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Poor Physical Function Trajectory Predicts Impaired Patient Survival in Older Recipients of Deceased Donor Kidneys: A Prospective Cohort Study

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Background. Optimized health-related quality of life (HRQOL) at the time of kidney transplantation (KT) is associated with improved survival. In older KT recipients, we aimed to prospectively evaluate if HRQOL evolution during the first posttransplant year was associated with long-term patient survival. **Methods.** Recipients older than 65 y at KT who received an organ from a deceased brain-dead donor and survived >12 mo posttransplant were eligible. HRQOL was assessed pre-KT, at 10 wk, 6 mo, and 12 mo post-KT, using the Kidney Disease Quality of Life Short Form version 1.3 survey. A mixed-effect model was used to explore HRQOL evolution during the first posttransplant year in long-term survivors compared with nonsurvivors. Distinct HRQOL clusters were identified using a group-based trajectory modeling and their association with patient survival was investigated with Cox proportional hazard regression models. **Results.** We included 192 elderly recipients of deceased brain-dead donor kidneys who were transplanted from 2013 to 2020. Eleven died during the first year leaving 181 for evaluation (male, 125; mean age at KT, 72 y [65–84 y]). During a median observation time post-KT of 4.9 y (11.1–8.5 y), 57 recipients died. In survivors, all the generic and kidney-specific HRQOL domains substantially improved during the first year, whereas in nonsurvivors HRQOL deteriorated. Three longitudinal HRQOL trajectories indicating poor, fair, and good HRQOL evolution were identified. Poor physical function trajectory was significantly associated with higher mortality risk independent of covariates, as compared with good physical trajectory (hazard ratio, 2.38; 95% confidence interval, 1.15–5.01). **Conclusions.** In elderly KT recipients, detection of declining posttransplant physical function may imply impaired survival. Systematic HRQOL monitoring following KT provides added value when evaluating mortality and may guide therapeutic decisions.

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Health-related quality of life (HRQOL) outcomes are widely accepted measures of patient's health status and treatment effectiveness in patients with end-stage kidney disease (ESKD), both before and following kidney transplantation (KT).[1-3] The use of HRQOL scores during the pretransplant evaluation and posttransplant follow-up has lately

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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.

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gained attention because of the association with clinical outcomes.[4-7] Inclusion of patients' pretransplant functional status scores in mortality risk models improved their predictive and discriminative ability.[8] Posttransplant physical, mental, and general health scores have been positively associated with long-term patient and graft survival outcomes.[9,10] Recently, Food and Drug Administration proposed systematic HRQOL monitoring following KT as an indicator of treatment responsiveness and adherence to medication.[11]

The population of older patients with ESKD is increasing and comprise half of the prevalent population in need for kidney replacement therapy in Europe and United States.[12-14] KT is considered the best treatment in selected older ESKD patients,[15-17] and KT recipients are expected to live approximately twice as long as their peers receiving dialysis.[13] However, advanced age is often associated with increased comorbidity that may result in impaired posttransplant outcome.[18,19]

Use of HRQOL data to identify recipients at risk of clinical impairment requires knowledge on how HRQOL changes early after KT in different patient groups, and if distinct HRQOL trajectories are associated with different posttransplant outcomes. Thus, in the current study, we prospectively evaluated HRQOL evolution during the first posttransplant year, in older recipients of deceased brain-dead donor (DBD) kidneys, and if distinct HRQOL trajectories were associated with long-term patient survival.

MATERIALS AND METHODS

Study Design

The current study is part of the ongoing Question 65 study, a national longitudinal prospective study that evaluates HRQOL outcomes in older KT candidates, from waitlisting until 10 y posttransplantation.[20] HRQOL status for each patient was collected prospectively from waitlisting and at every 6 mo until KT, permanent withdrawal from the waitlist, or death. HRQOL outcomes collected before KT and at 10 wk, 6 mo, and 12 mo post-KT were used to investigate the HRQOL evolution during the first posttransplant year and to examine possible association with long-term patient survival.

All patients ≥65 y, enlisted for KT between January 2013 and November 2016, at the Norwegian National Transplant Center, at Oslo University Hospital, were invited to participate. Intact cognitive function and adequate language skills were required for study participation. At our center, older patients with cognitive impairment are generally not accepted for KT. In total, 21 patients were excluded, all due to insufficient language skills.[20] Only patients receiving a DBD kidney who survived >12 mo were included in the current analyses. Since donation after circulatory death was not yet implemented as a routine in Norway, all participants received DBD organs.

All patients received induction therapy according to immunologic risk, and a triple maintenance immunosuppressive regime, consisting of a calcineurin inhibitor (tacrolimus), an antiproliferative agent (mycophenolate mofetil), and oral prednisolone tapered down to 5 mg/d during the first 4–6 mo according to our standard protocol.[21]

Comorbidity was assessed at enlisting, according to Liu comorbidity index.[22] Survival data were retrieved from the Norwegian Renal Registry on October 31, 2021, and clinical data were retrieved from the electronic patient records at Oslo University Hospital. All questionnaires were sent by mail to the patient's residence, and in case of no response, a single reminder was sent after 3–4 wk.

The study was approved by the regional ethics committee (2012/527) and followed the Helsinki Declaration. Before study inclusion, all participants received oral and written study information and signed an informed consent form.

Health-related Quality of Life

The self-reported Kidney Disease Quality Of Life Short Form version 1.3 survey was used to assess HRQOL and combines the generic short form health survey with the Kidney Disease Quality Of Life kidney-specific survey.[23-25] Eight generic domains, that is, physical function (PF), physical role, bodily pain, general health, vitality, social function, emotional role, and mental health, as well as 11 kidney-specific domains, that is, symptoms, effect of kidney disease, burden of kidney disease, work status, cognitive function, quality of social interaction, sexual function, sleep, social support, dialysis staff encouragement, patient satisfaction, and the total health item were evaluated on a 0 to 100 possible range, with higher scores reflecting better HRQOL.[25]

Statistical Analysis

Continuous variables are described as mean ± SD when normally distributed and as median with 25th–75th percentiles when skewed. Categorical data are presented as percentages. Statistically significant ($P \leq 0.05$) differences between groups were assessed by the independent samples t test or Mann-Whitney test for continuous variables and the Fisher exact test for categorical variables.

A mixed-effect linear regression model was used to evaluate the time evolution of HRQOL during the first posttransplant year in recipients who survived compared with recipients who died throughout the observation period. HRQOL domains were defined as outcome variables, and fixed-effects for time, group (survivors versus nonsurvivors), and their interaction were used as categorical variables of interest. The interaction term was included in the final model if it was statistically significant. All models included random intercepts and an unstructured covariance matrix; the random slope was added only if it improved the model, based on the Akaike Information Criterion.[26] Regression coefficients (β), with 95% confidence interval (CI), are reported.

A group-based trajectory modeling was used to identify different trajectories in the whole cohort analyzed together. Distinct trajectory groups represent clusters of individuals who follow the same time evolution of HRQOL.[27] For each HRQOL domain, different models including 2, 3, and 4 groups were applied, testing zero, linear, and quadratic specification for the trajectory shape. Individuals were assigned a probability of group membership and selection of the best model was based on: (1) the Bayesian information criterion; (2) close correspondence for each group between estimated probability of group membership and the proportion assigned to the group based on the posterior probability of group membership; and (3) an average of the posterior probabilities of group membership >0.7 for each group.[27,28]

Survival was estimated from the time of transplantation until death (censoring date October 31, 2021). The primary outcome of interest was all-cause mortality, with and without

a functioning transplant. Univariable and multivariable Cox proportional hazard regression was used to investigate the association between HRQOL trajectories and patient survival. All models were adjusted for age at KT, gender, pretransplant comorbidity,[29] history of cardiovascular disease and diabetes, and dialysis vintage (no dialysis, dialysis ≤2 and >2 y[29]). Hazard ratios (HRs) with 95% CI and *P* values are reported. Deviation from the proportionality assumption was tested globally and per covariate by Schoenfeld residuals.

A sensitivity analysis including recipients who died during the first posttransplant year was also conducted.

RESULTS

Study Population

Among 289 waitlisted KT candidates aged ≥65 y who were included, 222 (77%) had undergone transplantation by October 2020; 181 (82%) received a DBD kidney and survived throughout the first posttransplant year, being eligible for the current study (Figure 1). Their mean age at KT was 72.0 y (4.2 y), median waiting time was 17.0 mo (11.9–25.8 mo), mean donor age 67.2 y (10.6 y), and 80% of DBD organs were defined as expanded criteria donor organs, as previously described[30] (Table 1). Sixteen patients (8%) lost their graft; 2 died during the first posttransplant year, leaving 14 recipients eligible for evaluation. Seven survived throughout the whole observation period and 7 died. No HRQOL data were collected after graft loss while patients were returned in dialysis.

During a median posttransplant observation period of 4.9 y (3.7–6.6 y), 57 recipients (31%) died. Apart from a higher pretransplant comorbidity score (3.6 versus 2.3; $P < 0.001$), nonsurvivors did not differ significantly from survivors with regard to age, gender, waitlisting time, dialysis vintage, or cause of ESKD. Death was primarily caused by infections (37%), cardiovascular events (30%), and cancer (25%).

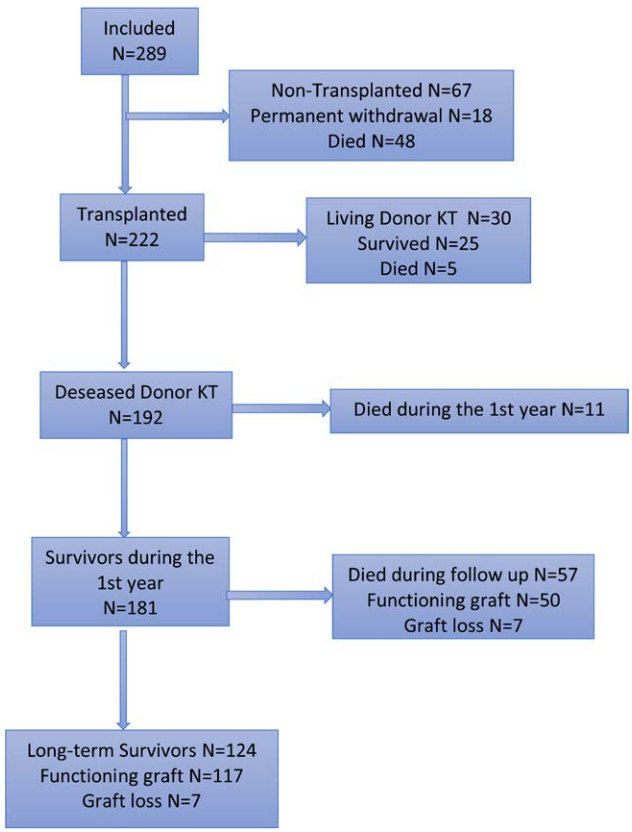

FIGURE 1. Flow chart of the study. KT, kidney transplantation.

HRQOL Evolution During the First Year After KT in Survivors Versus Nonsurvivors

Pretransplant reference HRQOL scores, collected at a mean time of 4.1 mo (4.2 mo) before KT, did not significantly differ between survivors and nonsurvivors, except for better mental health scores in survivors (76.7 versus 70.8; $P = 0.05$).

The evolution of HRQOL during the first year posttransplant differed between survivors and nonsurvivors. Compared with their reference values, recipients who survived experienced a statistically significant improvement in all the generic and kidney-specific HRQOL outcomes, in contrast to nonsurvivors whose HRQOL deteriorated throughout the first year (**Tables S1** and **S2**, **SDC**, http://links.lww.com/TXD/A441). In the latter, the domain of general health significantly declined already at 6 mo (β = –10.5; $P = 0.01$), and the decline in the other physical domains, that is, PF (β = –12.4; $P = 0.007$), physical role (β = –20.6; $P = 0.02$), and bodily pain (β = –21.7; $P < 0.001$) reached statistical significance at 1-y (Figure 2). Social and emotional functioning scores also decreased but not significantly. The same declining trend was observed in the kidney-specific domains, with the domains of symptoms (β = –6.1; $P = 0.01$), cognitive function (β = –6.6; $P = 0.01$), sleep (β = –8.1; $P = 0.008$), and total health (β = –11.3; $P = 0.001$) being statistically significantly impaired after 1 y.

Group-based Trajectory Modeling

The evolution of HRQOL during the first year after KT followed distinct separate patterns. Three longitudinal HRQOL trajectories representing good, fair, and poor evolution were revealed, in almost all the generic and kidney-specific domains (**Figures S1** and **S2**, **SDC**, http://links.lww.com/TXD/A441). Two groups were identified in the domains physical and emotional role.

Figure 3 illustrates typical trajectories for the domain of PF, yet this pattern was similar for all HRQOL domains. Recipients in the good evolutional group comprised 43% of our study population (N = 80), with mean PF scores across time being similar to the age-matched Norwegian population norms[31] (males 84.3 versus 80.3, $z = 0.2$; females 84.5 versus 71.6, $z = 0.5$). The second largest group included 40% of the study participants (N = 72) with fair physical evolution, whose mean PF scores across time deviated within 1 SD from population means (males 61.6 versus 80.3, $z = –0.9$; females 60.7 versus 71.6, $z = –0.4$). Poor PF evolution was observed in 17% of recipients (N = 29), with mean PF significantly deviating from the general population (males 31.3 versus 80.3, $z = –2.5$; females 31.8 versus 71.6, $z = –1.5$). Compared with the pretransplant values, mean PF significantly increased at the end of the first posttransplant year in recipients perceiving good (78.7 versus 88.8; $P < 0.001$) and fair physical evolution (54.1 versus 64.1; $P = 0.02$). In recipients experiencing poor physical outcomes mean PF scores declined (37.2 versus 25.8; $P = 0.08$). Patients with poor PF had significantly more diabetes and trended to be more prone to have cardiovascular diseases than their counterparts with good or fair PF trajectories. Recipients who experienced graft loss were equally divided between trajectories (6 good, 4 fair, 4 poor; $P = 0.4$; Table 1).

TABLE 1.

Characteristics of older KT recipients of DBD kidneys by developmental trajectories for physical function

	Physical function trajectories				
Study participants	**Total (N = 181)**	**Good (N = 80)**	**Fair (N = 72)**	**Poor (N = 29)**	***P***
Sex, male, n (%)	125 (69.1)	63 (78.7)	44 (61.1)	18 (62.1)	0.04
Age at KT[a], y	72.0 (4.2)	71.9 (4.2)	72.5 (4.3)	71.1 (3.8)	0.3
Comorbidity, n (%)					
CVD	95 (52.5)	35 (43.8)	42 (58.3)	18 (62.1)	0.1
Diabetes	41 (22.7)	10 (12.5)	20 (27.8)	11 (37.9)	0.006
Cancer	46 (25.4)	20 (25.0)	17 (23.6)	9 (31.3)	0.7
No comorbidity	41 (22.7)	25 (31.2)	14 (19.4)	2 (6.9)	0.02
LCI[a]	2.7 (2.4)	2.0 (1.8)	3.0 (2.3)	3.8 (3.3)	<0.001
LCI group, n (%)					<0.001
0–3	131 (72.4)	66 (82.5)	46 (63.9)	19 (65.5)	
4–6	36 (19.9)	12 (15.0)	22 (30.6)	2 (6.9)	
7–9	11 (6.1)	2 (2.5)	3 (4.2)	6 (20.7)	
≥10	3 (1.6)	0	1 (1.4)	2 (6.9)	
Waitlisting time[b], mo	17.1 (11.9–25.8)	15.9 (11.8–26.0)	17.1 (12.0–26.9)	19.8 (9.4–25.5)	1.0
Graft loss	14 (7.7)	6 (7.5)	4 (5.6)	4 (13.8)	0.4
Donor age[a], y	67.1 (10.6)	67.3 (9.0)	66.2 (12.8)	69.0 (8.8)	0.5
ECD, n (%)	144 (80.0)	64 (80.0)	56 (77.8)	24 (82.8)	0.9
Dialysis vintage[b], mo	27.4 (17.3–43.2)	23.5 (13.7–32.5)	27.2 (18.5–46.6)	30.0 (19.0–51.0)	0.09
Survival[b], y	4.9 (3.7–6.6)	5.2 (3.7–7.0)	4.8 (3.8–6.2)	4.7 (2.8–5.9)	0.2
Deaths, n (%)	57 (31.5)	19 (23.7)	22 (30.6)	16 (55.2)	0.009

[a]Age at KT, LCI, and donor age are presented as mean values ± SD.
[b]Waitlisting time, dialysis vintage, and survival are presented as median value and 25th–75th percentiles.
CVD includes congestive heart failure, coronary vascular disease/myocardial infarction, dysrhythmia, cerebrovascular disease, and peripheral vascular disease.
CVD, cardiovascular disease; DBD, deceased brain-dead donor; ECD, expanded criteria donor organ; KT, kidney transplantation; LCI, Liu comorbidity index.

Long-term patient survival was significantly associated with the longitudinal evolution of PF during the first posttransplant year. The 5-y survival rate was 84% (95% CI, 74%-91%) in recipients with good physical evolution, 71% (95% CI, 59%-81%) in recipients with fair physical evolution, and 49% (95% CI, 30%-66%) in recipients with poor physical evolution (logrank; $P = 0.006$) (Figure 4). In the univariable Cox regression model, mortality risk was 2.8 times higher (HR, 2.79; 95% CI, 1.44–5.44) in the poor physical trajectory and 1.4 times higher (HR, 1.38; 95% CI, 0.75–2.56) in the fair physical trajectory, as compared with the good physical trajectory. The significant association between poor PF trajectory and patient survival was still present after adjustment for age at KT, gender, pretransplant comorbidity assessed by Liu index,[22] and dialysis vintage (HR, 2.38; 95% CI, 1.15–5.01) (Table 2). Similarly, this association remained significant when we included specific pretransplant comorbidities such as cardiovascular disease (HR, 2.89; 95% CI, 1.46–5.76), diabetes (HR, 3.09; 95% CI, 1.56–6.14), or both (HR, 2.92; 95% CI, 1.43–5.99) in the model. The results remained unchanged in a sensitivity analysis including in the model also patients that died during the first posttransplant year (N = 11, data not shown). The domains of mental health and effect of kidney disease were also significantly associated with patient survival in the univariable models, but this association disappeared in the multivariable analyses.

DISCUSSION

This longitudinal analysis indicates that in older recipients of DBD kidneys HRQOL develops differently during the first posttransplant year, in long-term survivors versus nonsurvivors. Declining PF predicted impaired long-term patient survival, also when controlling for other factors in a multivariable analysis. Compared with patients with good PF, patients experiencing poor physical evolution had 2.4 times higher mortality risk. Our findings are novel for the KT population and indicate that systematic HRQOL monitoring during posttransplant follow-up may be used to identify patients at risk of impaired long-term outcome.

HRQOL outcomes, especially the domain of PF, evaluated before or after KT have been shown to be positively associated with risk of hospitalization, rate of KT, and patient and graft survival.[4-7,9,10,32] However, previous studies were often limited by their cross-sectional design and a single time-point evaluation of HRQOL and did not offer further insight in HRQOL evolution in different patient groups. We recently demonstrated that in older recipients, self-reported PF evaluated shortly before KT, was an independent predictor of patient survival, with scores ≤60 doubling the risk of posttransplant death.[29] In the current study, we additionally observed that decreasing HRQOL scores early after KT, starting already at 10 wk and persisting throughout the first year, were associated with inferior patient survival. Following these findings, one may elucidate that declining HRQOL can serve as a marker of clinical deterioration, and recipients who lack posttransplant improvement should be reevaluated and possible causes explored. In line with our findings, higher mortality risk was recently reported in recipients who physically declined during the first year after hemodialysis initiation, and proactive monitoring of the PF domain is thought to improve risk prediction modeling.[33]

Analyzing trajectories offers the advantage of revealing latent groups with the same evolutional pattern that may have common characteristics and experience similar clinical

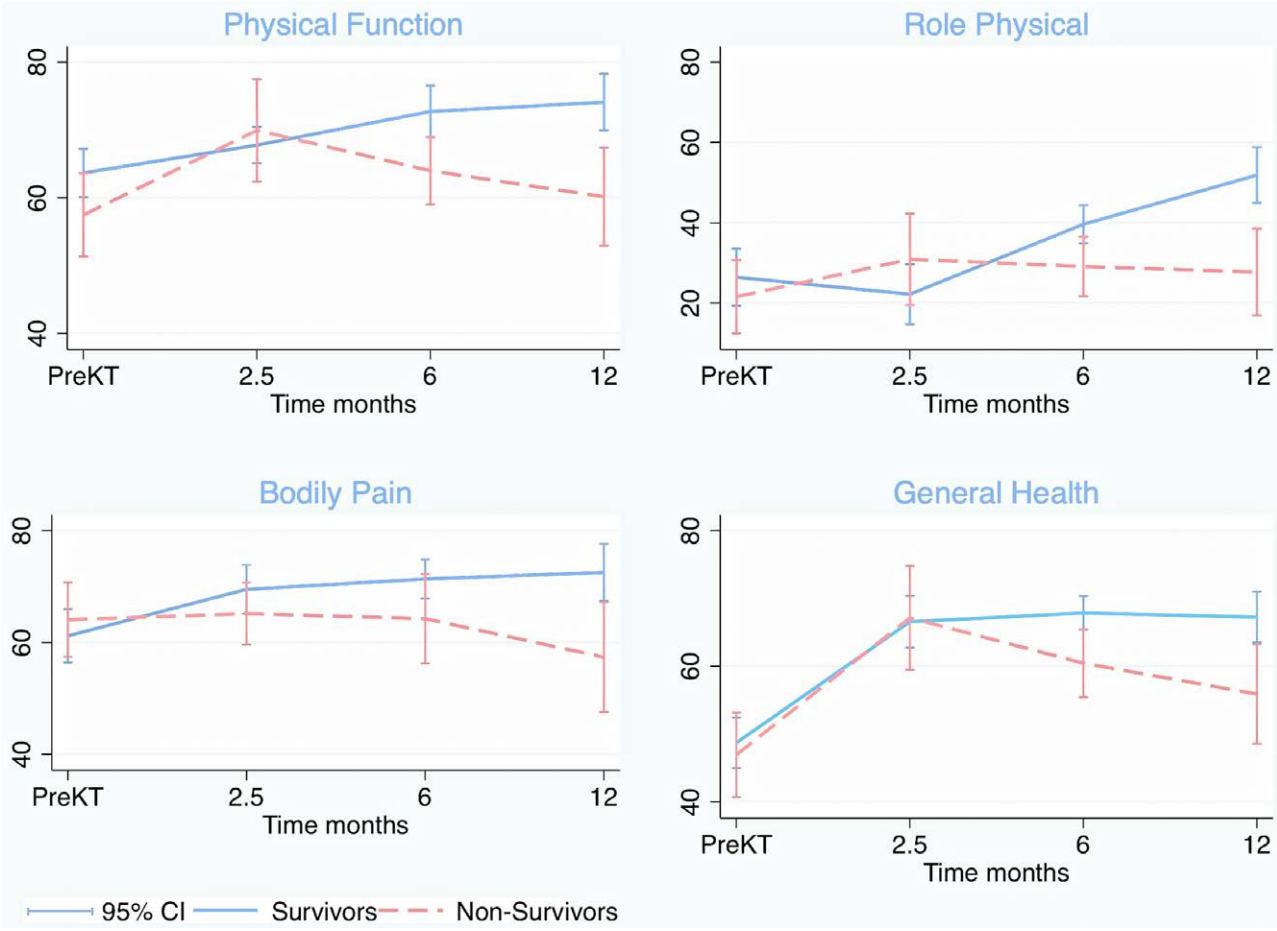

FIGURE 2. HRQOL evolution during the first posttransplant y in long-term survivors compared with nonsurvivors. CI, confidence interval; HRQOL, health-related quality of life; KT, kidney transplantation.

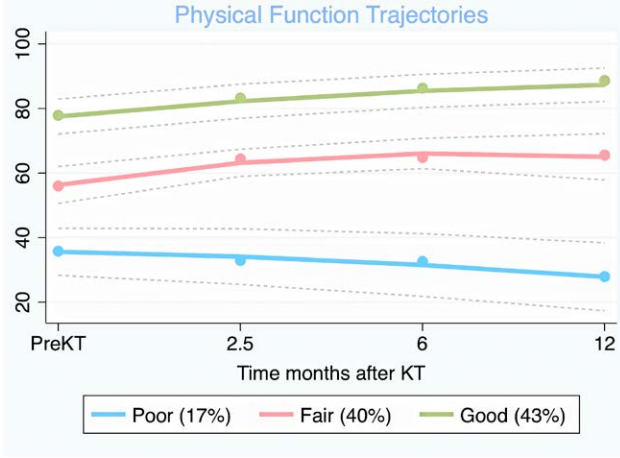

FIGURE 3. Physical function trajectories; good, fair, and poor evolution. KT, kidney transplantation.

outcomes.[27] In solid organ transplantation, a considerable number of recipients share a poor evolutional trajectory and will experience impaired outcomes, despite the average trend of HRQOL improvement.[34,35] Recently, 4 distinct HRQOL trajectories were identified in KT recipients who were followed up to 3 y, with poor generic HRQOL evolution indicating increased risk of graft failure.[36] Our findings, in a much older population, confirm the presence of distinct HRQOL trajectories during the first year posttransplant. The good, fair, and poor physical trajectories indicated no, slight, or large deviation from the population means, respectively, which corroborate previous reports.[35,36] The evolution of PF was an independent predictor of long-term patient survival, and in the adjusted model, recipients in the poor trajectory had a 2.4 times higher risk of death as compared with good trajectory.

The domain of perceived PF has been reported to correlate with the level of physical activity.[37] As a lifestyle behavior, physical inactivity is highly prevalent among KT recipients and predicts cardiovascular and all-cause mortality.[38,39] Even minor increases in physical activity generate marked health benefits.[40] In KT recipients, the short-term effects of exercise training initiated after KT are beneficial and include improved cardiorespiratory fitness, increased muscle strength, better PF, better blood lipid profile, lower blood pressure, less arterial stiffness, better bone health, less obesity, and improved quality of life.[39] However, very few studies have reported long-term data, up to 12 mo after initiating the intervention, and the effect of physical activity on patient survival is unknown. Given the observed adverse association between the evolution of PF after transplantation and survival, one should address whether early intervention, in the physically impaired population can alter the anticipated poor physical evolution, and in that case, if this may improve long-term outcomes.

Our study has several strengths. The national prospective design ensures uniform evaluation and common treatment

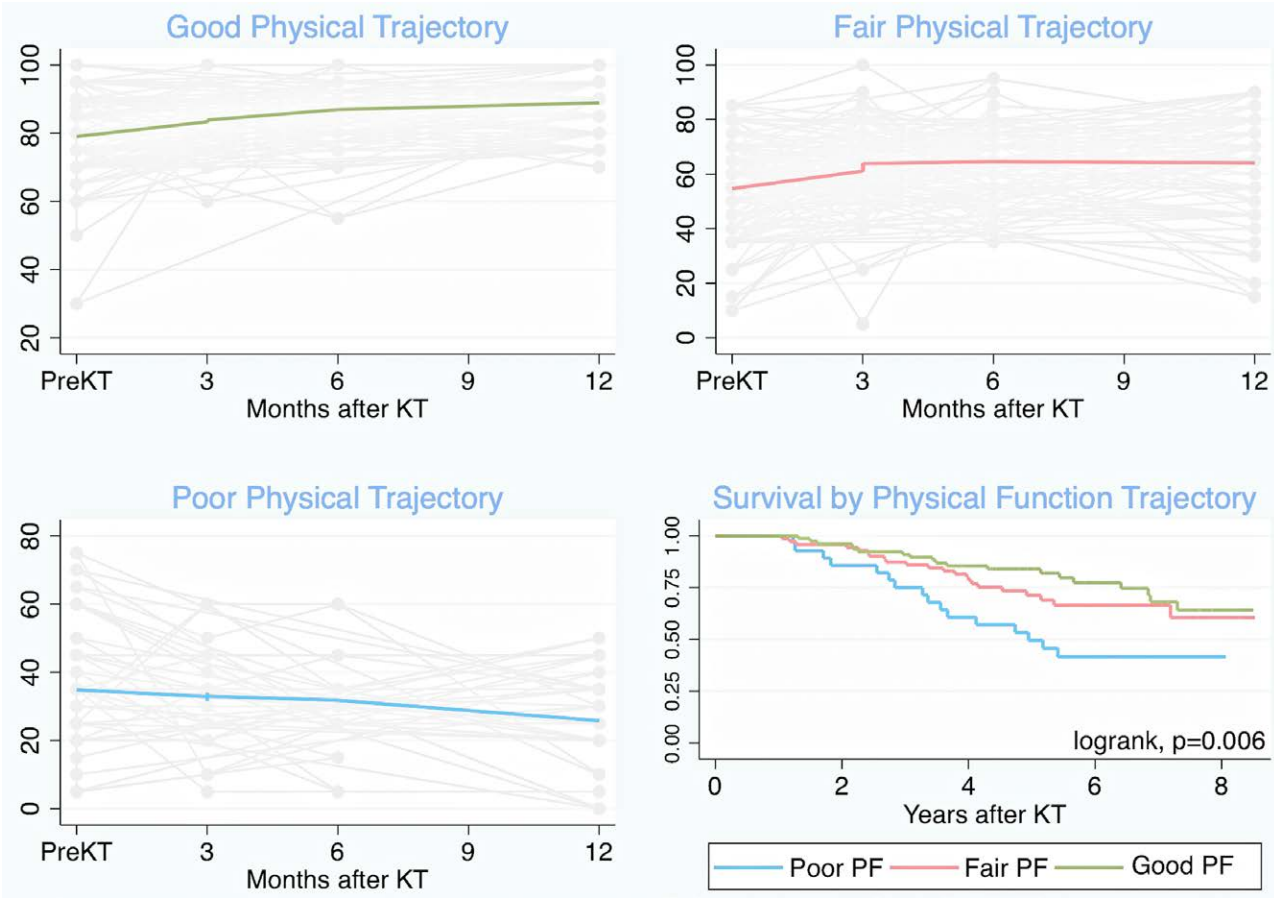

FIGURE 4. Illustration of individual PF trajectories together with each group mean trajectory. Observed patient survival by PF trajectory group. KT, kidney transplantation; PF, physical function.

TABLE 2.

Association between physical function trajectories and patient survival in older recipients of deceased donor organs

	Cox proportional hazard regression			
	Univariable		Multivariable	
PF trajectories	HR (95% CI)	*P*	HR (95% CI)	*P*
Poor PF	2.79 (1.44–5.44)	0.002	2.38 (1.14–5.01)	0.02
Fair PF	1.38 (0.75–2.56)	0.3	1.23 (0.65–2.34)	0.5
Sex			0.95 (0.51–1.74)	0.9
Age at KT			1.02 (0.96–1.09)	0.5
Liu comorbidity			1.07 (0.97–1.19)	0.2
Dialysis ≤2 y			1.90 (0.80–4.53)	0.1
Dialysis >2 y			2.25 (1.00–5.07)	0.05

The good developmental physical function trajectory is used as reference. Male sex is used as reference. No previous history of dialysis is used as reference. Age is given in y. Liu comorbidity score is a continuous variable.
CI, confidence interval; HR, hazard ratio; KT, kidney transplantation; PF, physical function.

protocols. To our knowledge, this is the first prospective study to longitudinally evaluate HRQOL trajectories during the first posttransplant year in older recipients and to address the association with patient survival. The evaluation of HRQOL shortly before KT and the regular posttransplant assessment provides an accurate depiction of its evolution after KT. All data are self-reported, always collected at the patient's residence, which minimizes the collection and interpretation biases. However, the participants in this single-center study had a relatively short waiting time compared with many other centers, which may reduce the generalizability of our findings. Frailty, which has been associated with impaired outcomes in ESKD and after KT,[41] was not assessed in our study. However, the dimension PF, may to some degree, describes physical frailty,[41] so it is unlikely that this has significantly confounded our results.

In conclusion, in older KT recipients declining HRQOL after KT indicates increased risk of clinical deterioration. Poor PF trajectory is a significant predictor of impaired patient survival. Implementation of regular posttransplant HRQOL monitoring may identify high-risk patients for clinical impairment and guide therapeutic decisions.

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