

Older candidates for kidney transplantation: Who to refer and what to expect?

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Abstract

The number of older end-stage renal disease patients being referred for kidney transplantation continues to increase. This rise is occurring alongside the continually increasing prevalence of older end-stage renal disease patients. Although older kidney transplant recipients have decreased patient and graft survival compared to younger patients, transplantation in this patient population is pursued due to the survival advantage that it confers over remaining on the deceased donor waiting list. The upper limit of age and the extent of comorbidity and frailty at which transplantation ceases to be advantageous is not known. Transplant physicians are therefore faced with the challenge of determining who among older patients are appropriate candidates for kidney transplantation. This is usually achieved by means of an organ systems-based medical evaluation with particular focus given to cardiovascular health. More recently, global measures of health such as functional status and frailty are increasingly being recognized as potential tools in risk stratifying kidney transplant candidates. For those candidates who are deemed eligible, living donor transplantation should be pursued. This may mean accepting a kidney from an older living donor. In the absence of any living donor, the choice to accept lesser quality kidneys should be made while taking into account the organ shortage and expected waiting times on the deceased donor list. Appropriate counseling of patients should be a cornerstone in the evaluation process and includes a discussion regarding expected outcomes, expected waiting times in the setting of the new Kidney Allocation System, benefits of living donor transplantation and the acceptance of lesser quality kidneys.

Key words: Kidney transplant outcomes; Frailty; Elderly; Expanded criteria donor; Quality of life

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Core tip: Transplant physicians must be well-versed in the intricacies of evaluating older kidney transplant candidates. This includes the appropriate selection of candidates which can be challenging due to the extent of comorbidity and frailty in this patient population. For patients who are deemed appropriate for transplant, physicians must be able to counsel them regarding expected outcomes and explain the expected benefit that transplantation confers over remaining on the deceased donor waiting list. Living donor kidney transplantation, even from older donors, should be encouraged. If no living donor is available, the rationale for accepting lesser quality kidneys should be discussed.

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INTRODUCTION

Although the incidence of end stage renal disease (ESRD) in the United States for patients ≥ 65 years old is declining, prevalence continues to increase due to increasing patient survival. Older patients (≥ 65 years) now constitute over 40% of the ESRD population and with an aging general population, this is likely to grow further. Among 116990 incident ESRD patients in 2013, 56977 (48.7%) were ≥ 65 years and the mean age was 62.5 years^[1]. Due to the above trends, the number of older patients referred for kidney transplantation will likely continue to increase as well. As such, transplant physicians must be well versed in the unique issues that arise in the evaluation of older candidates. In this review, we answer key questions that confront both physicians and patients during the evaluation process.

WHO IS AN APPROPRIATE CANDIDATE?

An appropriate candidate is a patient whose survival and quality of life are expected to improve with transplantation as compared to remaining on dialysis. Unfortunately, there are no clinical criteria that accurately and reliably predict this. Older age alone is not a contraindication to transplantation^[2]. Transplant centers, however, may arbitrarily set their own age cut-offs. For candidates who do not have a living donor, this may be influenced by the expected waiting time in an individual center. In choosing the appropriate candidate, it is logical to only consider patients with reasonable long-term prognosis. However, determining who these patients are can be quite complex and there may be an inherent bias to exclude older patients due to perceived poor outcomes. Grams *et al.*^[3] developed a prediction model specific to older patients (≥ 65 years) using United States Renal Data System (USRDS) data of 128850 incident Medicare-

primary older adults with ESRD and United Network for Organ Sharing (UNOS) data of 6988 Medicare-primary first kidney transplant recipients aged ≥ 65 years. They identified 19 variables (15 comorbidities, age, dialysis vintage, sex and transplantation year) that predicted post-transplant outcomes. Based on the model, 11756 (9.1%) were found to be excellent kidney transplant candidates with a predicted 3-year post kidney transplant survival of 87.6% or higher. Of note, 76.3% of these patients were never placed on the waiting list or referred for living donor kidney transplantation. The authors concluded that using a simple risk prediction model may help identify suitable candidates and ultimately improve older candidates' access to transplantation. In another more recent study, Dusseuz *et al.*^[4] developed a simple clinical scoring system using data from the French national prospective registry. By applying this scoring system on incident dialysis patients aged 70 or above, they identified a subgroup of patients that had a 70% probability of survival within 3 years, representing about 20% of the entire cohort. They suggested that this subgroup of patients, despite their older age, were worthy of being referred for kidney transplant evaluation.

Medical evaluation

The primary reason for graft loss in the older patient population is death with a functioning graft hence a great deal of emphasis is usually placed on the medical evaluation to determine suitability for transplant. Transplant centers may have variable selection criteria especially in older patients. Although several guidelines^[2,5,6] exist with regards to the medical evaluation of a kidney transplant candidate, these are not specific for the older population. In general, however, individual organ systems are evaluated by means of history taking, physical examination and ancillary testing. If there is end-stage or severe disease, for example multi-vessel coronary artery disease not amenable to revascularization, then this usually becomes a reason to exclude patients from transplantation. Screening for infection and malignancy is also inherent to the evaluation especially in older patients due to their heightened susceptibility for both^[7].

Particular focus is given to the cardiovascular work-up because cardiovascular causes comprise the leading cause of death among transplant recipients^[1]. Unfortunately, the optimal method of screening for cardiovascular disease, in particular coronary artery disease, is not known^[8,9]. Transplant centers may have variable approaches, usually ranging from cardiac stress testing to more invasive testing such as coronary angiography. Stress testing is relatively easy and inexpensive to perform, but has suboptimal sensitivity and specificity especially in diabetics^[10]. As such, some centers may opt to go straight to a coronary angiogram. For example, at our center patients who are older than 70 years of age are required to undergo coronary angiography and if there is a significant burden of coronary artery disease, then a patient is deemed to be "too high risk" and therefore unsuitable for kidney transplantation. As part of the

cardiovascular work-up, additional attention is also given to imaging the iliac vessels to assess for patency and calcification. The imaging modality of choice at our center is computed tomography ± angiogram but a non-contrast magnetic resonance angiogram may also be a reasonable alternative if calcific burden is the main concern. At our center, not surprisingly, the primary reasons for excluding patients aged 60 years old or above are coronary artery disease, peripheral vascular disease (PVD), or both. It must be noted, however, that there are no studies that specifically compare the survival of these “very high risk” patients with transplantation as opposed to remaining on dialysis. Therefore, the decision to exclude these patients from transplantation remains rather subjective.

Measures of global health

Although a medical evaluation is able to closely scrutinize individual medical conditions, measures of global health and overall burden of disease may be more predictive of an older patient’s prognosis post-transplant. Measures of global health that are increasingly being recognized as important predictors of outcome in kidney transplantation include comorbidity indices and measures of functional status, physical performance, and frailty.

Comorbidity refers to the presence of two or more chronic diseases or conditions. The Charlson Comorbidity Index (CCI) is the most widely used tool to quantify comorbidity. In the kidney transplant population, high CCI scores, indicating increased comorbidity, have been shown to correlate with an increased risk of death^[11,12]. However, in a study by Heldal *et al*^[13], although increasing CCI scores predicted mortality in younger patients (ages 45-54 and 60-69 years), these were not predictive in those aged 70 years or older. Additionally, the applicability of the CCI, however, has been questioned in kidney transplant candidates^[14]. In a recently published Dutch study, Laging *et al*^[14] developed the Rotterdam Comorbidity in Kidney Transplantation (RoCKeT) score as an alternative to the CCI. The RoCKeT score is determined by the presence of cardiovascular disease (3 points), cerebrovascular accident (2 points), PVD (2 points), diabetes mellitus (2 points), liver disease (2 points), lung disease (2 points), malignancy (2 points) and human immunodeficiency virus (1 point). Not surprisingly, comorbidity was highest in the oldest age group in that 75% of patients aged 70 to 79 had comorbidity (at least 1 point). When RoCKeT scores were categorized and analyzed for the influence on patient survival, the group with the highest scores (5-9) had a significantly lower survival than those without comorbidity (score of 0). After multivariate analysis, patients with a score of 5-9 had a 2.7 increased risk of death compared to patients with a score of 0. Despite this, 50% of patients in the highest comorbidity category survived more than 10 years. The authors concluded that patients with severe comorbidity should not be excluded from transplantation due to superior patient survival compared with published survival data of hemodialysis patients. Moreover, meticulous selection of high-risk patients for kidney

transplantation can lead to successful outcomes.

Functional status is measured by a patient’s self-report of his or her ability to perform certain tasks. These tasks may include the ability to walk a certain distance, climb stairs, or perform activities of daily living. Functional status measurements are subjective and are obtained *via* questionnaires such as the short form-36 (SF-36) Physical Function (PF) scale, Vulnerable Elderly Survey-13, or Physical Activity Scale for the Elderly. A number of studies have reported an association between functional status and patient survival^[15-19]. In the largest study to date, Reese *et al*^[19] analyzed 19242 *Fresenius* dialysis patients who had answered the SF-36 PF scale pre-transplant and had linked post-transplant data *via* the UNOS registry. Patient PF scores were divided into PF quartiles and these were correlated with time to kidney transplantation and the net survival benefit of kidney transplantation vs remaining on the waiting list. Patients in the lowest quartile were significantly older than those in the highest quartile (median age 54 years vs 46 years). In terms of survival, patients who were in the lowest PF quartile had the worst 3-year survival rates (84% compared to 92% for the highest quartile). When compared to remaining on the waiting list, patients across all PF quartiles had a survival benefit with transplantation. The lowest PF quartile had a survival benefit evident by 6 mo after transplantation. Another important finding in this study is that patients in the lowest PF quartile were more likely to be inactivated on the waiting list (adjusted hazard ratio vs highest quartile, 1.3) and less likely to be transplanted (adjusted hazard ratio vs higher quartile, 0.64). The authors concluded that functional status measures may be more useful in counseling patients regarding their probability of transplantation. It must be noted however that this study did not examine patients who were excluded from kidney transplant listing and who presumably had poorer baseline functional status, *i.e.*, the study only examined the best patients referred for transplant. Also, only 12% of the cohort were 65 years or older. Therefore, for patients referred for transplant who are older or with potentially worse baseline functional status, the applicability of this study’s findings in regards to the survival benefit of transplant vs remaining on the waiting list remains to be determined.

Physical performance is the measured ability to perform tasks or exercise. Examples include measurements of gait speed or grip strength. The short physical performance battery (SBBP) is a combination of tests with a sub-score assigned. Measures of physical performance are objective and may be superior to reports of functional status in that these avoid reporting bias and overestimation of patients of their health status. Hartman *et al*^[20] in a study of 26 patients aged ≥ 60 years and referred for kidney transplantation, found that these patients with renal failure had lower SBBP scores, gait speed and grip strength compared to patients with diastolic heart failure (71 patients), chronic obstructive pulmonary disease (176 patients) or those with high cardiovascular risk (294 patients). Interestingly, despite

their inferior physical performance, renal failure patients were less likely to report functional impairment on disability questionnaires. We are not aware of any studies to date that have measured physical performance and correlated these with outcomes in kidney transplant patients. In other solid organ transplant candidates, particularly in lung transplant, the six-minute walk test (6MWT)^[21] has been used routinely in pre-transplant evaluations and has been shown to be a predictor of morbidity and mortality^[22,23]. The 6MWT measures the distance that a patient can quickly walk on a flat, hard surface in a period of 6 min. It would certainly be interesting to see if the 6MWT can be used similarly in older kidney transplant candidates to predict outcomes.

Frailty is a state of decreased physiologic reserve and is defined by the presence of 5 features, namely unintentional weight loss, weakness as measured by decreased grip strength, slow walking speed, low physical activity and self-reported exhaustion. It has been shown by McAdams-DeMarco *et al.*^[24-26] in successive papers that frailty is associated with increased hospital readmission post-transplant, graft loss and mortality. In a prospective study of 537 kidney transplant recipients in a single center^[26], frailty was measured at time of transplantation. Those who were frail, defined as having at least 3 out of the 5 features, were found to have a hazard ratio for death post-transplant of 2.22 (1.03-4.81, $P = 0.042$) compared to patients who were non-frail. In the subgroup of patients who were 65 years or older, 1-year survival was 85.8% in the frail group as opposed to 97.4% and 97.5% in the intermediately frail and non-frail groups, respectively. The authors suggested that frail patients should be identified pre-transplant and that patient survival may improve with appropriate management and closer monitoring of these patients.

A common theme to all the global measures of health discussed above is that it is not clear as to who is "too sick", "too debilitated", "too weak" or "too frail" to undergo kidney transplantation. Although these tools may help risk stratify patients, each candidate should be assessed on an individual basis and all data considered as a whole in determining a patient's suitability for transplant.

WHAT OUTCOMES CAN BE EXPECTED POST-TRANSPLANT?

Older recipients have decreased patient and graft survival compared to younger patients^[27]. Graft loss is commonly due to patient death, the top 3 causes being cardiovascular disease, infection and malignancy^[28]. There is less acute rejection in older patients and if graft loss is censored for death, graft survival actually improves with increasing age^[7,29].

Despite inferior patient survival in older compared to younger patients, kidney transplantation is pursued due to the survival benefit that it confers when compared to remaining on the deceased donor waiting list. In a study by Rao *et al.*^[30], 5667 patients aged ≥ 70 years who

were waitlisted for kidney transplantation were analyzed based on scientific registry of transplant recipients (SRTR) data. Of these patients, 2438 ultimately underwent kidney transplantation and when compared to those who remained on the waiting list, the transplanted patients had a 41% reduction in risk of death (0.59 relative risk of death). The time to equal risk was 125 d and the time to equal survival was 1.8 years from transplant. Of note, the mortality benefit that was seen in this study extended to the subgroup of patients aged ≥ 75 years, those with diabetes and those who received an expanded criteria donor. This study confirmed the findings of an earlier study by Wolfe *et al.*^[31] wherein the subgroup of patients aged 60-74 years was found to have a 61% lower mortality (0.39 relative risk of death 18 mo after transplantation) compared to similar patients on the waiting list. This survival advantage was calculated to translate into a 4-year increase in life expectancy (from 6 to 10 years).

In addition to superior patient survival compared to remaining on the waiting list, kidney transplantation is pursued due to the improvement in quality of life (QOL) that it confers^[32,33]. Transplant patients have superior QOL compared to dialysis patients^[34], though this may not be a fair comparison given that transplanted patients are a highly selected group. Age may have an effect on post-transplant QOL^[35-37]. In a single center study by Weber *et al.*^[36], they compared the post-transplant health-related QOL of patients ≥ 65 years with younger patients and with the general population. They found that physical QOL in older patients was significantly lower compared to younger patients and the general population. However, mental QOL was better than younger patients and similar to the general population. Humar *et al.*^[37] compared QOL of patients ≥ 65 years to younger patients and with national norms for this age group. They found that older transplanted patients scored higher in their general health perception, social functioning and mental health compared to national norms and also scored higher on social functioning and mental health compared to younger transplanted patients. Both these studies, however, did not look at pre-transplant QOL data to determine if there was an actual improvement in QOL before and after transplant. In a study by Laupacis *et al.*^[38] of 166 patients, 22 of whom were ≥ 60 years, they found that mean health-related QOL scores of almost all measures improved from pre-transplant to 6 mo after transplantation.

WHICH TYPE OF KIDNEY IS BEST?

Clearly, living donor (LD) transplantation confers the best outcomes in terms of patient and graft survival^[39]. This eliminates time on the waiting list, reduces dialysis vintage and allows for preemptive transplantation, affords patients better quality kidneys, and reduces the incidence of delayed graft function and a potentially tumultuous immediate post-transplant course. Moreover, due to the

elective and scheduled nature of LD transplant surgery, recipient issues can be addressed in a controlled manner prior to surgery thereby reducing perioperative risk. This was shown in a study by Gill *et al*^[40] of 25468 patients aged ≥ 65 years based on USRDS data who were listed for kidney transplantation, of which 11072 received a kidney transplant either from a LD, standard criteria deceased donor (SCD), or expanded criteria deceased donor (ECD). All patients were categorized based on cardiovascular (CV) risk as either being high, intermediate, or low CV risk. Among patients transplanted and across all CV risk categories, the death rate was lowest for patients who received a LD transplant and highest for recipients of an ECD kidney. Compared to patients who remained on the waiting list, a survival advantage was obtained, but importantly, times to equal risk and equal survival differed depending on the type of kidney transplanted and a patient's risk category. For patients who received a LD transplant, those who were low or intermediate CV risk had an immediately lower risk and higher survival post-transplant, and those who were high CV risk had a time to equal risk of only 43 d compared to similar patients who received an SCD (110 d) or ECD (180 d).

Despite the known advantage that living donor transplantation confers, older patients may have more limited living donor options as they may be hesitant to accept kidneys from younger donors such as their children or grandchildren. An alternative would be to pursue living donor transplantation from older donors such as their spouses or peers. Several studies have shown that recipients of kidneys from older living donors have reasonable outcomes^[41-43]. Englum *et al*^[41] studied 250827 patients based on UNOS data who received a kidney transplant, of which 92646 were LD kidneys and 4186 from donors aged ≥ 60 years. Not surprisingly, graft and patient survivals of patients who received a kidney from an older LD were worse compared to those who received a kidney from a younger LD. However, patients who received a kidney from an older LD aged 60-64 years and 65-69 years had similar graft survivals to patients who received a SCD kidney, superior graft survivals to ECD recipients and superior patient survivals to both SCD and ECD recipients. Patients who received a kidney from a LD aged ≥ 70 years had graft survivals similar to ECD recipients but significantly better patient survival. Given the organ shortage and current waiting times for a deceased donor kidney, it would make sense for an older patient who has an available older LD to pursue transplantation from an older LD rather than wait for an SCD or ECD kidney.

For those without living donor options, patients are faced with an increasing waiting time on the deceased donor list. The median number of years to deceased donor transplant was 5.5 years in 2003 and 7.6 years in 2007^[39]. Waiting time could be shorter or longer depending on where a patient is listed and his or her sensitization status and blood type. As older patients' time on the waiting list increases, the less likely they are to be transplanted as their health deteriorates

and they are either removed from the waiting list or they die^[44]. Compared to younger patients, the risk of death while waiting for a transplant is higher for older patients^[39]. It is therefore of paramount importance for older patients to get transplanted sooner rather than later. Kidneys that are thought to be of lesser quality should be considered for older candidates as waiting times for these kidneys are usually shorter. Rao *et al*^[30] and Merion *et al*^[45] demonstrated that recipients of ECD kidneys had superior survival compared to similar patients who remained on the waiting list or those who received standard therapy (waiting list and non-ECD transplantation). Massie *et al*^[46] examined the outcomes of patients who received high kidney donor profile index (KDPI) kidneys and compared these to outcomes of patients who remained on the waiting list until receipt of a KDPI $< 70\%$ kidney. The times to equal risk and equal survival post-transplant with the comparison group were 6 and 18 mo, respectively for the KDPI 81%-90% group and 7.2 and 19.8 mo, respectively for the KDPI 91%-100% group. At 4 years post-transplant, the KDPI 81%-90% group and 91%-100% group had a 17% and 10% lower mortality, respectively, than the comparison group. However, after 4 years the mortality rate was not statistically significantly different. The study found that the benefit of the high KDPI kidneys was greatest in patients ≥ 50 years who were listed at centers with a median wait time of ≥ 33 mo. In another study, Rose *et al*^[47] found that among 5257 patients that received a kidney from a deceased donor aged ≥ 65 years (defined in this study as an ECD kidney) in the United States, 10-year mean death-censored graft survival exceeded patient survival in patients aged ≥ 60 years. Among those aged ≥ 70 years, the difference was over 20 mo. Of note, there was a 7-8 mo difference in the 10-year mean patient survival between those who received an ECD kidney and similar patients who received a kidney from a deceased donor aged < 65 with a KDPI of 60%-69%. The authors concluded that for patients aged ≥ 60 years, kidneys from older donors can provide a lifetime of allograft function and that ECD transplantation should be encouraged in this age group. In a study from Spain, Pérez-Sáez *et al*^[48] looked at outcomes of 2040 patients waitlisted for transplant, of whom 389 (mean age 68.9 ± 5.8 years) received a kidney from a deceased donor aged ≥ 75 years. They found that there was a 56% lower risk of death in patients who received a transplant compared to those who remained on the waiting list. However, patients ≥ 70 years, diabetics and those with chronic obstructive pulmonary disease did not derive any statistically significant benefit.

HOW DOES THE NEW KIDNEY ALLOCATION SYSTEM (KAS) AFFECT OLDER PATIENTS?

In an attempt to balance equity with utility, kidney allocation in the United States was changed in December

2014^[49]. One of the goals of the new KAS is to increase unrealized graft years by matching high quality kidneys with recipients who have longer life expectancy^[50,51]. As a result, transplant rates among older candidates are expected to decrease^[51]. In an analysis of the early impact of the new KAS a year after its implementation, Stewart *et al.*^[52] noted a significant reduction in transplants where donor and recipient age differed by more than 30 years (21.1% pre-KAS vs 16.3% post-KAS). Among recipients aged 65 years or older, transplant rates significantly decreased from 22.9% of all kidney transplants pre-KAS to 18.1% post-KAS across all donor KDPI's, with the most prominent reduction in transplants from donor kidneys with a KDPI of 0-20%. This occurred despite an increase in the number of waitlisted patients aged \geq 65 years (21.3% pre-KAS to 24.9% pre-KAS).

Another important feature of the new KAS is that kidneys from donors with a KDPI > 85% are now being allocated nationally. Whether this would lead to increased utilization of these organs and subsequent shorter waiting times remains to be seen. Broader sharing of these kidneys may lead to increased cold ischemic times and increased discard rates of marginal kidneys. In early analysis^[52], there was a significant reduction in transplant rates of kidneys from donors aged \geq 65 years (3.1% pre-KAS vs 2.5% post-KAS, $P = 0.0085$) and a non-significant reduction in transplanted kidneys with a KDPI of 86%-100% (8.6 pre-KAS vs 7.9% post-KAS, $P = 0.0645$). The kidney discard rate 1-year post KAS was slightly higher (19.4% post-KAS vs 18.5% pre-KAS, $P = 0.05$).

With these changes in the new KAS, we believe that older recipients should be motivated further to look for living donors including older living donors. If no living donor is available, then listing for kidneys with a KDPI > 85% should be highly considered. Consenting for KDPI > 85% kidneys should include a discussion regarding expected outcomes and rationale for accepting these kidneys.

CONCLUSION

Determining who among older kidney transplant candidates is appropriate for transplantation can be challenging and complex. A thorough medical evaluation with particular focus on cardiovascular health must be employed. Additional tools such as measures of comorbidity, functional status, physical performance, and frailty may be helpful. Those older patients who ultimately undergo transplantation have decreased patient and graft survival compared to younger counterparts, but have superior patient survival compared to those who remain on the deceased donor waiting list. Living donor transplantation confers the best outcomes for older recipients with reasonable outcomes from older living donors. If no living donor is available, most older patients will likely benefit from accepting lesser quality kidneys such as those that have a KDPI > 85%. In the era of the new KAS where transplant rates among older patients are expected to decrease, appropriate counseling of older recipients regarding their options is of paramount

importance.

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