



ORIGINAL ARTICLE

## Increased mortality after kidney transplantation in mildly frail recipients

María José Pérez-Sáez <sup>1,\*</sup>, Carlos E. Arias-Cabrales<sup>1,\*</sup>, Dolores Redondo-Pachón<sup>1</sup>, Carla Burballa<sup>1</sup>, Anna Buxeda<sup>1</sup>, Anna Bach<sup>1</sup>, Anna Faura<sup>1</sup>, Ernestina Junyent<sup>1</sup>, Ester Marco<sup>2</sup>, Leocadio Rodríguez-Mañas <sup>3</sup>, Marta Crespo<sup>1</sup> and Julio Pascual<sup>1,4</sup>, for the FRAIL-MAR Study Group

<sup>1</sup>Nephrology Department, Hospital del Mar, Barcelona, Spain, <sup>2</sup>Physical Medicine & Rehabilitation Department, Parc de Salut Mar (Hospital del Mar-Hospital de l'Esperança), Rehabilitation Research Group, Hospital del Mar Research Institute, Universitat Autònoma de Barcelona, Barcelona, Spain, <sup>3</sup>Geriatrics Department, Hospital Universitario de Getafe, Madrid, Spain and <sup>4</sup>Nephrology Department, Hospital Universitario 12 de Octubre, Madrid, Spain

\*These authors contributed equally to this work.

Correspondence to: Julio Pascual; E-mail: [julpascual@gmail.com](mailto:julpascual@gmail.com)

### ABSTRACT

**Background.** Physical Frailty Phenotype (PFP) is the most used frailty instrument among kidney transplant recipients, classifying patients as pre-frail if they have 1–2 criteria and as frail if they have  $\geq 3$ . However, different definitions of robustness have been used among renal patients, including only those who have 0 criteria, or those with 0–1 criteria. Our aim was to determine the impact of one PFP criterion on transplant outcomes.

**Methods.** We undertook a retrospective study of 296 kidney transplant recipients who had been evaluated for frailty by PFP at the time of evaluating for transplantation.

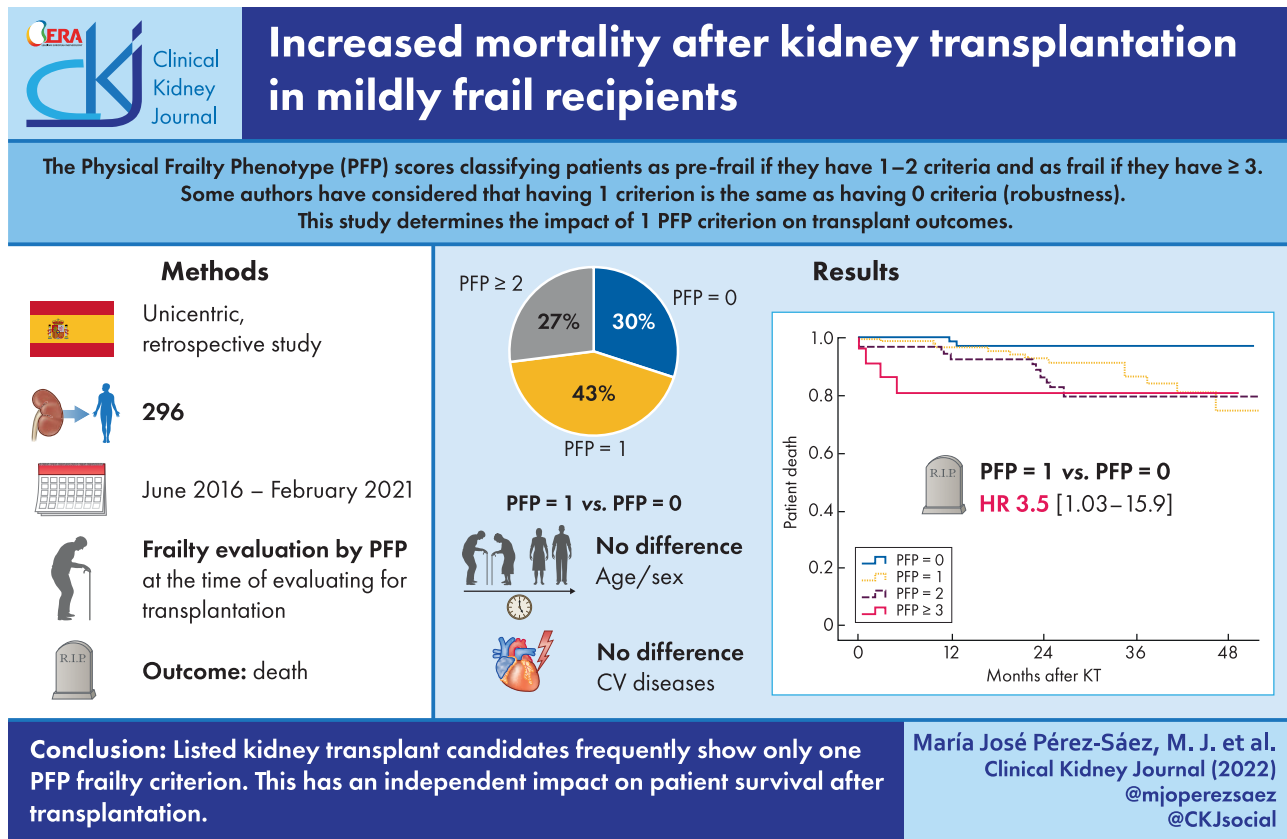
**Results.** Only 30.4% of patients had 0 criteria, and an additional 42.9% showed one PFP criterion. As PFP score increased, a higher percentage of women and cerebrovascular disease were found. Recipients with 0–1 criteria had lower 1-year mortality after transplant than those with  $\geq 2$  (1.8% vs 10.1%), but this difference was already present when we only considered those who scored 0 (mortality 1.1%) and 1 (mortality 2.4%) separately. The multivariable analysis confirmed that one PFP criterion was associated to a higher risk of patient death after kidney transplantation [hazard ratio 3.52 (95% confidence interval 1.03–15.9)].

**Conclusions.** Listed kidney transplant candidates frequently show only one PFP frailty criterion. This has an independent impact on patient survival after transplantation.

Received: 31.3.2022; Editorial decision: 1.6.2022

© The Author(s) 2022. Published by Oxford University Press on behalf of the ERA. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (<https://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact [journals.permissions@oup.com](mailto:journals.permissions@oup.com)

## GRAPHICAL ABSTRACT



**Keywords:** frailty phenotype, Fried, survival, transplant

## INTRODUCTION

Among kidney transplant (KT) recipients, the overall pooled prevalence of frailty before transplantation has been recently estimated at 17.1% [1]. This condition implies poorer results after transplantation, not only regarding clinical outcomes such as longer delayed graft function or inpatient stay [1], higher rate of early readmissions to the hospital [2], or poorer tolerance to immunosuppressants [3], but also in terms of higher mortality after transplantation [4–6].

Although many scales have been used to evaluate frailty in KT recipients [7, 8], the Physical Frailty Phenotype (PFP) [9] has been the most utilized [1]. Its original version comprises five domains and classifies patients as frail if they present with  $\geq 3$  criteria. Non-frail patients are considered with 0 criteria and intermediate or pre-frail patients those with 1 or 2 criteria. In the general population, not only frailty but also pre-frailty has been associated with poorer health outcomes [9–12]. In the setting of KT, pre-frailty has also been associated with worse outcomes after transplantation, although it has not been found to increase the risk of mortality after transplantation when adjusted models were performed [4]. In other studies, pre-frail and frail transplant recipients have been merged and outcomes have been considered together for both categories [3, 5, 13].

The problem may arise when robustness or pre-frailty concepts are modified from the original PFP definition. Several studies carried out both in dialysis patients and KT recipients have considered as non-frail patients those who had not only 0 but also 1 PFP criteria [4, 5, 14, 15] (instead of only those with 0 criteria). This responded to the claim that too few end-stage renal disease patients would have 0 criteria. Therefore, two misclassifications may potentially be present: (i) when analyzing intermediate frail patients, these studies only consider those recipients with 2 PFP criteria, and (ii) for non-frail patients, they are considering those recipients with not only 0 but also 1 PFP criterion. In other studies involving renal patients, the original PFP score to define different categories of robustness, pre-frailty, and frailty has been used [16]. Therefore, while there is consensus in considering as frail patients those who fulfill  $\geq 3$  PFP criteria and this is relevant for outcomes analyses [1], confusion might be present when analyzing results of pre-frail patients, a much more common condition among KT candidates and recipients, especially if we only consider 1 PFP criterion to define pre-frailty. To our knowledge, no studies have analyzed the relevance of the presence of 1 PFP criterion, and no studies have differentiated results after transplantation accordingly to the original PFP definition (0, 1–2, and  $\geq 3$  criteria) vs the modified PFP classification performed in renal population.

Table 1. Baseline characteristics and main outcomes of 296 KT recipients according to their PFP score

	All KT (n = 296)	PFP 0 (n = 90)	PFP 1 (n = 127)	PFP ≥2 (n = 79)	P-value
<b>Baseline characteristics</b>					
Age at transplantation (years, mean ± SD)	62.6 ± 12.3	60.9 ± 11.5	61.1 ± 14.1	63.2 ± 11.3	.412
Sex (female, n (%))	87 (29.4)	17 (18.9)	30 (23.6)	40 (50.6)	<.001
BMI (kg/m <sup>2</sup> , mean ± SD)	27.2 ± 4.8	27.2 ± 4.5	26.8 ± 4.8	27.8 ± 5.2	.288
Hypertension (n, %)	285 (96.3)	86 (95.6)	124 (97.6)	74 (94.9)	.553
Diabetes mellitus (n, %)	102 (34.5)	28 (31.1)	41 (32.3)	33 (41.8)	.275
Coronary artery disease (n, %)	41 (13.9)	12 (13.3)	18 (14.2)	11 (13.9)	.984
Peripheral vascular disease (n, %)	25 (8.4)	4 (4.4)	13 (10.2)	8 (10.1)	.262
Cerebrovascular disease (n, %)	22 (7.4)	8 (8.9)	2 (1.6)	12 (15.2)	.001
<b>Renal replacement therapy modality (n, %)</b>					
Hemodialysis	164 (65.5)	51 (56.7)	81 (63.8)	62 (78.5)	
Peritoneal dialysis	66 (22.3)	23 (25.6)	31 (24.4)	12 (15.2)	.037
Preemptive transplant	36 (12.2)	16 (17.8)	15 (11.8)	5 (6.3)	
Time on dialysis prior to KT (months, mean ± SD)	24.7 ± 21.1	21.0 ± 19.9	25.2 ± 22.0	27.5 ± 20.7	.162
Retransplant (n, %)	21 (7.1)	7 (7.8)	6 (4.7)	8 (10.1)	.325
<b>Transplant characteristics</b>					
<b>Type of donor (n, %)</b>					
Living donor	28 (9.5)	12 (13.3)	11 (8.6)	5 (6.3)	
Brain-death donor	146 (49.3)	37 (41.2)	69 (54.4)	40 (50.6)	.094
Circulatory-death donor	122 (41.2)	41 (45.5)	47 (37.0)	34 (43.1)	
Donor age (years, mean ± SD)	64.1 ± 15.3	64.1 ± 13.0	63.6 ± 16.3	65.1 ± 16.2	.794
Thymoglobulin induction (n, %)	37 (12.6)	10 (11.2)	11 (8.7)	16 (20.5)	.043
Calcineurin inhibitor + mycophenolic acid (n, %)	166 (57.8)	50 (57.5)	74 (60.2)	42 (54.5)	.734
Calcineurin inhibitor + mTOR inhibitors (n, %)	119 (41.5)	37 (42.5)	48 (39.0)	34 (44.2)	.751
Tacrolimus C <sub>0</sub> /D during first year after transplant (ng/mL/mg, mean ± SD) <sup>a</sup>	1.44 ± 0.56	1.44 ± 0.56	1.49 ± 0.57	1.37 ± 0.52	.409
Follow-up (months, median [IQR])	22 [10–38]	19 [11–38]	22 [10–39]	23 [6–38]	.850

KT, kidney transplant; PFP, Physical Frailty Phenotype; SD, standard deviation; mTOR, mammalian target of rapamycin; C<sub>0</sub>/D, concentration/dose; IQR, interquartile range.

<sup>a</sup>C<sub>0</sub>/D ratio = tacrolimus trough concentration (ng/mL)/daily dose (mg).

Comparisons were made among three categories: PFP 0, PFP 1, and PFP ≥ 2. Chi-square test was used to compare categorical variables, ANOVA test to compare quantitative variables with normal distribution and Kruskal–Wallis test for quantitative variables without normal distribution.

We have previously reported a high prevalence of pre-frailty between KT candidates and its negative impact on outcomes while waiting for transplantation [17, 18]. In the present study, we aim to analyze results after transplant according to the patient's frailty status, focusing on the specific weight of having only 1 PFP criterion on transplant outcomes.

## MATERIALS AND METHODS

### Study design

This is a retrospective cohort study carried out at Hospital del Mar, Barcelona, Spain. Between June 2016 and February 2021, 296 KT candidates who had been evaluated for frailty received a KT. Median time to follow-up after KT was 22 months [interquartile range (IQR) 10–38]. Clinical and epidemiological variables were collected from our local database.

### Ethics

The Institutional Review Board of Hospital del Mar approved the study, and all enrolled participants provided written informed consent at the time of frailty evaluation. The study followed the principles of the declaration of Helsinki, only relying on the official center database.

### Frailty assessment

Frailty was assessed according to PFP scale [9] at the time of KT waiting-list evaluation. Median time from evaluation to list-

ing was 12.4 [84.2–184.7] days. PFP comprises five components: shrinking (self-report of unintentional weight loss of 4.5 kg during the past year), weakness [grip strength below an established cut-off based on sex and body mass index (BMI)], exhaustion (self-report), low activity (kilocalories per week below an established cut-off) and slowed walking speed (walking time of 4.5 m below an established cut-off by sex and height). Each component or question scores 0 or 1 depending on its absence or presence, respectively. In the original version, robust patients were defined as a score 0, pre-frail as those who ranked 1–2, and frail patients were defined by a score ≥3. In previous studies involving dialysis and KT population, 0 and 1 scores were merged as a single category of robust patients, claiming that few patients with end-stage renal disease score 0 [4, 5, 14, 15]. We explored the potential misclassification of labeling as robust patients those who scored 1 and, therefore, both classifications were analyzed separately, including patients who scored 1 as robust and as pre-frail patients.

### Study variables

Baseline assessment included recipient's demographics (age, sex, ethnicity and BMI) and clinical data (comorbidities such as hypertension, diabetes mellitus, chronic cardiac and pulmonary diseases, type of renal replacement therapy, etc.), as well as donor characteristics and immunosuppression received.

Regarding outcomes, we analyzed the rate of delayed graft function (defined as the need of dialysis within the first week after transplantation); the length of the first transplantation

**Table 2.** Comparisons in clinical outcomes after kidney transplantation between different PFP classification strategies: (a) grouping 0–1 as a single category of robust patients, (b) considering PFP 0 patients as robust and grouping all patients with any frail PFP, and (c) comparing PFP 0 vs 1 subsets

	PFP 0–1 (n = 217)	PFP ≥2 (n = 79)	P-value
<b>Grouping PFP 0–1 as a single category of robust patients</b>			
Delayed graft function (n, %)	56 (26.8)	27 (35.5)	.151
Length of first inpatient (days, mean ± SD)	10.3 ± 7.8	12.3 ± 10.7	.219
Early readmission (≤90 days, n, %)	52 (24.0)	18 (22.8)	.833
Surgical complications (n, %)	10 (8.9)	10 (12.6)	.202
Opportunistic infections (n, %)	74 (34.1)	34 (43.0)	.158
Acute rejection (n, %)	14 (6.5)	3 (3.8)	.385
3-month serum creatinine (mg/dL, mean ± SD)	1.97 ± 1.12	1.79 ± 1.00	.252
1-year serum creatinine (mg/dL, mean ± SD)	1.94 ± 1.62	1.66 ± 1.26	.271
1-year graft loss (n, %)	23 (10.6)	17 (21.5)	.020
1-year death-censored graft loss (n, %)	19 (8.7)	9 (11.3)	.504
1-year patient mortality (n, %)	4 (1.8)	8 (10.1)	.003
	PFP 0 (n = 90)	PFP ≥ 1 (n = 206)	P-value
<b>Considering PFP 0 patients as robust and grouping any frail score</b>			
Delayed graft function (n, %)	22 (25.3)	61 (30.8)	.345
Length of first inpatient (days, mean ± SD)	10.1 ± 6.9	11.1 ± 9.4	.359
Early readmission (≤90 days, n, %)	20 (22.2)	50 (24.3)	.703
Surgical complications (n, %)	3 (3.3)	16 (7.7)	.704
Opportunistic infections (n, %)	30 (33.3)	78 (37.9)	.456
Acute rejection (n, %)	6 (6.7)	11 (5.3)	.652
3-month serum creatinine (mg/dL, mean ± SD)	2.06 ± 1.15	1.87 ± 1.07	.194
1-year serum creatinine (mg/dL, mean ± SD)	2.09 ± 1.69	1.79 ± 1.48	.197
1-year graft loss (n, %)	7 (7.7)	33 (16)	<.001
1-year death-censored graft loss (n, %)	6 (6.6)	22 (10.7)	<.001
1-year patient mortality (n, %)	1 (1.1)	11 (5.3)	<.001
	PFP 0 (n = 90)	PFP 1 (n = 127)	P-value
<b>Comparing patients PFP 0 vs 1</b>			
Delayed graft function (n, %)	22 (25.3)	34 (27.9)	.678
Length of first inpatient (days, mean ± SD)	10.1 ± 6.9	10.4 ± 8.4	.773
Early readmission (≤90 days, n, %)	20 (22.2)	32 (25.2)	.613
Surgical complications (n, %)	3 (3.3)	7 (5.5)	.884
Opportunistic infections (n, %)	30 (33.3)	44 (34.6)	.841
Acute rejection (n, %)	6 (6.7)	8 (6.3)	.914
3-month serum creatinine (mg/dL, mean ± SD)	2.06 ± 1.15	1.91 ± 1.11	.366
1-year serum creatinine (mg/dL, mean ± SD)	2.09 ± 1.69	1.85 ± 1.58	.370
1-year graft loss (n, %)	7 (7.7)	16 (12.6)	<.001
1-year death-censored graft loss (n, %)	6 (6.6)	13 (10.2)	<.001
1-year patient mortality (n, %)	1 (1.1)	3 (2.4)	.019

PFP, Physical Frailty Phenotype; SD, standard deviation.

inpatient stay; the rate of early readmission to the hospital (defined as admissions within 90 first days after transplant date); surgical complications (including wound infection and/or dehiscence, lymphocele, vascular complications, ureteral stenosis and ureteral leak); opportunistic infections (including cytomegalovirus, BK virus and others); biopsy-proven acute rejection; graft function (defined as serum creatinine at 3 months and 1 year after transplantation); and both graft survival (including death-censored graft survival) and patient survival.

## Statistics

Continuous variables were expressed as mean ± standard deviation (SD), or median and IQR, according to normal distribution. Categorical data were expressed as absolute numbers and percentages. Comparisons of baseline characteristics between two groups were made using Chi-square or Fisher's exact tests to analyze categorical variables, Student's t-test for continuous variables with normal distribution and Mann-Whitney test for non-parametric variables. When three categories were

present, Chi-square test was also used to compare categorical variables, ANOVA test to compare quantitative variables with normal distribution, and Kruskal-Wallis test for quantitative variables without normal distribution. Patient and graft survival were estimated using Kaplan-Meier curves, applying the log-rank test. Among those KT recipients who had 0 or 1 PFP criteria, univariable and multivariable Cox regressions were performed to estimate the hazard ratio (HR) and confidence intervals (CI) for patient survival. Clinical variables who resulted statistically significant in the univariable analysis were included in the multivariable analysis. Statistical analysis was performed using SPSS version 27 software (IBM, Armonk, NY, USA). P-values < .05 were considered statistically significant.

## RESULTS

From a total of 296 KT recipients, 90 (30.4%) had 0 PFP criteria at the time of KT waiting-list admission, 127 (42.9%) had 1 criterion, 57 (19.3%) had 2 criteria, 16 (5.4%) had 3 criteria and

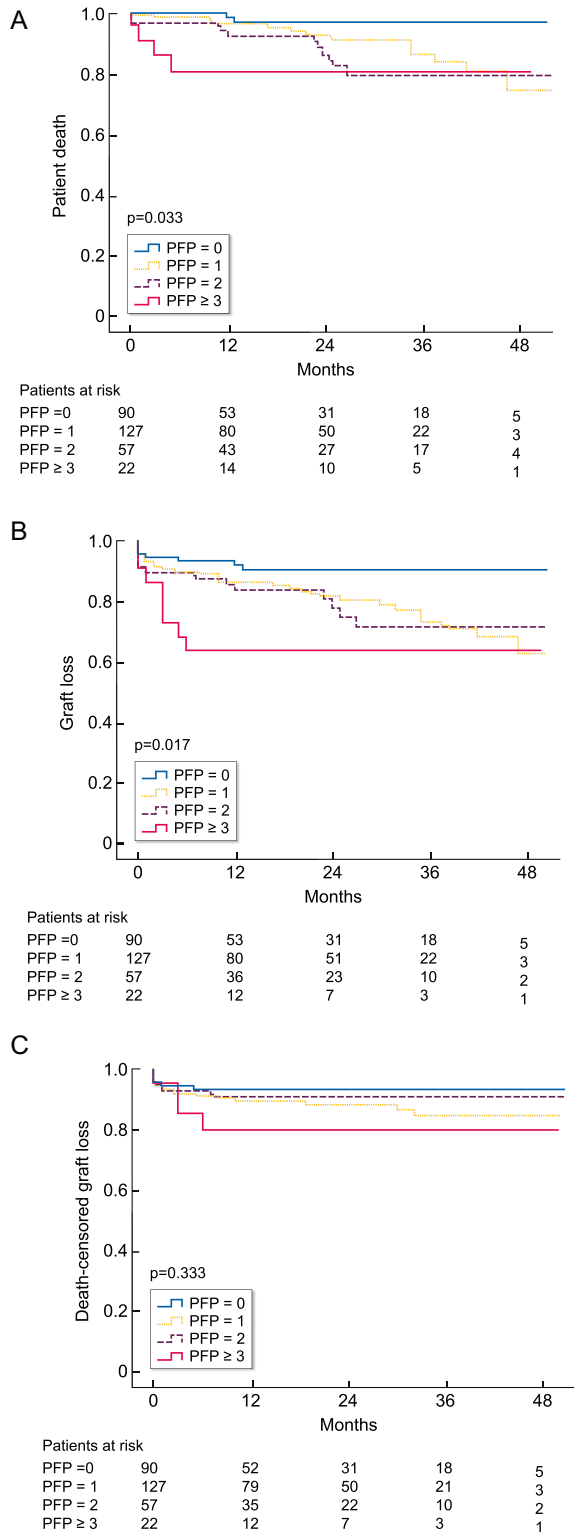


FIGURE 1: Kaplan-Meier survival curves of (A) patient death, (B) graft loss and (C) death-censored graft-loss among 296 KT recipients according to PFP score.

6 (2%) had 4 criteria. No patient presented with 5 criteria. Overall, 79 (26.7%) had  $\geq 2$  criteria. The PFP criteria distribution of those recipients who presented with 1 PFP criterion was as follows: 66.1% weakness, 15.7% weight loss, 15% exhaustion, 1.6% slow walking speed and 0.8% low physical activity. Table 1 displays the baseline characteristics of the cohort based on PFP criteria. Mean

age was not significantly different between groups. Female sex was progressively more frequent among those recipients with advanced stages of frailty (18.9% among patients with 0 criteria and 50.6% among those with  $\geq 2$  PFP criteria). Cerebrovascular disease was more frequent among recipients scoring  $\geq 2$  (15.2% vs 8.9% among patients with 0 criteria). Preemptive KT was a less frequent option among recipients scoring  $\geq 2$  (6.3% vs 17.8% among patients with 0 criteria). No differences were found in terms of time on dialysis prior to transplant, type of donor or donor age between groups. Thymoglobulin was more frequently used in those recipients with  $\geq 2$  PFP criteria. Follow-up was similar between groups.

Regarding transplant outcomes, Table 2 shows results according with three different PFP classifications: (i) merging 0 and 1 criteria and considering both as robust patients ( $n = 217$ , 73.3%) vs  $\geq 2$  as pre-frail or frail ( $n = 79$ , 26.7%); (ii) considering only 0 criteria for robust patients ( $n = 90$ , 30.4%) and comparing with  $\geq 1$  as pre-frail or frail ( $n = 206$ , 69.6%); and (iii) considering 0 criteria for robust patients ( $n = 90$ , 30.4%) and comparing with the subset of KT recipients who scored 1 ( $n = 127$ , 42.9%). In all the three classification models, no differences were found in delayed graft function rate, length of first inpatient stay, early readmission to the hospital, surgical complications, opportunistic infections, acute rejection rate, or graft function at both 3 and 12 months after transplantation. However, univariable analysis showed that graft and patient survival were different between groups, although death-censored graft survival was similar. Figure 1 represents the Kaplan-Meier survival curves of patient death (Fig. 1A), graft loss (Fig. 1B) and death-censored graft loss (Fig. 1C) according to PFP criteria.

To disaggregate data about patient survival, a subset of patients who had 0 PFP criteria ( $n = 90$ ) and 1 PFP criteria ( $n = 217$ ) were considered. Table 3 shows differences among those recipients who were alive and those who were deceased at the end of follow-up. The multivariable analysis reveals that recipient age (HR 1.1 per year), the presence of peripheral vascular disease (HR 9.0) and having 1 PFP criterion (HR 3.52) were independent factors for patient mortality (Table 4).

## DISCUSSION

In this study, we present transplant outcomes in a cohort of KT recipients according to different PFP classifications. Non-frail patients ranged from 30.4% to 73.3% if only those who had none PFP criteria vs those who had 0 or 1 were considered. Both graft and patient survival diverged among groups, being poorer among pre-frail and frail patients. Presenting with one PFP criterion conferred higher rate of patient death than having none.

Frailty has been well established as a risk factor for poorer outcomes after transplantation [1-6]. Most of the studies carried out in KT recipients have used the Fried phenotype [9] to evaluate frailty, considering as frail those patients who have  $\geq 3$  criteria [7]. However, intermediate frail status, originally defined as the presence of 1 or 2 PFP criteria, has been modified in renal population to the presence of 2 criteria, leaving 0 and 1 criteria to define non-frail patients. These thresholds have been recently described as 'specific' to the end-stage renal disease population [19], but no studies have evaluated whether patients with 0 criteria vs 1 criterion behave the same after transplantation.

In the general population, the original definition of pre-frailty has been associated with an increased risk of cardiovascular events [11], as well as disability, low quality of life and mortality [10, 12]. In the KT scenario, several studies have explored the relationship between the excess risk of mortality after

**Table 3. Comparison among patients who survived (n = 202) and those who died (n = 15) at the end of the follow-up (considering only those with 0 or 1 PFP criteria, n = 217)**

	Alive (n = 202)	Deceased (n = 15)	P-value
Age at transplantation (years, mean ± SD)	60.4 ± 12.7	69.9 ± 7.2	<.001
Sex (female, n, %)	44 (21.8)	3 (20)	.585
Hypertension (n, %)	195 (96.5)	15 (100)	.610
Diabetes mellitus (n, %)	62 (30.7)	7 (46.7)	.160
Coronary artery disease (n, %)	26 (12.9)	4 (26.7)	.135
Heart failure (n, %)	5 (2.5)	1 (6.7)	.353
Peripheral vascular disease (n, %)	12 (5.9)	5 (33.3)	.003
Cerebrovascular disease (n, %)	8 (4)	2 (13.3)	.145
PFP = 1	114 (56.4)	13 (86.6)	.018
Time on dialysis prior to KT (months, mean ± SD)	24 ± 22	22 ± 16	.787
Thymoglobulin induction (n, %)	19 (9.5)	2 (13.3)	.438
Tacrolimus C <sub>0</sub> /D during first year after transplant (ng/mL/mg, mean ± SD) <sup>a</sup>	1.44 ± 0.57	1.52 ± 0.43	.490

SD, standard deviation; PFP, Physical Frailty Phenotype; KT, kidney transplantation; C<sub>0</sub>/D, concentration/dose.<sup>a</sup>C<sub>0</sub>/D ratio = tacrolimus trough concentration (ng/mL)/daily dose (mg).**Table 4. Univariable and multivariable analysis of risk factors for patient mortality after transplantation (considering only those with 0 or 1 PFP criteria, n = 217)**

	Univariable			Multivariable		
	HR	95% CI	P-value	HR	95% CI	P-value
Age at transplantation (years)	1.09	1.04–1.14	<.001	1.10	1.03–1.17	.002
Sex (ref: female)	1.49	0.69–3.23	.302			
Hypertension (n, %)	1.70	0.22–12.6	.602			
Diabetes mellitus (n, %)	2.51	0.90–5.69	.070			
Coronary artery disease (n, %)	1.72	0.64–4.57	.275			
Heart failure (n, %)	1.29	0.17–9.5	.801			
Peripheral vascular disease (n, %)	3.36	1.35–8.35	.009	9.0	2.80–29.4	<.001
PFP = 1 (ref: 0)	4.49	1.01–19.9	.048	3.52	1.03–15.9	.048
Time on dialysis prior to KT (months)	1.00	0.98–1.02	.800			
1-year serum creatine	1.29	0.70–2.38	.405			
Tacrolimus C <sub>0</sub> /D ratio during first year after transplant <sup>a</sup>	1.39	0.72–2.68	.313			

HR, hazard ratio; CI, confidence interval; PFP, Physical Frailty Phenotype; KT, kidney transplantation; C<sub>0</sub>/D ratio, concentration/dose.<sup>a</sup>C<sub>0</sub>/D ratio = tacrolimus trough concentration (ng/mL)/daily dose (mg).

transplantation and the recipient frailty status [4–6]. These studies considered as pre-frail patients those who presented with two PFP domains, merging 0 and 1 criteria to define robust patients. One study found that frailty increased 2-fold the risk of death after KT [4], while adjusted models were unable to show an association between pre-frailty and mortality. Patients who had 1 PFP criterion were not analyzed in detail in these studies, as they were considered as robust, and therefore they served as the control group.

In our cohort, only 30.4% of the recipients accounted for 0 PFP criteria and they may be considered as non-frail. In addition, we found a high percentage of patients (42.9%) scoring one PFP criterion. This PFP 1 subgroup would have been considered as non-frail in some studies, or pre-frail in others. Aiming to disaggregate transplant results in this group of robust vs pre-frail patients, we analyzed clinical outcomes from different PFP classification perspectives. Although minor clinical outcomes were similar among patients with 0, 1 or ≥2 criteria, significant differences were found in terms of both graft and patient survival. When considering the PFP 'renal' classification, differences in early patient mortality (within the first 12 months after transplantation) were found among robust (0–1 criteria) and pre-frail (≥2 criteria) patients, which was significantly higher

among these pre-frail patients (10.1% vs 1.8%). Patients scoring for 2 or more PFP domains were at high risk of a premature death after transplantation. On the other hand, when considering original Fried classification for robustness (0 criteria) and pre-frailty or frailty (≥1 criteria), we also observed differences in early patient mortality (higher in pre-frail or frail recipients), as well as a higher rate of global graft loss during the first year after transplant. Finally, we decided to analyze whether they were any differences in terms of transplant outcomes between those patients who had been merged in previous studies from other groups as non-frail patients (0 criteria vs 1 criterion). Patients with 1 PFP criterion presented with higher 1-year patient mortality (2.4% vs 1.1%) and higher 1-year rate of death-censored graft loss (10.2% vs 6.6%) than patients with 0 criteria, and the multivariable analysis confirmed that having 1 PFP criterion increased almost 4-fold the risk of death after transplantation. As the Kaplan–Meier survival curves show, these patients do not seem to die as early as those who were frailer, but still, their risk of death is higher than the ones who did not score for any PFP criteria before transplantation.

Our study has the inherent limitations that an observational study implies and probably the sample size is not large enough to show statistically significant results in terms of other clinical

outcomes after transplantation. However, to our knowledge, this is the first study that explores the role of having one Fried criterion in transplant outcomes and presents the association between different PFP scores and these outcomes. Giving the large number of frailty scales, it is important to validate them in the renal population, clarifying their predictive value for bad outcomes [20] or analyzing the clinical significance of their definition for frailty. In addition, identifying pre-frail or frail patients may allow clinicians to establish proper strategies to revert the situation [21].

In accordance with the original PFP scale [9], being pre-frail has an impact on both graft and patient survival, and it starts with the presence of one Fried criterion. More studies are needed to corroborate these results and establish proper risks after transplantation according to frailty status before transplant.

## ACKNOWLEDGEMENTS

The authors of this study appreciate the contribution of all the members of the FRAIL-MAR Study Group.

## FUNDING

Frail-MAR project is currently supported by a FIS-FEDER grant PI19/00037 Instituto de Salud Carlos III (ISCIII) a 'Proyecto Estrella de Mejora de la Calidad', Parc de Salut Mar, Barcelona, Spain. M.J.P.-S. has received a grant from the Spanish Society of Transplant. A.Buxeda has support from a Rio Hortega contract CM19/00004, ISCIII.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

## CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

## APPENDIX

FRAIL-MAR Study Group members:

María José Pérez-Sáez, Carlos E. Arias-Cabrales, Dolores Redondo, Francesc Barbosa, Higinio Cao, Silvia Collado, Anna Buxeda, Carla Burbulla, Marta Crespo, Julio Pascual, Anna Faura, María Vera, Anna Bach, Guillermo Pedreira, Ernestina Junyent, Montserrat Folgueiras, Yolanda Castillo, Aida Martínez, Marisol Fernández, Eva Barbero, Rosa Causadías (Department of Nephrology, Hospital del Mar), Alicia Calvo (Department of Cardiology, Hospital del Mar), Jesús Carazo (Department of Anesthesiology, Hospital del Mar), Albert Frances, Lluís Cecchini (Department of Urology, Hospital del Mar), Ester Marco, Delky Meza de Valderrama, Andrea Morgado, Elena Muñoz (Department of Rehabilitation and Physical Medicine, Hospital del Mar), Xavier Nogués (Department of Internal Medicine, Hospital del Mar), Leocadio Rodríguez-Mañas (Department of Geriatrics, Hospital Universitario de Getafe, Madrid), Olga Vázquez (Department of Geriatrics, Hospital del Mar), María Dolores Muns (Dietary Unit, Department of Endocrinology and Nutrition, Hospital del Mar), Miguel Gárriz, María Polo Gómez (Psychology Department, Neuropsychiatric Institute, Hospital del Mar), Sara Hurtado, Maite López (Diagonal Hemodialysis Center, Fresenius

Medical Care), Laura Ribera, Margarita Guino (Glories Hemodialysis Center, Fresenius Medical Care), Ramón Roca, Jordi Calls, Alicia Rovira (Department of Nephrology, Hospital de Mollet), Josep Mora, Omar Ibrík, Florentina Liria (Granollers Hemodialysis Center, Fresenius Medical Care), Thais López, Jaume Almirall, Carmen Moya (Department of Nephrology, Hospital Parc Taulí), Fátima Moreno, Manel Ramírez de Arellano, Sandra Rubio (Department of Nephrology, Consorci Sanitari de Terrassa), Ignacio Cidraque, Carlota Pájaro (Cetirsa Terrassa Hemodialysis Center, Fresenius Medical Care), Núria Garra, Josep Galcerán, Marina Fenollar (Department of Nephrology, Hospital de Manresa), Sara Outón, Fabiola Dapena, Josep Jara (Department of Nephrology, Consorci Sanitari del Garraf), Rosa García, Mònica Manresa (Department of Nephrology, Hospital de Palamós).

## REFERENCES

1. Quint EE, Zogaj D, Banning LBD *et al.* Frailty and kidney transplantation: a systematic review and meta-analysis. *Transplant Direct* 2021; 7: e701; doi:10.1097/TXD.0000000000001156
2. Goldfarb DA. Re: frailty and early hospital readmission after kidney transplantation. *J Urol* 2014; 191: 1366–1367
3. McAdams-Demarco MA, Law A, Tan J *et al.* Frailty, mycophenolate reduction, and graft loss in kidney transplant recipients. *Transplantation* 2015; 99: 805–810
4. McAdams-Demarco MA, Law A, King E *et al.* Frailty and mortality in kidney transplant recipients. *Am J Transplant* 2015; 15: 149–154
5. McAdams-DeMarco MA, Ying H, Olorundare I *et al.* Individual frailty components and mortality in kidney transplant recipients. *Transplantation* 2017; 101: 2126–2132
6. McAdams-Demarco MA, King EA, Luo X *et al.* Frailty, length of stay, and mortality in kidney transplant recipients. *Ann Surg* 2017; 266: 1084–1090
7. Harhay MN, Rao MK, Woodside KJ *et al.* An overview of frailty in kidney transplantation: measurement, management and future considerations. *Nephrol Dial Transplant* 2020; 35: 1099–1112
8. Pérez-Sáez MJ, Gutiérrez-Dalmau Á, Moreso F *et al.* Frailty and kidney transplant candidates. *Nefrología* 2021; 41: 237–243
9. Fried LP, Tangen CM, Walston J *et al.* Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001; 56: M146–M156
10. Hanlon P, Nicholl BI, Jani BD *et al.* Frailty and pre-frailty in middle-aged and older adults and its association with multimorbidity and mortality: a prospective analysis of 493 737 UK Biobank participants. *Lancet Public Heal* 2018; 3: e323–e332
11. Sergi G, Veronese N, Fontana L *et al.* Pre-frailty and risk of cardiovascular disease in elderly men and women: the Pro.V.A. study. *J Am Coll Cardiol* 2015; 65: 976–983
12. Feng L, Zin Nyunt MS, Gao Q *et al.* Cognitive frailty and adverse health outcomes: findings from the Singapore Longitudinal Ageing Studies (SLAS). *J Am Med Dir Assoc* 2017; 18: 252–258
13. McAdams-DeMarco MA, Olorundare IO, Ying H *et al.* Frailty and postkidney transplant health-related quality of life. *Transplantation* 2018; 102: 291–299
14. McAdams-Demarco MA, Law A, Salter ML *et al.* Frailty as a novel predictor of mortality and hospitalization in individuals of all ages undergoing hemodialysis. *J Am Geriatr Soc* 2013; 61: 896–901

15. McAdams-Demarco MA, Suresh S, Law A et al. Frailty and falls among adult patients undergoing chronic hemodialysis: a prospective cohort study. *BMC Nephrol* 2013; **14**: 224
16. Pérez Fernández M, Martínez Miguel P, Ying H et al. Comorbidity, frailty, and waitlist mortality among kidney transplant candidates of all ages. *Am J Nephrol* 2019; **49**: 103–110
17. Pérez-Sáez MJ, Arias-Cabrales CE, Dávalos-Yerovi V et al. Frailty among chronic kidney disease patients on the kidney transplant waiting list: the sex-frailty paradox. *Clin Kidney J* 2021; **15**: 109–118
18. Pérez-Sáez MJ, Redondo-Pachón D, Arias-Cabrales CE et al. Outcomes of frail patients while waiting for kidney transplantation: differences between physical frailty phenotype and FRAIL scale. *J Clin Med* 2022; **11**: 672
19. McAdams-DeMarco MA, Chu NM, Segev DL. Frailty and long-term post-kidney transplant outcomes. *Curr Transplant Rep* 2019; **6**: 45–51
20. Pérez-Sáez MJ, Dávalos-Yerovi V, Redondo-Pachón D et al. Frailty in kidney transplant candidates: a comparison between physical frailty phenotype and FRAIL scales. *J Nephrol* Published online January 3, 2022; doi: 10.1007/s40620-021-01234-4
21. Pérez-Sáez MJ, Morgado-Pérez A, Faura A et al. The FRAILMar study protocol: frailty in patients with advanced chronic kidney disease awaiting kidney transplantation. A randomized clinical trial of multimodal prehabilitation. *Front Med* 2021; **8**: 675049