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Patient reported outcomes in a long-term perspective after kidney transplantation in patients older than 65 years

Main supervisor:

Consultant nephrologist

PhD, MHA **Kristian Heldal**

Oslo University Hospital HF, Rikshospitalet, 0424 Oslo
and Telemark Hospital Trust, 3710 Skien

Project leader/supervisor:

Consultant nephrologist, PhD **Karsten Midtvedt**

Oslo University Hospital HF, Rikshospitalet, 0424 Oslo

Co-Supervisors:

Head of the Research Unit

Professor Dr.philos **Tomm Bernklev**

Vestfold Hospital Trust

and Institute of Clinical Medicine, University of Oslo

Coordinating Nurse

RN, MSm, PhD **Kjersti Lønning**

Oslo University Hospital, Rikshospitalet

PhD candidate:

MD Vasiliki Tsarpali

Telemark Hospital Trust

Collaborators:

Professor, RN PhD **Marit Helen Andersen**

Oslo University Hospital, Rikshospitalet

and Institute of Health and Society, University of Oslo

Head of Section of Nephrology

Consultant nephrologist, PhD **Anna V Reisæter**

Oslo University Hospital, Rikshospitalet

and Norwegian Renal Registry

Consultant nephrologist, Professor emeritus PhD **Anders Hartmann**

Oslo University Hospital, Rikshospitalet

and Institute of Clinical Medicine, University of Oslo

Consultant nephrologist, PhD **Nanna Von Der Lippe**

Institute of Clinical Medicine, University of Oslo

1. Project title

Patient reported outcome in a long-term perspective after kidney transplantation in patients older than 65 years.

2. Introduction

The PhD project described in this protocol focus on long term health related quality of life (HRQoL) and survival in older kidney transplant candidates. In addition, we also aim to perform health economic evaluations to provide further information about the possible benefits of kidney transplantation in older patients from a health economic perspective.

Our research group has previously initiated a prospective study including kidney transplant candidates older than 65 years who are listed for transplantation at Oslo University Hospital, Rikshospitalet (QUESTION65). At present, 289 patients are included and 214 have been transplanted. Results have been presented at top international conferences (ERA-EDTA, ASN, ESOT, ATC). The first PhD protocol using data from this study was started in 2015 (PhD student Kjersti Lønning) the protocol focusing on short- and intermediate-term changes in HRQoL, effect of comorbidity on short-term complications and HRQoL and a qualitative evaluation of the patients' expectations.

For patients with end stage renal disease (ESRD), kidney transplantation is in general considered as the best treatment-option both with respect to survival (1), costs (2, 3) and HRQoL (4). Selected older patients have also been shown to improve survival after transplantation compared to dialysis (5, 6). For decades Oslo University Hospital, Rikshospitalet has been Europe's largest kidney transplantation center.

As a result of the general aging of the population, the number of older individuals with chronic diseases including chronic kidney disease is expected to increase significantly over the next 25 years. Consequently, the number of older kidney transplant candidates will also increase. Contrary to most other countries in the world, Norway has never had any upper age limit for kidney transplantation. In spite of this, we have had among the shortest waiting-time worldwide (7). Due to organ scarcity, transplant centers often have an upper formal or practical age limit for potential recipients. In some countries patients older than 50-55 years may end up spending the rest of their life in hemodialysis. The major challenge concerning allocation of donor organs is to find those patients who will derive the most benefit of transplantation in terms of improved patient outcome, less complications and increased survival time. Today, most centers use the same medical criteria for all patients, regardless of age. Based on the literature there is, however, a knowledge gap between what is documented for older patients versus younger patients.

Most data describing HRQoL after kidney transplantation have been collected from adult populations (median age ~ 50 years) (4, 8). Information on if/how HRQoL of older ESRD patients change during different phases of the treatment (dialysis, early post transplantation and long term transplantation) is very sparse (4) and for older patients the documentation is restricted to small cross sectional studies comparing a group of older recipients with either older patients on dialysis treatment or younger transplant recipients (9, 10). To our knowledge, no prospective study describing HRQoL longitudinally in older patients from pre-transplant through the immediate, short term and long-term phases post-transplant has been published. In 2018, RN Kjersti Lønning defended her PhD thesis on basis on the QUESTION65 study describing the short term HRQoL effects of kidney transplantation in the elderly (11-13). Consequently, there is a knowledge gap concerning how kidney transplantation affects HRQoL in the long term compared to the alternative; lifelong dialysis treatment.

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Older patients with ESRD often have a high burden of co morbidities. The most widely used comorbidity index is the Charlson comorbidity index (CCI) (14). The CCI has been validated in several populations including patients with ESRD (15). In recipients older than 70 years, the CCI has, however, not been shown to be associated with survival after kidney transplantation (16). More recently, other comorbidity scores have been developed for patients with ESRD (17, 18). However, these indexes are not validated in the elderly. We are consequently lacking instruments validated in older transplant candidates for standardized measurement of comorbidity.

Even though kidney transplantation is regarded as the most cost-effective treatment of ESRD, to our knowledge no proper health economic evaluation of transplantation in older patients exists.

2.1 Added value of the project

Added value for the patients: Increased knowledge of the outcomes after kidney transplantation will be important for the patient's choice of treatment. The findings will provide the patients and their families comfort and knowledge that timely specialist evaluation can help improve outcomes and reduce symptoms in older people with advanced kidney disease – whether they have selected conservative management, dialysis or kidney transplantation as their treatment plan. Improved selection criteria for transplantation will improve the patient outcomes by selecting the correct patient for the correct treatment.

Added value for the health service: The project will provide novel information that the clinicians can use to utilize the limited donor organ resources in an optimal way. The situation for kidney transplantation in Norway is currently changing. For the last decade we have had a stable situation with approximately 200 patients on the transplantation waiting list and a mean waiting-time of 9-12 months. Over the last years, the number of waitlisted patients has however increased significantly and consequently the waiting-time for kidney transplantation has become markedly longer. This situation has already resulted in some discussion on whether we should change our selection-criteria for including patients on the waiting list. One possibility is to set an upper age limit for potential kidney transplant recipients.

Our research group will argue that it is important not to set an upper age limit but rather improve the selection criteria for elderly kidney transplant candidates. The challenge is to improve the selection of recipients expected to go through the post-operative phase without major complications and thus being the ones most likely to profit from kidney transplantation.

We hypothesize that selection criteria of elderly recipients with ESRD can be improved by combining data from a pre-transplant comorbidity score and self-reported health related quality of life (HRQoL). We believe our research will improve the individual evaluation of each patient and provide each patient with the best treatment option available, both with respect to survival and quality of life. By identifying patients who will *not* benefit from transplantation, the organ can be allocated to another patient on the waiting list, thereby reducing the waiting time. The findings will be of strategic importance for future treatment of all patients in Norway with ESRD, regardless of age.

Added value for the society: Improved selection criteria combined with health economic evaluation will provide important guidance in the search for cost-effective treatment algorithms which is necessary if we should be able to utilize our health budget optimally. Evidence of the cost-effectiveness of various treatment options is required to facilitate appropriate resource planning and develop optimal treatment models across diverse health care settings. Policymakers need evidence that an intervention or program of care represents the most efficient use of available resources and

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provides value for money. Health economic evaluation is a systematic way of producing this evidence (19).

3. Aims

The overall aim of this study is to collect and evaluate long-term data on patient reported, clinical and health economic outcomes following kidney transplantation in older patients (≥ 65 years of age at enlisting). Further specific aims are:

Aim 1:

To evaluate patient reported HRQoL longitudinally from time of wait listing and up to 5 years after transplantation in kidney transplant candidates older than 65 years of age.

These data will describe if and how patient reported HRQoL changes over time and thereby evaluate whether the benefit of transplantation described for general adult patients is also valid for older recipients. The data will also make it possible to compare the effect on HRQoL and clinical outcomes for patients on long-term dialysis compared to patients several years after transplantation.

Aim 2:

To investigate the relationship between pre-transplant comorbidity, expressed as the Liu comorbidity index and post-transplant HRQoL at 1-3 years post transplant.

Detection of any association between pre-transplant comorbidity and post-transplant HRQoL, can improve the selection process of older transplant candidates by including the comorbidity score as part of the patient selection algorithm.

Aim 3:

To investigate the relationship between pre-transplant comorbidity, expressed as the Liu comorbidity index, pre-transplant HRQoL described by KDQOL-SF and post-transplant patient- and graft survival.

Aim 4:

To evaluate kidney transplantation in older patients in a health economic perspective, including evaluation of quality adjusted life years (QALY), and investigate if QALY values are changing over time. By collecting standard cost estimates for the different procedures, we should be able to calculate an incremental cost-effectiveness ratio (ICER) for kidney transplantation versus dialysis

This aim will provide further information about the benefits kidney transplantation can or cannot provide older patients from a health economic perspective. This analysis will be of major importance for present and future priority discussions.

4. Implementation

Data will be retrieved from the QUESTION65 database described previously, and the Norwegian Renal Registry. Missing data will be retrieved from the patient records at Oslo University Hospital, Rikshospitalet and from the patients' local hospital records. The key necessary for identification of patients will be stored at the registry and will not be available for the researchers.

4.1. Design, methods and analyses

Statistics

All statistical analyses will be performed using the statistical software package SPSS Statistics version 22 or later. Scores from KDQOL-SF will be calculated and compared using traditional statistical methods (two-sided unpaired t-test or paired t-test, ANOVA, logistic regression). Fisher's exact test will be used to analyze binary data. Other standard statistical methods as for example multiple variable logistic regression analyses will be used as needed. Survival analyses will be performed using the Kaplan-Meier method and Cox proportional hazard models.

Aim 1:

Data collection: Patient reported outcomes are collected in an on-going, prospective, longitudinal study (QUESTION65). By the end of inclusions in December 2016, we estimate that 280 patients should be included. All patients give their written informed consent before inclusion in the study. In addition, all patients have signed an informed consent when they were included in the Norwegian Renal Registry. This allows the use of unidentified data from the registry in research protocols.

HRQoL is assessed using the KDQOL-SF-36 health Survey (20, 21). This survey consists of two parts, a generic (SF-36) and disease specific (KDQOL) part. The same questionnaire is used before and after transplantation. The results will also be compared with data from an age matched Norwegian cohort (22).

All patients over the age of 65 years, who are accepted for the kidney transplantation waiting list or living donor transplantation, receive an invitation to participate in the study. In addition to provide baseline data, all patients receive additional forms with the same questionnaires every sixth months until they are transplanted, permanently removed from the transplant waiting list or deceased. Patients who are transplanted will receive a discharge form from Rikshospitalet (10 weeks after transplantation), after six months and at one-, three-, five-, seven- and ten years post-transplant.

Statistical power: The primary objective of the study is to detect differences in the QOL dimension general health (GH). According to the literature, SF-36 scores for GH varies between 47 and 69 for transplanted patients and between 36 and 44 for patients treated in haemodialysis (10, 23, 24). The standard deviation in these studies varies between 15 and 25. A clinically significant difference in SF-36 GH score is estimated to be around 10%. With a predicted SF-36 GH score of 50 for transplanted patients and 40 for patients in haemodialysis, we need a minimum of 63 patients to complete the study to reach a significance level (α) of 5% and a power (β) of 80%. According to previous analyses, 80% of patients > 70 years who are accepted for the kidney transplantation wait list will eventually be transplanted and five year survival in this age group is 64% (5). Consequently, a minimum of 100 patients must be transplanted and hence, an even higher number must be included at baseline. To have the possibility to evaluate the impact of gender and dialysis modality, the number of included patients has been further increased up to a total of 280. The regional committee of medical and health research ethics have approved this increase.

By August 2016, 261 patients are included, 152 are transplanted. Consequently, the number included and transplanted patients are already well above the minimum number.

Aim 2:

Data collection: From 2012 we have included pre-transplant data according to the Liu comorbidity index (17) as part of the routine work up of candidates for kidney transplantation. Complete data describing patient and transplant characteristics, including the Liu comorbidity index will be

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extracted from the Norwegian Renal Registry. The data will be exported from the registry without any identification except from a patient number. Post-transplant HRQoL values will be retrieved from the QUESTION65 database.

Statistical power: No previous studies describing the correlation between pre-transplant comorbidity and post-transplant HRQoL exist. Based on the same considerations as described for Aim 1, a similar number of patients should be necessary for Aim 2 to reach a significance level of 5% and a power of 80%.

Aim 3:

Data collection: Complete data describing patient and transplant characteristics, including the Liu comorbidity index will be extracted from the Norwegian Renal Registry as described for Aim 2. Pre-transplant HRQoL will be retrieved from the QUESTION65 database. Post-transplant survival data will be extracted from the Norwegian Renal Registry. The data will be exported from the registry without any identification except from a patient number.

Statistical power: No previous studies describing the correlation between pre-transplant comorbidity, pre-transplant HRQoL and post-transplant survival exist. Based on previous analyses on similar patient cohorts (25), 150 patients should be sufficient to detect statistically significant associations.

Aim 4:

Data collection: QALYs will be calculated from the SF-36 (SF-6D) scores available in the QUESTION65 database. From the SF-6D, a health index can be calculated. Patients who die during follow-up will have health index = 0 from time of death, and with this health index, QALYs can be calculated for each patient during follow-up. Costs necessary for estimation of cost/QALY and ICER will be estimated through use of information from the patient records at the patients' local hospitals as well as Oslo University Hospital. DRG weighted costs will be used for each contact (in-patient, out-patient and dialysis). In addition, medication costs will be estimated based on each patient's medication list and travel costs will be estimated based on the distance between the patient's home and the hospital.

Statistical power: No previous studies evaluating QALY in older kidney transplant recipients exist. Power calculation is therefore difficult to perform.

4.2. Organization and cooperation

This PhD project is organized as a collaborative project between researchers at Telemark Hospital Trust, Oslo University Hospital and Vestfold Hospital Trust. Project leader for the long-term study, Associate professor, consultant nephrologist Kristian Heldal works at Oslo University Hospital and is a member of the transplant research group at Oslo University Hospital. In addition, he has a position as researcher at Telemark Hospital Trust in Skien. He is the main supervisor for the PhD candidate. Professor Tomm Bernklev, head of Research Unit at Vestfold Hospital Trust is co-supervisor with major concern for analyses of HRQoL data and consultant nephrologist PhD Karsten Midtvedt is project leader and co-supervisor. The PhD candidate Vasiliki Tsarpali works as a nephrology fellow at Telemark Hospital Trust and is financed through a grant from Helse Sør-Øst. Regular project meetings are organized for the whole project group in addition to regular supervision. RN, PhD Kjersti Lønning who has been responsible for the QUESTION65 database as

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a part of her PhD project will continue to have a coordinating function with respect to the database and the Norwegian Renal Registry.

The study group has previously completed several successful projects in the context of kidney transplantation. In 2010 Kristian Heldal supervised by Karsten Midtvedt and Anders Hartmann, completed his PhD “Kidney transplantation in the elderly” describing the survival outcomes after kidney transplantation in patients older than 70 years. Professor, Dr. philos Tomm Bernklev has special competence regarding evaluation of patient reported outcome measurements (PROM) in patients with chronic diseases. Professor Marit Helen Andersen and consultant nephrologist Nanna von der Lippe also have scientific experience using the KDQOL-SF health survey on patients with ESRD. The other collaborators all have comprehensive experience from medical and epidemiological research. In addition to the regular members of the project group, statisticians from Oslo University Hospital will also be consulted for assistance regarding statistical analyses. Concerning the health economic analysis, Kristian Heldal has recently completed a Master in Health Administration (MHA) and his master thesis was a study of short-term health-economic effects of kidney transplantation in elderly patients and this thesis has served as a “Pilot study” for the long-term study planned in this project. In addition, the study group has established a collaboration with the Clinical Trial Unit at Oslo University Hospital for assistance with the health economic subprotocol.

The PhD student is responsible for registration and analyses of new HRQOL data from the surveys, survival data from the Norwegian Renal Registry and clinical data/cost data from the patient records. The PhD student will also be first author of all papers. The PhD project is planned as a 100% project over three years and is financed through a PhD grant from Helse Sør-Øst.

4.3. Budget

Budget (in NOK 1000)	2019	2020*	2021	2022	Total
Personnel costs (PhD student)	955	0	955	955	2865
Travel grant	30	0	30	30	90
Other operating costs: Courses, Literature	15	0	15	15	45
Total	1000	0	1000	1000	3000

* No expences registered for 2020 because the PhD student is on maternity leave

4.4. Schedule:

Activity	2019	2020	2021	2022
Data collection of HRQoL study - aim 1	x			
Data collection - aim 2	x	x	x	
Data collection - aim 3	x	x	x	
Data collection - aim 4	x	x	x	x
Data analysis	x	x	x	x
Publication		x	x	x
Writing PhD thesis				x
Dissertation for the degree of PhD				x

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Five years HRQoL data will be available for the first patient in 2018 and by the end of 2020, the database is expected to be complete also with long-term data necessary for evaluating long-term HRQoL (aim 1). Data from the other aims will be available for analysis and evaluation from 2019.

Planned publications: All manuscripts will be published in international nephrology, transplant or geriatric journals. Abstracts will be presented at international meetings.

Tentative papers:

1. Changes in health-related quality of life in older kidney transplant recipient up to three years post-transplant (2020)
2. Association between pre-transplant comorbidity and health related quality of life in older kidney transplant recipients (2021)
3. Association between pre-transplant comorbidity, pre-transplant health related quality of life and long-term (three years) post-transplant survival in kidney transplant recipients older than 65 years (2021)
4. Cost-effectiveness of kidney transplantation in the elderly (2022)

4.5 Implementation plan:

Results from our study will have implications for clinicians in selection and treatment of elderly patients with chronic kidney disease throughout the world. With increasing transplantation wait lists and organ scarcity it is important to give organs to the “most suitable candidates”. The aging of the general population means that older people now account for much greater proportion of patients with or at risk for kidney disease and kidney failure. Chronological age alone is not sufficient as the basis for clinical decision and a more nuanced approach is required – based on comorbidities, quality of life and obviously preference of each patient. Improved selection of the elderly population with ESRD will obviously also profit the younger recipients waiting for a kidney transplant. New knowledge about this group of patients can provide better information both to the patients and their health providers.

5. Patient involvement:

The first PhD protocol from this project;” Does kidney transplantation in older patients add life to years (Question 65)” was supported by the Norwegian patient organization for patients with kidney disease and transplant recipients (Landsforeningen for nyresyke og transplanterte, LNT) through a PhD grant from the Extra foundation. LNT is also involved in the new protocol and the results will be presented for the patient organization at meetings and in their magazine “LNT nytt.”

In addition, the project has been presented and discussed in the Telemark Hospital Research Committee, the members of which include a patients' representative.

6. Ethical considerations:

No experimental treatment is planned. As a consequence, it is considered to be ethical correct to include more patients than are required as a minimum. A higher number of patients included will provide more robust results. Informed consent will be obtained from all included patients. Each patient will receive a unique identification number that will be used for identification of individual data. The key necessary to identify the patients will be stored at Rikshospitalet (Section of

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Nephrology) and will not be available for the involved researchers. The sub-protocol for the longitudinal evaluation of HRQoL (Aim 1) has been approved by the regional committee for medical and health research ethics (2012/527). Data collection for Aim 1 started in 2012 and was completed in November 2016.

All patients included in the Norwegian Renal Registry have in addition given their informed consent that includes the use of registry data in research studies.

All data are made non-identifiable. In addition, all patients transplanted at Oslo University Hospital, Rikshospitalet after 2000 have signed a consent allowing data to be used in research, as have all patients included in the Norwegian Renal Registry done.

7. Date of protocol update: 04/05/2020

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