Table 1. Unadjusted risk associates of frailty in CKD patients

Category	Type	Prevalence (F vs. NF, %), values, or correlation	Patient CKD Severity	Frail 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 Phenotypes	61	[41] HQoLO

		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-based frailty	80	[36] J Ren Nutr

		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	stage 5D (PD)	In-house frailty	193	[18] 2016 KBPR

		vs. NF)		questionnaire		
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 Phenotypes	61	[3] 2012 Mansur
		40.2% vs. 30.5% (severe F vs. NF) (high fat	stage 5D (PD)	In-house frailty questionnaire	193	[18] 2016 KBPR

		prevalence)			
		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 questionnaire	178	[15] 2018 KBPR
			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. NF/mild)	stage 5D (HD)	FRAIL scale	46	[16] 2017 BMCG

			Value	Stage	Frailty scale	N	Reference
			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 (severe F vs. NF)	stage 5D (PD)	In-house frailty questionnaire	193	[18] 2016 KBPR
			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% (moderate/severe vs. NF/mild)	stage 5D (HD)	FRAIL scale	46	[16] 2017 BMCG
	Daily exchange volume (L)	6.5 vs. 7.0 (severe F vs.	stage 5D (PD)	In-house frailty	193	[18] 2016 KBPR

		NF)		questionnaire		
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 area)	Lower in F group				

		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 component (men)	stage 5D (online-HDF)	N/A	97	[22] NDT

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	95 vs. 735	stage 5D (HD)	Fried Phenotypes	68	[25] J Ren Nutr
	Low Physical Activity Questionnaire	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

			Value	Stage	Tool	N	Reference
			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 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

ADL, activity of daily living; AVF, arteriovenous fistula; AVG, arteriovenous graft; BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; DW, dry weight; EEG, electroencephalography; eGFR, estimated glomerular filtration rate; HCV, hepatitis C virus; HD, hemodialysis; HDL, high density lipoprotein; IADL, instrumental activity of daily living; IL-6, interleukin-6; iPTH, intact parathyroid hormone; LDL, low density lipoprotein; MIS, malnutrition-inflammation score; MNA, mini-nutritional assessment; nPNA, normalized protein equivalent of total nitrogen appearance ; OR, odds ratio; PD, peritoneal dialysis; SGA, standardized global assessment; TO, temporo-occipital; URR, urea reduction ratio

Table 2. 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

CKD, chronic kidney disease; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ECW, extracellular water; ICW, intracellular water; HD, hemodialysis; OR, odds ratio; RR, relative risk

Table 3. 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 5T	Fried Phenotypes	569	[53] Transplantation
Biological						
Endocrinologic/ Metabolic	Diabetes	Remain frail after transplantation (RRR 2.56 [1.22-5.39])	stage 5T	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 5T	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

CKD, chronic kidney disease; CI, confidence interval; HD, hemodialysis; IL-6, interleukin-6; OR, odds ratio

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
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	Lower in Frail group (adjusted *p* < 0.05)	stages 1-5	Edmonton Frail Scale	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
Functional status	Physical functioning		Lower in Frail group (adjusted *p* = 0.004)	stages 1-5	Edmonton Frail Scale	41	[14] 2019 Can 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
	Anxiety/depression	Hospital anxiety and depression scale	OR 1.21 (1.11-1.31)	stage 5D	Clinical Frailty Scale	251	[42] 2016 CJASN
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] Transplanta
		Physical functioning	Difference -14.17 (-18.58 to -9.76)				

	Role limitations	Difference -15.37 (-22.96 to -7.78)			tion
	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 follow-up	RR 2.91 (1.08-7.80)			
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					
Lower MCS	OR 0.94 (0.91-0.97)	stage 5D	Clinical Frailty Scale	251	[42] 2016 CJASN
Lower PCS	OR 0.88 (0.84-0.91)				
Symptom scores (high)	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 obesity	stage 5D (HD)	Fried Phenotypes	370	[59] NDT
		HR 2.43 (1.48-3.99)	stage 5D and	Inability to walk	425	[60] QJM

			5T from ANCA vasculitis	without help		
		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/ 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 5T	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	HR 23.58 (1.61-346.03)	Elderly with	Multidimensional	46	[62] JKMS

		stage 5D (HD)	frailty score		
cardiovascular hospitalization					
30-day post-transplant complications	β=13.31 (5.72-20.89), p = 0.0007	stage 5T	Groningen Frailty Indicator	150	[63] Transplant Int

ADL, activity of daily living; BUA, broadband ultrasound attenuation; CI, confidence interval; CKD, chronic kidney disease; HD, hemodialysis; HR, hazard ratio; HRQoL, health-related quality of life; LOS, length of stay; KDQOL-SF, Kidney disease quality of life instrument – short form; MCS, mental component score; MMF, mycophenolate mofetil; OR, odds ratio; PCS, physical component score; PD, peritoneal dialysis; QUS, quantitative ultrasound; SGA, standardized global assessment; SOS, speed of sound