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.
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 outcomes 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 account.
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 tar-
get specific interventions. Furthermore, it will allow future re-
search 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 analy-
sing 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 partici-
pants provided written informed consent. The study was under-
taken 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 compo-
nents: 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 trans-
plantation 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, represent-
ing 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 ≥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 ≥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 in-
cluded demographics (age, sex, ethnicity); social (education de-
finite 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 (comor-
bidities 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 ≤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 spec-
troscopy (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 ≤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 hae-
modialysis 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 trans-
plantation, pre-dialysis waitlisting and time to transplantation
were analysed.

Statistics

Continuous variables are expressed as mean ± standard devia-
tion (SD) or median and interquartile range (IQR) according to
their normal distribution. Categorical data are expressed as per-
centages. 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 esti-
mate the odds ratio (OR) for frailty status. All variables with ob-
served 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 soft-
ware (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 cri-
teria distribution are presented in Figure 1. For frail patients
(score ≥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 candi-
dates, present in 50% of candidates (Figure 1B).

Merging pre-frail and frail patients in a unique category of frail
patients (score ≥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% vs
22.5%, P < 0.001). Similarly, among frail patients, the per-
centage of women was much higher than the percentage of men
(49.3% vs 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 bur-
den and disability rates and presented with less lean mass and
more fat mass in their body composition. The multivariate analy-
sis 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<sup>a</sup> |
|--------------------------|-------------|----------------|---------------------------|---------------------|
| **Sociodemographics**    |             |                |                           |                     |
| Age, years (mean ± SD)   | 60.6 ± 12.4 | 60.5 ± 12.6    | 61.2 ± 11.3               | 0.380               |
| Caucasian, n (%)         | 144 (31.6)  | 76 (24.0)      | 68 (49.3)                 | -0.001              |
| Medical treatment adherence<sup>b</sup>, n (%) | 412 (95.8) | 284 (95.9) | 128 (95.5) | 0.922 |
| 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 (%)      | 257 (59.4)  | 171 (57.2)     | 86 (64.2)                 | 0.194               |
| Haemodialysis            | 93 (21.5)   | 64 (21.4)      | 29 (21.6)                 |                     |
| Peritoneal dialysis      |             |                |                           |                     |
| Disability status        |             |                |                           |                     |
| Disability for activities of daily living<sup>c</sup>, n (%) | 91 (20.0) | 52 (16.4) | 39 (28.3) | -0.001 |
| Disability for instrumental activities of daily living<sup>d</sup>, n (%) | 136 (29.9) | 75 (23.6) | 64 (46.4) | -0.001 |
| **Nutrition and inflammation status** |         |                |                           |                     |
| BMI, kg/m<sup>2</sup> (mean ± SD) | 27.8 ± 12.4 | 27.7 ± 5.4 | 28.1 ± 5.7 | 0.538 |
| Risk for malnutrition<sup>e</sup>, n (%) | 111 (24.4) | 64.0 (23.3) | 47.0 (37.3) | 0.003 |
| Lean mass, kg/m<sup>2</sup>, 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<sup>2</sup>, 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 |

<sup>a</sup>Comparisons were made among robust and frail patients.

<sup>b</sup>Morisky–Green = 0.

<sup>c</sup>Barthel ≤ 90.

<sup>d</sup>Lawton–Brody < 8 if women and < 5 if men.

<sup>e</sup>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

| Factor                                      | 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$^2$)                          | 1.00 (0.96–1.04)| 0.966   |

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

| Sociodemographics                              | Female $n = 68$ | Male $n = 70$ | P-value |
|-----------------------------------------------|-----------------|---------------|---------|
| 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*, 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 living¹    | 20 (29.4)       | 19 (27.1)     | 0.487   |
| Disability for instrumental activities of daily living² | 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 malnutrition³, 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   |

### Table 4. Comparison 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 1.34–4.85) (Table 2).

### 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 3 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 1.34–4.85) (Table 2).
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 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 (0.1–2.3) | 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 |

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

| Sociodemographics                                      | Robust (n = 70) | Frail (fried ≥2) (n = 68) | P-value |
|---------------------------------------------------------|-----------------|---------------------------|---------|
| 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<sup>a</sup>, n (%)          | 59 (85.5)       | 42 (66.7)                 | 0.031   |
| Education, no/primary, n (%)                            | 52 (74.4)       | 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 (30.5)       | 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<sup>b</sup>, n (%) | 2 (2.8)         | 20 (29.4)                 | <0.001  |
| Disability for instrumental activities of daily living<sup>c</sup>, n (%) | 24 (34.3)       | 24 (64.7)                 | <0.001  |
| Nutrition and inflammation status                       |                 |                           |         |
| BMI, kg/m<sup>2</sup>, median (IQR)                     | 26.2 (22.2–31.4) | 28.1 (24.3–33.1) | 0.216   |
| Risk for malnutrition<sup>d</sup>, n (%)                | 27 (35.5)       | 30 (44.1)                 | 0.354   |
| Lean mass, kg/m<sup>2</sup>, median (IQR)               | 12.9 (10.0–13.0) | 11.4 (10.3–12.0) | 0.046   |
| Fat mass, kg/m<sup>2</sup>, median (IQR)                 | 14.5 (10.0–19.2) | 15.2 (11.9–20.5) | 0.115   |
| Over hydration, L, median (IQR)                          | 0.6 (0.1–2.0)   | 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   |

<sup>a</sup>Morrisky–Green = 0.

<sup>b</sup>Barthel ≤90.

<sup>c</sup>Lawton–Brody ≤8 if women and <5 if men.

<sup>d</sup>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

| Factors                                              | 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<sup>2</sup>)                          | 0.86 (0.7–1.06) | 0.166   |

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.

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
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**

**FRAIL-MAR Study Group members**

María José Pérez-Sáez, Carlos E. Arias-Cabrales, Dolores Redondo, Francesc Barbosa, Higini Cao, Silvia Collado, Maria Dolores Arenas, Anna Buxeda, Carla Burballa, 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 Causadias (Department of Nephrology, Hospital del Mar), Alicia [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.

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.

![FIGURE 2: Frailty phenotype prevalence and criteria distribution differences between male and female kidney transplant candidates.](image-url)
Sex differences in frailty among KT candidates

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