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ORIGINAL ARTICLE

# The 60:40 conundrum: are women with CKD discriminated after referral to a nephrology clinic?

Adele Vautcranne<sup>1,\*</sup>, Lavinia Bianco<sup>1,\*</sup>, Béatrice Mazé<sup>1</sup>, Antioco Fois<sup>1</sup>, Antoine Chatrenet<sup>1</sup>, Maria Rita Moio<sup>1</sup>, Gulia Santagati<sup>1</sup>, Linda Njandjo<sup>1</sup>, Pierre-Yves de Müllenheim<sup>2</sup>, Massimo Torreggiani<sup>1,†</sup> and Giorgina Barbara Piccoli<sup>1,†</sup>

<sup>1</sup>Néphrologie et dialyse, Centre Hospitalier Le Mans, 194 Avenue Rubillard, Le Mans, France; and <sup>2</sup>APCoSS – Institute of Physical Education and Sports Sciences (IFEPSA), UCO, Angers, France

\*equal contribution

†equal contribution

Correspondence to: Giorgina Barbara Piccoli. E-mail: [gbpiccoli@yahoo.it](mailto:gbpiccoli@yahoo.it)

## ABSTRACT

**Background.** Epidemiological data show that chronic kidney disease (CKD) is more prevalent among females than males but the prevalence of women in dialysis is lower, as is their representation in nephrology trials. We aimed to test whether sex distribution varies at nephrology referral, inclusion in a trial, or at the starting of dialysis.

**Methods.** We evaluated patients' characteristics at the time of the first consultation in the Unit for the Care of Advanced CKD (UIRAV), at the inclusion in an observational study (PRO-RE-RE-PRO) and at the beginning of dialysis. Patient and renal survival analysis was performed in the pre-dialysis phase and after dialysis start. Reasons for denying participation to the proposed study and causes of death or withdrawal from follow-up and dialysis were likewise examined.

**Results.** During the period 2017–2023, 866 patients were referred to the UIRAV, 59% males and 41% females. Female patients were older, had lower comorbidity and were referred at the same eGFR than males. The same male/female proportion was observed in patients included in the PRO-RE-RE-PRO study and at dialysis start. Survival was significantly higher in females. Overall, distribution across sex remained stable over time.

**Conclusions.** Males and females are referred at similar eGFR levels, which appears to be the main reason for seeking nephrology care. Afterward, the ratio between males and females remains stable, suggesting that if a sex-selection bias exists, it should be sought before the first nephrology referral. However, further studies are needed to ensure that health equity is respected across sexes.

**Keywords:** dialysis, gender medicine, recruitment in studies, referral, selection

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## KEY LEARNING POINTS

### What was known:

- Epidemiological data show a disparity between the prevalence of CKD between males and females: CKD is more prevalent among women but there are more men on dialysis.
- Women are also less represented in clinical trials.
- We wanted to test whether sex distribution varies during nephrology care and whether sex influences inclusion in a trial or in the prescription/access to kidney replacement therapy.

### This study adds:

- According to our results, the male to female proportion of nephrology patients from the first consultation to the start of kidney replacement therapy remains stable.
- The same is true for the inclusion in a clinical trial.
- If a sex-selection bias exists, it should be sought before the referral to nephrology.

### Potential impact:

- Our data are reassuring about the fact that males and females are equally treated in the nephrology setting and dialysis is offered to everybody without discriminations.
- Further longitudinal studies are warranted to confirm our results and promote education of general practitioners and other specialists on nephrology referral.

## INTRODUCTION

Increased acknowledgment of the importance of sex and gender issues in health care in general and in nephrology in particular has led to focus attention on the discrepancy between the distribution of male and female individuals in different stages of chronic kidney disease (CKD) [1, 2].

Epidemiological data suggest that, in the general population, the overall prevalence of CKD is higher in females than males; however, women are less represented in dialysis and after kidney transplantation, even in settings in which the bias linked to preferential kidney donation from female to males is not recorded [1–10]. Being a woman has been identified, for more than a decade, as a factor associated with a lower likelihood of initiating kidney replacement therapy (KRT) [11]. Several explanations have been proposed to explain these differences, including lesser care delivered to women, for cultural or economic reasons, longer female life expectancies, and slower kidney disease progression [1]. Furthermore, it is possible that the current reference equations underestimate kidney function in females, thus mostly increasing the prevalence of “mild” CKD [1, 12, 13].

The difference is not limited to the clinics: the representation of women in nephrology trials is lower than that of males, and this difference persists also when inclusion in trials (for example in dialysis) is adjusted for the lower prevalence of females and for the eventual exclusion of women in childbearing age, thus suggesting an active sex bias in the selection of participants [14–17].

While it is presumable that in different settings different elements are involved, knowledge gaps persist due to the lack of studies aimed at analyzing sex issues through pathway from diagnosis of CKD, to referral to nephrology, and ultimately, to the start of dialysis, also including participation in clinical trials.

We undertook the present study in a large public nephrology center in central France serving a well-defined area where a unit dedicated to the care of advanced CKD and fragile patients (including women after an episode of preeclampsia) has been available since 2017. In our setting, an observational study on the effect of nutritional management in CKD stage 3 to 5 has been undertaken since 2019 [PRO-RE-RE-PRO: PROTéger les REins avec un REgime bas en PROtéines (protecting the kidneys with a

low-protein diet)]. The detailed clinical phenotyping of the population, in terms of comorbidity and nutritional status and the prospective recording of the reasons why patients were not recruited in the ongoing study (refusing participation, short life expectancy, language barriers, cognitive impairment, etc.) allowed granular analysis of the selection process. The information was integrated with data regarding dialysis start in the same center, in the same period, including patients referred from the outpatient clinic for the care of advanced kidney disease and from other sources.

The study aimed to test four hypotheses: (i) whether sex distribution is actually unbalanced at nephrology referral; (ii) whether sex influences inclusion in a trial, (iii) what the main influencing factors are; and (iv) whether “persistence” in the system of care differs between males and females.

## MATERIALS AND METHODS

### Setting of study

This study was conducted in central France at the Centre Hospitalier le Mans (CHM), one of the largest non-university hospitals in the country. CHM has ~1600 beds, 20 of which are in nephrology and immune-nephrology. It serves an area corresponding to the main city in the department, Le Mans (~147 000 inhabitants), and the Department of Sarthe (~570 000 inhabitants) [18]. The male to female ratio in our department is 1:1.06 [19]. According to the most recent estimation, CKD prevalence in France is ~10.5% with a male to female ratio equal to 1:1.36 [20].

CHM has a nephrology service with a network of outpatient care facilities (consultations and day-hospital facilities); there is a consultation service dedicated to patients who have experienced an episode of preeclampsia, as well as a consultation service for patients with kidney stones, but our study focuses on the unit for the care of advanced kidney disease and of fragile patients (including women after an episode of preeclampsia or during high-risk pregnancies) (UIRAV, Unité pour l'Insuffisance Rénale chronique AVancée) [21] and the dialysis unit (which includes 25 beds for both chronic HD patients and patients with acute kidney injury needing dialysis outside of the intensive care unit, and an outpatient peritoneal dialysis (PD) and

home hemodialysis program). Seven nephrologists work in the nephrology department, three of them in the UIRAV and the dialysis unit. The UIRAV team also includes a geriatrician, four nurses, and three trained dietitians, and also provides home HD and PD training. Nearby university hospitals (Angers, Nantes, Tours) perform kidney transplantations, and a dedicated outpatient unit is responsible for their follow-up.

More than 1100 patients have been referred to the UIRAV since the start of its activity in 2017 up to June 2023, 866 of whom were in CKD stages 3 to 5 not on dialysis, on which this analysis is mainly focused. Excluded patients were those referred for clinical or social fragility in lower CKD stages, as well as the young women referred to the unit during or after a complicated pregnancy (>200 cases).

In the same period, 332 patients started hemodialysis (HD) and 54 started PD and were included in the analysis.

### Referral and selection criteria

Patients are referred to the UIRAV by general practitioners and other hospital wards in case of advanced CKD irrespective of the cause, either due to primary or secondary glomerular diseases, genetic, systemic, or interstitial diseases, and chronic kidney failure in the context of advanced age [21].

PRO-RE-RE-PRO is an observational study whose aim was to explore the relationship between protein intake and the progression of kidney disease. The study was approved on 7 December, 2018 and will continue until April 2025. The exclusion criteria for the PRO-RE-RE-PRO study are age <18 years, patient's refusal to participate, life expectancy estimated as <3 months, dementia or severe cognitive impairment, and/or language barriers that might impede understanding, all causes of patient's inability to give or deny informed consent [22].

Patients were referred for dialysis from the UIRAV, hospitalization wards (nephrology and others), and other outpatient units in the CHM or in nearby hospitals.

The indications for dialysis start are the usual ones in the context of an intent to defer policy, promoting incremental start for all patients without contraindications (i.e. low residual kidney function, menacing fluid overload, or signs of decompensated uremia) as reported in detail elsewhere [23].

### Definitions

Chronic kidney disease was defined as is customary, in keeping with the K-DIGO guidelines, based on the presence of either decreased kidney function [estimated glomerular filtration rate (eGFR) <60 ml/min] or other morphological or urinary alterations lasting for at least 3 months [24]. All the patients enrolled in the study were diagnosed as having CKD with at least one confirmatory eGFR, assessed using the CKD Epidemiology Collaboration (CKD-EPI) formula [25].

Comorbidity was assessed using the Charlson Comorbidity Index (CCI, scale 0–33) [26].

The patient's nutritional status was assessed by means of the Malnutrition-Inflammation Score (MIS, scale 0–30) and the Subjective Global Assessment (SGA: A, B, or C) [27, 28]. All definitions were periodically reviewed by the senior physicians (G.B.P., A.F., M.T.).

### Statistical analysis

Statistical analyses were performed using JASP v.0.14.1 (JASP Team 2020, Amsterdam University, The Netherlands) or the

R programming language (v.4.3.1; R Core Team 2021, Vienna, Austria) along with the RStudio environment depending on the analysis. Descriptive statistics are presented as median (Q1–Q3) for numeric variables due to their asymmetrical distributions, and as counts and percentages for categorical variables.

Proportions of males and females at nephrology referral and at trial inclusion were compared to 60:40 proportion (60% males, 40% females) using the goodness of fit test.

We also tested between-sex differences in the numerical and categorical outcomes available at the first consultation under two different scenarios: considering the entire initial group (at referral) and the PRO-RE-RE-PRO study participants only (at trial initiation). Regarding numeric outcomes, normality and/or homoscedasticity assumptions assessed respectively using the Shapiro–Wilk and Levene's tests were never met. Consequently, we conducted two-tailed Wilcoxon rank-sum tests. Regarding categorical outcomes, we conducted chi-square tests of homogeneity or Fisher's exact test in cases of small cross-classified samples (fewer than five individuals) to detect differences in the male and female distributions across the categories of the outcomes of interest.

Survival analysis comparing males and females was conducted using the time elapsed between the first visit (referral) in the UIRAV unit and death. This analysis was performed without any further stratification (analysis 1) and with additional stratification based on the CGI level (CCI <7 vs. CCI ≥7; analysis 2). For both analyses, patients were censored in case of dialysis initiation, kidney transplantation, loss to follow-up (date of the last update), transfer to another unit, whichever came first. Finally, we also conducted a “persistence in the system” analysis, based on the time elapsed between the first visit (referral) and either death or dialysis initiation as event outcomes, while using the same censoring strategy as presented for analyses 1 and 2. For all survival analyses, between-sex differences were investigated based on Kaplan–Meier plots and using log rank tests.

Finally, we explored potential factors of participating or not to the PRO-RE-RE-PRO study using logistic regressions and age, comorbidity (CCI), body mass index (BMI), and sex as explanatory variables. These explanatory variables were chosen based on their potential clinical relevance. We first tested all explanatory variables with the outcome of interest in univariable regressions. Since age and CCI are collinear, we developed two models, one including age (model A) and another including CCI (model B). The relationships between the potential factors of interest and the fact of participating or not to the PRO-RE-RE-PRO study were reported as odds ratios (OR) along with their corresponding 95% confidence intervals.

For all analyses, claims about between-group differences and coefficients that would be significantly different from the null were based on the *P* values assuming an alpha risk ≤5% in the long run.

### Ethical issues

The study was conducted in accordance with the Declaration of Helsinki.

The observational study, PRO-RE-RE-PRO, involving all patients who attended at least one consultation at the UIRAV was approved by the Ethical Committee of the University Hospital of Toulouse (favorable opinion, session of 7 December 2018, prolonged and updated on 20 April 2023). All patients who started dialysis signed an informed consent form authorizing the anonymous use of their clinical data for research purposes. The observational study on incremental dialysis was approved

Table 1: Baseline data at the first consultation in UIRAV (patients with CKD stage 3 to 5 not on dialysis).

	All	Females	Males	P values F vs. M
N	866	352 (41%)	514 (59%)	.838 *
Age (years), median (Q1–Q3)	77 (67–86)	80 (68–87)	76 (67–84)	.002
Patients living at home, n (%)	774 (89.4%)	304 (86.4%)	470 (91.4%)	.017
Patients with only one consultation, n (%)	106 (12.2%)	42 (11.9%)	64 (12.5%)	.819
BMI (kg/m <sup>2</sup> ), median (Q1–Q3)	27.8 (24.3–32.3)	27.6 (23.4–32.8)	27.9 (24.8–32.1)	.242
Primary kidney disease				.158
ADPKD, n (%)	22 (2.5%)	7 (2.0%)	15 (2.9%)	
Diabetes mellitus, n (%)	43 (4.9%)	16 (4.5%)	27 (5.2%)	
NAS/hypertensive, n (%)	262 (30.3%)	116 (33.0%)	146 (28.4%)	
Glomerulonephritis, n (%)	18 (2.1%)	9 (2.6%)	9 (1.8%)	
CAKUT/obstructive disease/isolated urinary abnormalities, n (%)	30 (3.5%)	11 (3.1%)	19 (3.7%)	
Multifactorial, n (%)	374 (43.2%)	135 (38.4%)	239 (46.5%)	
Unknown, n (%)	35 (4.0%)	16 (4.5%)	19 (3.7%)	
Other, n (%)	82 (9.5%)	42 (11.9%)	40 (7.8%)	
CCI, median (Q1–Q3)	8 (6–9)	7 (6–8)	8 (7–9)	<.001
Cardiopathy, n (%)	333 (38.5%)	107 (30.4%)	226 (44.0%)	
Peripheral vascular disease, n (%)	213 (24.6%)	63 (17.9%)	150 (29.2%)	
Cerebrovascular disease, n (%)	114 (13.2%)	43 (12.2%)	71 (13.8%)	
Dementia, n (%)	50 (5.8%)	24 (6.8%)	26 (5.1%)	
Chronic pulmonary disease, n (%)	110 (12.7%)	39 (11.1%)	71 (13.8%)	
Liver disease, n (%)	45 (5.4%)	8 (2.3%)	37 (7.4%)	
Diabetes, n (%)	387 (45.5%)	131 (38.1%)	256 (50.6%)	
Hemiplegia, n (%)	16 (1.8%)	9 (2.6%)	7 (1.4%)	
Neoplasia, n (%)	176 (20.9%)	51 (15.0%)	125 (25.0%)	
AIDS, n (%)	7 (0.8%)	2 (0.6%)	5 (1.0%)	
Other, n (%)	49 (5.7%)	12 (3.4%)	37 (7.2%)	
MIS, median (Q1–Q3)	5 (3–7)	5 (3–7.5)	5 (3–7)	.019
SGA, n (%)				.005
A	638 (78.5%)	241 (73.7%)	397 (81.7%)	
A–B	14 (1.7%)	9 (2.8%)	5 (1.0%)	
B	142 (17.5%)	72 (22.0%)	70 (14.4%)	
B–C	2 (0.2%)	1 (0.3%)	1 (0.2%)	
C	17 (2.1%)	4 (1.2%)	13 (2.7%)	
Follow-up				.141
Death, n (%)	201 (23.2%)	66 (18.8%)	135 (26.3%)	
Transfer, n (%)	56 (6.5%)	27 (7.7%)	29 (5.6%)	
Refusal to continue follow-up, n (%)	19 (2.2%)	10 (2.8%)	9 (1.8%)	
Transplantation/hemodialysis, n (%)	131 (15.1%)	55 (15.6%)	76 (14.8%)	
Palliative care, n (%)	4 (0.5%)	2 (0.6%)	2 (0.4%)	
Lost to follow-up, n (%)	23 (2.7%)	7 (2.0%)	16 (3.1%)	
Follow-up ongoing <sup>b</sup> , n (%)	432 (59.9%)	185 (52.6%)	247 (48.0%)	

Q1: Quartile 1, 25th percentile; Q3: Quartile 3, 75th percentile.

\*Goodness of fit test, compared with theoretical proportion set at 40:60.

<sup>b</sup>Includes patients followed at CHM or at a peripheral hospital.

Bold indicates statistical significant differences.

by the ethics committee of the Le Mans Hospital (1 July 2021, updated 1 March 2022).

## RESULTS

### Baseline data of non-dialysis CKD patients

Table 1 reports the main clinical characteristics of the 866 patients in stages 3 to 5, not on dialysis, referred to the UIRAV; males accounted for 514 individuals (59%) and females for 352 (41%) while the 60:40 proportion is respected ( $P = .838$ ). The median age was 4 years older for females at time of referral (median 80 vs. 76 years), but in spite of their older age, the CCI was lower (median 7 vs. 8). Possibly as a reflection of younger age,

the prevalence of good nutritional status (SGA A) was higher in males, but no difference was found in the prevalence of mildly or severely impaired nutritional status (SGA B–C and C). During the follow-up period, 201 patients died and 131 started dialysis or received a pre-emptive kidney graft. Loss to follow-up was minimal: 23 patients were lost to follow-up and 19 decided to discontinue nephrology follow-up. Overall, at the time of our analysis, 432 patients were still on regular pre-dialysis care in the unit.

Table 2 reports the main biochemical data at the beginning of follow-up in the UIRAV.

Of note, at referral, the eGFR was almost identical in males and females (25 and 25.5 ml/min), while, as expected, serum creatinine was higher in males; proteinuria was likewise greater in males than females (0.4 vs. 0.2 g/24 h). The difference in serum

Table 2: Biochemical data at the first consultation in UIRAV (patients with CKD stage 3 to 5 not on dialysis).

	All	Females	Males	P value F vs. M
N	866	352 (41%)	514 (59%)	
Hemoglobin (g/dl), median (Q1–Q3)	11.7 (10.5–13.0)	11.4 (10.3–12.6)	11.9 (10.7–13.3)	<.001
<9 g/dl, n (%)	35 (4.1%)	18 (5.1%)	17 (3.3%)	.189
<10 g/dl, n (%)	141 (16.3%)	65 (18.5%)	76 (14.8%)	.157
Creatinine (μmol/l), median (Q1–Q3)	190 (149–261)	170 (131–240)	202 (163–268)	<.001
eGFR <sup>a</sup> (ml/min), median (Q1–Q3)	25.0 (17.0–34.0)	25.0 (17.0–35)	25.5 (18.0–34.0)	.692
Urea (mmol/l), median (Q1–Q3)	15.2 (11.0–20.7)	15.0 (10.4–20.1)	15.3 (11.1–21.3)	.111
≥40 mmol/l, n (%)	16 (1.9%)	5 (1.4%)	11 (2.1%)	.609
Total serum proteins (g/l), median (Q1–Q3)	72 (68–76)	72 (67–75)	72 (68–76)	.035
Albumin (g/dl), median (Q1–Q3)	3.7 (3.3–4.0)	3.6 (3.3–3.9)	3.7 (3.4–4.0)	.009
3.0–3.5 g/dl, n (%)	252 (30.5%)	117 (34.3%)	138 (30.5%)	<b>0.012</b>
<3.0 g/dl, n (%)	76 (9.1%)	38 (11.1%)	38 (7.7%)	
Proteinuria (g/24 h), median (Q1–Q3)	0.3 (0.1–1.5)	0.2 (0.1–0.9)	0.4 (0.2–1.7)	<.001
≥1 g/24 h, n (%)	160 (32.2%)	45 (23.6%)	115 (37.6%)	.001
Bicarbonate (mmol/l), median (Q1–Q3)	24 (22–27)	24 (22–27)	24 (22–27)	.957
<17 mmol/l, n (%)	16 (1.9%)	7 (2.0%)	9 (1.8%)	.793

Q1: Quartile 1, 25th percentile; Q3: Quartile 3, 75th percentile.

<sup>a</sup>eGFR calculated using the CKD-EPI formula.

Bold indicates statistical significant differences.

albumin at referral, although statistically significant (3.7 vs. 3.6 g/dl), is of doubtful clinical relevance.

### Inclusion in the observational study

The flow chart of patients from referral to inclusion in the PRO-RE-RE-PRO study is shown in Fig. 1. Among the 383 patients included in the study, no significant difference in the proportion of included males (59%) and females (41%) was observed with respect to the 60:40 proportion ( $P = .683$ ). Furthermore, no single reason for not being included in the study appears to be sex specific, including patients' refusal to participate (Fig. 1).

Table 3 reports the main clinical data of patients who were included in the PRO-RE-RE-PRO study and Table 4 reports their main biochemical data at recruitment. Once more, the eGFR was not significantly different in the included male and female patients, while, reflecting what was observed in the overall referred population, proteinuria and comorbidity were higher and age was lower in males than in females. The clinical and biochemical data of the patients not included in the study, and of those on the waiting list for inclusion are available in Supplementary Tables 1–4.

### Survival analysis in the pre-dialysis phase

During a median follow-up per patient of 1.158 years (0.400–2.383), in the overall cohort referred to the UIRAV, survival was significantly higher in females (Fig. 2a), and the difference persisted after stratification per CCI, dichotomized at 7 (Fig. 2b). Due to lower mortality, and to a non-significantly lower incidence of dialysis start, persistence in outpatient follow-up was higher in females (Fig. 2c).

### Determinants of the probability of being included in the study

In the two multivariable models (Table 5), built separately to avoid collinearity between age and CCI, sex was not associated with the probability of non-inclusion in the ongoing study, at difference with older age and higher comorbidity.

### Patients not included into the study

Compared to patients included in the study, patients not included were older, more comorbid, less likely to live at home and more likely to have undergone a single nephrology consultation (Supplementary Table 5). They had a higher MIS and a lower nutritional status (Supplementary Table 5). However, the male to female proportion was not different compared to patients included in the study (Supplementary Table 5). Regarding biochemical parameters, patients not included in the study had a slightly lower Hb, a lower eGFR and serum albumin (although of limited clinical relevance) (Supplementary Table 6). Comparing by sex, male patients showed the same features (Supplementary Tables 7 and 8) while female patients were not older or more comorbid (Supplementary Tables 9 and 10).

### Dialysis patients

Supplementary Table 11 reports the main clinical characteristics of patients starting HD and PD in our center. The distribution between males and females is not significantly different from the tested proportion (60:40). Supplementary Table 12 reports the main biochemical characteristics of patients starting dialysis: no significant differences in biochemical data at dialysis start was found between males and females, in the context of our intent to defer policy. The flow chart of dialysis patients is reported in Supplementary Fig. 1.

## DISCUSSION

The present study, conducted in a large public hospital, serving a well-defined, mainly rural area in central France, was undertaken to gather information on the possible variations of the male to female ratio since nephrology referral, to control for the presence of sex-related selections in the recruitment in an observational study focused on the implementation of nutritional management in advanced CKD and in dialysis start.

The first result is the stability of the ~35–40% female to 60–65% male ratio since start of follow-up in different subsets of cases: patients referred to the unit dedicated to

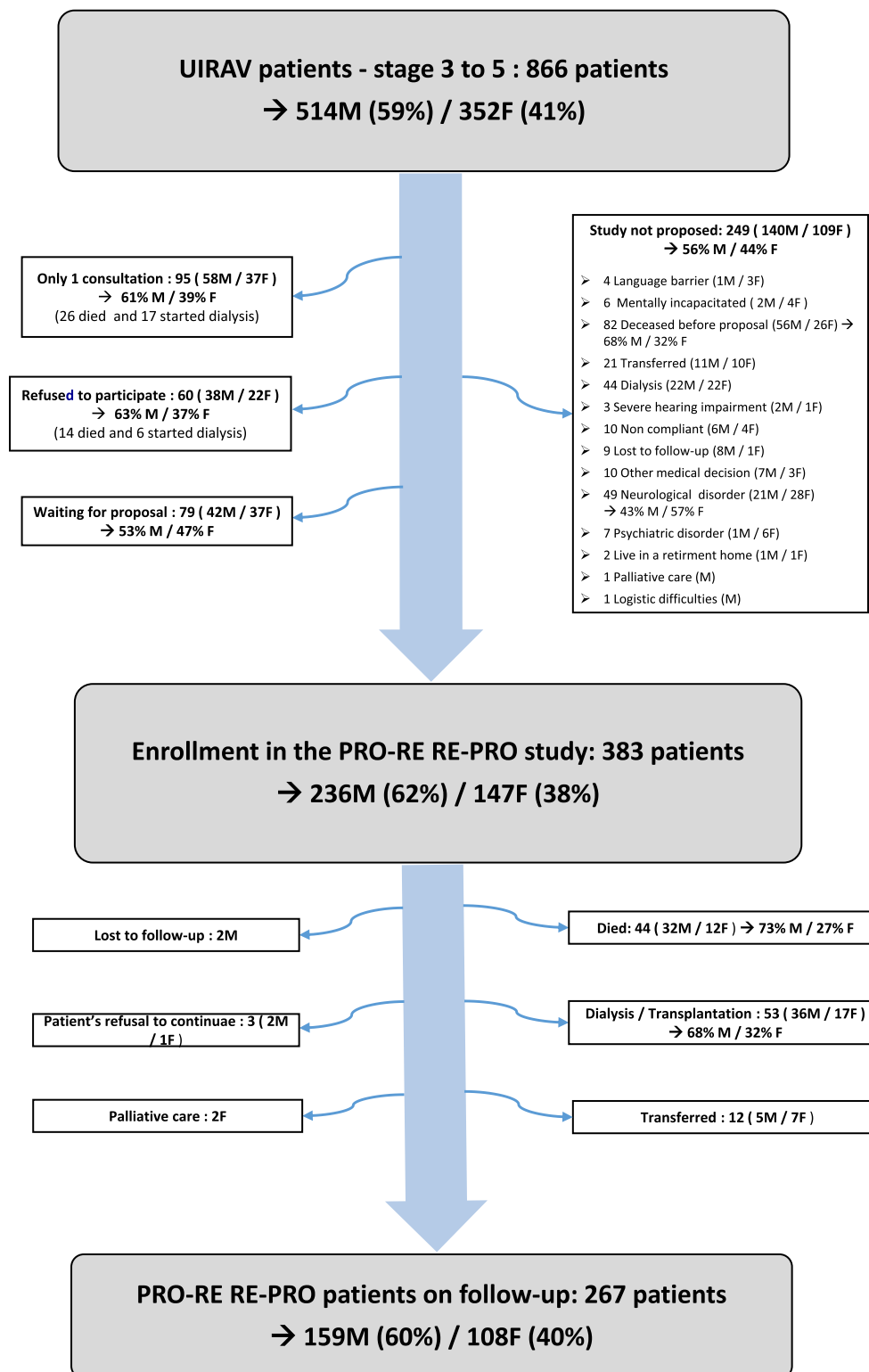


Figure 1: Flow chart of patients from referral to inclusion in the PRO-RE-RE-PRO study.

advanced CKD, patients recruited in the observational study on the effect of diet on CKD progression, currently active in the setting of study, patients not included, patients on follow-up at the completion of the database (Fig. 1, Tables 1–4). Furthermore, the same distribution is observed in patients start-

ing dialysis (Supplementary Fig. 1, Supplementary Tables 11 and 12).

This first result is thus reassuring on the absence of a deliberate sex-specific selection for inclusion in research studies in an overall elderly, high-comorbid cohort of patients with CKD

**Table 3: Baseline data at the first consultation in UIRAV of patients included in the PRO-RE RE-PRO study (patients with CKD stage 3 to 5 not on dialysis).**

	All	Females	Males	P value F vs. M
N	383	147 (38%)	236 (62%)	.683 <sup>a</sup>
Age (years), median (Q1–Q3)	75 (66–83)	78 (66–87)	74 (66–81)	<b>.003</b>
Patients living at home, n (%)	363 (95.0%)	135 (91.8%)	228 (96.6%)	<b>.041</b>
Patients with only one consultation, n (%)	11 (2.9%)	5 (3.4%)	6 (2.5%)	.755
BMI (kg/m <sup>2</sup> ), median (Q1–Q3)	28.8 (25.3–33.2)	28.5 (24.9–33.7)	29.1 (25.6–32.9)	.716
Primary kidney disease				.173
ADPKD, n (%)	12 (3.1%)	5 (3.4%)	7 (3.0%)	
Diabetes mellitus, n (%)	30 (7.8%)	13 (8.8%)	17 (7.2%)	
NAS/hypertensive, n (%)	109 (28.5%)	43 (29.3%)	66 (28.0%)	
Glomerulonephritis, n (%)	6 (1.6%)	4 (2.7%)	2 (0.8%)	
CAKUT/obstructive disease/isolated urinary abnormalities, n (%)	9 (2.4%)	3 (2.0%)	6 (2.5%)	
Multifactorial, n (%)	171 (44.6%)	55 (37.4%)	116 (49.2%)	
Unknown, n (%)	14 (3.7%)	9 (6.1%)	5 (2.1%)	
Other, n (%)	32 (8.4%)	15 (10.2%)	17 (7.2%)	
CCI, median (Q1–Q3)	7 (6–9)	7 (6–8)	8 (6–9)	<b>.008</b>
Cardiopathy, n (%)	126 (32.9%)	36 (24.5%)	90 (38.1%)	
Peripheral vascular disease, n (%)	92 (24.0%)	26 (17.7%)	66 (28.0%)	
Cerebrovascular disease, n (%)	38 (9.9%)	11 (7.5%)	27 (11.4%)	
Dementia, n (%)	10 (2.6%)	7 (4.8%)	3 (1.3%)	
Chronic pulmonary disease, n (%)	40 (10.4%)	13 (8.8%)	27 (11.4%)	
Liver disease, n (%)	21 (5.6%)	6 (4.1%)	15 (6.4%)	
Diabetes, n (%)	188 (50.0%)	59 (40.1%)	129 (54.7%)	
Hemiplegia, n (%)	4 (1.0%)	2 (1.4%)	2 (0.8%)	
Neoplasia, n (%)	83 (22.3%)	24 (16.3%)	59 (25.0%)	
AIDS, n (%)	2 (0.5%)	0 (0.0%)	2 (0.8%)	
Other, n (%)	26 (6.8%)	6 (4.1%)	20 (8.5%)	
MIS, median (Q1–Q3)	4 (2–6)	4 (3–6)	4 (2–5)	<b>.027</b>
SGA, n (%)				<b>.033</b>
A	340 (89.0%)	124 (84.4%)	216 (91.9%)	
A–B	2 (0.5%)	1 (0.7%)	1 (0.4%)	
B	39 (10.2%)	22 (15.0%)	17 (7.2%)	
B–C	0 (0.0%)	0 (0.0%)	0 (0.0%)	
C	1 (0.3%)	0 (0.0%)	1 (0.4%)	
Follow-up				<b>.108</b>
Death, n (%)	44 (11.5%)	12 (8.2%)	32 (13.6%)	
Transfer, n (%)	12 (3.1%)	7 (4.8%)	5 (2.1%)	
Refusal to continue follow-up, n (%)	3 (0.8%)	1 (0.7%)	2 (0.8%)	
Transplantation/hemodialysis, n (%)	53 (13.8%)	17 (11.6%)	36 (15.3%)	
Palliative care, n (%)	2 (0.5%)	0 (0.0%)	2 (0.8%)	
Lost to follow-up, n (%)	2 (0.5%)	2 (1.4%)	0 (0.0%)	
Follow-up on going <sup>b</sup> , n (%)	267 (69.7%)	108 (73.5%)	159 (67.4%)	

Q1: Quartile 1, 25th percentile; Q3: Quartile 3, 75th percentile.

<sup>a</sup>Goodness of fit test, compared with theoretical proportion set at 40:60.

<sup>b</sup>Includes patients followed at CHM or a peripheral hospital.

Bold indicates statistical significant differences.

stage 3–5 referred to a nephrology center. Our figures are in line with the sex distribution found in other European studies dealing with nutritional approaches in advanced CKD: in the highly selected population in the Garneata study on very low-protein diets, 63% and 59% of the participants in each group were males, while in the pragmatic ERIKA study 61% of the recruited patients were males [29, 30]. In a previous large observational multicentre Italian study (the TOPI study) the prevalence of males recruited in the four centers was 62.3% [31].

In our study, the outcome of “not being included” (for all causes, including refusal, short follow-up, contraindications, cognitive impairment) in the ongoing study was not associated

with sex, but, in this overall elderly population, whose age is albeit in line with patients under kidney care in Europe, was significantly associated with older age and higher comorbidity [32–36]. Likewise, refusal to participate was not different in males and females. Similarly for dialysis, a recent report described that the median age at KRT start in France was 71 years, according to the analysis of the official French registry data [37].

Referral to the nephrology is a complex issue. We clearly do not see all CKD patients [38]. While some guidelines, such as the recent KDOQI guidelines on nutritional treatment in CKD, arguing in favor of nutritional interventions since early

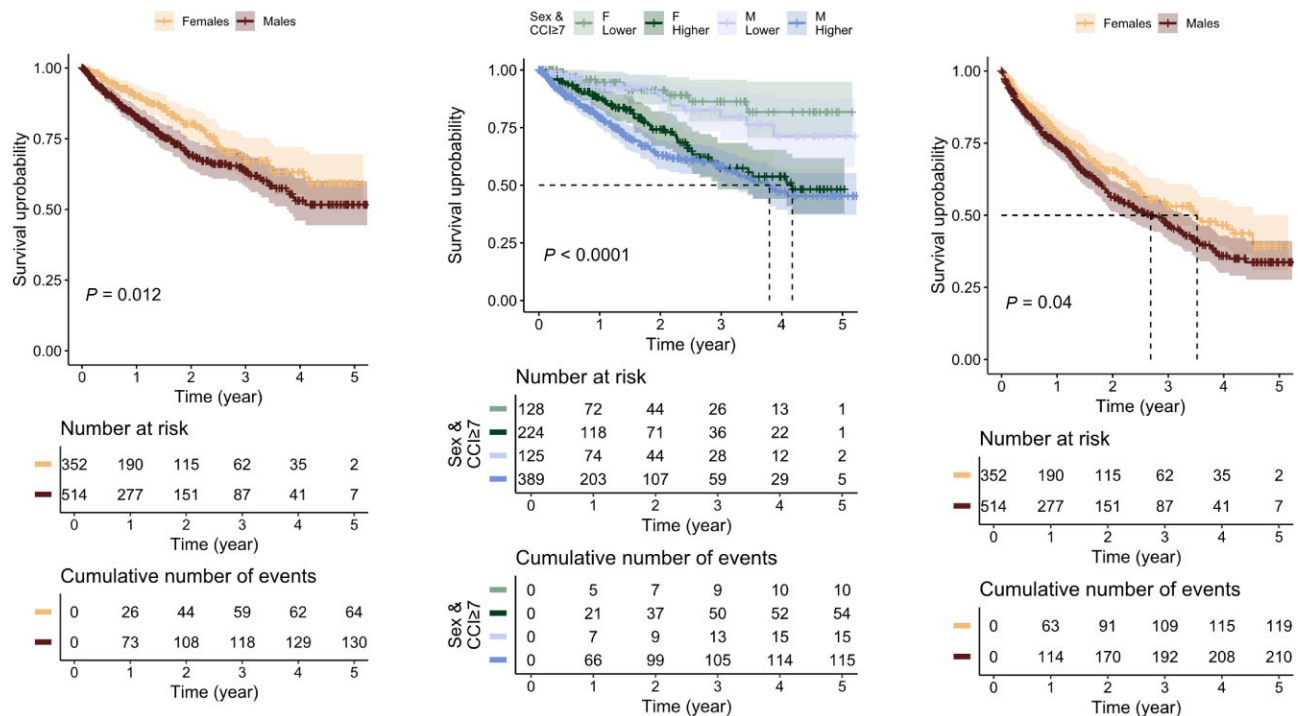
**Table 4: Biochemical data at the first consultation in UIRAV of patients included in the PRO-RE RE-PRO study (patients with CKD stage 3 to 5 not on dialysis).**

	All	Females	Males	P value females vs. males
N	383	147 (38%)	236 (62%)	
Hemoglobin (g/dl), median (Q1–Q3)	11.9 (10.8–13.2)	11.4 (10.5–12.5)	12.3 (11.0–13.6)	<.001
<9 g/dl, n (%)	11 (2.9%)	6 (4.1%)	5 (2.1%)	.347
<10 g/dl, n (%)	45 (11.7%)	24 (16.3%)	21 (8.9%)	.028
Creatinine (μmol/l), median (Q1–Q3)	187.0 (152.5–246.5)	167.0 (133.4–216.0)	199.5 (167.8–257.3)	<.001
eGFR <sup>a</sup> (ml/min), median (Q1–Q3)	27.0 (18.0–35.0)	25.5 (15.8–30.3)	29.0 (20.0–36.8)	.964
Urea (mmol/l), median (Q1–Q3)	14.6 (10.8–19.8)	14.7 (10.8–19.4)	14.5 (10.9–20.1)	.674
≥40 mmol/l, n (%)	6 (1.6%)	2 (1.4%)	4 (1.7%)	.999
Total serum proteins (g/l), median (Q1–Q3)	72 (68–76)	71 (67–75)	73 (69–76)	.004
Albumin (g/dl), median (Q1–Q3)	3.7 (3.5–4.0)	3.7 (3.4–4.0)	3.8 (3.5–4.0)	.028
3.0–3.5 g/dl, n (%)	103 (27.6%)	43 (30.3%)	60 (26.0%)	.032
<3.0 g/dl, n (%)	17 (4.6%)	11 (7.7%)	6 (2.6%)	
Proteinuria (g/24 h), median (Q1–Q3)	0.4 (0.1–1.6)	0.2 (0.1–0.8)	0.6 (0.2–2.0)	<.001
≥1 g/24 h, n (%)	87 (34.4%)	17 (19.3%)	70 (42.4%)	<.001
Bicarbonate (mmol/l), median (Q1–Q3)	24 (21.9–26.4)	24 (22.0–26.6)	24 (21.8–26.4)	.797
<17 mmol/l, n (%)	7 (1.8%)	3 (2.1%)	4 (1.7%)	.999

Q1: Quartile 1, 25th percentile; Q3: Quartile 3, 75th percentile.

<sup>a</sup>eGFR calculated using the CKD-EPI formula.

Bold indicates statistical significant differences.



**Figure 2: (a) UIRAV patient survival according to sex. (b) UIRAV patient 2 survival according to sex and CCI (dichotomized at 7). (c) Persistence in the system (outcome death or dialysis start).**

CKD stages, implicitly recognize that all CKD patients should be seen and nutritionally evaluated, specific guidelines for nephrology referral are more restrictive (stage 3b and 4, in the absence of relevant proteinuria), raising further, thus far unanswered, questions [39–42]. Data on the sex distribution of patients referred to nephrology centers in Europe are scant; we have previously reported a similar sex distribution, during one test year, in all patients who had at least one nephrology con-

sultation in all our outpatient units regardless of their kidney function [38]. However, we estimate that, at least in the setting of study most patients with stage 3 CKD are not referred to a nephrologist [38].

The second interesting finding in our study is a superimposable residual kidney function in males and females at referral to the UIRAV (median eGFR 25–25.5 ml/min) and in males and females at dialysis start (6–7 ml/min) suggesting that decisions

**Table 5: Univariable and multivariable analysis on the probability not to participate in the PRO-RE-RE-PRO study.**

Univariable analysis: OR not to participate in PRO-RE-RE-PRO study				
	OR	95% CI		P value
		Lower	Higher	
Age	1.041	1.016	1.067	.002
CCI	1.127	1.008	1.259	.035
BMI	0.973	0.930	1.016	.230
Sex (M)	1.083	0.628	1.906	.777
Model A: multivariable analysis:				
	OR	95% CI		P value
		Lower	Higher	
Age	1.043	1.017	1.073	.002
BMI	0.984	0.937	1.029	.491
Sex (M)	1.297	0.737	2.338	.375
Model B: multivariable analysis:				
	OR	95% CI		P value
		Lower	Higher	
CCI	1.120	1.002	1.252	<b>.045</b>
BMI	0.976	0.932	1.019	.294
Sex (M)	1.006	0.578	1.783	.984

CI, confidence intervals.

Bold indicates statistical significant differences.

of referral and dialysis start are mainly based on kidney function and not on sex, leaving the open issue of lack of medical resources, leading to long waiting times for a first nephrology consultation, one of the bottlenecks in the widening nephrology care [43].

The third issue regards dialysis start. The sex distribution we found in our study is not significantly different from those found at referral to the UIRAV (or at recruitment in the study), and is in line with the European Renal Association Registry Annual Report, which found that 61% of patients receiving KRT were men [36]. The similar eGFR at dialysis start, in the context of a lower mortality and higher “persistence” in the pre-dialysis phase (Supplementary Table 12 Fig. 2c) are in line with a lack of a selection bias, referring to dialysis for more men than women.

While our data give no clue to support the idea that women's kidney health is systematically neglected in our setting, they should be seen only as hypothesis generators, since our study has several limitations. The first limitation is due to the fact that it was conducted in only one hospital, albeit a large one; the absence of evidence of selection may reflect the particular attention to sex-related issues in our setting. Since few settings recruit patients for observational studies on advanced CKD, we limited our comparison to literature data.

The second major limitation is the lack of data or CKD prevalence in our area, allowing us to confirm or to refute the hypothesis that selection is unbiased by sex and based mainly on kidney function. Filling this knowledge gap should be a priority, making it possible to plan better interventions for all CKD patients, and efficiently put an end to late referral.

Third, our database did not allow us to control for other types of discrimination, for instance income, education, or setting of residence (rural versus urban). Further studies are needed to en-

sure health equity, thereby improving the care of our patients with advanced CKD and those on dialysis.

Last, only further stepwise analyses (diagnosis of CKD, referral to nephrology, enrollment in studies, referral to dialysis, death rates, and other causes of discontinuation of follow-up) focused on sex distribution in kidney care in different settings, could allow our findings to be validated.

## SUPPLEMENTARY DATA

Supplementary data are available at *Clinical Kidney Journal* online.

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## DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

## CONFLICT OF INTEREST STATEMENT

None declared.

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