Depression and quality of life in patients with chronic kidney disease

Thesisbook

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INTRODUCTION

The increasing prevalence of chronic conditions and the advanced mean age of the population increases the health care expenses of developed countries. The end-stage renal disease (ESRD) population, similarly to the general population, has grown much older over the last 15-20 years. Due to the rapidly increasing prevalence, the substantial disease burden and costs of renal replacement therapies (RRTs), renal failure has become one of the most important health care related concerns in the industrialized societies.

Chronic kidney disease (CKD) is defined by structural or functional abnormalities of the kidney, with or without decreased glomerular filtration rate (GFR) that persists for more than three months. In many patients the condition is progressive, the GFR will relentlessly decrease. In its early stages the condition is indolent but the normal functioning of several organ systems is affected in more advanced stages and an increasing number of symptoms will appear. When the GFR drops to or below 10-15% (end stage renal disease - ESRD) the patient will need to consider renal replacement therapy (RRT) in the form of peritoneal dialysis (PD) or hemodialysis (HD) or kidney transplantation (KTx). With the availability of renal replacement therapies patients with ESRD can survive the potentially lethal condition. At the same time, RRTs will not cure renal failure. We can not prevent, only slow down the progression of many of the complications of CKD. Furthermore, RRTs are very intrusive therapies and have a significant impact on patient's lives - sometimes this is similar in magnitude to the effect of the disease itself.

Depression has been identified as a complicating comorbid diagnosis in a variety of chronic medical conditions. The two main symptoms of depression are depressed mood and markedly diminished interest or pleasure (anhedonia), accompanied by somatic symptoms (fatigue, sleep and appetite/ weight problems) and cognitive dysfunctions (diminished ability to think or concentrate, feelings of worthlessness or inappropriate guilt, recurrent thoughts of death).

The risk of clinically significant depression is particularly high in patients with chronic somatic conditions (cardiovascular diseases, diabetes). Depression is associated with non-compliance, lower quality of life and negatíve clinical outcome. Comorbid depression increases the burden of chronic diseases and health care utilization of the patients.

Depression is one of the most common psychological disorders in ESRD patients, with a prevalence rate as high as 7% to 65% by some contemporary estimates. Accurate estimation of the prevalence has been difficult due to the use of different definitions of depression and varied assessment techniques. Although depression is a common problem, it is often underdiagnosed and undertreated in this population. In the DOPPS, only one third of

depressed patients used any kind of antidepressants. We suggest that depressive symptoms should be assessed on a regular basis in chronic kidney disease patients, because of the high prevalence and the association with clinical outcomes.

In my disseartation I introduced results of three different studies. Two of them were done by the Psychonephrology Study Group at Semmelweis University Budapest. In a cross-sectional study we measured the prevalence of depressive symptoms in kidney transplanted and waitlisted dialysis patients, and we analyzed the parameters associated with the presence of depression in the transplanted group. Thereafter, the transplanted population was followed up in a prospective study, to assess whether the severity and presence of depressive symptoms is an independent predictor of clinical outcome. As a visiting scholar, I had the opportunity to analyze data from an international, multicenter study. In that study, I tested whether self-reported measures of subjective well-being (i.e. HR-QoL) and depressive symptoms are associated with the odds of being on the kidney transplant waiting list. I also assessed whether depressive symptoms and HR- QOL are associated with receipt of a deceased donor kidney transplant in waitlisted hemodialysis patients.

AIMS AND HYPOTHESES

1. Symptoms of Depression in Kidney Transplant Recipients: Cross-Sectional Study

Depression is one of the most common psychiatric conditions in patients on maintenance dialysis. However, only few papers assessed depressive symptoms in kidney transplanted patients. Smaller studies reported that severity of depression was lower in transplanted than in maintenance dialysis patients, however, it is not clear whether the groups were comparable on socio-demographic and clinical characteristics. Furthermore, little is known about the clinical and socio-demographic correlates of depression in kidney transplanted patients.

In response to the obvious lack of relevant data, we conducted a large, cross-sectional study to compare the prevalence of depressive symptoms between comparable groups of kidney transplanted and waitlisted dialysis patients. Furthermore, we assessed the association between clinical and socio-demographic factors and depressive symptoms in kidney transplanted patients. Specifically, we wanted to analyze whether the modality of renal replacement therapy (dialysis vs. transplantation) is associated with depressive symptoms in patients with end-stage renal disease. The hypotheses were:

- Depressive symptoms are significantly less prevalent in kidney transplanted than in waitlisted dialysis patients,

- Symptoms of depression are significantly more prevalent in women, patients with lower renal function and more somatic comorbid conditions,
- The modality of renal replacement therapy is an independent predictor of the severity and prevalence of depressive symptoms.

2. Depressive Symptoms and Mortality in Patients after Kidney Transplantation – a Prospective Prevalent Cohort Study

Several studies found that increased mortality among depressed chronic dialysis patients. There is only little data available regarding the association of depression and mortality in kidney transplanted patients.

New information about the association between depressive symptoms and negative outcomes can further improve our understanding of the psychosomatic context of chronic kidney disease and it also may point to potentially treatable factors associated with clinical outcome. In this prospective prevalent cohort study we wanted to determine if the severity of depressive symptoms and the presence of clinically potentially significant depression, are associated with increased mortality and death censored graft loss after renal transplantation.

The hypothesis was:

- The severity of depressive symptoms and the prevalence of clinically potentially significant depression are independent predictors of mortality and death censored graft loss in kidney transplanted patients.

3. Psychosocial Variables Associated with being Waitlisted and Receiving a Transplant in Patients on Hemodialysis in the Dialysis Outcomes and Practice Patterns Study (DOPPS)

Kidney transplantation is associated with longer survival, better quality of life and lower costs than chronic dialysis. Therefore, transplantation should be the treatment of choice for patients with advanced CKD who are medically suitable and who desire this treatment modality. Numerous studies have demonstrated that inequalities exist in access to transplantation for different subgroups. Several patient and healthcare-related barriers to the transplantation process have been identified.

Developing and maintaining interest in renal transplantation among potential candidates is the first step in the transplantation process, which could be affected by several subjective factors (negative patient perceptions about transplantation, fears about transplant surgery). However, to date little attention has focused on the association between subjective self- reported measures of well- being versus access to transplantation. In previous studies, the presence of

psychiatric disorders (severe depression or other psychiatric disorder) independently was associated with lower access to the transplantation waitlist, and the presence of psychiatric diseases was associated with 32% lower rate of kidney transplantation. However, these studies only collected data from patients' charts on the presence of psychiatric disorders.

In the present study, we tested whether self- reported measures of subjective well-being (i.e. HR-QoL) and depressive symptoms are associated with the odds of being on the kidney transplant waiting list in a representative, prevalent cross-section of hemodialysis patients. We also assessed whether depressive symptoms and HR- QOL are associated with receipt of a deceased donor kidney transplant in waitlisted hemodialysis patients.

The hypotheses were:

- Patients with more severe depressive symptoms and lower quality of life are less likely to be on the waiting list,
- More severe depressive symptoms and lower quality of life decrease the odds of getting a transplant.

METHODS

1. Symptoms of Depression in Kidney Transplant Recipients: Cross-Sectional Study

Sample of patients and data collection

This prevalent cohort of stable kidney transplanted patients (Tx) was selected by inviting all patients 18 years or older (n=1067) who were regularly followed at a single kidney transplant outpatient clinic at the Department of Transplantation and Surgery at Semmelweis University, Budapest on June 30, 2002, to participate in our cross-sectional study (Transplantation and Quality of Life- Hungary Study, TransQoL-HU Study). All patients received renal transplant between 1977 and 2002. We also approached all waitlisted dialysis patients (n=214)(WL), who were listed with the above transplant center on June 30, 2002, and had been receiving dialysis for at least one month in any of the nine dialysis centers in Budapest. Data were collected between August 2002 and February 2003. Patients who had an acute rejection or infection within one month of data collection, had dementia or refused to participate, were excluded.

Socio- demographic data

Socio-demographic parameters collected at enrollment were: age, sex, level of education, marital status (married/common-law or single/separated/widowed), occupation (full time or

part time job, unemployed/disability benefit) and perceived financial situation (good, fair or poor).

Transplant and dialysis related data

Transplant and dialysis related data extracted from the medical records included the following information: etiology of CKD, medications (including current immunosuppressive treatment), single pool (sp) Kt/V, 'vintage', i.e. time elapsed since the time of the transplantation or since starting dialysis treatment. Cumulative End Stage Renal Disease (ESRD) time (time elapsed since the initiation of the first treatment for ESRD), donor type (cadaver vs. living), sex and age of the donor were also computed.

Laboratory parameters

Laboratory data were extracted from patients` charts and from the electronic laboratory databases of the hospitals. The following laboratory parameters were tabulated: hemoglobin, serum C-reactive protein, serum creatinine and serum albumin. Estimated glomerular filtration rate (eGFR) was calculated using the 4-variable Modification of Diet in Renal Disease (MDRD) Study equation: GFR (ml/min/1.73m^2) (to convert to ml/s/1.73m^2, multiply by 0.01667) = 186 x $(S_{Cr})^{-1.154}$ x $(Age)^{-0.203}$ (x 0.742 if female).

Based on the eGFR, patients were classified into groups corresponding to CKD stages: group 1: GFR≥60ml/min/1.73 m^2; group 2: GFR 30-59 ml/min/1.73 m^2; group 3: GFR<30 ml/min/1.73 m^2.

Assessment of depressive symptoms

Symptoms of depression were assessed by the Hungarian version of the Center for Epidemiologic Studies- Depression (CES-D) scale. In the present analysis, the CES-D score was used to describe the severity of depressive symptoms in the sample. In addition, cut-off score of 18 was used to identify patients with high risk for clinically significant depressive symptoms, as suggested in chronic kidney disease patients by Hedayati et al.

Self-reported co-morbidity

Information about the presence or absence of co- morbid conditions was obtained from the patients, as described. Self-reported co- morbidity score was calculated by summing up the number of co- morbid conditions the patients reported.

Immunosuppressive therapy in transplanted patients

Standard maintenance immunosuppressive therapy generally consisted of prednisolone, either cyclosporine A microemulsion formulation (CsA) or tacrolimus, combined with mycophenolate mofetil (MMF) or azathioprine or sirolimus. Based on the actual immunosuppressive therapy patients were also grouped into six mutually exclusive categories: 1) patients receiving CsA, MMF with or without steroids; 2) CsA, azathioprine and steroids; 3) CsA and steroids; 4) tacrolimus, MMF and/or steroids; 5) tacrolimus, azathioprine and steroids or 6) other immunosuppressive therapy.

Statistical Analysis

Statistical analysis was carried out using the SPSS 13.0 software. Continuous variables were compared using the Mann-Whitney U test and categorical variables were analyzed with the chi-square test. The Kruskall-Wallis test was used to analyze the relationship between continuous and categorical variables. Bivariate analysis was performed using the Spearman rank correlation analysis. For multivariate analysis, linear and logistic regression analysis was used. To analyze factors independently predicting the CES-D score linear regression with square- root (CES-D score) as dependent variable was used, as the distribution of the depression score deviated substantially from the normal distribution. In these models, square-root of the depression score or the presence of depression (CES-D≥18) were the dependent variables. Variables that showed significant association with depressive symptoms in the bivariate analysis were entered into the multivariate model. Additional variables were selected on a theoretical basis, variables which are known to be associated with depressive symptoms from previous research or which are thought to impact on depressive symptoms based on clinical experience were entered into the models.

2. Depressive Symptoms and Mortality in Patients after Kidney Transplantation – a Prospective Prevalent Cohort Study

Follow-up

Patients were followed from the day of the baseline visit to the time they returned to dialysis or died or until December 31 2007. Patients were censored if returned to dialysis or lost to follow- up. Median, [interquartile range - IQR] follow- up time was 58 [7] months (follow- up range: 59 months). Data on outcomes were collected during the follow-up period by persons who were blind to patients' CES-D score at baseline and entered in our electronic database. The cause of death was extracted from the charts. Two primary outcome measures were

defined: mortality with working graft (1) and death censored graft loss - return to dialysis (2). Initiation of dialysis was based on clinical decision made by the main responsible nephrologist of the patient.

Statistical Analysis

Statistical analysis was carried out using the SPSS 15.0 software. Continuous variables were compared using Student's t-test or the Mann-Whitney U test and categorical variables were analyzed with the chi-square test. To assess variables associated with the outcome measures, univariate and multivariate Cox proportional hazards analyses and Kaplan-Meier survival plots were used. To assess the independent association between depressive symptoms and outcomes all variables known to be associated with mortality/ death censored graft loss based on external evidence and clinical knowledge were included in the final multivariate models. As the number of deaths was relatively small and the number of potential co-variables to adjust for was relatively high, we did the multivariate analysis in three steps. In the first model, we adjusted for age and gender. In the next step, we also adjusted for the number of self- reported comorbid conditions and ESRD "vintage". All potentially important variables were included in the final model.

3. Psychosocial Variables Associated with being Waitlisted and Receiving a Transplant in Patients on Hemodialysis in the Dialysis Outcomes and Practice Patterns Study (DOPPS)

Study sample

DOPPS is an international, prospective cohort study of hemodialysis practice patterns and associated outcomes. DOPPS phase II included 322 and DOPPS phase III 198 dialysis facilities in 12 countries (Australia, Belgium, Canada, France, Germany, Italy, Japan, New Zealand, Spain, Sweden, United Kingdom and United States), with data collected between 2002- 2004 (DOPPS II) and 2005- 2008 (DOPPS III). Further details of the DOPPS data collection protocol and study design have been described elsewhere.

Included in the present analyses were 18-65 year-old patients from the United States and 7 European countries (Belgium, France, Germany, Italy, Spain, Sweden, United Kingdom) participating in DOPPS II (N=2149) and DOPPS III (N=4360). Analyses were based on a prevalent cross- section of patients in each facility. Socio-demographic factors, laboratory parameters, and co- morbidities were collected from medical charts at patient entry into the study.

Depressive symptoms

Depressive sympoms were assessed by the 10-item version of the Center for Epidemiologic Studies- Depression (CES-D) scale. Each response item is coded on a scale of 0 to 3 points; a CES-D score ranging from 0 to 30 is calculated by summing up the score of each item. Higher scores indicate greater level of depressive symptoms. A cut-off value of ≥10 was used to identify patients with high risk of clinically significant depressive symptoms based on prior work.

Health- related quality of life (HR-QoL)

Patient responses to the Kidney Disease Quality of Life- Short Form 12 (KDQOL- SF-12) were used to determine scores of HR-QoL. In the present analysis, the Physical Component Summary (PCS) score was used to describe physical aspects of HR-QoL.

Follow-up

Waitlisted patients aged 18 to 65 years (N=1905) were followed from study entry to deceased donor kidney transplantation. Patients were censored if they died or left the study for any reason (i.e., change in modality, transferred to another unit, etc.) other than the main outcome. The median follow up time was 1.57 patient- years (interquartile range, IQR=1.57 years).

Statistical analysis

Differences in baseline demographics and clinical characteristics between waitlisted and non-waitlisted patients were analysed using Student's t-test for continuous variables, and Chi-square test for categorical variables.

Multivariable logistic regression was used to estimate the adjusted odds ratio (AOR) for being on the transplantation waiting list among hemodialysis patients aged 18 to 65 years.

Transplantation rates by country are reported per 100 patient years and left- truncated for the time since the start of ESRD, for patients of age 18 to 65 years and who were on a kidney transplant waiting list (N=1905).

The association between socio-demographic factors, clinical variables, and self- reported measures and receiving a transplant in 18-65 year-old waitlisted patients was examined using Cox proportional hazards regression. All Cox models were left-truncated with regard to the date the patient started ESRD.

All analyses were performed with the SAS statistical package, version 9.2 (SAS Institute, Cary, NC).

RESULTS

1. Symptoms of Depression in Kidney Transplant Recipients: Cross-Sectional Study

Demographics and baseline characteristics of the sample

Data on depression was not available due to refusal or inappropriate completion of the questionnaire for 20% (213/1067) of the transplanted (Tx) and 18% (38/214) of the waitlisted (WL) patients (non-participants). The final sample analyzed, therefore, consisted of 854 Tx and 176 WL patients. Participants and non-participants were similar in age, sex distribution, number of co-morbid conditions, hemoglobin, albumin, eGFR or spKt/V, education and self-reported financial status in both the Tx and the WL group.

The mean spKt/V of the WL patients was 1.27±0.24. The mean eGFR in the Tx group was 49.61±22.37 mL/min/1.73 m^2. Dialysis or transplant "vintage" (median [interquartile range - IQR]) was 35 [39] and 54 [64] months for the WL vs. the Tx group, respectively.

Sixty nine percent (563) of the Tx patients were taking CsA, 708 (87%) were administered prednisolone, 64% were on MMF, 147 (18%) patients were administered tacrolimus and 96 patients (12%) were on azathioprine. Only 20 transplanted patients (2%) were given sirolimus.

Severity of depressive symptoms in transplanted versus waitlisted dialysis patients

Unadjusted severity of depressive symptoms was significantly higher in the WL vs. the Tx group. Median [interquartile range, IQR] CES-D score was 12 [15] vs. 9 [11] for the WL vs. Tx groups, respectively (p=0.001). Similarly, depression (defined as CES-D≥18) was significantly more prevalent in the WL than in the Tx group (33% vs 22%, p=0.002). Antidepressants were prescribed for 1.2% (10/854) of Tx and 1.7% (3/175) of WL patients. 6.7% of the transplanted and 5.7% of the waitlisted patients were taking anxiolytics.

In multivariate analysis, receiving dialysis remained significantly and independently associated with the CES-D score and the presence of depression (odds ratio: 2.01 95% confidence interval: 1.25-3.23, p=0.004).

Correlates of depressive symptoms in kidney transplanted patients

Socio- demographic characteristics

Increasing age was weakly, but significantly correlated with increasing CES-D score (rho=0.089, p=0.009). The median [IQR] CES-D score was significantly higher in female than in male patients (11 [13] vs. 9 [10]; p=0.04) and the proportion of depressed patients was

significantly higher in females than in males (26% vs. 19%, female vs. male, p=0.02). The severity of depressive symptoms was significantly associated with self- reported socio-economic status, assessed by both perceived financial situation and by the level of education. The prevalence of depression was significantly lower among those who had at least part time job versus among patients without a job (13% vs. 25%; p<0.001). Depression was significantly less frequent in married vs. single/separated/widowed patients (18% vs. 30% in married vs. single/separated/widowed patients, respectively; p<0.001).

Renal function

eGFR showed a weak but significant negative correlation with the CES-D score (rho= -0.133, p<0.001). Furthermore, both the prevalence of depression and the median CES-D score increased with declining graft function in groups formed by eGFR. The median [IQR] CES-D score was 8 [11], 10 [11] and 12 [14] for group 1, group 2 and group 3, respectively (p<0.001).

Self-reported co-morbidity and laboratory parameters

The prevalence of depressive symptoms was similar in patients with and without diabetes (25% vs. 22%, p=0.44). Increasing number of self-reported co-morbid conditions was significantly associated with increasing prevalence of depression (12% vs. 19% vs. 32% for patients with 0 vs. 1 or 2 vs. 3 or more co-morbid conditions, respectively; p<0.001).

Serum albumin, hemoglobin and serum C- reactive concentrations were similar in patients with and without depression. The CES-D score showed a weak, but significant positive correlation with serum C-reactive protein (CRP) (rho=0.112, p=0.007).

Immunosuppressive medications

None of the immunosuppressive drugs were significantly associated with the presence of depressive symptoms. We also performed analyses across groups managed with mutually exclusive combinations of immunosuppressive medications. There were no differences in the CES-D score and the prevalence of depressive symptoms among these groups either.

Transplantation- related variables and donor characteristics

We did not find any differences in total ESRD- time or transplantation ‘vintage’ in patients with vs. without depression. The type, age and sex distribution of donors was similar between depressed and non- depressed kidney transplant patients.

Multivariate analysis

Logistic regression model was built to assess the independent association between the presence of depression (CES-D≥18) and clinical and socio-demographic parameters. CES-D≥18 was the dependent variable and the following were included as independent variables: age, sex, occupation, perceived financial situation, marital status and level of education, number of co- morbid conditions, BMI, serum albumin, hemoglobin, CRP, eGFR and transplant 'vintage'. In this model, perceived financial situation, marital status,the number of co-morbid conditions and eGFR were significantly associated with the presence of depression.

Financial situation, marital status, the number of self- reported co- morbid conditions, eGFR and serum CRP were significantly and independently associated with the square- root of the CES-D score in a linear regression model which included the same independent variables as the model above.

2. *Depressive Symptoms and Mortality in Patients after Kidney Transplantation – a Prospective Prevalent Cohort Study*

Baseline characteristics of the sample

The cohort was followed-up over a median of 58 months. Over 3521 person-years, 125 patients died (crude mortality rate = 28/1000 person-years) and over 3245 person-years of follow-up, 95 kidney grafts were lost (crude rate of death censored graft loss = 34/1000 person-years). During the follow-up 23% of mortality was due to cardio- or cerebrovascular diseases, 27% to infections, 19% to malignant disorders and 31% to other or unknown cause. We did not find any association between the cause of death and the presence of depression.

Multivariate analyses of transplanted patients' mortality and death censored graft loss

To analyze the independent association between the CES-D score and mortality three multivariate models were built. In the first model (Model 1) we adjusted for age and gender. In the next step we also adjusted for the number of self- reported comorbid conditions (including diabetes) and ESRD "vintage". Finally, all potentially important variables associated with outcomes were included in Model 3. Accordingly, age, gender, the number of self- reported comorbid conditions, ESRD "vintage", eGFR, serum albumin, hemoglobin and serum CRP were the co-variables entered into the final Cox model, in addition to the CES-D score, respectively.

In the final model (Model 3) the CES-D score ($HR_{\text{for each 1 point increase}}$= 1.02; 95% CI: 1.00-1.04) was significantly associated with mortality. The CES-D score was also significantly associated with death censored graft loss ($HR_{\text{for each 1 point increase}}$= 1.03; 95% CI: 1.01-1.05). The CES-D score remained a significant predictor of mortality and death censored graft loss even if transplant „vintage" instead of total ESRD „vintage" was included in the models (not shown).

Analyses using the "presence of depression" (CES-D≥18) as independent variable

In the study population, the frequency of negative outcomes was significantly higher in patients with versus without CES-D≥18 (depression)(mortality: 21% vs 13%; p=0.004; death censored graft loss: 14% vs 11%; p=0.1). Patients without depression had significantly better survival chance than those with depression, as it is presented by the Kaplan-Meier survival plot. A similar trend was seen for death censored graft loss.

In univariate Cox proportional hazards model mortality and the presence of depression were significantly associated (CES-D≥18)(HR_{presence}= 1.72; 95% CI: 1.18-2.51). A trend for increased risk of death censored graft loss in patients with depression was also seen (HR_{presence}= 1.46; 95% CI: 0.93-2.29) but this was not statistically significant.

In the final multivariate Cox model, the presence of depression at baseline significantly predicted mortality (HR_{presence}= 1.66; 95% CI: 1.12-2.47). The association between the presence of depression and death censored graft loss did not quite reach statistical significance, although a trend for worse graft survival in depressed patients is suggested by the Kaplan- Meier plot. When the multivariate analyses were repeated using a CES-D cut off score of 16, which is suggested for the general population, qualitatively similar results were obtained.

3. Psychosocial Variables Associated with being Waitlisted and Receiving a Transplant in Patients on Hemodialysis in the Dialysis Outcomes and Practice Patterns Study (DOPPS))

Differences in baseline characteristics between waitlisted and non-waitlisted patients:

Expectedly, there were significantly more patients in younger age categories among waitlisted than among non- waitlisted patients. Fifty six percent (US) and 60% (Eur) of the patients were male. Most patients had been on dialysis for more than 24 months and only small percent of waitlisted patients had ESRD time less than 6 months (10.3 % (US) vs 12.6% (Eur)). As expected, waitlisted patients had less co-morbidities than the non- waitlisted group. Differences in serum albumin and hemoglobin concentrations between waitlisted and non-

waitlisted patients did not appear to be clinically significant. BMI was also similar in the two subgroups.

Differences in HR- QoL and depressive symptoms

Patients on the waiting list had significantly lower depression scores than non- waitlisted patients. In Europe, 32.5% of waitlisted vs 41.4% of non-waitlisted patients, while in the US 30.3% of waitlisted vs 38.3% of non-waitlisted patients had CES-D scores ≥10, indicating high risk of clinically significant depressive symptoms ($p<0.001$). In both regions, median HR- QoL scores were significantly higher (representing better HR- QoL) among waitlisted vs. non- waitlisted patients.

Wait- listing rates in the whole study sample by countries

Percentage of waitlisted patients varied widely, ranging from 14% in Sweden to 31% in the United Kingdom. There was a decreasing trend in wait-listing with increasing age in each country. Only a few patients over 65 years were on the transplant waitlist (1% in Italy, to 7% in the UK).

Registration on the kidney transplantation waiting list- multivariable logistic regression models

A series of multivariable logistic regression models were built to analyze the independent associations of potential explanatory variables and being on the waitlist in 18-65 year-old patients. First we adjusted for socio-demographic variables (age, gender, race/ethnicity, level of education). In the next step (Model 2) clinical variables (serum albumin, hemoglobin, dialysis vintage and 8 summary comorbid conditions) were also included. Model 3A was adjusted for PCS scores and Model 3B for CES-D scores, as well. The final model included all variables above.

In the final model older age, less education, lower serum albumin and hemoglobin levels, shorter time on dialysis, presence of diabetes mellitus (DM), congestive heart failure (CHF), peripheral vascular diseases (PVD) and cerebrovascular diseases were independently associated with decreased odds of being on the waitlist.

Self- reported measures of subjective well- being and self- reported depressive symptoms were significantly associated with wait-listing. Each 5-point decrease in the PCS scores (i.e. worse HR- QoL) was associated with 9% reduced odds of being waitlisted. Increasing CES-D

score was an independent predictor of reduced odds of being waitlisted, 5-point increase in the depression score reduced the odds of being waitlisted with 9%.

Kidney transplantation rates among 18-65 year-old patients

Overall 35% of waitlisted hemodialysis patients ages 18 to 65 years received a kidney transplant during the follow-up period. Transplantation rates reported per 100 patient-years and left- truncated for the time since the start of ESRD varied between 4 (Germany, Italy and United Kingdom) and 11 (Sweden) among the eight participating countries.

Kidney transplantation rates - Cox regression models

A series of multivariable Cox regression models were built to analyze the relative risk (95% CI) for receiving a kidney transplant within the follow-up period among patients 18-65 years of age who were on the transplant waitlist, similarly to the logistic regression models.

The results of the final model indicated a HR of receiving a transplant of 0.75 (0.61-0.91) for females, 0.66 (0.44-1.00) for blacks and 0.67 (0.52-0.87) for patients having less than 12 years of education. Patients having lower hemoglobin levels (HR=0.93 for each 1 g/dl decrease in hemoglobin, 95% CI= 0.87-1.00) and being on dialysis for longer time (HR=0.92 for each 6-month increase in vintage, 95% CI= 0.86-0.98) were less likely to get a transplant. Furthermore, patients having coronary artery disease (HR=0.74, 95% CI= 0.60-0.91) or congestive heart failure (HR=0.66, 95% CI= 0.51-0.86) also had reduced rates of transplantation.

CES-D scores and PCS scores were not an independent predictor of receiving a transplant over the follow-up period.

CONCLUSIONS, NEW RESULTS

In my dissertation, I have assessed the severity and significance of depression, and analysed the parameters associated with depressive symptoms in dialyzed and kidney transplanted patients. The new results of this work are the following:

- We demonstrated that the severity of depressive symptoms and the prevalence of depression is significantly lower in transplanted than in waitlisted dialysis patients with comparable characteristics;
- The modality of renal replacement therapy (dialysis vs transplantation) is an independent predictor of the severity of depressive symptoms and the presence of

clinically significant depression in patients with CKD, even after … for socio-demographic and clinical parameters;

- We showed that socio- demographic factors (marital status, self-reported financial situation), renal function, and co- morbidity are independently associated with depressive symptoms in kidney transplanted patients
- We have found that depressive symptoms are independently associated with mortality and death censored graft loss - return to dialysis in a large sample of renal transplant recipients.
- We reported that worse self- reported HR- QoL and self- reported depressive symptoms are associated with lower odds of being wait-listed.
- Subjective measures of well-being, however, were not associated with receiving a kidney transplant during the follow-up period.

In summary, we have shown here that the severity of depressive symptoms is significantly lower in kidney transplanted than in waitlisted dialysis patients with comparable characteristics. The prevalence of significant depression, however, was still quite high in the transplanted group - comparable to patients with other chronic medical conditions. Several socio- demographic and clinical variables are independent predictors of depressive symptoms in kidney transplanted patients. Further longitudinal assessment and interventional studies are needed to better understand the development and the causes of depressive symptoms in these patient populations.

We showed that depressive symptoms are independent predictor of patient survival and death censored graft loss in kidney transplanted patients. We, therefore, believe that screening for depressive symptoms could be advised during the regular follow-up of kidney transplanted patients. Patients who have scores above the suggested cut-off on a screening scale, should be further evaluated by mental health professionals. Our results call for randomized studies assessing the effect of treating depression on various outcomes, including mortality and quality of life, in this patient population.

We identified for hemodialysis patients two new factors, self-reported depressive symptoms and health-related quality of life, which are associated with being on the transplant waitlist. Depressive symptoms are often modifiable, both pharmacotherapeutical and psychotherapeutical interventions could successfully treat depression in patients with chronic kidney disease. Furthermore, HR-QoL assessment could provide important additional information about the well-being of individuals with CKD which is not readily available from

other sources that are currently used to monitor the patients. We suggest that depressive symptoms and health-related quality of life should be assessed on a regular basis in chronic hemodialysis patients, because these are important factors to identify patients with diminished access to transplant waitlisting and therefore kidney transplantation.

PUBLICATIONS

Publications associated with the dissertation

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