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ORIGINAL ARTICLE

The association between CKD and frailty in the FRASNET study: suggestion of a novel eGFR threshold as a key determinant of frailty in the elderly

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Abstract

Background Frailty, a geriatric syndrome marked by reduced physiological reserves, has been linked to organ dysfunction. However, the specific contribution of kidney function to frailty remains underexplored. This study aims to assess the impact of kidney function on frailty in a large population of older adults.

Methods The FRASNET cohort, including elderly individuals non-hospitalized, was evaluated for frailty, markers of kidney glomerular and tubular function, and for anthropometric parameters.

Results We included 1183 individuals in this study (59.9% females, age 65–93). Among them, 27.7% of subjects were classified as robust, 37.6% were pre-frail, and 34.7% were frail. The prevalence of frailty increased with age (43% in individuals over 76 years of age) and was associated with obesity (28.3%) and polytherapy (23.2%). Whole estimated glomerular filtration rate (eGFR) was 73.8 (IQR 62.4, 84.7) ml/min/1.73 m^2. The prevalence of chronic kidney disease (CKD) increased across frailty classes from 15.2% in robust to 29.0% in frail individuals ($P < 0.001$). Among young-old subjects (65–75 years old), comorbidity was the main determinant of frailty, whereas in older subjects, when eGFR was below 53.5 ml/min/1.73 m^2, it was associated with frailty ($P < 0.002$). Fractional excretion of sodium progressively increased across frailty classes, from 0.71% in robust individuals (IQR 0.46–1.03) to 0.79% in frail subjects (IQR 0.48–1.17) ($P = 0.04$).

Conclusion This study revealed a strong relationship between CKD and frailty, identifying a new eGFR threshold associated with frailty in older adults. The alterations in age- and frailty-dependent sodium handling highlight the potential role of the often-overlooked tubular function in older individuals.

Keywords Frailty · Renal aging · Estimated glomerular filtration rate · Tubular function

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Introduction

Frailty, defined as a decline in physiological reserve and increased vulnerability to stressors, remains challenging to quantify, and the role of organ function deterioration in the overall picture remains unclear. Frailty prevalence ranges from 12 to 30% depending on age, sex, and classification criteria [1], rising to 25–50% in those over 85 years of age.

The kidney is one of the organs that progressively loses function with aging [2, 3]. Approximately 20–50% of older adults suffer from stage 3–5 chronic kidney disease (CKD). However, it is still debated whether the decrease in estimated glomerular filtration rate (eGFR) below 60 mL/min in the elderly is an expression of a potentially progressive kidney disease or if it is the result of physiological aging of

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the kidney [4]. Moreover, the actual clinical relevance of this condition is still unclear [2]. An accurate assessment of kidney function may allow risk stratification and support decision-making regarding the choice of therapy and drug dosage [5].

Kidney aging is the result of a multifactorial physiological process characterized by progressive and irreversible cellular aging, which is accelerated by comorbidities such as arterial hypertension, ischemic heart disease and diabetes. The structural changes of the renal parenchyma include glomerular sclerosis, interstitial fibrosis and tubular atrophy, which are also modulated by inflammatory processes related to comorbidities [4, 6, 7].

Senile involution of the kidney is characterized by progressive functional changes which lead to a reduction in glomerular filtrate and renal blood flow coupled with an increase in vascular resistance and filtration fraction. These alterations may result in an increase in plasma creatinine, a decrease in GFR and an increase in the filtration fraction of electrolytes such as sodium and potassium. The increase in vascular resistance and the reduction in glomerular filtration rate contribute to the increase in blood pressure and sodium sensitivity [7], [8, 9].

Although life expectancy varies by country, people are generally living longer. However, a major goal of modern medicine is to preserve quality of life. Applied to older people, this translates into concepts such as "successful", "healthy", or "optimal" aging, which means avoiding disease and disability, maintaining good cognitive and physical function, and remaining actively engaged in life.

The physical frailty phenotype is the most widely used to describe frailty and is based upon the presence of at least three of the following characteristics: reduced grip strength, reduced gait speed, low physical activity, self-reported exhaustion, and unintentional weight loss [8].

The current study aimed at assessing the association between kidney and frailty in a large population of older subjects as is the FRASNET cohort. A multilevel analytical approach incorporated different anthropometric and renal parameters.

Materials and methods

Study participants

The FRASNET study is a cross-sectional multicenter observational cohort study involving healthy volunteers [9]. The study was approved by the San Raffaele Ethics Committee on 9th March, 2017, Protocol N. 24/INT/2017. All participants provided written informed consent. Subjects were enrolled between 1st April, 2017 and 16th October, 2020 in recreational and cultural centers and retirement homes in Milan and Monza Brianza, Italy. Evaluation visits were performed at the San Raffaele Scientific Institute in Milan, and at Cuggiono Hospital, near Milan, Italy. The inclusion criteria were: (i) age above 65 years, (ii) able to walk more than 500 m without assistance; (iii) life expectancy greater than 6 months. The exclusion criteria were: i) severe cognitive impairment, defined as a Mini-Mental State Examination (MMSE) score < 18/30; (ii) inability to provide written informed consent; (iii) severe health problems (e.g., uncontrolled hypertension, recent upper or lower extremity fractures, myocardial infarction within the past year).

Data collection

Participants underwent comprehensive geriatric assessment, demographic and psychosocial data were collected via self-administered questionnaires. Additional evaluations covered comorbidities, pharmacological therapy, and the incidence and number of falls and of emergency department visits in the year preceding the assessment. Anthropometric measurements, including weight, height, waist circumference, and body mass index (BMI), were also recorded. Age was classified in groups following the guidelines set by the Istituto Superiore di Sanità. Cognitive function was assessed using the Mini Mental State Examination (MMSE), while mood was evaluated by the 15-item Geriatric Depression Scale (GDS). Fatigue was measured using the Fatigue Severity Scale (FSS), quality of life with the Short Form 36 (SF-36) Health Survey, and physical activity level using the Physical Activity Scale for the Elderly (PASE) questionnaire [9].

Body composition was determined using the Full Body Sensor Body Composition Monitor and Scale (OMRON) (https://omronhealthcare.com/wp-content/uploads/hbf-510w-instruction-manual.pdf). Muscle performance was evaluated through the Short Physical Performance Battery (SPPB), which includes three subtests: standing balance, usual gait speed over a short distance, and the ability to rise from a chair. The chair-stand test of the SPPB was specifically used to assess muscle strength [12]. Sarcopenia was defined according to the revised criteria of the European Working Group on Sarcopenia in Older People 2 (EWGSOP2, 2019). Based on these guidelines, *low muscle strength* was considered the main criterion for case finding (probable sarcopenia), while the diagnosis of *confirmed sarcopenia* required the presence of both low muscle strength and low muscle mass [10].

Muscle strength was assessed using the chair-stand subtest of the SPPB. Participants were instructed to rise from a chair five times as quickly as possible with their arms folded across their chest [11]. A total time exceeding 15 seconds to complete the five repetitions was considered indicative

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of reduced lower limb muscle strength, as per EWGSOP2 thresholds for identifying probable sarcopenia.

Muscle mass was estimated using a Full Body Sensor Body Composition Monitor and Scale (OMRON), which employs bioelectrical impedance analysis (BIA). This method uses a very low electrical current (50 kHz, <500 µA) to estimate body composition based on the conductivity of body tissues. Tissues with higher water content, such as muscle, conduct electrical current more easily, whereas fat has lower conductivity. This allows estimation of fat-free mass, total body fat, visceral fat, and skeletal muscle mass. On the basis of Omron Healthcare reference values, skeletal muscle mass was considered reduced if <23.9% in women aged ≥60 years and <32.9% in men aged ≥60 years.

Participants were classified as: Pre-sarcopenic (probable sarcopenia): low muscle strength only. Sarcopenic (confirmed sarcopenia): low muscle strength + low muscle mass—as per EWGSOP2 recommendations.

Frailty was measured using a modified Fried phenotype, as previously reported [9, 12] excluding unintentional weight loss since older adults often have difficulty recalling their usual weight [9]. The four domains considered in the Modified Fried Phenotype were derived from the geriatric assessment.

The four-items version of the Fried (Fried 2001) criteria included: (1) exhaustion, (2) low strength, (3) slow walking speed, (4) low physical activity. The final score was calculated as the sum of the individual component scores (range 0–4). Subjects with three or more criteria were classified as frail, those with one or two as pre-frail, and those meeting none as robust.

Low physical activity was determined by a PASE score below 76, corresponding to the 40th percentile of physical activity levels in the older Italian population (www.epicentro.iss.it/passi-argento).

Kidney function evaluation

Kidney function was evaluated considering both glomerular and tubular function. Glomerular filtration rate (eGFR) was evaluated applying the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation. eGFR was analysed both as a continuous variable and for classifying subjects into the following stages: Stage 1—GFR ≥ 90 ml/min/1.73 m^2; Stage 2—GFR 60–89 ml/min/1.73 m^2; Stage 3a—GFR 45–59 ml/min/1.73 m^2; Stage 3b—GFR 30–44 ml/min/1.73 m^2; Stage 4—GFR 15–29 ml/min/1.73 m^2; Stage 5 –GFR < 15 ml/min/1.73 m^2 (kidney failure).

We also collected a morning urine sample (second micturition) in order to measure urinary sodium, urinary potassium, and urinary creatinine. We calculated 24-h urinary sodium excretion by applying the Kawasaki formula [13] to estimate dietary sodium intake and fractional excretion of sodium (FeNa) as a ratio between sodium clearance and creatinine clearance.

The data were collected and reported in an electronic case report form (eCRF) created using FileMaker Pro v. 11.

Statistical analyses

Since continuous variables were not normally distributed, they were presented as median and interquartile range (IQR), where as dichotomous variables as number (N) and percentage (%). The Kruskal–Wallis rank sum test and Pearson's Chi-squared or Fisher's Exact tests were performed to verify differences in distribution of frailty groups for each continuous variable of interest (i.e., age, eGFR, etc.) and categorical risk factor (i.e., gender, sarcopenia etc.).

To determine the influence of selected explanatory variables (sex, age group, weight group, number of daily drugs and eGFR) on frailty, we applied the conditional inference tree analysis using the ctree function of the Partykit package of R (https://cran.r-project.org/web/packages/partykit/vignettes/partykit.pdf). This statistical method is very useful for obtaining results in studies with subgroups with different levels of response to the explained variables. Briefly, the global null hypothesis of independence between the explanatory variables and the response is tested. If this hypothesis cannot be rejected based on a Bonferroni correction ($\alpha = 0.05$), the algorithm selects the explanatory variable with the strongest association with response and implements a binary split in the selected explanatory variable. This approach is repeated recursively until $\alpha > 0.05$.

All statistical analyses were performed with R statistical software v. 4.3.2. (R Core Team. R: A Language and Environment for Statistical Computing; R Foundation for Statistical Computing: Vienna, Austria, 2015; https://www.r-project.org/) and SPSS version 25.0 (SPSS Inc., Chicago, IL, USA).

Results

General characteristics of the participants

Altogether,l 1250 volunteers aged 65 years old or older (753 males, and 497 females) were included in the study. Kidney function parameters were available for 1183 individuals (aged 65–93). Frailty classes were as follows: 328 (27.7%) subjects were robust; 445 (37.6%) were pre-frail, and 410 (34.7%) were frail. Table 1 reports the characteristics of the participants in the whole cohort and by frailty group.

No difference in frailty distribution was observed according to gender (Pearson Chi-squared Test, $P > 0.05$). Overall, median age was 72 [IQ 69–77] years, and the highest percentage of subjects was in the first age class (65–75 years,

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Table 1 Sample characteristics in the FRASNET study. Data are reported for all samples and by frailty categories

	All cases $N=1183$	Frailty–Robust $N=328$	Frailty–Pre frail $N=445$	Frailty–Frail $N=410$	*P* value
Age, min–max	65–93	65–89	65–93	65–93	
Age, years	72 (69, 77)	71 (68, 75)	72.0 (69, 76.)	74 (69, 80)	< .001
Gender					.2
Female	709 (59.9%)	194 (59.2%)	256 (57.5%)	259 (63.2%)	
Male	474 (40.1%)	134 (40.8%)	189 (42.5%)	151 (36.8%)	
Age groups					< .001
65–75 years	804 (68.0%)	247 (75.3%)	325 (73.0%)	232 (56.6%)	
76–85 years	342 (28.9%)	79 (24.1%)	113 (25.4%)	150 (36.6%)	
> 85 years	37 (3.1%)	2 (0.6%)	7 (1.6%)	28 (6.8%)	
BMI, kg/m^2	26.7 (24.0, 29.5)	26.3 (23.7, 29.1)	26.6 (23.8, 28.9)	27.4 (24.5, 30.4)	< .001
BMI groups					.002
BMI < 18.5 kg/m^2	7 (0.6%)	0 (0.0%)	4 (0.9%)	3 (0.7%)	
BMI ≥ 18.5 & BMI < 25 kg/m^2	388 (32.8%)	114 (34.7%)	159 (35.7%)	115 (28.1%)	
BMI ≥ 25 & BMI < 30 kg/m^2	537 (45.4%)	159 (48.5%)	202 (45.4%)	176 (42.9%)	
BMI ≥ 30 & BMI < 40 kg/m^2	247 (20.9%)	55 (16.8%)	79 (17.8%)	113 (27.6%)	
BMI ≥ 40 kg/m^2	4 (0.3%)	0 (0.0%)	1 (0.2%)	3 (0.7%)	
eGFR, ml/min/1.73 m^2	73.8 (62.4, 84.7)	74.9 (64.3, 86.3)	74.9 (64.1, 84.6)	70.3 (56.9, 82.8)	< .001
Number of daily medications	3.0 (1.0, 5.0)	2.0 (1.0, 4.0)	3.0 (1.0, 4.0)	3.0 (2.0, 5. 0)	< .001
Number of daily medications -quartile					< .001
0–1 medication	323 (27.3%)	114 (34.7%)	121 (27.2%)	88 (21.4%)	
2–3 medications	407 (34.4%)	121 (36.9%)	159 (35.7%)	127 (31.0%)	
4–5 medications	270 (22.8%)	62 (18.9%)	108 (24.3%)	100 (24.4%)	
> 5 medications	183 (15.5%)	31 (9.5%)	57 (12.8%)	95 (23.2%)	
Sarcopenia ($n=1163$)					< .001
Robust	658 (56.6%)	201 (61.8%)	256 (58.1%)	201 (50.6%)	
Pre-sarcopenic	347 (29.8%)	111 (34.2%)	151 (34.2%)	85 (21.4%)	
Sarcopenic	158 (13.6%)	13 (4.00%)	34 (7.7%)	111 (28.0%)	
FE Na % ($n=1153$)	0.75 (0.49, 1.14)	0.71 (0.46, 1.03)	0.75 (0.51, 1.18)	0.79 (0.48, 1.17)	.04
FE Na class ($n=1153$)					.021
≤ 1%	785 (68.1%)	236 (74.2%)	290 (66.2%)	259 (65.2%)	
> 1%	368 (31.9%)	82 (25.8%)	148 (33.8%)	138 (34.8%)	
Urine Na/creatinine mmmol/meq (n = 1156)	121.1 (76.8, 176.6)	113.3 (76.8, 161.5)	122.4 (79.4, 180.9)	124.3 (74.8, 180.0)	.2
Kawasaki_Na_24h, mEq/24 h (n = 1156)	188.9 (150.6, 230.4)	186.5 (152.9, 224.5)	190.1 (15.0, 232.6)	188.7 (144.1, 232.6)	.2
CKD stages					< .001
eGFR > 90, stage 1	137 (11.6%)	42 (12.8%)	51 (11.5%)	44 (10.7%)	
eGFR 60–90, stage 2	796 (67.3%)	236 (72.0%)	313 (70.3%)	247 (60.2%)	
eGFR 30–60, stage 3	228 (19.2%)	50 (15.2%)	76 (17.1%)	102 (24.9%)	
eGFR 10–30, stage 4	14 (1.2%)	0 (0.00%)	3 (0.6%)	11 (2.7%)	
eGFR < 10, stage 5	8 (0.7%)	0 (0.00%)	2 (0.5%)	6 (1.5%)	
eGFR categories					< .001
eGFR ≥ 60	933 (78.9%)	278 (84.8%)	364 (81.8%)	291 (71.0%)	
eGFR < 60	250 (21.1%)	50 (15.2%)	81 (18.2%)	119 (29.0%)	

Data are Median (IQR) or *n* (%). IQR: interquartile range. *P* values refer to the differences among frailty classes and were calculated using the Kruskal–Wallis rank sum test for continuous variables and Pearson's Chi-squared or Fisher's Exact test for categorical variables

BMI body mass index; *eGFR* estimated glomerular filtration rate; *FE Na* fractional excretion of sodium; *Urine Na/creatinine* ratio between urine sodium and urine creatinine; *Kawasaki_Na_24h, mEq/24 h* estimated 24 h-urinary sodium excretion (Kawasaki formula); *CKD* chronic kidney disease

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68.0%; 76–85 years, 28.9%, and > 85 years, 3.1%). Less than 30% of the robust and pre-frail individuals were 76 years of age or older (24.7% and 27.0%, respectively), compared to 43.4% of frail individuals. Frail individuals showed a higher prevalence of obesity (BMI ≥ 30 kg/m^2, 28.3% versus 16.8% and 18.0% of robust and pre-frail, respectively) and a higher percentage of subjects treated with more than 5 drugs (23.2% versus 12.8% and 9.5%, respectively).

The overall median eGFR was 73.8 (IQR 62.4, 84.7) ml/min/1.73 m^2. Median estimated 24-h urinary sodium excretion was 188.9 (IQR 150.6, 230.4) mEq/24 h corresponding to a high-salt-content diet with a median fractional excretion of sodium of 0.75% (IQR 0.49, 1.14). In 31.9% of the cases, fractional excretion of sodium was greater than 1%, which is considered a pathological level.

Prevalence of CKD in the FRASNET cohort

Only 60% of subjects were able to provide information about kidney function, and only 3% of them reported CKD. However, in this cohort, blood tests showed that 21.1% of subjects had an eGFR within the range of kidney failure (eGFR < 60, $n = 250$) (Table 1). Subjects included in this study were expected to have been clinically stable for 6 months after an acute event, allowing us to assume that this kidney function value represents a condition of chronic kidney disease.

Table 2 summarizes CKD classification according to gender, age group and daily medication quartiles. The proportion of males with low eGFR was higher than in females (23.8% versus 19.3% p = n.s.). Considering the distribution of CKD classes according to age, 12.4% of subjects aged < 75 had CKD class 3 or above (11.6% in class 3). The prevalence of CKD stages 3–5 increased across age classes from 36.5% of subjects in age class 75–85 with CKD stages 3–5 to 70.3% in individuals aged over 85.

The prevalence of CKD increased across frailty classes, from 15.2% in robust individuals to 29.0% in frail ones. We observed that CKD patients were receiving a greater number of drugs. In the overall population, 27.3% of the individuals reported taking none or one drug per day (Table 1), while 82 subjects out of 250 (32.8%) reported taking more than five drugs per day (Table 2).

The median number of daily medications increased with age: 2 (IQR 1–4) in the younger age class, 3 (IQR 2–5) in the middle group, and 5 (IQR 3–8) in the older age class.

Impact of CKD on frailty

Conditional inference tree analysis confirmed the association with age, number of drugs and BMI group, eGFR and frailty (Fig. 1). In younger FRASNET subjects (65–75 years) the number of drugs was the main determinant of frailty

Table 2 Characteristics of the FRASNET cohort regarding CKD classification, according to gender, age group, and number of daily medications

	Gender			Age groups				Number of daily medications				
	Females $N = 709$	Males $N = 474$	P value	65–75 y $N = 804$	76–85 y $N = 342$	> 85 y $N = 37$	P value	0–1 $N = 323$	2–3 $N = 407$	4–5 $N = 270$	> 5 $N = 183$	P value
eGFR Classification			0.062				< 0.001					< .001
eGFR ≥ 60, $N = 933$	572 (80.7)	361 (76.2)		705 (87.7)	217 (63.5)	11 (29.7)		287 (88.9)	351 (86.2)	194 (71.9)	101 (55.2)	
eGFR < 60, $N = 250$	137 (19.3)	113 (23.8)		99 (12.3)	125 (36.5)	26 (70.3)		36 (11.1)	56 (13.8)	76 (28.1)	82 (44.8)	
CKD Groups			0.3				< 0.001					< .001
Stage 1, $N = 137$	81 (11.4)	56 (11.8)		129 (16.0)	8 (2.3)	0 (0.0)		46 (14.2)	53 (13.0)	25 (9.3)	13 (7.1)	
Stage 2, $N = 796$	491 (69.3)	305 (64.3)		576 (71.6)	209 (61.1)	11 (29.7)		241 (74.6)	298 (73.2)	169 (62.6)	88 (48.1)	
Stage 3, $N = 228$	126 (17.8)	102 (21.5)		93 (11.6)	112 (32.7)	23 (62.2)		34 (10.5)	55 (13.5)	70 (25.9)	69 (37.7)	
Stage 4, $N = 14$	6 (0.8)	8 (1.7)		3 (0.4)	8 (2.3)	3 (8.1)		0 (0.0)	0 (0.0)	3 (1.1)	11 (6.0)	
Stage 5, $N = 8$	5 (0.7)	3 (0.6)		3 (0.4)	5 (1.5)	0 (0.0)		2 (0.6)	1 (0.2)	3 (1.1)	2 (1.1)	

Data are n (%). P values refer to Pearson's Chi-squared or Fisher's Exact test. eGFR unit of measurement: ml/min/1.73 m^2

CKD chronic kidney disease; *eGFR* estimated glomerular filtration rate

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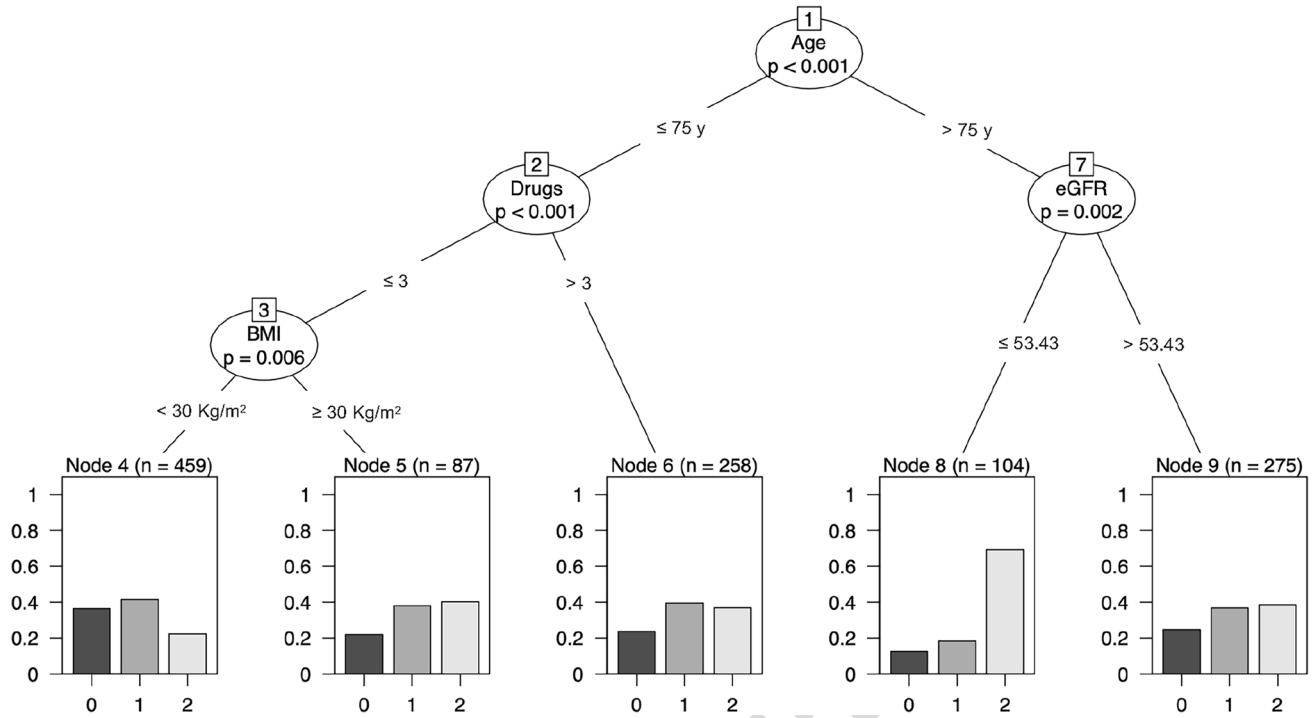

Fig. 1 Binary tree computed by conditional recursive partitioning of the effect of gender, age groups, BMI groups, number of daily drugs, and eGFR, on frailty classes (0 = robust, 1 = pre-fail, 2 = frail). The terminal nodes showed the direct impact of these variables on frailty. BMI: body mass index; eGFR: estimated glomerular filtration rate.

followed by BMI, whereas in older subjects, kidney function played a pivotal role.

Considering the relationship between eGFR and frailty, in the FRASNET population we noticed that an eGFR below 53.5 ml/min/1.73 m^2 in older subjects (> 75 years old) was strongly associated with frailty (Fig. 1). This may support the hypothesis that, in older individuals, a slightly reduced eGFR does not necessarily reflect the real burden of the disease, which becomes evident at a lower level of kidney function (in the elderly this is considered to be below 45 ml/min/1.73 m^2).

Association between sodium intake and tubular function and frailty

No differences in sodium excretion were observed across frailty classes, but the overall mean estimated value is high compared to the recommended intake (Table 1), thus confirming a high dietary salt intake.

With regard to tubular function, we observed an increase in fractional excretion of sodium across frailty classes, from 0.71% in robust individuals (IQR 0.46, 1.03) to 0.79% in frailty (IQR 0.48, 1.17) (Table 1), suggesting that sodium handling may differ among these groups. Moreover, in the frail group, high fractional excretion of sodium (> 1%) was more frequent than in robust and pre-fail subjects (χ^2 $P < 0.05$) (Table 1).

Supplementary Table 1 shows the values of fractional excretion of sodium according to gender, age group, drugs, and CKD class. A fractional excretion of sodium > 1% was more frequent in older subjects ($P < 0.001$), in those taking more than five drugs daily ($P = 0.005$), and in patients with CKD ($P < 0.001$).

Conditional inference tree analysis showed no relationship between sodium intake or tubular function and frailty class. Even after the introduction of fractional excretion of sodium or the Kawasaki estimation of 24-h urinary sodium excretion variables in inferential trees, the eGFR (with a proposed cut-off of 53 ml/min/1.73 m^2) was the main determinant of frailty in the older group (> 75 years), whereas in young-old subjects comorbidity and obesity were associated with frailty (Supplementary Fig. 1, Supplementary Fig. 2).

Discussion

The present study aims to add understanding to the ongoing discussion regarding the intricate relationship between kidney function, aging and frailty in older people [14–17]. Declining kidney function, characterized by reduced tubular salt and water reabsorption, is associated

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with glomerular sclerosis, tubular atrophy, and vascular sclerosis, all of which can be exacerbated by comorbid conditions [14]. However, the clinical significance of this decline remains debated. The 2024 KDIGO guidelines [18] address whether decreased eGFR in older adults is an indication of the disease or is a feature of normal aging. KDIGO recommends using an eGFR of 45 mL/min/1.73 m^2 as a CKD diagnostic threshold in older adults without proteinuria or known kidney disease, acknowledging its impact on cardiovascular (CV) risk and mortality [19].

Moreover, KDIGO 2024 highlighted that the interpretation of creatinine in older adults may be affected by sarcopenia and introduced the creatinine and cystatin C–based estimated glomerular filtration rate (eGFRcr-cys).

The rationale for using a combination of both eGFR equations when evaluatiog the elderly is that creatinine, which is directly linked to muscle mass, may be misleading in the presence of sarcopenia, but cystatin C is impacted by different variables (steroid use, thyroid disease, and cancer). Moreover cystatin C is currently not routinely tested.

Our study explored the relationship between kidney function, aging, and frailty, and showed a strong association between eGFR and frailty even when eGFR is not within the range of kidney disease. Although previous research has linked CKD to frailty, the majority of data were collected from the electronic health records of hospitalized patients [20]. In contrast, we analyzed data concerning non-hospitalized individuals who had not undergone any recent acute events. This characteristic of our cohort, of which the majority, (68.0%) was made up of the so-called young-old, allowed us to translate our conclusions in particular to healthy elderly people.

Notably, the relationship between kidney function and frailty varies with age. Among individuals ≤ 75 years old, comorbidities (number of drugs and BMI) are the primary drivers of frailty, whereas in those > 75 we identified an eGFR < 53.5 mL/min/1.73 m^2 as a key element associated with frailty. This supports previous findings that eGFR decline in older adults, while not a strict disease marker [21], may be associated with frailty. Identifying a specific eGFR threshold could help define which older adults should be targeted for frailty prevention [22]. Additionally, we frequently observed tubular dysfunction in frail individuals [14, 15].

Various factors contribute to the increased frailty observed with declining kidney function. First, reduced kidney function is associated with higher CV risk and impaired calcium-phosphorus balance, predisposing to osteoporosis. Additionally, kidney function decline is associated with comorbidities that contribute to frailty. Lastly, alterations in glomerular filtration and tubular function complicate drug therapy management, increasing the risk of adverse effects [23, 24].

A key strength of our study is the FRASNET cohort, composed of elderly, non-hospitalized volunteers. Furthermore, this is the first investigation into the relationship between frailty and CKD in a large sample of older, non-institutionalized or hospitalized adults. However, the study's primary limitation is its observational design, which prevents establishing a causal relationship between kidney function decline and frailty.

Furthermore, the inclusion and exclusion criteria may make it difficult to apply the conclusions to the general population of elderly individuals, which also includes patients with severe diseases. Another limitation of the study lies in the definition of kidney function, which was assessed by a single measurement of serum creatinine, and not by two measurements taken three months apart, to define chronicity. This limitation is mitigated by the inclusion and exclusion criteria, which required clinical stability.

In conclusion, glomerular filtration rate, rather than the presence of CKD, is a key factor associated with frailty. An eGFR below 53.5 ml/min/1.73 m^2 is significantly associated with frailty, potentially representing the critical threshold where the physiological decline of kidney function transitions toward clinically relevant impairment. We recommend incorporating kidney function assessment into routine frailty screening and in the planning of targeted interventions for the geriatric population, especially in those over 75 years of age.

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Author contributions CL, LC, MS, PRQ, AAM, PM, designed the study; CL, LC, AB, LZ, MS, EB, MEB collected data; CL, LC, MPC, MS, SD, PRQ, AM analyzed and interpreted the data; CL, LC, MPC, MS drafted the manuscript. All the authors read and approved the final draft. The results presented in this article have not been published previously in whole or part. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Data availability The datasets collected and analyzed during in the current study are available from the corresponding author on reasonable request.

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Declarations

Conflict of interest The authors report no conflicts of interest in this work.

Ethical approval All procedures used in this study adhere to the tenets of the Declaration of Helsinki. Approval was granted by the Ethics Committee of IRCCS San Raffaele Scientific Institute, Milan, Italy (N. 24/INT/2017).

Human and animal rights No animals were used in this study.

Informed consent to participate Written informed consent was obtained from all participants.

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