episodes, the requirement for surgical procedures and less time missed at work. Prophylaxis increased mobility and the ability to do everyday activities and improved the HRQoL of people with severe haemophilia. Health care utility in patients with on-demand therapy was significantly lower than other groups who spent at minimum 50% of their life on prophylaxis (Chapters 9, 10).

11.2 DISCUSSION OF MAIN FINDINGS

The main focus of this thesis was to explore the associations between HRQoL, medication-related factors and patient outcomes in two samples – patients after KT and patients with bleeding disorders. Our findings can be integrated into the model which was proposed in Chapter 1 (Figure 11.1). Based on the research questions, the main findings are grouped into two topics, which structure this discussion. The first topic concerns HRQoL and long-term outcomes in patients after KT (RQ1-4). The second topic is dedicated to the level of haemophilia care in the EU and its association with patient outcomes and their HRQoL (RQ5-6).

Figure 12.1 Model of the relationships of the key constructs examined in this thesis



11.2.1 HRQoL and long-term outcomes in patients after KT

An effect of HRQoL on long-term outcomes has been suggested by previous cross-sectional studies.²⁻⁵ Our study, however, confirms that physical and mental HRQoL already at 3 months post-KT is a reliable independent indicator of survival with a functioning graft over 10 years.

According to Griva et al. (2013), a substantial proportion of KT recipients report impaired physical HRQoL in spite of being leaner, younger and mostly non-diabetic. These impairments are an independent risk factor for poor outcomes over 12 years.⁵ In line with their findings, our results indicate that HRQoL assessment early after KT might provide additional information regarding patient outcomes and disease course that is not captured by traditional indices of clinical status, independently of demographic, socioeconomic and clinical risk factors.⁶ Regular assessment of HRQoL in a clinical setting may help to identify high-risk patients who may benefit from increased attention.

MEDICAL DETERMINANTS OF HRQoL AND LONG-TERM OUTCOMES IN PATIENTS AFTER KT

Several medical factors that have been previously linked with HRQoL⁷ have been explored in this thesis. Our study focused predominantly on the role of kidney function, comorbidity or perceived side-effects of immunosuppressive treatment; however, we explored their associations with HRQoL while controlling them for relevant sociodemographic and psychosocial factors.

Kidney function, in contrast to previous findings^{6, 8-11}, was not associated with HRQoL in either study from Chapter 3 or Chapter 4, although it was confirmed as a significant predictor of long-term patient outcomes. Legendre et al. (2014) found that in stable KT recipients a lower estimated glomerular filtration rate is independently associated with cardiovascular events¹², which may also influence survival.¹³ Further prospective studies need to explore cardiovascular comorbidity and other potential cofounders that may influence the overall estimated glomerular filtration rate, HRQoL and survival.

Comorbidity, on the other hand, was found to be significantly associated with physical HRQoL as well as with future mortality, in line with previous findings.¹⁴⁻¹⁶ According to Ojo et al. (2013), comorbidities and their management in each country's health system are a possible explanation for the differences in long-term mortality rates, which vary hugely between different countries.¹⁷

Special attention was paid to the role of perceived side-effects of immunosuppressive treatment. Modern immunosuppression methods have decreased the incidence of acute rejection episodes in the first months post-KT; however, this has not resulted in significant improvements over the long term.¹⁸ Legendre et al. (2014) suggest that in the long term, the role of a specific drug is minimal and that although immunosuppressive drugs play an important beneficial role in preventing rejection, they also play a deleterious role because of their side-effects.¹² Higher levels of perceived side-effects were previously linked with lower perceived HRQoL¹⁹⁻²² as well as with poor adherence.²³⁻²⁵ We also showed that side-effects played an important role in HRQoL at 3 months after KT and in adherence to immunosuppressive treatment during the first year post-transplant as well as in restrictions of social participation 3 months – 6 years post-transplant. 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 physical and mental HRQoL, adherence and social participation, and it is possible that they thereby had an indirect effect on survival. Although the effects of adverse effects of immunosuppressive treatment on HRQoL depend on the type of immunosuppressive used^{9, 26-28}, they tend to worsen over time.²⁹ In spite of this phenomenon, long-term kidney transplant recipients experience levels of perceived health similar to the short term, despite more symptoms and comorbidities.³⁰ Our findings underline the need for ongoing screening for adverse effects in patients after KT, due to their paramount effect on the life of patients after KT. As Peters et al. pointed out in their study, due to the big gap between the levels of side-effects reported by the patient versus those observed by physicians³¹, it is important to increase awareness of the impact of physical side effects from the patient's perspective in order to improve overall HRQoL, adherence and social participation. Adequate management of symptoms and interventions to prevent comorbidity could prove useful to increase the long-term perceived health of KT recipients.

Finally, our study explored the effect of adherence on future patient outcomes, such as mortality and graft loss over 12 years. In line with previous findings³²⁻³⁶, poor adherence predicted worse outcomes: patients who admitted or were considered as delaying, skipping or altering their medication twice a month in the first year after kidney transplantation were more likely to lose their graft or to die during the follow-up. However, subclinical non-adherence (delaying, skipping or altering their medication once a month) did not predict either graft loss or mortality. Israni et al. (2011) found that non-adherence with a single immunosuppressive medication was not associated with a decline in eGFR.³⁷ Massey et al. (2013) found an increase in self-reported non-adherence from 17% to 27% in the period from 6 weeks to in 6 months post-transplant. The importance of adherence and the necessity of immunosuppressive medication significantly decreased over time, and an increase in perceived graft longevity was related to a higher likelihood of non-adherence.³⁸ It is therefore possible that patients who only occasionally broke their regimen did not increase their non-adherence as rapidly and therefore avoided affecting their long-term outcomes as those who behaved non-adherently every second week in their first year after KT.

PSYCHOSOCIAL DETERMINANTS OF HRQOL AND LONG-TERM OUTCOMES IN PATIENTS AFTER KT

This thesis also explored the psychosocial determinants of HRQoL and the long-term outcomes in patients after KT, such as personality traits, psychological distress, self-efficacy and social participation. According to Goetzmann et al. (2008) the experience of the transplant process may vary greatly from patient to patient, and a considerable number of transplant recipients require psychosocial support, despite the majority of patients showing an unquestionable

post-transplant improvement in psychosocial well-being.³⁹ Our results indicated the superior effect of psychosocial distress over personality, similar to other studies^{40, 41}, such as the one performed by Schulz et al. (2012), who found that personal characteristics act as a mediator between psychological distress and objective health.⁴² He also suggests that poor health and poor subjective interpretations of health in turn cause psychological distress by increasing coping demands while simultaneously decreasing coping resources. KT-specific distress, such as worry about the transplant, was previously confirmed to explain mental and physical HRQoL variance.⁴³ In line with this, we also found that higher efficacy in stopping unpleasant emotions was associated with both higher physical and mental HRQoL at 3 months post-KT, similar to findings in other chronic disease patients.⁴⁴ Self-efficacy was found to enhance self-care and thereby also HRQoL.⁴⁵ This could explain why lower efficacy in getting support from family and friends was associated with higher mental HRQoL – the ability to maintain a certain level of independence and self-management could be more beneficial for one's HRQoL than the ability to find support among peers.

When it comes to social participation, most previous studies concern employment status; however, it is important to also consider other aspects of social participation outlined by the ICF framework.⁴⁶ In line with previous findings⁴⁷⁻⁵⁰, our study has confirmed the association of social participation and physical HRQoL. A study conducted in the USA found that when KT recipients bear the label of disabled, regardless if the disability is real or perceived, they are less likely to participate in work and social activities. The author suggests that given the magnitude of influence of perceived disability, it is conceivable that its presence or absence should be the newest metric for success or failure of KT.⁵¹ In our sample, restrictions in social participation were also linked to future graft loss and mortality. To the best of our knowledge, similar findings have not yet been published.

11.2.2 LEVEL OF HAEMOPHILIA CARE IN EU, PATIENT OUTCOMES AND THEIR HRQOL

As the management of haemophilia is complex, it is essential that those with the disorder should have ready access to a range of services provided by a multidisciplinary team of specialists.⁵² The management of haemophilia should not be based solely on achieving access to better treatment with safe factor concentrates; it should also include providing specialized comprehensive care by a multidisciplinary team of specialists trained in haemophilia management.⁵³ Our studies highlighted differences across all levels of care, from home treatment to access to specialist care, despite the recent promulgation of consensus guidelines designed to standardize the care for haemophilia throughout the European continent. Similar findings were later confirmed by Fischer et

al. (2013), who found that the principles of haemophilia care were generally applied throughout 14 European countries; however, some aspects of centralisation, national organisation of care, use of registries, formal paediatric care and prophylaxis for adults may be improved. This study, however, only included developed countries.⁵⁴

Based on the information obtained from the National Member Organisations of the World Federation of Haemophilia, we explored what is established as modern haemophilia care – recombinant home treatment^{55, 56} – was still inaccessible in a number of Eastern European countries, and some countries resort to the use of cryoprecipitate. Our study is in line with findings of Schramm et al. (2012), who found that access of European patients with haemophilia to optimal care with safe factor VIII concentrates is limited and depends on the region of residence.⁵⁷ The same applied for prophylaxis, due to its increased cost – in 5 countries no prophylaxis was available for adults or even for children. The follow-up study revealed a significant improvement in access to prophylaxis and home treatment in the 19 countries that responded to the previous survey.

The superior effect of prophylaxis as opposed to on-demand treatment due to its health and social benefits, such as decreased number of bleeds or ability to work, has been previously established.^{58–60} Accordingly, long-term prophylaxis resulted in a lower presence of target joints, occurrence of serious bleeding episodes, recurring bleeding episodes and requirement for surgical procedures. New studies confirm our results, finding that prophylaxis started early and continuing throughout the lifespan has been successful in eliminating joint bleeds, preserving a nearly normal joint status⁶¹ and that on-demand therapy is not effective in preventing the development of haemophilic arthropathy in a severe haemophilic population.⁶² In a paired-sample study, Ingerslev et al. (2014) confirmed that long-term prophylactic factor administration during childhood and adolescents prevents joint destruction, and that these patients also report lower pain, better HRQoL and functional independence.⁶³

The results also demonstrated consistently higher HRQoL in individuals who were on long-term prophylactic treatment when compared with on-demand treatment or intermittent prophylaxis and on-demand treatment, in line with previous literature.^{64–66} Since then, Aznar et al. (2014) have conducted a study exploring the effects of secondary prophylaxis in adults with severe haemophilia and its effect on their QoL, musculoskeletal assessment and haemarthrosis.⁶² They found significant improvements in all three factors over a 12-month period with only a small increase in factor use.⁶² Our results show that on-demand treatment results in more bleeding, more damage to joints, more time missed at work and worse HRQoL, but secondary prophylaxis may prevent further issues without dramatically increasing health care costs themselves, refraining from the gains mentioned before.

11.3 STRENGTHS AND LIMITATIONS OF THE STUDY

The strength of this thesis is its combination of cross-sectional and longitudinal design in two groups of chronic disease patients. The KT study was performed with up to 11 years of follow-up, which enabled us to explore the impact of medical and psychological factors on long-term patient outcomes. Therefore, the impact of our findings has a greater informative value in Chapter 4 and 5 because of the uniformity of post-transplant time at baseline assessment. During the observation period the average number of patients undergoing KT at the Louis Pasteur University Hospital Transplantation centre in Kosice, Slovakia, was 31.4 per year – or about one quarter of all KT carried out in Slovakia. Therefore, our cohort explained a relevant number of national transplant 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 centre, and the sample consisted of rather younger and predominantly white Caucasian patients; therefore, our findings cannot be generalized without further consideration. However, we used consecutive patients without selection. Similarly, we have limited information on patients who dropped out prior to the start of this study due to graft loss or mortality or on those who provided incomplete data at baseline. In kidney transplant recipients, the initial assessment was not conducted immediately after transplantation to prevent false findings due to perioperative stress, complications and subjective anticipation or suspense. Therefore, patients who died or lost their transplanted kidney before the first 3 months after KT were not incorporated into the study.

The haemophilia study included data from over 36 countries with varying level of access to haemophilia treatment, thus enabling a better understanding of the effects of long-term prophylaxis on the individual and national level. All surveys were conducted through the National Member Organisations and self-reported, so respondents may have some recall bias. The sample in Chapters 9 and 10 was defined by only two criteria – age and severity of the haemophilia – and future studies should also consider alternative factors, such as comorbidities. Also, there were concerns regarding the use of EQ-5D, since it may not adequately describe the health of people with disabilities. The UK-specific EQ-5D value set was used due to unavailability of value sets specific for other participating countries. However, as the EQ-5D is the preferred utility measurement questionnaire for agencies carrying out Health Technology Assessments (HTA), such as the National Institute for Clinical Excellence (NICE, UK) and the Scottish Medicines Consortium (SMC, Scotland), it was considered an adequate tool to utilise in terms of health utilities and quality of life. Finally, for both studies it is important to stress that as these were observational studies; causal associations between predictors and outcomes cannot be definitely confirmed.

11.4 PRACTICE IMPLICATIONS

KIDNEY TRANSPLANT RECIPIENTS

Due to extensive research in the area of KT, the long-term outcomes across all age groups have vastly improved over the last two decades. In spite of this progress, successful KT is still associated with a relatively high rate of long-term mortality, which may be explained by pre- and post-transplant medical care.¹⁷ Our study indicates that in order to keep on improving HRQoL and both graft and patient survival, adequate management of symptoms and interventions to prevent comorbidity could prove useful to increase long-term perceived health of kidney transplant recipients. Regular assessment of HRQoL in the clinical setting may help to identify high-risk patients who might benefit from the increased attention, and HRQoL may also be a reliable indicator of future patient outcomes.

HRQoL was found, in line with previous findings⁴⁹, to be strongly associated with personal and environmental factors, such as psychological distress, coping efficacy, social participation or social support. Psychological distress was associated with poorer HRQoL, and other studies have shown that certain types of distress⁴⁰, such as depression, were very commonly found in patients living alone.⁶⁷⁻⁷¹ Our study also revealed the inverse relationship between social support and non-adherence as well as the impact of restrictions in social participation on graft loss and mortality. A multidisciplinary team should strive to be familiar with indicators of depression or lack of supportive network, to be able to recognize these indicators in their patients and to provide them with instrumental and emotional support in dealing with these issues.

Similarly, alternative ways to improve HRQoL and long-term patient outcomes, such as intervention programmes, should be explored. In patients awaiting KT, certain types of cognitive-behaviour therapy, such as the quality of life therapy, was found to be effective in improving overall quality of life⁷² and therefore it could also be adapted for patients after KT. Alternatively, a multi-disciplinary team could assist their patients in improving their future HRQoL by providing intervention programmes focused on dealing with depression and anxiety by providing patients with alternative coping strategies and with peer support from other patients experiencing a similar situation.

PATIENTS WITH HAEMOPHILIA

As a rare, hereditary lifelong condition, haemophilia can be successfully treated to lengthen lifespan and to increase the ability of these patients to contribute to society, if an appropriate level of care is provided. The findings from this study can and should be used by national member organisations in collaboration with their haemophilia clinicians to advocate for improving care in their specific country where deficiencies have been identified. In most countries, the life expectancy of

persons with haemophilia has increased over the recent years due to safe and largely available replacement therapy, and therefore also the incidence of age-related comorbidities.⁷³ Already there has been an indication that ageing males with haemophilia have concerns about the health care system and its ability to respond to the need of the ageing patients with haemophilia.⁷⁴ We would therefore suggest not only continuing with the implementation of the principles of haemophilia care but also their regular updating in order to ensure the best care for the entire haemophilia cohort. Our findings, along with previous studies, also stress the need for continuous monitoring of HRQoL and its determinants to identify an increased need of care in the haemophilia population.⁷⁵ Specific attention should be paid to any psychosocial distress and symptoms of depression, which have been shown to have a stronger effect on overall HRQoL in persons with haemophilia than their physical health.⁷⁶

Finally, in order to ensure the best outcomes, assessment of adherence should become a routine part of hospital appointments. Previous studies indicate that when there is any change in a treatment regimen, such as moving from being infused by a parent to self-infusion or from prophylaxis to on-demand, adherence may be compromised.⁶⁶ Better adherence was found in persons with longer exposure to prophylaxis⁷⁷, indicating that continuous education and health promotion play an important role in maintaining adherence.

To reach these objectives, it is essential to have the participation of the patient and family members and to strive for the financial and legislative support from the government in order to improve the HRQoL for the community of patients with haemophilia.

11.5 IMPLICATIONS FOR FUTURE RESEARCH

IN KIDNEY TRANSPLANT RECIPIENTS

Based on our findings on the association between medical and psychosocial factors, HRQoL and patient outcomes in a prospective observation design from a single centre cohort study, we suggest extending this research to all four transplant centres in the Slovak Republic and if possible also involving international cooperation. A robust study obtaining a larger sample of KT patients in a longitudinal design would enable the modelling of causal pathways between the factors outlined in this thesis, such as side-effects, HRQoL, adherence and patient outcomes, as well as additional clinical indicators, such as factors of the donor, pre-transplant period or early post-transplant recovery. Secondly, the effectiveness of intervention programmes focused on improving HRQoL should be explored. Our findings indicate that certain factors, such as psychological distress, self-efficacy or social participation, may affect patients' HRQoL and thereby also their long-term outcomes; however, these pathways need to be verified.

IN HAEMOPHILIA PATIENTS

Future research should verify our findings using a more robust methodology. It would be instructive to extend the survey to even more countries, especially those which use low levels of FVIII per capita, in order to assess what may well be, in effect, a baseline utility figure. A longitudinal design should be implemented in order to allow for a more extensive analysis of factors impacting patient outcomes and HRQoL. Similarly, future studies should also include the aging haemophilia population and explore the effect of comprehensive care and access to prophylactic treatment on patient outcomes over an even longer period of time. The prosperity of a country and the amount of money it spends on its health care system should play a role in such studies.

Additional data, such as social participation, assessment of adherence or psychosocial variables, should be collected to allow the interpretation in a broader context. The literature relating to psychosocial issues in persons with haemophilia is extremely heterogeneous.⁷⁸ There is a need for more robust research to explore the social and psychological aspects of life with haemophilia, such as depression, coping and social support. The assessment of social participation, currently involving predominantly the ability to work, a perspective which should be broadened, should expand to include all factors outlined by the ICF framework. Finally, more research on health promotion and behaviour change is needed to develop more effective intervention strategies to promote continued prophylaxis in adolescents and young adults.

11.6 CONCLUSION

This thesis analysed the sociodemographic, psychological and medical determinants of HRQoL as well as the effect of adherence to the immunosuppressive regimen and restrictions in social participation in patients after kidney transplantation and in patients with haemophilia. We found that they were associated with long-term patient outcomes such as graft loss and mortality in kidney transplant recipients. A number of medical factors were identified as being associated with HRQoL, such as kidney function, comorbidities, or side-effects of immunosuppressive treatment, along with psychosocial variables, such as personality, distress and coping efficacy. HRQoL 3 months after KT was established as a significant predictor of patient and graft survival over 10 years' time. Poor adherence to immunosuppressive treatment in the first year post-transplant and restrictions in social participation, on the other hand, increased the risk of graft loss and mortality over 12 and 10 years, respectively.

We also found that prophylactic vs. on-demand treatment was significantly associated with a different number of bleeds, joint damage, social participation and quality of life in adults with haemophilia in Europe and Canada. When analysing the level of implementation of European prin-

ciples of haemophilia care across Europe, we found large disparities in access to treatment and medical care in patients with haemophilia. There has been improvement in this area, however, in a number of countries, which is mostly due to the involvement of National patient organisations advocating in the interest of their members.

Our study indicates that in order to keep on improving long-term patient outcomes, adequate access to medical care, including management of symptoms and interventions to prevent comorbidity, could be useful to increase long-term perceived health of chronic disease patients. Regular assessment of HRQoL in a clinical setting may help to identify high-risk patients who may benefit from the increased attention and act as a reliable indicator of future patient outcomes. In addition, such assessment should be integrated into research as a component of the evidence required to justify the high costs of lifelong therapy. Aside from striving to improve HRQoL and long-term patient outcomes by managing clinical indicators, such as comorbidity and side-effects, complementary programmes and services to enhance long-term outcomes should be explored. This would include ongoing education on adherence and training programmes designed to enhance different ways of coping with distress. To reach these objectives, it is essential to involve the community of patients and family members and their medical team and to strive for financial and legislative support from the government.

Future research should explore the causal pathways between the factors outlined in this thesis, such as side-effects, access to treatment, HRQoL, adherence and patient outcomes, as well as additional clinical indicators. In addition, the effectiveness of intervention programmes focused on improving HRQoL should be explored. The findings presented in this thesis need to be verified and further developed in more robust research, including transnational studies and those with a longitudinal design.

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Summary

From the time of diagnosis, patients with a chronic condition have to deal with the many consequences of their illness and have to adapt to a new lifestyle and to changes in their health-related quality of life (HRQoL). This is particularly difficult in patients for whom the most effective treatment is associated with significant side effects, such as immunosuppressive treatment in patients after kidney transplantation (KT), or for whom treatment is not always available, such as prophylactic treatment in patients with haemophilia.

The aim of this thesis was to explore the associations between HRQoL, medication-related factors and patient outcomes in these two chronic disease groups – patients after KT and patients with bleeding disorders. Additionally, we explored specific issues in each group: psychosocial factors determining HRQoL, adherence to immunosuppressive treatment and social participation in patients after KT, and access to treatment and medical services in patients with haemophilia throughout Europe.

Chapter 1 provides a general introduction to quality of life, factors associated with treatment and quality of life in patients after KT and in patients with a bleeding disorder. Furthermore, a model and 6 research questions regarding quality of life, treatment factors and patient outcomes are formulated.

Chapter 2 provides information about the design of the study. It provides information about the samples, data sources, measures and statistical analyses used in this thesis.

Chapter 3 explores the associations between personality traits (neuroticism, extroversion), the level of psychological distress and HRQoL in patients after KT, when controlled for mutually and when controlled for sociodemographic and medical variables. Higher physical HRQoL was associated with younger age, higher education and income, a low number of comorbid diseases, lower neuroticism and distress. Higher mental HRQoL was associated with higher education and income, longer time from KT, higher extroversion, lower neuroticism and distress. In both physical and mental HRQoL, actual distress was the best predictor, even when controlled for neuroticism.

Chapter 4 examines how HRQoL reflects the coping efficacy and side-effects of immunosuppressive treatment as well as the ability to predict long-term patient and graft survival based on the HRQoL of patients at baseline. Higher efficacy in stopping unpleasant emotions was associated with both higher physical and mental HRQoL at baseline. Additionally, lower efficacy in getting support from family and friends was associated with higher mental HRQoL. Regarding the impact of physical and mental HRQoL at baseline on patient and graft survival for up to 10 years, patients reporting higher physical and mental HRQoL at baseline had higher odds of surviving with a functioning graft over 10 years, as did higher age and better kidney function.

Chapter 5 investigates the association between sociodemographic factors, medical factors (kidney function, side-effects) and social support and different levels of adherence. Female sex, higher education, higher perceived side-effects of corticosteroids, better perceived cardiac and

renal function, higher perceived family social support and lower support from significant others in the first year post-transplantation were associated with full adherence to immunosuppressive treatment. The predictive value of adherence to immunosuppressive medication in the first year after KT as a determinant of graft loss and mortality up to 12 years was also explored. Poor adherence to immunosuppressive medication in the first year after KT increased the likelihood of graft loss and mortality over 12 years compared with adherent patients.

Chapter 6 analyses the association between physical and mental HRQoL and relevant post-KT factors such as kidney function, side-effects of immunosuppressive treatment, comorbidity and social participation (SP). Restrictions in SP were associated with living alone, worse kidney function, more severe side-effects of immunosuppressive treatment and lower physical HRQoL. Furthermore, we explored the impact of SP on future graft loss and mortality for up to 10 years when controlled for relevant sociodemographic and medical factors at baseline. Restrictions in SP at baseline were associated with an increased risk of graft loss and mortality at follow-up, along with lower education, worse kidney function and a higher number of comorbidities.

Chapter 7 comprises information about the organisation of haemophilia care and treatment available at a national level in 19 European countries, with a specific focus on consensus guidelines designed to standardise the care of haemophilia throughout Europe. The received responses highlighted differences in the level of care. There was a wide range in factor VIII consumption, and in some Eastern European countries cryoprecipitate is still used.

Chapter 8 provides information about the organisation of haemophilia care and treatment available at the national level in 35 European countries and its main objective is to identify differences in the availability of treatment and care. Similar to Chapter 7, the responses highlighted major differences in the availability of treatment and care. There was a wide range in factor VIII consumption, with usage ranging from 0.10 IU/capita in Armenia to 8.56 IU/capita in Sweden (median: 3.59 IU/capita). The decrease in health budgets in many countries was not matched by decreases in the use of FVIII per capita. In the 19 countries which responded to the previous survey, there was a significant improvement in access to prophylaxis and home treatment.

Chapter 9 presents information about the organisation of haemophilia care and treatment available at the national level of four countries. The differences in quality of life, level of treatment and implications for national health care are also explored. Long-term prophylaxis was associated with a lower presence of target joints, the occurrence of serious bleeding episodes, recurring bleeding episodes, the requirement of surgical procedures and less time missed at work. Prophylaxis increased mobility and the ability to do everyday activities and improved the HRQoL of people with severe haemophilia. Health care utility in patients with on-demand therapy was significantly lower than other groups who spent a minimum of 50% of their life on prophylaxis.

Chapter 10 presents information about the organisation of haemophilia care and treatment available at the national level of six countries. This study shows that the benefit of prophylaxis continued into adulthood significantly increases HRQoL. On-demand treatment results in a lower utility value in relation to quality of life for people with severe haemophilia. Prophylaxis started at an early age and continued into adulthood results in less bleeding, less damage to joints and less time missed at work. Prophylaxis increases mobility and the ability to do everyday activities and improves the health-related quality of life of people with severe haemophilia.

Finally, *Chapter 11* 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.

In KT recipients, a number of medical factors were identified to be associated with HRQoL, such as kidney function, comorbidities or side-effects of immunosuppressive treatment, along with psychosocial variables, such as personality, distress and coping efficacy. HRQoL at baseline was established as a significant predictor of patient and graft survival over 10 years' time. On the other hand, poor adherence to immunosuppressive treatment in the first year post-transplant and restrictions in social participation increased the risk of graft loss and mortality over 12 and 10 years, respectively.

In patients with haemophilia, prophylactic vs. on-demand treatment were significantly associated with a different number of bleeds, joint damage, social participation and quality of life in adults in Europe and Canada. When analysing the level of implementation of European principles of haemophilia care across Europe, we found large disparities in access to treatment and medical care in patients with haemophilia. There has been, however, improvement in this area in a number of countries, which is mostly due to the involvement of national patient organisations advocating for the interest of their members.

The findings of this thesis indicate that in order to improve long-term outcomes, adequate access to medical care, including management of symptoms and interventions to prevent comorbidity, could be useful to increase long-term the perceived health of chronic disease patients. Regular assessment of HRQoL in a clinical setting may help to identify high-risk patients who may benefit from the increased attention, as HRQoL may act as an indicator of their future outcomes. Potential benefits of complementary programmes, such as education programmes on adherence or training programmes designed to enhance coping strategies, should be also explored. Finally, in order to reach these objectives, it is essential to involve the community of patients and family members and their medical team as well as to strive for the financial and legislative support from the government.

More robust and transnational research is needed to explore the underlying mechanisms between

the factors outlined in this thesis, such as side-effects, access to treatment, HRQoL, adherence and patient outcomes, as well as additional clinical indicators. In addition, the effectiveness of intervention programmes focused on improving HRQoL should be explored.

Zhrnutie

Od momentu stanovenia diagnózy sa jednotlivci s chronickým ochorením musia vysporiadať s mnohými dôsledkami ich ochorenia, prispôbiť sa novému životnému štýlu a zmenám v ich so zdravím súvisiacou kvalitou života (ZSKŽ). To je obzvlášť náročné, ak je najúčinnější liečba spojená s výraznými vedľajšími účinkami ako v prípade imunosupresívnej liečby u pacientov po transplantácii obličky (TO) alebo nie je vždy k dispozícii ako v prípade profylaktickej liečby pacientov s hemofíliou.

Cieľom tejto práce bolo preskúmať vzťah medzi ZSKŽ, faktormi spojenými s liečbou a dlhodobými výsledkami v dvoch skupinách pacientov s rozdielnymi chronickými ochoreniami – pacienti po TO a pacienti s poruchou zrážanlivosti krvi. Taktiež sme sa zaoberali konkrétnymi problémami v každej skupine: v skupine pacientov po TO sme zisťovali psychosociálne faktory podmieňujúce ZSKŽ, dodržiavanie imunosupresívnej liečby a sociálnu participáciu jednotlivcov; na druhej strane u pacientov s hemofíliou sme skúmali prístup k liečbe a zdravotným službám v rámci Európy.

Prvá kapitola poskytuje všeobecný úvod do kvality života a popisuje faktory spojené s liečbou a kvalitou života u pacientov po TO a s hemofíliou. Súčasne táto kapitola predstavuje teoretický model a 6 výskumných otázok týkajúcich sa ZSKŽ, faktorov liečby a dlhodobých výsledkov pacientov.

Druhá kapitola podáva informácie o dizajne štúdie, skúmanej vzorke respondentov, použitých dátach, metodikách a štatistických analýzach aplikovaných v tejto práci.

Tretia kapitola sa zaoberá vzťahmi medzi osobnostnými rysmi (neuroticismus, extroverzia), úrovňou psychického distresu a ZSKŽ pacientov po TO, kontrolovaných vzájomne ako aj sociodemografickými a medicínskymi premennými. Vyššia telesná ZSKŽ bola spojená s mladším vekom, vyšším vzdelaním a príjmom, nižším počtom komorbídít, nižším neuroticismom a distresom. Vyššia duševná ZSKŽ bola spojená s vyšším vzdelaním a príjmom, dlhším časom po TO, vyššou extroverziou, nižším neuroticismom a distresom. Distres sa ukázal ako najlepší prediktor fyzických a súčasne aj duševných ZSKŽ, a to aj keď bol kontrolovaný pre neuroticizmus.

Štvrtá kapitola skúma, ako ZSKŽ odráža účinnosť zvládania a vedľajšie účinky imunosupresívnej liečby, rovnako ako schopnosť predpovedať dlhodobé prežitie štepu a pacienta na základe ZSKŽ pacientov tri mesiace po TO. Vyššia účinnosť potlačiť nepríjemné emócie bola spojená ako s vyššou fyzickou a psychickou ZSKŽ tri mesiace po TO. Navyše nižšia schopnosť získavať podporu od rodiny a priateľov bola spojená s vyššou psychickou ZSKŽ. Vyšší vek, lepšia funkcia štepu a vyššia fyzická a psychická ZSKŽ tri mesiace po TO zároveň zvýšili pravdepodobnosť prežitia s funkčnou obličkou v priebehu nasledujúcich desiatich rokov.

Piata kapitola sa zaoberá vzťahom medzi sociodemografickými faktormi, medicínskymi faktormi (funkcia štepu, nežiaduce účinky), sociálnou oporou a úrovňou dodržiavania predpísanej liečby. Ženské pohlavie, vyššie vzdelanie, subjektívne viac vnímané nežiaduce účinky imunosupresív, subjektívne lepšia funkcia srdca a obličiek, vyššia sociálna opora od rodiny a nižšia opora od signifikantnej osobz v prvom roku po transplantácii boli spojené s plným dodržiavím imunosu-

presívnej liečby. Navyše, nedostatočné dodržiavanie imunosupresívnej liečby v prvom roku po TO signifikantne zvýšilo pravdepodobnosť straty štetu a úmrtia v priebehu nasledujúcich dvanástich rokov v porovnaní s pacientami, ktorí plne dodržiavali liečbu.

Šiesta kapitola analyzuje vzťah medzi fyzickou a duševnou ZSKŽ, sociálnou participáciou (SP), subjektívnymi a objektívnymi ukazovateľmi po TO, ktorými boli vedľajšie účinky imunosupresívnej liečby, funkcia štetu, a komorbidity. Obmedzenia v SP boli spojené so životom osamote, horšou funkciou štetu, vážnejšími vedľajšími účinkami imunosupresívnej liečby a horšou fyzickou ZSKŽ. Obmedzenia v SP, nižšie vzdelanie, horšia funkcia štetu a väčší počet komorbidít boli súčasne asociované so zvýšeným rizikom straty štetu a úmrtnosťou v priebehu nasledujúcich desiatich rokov.

Siedma kapitola obsahuje informácie o organizácii starostlivosti a dostupnosti liečby pre pacientov s hemofíliou v devätnástich Európskych krajinách, s osobitným zameraním na dodržiavanie smerníc o štandardizácii hemofilickej starostlivosti v celej Európe. Výsledky prieskumu zvýraznili rozdiely v úrovni starostlivosti, v spotrebe faktora VIII (FVIII) a taktiež trvalé používanie kryoprecipitátu v niektorých východoeurópskych krajinách.

Ôsma kapitola skúma dostupnosť liečby a organizáciu starostlivosti u pacientov trpiacich hemofíliou v tridsiatich piatich Európskych krajinách s hlavným cieľom identifikovať ich odlišnosti. Podobne ako v siedmej kapitole, výsledky preukázali významné rozdiely v dostupnosti liečby a starostlivosti, ako napríklad v spotrebe FVIII, s rozmedzím od 0.10 IU na obyvateľa v Arménsku do 8.56 IU na obyvateľa vo Švédsku (medián: 3.59 IU na obyvateľa). V mnohých krajinách zníženie rozpočtu pre zdravotníctvo nekorešpondovalo s poklesom v užívaní FVIII. V devätnástich krajinách, ktoré sa zúčastnili predchádzajúceho prieskumu, došlo k výraznému zlepšeniu v dostupnosti prevencie a domácej liečby.

Deviata kapitola sa zaoberá organizáciou hemofilickej starostlivosti a dostupnej liečby v štyroch krajinách a súčasne skúma rozdiely v kvalite života, v úrovni liečby a dôsledky pre národnú zdravotnú starostlivosť. Dlhodobá profylaktická liečba bola spojená s nižším výskytom takzvaných cieľových kĺbov, závažných a opakovaných krvácaní, chirurgických zákrokov, ale aj kratším obdobím práceneschopnosti. Navyše profylaxia zvyšovala mobilitu a schopnosť vykonávať každodenné činnosti a tiež zlepšila ZSKŽ u ľudí s ťažkou hemofíliou. ZSKŽ u pacientov s liečbou „podľa potreby“ bola významne nižšia ako u pacientov ktorí strávili minimálne 50% svojho života na profylaxii.

Desiata kapitola prezentuje organizáciu hemofilickej starostlivosti a dostupnosť liečby v šiestich krajinách. Poukazuje na to, že profylaxia, ktorá pokračuje do dospelosti, výrazne zvyšuje ZSKŽ. Avšak liečba „podľa potreby“ má za následky nižšiu ZSKŽ u pacientov trpiacich ťažkou hemofíliou. Profylaxia od ranného veku s pokračovaním do dospelosti má za následok menej krvácaní, menšie poškodenie kĺbov a menej vymeškaného pracovného času. Profylaxia navyše zvyšuje pohyblivosť a schopnosť vykonávať každodenné činnosti a zlepšuje ZSKŽ u ľudí s ťažkou hemofíliou.

Posledná *jedenásta kapitola* uvádza skrátene výsledky celej práce, diskutuje o nich v rámci existujúcich vedomostí, poukazuje na ich silné stránky, ale aj slabiny výskumu, uvádza dôsledky pre prax a ponúka nové možnosti pre budúci výskum.

U pacientov po TO boli v tejto práci identifikované zdravotné, ale aj psychosociálne faktory s dopadom na ZSKŽ, napríklad: funkcia štepu, komorbidity, vedľajšie účinky imunosupresívnej liečby, typ osobnosti, úzkosť a účinnosť zvládania. Navyše ZSKŽ v prvom roku po transplantácii obličky predikovala prežívanie pacienta a štepu v priebehu nasledujúcich desiatich rokov. Na druhej strane, nedostatočné dodržiavanie predpísanej imunosupresívnej liečby v prvom roku po transplantácii a obmedzenia v sociálnej participácii zvyšovali riziko straty štepu a úmrtnosti počas nasledujúcich dvanástich, respektíve desiatich rokov.

U pacientov s hemofíliou sme preukázali významnú rozdielnosť medzi užívaním profylaktickej liečby a liečby „podľa potreby“, v zmysle asociácie s frekvenciou a intenzitou zakrvácania, poškodením kĺbov, sociálnou participáciou a kvalitou života u dospelých v Európe a Kanade. Analýza úrovne implementácie európskych princípov hemofilickej starostlivosti v Európe upozornila na veľké rozdiely v prístupe k liečbe a zdravotnej starostlivosti u pacientov s hemofíliou. V mnohých krajinách ale došlo k pokroku v tejto oblasti, čo je väčšinou dôsledok zapojenia národných patientskych organizácií v obhajovaní záujmov svojich členov.

Výsledky tejto práce naznačujú, že pre zlepšenie dlhodobých výsledkov je potrebný dostatočný prístup k lekárskej starostlivosti, vrátane usmernenia symptómov a intervencií, ktoré spolu môžu ovplyvniť nielen rozsah a symptómy základného ochorenia, ale aj pridružené komorbidity. Týmto spôsobom môžeme byť nápomocní pre zvýšenie dlhodobého pocítovaného zdravia pacientov s chronickou chorobou. Navyše pravidelná monitorácia ZSKŽ v klinickom prostredí môže pomôcť identifikovať vysoko rizikových pacientov, ktorí by mohli mať prospech zo zvýšenej lekárskej starostlivosti, keďže ZSKŽ môže slúžiť ako ukazovateľ ich dlhodobých výsledkov. Potenciálny prínos doplnkových projektov, ako napríklad vzdelávacie programy pre dodržiavanie liečby alebo programy s cieľom zvýšiť copingové stratégie, by mal byť tiež preskúmaný. V záujme dosiahnutia týchto cieľov, je však nevyhnutné do celého procesu zapojiť komunitu pacientov, ich rodinných príslušníkov a lekárske tímy, so súčasnou apeláciou o finančnú a legislatívnu podporu zo strany vlády.

Na preskúmanie základných mechanizmov medzi faktormi uvedenými v tejto práci je potrebný robustnejší a nadnárodný výskum, ktorý by dodatočne zahŕňal aj ďalšie klinické ukazovatele. Budúci výskum by mal taktiež skúmať účinnosť intervenčných programov zameraných na zlepšenie ZSKŽ v oblasti chronických chorôb.

Samenvatting

Vanaf het moment dat de diagnose wordt gesteld, hebben patiënten met een chronische aandoening te maken met de vele gevolgen van hun ziekte en moeten ze zich aanpassen aan een nieuwe levensstijl en veranderingen in hun aan gezondheid gerelateerde kwaliteit van leven (GGKvL). Dit is bijzonder moeilijk bij patiënten bij wie de behandeling wordt geassocieerd met significante bijwerkingen, zoals de immunosuppressieve behandeling bij patiënten na niertransplantatie (KT), of voor wie behandeling niet altijd beschikbaar is, zoals de profylactische behandeling van patiënten met hemofilie.

Het doel van dit proefschrift was om de verbanden tussen GGKvL, medicatie-gerelateerde factoren en patiëntuitkomsten in deze twee chronische ziekte groepen te onderzoeken - patiënten na KT en patiënten met hemofilie. Daarnaast hebben we in beide groepen specifieke vragen verkend: of psychosociale factoren GGKvL, therapietrouw aan immunosuppressiva en sociale participatie bij patiënten na KT bepalen, en de toegang tot de behandeling en medische voorzieningen bij patiënten met hemofilie in Europa.

Hoofdstuk 1 geeft een algemene inleiding in GGKvL, factoren die samenhangen met de behandeling en GGKvL bij patiënten na KT en bij patiënten met hemofilie. Verder zijn een model en zes onderzoeksvragen met betrekking tot GGKvL, behandelfactoren en de patiëntuitkomsten geformuleerd.

Hoofdstuk 2 geeft informatie over de opzet van het onderzoek. Verder wordt ingegaan op de gebruikte steekproeven, gegevensbronnen, maatregelen en statistische analyses die in dit proefschrift gebruikt worden.

In *Hoofdstuk 3* wordt het verband onderzocht tussen persoonlijkheidskenmerken (neuroticisme, extraversie), het niveau van psychische distress en GGKvL bij patiënten na KT, wanneer met controle van deze variabelen en voor sociaal-demografische en medische variabelen. Hogere fysieke GGKvL werd geassocieerd met jongere leeftijd, hoger onderwijs en inkomen, een laag aantal comorbide aandoeningen, en lagere neuroticisme en distress. Hogere mentale GGKvL werd geassocieerd met een hogere opleiding en inkomen, langere tijd sinds KT, hogere extraversie, neuroticisme en lagere distress. In zowel de fysieke en mentale kwaliteit van leven was de werkelijke distress de beste voorspeller, ook na controle voor neuroticisme.

Hoofdstuk 4 onderzoekt het verband tussen GGKvL en de effectiviteit van coping en bijwerkingen van immunosuppressieve behandeling alsmede het vermogen om langdurige patiënt- en transplantaatoverleving op basis van de GGKvL van patiënten bij de beginmeting te voorspellen. We vonden een verband tussen een grotere effectiviteit in het stoppen van onaangename emoties en zowel een hogere fysieke als mentale GGKvL bij de beginmeting. Bovendien vonden we een verband tussen lagere effectiviteit bij het verkrijgen van steun van familie en vrienden en hogere mentale GGKvL. Over de impact van fysieke en mentale GGKvL bij de beginmeting van de patiënt

op patiënt- en transplantaatoverleving voor maximaal 10 jaar, hadden patiënten met een hogere fysieke en mentale GGKvL bij de beginmeting een hogere kans op overleven met een functionerend transplantaat, evenals bij een hogere leeftijd en een betere nierfunctie.

In *Hoofdstuk 5* wordt het verband tussen sociaal-demografische factoren, medische factoren (nierfunctie, bijwerkingen), sociale steun en de verschillende niveaus van therapietrouw onderzocht. We vonden een verband tussen vrouwelijk geslacht, hoger onderwijs, meer waargenomen bijwerkingen van corticosteroïden, beter waargenomen hart- en nierfunctie, hoger gepercipieerde sociale steun van familie en minder steun van belangrijke anderen in het eerste jaar na de transplantatie en de volledige therapietrouw met betrekking tot immunosuppressieve behandeling. De voorspellende waarde van de therapietrouw met betrekking tot immunosuppressieve medicatie in het eerste jaar na KT als determinant van het verlies van het transplantaat en sterfte tot 12 jaar na KT werd ook onderzocht. Gebrekkige therapietrouw met betrekking tot immunosuppressieve medicatie in het eerste jaar na KT verhoogde de kans op verlies van het transplantaat en op sterfte in vergelijking met de meer therapietrouwe patiënten.

In *Hoofdstuk 6* wordt het verband onderzocht tussen fysieke en mentale GGKvL en relevante post-KT factoren zoals nierfunctie, bijwerkingen van immunosuppressieve behandeling, comorbiditeit en sociale participatie (SP). We vonden een verband tussen beperkingen in de SP met zelfstandig wonen, een verslechterde nierfunctie, meer ernstige bijwerkingen van de immunosuppressieve behandeling en slechtere fysieke GGKvL. Verder werd de impact van de SP onderzocht op het toekomstig verlies van het transplantaat en de sterfte tot 10 jaar bij controle voor relevante sociaal-demografische en medische factoren bij de beginmeting. We vonden een verband tussen de beperkingen in de SP bij de beginmeting en een verhoogd risico op verlies van het transplantaat en sterfte bij follow-up, samen met een lagere opleiding, slechtere nierfunctie en een hoger aantal comorbide aandoeningen.

Hoofdstuk 7 bevat informatie over de organisatie van de zorg voor hemofilie en de behandeling die beschikbaar is op nationaal niveau in 19 Europese landen, met een specifiek focus op consensus richtlijnen die ontwikkeld zijn om de zorg voor hemofilie in heel Europa te standaardiseren. De ontvangen reacties wezen op verschillen in het niveau van de zorg. Tussen landen bestond er een groot verschil in factor VIII consumptie, terwijl in sommige Oost-Europese landen cryoprecipitaat nog steeds gebruikt werd.

Hoofdstuk 8 geeft informatie over de organisatie van de zorg voor hemofilie en de behandeling die beschikbaar is op nationaal niveau in 35 Europese landen; de voornaamste doelstelling is om verschillen in de beschikbaarheid van de behandeling en zorg te identificeren. Net als in *Hoofdstuk 7*, wezen de antwoorden op grote verschillen in de beschikbaarheid van behandeling en zorg. Er was een groot verschil in factor VIII consumptie, met gebruik variërend van 0,10 IU/

capita in Armenië tot 8,56 IU/capita in Zweden (mediaan: 3,59 IU/capita). De afname van de gezondheidsbegrotingen is in veel landen niet gekoppeld aan de afname in het gebruik van factor VIII per capita. In de 19 landen die reageerden op de vorige enquête, was er een significante verbetering van de toegang tot profylaxe en thuisbehandeling.

Hoofdstuk 9 geeft informatie over de organisatie van de zorg voor hemofilie en de behandeling die beschikbaar is op nationaal niveau van vier landen. De verschillen in kwaliteit van leven, het niveau van de behandeling en de gevolgen voor de nationale gezondheidszorg worden ook onderzocht. Wij vonden een verband tussen een langdurige profylaxe en een lagere aanwezigheid van gewrichten met bloedingen, het optreden van ernstige bloedingsepisodes, terugkerende bloedingen, de noodzaak van chirurgische procedures en minder tijd die men verzuimde. Profylaxe deed de mobiliteit toenemen alsmede het vermogen om dagelijkse activiteiten te ondernemen en een verbetering van de kwaliteit van leven van mensen met ernstige hemofilie. Het gebruik van gezondheidszorg bij patiënten met on-demand therapie was beduidend lager dan andere groepen die ten minste 50% van hun leven profylaxe kregen.

Hoofdstuk 10 geeft informatie over de organisatie van de zorg voor hemofilie en de behandeling die beschikbaar is op nationaal niveau van zes landen. Deze studie laat zien dat de voordelen van profylaxe voortgezet in de volwassenheid de kwaliteit van leven aanzienlijk verhoogt. On-demand behandeling resulteert in een lagere kwaliteit van leven voor mensen met ernstige hemofilie. Profylaxe begonnen op jonge leeftijd en voortdurend tot in de volwassenheid resulteert in minder bloedingen, minder schade aan de gewrichten en minder verzuim. Profylaxe vergroot de mobiliteit en het vermogen om dagelijkse activiteiten te verrichten en verbetert de GGKvL van mensen met ernstige hemofilie.

Tot slot presenteert *Hoofdstuk 11* de gecondenseerde uitkomsten van dit onderzoek, bespreekt ze in het kader van de bestaande kennis, geeft de sterke en zwakke punten weer, alsmede hun implicaties voor de praktijk en voor nieuwe mogelijkheden van verder onderzoek.

Bij KT ontvangers werd een aantal medische factoren geïdentificeerd dat verband hield met GGKvL zoals nierfunctie, comorbiditeit of de bijwerkingen van de immunosuppressieve behandeling samen met psychosociale variabelen, zoals persoonlijkheid, angst en de effectiviteit van coping. We vonden dat GGKvL bij de beginmeting een belangrijke voorspeller was van de overleving van de patiënt en het transplantaat tot 10 jaar later. Aan de andere kant, gebrekkige therapietrouw aan de immunosuppressieve behandeling in het eerste jaar na transplantatie, en beperkingen in sociale participatie verhogen het risico op verlies van het transplantaat en de sterfte respectievelijk tot 12 en 10 jaar nadien.

Bij patiënten met hemofilie werd bij de profylactische versus on-demand behandeling een significant verband gevonden met een verschillend aantal bloedingen, gewrichtschade, sociale par-

ticipatie en kwaliteit van leven bij volwassenen in Europa en Canada. Bij het analyseren van het niveau van de uitvoering van de Europese principes van de zorg voor hemofilie over heel Europa vonden we grote verschillen in de toegang tot de behandeling en de medische zorg bij patiënten met hemofilie. Er is echter verbetering op dit gebied in een aantal landen, dat vooral toe te schrijven is aan de betrokkenheid van de nationale patiëntenorganisaties die pleiten voor het belang van hun leden.

De bevindingen van dit proefschrift geven aan dat om de lange termijn resultaten te verbeteren een adequate toegang tot medische zorg, waaronder de behandeling van de symptomen en interventies om comorbiditeit te voorkomen nuttig zouden kunnen zijn om de ervaren gezondheid van patiënten met chronische aandoeningen te verhogen. Regelmatige evaluatie van de GGKvL in een klinische setting kan helpen om hoog-risico patiënten te identificeren; aldus kunnen die profiteren van de toegenomen aandacht, omdat de GGKvL kan fungeren als een indicator voor hun toekomstige resultaten. Potentiële voordelen van aanvullende programma's, zoals onderwijsprogramma's met betrekking tot therapietrouw of trainingsprogramma's om coping-strategieën te verbeteren, moeten ook worden onderzocht. Tot slot, om deze doelstellingen te bereiken, is het essentieel om de gemeenschap van patiënten en familieleden en hun medisch team hierbij te betrekken en tevens te streven naar financiële en juridische steun van de overheid.

Robuuster en transnationaal onderzoek is nodig om de onderliggende mechanismen tussen de factoren die beschreven zijn in dit proefschrift te onderzoeken, zoals bijwerkingen, toegang tot de behandeling, GGKvL, therapietrouw en patiëntuitkomsten, evenals aanvullende klinische indicatoren. Daarnaast moet de effectiviteit van interventieprogramma's gericht op het verbeteren van GGKvL worden onderzocht.

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About the author

Lucia Prihodova was born on April 23rd , 1983 in Šaľa, Slovakia. She completed her master's degree in psychology at the University of Trnava, Slovakia. Her qualifying areas were clinical, counselling and educational psychology, and in her master thesis she explored the interactions between coping skills, hope, social support and quality of life in patients with an oncologic disease. After graduating in the year 2006, she started to work as a researcher at the Safarik University in Kosice and at the same time, she started a PhD program at the University of Groningen, the Netherlands. Simultaneously, she worked part time at the Fresenius dialysis department as a psychologist, where she utilized her training in relaxation-imaginative psychotherapy. In her research, she focused at psychosocial and medical determinants of quality of life in patients with a chronic disease and their long term outcomes. While working at the Safarik University, she also delivered a training focused on improving the communication skills of students and supervised students working on bachelor degree dissertations. In the year 2008, she relocated to Ireland, broadened her project by establishing a connection with the Irish Haemophilia Society and continued the work on her PhD project on an external part-time basis, while also working at residential camps for children affected by life-threatening diseases and their families. She currently lives in Ireland and is employed as a research fellow on a research project aimed at developing and implementing a system of structured network-wide dissemination and knowledge transfer activities in palliative care at the School of Psychology, University College Dublin.

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Co-Supervisors: Assoc. Prof. Dr. JP van Dijk, Assoc. Prof. A Madarasova Geckova

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Assoc. Prof. A Madarasova Geckova

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CO-SUPERVISORS: Assoc. Prof. Dr. JP van Dijk, Dr. I Nagyova,
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Co-Supervisors: Assoc. Prof. Dr. JP van Dijk, Dr. J Rosenberger, Assoc. Prof. Dr. Z Gdovina,
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Supervisor: Prof. Dr. JW Groothoff, Prof. Dr. WJA van den Heuvel

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Co-Supervisors: Dr. JP van Dijk

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Supervisor: Prof. Dr. D Post, Prof. Dr. JW Groothoff

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