Sociedad Española de Nefrología

nefrología
Revista de la Sociedad Española de Nefrología
www.revistanefrologia.com

Review

Frailty in end stage renal disease: Current perspectives

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ARTICLE INFO

Keywords:
Frailty
End stage renal disease
Dialysis
Sarcopenia
Senescent nephropathy

ABSTRACT

Frailty is common in end stage renal disease (ESRD) and is a marker of poor outcomes. Its prevalence increases as chronic kidney disease (CKD) progresses. There are different measurement tools available to assess frailty in ESRD. The pathogenesis of frailty in ESRD is multifactorial including uraemia and dialysis related factors. In this current review, we discuss the importance of frailty, its pathogenesis, screening methods, prognostic implications and management strategies in context of ESRD.

Fragilidad en la enfermedad renal en etapa terminal: perspectivas actuales

Palabras clave:
Fragilidad
Enfermedad renal en etapa terminal
Diálisis
Sarcopenia
Nefropatía senescente

RESUMEN

La fragilidad es común en la enfermedad renal en etapa terminal (ESRD) y es un marcador de malos resultados. Su la prevalencia aumenta a medida que avanza la enfermedad renal crónica (ERC). Hay diferentes herramientas de medición disponibles para evaluar la fragilidad en la ERT. La patogenia de la fragilidad en la ESRD es multifactorial que incluye uremia y factores relacionados con la diálisis. En esta revisión actual, discutimos la importancia de la fragilidad, su patogénesis, métodos de cribado, implicaciones pronósticas y estrategias de manejo en el contexto de la ESRD.

Introduction

Frailty is a state of increased vulnerability to physical stressors like illness which leads to poor clinical outcomes.[1] It is a condition usually found in elderly people and occurs as a result of progressive and sustained degeneration in multiple physiological systems in our body. This is further worsened because of a decline in psychological health and inadequate

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http://dx.doi.org/10.1016/j.nefroe.2021.05.008

social support.[1–3] The prevalence of frailty is around 11% in elderly without end stage renal disease (ESRD), whereas in patients with ESRD on dialysis it is more than 60%.[4,5] It is characterized by weakness, balance and motility issues, and a decreased ability to resist stressors.[6,7] Impaired physical function, sarcopenia, and an increased risk of falls are hallmarks of the frailty syndrome. Other adverse health outcomes include fractures, hospitalization, institutionalization, disability, dependence, dementia, poor quality of life, and death.[8] Frailty in chronic kidney disease (CKD) has been described as "senescent nephropathy" – a state characterized by a synergistic decline in physical and renal function, proposed to be caused by increased levels of inflammation associated with each condition.[6] Inspite of being an important prognostic marker, frailty screening is yet to be widely implemented in routine renal care. Patients with CKD, especially ESRD are at a high risk of being frail. Though there are many frailty measuring tools available, the optimal means of screening for frailty in patients with kidney disease remains perplexing.

The pathogenesis of frailty in ESRD is multifactorial and is different from the general population since uraemia and dialysis are significant contributors. Additionally, standard management of ESRD, including kidney replacement therapies, may have a lower benefit or may be even potentially harmful in the presence of frailty. Recently, several interventions to modify frailty in ESRD have been proposed.[9] In this review, we highlight the importance of frailty screening in ESRD, different tools for its measurement and its pathogenesis. We also recapitulate the available evidence on frailty as a predictor of poor clinical outcomes, as well as current guidelines for its management.

Definitions and frailty measurement tools

Frailty has been defined as a state of increased vulnerability to stressors like illness or trauma due to degeneration in multiple systems in our body leading to poor outcomes.[1] Recently efforts have been put to create an operational definition for frailty, so that it aids in its identification and severity. In literature, two principal concepts are described: the Fried Phenotype Model of Frailty, which focuses frailty as a physical phenotype characterized by sarcopenia, and the other more holistic Frailty index (Cumulative Deficit Model of Frailty) which additionally incorporates other domains like comorbidities and psychological conditions.[10–14]

Frailty Phenotype (FP) is described as 'a clinical syndrome involving at least three of the following: unintentional weight loss, self-reported exhaustion, weakness, slow walking speed and low physical activity'.[14] (Table 1) The presence of one or two of the above characteristics defines a patient as pre-frail. In FP, the measures of weakness and walking speed examination is cumbersome and time consuming. So the FP has been modified in an attempt to reduce the burden of data collection by several studies on CKD populations which have used modified versions of the FP, where questionnaire-based assessments for the objective measures of weakness and slowness are used. Though these methods may overestimate the prevalence of frailty, they also predict outcomes similar to FP.[15–18] A study demonstrated that modified FP was independently associated with increased mortality risk in dialysis-dependent CKD [HR 2.24 (95% CI 1.60–3.15)] and also with an increased risk of the combined endpoint of hospitalization or death [HR 1.56 (95% CI 1.36–1.79)].[16] Similar to the FP, the short physical performance battery (SPPB) is comprised of three physical assessments: standing balance, gait speed, and a chair stand test. Like the FP, its strengths also lie in its objectivity. In addition, it provides a range of scores, from 0 (worst performance) to 12 (best performance), allowing some quantification of a patient's level of frailty. Importantly, in patients with CKD, the SPPB is reliable, [19] associated with disease progression and is predictive of mortality.[20]

A contrasting and holistic approach to the Cumulative Deficit Model of Frailty was described in the older population. [11] A remodification of this model included a total of 70 variables consisting of a variety of medical, psychological and functional impairments.[13] This led to the creation of a more global and complete frailty assessment, the frailty index (FI). FI score was calculated by dividing the total number of deficits for an individual patient by all the predetermined clinical variables.[3] A study compared FI with FP in elderly individuals and demonstrated that these operational definitions of frailty correlated moderately well with each other.[12] They categorized participants as robust, pre-frail (intermediate frailty) and frail as per FP.[12] FI and FP were found to be comparable in frailty assessment in CKD.[21] But the FI is demanding to implement into routine clinical care, as at least 30 variables are required to calculate the score making it a relatively time-consuming alternative.[22,23] However, with the advent of electronic health records, it may be possible to surpass this challenge.

The Groningen frailty indicator (GFI) is another multidimensional method of assessing frailty. It consists of 15 questions across 8 domains, including mobility, vision, hearing, nutrition, comorbidity, cognition, psychosocial, and physical fitness. The absence of physical testing and a better assessment of psychosocial status makes its afavoured screening test.[24] GFI was equally predictive of death and hospitalization in CKD population as other approaches, but it failed to distinguish specific deficits, especially of a physical nature.[25] This could be due to the reason that physical impairment is screened with a single question, asking the patient to rate their fitness from 0 to 10.[24]

The multidimensional prognostic index (MPI) has been developed to predict the longevity of hospitalized adults. In MPI, frailty status is assessed through eight individual assessments including function (activities of daily living), polypharmacy, mental status, nutrition, comorbidity, risk of pressure sores and social circumstances. Deficits in each domain are graded as 0 (none), 0.5 (minor), or 1 (major), and then averaged.[26] A score greater than 0.66 is indicative of frailty and associated with increased hospital mortality and length of stay in the general population.[27] In the elderly CKD population, the addition of the MPI to the estimated GFR drastically improved prediction of mortality.[28] A study revealed that maintenance haemodialysis (HD) patients had higher MPI scores than the global geriatric population.[29] The limitation of the MPI score is that it is only been validated in admitted CKD patients and needs endorsement before generalization to the outpatient CKD population.

Table 1 – Measures of frailty in end stage renal disease.

Tool	Components/domains	Advantages	Disadvantages
Fried's frailty criteria (Fried et al., 2001)[14]	Physical – weight loss, low physical activity, exhaustion, slowness, weakness	Most commonly used and extensively validated in chronic kidney disease (CKD) and end stage renal disease (ESRD) population Objective measures also used hence reproducible	Need to perform physical tests Assesses only physical domain Categorical grading of components, hence may identify only moderate to severe cases Weight loss criteria may not be practical in dialysis patients
Short Physical Battery performance (Guralnik et al., 1994)[34]	Physical – Balance, gait, strength, and endurance	Validated in CKD and ESRD population Objective assessment Risk scoring is on a continuous scale hence can help identify mild cases and also monitor progress	Only physical domains assessed Physical testing may be cumbersome
Groningen Frailty Indicator (Steverink et al., 2001)[24]	Multiple – Physical, cognitive, social and psychological	No physical tests to be performed hence easier Gives information of day to day functionality of the patient	Not well validated in CKD and ESRD Subjective assessment in many domains Less sensitive to detect defects in physical domains
Clinical Frailty Scale (Rockwood et al., 2005)[13]	Multiple – Physical cognitive, functional, comorbid illness	Based on clinical judgement, simple to use Allows for gradation and monitoring progress	Many components subjective Very fit ESRD patients will also be scored as 3 (Managing Well) on account of co-morbidity Not well validated CKD/ESRD
Frailty Index (Rockwood and Mitnitsky 2001)[11]	Multiple – Physical, cognition, co morbid illness, symptoms, disabilities	Covers multiple domains, which can be created specifically for a target population Patients can be graded	Time consuming to calculate because of mathematical nature
Multidisciplinary prognostic index (Pilotto et al., 2008)[26]	Multiple – medication number, instrumental activities of daily living (IADLs), ADLs, cognitive status, nutritional status, risk of developing pressure sores co-morbidity and living status	Help predict the longevity of hospitalization	Validated predominantly for hospitalized patients only

Finally, to produce a simple yet global frailty assessment for screening purposes, a clinical frailty scale (CFS) has been proposed.[13] Simplicity is the hallmark of the CFS when compared to other methods of assessing frailty. CFS relies on clinical judgement alone and higher scores on the CFS were associated with an increased risk of death [HR 1.30 (95% CI 1.27–1.33)] and hospitalization [HR 1.46 (95% CI 1.39–1.53)].[13] In its original form, the CFS was a 7-point scale[13] and later updated to include nine descriptors.[23] The CFS has been shown to have similar predictive characteristics as the FP and FI in the general population.[12,13] In addition, like the SPPB and FI, the CFS is graduated and allows for monitoring of changes in frailty severity over time.[30] CFS scores at dialysis initiation are associated with higher mortality[31] and worse health-related quality of life scores in older patients on assisted peritoneal dialysis (PD) and HD.[32] CFS seemingly agreed with the FP better than the SPPB and FI, suggesting that the CFS may be a valuable option for accurate screening of frailty when it is not practical to perform a physical assessment.[33] So CFS is a promising frailty screening tool that could be incorporated into routine clinical renal care. The limitations of the CFS are being a subjective tool and yet to have robust validation data in CKD. Currently there is no consensus as to which measurement of frailty is superior. Since all approaches are associated with clinical outcomes, it is more important that efforts are made to identify frailty in ESRD, regardless of the adopted methodology.

Pathogenesis of frailty in ESRD (Fig. 1)

The pathogenesis of frailty in ESRD is multifactorial. Reduced intake contributes to sarcopenia and later physical frailty.[35] The contributing factors for loss of appetite include the uraemic milieu, inflammation, comorbid illnesses, medications and associated low mood and cognitive impairment.[35,36]

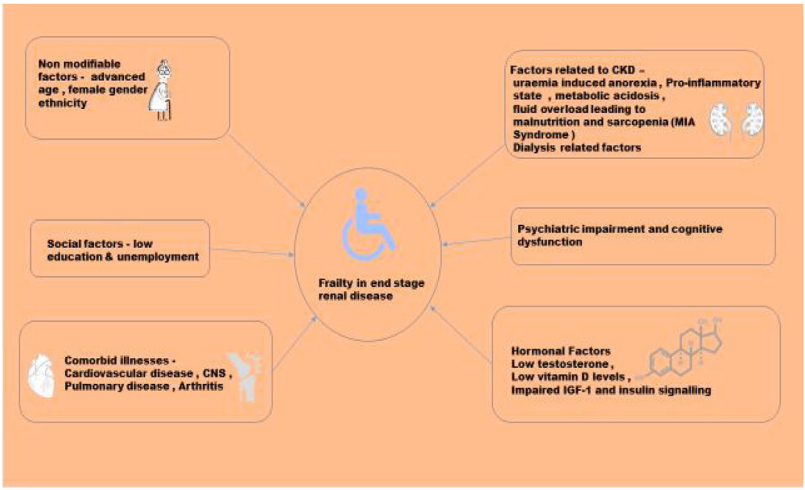

Fig. 1 – Pathogenesis of frailty in end stage renal disease (Abbreviations: CNS – central nervous system, CKD – chronic kidney disease, MIA – malnutrition inflammation-atherosclerosis, IGF – insulin like growth factor).

Physical inactivity is the other important factor in CKD which contributes for sarcopenia.[37] The increased levels of pro-inflammatory cytokines like interleukin (IL-6) and tumour necrosis factor alpha (TNF-a)[38] leads to impaired signalling of the anabolic hormones insulin and insulin-like growth factor-1 (IGF)-1.[35,39] This leads to muscle protein breakdown via the caspase-3 and ubiquitin proteasome system.[38] Metabolic acidosis also activates caspase-3 and inhibits intracellular signalling of insulin and IGF-1.[35,38] All of the above results in a state of protein catabolism leading to sarcopenia. It has been shown that 1, 25$(OH)_2$ D is a determinant of physical function and muscle size in those with CKD.[40] So deficiency of Vitamin D also may be a factor in the development of frailty in CKD. Finally, cellular senescence, loss of telomeric structures, mitochondrial dysfunction, increased free radical production and poor DNA repair capability are important in the ageing process and the development of frailty.[41] These processes occur prematurely in CKD population ultimately leading to sarcopenia, vascular dysfunction and progressive organ damage.[42]

Frailty as a marker of prognosis in ESRD

Frailty is independently predictive of adverse outcomes, including falls, hospitalization and mortality in the elderly general population.[14] Furthermore, the presence of intermediate frailty (or pre-frailty), was predictive of becoming frail over the next 3–4 years.[14] Studies that were done in the ESRD patients also show a similar pattern. A study demonstrated that frailty at dialysis initiation was associated with an increased risk of mortality [hazard ratio [HR] 1.57 (95% CI 1.25–1.97)] and first hospitalization [HR 1.26 (95% CI 1.09–1.45)].[5] Another study categorized dialysis patients as either non-frail, intermediately frail or frail. It was seen that proportion of participants admitted to hospital on two or more occasions over the subsequent year after enrolment was 43% for frail dialysis patients compared to 28% for nonfrail dialysis patients.[43] The 3-year mortality was 40% for frail dialysis patients. 34% of those categorized as intermediately frail patients died within the 3-year follow-up period, compared with only 16% of those who are non-frail.[43] Thus, differentiating degrees of frailty offers even greater clinical utility. Another study by the same group assessed frailty in 95 dialysis patients for falls. Over a 6.7-month follow-up period, there were 3.09-fold (95% CI 1.38–6.90) more falls in frail patients.[44] The other studies in dialysis patients are listed in Table 2. With the present evidence, it is clear that assessment of frailty is an important prognostic indicator in dialysis patients and it predicts mortality, hospitalization and falls irrespective of the methods used for assessment.

Current guidance

Among present guidelines on dialysis, the frailty is being addressed in the 2016 European renal best practice (ERBP) guideline. Frailty screening should be considered in all older adults who are not otherwise at risk of imminently dying or at low risk for progression to ESRD. It emphasizes that frailty scores may help in providing additional information during assessment and shared decision-making on the planning of patients. No specific screening test was recommended. It suggested that after an initial assessment, functional status be reassessed every 6–8 weeks for dialysis patients. It also recommends exercise therapy and dietary interventions as potential means of modifying frailty and frailty assessment to be a part of advanced care planning (ACP).[51] In 2015, Kidney Disease: Improving Global Outcomes (KDIGO) in partnership with the International Society of Nephrology (ISN), hosted a controversies conference on supportive care in CKD. The conference highlighted the need for identifying patients pre-dialysis and as well on dialysis who may be frail and may not benefit or may worsen with continuation of dialysis. There was no consensus on ideal tools to decide on patients requiring conservative care. However, there was a stress on using appropriate tools like the modified Karnofsky activity scale or screening activities of daily living, use of “surprise question” to assess and

Table 2 – Studies on outcomes in patients with frailty in end stage renal disease.

Study authors	Frailty measurement tool used	Study characteristics	Outcomes
Johansen et al. (2007)[16]	Modified fried phenotype	2275 incident haemodialysis (HD) patients of Dialysis Morbidity and Mortality Wave 2 study	Frailty was independently associated with higher risk of death (adjusted hazard ratio [HR] 2.24, 95% confidence interval [CI] 1.60–3.15) and composite of death or hospitalization (adjusted HR 1.63, 95% CI 1.41–1.87)
Bao et al. (2012)[5]	Modified fried phenotype	1576 incident HD patients from the comprehensive dialysis study cohort of the United States renal data system	73% prevalence of frailty Frail patients had increased mortality (HR 1.57, 95% CI 1.25–1.97) and faster time to hospitalization (HR 1.26, 95% CI 1.09–1.45)
McAdams de Marco et al. (2013)[43]	Fried phenotype	146 maintenance HD patients at single centre	Intermediate frailty and frailty were associated with a 2.7 times (95% (CI) = 1.02–7.07, $p = 0.046$) and 2.6 times (95% CI = 1.04–6.49, $p = 0.04$) greater risk of death independent of age, sex, comorbidity, and disability. Frailty was associated with 1.4 times (95% CI = 1.00–2.03, $p = 0.049$) more hospitalizations
McAdams de Marco et al. (2013)[44]	Fried phenotype	95 maintenance HD patients	Frailty independently predicted a 3.09-fold (95% CI: 1.38–6.90, $p = 0.006$) higher number of falls.
Alfaadhel et al. (2015)[31]	Clinical Frailty Scale (CFS)	390 patients on maintenance HD	HR for mortality associated with each 1-point increase in the CFS was 1.22 (95% CI, 1.04–1.43; $p = 0.02$).
Lee et al. (2017)[45]	Modified cardiovascular health study frailty (CHS) phenotype	1255 HD and 403 PD patients, multicentre	Frailty was associated with hospitalization (adjusted HR, 1.80; 95% CI: 1.38–2.36) and mortality (HR, 2.37, 95% CI: 1.11–5.02)
Lee et al. (2017)[46]	Multidimensional frailty score	46 elderly incident HD patients	Mortality or cardiovascular Hospitalization for frailty group HR 23.58 (1.61–346.03)
McAdams de Marco et al. (2018)[47]	Frieds phenotype	1975 HD patients on transplant wait list, multicentre cohort	Frailty associated with increased mortality (HR 2.19, 95% CI: 1.26–3.79)
Fitzpatrick et al. (2019)[48]	Frieds phenotype	370 incident HD patients enrolled in the Predictors of Arrhythmic and Cardiovascular Risk in End Stage Renal Disease (PACE) study	Frail patients had 1.66-fold increased mortality risk [95% (CI) 1.03–2.67].
Johansen et al. (2019)[49]	Frieds phenotype	727 maintenance HD patience, multicentre	HR of 2.73 for one frailty component fulfilled to 10.07 for five components
Aurora et al. (2020)[50]	Fried phenotype, short physical performance battery	117 elderly (>69 years) HD patients	Frail patients had higher mortality risk, HR 2.6 (95% CI 0.9–7.9) versus non frail at 12 months

prognosticate the patients for conservative care versus conventional kidney replacement therapy (KRT).[52]

Management

Frail patients with CKD are a distinct population, their risk profile will be different from fit patients. Although, frailty most commonly follows a downward trajectory, there is growing evidence to suggest that it can be improved with intervention. A holistic assessment with individualized assessment and targeted management strategy will be the key.

First and foremost, it is important to address undernutrition. The possible causes for decreased appetite, like uraemia, metabolic acidosis, intercurrent illness, medications, and comorbid conditions such as depression should be identified and treated.[35,39,53] Though there might not be a survival benefit ($p = 0.29$), but oral nutritional supplementation was associated with fewer hospital admissions, in those with ESRD and hypalbuminaemia.[54] The dietary phosphate restriction in ESRD patients with frailty may outweigh the benefits and result in further worsening of undernutrition and protein-energy. So dietary phosphate restriction should be individualized to allow adequate nutritional intake. Recent guidelines by ERBP in 2016 state that 'preserving nutritional status should prevail over any other dietary restriction'.[51]

Exercise has well-established, multifaceted benefits for improving the frailty in ESRD patients. Dialysis patients, in general, live a sedentary lifestyle. Decreased physical activity in elderly haemodialysis patients has been associated with a risk of increased mortality.[55] Exercise helps in improvements in muscle strength, cardiovascular function, physical function and health-related quality of life.[56] Even a modest amount of exercise in severely frail patients have shown a variety of

benefits like better mobility, independence, quality of life, bone mineral density and reduced falls.[57] Aerobic, resistance and combined exercise programmes have demonstrated substantial benefits. Both intradialytic and interdialytic exercise programmes are helpful in improving frailty.[58–60] Regular exercise increased muscle mass and reduced systemic inflammation in CKD population.[61,62] A study concluded that exercising during non-dialysis days was most effective, but intra-dialysis exercising was both effective and preferable.[59] Individualized exercise programme should be part of targeted therapy for all frail ESRD patients and seems to be valuable regardless of the type or mode of exercise. Apart from nutritional care and exercise, falls prevention measures, and timely control of ESRD complications, the inclusion of frailty management as part of ACP may help frail ESRD patients to improve their overall outcomes.

Choice of KRT in frail ESRD

Dialysis and transplant are significant stressors to an ESRD patient, and therefore should only be expected to benefit who are adequately robust.[63] The severity of frailty significantly impacts on patient's experience of different kidney replacement therapies. As a patient's frailty severity progresses, the nephrologist's focus should shift to potentially modifying care to less invasive treatment options like incremental dialysis or conservative management.

Incremental HD is one of the proposed strategies for limiting frailty. It has been shown to slow the loss of residual kidney function in ESRD.[64] It means to start with one/week or two/week HD regimens which are shorter or less frequent than standard three times per week maintenance therapy. Later it can be increased over time to accommodate a further decline in residual kidney function. By starting frail patients on incremental HD, the physiologic stress of dialysis is decreased. It leads to reduced post dialysis recovery time, less interference with social and family life, and ultimately better quality of life.[65] Incremental PD may be considered as an option as well. Home HD (either conventional, frequent, or intensive) in frail patients may be another solution. But the evidence on peritoneal or home HD is not substantial.[32,66] Similar to PD, home HD allows greater involvement of family, no travel burden of in-centre haemodialysis, and more flexibility. An important future consideration is an evaluation of the impact of PD or home HD on frailty.

Kidney transplant is a significant physiologic stress to frail ESRD patients. Frail patients have an increased risk of postoperative complications and mortality.[67,68] It is currently unclear at what degree of frailty the risks of transplantation outweigh the benefits. But transplant itself may be one of the "interventions" that could improve a patient's frailty significantly. Although frailty initially worsens post-transplant, it has been shown to improve as early as three months post transplantation.[69] A study showed a similar survival benefit in frail and fit patients by 9 months post-transplant.[70] As frailty advances, the risks and benefits of more invasive options for KRT should be reassessed. The option of conservative treatment with symptomatic management without any dialytic support must be explored with patients and families.[51]

Conclusion

Frailty is highly prevalent in ESRD patients independent of age. The pathogenesis of frailty in ESRD is multifactorial. Frail patients are likely to have higher morbidity and mortality compared to non-frail counterparts. Many frailty screening tools have been studied and validated in different settings of CKD and ESRD. In the absence of a consensus on the ideal screening tool, the emphasis should be placed on to use any one of the tools to identify frailty. A holistic individual assessment to address risk factors that may exacerbate its progression should be considered. Adequate nutritional intake is essential and individualized exercise programmes should be offered to all frail ESRD patients along with psychological and social support. Though the ERBP in 2016 and KDIGO in 2015 have attempted to incorporate frailty screening in ESRD population, it is yet to receive widespread acceptance. It is the time for the nephrology community to include it in routine practice to inform discussions with patients about conservative treatment or select a suitable mode of kidney replacement therapy, tailor the dialysis prescription as per the needs of the individual rather have a "one size fits all" approach.

Data availability

Not required.

Ethical approval

The procedures followed were in accordance with Declaration of Helsinki and its revisions. Informed consent from the subjects is not required

Funding

Not required.

Conflicts of interest

None.

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