Criteria for and Appropriateness of Renal Transplantation in Elderly Patients With End-Stage Renal Disease: A Literature Review and Position Statement on Behalf of the European Renal Association-European Dialysis and Transplant Association Descartes Working Group and European Renal Best Practice

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Abstract: During the last 20 years, waiting lists for renal transplantation (RT) have grown significantly older. However, elderly patients (ie ≥65 years of age) are still more rarely referred or accepted to waiting lists and, if enlisted, have less chances of actually receiving a kidney allograft, than younger counterparts. In this review, we looked at evidence for the benefits and risks of RT in the elderly trying to answer the following questions: Should RT be advocated for elderly patients? What should be the criteria to accept elderly patients on the waiting list for RT? What strategies might be used to increase the rate of RT in waitlisted elderly candidates? For selected elderly patients, RT was shown to be superior to dialysis in terms of patient survival. Virtually all guidelines recommend that patients should not be deemed ineligible for RT based on age alone, although a short life expectancy generally might preclude RT. Concerning the assessment of comorbidities in the elderly, special attention should be paid to cardiac evaluation and screening for malignancy. Comorbidity scores and frailty assessment scales might help the decision making on eligibility. Psychosocial issues should also be evaluated. To overcome the scarcity of organ donors, elderly RT candidates should be encouraged to consider expanded criteria donors and living donors, as alternatives to deceased standard criteria donors. It has been demonstrated that expanded criteria donor RT in patients 60 years or older is associated with higher survival rates than remaining on dialysis, whereas living donor RT is superior to all other options.

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Patients over 65 years old are the fastest growing age group among the population with end-stage renal disease (ESRD) worldwide.[1] In the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) Registry Annual Report of 2012, patients aged 65 to 74 years and 75 years or older constitute 22% and 20%, respectively, of the prevalent renal replacement therapy population.[2] The proportions are even higher in the United States, with 24% and 34%, respectively.[3]

Several studies have shown that renal transplantation (RT) is safe and provides better survival, compared with dialysis, in patients of advanced age.[4] However, many centers and specialists are still reluctant to register elderly patients on waiting lists for RT; this reluctance may often be due to biased opinions, because, unfortunately, objective selection criteria for RT are poorly defined for this population.[5] Furthermore, in the context of donor shortage, the probability for waitlisted elderly patients of actually receiving a kidney transplant is still lower than that for younger counterparts.[6] Nevertheless, another important reason for this lower transplant rate in the elderly may be that incurring events (eg, infections or cardiovascular complications) might alter their transplant status, at least temporarily.

Management of elderly patients is often complex and specific evidence-based treatment guidelines are often lacking. A European multidisciplinary initiative recently identified and prioritized potential topics to be addressed for this population. This joint initiative of the ERA-EDTA and the European Union Geriatric Medicine Society prioritized the development of guidance on benefits and risks of RT in elderly patients with ESRD as a topic of interest.[7]

In this review, we looked at relevant data in the literature concerning the benefits and risks of RT in the elderly (ie, patients ≥65 years of age), trying to find answers to the following questions:

1. Should RT be advocated for elderly patients?
2. What should be the criteria to accept elderly patients on the waiting list for RT?
3. What strategies might be used to increase the rate of RT in waitlisted elderly candidates?

BENEFITS OF RT COMPARED WITH DIALYSIS IN ELDERLY ESRD PATIENTS

The superiority of RT over dialysis in terms of survival duration has been suggested by several studies performed over the last 20 years in ESRD patients, including the elderly[8-17] (Table 1). However, RT recipients 70 years or older and, particularly, 80 years or older have a higher mortality risk, compared with those 60 to 69 years.[18]

Furthermore, elderly RT recipients may also experience better quality of life (QOL), as compared with dialysis,[1] although there are very few good studies in this field.[19] Benedetti et al[20] found that over 80% of RT recipients 60 years or older felt cheerful, independent, and healthy; they reported that health problems were either a minor drawback or no drawback to enjoying life, and 100% of them felt that opting for RT was the correct decision. Rebollo et al[21] reported significantly better physical functioning, bodily pain, general health, vitality, and social functioning scores in elderly RT patients compared with their counterparts staying on dialysis. Humar et al[22] showed that elderly RT recipients scored higher in their general health perception, social functioning, and mental health, as compared with the national US norms.

In addition, RT in the elderly may also be cost-effective. Laupacis et al[23] found that in patients 60 years or older, the annual cost of dialysis was 65 720 Canadian dollars ($CA), whereas the cost of the first year after RT was $CA 63 708; however, in year 2, the cost of RT was only $CA 21 160.

RISKS OF RT IN THE ELDERLY

Elderly RT recipients have an increased risk of infections and cardiovascular events than younger patients.[1,24]

With aging, the immune system undergoes structural and functional changes, including qualitative alterations in T cell activation and/or quantitative differences in T cell subsets.[25] This results in higher incidence and severity of infectious complications in the elderly compared with younger transplant recipients for the same degree of immunosuppression. Meier-Kriesche et al[26] reported an exponential increase in deaths caused by infections in elderly RT patients, whereas the increase was linear in their age-matched waitlisted counterparts. The risk of death due to infection was 5-fold higher in transplant recipients 65 years or older than in those aged 30 to 39 years.[27] Kauffman et al[28] showed that infection is the most common cause of mortality in the first posttransplant year in recipients 60 years or older. However, it should be emphasized that the mortality risk from infections is even higher for elderly patients who remain on dialysis.[29]

On the other hand, the decreased immune reactivity also seems to be associated with a lower risk of acute rejection episodes after RT in the elderly.[25] In more than 70 000 RT recipients, Meier-Kriesche et al[27] showed that the incidence of acute rejection decreased with increasing age; in patients aged 18 to 29 years, the 6-month acute rejection rate was 28%, compared with only 19.7% in those 65 years or older. Using the United Network of Organ Sharing (UNOS) database, Tullius and Milford[30] found that in patients 70 years of age, the rejection rate was 14% versus 28% in those aged 18 years. Another study[31] showed an incidence of acute rejection of 37.6% in patients 50 to 59 years versus 22.7% in those 60 years or older. In a group of RT recipients 70 years or older, acute rejection rates of 35% were seen within the first 12 weeks posttransplantation, as compared with 44% in patients aged 60 to 69 years and 45% in those aged 40 to 54 years.[32] However, the consequences of acute rejection may be more severe in the elderly. In a study of 48 821 RT recipients,[33] acute rejection was associated with a rate of graft loss of 116 per 1000 patients in those 65 years or older, compared with only 43 per 1000 patients in those aged 18 to 35 years, after adjustment for confounders like donor age, donor source, and delayed graft function. In another study,[34] the presence of acute rejection episodes during the first 3 months posttransplant was a strong predictor of premature death in the elderly (≥60 years), as opposed to the control group (45-54 years).

In the long term, death-censored graft survival in the elderly appears to be comparable to or even better than that in younger RT recipients. For example, in a study by Heldal et al[32] death-censored graft survival was similar among different age groups: 89% in elderly (≥70 years), 88% in senior (60-69 years), and 90% in control (45-54 years) patients.

TABLE 1.

Survival studies in elderly ESRD patients on RT waiting list: RT recipients compared with patients staying on dialysis

Study	Patients	Main findings
Wolfe et al, USA, 1999[8]	228 552 patients on maintenance dialysis (USRDS data)	Among patients who were 60-74 y of age, the cumulative survival rate improved after the first year post-RT, with a projected increase in life span of 4 y and a decrease in the long-term risk of death of 61%. When this group was further subdivided into age subgroups of 60-64, 65-69, and 70-74 y, the projected increases in life span were 4.3 y, 2.8 y, and 1 y, respectively.
Ojo et al, USA 2001[9]	Patients registered on the UNOS RT waiting list	Among patients ≥65 y, the 5-y mortality risk in ECD recipients relative to those who stayed on dialysis was 0.71, with a projected extra life time of 3.8 y.
Rao et al, USA 2007[10]	5667 RT candidates ≥70 y from the SRTR, who were waitlisted between 1990 and 2004	Transplant recipients had a 41% lower overall risk of death compared with waitlisted candidates remaining on dialysis, after adjustment for several demographic and medical factors (RR, 0.59; P <0.0001). Further subgroup analyses found that patients aged 70-74 y (RR, 0.58; 95% CI, 0.52-0.65), as well as those older than 74 y (RR, 0.67; 95% CI, 0.53-0.86), had improved survival with RT compared to those who stayed on dialysis.
Gill et al, Canada, 2005[11]	63,783 RT candidates who started dialysis between 1995 and 2000	Among patients aged ≥70 y, the expected survival rates were 8.2 y for those who received a kidney transplant, compared to only 4.5 y for those remaining on dialysis.
Johnson et al, Australia, 2000[12]	174 consecutive patients ≥60 y of age who were accepted on the Queensland cadaveric RT waiting list between 1993 and 1997	There were 67 patients receiving a RT, whereas the other 107 continued to undergo dialysis. These two groups were well matched at baseline with respect to age, gender, body mass index, renal disease etiology, comorbid illnesses, and dialysis duration and modality. Respective 1-, 3- and 5-y survival rates were 92%, 62%, and 27% for the dialysis group and 98%, 95%, and 90% for the transplant group (P <0.01).
Bayat et al, France, 2010[13]	1495 adults starting renal replacement therapy from 1997 to 2003 in the Lorraine region of France, of which 994 were ≥60 y	Among the elderly, RT recipients had a 78% lower risk of death compared with patients on dialysis (HR, 4.6; 95% CI, 2.2-9.7), after adjusting for comorbidities, serum albumin and body mass index.
Savoye et al, France, 2007[14]	3001 patients ≥60 y waitlisted for RT, of which 2099 were transplanted	Patients who did not undergo RT had an adjusted risk of death 2.54 times higher than that of transplanted patients of the same age (P<0.0001), regardless of the type of graft. The risk was 3.78 times higher than that for patients receiving SCD grafts (P < 0.0001) and 2.31 for patients receiving ECD grafts (P<0.0001).
Oniscu et al, Scotland, 2004[15]	325 patients >60 y listed for RT	128 patients (39.4%) received a first transplant within the study period and the remaining 197 (60.6%) continued to undergo dialysis. The RT recipients were younger at listing (P<0.0001), spent less time on the active waiting list (P<0.0001), and had less ischaemic heart disease (P = 0.024) and cerebrovascular disease (P = 0.03). There was a significantly lower risk of death (RR = 0.35, 95% CI 0.22-0.54; P<0.0001) and a longer life expectancy after listing with a transplant (8.17 vs 4.32 y).
Heldal et al, Norway, 2010[16]	286 ESRD patients ≥70 y of age waitlisted for RT	Patients starting dialysis between 1990 and 1999 appeared to have no survival advantage after RT (HR for death, 1.01; 95% CI, 0.58-1.75), whereas, in contrast, a substantial long-term benefit of RT was seen among those starting dialysis after 2000 (HR for death, 0.40; 95% CI, 0.19-0.83; P=0.014).
Lloveras et al, Spain, 2015[17]	Matched-pair analysis of 823 RT recipients from elderly donors (65 y or older), compared to 823 controls that remained on dialysis.	In all age groups, the dialysis patients had higher adjusted risk of death than the transplanted patients. In the elderly groups, the RR was 2.20 (95% CI, 1.60-3.09) in those aged 65-69 y and 1.86 (95% CI, 1.11-3.11) in those ≥70 y

HR, hazard ratio; USRDS, United States Renal Data System.

Based on UNOS data, Keith et al[35] and Tullius et al[36] showed that the death-censored risk of graft loss declined with each successive decade increase in age. Molnar et al,[37] in an analysis using US Scientific Registry of Transplant Recipients (SRTR) data of 145 470 adult RT recipients, found that, compared with patients 18 to 34 years, death-censored allograft failure risk was lower in patients aged 65 to 69 years by 37%, 70 to 74 years by 36%, and 75 years or older by 20%. Faravardeh et al[38] reported death-censored graft survival rates at 5, 10, and 15 years of 90.7%, 80.4%, and 73.7%, respectively, for patients 65 years or older, 87.2%, 77.6%, and 71.5% for those 50 to 64 years, and 79.8%, 70.3%, and 60.8% for those younger than 50 years. A possible explanation for the better graft survival

in elderly patients might again be the depression of the immune system associated with advanced age, as discussed above, although selection bias could also explain this outcome, to some extent. Furthermore, death censoring may be misleading, as graft survival may thus appear to be better in the elderly than in the younger patients simply because of a shorter life duration in the former age-group.

Although randomized controlled studies are lacking, it is conceivable that, given the immunosenescence, using lower doses or alternative drug combinations could minimize side effects like infection or malignancy in elderly RT patients, while still being able to provide an adequate level of immunosuppression.[39] A small study by Badowski et al[40] showed that reduced immunosuppression was associated with improved graft and patient survival in RT recipients 60 years or older.

Relatively few studies have compared patient survival between older and younger RT recipients, because older age is undoubtedly associated with higher risk of death in all populations.[4] In a study by Karim et al[41] including 19 103 RT recipients, with a median follow-up of 4.4 years, mortality risk increased with age, as follows: below 50 years (5.8%), 50 to 59 years (14.2%), 60 to 69 years (22.0%), 70 to 79 years (31.9%), and 80 years or older (45.5%). The 3 most common causes of deaths for recipients 70 years or older were cardiac (21.2%), infection (21.2%), and malignancy (20.2%). Similar findings were reported by Faravardeh et al[38] and Mendonça et al.[31] Surprisingly, however, Hatamizadeh et al[42] found a 75% and 92% lower death risk in RT recipients than in the general population, among individuals aged 65 to 75 years and 75 years or older, respectively. Part of the explanation of this phenomenon might be the presence of selection bias, where older patients selected for RT may be relatively healthier compared to age-matched non-ESRD individuals.[4]

TRENDS AND CURRENT PRACTICES IN WAITLISTING FOR RT AND ALLOCATION OF KIDNEY ALLOGRAFTS TO ELDERLY ESRD PATIENTS

Over the last decades, the emerging evidence of the benefits and safety of RT in the elderly, as well as the ageing of the overall ESRD population, has led to waiting lists for RT growing significantly older in many countries, with the largest absolute and relative increase in the 65 years or older age group.[43] In the United States between 1997 and 2014, whereas the waiting list for RT increased from 30 000 to more than 100 000 candidates, the proportion of candidates 65 years or older has grown from 7% to over 21%.[44] In France, this proportion increased from 2.4% in 1998 to 11.7% in 2011, with individuals 70 years or older, representing almost half of this elderly group.[45]

However, although the numbers of elderly on waiting lists has increased, the percentage of waitlisted patients among those with ESRD continues to decrease with advancing age.[25] For example, in the United States, the relative proportion of patients waitlisted for RT decreases from 21% among ESRD patients aged 18 to 39 years to only 3.4% among those 70 years or older and 0.5% among those 80 years or older.[46] In France, the percentages of ESRD patients waitlisted for RT before dialysis initiation and after 5 years on dialysis are 11.2% and 66%, respectively, among individuals younger than 60 years, but only 3.4% and 26.8% among those 60 to 69 years and as low as 0.2% and 1.6% among those 70 years or older.[47] Bayat et al[48] analyzed data of incident patients aged 18 to 80 years in 11 French regions, who started dialysis between 2006 and 2008. Compared with patients aged l8 to 39 years, those 70 years or older were found to be almost twice less likely to be placed on the waiting list, after adjustment for other patient-related and region-related factors.

In a recent systematic review, Tong et al[49] showed that there is significant variability among nephrologists in considering RT for elderly patients, with the percentage of those who recommend it to ESRD patients 60 years or older ranging from 10% to 59%. Low rates of waitlisting for the elderly can be explained by increasing comorbidity in this population.[50] However, some studies suggest that elderly patients are often not listed, despite having no formal contraindications.[25] Another aspect of the inequity, as shown in a study by Salter et al[51] is that discussions on RT are not maintained with patients 65 years or older (44% vs 75% in the younger age groups). Other reasons for not listing the elderly, as suggested by Knoll,[52] could be that (a) patients may not see themselves as potential candidates and, therefore, decline this option; (b) physicians may feel that they would "displace" a kidney from a younger potential recipient; and (c) unlike kidney allocation, which is generally governed by stronger oversight, referral for waitlisting is largely at the discretion of referring physicians.[52] Misconceptions regarding the criteria for RT could prevent early referral to a transplant centre, leading to longer time spent on dialysis by the elderly.[1]

Regarding the RT allocation practices, in the United States, the probability for elderly candidates of actually receiving a kidney transplant has steadily increased during the last decades. The proportion of patients 65 years or older among those living with a renal transplant has grown from 3.8% in 1990 to 23.3% in 2012.[6] The chance of getting an RT within 3 years is still slightly lower in the elderly (36%), as compared with the youngest population (44%); however, the mortality risk while waiting is, not surprisingly, much higher in the former (16.9% vs 3.4%), which highlights the interest in increasing the RT rate in this age group.[6] The trends are similar in Europe. Data from Eurotransplant indicate that the proportion of deceased donor (DD) RT recipients among candidates 65 years or older increased from 3.6% in 1991 to 19.7% in 2007.[43] In Denmark, for example, the group 60 years or older accounted for 18% of prevalent RT patients in 2000 and has increased to 30% in 2012.[6] However, the rate of RT still remains lower in the elderly than in younger candidates. The United Kingdom Renal Registry 2013 data show that the ratio between the number of transplants and the number of active patients on the waiting list in different age groups from 35 to 70 years or older decreases from 0.57 to 0.40. In France, the probability of receiving a kidney transplant after 5 years on dialysis is 58.6% among patients younger than 60 years of age, but only 21.6% among those 60 to 69 years and 1.3% among those 70 years or older.[47]

EVALUATION OF ELDERLY PATIENTS AS POTENTIAL CANDIDATES FOR RT: RECOMMENDATIONS FROM AVAILABLE GUIDELINES

Practice guidelines from major medical societies state that age alone should not be a reason to withhold waitlisting.[52] In fact, due to laws that prohibit age discrimination in

the delivery of healthcare services, age-based transplant allocation is illegal in many countries.

A few years ago, Batabyal et al[53] performed a systematic review of clinical practice guidelines on waitlisting for RT, including 15 such guidelines published from 2001 to 2011. Six guidelines[54-60] recommended that patients should not be deemed ineligible based on age alone, but that age-related comorbidities, however, could be considered a relative contraindication to RT. For example, the UK Renal Association guidelines state that "age is not a contraindication to transplantation, but age-related comorbidity is an important limiting factor,"[54] whereas the American Society of Transplantation guidelines maintain that "there should be no absolute upper age limit for excluding patients whose overall health and life situation suggest that transplantation will be beneficial."[55] Only 1 guideline[61] recommended exclusion of patients 65 years or older and proposed that patients aged 55 to 65 years be evaluated individually, whereas another guideline[62] stated that candidates 70 years or older may be waitlisted, although no clear evidence was available to support improved outcomes.

Almost all guidelines recommended that patients with a reduced life expectancy should not be waitlisted, rather than defined a specific age cutoff.[53] However, it has been acknowledged that this principle is difficult to interpret and apply in clinical practice, because assessment for waitlisting involves complex decisions based on multiple factors and because we do not actually possess reliable tools to accurately estimate survival duration. Three guidelines[61,63,64] recommended a minimum life expectancy of 5 years posttransplantation to be considered for RT. One consensus statement[60] declared that patients with "an anticipated likelihood of less than 80% chance of surviving a minimum of 5 years after transplantation" should be excluded. An anticipated survival rate of less than 2 years was an absolute contraindication in 1 guideline,[58] because "RT does not offer any advantage and may instead accelerate the death." Three guidelines made qualitative recommendations, that is, to exclude patients with a "short life expectancy,"[57] who were "predicted to have their lives shortened by transplant or experience worsening QOL,"[54] or who did not have "reasonable probability of surviving beyond current waiting times."[56]

For elderly transplant candidates, careful selection based on thorough medical and psychosocial evaluation is recommended in most studies.[19] As shown by Kauffman et al,[28] elderly patients with significant comorbidities may experience high mortality rates early post-RT, thus drawing no survival benefit from RT as compared with staying on dialysis. However, no clear guidelines on the criteria to use for selecting elderly candidates for RT are currently available.[5] Although many guidelines recommend that elderly patients should be screened more aggressively for cardiovascular disease and cancer, they do not provide specific criteria to determine which patients may be suitable candidates. In addition to investigations for comorbidity, some authors suggest that elderly candidates should also be screened for frailty and adherence to prescriptions, because each of these factors can put RT recipients at risk of death or graft failure.[5]

Evaluation of elderly patients basically has the same objectives and uses the same methods as for all RT candidates. This includes assessment of surgical and vascular suitability, cardiovascular tolerance to stress, malignancy, nutritional status, serologic suitability, behavioral and medication compliance, psychosocial and financial status.[65] Such assessments need to be repeated periodically in all waitlisted patients, but probably more frequently in high-risk individuals, such as the elderly.[66] The purpose of the evaluation is to identify contraindications for RT and address and correct medical and psychological conditions that may affect transplant outcomes. This evaluation commonly involves several investigations, as shown, for example, in Table 2.[62]

Screening for Cardiovascular Disease and Cancer

Patients with chronic kidney disease and ESRD, in general, have a high prevalence of cardiovascular diseases.[62] These, in fact, represent one the most common causes of mortality in RT recipients, with highest rates in the peritransplantation period.[67] In RT candidates, older age is considered a high-risk factor for cardiovascular events perioperatively and later post-RT.[59] Therefore, potential RT recipients—and particularly the elderly—should have a careful evaluation of cardiovascular comorbidity. Assessment for cardiovascular disease includes history taking, physical examination, and ECG for all patients; abnormal results warrant further cardiac evaluation.[62] In addition, for asymptomatic patients 60 years or older, some guidelines recommend noninvasive stress testing, although they acknowledge that there is little or no evidence to support this recommendation. The 2012 scientific statement from the American Heart Association and the American College of Cardiology Foundation concerning cardiac disease evaluation and management among RT candidates[67] suggests that noninvasive stress testing may be considered in patients 60 years or older with no active cardiac conditions who also have at least 2 other risk factors for coronary artery disease, including diabetes, prior cardiovascular disease, more than 1 year on dialysis, left ventricular hypertrophy, smoking, hypertension, and dyslipidemia (class IIb; level of evidence C). The statement does not indicate any particular technique(s) to be used for noninvasive testing nor the optimal frequency for repeat testing. The ERA-EDTA guidelines[59] recommend performing a standard exercise tolerance test and cardiac ultrasound in asymptomatic high-risk patients, including those with older age, diabetes, and history of cardiovascular disease (grade 1C). Further investigation with noninvasive stress imaging (dobutamine stress echocardiography or myocardial perfusion scintigraphy) is recommended only in those with a positive or inconclusive exercise tolerance test (1C). In those with a positive test for ischemia, coronary angiography is subsequently indicated (1D).

Cancer is also very frequent in elderly dialysis patients.[68] European[59] and US guidelines[55] maintain that age-appropriate screening for malignancy as recommended for the general population should also be applied to RT candidates, in the absence of specific guidelines for these patients. This usually includes colonoscopy in patients 50 years or older, mammogram in women 40 years or older, and serum immunoelectrophoresis in patients older than 60 years, as shown in Table 2.[62]

Charlson Comorbidity Index and Other Mortality Risk Prediction Scores

Several comorbidity scores have been proposed to predict posttransplantation mortality in RT candidates, which might be used to guide decision-making for RT eligibility.

TABLE 2.

General evaluation of kidney transplant candidates[62]

(1) Comprehensive history and physical examination, with emphasis on:
(a) Documentation of the cause of renal disease and assessment of the risk of recurrence in the transplanted kidney
(b) Family history, especially kidney disease, hypertension, and diabetes
(c) Evidence of coronary heart disease, cerebrovascular disease, and peripheral vascular disease
(d) Evidence of defects in coagulation
(e) Evidence of abnormalities of the urinary tract and bladder
(f) Financial evaluation to assess ability to afford transplant medications
(g) Psychosocial evaluation
(h) Sensitization risks, including a history of blood or platelet transfusions, pregnancies, abortions, and previous transplants
(i) In retransplantation candidates, a detailed history of the prior transplantation courses and cause of graft loss, medication compliance, and previous transplant complications
(2) General laboratory tests:
(a) Blood type
(b) Complete blood count and comprehensive metabolic panel
(c) PT and PTT
(d) Serological tests for: viral hepatitis, VDRL, cytomegalovirus, and so on
(e) Tissue typing for HLA and PRA
(f) ECG
(g) Chest X-ray and lung function testing
(h) Renal ultrasound for those on dialysis therapy for more than 5 y in patients without recent imaging
(3) Particular laboratory tests, as indicated:
(a) PPD test in those with a history of exposure to tuberculosis, prior residence in an endemic area, or chest X-ray suspicious of tuberculosis
(b) Colonoscopy in patients older than 50 y
(c) Gynecological evaluation, including Papanicolaou smear in women of childbearing age
(d) Mammogram in women older than 40 y
(e) Serum immunoelectrophoresis in patients older than 60 y and those with unexplained renal failure and anemia
(f) Stress test, echocardiogram, and coronary angiogram
(g) Doppler studies of iliac and lower-extremity vessels or other imaging study may be performed in patients with symptoms and signs suggestive of peripheral vascular disease to evaluate the feasibility of allograft placement
(h) Detailed coagulation study in those with history of deep venous thrombosis, spontaneous abortion, recurrent clotting of a dialysis fistula or graft, or bleeding tendency
(i) Toxoplasmosis, coccidioidomycosis, and histoplasmosis titers in residents of endemic areas

PT, prothrombin time; PTT, partial thromboplastin time; VDRL, venereal disease research laboratory; PPD, purified protein derivative; PRA, panel-reactive antibody; ECG, electrocardiogram

The Charlson Comorbidity Index (CCI) is the most widely used scoring system for comorbidities in research and clinical practice. It assesses comorbidity level by taking into account the number and severity of 19 predefined comorbid conditions, and it provides a weighted score, which can be used to predict short- and long-term outcomes, such as physical function, hospitalization duration, and mortality rates.[69] Wu et al[70] found that baseline CCI score was a significant predictor of survival of RT recipients of any age, including those 60 years or older; however, among the elderly, this relation between comorbidity and survival was seen only in recipients of DD kidneys, but, surprisingly, not in recipients of living donor (LD) kidneys. Heldal et al[34] found that CCI predicts mortality in RT patients aged 60 to 69 years, but not in those 70 years or older.

Based on data from the United States Renal Data System, Grams et al[71] used logistic regression to develop a prediction model for post-RT outcomes of ESRD patients 65 years or older, involving 4 demographic and 15 comorbidity variables. Application of the model to a Medicare population of elderly ESRD patients (n = 128 850) identified 11 756 excellent RT candidates (defined as >87% predicted 3-year post-RT survival), of whom 76.3% were never actually referred for RT. It was estimated that 11% of these candidates would have found a suitable LD had they been offered the option of RT.

In a similar manner, Dusseux et al,[72] using logistic regression in a cohort of dialysis patients from the French national registry, developed and then validated in another cohort a 3-year mortality risk score for elderly patients 70 years or older, based on 14 demographic and comorbidity factors. Using this score system, they identified a group of patients with a good prognosis (risk score ≤6 points, ie, ≥65% survival rate at 3 years), representing 21% of the entire study group, which could have been considered as appropriate candidates for RT.

Evaluation of Frailty

Elderly RT recipients with a poor functional status, incapable of performing daily living activities and light exercise, have a significantly increased short- and intermediate-term risk of graft loss and mortality.[73] Friedman[65] believes that "the patient's activity level and exercise capacity are the best objective measures of this overall recovery potential (post-RT)" and that "it is neither reasonable, nor realistic to offer transplantation to an inactive, uninvolved old person for whom reengagement in life represents excessive optimism."

Physical frailty is defined as "a medical syndrome with multiple causes and contributors that is characterized by diminished strength, endurance, and reduced physiologic function that increases an individual's vulnerability for developing increased dependency and/or death."[74] Various scales have been proposed by geriatric specialists to identify and assess the severity of frailty. The phenotypic frailty scale designed by Fried et al[75] consists of 5 items (fatigue, resistance, ambulation, illnesses, and weight loss) and is based on patients' self-assessment. Frailty is classified by scoring 4 to 5, intermediate frailty by scores between 2 and 3, and no frailty by scores 0 to 1. To reduce subjectivity, this scale has been modified to include some objective measurements of weakness, weight loss, and slow walking speed.[76] These 2 scales are presented in Table 3.[5]

Frailty is highly prevalent in dialysis patients, and this prevalence increases with age. According to a study by Johansen et al,[77] 44% of dialysis patients younger than 40 years met the criteria for frailty, compared with 78% of patients 70 years or older. Frailty is a significant predictor of hospitalization and mortality in dialysis patients[52] and has also been associated with increased risk of delayed graft function,[78] early rehospitalization, and death[79] after RT, among recipients of all ages. The assessment of frailty might play a role in the selection of elderly patients for RT.[80] However, there is still very limited information about the impact

TABLE 3.

Two phenotypic frailty scales[5]

A phenotypic frailty scale based on questions[75]	A phenotypic frailty scale based on questions and measurements[76]
Fatigue. Are you fatigued?	Weakness. Decreased grip strength as measured by a handed dynamometer
Resistance. Are you unable to climb stairs?	Exhaustion. Measured by responses to questions about effort and motivation
Ambulation. Are you unable to walk 1 block?	Slow walking. Measured walking time to walk 4.5 m
Illnesses. Do you have ≥5 illnesses?	Low physical activity. Determined by asking about leisure time and activity
Loss of weight. Have you lost 5% of your weight in the last 6-12 mo?	Shrinking. Unintentional weight loss ≥4.5 kg in the last 12 mo

of frailty on mortality in elderly transplant recipients, and there are no guidelines indicating at which level of frailty a patient should be excluded from a waiting list.[5] Further studies of frailty as a predictor of post-RT outcomes are needed before its routine use in such decision-making can be recommended.

Evaluation of Psychosocial Issues and Adherence to Prescriptions

Mild cognitive impairment and dementia are common among patients with ESRD, affecting 16% to 38% of them, particularly the elderly. Dementia is associated with high risks of death, hospitalization, and disability in this population.[81] However, practice guidelines do not recommend routine cognitive testing before RT, not even in elderly patients.[80]

Successful RT (in terms of improved long-term survival and QOL) requires a good cooperation of patients and their supporters (family members, residence nurses) with the transplant team, to ensure adherence to recommended lifestyle, nutrition, medication, and follow-up visits.[65] This adherence may be considerably affected in elderly patients with cognitive impairment, but also in those with visual or physical deterioration, depression, social isolation, and/or financial restraint. It is crucial that such issues are identified and addressed properly, considering that poor adherence can contribute to acute rejection episodes, graft loss, and other complications.

Signs of cognitive deterioration or depression, as well as previous medical nonadherence, may predict poor adherence after RT. In addition, specific questionnaires can be used to identify patients who are more likely to be nonadherent, such as the Basel Assessment of Adherence to Immunosuppressive Medications Scale or the Theory of Planned Behaviour instrument; the latter may also help understanding the reasons of nonadherence and guide interventions to reduce it.[5]

STRATEGIES TO INCREASE ACCESS TO RT FOR THE ELDERLY

In a retrospective analysis from 2009, which included 54 669 candidates 60 years or older from the SRTR database, Schold et al[82] estimated that 46% of these candidates were expected to die before receiving a DD RT. The authors claimed that this information should be shared with the elderly candidates and their caregivers to encourage them to consider the option of LD RT as a probably more promising alternative. Indeed, Schaeffner et al[83] showed that in the United States, in ESRD patients aged 60 to 75 years, access to RT doubled between 1995 and 2006, and this improvement in access was largely due to a 3-fold increase in the number of both LD and expanded criteria donor (ECD) RT cases.

To overcome the growing discrepancy between supply and demand of kidney allografts, ECDs (ie, donor age 60 years or older or 50 to 59 years and additional comorbidity), as well as donors after cardiac death, are increasingly used for RT in many countries.[4] Furthermore, a "young-for-young and old-for-old" strategy (young-for-young particularly in the United States, and old-for-old in several European countries) has been implemented in recent years for utility reasons, that is, to reduce the need for repeat RT in the young and the rate of allograft loss due to recipient's death in the elderly.[4] This strategy is also thought to be equitable, at least from the perspective of the principle of "fair innings," which maintains that "patients developing ESRD at younger ages are worse off than those developing ESRD when older, because they have had fewer healthy life years."[84] Thus, ECD listing is particularly advisable for older patients who lack an LD and in whom a prolonged wait for a standard criteria donor (SCD) kidney is anticipated.[62]

Kidneys from elderly donors are associated with an increased risk of rejection when transplanted into younger recipients. However, when older grafts are allocated to older recipients, this effect is blunted, conceivably because of the immunosenescence.[4] Expanded criteria donor RT was shown to yield good results in the elderly in most studies. In a French study,[14] ECD RT in patients 60 years or older was associated with higher survival rates than remaining on the waiting list (relative risk [RR], 2.31; $P < 0.0001$). Using the SRTR database, Rao et al[10] confirmed that patients 70 years or older also have a survival advantage with an ECD kidney (RR, 0.75; 95% confidence interval [95% CI], 0.65-0.86) compared with nontransplanted waitlisted candidates. In another study of SRTR data of 145 470 RT patients,[37] ECD versus SCD kidneys were significant predictors of mortality in patients younger than 70 years, but not in those 70 years or older, after a median follow-up of 3.9 years. Hernandez et al,[85] based on UNOS data analysis of about 137 000 transplants, showed that recipients 70 years or older had comparable outcomes if they received low-quality kidneys compared with medium-quality kidneys, as measured by the Kidney Donor Profile Index; however, very low-quality kidneys had significantly worse outcomes. In a study of 109 127 patients from a US national registry, Merion et al[86] compared mortality after ECD RT with that in a standard-therapy group consisting of SCD recipients and patients staying on dialysis. Overall, the 3-year RR of mortality was 17% lower for ECD recipients (RR, 0.83; 95% CI, 0.77-0.90; $P < 0.001$). For patients 60 years or older, the survival benefit was even greater, with a 22% decrease in mortality (RR, 0.78; 95% CI, 0.68-0.90). Schold and Meier-Kriesche[87] found that patients 65 years or older had a slightly longer life expectancy if they accepted an ECD kidney within 2 years of starting dialysis therapy (5.6 years), rather than waiting 4 years to receive a SCD (5.3 years) or a LD (5.5 years) kidney.

Eurotransplant—an organization responsible for the allocation of donor organs in 8 European countries (Austria, Belgium, Croatia, Germany, Hungary, Luxembourg, the Netherlands, and Slovenia)—introduced in 1999 the Eurotransplant Senior Program (ESP) to offer elderly candidates rapid access to transplantation. The ESP preferentially allocates kidneys from donors 65 years or older locally or over a narrow geographic area to unsensitized recipients 65 years or older. A report of the program's first 5 years[88] compared the ESP group (old to old [O/O]) to 2 groups allocated via the standard Eurotransplant Kidney Allocation System with either old donor age (old to any [O/A], donor age ≥65 years) or old recipient age (any to old, [A/O], recipient age 60-64 years). Patients from ESP had worse 5-year survival than A/O patients in Eurotransplant Kidney Allocation System (60% vs 74%, $P < 0.001$) and worse 5-year graft survival (47% vs 64%, $P < 0.001$). On the other hand, the authors found that ESP led to significantly shorter waiting time (3.55 years in ESP vs 4.64 years in A/O; $P < 0.001$), as well as shorter cold ischemia time and less delayed graft function for the elderly recipients. Also, the number of older grafts accepted for RT significantly increased and the discard rates decreased since the initiation of ESP, suggesting that more elderly patients could be transplanted under ESP. Considering that RT confers a survival benefit compared to dialysis, the authors believe that the trade-off might be warranted.[88] Rose et al[89] compared 5-year outcomes in the ESP and United States Renal Data System. They found that among European recipients 65 years or older, patient survival exceeded graft survival, and ECD recipients returned to dialysis for an average of 5.2 months after transplant failure, whereas among US recipients 60 years older, graft survival exceeded patient survival. The average difference in patient survival at 10 years in elderly recipients in the United States with an ECD versus non-ECD transplant was only 7 months.

However, not all studies reported benefits of this O/O strategy. Veroux et al[90] showed that patients 65 years or older who received kidneys from DD also 65 years older had worse survival rates than patients of similar age remaining on the waiting list. Such results suggest that maybe there should be a donor age upper limit and/or a minimum quality standard for ECD kidneys to be accepted for RT. In some cases, an alternative to discarding is to transplant 2 ECD kidneys that are declined for use as single organs due to poor function; however, this requires more extensive and risky surgery, which can be problematic for elderly patients.[65]

Another very important strategy to increase RT in elderly candidates is to promote living donation.[24] The proportion of LD recipients 65 years or older doubled in the United States from 6.8% in 2001 to 13.7% in 2011.[66] Several studies[10,91-93] showed that LD RT was associated with better graft survival rates than DD RT in elderly recipients, as well as in younger ones. With respect to donor age, an analysis of UNOS data by Gill et al[94] demonstrated that in recipients 60 years or older RT from LDs 55 years or older have similar 3-year graft survival (83.4 vs 85.7%; P = NS) and patient survival rates (87.4 vs 88.4%; P = NS) as RT from younger LDs, and that kidneys from LDs 65 years or older showed graft survival rates comparable to deceased SCD and superior to deceased ECD transplants. Furthermore, in an analysis of SRTR data, Berger et al[95] found that graft survival for kidneys from LDs 70 years or older was similar to that of kidneys from deceased SCDs 50 to 59 years.

CONCLUSIONS AND RECOMMENDATIONS

1. For selected elderly ESRD patients, RT was shown to be superior to dialysis in terms of patient survival and, possibly, QOL and cost-effectiveness.
2. Death-censored graft survival is similar or even better in elderly RT recipients, as compared with younger counterparts.
3. RT appears to be safe in the elderly, if candidates are carefully selected. Given the senescence of the immune system, the use of lower doses of immunosuppressive drugs is likely to minimize side effects, without excess rejections; however, specific options need to be tested in randomized controlled trials.
4. Virtually all guidelines recommend that patients should not be deemed ineligible for RT based on age alone.
5. A short life expectancy generally precludes RT; however, this principle may be difficult to interpret and apply in clinical practice, because there is no general consensus over the definition of "short," and it is often unclear how life expectancy can be estimated.
6. The evaluation of elderly patients for RT basically has the same objectives and uses the same methods as for all RT candidates. This involves thorough medical and psychosocial assessment. However, the existing guidelines contain very few specific recommendations on the criteria to use for selecting elderly candidates for RT.
7. Many guidelines recommend that elderly potential candidates for RT should be screened more aggressively and more frequently for cardiovascular disease and cancer. Significant age-related comorbidities could be considered as relative contraindications to RT. However, the specific investigation methods and time intervals to be used, as well as criteria for exclusion, are still poorly defined and not supported by evidence.
8. For cardiac evaluation, noninvasive stress testing may be considered in asymptomatic patients 60 years or older who also have at least 2 other risk factors for coronary artery disease, although there is little evidence to support this recommendation.
9. With regard to malignancy, age-appropriate screening as indicated for the general population should be performed for RT candidates, in the absence of specific guidelines for these patients. This usually includes colonoscopy in patients 50 years or older and mammogram in women 40 years or older.
10. Several comorbidity scores can predict post-RT mortality and might be used to guide decision-making on eligibility. However, such scores should be validated in additional studies.
11. The assessment of frailty might also play a role in the selection of elderly patients for RT. Various scales have been proposed in this regard. However, there is still very limited information about the impact of frailty on mortality in elderly RT recipients, and there are no guidelines indicating at which level of frailty (if any) a patient should be excluded from a waiting list.
12. Psychosocial issues, including cognitive deterioration, depression, social isolation, and financial problems, are common in elderly patients and may have a significant impact on compliance to prescriptions and, ultimately, on patient and graft outcomes. Therefore, these issues should be assessed prior to RT waitlisting, as well as thereafter. Specific questionnaires can be used to identify patients who are more likely to be nonadherent.

13. Elderly patients should be encouraged to consider ECD and LD, as alternatives to deceased SCD, in order to increase their chances of access to RT. It has been demonstrated that ECD RT in patients 60 years or older is associated with higher survival rates than remaining on dialysis, while LD RT is superior to all other options. Systems like the ESP—which offers preferential allocation of ECDs to this age group—should be promoted.

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