End-Stage Kidney Disease in the Elderly: Approach to Dialysis Initiation, Choosing Modality, and Predicting Outcomes

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The number of patients with end-stage kidney disease 65 years and older is growing, and this growth is expected to continue. The presence of medical comorbidities, limited life expectancy, frailty, and poor functional status in these patients poses substantial challenges in clinical decision-making and provision of optimal care. Frailty is more common in elderly patients with CKD than without and is associated with poor outcomes. Several prognostic tools were developed to estimate the rate of CKD progression among elderly, and risk of mortality after dialysis initiation. Risk factors for CKD progression among elderly include low estimated glomerular filtration rate, high baseline proteinuria, acute kidney injury, low serum albumin, and presence of congestive heart failure. The decision to initiate dialysis in the elderly should take into consideration life expectancy, risks and benefits of each dialysis modality, quality of life, and patient and caregiver preferences. This article discusses common issues in the elderly with end-stage kidney disease, with particular emphasis on the impact of frailty and functional status, choice of dialysis modality and vascular access, and prognosis after dialysis initiation, to assist the nephrologist in making decisions regarding optimal care for this complex group of patients.

Key Words: End-stage kidney disease, Dialysis, Elderly, Frailty, Prognosis

INTRODUCTION

CKD and end-stage kidney disease (ESKD) have become increasingly geriatric conditions. In addition to a higher burden of medical comorbidities, older patients are also more likely to be affected by frailty and functional impairment, which are associated with increased morbidity and mortality.[1] Consequently, there is great interest in the ability to predict which older patients with CKD will progress to ESKD, to discern who is less likely to gain benefit from renal replacement therapy (RRT), and to understand how syndromes such as frailty and functional impairment influence the disease process and trajectory.[2]

Prevalence of CKD, when defined as an estimated glomerular filtration rate (eGFR) ≤60 mL/min/1.73 m^2, is high in the United States, particularly among those aged 65 years and older.[3-6] It is established that renal function declines with normal aging[7-9] consistent with observed histopathologic findings of tubular atrophy, interstitial fibrosis, glomerular dropout, and vascular sclerosis.[6] However, evidence suggests that an eGFR ≤ 60 mL/min/1.73 m^2 should not be viewed simply as a consequence of normal aging, as the prevalence of CKD-associated complications such as anemia, acidosis, hyperphosphatemia, and hyperparathyroidism increase when eGFR ≤ 60 vs >60 mL/min/1.73 m^2,[6,10,11] particularly with more severe declines in eGFR.[11]

FACTORS ASSOCIATED WITH PROGRESSION TO END-STAGE KIDNEY DISEASE

Although it is clear that CKD is a pathologic process in the elderly, progression is not uniform. The competing risk of ESKD vs death declines with advancing age except for those with eGFR < 15 mL/min/1.73 m^2 or higher baseline proteinuria, as evidenced in the following studies.[12-17] A retrospective study of 116 patients with CKD demonstrated a slower rate of progression with increasing age, with the smallest changes among those aged 76 to 87 years.[12] A larger prospective study of 1248 CKD Stages 3 to 5 patients showed for those aged <60 years, risk of ESKD exceeded risk of death.[13] The competing risk of ESRD vs. mortality declined with aging, but still exceeded the risk of death for eGFRs of 25-35 mL/min/m^2 in those aged 65 to 75 years, and for an eGFR <15 mL/min/m^2 in those up to 85 years old.[13] Proteinuria was also associated with increased risk of progression to ESKD in all age groups.[13] O'Hare and colleagues[16] demonstrated among a large group of US veterans that the association of eGFR with mortality decreased with increasing age. For those aged 18 to 44 years, risk of ESKD exceeded risk of death if eGFR < 45 mL/min/1.73 m^2, and for those aged 65 to 84 years if eGFR < 15 mL/min/1.73 m^2.[17] For those aged >85 years, risk of death persistently exceeded risk of ESKD.[17] A retrospective study of 461 CKD patients also demonstrated a very low likelihood of progression to ESKD for patients aged >65 years with CKD 3 and no overt proteinuria.[14] Among CKD 4 patients, those aged >74 years were significantly less likely to progress to ESKD than those aged <65 years, although progression to RRT was associated with higher baseline proteinuria and larger early decline in eGFR.[15]

Another factor associated with progression to ESKD in the elderly is acute kidney injury (AKI).[18] Among

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233,803 Medicare beneficiaries aged ≥67 years, the hazard ratio (HR) for ESKD was 41.2 (95% confidence interval [CI] 34.6-49.1) for those with AKI and prior CKD, 13.0 (95% CI 10.6-16.0) for those with AKI and no prior CKD, and 8.4 (95% CI 7.4-9.6) for those without AKI but with CKD.[18]

Given the heterogeneity of risk for ESKD, models to predict CKD progression have been developed. Tangri and colleagues[19] validated a model in patients of all ages with eGFR < 60 mL/min/1.73 m^2 for CKD progression at 1, 3, and 5 years using clinical variables: eGFR, albuminuria, serum calcium, serum phosphate, serum bicarbonate, and serum albumin. This model was also validated in a cohort of European patients.[21] Recently, Drawz and colleagues[20] described a 1-year model to predict progression to ESKD in a cohort of veterans with eGFR < 30 mL/min/m^2, all aged ≥65 using age, congestive heart failure, systolic blood pressure, eGFR, potassium, and albumin. The authors chose 1 year of observation to approximate time required for RRT planning in patients with advanced CKD.[20]

PROGNOSIS AFTER DIALYSIS INITIATION

Once initiated on chronic dialysis, elderly patients in general are at increased risk for poor outcomes, particularly those with cognitive dysfunction, comorbidities, and ischemic cardiovascular disease.[22-31] Early initiation of dialysis (ie, at eGFR > 15 mL/min/1.73 m^2) has been associated with worsened unadjusted 1-year mortality in elderly ESKD patients.[22] Burden of comorbidity is also associated with poor outcomes in elderly patients. A single-center observational study of 129 ESKD patients compared 52 patients who chose RRT with 77 who opted for non-dialytic treatment.[24] Those on dialysis had a significant 2-year survival benefit. Selection or indication bias could have been potential confounders, as RRT may have been chosen for less sick and more motivated patients. However, this benefit was not present in patients with higher comorbidity burden or ischemic cardiovascular disease.[24] Similar findings were reported by other observational studies.[25-31] The largest such study also noted a loss of survival benefit for those aged >80 years and lower performance scores, as well as attenuation of benefit with higher Charlson Comorbidity Index.[28] A study comparing elderly patients treated with peritoneal dialysis (PD) vs non-dialytic management found a lack of survival benefit for those with high comorbidity and difficulty with activities of daily living (ADLs).[30]

Prognostic tools have been developed for prevalent dialysis patients. A palliative care screening tool assessed the surprise question (ie, "Would I be surprised if this patient died in the next 12 months?") in dialysis patients of all ages.[32] The 1-year mortality was 29% for those with a "no" answer compared with 10% for those with a "yes" answer.[32] The surprise question was subsequently used in a 6-month prognostic tool (along with age, serum albumin, dementia, and peripheral vascular disease) validated in elderly dialysis patients, which is now available as an online tool.[33] The French Renal Epidemiology and Information Network risk score is also available to estimate 6-month prognosis in elderly dialysis patients.[34]

It is worth mentioning that the reported survival benefit for RRT vs no RRT is not necessarily associated with improved quality of life. Elderly patients managed with RRT are more likely to spend more time in health-care settings away from home, have decreased life satisfaction scores, and die away from home.[25,27] Therefore, the decision to initiate RRT must take into consideration a number of factors, including life expectancy, risks and benefits of each RRT modality, type of access required, and the quality of life, and preferences of the patient and caregiver.

CLINICAL SUMMARY

- The competing risk of end-stage kidney disease vs death appears to decline with advancing age except for those with estimated glomerular filtration rate < 15 mL/min/1.73 m^2 or higher baseline proteinuria.
- After dialysis initiation, elderly patients with cognitive dysfunction, comorbidities, or ischemic cardiovascular disease are at particular risk for poor outcomes.
- Frailty, poor functional status, and falls are highly prevalent in elderly dialysis patients and are associated with mortality.
- Choice of renal replacement therapy modality and dialysis vascular access should take into consideration age, comorbidities, life expectancy, and quality of life.
- Elderly patients managed with dialysis are more likely to spend more time in health-care settings away from home and have poorer quality of life.

COMPARISON OF RENAL REPLACEMENT THERAPY MODALITIES

In the United States, the initial forms of RRT in patients aged >65 years are in-center hemodialysis (93%-98%), PD (2.5%), preemptive kidney transplant (<2%), and home hemodialysis (<1%).[35,36] Observational studies suggest that mortalities for incident HD and PD patients are similar.[37,38] However, for those with diabetes aged ≥65 years, survival was worse on PD compared with HD.[37,38] Multiple studies from Europe compared outcomes for elderly patients on PD and HD. The North Thames Dialysis Study found no difference in mortality at 1 year for 125 patients aged ≥70 years.[39] Similarly, the Broadening Options for Long-term Dialysis in the Elderly study found similar quality life for those aged >65 years on PD compared with HD.[40] Among 3512 incident dialysis patients aged >75 years in France, the 2-year PD survival rate was 64%, similar to that observed with HD.[41] Several studies suggested equivalence in quality of life for patients on PD compared with HD.[39,40,42,43] However, caregivers related a substantial burden and adverse effects on their quality of life, particularly if caring for elderly PD patients.[44] Kidney transplantation in the elderly is covered elsewhere in this series.

Infection rates have declined in the United States for both HD and PD patients aged 65 to 85 years.[36] Rates have increased for those aged >85 years on HD,[36] likely because life-threatening sepsis is more common among

HD patients who dialyze using a catheter than among patients who dialyze using permanent vascular access (either arteriovenous fistula (AVF) or arteriovenous graft (AVG)), and most elderly aged >85 years initiate HD via catheters.[45] Consequently, a patient aged >85 years requiring RRT without a functional vascular access may benefit from initiating RRT via PD (if feasible) in an attempt to avoid complications associated with a tunneled dialysis catheter.[46] However, compared to younger patients, there is higher incidence of technique failure and an increased need for transfer to HD via catheter.[46] Therefore, such patients require close monitoring for signs of technique failure with the goal of creation of permanent vascular access in preparation for transition to HD, if required.[46]

CHOICES FOR HEMODIALYSIS VASCULAR ACCESS

For patients choosing to pursue HD, important considerations include the best timing of access placement and selection of the appropriate access type (ie, AVF or AVG). Given the risk of death exceeds the risk of progression to ESKD for most elderly, especially those aged >85 years,[17,47,48] care should be taken not to create unnecessary vascular accesses, which could potentially result in complications from procedures, as well as increased health-care costs. Using mathematical models, O'Hare and colleagues[49] demonstrated that if a cohort of elderly patients was referred for access surgery based on guideline recommendations, the ratio of unnecessary to necessary procedures for patients aged 85 to 100 years would be 5:1 compared with 0.5:1 for patients aged 18 to 44 years.

Once the decision is made to proceed with permanent vascular access for HD, the life expectancy of the patient is an important factor to consider in choosing the type of vascular access. Clinical practice guidelines have promoted the preference for AVFs rather than AVGs, with the rationale that AVFs reaching maturity require fewer interventions to maintain patency and are associated with fewer infectious complications than AVGs.[50] However, AVFs require more time to mature, and increased age was associated with nonmaturation of AVFs with worse primary cumulative AVF survival.[51] This may lead to an increased number of surgeries with the aim of establishing vascular access and increased risk of ultimately initiating HD via a tunneled dialysis catheter. In addition, in elderly patients with limited life expectancy, AVFs confer a very modest reduction in the risk of bacteremia compared with AVGs.[35] It has been estimated that among patients aged 90 years or older with an estimated life expectancy in the 25th percentile for that age group, 219 AVF placements would be required to prevent 1 episode of AVG-related bacteremia.[35] For those aged 85 to 89 years with an estimated life expectancy in the 25th percentile, 167 AVF placements would be required, and 110 would be required for those aged 80 to 84 years with an estimated life expectancy in the 25th percentile.[35] In addition, there may be no difference in survival for elderly patients using AVFs compared with AVGs. DeSilva and colleagues[50] found no such benefit for patients aged >80 years. This finding may have been due to a lower percentage of patients initiated via a tunneled dialysis catheter when an AVG was chosen (25.4%) compared with when an AVF was chosen (43.2%).[50]

Tunneled dialysis catheters are usually not the most appropriate choice for the elderly. However, aggressive placement of AVFs or AVGs in an elderly population may result in unnecessary surgeries with associated higher cost. O'Hare and colleagues[49] demonstrated that among patients aged 85 to 100 years with an eGFR < 15 mL/min/1.73 m^2, only 1 in 4 patients started HD within 6 months of access creation, and only 1 in 3 had started HD within 1 year. Therefore, the timing of access creation needs to be individualized with consideration of life expectancy and rate of progression of kidney disease. There may be special circumstances in which they may be appropriate, for example, as a last resort when all other options for vascular access have been exhausted or life expectancy is very low. Consequently, a tunneled catheter may be a viable option for those with a life expectancy < 6 months.

FRAILTY, FUNCTIONAL STATUS, FALLS, AND COGNITIVE IMPAIRMENT IN ELDERLY WITH CKD

A geriatric syndrome that has become increasingly recognized as a predictor of adverse outcomes in patients with kidney disease is frailty. Frailty is commonly defined as a geriatric syndrome of decreased reserve and resistance to stressors resulting from cumulative declines across multiple physiologic systems, causing vulnerability to adverse health outcomes, including falls, hospitalization, institutionalization, and mortality.[52-54] The concept of frailty can include physical domains as well as cognitive function and psychological and psychosocial factors. Several different models of frailty were described, which use different combinations of these domains.[54]

The first and most commonly discussed frailty phenotype was originally described by Fried and colleagues[52] among participants of the Cardiovascular Health Study (CHS) and is diagnosed if 3 of 5 criteria are present (Table).

The prevalence of frailty was found to be 7% if aged >65 years and 40% if aged >80 years. Frailty was associated with increased risk for falls, hospitalization, disability, and death.[52] In a secondary analysis of this cohort, CKD (defined as serum creatinine > 1.5 mg/dL for men and >1.3 mg/dL for women) was associated with frailty (adjusted odds ratio 1.76; 95% CI 1.28-2.41), and frailty was more prevalent in those with CKD compared with those with normal renal function (15% vs 6%).[55]

Despite the common definition of frailty, chronologic age is not necessarily a criterion, which underscores the concept that the phenotype represents a state of diminished physiologic reserve that leaves patients vulnerable to adverse outcomes. This phenotype has been associated with abnormalities of inflammatory markers, altered glucose metabolism, and coagulation disturbances.[56] Frailty is also known to be associated with sarcopenia.[54] Johansen and colleagues[57] performed a cross-sectional analysis of 638 HD patients using bioelectrical impedance spectroscopy estimates of body composition. Increased fat mass and increased extracellular water were associated with a higher likelihood of frailty, whereas higher intracellular water (a surrogate for muscle mass) was associated with lower likelihood of frailty.[57] In a smaller observational study of 80 HD patients, frailty was associated

Table. Criteria for Frailty Phenotype

Criteria for Frailty
Exhaustion
Low physical activity
Unintentional weight loss
Slow walking speed
Weakness

Three of 5 criteria must be present to diagnose frailty.
Data adapted from Fried, et al[52].

with smaller quadriceps muscle mass.[58] Consequently, there is overlap with the metabolic and inflammatory abnormalities, as well as changes in body composition, associated with CKD, although it is difficult to say whether kidney disease causes frailty or factors that cause frailty play pathogenic roles in CKD development. To date, the research on frailty and kidney disease has focused on the physical construct of the phenotype although it is likely that other domains of frailty also have significant interactions with kidney disease.[54]

The reported prevalence of frailty among CKD patients differs based on criteria used to define frailty. In the original CHS cohort, weakness was measured using handgrip strength, and walking speed was measured using timed 15-minute walk.[52] Subsequent studies substituted responses to the Physical Function (PF) Scale from the self-reported short form-36 questionnaire, based on strong correlations of this scale with weakness and slowness.[54] In a retrospective analysis of 188 HD patients, 78% met criteria for frailty using self-report measures, whereas 24% met criteria using the more objective CHS criteria.[54] Although the self-report measures may overestimate the prevalence of frailty in dialysis patients, the rate using objective measurements is still very high.

A retrospective analysis of National Health and Nutrition Examination Survey-III using the PF scale revealed age-adjusted risk for frailty to be 2-fold higher for patients with mild CKD (eGFR > 45 mL/min/1.73 m^2 or proteinuria) compared with those without CKD, and the risk was 6-fold higher for those with eGFR < 45 mL/min/1.73 m^2, relationships that persisted after correction for multiple comorbidities.[59] Frailty was also associated with increased morality.[59] Using strict CHS criteria, Roshanravan and colleagues[60] performed a prospective analysis of 336 patients in the Seattle Kidney Study (cystatin C-based eGFR $<$ 90 mL/min/1.73 m^2). Frailty was prevalent in 14.0%, and compared with patients with eGFR $>$ 60 mL/min/1.73 m^2, those with Stage 4 CKD had a 2.8-fold (95% CI 1.3-6.3) increase in prevalence of frailty, and those with 3b CKD had a 2.1-fold (95% CI 1.0-4.7) increase.[60]

In chronic HD patients, frailty is common at all ages using both PF[61] and CHS[62] criteria, and the prevalence increased with increasing age (44% if aged <40 years; 74% if aged 60-70 years; and 79% if aged >80 years).[61] Even after adjusting for age, frailty was associated with higher mortality and hospitalization, with adjusted HRs of 2.24 (95% CI 1.60-3.15) and 1.56 (95% CI 1.36-1.79), respectively.[61,62] In another prospective cohort of 95 prevalent HD patients, frailty using strict CHS criteria was an age-independent predictor for falls.[63]

Initiation of dialysis at a higher eGFR has been associated with poor outcomes in elderly ESKD patients.[22] In a retrospective analysis of 1576 participants in the Comprehensive Dialysis Study, frailty (using PF scale) was associated with earlier initiation of dialysis.[64] Furthermore, the association of early initiation with mortality became statistically nonsignificant when frailty was included, suggesting that frailty may be a factor in the observed association between early initiation and mortality.[64] Bias by indication could have confounded this and similar studies, as the self-reported symptoms of frailty may have been perceived as uremic symptoms, resulting in earlier referral for dialysis initiation at higher eGFRs.

Associations between frailty and adverse outcomes in kidney transplant recipients have also been described. In a prospective study of 183 transplant recipients, preoperative frailty using strict CHS criteria was associated with a 1.94-fold increase in delayed graft function (95% CI 1.13-3.36).[65] In a prospective analysis of 383 transplant recipients using strict CHS criteria, frail patients had a higher risk of early hospital readmission (adjusted risk ratio 1.61; 95% CI 1.18-2.19).[66]

Physical activity and functional status have been recognized as important clinical markers in kidney disease.[67] Among 256 patients with CKD 3 to 5, a higher level of physical activity, measured by the Four-Week Physical Activity History Questionnaire, was associated with a slower rate in eGFR decline.[68] Using the self-report Human Activity Profile, dialysis patients had extremely low levels of physical activity at the 5th percentile when compared to age-adjusted norms, with 95% of patients classified as having low fitness.[69] An analysis of the United State Renal Data System Dialysis Morbidity and Mortality Study Wave 2 demonstrated that those sedentary at the time of dialysis initiation had a 62% increased risk for mortality compared with non-sedentary patients, after adjustment for comorbidities.[70,71] Among HD patients in the Dialysis Outcomes and Practice Patterns Study, those who reported exercising more than 1 time per week had a decreased mortality risk (adjusted HR 0.73; 95% CI 0.69-0.78).[72]

Functional impairment or disability, defined as loss of ability to perform ADLs and instrumental activities of daily living (IADLs) is common in the elderly at dialysis initiation and continues to decline among prevalent dialysis patients.[73-77] In a prospective cohort of 162 elderly HD patients, only 8 reported no loss of function, whereas 69 had impairment of at least 1 IADL, and 85 has losses of both ADLs and IADLs.[74] In a retrospective study of 1286 hospitalized dialysis patients, >70% had impairment in ADLs at the time of admission.[75] Age-adjusted risk of in-hospital death or discharge to an assisted care facility was observed with increasing levels of functional impairment.[75] Among 3702 patients with baseline functional impairment before dialysis initiation, 39% had maintenance of function 3 months after initiation, dropping to 13% at 12 months after initiation, with a 12-month mortality rate of 58%.[76] Even among independent, community-dwelling elders, a significant decline in functional status was observed 6 months after starting dialysis.[77]

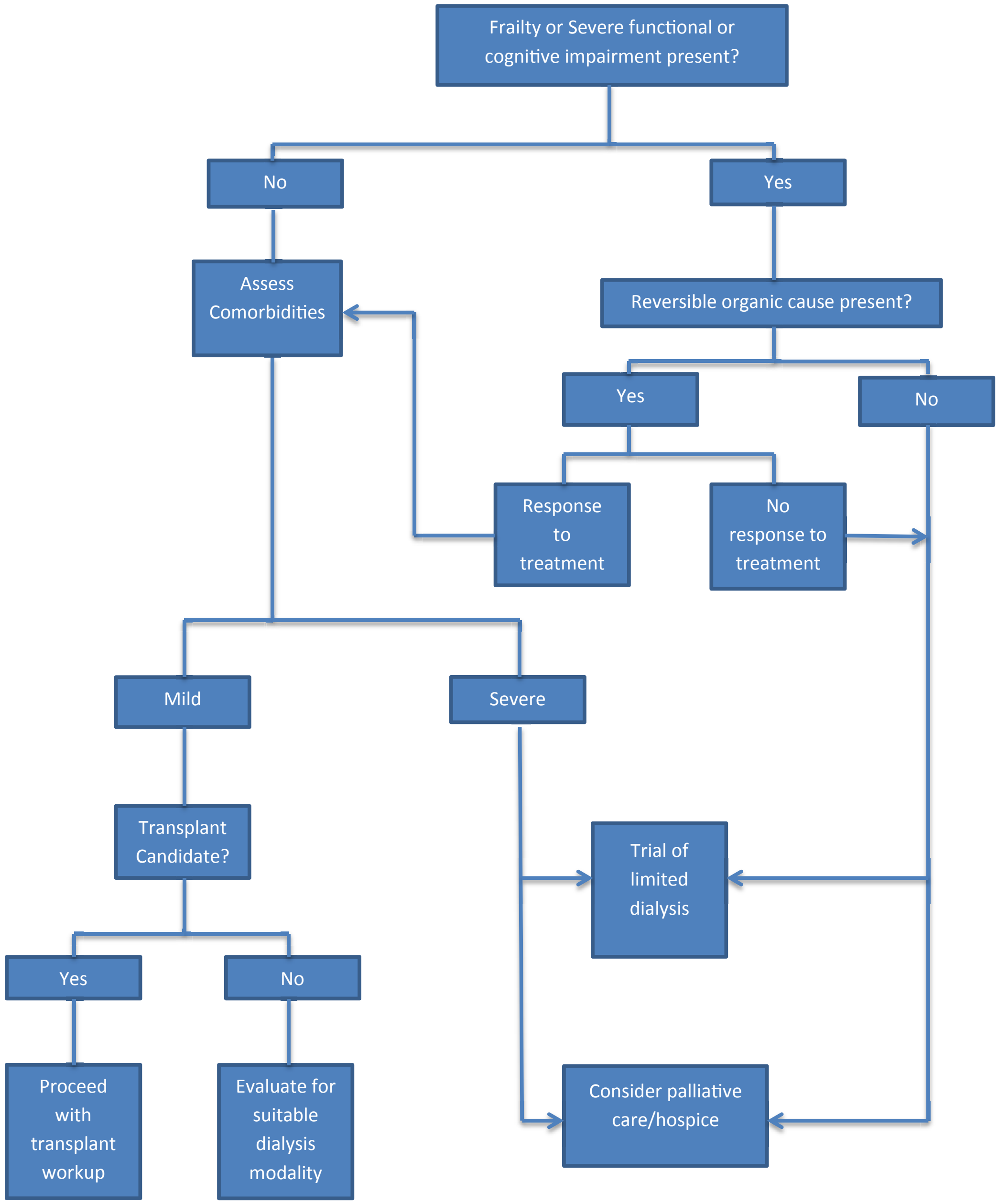

Figure 1. Suggested approach to the elderly patient with end-stage kidney disease.

Falls occur in >45% of elderly chronic dialysis patients and were shown to be associated with morbidity and mortality in this patient population.[78,79] In a prospective cohort study of HD patients (mean age 75 years), an increase in mortality was observed in those with at least 1 fall compared with no falls (HR 1.63; 95% CI 1.02-2.28), even after excluding falls deemed to be related to an acute illness.[80]

In total, these observations on frailty, functional impairment, and falls point to the possibility that focused rehabilitative efforts could be beneficial for elderly dialysis patients. A small ($N = 22$) study suggested that a supervised, intradialytic exercise program (combining strength and aerobic training) can improve muscle strength as well as mental and PF.[81] Individual dialysis units reported success with the implementation of in-center physical therapy programs and reported that age alone is not a barrier to achievement of goals for improved physical functioning and overall sense of well-being.[82-84] Retrospective data from dialysis facilities in Texas indicate that facilities with higher levels of rehabilitation activity implementation had higher scores on the patient self-reported mental component scale.[85] A Canadian pilot study demonstrated the effectiveness of a dedicated inpatient geriatric renal rehabilitation unit in terms of meeting rehabilitation goals and improving PF for elderly HD patients requiring inpatient rehabilitation.[86] It remains to be seen whether such programs can be widely implemented and whether they will have an impact on reducing morbidity and mortality among this vulnerable patient group.

Cognitive impairment is another geriatric syndrome that must be considered in patients with CKD and ESKD. In the Chronic Renal Insufficiency Cohort Study, among patients aged 55 years and older, lower eGFR (particularly <30 mL/min/1.73 m^2) was associated with cognitive impairment.[87] In ESKD patients, dementia has been observed to be 2-fold more prevalent than in patients without ESKD,[88] and cognitive impairment has been observed to be an independent predictor of mortality in dialysis patients.[23] Furthermore, cognitive decline has been associated with early dialysis initiation[89] (as was frailty, as discussed earlier). Unfortunately, chronic dialysis may not readily and consistently lead to improvement in cognitive function.[90]

Frailty, functional impairment, and cognitive impairment are common problems among elderly dialysis patients, which are often present simultaneously (Fig 1) and may be mechanistically related. For example, a cognitively impaired patient may have increased difficulty completing ADLs. Sarcopenia associated with frailty can lead to impaired functional status. An injury leading to functional impairment may make a patient more likely to become frail. Regardless of the direction of causality, the presence of any of these geriatric syndromes predisposes the elderly patient approaching the need for RRT to adverse outcomes and should trigger a careful consideration of whether pursuit of RRT is appropriate.

CONCLUSIONS

Decision-making can be very challenging for elderly CKD patients approaching ESKD, and awareness of factors associated with, as well as options to prevent adverse clinical outcomes, is important in guiding patients, caregivers, and providers on whether to pursue RRT and what modality of RRT would be most appropriate. Despite best efforts at prognostication, disease progression, treatment response, and patient-specific goals are highly heterogeneous in the elderly population, and a patient-centered approach is critical.[91] Importantly, effects on continued decline in functional impairment and health-related quality of life need to be addressed. Ideally, a shared decision-making, multidisciplinary approach is preferred where information about prognosis and estimated risks and benefits of treatment interfaces with individual preferences and values.[92]

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