Kidney Transplantations For The Elderly

- Is there a significant difference in outcome?

Version 2

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Abstract

**Background:** Kidney transplantation is the most adequate treatment for end stage renal disease patients and the group of patients, who undergo kidney transplantation, increase in age. Therefore it is of interest to observe if the age in itself affects the patient and graft survival for the elderly recipients compared to the younger. The primary aim is to see if the combined patient and graft survival is similar in different age groups.

**Method:** This is a single center retrospective study based on data collected from local and national registry (TIGER and SNR). The patients were stratified into four ages cohorts; 55-60, 60-65, 65-70 and 70+. The primary endpoint was the combination of graft and patient survival after 10 years.

**Result:** The study involves 654 patients transplanted for the first time with a kidney from a deceased donor between 1995-01-22 and 2015-11-30. The observation time was in median 11.8 years. There was no significant difference in graft and patient survival between the age groups, but the report shows a tendency that until 5,4 years, the 70 and over has better graft and patients survival rate than the other groups.

**Conclusion:** This study concludes that the results of kidney transplantation in patients older than 70 years of age are excellent and the combined patient and graft survival is similar to younger patients when observed up 10 years. At the end of the observation time there is a tendency to a decline in survival as the elderly patients dies more frequently.
**Abbreviations**

CKD – Chronic kidney disease  
DD – Deceased donor  
ECG - Electrocardiogram  
ESRD – End stage renal disease  
GFR – Glomerular filtration rate  
HLA- Human leukocyte antigen  
LD – Living donor  
NOS – Not otherwise specified  
SNR – Svenskt Njurregister (The Swedish Renal registry)  
SU/GOT - Sahlgrenska University Hospital, in Gothenburg
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Background

Kidney disease prevalence in the population varies after how the definition is set and generally kidney diseases are detected in a late stage because uremic symptoms, like fatigue and weight loss, occur first when the kidney has an 80-90% kidney function loss. The treatments for chronic kidney disease (CKD) are:

- Dietary protein restriction in order to decrease the level of urea under the limit for symptoms and nitrogenous metabolites.
- Dialysis treatment.
- Kidney transplantation.

Common co-morbidities are hypertension and renal anaemia. Hypertension is important to pay attention to and control since the blood pressure is generally dependent on salt and volumes. Renal anaemia affects almost all patients with CKD and is treated with erythropoiesis-stimulating agents.

About 3500 patients in Sweden have chronic dialyse treatment and 4600 patients have a functional kidney transplant [1].

CKD is defined as:

1. ‘Kidney damage for \( \geq 3 \) months, as defined by structural or functional abnormalities of the kidney, with or without decreased glomerular filtration rate (GFR), manifest by *either:* Pathological abnormalities; or Markers of kidney damage, including abnormalities in the composition of the blood or urine, or abnormalities in imaging tests.

2. GFR \(<60\text{mL/min/1.73m}^2\) for \( \geq 3 \) months, with or without kidney damage’ [2].

There are five stages of CKD in regard to the level of GFR. During the first two stages, the GFR is around \( \geq 90 \) respectively 60-89, and the patient often has no symptoms. A CKD diagnosed in these stages is often detected during an investigation of hypertension or cardiovascular diseases. Regardless of the etiology a vicious circle of self-destruction occurs because the remaining nephrons increases its function to an unsustainable point and in stage 4 the GFR is around 15-29 [1,2]. The main etiologies for patients with end stage renal disease (ESRD), who are transplanted, are chronic glomerulonephritis, diabetic nephropathy, chronic pyelonephritis, nephrosclerosis and polycystic kidney disease [3]. When the GFR is \(<15\), the
kidney has very few functional nephrons and the body still tries to uphold the homeostasis. This is called kidney failure and kidney replacement therapy is required [1,2].

For patients with ESRD, kidney transplantation is the most adequate treatment because of its improvement of life quality. Compared to patients on the transplant waiting list, remaining on dialysis, the transplanted patients have longer survival and patients remaining on dialysis accumulate more co-morbidities and complications [4,5]. Most kidney transplanted patients experience that they have received their life back after the surgery and the thought of returning to dialysis treatment is frightening (personal communication). In terms of value for the society, kidney transplantation is to prefer as it costs five times less than chronic dialysis during a period of five years [3].

At kidney transplantation the new kidney is placed extra peritoneal in the recipient’s iliac fossa. An anastomosis is then created between the iliac artery and vein and the kidneys vessels. The kidney’s ureter is implanted in the bladder. The recipients own kidneys are left untouched. The donated kidney can be from living donors (LD) or from deceased donors (DD) [3]. In Sweden about 60 % originate from a DD and in the remaining cases from a friend or relative [1]. Most of the transplants function from the start, especially kidneys from LD. Some of the kidneys from DD have sustained ischemic injury and do not function immediately. The kidney transplant has then delayed graft function, and the patient have to go on dialysis during the first period of time [3].

In Sweden there are four units who perform kidney transplantations; Stockholm, Gothenburg, Malmö and Uppsala, each with their own waiting list [6]. In 2014 there were 440 kidneys transplanted and 151 of them were from LD. 626 patients were on the waiting list for a kidney after the first 6 months of 2015, so the limiting factor is the number of kidneys [7]. The four units are similar when it comes to routines for investigations, the medical criteria for acceptance of kidney transplantations and they are all following national and international guidelines [6,8]. There is no difference in graft survival and patient survival after kidney transplantation between the four units and when the results are compared with centres from Canada and USA [8]. A study from a European material showed that overall 5- and 10-year graft survival rates are 77 % respectively 56 % [5].
The allocation of the kidneys for transplantation is based on the main criteria’s: to achieve justice and be beneficial [9], also called utilitarianism. Which means to ‘benefit morality; a moral doctrine means that one should always act so that the consequences of what you do will be as good as possible in the sense that the total welfare of all sentient beings will be as great as possible’ [10]. The main principle of the distribution is that the patient on top of the waiting list, in their blood group, gets the kidney that is offered [9]. All patients on the waiting list are patients who have not found a LD. Once a year all the patients on the waiting list has to do an autologous cytotoxic B cells cross-match test, between patient serum and patient cells, to detect nonspecific (irregular) antibodies. The cytotoxic T- and B cells cross-match, that is done when a kidney is available, and frozen patient serum (not older than 3 months) is used against donor cells to detect donor-specific HLA antibodies of IgM and IgG type. At last, a more sensitive cross-match test is then performed, named flow cytometric T cells cross-match, to detect donor-specific HLA antibodies of the IgG type before the kidney transplantation can be executed [11]. Patients with antibodies are an exception and always go first in line if a kidney is available and the cross-match is negative. With the current strategy to allocate kidneys the patient age in itself not an obstacle, only the medical conditions that often come by age [9].

Factors that potentially increase the risk of death after kidney transplantations are;

- Age at transplantation.
- Time in dialysis before renal transplantation.
- Presence of diabetes.
- Transplantation of a kidney from a DD.

It have also been seen that cardiovascular diseases, obesity, HLA-mismatch and type of immunosuppression that is used also influences the graft and patient survival [8]. The population of patients are aging though and it is a more complex issue to transplant patients over 65 years than younger patients. One reason is the higher risk for the elderly recipient to get post-operative infections, and they have therefore an increased risk of transplant loss. As a result younger recipients potentially have a better survival outcome than older transplant recipients. It has also been shown that kidney transplantation with the use of a LD to an elderly recipient has a significant improvement in survival compared to the use of DD [12].
The investigation of whether a patient is suitable for kidney transplantation apply to all patients. Patients that are over 50 years old, with diabetes or with risk factors for cardiovascular disease have even more specified routines. These patients need to do an ECG during strain and a Doppler sonographer of the pelvic arteries [13]. The extra tests are made as elderly patients often have more co-morbidities and it’s therefore very important to do a proper investigation regarding the patient’s transplantability (personal communication).

As the group of patients that undergo kidney transplantation increase in age it is of interest to observe if the age in itself affects the patient and graft survival for the elderly recipients compared to the younger.

The primary aim is to see if the combined patient and graft survival is similar in different age groups.

The secondary aim is to observe how the primary diseases differ between age groups and if the causes of death differ.

**Materials and method**

The research aims to be used for clinical evaluation at the Transplantation center of Sahlgrenska University hospital. It’s a single center research designed as a retrospective study based on data collected from local (TIGER) and national transplantation registries (Svenskt Njurregister, SNR)

2.1 Study Population

The analysis is based on data received from SNR, between the dates 1995-01-22 to 2015-11-30 at the Transplantation Centre, Sahlgrenska University Hospital, in Gothenburg (SU/GOT). According to the report 2 777 patients between the ages of 18 to over 70 were transplanted at the centre during that time.

The patients were selected so that only patients kidney transplanted for the first time, between the age 55 to over 70, with kidneys from a DD and with the kidney transplantation as their only type of organ transplantation were analysed. A total number of 654 patients were identified.
The patients were stratified into four age cohorts; 55 to 60 (age cohort 1), 60 to 65 (age cohort 2), 65 to 70 (age cohort 3) and finally 70 and over (age cohort 4). The first group, 55 to 60, was used as a control group to compare between the other groups that were classified as elderly patients.

2.2 Endpoints

The study’s endpoint variables were chosen based on clinical knowledge, that they had a value for the patients.

The primary endpoint was the combination of graft and patient survival after 10 years. The observed event was when a graft is lost (defined as when a patient return to dialysis) or the patient dies.

The secondary endpoint was the combination of graft and patient survival after 5 years, graft survival (death censored) and patient survival after 5 and 10 years.

Overall survivals for the patients were defined as when the event of death was reported. The different death causes were categorized: infections, cardiac, malignancy, uraemia, vascular and other. Graft survival (the transplanted kidneys survival) was observed by looking at the transplant survival time, calculated in days, and reported events (that the graft died). The end of the follow-up period was 2015-11-30 and the event will probably not have occurred for all patients and these patients survival time is said to be censored.

Primary renal diseases are categorized in the data from SNR as adult polycystic kidney disease, diabetic nephropathy, chronic glomerulonephritis, hypertension, chronic pyelonephritis, uraemia NOS and other.

2.3 Statistics

In each age cohort the distribution of the different the primary renal diseases was observed by comparing the elderly patients with the control group. In the same way the graft survival was observed in each age cohort. The patient survival was observed by looking into the deceased patient’s death causes and when the death event occurred. Chi-Square tests were used to compare the distribution of primary renal diseases and causes of death between the groups.
The stratified data of the graft and patient survival were analyzed by using of the survival curve analysis with Kaplan-Meier methodology [14]. All analyses were performed in IBM SPSS (Statistical Package for Social Sciences, Microsoft Inc., version 23) and Excel. The significance level was set by a p-value of 0.05 and a confidence interval with 95% threshold.

2.4 Ethics

The evaluation is done as part of a quality review of the kidney transplantations performed at the Transplantation Centre and contains information about patients divided in cohorts and not individuals. It has therefore not been needed to apply for ethical approval, the patients will not be identified and results will be presented on group level.

Results

The study involves 654 patients transplanted for the first time with a DD at the Transplantation Centre, SU/GOT between 1995-01-22 and 2015-11-30. The mean age of all the patients were 63 and in the four cohorts the mean age was 58, 63, 67 respectively 72.

Table 1. Observation time of the patients (n=654) transplanted between 1995-01-22 and 2015-11-30. The time of the observation was measured in years and between the transplantation dates and when the patient deceased or the graft was lost.

<table>
<thead>
<tr>
<th>Age Cohort</th>
<th>Observation time</th>
<th>Std. Error</th>
<th>95 % Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td></td>
<td>Lower Bound</td>
</tr>
<tr>
<td>55-60</td>
<td>12.5</td>
<td>1.0</td>
<td>10.5</td>
</tr>
<tr>
<td>60-65</td>
<td>10.4</td>
<td>0.9</td>
<td>8.6</td>
</tr>
<tr>
<td>65-70</td>
<td>11.5</td>
<td>1.4</td>
<td>8.7</td>
</tr>
<tr>
<td>70+</td>
<td>8.9</td>
<td>2.3</td>
<td>4.4</td>
</tr>
<tr>
<td>Overall</td>
<td>11.8</td>
<td>0.7</td>
<td>10.4</td>
</tr>
</tbody>
</table>

The median for the observation time was 11.8 years overall in the study population with a lower bound of 10.4 years and an upper bound of 13.2 years (Table 1).
3.1 Primary renal diseases

Chronic glomerulonephritis is the disease that is most common overall, as displayed in Figure 1. There was a significant difference p=0.002 in the underlying diseases that caused CKD.

Among elderly patients there were more patients with hypertension. The adult polycystic kidney disease was the disease that varied the most between the cohorts and progressively became less common with age as displayed in Figure 2.

![Figure 1](image1.png)

**Figure 1.** This circle diagram illustrates the distribution of the primary renal diseases for all patients between the ages 55-70+. 1. Adult polycystic kidney disease, 2. Diabetic nephropathy, 3. Chronic glomerulonephritis, 4. Hypertension, 5. Chronic pyelonephritis, 6. Uraemia NOS and 7. Other.
3.2 Secondary diseases

68,7 % of the patients (n=654) had hypertension as a secondary disease when they were transplanted and it was therefore the most common one. The distribution between the cohorts was equal. In the population there were also 14,5 % with diabetes and 8,7 % with ischaemic heart disease.
3.3 Graft survival (death censored)

There was no significant difference in graft survival between the age groups. The 5-year graft survival was numerically higher, 96% in the 70+ cohort compare to the other cohorts (90-91%) (Figure 3).

![Graft survival (Death censored) after 5 years](image)

**Figure 3.** Kaplan-Meier-analysis shows the graft survival of the 654 patients, allocated in four cohorts, transplanted between 1995-01-22 and 2015-11-30 after 5 years.
When the analysis was expanded to 10 years the graft survival was 80, 86, 85 and 93% in the four age groups.

After 8,9 years there were only 2 grafts still functional in the 70+ cohort and most patients were censored due to death (Figure 4).

3.4 Graft and patient survival

There was no significant difference in graft and patient survival between the age groups. When the combined endpoint was analysed after 5-year the combined survival was 82, 80, 79 and 91% in the four age groups (Figure 5).

When the analysis was expanded to 10 years the combined survival was 63, 64, 64 and 76% in the four age groups (Figure 6).

**Figure 4.** Kaplan-Meier-analysis shows the graft survival of the 654 patients, allocated in four cohorts, transplanted between 1995-01-22 and 2015-11-30 after 10 years.
Figure 5. Kaplan-Meier-analysis shows the graft and patient survival of the 654 patients, allocated in four cohorts, transplanted between 1995-01-22 and 2015-11-30 after 5 years.

Figure 6. Kaplan-Meier-analysis shows the graft and patient survival of the 654 patients, allocated in four cohorts, transplanted between 1995-01-22 and 2015-11-30 after 10 years.
Until 5.4 years the patients above 70 had better graft and patients survival rate than the other groups (Figures 5 and 6). The overall cumulative proportion survival half time was estimated at 9.7 years with 0.026 as std. error. For the four cohorts the estimation was 10.7, 9.7, and 9.2 respectively 6.0 years.

3.5 Causes of death

Of the patient population 228/654 of the patients died between 1995-01-22 and 2015-11-30 and the most common death causes were cardiac as displayed in Figure 7. The most common cause of in the cardiac category was myocardial ischemia and infarction.

There was no significant difference in the causes of death in the four different age cohorts. Numerically there were more patients that died from an infection in cohort 1, 2 and 3 compared to cohort 4 were none of the patients deceased from it. The cause of death that was the most common in cohort 4 was malignancies. That cause was common in all ages and together with infections the second most common cause of death for all the 228 patients. Vascular causes of deaths had a tendency to be more common in cohort 4 than in the others, but these differences were not significant (Figure 8).
Totally 12 out of 228 deceased patients had no reported death cause and they were therefore included in the “Other”-category. Overall 34 % of the deceased patients (n=228) were dead after 5 years and 74 % after 10 years. 27 % of deceased patients had a graft failure before they deceased.

There were no patterns found between the deceased patient’s death causes and their primary renal disease. All 228 deceased patients had hypertension as secondary diseases. Nor was there a pattern found between death causes and diabetes respectively ischaemic heart disease.

**Figure 8.** This circle diagram illustrates the distribution of the death causes for all the patients between the ages 55-70+. The percentage refers to the proportion of deaths in each cohort. 1. Infections, 2. Cardiac, 3. Malignancy, 4. Uraemia, 5. Vascular and 6. Other.
Discussion

With the long waiting list for kidney transplants both in Sweden and in the rest of the Western world there is a need to utilize this scarce resource in the best manner possible. It has therefore been proposed that kidney transplants should be allocated according to a principle where the kidneys were allocated to those that could benefit most years from the kidneys. This would benefit younger patients on the behalf of elderly patients [15]. It would also be in conflict with Hälso- o sjukvårdslagen (The Swedish Health Care Act), which says that health care should be provided equally for the entire population irrespectively of age, sex and ethnicity and whoever has the greatest need of health care should take precedence to care [16]. It is therefore of great interest to have knowledge how the kidney transplants function in different age cohorts.

The primary aim was to see if the kidney transplants perform differently in different age groups and if the risk for mortality is higher in elderly patients. The kidney transplant in elderly works similar as the kidneys in the younger patients but the elderly’s kidneys don’t work for as long because the elderly patients dies, but not because of kidney diseases.

In this study the Kaplan-Meier methodology was used to observe survival rate and comparing between different groups and it is the commonly used method for this kind of studies and was therefore the natural choice for the study. When comparing the different groups distribution of primary renal diseases and death causes Excel was a great tool when doing diagrams.

The study was based on reports from TIGER and SNR that health staffs have manually reported into and the human factor must therefore take into account. The number of patients was decided after the selection was done, based on the different criteria. Therefore the cohort with the ages 70+ became fewer than in the other groups, which weakens the strengths of the results. A few patients in the study had not available data on whether the patients had been heart transplanted or not. We anticipated that they were not heart transplanted and were therefore included. A factor that was not considered in the study was the difference between different genders and that was because usually the outcome of kidney transplantation is not affected by gender (personal communication).

The kidneys in all the cohorts worked similar and a more appropriate endpoint was therefore the combined endpoint of freedom from patient death or graft loss also described as the combined patient and graft survival. This showed that over time the elderly patients succumb
due to age and concomitant diseases, especially malignancies and not because of graft failure. A reason for the few graft failures in the elderly cohort could be that the elderly patients are better selected patients than the younger and therefore their grafts function better. Hellemans et al. [5] and Elinder et al. [8] highlights the increased risk for mortality that comes with time on dialysis before transplantation and this could be a reason for the greater loss of kidneys in the control group since Hellemans et al. shows that almost all patients on the waiting list over 65 years old get a kidney transplant within a year and the younger patients then get more co-morbidities. The fact that there was less graft lost for the elderly is contradicted by Knoll [12], who means that post-operative infections cause more graft lost in elderly.

The secondary aim was to observe how the primary diseases contribute to the prognosis and what the most common causes are of death. There were no patterns found between the deceased patient’s death causes and their primary renal disease and the most common death cause overall was cardiac, which then shows more of the effect of the secondary disease hypertension.

The results that the primary renal disease’s distribution overall and that chronic glomerulonephritis was the most common overall were expected since it been observed before [3]. The fact that polycystic kidney disease was more common in the younger cohorts is expected as it is one of the most frequently inherited renal diseases worldwide and 50 % of the patients will progress to ESRD by the age of 60 years old [17].

There were no patterns found between the primary diseases and the causes of death, therefore a conclusion can be made that the primary disease don’t have a great impact of the prognosis. The secondary disease, hypertension, though showed an impact of the cause of death since all of the patients that deceased had hypertension and most common casus of death were cardiac. Co-morbidities in general could be of greater impact to the cause of death than the primary diseases. It is difficult to determine how much impact the fact that all patients who deceased had hypertension made. It is a possibility that there were other reasons for the hypertension, for example obesity, and those factors were not included in the study. But on the other hand is hypertension a very common disease and co-morbidities among patients with ESRD, and very closely related to kidney diseases that then have a possibility to affect the prognosis of the transplanted patients. Cardiovascular disease in general and obesity are risk factors that increase the risk for mortality according to Elinder et al. [8] but it’s hard to say how they affected the patients in this report. Another risk factor for mortality that is also mentioned in
Elinder et al is the presence of diabetes. 14,5 % of the patient population was diagnosed with it and 11 % of the patients had diabetic nephropathy as the primary renal disease, but no increased risk among these patients was found compared to the others in general. But since diabetes is a severe disease that affects the whole body it’s hard to estimate how much impact it had on the patients.

The result of the study confirms that the strategy to also transplant patients older than 70 after a careful selection is valid and no changes will be made in that strategy.

**Conclusion**

This study concludes that the results of kidney transplantation in patients older than 70 years of age are excellent and the combined patient and graft survival is similar to younger patients when observed up 10 years. At the end of the observation time there is a tendency to decline in survival as the elderly patients dies. No true pattern was made between the primary renal disease and the cause of the death and it is therefore hard to say how much impact they had on the prognosis.

**References**


