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Renal transplantation in elderly patients. How to select the candidates to the waiting list?

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A B S T R A C T

Today, old age does not represent a formal contraindication to kidney transplantation. Rather, there is evidence that in elderly patients renal transplantation offers longer life expectancy and better quality of life in comparison with dialysis. Yet, the results of renal transplantation in recipients older than 65 years are inferior to those observed in younger adults, death with functioning graft representing a major cause of failure. Therefore, the selection of aged patients is of paramount importance. Apart from the routine clinical and biological investigations, three aspects have been relatively neglected by the transplant community and may require a careful analysis in elderly candidates to transplantation: the presence and degree of frailty, the presence of comorbidities and the adherence to prescriptions. Although there are rapid and simple tests for assessing the degree of frailty in the elderly, there is no clear cut-off value to decide whether a patient should be accepted or not. With advanced age the prevalence and severity of cardiovascular events and other diseases tend to increase. The use of combined age–comorbidity indices may be helpful to identify patients at high risk of mortality. Another critical point is the poor unintentional adherence to treatment, often caused by forgetfulness and mild cognitive impairment. These drawbacks may be further enhanced by a high number of pills to take and by changes in the dosage or type of prescriptions. A careful screening of the presence and degree of frailty, comorbidity and poor compliance to treatment is highly recommended before admitting older candidates to the waiting list for transplantation.

1. Introduction

For many years old age has represented a barrier to kidney transplantation. In the USA, the number of patients older than 65 years on dialysis approached 40% by 1989. However, the percentage of patients with a functioning kidney transplant was only 2.7% in this age group [1]. Nonetheless, the continuous advances in immunosuppressive and supportive therapies improved the results of kidney transplantation and allowed to extend the criteria for admitting even high-risk patients to the waiting list. Today, both the American and the European guidelines state that old age does not represent a contraindication to renal transplantation [2,3]. Rather, there are advantages offered by renal transplantation in comparison with dialysis. Compared to coetaneous patients on dialysis, life expectancy has been shown to be significantly longer in old patients who received a transplant than in those who remained in the waiting list [4–7], particularly when transplant recipients are given drugs which tend to lessen adverse events [8]. The quality of life was also better in transplant recipients, and the economic costs were lower [9,10]. These differences between transplantation and dialysis were particularly evident if patients received a kidney from a living donor [4,10], but remained in favor of transplant even if the kidney came from a deceased donor with expanded criteria [11].

However, in spite of improved graft outcome in older transplant recipients, elderly population is at a higher risk to develop cardiovascular disease, infections and malignancy in the post-transplant period and death with functioning graft still represents the leading cause of graft failure [12–15]. Thus a detailed evaluation of old candidates to kidney transplantation is warranted before admitting them to the waiting list for transplantation. Absolute contraindications to transplant include active infection, recent malignancy and/or uncontrolled psychiatric disorders. Patients with severe and irreversible failure of heart, lung or liver are also excluded from the waiting list unless a double organ transplant is indicated. However, apart from these contraindications that are valid for any age, the criteria for selecting old patients for transplantation are still poorly defined and the impression remains that old age per se may discourage some centers to admit these patients to the waiting list. Actually, older adults undergoing dialysis are less likely than younger adults to have discussions about kidney transplantation [16], as confirmed by the fact that less than 20% of patients aged ≥ 65 years are admitted to the waiting list [17]. This disparity with younger adults may be partially explained by the lack of guidelines or recommendations to select old candidates. Actually, in the absence

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of objective criteria, the decision to admit or reject old persons to the waiting list still rests on the subjective opinion of a team of experts or of a single doctor. In particular, little attention has been paid by the transplant community to three main aspects that can have a great impact on the outcome of kidney transplantation in the elderly, i.e. frailty, comorbidity and unintentional poor adherence to prescriptions. In this paper we will outline the importance of these drawbacks in influencing the deadly risk in the elderly subjects and will review the few papers that reported their impact on the outcome of renal transplant recipients.

2. Frailty

Gerontologists have long argued over the definition of frailty. Recently a consensus group defined physical frailty 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" [18]. Frailty is frequent in the elderly patients, and the presence of chronic kidney disease can double the risk of frailty [19]. Indeed even though a number of old uremic patients maintain an efficient physical status, degree assessment of elderly patients with end-stage renal disease (ESRD) plays a pivotal role in making clinical decision for these patients. Indeed, even though a number of old uremic patients do not suffer from severe comorbidities, many old patients in dialysis treatment tend to become sedentary and, in general, match with the definition of frailty.

Age per se is an unreliable indicator of frailty since health and aging rate of individuals are highly heterogeneous. Many nephrologists and transplant surgeons feel to be able to recognize the presence and the degree of frailty of old candidates to transplant. Yet, such a distinction is often elusive and it is certainly difficult for intermediate cases. Different scales have been proposed by geriatrists to identify the presence and severity of frailty. By reviewing seven scales of frailty in general old population, Theou et al. found that on each frailty scale, frailty score increased with age and the mortality risk increased with frailty score [20]. Many of these scales actually have predictive value but are time-consuming and are not widely used. The aforementioned consensus group indicated that simple, rapid screening tests can allow physicians to objectively recognize frail people. The phenotypic FRAIL scale proposed by Fried et al. [21] is composed by 5 items (fatigue, resistance, ambulation, illnesses, and loss of weight). Patients are asked five simple questions. Frailty is classified by scoring 4 to 5, intermediate frailty by scores between 2 and 3, no frailty by scores 0 to 1 [22]. This scale has been validated. To reduce subjectivity, the FRAIL scale has been modified by including some objective parameters to measure weakness, exhaustion and slow walking [23] (Table 1). Thus, it is possible and also rather easy to identify the presence and the degree of frailty.

Table 1
Two phenotypic frailty scales based respectively in simple questions [21] or objective measurements of weakness, exhaustion, and slow walking [22].

A phenotypic frail scale based on questions [19]	A Phenotypic Frail Scale Based On Questionsand Measurements [20]
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
Ilnesses. 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

Yet, the impact of frailty on the outcome of kidney transplant has been rarely assessed. To the best of our knowledge, only two studies have been reported, both of them were performed by the transplant team of the Hopkins Hospital in Baltimore. In a study on 183 renal transplant recipients aged 53 ± 14 years, preoperative frailty was assessed by the two phenotypic scales reported in Table 1. Frailty was independently associated with a 1.94-fold increased risk for delayed graft function within the first post-transplant week [24]. In the other study on 383 transplant recipients with a mean age of 53.5 ± 13.9 years, 18.8% of patients were considered to be frail. Frail patients were significantly more likely to experience hospital readmission in the first month after surgery and had an increased rate of morbidity [25]. However, little information about the impact of frailty on mortality in old transplant recipients can be drawn from these reports since the mean follow-ups were very short and only a minority of patients was older than 65 years.

In summary, one should keep in mind that frailty is an independent variable that may predict a higher risk of death. Frailty may be associated with comorbidity or may be a direct consequence of multiple diseases, but it should be remembered that these terms are not synonyms. Frailty is not identical to comorbidity. Therefore, identifying frail patients may prove to be an important criterion for selecting candidates to transplantation, and we feel that the presence and degree of frailty should be the first aspect to evaluate in an old transplant candidate. However, although the FRAIL and other scales can assess the presence and the degree of frailty, we still do not have clear guidelines indicating at which level of frailty a patient should be excluded from a program of kidney transplantation.

3. Comorbidity

With advanced age the prevalence and severity of comorbidities tend to increase. In a large British review, Tomson et al. found that among incident patients older than 65 years who started regular replacement therapy (RRT) only 39% of new entries aged ≥ 65 years had no comorbidity [26]. In a European survey on patients in RRT aged in mean of 61 years, 28% had diabetes mellitus, 23% ischemic heart disease, 24% peripheral vascular disease, 14% cerebrovascular disease, and 11% malignancy [27]. The UK renal registry reported that 56.5% of 5617 patients entered in the registry between 2008 and 2009 had one or more comorbidities, the most frequent being diabetes 39% and heart disease 22%; comorbidities became more frequent with advanced age [28].

The association between each comorbidity and mortality was evaluated in a European survey: the hazard ratio for death, adjusted for confounding effects was 1.65 for diabetes, 1.43 for ischemic heart disease, 1.40 for peripheral vascular disease, 1.41 for cerebrovascular disease and 1.64 for malignancy. An age over 60 years increased the risk of mortality by 11.2% [29]. By reviewing the data from United Network for Organ Sharing Standard Transplant Analysis and Research File, Baskin-Bey et al. found that the four strongest predictors of recipient survival after transplantation were age, diabetes mellitus, angina and waiting time on dialysis. At multivariate analysis the risk of mortality increased of 56% for every decade of age over 48 years, doubled for patients with diabetes, increased by 35% for patients with a history of angina, and increased by 52% if the duration of dialysis was longer than 1 year. Combining these factors, the relative risk of death fluctuated from less than 2.5 to more than 3.9 [30]. Apart from single comorbid conditions, little attention has been paid to the cumulative effects of different comorbidities. Charlson et al. proposed to use a comorbidity index to assess whether a patient would live long enough to benefit from a specific screening measure or medical intervention [31]. Accordingly, 20 comorbid conditions were considered and each condition was given a score of 1, 2, 3, or 6, depending on the associated mortality risk. This comorbidity index was validated and largely used in different instances. Years later,

Table 2
The Charlson combined ACI (to adjust for age, a score of 1 should be added for each decade over 40 years) and the comorbidity index for ESRD developed by Liu et al.

Charlson ACI [32]	Comorbidity index for ESRD [36]
Score 1	Score 1
Myocardial infarction	Atherosclerotic heart disease
Congestive heart failure	Diabetes
Peripheral vascular disease	
Dementia	
Cerebrovascular disease	
Chronic lung disease	
Connective tissue disease	
Ulcer	
Chronic liver disease	
Diabetes mellitus	
Score 2	Score 2
Hemiplegia	Cerebrovascular accident
Moderate/severe kidney disease	Peripheral vascular disease
Diabetes with end-stage organ damage	Chronic obstructive pulmonary disease
Tumor	Gastro-intestinal bleeding
Leukemia*	Dysrhythmia
Lymphoma*	Other cardiac disease
	Liver disease
	Cancer*
Score 3	Score 3
Moderate/severe liver disease	Chronic heart failure
Score 6	
Malignant tumor*	
Metastasis*	
AIDS*	

* Items included in the indices represent formally absolute contraindications to renal transplantation.

Charlson et al. adjusted the comorbidity index by age [32]. In the combined age–comorbidity index (ACI) 1 point was added to the final score for each decade over 40 years (Table 2). Jassal et al. reported that the 5-year survival in transplant patients with a Charlson score > 6 was 81% for patients aged 40–44 years and 62% for those older than 65 years [33], showing that the age adjustment is of paramount importance when considering elderly patients. Wu et al. assessed outcomes in 715 kidney transplant recipients. They found that high ACI was associated with a 2.88 times increased risk for patient death, both in the peri-transplant period and more than 3 months after transplantation. However the mean age of patients was 49.8 ± 14.2 years so that no information about the risk in old transplant recipients can be drawn from this study [34]. In a large retrospective review of risk factors that could predict renal allograft outcome, Heldal et al. found that the Charlson comorbidity index (CCI) at transplantation can play a significant role in patients under 70 years of age but does not seem helpful in the selection for kidney transplantation of patients older than 70 years [35]. The authors hypothesized that age itself and/or other confounders may be more important than comorbid conditions. In this regard, it is likely that the impact of comorbidity may have been overwhelmed by frailty or poor adherence to prescriptions, two frequent drawbacks of older age. The main limitation of the CCI/ACI lies in the fact that it has been developed for general populations. Comorbid conditions included in this score have a different impact on survival for the general population than for ESRD patients. Recently, Liu et al. ideated and validated a new simple score based on administrative data, specifically designed for ESRD patients (Table 2). The score proved to be better than the CCI in predicting mortality, hospitalization and medical costs, but it was only validated for dialysis patients. No data are available for renal transplant recipients at the moment, thus further work will be needed to determine if the new score outperforms the CCI even in this population [36].

In summary, comorbidity can strongly influence the probability of survival both before and after transplantation. Several scales may be used to assess the impact of comorbidity on life expectancy of an elderly patient after renal transplantation. Yet, there are no guidelines and the transplant specialists admit or reject a patient to the waiting list for transplant on the basis of their own decisions, usually based on personal clinical evaluation.

4. Adherence to prescriptions

Unintentional low medication adherence is a real, complex problem for older patients receiving polypharmacy. In a recent survey among non transplant patients older than 65 years, non-adherence one month after hospital discharge was found in 55% and it reached 69% after 3 months. Voluntary withdrawal of a drug and change of dosage without medical consultation were the main reasons for non-adherence. The number of drugs prescribed at discharge was related to medication non-adherence at both follow-up interviews [37]. The number of doses per day can also influence the adherence. A review of studies that measured compliance using electronic monitoring showed that compliance declined as the number of daily doses increased. Compliance was 79% for 1 dose, 69% for 2 doses, 65% for 3 doses and 51% for 4 doses [38].

The problem is of particular concern for transplant patients who have to take an elevated number of pills every day. In a survey of 1130 renal transplant recipients with stable kidney function in a mean of 5.9 years after transplantation, each patient was taking on average 11 pills per day, 6 immunosuppressants and 5 non-immunosuppressants [39]. It is difficult to believe that even an adherent young adult does not make any mistakes with such a high number of pills to be taken every day. Elderly transplant recipients tend to be more compliant to therapy than younger adults, but they either do not remember to refill prescriptions or get confused whenever changes to prescriptions or dosages are made. As a consequence, the rate of adherence to immunosuppressive and supportive therapy in renal transplant recipients decreases as patient age increases [40]. This unintentional poor compliance is more frequent in older patients with social isolation, depression, forgetfulness, and/or poor socio-economic conditions [40,41]. It should also be taken into account that 3% to 19% of persons older than 65 years have a mild cognitive impairment that does not interfere notably with activities of daily life. Some people with mild cognitive impairment seem to remain stable or return to normal over time, but more than half progress to dementia within 5 years [42], a condition leading to a number of consequences, including poor adherence to prescriptions [43]. In a study, about 1/3 of transplant patients older than 65 years who passed a Mini Mental State Examination forgot their medication at least once a month. Of note, all these patients were independent and active in their social work, suggesting that the risk of poor compliance could be quite higher in old transplant recipients with social isolation, depression or poor cognitive function [44].

Poor adherence contributes substantially to graft loss. In a systematic review a median of 36% of graft losses were associated with prior non-adherence and a meta-analysis showed that the odds of graft failure increased sevenfold in non-adherent patients compared with adherent subjects [45]. Another review reported that non-adherence contributed to 20% of late rejection episodes and 16% of the graft losses [46]. Moreover, poor adherence to clinical visits and/or to non-immunosuppressive medications may favor the occurrence of infection, tumor and cardiovascular disease [47], the three more frequent causes of death in transplant recipients.

Some clues may predict poor adherence after transplantation. Poorer performance in solving everyday problems and depressive symptoms are associated with post-transplant poor compliance [48]. Moreover, pre-transplant medical non-adherence strongly predicts post-transplant non adherence. In a recently published study on solid organ transplantation, pre-transplant non-adherence was associated with threefold higher odds of post-transplant immunosuppressive medication non-adherence [49]. About 60% of patients cannot

correctly report what their physicians told them about medication use 10 to 80 minutes after receiving the information [50]. Older patients often forget to take medications and the greater is the number of drugs to take, the higher is the risk of forgetfulness. Moreover, changes in the dosage or type of medications can often be misunderstood, leading to mistakes. These problems outline how cognitive impairment plays a fundamental role for non-adherence in this population and how a thorough assessment of cognitive functions needs to be undertaken in the evaluation of elderly candidates.

Particular care should be paid to those elderly patients who are considered as suitable for renal transplantation and who present risk factors for post-transplant non-adherence. Dedicated questionnaires may be helpful in identifying patients who are more likely to be non-adherent to immunosuppressive regimens. The Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS®) is a simple four-item questionnaire with a short recall period (4 weeks) that can be performed in interview format. Any positive answer to the questions is considered as non-adherence [51]. This scale, although still needing validation in renal transplant recipients, holds the premises to be a useful tool in this cohort of patients.

Other questionnaires, such as the Theory of Planned Behavior instrument, may be helpful in understanding the reason of non-adherence and guide interventions to ameliorate compliance [52]. The test comprises 23 different simple questions that evaluate the patient's attitude, subjective norms (perceptions of pressure/support from important others), perceived control over the therapy, intentions and past behavior. A poor performance in a specific area/set of questions may increase the physicians' ability to plan early interventions, targeted towards individual needs.

Cognitive-educational interventions are potentially effective approaches to enhance patient adherence to medication. Different kinds of strategies to aid in remembering prescriptions were identified by Gordon et al. in a study on renal transplant recipients. Visual cues, external reminders (i.e. people or simple technological devices) and organizing medicines/schedules, along with medicine toting, seemed to be the most widely used approaches [53].

The collaboration between caretakers and patient is of paramount importance. The transplant staff should provide clear instructions about prescriptions and check that patient has fully understood the prescription. A regular contact with the patient should be established and the adherence to prescriptions should be verified during follow-up visits. Some increase in adherence can also be obtained by simply asking the patients a feedback of their recent dosing history [54].

5. Conclusions

Today, age does not represent a contraindication to transplant anymore. Yet, older patients are more frequently affected by frailty, comorbidity and/or poor adherence to prescriptions. Each of these factors can put transplant patients at risk of death or graft failure. At present, no clear guidelines on the criteria to use for selecting elderly candidates to transplant are available and the scores indicating the degree of frailty and comorbidity are being used only by few centers. In clinical practice, decisions on the suitability of a transplant candidate are often based on the opinion of a team of experts or by a single transplant doctor. Such an approach can be biased by subjectivity and can raise conflicts between patients and caretakers or among doctors themselves. The transplant community urgently needs clear recommendations coming from panels of transplant experts, ethicists, and renal patients in order to know which criteria to use for admitting elderly patients to a program of kidney transplantation. Indeed, providing care that meets the needs of individuals is not always easy when faced with demands to make efficient use of resources. Furthermore, one must consider the interests of the public at large and practice within legal boundaries. Waiting for formal recommendations, we propose that in addition to the routine analyses older candidates to transplant should be screened for frailty, comorbidity and adherence to prescriptions.

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