Frailty and Cognitive Deficits Limit Access to Kidney Transplantation

Unfair or Unavoidable?

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Only one out of every seven incident dialysis patients in the United States is added to a kidney transplant waiting list or receives a transplant within 1 year of initiating dialysis (1). Kidney transplantation is associated with better survival relative to dialysis even among high-risk subgroups, including older adults and those with functional limitations (2). However, concerns about the scarcity of organs and scrutiny of transplant center outcomes may motivate centers to preferentially select the most resilient candidates for waitlisting—individuals who seem most capable of withstanding the punishing effects of years of maintenance dialysis followed by transplant surgery and immunosuppression. In this issue of the *Clinical Journal of the American Society of Nephrology*, Haugen *et al.* (3) and Gupta *et al.* (4) reveal how individuals affected by frailty and cognitive impairment, respectively, are less likely to be added to the transplant waiting list and receive a kidney transplant. Together, these works draw attention to the opaque process of deciding who is and who is not a suitable kidney transplant candidate and challenge the nephrology community to decide if the authors have uncovered a fairness problem.

Frailty is very common in the dialysis unit. By one estimate, one half of patients ≥65 years old on dialysis are frail (5). Frailty is a syndrome of limited capacity to recover from health stressors, such as infections, heart failure episodes, or falls. Although nephrologists might contend that they can easily recognize frailty at the bedside, the most widely used research definition of frailty is the Fried Frailty Phenotype, which involves a series of formal tests to identify frail patients. This approach assigns the category of frailty when three or more of the following characteristics are present: unintentional weight loss of >10 pounds in the past year, weak grip strength, slow walking speed, self-reported exhaustion, and self-reported low physical activity. Over the past two decades, an impressive set of studies across gerontology, nephrology, and other domains of medicine has shown that frail patients are more likely to die and suffer adverse health outcomes than their nonfrail peers. Given the increasing awareness of the adverse health outcomes associated with frailty in nephrology, many frail patients may never be referred for transplant evaluation at all.

Haugen *et al.* (3) prospectively measured frailty among 7078 individuals who were evaluated for kidney transplant candidacy at three United States transplant centers from 2009 to 2018. Two of the three centers blinded their transplant selection committees to the results of frailty testing. Frailty prevalence varied from 11% to 21% across centers. Compared with nonfrail patients, frail patients had a 38% lower rate of listing (adjusted hazard ratio [aHR], 0.62; 95% confidence interval [95% CI], 0.56 to 0.69) and a 1.7-fold higher death rate after they were on the waiting list (adjusted subhazard ratio, 1.70; 95% CI, 1.36 to 2.14). The association between frailty and longer time to listing was not modified by patient age or sex, but it was more pronounced among nonblack candidates than black candidates. A limitation is that the investigators did not provide reasons why committees waitlisted frail candidates at lower rates or the mechanisms that limited their progress to transplantation. Nonetheless, this study adds valuable data to an existing body of knowledge that frailty is an independent risk factor for waiting list mortality, increased health care utilization, and death after transplantation (6).

Whereas frailty is most typically conceptualized as a physical syndrome, patients with kidney disease may also be more vulnerable to health stressors if they are cognitively impaired. Cognitive impairment is observed among 30%–70% of patients on hemodialysis (7). Executive function—the ability to pay attention, plan, and organize—is the cognitive domain affected most often. Recent studies have begun to describe potential effects of cognitive deficits on patients who are tasked with preparing for dialysis or managing complex medication regimens. For example, cognitive impairment is associated with higher venous catheter use at dialysis initiation (8) and greater risks of all-cause graft loss after kidney transplantation (9).

The study by Gupta *et al.* (4) was a single-center, longitudinal cohort of 349 kidney transplant candidates. The investigators tested transplant candidates' global cognitive function using the Montreal

Cognitive Assessment (MoCA). The primary outcome was time to active waitlisting. A MoCA score between 19 and 25 (of 30) was used to define mild cognitive impairment (49% of the cohort), and a score ≤18 was used to define severe cognitive impairment (6% of the cohort). The transplant center's selection team was blinded to the testing results. Compared with candidates without cognitive impairment (*i.e.*, MoCA≥26; 45% of the cohort), those with mild cognitive impairment were more likely to be older, be black, have lower educational attainment, and smoke. In unadjusted analysis, individuals with MoCA<26 had longer median time to listing than those with higher scores (10.6 versus 6.3 months; P=0.01). However, the association between time to listing and MoCA<26 was attenuated after multivariable adjustment (aHR, 1.41; 95% CI, 0.98 to 2.02; P=0.06). The lack of an independent association between waitlisting and this cutoff score on the MoCA may reflect a cutoff that was too high, because other studies have suggested that lower thresholds of MoCA scores would include more patients with meaningful cognitive deficits (10). The authors also describe a linear relationship between MoCA score and time to waitlisting, such that a one-point increase in MoCA score was associated with a 1.07-fold increase in the rate of waitlisting (aHR, 1.07; 95% CI, 1.01 to 1.13; P=0.02). However, it seems unexpected that the association between MoCA score and access to transplantation would be linear; testing for nonlinear relationships may have identified alternative threshold scores that could be used to inform clinical practice.

The studies by Haugen *et al.* (3) and Gupta *et al.* (4) do not explain why transplant selection committees seemed less likely to accept frail and cognitively impaired patients, but there are plausible reasons. Committee members might have worried that patients with physical or cognitive impairment would suffer undue complications from transplant surgery and immunosuppression. Cognitively impaired patients might have been judged at greater risk of medication nonadherence. The committees might have suspected that worse outcomes among frail or cognitively impaired patients would imperil center evaluations or lead to too many costly complications, such as intensive care or long hospital stays. Alternatively, it is possible that the complex transplant evaluation process is too challenging for frail and cognitively impaired patients to navigate successfully (11). However, we suspect that the selection committees' preferences toward transplanting the most "fit" patients reflect an understandable sense of duty to maximize the benefits of the scarce resource of organs.

If that suspicion is correct, it would reflect the current reality that selection of patients for the waiting list is mainly left to transplant center judgment, and as such, it may overwhelmingly reflect transplant center priorities. Furthermore, the lack of consistency and transparency in the candidate selection process may be particularly unfair to certain higher-risk subgroups, especially in regions of the country with few transplant centers that have little competition for patients. Prior work by our group showed that patients with limited functional status live longer with transplant compared with dialysis (2), and it is likely that many frail and cognitively impaired patients would also live longer if transplanted. If the main problem for patients with cognitive impairment after transplantation is nonadherence, then this problem could reasonably be overcome with strong social support in some patients. Haugen *et al.* (3) also contend that post-transplant health outcomes for frail patients might improve with targeted treatments, such as physical therapy or dietary interventions. However, whether these rehabilitation efforts will work and whether the cost seems reasonable to payers are open questions.

Referring nephrologists, patients, and families may read these results by Haugen *et al.* (3) and Gupta *et al.* (4) and worry that some frail or cognitively impaired patients may not be taken seriously as transplant candidates. Although cognitively impaired patients have often been thought of as a vulnerable group that needs protections and advocacy, the transplant ethics literature has never conceptualized frail patients this way.

Conversely, transplant center leadership may raise valid concerns about flawed procedures for grading center quality. That is, frailty and cognitive impairment are not included in current risk adjustment algorithms for waiting list and transplant outcomes. Centers that choose to select frail and cognitively impaired candidates for transplant do not receive "credit" (*i.e.*, adequate risk adjustment) for managing these potentially higher-risk patients before and after transplantation (12). Finally, from a public health perspective, associations between frailty, cognitive impairment, and graft loss introduce questions about how to best use a rare and precious resource.

At the least, these provocative studies by Haugen *et al.* (3) and Gupta *et al.* (4) provide an argument for greater transparency and consistency in the process of educating, referring, and selecting potential kidney transplant candidates, and they should motivate us to look more closely at frail and cognitively impaired patients who seek transplantation. Their results also underscore the urgent need for identifying interventions to prevent or reverse the functional burdens of kidney disease.

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