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A Comorbidity Index and Pretransplant Physical Status Predict Survival in Older Kidney Transplant Recipients: A National Prospective Study

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Background. Kidney transplantation (KT) is considered the best treatment for end-stage kidney disease (ESKD). In the increasing elderly ESKD population, KT should be reserved for carefully selected candidates who are expected to experience favorable outcomes. We aimed to prospectively evaluate pretransplant recipient factors that may predict patient survival and can eventually guide therapeutic decisions in elderly with ESKD. **Methods.** Recipient factors were evaluated in KT candidates aged ≥65 y. Comorbidity was assessed at waitlisting according to the Liu comorbidity index (LCI). Health-related quality of life outcomes were measured using the Kidney Disease Quality of Life Short Form, version 1.3. The Cox proportional hazard regression was used to evaluate predictors of patient survival. **Results.** We included 192 recipients, with a mean age of 72.1 (4.1) y, who were transplanted with kidneys from deceased brain-dead donors. During a median observation period of 4.6 (3.2–6.3) y, 66 recipients died. Elevated LCI consistently predicted poor patient survival. In recipients with LCI ≥4, dialysis >2 y comprised a 2.5-fold increase in mortality risk compared with recipients on dialysis ≤2 y. Self-reported pretransplant physical function was also proven to be a significant positive predictor of survival. **Conclusion.** The implementation of LCI and a physical function score during the evaluation of older kidney transplant candidates may improve the selection and thereby optimize posttransplant outcomes.

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INTRODUCTION

The end-stage kidney disease (ESKD) population is growing old, and it is expected that, by 2030, 60% of patients in need of kidney replacement therapy will be older than 65 y.[1] Regardless of age, kidney transplantation (KT) is considered the best treatment, and older recipients have been reported to live longer and to improve in their health-related quality of life (HRQOL) compared with their counterparts receiving dialysis.[2-5]

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The data that support the findings of this study are available upon request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Additional supporting information may be found in the Supporting Information section, SDC, http://links.lww.com/TXD/A408.

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Due to increased comorbidities and age, older ESKD patients are at high risk for adverse events early postoperatively.[6,7] Current allocation policies attempt to match recipient and graft survival by directing expanded criteria donor organs (ECD) to older recipients. Compared with organs from standard criteria donors, ECD kidneys are associated with impaired survival outcomes[8,9] but with increased life expectancy over dialysis in older recipients[10-12]; however, less than two thirds of patients older than 65 y are willing to undergo transplantation with ECD kidneys, resulting in a high discard rate of this useful source.[13] Although many older individuals are suitable and should be offered a transplant, they are not routinely referred to KT, and their chance of actually receiving a transplant is low.[14,15] Only a minority of older dialysis patients have neither cardiovascular comorbidity nor diabetes, raising the question whether KT in general should be offered to elderly with ESKD.[8,15,16]

Optimizing outcomes in older KT recipients requires allocation of all available organs in carefully selected candidates, whose transplantation risk is lower than their expected benefit; however, a lack of consensus regarding which recipient factors should be considered during the evaluation process[17] has resulted in various selection policies between transplant centers. In the current study, we aimed to describe posttransplant patient survival in older patients who were transplanted with kidneys from deceased brain-dead (DBD) donors and to identify which pretransplant recipient factors were associated with patient survival after KT and if they could potentially guide therapeutic decisions.

MATERIALS AND METHODS

Study Design

The current study is a part of the prospective cohort study "Health-Related Quality of Life in ESKD Patients Older than 65 y," also known as Question 65, designed to evaluate HRQOL in older KT candidates from waitlisting until 10 y posttransplantation.[18] All patients aged ≥65 y who were waitlisted for KT between January 2013 and November 2016 were invited to participate. Patients with insufficient Norwegian language skills or cognitive impairment evaluated during the pretransplant workout were excluded from the study.[18]

The study is conducted at the Norwegian National Transplant Center at Oslo University Hospital, performing 240 to 275 KTs per year, 25% with a living donor. The active waitlist currently contains approximately 400 patients, whose median waiting time for a first DBD transplant is 13 mo. Because of short waitlisting, preemptive KT is also possible with DD organs. In 2020, 34% and 5% of eligible waitlisted candidates were older than 65 and 75 y, respectively.

Initially, all patients received induction with basiliximab; thereafter, the center standard triple immunosuppressive regime, consisting of a calcineurin inhibitor (tacrolimus), an antiproliferative agent (mycophenolate mofetil), and oral corticosteroids tapered down to 5 mg/d during the first 4 to 6 mo.[19]

The Kidney Disease Quality of Life Short Form questionnaire, version 1.3,[20] was used to assess HRQOL outcomes. HRQOL was collected from waitlisting and at every 6 mo until KT, permanent withdrawal from the waiting list, or death. Kidney Disease Quality of Life Short Form questionnaire, version 1.3, scores were converted to a 0 to 100 possible range, with higher scores reflecting better HRQOL.[20] The last values obtained before KT were evaluated in the current study, whereas posttransplant HRQOL outcomes were not included. Survival data were retrieved from the Norwegian Renal Registry on June 30, 2021. Clinical data were retrieved from the electronic patient records at the Oslo University Hospital.

The study was approved by the Regional Ethics Committee (2012/527) and followed the regulations of the Helsinki Declaration. Before study inclusion, all participants received oral and written study information and signed an informed consent form.

Comorbidity

Pretransplant comorbidity was assessed at waitlisting[21] according to the Liu comorbidity index (LCI)[22] (Table 1). The LCI index was originally developed based on data from a US incident dialysis population with a mean age of 65 y and has been reported to predict survival in elderly dialysis patients[23] as well as posttransplantation.[24] Comorbidity scores range from 0 to 21, and patients were grouped in the intervals ≤3, 4 to 6, and ≥7, as originally proposed.[22]

For comparison, the Charlson comorbidity index (CCI; Table 2), without age adjustment, was also calculated, as originally described,[25] and patients were grouped into 4 groups of gradating comorbidity (low, moderate, high, and very high) in the intervals ≤3, 4 to 5, 6 to 7, and ≥8, as previously proposed.[26]

Statistical Analysis

Continuous variables are described as mean ± SD when normally distributed and as median with 25th to 75th percentiles when skewed. Dichotomous variables are presented as frequency distributions. Statistically significant ($P \leq 0.05$) differences between groups were assessed using the 2-sample *t* test or Mann-Whitney *U* test for continuous variables and chi-squared tests for categorical variables.

Survival was estimated from the time of KT until death (censoring date: June 30, 2021). Recipients experiencing graft loss remained in the analysis according to intention-to-treat principles. Survival between subgroups was assessed using the Kaplan-Meier method and log-rank test, and the survivor function with 95% confidence intervals (CIs) is reported.

TABLE 1.

Liu comorbidity index

Comorbid conditions	Score
Diabetes	1
Congestive heart failure	3
Coronary artery disease	1
Cerebrovascular disease/TIA	2
Peripheral vascular disease	2
Other cardiac	2
Dysrhythmia	2
Chronic obstructive pulmonary disease	2
Gastrointestinal bleeding	2
Liver disease	2
Cancer	2

Other cardiac: pericarditis, myocarditis, endocarditis, complications of heart disease, heart transplant, heart devices. Age is not included.
TIA, transient ischemic attack.

TABLE 2.

Charlson comorbidity index

Comorbid conditions	Score
Myocardial infarct	1
Congestive heart failure	1
Peripheral vascular disease	1
Cerebrovascular disease	1
Dementia	1
Chronic obstructive pulmonary disease	1
Connective tissue disease	1
Gastrointestinal bleeding	1
Mild liver disease	1
Diabetes without end organ damage	1
Hemiplegia	2
Moderate/severe renal disease	2
Diabetes with end organ damage	2
Cancer	2
Leukemia	2
Lymphoma	2
Moderate/severe liver disease	3
Metastatic solid tumor	6
AIDS	6

Univariable and multivariable Cox proportional hazard regressions were used to identify pretransplant predictors of patient survival.

Factors yielding $P \leq 0.10$ in the univariable models were included in the multivariable analyses, and a backward manual elimination procedure was performed. Factors yielding P values ≤0.05 were included in the final model. Hazard ratios (HRs) with 95% CIs and P values are reported. Deviation from the proportionality assumption was tested globally and per covariate by Schoenfeld residuals.

Comparison between LCI and CCI was performed using a receiver operating characteristic curve analysis, and the area under the curve for the 2 indices was compared.[27] The predictive ability of the multivariable Cox regression model was assessed using C statistics, as proposed by Harrell et al.[28,29] The same index was also used for comparison between the Cox regression model containing the CCI versus the LCI.

Recipient factors evaluated in the univariable analyses included sex, age at KT, waiting time, time on dialysis at KT (continuous and categorical), marital status (partnered or not), cause of ESKD (hypertension or diabetes or other), LCI and CCI (continuous and categorical), donor age, ECD status, HLA mismatch (A, B, DR), cold ischemia time, and the last pretransplant generic and kidney-specific HRQOL scores.

RESULTS

Study Population

Among 289 transplant candidates older than 65 y who were included in the study, 222 (77%) had undergone KT by June 2021; 192 (87%) received a DBD organ, of whom 47 (24%) were transplanted preemptively (study flowchart; Figure S1, SDC, http://links.lww.com/TXD/A408).

The mean age at KT was 72.1 (4.1) y, ranging from 65 to 84 y, a median waiting time of 17.0 (11.9–26.0) mo, and a mean donor age of 67.2 (10.5) y, and 80% of DBD organs were defined as ECD, as described previously[30] (Table 3). Among the 145 nonpreemptive KT recipients, the median time on dialysis was 27.5 (17.6–43.2) mo; 62 recipients had received dialysis ≤2 y and 83 recipients >2 y.

During a median posttransplant observation period of 4.6 (3.2–6.3) y, 66 patients died, 58 (88%) with a functioning graft. The overall 1-, 3-, and 5-y patient survival was 95% (0.91–0.97), 83% (0.76–0.88), and 69% (0.61–0.75). The main causes of death were infections (33%), cardiovascular events (26%), and cancer (21%).

Table 4 presents the effect of the interaction between dialysis time and comorbidity on patient survival. Tables S1 and S2 (SDC, http://links.lww.com/TXD/A408) present the univariable and multivariable Cox proportional hazard regression models, respectively.

Impact of Pretransplant Comorbidity on Survival

Seventy-one percent of our study population had LCI ≤3, 20% between 4 and 6, and 9% ≥7. The median LCI score was 2.0 (1.0–4.0). In the univariable analyses, increasing comorbidity score (continuous variable) was linearly associated with increased death risk in DBD KT (HR, 1.15; 95% CI, 1.06-1.24).

Based on data from the current study, indicating beneficial survival for recipients with comorbidity scores ≤3 (Figure S2, SDC, http://links.lww.com/TXD/A408), the patients were divided into a low (LCI, ≤3) and a high (LCI, ≥4) comorbidity group. Recipients (n = 136) with LCI ≤3 had estimated 1-, 3-, and 5-y survival rates of 97% (0.92–0.99), 88% (0.81–0.92), and 76% (0.67–0.82) versus 91% (0.80–0.96), 71% (0.57–0.81), and 53% (0.39–0.66) in recipients (n = 56) with LCI ≥4 (log-rank, $P = 0.001$; Figure 1). In the univariable regression models, LCI ≥4 was associated with a 2.2-fold (HR, 2.19; 95% CI, 1.35-3.56) increase in mortality risk.

For comparison, comorbidity was also assessed by the CCI. The 1-, 3-, and 5-y survival rate for recipients with CCI ≤4 (n = 101) was 96% (0.90–0.98), 86% (0.77–0.91), and 76% (0.65–0.83) versus 94% (0.87–0.98), 79% (0.69–0.86), and 61% (0.50–0.71) in recipients with CCI ≥4 (n = 91). CCI at waitlisting was not a significant independent predictor of survival, neither as a continuous (HR, 1.16; 95% CI, 0.99-1.35) nor as a categorical variable in the intervals CCI ≥4 (HR, 1.56; 95% CI, 0.96-2.53) or CCI ≥7 (HR, 1.60; 95% CI, 0.69-3.72). The receiver operating characteristic curve analysis indicated that CCI was inferior in predicting mortality in older recipients of DBD kidneys than LCI (area under the curve, 0.59 versus 0.66; $P = 0.02$; Figure 2). Inclusion of CCI, instead of LCI, in the final multivariable Cox proportional hazard regression reduced its predictive power (C index, 0.62 versus 0.66), indicating that comorbidity assessed by LCI was a better predictor in the model.

Impact of Dialysis Time on Survival

Longer time on dialysis, as a continuous variable in months, increased mortality risk (HR, 1.02; 95% CI, 1.01-1.03), and a significant interaction was observed between dialysis time and comorbidity in the multivariable regression model (Table 4). Recipients with both LCI ≥4 and total dialysis >2 y (n = 32) had a 2.5-fold increase in mortality risk (HR, 2.48; 95% CI, 1.04-5.92) and poor survival outcomes; the 5-y survival rate was 44% compared to 77% observed in recipients with the same level of comorbidity and total dialysis ≤2 y (n = 19; log-rank, $P = 0.053$) In recipients with LCI ≤3, no

TABLE 3.

Demographic and clinical characteristics of the study population

	Included population (N = 289)	DBD KT (n = 192)	Survivors (n = 126)	Deceased (n = 66)	*P*
Sex (male), n (%)	196 (67.8)	133 (69.3)	86 (68.3)	47 (71.2)	0.73
Age at KT, y; mean (±SD)	71.8 (4.1)	72.1 (4.1)	72.0 (4.0)	72.2 (4.2)	0.79
Married, n (%)	222 (76.8)	152 (79.2)	103 (81.8)	49 (74.3)	0.66
Comorbidity, n (%)					
CVD	166 (57.4)	104 (54.2)	31 (24.6)	24 (36.4)	0.02[a]
Diabetes	73 (25.3)	45 (23.4)	29 (23.0)	16 (24.2)	0.50
COPD	33 (11.4)	20 (10.4)	9 (7.1)	11 (16.7)	0.08
GI bleeding	35 (12.1)	21 (11.0)	7 (7.1)	12 (18.2)	0.16
Liver disease	4 (1.4)	2 (1.0)	1 (0.8)	1 (1.5)	0.64
Cancer	80 (27.7)	47 (24.5)	29 (23.0)	18 (27.3)	0.52
No comorbidity	62 (21.4)	43 (22.4)	34 (26.7)	9 (13.6)	0.04[a]
LCI, mean (±SD)	3.2 (2.6)	2.75 (2.4)	2.3 (2.1)	3.6 (2.7)	<0.001[a]
LCI group, n (%)					0.004[a]
0–3	183 (63.3)	136 (70.8)	100 (79.4)	36 (54.6)	
4–6	72 (24.9)	39 (20.3)	19 (15.1)	20 (30.3)	
7–9	27 (9.4)	14 (7.3)	6 (4.8)	8 (12.1)	
≥10	7 (2.4)	3 (1.6)	1 (0.8)	2 (3.0)	
Waitlisting time, mo; median (±25th to 75th percentiles)	15.2 (9.2–25.3)	17.0 (11.9–26.0)	17.6 (12.8–27.6)	15.3 (9.4–24.5)	0.06
Donor age, y; mean (±SD)	65.2 (11.8)	67.2 (10.5)	67.0 (10.8)	67.5 (9.8)	0.73
ECD, n (%)	164 (73.9)	154 (80.2)	101 (80.2)	53 (80.3)	0.98
Dialysis vintage, mo; median (±25th to 75th percentiles)	25.8 (15.7–41.7)	27.5 (17.6–43.2)	27.1 (17.8–42.9)	28.0 (16.3–44.2)	0.55
Acute rejection, n (%)	34 (15.3)	29 (15.1)	15 (11.9)	14 (21.2)	0.09
Delayed graft function, n (%)	62 (27.9)	61 (31.8)	35 (27.8)	26 (39.4)	0.10
Infections, n (%)	62 (27.9)	54 (28.1)	28 (22.2)	26 (39.4)	0.01[a]
Complications, n (%)					0.64
Urologic	46 (20.7)	45 (23.4)	28 (22.2)	17 (25.8)	
Vascular	16 (7.2)	14 (7.3)	10 (7.9)	4 (6.0)	
Cardiovascular	16 (7.2)	15 (7.8)	8 (6.4)	7 (10.6)	

[a]*P* values ≤0.05 are considered significant.

Acute rejection is defined when rejection occurred during the first 10 wk. Urologic complications include urine leakage, lymphocele, bladder outlet obstruction, and ureter necrosis. Vascular complications include hemorrhage/hematomas, renal artery stenosis, and renal vein thrombosis. Cardiovascular events include unstable angina pectoris/myocardial infarction, pulmonary embolism, cerebrovascular event, peripheral vascular thrombosis, and cardiac arrest. CVD includes congestive heart failure, coronary vascular disease/myocardial infarction, dysrhythmia, cerebrovascular disease, and peripheral vascular disease.

COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; DBD, deceased brain-dead donor; ECD, expanded criteria donor; GI, gastrointestinal; KT, kidney transplantation; LCI, Liu comorbidity index.

difference in survival was observed with regard to dialysis shorter (n = 43) or longer than 2 y (n = 51; 68% versus 66%; *P* = 0.59; Figure 3). The dialysis groups were comparable in terms of LCI score (3.1 versus 3.2; *P* = 0.8), age (71.8 versus 72.1; *P* = 0.6), and male sex (72% versus 72%; *P* = 1.0).

The use of 1 y as a threshold for time on dialysis did not predict survival. The inclusion of 3 dialysis groups in the model (≤2, 2–3, and >3 y) did not improve its predictive ability (C index, 0.66), and the graphical assessment of the data indicated that 2 y of dialysis is a reasonable cutoff point in the analysis (Figure S3, SDC, http://links.lww.com/TXD/A408).

TABLE 4.

Interaction effect between time on dialysis and Liu score on patient survival

	Time on dialysis					
	Dialysis ≤2 y			Dialysis >2 y		
Liu comorbidity	HR	95% CI	*P*	HR	95% CI	*P*
Liu score ≤3	Ref			0.77	0.38-1.57	0.5
Liu score ≥4	2.19	1.09-4.37	0.03	2.48	1.04-5.92	0.04

P values ≤0.05 are significant.

CI, confidence interval; HR, hazard ratio; Ref, reference.

Impact of Pretransplant Physical Function on Survival

By study design, self-reported HRQOL was regularly assessed every 6 mo during waitlisting, and the last HRQOL scores obtained at a mean time of 4.8 (4.7) mo before KT were evaluated.

Increasing pretransplant physical function (PF) scores were linearly associated with improved survival outcomes (HR, 0.98; 95% CI, 0.97-0.99). The mean pretransplant PF score was 61.5 (22.4), and survival was compared between recipients with PF scores ≤60 and >60. The estimated 5-y survival rate was 77% (0.68–0.84) for recipients with PF score >60 versus 55% (0.41–0.66) for their counterparts with PF scores ≤60 (log-rank, *P* = 0.01). In the adjusted regression model, PF ≤60 was associated with a 2-fold increase in mortality risk (HR, 2.03; 95% CI, 1.18-3.46), whereas no interactions were observed with time on dialysis or comorbidity.

In the univariable analysis, pretransplant social support was significantly associated with survival, but this association disappeared in the multivariable regression model (Table S1, SDC, http://links.lww.com/TXD/A408).

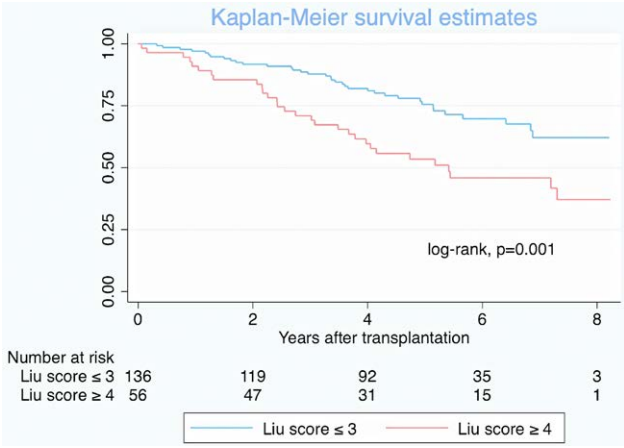

FIGURE 1. Observed patient survival in recipients of low vs high comorbidity.

DISCUSSION

Our findings indicate that elevated pretransplant comorbidity evaluated by LCI can serve as a marker of 5-y patient survival in older recipients of DBD kidneys. In the presence of elevated comorbidity, dialysis longer than 2 y was adversely associated with survival outcomes. Poor pretransplant PF scores independently predicted increased mortality after KT. These observations are novel, and their implementation during the selection process may optimize outcomes in older KT patients.

In the current study, elevated LCI at waitlisting was an independent predictor of 5-y survival in recipients transplanted older than 65 y. In contrast, CCI did not predict mortality in our analyses. The value of CCI in predicting survival in older KT recipients is not appropriately defined because previous findings have been contradictory. In the elderly, CCI was adversely associated with survival in recipients followed up for a decade[31] but not in those older than 70 y who were observed for 5 y.[32] Our research group has previously reported that elevated LCI pretransplant predicted mortality risk in recipients older than 55 y[24] and decline in HRQOL 3 y after KT in those older than 65 y.[5] These observations are novel and indicate that LCI may serve as a marker of both longevity and HRQOL in older KT recipients. Our results suggest that the LCI should be preferred over the CCI in the assessment of comorbidity in older KT patients, and its implementation during the selection process may identify candidates with the best chance for a good outcome after KT.

In line with our results, prolonged time on dialysis before KT is considered the most consistent predictor of poor renal transplant outcomes in older KT recipients.[15,32-34] Interestingly, we observed a significant interaction between time on dialysis and comorbidity, indicating that, at least in the elderly, elevated comorbidity amplifies the effect of dialysis on survival. In recipients with LCI ≥4, the 5-y survival rate was significantly impaired when dialysis time exceeded 2 y, which was not observed in recipients with LCI ≤3. We conclude that in older ESKD patients with LCI ≥4 at waitlisting, dialysis >2 y is associated with impaired posttransplant survival and should, if possible, be avoided.

In this older cohort, the 1-, 3-, and 5-y survival rates were estimated to be 95%, 83%, and 69%, respectively, corroborating previous reports.[8,35] Neither donor age nor ECD organ affected posttransplant survival. Consistent with our findings, older recipients with short dialysis time have been reported to survive longer even when transplanted with high kidney donor profile index organs, compared with those who remained waitlisted, and subsequently received a kidney donor profile index organ 0% to 85%.[35] Survival probabilities following KT with lower quality organs were good, even in moderately physically impaired recipients,[36] and HRQOL outcomes have been reported favorable.[37] Based on these observations, we support that older candidates should preferentially be

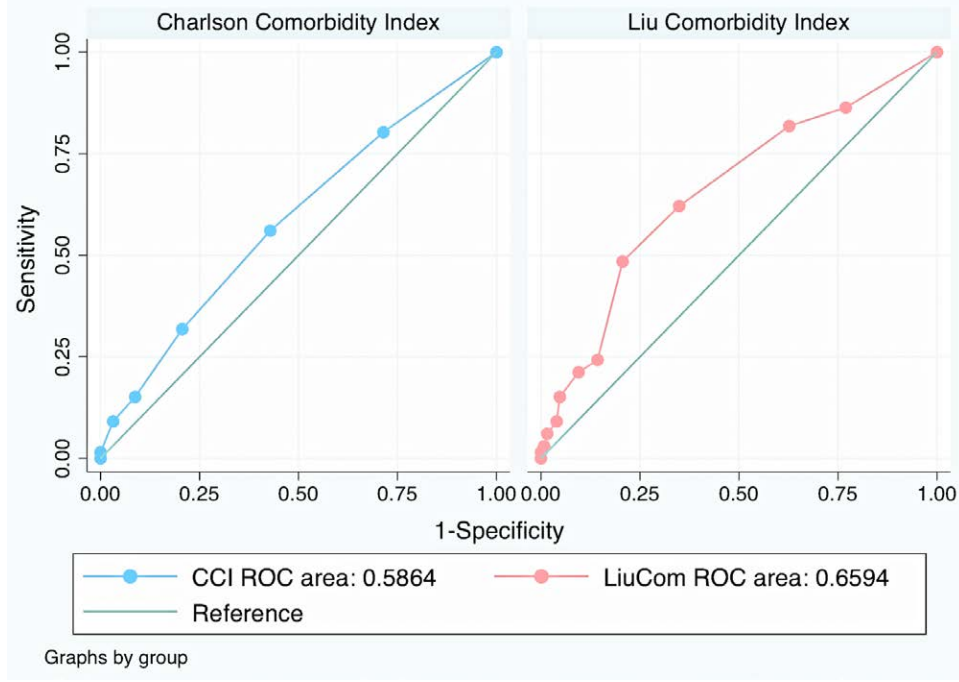

FIGURE 2. Receiver operating characteristic (ROC) curve analysis. Comparison between Liu index vs Charlson Comorbidity Index (CCI).

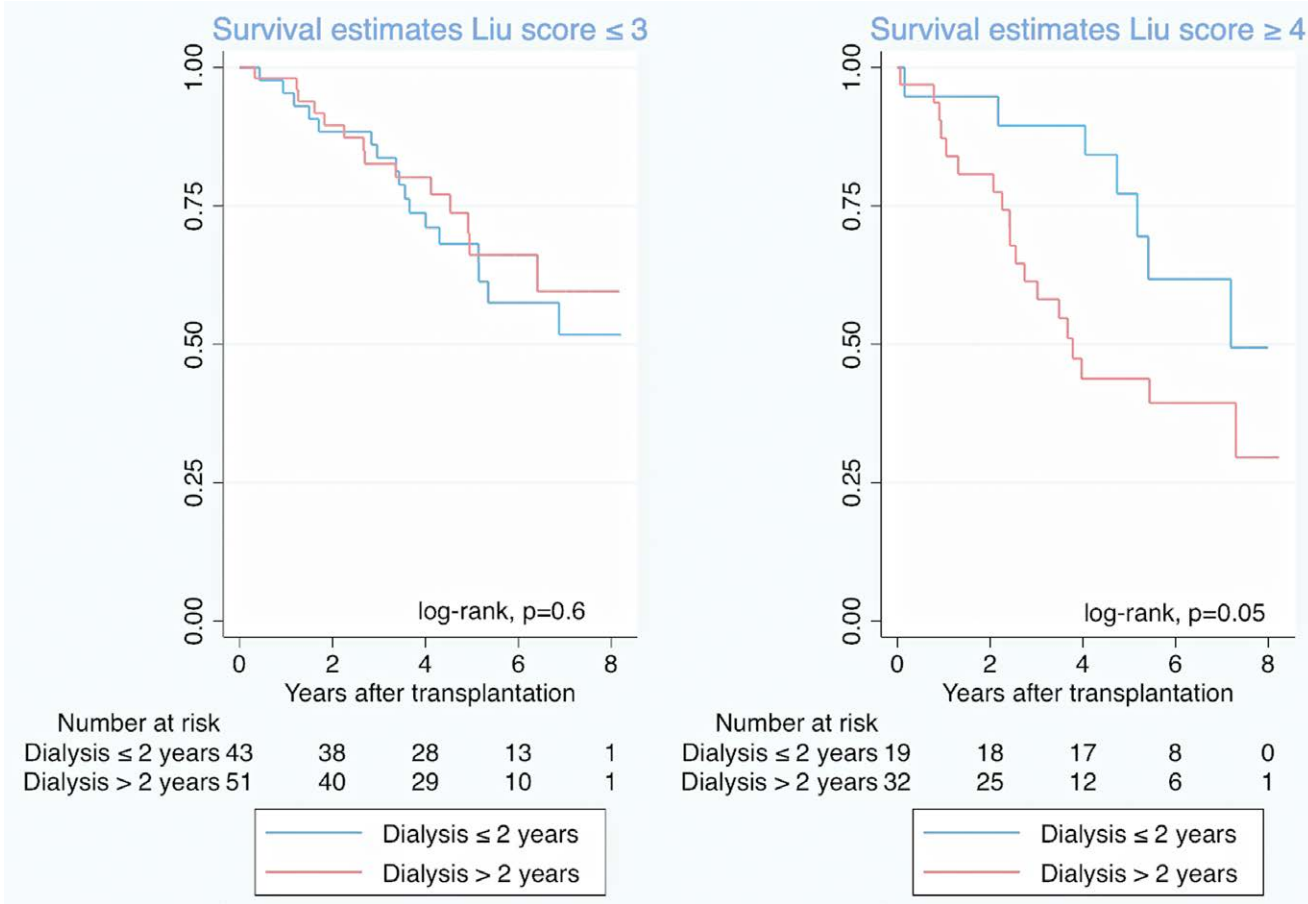

FIGURE 3. Impact of dialysis vintage on patient survival outcomes. Interaction between time on dialysis and comorbidity.

transplanted preemptively, even with the cost of receiving a lower quality organ, because the beneficial effect of avoiding dialysis on survival exceeds the risk linked to ECD organ KT.

Self-reported pretransplant PF was proven to be a significant predictor of posttransplant survival, with increasing scores indicating improved outcomes. Previously low pretransplant PF score has been associated with impaired survival in younger recipients[38,39] and corroborates our findings in an older cohort. Inclusion of patients' PF scores in models predicting survival after KT improved their predictive and discriminative ability.[36] In line with Bui et al, we support that the use of patient's PF score during selection may improve current listing and transplantation strategies and optimize outcomes.

In comparison of survival outcomes with regard to treatment modality, dialysis versus transplantation is out of the scope of this study, and we have no evidence to recommend preclusion from KT of candidates with increased comorbidity, longer dialysis, or impaired pretransplant PF. Instead, posttransplant outcomes have been reported to be favorable compared to dialysis, even in such recipients.[38,40,41]

The national prospective design of this study ensures uniform evaluation and treatment protocols. All HRQOL data are self-reported and always collected at the patient's residence, which minimizes the collection and interpretation biases; however, the participants in this study had a relatively short waiting time compared to many other centers, which may reduce the generalizability of our findings. Frailty, which has been associated with impaired outcomes in ESKD and after KT,[42] was not assessed in our study; however, it is possible that the HRQOL dimension PF, to some degree, can describe physical frailty,[42] so it is unlikely that this has significantly confounded our results. Finally, comorbidity was assessed only at waitlisting and not at the time of KT. It is plausible that comorbidity progression differs with respect to dialysis time and might have partly accounted for the observed results.

Conclusively, in older recipients of DBD organs, LCI ≥4 predicted impaired patient survival. In the presence of elevated comorbidity, mortality risk increased by 2.5 times when dialysis exceeded 2 y. Self-reported pretransplant PF score predicted posttransplant survival, and scores ≤60 increased mortality by 2 times. Implementation of the LCI and PF score during the evaluation of older KT candidates could be considered.

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