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ORIGINAL ARTICLE

Frailty in kidney transplant candidates: a comparison between physical frailty phenotype and FRAIL scales

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Abstract

Background Frailty is common among advanced chronic kidney disease (CKD) patients who are kidney transplant (KT) candidates, and predisposes to poor outcomes after transplantation. However, frailty is not routinely measured during pre-transplant work-up and it is unknown which metric should be used in this specific population. Our aim was to establish frailty prevalence in KT candidates according to different frailty scales.

Methods Prospective longitudinal study of 451 KT candidates evaluated for frailty by both Physical Frailty Phenotype (PFP) and FRAIL scale at the time of inclusion on the KT waiting list. Clinical and functional characteristics including sociodemographics, comorbidities, disability and nutritional status were recorded. Agreement between PFP and FRAIL scales as well as dissonant patients were analyzed.

Results Mean age was 60.9 years and 31.7% were female. Comorbidity burden among patients was high, with 36.9% and 16.2% presenting with diabetes and ischemic coronary disease, respectively. Disabilities were also frequent. More than 70% of patients presented with ≥ 1 PFP criteria while this percentage for ≥ 1 FRAIL criteria was 45.4%. Agreement between PFP and FRAIL was not good (kappa index 0.317). There were 132 patients who were pre-frail or frail according to PFP but non-frail according to the FRAIL scale and they presented with fewer comorbidities and less disability.

Conclusions Frailty is frequent in advanced CKD patients, although its prevalence may vary according to different scales. Agreement between PFP and FRAIL scale is not good, and FRAIL scale might misclassify as robust patients those frail/prefrail patients who are in better health conditions.

The FRAIL-MAR Study Group members are list in the supplementary list.

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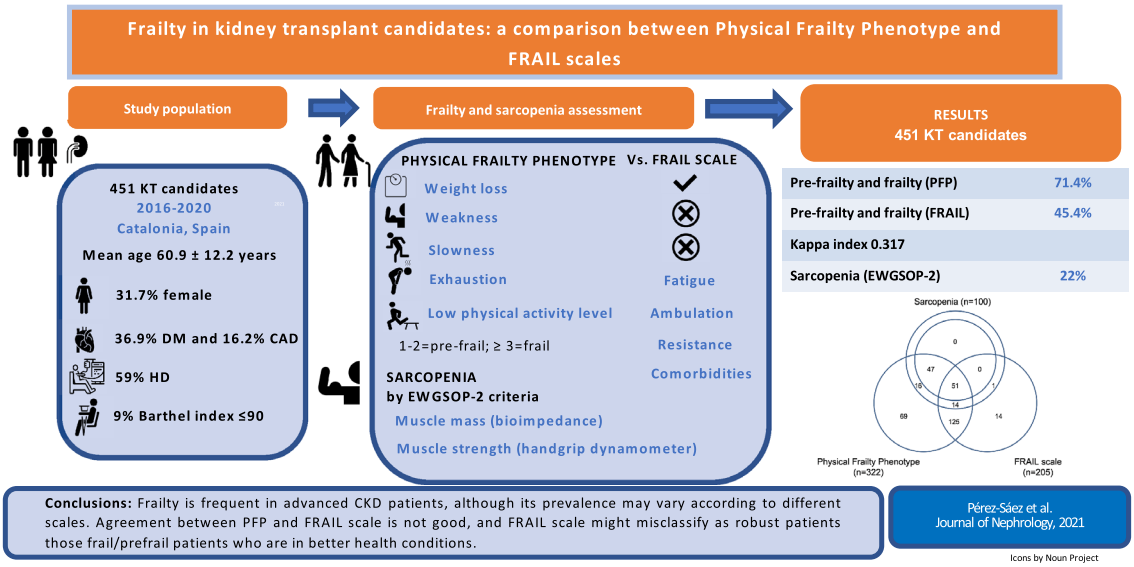
Graphical abstract



Keywords Frailty · FRAIL · Kidney transplantation · Physical frailty phenotype

Introduction

The concept of frailty was first developed in geriatrics to help identify older adults with increased vulnerability when confronted with a health stressor [1]. Kidney transplantation (KT) represents the optimal treatment for advanced chronic kidney disease (CKD) patients, even when elderly recipients are considered [2, 3]. However, it represents a stressor to the patient's health that may imply a challenge in many KT candidates, increasing their risk of death especially during the first months after transplantation [3]. As CKD patients are aging [4, 5], frailty has been progressively introduced as a prognostic tool in this population, and different studies have evaluated their prevalence and impact on outcomes both in CKD-non dialysis [6–9] and dialysis patients [10–17].

Furthermore, frailty is also an independent risk factor for adverse results after transplantation [18–22] and awareness among the transplant community is increasing [23]. Frailty metrics could improve the ability to identify KT candidates at risk for adverse health outcomes and those who could potentially benefit from interventions to improve their frail status. However, frailty is not routinely assessed during pre-transplant work-up. Although there is agreement regarding the underlying conceptual framework of frailty, there is a low level of consensus regarding the constituent elements to be included in operational definitions of frailty. Thus, to date, many frailty metrics considering different aspects such as physical reserve, morbidity, cognition or social factors have been developed [24]. The most used frailty scale in research in the CKD population is the Physical Frailty Phenotype (PFP) [25], but other less time-consuming metrics such as the FRAIL scale [26] have also been utilized [27]. There is substantial heterogeneity regarding the metrics used to assess pre-KT frailty, although PFP has been proposed as the elected one for physical reserve measurement [23]. However, different scales might catch different phenotypes of frail patients and the comparison of their specific predictive value for bad outcomes in the CKD population remain unclear [28].

Sarcopenia, defined by the European Working Group on Sarcopenia in Older People 2 (EWGSOP2) as a muscle disease [29], has also been associated with adverse clinical outcomes in the CKD population [30, 31]. The loss of muscle function is nowadays the stronger sarcopenia criterion, and might precede frailty or even overlap it [32].

The aims of our study were: (1) to assess the prevalence of frailty according to two different frailty methods (PFP and FRAIL scales) in a cohort of CKD KT candidates, and to analyze clinical and functional characteristics of patients differently classified according to each frailty metric; and

(2) to assess the prevalence of sarcopenia according to the EWGOSP2 criteria.

Methods

Study design

Prospective cohort study of patients with advanced CKD reported according to the Strengthening the Reporting of Observational Studies in Epidemiology recommendations (STROBE).

Setting

The cohort study was carried out in the Nephrology unit of the Hospital del Mar (Barcelona, Spain) between June 2016 and June 2020.

Participants

Four hundred and fifty-one patients with advanced CKD who were candidates to KT were eligible for study participation. All patients were evaluated for frailty at the time of inclusion on the waiting list. Other study variables, along with clinical and epidemiological characteristics were collected from the local database.

Study variables

Main study variables were **frailty, sarcopenia** and **nutritional status**.

- ***Frailty assessment***

  Two different frailty assessment tools were used: PFP [25] and FRAIL scale [26]. The PFP scale 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 on the basis of 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). The FRAIL scale includes five self-reported questions assessing fatigue, resistance, ambulation, illness, and loss of weight. In both scales, each component or question was coded into a dichotomous variable (0 or 1). Pre-frail patients were defined by scores of 1–2, frail patients by scores ≥ 3; patients ranging 0 were considered as robust. To increase the power of the study, pre-frail and frail categories were joined for the analysis, considering those patients as frail ones.
- ***Sarcopenia assessment***

  According to the updated EWGSOP definition of sarcopenia (EWGSOP2), the diagnosis of sarcopenia is based on the presence of reduced muscle mass and strength [29]. Muscle mass was assessed using bioimpedance spectroscopy by Body Composition Monitor (Fresenius Medical Care, Bad Homburg, Germany). Measures were expressed in Kg and as a percentage of the European population

Table 1 Kidney transplant candidates' baseline characteristics

Kidney transplant candidates ($n = 451$)	
Sociodemographics	
Age (years, mean ± sd)	60.9 ± 12.2
Sex (female, *n* (%))	143 (31.7)
Caucasian, *n* (%)	408 (95.8)
Education (no/primary, *n* (%))	271 (62.4)
Deficient family support, *n* (%)	64 (14.5)
Socioeconomic status (non-regular incomes, *n* (%))	41 (9.5)
Comorbidities	
Hypertension, *n* (%)	434 (96.4)
Diabetes mellitus, *n* (%)	166 (36.9)
Heart Failure, *n* (%)	26 (5.8)
Ischemic coronary disease, *n* (%)	73 (16.2)
Peripheral vasculopathy, *n* (%)	42 (9.3)
Cerebral vasculopathy, *n* (%)	35 (7.8)
Chronic obstructive pulmonary disease, *n* (%)	31 (7.8)
Hemodialysis as RRT modality, *n* (%)	253 (59)
Disabilities	
Disability for activities of daily living[#], *n* (%)	36 (9)
Disability for instrumental activities of daily living[$], *n* (%)	88 (22)
Sarcopenia assessment* and nutrition evaluation	
Sarcopenia according to EWGSOP2 criteria, *n* (%)	100 (22)
Severe sarcopenia according to EWGSOP2 criteria, *n* (%)	22 (4.8)
Low muscle mass, *n* (%)	240 (53)
Low muscle strength, *n* (%)	161 (35)
Slow gait speed, *n* (%)	61 (13.5)
BMI (Kg/m^2, mean ± sd)	27.9 ± 5.3
At risk of malnutrition[&], *n* (%)	111 (27.9)
Albumin (g/L, mean ± sd)	4.2 ± 0.5
Frailty	
Frailty and pre-frailty prevalence according to PFP, *n* (%)	322 (71.4)
Frailty and pre-frailty prevalence according to FRAIL *n* (%)	204 (45.4)

SD standard deviation, *RRT* renal replacement therapy, *EWGSOP* European Working Group on Older People, *BMI* body mass index, *IQR* interquartile range, *PFP* Physical Frailty Phenotype

*Bioimpedance data were obtained in 352 subjects

[#]Barthel Index ≤ 90

[$]Lawton–Brody < 8 (women) and < 5 (men)

[&]SNAQ ≤ 14

Table 2 Prevalence of frailty (according to PFP and FRAIL scale) among kidney transplant candidates

	n (%)
Physical frailty phenotype ($n=451$)	
No (0)	129 (28.6)
Pre-Frail (1–2)	275 (61)
Frail (≥3)	47 (10.4)
FRAIL scale ($n=451$)	
No (0)	246 (54.6)
Pre-Frail (1–2)	181 (40.1)
Frail (≥3)	24 (5.3)

PFP Physical frailty phenotype

Table 3 Contingency table showing the frequency distribution of robust, pre-frail and frail patients according to the Physical Frailty Phenotype (PFP) and the FRAIL scale

	PFP Robust	PFP Pre-Frail	PFP Frail	Total
FRAIL Robust	114 (25.3)	131 (29.1)	1 (0.2)	246 (54.6)
FRAIL Pre-Frail	15 (3.3)	137 (30.4)	29 (6.4)	181 (40.1)
FRAIL Frail	0	7 (1.5)	17 (3.8)	24 (5.3)
Total	129 (28.6)	275 (61)	47 (10.4)	451 (100)
				Kappa = 0.317 $p<0.001$

reference values [33]. For the purpose of this study, values less than 80% of the reference data were considered decreased, according to previous data [34, 35]. Muscle strength was measured by a handgrip dynamometer (JAMAR, Nottinghamshire, UK), and expressed in kilograms (Kg). Patients performed a maximum voluntary isometric contraction of finger flexor muscles. The highest value of three reproducible maneuvers (< 10% variability between values) was used for analysis following standardized methods [36]. Handgrip strength values < 27 kg for men and < 16 kg for women, were considered decreased [29]. Confirmed sarcopenia was defined when both grip strength and muscle mass were reduced, being severe when gait speed was < 0.8 m/s [29].

- ***Nutritional assessment***

The Short Nutritional Assessment Questionnaire (SNAQ) for risk of malnutrition [37], is a 4-item, efficient and valid tool that has proved to identify patients at risk of severe weight loss. Each item has 5 options scoring 1-to-5 depending on the patient's answer (a = 1, b = 2, c = 3, d = 4, e = 5). Scores ≤ 14 classify individuals at risk of weight loss. Additionally, albumin levels were collected.

Besides demographic characteristics (age, sex, ethnicity), other data were collected: education defined by 4 categories (no, primary education, secondary education, and tertiary education), family or social support, economic incomes (non regular incomes, retired with pension, active worker

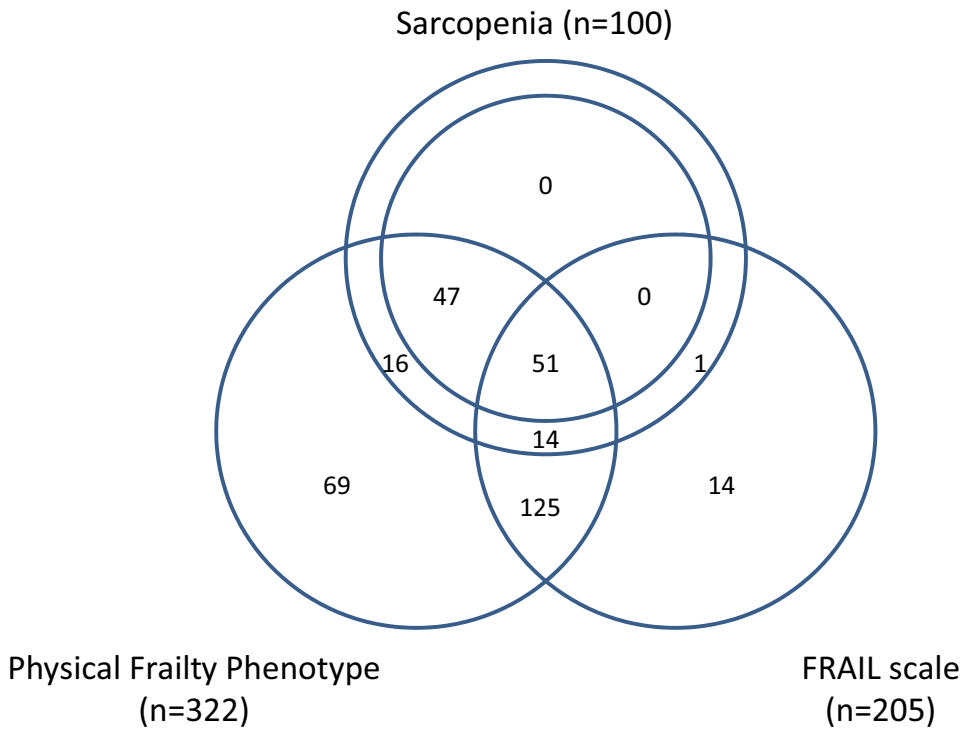


Fig. 1 A modified Venn diagram showing the overlap between the two different frailty criteria and sarcopenia in 352 patients (all patients with PFP, FRAIL and sarcopenia measurements). *PFP* Physical Frailty Phenotype

with salary), basic and instrumental activities of daily living assessed by the Barthel index [38, 39], and the Lawton–Brody scale [40], respectively. Cutoff points for disability were ≤ 90 (Barthel index), and < 8 in women and < 5 in men (Lawton–Brody scale), and clinical data (comorbidities such as hypertension, diabetes mellitus, chronic cardiac and pulmonary diseases, type of renal replacement therapy, etc.).

Ethics

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

Statistics

Continuous variables were expressed as mean ± standard deviation (SD), or median and interquartile range (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

Table 4 Comparison among frail and pre-frail KT candidates (≥ 1 criteria) according to PFP and FRAIL (n = 90) and those who were frail and pre-frail according to PFP but not according to FRAIL (n = 132)

	PFP ≥ 1 and FRAIL ≥ 1 n = 190	PFP ≥ 1 and FRAIL = 0 n = 132	P value
Sociodemographics			
Age (years, mean ± sd)	60.4 ± 11.9	62.3 ± 13.8	0.049
Sex (female, *n* (%))	82 (43.2)	36 (27.3)	0.002
Caucasian, *n* (%)	171 (90)	123 (93.2)	0.463
Education (no/primary, *n* (%))	122 (64.2)	84 (64.6)	0.274
Deficient family support, *n* (%)	36 (18.9)	19 (14.4)	0.328
Socioeconomic status (non-regular incomes, *n* (%))	25 (13.5)	6 (4.5)	0.010
Comorbidities			
Hypertension, *n* (%)	183 (96.3)	129 (97.7)	0.473
DM, *n* (%)	80 (42.1)	42 (31.8)	0.061
Heart Failure, *n* (%)	14 (7.3)	5 (3.8)	0.180
Ischemic coronary disease, *n* (%)	35 (18.4)	16 (12.1)	0.128
Peripheral vasculopathy, *n* (%)	21 (11)	14 (10.6)	0.899
Cerebral vasculopathy, *n* (%)	24 (12.6)	2 (1.5)	< 0.001
COPD, *n* (%)	19 (10)	5 (3.8)	0.037
Hemodialysis as RRT modality, *n* (%)	104 (54.7)	81 (61.3)	0.232
Disabilities			
Disability for activities of daily living[#], *n* (%)	30 (15.8)	2 (1.5)	< 0.001
Disability for instrumental activities of daily living[$], *n* (%)	56 (29.5)	23 (17.4)	0.012
Sarcopenia assessment*			
Sarcopenia according to EWGSOP2 criteria, *n* (%)	49 (27.8)	47 (40.9)	0.24
Low muscle mass, *n* (%)	107 (56.3)	72 (54.5)	0.54
Low muscle strength, *n* (%)	73 (38.4)	85 (64.4)	< 0.001
Nutrition and inflammation status			
BMI (median [IQR])	27.9 ± 5.5	27.8 ± 5.1	0.760
At risk of malnutrition[&], *n* (%)	62 (32.6)	29 (22.5)	0.029
Albumin (g/L, mean ± sd)	4.2 ± 0.5	4.2 ± 0.4	0.821
CRP (mg/dl, median [IQR])	0.4 [0.2–1.0]	0.3 [0.1–0.7]	0.161

KT kidney transplant, *PFP* Physical Frailty Phenotype, *sd* standard deviation, *DM* diabetes mellitus, *COPD* chronic obstructive pulmonary disease, *RRT* renal replacement therapy, *EWGSOP2* European Working Group on Older People, *BMI* body mass index, *IQR* interquartile range, *CRP* C-reactive protein

*Bioimpedance data were obtained in 176 and 115 subjects, respectively

[#]Barthel Index ≤ 90

[$]Lawton–Brody < 8 (women) and < 5 (men)

[&]SNAQ ≤ 14

categorical variables, Student's *t* test for continuous variables with normal distribution, and Mann–Whitney test for non-parametric variables. The Cohen's *kappa* coefficient was calculated to assess agreement between the PFP and the FRAIL scale; *kappa* values 0–0.20 indicate low agreement; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.80, substantial; and 0.81–1, high agreement [41]. Statistical analysis was performed using SPSS version 21 software (IBM, Armonk, NY, USA). *P*values < 0.05 were considered statistically significant.

Results

Baseline characteristics of 451 KT candidates are shown in Table 1. Mean age was 60.9 years and 31.7% of them were women. A considerable number of patients presented with poor social results such as low level of education (62.4%), deficient family support (14.5%) or lack of regular economic incomes (9.5%). Comorbidity burden, as expected in the CKD population, was high, especially in terms of hypertension (96.4%), diabetes mellitus (36.9%), and coronary ischemic disease (16.2%). Disabilities were also frequent, both for basic and instrumental activities of daily living (9% and 22%, respectively).

Sarcopenia was assessed in 420 subjects. According to EWGSOP2 criteria, 22% of patients were sarcopenic, and one out of every four had severe sarcopenia. Low muscle mass was the most frequent finding, and was present in 53% of 352 patients with available bioimpedance data. In addition, although BMI showed slight overweight among patients (27.9 kg/m^2) and albumin levels were normal (4.2 g/L), 27.9% of them were at risk for malnutrition according to the SNAQ (Table 1).

Frailty prevalence differed depending on the scale used. The PFP classified a higher number of subjects as frail (71.4% as opposed to 45.4% of the FRAIL scale) (Table 2). A contingency table shows the distribution of robust (25.3%), pre-frail (30.4%) and frail patients (3.8%) according to both scales (Table 3). The Cohen's Kappa coefficient (0.317) established fair agreement between the two assessment tools.

The PFP, FRAIL scale and sarcopenia assessment were available in 420 individuals. A frailty-sarcopenia overlap was observed in 98 patients when using the PFP in front of 51 patients with the FRAIL scale, as shown in a modified Venn diagram (Fig. 1).

In an attempt to clarify which patients could be at risk to be identified as frail using self-reported questions (e.g. FRAIL scale), frail patients according to the PFP and FRAIL scales ($n = 190$) were compared to those classified as frail with the PFP and did not meet the FRAIL scale criteria ($n = 132$). In this group of patients, there was a higher percentage of men and they had better socioeconomic status (only 4.5% without regular incomes). They presented with fewer comorbidities (cerebral vasculopathy of 1.5 vs 12.6% in those who scored positive for both PFP and FRAIL) and less disability for both activities of daily living (1.5 vs 15.8%, respectively), and instrumental ones (17.4 vs 29.4%, respectively), as shown in Table 4. Moreover, prevalence of sarcopenia was higher in these patients (40.9 vs 27.8%).

Discussion

In this study, we aimed to compare frailty prevalence by two different tools (PFP and FRAIL scale) in a cohort of 451 CKD KT candidates. The PFP identified 71.4% of patients as pre-frail or frail (≥ 1 criteria), while the FRAIL scale identified 45.4% of them. Agreement between both scales was fair, with a *kappa* index of 0.317. Sarcopenia and risk of malnutrition were prevalent conditions, with 22% of patients meeting EWGSOP2 criteria for sarcopenia and 27.9% of patients being at risk of malnutrition.

Although frailty is considered a significant risk factor for poorer outcomes both in KT candidates [14, 15] and recipients [18–22], systematic frailty assessment during transplant candidacy evaluation is not established in many transplant units. This may be explained by several factors. First, there is a lack of consensus in the transplant community about how frailty should be assessed. Although the most commonly used scale to date in both KT candidates and recipients is the PFP [25], other instruments have also been utilized [24, 28], and their specific predictive value for bad outcomes in the KT candidate population has not been compared. This underscores the unmet need for a disease-specific frailty metric that could be used to monitor KT candidates and recipients [24, 42]. Secondly, the feasibility of the frailty metric performance in the setting of the pre-transplant work-up may be a matter of importance when considering many medical tests and scales. While, ideally, a comprehensive geriatric assessment should be of choice for at least the older KT candidates, enforcing different evaluations that sometimes can be time- and resource-consuming may be difficult in the real-world clinical practice.

Considering the evidence towards frailty status as a risk factor for mortality after transplantation [20–22], it should be routinely screened before transplantation (in order to prevent or improve it) and factored into the current transplant program risk-adjustment equations [24]. Therefore, the search for both a disease-specific and also feasible frailty metric tool becomes necessary in order to implement its systematic assessment during KT candidate evaluation. However, different frailty indicators include different components of frailty and it might respond to the existence of different frailty phenotypes [43, 44]. While PFP evaluates

both subjective and objective components of frailty [25], the FRAIL scale accounts for subjective components but also includes morbidity [26]. In fact, although the comparison among scales has demonstrated consistent relationships with clinical variables (age, sex) and outcomes [43], agreement between frail metrics has been described to be poor, with the reported *kappa* index between PFP and FRAIL scale ranging between 0.194 and 0.46, depending on settings [44–47]. In our study, agreement between PFP and FRAIL scale was fair, and PFP identified a higher number of frail patients. Therefore, although the FRAIL scale is a validated instrument that is quicker and simpler to apply than PFP [44], concerns may arise with scales that do not directly measure the physiologic reserve of the patient. In our study, 132 patients were identified as frail by PFP and non-frail by the FRAIL scale, while the opposite situation only happened in 15 patients. These 132 patients had fewer comorbidities and less disability than the ones who were diagnosed as frail by the two scales. On the contrary, they were more frequently sarcopenic and had low muscle strength. This responds to the PFP criteria accounting for low muscle strength. Patients who scored positive only for grip strength were classified as pre-frail by PFP and non-frail by the FRAIL scale. Whether the FRAIL scale is misclassifying these patients as robust and they are actually frail and the consequences in terms of outcomes that it might have is unknown. On the other hand, the best frailty metric should be individualized for each setting and, in many cases, the FRAIL scale will be the tool of choice as it has proven to be more feasible than PFP in the real world. In fact, the FRAIL scale has been reported as a better frailty metric tool than other tools in a rural dialysis population [27].

Sarcopenia is defined by loss of muscle mass accompanied by low muscle function [29]. Skeletal muscle mass and muscle function are negatively affected by a variety of conditions inherent to CKD and to dialysis treatment [30, 31]. In CKD patients, sarcopenia has been reported as frequently as 10–60%, depending on the methods used to measure muscle mass function, and criteria applied [30]. The recently revised EWGSOP2 criteria aim to increase awareness of sarcopenia, in order to promote early detection and treatment [29]. It was recently applied to a cohort of 85 CKD stage 3–5 patients, finding 7.5% of sarcopenia [48]. In our cohort of advanced CKD stage 5 patients, 22% met the EWGSOP2 criteria for sarcopenia and, more importantly, it was present in 40.9% of patients who ranked as non-frail by the FRAIL scale. Although frailty and sarcopenia overlap, and in fact, PFP measures muscle mass functionality with the hand-grip strength test and the walking test, muscle functionality has been described to be more important than muscle mass in terms of correlation with outcomes in the dialysis population [49]. However, we must take into account that frail patients do not necessarily have sarcopenia, and statistical differences have been observed when comparing patients with sarcopenia and with the Fried phenotype (Chi-square $p < 0.001$, data not shown).

This observational study is limited by its cross-sectional nature. However, to our knowledge, this is the largest study so far comparing two different frailty metrics in KT candidates [28]. In addition, sarcopenia was established according to EWGSOP2 criteria and overlapping between different frailty phenotypes and sarcopenia was analyzed. Our study is also interesting because most studies on frailty prevalence come from US cohorts [6, 7, 10–12, 14–24, 50, 51], and European data are mostly lacking.

Frailty is frequent among CKD KT candidates and may be assessed by different frailty metrics. Agreement between these scales is poor and it is unknown which one correlates better with transplant outcomes. FRAIL scale might misclassify as robust patients those who are in better health conditions but are frail due to sarcopenia, excluding them from potential interventions improving their functional status and, accordingly, their prognosis. On the contrary, FRAIL is more feasible for screening during the pre-transplant work-up. The search for the best frailty metric in this population requires further investigation but the evaluation for frailty in all KT candidates seems to be necessary.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40620-021-01234-4.

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Author contributions MJPS and JP conceptualized the study, performed the analysis and wrote the manuscript. VD contributed with database and sarcopenia data. DRP, CEAC, ABu and CB participated in frailty assessment and contributed with the analysis. AF, ABa and EJ performed frailty metrics in the participants. XN, MC, EM, LRM gave their insight and contributed to the manuscript development.

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Data availability Data supporting this article are available upon request.

Declarations

Conflict of interest The authors of this study declare no conflict of interest.

Ethical approval The Institutional Review Board of Hospital del Mar approved the study.

Consent to participate All enrolled participants provided written informed consent.

Consent for publication The manuscript has not been and will not be submitted, in part or in its entirety, elsewhere for publication.

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