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ORIGINAL ARTICLE

Frailty among chronic kidney disease patients on the kidney transplant waiting list: the sex–frailty paradox

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ABSTRACT

Background. Frailty is defined as decreased physiologic reserve and resistance to stressors that predisposes patients towards poor health results. Its prevalence in chronic kidney disease (CKD) patients who are kidney transplant (KT) candidates is high. Frailty is associated with a higher rate of complications and mortality after transplant. It is unknown whether frailty phenotype differs depending on sex in this population.

Methods. This was a prospective longitudinal study of 455 KT candidates evaluated for frailty by physical frailty phenotype at the time of inclusion on the KT waiting list. Pre-frailty was defined as the presence of two criteria and frailty as three or more criteria. Univariate and multivariate analyses searched for associations of frailty status, frailty components and gender differences.

Results. Thirty percent of the total cohort resulted to be pre-frail (20%) or frail (10.3%), but disparities were observed between sexes, with 22.5% of men and 47.2% of women falling into one of these categories. Among frailty criteria, women presented with a higher percentage of exhaustion (39.6% versus 17%) and slowness (22.2% versus 9.6%) compared with men. Comorbidity burden was higher among frail men, whereas social factors were poorer between frail women. Disability was common among those patients who were frail, both men and women.

Conclusions. Frailty is twice as frequent in advanced CKD women as men. Frailty criteria distribution and phenotype seem to differ among sexes, which might have implications in terms of specific and individualized interventions to improve their status before transplantation.

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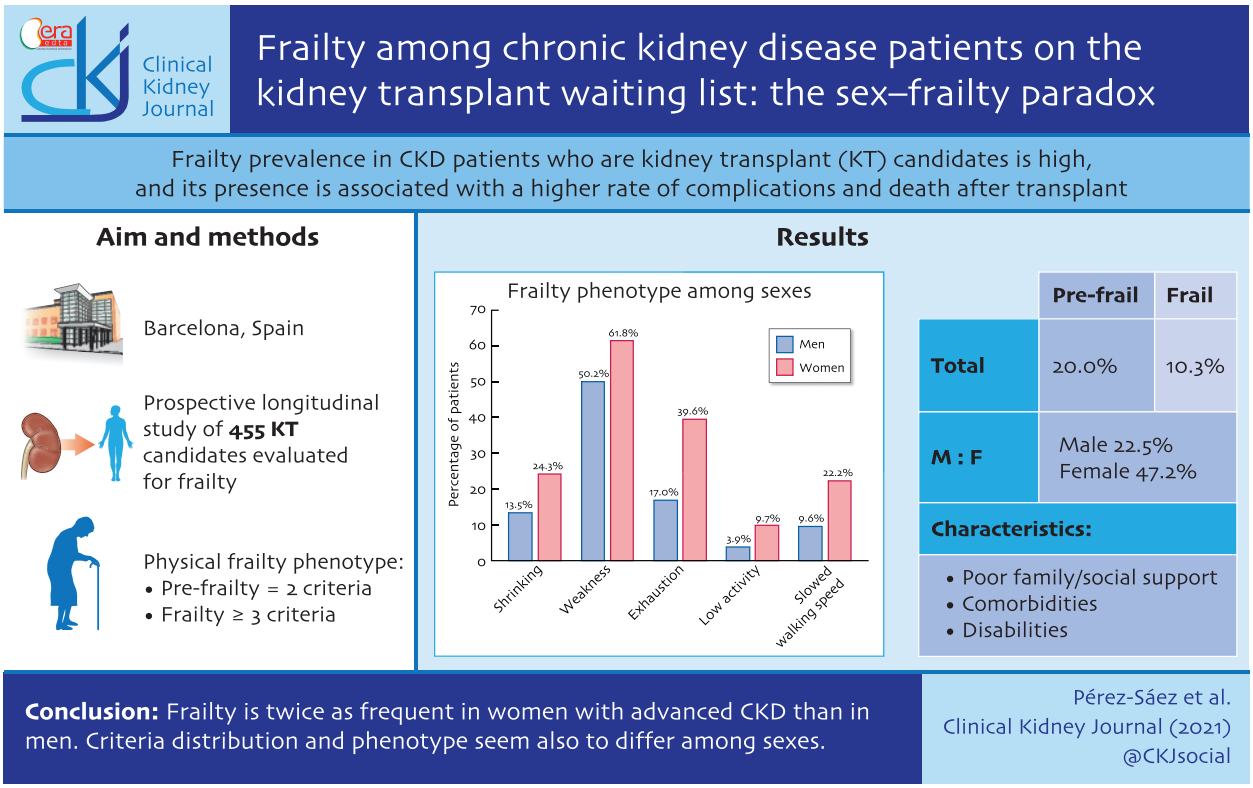
GRAPHICAL ABSTRACT



Keywords: frailty, gender, kidney transplantation, risk factor, sex

INTRODUCTION

Frailty is characterized by decreased physiologic resistance to stressors and was first studied in the community-dwelling aged population [1]. It is a frequent condition among chronic kidney disease (CKD) patients, representing between 15% and 21% of those in whom advanced CKD is present [2]. In the setting of haemodialysis, up to 70% of patients have been reported to have some degree of frailty [3, 4] and this is related to poorer outcomes, including poor cognitive function, falls, hospitalizations and mortality [5–8]. Access to the kidney transplantation (KT) waiting list may also be diminished in frail CKD patients, and even when they reach the KT waiting list, the probability of getting a transplant is lower [9, 10]. In the end, around 20% of KT recipients are frail [11], and these patients present with a higher rate of complications and mortality after KT [11–16].

In Spain, <25% of dialysis patients have access to transplantation [17], and despite the well-known weight of frailty in KT outcomes, clinicians often struggle with frailty measurement at the outpatient clinic. However, identifying patients at risk for poor results is of crucial importance to assess prognosis, establish prevention strategies and implement therapeutic approaches like prehabilitation. A complete frail profile characterization, added to information about both social and medical variables, might help to mitigate or reverse some of them, and, therefore, improve frailty in candidates for transplantation [18].

In recent years, many medical disciplines have shown increasing awareness of how diseases manifest differently between men and women. CKD is no exception, and, despite more women than men suffering advanced CKD, a higher percentage of men initiate dialysis or undergo transplantation [19–21]. This discrepancy may be attributed to biological (sex) differences, such as the CKD progression rates [20, 22], or to sociocultural (gender) differences, including access to care or attitudes towards disease [20, 23].

Mortality is also different among women and men with CKD: while men present higher rates within non-dialysis CKD stages, they become equal among sexes once renal replacement therapy (RRT) is started [20, 22].

Frailty studies of community-dwelling populations have found that females have higher frailty prevalence than males [24]. However, the so-called male–female health-survival paradox shows a higher survival rate in women than in men, resulting in longer times with disability and poor health status in women compared with men [24–26]. In contrast, among liver transplant candidates, women have higher frailty scores but also higher mortality while listed [27]. In the CKD setting, frailty seems also to be more frequent in women [4, 5, 28–31], but their mortality rates on the KT waiting list are lower than that observed in men [30, 31]. On the other hand, not only prevalence but also frailty components and characteristics between male and female frail patients may differ [27, 28, 32]. This may be of importance to identify frailty sex-specific factors to take into

consideration and intervene on if possible before KT. Assessing sex differences in frailty among CKD patients waiting for KT may improve risk stratification before transplant and help target specific interventions. Furthermore, it will allow future research about the sex-related impact of frailty on outcomes and mortality both in patients on dialysis and after transplant.

The aim of this study was to analyse the frailty phenotype in a cohort of CKD transplant candidates from a sex-perspective point of view.

MATERIALS AND METHODS

Study design

This is a prospective longitudinal clinical cohort study analysing baseline frailty status in advanced CKD patients who were being studied for transplantation at Hospital del Mar, Barcelona, Spain. Clinical and epidemiological information were collected from our local database. The Institutional Review Board of Hospital del Mar approved this study and all enrolled participants provided written informed consent. The study was undertaken following the principles of the declaration of Helsinki, only relying on the official centre database.

Patient cohort and frailty measurement

Between June 2016 and June 2020, 455 KT candidates were prospectively evaluated for frailty at the time of inclusion on the KT waiting list. Physical frailty phenotype defined by Fried *et al.* [1] was used. The frailty phenotype has been validated before in CKD patients [5, 7–9, 33] and 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) [1]. Frailty assessment was performed at the transplantation outpatient clinic. Supplementary data, Table S1 shows the specifics regarding methods for Fried criteria assessment.

Each of the five components was scored as 0 or 1, representing the absence or presence of that component. The aggregate frailty score was calculated as the sum of the component scores (range 0–5). Robust patients were defined as a score 0–1, pre-frail as those who ranked 2 and frail patients were defined by a score $\geq$3 as previously described by other groups [9, 11, 34, 35]. The cut points for robust and pre-frail patients differed from the standard Fried physical frailty phenotype classification because there are too few adults with advanced CKD who had none of the frailty components. To increase the power of the study, pre-frail and frail categories (score $\geq$2) were joined for the analysis [36, 37]; we refer to this group as frail throughout the rest of this article.

Study variables

Study variables were retrieved from our local database. We included demographics (age, sex, ethnicity); social (education defined by four categories: no, primary education, secondary education and tertiary education; family or social support, defined by its presence or absence; economic incomes, defined by three categories: non-regular incomes, retired with pension and active worker with salary) and clinical data (comorbidities such as hypertension, diabetes mellitus, chronic cardiac and pulmonary diseases, type of RRT, etc.). In addition, we assessed self-reported pharmacological treatment adherence by four-item Morisky–Green–Levine Medication Adherence Scale [38], considering the patient adherent if none of the items were present, basic activities of daily living by Barthel scale (disability if score $\leq$90) [39, 40], and instrumental activities of daily living by Lawton–Brody scale (disability if $<$8 in women and $<$5 in men) [41]. Nutritional evaluation included bioimpedance spectroscopy (BIS) by Body Composition Monitor (Fresenius Medical Care, Bad Homburg, Germany) at the time of inclusion; Simplified Nutritional Appetite Questionnaire (SNAQ) questionnaire for risk of malnutrition, positive if $\leq$14 [42]; and albumin levels at the time of inclusion. Unfortunately, BIS was assessed at the time the patient attended to the transplantation clinic, regardless of haemodialysis session, so we could not adjust for this variable. For inflammation information, we also collected C-reactive protein (CRP) levels at the time of inclusion. To evaluate access to transplantation, pre-dialysis waitlisting and time to transplantation were analysed.

Statistics

Continuous variables are expressed as mean ± standard deviation (SD) or median and interquartile range (IQR) according to their normal distribution. Categorical data are expressed as percentages. Comparisons of baseline characteristics between two groups were made using Chi-square or Fisher's exact tests to analyse categorical variables, Student's *t*-test for continuous variables with normal distribution and Mann–Whitney test for non-parametric variables. Logistic regression was used to estimate the odds ratio (OR) for frailty status. All variables with observed differences between groups ($P < 0.10$) were included in the analysis for adjustment except for SNAQ test as it may have collinearity with one of the Fried criteria for frailty (shrinking). Statistical analysis was performed using SPSS version 21 software (IBM, Armonk, NY, USA). P-values $<$0.05 were considered statistically significant.

RESULTS

Characteristics of frail and robust patients

During the study period, 455 KT candidates were evaluated for frailty phenotype at the time of KT waiting list inclusion. Of them, 317 (69.7%) resulted to be robust, 91 (20%) pre-frail and 47 (10.3%) were frail patients. Frailty phenotype total score and criteria distribution are presented in Figure 1. For frail patients (score $\geq$3), the majority scored 3, eight patients scored 4 and one patient scored 5 (Figure 1A). Regarding criteria distribution, weakness was the most prevalent frailty criterion among candidates, present in 50% of candidates (Figure 1B).

Merging pre-frail and frail patients in a unique category of frail patients (score $\geq$2), the comparison between robust and frail patients is summarized in Table 1. Frail patients had a similar age to robust ones. Among women, the percentage of patients with a frail phenotype was much higher than among men (47.2% versus 22.5%, $P < 0.001$). Similarly, among frail patients, the percentage of women was much higher than the percentage of men (49.3% versus 24.0%, $P < 0.001$). Frail patients had lower self-reported pharmacological adherence, poorer family support and lower economic incomes. They had also higher comorbidity burden and disability rates and presented with less lean mass and more fat mass in their body composition. The multivariate analysis for frailty status demonstrated that women were more likely

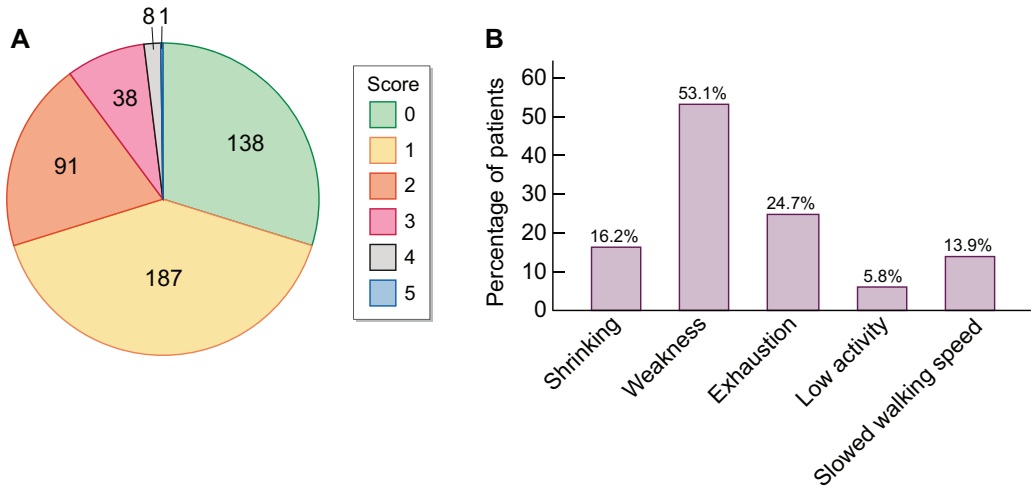


FIGURE 1: Frailty phenotype prevalence and criteria distribution among 455 kidney transplant candidates. A: Number of patients who scored positive 0 to 5 criteria. B: Percentage of patients who presented each different criteria.

Table 1. Baseline characteristics of 455 KT candidates stratified by frailty status (two categories)

	All $n = 455$	Robust $n = 317$	Frail (Fried ≥ 2) $n = 138$	P-value[a]
Sociodemographics				
Age, years (mean ± SD)	60.6 ± 12.4	60.5 ± 12.6	61.2 ± 11.3	0.380
Sex, female, *n* (%)	144 (31.6)	76 (24.0)	68 (49.3)	<0.001
Caucasian, *n* (%)	412 (95.8)	284 (95.9)	128 (95.5)	0.922
Medical treatment adherence[b], *n* (%)	333 (82.4)	238 (85.6)	95 (75.4)	0.010
Education, no/primary, *n* (%)	273 (62.4)	184 (58.0)	89 (64.5)	0.363
Deficient family support, *n* (%)	64 (14.4)	35 (11.3)	29 (21.0)	0.017
Socioeconomic status, no incomes, *n* (%)	41 (9.4)	23 (7.3)	18 (13.0)	0.047
Comorbidities				
Hypertension, *n* (%)	438 (96.5)	305 (96.5)	133 (96.4)	0.940
DM, *n* (%)	168 (37.0)	110 (34.8)	58 (42.0)	0.143
Heart failure, *n* (%)	26 (5.7)	13 (4.1)	13 (9.4)	0.025
Ischaemic coronary disease, *n* (%)	75 (16.5)	52 (16.4)	23 (16.7)	0.945
LV ejection fraction, %, median (IQR)	63.0 (59.0–67.0)	63.0 (58.5–66.2)	64.0 (59.0–69.0)	0.103
Peripheral vasculopathy, *n* (%)	43 (9.5)	26 (8.2)	17 (12.3)	0.168
Cerebral vasculopathy, *n* (%)	35 (7.7)	15 (4.7)	20 (14.5)	<0.001
COPD, *n* (%)	35 (7.7)	26 (8.2)	9 (6.5)	0.536
RRT modality, *n* (%)				
Haemodialysis	257 (59.4)	171 (57.2)	86 (64.2)	0.194
Peritoneal dialysis	93 (21.5)	64 (21.4)	29 (21.6)	
Disability status				
Disability for activities of daily living[c], *n* (%)	91 (20.0)	52 (16.4)	39 (28.3)	<0.001
Disability for instrumental activities of daily living[d], *n* (%)	136 (29.9)	75 (23.6)	64 (46.4)	<0.001
Nutrition and inflammation status				
BMI, kg/m^2 (mean ± SD)	27.8 ± 12.4	27.7 ± 5.4	28.1 ± 5.7	0.538
Risk for malnutrition[e], *n* (%)	111 (24.4)	64.0 (23.1)	47.0 (37.3)	0.003
Lean mass, kg/m^2, median (IQR)	13.9 (11.6–16.5)	14.5 (12.5–16.9)	12.2 (10.8–14.8)	<0.001
Fat mass, kg/m^2, median (IQR)	12.7 (9.1–16.5)	11.9 (8.5–16.4)	13.6 (11.0–18.2)	0.031
Overhydration, L, median (IQR)	1.0 (0.1–2.1)	1.0 (0.0–2.0)	1.1 (0.2–2.5)	0.486
Albumin, g/dL, mean ± SD	4.2 ± 0.5	4.2 ± 0.5	4.1 ± 0.6	0.123
CRP, mg/dL, median (IQR)	0.3 (0.1–0.8)	0.3 (0.1–0.7)	0.3 (0.1–0.9)	0.932
Access to transplantation				
Pre-dialysis waitlisted, *n* (%)	83 (19.2)	64 (21.4)	19 (14.2)	0.087
Time to transplantation, months, median (IQR)	22.2 (10.5–32.1)	19.7 (9.3–30.2)	23.0 (12.5–34.2)	0.125

[a]Comparisons were made among robust and frail patients.
[b]Morisky–Green = 0.
[c]Barthel ≤90.
[d]Lawton–Brody <8 if women and <5 if men.
[e]SNAQ ≤14. DM, diabetes mellitus; LV, left ventricular; COPD, chronic obstructive pulmonary disease.

to be frail [OR 1.91; 95% confidence interval (CI) 1.00–3.60] (Table 2). Other factors associated with frailty were deficient family support (OR 2.57; 95% CI 1.28–5.13), comorbidities such as heart failure (OR 2.97; 95% CI 1.03–8.54) or cerebrovascular disease (OR 3.95; 95% CI 1.35–11.6) and disability for activities of daily living, both basic (OR 2.67; 95% CI 1.05–6.81) and instrumental (OR 2.55; 95% CI 1.34–4.85) (Table 2).

Table 2. Multivariate analysis for factors associated with frailty in the whole cohort

	OR (95% CI)	P-value
Female sex	1.91 (1.00–3.60)	0.047
Deficient family support	2.57 (1.28–5.13)	0.008
Heart failure	2.97 (1.03–8.54)	0.043
Cerebral vasculopathy	3.96 (1.35–11.6)	0.012
Daily living activities disability	2.67 (1.05–6.81)	0.039
Instrumental daily living activities disability	2.55 (1.34–4.85)	0.003
Medical treatment adherence (yes)	1.46 (0.75–2.86)	0.266
Socioeconomic status (no incomes)	1.48 (0.60–3.69)	0.391
Lean mass (kg/m^2)	0.93 (0.85–1.02)	0.116
Fat mass (kg/m^2)	1.001 (0.96–1.04)	0.966

Sex differences in frailty phenotypes

Considering the higher risk for women to be frail, we aimed to analyse male ($n=70$, 22.5%) and female ($n=68$, 47.2%) frailty phenotypes separately (Table 3). Frail women had poorer results in social variables like level of education (72.1% with low level of education versus 57.1% of men) or economic incomes (20.6% with no incomes versus 5.7% of men). On the other hand, frail men had a stronger presence of comorbidities like ischaemic coronary disease, peripheral and cerebral vasculopathy, or pulmonary disease (Table 3). In terms of disability, both frail women and men presented similar rates of disability for activities of daily living (29.4% versus 27.2%, respectively), but frail women had more difficulties with instrumental activities than frail men, with 64.7% of them presenting with disability (Table 3).

Table 4 shows all differences between robust and frail male KT candidates, showing a higher percentage of comorbidities (peripheral and cerebral vasculopathy) and disability among those who were frail. In addition, more male frail patients were on haemodialysis as RRT modality compared with robust patients (73.5% versus 52.8%, respectively). Factors associated with frailty in male patients included deficient family support (OR 3.35; 95% CI 1.37–8.23), cerebral vasculopathy (OR 3.28; 95% CI 1.01–10.62), haemodialysis as RRT modality (OR 2.51; 95% CI

Table 3. Comparison between male and female frail (Fried ≥2) KT candidates

	Female $n=68$	Male $n=70$	P-value
Sociodemographics			
Age, years, mean ± SD	62.7 ± 11.3	60.1 ± 11.6	0.208
Caucasian, *n* (%)	65 (95.6)	67 (95.7)	0.999
Medical treatment adherence[a], *n* (%)	42 (61.7)	53 (75.7)	0.066
Education, no/primary, *n* (%)	49 (72.1)	40 (57.1)	0.008
Deficient family support, *n* (%)	14 (20.6)	15 (21.4)	0.800
Socioeconomic status, no incomes, *n* (%)	14 (20.6)	4 (5.7)	0.018
Comorbidities			
Hypertension, *n* (%)	64 (94.1)	69 (98.6)	0.162
DM, *n* (%)	27 (39.7)	31 (44.3)	0.586
Heart failure, *n* (%)	5 (7.3)	8 (11.4)	0.413
Ischaemic coronary disease, *n* (%)	5 (7.3)	18 (25.7)	0.004
LV ejection fraction, %, median (IQR)	64.0 (58.0–69.5)	63.0 (59.0–67.7)	0.959
Peripheral vasculopathy, *n* (%)	3 (4.4)	14 (20.0)	0.005
Cerebral vasculopathy, *n* (%)	5 (7.3)	15 (21.4)	0.019
COPD, *n* (%)	1 (1.5)	8 (11.4)	0.018
Haemodialysis as RRT modality, *n* (%)	36 (52.9)	50 (71.4)	0.022
Dependency status			
Disability for activities of daily living[b], *n* (%)	20 (29.4)	19 (27.1)	0.487
Disability for instrumental activities of daily living[c], *n* (%)	44 (64.7)	20 (28.6)	<0.001
Nutrition and inflammation status			
BMI, kg/m^2, median (IQR)	27.8 (23.7–32.6)	27.6 (25.0–31.4)	0.858
Risk for malnutrition[d], *n* (%)	30 (44.1)	17 (24.3)	0.055
Lean mass, kg/m^2, median (IQR)	11.4 (10.3–12.3)	14.6 (11.3–16.8)	<0.001
Fat mass, kg/m^2, median (IQR)	15.2 (11.9–20.5)	13 (9.5–16.2)	0.012
Overhydration, L, median (IQR)	0.5 (0.1–1.9)	1.5 (0.3–3.2)	0.025
Albumin, g/dL, mean ± SD	4.1 ± 0.63	4.12 ± 0.49	0.583
CRP, mg/dL, median (IQR)	0.4 (0.2–1.1)	0.3 (0.2–0.8)	0.925
Access to transplantation			
Pre-dialysis waitlisted, *n* (%)	16 (23.5)	3 (4.3)	0.001
Time to transplantation, months, median (IQR)	29.1 (15.0–40.2)	19.5 (10.3–27.2)	0.125

[a]Morisky–Green = 0.
[b]Barthel ≤90.
[c]Lawton–Brody <8 if women and <5 if men.
[d]SNAQ ≤14. DM, diabetes mellitus; LV, left ventricular; COPD, chronic obstructive pulmonary disease.

Table 4. Baseline characteristics of 311 KT male candidates stratified by frailty status (two categories)

	Robust $n = 241$	Frail (fried ≥2) $n = 70$	P-value
Sociodemographics			
Age, years, mean ± SD	60.2 ± 13.5	60.4 ± 12.4	0.986
Caucasian, *n* (%)	213 (95.9)	65 (95.6)	0.934
Medical treatment adherence[a], *n* (%)	179 (85.6)	53 (84.1)	0.189
Education, no/primary, *n* (%)	132 (54.8)	40 (57.1)	0.725
Deficient family support, *n* (%)	24 (10.1)	15 (21.4)	0.078
Socioeconomic status, no incomes, *n* (%)	12 (5.0)	4 (5.7)	0.806
Comorbidities			
Hypertension, *n* (%)	231 (96.3)	69 (98.6)	0.333
DM, *n* (%)	87 (36.3)	31 (44.3)	0.223
Heart failure, *n* (%)	11 (4.6)	8 (11.4)	0.035
Ischaemic coronary disease, *n* (%)	43 (17.8)	18 (25.7)	0.144
LV ejection fraction, %, median (IQR)	62.0 (57.0–65.0)	63.0 (59.0–68.0)	0.611
Peripheral vasculopathy, *n* (%)	22 (9.1)	14 (20.0)	0.012
Cerebral vasculopathy, *n* (%)	11 (4.6)	15 (21.4)	<0.001
COPD, *n* (%)	22 (9.1)	8 (11.4)	0.566
Haemodialysis as RRT modality, *n* (%)	121 (52.8)	50 (73.5)	0.003
Dependency status			
Disability for activities of daily living[b], *n* (%)	44 (18.2)	19 (27.1)	0.007
Disability for instrumental activities of daily living[c], *n* (%)	45 (18.6)	20 (28.5)	<0.001
Nutrition and inflammation status			
BMI, kg/m^2, median (IQR)	27.4 (24.1–31.6)	28.2 (25.3–31.4)	0.949
Risk for malnutrition[d], *n* (%)	37 (15.3)	17 (24.3)	0.095
Lean mass, kg/m^2, median (IQR)	15.2 (13.5–17.5)	14.6 (11.4–16.7)	0.121
Fat mass, kg/m^2, median (IQR)	11.7 (8.2–15.4)	13.0 (9.5–16.1)	0.728
Overhydration, L, median (IQR)	1.3 (0.1–2.1)	1.5 (0.3–2.9)	0.356
Albumin, g/dL, mean ± SD	4.3 ± 0.5	4.2 ± 0.5	0.289
CRP, mg/dL, median (IQR)	0.3 (0.1–0.7)	0.3 (0.2–0.8)	0.898
Access to transplantation			
Pre-dialysis waitlisted, *n* (%)	56 (24.5)	3 (4.4)	<0.001
Time to transplantation, months, median (IQR)	20.2 (9.0–33.1)	19.4 (10.2–27.1)	0.785

[a]Morisky–Green = 0.
[b]Barthel ≤90.
[c]Lawton–Brody <8 if women and <5 if men.
[d]SNAQ ≤14. DM, diabetes mellitus; LV, left ventricular; COPD, chronic obstructive pulmonary disease.

Table 5. Multivariate analysis for factors associated with frailty in male patients

	OR (95% CI)	P-value
Deficient family support	3.35 (1.37–8.23)	0.008
Instrumental activities disability	5.32 (1.86–15.15)	0.002
Haemodialysis as RRT (yes)	2.51 (1.13–5.57)	0.024
Cerebral vasculopathy	3.28 (1.01–10.62)	0.047
Heart failure	3.35 (0.95–11.92)	0.061
Peripheral vasculopathy	1.72 (0.58–5.02)	0.324
Basic activities disability	1.35 (0.38–4.77)	0.641

1.13–5.57) and disability for instrumental activities of daily living (OR 5.32; 95% CI 1.82–15.15) (Table 5). In contrast to men, frail women did not present a higher comorbidity burden, but they had more disability and less lean mass in their body composition (11.4 versus 12.0 kg/m^2, Table 6). The multivariate analysis showed that women were more frequently non-adherent to pharmacological treatment (OR 2.75; 95% CI 1.1–7.47) and showed an increased disability in basic (not instrumental, like in men) activities (Table 7).

Although all frailty criteria were more frequent in women than in men, self-reported exhaustion (39.6 versus 17.0%, respectively) and slowness in walking speed (22.2% versus 9.2%) were the two of them more differently distributed among sexes (Figure 2).

DISCUSSION

This prospective study describes the frail profile characterization in a Spanish cohort of advanced CKD patients waiting for KT. Pre-frailty (score 2, 20%) and frailty (score ≥3, 10.3%) were common, but were much more frequent in women (47.2%). Sex-related differences in frailty phenotype are relevant: first, in terms of frailty criteria, with women experiencing more exhaustion and slowness than men; and secondly, regarding frailty characteristics, with more burden of disease associated with men and more social factors associated with women.

Frailty is a common condition among CKD patients. It ranges from 15% to 21% [2] of CKD non-dialysis patients to >70% of haemodialysis patients [3]. In Spain, only two studies with reduced sample sizes have analysed frailty in haemodialysis patients, reporting disparities from 6% to >40% of patients [29, 43] presenting three or more Fried criteria [1]. Regarding KT candidates, studies have reported lower incidence of frailty—around 14%—but this percentage increases up to 18–20% when KT recipients are considered [11, 35]. We report a 30%

Table 6. Baseline characteristics of 144 KT female candidates stratified by frailty status (two categories)

	Robust $n = 70$	Frail (fried ≥2) $n = 68$	P-value
Sociodemographics			
Age, years, mean ± SD	61.3 ± 12.1	63.2 ± 11.3	0.318
Caucasian, *n* (%)	71 (95.9)	63 (95.5)	0.994
Medical treatment adherence[a], *n* (%)	59 (85.5)	42 (66.7)	0.031
Education, no/primary, *n* (%)	52 (68.4)	49 (72.1)	0.634
Deficient family support, *n* (%)	11 (15.1)	14 (20.6)	0.432
Socioeconomic status, no incomes, *n* (%)	11 (15.1)	14 (20.6)	0.334
Comorbidities			
Hypertension, *n* (%)	74 (97.4)	64 (94.1)	0.330
DM, *n* (%)	23 (30.3)	27 (39.7)	0.235
Heart failure, *n* (%)	2 (2.6)	5 (7.4)	0.188
Ischaemic coronary disease, *n* (%)	9 (11.8)	5 (7.4)	0.364
LV ejection fraction, %, median (IQR)	65.0 (60.0–68.0)	64.0 (58.0–69.0)	0.398
Peripheral vasculopathy, *n* (%)	4 (5.3)	3 (4.4)	0.813
Cerebral vasculopathy, *n* (%)	4 (5.3)	5 (7.4)	0.605
COPD, *n* (%)	4 (5.3)	1 (1.5)	0.215
Haemodialysis as RRT modality, *n* (%)	50 (71.4)	36 (54.5)	0.041
Dependency status			
Disability for activities of daily living[b], *n* (%)	2 (2.8)	20 (29.4)	<0.001
Disability for instrumental activities of daily living[c], *n* (%)	24 (34.3)	24 (64.7)	<0.001
Nutrition and inflammation status			
BMI, kg/m^2, median (IQR)	26.2 (22.2–31.4)	28.1 (24.3–33.1)	0.216
Risk for malnutrition[d], *n* (%)	27 (35.5)	30 (44.1)	0.354
Lean mass, kg/m^2, median (IQR)	12.0 (10.0–13.0)	11.4 (10.3–12.0)	0.046
Fat mass, kg/m^2, median (IQR)	14.5 (10.0–19.2)	15.2 (11.9–20.5)	0.115
Over hidratation, L, median (IQR)	0.6 (−0.5 to 1.3)	0.6 (0.1–2.0)	0.118
Albumin, g/dL, mean ± SD	4.2 ± 0.4	4.1 ± 0.6	0.558
CRP, mg/dL, median (IQR)	0.4 (0.1–0.8)	0.4 (0.2–1.1)	0.833
Access to transplantation			
Pre-dialysis waitlisted, *n* (%)	8 (11.4)	16 (24.2)	0.050
Time to transplantation, months, median (IQR)	17.2 (9.1–25.0)	29.2 (15.1–40.0)	0.017

[a]Morisky–Green = 0.
[b]Barthel ≤90.
[c]Lawton–Brody <8 if women and <5 if men.
[d]SNAQ ≤14. DM, diabetes mellitus; LV, left ventricular; COPD, chronic obstructive pulmonary disease.

Table 7. Multivariate analysis for factors associated with frailty in female patients

	OR (95% CI)	P-value
Medical treatment adherence (no)	2.75 (1.1–7.47)	0.046
Basic activities disability	8.80 (1.00–77.21)	0.050
Haemodialysis as RRT (yes)	2.22 (0.91–5.42)	0.079
Instrumental activities disability	1.91 (0.82–4.46)	0.132
Lean mass (kg/m^2)	0.86 (0.7–1.06)	0.166

prevalence of frailty among KT candidates, although not only patients with ≥3 Fried criteria [1], but also patients with ≥2 criteria were considered. This consideration has been previously reported in other studies [36, 37], where outcomes have been found similar if two or three of frailty criteria were present. This frailty status has been related to comorbidity burden and disability [44], and its presence implies poorer outcomes after transplantation [11–16]. Our data show that frail patients had a greater number of comorbidities such as heart failure or cerebral vasculopathy, and higher disability for activities of daily living. Other social aspects like family support or economic incomes were worse among frail patients, as has been previously described [45, 46]. However, the multivariate analysis establishes that comorbidity burden is associated with frailty status only in men, while social factors were present in both sexes.

Female sex was associated with frailty in our cohort, women being 2-fold more inclined to be frail than men. This difference has been analysed in the general population [24]. In a systematic review, Gordon *et al.* [24] found that females presented with higher frailty index scores [47] than males at all ages. The specific role of sex in frailty status has also been explored in the setting of some clusters of chronic disease patients, such as the human immunodeficiency virus (HIV) population [32] or liver transplant candidates [27], with a higher percentage of women among frail patients in both settings. Therefore, the logic sequence is likely to be as follows: women have higher rates of frailty, frailty is associated with poorer health results and women have higher mortality rates than men. However, the concept of the male–female health-survival paradox refers to the marked discrepancy between the health and survival of the sexes: females have greater levels of disability, more comorbidities and poorer self-rated health, but longer life expectancy [25, 48]. Narrowing down to the point, the sex–frailty paradox also arises from the higher rate of frailty among women, but the lower mortality that they present compared with men in the general population [24, 26]. In a similar setting to CKD, Lai *et al.*

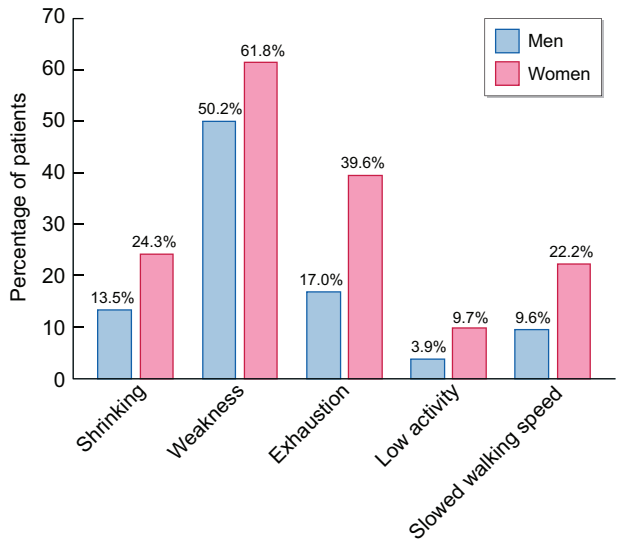


FIGURE 2: Frailty phenotype prevalence and criteria distribution differences between male and female kidney transplant candidates.

[27] evaluated 1405 candidates for liver transplantation and found higher frailty scores in women than men. However, in this case, waitlisted mortality was also higher among women and frailty could explain part of that excess of mortality [27]. In CKD patients, frailty has been reported to be more frequent in women [4, 5, 28–31], but this issue has not been precisely addressed and requires further investigation. Some sex differences have been well established in CKD epidemiology and evolution. Women present with advanced stages of CKD more frequently than men, perhaps due to the longer life expectancy they have and possibly because glomerular filtration rate equations tend to overdiagnose CKD in female patients [19, 20, 49]. In addition, kidney function declines faster in men and they more often need RRT. The potential protective effects of estrogens or the damaging effects of testosterone may also play a role [20, 22].

In terms of transplantation, women have reduced access to the KT waiting list compared with men and fewer chances to receive a transplant from a deceased donor [20, 21, 50, 51]. This might be partly explained by sex itself and the biological effect of pregnancy sensitization, but also by gender and therefore social factors, such as lower probability of having a KT discussion with their nephrologist [23]. More importantly, mortality is higher among men at all levels of advanced CKD, whereas mortality among individuals on dialysis or after transplant is similar in both sexes [20, 22]. In the setting of frailty, two studies have shown that CKD women who were KT candidates had longer hospitalizations than men while listed. Hospitalization was a marker of reduced survival on dialysis, decreased likelihood of transplantation, readmissions after transplant and diminished patient survival. However, although readmissions after transplant were more frequent between women, they did not experience higher rates of graft loss or mortality [30, 31]. So far, the consequences of sex disparities in frailty prevalence among CKD patients remain uncertain.

Regarding frailty criteria distribution, women have shown a different frailty phenotype than men among HIV patients [32], liver transplant candidates [27] and KT candidates [28, 50], with poorer results also in the Short Physical Performance Battery test in the latter study. Our study describes frailty criteria distribution between sexes and frail patients' characteristics depending on sex. CKD women experienced a higher percentage of exhaustion and slowness than men. These two criteria can be the result of the lower lean mass that women had compared with men and might translate a higher level of sarcopenia among women [52]. In addition, comorbidities were more related to frail men, whereas social factors were more related to frail women. Again, whether this difference in frailty criteria distribution between sexes has an impact on CKD and transplant outcomes requires further investigation.

This study has the inherent limitations of a descriptive one-centre study, so external validation may not be assumed. In addition, the study was designed based on previous reports from other groups, assuming similarity among US and European populations, and classifying as robust patients those with 0–1 frailty criterion. We also merged pre-frail (≥2 criteria) and frail patients (≥3 criteria) due to the low number of patients with ≥3 criteria (only 10.3%), which might have an impact on the results. However, to our knowledge, this is the first study to disaggregate frailty data between men and women in a cohort of KT candidates. This may have implications for the detection of patients at risk, and for specific and targeted interventional approaches to improve frailty before transplantation.

Frailty is very frequent among CKD patients on the KT waiting list. Prevalence, criteria distribution and associated factors are different between men and women. Further studies are needed to elucidate if this frailty has similar impact on outcomes between different sexes.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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CONFLICT OF INTEREST STATEMENT

The authors of this study declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

APPENDIX

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