Frailty in chronic kidney disease: identification and intervention

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Background

CKD increases in prevalence with age

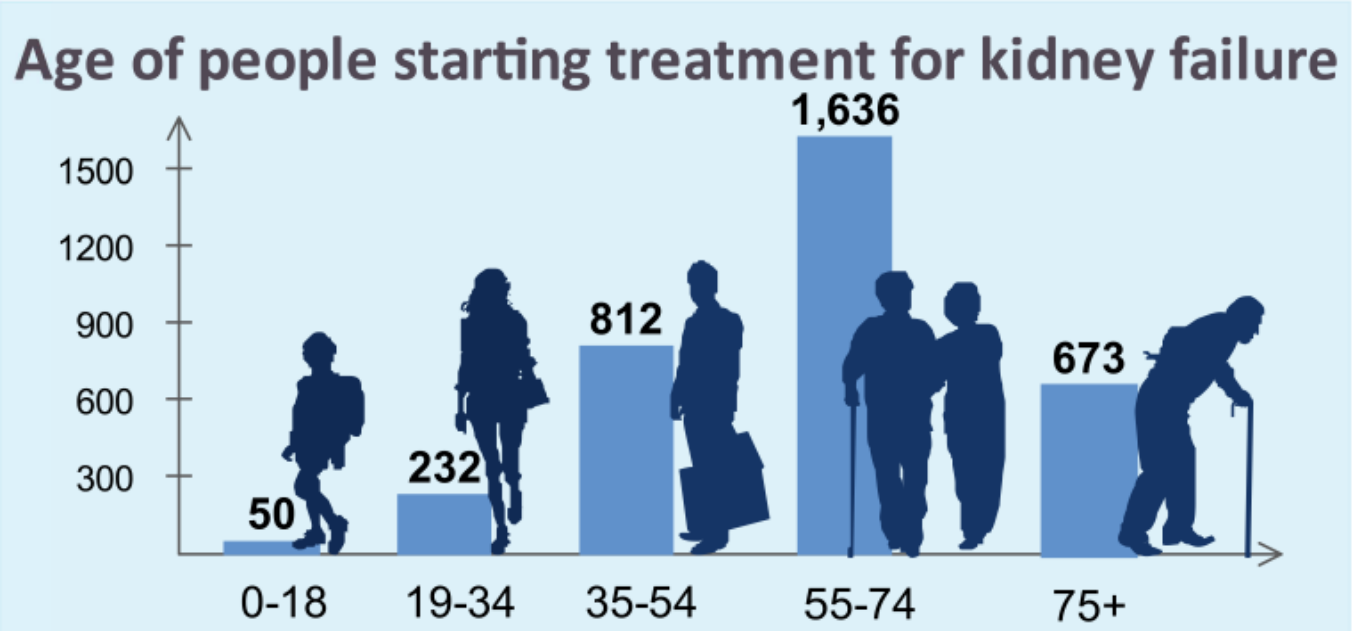
High proportion of patients commencing dialysis for end stage kidney disease are elderly aged 65-85 years

Frailty is under-recognised and suboptimally resourced and managed in nephrology care models

- Highly prevalent[1,2]
- Greater impairment in CKD[3]
- Younger age onset[4]

Lack of consensus for frailty assessment

No evidence-based frailty intervention to date



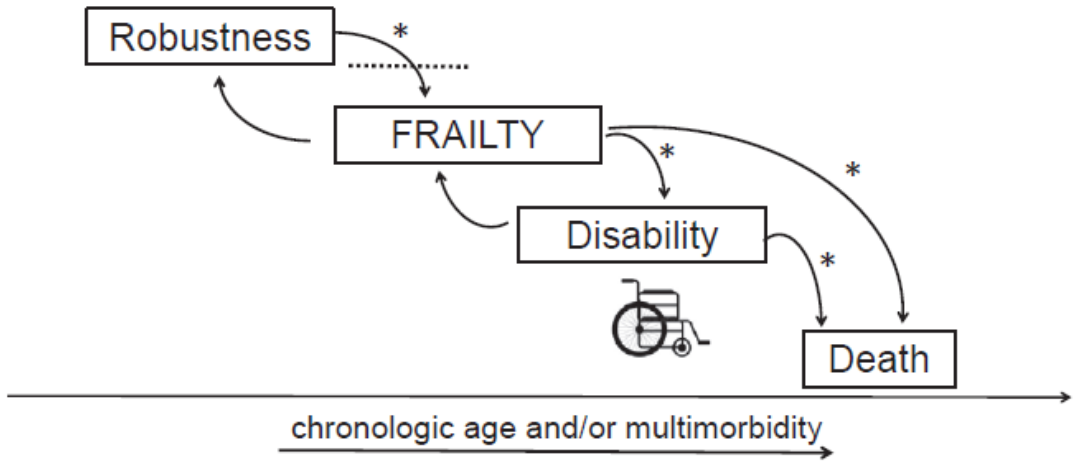
[1] Lee SY, et al. Journal of Renal Nutrition 2017
[2] Walker SR, et al. BMC Nephrology 2013
[3] Hartmann EL, Clin J Am Soc Nephrol. 2009
[4] Bao Y, Arch Intern Med 2012

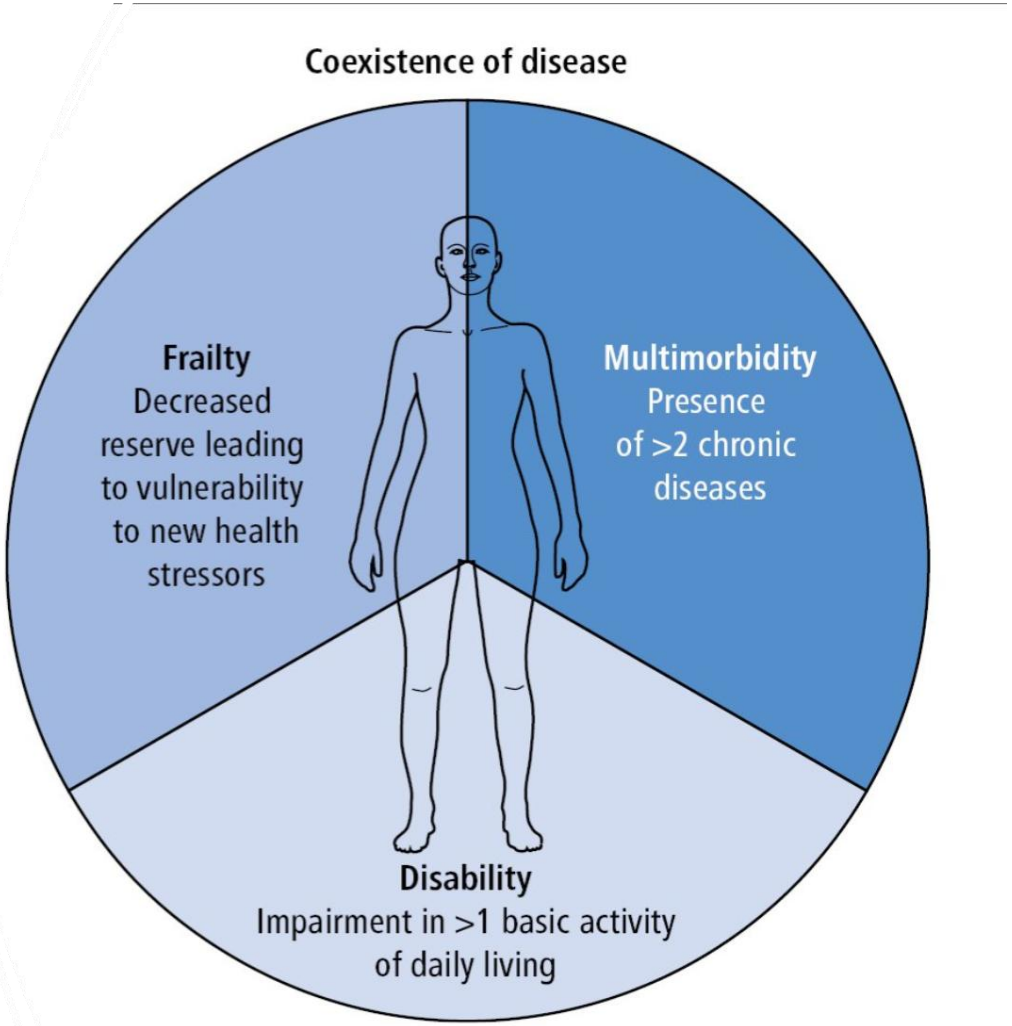
Kidney Int Suppl 2022
ANZDATA 2022

Frailty concepts: Geriatric literature

- Definition: diminished physiological **reserve** and **accumulation** of subclinical **organ dysfunction** implies concern about a person's **disproportionate** change in health state and prognosis following a relatively **minor insult**.

Clegg, Peel et al. The Lancet 2013.





Prevalence of frailty in advanced kidney disease

- Frailty prevalence increases with progression of CKD

- Particularly high prevalence and impact in dialysis populations

  14%-40.4% in individuals with chronic kidney disease (CKD),

  31%-82% in haemodialysis,

  14.2%-69.4% in peritoneal dialysis

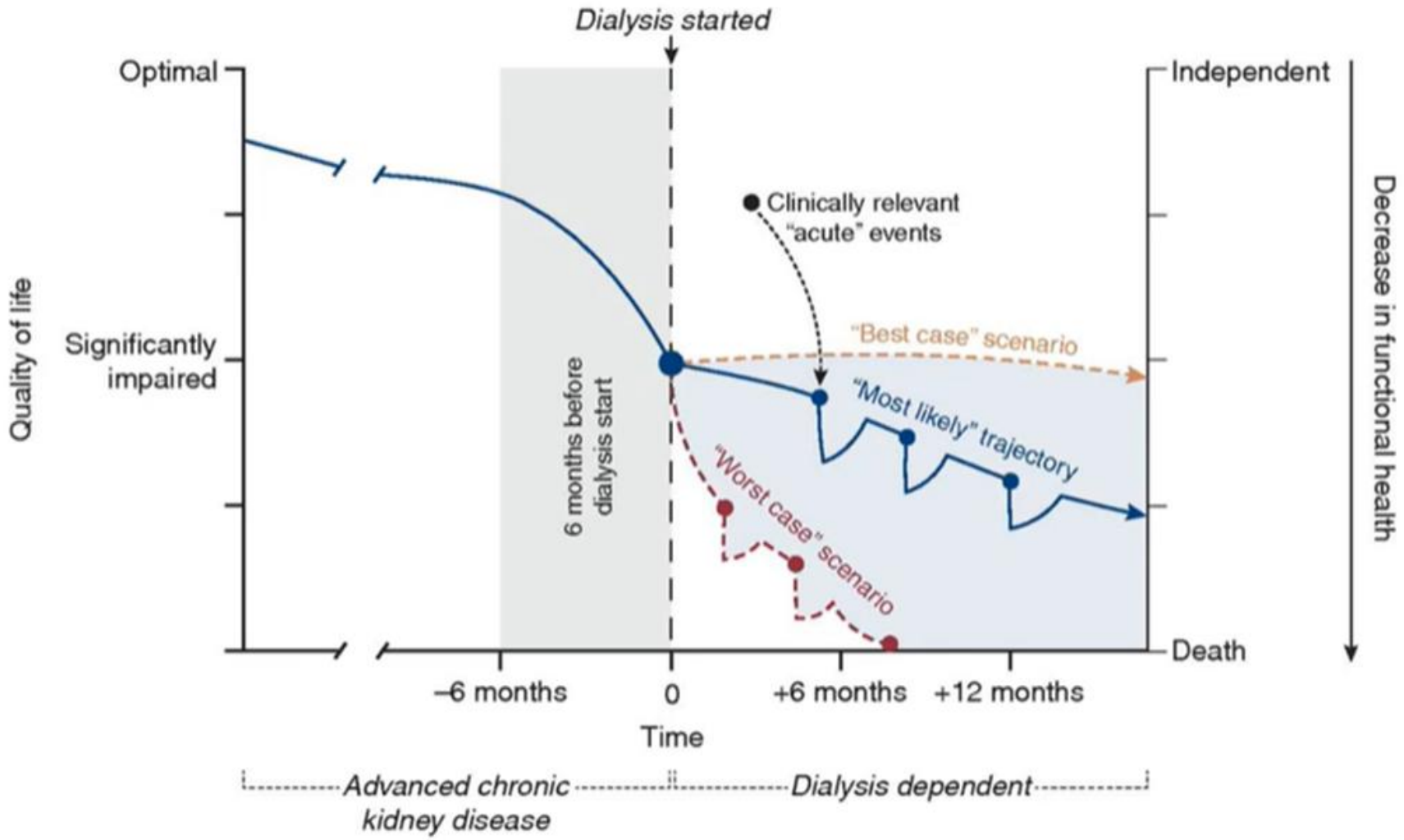
  13.3%-17.1% in kidney transplant populations

- CKD: Greater impairment compared to other end organ disease patient groups
  - Eg advanced COPD and advanced heart failure
- CKD populations: younger age of onset; Functional impairment progresses within 3 months and 12 months of dialysis initiation.

Kennard et al BMC geriatrics. 2023;23(1):449
Nair et al Am J Kidney Dis. 2025 85(1):89-103.

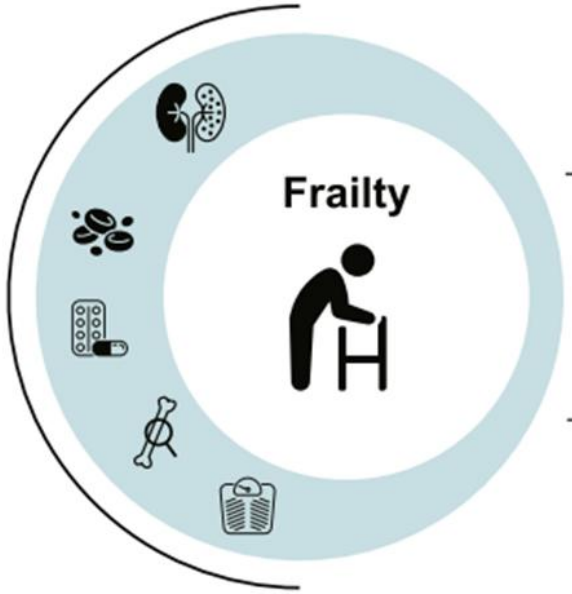
Frailty: understanding the impact of dialysis

Fonseca-Carerra & Jassal
Clin J Am Soc Nephrol. 2022



Physiologic not chronological age

- Age is a separate construct
- Age just one risk factor
- CKD context: accelerated aging, premature onset of frailty
- Present in 63% of patients younger than 40 years
- Approaching 50% age <65years undergoing HD



Risk Factors

- Older age
- Female sex
- Diabetes
- Peripheral artery disease
- Polypharmacy

Pathophysiology

- Senescent cells
- Inflamation and oxidative stress
- Sarcopenia
- Cortisol concentrations
- Anaemia
- Extensive vascular calcification
- Bone demineralisation
- Malnutrition

Clinical Markers

- Cortisol concentrations
- Inflammatory markers; increased neutrophil count
- Protein energy wasting
- Hypoalbuminemia
- Decreased transferrin levels
- Anaemia and erythropoietin resistance

Figure 1. Risk factors, pathophysiological mechanisms, and clinical markers of frailty in the kidney disease context.

Bao et al. Arch Intern Med 2012
Chu et al Am J Nephrol. 2020;51(7):501-510

Unique pathophysiologic mechanisms

Nair et al Am J Kidney Dis. 2025 85(1):89-103.

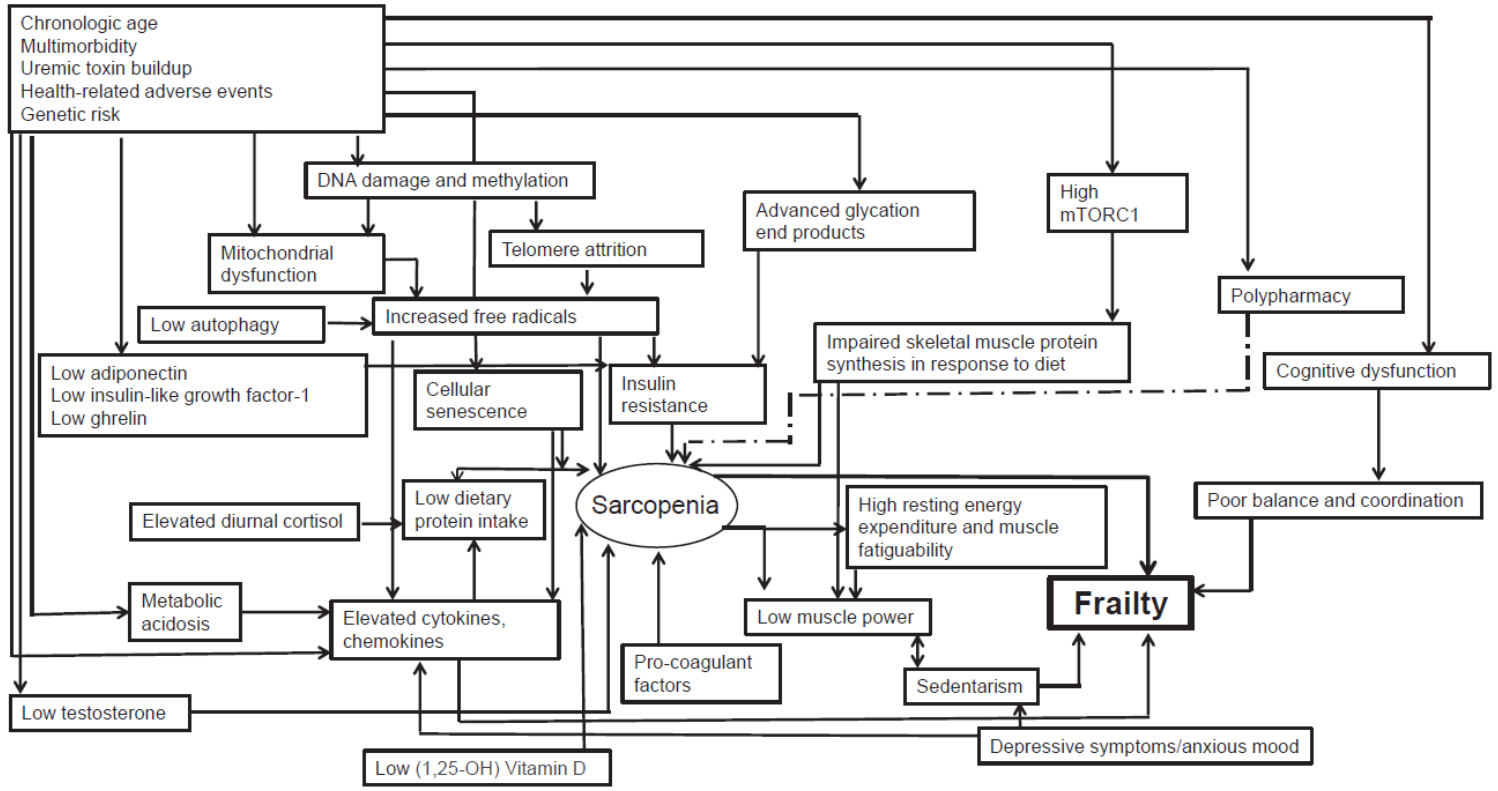


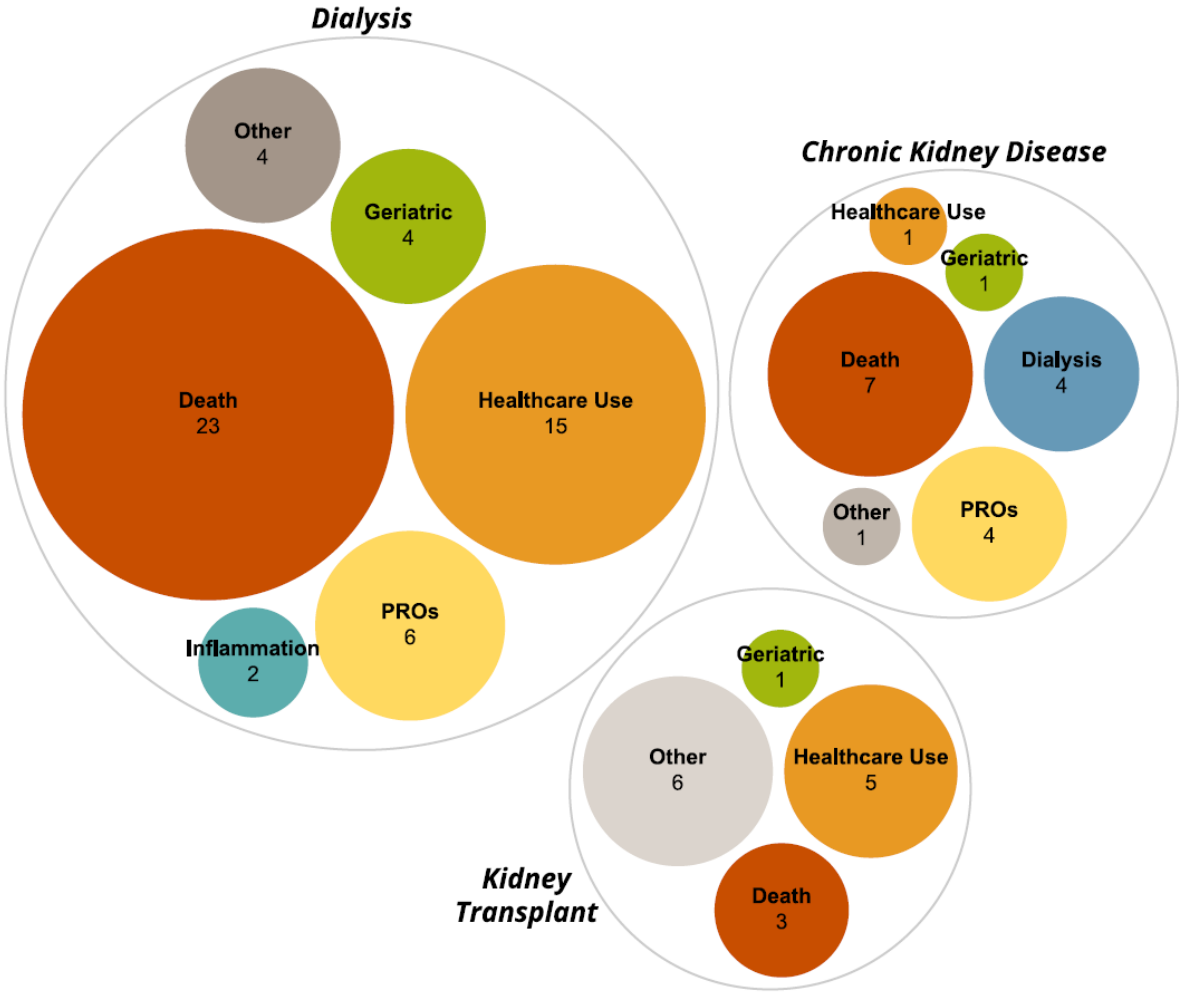
Figure 2. Mechanisms of frailty in kidney disease. All possible associations between constructs are not represented. Dotted line indicates hypothesized relationship. Abbreviation: mTORC1, mammalian target of rapamycin complex 1.

Clinical implications of frailty

- Predicts 2-6 fold increased risk of death, hospitalisation, progression to dialysis
- Treatment choice:
  - Not-for-dialysis conservative kidney care
  - In-centre vs at-home dialysis modality
  - No survival benefit of dialysis over conservative kidney management
- Complications on dialysis
  - Greater symptom burden and impaired quality of life
  - Infection, cardiovascular events
  - Intradialytic hypotension
  - Primary and secondary vascular access failure
- Reduced access to transplantation
- Surrogate measures, qualitative research: greater probability of dialysis withdrawal
- Assessment: better transplant outcomes, improved advanced care planning and care scaffolding

Comprehensive Review: Kennard et al IMJ 2022, Kennard et al KI Reports 2024

Excellent prognostic ability



Nair et al Am J Kidney Dis. 2025 85(1):89-103.

Do we recognise frailty when we see it?

Clinician misclassification

- Practice patterns: Clinicians preference subjective clinical impressions of frailty over objective frailty assessment[1,2]

- Compared blinded Fried frailty objective assessment to clinical acumen of experienced nephrologists[3]
  - 89 participants assessed by six primary nephrologists (all male, median age 52 years (IQR 43–54 years), median years of physician practice 19 (IQR 13–20 years)).
- **Minimal to moderate** correlation between objective frailty and subjective assessment

  (r = 0.50, P = 0.00, κ – 0.25, p = 0.00)
- Influenced by surrogate measures of frailty: female sex, comorbidity, walking aid

- Equally likely to over-classify or under-recognise frailty : **missed opportunity, inequity**

[1] McAdams-DeMarco et al Transplantation 2020
[2] Kennard et al Ren Soc Australas 2022
[3] Kennard et al IMJ 2024

How should we assess frailty?

Frailty assessment tools

	Fried phenotype[1]	Clinical Frailty Scale[2]	Frailty Index[3]	Comprehensive Geriatric Assessment
Tool	3 or more of 5: Inactivity Fatigue/exhaustion Poor strength Unintentional weight loss Slow walk speed	9-point scale based on clinical descriptors Emphasises disability	Concept of multi-organ deficits and redundancy until a critical threshold of disability	Specialist geriatric and multidisciplinary assessment of physical, cognitive and socioemotional domains
Strengths	Objective assessment Pre-frail state Excellent interrater validity Easy to train, 10 min	Common theme "slowing" Excellent interrater validity Smart-phone App	Retrospective application Can accompany routine admission	Gold standard Objective tests of upper and lower limb function Only tools to assess cognitive, social caregiver components
Limitations	Non-inclusion of cognitive impairment Weight loss can be problematic	Not validated for use among younger people Insensitive to dynamic changes	Not validated for use among younger people Not valid for use among non-specialists Limited studies in dialysis populations ~30 min	Not validated for use among younger people **Resource intensive**
Comparator Nixon et al Nephron 2018	Sens 89%, spec 96%, PPV 84% NPV 96%	Sens 79%, spec 87%, PPV 63%, NPV 94%	Sens 100%, spec 37%, PPV 30%, NPV 96%	

[1]Fried et al J Geront A Biol Sci Med Sci 2001, [2] Rockwood et al Can Med Assoc J 2005, [3] Rockwood et al J Geront A Biol Sci Med Sci 2007

Fried equipment

Clinical frailty scale

Fig 1. **Clinical Frailty Scale**

1. Very fit
People who are robust, active, energetic and motivated. They commonly exercise regularly and are among the fittest for their age

2. Well
People who have no active disease symptoms but are less fit than category 1. Typically, they exercise or are very active occasionally, such as seasonally

3. Managing well
People whose medical problems are well controlled but are not regularly active beyond routine walking

4. Vulnerable
While not dependent on others for daily help, often symptoms limit activities. A common complaint is being 'slowed up' and/or being tired during the day

5. Mildly frail
People often have more evident slowing and need help with high-order IADLs. Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework

6. Moderately frail
People need help with all outside activities, housework and cooking. They often need help with stairs and bathing, and might need minimal assistance with dressing

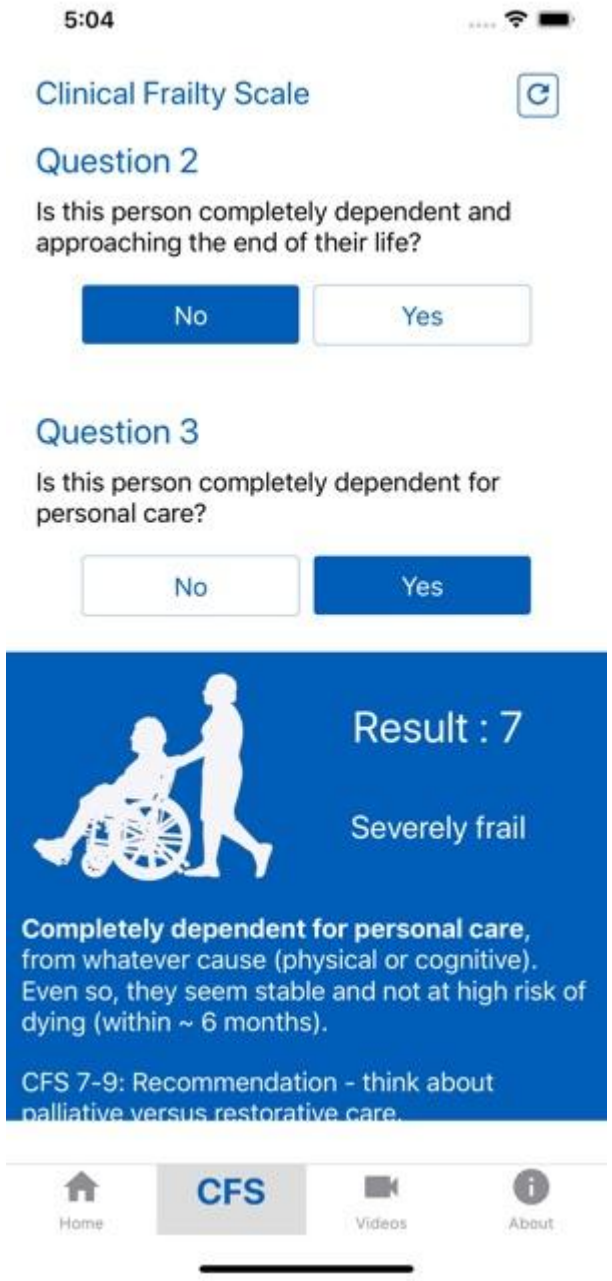
7. Severely frail
People completely dependent for personal care. However, they seem stable and not at high risk of dying (within ~6 months)

8. Very severely frail
People completely dependent and approaching the end of life. Typically, they could not recover even from a minor illness

9. Terminally ill
People approaching the end of life. This category applies to people with a life expectancy of <6 months, who are not otherwise evidently frail

IADL = instrumental activity of daily living (such as finances, transport, heavy housework or medications)

Source: Rockwood et al (2005)



Clinical utility of Fried frailty assessment

- Prospective observational cohort study advanced CKD (eGFR <20ml/min) or maintenance HD
- Frailty assessment aligned with outpatient visit baseline, 6 and 12 months
- Explored frailty dynamics, hospitalisation and healthcare utilisation, transplant outcomes, survival
- 256 participants (147 CKD, 109 HD), median 70.5y (IQR 57-80, 98 <65y), 62.7% male
- Median follow-up 510 days (IQR 429-541)

Table 2 Fried frailty phenotype at baseline for the study population at baseline

Fried phenotype	CKD N=147	HD N=109	
Frail (%)	55 (37.4)	38 (34.9)	$\chi 2=0.35$, p=0.84
Pre-frail (%)	66 (44.9)	53 (48.6)	
Robust (%)	26 (17.7)	18 (16.5)	

CKD, chronic kidney disease; HD, haemodialysis.

Not a vicious cycle: Frailty is dynamic

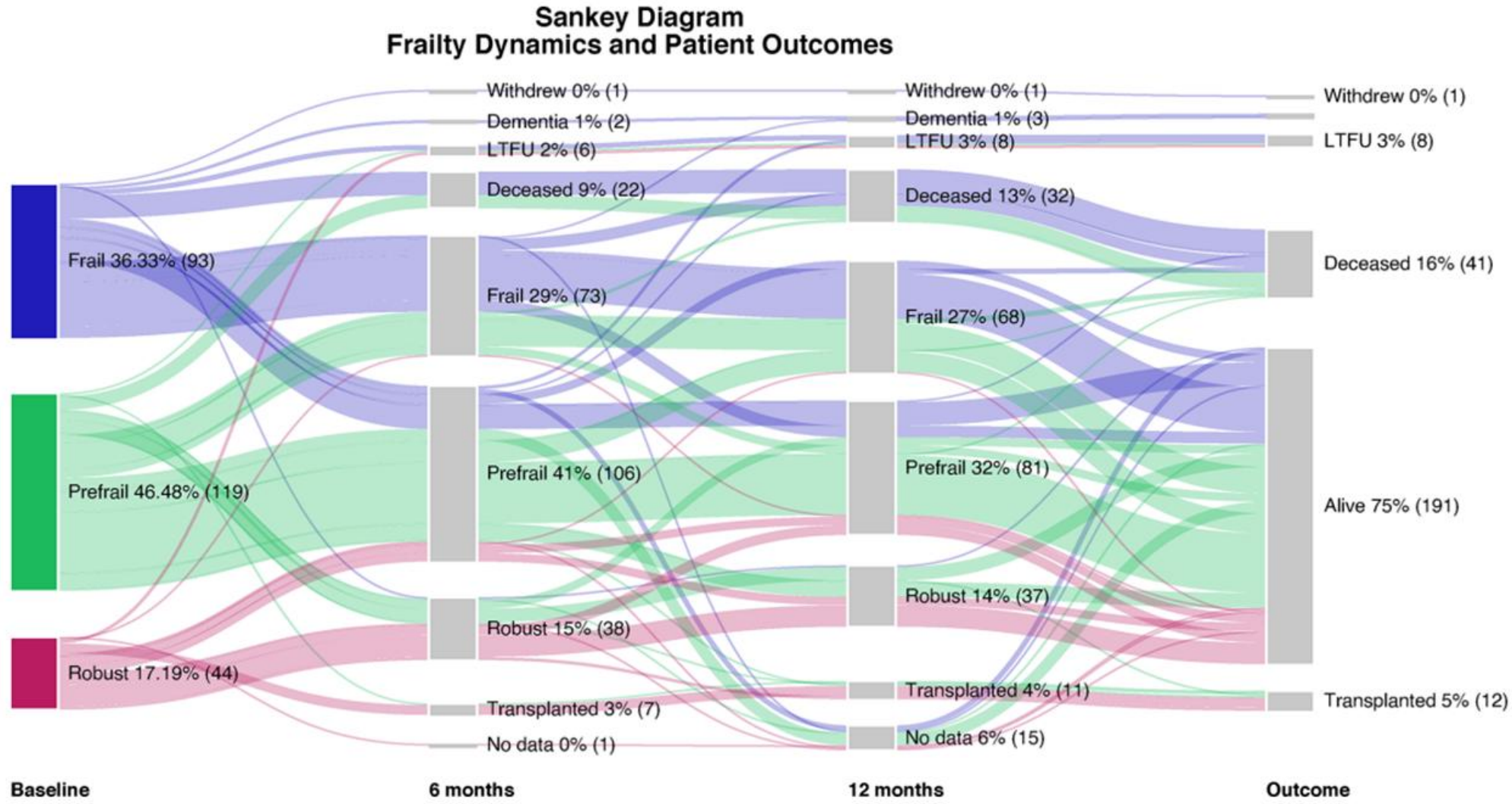


Figure 1 Sankey diagram illustrating frailty dynamics and outcomes over longitudinal follow-up.

Predicting frailty progression

Table 5 Cox proportional hazards modelling for frailty progression

Variable	Frailty progression model (95% CI) adjusted for demographics
Female sex	HR 1.79 (1.04 to 3.07), p=0.03
Usual walking aid	HR 1.28 (0.91 to 1.81), p=0.15
Symptom burden	HR 1.03 (1.01 to 1.05), p=0.02
Depressed	HR 0.77 (0.59 to 1.00), p=0.05

Frailty outcomes

- Frailty predicted survival HR 3.60 (1.86 to 6.97), p<0.001
- **Dynamic frailty clinically relevant: improved survival**
- Frailty predicted increased Emergency Department presentations, admission to hospital and total days of hospitalisation
- **Independent** of age, sex, stage of CKD, comorbidity, disability or inflammatory state
- Hospitalisation events occurred a median 152 days (IQR 44-251) after enrolment: **window of opportunity**
- Poor utilisation of referral services that might improve frailty outcomes: rehabilitation, geriatrician specialist involvement, palliative care
    - **Frailty goes unrecognised**

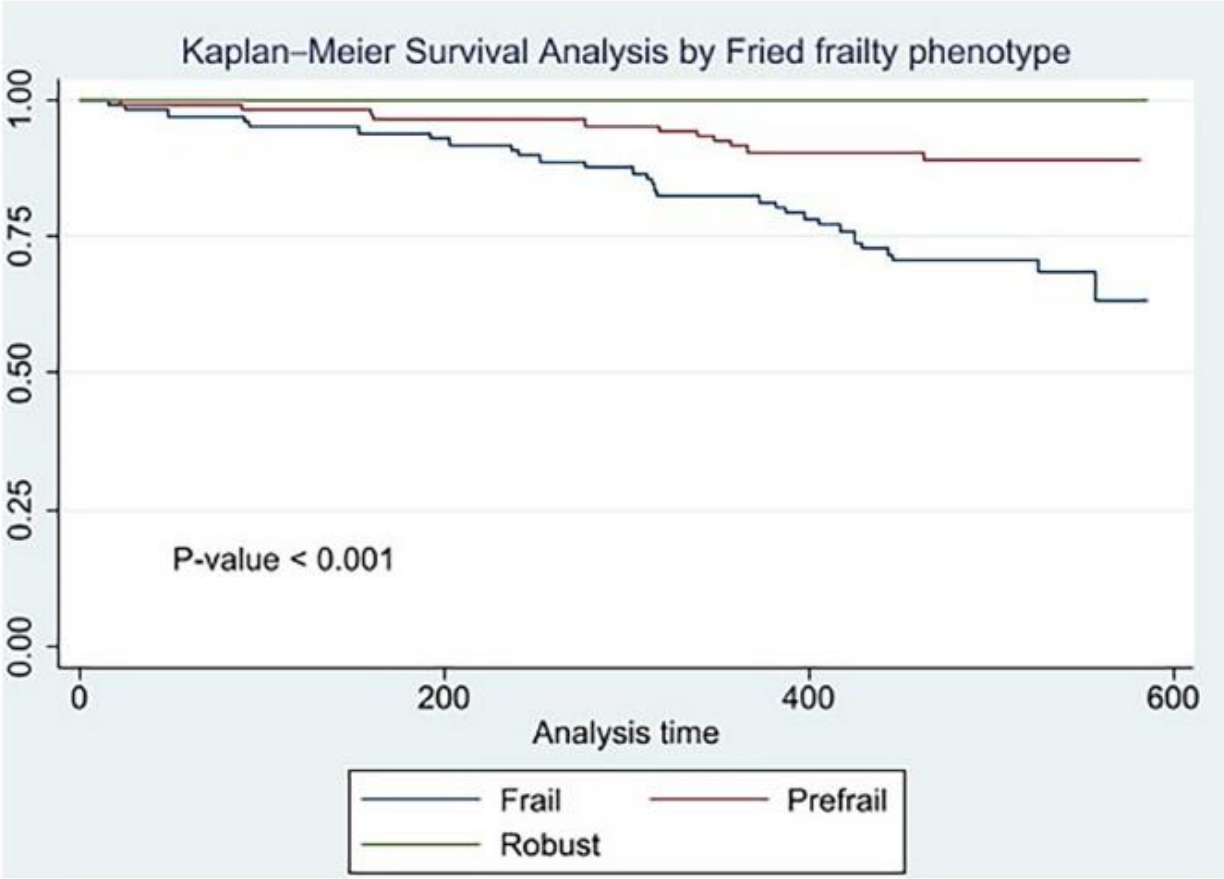


Figure 2 Kaplan-Meier survival analysis by Fried frailty phenotype.

Kennard et al BMJ Open 2024
Kennard et al KI Reports 2025

Table 2. Emergency department and hospitalization patterns by Fried phenotype

Health care utilization	Frail $n = 93$ 36.3%	Prefrail $n = 119$ 46.5%	Robust $n = 44$ 17.2%	Full cohort $N = 256$	*P*-value for difference between groups
ED presentations					
Total	256	225	36	517	< 0.01
Median (IQR)	2 (1–3)	1 (0–3)	0 (0–1)	1 (0–3)	
95% centile range	(0–8)	(0–6)	(0–3)	(0–7)	
Rate of ED presentations Median (IQR)	1.64 (0.69–3.98)	0.75 (0.00–2.31)	0 (0.00–0.85)	0.82 (0–2.34)	< 0.01
Hospital admissions					
Total	336	321	61	718	< 0.01
Median (IQR)	2 (1–5)	2 (0–4)	1 (0–2)	2 (1–4)	
95% centile range	(0–13)	(0–11)	(0–4)	(0–10)	
Rate of admission per 365 days Median (IQR)	2.32 (0.80–4.23)	1.54 (0.00–2.74)	0.69 (0.00–1.80)	1.53 (0.64–3.33)	< 0.01
Days of hospital admission					
Total	3076	2114	108	5298	< 0.01
Median (IQR)	14 (2–40)	4 (0–14)	1 (0–3)	4 (1–20)	
95% centile range	(0–181)	(0–63)	(0–8)	(0–72)	

ED, emergency departments; IQR, interquartile range.

How do changes in frailty affect hospitalizations and all-cause mortality among patients on hemodialysis?

Kidney Medicine

Methods

Prospective cohort study
Canada

N = 985 adults on maintenance HD

Frailty evaluated at:
- baseline (HD start)
- 6, 12, 24 & 60 months

Median follow-up 33 months

Frailty classified using **5-point score:**

- 1p **Physical inactivity**
- 2p **Slowness and/or weakness**
- 1p **Poor endurance and/or exhaustion**
- 1p **Malnutrition**

Frailty present if score ≥ 3 points
77% of adults had frailty during follow-up

Results

Associations with frailty 95% CI	All-cause mortality	Hospitalization
High frailty score	**aHR 1.58** (1.39,1.80) per unit increase in frailty	**RR 1.16** (1.09,1.23) per unit increase in frailty
Improvement in frailty (compared to frail across follow-up)	**HR 0.59** (0.42,0.81)	**RR 0.70** (0.56,0.87)

Conclusion: Frailty was associated with higher risk of poor outcomes, and participants whose status improved from frail to non-frail had better clinical outcomes than those who remained frail. These findings emphasize the importance of identifying and implementing effective treatments for frailty in maintenance HD patients.

Reference: Tonelli M, Wiebe N, Gill JS, et al. Frailty and clinical outcomes in hemodialysis patients: a prospective cohort study. *Kidney Medicine*, 2023.

Visual abstract by Corina Teodosiu, MD @CTeodosiu

The marginal cost of frailty

Table 2. Adjusted[a] mean point estimates and percentage differences in expenditures between frail and nonfrail patients

	Nonfrail ×1000 $/pppy (95% CI)	Frail ×1000 $/pppy (95% CI)	Percentage difference in expenditures (95% CI)
Total costs	71.8 (64.8–79.6)	87.6 (76.8–100.0)	+22.0% (+9.6 to +35.8)
Dialysis	23.7 (21.8–25.6)	22.0 (19.9–24.4)	−7.0% (−14.9 to +1.7)
Outpatient	11.4 (9.9–13.2)	14.3 (12.2–16.6)	+24.6% (+7.8 to +44.1)
Inpatient	18.4 (14.4–23.3)	29.9 (22.4–39.9)	+62.9% (+27.3 to +108.3)
Physician	9.2 (7.9–10.7)	10.3 (8.6–12.3)	+11.9% (−1.8 to +27.6)
Medication	7.8 (6.3–9.6)	8.0 (6.3–10.0)	+2.4% (−8.4 to +14.5)

CI, confidence interval.
[a]Adjusted for age, sex, body mass index, race, and comorbidities (diabetes, coronary artery disease, and congestive heart failure).
Point estimates standardized to average age and body mass index of all study participants.

Sy et al. KI Reports 2019

Incorporating the Clinical Frailty Scale into routine outpatient nephrology practice: an observational study of feasibility and associations

Anuttara Panchali Kumarasinghe [1,3,4] Aron Chakera,[1,2] Kien Chan,[1] Sharan Dogra,[5] Sally Broers,[5] Sean Maher,[1] Charles Inderjeeth [1,2] and Angela Jacques[1]

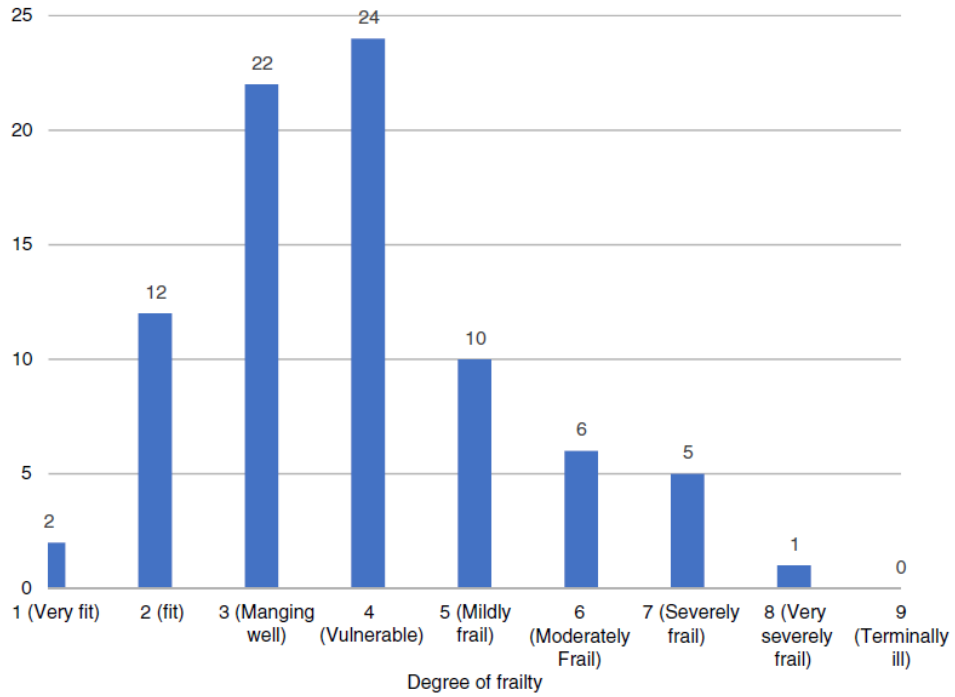
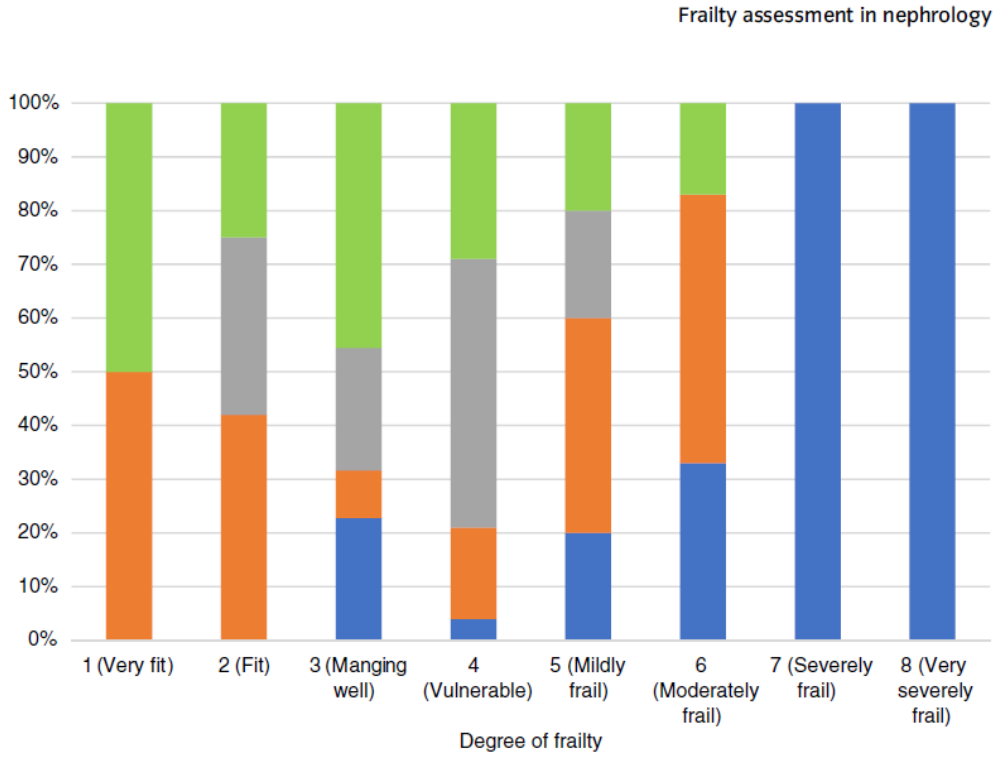


Figure 3 Distribution of Clinical Frailty Scale scores among older adults with advanced kidney disease attending nephrology outpatient clinics.

Clinician perception:
CFS assisted decision-making in 39% of patient-visits

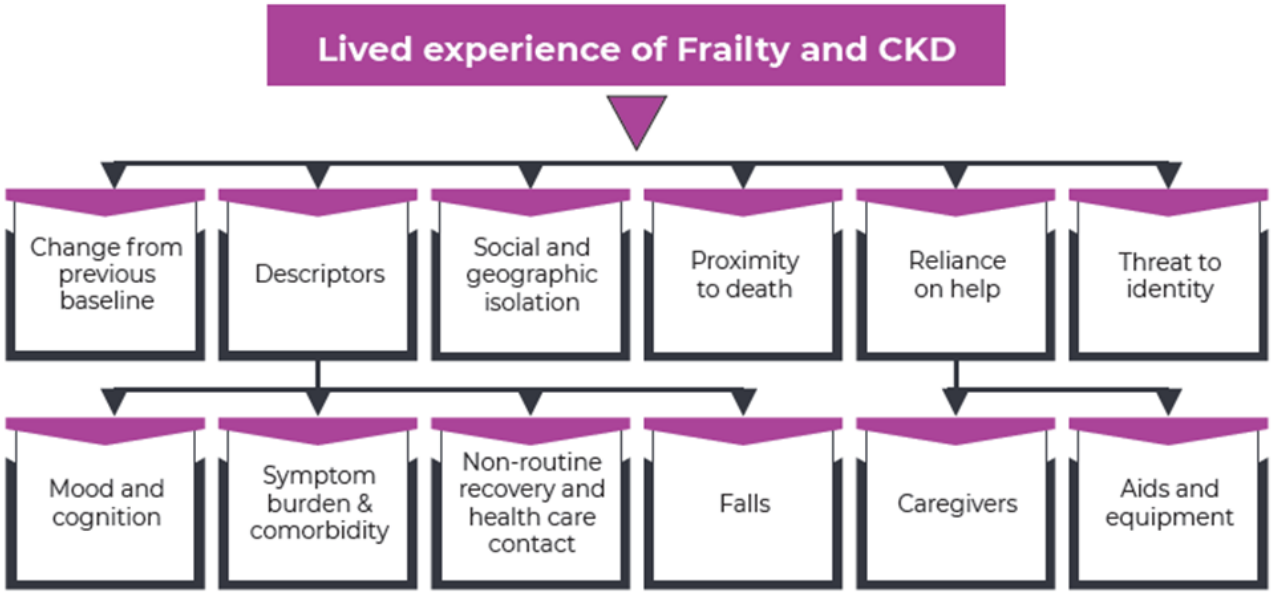


Goal: Screen all patients >50y attending low clearance clinic
Achieved: 59%

Figure 6 Planned end-stage kidney disease management variation with degree of frailty. (■), Conservative management; (■), haemodialysis; (■), peritoneal dialysis; (■), not documented.

What do our patients know about frailty?

Qualitative enquiry



- Negative, stigmatised condition
- Cultural stereotypes prominent
- Aligned with suffering
- Psycho-emotional-social experience
- Threat to health and well-being
- Punctuated by falls
- Non-routine recovery… highly dynamic and unpredictable
    - Disruptor to advance care planning efforts

Key findings

Frailty interacts with the physical manifestations of uraemia to produce characteristic **symptom clusters.**

"I've got very poor sleep habits. ... I find at times I can be lethargic, don't quite have the same amount of energy as I used to... I'm really tired all the time."

"Ten minutes and I'm buggered. You know, my legs are aching, my – get short of breath."

"I think this kidney disease depletes you of a lot of things, right? It makes you know you're ill, right? But it just plays on your brain all the time and it makes you angry... You just feel depressed."

Frailty was articulated as an inability to manage the home **environment** and loss of functional independence.

"[He] is basically a prisoner in his own home."

"My biggest outing is really my doctor's appointment."

Frailty was accompanied by social and geographic **isolation**

"You had to be strongminded to just pace yourself and get through it."

CKD/Frailty is **dynamic**

Participants held **expectations of improvement** with appropriate time and care

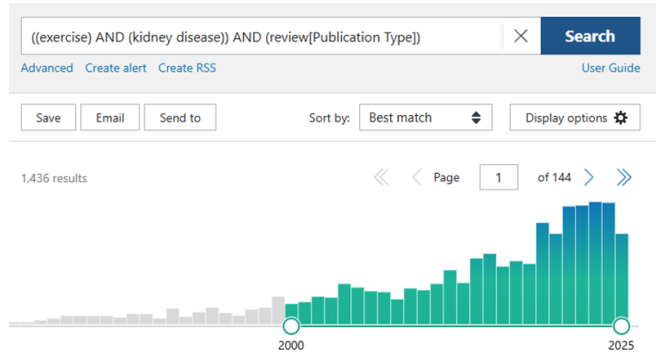
"Frailty for me (was in this time), was would I ever wake up and feel like I was alive. Because I felt so exhausted and weak and empty that I didn't know if I was ever going to get past that feeling... I was very, very fragile and unwell...so as it has progressed to where I am now I'm quite quietly sort of excited that I might have a bit longer to live..."

The lived experience of CKD/frailty is imbued with a sense of **optimism and resilience.**

Kennard et al International Journal of Geriatrics and Gerontology 2024

How should we respond to frailty?

Exercise-based frailty interventions



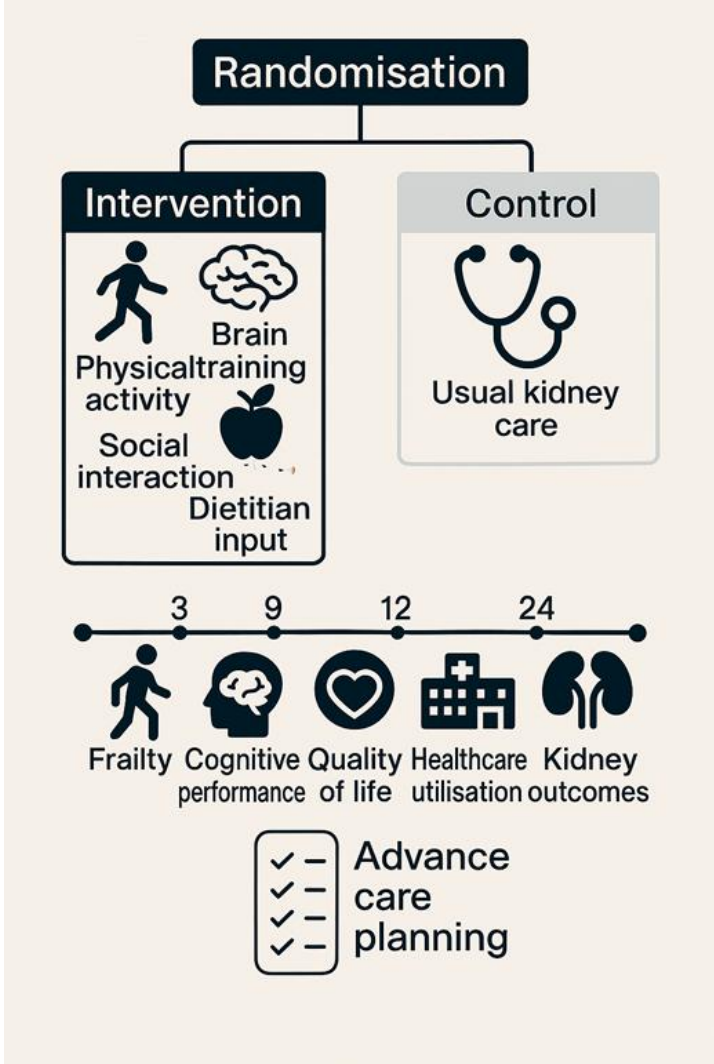
- Evidence is sparse: little research focus on frailty
- KDIGO 2024 recommendations: graduated supervised physical activity
- UK Kidney Assoc 2021: movement and function-focused programs can support symptom control and maintain dignity and autonomy
- Italian Society of Nephrology 2024: beneficial, safe, tailored
- ISPD: specific recommendations for PD populations
- HD: intradialytic and home-based exercise programs have equal benefit in performance outcomes
  - Safe
  - No long-term outcomes such as hospitalisation or mortality
- CKD: improved inflammatory markers, fitness and muscle function, improved cardiac function and slowed or resolved proteinuria.
  - Psychological benefit, improved sleep and QOL

Promising studies… and some ideas

- Ex-FRAIL… home based exercises
- CYCLE-HD… intradialytic cycling

- Frail to Fit Study: Chair-based modified yoga/cycling/activity circuit + multimodal intervention + codesign

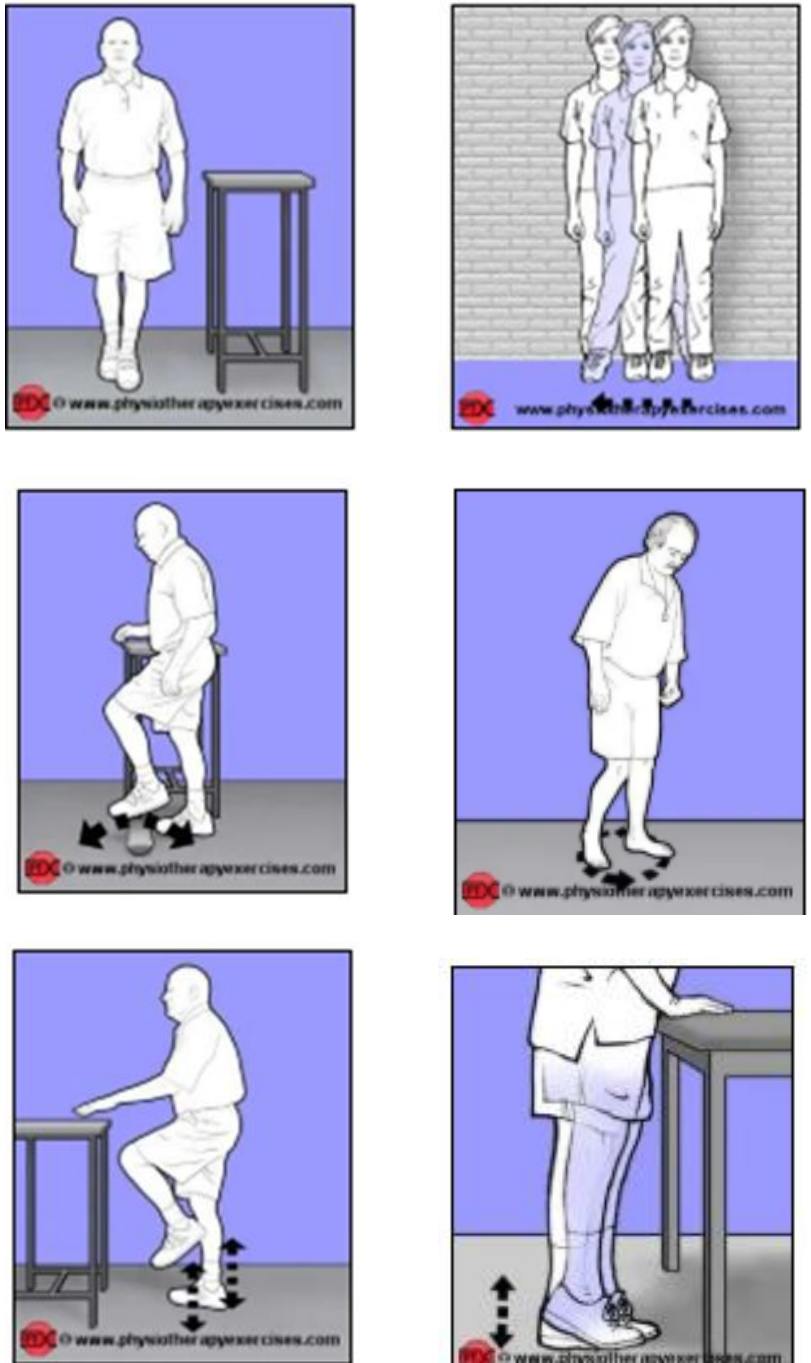
- Comprehensive geriatric review facilitates future care planning and advance care planning



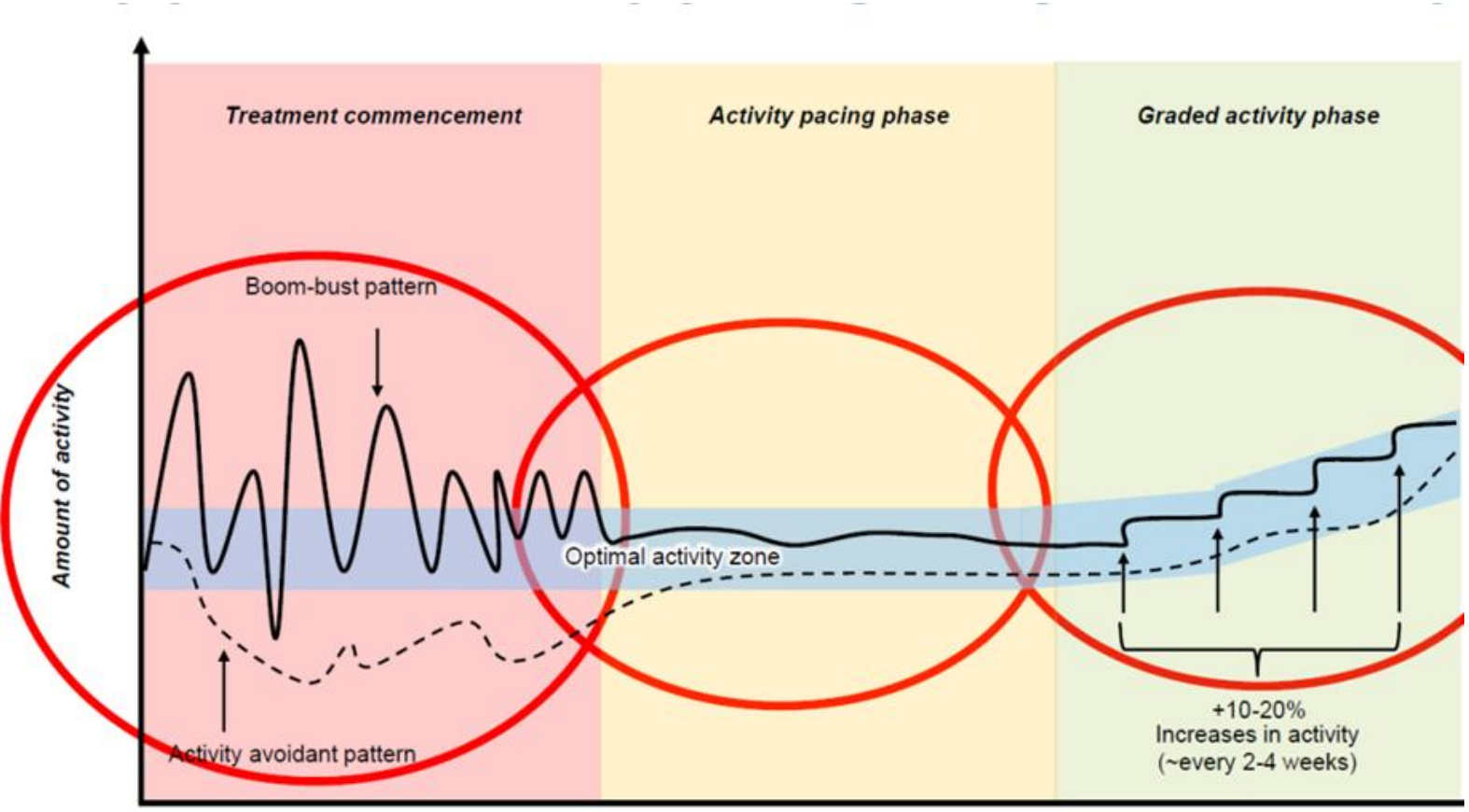
Exercise prescription

- Falls prevention: Standing balance and stepping
- Mobility and walking strategies
- Managing dyspnoea
  - Maintain cardiorespiratory fitness
  - Add in small additional activities (marching 10 steps)
  - Seated movement
  - Chest opening, breathing
  - Pursed-lip breathing, belly breathing
- Address the fistula fallacy

Acknowledgement: A/Prof Arnold



Managing fatigue



- Understanding fatigue
- Rest ≠ more energy
- “Spending” energy wisely
- Finding thresholds
- Avoiding exacerbations
- Not a conventional progression model

Acknowledgment: A/Prof Arnold

MJA 2020 Sandler & Lloyd

Renal rehabilitation

- “a long-term comprehensive program consisting of exercise therapy, diet therapy and water management, drug therapy, education, psychological and mental support to alleviate the physical and mental effects of kidney disease and dialysis therapy, prolong life, and improve psychological and occupational circumstances”
- “exhaust all support options to help kidney disease patients smoothly achieve social rehabilitation instead of simply implementing exercise therapy”

Matsuzawa Renal Replacement Therapy 2022

- Wrap-around frailty management
  - Deprescribing polypharmacy: PPIs, Statins, gabapentinoids, insulin, GLP1 analogues & DPP-4 inhibitors, phosphate binders
  - Assessing and responding to symptom burden
  - Targeted multidisciplinary care: Dietitian, social work, physio/ex-phys, Geriatrician
  - Caregiver support
  - Future care planning

Final thoughts

- Consider use of cystatin-c based estimates of glomerular filtration
  - Among older adults (where frailty/sarcopenia common), the lower eGFR between eGFRcys and eGFRcr was a more accurate and less biased estimate of mGFR when comparing the groups. Potock Kidney Medicine 2023
  - KDIGO Guidelines: **eGFRcr-cys gives improved performance** versus either marker alone in groups with abnormal muscle mass
- Urine albumin:creatinine inaccurate when the denominator (creatinine) is very low
  - In frail or sarcopenic patients, **spot ACR may overstate albuminuria** (and therefore CKD risk) purely because of **low creatinine generation**.
  - ?Albumin excretion rate and context-aware interpretation. Vart et al AJKD 2016

Summary

- Assess frailty objectively: can be feasibly incorporated into clinic spaces and activity
- Recognise the prognostic implications of frailty
- Discuss frailty implications to support shared decision making
- Avoid therapeutic nihilism
  - Deprescribing and attention to symptom burden
  - Recognition of frailty should prompt exercise physiology/physio, dietitian, social work, geriatrician

Thank you

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Consumers and caregivers TCH Department of Nephrology

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