ORIGINAL ARTICLE

Observational study of risk factors associated with clinical outcome among elderly kidney transplant recipients in Sweden – a decade of follow-up

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SUMMARY

Kidney transplantation (Ktx) in elderly has become increasingly accepted worldwide despite their higher burden of comorbidities. We investigated important risk factors affecting long-term patient and graft survival. We included all (n = 747) Ktx patients >60 years from 2000 to 2012 in Sweden. Patients were age-stratified, 60–64, 65–69 and >70 years. Follow-up time was up to 10 years (median 7.9 years, 75% percentile >10 years). Primary outcome was 10-year patient survival in age-stratified groups. Secondary outcomes were 5-year patient and graft survival in age-stratified groups and the impact of risk factors including Charlson comorbidity index (CCI) on patient and graft survival. Mortality was higher in patients >70 years, after 10 years (HR 1.94; 95% CI 1.24–3.04; P = 0.004). Males had a higher 10-year risk of death (HR 1.39; CI 95% 1.04–1.86; P = 0.024). Five-year patient survival did not differ between age groups. In multivariate Cox analysis (n = 500), hazard ratio for 10-year mortality was 4.6 in patients with CCI ≥7 vs. <4 (95% CI 2.42–8.62; P = 0.0001). Higher CCI identified ESKD patients with 4.6 times higher risk of death after Ktx. We suggest that this index should be used as a part of the preoperative evaluation in elderly.

Introduction

Kidney transplantation (Ktx) in the elderly has increased worldwide during the recent decades, which reflects the increase in incidence and prevalence of end-stage kidney disease (ESKD) during the same time period [1–5]. In 2000, only 16% of Ktx in Sweden were >60 years and this percentage more than doubled to 35% by the year of 2019 [6]. Retrospective registry studies have shown a survival benefit in elderly Ktx recipients compared to staying on the waiting list [3–5,7,8].

In a position statement from ERA-EDTA, Segall *et al.* [9] recommends that patients should not be excluded from the waiting list based on chronological age alone. Instead factors like frailty, psychosocial issues and possible comorbidity scores should be included in the preoperative evaluation [9]. Prognostic risk scores may increase the precision of preoperative assessment in the elderly and contributes to a standardization of the evaluation. The Charlson comorbidity index (CCI) and Framingham risk score has been evaluated in earlier studies [10,11]. Modified versions of CCI have been used, and data have been retrieved mainly from registries, comprising the limitations that follows with registry studies [12–14]. Jassal *et al.* [12] investigated four different risk scores in Ktx (*n* = 6324), with the conclusion that 'CCI is a suitable tool for the measurement of comorbidity in renal transplant recipients'. Thus, CCI had the best accuracy of the four risk scores when compared. However, Jassal *et al.* [12] retrieved data from Canadian Organ Replacement Registry (CORR), which is a voluntary countrywide registry. Moreover, CCI was not calculated from all 19 diagnoses but from a subset of diagnoses. It is possible that these limitations in earlier registry studies have diluted the association between CCI and mortality in Ktx. To our knowledge, there is only one previous study (*n* = 130), which has evaluated CCI´s predictive value were all 19 diagnoses were included, in Ktx [15]. The RoCKeT score [14] had an even more precise predictive value than CCI, but this was in comparison with a modified CCI and the RoCKeT score was developed to predict mortality in one specific cohort, retrospectively.

It has been suggested that if we push the age and comorbidity limit in elderly Ktx recipients further, we may eventually lose the advantage of Ktx. The increasing mean lifespan and improved health in many populations in the world [16] might imply a need to expand the upper age limit for Ktx. Consequently, increased awareness of which preoperative clinical factors influences Ktx outcome in the elderly, may improve the possibility for more accurately predicting which patients are most likely to benefit from Ktx and which probably would do better by remaining in dialysis. It is likely that biological age of Ktx recipients should predict outcome after Ktx in a more precise manner than chronological age. The term 'biological age' refers to a combination of an individual´s chronological age and epigenetic changes because of allostatic overload. Allostatic overload, or the wear and tear of the body, is caused by different factors as for example lifestyle burden, inflammation and oxidative stress because of chronic consequences of lifestyle diseases, such as CVD, diabetes, obesity and others [17–19].

In this study based on data retrieved from patient files and national registry data, we have evaluated long-term patient and graft survival and the importance of preoperative risk factors in elderly Ktx recipients. One of the main objectives was to evaluate the complete CCI´s (including all 19 diagnoses) predictive value in a subset of our national cohort of elderly patients. Our hypothesis was that extensive comorbidity at baseline, presented by higher CCI score, predicts patient and graft survival in elderly Ktx.

Methods

We included all 747 patients >60 years of age who received a kidney transplant from year 2000 to year 2012 in Sweden. To avoid selection bias, we included all recipients transplanted during this period. All Ktx centres in Sweden participated in the study (Gothenburg *n* = 199, Malmö *n* = 199, Uppsala *n* = 198 and Stockholm *n* = 151). We stratified the patients in groups according to age at transplantation, 60–64, 65–69 and >70 years. We did not have access to information about the patients' socio-economic status. The patients were transplanted at one of the four transplant centres in Sweden, whereas clinical follow-up was taken place in the whole country, at local, regional or University hospitals. The Regional Ethics Committee of Gothenburg approved the study protocol, ref 1030-16. The study was conducted in accordance with the Helsinki Declaration as revised in 2013. Patient and graft survival were determined in all patients (*n* = 747). Cause of death was recorded in all deceased patients (*n* = 253). When the cause of death was unknown, it was classified as other causes.

Post-transplant diabetes mellitus (PTDM), graft function, immunosuppressive treatment, graft and patient survival were recorded at 1, 5 and 10 years after Ktx. In a subgroup, a detailed analysis of biopsy proven acute rejection (BPAR) and CCI was performed. BPAR was diagnosed by kidney biopsies which were performed on clinical indication. No protocol biopsies were performed. BPAR was classified according to Banff criteria. To evaluate BMI as a risk factor for patient and graft survival in elderly, we stratified for BMI in different categories according to WHO, <18, 18–24.9, 25–29.9 and >30 kg/m^2, respectively. To investigate a possible association between donor age and recipient outcome, the donors were stratified according to chronological age: >70 years or <70 years.

All demographic and clinical data were retrieved from patient files, the Swedish Renal registry (SRR) and from the Scandiatransplant database. All collection of data was coded and approved by the Regional Ethics Committee. A list of missing data is provided in Table S1. Cause of death was retrieved from SRR or from patient files. Patient and graft survival, cause of death, dialysis vintage, comorbidities, BPAR, CMV status in donor and recipients, donor age and PTDM were determined. In the present study, data on HbA1c or oral glucose tolerance test were not available in all patients before transplantation. Thus, the definition of PTDM was based on a new diabetes diagnose stated in patients files or a new onset of the need for treatment with insulin >30 days after Ktx. The diabetes diagnosis was defined by the criteria of the American Diabetes Association. Information on donor characteristics was retrieved from the Scandiatransplant database in deceased donors and from the patient files in living donors.

Charlson comorbidity index

Charlson comorbidity index was calculated at baseline (at the date of Ktx) in a subgroup of patients. There is no evidence that the group of patients without CCI scores was fundamentally different. CCI was modified by extracting the age-generating points from the total score, to enable an analysis of an age-independent CCI. We stratified CCI into clinically relevant groups according to total score (age-excluded): low CCI: <4 points, intermediate CCI: ≥4 and <7, high CCI: ≥7 points. All diagnoses included in the CCI were recorded, and data were retrieved from patient records by transplant physicians or research nurses. The diagnoses included in CCI are as follows: myocardial infarction (1p), cardiac failure (1p), peripheral vascular disease (1p), cerebrovascular disease or TIA (1p), hemiplegia (2p), COPD (1p), mild liver disease (1p), moderate–severe liver disease (3p), diabetes mellitus none or diet-controlled (0p), diabetes mellitus uncomplicated (1p), diabetes mellitus with end organ damage (2p), dementia (1p), lymphoma (2p), leukaemia (2p), malignancy without metastasis (2p), malignancy with metastasis (6p), AIDS (6p), connective tissue disease (1p) and peptic ulcer disease (1p). Each diagnosis included in the CCI was considered in each patient in the subgroup. This was possible by means of an electronic CRF with mandatory yes or no answers for each diagnosis.

Potential confounders as recipient and donor age, recipient and donor sex, type of donor, cause of CKD, transplant centre and dialysis vintage were all included in the Cox multivariate analysis when analysing graft and patient survival. We adjusted for the same potential confounders and CCI in the subgroup of 500 patients, to analyse the importance of comorbid conditions. We used the 'one-at-a-time' sensitivity analysis from different regions. All factors that were affecting outcome one at a time were used in multivariate Cox proportional hazards model for patient and graft survival. When comparing transplantation centres, Gothenburg was chosen as reference.

Statistical analyses

Data are expressed as median (interquartile range, IQR), mean (standard deviation, SD), number or percentage, as appropriate. Statistical significance was set at the level of $P < 0.05$. Comparisons between two groups were assessed with the nonparametric Wilcoxon test for skewed continuous variables and t-test for normally distributed variables and chi-square test Fisher's exact test for nominal variables. Kaplan–Meier survival curves were used to analyse univariate models. Patients were censored at 10 years or time for death or at time for graft failure whichever came first. Multivariate Cox regression analysis was used to evaluate risk factors for 10-year patient survival and graft survival. To evaluate the impact of CCI, we performed one multivariate cox regression analysis including confounders except for CCI and compared it with a multivariate cox regression analysis including the same confounders and CCI. In case of missing data, the patient was excluded from the statistical analysis and we did not perform multiple imputation for the missing values. There were 14 patients who were lost to follow-up, and they were censored. Statistical analyses were performed using statistical software SAS version 9.4 (SAS Campus Drive, Cary, NC, USA) and STATA 16.1 (Stata Corporation, College Station, TX, USA).

Results

Patient characteristics

Recipient median age was 64, (range 60–78) years (Table 1). Median donor age was 62, (IQR 55–67) years. All patients in Sweden >60 years of age who had received a kidney transplant between 2000 and 2012 were included (Fig. S1). Median follow-up time was 7.9 years, in the 75% quartile 10 years and the 25% quartile 6.1 years.

Patient and graft survival

At 10-year follow-up, 253 patients had died, and 51 death-censored graft loss occurred. There were no significant differences in patient survival after five years

Table 1. Baseline characteristics of 747 elderly kidney transplant recipients.

	Total N = 747	Deceased N = 575	Living N = 172	P-value
Age, years	64 (62–67)	64 (62–67)	64 (62–67)	0.65
Recipient sex (males %)	500 (66.8%)	379 (65.9%)	121 (70.3%)	0.27
Presence of diabetes nephropathy	90 (12.0%)	75 (13.0%)	15 (8.7%)	0.13
Pre-emptive kidney transplantation (Ktx)	65 (8.7%)	25 (4.3%)	40 (23.3%)	<0.001
Patients in PD/HD before Ktx, n = 676	251/425	196/348	55/77	0.23
Donor age, years	62 (55–67)	62 (56–68)	61 (52–65)	0.001
Donor sex (males %)	323 (43.4%)	277 (48.3%)	46 (26.7%)	<0.001
Dialysis vintage, months	27 (16–40)	29 (17–43)	18 (10–27)	<0.001
Waiting list time, months	8 (1–21)	12 (5–25)	0 (0–0)	<0.001
Charlson comorbidity index, n = 559	3 (2–4)	3 (2–4)	3 (2–5)	0.002
First Ktx recipient n (%)*	680 (91%)	520 (90%)	160 (93%)	0.33
Second or third Ktx, recipient n (%)	62 (8.3%)	50 (9%)	12 (7%)	

Continuous data expressed as median and IQR. Nominal data expressed as count and percentage. The grey shade represent data from the entire cohort.
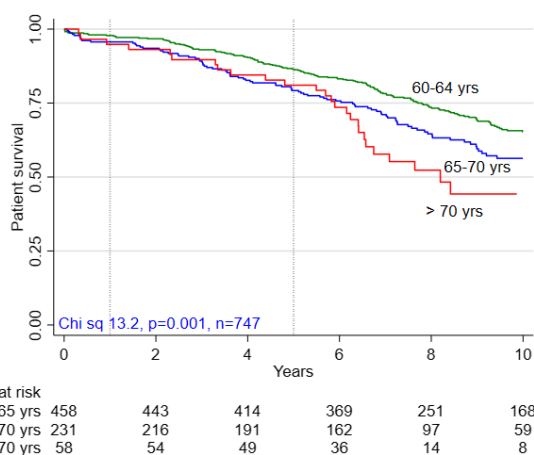
*Ktx recipients information missing (n = 5).

Figure 1 Patient survival stratified by recipient age group, n = 747.

between the age groups 65–69 years and >70 years (Fig. 1). Patient survival at 10 years was 65%, 56% and 44%, respectively (60–64 years, 65–69 years and >70 years). Patients >70 years had a higher hazard ratio of death at 10 years follow-up (HR 1.94; CI 95% 1.24–3.04, P = 0.004) compared to patients 60–64 years after adjustment for confounders (Fig. 2a). In multivariate Cox hazard analysis, males had a higher hazard risk of death compared to females after 10 years (HR 1.39; CI 95% 1.04–1.87, n = 673, P = 0.024; Fig. 2a). This difference in hazard risk for death between males and females remained after adjustment for comorbidity at baseline (Fig. 2b). In the multivariate Cox hazard analysis including CCI (n = 500), recipients with living donors had a lower hazard risk of death over 10 years (HR
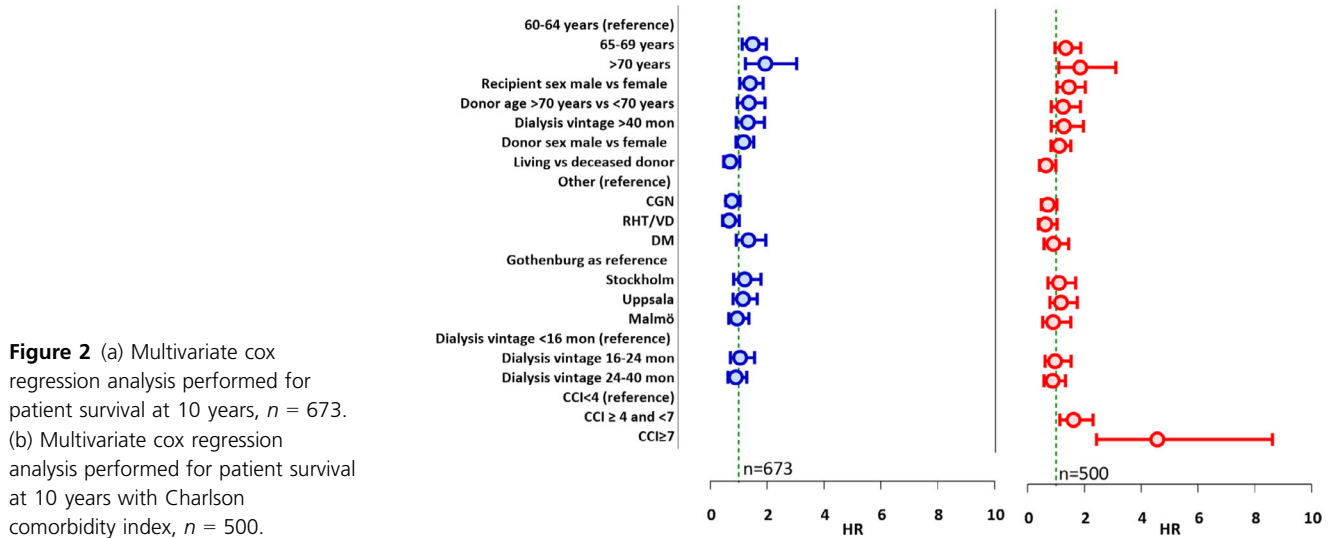
0.64; CI 95% 0.42–0.99, P = 0.049) (Fig. 2b). Death-censored graft survival was 78% at 10 years, all age groups included. We found that recipient age (Fig. 3) was not associated with death-censored graft survival (P = 0.77).

Causes of death

There were no significant differences in causes of death between the different age groups (P = 0.77), sexes (P = 0.11) or regions (P = 0.07). Cardiovascular disease was the most common cause of death 35.6% (n = 90), followed by infections 19.4% (n = 49), malignancy 18.2% (n = 46) and other causes of death 26.9% (n = 68).

Impact of various risk factors

In 548 patients, we analysed the incidence and risk factors of BPAR (Table 2). Most patients had immunosuppression consisting of tacrolimus, mycophenolate and prednisolone (Table 2). Induction therapy (basiliximab) was given to 55% of the patients and did not affect patient survival or the incidence of BPAR. During the first year after Ktx, only 3% received thymoglobulin (as induction or rejection therapy). BPAR occurred in 22% of the patients during the first 6 months and in 5.5% after 6 months. BPAR did not affect death censor graft survival (P = 0.33) or patient survival (P = 0.27). When analysing early and late BPAR, rejections occurring <6 and >6 months did not affect graft survival (P = 0.75).

Figure 2 (a) Multivariate cox regression analysis performed for patient survival at 10 years, n = 673. (b) Multivariate cox regression analysis performed for patient survival at 10 years with Charlson comorbidity index, n = 500.

The frequency of BPAR did not differ in the stratified age groups (data not shown).

BMI was available in 534 patients; among these, 44.5% of patients had BMI ranging from 18 to 24 kg/m^2 and 43% of patients had BMI between 24 and 29 kg/m^2. Only 12% had a BMI >29 kg/m^2, and 0.5% had BMI <18 kg/m^2. BMI was not statistically associated with patient or death-censored graft survival (data not shown). The incidence of PTDM was available in 572 patients and occurred in 8% of these patients. PTDM was not associated with patient or death-censored graft survival (data not shown). In a multivariate Cox regression analysis, dialysis vintage and donor age was not associated with death-censored graft survival (data not shown) or patient survival (Fig. 2a,b).
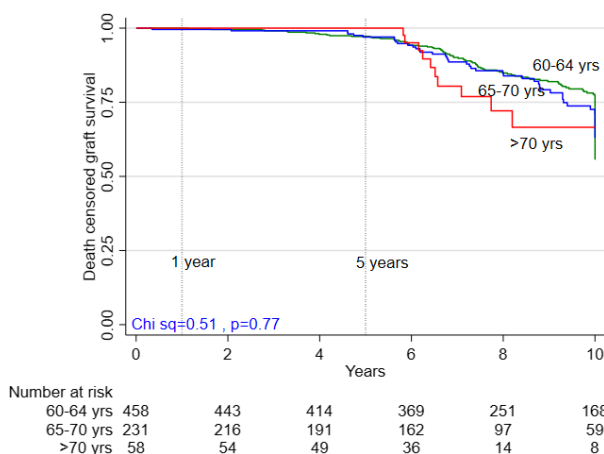
Charlson comorbidity index

CCI median was 3.0 (IQR 2.0–5.0). CCI median and IQR was the same in age groups 60–64, 65–69 and >70 years (P = 0.64). The unadjusted association between CCI and patient survival was analysed in 559 patients (Fig. 4). We found an unadjusted association between CCI and patient survival also when dividing patients in >65 years (n = 209, P = 0.002) and <65 years (n = 350, P = 0.001). We performed multivariate Cox regression analysis (n = 500) adjusted for CCI, recipient sex, donor age group, dialysis vintage, region, donor sex, living or deceased donor, cause of CKD and found a higher hazard risk of death

Figure 3 Death-censored graft survival stratified by recipient age group, n = 747.

Table 2. Immunosuppression, Post-transplant diabetes mellitus during the first 12 months after transplantation and biopsy proven acute rejection (BPAR).

|	Total (%)
Basiliximab, n = 514	282 (55)
Thymoglobulin, n = 514	13 (3)
Tacrolimus, n = 536	394 (74)
CyA, n = 549	173 (32)
Azathioprine, n = 514	35 (6)
Mycophenolate mofetil, n = 563	440 (78)
Everolimus, n = 511	17 (3)
Belatacept, n = 511	3 (1)
Corticosteroid, n = 556	529 (95)
Post-transplant diabetes mellitus, n = 572	44 (8)
Biopsy proven acute rejection <6 months, n = 548	122* (22)
Biopsy proven acute rejection >6 months, n = 548	30* (5.5)

*Excluding patients from Malmö region.
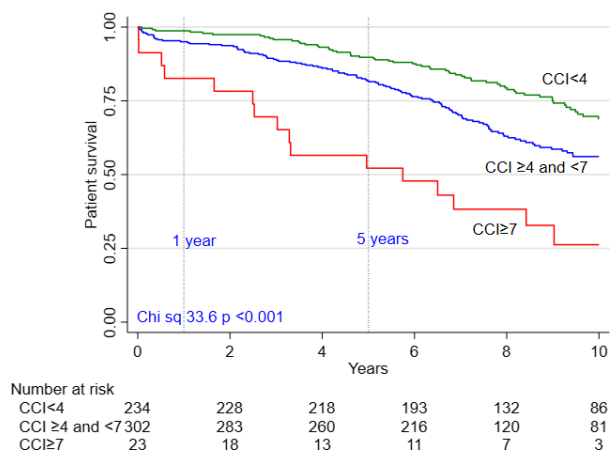
Figure 4 Patient survival stratified by Charlson comorbidity index, *n* = 559.

after 10 years in patients with CCI≥7 vs. <4 (HR 4.57; 95% CI 2.42–8.62; *P* = 0.0001; Fig. 2b). CCI was associated with death-censored graft survival after 10 years (*P* = 0.003; Fig. S2). When dividing patients in age groups >65 and <65 years, CCI was associated with death-censored graft survival in patients <65 years, but not in patients >65 years. There was no association between CCI and BPAR (*P* = 0.23).

Discussion

In this study of all Ktx patients >60 years in Sweden from 2000 to 2012, there was no significant difference in patient survival at 5 years in the age groups 65–69 and >70 years. The higher 10-year mortality in the oldest age group (>70 years) might not have been a consequence primarily of Ktx, since similar mortality trends occur in people aged >80 years in the general population. There were no significant statistical differences between causes of death in the age-stratified groups. Furthermore, there were no significant difference between age groups in death-censored 10-year graft survival. For these reasons, it is reasonable to suggest that Ktx should not be withheld in patients >70 years.

The main finding of our study was that high CCI (age-excluded) identified patients with almost five times higher risk of death after Ktx. Thus, our results suggest that CCI should be used as a part of the preoperative evaluation as a predictive marker. In the Cox multivariate analysis, CCI had a stronger significance than chronological age in predicting 10-year patient survival. Provided that comorbidity can be an accurate surrogate marker for biological age, our study supports that biological age (i.e., physiological age) is a better predictor

than chronological age in elderly kidney recipients. When we stratified for sex, female recipients had a higher 10-year patient survival although females >60 years are postmenopausal. Our observation concurs with data in the general population showing that older males experience greater declines in biological age than females [20]. It is thus of importance to stratify for sex in future studies of long-term outcome in Ktx.

Dialysis vintage >40 months has previously been associated with impaired patient survival after Ktx [21], but this was not the case in a multivariate analysis adjusting for CCI in our present study. It is well known that prolonged dialysis vintage both enhances and adds risk of comorbidity. This highlights the importance of preemptive Ktx also in the elderly and likewise early wait listing after start of dialysis. It is well established that cardiovascular event rates are particularly high during the first weeks after haemodialysis initiation [11]. As dialysis vintage is one of the few risk factors possible to modify, unawareness or administrative difficulties that delays Ktx must be avoided. We report that PTDM and BMI did not affect 10-year patient or death-censored graft survival. Higher BMI in elderly CKD patients may indicate good nutritional status and appetite as well as absence of catabolism which has been demonstrated in HD patients and is known as the 'obesity paradox' [22]. Our finding that BMI <18 kg/m^2 did not affect outcome might be because of the low number of patients. Contradictory to results in two previous studies, we found no difference in the incidence of rejections in the basiliximab group compared to the group that was not given basiliximab as induction [23,24]. This might be explained by 'bias by indication', because of the likelihood that immunized patients received basiliximab to a greater extent than patients without HLA-antibodies. Panel reactive antibodies (PRA) and HLA-mismatch status preoperatively should ideally have been included in the study (to evaluate induction therapy in elderly in a more precise way), but this was not possible because of logistical reasons, unfortunately. Rejections were analysed in a subgroup of 548 patients. In this subgroup, we did not find any association between rejections and graft or patient survival. In contrast, Heldal *et al.* [25] concluded that clinical outcome in elderly Ktx was more related to acute rejection than pretransplant comorbidity.

Some strengths and limitations of the study should be acknowledged. The major strength of our study was the inclusion of all (100%) Ktx recipients >60 years of age in Sweden during the years 2000–2012, which results in a great external validity and reduces selection bias. Another strength is that validity of graft and patient survival is reliable and trustworthy, because of

reproducible results by the Swedish renal registry, patient files and the Swedish Population Registry. We believe this is the reason for the strong association of CCI and patient survival. Moreover, there were no significant variations in death-censored graft survival or patient survival over time at the participating transplant centres indicating sufficiently good quality of data. Finally, Swedish national renal registry data confirm similar graft and patient survival in the different transplant centres. The results of our study should, however, be interpreted with some caveats. Ideally, a comparison of outcome in patients with the same age and CCI score before KTx versus dialysis treatment should be done. CCI data were not available in a comparable dialysis population. Ideally, this group should have been accepted to the waitlist, but not transplanted. Another limitation is missing data on BPAR from one of the study centres. We excluded this centre from the rejection analysis since they did not perform a systematic registry of BPAR at the time. We did a rejection analysis comprising the three other transplant centres to reduce the risk of information bias. The incidence of rejections in the three remaining centres was similar. Possibly, a relatively small number of observations, and especially a small number of rejections of higher grade, could have affected the impact of BPAR on graft and patient survival. Our results convincingly suggest that preoperative evaluation in the elderly should include proper evaluation of comorbidity and preoperative risk factors by using a suitable risk score as recommended by ERA-EDTA [9]. Because of the retrospective design of the study, frailty was not possible to include in the statistical analysis. Still, there was a strong association between patient survival and CCI. Ideally, frailty and CCI should be evaluated in combination to enable an optimal preoperative evaluation [26,27]. We believe that all comorbidities should be included in CCI to enable the best predictive value in a cohort [28].

In conclusion, since an association between clinical long-term outcome and age, sex and the CCI >60 years in Ktx was observed, careful classification of comorbidity including all 19 diagnoses in CCI should be part of the preoperative assessment of elderly Ktx recipients.

Authorship

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Conflict of interest

None declared.

Acknowledgements

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Flow chart showing recruitment of patients and selection of patients.

Figure S2. Death-censored graft survival stratified by Charlson comorbidity index, $n = 559$.

Table S1. Missing data.

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