Table 1. Potential causes of frailty in patients with CKD reported in the literature

Category	Type		Risk Difference (95% CI)	Patient CKD severity	Frailty Assessment method	Sample Size	Ref
Demographic profile	Advanced age	Age > 60 years	OR 4.0 (1.0-16.2)	stages 3-5	Modified Fried Phenotypes	61	[3] 2012 Mansur
		per year	OR 1.02 (1.01-1.03)	stages 5D	Modified Fried Phenotypes	2275	[4] 2007 JASN
			OR 1.03 (1.01-1.04)	stage 5D	Modified CHS scale	1658	[49]J Ren Nutr
	Female gender		OR 11.3 (2.3-55.6)	stages 3-5	Modified Fried Phenotypes	61	[3] 2012 Mansur
			OR 1.55 (1.27-1.88)	stage 5D	Modified Fried Phenotypes	2275	[4] 2007 JASN
			OR 11.6 (1.7-79.1)	Elderly with stage 5D (HD)	Multidimensional frailty score	46	[62] JKMS
	Male gender		OR 0.49 (0.39-0.62)	stage 5D (incident)	Modified Fried Phenotypes	1576	[46] JAMA-IM
	Non-white race		OR 1.9 (1.1-1.3)	stages 1-4	Modified CHS scale	336	[7] 2012 AJKD
	Unemployed status		OR 1.89 (1.36-2.62)	stage 5D	Modified CHS scale	1658	[49]J Ren Nutr
	Higher education level		OR 0.67 (0.49-0.91) for 7th-12th grade, 0.53 (0.35-0.82) for >12th grade				
Lifestyle	Smoking		RR 1.18 (1.04-1.34)	stage 5D (HD)	Fried Phenotypes	205	[1] 2017 SJKDT

Anthropometric parameters	BMI	OR 1.2 (1.0-1.4) per 5 kg/m^2	stages 1-4	Modified CHS scale	336	[7] 2012 AJKD
		OR 1.06 (1.02-1.1) per kg/m^2	stage 5D	Modified CHS scale	1658	[49] J Ren Nutr
		OR 0.58 (0.38-0.88) per kg/m^2	Elderly with stage 5D	Multidimensional frailty score	46	[62] JKMS
	Waist circumference (cm)	OR 3.84 (1.39-10.61; 3rd tertile)	stage 5D (HD)	Fried Phenotypes	151	[26] J Ren Nutr
CKD severity	Mild	OR 2.21 (1.49-3.28)	stages 1/2	Modified Fried Phenotypes	10256	[5] 2009 AJM
		OR 1.48 (1.00-2.19)	Cre > 1.3 mg/dL	CHS scale	5888	[6] 2004 AJKD
	Moderate	OR 2.48 (1.57-3.93)	stages 3a	Modified Fried Phenotypes	10256	[5] 2009 AJM
	Severe	OR 5.88 (3.40-10.16)	stages 3b-5			
		OR 2.8 (1.3-6.3)	stage 3b	Modified CHS scale	336	[7] 2012 AJKD
		OR 2.1 (1.0-4.7)	stage 4			
Biological						
Cardiovascular	Hypertension	RR 1.6 (1.26-2.04)	stage 5D (HD)	Fried Phenotypes	205	[1] 2017 SJKDT
	Peripheral vascular disease	RR 1.58 (1.34-1.8)	stage 5D (HD)	Fried Phenotypes	205	[1] 2017SJKDT
		OR 1.67 (1.16-2.41)	stage 5D (incident)	Modified Fried Phenotypes	1576	[46] JAMA-IM
	Left ventricular dysfunction	RR 1.18 (1.03-1.36)	stage 5D (HD)	Fried Phenotypes	205	[1] 2017SJKDT

		Cardiac disorder (any)	OR 1.43 (1.01-1.98)	stage 5D	Modified CHS scale	1658	[49]J Ren Nutr
		Endothelial dysfunction	OR 3.86 (1.00-14.88)	stages 3-5	Modified Fried Phenotypes	61	[3] 2012 Mansur
	Central nervous system	Cerebrovascular Accident	RR 1.34 (1.19-1.5)	stage 5D (HD)	Fried Phenotypes	205	[1] 2017SJKDT
			OR 1.55 (1.05-2.29)	stage 5D	Modified Fried Phenotypes	2275	[4] 2007 JASN
			OR 1.85 (1.04-3.28)	stage 5D (incident)	Modified Fried Phenotypes	1576	[46] JAMA-IM
			OR 1.56 (1.04-2.35)	stage 5D	Modified CHS scale	1658	[49]J Ren Nutr
	Pulmonary	COPD	OR 2.20 (1.20-4.03)	CKD stages 1-5	Modified Fried Phenotypes	10256	[5] 2009 AJM
	Endocrinologic/ Metabolic	Diabetes	OR 1.68 (1.16-2.45)	CKD stages 1-5	Fried Phenotypes	10256	[5] 2009 AJM
			OR 1.35 (1.10-1.65)	stage 5D	Modified Fried Phenotypes	2275	[4] 2007 JASN
			OR 1.52 (1.18-1.96)	stage 5D (incident)	Modified Fried Phenotypes	1576	[46] JAMA-IM
			OR 1.44 (1.11-1.87)	stage 5D	Modified CHS scale	1658	[49]J Ren Nutr
		Obesity	OR 6.63 (1.16-36.77)	stages 3-5	Modified Fried Phenotypes	61	[3] 2012 Mansur
	Cancer	Cancer	OR 1.89 (1.19-2.99)	CKD stages 1-5	Modified Fried Phenotypes	10256	[5] 2009 AJM

	Musculoskeletal	Arthritis	OR 3.34 (2.08-5.38)	CKD stages 1-5	Modified Fried Phenotypes	10256	[5] 2009 AJM
	Body composition	Fat mass	OR 3.27 (1.17-9.09; 2nd tertile) and 4.97 (1.7-14.55; 3rd tertile)	stage 5D (HD)	Fried Phenotypes	151	[26] J Ren Nutr
		ECW to ICW ratio	OR 3.85 (1.18-10.50; 3rd tertile)				
Psychological		Depression	OR 3.97 (2.28-6.91)	stage 5T	Fried Phenotypes	773	[48] Clin Transplant
Functional status		Disability	OR 5.6 (4.12-7.62)	stage 5D	Modified CHS scale	1658	[49]J Ren Nutr
Vascular access		Permanent vascular access (fistula or graft)	OR 0.71 (0.51-0.98)	stage 5D (HD)	Modified Fried Phenotypes	2275	[4] 2007 JASN
Laboratory Data		Creatinine < 4 mg/dL*	RR 1.46 (1.22-1.71)	stage 5D (HD)	Fried Phenotypes	205	[1] 2017SJKDT
		eGFR (per 5 mL/min/1.73m^2 increase)	OR 1.44 (1.23-1.68)	stage 5D (incident)	Modified Fried Phenotypes	1576	[46] JAMA-IM
		Albumin < 3.2 (g/dL)	OR 1.89 (1.43-2.49)	stage 5D	Modified Fried Phenotypes	2275	[4] 2007 JASN
		Lower free testosterone, (per 50% lower)	OR 1.30 (1.03-1.58)	Male stage 5D (HD)	Fried Phenotypes	440	[8] 2018 NDT

Table 2. Potential modifiers of frailty trajectories in patients with CKD reported in the literature

Category		Type	Risk Difference (95% CI)	Patient CKD severity	Frailty Assessment method	Sample Size	Ref
Ethnicity		Hispanic	Frailty scores increase 0.6 (0-1.1) per year	stage 5D (HD)	Fried Phenotypes	762	[2] 2017 CJASN
		Black	Frail to non-frail after transplantation (RRR 1.98 [1.07-3.67])	stage 5	Fried Phenotypes	569	[53] Transplantation
Biological							
	Endocrinologic/ Metabolic	Diabetes	Remain frail after transplantation (RRR 2.56 [1.22-5.39])	stage 5	Fried Phenotypes	569	[53] Transplantation
			Frailty scores increase 0.7 (0.3-1.0) per year	stage 5D (HD)	Fried Phenotypes	762	[2] 2017 CJASN
	Laboratory data	IL-6	Frailty scores increase 0.3 (0.1-0.4) per year				
		Serum Albumin Concentrations (g/dL)	Frailty scores decrease 1.1 (0.7-1.5) per g/dL				
		Low free testosterone (< 147 pmol/L)	Developing Frailty over 12 months (OR 1.56, 1.04-2.33)	Male stage 5D (HD)	Fried Phenotypes	440	[8] 2018 NDT
Dialysis course		Time of dialysis	Frail to non-frail after	stage 5	Fried Phenotypes	569	[53]

		(year)	transplantation (RRR 0.88 [0.78-1])				Transplantation
Healthcare utilization							
	Hospitalization	Hospitalization during past year	Frailty scores increase 0.6 (0.3-0.8) per year	stage 5D (HD)	Fried Phenotypes	762	[2] 2017 CJASN

Table 3. Unadjusted associates of frailty in CKD patients

Category	Type	Prevalence (Frail vs. non-frail, %), values, or correlation	Patient CKD Severity	Frailty Assessment method	Sample Size	Ref
Demographic profile	Age (years)	r = 0.24, p = 0.04	stage 5D (HD)	Fried Phenotypes	74	[9] 2018 Clinics
		57.0 vs. 52.0	stage 5D (HD)	Fried Phenotypes	324	[10] 2015 CJASN
		82.5 vs. 65.4	stage 5D (PD)	Clinical Frailty Scale	119	[12] 2018 PDI
		62.1 vs. 58.5	stage 5D (PD)	In-house frailty questionnaire	178	[15] 2018 KBPR
		69.4 vs. 56.6 (severe F vs. NF)	stage 5D (PD)	In-house frailty questionnaire	193	[18] 2016 KBPR
		69 vs. 59	stage 5D (HD)	Fried Phenotypes	151	[26] J Ren Nutr
		78.4 vs. 65.5	stage 5D (HD)	FRAIL scale	51	[29] Nephrology
		71.7 vs. 61.5	stage 5D (HD)	CHS scale	214	[35] JBMM
		58 vs. 53	stage 5D (HD)	Performance-based frailty	80	[36] J Ren Nutr
		75.3 vs. 65.1	stage 5D (HD)	FRAIL scale	46	[37] Nephrology
		69.5 vs. 63.7	stage 2-4	Modified Fried Phenotypes	168	[40] HQoLO
		64.9 vs. 57.3	stages 3-5	Modified Fried	61	[41] HQoLO

				Phenotypes		
		62.9 vs. 55.1	stage 5D (HD)	Fried Phenotypes	146	[50] JAGS
		55.8 vs. 50.7	stage 5T	Fried Phenotypes	537	[54] Am J Transplant
	Gender (male)	56% vs. 21% (moderate/severe vs. NF/mild)	stage 5D (HD)	FRAIL scale	46	[16] 2017 BMCG
		55% vs. 72%	stage 5D (HD)	Performance-based frailty	80	[36] J Ren Nutr
		11% vs. 51%	stage 5D (HD)	FRAIL scale	46	[37] Nephrology
		42.3% vs. 71.4%	stages 3-5	Modified Fried Phenotypes	61	[41] HQoLO
		51.2% vs. 68.2%	stage 5D (HD)	Self-reported frailty	1646	[47] AJN
		60.8% vs. 57.9%	stage 5T	Fried Phenotypes	383	[51] Am J Transplant
Anthropometric parameters	BMI (kg/m^2)	31.5 vs. 27.6 (based on DW)	stage 5D (HD)	Fried Phenotypes	324	[10] 2015 CJASN
		22.53 vs. 26.16	stage 5D (HD)	Fried Phenotypes	320	[11] 2017 J Aging Res
		28.3 vs. 25.6	stage 5D (HD)	Fried Phenotypes	151	[26] J Ren Nutr
		28.8 vs. 24.9	stage 5D (HD)	Performance-	80	[36] J Ren Nutr

				based frailty		
		30.1 vs. 28.1	stage 5D (HD)	Self-reported frailty	1646	[47] AJN
	Waist circumference (cm)	101.0 vs. 97.7	stage 5D (PD)	In-house frailty questionnaire	178	[15] 2018 KBPR
		103.0 vs. 93.6	stage 5D (HD)	Fried Phenotypes	151	[26] J Ren Nutr
Multimorbidity	Charlson comorbidity index	5.0 vs. 2.0	stage 5D (PD)	Clinical Frailty Scale	119	[12] 2018 PDI
		5.8 vs. 5.1	stage 5D (PD)	In-house frailty questionnaire	178	[15] 2018 KBPR
		6.6 vs. 4.3 (severe F vs. NF)	stage 5D (PD)	In-house frailty questionnaire	193	[18] 2016 KBPR
	Number of comorbidities	6 vs. 5	stages 1-5	Edmonton Frail Scale (EFS)	41	[14] Can J Diabet
Dialysis duration	Duration	70.5 vs. 162.1 (weeks)	stage 5D (PD)	Clinical Frailty Scale	119	[12] 2018 PDI
		47.9 vs. 34.3 (months)	stage 5D (PD)	In-house frailty questionnaire	178	[15] 2018 KBPR
		61.5 vs. 45.8 (months) (severe F vs. NF)	stage 5D (PD)	In-house frailty questionnaire	193	[18] 2016 KBPR
Physical examination	Diastolic blood pressure (mmHg)	75.6 vs. 80.2	stage 5D (PD)	In-house frailty questionnaire	178	[15] 2018 KBPR

		72.7 vs. 82.5 (severe F vs. NF)	stage 5D (PD)	In-house frailty questionnaire	193	[18] 2016 KBPR
Biological						
Cardiovascular	Heart Failure (%)	30% vs 12%	stages 1-4	Modified CHS scale	336	[7] 2012 AJKD
		44% vs. 11%	stage 5D (HD)	FRAIL scale	46	[37] Nephrology
		36.4% vs. 25.3%	stage 5D (HD)	Self-reported frailty	1646	[47] AJN
	Peripheral vascular disease (%)	38.8% vs. 17.21%	stage 5D (HD)	Fried Phenotypes	320	[11] 2017 J Aging Res
		13.6% vs. 0% (severe F vs. NF)	stage 5D (PD)	In-house frailty questionnaire	193	[18] 2016 KBPR
		42.6% vs. 10.5%	stage 5D (HD)	Fried Phenotypes	146	[50] JAGS
	Angina (%)	34% vs. 22%	stages 1-4	Modified CHS scale	336	[7] 2012 AJKD
	Coronary heart disease (%)	27.3% vs. 5.1% (severe F vs. NF)	stage 5D (PD)	In-house frailty questionnaire	193	[18] 2016 KBPR
	Atherosclerosis (%)	40.1% vs. 30.6%	stage 5D (HD)	Self-reported frailty	1646	[47] AJN
Central nervous system	Cerebrovascular Disease (%)	26.4% vs. 12%	stage 5D (HD)	Fried Phenotypes	324	[10] 2015 CJASN

Endocrinologic/ Metabolic	Diabetes (%)	64% vs. 49%	stages 1-4	Modified CHS scale	336	[7] 2012 AJKD
		63.6% vs. 27.1% (severe F vs. NF)	stage 5D (PD)	In-house frailty questionnaire	193	[18] 2016 KBPR
		65% vs. 45%	stage 5D (HD)	Fried Phenotypes	151	[26] J Ren Nutr
		80% vs. 44%	stage 5D (HD)	FRAIL scale	51	[29] Nephrology
		60% vs. 36%	stage 5D (HD)	Performance-based frailty	80	[36] J Ren Nutr
		63% vs. 43.7%	stage 5D (HD)	Self-reported frailty	1646	[47] AJN
		75.4% vs. 44.7%	stage 5D (HD)	Fried Phenotypes	146	[50] JAGS
	Obesity (%)	64% vs. 50%	stages 1-4	Modified CHS scale	336	[7] 2012 AJKD
		51.8% vs. 23.9%	stage 5D (HD)	Fried Phenotypes	324	[10] 2015 CJASN
Musculoskeletal	Osteoporosis	Higher in frail patients (p = 0.01)	stages 3-5	Modified Fried Phenotypes	61	[3] 2012 Mansur
Immunological	Viral infection					
	HCV infection	21.5% vs. 2.6%	stage 5D (HD)	Fried Phenotypes	205	[1] 2017 SJKDT
Body Composition	Fat mass	r = 0.25, p = 0.04	stages 3-5	Modified Fried	61	[3] 2012

					Phenotypes		Mansur
			40.2% vs. 30.5% (severe F vs. NF) (high fat prevalence)	stage 5D (PD)	In-house frailty questionnaire	193	[18] 2016 KBPR
			40.7% vs. 35.0%	stage 5D (HD)	Fried Phenotypes	151	[26] J Ren Nutr
			30.7 vs. 24.4 kg				
		Total mass					
		trunk mass (kg)	40.8 vs. 48.88	stages 1-5	Edmonton Frail Scale	41	[14] Can J Diabet
			29.4 vs. 33.5	stage 5D (HD)	FRAIL scale	44	[32] JPSM
		Cephalic mass (kg)	4.64 vs. 4.93				
		Lower lean body mass	57.1% vs .14.7%	stages 1-5	Edmonton Frail Scale	41	[14] Can J Diabet
			45.49 vs. 53.62 kg				
			34.7 vs. 43.1 kg	stage 5D (HD)	FRAIL scale	44	[32] JPSM
		Trunk lean mass (kg)	17.4 vs. 22.1				
			23.05 vs. 27.98	stages 1-5	Edmonton Frail Scale	41	[14] Can J Diabet
		Cephalic lean mass (kg)	3.74 vs. 4.69				
			3.06 vs. 3.29	stage 5D (HD)	FRAIL scale	44	[32] JPSM
		Gynoid lean mass (kg)	6.64 vs. 7.91	stages 1-5	Edmonton Frail Scale	41	[14] Can J Diabet
		Lean tissue mass	37.2 vs. 41.4 kg	stage 5D (PD)	In-house frailty	178	[15] 2018 KBPR

					questionnaire		
			53.6% vs. 67.5% (severe F vs. NF)	stage 5D (PD)	In-house frailty questionnaire	193	[18] 2016 KBPR
		Skeletal muscle index (kg/m^2)	6.55 vs. 7.41	stage 5D (PD)	Clinical Frailty Scale	119	[12] 2018 PDI
		Phase angle (degree)	5.24 vs. 6.24	stage 5D (HD)	Performance-based frailty	80	[36] J Ren Nutr
		Over-hydration (L)	4.19 vs. 2.49 (severe F vs. NF)	stage 5D (PD)	In-house frailty questionnaire	193	[18] 2016 KBPR
		Bone mineral density (g/cm^2)		stage 5D (HD)	FRAIL Scale	43	[34] JAGS
		L3	0.81 vs. 0.97				
		L4	0.73 vs. 0.92				
		Femoral neck	0.43 vs. 0.63				
		T-score					
		L3	-1.97 vs. -0.64				
		L4	-2.6 vs. -0.95				
		Femoral neck	-3.47 vs. -1.68				
Laboratory Data		Prealbumin (mg/dL)	28.9 vs. 38.3	stage 5D (PD)	Clinical Frailty Scale	119	[12] 2018 PDI
		Serum albumin (g/dL)	3.6 vs. 3.9	stages 1-4	Modified CHS scale	336	[7] 2012 AJKD

			r = -0.263, p = 0.025	stage 5D (HD)	Fried Phenotypes	74	[9] 2018 Clinics
			3.8 vs. 4.1	stages 1-5	Edmonton Frail Scale (EFS)	41	[14] Can J Diabet
			2.92 vs. 3.48	stage 5D (PD)	Clinical Frailty Scale	119	[12] 2018 PDI
			3.61 vs. 3.85	stage 5D (HD)	Fried Phenotypes	320	[11] 2017 J Aging Res
			3.29 vs. 3.49 vs. 3.58 (F + D vs. F – D vs. NF)	stage 5D (PD)	In-house frailty questionnaire	178	[15] 2018 KBPR
			3.17 vs. 3.62 (severe F vs. NF)	stage 5D (PD)	In-house frailty questionnaire	193	[18] 2016 KBPR
			3.7 vs. 3.9	stage 5D (HD)	Fried Phenotypes	151	[26] J Ren Nutr
			3.5 vs. 3.9	stage 5D (HD)	FRAIL scale	51	[29] Nephrology
			3.7 vs. 3.9	stage 5D (HD)	CHS scale	214	[35] JBMM
			3.5 vs. 3.8	stage 5D (HD)	FRAIL scale	46	[37] Nephrology
			3.2 vs. 3.4	Elderly with stage 5D	Multidimensional frailty score	46	[62] JKMS
		Creatinine	299 vs. 115 umol/L	stages 1-5	Edmonton Frail Scale (EFS)	41	[14] Can J Diabet
			11.6 vs. 9.9 mg/dL (moderate/severe vs.	stage 5D (HD)	FRAIL scale	46	[16] 2017 BMCG

			NF/mild)				
			12.2 vs. 10.4 mg/dL (F/PF vs. NF)	stage 5D (HD)	FRAIL scale	44	[32] JPSM
			8.1 vs. 11.1 mg/dL	stage 5D (HD)	FRAIL scale	46	[37] Nephrology
		eGFR (mL/min/1.73m^2)	41.1 vs. 52.5 (cystatin C)	stages 1-4	Modified CHS scale	336	[7] 2012 AJKD
			18 vs. 50	stages 1-5	Edmonton Frail Scale (EFS)	41	[14] Can J Diabet
		Albuminuria (mg/g Cre)	311.2 vs. 102	stages 1-4	Modified CHS scale	336	[7] 2012 AJKD
		Phosphate (mg/dL)	4.1 vs. 3.7	stages 1-4	Modified CHS scale	336	[7] 2012 AJKD
		Hemoglobin (g/dL)	10.35 vs. 10.97	stage 5D (HD)	Fried Phenotypes	320	[11]2017 J Aging Res
			r = -0.336, p = 0.004	stage 5D (HD)	Fried Phenotypes	74	[9] 2018 Clinics
			12.2 vs. 13.2	stages 1-4	Modified CHS scale	336	[7] 2012 AJKD
			10.1 vs. 9.2 (moderate/severe vs. NF/mild)	stage 5D (HD)	FRAIL scale	46	[16] 2017 BMCG
		Total cholesterol	4.48 vs. 5.18 mmol/L	stage 5D (PD)	In-house frailty	193	[18] 2016 KBPR

			(severe F vs. NF)		questionnaire		
			134 vs. 148 mg/dL	stage 5D (HD)	Fried Phenotypes	151	[26] J Ren Nutr
		LDL cholesterol (mmol/L)	2.51 vs. 3.02 (severe F vs. NF)	stage 5D (PD)	In-house frailty questionnaire	193	[18] 2016 KBPR
		HDL cholesterol	1.18 vs. 1.38 mmol/L (severe F vs. NF)				
			40 vs. 46 mg/dL	stage 5D (HD)	Fried Phenotypes	151	[26] J Ren Nutr
		iPTH (pg/mL)	248.8 vs. 127.9	stages 3-5	Modified Fried Phenotypes	61	[3] 2012 Mansur
		Ferritin (ng/mL)	1202 vs. 534	stage 5D (HD)	FRAIL scale	46	[37] Nephrology
		Transferrin saturation (%)	30.1 vs. 37.1	stages 3-5	Modified Fried Phenotypes	61	[3] 2012 Mansur
		25-OH-D (ng/dL)	r = -0.363, p = 0.002	stage 5D (HD)	Fried Phenotypes	74	[9] 2018 Clinics
		CRP (mg/dL)	3.8 vs. 2.1	stages 1-4	Modified CHS scale	336	[7] 2012 AJKD
			1.12 vs. 0.28 (natural Log transformed)	stage 5D (PD)	Clinical Frailty Scale	119	[12] 2018 PDI
		IL-6 (pg/mL)	2.45 vs. 1.58 (natural Log transformed)	stage 5D (PD)	Clinical Frailty Scale	119	[12] 2018 PDI
		nPNA (g/kg/day)	1.10 vs. 1.19	stage 5D (PD)	In-house frailty questionnaire	178	[15] 2018 KBPR

CKD-related complications	Counts of complications	r = 0.666, p < 0.0001	Elderly with unknown CKD stages	Edmonton Frail Scale	35	[17] 2016 Rev Rene
Residual renal function	Residual eGFR (ml/min/1.73m^2)	1.54 vs. 2.46	stage 5D (PD)	In-house frailty questionnaire	178	[15] 2018 KBPR
		0.9 vs. 2.2	stage 5D (PD)	In-house frailty questionnaire	193	[18] 2016 KBPR
Care modality	Assisted PD	38.6% vs. 0% (severe F vs. NF)	stage 5D (PD)	In-house frailty questionnaire	193	[18] 2016 KBPR
	Living with caregivers	45% vs. 72%	Elderly with stages 4/5 CKD	Groningen frailty indicator	65	[19] Ren Fail
	Renal conservative care	45% vs. 2%	Elderly with stages 4/5 CKD	Groningen frailty indicator	65	[19] Ren Fail
Dialysis related parameters	Kt/V	1.69 vs. 1.55 (moderate/severe vs. NF/mild)	stage 5D (HD)	FRAIL scale	46	[16] 2017 BMCG
		1.44 vs. 1.58	stage 5D (HD)	Fried Phenotypes	151	[26] J Ren Nutr
	Weekly total Kt/V	1.74 vs. 1.96 (severe F vs. NF)	stage 5D (PD)	In-house frailty questionnaire	193	[18] 2016 KBPR
	URR	76.2% vs. 72.5%	stage 5D (HD)	FRAIL scale	46	[16] 2017

		(moderate/severe vs. NF/mild)				BMCG
	Daily exchange volume (L)	6.5 vs. 7.0 (severe F vs. NF)	stage 5D (PD)	In-house frailty questionnaire	193	[18] 2016 KBPR
Vascular access	Catheter, AVF, and AVG use	Catheter: 61.6% vs. 17.8% AVF: 27.78% vs. 77.5% AVG: 11.11% vs. 5%	stage 5D (HD)	Fried Phenotypes	320	[11] 2017 J Aging Res
Microbiota	Bacterial Abundance of some genera (Mogibacteriacee, Coriobacteriacee, Eggerthella, Erwinia, Coprobacillus, Anaerotruncus, etc)	Higher in F group	stages 3b/4	Fried Phenotype	79	[20] NDT
Neurological	Quantitative EEG findings		stage 5D (HD)	FRAIL scale	46	[16] 2017 BMCG
	Delta wave (central, right/left TO, left frontal area)	Lower in F group				
	Delta to alpha ratio (global, central, left frontal, right/left TO	Lower in F group				

	area)					
	Delta/theta to alpha/beta ratio (global, central, left frontal, right/left TO area)	Lower in F group				
Cognitive impairment			stage 5T	Fried phenotypes	665	[30] JASN
	Prevalence	11% vs. 6.6%				
	Pre-transplant 3MS scores	93.0 vs. 96.0				
	3MS memory	20.0 vs. 21.0				
	3MS identification/association	23.0 vs. 24.0				
Psychological						
Mood	Mood Change	Negative correlation	stage 5D (HD)	Edmonton Frail Scale	60	[21] Act Paul Enferm
Anxiety	Hospital Anxiety and Depression Scale	Higher global, psychological and social components (women) Higher physical	stage 5D (online-HDF)	N/A	97	[22] NDT

		component (men)				
Depression	Depression	38.8% vs. 12.58%	stage 5D (HD)	Fried Phenotypes	320	[11] 2017 J Aging Res
	Hospital Anxiety and Depression Scale	Higher global, psychological, physical component (men)	stage 5D (online-HDF)	N/A	97	[22] NDT
	Self-reported major depression	83% vs. 6%	stages 1-5	Edmonton Frail Scale (EFS)	41	[14] Can J Diabet
Physical activity	Minnesota Leisure Time Activity (LTA)	95 vs. 735	stage 5D (HD)	Fried Phenotypes	68	[25] J Ren Nutr
	Low Physical Activity Questionnaire (LoPAQ)	280 vs. 798				
	Sitting (hours/day)	6.5 vs. 5				
	Grip strength (kg)	16.4 vs. 24.6	stage 5D (PD)	Clinical Frailty Scale	119	[12] 2018 PDI
	Walk speed (m/s)	0.79 vs. 1.67				
Nutritional Status	SGA scores	5.25 vs. 5.75	stage 5D (PD)	In-house frailty questionnaire	178	[15] 2018 KBPR
		4.2 vs. 5.3 (severe F vs. NF)	stage 5D (PD)	In-house frailty questionnaire	193	[18] 2016 KBPR
	MIS scores	8.14 vs. 5.12	stage 5D (PD)	In-house frailty questionnaire	178	[15] 2018 KBPR

		12.2 vs. 6.0 (severe F vs. NF)	stage 5D (PD)	In-house frailty questionnaire	193	[18] 2016 KBPR
		7.6 vs. 3.9	stages 3b/4	Fried Phenotype	79	[20] NDT
	MNA scores	18.0 vs. 22.0	Elderly with stage 5D	Multidimensional frailty score	46	[62] JKMS
Quality of Life	Kidney Disease Quality of Life (KDQoL) components					
	Mental health	43.6 vs. 48.9	stage 5D (HD)	Fried Phenotypes	151	[26] J Ren Nutr
	Kidney disease symptoms	67.8 vs. 79.1				
	SF-36					
	Physical functioning	46 vs. 84	stages 3-5	Modified Fried Phenotypes	61	[41] HQoLO
	Role physical	53.8 vs. 75				
	Bodily pain	58.4 vs. 76.5				
	General health	48.9 vs. 62				
	Vitality	58.8 vs. 77.4				
	Mental health	69.5 vs. 80.8				
Functional outcomes	Ability for basic ADL	33.33% vs. 76.4%	stage 5D (HD)	Fried Phenotypes	320	[11] 2017 J Aging Res
		55% vs. 91%	Elderly with stages	Groningen frailty	65	[19] Ren Fail

				4/5 CKD	indicator		
		Ability to transfer	38.8% vs. 84.7%	stage 5D (HD)	Fried Phenotypes	320	[11] 2017 J Aging Res
		Barthel Index	90 vs. 100	stage 5D (PD)	Clinical Frailty Scale	119	[12] 2018 PDI
	Disability	≥1 disability in ADL	15% vs. 5%	CKD stages 1-4	Fried Phenotypes	336	[7] 2012 AJKD
		≥1 disability in IADL	60% vs. 28%				
		≥1 disability in mobility	40% vs. 18%				
	Functional status	Karnofsky scores	44.4 vs. 95.36	stage 5D (HD)	Fried Phenotypes	320	[11] 2017 J Aging Res
Health-care utilization		Hospitalization >= 1 time per year	90% vs. 53%	Elderly with stages 4/5 CKD	Groningen frailty indicator	65	[19] Ren Fail
		Hospitalization frequency (per year)	0.78 vs. 0.28 episodes	stage 5D (HD)	Fried Phenotypes	320	[11] 2017 J Aging Res
		Hospitalization episode count	3.31 vs. 2.12 vs. 0.9 (in 2 years) (F + D vs. F – D vs. NF)	stage 5D (PD)	In-house frailty questionnaire	178	[15] 2018 KBPR
			5.2 vs. 2.4 per year (severe F vs. NF)	stage 5D (PD)	In-house frailty questionnaire	193	[18] 2016 KBPR
		Cardiovascular origin hospitalization count	1.4 vs. 0.5 per year (severe F vs. NF)				

	Hospital stay (days per year)	26.62 vs. 14.05 vs. 8.04 (2 years) (F + D vs. F – D vs. NF)	stage 5D (PD)	In-house frailty questionnaire	178	[15] 2018 KBPR
		58.5 vs. 18.3 per year (severe F vs. NF)	stage 5D (PD)	In-house frailty questionnaire	193	[18] 2016 KBPR
Technique survival	Technique failure	42.5% vs. 35.8% vs. 13.7% (2 years) (F + D vs. F – D vs. NF)	stage 5D (PD)	In-house frailty questionnaire	178	[15] 2018 KBPR
Mortality	Overall mortality	20.45% vs. 12.36% (1 year)	stage 5D (HD)	Fried Phenotypes	320	[11] 2017 J Aging Res
		37.5% vs. 28.6% vs. 13.4% (2 years) (F + D vs. F – D vs. NF)	stage 5D (PD)	In-house frailty questionnaire	178	[15] 2018 KBPR
		30% vs. 10% (1 year)	Elderly with stages 4/5 CKD	Groningen frailty indicator	65	[19] Ren Fail

Table 4. Confounder-adjusted risk of complications resulting from frailty in CKD patients

Category	Type		Hazard/odds ratio, Risk Difference (95% CI), or values in F vs. NF groups	Patient CKD Severity	Frailty Assessment method	Sample Size	Ref
Physical examination	Blood pressure		Lower in Frail group (adjusted *p* = 0.001)	stages 1-5	Edmonton Frail Scale	41	[14] 2019 Can J Diabet
Biological							
Cardiovascular	QRS duration		β= −0.29, t = −2.03, p = 0.048	stage 5D (HD)	Edmonton frailty scale	41	[28] PeerJ
			β= −0.27, t = −1.84, p = 0.05		FRAIL scale		
Musculoskeletal	Vertebral compression fracture (any)		OR 1.8 per FRAIL score (p = 0.01)	stage 5D (HD)	FRAIL Scale	43	[34] JAGS
Cognitive function	3MS scores	At baseline	-2.37 (-4.21 to -0.53) compared to NF	stage 5D (HD)	Fried Phenotypes	324	[10] 2015 CJASN
		1-year	-2.80 (-5.37 to -0.24) compared to NF				
		Pre-transplant	-1.8 compared to NF	stage 5T	Fried phenotypes	665	[30] JASN
		1-4 years post-transplant	-0.04 per year (-0.06 to -0.01)				
	TMT-A	At baseline	12.08 (4.73 to 19.43) compared to NF	stage 5D (HD)	Fried Phenotypes	324	[10] 2015 CJASN
	TMT-B	At baseline	33.15 (9.88 to 56.42) compared to NF				

	Body composition	Lean mass	Lower lean mass over cephalic, trunk, and 4 extremities than NF group	stage 5D (HD)	FRAIL scale	44	[32] JPSM
		BMD at 1 year follow up		stage 5D (HD)	FRAIL Scale	43	[33] PeerJ
		Total	ß = −0.53, t = −3.27, p < 0.01				
		L1	ß = −0.4, t = −2.18, p = 0.04				
		L4	ß = −0.39, t = −2.1, p = 0.046				
		Femoral neck	ß = −0.5, t = −2.96, p < 0.01				
		Average L-spine areas					
		1 year of follow up	ß = −0.48, t = −2.84, p < 0.01				
		Interval changes	ß = −0.5, t = −3.02, p < 0.01				
		Interval changes in L-spine Z-score percentages	ß = −0.45, t =−2.11, p=0.049				
		QUS parameters					
		SOS	1487.8 vs. 1537.8 (female) 1493.7 vs. 1542.2 (male)	stage 5D (HD)	CHS scale	214	[35] JBMM
		BUA	86.2 vs. 100.7 (female) 93.8 vs. 107.8 (male)				

		Stiffness index	54.0 vs. 77.7 (female) 60.9 vs. 83.6 (male)				
		Muscles					
		Quadriceps muscle area	r = -30.28, p = 0.02	stage 5D (HD)	Performance-based frailty	80	[36] J Ren Nutr
		Appendicular skeletal muscle mass index (ASMI)	Lower in Frail group (adjusted p < 0.05)	stages 1-5	Edmonton Frail Scale (EFS)	41	[14] 2019 Can J Diabet
		Appendicular fat percentage		stage 5D (HD)	FRAIL scale scores	44	[32] JPSM
		Left/Right lower extremity	β =0.34, t = 2.32; p = 0.03 (left); β =0.3, t = 2.05; p = 0.048 (right)				
		Left/Right upper extremity	β =0.37, t = 2.66; p = 0.01 (left); β =0.43, t = 3.09; p <0.01 (right)				
		Sarcopenia	OR 12.2 (2.27-65.5)	stage 5D (PD)	Clinical Frailty Scale	119	[12] 2018 PDI
Laboratory data		Serum albumin (g/dL)	Negative relationship (p = 0.01)	stage 5D (HD)	FRAIL scale	46	[37] Nephrology
Psychological		Hospital anxiety and depression scale	OR 1.21 (1.11-1.31)	stage 5D	Clinical Frailty Scale	251	[42] 2016 CJASN
Functional status		Physical functioning	Lower in Frail group (adjusted p =	stages 1-5	Edmonton Frail Scale	41	[14] 2019 Can

		0.004)		(EFS)		J Diabet
	Need assistance in ADL	OR 1.93 (1.01-3.68) for pre-frail OR 11.32 (5.49-23.32) for frail	stage 5D (HD)	Modified Fried Phenotypes	742	[31] HDI
	Barthel index scores	OR 0.89 (0.86-0.93)	stage 5D	Clinical Frailty Scale	251	[42] 2016 CJASN
Psychological						
Delirium	Post-transplantation delirium	OR 2.05 (1.02-4.13)	stage 5T	Fried Phenotypes	893	[23] JASN
Distress	Self-reported distress thermometer	β = 0.35 (0.12-0.58), t = 3.0, p = 0.003	stage 5D (HD)	Canadian frailty score	382	[38] Nutr Clin Pract
Fall	Any fall	HR 2.1 (1.21-3.92)	stage 5D (HD)	Fried Phenotypes	205	[1] 2017SJKDT
		OR 2.39 (1.22-4.71)	Stage 5D (HD)	Modified Fried Phenotype	762	[44] CKJ
	Increased numbers of falls	HR 3.09 (1.38-6.90)	stage 5D (HD)	Modified Fried Phenotype	95	[45] BMCN
	Time to first fall	HR 1.60 (1.16-2.20)	stage 5D (HD)	Self-reported frailty	1646	[47] AJN
Quality of Life	KDQoL					
	Physical health	33.7 vs. 40.7	stage 5D (HD)	Fried Phenotypes	151	[26] J Ren Nutr
	Effects of disease	51.6 vs. 66.8				
	KDQoL short form					

	Physical component	Difference -6.31 (-8.16 to -4.46)	stage 5T	Fried Phenotypes	443	[43] Transplantation
	Physical functioning	Difference -14.17 (-18.58 to -9.76)				
	Role limitations	Difference -15.37 (-22.96 to -7.78)				
	Bodily pain	Difference -9.45 (-14.33 to -4.57)				
	General health	Difference -11.76 (-15.94 to -7.59)				
	Emotional well-being	Difference -3.05 (-6.01 to -0.09)				
	Social functioning	Difference -6.19 (-10.98 to -1.41)				
	Energy	Difference -11.66 (-16.3 to -7.03)				
Kidney disease-specific HRQoL		Difference -6.53 (-9.17 to -3.89)				
	Symptoms	Difference -5.5 (-8.2 to -2.79)				
	Effects	Difference -7.69 (-11.66 to -3.72)				
	Burden	Difference -10.19 (-15.94 to -4.44)				
	Cognitive function	Difference -5.51 (-9 to -2.02)				
	Social interaction	Difference -4.7 (-7.85 to -1.56)				
	Sleep	Difference -6.29 (-10.56 to -2.02)				
	Social support	Difference -5.69 (-9.92 to -1.47)				
HRQoL						
	Fair/Poor HRQoL at follow-up	OR 2.79 (1.32-5.90)	stage 5D	Fried Phenotypes	233	[39] J Frailty Aging
	Worse HRQOL after	RR 2.91 (1.08-7.80)				

	follow-up					
SF-36						
	Physical components	Lower in Frail group (adjusted *p* = 0.002)	stages 1-5	Edmonton Frail Scale	41	[14] 2019 Can J Diabet
		β = -0.566, t = -8.792, p < 0.001	stage 2-4	Modified Fried Phenotypes	168	[40] HQoLO
		Mean difference -1.12 (-1.47 to -0.76)	stages 3-5	Modified Fried Phenotypes	61	[41] HQoLO
	Mental components	Mean difference -0.75 (-1.4 to -0.16)				
		β = -0.485, t = -6.709, p < 0.001	stage 2-4	Modified Fried Phenotypes	168	[40] HQoLO
SF-12						
	MCS	OR 0.94 (0.91-0.97)	stage 5D	Clinical Frailty Scale	251	[42] 2016 CJASN
	PCS	OR 0.88 (0.84-0.91)				
Symptom scores		OR 1.23 (1.13-1.34)				
KDQOL-SF scores 3 months after transplant			stage 5T	Fried Phenotypes	443	[43] Transplantation
	Physical HRQoL	0.34/month vs. 1.35/month				
Kidney disease-specific HRQoL		2.41/month vs. 3.75 points/month				
	Effects	4.01/month vs. 7.1/month				

	Cognitive function	1.28/month vs. 2.88/month				
	Social interaction	-0.57/month vs. 1.18/month				
Graft Loss	Risk of graft loss in depressive patients	aHR 6.20 (1.67 to 22.95)	stage 5T	Fried Phenotypes	773	[48] Clin Transplant
Immunosuppressant use	MMF dose reduction	HR 1.29 (1.01-1.66)	stage 5T	Modified Fried Phenotypes	525	[13] 2015 Transplant
Dialysis access survival	Access failure	HR 2.63 (1.03-6.71)	stage 5D (HD)	FRAIL scale	51	[29] Nephrology
Health-care utilization	Hospitalization or mortality	HR 1.56 (1.36-1.79)	stage 5D	Modified Fried Phenotypes	2275	[4] 2007 JASN
	Hospitalization	HR 2.06 (1.18-3.58)	stage 5D (HD)	Fried Phenotypes	205	[1] 2017SJKDT
		aHR 1.83 (1.41-2.37)	stage 5D	Modified CHS scale	1658	[49]J Ren Nutr
		HR 1.43 (1.00-2.03)	stage 5D (HD)	Fried Phenotypes	146	[50] JAGS
	Number of all-cause hospitalizations	beta = 0.29, $p < 0.0001$	stage 5D (PD)	In-house frailty questionnaire	193	[18] 2016 KBPR
	Number of cardiovascular hospitalizations	beta = 0.37, $p < 0.0001$				

	Time to first hospitalization	HR 1.26 (1.09-1.45)	stage 5D (incident)	Modified Fried Phenotypes	1576	[46] JAMA-IM
	Early Hospital Readmission	RR 1.59 (1.17-2.17)	stage 5T	Fried Phenotypes	383	[51] Am J Transplant
	Longer Length of Stay					
	LOS (days)	RR 1.15 (1.03-1.29)	stage 5T	Fried Phenotypes	589	[52] Ann Surg
	> 2 weeks	OR 1.57 (1.06-2.33)				
		OR 2.02 (1.20-3.40) for increased frail category; OR 1.92 (1.13-3.25) for increased frail scores	stage 5	Fried Phenotypes	569	[53] Transplantation
	In depressive patients	aRR 1.88 (1.70-2.08)	stage 5T	Fried Phenotypes	773	[48] Clin Transplant
	Hospitalization frequency	Higher in Frail group (adjusted $p < 0.001$)	stages 1-5	Edmonton Frail Scale (EFS)	41	[14] 2019 Can J Diabet
	Emergency department visit frequency	Higher in Frail group (adjusted $p = 0.002$)				
	Total medical visit frequency	Higher in Frail group (adjusted $p = 0.001$)				
Mortality	Overall mortality	HR 2.17 (1.01-4.65) after transplantation	stage 5T	Fried Phenotypes	537	[54] Am J Transplant

		HR 2.0 (1.5-2.7)	stages 1-5	Modified Fried Phenotypes	10256	[5] 2009 AJM
		HR 1.57 (1.25-1.97)	stage 5D (incident)	Modified Fried Phenotypes	1576	[46] JAMA-IM
		HR 2.24 (1.60-3.15)	stage 5D	Modified Fried Phenotypes	2275	[4] 2007 JASN
		HR 1.22 (1.04-1.43)	stage 5D	Clinical Frailty Scale	390	[55] 2015 CJASN
		HR 4.28 (1.22-14.98)	stages 4/5	PRISMA questionnaire & TUGT	104	[56] SJKDT
		HR 9.83 (1.80-53.7)	stage 5D (PD)	Clinical Frailty Scale	119	[12] 2018 PDI
		HR 2.60 (1.04-6.49)	stage 5D (HD)	Fried Phenotypes	146	[50] JAGS
		HR 2.08 (1.04-4.16)	stage 5D	Modified CHS scale	1658	[49]J Ren Nutr
		HR 1.78 (1.15-2.8) for performance-based frailty; HR 1.66 (1.06-2.6) for self-reported frailty; HR 1.95 (1.19-3.2) for both definition positivity	stage 5D (HD)	Modified Fried Phenotypes and self-reported frailty	771	[57] CJASN
		HR 1.66 (1.03-2.67) in general; HR 3.77 (1.10-12.92) in general obesity; HR 2.38 (1.17-4.82) in abdominal	stage 5D (HD)	Fried Phenotypes	370	[59] NDT

		obesity				
		HR 2.43 (1.48-3.99)	stage 5D and 5T from ANCA vasculitis	Inability to walk without help	425	[60] QJM
		HR 1.93 (1.58-2.36)	stage 5D and 5T from MM or amyloidosis	Inability to walk without help	1462	[61] CJASN
	In depressive patients	aHR 2.62 (1.03 to 6.70)	stage 5T	Fried Phenotypes	773	[48] Clin Transplant
	Modify the association between comorbidity and mortality	HR 0.75 (0.44-1.29) in F group vs. 1.66 (1.17-2.35) in NF group	stage 5	Fried Phenotypes	2086	[58] Am J Nephrol
		HR 1.93 (1.58-2.36)	stage 5D and 5T from MM or amyloidosis	Inability to walk without help	1462	[61] CJASN
	Post-transplant mortality	HR 2.27 (1.11-4.65) for increased frail category; OR 2.36 (1.12-4.99) for increased frail scores	stage 5	Fried Phenotypes	569	[53] Transplantation

Composite	Mortality or dialysis	HR 2.5 (1.4-4.4)	stages 1-4	Modified CHS scale	336	[7] 2012 AJKD
	Mortality or cardiovascular hospitalization	HR 23.58 (1.61-346.03)	Elderly with stage 5D (HD)	Multidimensional frailty score	46	[62] JKMS
	30-day post-transplant complications	β=13.31 (5.72-20.89), p = 0.0007	stage 5T	Groningen Frailty Indicator	150	[63] Transplant Int

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