Frailty and Kidney Transplantation

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ABSTRACT

Two significant policy changes, one in the way people are put forward for kidney transplants and the other in the way in which kidneys are distributed to people on the waiting list, make the question of whether someone is too frail to receive a transplant all the more relevant, particularly in Rhode Island. An executive order signed by President Donald Trump stresses that efforts to treat kidney disease need to concentrate on providing more people with kidney transplants and increasing the number of organs transplanted rather than discarded. An effort to decrease waiting times for kidneys in large metropolitan areas potentially means that young, more desirable kidneys will be shipped out of New England, leaving longer waiting times and less desirable organs for transplantation in our region. The net effect of these changes may mean that potential older or more frail recipients could be faced with accepting kidneys from older or less desirable donors or spend more time on the waiting list and never receive a credible kidney offer. This raises the specter of poor outcomes from marginally functioning kidneys transplanted into marginally functioning recipients or increased rates of death on the waiting list. While organ allocation policies are beyond the ability of transplant nephrologists in Rhode Island to change, we will need to assess patients more closely for signs of frailty and work with referring doctors to reverse frailty when possible so that patients can take advantage of a kidney transplant even if the organ isn’t ideal. This article will review the concept of frailty; how to assess it in general and in the context of a transplant evaluation; the risk of frailty in transplant outcomes and the benefits of transplant in reversing frailty; whether markers of frailty can be improved and whether that improves transplant outcomes.

KEYWORDS: kidney transplant, chronic kidney disease, frailty assessment, donor waitlists

INTRODUCTION

Chronic kidney disease is a growing worldwide problem and one from which the US is not immune. And while a functioning kidney transplant is seen as the ideal and ultimate renal replacement therapy, there is an overall shortage of organs compared to the number of people on the waiting list. The number of people waiting for a deceased donor kidney has decreased steadily from over 100,000 in 2014 to 92,906 at the start of 2018. Some 33,879 candidates were added to the list in 2018 while 34,591 were removed from the list. The ranks of those removed included 14,784 who received a deceased donor kidney transplant and 6,120 who received a living donor transplant. It also included 4,193 who died on the waitlist and 4,240 who were removed as too sick. The decline in numbers on the waiting list reflects the effects of an earlier change in kidney allocation policies to help better match survival of the organ with expected survival of the recipient, decrease the number of organs discarded, and that backdated credit for waiting time to when a candidate initiated dialysis.

In 2019, President Trump signed an executive order that sought to decrease the number of people receiving in-center hemodialysis and increase the number of people getting dialyzed at home and getting kidney transplants. The order envisioned an additional 17,000 kidney transplants. More recently, efforts to reduce large disparities in waiting times around the country have led to changes in the way points are awarded that are used to determine one’s standing on the list when an organ is offered. The net effect of this change is that organs that might have stayed in New England, where average wait times for a deceased donor kidney are around 5 years, would be transported to regions like New York, where wait times are closer to 10 years. While the changes in kidney allocation will reduce waiting times in some regions, waiting times will increase in regions that become net exporters of kidneys. These changes raise the possibility that as older or more frail candidates move on to list, they will have to wait longer and will receive kidneys offers that reflect the diminished survival prospects of the recipient, or risk dying on the list before they are matched with a kidney.

To keep transplantation going in the region will require more careful evaluation of candidates as well as increased efforts to improve candidates’ chances of surviving on the waiting list to receive an organ offer and thrive after
transplantation. The concept of frailty plays into this calculus. This paper will review the concept of frailty and address ways to assess it in general and as part of the transplant evaluation. The paper will look briefly at the risk to patient and transplant outcomes from frailty versus the potential benefit from transplant toward reversing frailty. The paper will examine potential ways to reverse elements of frailty to improve transplant prospects and whether such preconditioning works. The literature is vast, but this review will try to touch briefly on these important concepts.

**FRAILTY**

Frailty is often equated with old age or increased comorbidities. And while age and illness can factor into frailty, they are not substitutes for frailty. In their seminal paper on describing a frailty phenotype, Fried and colleagues wrote that frailty “may have a biological basis and be a distinct clinical syndrome” and sought to develop a standardized definition. Using data from the Cardiovascular Health Study, they evaluated 5,317 men and women, including 582 Blacks, from 4 to 7 years of follow-up. They defined frailty as a clinical syndrome based on three or more of five characteristics: unintentional weight loss of 10 pounds or more in the previous year (shrinkage), self-reported exhaustion, weakness on a test of grip strength, slow walking speed over a set distance and low physical activity as defined on a standardized questionnaire. In their study, frailty was associated with increased age, female gender, Black race, having a lower level of education and income, poorer health, and higher rates of chronic comorbid diseases and disability. They found that the frailty phenotype independently predicted falls, worsening mobility, hospitalization and death over three years. They defined intermediate frailty as having one or two of the characteristics, signaling an increased risk of becoming frail over 3–4 years. They defined frailty as a downwardly spiraling physiologic process of declining energy utilization and “loss of homeostatic capability to withstand stressors and resulting vulnerabilities.” While they noted some overlap with disability and illness, they stressed that those concepts are not synonymous with frailty.

**NEED TO ASSESS FRAILTY**

There is a clear consensus, however, that frailty is a common feature of people with end-stage organ damage awaiting a transplant. The data also bear this out. According to a national study pooling data from three major centers, an estimated 16.4% of all kidney transplant candidates were considered frail between 2008 and 2018 while 14.3% of all kidney transplant recipients were considered frail during the same time.

The American Society of Transplantation (AST) sponsored a consensus conference on frailty in February 2018 to standardize assessment of frailty in transplant candidates and generate ideas for further research. In a survey of AST members concerned with kidney transplantation, 98.9% considered frailty in transplant candidates a risk factor for poor outcomes after transplantation, while 93.3% felt the need for a frailty score in making decisions on whether to transplant, and 67.1% thought age should be included in assessing frailty. Optimizing dialysis and volume status, nutrition, physical therapy and psychotherapy were thought essential components in improving frailty in patients with kidney disease awaiting transplant in the AST survey.

Much work has gone into looking at individual components of frailty, as well as association of age, comorbidities and frailty. Reviews on measuring frailty cite up to 75 functional assessment tools available currently, including questionnaires assessing physical capacity, tools like the Karnosky Performance Scale to assess physical performance, tools to quantify perceived frailty like the Fried's frailty phenotype (FFP), a frailty index of cumulative deficits, physical performance scores like walking speed, grip strength, ability to stand and balance, involuntary loss of muscle mass (sarcopenia), cardiopulmonary fitness testing to assess oxygen utilization.

In a recent survey of US kidney transplant programs, McAdams-DeMarco and colleagues found the bulk of programs that responded to the survey (133/202) considered frailty a clinically relevant concept (99.2%) but only 96% said they thought frailty should be used in making decisions about whether someone was a transplant candidate. The survey found great heterogeneity in assessing frailty with respondents reporting that they used some 18 different tools to assess it. The most used test – by 19% of respondents – was a timed walk. Some 8% of respondents used the FFP while 8% used the Montreal Cognitive Assessment, and 8% also used sarcopenia. Two-thirds of respondents said they used more than one test.

Without a standardized method to assess frailty, clinicians often fall back on perceptions of frailty, which can be deceiving, with the consequence of potentially denying access to transplantation among those perceived as frail. Salters and colleagues looked at differences in perceived and measured frailty in 146 adults undergoing hemodialysis at a single dialysis unit in Baltimore. Patient characteristics of frailty as perceived by nurse practitioners, nephrologists or patients were compared with measured assessment of frailty using the FFP. Older age and comorbidities were associated with a greater likelihood of being perceived as frail by nephrologists while women and non-African Americans were more likely perceived as frail by nurse practitioners. At the same time, patients classified by the FFP as frail, only 42% were perceived as frail by nephrologists, 39.2% by NPs and 4.9% by patients themselves. The risk, according to the authors, was that older dialysis patients and women perceived as frail but not actually demonstrating frailty risked not being listed for transplantation.
And yet for frail patients, the risk of not being listed is significantly higher. In study of 7,078 transplant candidates between 2009–2018, frail patients were 38% less likely to be listed for transplant, regardless of age or other demographic factors. Frail Black kidney transplant candidates were 46% less likely to be listed than non-frail, non-Black candidates. They were 32% less likely to be transplanted compared to non-frail patients and they were 70% more likely to die on the waiting list.14

The relationship between aging, frailty and chronic kidney disease is central since aging increases the risk of poor outcomes from the cumulative burden of correlates for frailty like cognitive impairment, poly-pharmacy, disability, multiple comorbidities, malnutrition, and dialysis.15 In the Rhode Island experience, the relationship between age and loss of kidney transplant and death after transplant was significant in patients who were inactive, smoked, had COPD, had peripheral vascular disease or required dialysis within a week after transplantation (delayed graft function).16

Age alone does not seem to define frailty in patients undergoing dialysis and transplantation and as a single entity, does not portend poorer outcomes. Researchers at Johns Hopkins, the University of Michigan and the University of California, San Francisco, pooled cohorts to compare frailty in subjects older than 65 and younger than 65 at three time points: within six months of starting dialysis; at time of kidney transplant evaluation; at time of admission for kidney transplant. Overall, frailty in all three time points was more prevalent in older patients who were also more likely to have slowness and weakness. Younger subjects were more likely to experience exhaustion in all three time points. The authors concluded that while frailty was more prevalent in older subjects, younger subjects still had a high burden.17 A registry-based study at Oslo Hospital of all potential kidney transplant recipients age 65 or older who received a deceased donor kidney transplant between 2000 and 2014 found no difference in outcomes between those who received a first kidney and those who received a second kidney re-transplant. Five-year survival censored for death with a functioning graft in those receiving a second transplant was 88% versus 90% for those receiving a first transplant (P = 0.475%).18 Risk factors for increased chance of death with a functioning graft also included longer time on the waiting list before re-transplantation, although the authors noted that overall waiting time at their center was small such that their findings might be even more applicable at centers with longer waiting times.

FRAILTY WHILE WAITING

The risk of death on the waiting list for frail patients has led to much thought about whether chances to receive a kidney can be enhanced by “preconditioning” of frail candidates to improve physical stamina. Researchers at the Mayo Clinic identified what they described as high-risk kidney transplant patients (59 years or older, diabetes and or more than three years on dialysis) and evaluated them using the FFP and Short Physical Performance Battery. They found that both frailty and physical performance were significantly associated with death on the waiting list [hazard ratio 6.7, 95% confidence interval 1.5–30.1; P=0.01]. They also found that the relationship between frailty, physical performance score and death on the waiting list were independent of age, diabetes or length of time of dialysis.19

Time on the waiting list can also increase frailty, such that some suggest measuring changes in frailty over the course of time between listing and transplantation. Researchers at Johns Hopkins noted that 22% of 569 kidney transplant candidates enrolled in their cohort study of frailty became increasingly frail while 24% became less so. While Black race was associated with becoming less frail and diabetes was associated with remaining stably frail, the longer candidates remained on dialysis, the less likely they were to become less frail. Given the dynamic change in frailty in some patients, these researchers recommended assessing frailty at the time of listing and time of transplantation since candidates who became more frail faced longer hospitalization times post-transplant as well as a higher risk of mortality post-transplant.20 Researchers at Columbia University used a timed “get up and go” test for patients on the waiting list to see if that might predict outcomes after transplant. In the end, participants in the study who were transplanted had shorter times on the test than those who remained on the waitlist. However, there was no association between test time and probability of removal from the waitlist or prolonged hospitalization after transplantation or 30-day readmissions.21

In an ongoing trial, a group of Canadian researchers hopes to better evaluate whether frailty is associated with death on the waitlist, withdrawal from the waitlist as well as whether frailty is associated with hospitalization, quality of life and even being listed. Their plan is to evaluate potential candidates using the FFP, the frailty index, the Short Physical Performance Battery and the Clinical Frailty Scale (CFS) at the time of initial evaluation for listing and annually after that. The goal is to understand the association of frailty and outcomes from patient on the waitlist before incorporating measurement of frailty into the regular waitlist workup.22

The association between waitlist mortality and frailty is not clear. The CFS, a validated instrument in dialysis patients, uses overall clinical impression to award a single point for each degree of perceived frailty. In a cohort of incident dialysis patients assessed between 2009 and 2013, each point increase in the CFS was associated with an increase in the hazard ratio of death [HR 1.22; 95% CI, 1.04–1.43; P=0.02].23 In a separate multi-center study, researchers assessed whether an association existed between frailty on the waitlist and accumulated burden of comorbidities as
assessed by the Charlson Comorbidity Index. In a study of 2,086 candidates on the kidney transplant waitlist, 18.1% were frail and 51% had a high comorbidity burden. They found that among non-frail patients, a high comorbidity score was associated with a statistically significant risk of mortality [HR 1.66 95% CI 1.17–2.35]. But among frail patients, high burden of comorbid conditions did not show an association with mortality. Stratified by age, the higher comorbidity index portended worse mortality in patients waiting for kidney transplantation who were under 65, while a high burden of comorbidities was not associated with waitlist mortality in patients age 65 and greater on the waitlist.

INTERVENTIONS

The question then becomes whether one can intervene with frail candidates to improve their survival on the waitlist, their chances of getting a kidney and survival after transplantation. Part of the problem in increasing exercise tolerance among kidney transplant candidates is that people enter the waitlist already in poor physical shape. According to one study, 95% of new starts on dialysis have physical fitness levels below the 20th percentile for the general population, and just over half (56.4%) are able to walk one block, 23.8% can climb 24 stairs, and only 18.5% said they could walk a mile. Researchers at several centers are looking into adapting an exercise module developed by the American College of Sports Medicine to create an exercise module for people transitioning to dialysis. The idea is to develop a practical and cost-effective package to help patients starting dialysis overcome barriers to exercise.

Researchers at the Mayo Clinic used supervised exercise sessions in frail patients with stage IV chronic kidney disease or greater to see whether their intervention could improve strength. They enrolled 21 patients in two supervised outpatient exercise sessions per week for eight weeks. The intervention, which included strength, endurance and flexibility training, led to improvement in frailty parameters like walk speed, grip strength and fatigue, although none of the changes were statistically significant. Scores on the Short Physical Performance Battery did improve significantly. The authors suggest that their results are encouraging and warrant evaluation in a larger, multi-site study.

The transplant clinic at Stanford University began doing physical assessments of transplant candidates once their accumulated waiting time put them in the top of the center’s waitlist. Rather than assessing frailty, the clinic assessed 60 second sit-to-stand and 6-minute walk tests. They found that the lower the scores on the two tests, the higher risk of removal from the waitlist or death on the waitlist.

FRAILTY AFTER TRANSPLANT

Does transplantation improve frailty among kidney recipients? Again, the data appear mixed. Researchers in the Netherlands studied 176 kidney transplant recipients at their center in Groningen between 2015 and 2017 and followed for up to three years. Using their own frailty scale [Groningen Frailty Indicator], they found that 34 non-frail patients became frail after transplantation, 125 patients remained unchanged, and 19 frail patients were no longer frail. The GFI includes 15 questions in eight functional domains including mobility, vision, hearing, nutrition, comorbidities, cognition, psychosocial functioning and physical fitness. Changes in cognition and psychosocial functioning contributed most to the shift from not frail to frail after transplantation. In contrast, researchers at Johns Hopkins and the University of Michigan assessed frailty using the FFP and then examined changes in health-related quality of life [HRQOL] in 443 kidney transplant patients at their centers between 2014 and 2017 for three months post-transplant. At the time of transplant, frail patients had worse HRQOL scores than non-frail patients, but both groups showed improvement one month post-transplant. At three months, frail transplant recipients had statistically significant continued improvement in physical HRQOL but non-frail patents did not. The same held true for changes in mental HRQOL. Both frail and non-frail transplant recipients reported improvement in kidney disease specific HRQOL.

CONCLUSION

The topic of frailty in chronic kidney disease and transplantation remains in flux. The transplant community knows that frailty is a poor indicator for outcomes in transplantation. Frailty can affect not only if patient can get transplanted once placed on the waitlist but also whether that person can even get on the list to begin with. As older people undergo transplant evaluation and face the prospect of only getting offers of kidneys from more marginal donors, assessing candidates for frailty and finding ways to reverse the components of frailty that are amenable to improvement becomes all the more important. However, the transplant community remains divided on the best tool[s] to use to make the assessment and whether exercise conditioning can help give people more strength, stamina and improve energy metabolism. The Organ Procurement and Transplantation Network [OPTN] has temporarily put on hold the implementation of changes in the kidney allocation system while the Department of Health and Human Services reviews concerns about the changes that were submitted just before the new rules were due to take effect December 15, 2020. Whatever the outcome of that review, efforts to improve a transplant candidate’s conditioning and stamina could also be important tools in improving access to and survival after kidney transplantation.
References


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