Comorbidities and Kidney Transplant Evaluation in the Elderly

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Key Words

Elderly · Evaluation · Kidney transplant

Abstract

Background/Aims: The elderly are the fastest growing subpopulation with end-stage renal disease. The goal of our study was to define characteristics of elderly patients who were considered ineligible for transplantation compared to those who were listed. **Methods:** 984 patients were referred for evaluation during a 2-year period. Records of patients ≥ 65 years of age ($n = 123$) were reviewed. Patients who were listed versus not listed were characterized. Factors associated with waitlisting were determined using standard statistical tools. **Results:** Half of elderly transplant candidates were accepted for listing compared to 75.4% of those aged < 65 years. In multivariable logistic regression, older age (OR 1.29 per year ≥ 65 , 95% CI 1.14–1.45), coronary artery disease (OR 8.57, 95% CI 2.41–30.53), and poor mobility (OR 13.97, 95% CI 4.76–41.00) were independently associated with denial of listing. The receiver operating characteristic curve showed good discrimination for denial of listing (area under the receiver operating characteristic curve of 0.88). **Conclusion:** Elderly candidates carry a heavy burden of comorbidities and over half of those evaluated are deemed unsuitable for waitlisting. Better delineation of characteristics associated with suitability for transplant candidacy in the elderly is warranted to facilitate appropriate referrals by physicians and management of expectations in potential candidates.

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Introduction

Patients ≥ 65 years of age are the largest growing age group of the end-stage renal disease (ESRD) population and comprise 40% of all patients with ESRD [1]. Mortality in ESRD patients is significantly higher than the general population and this effect is most marked in the elderly [2]. Kidney transplantation has been shown to be associated with improved survival and quality of life compared to remaining on the waiting list in patients with ESRD irrespective of age [3, 4].

The widespread use of expanded criteria kidney donor (ECD) transplantation has improved access to kidney transplantation in the elderly, where standard deceased donor pool waiting times are prohibitively long [5, 6]. However, the transplant waitlist evaluation process, a prerequisite for deceased donor kidney transplantation, is an obstacle that many elderly patients with advanced CKD do not surmount as evidenced by the low proportion of the elderly patients with advanced CKD or ESRD who are evaluated, waitlisted and transplanted [7].

The deceased donor waitlist evaluation process for kidney transplantation is different than that of other solid organ transplants in that the medical assessment may precede transplantation by many years. Therefore the assessment must not only take into account the candidate's current state of health but also his or her likelihood of

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survival to successful transplantation. Low referral and waitlisting rates of elderly patients may reflect physician concern over additional consultations and testing required for transplant listing combined with unrealistic expectations by such patients in the setting of lower life expectancy and longer transplant waiting times.

Transplant evaluation in these complex patients is therefore a somewhat subjective process that must combine careful medical and psychosocial assessment of each candidate with an educated assessment of their life expectancy. The primary goal of our study was to define the demographic and clinical characteristics of elderly patients who were considered ineligible for transplantation compared to those who met criteria for listing.

Subjects and Methods

Study Population

We identified all adult patients who were referred for kidney transplant evaluation at our center between September 2008 and September 2010 and conducted a detailed chart review of all candidates aged ≥ 65 years. Candidates for kidney transplant evaluation are referred to our center from a broad referral base and are required to undergo teaching sessions prior to evaluation by a physician. After completion of the teaching session, patients may proceed to evaluation by the transplant team. Group teaching sessions are offered monthly for patients who are referred, during which basic information on kidney transplantation is given. While all patients are encouraged to proceed with medical evaluation, some patients opt not to proceed after the teaching session. Medical data on the proportion of patients who opted not to proceed with the formal evaluation process were not available. The evaluation process entails a comprehensive assessment by a transplant nephrologist, social worker and nurse specialist. For each candidate, a multidisciplinary panel determines eligibility for transplantation.

We stratified patients by age (18–29, 30–49, 50–64 and ≥ 65 years) and determined the proportion of candidates accepted to the waitlist in each group. We performed a detailed chart review of all candidates aged ≥ 65 years. Data extracted included demographics: age, sex, race/ethnicity and marital status; renal history: etiology of renal disease, mode of renal replacement therapy and time from initiation of dialysis to transplant evaluation; medical comorbidities: cardiac, cerebral and peripheral vascular disease, diabetes, body mass index (BMI) and cancer history. To delineate further the important issue of social support, we identified with whom the patients live – categorized as alone versus not alone (i.e. with spouse/partner, siblings, children, grandchildren or nursing home). In addition, distance to our center from the patient's home was assessed and used as a proxy for accessibility to the transplant center.

In the absence of a formal standardized mobility test, we graded mobility on a simple 1–3 scale based on information provided in the medical records, with 3 representing no functional impairment, 2 representing moderate functional impairment, and 1 representing significant disability (e.g. wheelchair use or inability to move to the examination table). Standardized measures of frailty have not been routinely assessed, and whether the patients can

perform the medical workup as suggested was not formally assessed. Because of the long-wait period in our region, further medical tests that are required for transplantation are deferred until the estimated time to transplantation is within 1–2 years.

Our primary outcome was the status of waitlisting (list vs. denial). Secondary outcomes were death or transplantation following evaluation. Death was ascertained using patient medical records and the social security death index.

We obtained a waiver of consent for this study from the institutional review board at Stanford University School of Medicine.

Statistical Analysis

We assessed associations among categorical variables and the outcome (list vs. denial) using the χ^2 test or Fisher's exact test when appropriate. Student's t-test or the Wilcoxon rank sum test was used to assess any associations among continuous variables and the same outcome.

We performed univariate analysis using unconditional logistic regression to generate crude odds ratios. Continuous variables in the model were checked for linearity in the logit. All significant predictors in univariate analysis were assessed in multivariate models. Our final model was ascertained through backward stepwise elimination. Model fit was ascertained using the likelihood ratio χ^2 test. A receiver operating characteristic (ROC) curve was generated to determine the discriminative ability of our final model, wherein model performance was assessed using the area under the curve (AUC). In addition, a 10-fold cross-validation was performed in order to assess the generalizability of our model. The data was partitioned into 10 random subsets, of which a fitted model based on 9 subsets was applied to the last, independent subset 10 times. We conducted statistical analyses using SAS 9.3 (SAS Institute, Cary, N.C., USA). We considered two-tailed p values < 0.05 as statistically significant.

Results

Referral, Evaluation and Waitlisting Rates by Age Categories

A total of 984 adult patients were referred during the study period and 699 (71%) completed a full evaluation. Of the 699 patients who were evaluated, 496 (71%) were accepted to the waitlist (fig. 1). Among the patients referred, 57% of those ≥ 65 years of age were evaluated compared to 73–82% in other age groups (table 1). Once evaluated, 50% of those ≥ 65 years of age were placed on the waitlist compared to 66–92% in other age groups (table 1).

Characteristics of Elderly Candidates

Baseline characteristics of the 123 candidates ≥ 65 years of age are shown in table 2. The mean age was 70.4 ± 4.4 years, 43% were female, and the most common presumed etiology of CKD was diabetic nephropathy (42%). For elderly patients with CKD, there was a heavy burden of cardiac disease (25%) and diabetes mellitus (53%). 62% of

Table 1. Referral, evaluation, and waitlisting of all adults by age category

Age groups	Referred n	Evaluated n (%) ^a	Waitlisted n (%) ^b
18–29	76	62 (82)	57 (92)
30–49	309	235 (76)	193 (82)
50–64	382	279 (73)	185 (66)
>65	217	123 (57)	61 (50)
All adults	984	699 (71)	496 (71)

^a Per referred patients. ^b Per evaluated patients.

Fig. 1. Patients referred, evaluated and waitlisted. We define elderly as patients who were ≥65 years of age at the time of referral.

patients evaluated were on hemodialysis, 9% on peritoneal dialysis and 29% were non-dialysis-dependent. The time to evaluation for transplant candidacy was more than 6 months after initiation of dialysis in 56 patients (46%). Among the older cohort, 20% indicated the presence of potential living donors compared to 43% of the younger cohort.

Factors Associated with Denial of Transplant Listing

Table 3a summarizes the characteristics of candidates according to waitlist status (accepted vs. denied). Univariate analysis showed that variables associated with waitlist denial were impaired mobility (OR 10.49, 95% CI 4.30–25.85), coronary artery disease (CAD) (OR 6.19, 95% CI 2.32–16.56), older age (OR 1.26 per year, 95% CI

Table 2. Elderly patient demographics and characteristics

Parameter	n (%) or mean ± SD
Mean age, years	70.4±4.4
Female	53 (43)
Race	
White	41 (33)
Black	6 (5)
Asian	40 (33)
Hispanic	33 (27)
Pacific islander	3 (2)
Marital status	
Married	76 (62)
Single	7 (6)
Divorced	21 (17)
Widowed	19 (15)
Lives alone	23 (19)
Distance to transplant center	
≤50 miles	101 (82)
>50 miles	22 (18)
BMI ≥30	34 (30)
Renal diagnosis	
Diabetes mellitus	52 (42)
Unknown	33 (27)
Hypertension	14 (11)
PKD	7 (6)
Calcineurin toxicity	6 (5)
Glomerulonephritis	6 (5)
Obstructive	1 (1)
Tubulonephritis	4 (3)
Comorbidities	
CAD	31 (25)
Cancer	12 (10)
Liver	10 (8)
PVD	14 (11)
CVD	13 (11)
Hypertension	110 (89)
Diabetes mellitus 2	63 (51)
Diabetes mellitus 1	2 (2)
Mobility	
Normal	77 (63)
Limited	30 (24)
Poor	16 (13)
Modality	
Hemodialysis	76 (62)
Peritoneal dialysis	11 (9)
Referral timing	
Preemptive	36 (29)
≤6 months on dialysis	30 (24)
>6 months on dialysis	57 (46)
Potential living donor	25 (20)

CAD = Coronary artery disease; BMI = body mass index; PVD = peripheral vascular disease; CVD = cerebrovascular disease; PKD = polycystic kidney disease.

Table 3a. Differences in characteristics between waitlisted and denied patients

	n (%) or mean $\pm$ SD		p value
	waitlisted n = 61	not waitlisted n = 62	
Mean age, years	68.5 $\pm$ 3.3	72.2 $\pm$ 4.6	<0.0001
Female	26 (43)	27 (44)	0.92
Race			0.52
White	18 (30)	23 (37)	
Black	4 (7)	2 (3)	
Other	39 (64)	37 (60)	
Marital status			0.007
Married	45 (74)	31 (50)	
Unmarried	16 (26)	31 (50)	
Lives alone	9 (15)	14 (23)	0.2657
Distance to transplant center			0.6082
$\leq$ 50 miles	49 (80)	52 (84)	
>50 miles	12 (20)	10 (16)	
BMI $\geq$ 30	11 (19)	23 (43)	0.007
Renal diagnosis			0.080
Diabetes mellitus	21 (34)	31 (50)	
Other	40 (66)	31 (50)	
Comorbidities			
CAD	6 (10)	25 (40)	<0.0001
Cancer	3 (5)	9 (15)	0.0729
Liver	5 (8)	5 (8)	1
PVD	4 (7)	10 (16)	0.0947
CVD	7 (11)	6 (10)	0.7457
Hypertension	51 (84)	59 (95)	0.0372
Diabetes mellitus	28 (46)	37 (60)	0.1260
Mobility			<0.0001
Normal	53 (87)	24 (39)	
Limited	8 (13)	22 (35)	
Poor	0 (0)	16 (26)	
Modality			0.0521
Hemodialysis	30 (49)	46 (74)	
Peritoneal dialysis	8 (13)	3 (5)	
On dialysis	38 (62)	49 (79)	0.0414
Referral timing			0.0532
Preemptive	23 (38)	13 (21)	
$\leq$ 6 months on dialysis	16 (26)	14 (23)	
>6 months on dialysis	22 (58)	35 (73)	
Potential living donor	18 (30)	7 (11)	0.0121

1.13–1.40), BMI >30 kg/m² (OR 3.17, 95% CI 1.36–7.41), being unmarried (OR 2.81, 95% CI 1.32–6.0), hypertension (OR 3.86, 95% CI 1.01–14.78), on dialysis (vs. predialysis) (OR 2.28, 95% CI 1.02–5.08), hemodialysis (vs. peritoneal dialysis) (OR 4.09, 95% CI 1.00–16.65), late evaluation (>6 months after initiation of dialysis; OR 2.82, 95% CI 1.19–6.68) (table 3b). Having a potential liv-

Table 3b. Predictors of waitlist denial in univariate model

Parameter	OR	95% CI
Age	1.26	(1.13, 1.40)
Age (5 years)	3.18	(1.86, 5.46)
Marital status		
Married	Ref	
Unmarried	2.81	(1.32, 6.00)
BMI		
<30	Ref	
≥ 30	3.17	(1.36, 7.41)
CAD	6.19	(2.32, 16.56)
Hypertension	3.86	(1.01, 14.78)
Mobility		
Normal	Ref	
Limited/poor	10.49	(4.30, 25.85)
On dialysis	2.28	(1.02, 5.08)
Modality*		
Peritoneal	Ref	
Hemodialysis	4.089	(1.00, 16.65)
Referral timing		
Preemptive	Ref	
≤ 6 months	1.55	(0.58, 4.16)
>6 months	2.82	(1.19, 6.68)
Potential living donor	0.30	(0.12, 0.79)

CAD = Coronary artery disease; BMI = body mass index.

* Calculated only for those patients receiving dialysis (n = 86; 38 waitlisted and 48 not waitlisted).

Fig. 2. Independent predictors of waitlist denial. Age, mobility and CAD were associated with waitlist denial after multivariable analysis. ORs and 95% CIs are displayed.

ing donor was associated with decreased odds of denial (OR 0.30, 95% CI 0.12, 0.79).

When entered into a multivariable logistic regression model, three factors remained independently associated with waitlist denial; older age (OR 1.29 per year >65 , 95% CI 1.14–1.45), CAD (OR 8.57, 95% CI 2.41–30.53), and poor mobility (OR 13.97, 95% CI 4.76–41.00) (fig. 2). For

Fig. 3. ROC curve of the multivariate waitlist denial prediction model. AUC = 0.8830.

the three-variable model (age, CAD, and poor mobility), the ROC curve showed good discrimination for waitlist denial with an AUC of 0.88 (fig. 3). A 10-fold cross-validation only slightly attenuated the AUC to 0.87, indicating that our model, and hence our predictors, are fairly consistent and robust. Figure 4 illustrates the relation between candidate age and the predicted probability of waitlist denial in our model, dependent on CAD history and mobility. Mobility seems to have a larger effect at baseline relative to CAD history.

Reasons for Waitlist Denial and Post-Evaluation Outcomes

Decision letters to patients regarding transplant candidacy were reviewed. Following evaluation, 5% of elderly candidates chose not consider transplantation. The most common reason documented for waitlist denial was medical unfitness (83.9%); specified as multiple medical issues in 46.3%, severity of cardiovascular disease in 25.8%, active cancer in 6.5%, and obesity in 4.8% (at our institution, BMI <40 is required for listing at any age). Other reasons for waitlist denial included poor psychosocial support in 4.8% and renal recovery in 3.2%. In the short follow-up period following evaluation, 5 patients denied waitlisting and 2 patients on the waitlist died, while 4 waitlisted patients were transplanted (3 living donor, 1 deceased donor).

Fig. 4. Effect of age on the predicted probability of waitlist denial. **a** Effect of CAD history on the probability of waitlist denial and age, holding mobility constant. **b** Effect of mobility on the probability of waitlist denial and age, holding CAD history constant.

Discussion

In this single-center analysis of kidney transplant evaluations, nearly half of elderly patients evaluated were deemed ineligible for waitlisting. While studies have reported a significant benefit of transplantation over dialysis in older age groups, elderly patients who are referred for transplant evaluation are highly selected even prior to referral, and generally are thought to represent the healthiest among the ESRD population in their age cohort. At our center, potential candidates who are referred by their physician undergo basic education on the transplant process by a team of transplant coordinators prior to a formal evaluation. Among patients ≥ 65 years of age, 57% proceeded to a formal comprehensive evaluation, compared to 76% among the 50- to 65-year age group.

Only half of those patients ≥ 65 years of age evaluated were placed on the waitlist. Three variables, poor mobility, age and CAD, were independently associated with waitlist denial, and taken together, were highly predictive of waitlist denial.

American and European guidelines published for transplant evaluation have been evolving, and has promoted consistency of evaluation across transplant centers [8–10]. Our evaluation process includes a comprehensive education session, assessment of patient motivation, psychosocial factors and support structures as well as a detailed medical evaluation [10]. Judicious waitlist selection has never been more important. There is an increasing discrepancy in the USA between the size of the deceased donor kidney waiting list and available organs. In 2009, there were 14,394 kidneys procured from 7,248 deceased donors and a total of 85,920 patients on the transplant waiting list [11]. The elderly are the fastest growing among those with ESRD, yet they are the most vulnerable to medical decline and death while awaiting transplantation. How best to select those who would benefit from transplantation is not well defined.

There is no absolute age limit beyond which kidney transplantation should not be considered, and consideration of the biological, rather than chronological age of each candidate, has been advocated [12]. Indeed, life expectancy after initiation of dialysis is quite heterogeneous among similarly aged patients on dialysis. For example, while the median life expectancy of patients initiated on dialysis at ages 65–69 is 2.5 years, those in the highest quartile have a median life expectancy of 4.6 years compared to the 0.9 years in the lowest quartile [13]. While it is important to carefully assess the potential benefit of transplantation in terms of life expectancy and quality of life for the older candidate, lack of a standardized tool for assessing biological age may render the transplant evaluation process for elderly candidates more subjective than that for younger candidates. More precise and consistent ways of determining biological age and functional status would aid in the transplant evaluation of the elderly, such that the selection process is clearer to the patient and referring physician.

Around half of elderly candidates who underwent medical evaluation were deemed ineligible for deceased donor transplant listing. Candidates may have outright contraindications to transplantation including non-correctable CAD, severe heart failure, malignancy, morbid (grade 3) obesity or inadequate social or financial support. Waitlisting is not a passive process and places a

number of demands on the patient including regular clinic follow-up visits and diagnostic testing including some that are invasive (e.g. coronary angiography) and carry risk. Therefore, the evaluation process must also assess whether there is a *reasonable expectation* that the candidate will be alive and fit for transplantation, and whether the patient would want to undergo some of the risks of the evaluation process itself. In centers with long median wait-times, consideration of the ECD list may be advised for older candidates [14]. Regular routine follow-ups with the transplant center may be necessary to assess whether the patient remains a reasonable candidate for transplantation and to facilitate communication of expectations after transplantation with the patient and his or her loved ones.

A large proportion of elderly dialysis patients have significant limitation in mobility and activities of daily living [15] and, at least in the first year following transplantation, physical performance does not significantly improve [16]. In our elderly cohort, we found that impaired mobility was among the strongest predictors of denial of candidacy (OR 10.5, 95% CI 4.3–25.85). Recent reports highlighted that a staggering proportion of elderly patients with ESRD [17], even among those who were eventually referred for kidney transplantation, had poorer physical performance than similarly aged adults with other common chronic diseases such as heart failure, COPD and severe cardiovascular disease [18]. Standardized assessments of mobility and frailty that have been used in geriatrics [19, 20] have now been implemented in the ESRD population to help guide the decision to initiate dialysis in octo- and nonagenarians [21] and to aid the selection of dialysis modality [22]. With the projected increase in the number of elderly patients referred for transplant evaluation, adoption of such measures in the setting of transplant evaluation may be warranted.

Many centers with long waiting times wrestle considerably with waitlist management, especially of the elderly. Wait-times at our center for blood group O are 7–10 and 4–5 years for standard and ECD transplants, respectively. Patients with ESRD have accelerated progression of comorbid diseases such as cardiovascular disease, and the medical suitability for transplantation diminishes rapidly while on the waitlist. The elderly are especially vulnerable to rapidly declining health. The threshold for waitlisting in the elderly varies significantly, with inhomogeneous weights on factors such as regional wait-time and the presence of a living donor. The practice at our center has been to accept patients for waitlisting if they are suitable

for transplantation at the time of evaluation regardless of whether the donor has potential living donors. We found a crude association (approximately 3-fold higher odds) between acceptance on the waitlist and the presence of a potential living donor, and it would be tempting to interpret this as a selection bias toward those with living donors. However, having a potential living donor may also indicate a better and wider network of social support. Access to transplant center, as measured by distance to our center, was not associated with transplant candidacy. However, only 20% of patients had to travel >50 miles, and this must be interpreted with caution. Larger national data have been used to address issues of psychosocial barriers to referral [23–27]. All patients 60 years of age or older are encouraged to consider concurrent ECD listing, and their candidacies are reexamined every 1–2 years while on the waitlist. While geriatric consultation, formal cognitive assessment or depression screening are not systematically used, these may be useful and necessary tools in the future to better serve our growing geriatric population.

A major strength of this study is that it captures data on patients at the time of referral and evaluation, rather than at the later time point of transplant listing. Preexisting large national transplant databases, e.g. the UNOS database registry, capture data on patients after placement on the waitlist, and therefore preclude analyses of patients prior to transplant listing. Other databases such as USRDS record data on patients with ESRD and waitlisting status, but do not ascertain whether patients have been formally evaluated for transplantation. A major obstacle in delineating the factors that lead to the denial of transplant candidacy is that data on patients who are evaluated but not listed for transplantation are seldom recorded, and certainly unavailable in a standardized way, unlike the registry data obtained for listing by UNOS. To our knowledge, our study is the first to characterize all patients referred to a transplant center and analyze the decision-making process.

Our study has several limitations. As with all single-center studies there are issues with generalizability; racial and socioeconomic case-mix vary from region to region and our deceased donor waiting times are some of the longest in the country, although all candidates >60 years of age are routinely offered parallel ECD listing and are informed about, and encouraged to pursue, multiple center listing. In addition, the relatively small sample size limits identification of factors modestly associated with denial of listing, or rare factors (e.g. active HIV or hepatitis) with strong associations. This retrospective

analysis did not have the granularity of data needed to ascertain the precise and standardized measurements of the extent of conditions such as mobility, CAD or hypertension. However, given the large strength of the association of these factors with waitlisting status, it is likely to have external validity. Future multicenter studies using standardized, precise measures of these factors will help define better selection criteria for transplantation in the elderly. Finally, while we were able to identify the patients who died during the study period (5 who were not waitlisted vs. 2 on the waitlist), longer follow-up would be needed to determine whether those who were listed were likely to die during the wait period had they been listed.

Other factors that showed statistically significant but weaker associations with denial of transplant candidacy in our study warrant validation in larger studies. Some factors are likely to represent proxies for more direct causes of non-listing. For example, marital status is likely a surrogate measure for social support. Similarly, patients who are referred later may have lower socioeconomic status and poorer access to transplant referral. Schold et al. [7] have reported that insurance status and income are among the predominant factors associated with patient progress to transplantation. From our recent analysis and modeling of data from the USRDS database, we showed that the benefits of transplantation in the elderly diminish significantly when the lag-time to waitlist is factored into the model compared to listing at the time of dialysis initiation [13].

In summary, elderly patients being evaluated for transplantation carry a heavy burden of comorbidities and (at our center) over half of those evaluated were deemed unsuitable for waitlisting. With the continuing rapid growth of elderly with CKD, we anticipate that proportionately more time and resources will be spent in the evaluation of elderly candidates by transplant centers. Better delineation of characteristics associated with suitability for transplant candidacy in the elderly is warranted. Poor mobility and CAD were the strongest factors associated with denial of transplant candidacy in the elderly. Prospective studies with better adaptation and utilization of geriatric measures of frailty, mobility and medical comorbidities are needed to better define biologic age over chronologic age in elderly transplant candidates in order to help optimize access to transplantation while assuring good outcomes in this population. Such studies will also facilitate appropriate referrals to transplant centers, promote transparency for patients and help physicians set reasonable expectations.

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Disclosure Statement

The results presented in this paper have not been published previously in whole or part, except in abstract format.

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