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ORIGINAL RESEARCH

Association Between Residual Kidney Function and Frailty in End-Stage Renal Disease Patients Undergoing Hemodialysis: A Cross-Sectional Study

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Background: Residual kidney function (RKF) plays a crucial role in maintaining biochemical balance in hemodialysis patients. Frailty, commonly observed in end-stage renal disease (ESRD) patients, is associated with metabolic derangements, inflammation, and fluid overload. However, the relationship between RKF and frailty in this population remains unclear.

Purpose: This study aimed to investigate the association between RKF and frailty in ESRD patients undergoing hemodialysis. Secondary objectives included assessing the prevalence of frailty and sarcopenia, and identifying clinical correlates.

Patients and Methods: A cross-sectional study was conducted involving 110 adult ESRD patients undergoing maintenance hemodialysis for ≥6 months at an urban teaching hospital in Bangkok, Thailand between October 2023 and February 2024. RKF was assessed by 24-hour urine volume, with <100 mL defined as absent RKF. Frailty was evaluated using the Thai version of the FRAIL scale, and sarcopenia was diagnosed based on the 2019 Asian Working Group for Sarcopenia (AWGS) criteria. Demographic, clinical, and laboratory data were analyzed using chi-squared tests, logistic regression, and multivariable models.

Results: Among 110 participants, 78 (70.91%) had no RKF. Frailty prevalence was 13.64%, and sarcopenia prevalence was 65.45%. Frailty was associated with a history of cerebrovascular accident [adjusted odds ratio (OR) 10.303; P = 0.036] and lower total iron-binding capacity (TIBC) (adjusted OR 0.972; P = 0.047). Sarcopenia was linked to advanced age (adjusted OR 1.054; P = 0.020) and lower Kt/V values (adjusted OR 0.417; P = 0.002). RKF was not significantly associated with frailty.

Conclusion: While RKF was not directly associated with frailty, this study highlights other significant factors, such as cerebrovascular accidents and low TIBC, contributing to frailty and advanced age associated with sarcopenia. These findings emphasize the need for comprehensive frailty screening and tailored interventions to improve outcomes in ESRD patients.

Keywords: residual kidney function, frailty, sarcopenia, hemodialysis

Introduction

Currently, renal replacement therapy (RRT) extends life and alleviates symptoms in patients with end-stage renal disease (ESRD) by removing metabolic waste products and excess fluid from the blood. Despite advancements in dialysis technology and management strategies, hemodialysis patients continue to experience high rates of morbidity and mortality. ESRD patients often have an average life expectancy of only about 30% compared to the general population of the same age.[1] This reduced life expectancy is influenced by multiple factors, often overlooked or inadequately addressed, including frailty[2] and sarcopenia.[3]

Frailty, a syndrome characterized by decreased physiological reserve and increased vulnerability to stressors,[4] is increasingly prevalent in ESRD patients, with rates two to four times higher than in individuals with normal kidney function.[5] In Thailand, frailty affects 22.1% of the general aged population, while in ESRD patients, the prevalence

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ranges from 14% to 73%, significantly impacting health by increasing mortality rates, hospitalization rates, confusion, falls, and the likelihood of becoming bedridden.[6] Anemia, inflammation, reduced food intake, acid-base abnormalities, and hormone imbalances all contribute to frailty and protein-energy wasting in ESRD patients.[7]

Sarcopenia, characterized by decreased muscle mass, muscle strength, and physical performance, leads to reduced physical ability, decreased quality of life, increased falls, morbidity, and mortality in older adults.[8] The prevalence of sarcopenia in ESRD patients can be as high as 28.5%.[9] Sarcopenia in these patients is associated with higher rates of physical disability and nearly doubles the mortality risk compared to those without sarcopenia. The key mechanism involves both increased muscle breakdown and decreased muscle synthesis, associated with heightened inflammation in ESRD patients.[10]

Residual kidney function (RKF), defined as a urine output of at least 100 mL per day in patients undergoing RRT, plays a crucial role in maintaining adequate blood filtration, fluid balance, acid-base regulation, and erythropoietin production.[11]

The relationship between RKF and frailty in hemodialysis patients remains poorly understood. To address this gap in knowledge, this study aims to investigate the association between RKF and frailty in hemodialysis patients. Recognizing the role of RKF in frailty could prompt healthcare providers to refer ESRD patients without RKF for frailty assessment. Early detection of frailty would enable tailored prevention and treatment strategies, such as optimizing dialysis, managing anemia, reviewing, and minimizing unnecessary medications, preventing falls, recommending appropriate exercise, and addressing nutritional deficiencies, depression, and cognitive impairment.

The primary objective of this study was to investigate the association between residual kidney function (RKF) and frailty in patients with end-stage renal disease (ESRD) undergoing hemodialysis. Secondary objectives included determining the prevalence of frailty and sarcopenia in this population, as well as exploring the association between frailty, sarcopenia, and RKF with baseline demographic and clinical characteristics.

Materials and Methods

Study Design

This was a cross-sectional study conducted from October 2023 to February 2024 on ESRD patients attending the Division of Nephrology and Renal Replacement Therapy, at one urban teaching hospital in Bangkok, Thailand. Participants included adults aged over 18 years who had been undergoing regular hemodialysis for more than six months. Exclusion criteria comprised patients with neurological deficits, recent cerebrovascular accidents within the previous 6 months, severe cognitive impairment or dementia, secondary hypertension, cancer, overt cardiovascular disease, obstructive pulmonary disease, other severe illnesses, wheelchair dependency, a life expectancy of less than six months, or an inability to comply with medical treatment. The sample size was calculated using statistical methods, setting α at 0.05, a power of 80%, and incorporating risk differences in frailty occurrence between patients with and without residual kidney function (RKF). Based on these parameters, the required sample size was determined to be 89 participants, adjusted to 107 to account for a 20% loss to follow-up.

This study was conducted following the approval of the Clinical Research Ethics Committee of the Faculty of Medicine Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand (Certificate of Approval No. 044/2566). The Institutional Review Board is in full compliance with international guidelines for human research protection, including the Declaration of Helsinki, The Belmont Report, CIOMS Guideline, and the International Conference on Harmonization in Good Clinical Practice (ICH-GCP).

Data Collection

Written informed consent was obtained from all participants after providing detailed information about the study objectives, procedures, and potential risks. Confidentiality and privacy of the participants' data were ensured, adhering to the principles of the Declaration of Helsinki.

Participants were recruited through the hospital's electronic medical record system. Demographic data, including age, gender, and body mass index (BMI), and clinical information, such as underlying medical conditions, current

medications, original kidney disease, dialysis duration, vascular access type, dialysis frequency, adequacy of dialysis, urea reduction ratio (URR), normalized protein catabolic rate (nPCR), history of intradialytic hypotension, oral nutrition supplementation (ONS), and dialysis ultrafiltration volumes, were extracted. Dialysis adequacy was assessed using Kt/V, calculated as the product of dialyzer urea clearance (K) and dialysis time (t), divided by the volume of distribution of urea (V).

Laboratory and Residual Kidney Function Measurement

Participants received instructions and containers for collecting a 24-hour urine sample prior to a dialysis day. The collected urine samples were brought to the hospital, where blood samples were also drawn. The following laboratory parameters were assessed:

Pre-Dialysis Blood Parameters

Hemoglobin, potassium, alkaline phosphatase (ALP), calcium, phosphorus, parathyroid hormone, albumin, vitamin D, blood urea nitrogen (BUN), iron, total iron-binding capacity (TIBC), and ferritin.

Residual Kidney Function (RKF)

Calculated using the residual renal urea clearance (KRU) formula:[12]

$$KRU = \frac{UUN(mg/dl) \times \ urine\,flow\,rate(mg/dl)}{Time - averaged\,concentration\,SUN(mg/dl)}$$

Where:

KRU: Residual renal urea clearance,

UUN: Urine urea nitrogen concentration from the 24-hour urine sample.

Urine Flow Rate: Calculated as:

$$Urine\,flow\,rate = \frac{Total\,Urine\,Volume\,(ml)}{Collection\ \ Duration\,(min)}$$

TAC of SUN: Time-averaged concentration of serum urea nitrogen, derived as:[13]

$$Time - averaged\,concentration\,(TAC)\,of\,serum\,urea\,nitrogen\,(SUN) = 0.9\,x\,predialysis\,SUN\,(mg/dl)$$

Within two weeks of submitting the 24-hour urine sample, participants underwent assessments for frailty, nutritional status, and sarcopenia, conducted by physiotherapists at the Department of Rehabilitation Medicine, Faculty of Physical Therapy, Vajira Hospital.

Frailty Assessment

Frailty was assessed using the Thai version of the FRAIL Scale,[14] a validated translation of the Simple Frailty Questionnaire[15] for use in Thailand. This tool comprises five domains: Fatigue, Resistance, Ambulation, Illnesses, and Loss of Weight. Each domain is evaluated through self-reported responses, scored as either 0 or 1 point based on the presence of specific criteria. The total score ranges from 0 to 5, with higher scores reflecting a greater degree of frailty. A cutoff score of 3 or higher indicates frailty.

Sarcopenia Assessment

Sarcopenia was diagnosed following the Asian Working Group on Sarcopenia (AWGS) 2019 recommendations. Diagnosing sarcopenia involves three main components: reduced muscle mass, decreased muscle strength, and impaired physical performance. Additionally, this condition can be categorized into three levels: pre-sarcopenia, sarcopenia, and severe sarcopenia, as shown in Table 1. Muscle strength was evaluated with the Handgrip Strength Test using a digital dynamometer, with normal values defined as <28 kg for males and <18 kg for females. Physical performance was measured using the Five Time Chair Stand Test, with an abnormal score ≥12 seconds. Muscle mass was determined using the Fresenius Bioelectrical Impedance Analysis (BIA) device, and the appendicular skeletal muscle mass index (ASMI) was calculated as follows.[16] Low muscle mass was defined as <7 kg/m² for males and <5.7 kg/m² for females.

Table 1 The Diagnostic Criteria for Sarcopenia According to the Recommendations of the European Working Group on Sarcopenia in Older People (EWGSOP) in 2010[17] and the Asian Working Group of Sarcopenia (AWGS) in 2019[8]

Diagnosis	Physical Performance		Muscle Strength		Muscle Mass
Pre-sarcopenia	-	-	-	-	Decrease
Sarcopenia	Decrease	Or	Decrease	And	Decrease
Severe sarcopenia	Decrease	And	Decrease	And	Decrease

$$ASMI\left(\mathrm{kg/m^2}\right) = \frac{ASM(kg)}{Height^2(\mathrm{m^2})}$$

Where: ASM: Appendicular skeletal muscle mass, calculated as:

$$ASM(kg) = -1.838 + 0.395 \times Total\,body\,water\,(L) + 0.105 \times Body\,weight\,(kg) + 1.231 \times Male\,sex(1),\ Female\,sex(0) - 0.026 \times age\,(years)$$

Nutritional Status Assessment

Nutritional status was assessed using the Thai version of the Malnutrition Inflammation Score (MIS), based on the Clinical Practice Recommendation for Nutritional Management in Adult Kidney Patients 2018 by the Society of Parenteral and Enteral Nutrition of Thailand and the Nephrology Society of Thailand.[18] MIS scores were categorized as follows: 1–2: Well-nourished, 3–5: Mild to moderate malnutrition, and ≥6: Severe malnutrition.

Statistical Analysis

The general data analysis of the sample group involved analyzing and presenting the data in two parts based on the data types. These included qualitative data presented in reports through frequency distribution and percentages, categorized by the RKF into two groups: one with RKF and the other without. The comparison of the groups was performed using either the Chi-squared test or Fisher's exact test, depending on the appropriateness of the data.

For quantitative data presented in reports, the mean, standard deviation, median, and interquartile range were used. The data were classified by the RKF into two groups: one with RKF and the other without. The comparison between groups was done using either the Student's *t*-test or Mann–Whitney *U*-test, depending on the appropriateness of the data.

The prevalence of frailty and sarcopenia conditions was reported through frequency distribution and percentages, along with a 95% confidence interval. The comparison of the differences between the group with RKF and the group without was conducted using either the Chi-squared test or Fisher's exact test, depending on the appropriateness of the data.

The relationship between RKF and factors associated with frailty and sarcopenia in ESRD patients undergoing hemodialysis was analyzed using a multivariable logistic regression approach. Odds Ratios (OR) and 95% confidence intervals (95% CI) were reported to evaluate the strength and direction of associations between variables. Variables with a p-value < 0.2 from the univariable logistic regression analysis were considered for inclusion in the multivariable model. The final model was developed using a stepwise selection method, with criteria for variable entry set at $p < 0.10$ and removal at $p < 0.05$.

All data analyses were performed using the computer program SPSS version 24.0, with the statistical significance level set at 0.05.

Results

Baseline Characteristics

A total of 138 patients were initially enrolled in the study after meeting the inclusion criteria. However, 28 patients were unable to provide a 24-hour urine sample prior to a dialysis day and were lost to follow-up for assessments of frailty,

nutritional status, and sarcopenia, which were conducted by physiotherapists. Consequently, the final study population consisted of 110 patients. Among them, 78 patients (70.91%) were classified as having no RKF, while 32 patients (29.09%) had RKF (Figure 1).

Baseline demographic analysis revealed that patients without RKF were younger, with a mean age of 58.58 ± 11.76 years, compared to 64.65 ± 11.28 years in those with RKF (P = 0.014). Additionally, the dialysis duration was significantly longer in the group without RKF (56 months vs 30 months; P = 0.002). While there were no significant differences between the two groups in terms of gender, comorbidities, causes of chronic kidney disease, or laboratory parameters, beta-blocker use was markedly more prevalent among patients without RKF compared to those with RKF (75.95% vs 37.50%; P = 0.001) (Table 2).

In the frailty analysis, frail participants were predominantly female. The Charlson Comorbidity Index was significantly higher in the frail group compared to the non-frail group [median in frail group=6 (IQR 3,7) vs median in non-frail group =5 (IQR 3,6); P = 0.041]. Additionally, the frail group had a lower mean ultrafiltration (UF) rate (2.3 L vs 2.77 L; P = 0.032), lower hemoglobin levels (9.95 g/dL vs 10.93 g/dL; P = 0.027), and lower blood urea nitrogen (BUN) levels (36.93 mg/dL vs 47.29 mg/dL; P = 0.036) (Table 2).

In the sarcopenia analysis, participants with sarcopenia were older, with a mean age of 62 years compared to 57 years in those without sarcopenia (P = 0.028). The sarcopenia group also had a significantly lower BMI (21.49 kg/m² vs 27.09 kg/m²; P = 0.001). The prevalence of diabetes mellitus (DM) and dyslipidemia (DLP) was lower among participants with sarcopenia compared to those without (DM: 41.67% vs 63.16%, P = 0.032; DLP: 33.33% vs 60.53%, P = 0.006). Measures of dialysis adequacy, including Kt/V and the urea reduction ratio (URR), were higher in the sarcopenia group (Kt/V: 1.84 vs 1.54, P = 0.002; URR: 77.23 vs 73.37, P = 0.001). In contrast, the ultrafiltration (UF) rate was significantly lower in the sarcopenia group (2.59 L vs 2.93 L; P = 0.029). The use of calcium channel blockers (CCBs) was less frequent in the sarcopenia group (59.72% vs 84.21%; P = 0.010). Laboratory analysis revealed that hemoglobin levels were significantly higher in the sarcopenia group (11.03 g/dL vs 10.35 g/dL; P = 0.029), while blood urea nitrogen (BUN) levels were lower (43.25 mg/dL vs 50.86 mg/dL; P = 0.032) (Table 2).

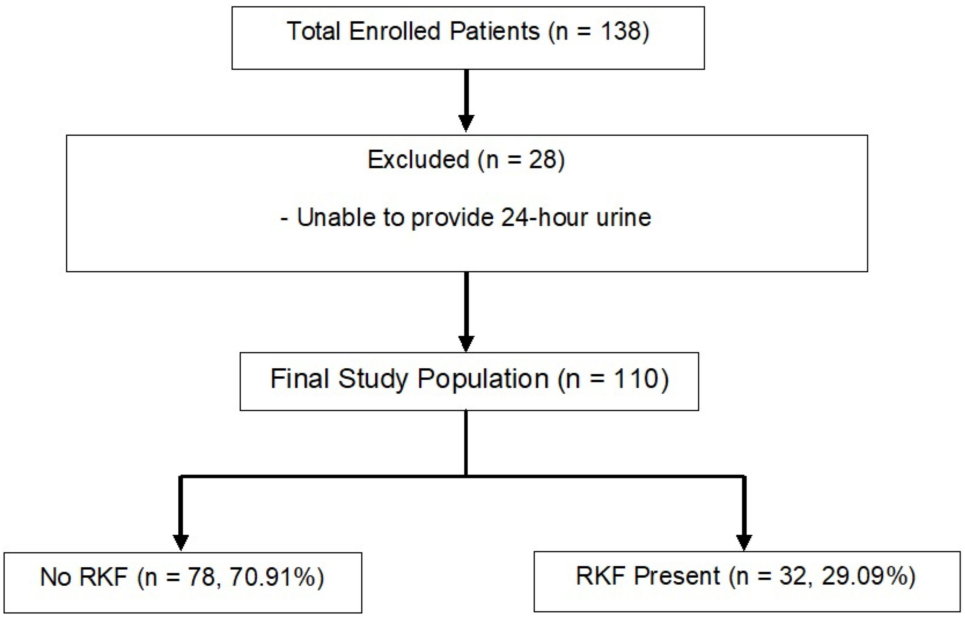

Figure 1 Flowchart of patient enrollment and classification based on the presence of RKF.

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Table 2 Demographic, Clinical and Laboratory Data According to Residual Renal Function (RKF), Frailty, and Sarcopenia

	Total	RKF <100	RKF ≥ 100	P	No Frail	Frailty	P	No Sarcopenia	Sarcopenia	P
	n=110	n=78	n=32		n=95	n=15		n=38	n=72	
Age: Mean (SD)	60.35(11.89)	58.58(11.76)	64.65(11.28)	0.014*	59.51(11.28)	65.73(14.54)	0.059	56.94(10.51)	62.15(12.25)	0.028*
Gender										
Male: (N%)	64(58.18)	45(57.69)	19(59.38)	0.871	59(62.10)	5(33.33)	0.035*	23(60.53)	41(56.94)	0.717
BMI (kg/m2): Mean (SD)	23.42(4.27)	23.51(3.94)	23.22(5.05)	0.750	23.55(4.31)	22.59(4.08)	0.420	27.09(4.29)	21.49(2.73)	0.001*
Comorbid: N%										
HT	99(90.00)	70(89.74)	29(90.62)	0.889	85(89.47)	14(93.33)	0.538	37(97.37)	62(86.11)	0.093
DM	54(49.09)	36(46.15)	18(56.25)	0.336	47(49.47)	7(46.66)	0.840	24(63.16)	30(41.67)	0.032*
DLP	47(42.73)	32(41.03)	15(46.88)	0.573	42(44.21)	5(33.33)	0.429	23(60.53)	24(33.33)	0.006*
CAD	11(10.00)	9(11.54)	2(6.25)	0.401	8(8.42)	3(20)	0.172	1(2.63)	10(13.89)	0.093
PAD	1(0.91)	1(1.28)	0	0.520	1(1.05)	0	0.864	0	1(1.39)	0.999
CHF	3(2.73)	2(2.56)	1(3.12)	0.870	2(2.10)	1(6.66)	0.359	1(2.63)	2(2.78)	0.999
CVA	9(8.18)	7(8.97)	2(6.25)	0.636	6(6.31)	3(20)	0.104	3(7.89)	6(8.33)	0.999
Cancer	10(9.09)	8(10.26)	2(6.25)	0.507	9(9.47)	1(6.66)	0.591	4(10.53)	6(8.33)	0.735
Cirrhosis	2(1.82)	2(2.56)	0	0.361	2(2.10)	0	0.745	1(2.63)	1(1.39)	0.999
CNT diseases	2(1.82)	2(2.56)	0	0.361	2(2.10)	0	0.745	0	2(2.78)	0.544
Charlson comorbidity index: Median (p25, p75)	5(3,6)	4.5(3,6)	5(4,6)	0.050	5(3,6)	6(3,7)	0.041	5(4,6)	5(3,6)	0.931
Original kidney disease: N%										
HT	3(2.73)	2(2.56)	1(3.12)	0.870	3(3.15)	0	0.641	2(5.26)	1(1.39)	0.274
DN	3(2.73)	2(2.56)	1(3.12)	0.870	3(3.15)	0	0.641	2(5.26)	1(1.39)	0.274
PIGN	1(0.91)	1(1.28)	0	0.520	1(1.05)	0	0.864	1(2.63)	0	0.345
LN	1(0.91)	1(1.28)	0	0.520	1(1.05)	0	0.864	0	1(1.39)	0.999
CGN	2(1.82)	2(2.56)	0	0.361	2(2.10)	0	0.745	0	2(2.78)	0.544
IgAN	5(4.55)	4(5.13)	1(3.12)	0.647	5(5.26)	0	0.473	3(7.89)	2(2.78)	0.338
Amyloidosis	1(0.91)	1(1.28)	0	0.520	1(1.05)	0	0.864	0	1(1.39)	0.999
FSGS	5(4.55)	3(3.85)	2(6.25)	0.583	5(5.26)	0	0.473	1(2.63)	4(5.56)	0.657
ADPKD	3(2.73)	3(3.85)	0	0.261	3(3.15)	0	0.641	0	3(4.17)	0.550
Unknown	88(80.00)	61(78.21)	27(84.38)	0.462	73(76.84)	15(100)	0.027	29(76.32)	59(81.94)	0.617
Dialysis										
Dialysis vintage (month): Median (p25, p75)	43(23,84)	56(26,109)	30.5(17,46.5)	0.002*	43(22,84)	46(26,84)	0.861	41(20,72)	45.5(24,87.5)	0.380
Vascular access: N%										
AVF	94(85.45)	67(85.90)	27(84.38)	0.250	80(84.21)	14(93.33)	0.497	34(89.47)	60(83.33)	0.482
AVBG	8(7.27)	4(5.13)	4(12.50)		8(8.42)	0		3(7.89)	5(6.94)	
CVC	8(7.27)	7(8.97)	1(3.12)		7(7.36)	1(6.66)		1(2.63)	7(9.72)	

HD session (session /week) N%										
2	9(8.18)	4(5.13)	5(15.62)	0.068	6(6.31)	3(20)	0.104	2(5.26)	7(9.72)	0.716
3	101(91.82)	74(94.87)	27(84.38)	0.068	89(93.68)	12(80)		36(94.74)	65(90.28)	
KT/V: mean (SD)	1.73(0.51)	1.78(0.53)	1.61(0.44)	0.104	1.73(0.53)	1.80(0.31)	0.605	1.54(0.34)	1.84(0.55)	0.002*
IDH: N%	15(13.64)	11(14.10)	4(12.50)	0.824	13(13.68)	2(13.33)	0.666	7(18.42)	8(11.11)	0.382
nPCR (g/kg/d): Median (p25, p75)	1.14 (0.91,1.42)	1.20 (0.91,1.43)	0.64 (0.93,1.40)	0.666	1.14 (0.94,1.45)	1.02 (0.80,1.30)	0.180	1.25 (0.94,1.42)	1.13 (0.91,1.42)	0.619
URR (%): median (p25, p75)	76.04(71.01,80.20)	76.29(71.01,80.24)	74.88(71.10,78.46)	0.366	75.68 (71,79.49)	78.87 (73.33,81.58)	0.250	73.37 (64,76.5)	77.23 (72.15, 81.74)	0.001*
UF (L): mean (SD)	2.71(0.80)	2.79(0.74)	2.52(0.93)	0.117	2.77(0.76)	2.30(0.92)	0.032*	2.93(0.77)	2.59(0.79)	0.029*
Drug: N%										
Furosemide	15(13.64)	8(10.26)	7(21.88)	0.107	13(13.68)	2(13.33)	0.666	7(18.42)	8(11.11)	0.382
ACEI/ARB	26(23.64)	22(28.21)	4(12.50)	0.078	25(26.31)	1(6.66)	0.083	12(31.58)	14(19.44)	0.165
Beta blocker	71(64.55)	59(75.64)	12(37.50)	0.001*	61(64.21)	10(66.66)	0.853	28(73.68)	43(59.72)	0.146
CCB	75(68.18)	54(69.23)	21(65.62)	0.712	63(66.31)	12(80)	0.228	32(84.21)	43(59.72)	0.010*
Laboratory										
Hb (g/dl): mean (SD)	10.80(1.60)	10.92(1.54)	10.50(1.73)	0.211	10.93(1.62)	9.95(1.19)	0.027*	10.35(1.72)	11.03(1.49)	0.032*
K (mmol/L): mean (SD)	4.44(0.57)	4.48(0.57)	4.34(0.58)	0.214	4.46(0.59)	4.28(0.37)	0.250	4.57(0.57)	4.37(0.56)	0.089
ALP (U/L): median (p25, p75)	98(67,127)	102(67,145)	73.5(61.5,94)	0.138	98(67,127)	125(55,195)	0.952	77(60,112)	101.5(68,157)	0.143
Ca (mg/dl): mean (SD)	9.12(0.83)	9.08(0.83)	9.20(0.83)	0.498	9.07(0.83)	9.44(0.79)	0.104	9.25(0.70)	9.05(0.89)	0.214
PO4 (mg/dl): median (p25, p75)	4.4(3.4. 5.5)	4.4(3.3,5.6)	4.45(3.5,5.4)	0.774	4.5(3.5,5.5)	4.2(2.8,5.4)	0.398	4.7(3.4,5.5)	4.4(3.4,5.5)	0.722
PTH (pg/mL): median (p25, p75)	290(100, 539)	313(145,611.5)	226(84.15,419)	0.229	306(96,580)	231(104,444)	0.508	311(166,502)	253(82.3, 684)	0.589
Albumin (g/dl): median (p25, p75)	4.2(3.9,4.4)	4.2(3.9,4.4)	4.15(4,4.4)	0.886	4.2(4,4.4)	4(3.8,4.2)	0.060	4.2(4,4.5)	4.1(3.9,4.4)	0.277
Vitamin D(ng/mL): median (p25, p75)	26(19.15, 39.3)	26(18.6,39)	28.65(20.5,53.4)	0.317	26.05(19.75,39.3)	26.3(16.6,38.7)	0.759	27.8(18.6,38.4)	26(19.5,42)	0.852
BUN (mg/dl): mean (SD)	45.88(17.83)	45.01(18.90)	45.56(15.16)	0.904	47.29(17.85)	36.93(15.33)	0.036*	50.86(22.31)	43.25(14.43)	0.032*
Iron (mcg/dl): median (p25, p75)	53(42,77)	53(41,72)	56.5(48,78)	0.214	56(42,78)	52(39,65)	0.278	53(44,64)	59.5(42,78.5)	0.567
TIBC (mcg/dl): median (p25, p75)	204.5(184, 229)	203(183,226)	213(190.5,245)	0.232	206(186,238)	186(171,215)	0.050	204(184,239)	204.5(184.5,226)	0.897
Ferritin (mcg/mL): median (p25, p75)	363(172.5,635.5)	358(187.5,568)	426.5(164.5,756)	0.614	356(171,571)	565(247,782)	0.229	399(257,565)	361(166,723)	0.673

Notes: Statistically significant values (P < 0.05) are marked with *.

Abbreviations: ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin II receptor blocker; ADPKD, autosomal dominant polycystic kidney disease; ALP, alkaline phosphatase; AVBG, arteriovenous bridge graft; AVF, arteriovenous fistula; BMI, body mass index (the weight in kg divided by height in m^2); BUN, blood urea nitrogen; Ca, calcium; CAD, coronary artery disease; CCB, calcium channel blocker; CVC, central venous catheter; CGN, chronic glomerulonephritis; CHF, chronic heart failure; CNT, connective tissue; CVA, cerebral vascular accident; DM, diabetes mellitus; DLP, dyslipidemia; DN, diabetic nephropathy; FSGS, focal segmental glomerulosclerosis; HD, hemodialysis; HT, hypertension; IDH, intradialytic hypotension; IgAN, IgA nephropathy; K, potassium; LN, lupus nephritis; nPCR, normalized protein catabolic rate; PAD, peripheral artery disease; PIGN, post-infectious glomerulonephritis; PO4, phosphorus; PTH, parathyroid hormone; TIBC, total iron-binding capacity; UF, ultrafiltration; URR, urea reduction ratio.

Table 3 Frailty According to Residual Renal Function (RKF) Status

	No Frailty (N=95)	Frailty (n=15)	P-value
No RKF (N=32)	25(26.32%)	7(46.67%)	0.130
RKF (N=78)	70(73.68%)	8(53.33%)	

Primary Outcomes

The comparison of Frailty according to RKF status between the two groups is summarized in Table 3. Frailty rates did not differ significantly between groups with and without RKF (21.88% vs 10.26%; P > 0.05). Multivariate logistic regression found no association between RKF and frailty (Table 4).

Secondary Outcomes

Frailty classifications included robust (37 patients, 33.64%), pre-frailty (58 patients, 52.73%), and frailty (15 patients, 13.64%) (Figure 2).

Sarcopenia was classified into three categories: no sarcopenia (38 patients, 34.55%), sarcopenia (35 patients, 31.82%), and severe sarcopenia (37 patients, 33.64%). The overall prevalence of sarcopenia, including both sarcopenia and severe sarcopenia, was 72 patients (65.45%) (Figure 3).

Table 4 Univariate and Multivariate Analysis of Factors Associated with Frailty

Variable	Univariate			Multivariable		
	OR	95% CI	P-value	aOR	95% CI	P-value
Age	1.046	0.997,1.099	0.064	1.021	0.928,1.124	0.656
Male	0.305	0.096,0.964	0.043*	0.292	0.060,1.422	0.128
HT	1.647	0.195,13.887	0.646			
Charlson comorbidity index	1.478	1.035, 2.110	0.031	1.077	0.546,2.123	0.830
DM	0.894	0.300,2.661	0.840			
CAD	2.719	0.633,11.680	0.179	1.989	0.193,20.471	0.563
CHF	3.321	0.282,39.085	0.340			
CVA	3.708	0.818, 16.80	0.089	10.303	1.168, 90.887	0.036*
HD duration	0.998	0.987, 1.010	0.750			
Hemoglobin	0.678	0.476,0.966	0.031*	0.616	0.369,1.027	0.063
Calcium	1.745	0.887,3.435	0.107	2.812	0.988,7.997	0.052
Phosphorus	1.119	0.996,1.258	0.059	1.129	0.924,1.379	0.234
PTH	0.999	0.998,1.001	0.432			
Albumin	0.318	0.085,1.197	0.090	0.555	0.050,6.086	0.631
KT/V	1.308	0.478,3.576	0.601			
URR	1.032	0.965,1.104	0.360			

(*Continued*)

Table 4 (Continued).

Variable	Univariate			Multivariable		
	OR	95% CI	P-value	aOR	95% CI	P-value
Vitamin D	0.999	0.965,1.035	0.992			
nPCR	0.328	0.059,1.820	0.202			
MIS Score	1.152	0.972,1.364	0.103	0.978	0.739,1.295	0.879
Sarcopenia	0.553	0.184,1.665	0.293			
RKF (< 100 mL)	0.408	0.134,1.241	0.114	0.401	0.080,1.999	0.265
TIBC	0.985	0.968, 1.001	0.074	0.972	0.946,0.999	0.047*
Ferritin	1.000	0.999,1.001	0.514			

Notes: Statistically significant values (P < 0.05) are marked with*. Multivariable model adjusted for: age, gender, Charlson comorbidity index, CAD, CVA, hemoglobin, calcium, phosphorus, albumin, MIS score, residual kidney function (RKF), and total iron-binding capacity (TIBC). Covariates were selected based on bivariate logistic regression with a P-value < 0.20. The significance level for variable entry was set at 0.05, and for variable removal at 0.10. The Hosmer-Lemeshow goodness-of-fit test yielded a p-value of 0.996, indicating good model fit. Pseudo R^2 = 0.3574, suggesting that approximately 35.74% of the variance in the dependent variable is explained by the independent variables included in the model.
Abbreviations: ASMI, appendicular skeletal muscle mass index; BMI, body mass index (the weight in kg divided by height in m^2); CAD, coronary artery disease; CHF, chronic heart failure; CVA, cerebral vascular accident; DM, diabetes mellitus; HD, hemodialysis; HT, hypertension; MIS score, Malnutrition-Inflammation Score; nPCR, normalized protein catabolic rate; PTH, parathyroid; RKF, residual kidney function; TIBC, total iron-binding capacity; URR, urea reduction ratio.

Factors associated with frailty included a history of cerebrovascular accident (CVA) (adjusted OR 10.303, 95% CI 1.168–90.887; P=0.036) and TIBC levels (adjusted OR 0.972, 95% CI 0.946–0.999; P=0.047) (Table 4). Factors associated with the absence of RKF included age (adjusted OR 0.93, 95% CI 0.888–0.974; P=0.002), longer dialysis duration (adjusted OR 1.020, 95% CI 1.004–1.036; P=0.009), and higher Malnutrition Inflammation Score (MIS) (adjusted OR 1.203, 95% CI 1.007–1.437; P=0.041) (Table 5). Sarcopenia was associated with age (adjusted OR 1.054, 95% CI 1.008–1.102; P=0.02) and Kt/V values (adjusted OR 0.417, 95% CI 0.238–0.728; P=0.002) (Table 6).

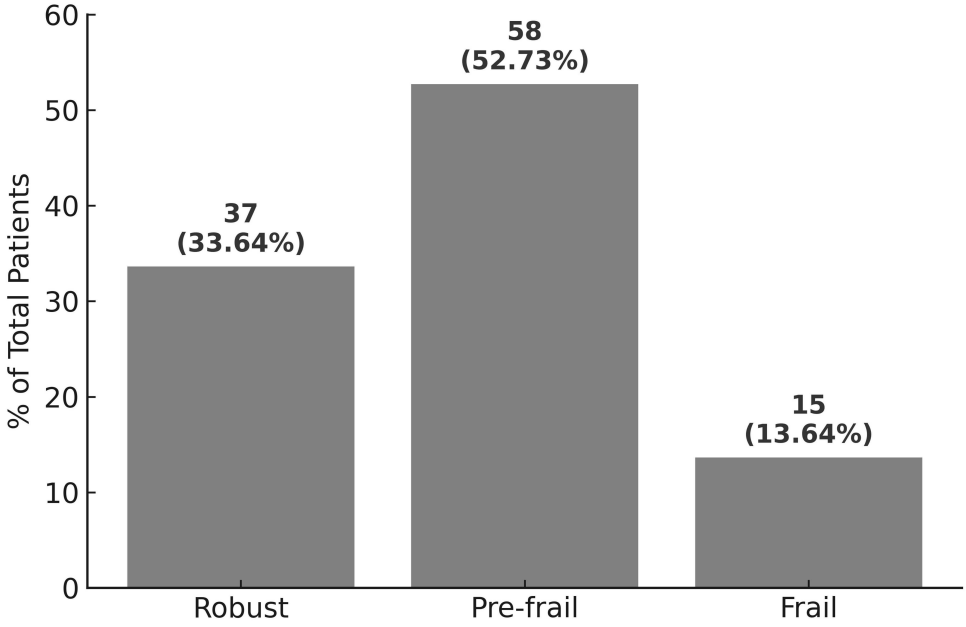

Figure 2 Rate of frailty.

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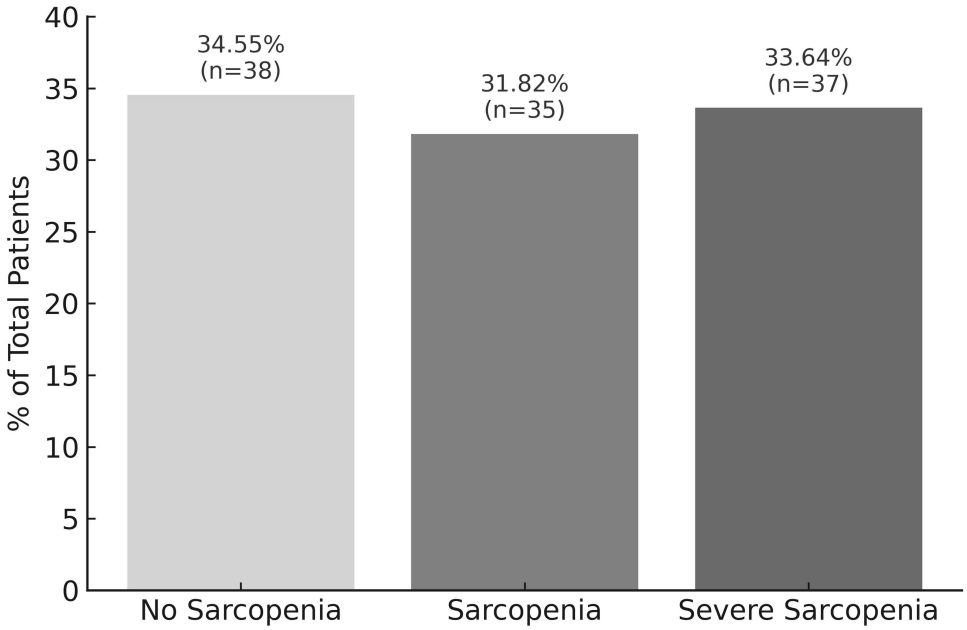

Figure 3 Rate of sarcopenia.

Discussion

Previous studies have demonstrated an association between kidney function and frailty in patients with chronic kidney disease (CKD). Lower estimated glomerular filtration rate (eGFR) levels have been linked to a higher prevalence of frailty, while an increase of 5 eGFR units has been inversely associated with frailty.[19] As CKD progresses to end-stage renal disease (ESRD) requiring hemodialysis, most patients retain some residual kidney function (RKF), which is essential for maintaining fluid and metabolic balance and positively contributing to overall health.

Frailty and sarcopenia prevalence were examined in this study. The prevalence of frailty was 13.64% (15 patients), consistent with global data showing frailty rates among ESRD patients on dialysis range from 14% to 73%.[6] Conversely, sarcopenia was observed in 31.82% (35 patients), higher than the reported prevalence of 28.5% in ESRD patients.[9]

Our study provides insights into the relationship between RKF and frailty in ESRD patients undergoing hemodialysis. However, we did not find a significant correlation between RKF and frailty in this population. This contrasts with CKD patients, where kidney function appears to play a central role in the development of frailty. One possible explanation is the multifactorial nature of frailty in ESRD, which involves factors beyond kidney function alone. For instance, a history of cerebrovascular accident (CVA) emerged as a significant predictor of frailty, increasing the risk by up to 10-fold. This aligns with existing data linking CVA and frailty, often referred to as "cognitive frailty." Features of cognitive frailty, such as leukoaraiosis, atrophy, and old vascular lesions or infarcts, are associated with poorer functional and cognitive outcomes post-stroke.[20] These findings underscore the need for further research to elucidate the mechanisms linking CVA and frailty in ESRD patients.

Our study also identified an intriguing association between frailty and lower total iron-binding capacity (TIBC). Frail patients in this study had a median TIBC of 186 μg/dL, which is significantly lower than the normal range of 250–450 μg/dL. This finding is consistent with previous research showing that low TIBC levels are linked to slower walking speeds, a key component of frailty syndrome.[21] The role of TIBC in frailty development may be related to its influence on nutritional status and iron metabolism. These results underscore potential intervention points, such as optimizing nutritional and hematologic parameters, to reduce frailty risk in patients with end-stage renal disease (ESRD).

Factors contributing to RKF loss include younger age, longer dialysis duration, and higher Malnutrition Inflammation Score (MIS). Younger patients often experience acute, severe kidney failure necessitating dialysis initiation, which may lead to RKF loss over time. Prolonged dialysis is associated with a decline in RKF, with an estimated decrease of 0.18–0.33 mL/min/month during the first year, followed by a gradual decline.[22] Additionally, higher MIS scores,

Table 5 Univariate and Multivariate Analysis of Factors Associated with Absence Residual Renal Function

Absence Residual Renal Function	Univariate			Multivariable		
Variable	**OR**	**95% CI**	**P-value**	**aOR**	**95% CI**	**P-value**
Age	0.955	0.921,0.992	0.017*	0.930	0.888,0.974	0.002*
Male	0.933	0.404,2.153	0.871			
HT	0.905	0.224,3.655	0.889			
DM	0.666	0.291,1.526	0.337			
CAD	1.956	0.385,9.297	0.408			
CHF	0.816	0.071,9.327	0.870			
CVA	1.478	0.290, 7.535	0.638			
HD Session	3.425	0.856,13.708	0.082	4.502	0.902,22.468	0.067
HD duration	1.020	1.007,1.033	0.003*	1.020	1.004,1.036	0.009*
Hemoglobin	1.181	0.911,1.531	0.210			
Calcium	0.840	0.510,1.385	0.495			
Phosphorus	0.993	0.900,1.098	0.903			
PTH	1.001	1.000,1.002	0.188			
Albumin	1.349	0.473,3.847	0.576			
KT/V	0.714	0.439,1.159	0.173			
URR	1.007	0.970,1.046	0.715			
nPCR	0.761	0.429,1.347	0.348			
MIS Score	1.173	1.014,1.358	0.032*	1.203	1.007,1.437	0.041*
Frailty	0.408	0.134,1.242	0.114			
Sarcopenia	0.574	0.243,1.358	0.206			
TIBC	1.001	0.998,1.003	0.668			
Ferritin	0.999	0.998,1.001	0.448			

Notes: Statistically significant values (P < 0.05) are marked with *. Multivariable model adjusted for: age, HD session, HD duration, PTH, KT/V, Frailty and MIS Score. Covariates were selected based on bivariate logistic regression with P-value < **0.20**. The significance level for variable entry was set at 0.05, and for variable removal at 0.10. The Hosmer-Lemeshow goodness-of-fit test yielded a p-value of 0.611, indicating good model fit. Pseudo R^2 = 0.2066, suggesting that approximately 20.66% of the variance in the dependent variable is explained by the independent variables included in the model.

Abbreviations: CAD, coronary artery disease; CHF, chronic heart failure; CVA, cerebral vascular accident; DM, diabetes mellitus; HD, hemodialysis; HT, hypertension; MIS score, Malnutrition-Inflammation Score; nPCR, normalized protein catabolic rate; PTH, parathyroid; TIBC, total iron-binding capacity; URR, urea reduction ratio.

indicative of malnutrition, are linked to the accumulation of waste products and metabolic abnormalities, further contributing to RKF loss.[23] Risk factors for sarcopenia include advanced age and low Kt/V, a measure of dialysis adequacy in hemodialysis patients. Insufficient Kt/V values are associated with the development of uremic sarcopenia, a specific type of sarcopenia caused by inadequate dialysis. Inadequate dialysis leads to metabolic acidosis, insulin resistance, systemic inflammation, and increased expression of angiotensin II and myostatin.[24] These factors activate the ATP-dependent ubiquitin-proteasome system, the primary pathway for skeletal muscle protein degradation. Additionally,

Table 6 Univariate and Multivariate Analysis of Factors Associated with Sarcopenia

Sarcopenia Group	Univariate			Multivariable		
Variable	**OR**	**95% CI**	**P-value**	**aOR**	**95% CI**	**P-value**
Age	1.039	1.003,1.076	0.031*	1.054	1.008,1.102	0.020*
Male	0.862	0.387,1.920	0.717			
HT	0.167	0.020,1.362	0.095	0.143	0.015,1.296	0.084
DM	0.416	0.185,0.935	0.034*	0.406	0.149,1.109	0.079
CAD	5.967	0.734,48.517	0.095			
CHF	1.057	0.092,12.047	0.964			
CVA	1.060	0.249,4.499	0.936			
HD duration	1.004	0.996,1.013	0.279			
Hemoglobin	1.316	1.018,1.701	0.036*			
Calcium	0.735	0.452,1.195	0.215			
Phosphorus	1.039	0.919,1.174	0.538			
PTH	1.001	0.999,1.001	0.388			
Albumin	0.510	0.173,1.502	0.222			
Vitamin D	1.003	0.978,1.029	0.797			
KT/V	0.387	0.232,0.645	0.001*	0.417	0.238,0.728	0.002*
URR	1.054	1.004,1.106	0.032*			
nPCR	1.080	0.600,1.943	0.795			
MIS Score	1.052	0.926,1.195	0.433			
RKF	0.811	0.336,1.955	0.642			
Frailty	0.553	0.184,1.665	0.293			

Notes: Statistically significant values ($P < 0.05$) are marked with *. Multivariable model adjusted for: age, hypertension (HT), diabetes mellitus (DM), Hemoglobin, Kt/V and URR. Covariates were selected based on bivariate logistic regression with P-value < 0.20. The significance level for variable entry was set at 0.05, and for variable removal at 0.10. The Hosmer-Lemeshow goodness-of-fit test yielded a p-value of 0.181, indicating good model fit. Pseudo $R^2 = 0.193$, suggesting that approximately 19.3% of the variance in the dependent variable is explained by the independent variables included in the model.

Abbreviations: CAD, coronary artery disease; CHF, chronic heart failure; CVA, cerebral vascular accident; DM, diabetes mellitus; HD, hemodialysis; HT, hypertension; KRU, residual renal urea clearance; MIS score, Malnutrition-Inflammation Score; nPCR, normalized protein catabolic rate; PTH, parathyroid; RKF, residual kidney function; URR, urea reduction ratio.

the retention of indoxyl sulfate, a uremic toxin, exacerbates mitochondrial dysfunction and promotes the overexpression of muscle atrophy-related genes, including atrogin-1 and myostatin, further driving muscle loss in uremic sarcopenia.[25]

This study has several strengths worth acknowledging, although these should be interpreted within the study's context and limitations. To our knowledge, it is among the first studies to explore the relationship between RKF and frailty in ESRD patients undergoing hemodialysis, with an adequate sample size to allow for meaningful analysis. Additionally, 24-hour urine samples were collected prior to dialysis sessions to minimize reliance on self-reported urine volumes, and frailty screening was conducted within two weeks of urine collection, alongside laboratory testing, to reduce confounding from acute illness. The study also assessed malnutrition using the MIS and sarcopenia using hand grip tests, the five-time

chair stand test, and bioelectrical impedance analysis (BIA), with trained physical therapists ensuring consistency in evaluations.

Nevertheless, this study has its limitations. The cross-sectional design restricts our ability to establish causality or determine temporal relationships between RKF and frailty. Prospective longitudinal studies are needed to better understand these associations. Additionally, the lack of a standardized frailty assessment tool for ESRD patients introduces variability, as different tools might yield different results. Potential unmeasured confounders, such as socioeconomic status, dietary habits, and physical activity, could also influence the outcomes. Lastly, self-reporting bias or misclassification in variables like the Thai version of the FRAIL Scale and MIS score may have affected the findings.

Conclusion

While there was no significant association between RKF and frailty in hemodialysis patients, our study did reveal that a history of CVA and low TIBC levels were significant contributing factors for frailty. These findings underscore the importance of comprehensive frailty screening and interventions targeting nutritional and hematologic parameters. Future longitudinal studies are needed to explore causal relationships and inform strategies for improving patient outcomes.

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Disclosure

The authors reported no conflicts of interest in this work.

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