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Review Article

Expanded Criteria Donors in Kidney Transplantation: The Role of Older Donors in a Setting of Older Recipients

Paride De Rosa,[1] Giovanna Muscogiuri,[2] and Gerardo Sarno[1]

[1] *Department of General Surgery and Transplantation Unit, "San Giovanni di Dio e Ruggi D'Aragona" University Hospital, Scuola Medica Salernitana, Largo Città di Ippocrate, 84131 Salerno, Italy*
[2] *Division of Endocrinology and Metabolic Diseases, Catholic University of the Sacred Heart "Agostino Gemelli" University Hospital, Rome, Italy*

Correspondence should be addressed to Gerardo Sarno; gsarno79@yahoo.it

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Kidney transplantation (KT) is the therapy of choice for end-stage renal disease (ESRD). The ESRD population is aging and so are patients waiting for KT. New strategies have been made for increasing the donor and recipient pools, and as a consequence kidneys from older donors or donors with significant comorbidities, the so-called "expanded criteria donor" (ECD) kidneys, are used for transplantation. Although good outcomes have been achieved from ECD, several issues are still waiting for clarification and need to be discussed. The concept of age matching is accepted as a method to ameliorate utilization of these allografts, but an optimal and widely accepted strategy is still not defined. The development of machine perfusion and the dual kidney transplantation are techniques which further improve the outcome of transplants from ECD, but the described experiences are scarce or coming from small single institutional reports. Also due to age-related immune dysfunction and associated comorbidities, the elderly recipients are more susceptible to immunosuppression related complications (e.g., infections and malignancy), although a widely accepted and validated immunosuppressive regimen is still lacking. In this paper, we review the issues related to KT employing allografts from marginal donors with a particular interest for the elderly patients.

1. Introduction

In the last two decades while kidney transplantation (KT) has been definitively recognized as the therapy of choice for end-stage renal disease (ESRD), the elderly population has progressively and largely increased over the years, all around the world [1]. At present there are two renal replacement therapies for ESRD: dialysis (including hemodialysis and peritoneal dialysis) and KT. The superiority of KT over dialysis is well established, warranting a better quality of life and an improved survival for all patients, including those with advanced age [2]. In the recent past, advanced age was considered by most to be a contraindication to KT, with advanced age of the donor also being among the most common reasons for discarding the offered kidneys [3]. The increasing disparity between the limited supply of cadaveric donors and the rising demand for kidneys has led to the consideration of alternative strategies to expand the availability of organs for transplant [4] as well as better ways of using the suitable allografts. Since the early 1990s the criteria for accepting kidneys for transplantation have been extended to allow the use of organs from "marginal donors" [5], and as a result the mean age of donors has progressively increased [6]. As a consequence there has been an increase in the number of performed transplants, but unfortunately the number of patients on the waiting list has remained stable, mostly because of expansion of the number of elderly recipients [7]. Out of more than 35000 candidates added to the waiting list for KT in 2011 in the USA, those aged 50–59 years were greater than 27% and more interestingly more than 30% were over the age of 60 years [8].

Aging is associated with a higher risk of renal failure, reason for which the number of patients with ESRD undergoing dialysis is increasing. In Europe in 2009 the number of new admissions on dialysis because of ESRD was of 125 per million population, with a median age of 67.2 years [9].

These data confirm the trend toward a progressive aging of the ESRD patients associated with an increasing need for KT among older adults. The need for more accurate selection and better ways of using the available allografts is still critical. In the United States in 1994 approximately 7% out of 9531 offered kidneys were discarded [10], and in 2003 along with an increase of offered kidneys up to 11437, the percentage of discard raised up to 12% [11]. In Italy in 2011, there have been 1113 available deceased donors, but the performed KTs have been 1331 (corresponding to only 59.8% of the available kidneys), again highlighting the need for a specific tool for allograft selection and assignment [12].

In this paper, we review the issues related to KT employing allografts from marginal donors with particular interest on elderly patients.

2. The "Marginal Donors"

What defines a "marginal donor" still requires clarification. The definition of Expanded Criteria Donor (ECD) codified in 2002 is employed to describe kidneys donors over the age of 60 years without comorbidities or donors over the age of 50 years with two comorbidities among blood hypertension, death from cerebrovascular accident, or terminal serum creatinine levels >1.5 mg/dL [13]. It is still not clear which upper limit of age should be considered as a barrier to donation. Collini et al. [14] described a series of 38 patients undergoing KT (16 as single and 22 as double transplants) matched for age with donors aged 75 years or older (mean age 79.1 years, range 75–90 years). The 3-year actuarial graft survival rate was 64%, while the patient survival rate was 81.2%, with an acceptable renal function along the study period. More recently Gallinat et al. [15] carried out a similar evaluation on the outcome of 52 patients (median age: 66 years, range 52–82 years) undergoing 41 single and 11 double KTs, transplanted with grafts from deceased donors aged 75 years or older (median age 79 years, range 75–86 years). Graft and patient survival at 5 year were 53% and 64%, respectively, the better results achieved when dual kidney grafting was used and when retransplantations and high grade surgical complications were avoided.

The survival benefits seen in recipients of marginal kidney transplants are inferior compared with those in recipients of standard criteria donor kidneys, but significantly better than in those remaining on hemodialysis [16, 17], and also economic analysis suggests that transplantation with a marginal donor kidney is more cost effective than dialysis treatment [18, 19]. Ojo et al. [17] demonstrated that although patient survival in marginal donor kidney recipients was worse than in nonmarginal kidney recipients (5-year survival 77% versus 85%; $P < 0.001$), the death rate for marginal donor kidney recipients was significantly better than for wait-listed patients still receiving hemodialysis (4.7% versus 6.3% per year; $P < 0.001$). Thus KT with a marginal kidney increased life expectancy by 5.1 years over maintenance dialysis treatment. Similarly Merion et al. [16] evaluated a cohort of 109127 patients receiving dialysis over a 9-year period of study. Patients who never received a transplant were 45082, of whom 44% died before the study end, while the percentages of death were 14% and 23% among standard and marginal donor kidney recipients, respectively. Interestingly the adjusted long-term mortality risk at 3 years was 60% lower for ECD recipients compared to patients on the waiting list, with the better survival benefit achieved in recipients aged 40 years and older. Anyway perioperative mortality risk for ECD recipients was 5.2-fold higher during the first two post-transplant weeks when compared to patients on the waiting list and those receiving a standard kidney transplant. More relevantly due to the excess deaths accumulated among ECD recipients during the period of higher risk, overall cumulative mortality did not become equal to the other groups of patients until 3.5 years after transplantation, so highlighting the need of a careful recipients selection before transplantation, of a meticulous surgical technique and postoperative care.

The risk of graft failure (e.g., return to maintenance dialysis or graft nephrectomy) is more frequent in marginal donor kidney recipients [6, 16, 17], as largely documented in recently published series [20–27] (Table 1). Aging of the donors directly impacts on long-term graft survival, and, in a recent series, among 407 KTs, graft survival was significantly lower for the ECD when compared to the non-ECD (5-year survival rate: 74% versus 90%, $P < 0.001$) [21]; the older the donor, the greater seems to be the decrease in survival [6]. A similar correlation between age and graft outcome has been described in living donor KT [28]. Living donor age was related to worse patient survival and to reduced death-censored graft survival for every decade increase in age ($P = 0.001$), with a significant increase of the risk of graft failure when the living donor age increased beyond 40 years [28].

Marginal donors are also considered those with diabetes, the non-heart-beating cadaver donors, or those with anatomical abnormalities [1, 29]. These factors are usually considered during the clinical decision to accept or decline a marginal graft. Interestingly in the report by Dahmane et al. [30], evaluating allografts collected from this class of donors, the 5-year graft survival of marginal discarded kidneys was not significantly different in comparison with the control group of standard donors, so demonstrating that such marginal discarded kidneys provide acceptable survival rates and suggesting that in numerous situations the decision to refuse them has to be carefully evaluated.

3. The Marginal Kidney

Whether the definition of marginal donor is still debated what defines a marginal kidney has only seldom been discussed [29]. The aging causes a series of morphological and physiological changes to the kidneys leading to an increased glomerular, vascular, and tubular senescence [31, 32]. Such morphological changes can result in significant functional changes including a decrease in renal blood flow and glomerular filtration rate, leading to an overall deterioration in renal function [6]. Furthermore these changes may be aggravated by atherosclerosis [33], blood hypertension [34, 35], smoking [33, 34], dyslipidemia [34], obesity [36, 37], and diabetes [6, 38] which are highly prevalent in older

Table 1: Graft survival: comparison between standard and expanded criteria donor (ECD).

Author	Year	No. of KTs	<60 yr ≥60 yr (ECD)	Graft survival		*P*
Collini et al. [22]	2006	238	113 125	81.5% 71%	(3 yr)	nd
Andrés et al. [20]	2009	1343	900 443	89% 83%	(3 yr)	n.s.
Ferrer et al. [24]	2009	409	309 100	84% 75%	(3 yr)	0.003
Resende et al. [26]	2009	441	368 73	88% 77%	(5 yr)	0.72
Fraser et al. [25]	2010	1053	819 234	80.5% 79.1%	(5 yr)	0.32
di Cocco et al. [23]	2011	208	176 32	94.9% 87.5%	(3 yr)	n.s.
Nardo et al. [27]	2011	478	229 249	93.7% 86.9%	(5 yr)	n.s.
Barba et al. [21]	2012	407	244 163	90% 74%	(5 yr)	<0.001

individuals. The glomerular filtration rate (GFR), maintained at approximately 140 mL/min/1.73 m^2 until the fourth decade, declines by about 8 mL/min/1.73 m^2 per decade thereafter [32, 39, 40]. Similar changes, with a decrease in renal blood flow by about 10 percent per decade, particularly to the renal cortex have been further documented [32, 41]. Moreover animal studies suggest that another functional abnormality in aging is an increase in glomerular basement membrane permeability, leading to an increase in urinary excretion of proteins, including albumin [42]. The evidence of an increase in both microalbuminuria and overt proteinuria with aging has been confirmed in population studies [43], even in the absence of diabetes and hypertension. The kidney weight declines with age, primarily due to loss of renal mass to the cortical, with a relative sparing of the medulla [44, 45]. Degeneration of the cortical is based on a progressive sclerosis and hyalinosis of the glomeruli whose total number decreases, leading to a progressive atrophy [32]. In addition senescence of renal tissue is associated with impaired cellular repair mechanism [46]. The progressive loss of the renal mass and the decrease in the total number of functioning glomeruli cause a marked reduction of the functional reserve of the kidney, with the glomerulopenia being at the basis of a "remnant kidney" phenomenon causing progressive allograft failure [47].

Along with the changes caused by aging, "marginal kidney" has been defined not only those organs obtained from marginal donors, but also kidneys that, though collected from standard donors, have complex arterial anomalies (e.g., more than 2 arteries though on a single patch or separated in such a way to need a double anastomosis or a bench reconstruction), kidneys with noticeable parenchymal damage (macroscopic sclerosis areas or sutured polar branches accidentally damaged during removal), and kidneys with complex anomalies of the excretory tract (complete double district), all conditions causing a loss functional mass [29].

Kidneys from older donors have been shown to be particularly susceptible to the negative impact of long cold ischemic time [48–51], which may contribute to the ultimate discard of the kidney. Cold ischemia time is a well-known independent risk factor for delayed graft function (DGF), which is associated with inferior graft survival [52–55]. Interestingly Kayler et al. [56] demonstrated in ECD kidney transplants a higher incidence of DGF in those with longer cold ischemia time, but the overall graft loss rates were not significantly different between recipients with longer or shorter cold ischemia time.

Age related physiological changes are also responsible of an increased risk of nephrotoxicity due to medications, including the commonly employed immunosuppressive compounds calcineurin inhibitors (CNIs) cyclosporine and tacrolimus [57]. Kidneys from ECD may be particularly susceptible to CNI-mediated vasoconstriction and nephrotoxicity. In the early posttransplant phase, using CNI may prolong ischemic injuries [58]. Although it is difficult to prove that older age is specifically associated with increased susceptibility to CNI nephrotoxicity because no lesions are really specific for any process, a lesser improvement of GFR after CNIs cessation has been reported in older kidneys when compared to younger allografts [59], suggesting that CNI induce more irreversible damage to the kidneys from older donors. Functional and structural senescence also leads to an increase in kidney immunogenicity and a reduced resistance to unspecific damages. Experimental studies have shown a more intense host immune response to elderly grafts especially in the early post-transplant period as reflected by a higher number of peripheral T and B cells, increased T-cell alloreactivity, and elevated frequencies of intragraft dendritic cells [60].

Based on these evidences the goal should be therefore to optimize renal functional reserve and the number of functioning nephrons in order to allow a post-transplant renal

function similar to that of standard kidneys. In order to improve the graft selection process, histological criteria have been introduced, based on pretransplant kidney biopsy. Pretransplant biopsy is performed in up to 75% of marginal kidneys, and it represents the main tool for accepting or discarding the allograft [61]. In a histologic-scoring panel, with 0 representing no lesions and 12 representing marked changes in the renal parenchyma (vessels/glomeruli/tubules/connective tissue), kidneys with score of 3 or less should have enough viable nephrons for single kidney transplants, those with scores 4–6 should have enough viable nephrons for dual kidney transplant, and kidneys with higher scores are not suitable for transplantation [62, 63].

4. The Older Recipient

In the recent past advanced age has been considered a contraindication for KT, mainly because of the belief of a higher risk of post-transplant complication, graft loss, or even death with a functioning graft [64, 65]. More recently several studies have demonstrated acceptable graft survival among older recipients. Wolfe et al. [2] evaluated 228552 patients receiving long-term dialysis for end-stage renal disease (ESRD) in the US. Among them 46164 patients were placed on a waiting list for transplantation, and 23275 of these received a transplant between 1991 and 1997. When compared to those still on dialysis or those still on the waiting list, the survival of patients who were 60–74 years improved from the first year after transplantation, with a projected increased life span of four years and a 61% decrease in the long-term risk of death; when this group was divided into three subgroups 60–64 years old, 65–69 years old, 70–74 years old, the projected increases in the life span were 4.3 years, 2.8 years, and 1 year, respectively. Kauffman et al. [66] evaluated the impact of age and comorbid conditions over survival. When evaluating patients without comorbid conditions, the one year mortality rate for those aged 60 years and older was 9.2%, more than twice that of 3.5% observed for patients with age ranging between 18 and 59 years. The percentage of death at one year increased significantly when one or more comorbid conditions were present ranging from 10.6% for patients with history of malignancy to 21.4% for patients with chronic obstructive pulmonary disease. Furthermore when patients aged 60 years and older with comorbidities received an ECD kidney, there was a further substantial increase in 1-year mortality ranging from 16% for patients with diabetes to 42.3% for patients with chronic obstructive pulmonary disease. Comorbid conditions such as diverticular disease, diabetes, vascular insufficiency, and urinary tract abnormalities can also lead to a higher risk of post-transplant infections [1]. An increase in incidence of infections with aging has been described [67–69], which in turn can be responsible of a higher post-transplant mortality [69].

Aging is also characterized by an increased incidence of malignancy [70]. When compared to younger patients (age ranging 18–34 years), transplant recipients aged 65 year or older showed a fivefold increase in the risk of malignancies [71].

5. Strategy to Optimize the Outcome of Marginal Donors and Kidney Grafts

Although advanced age is not recognized as a contraindication to kidney transplantation, KT in the elderly remains challenging and a careful selection of candidates, taking into account all the comorbidities being mandatory [72]. Each patient deserves a thoughtful review of his own health status, and the risk of infections and malignancies needs a meticulous evaluation in order to avoid major post-transplant complications that can lead to a progressive loss of independence and even death. Clinicians may be reluctant to perform transplants on older patients with lower life expectancy, and also clinicians may have reservations about the use of a marginal kidney for the previously described reasons. The solution to this issue is to collect older kidneys for use in older recipients, the so-called "old-for-old" program. This form of donor and recipient age matching is ethically fair and physiologically logical. On this basis Eurotransplant Senior Program (ESP), a well-established old-for-old allocation program exists in Europe since 1999 [73]. Deceased donors aged 65 years and older are allocated to unsensitized recipients aged 65 years and older. Donor HLA-typing is not required, so allocation is done by using only ABO group matching, negative crossmatch,and a local allocation based on waiting time in order to keep cold ischemia time to a minimum. In the preliminary report by Fritsche et al. [74], this policy allowed the expansion of the donor and recipient pools without significantly affecting patient and graft survival. Anyway an increase in rate of acute rejections due to a higher number of HLA mismatches causing longer hospitalization and a major risk of graft loss was recorded. Subsequently Frei et al. [49] confirmed the results which were previously reported and described a doubling of elderly donors within the program with a decrease in waiting time for elderly recipient, so confirming the ESP age matching of elderly donors and recipients as an effective allocation system for organs from elderly donors.

More recently Lim et al. [75] by analyzing a cohort of 4616 renal transplant recipients along a 16 years followup demonstrated a significant increase in long-term graft survival when elderly donor (60 years and older) kidneys were allocated to older recipients (55 years and older) with the worst allocation when these organs were allocated to young recipients (younger than 55 year).

Along with a local allocation policy, in order to reduce the damage related to cold ischemia time, the use of machine perfusion has been advocated [76]. Treckmann et al. [77] evaluated the outcome of ECD kidneys comparing the use of machine perfusion and cold storage. When machine perfusion was employed, the risk of DGF decreased significantly (OR 0.460, $P = 0.047$) while the incidence of primary nonfunction in the cold storage group was four times higher than in the machine perfusion group. Also one-year graft survival was significantly higher in the machine perfusion kidneys (92.3% versus 80.2%, $P = 0.02$). Unfortunately the heavy initial costs of these devices are the major limit to a further diffusion of this technique, and, even if some retrospective

analysis found that the use of machine perfusion correlates with lower costs for the transplant hospitalization of ECD, prospective trials based on a large cohorts of patients are still lacking so that this evidence needs to be confirmed [78].

As previously reported, pre-transplant biopsy is the most used and reliable tool to discard or accept ECD kidneys. On the basis of the biopsy findings the transplant strategy can be planned, allowing the allocation of kidneys to single or dual kidney transplant. The dual kidney transplant, transplantation of two allografts in the same recipient, is a strategy employed for providing recipients an adequate number of functioning nephrons. Remuzzi et al. [62] firstly reported the successful use of this technique. The authors demonstrated that the survival of kidneys collected from donors aged 60 years and older allocated for single or dual KT according to pre-transplant biopsy was similar to that of single grafts from younger donors and was better than that of single grafts from donors older than 60 years when those grafts were selected and allocated on the basis of clinical criteria. Anyway although this technique along with the use of histological parameters has shown good results, the experience is limited to a single center analyzing a small cohort of patients, and for this reason further validation in large prospective trials is mandatory. The employment of functionality parameters has also been advocated. Snanoudj et al. [79] reported their experience in allocating kidneys for single or dual KT by evaluating the donor estimated glomerular filtration rate (eGFR). Dual KT was performed if eGFR was between 30 and 60 mL/min, single KT if eGFR greater than 60 mL/min. Patient and graft survival rates were similar in the two groups.

Among the issues still needing clarification, an optimal immunosuppressive regimen to be employed in the elderly has not yet been assessed. Elderly patients are usually excluded from transplantation trials [1, 80], and the available evidences derive from small, single center, observational studies [1]. Due to this lack of evidences, the choice of the immunosuppressive therapy remains largely subjective, usually based on data from younger recipients. However, in the case of elderly patients the definition of a tailored immunosuppressive regimen is mandatory taking into account, as previously mentioned, the different immunological status along with the increased risk of infections and malignancy. The goal of immunosuppression should consist of a reduction of the risk of CNI nephrotoxicity along with a limited use of steroids because of the increased risk of infections, fractures, myopathy, and other steroid-related side effects [1, 81, 82].

Furian et al. [58] compared the outcome of 31 patients undergoing dual kidney transplant with ECD kidneys receiving a CNI-free immunosuppression based on antilymphocyte antibodies induction, sirolimus, mycophenolate mofetil (MMF), and steroids with the outcome of 25 patients treated with CNI-based therapy. Incidence of acute rejection was not significantly different between the two groups, incidence of DGF was higher in the CNI-based group ($P = 0.008$). No differences in terms of medical complication were recorded in the two groups. At one year the renal function was significantly better in the CNI-free immunosuppression group, so suggesting that a CNI-free immunosuppressive regimen allows good results with a lower DGF rate and a better renal function. More recently the results of a randomized phase III study have become available, which has compared the outcome of an immunosuppressive regimen based on Belatecept, a new immunosuppressive drug that selectively inhibits T-cell activation, to the outcome of a CNI-based protocol [83]. Acute rejection rate and overall patient survival were similar among the groups. In the Belatacept-based group a better renal function and a reduced incidence of chronic kidney disease were recorded but these patients experienced a higher incidence of lymphoproliferative disorders and tuberculosis; therefore safety still remains an issue which needs to be solved in future trials.

The need of minimizing the use of steroids has also been evaluated. Segoloni et al. [82] described a series of 88 patients receiving kidneys from marginal donors whose immunosuppressive protocol consisted of monoclonal anti-IL-2 receptor antibodies, MMF, and steroids. When serum creatinine levels were less than 2.6 mg/mL, tacrolimus was started and MMF was subsequently withdrawn when the tacrolimus through level increased above 15 ng/mL. Steroid was tapered to 5 mg at day 45 and then progressively reduced. The acute rejection rate was 13.6%. At 3 years and 4 years after transplant, 80% and 100% of patients, respectively, were off steroids with a 4-year patient and graft survival of 98% and 79%, respectively. Incidence of infections and malignancy were also acceptable.

6. Conclusions

Kidney transplantation is the treatment of choice for patients suffering from ESRD including those with advanced age, whose number is increasing along the years. Older age by itself is no more recognized as a barrier to transplantation, and good results can be achieved also in elderly recipients after a careful selection, by employing meticulous surgical technique and post-transplant care. An increasing use of "marginal kidneys" from expanded criteria donors, as a strategy to reduce the allograft shortage, has been successfully employed. Anyway several issues still need to be resolved in order to make transplantation in the elderly as safe as in younger recipients. Consequently further efforts are needed in order to better define the strategy to allocate these organs for reducing the risks of allograft rejection and increase patient and graft survival, to define the best surgical technique (single or dual transplantation), when and how to use machine perfusion, and above all to define the best immunosuppressive regimen because the higher risks of infection and malignancy in the elderly patients render them increasingly susceptible to complications associated with immunosuppressive compounds.

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References

[1] R. Saxena, X. Yu, M. Giraldo et al., "Renal transplantation in the elderly," *International Urology and Nephrology*, vol. 41, no. 1, pp. 195–210, 2009.

[2] R. A. Wolfe, V. B. Ashby, E. L. Milford et al., "Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant," *The New England Journal of Medicine*, vol. 341, no. 23, pp. 1725–1730, 1999.

[3] *United Network for Organ Sharing*, Annual Report, 2006.

[4] B. Gridelli and G. Remuzzi, "Strategies for making more organs available for transplantation," *The New England Journal of Medicine*, vol. 343, no. 6, pp. 404–410, 2000.

[5] N. Perico, P. Ruggenenti, M. Scalamogna, and G. Remuzzi, "Tackling the shortage of donor kidneys: how to use the best that we have," *American Journal of Nephrology*, vol. 23, no. 4, pp. 245–259, 2003.

[6] F. Oppenheimer, P. Aljama, C. Asensio Peinado, J. Bustamante Bustamante, J. F. Crespo Albiach, and L. Guirado Perich, "The impact of donor age on the results of renal transplantation," *Nephrology Dialysis Transplantation*, vol. 19, supplement 3, pp. 11–15, 2004.

[7] US Renal Data System, "USRDS 2011 Annual Data Report: Atlas of Chronic Kidney Disease and End-stage Renal Disease in the United States," *American Journal of Kidney Diseases*, vol. 59, pp. e1–e420, 2012.

[8] Organ Procurement and Transplantation Network, Septmber 2012, http://optn.transplant.hrsa.gov/data/citing.asp.

[9] M. W. M. van de Luijtgaarden, C. Wanner, and K. J. Jager, "Renal replacement therapy in Europe-a summary of the 2009 ERA-EDTA Registry Annual Report," *Clinical Kidney Journal*, vol. 5, pp. 109–119, 2012.

[10] United Network for Organ Sharing, *Annual Report 1999: UNOS Registry 1999*, United Network for Organ Sharing, Richmond, Va, USA, 1999.

[11] United Network for Organ Sharing, *Annual Report 2004*, United Network for Organ Sharing, Richmond, Va, USA, 2004.

[12] Centro Nazionale Trapianti, http://www.salute.gov.it/imgs/C_17_pubblicazioni_1696_allegato.pdf.

[13] F. K. Port, J. L. Bragg-Gresham, R. A. Metzger et al., "Donor characteristics associated with reduced graft survival: an approach to expanding the pool of kidney donors," *Transplantation*, vol. 74, no. 9, pp. 1281–1286, 2002.

[14] A. Collini, P. Kalmar, A. Dhamo, G. Ruggieri, and M. Carmellini, "Renal transplant from very old donors: how far can we go?" *Transplantation*, vol. 87, no. 12, pp. 1830–1836, 2009.

[15] A. Gallinat, T. Feldkamp, R. Schaffer et al., "Single-center experience with kidney transplantation using deceased donors older than 75 years," *Transplantation*, vol. 92, no. 1, pp. 76–81, 2011.

[16] R. M. Merion, V. B. Ashby, R. A. Wolfe et al., "Deceased-donor characteristics and the survival benefit of kidney transplantation," *Journal of the American Medical Association*, vol. 294, no. 21, pp. 2726–2733, 2005.

[17] A. O. Ojo, J. A. Hanson, H.-U. Meier-Kriesche et al., "Survival in recipients of marginal cadaveric donor kidneys compared with other recipients and wait-listed transplant candidates," *Journal of the American Society of Nephrology*, vol. 12, no. 3, pp. 589–597, 2001.

[18] A. Laupacis, P. Keown, N. Pus et al., "A study of the quality of life and cost-utility of renal transplantation," *Kidney International*, vol. 50, no. 1, pp. 235–242, 1996.

[19] J. F. Whiting, E. Y. Zavala, J. W. Alexander, and M. R. First, "The cost-effectiveness of transplantation with expanded donor kidneys," *Transplantation Proceedings*, vol. 31, no. 1-2, pp. 1320–1321, 1999.

[20] A. Andrés, N. Polanco, M. P. Cebrian et al., "Kidneys from elderly deceased donors discarded for transplantation," *Transplantation Proceedings*, vol. 41, no. 6, pp. 2379–2381, 2009.

[21] J. Barba, J. J. Zudaire, J. E. Robles, D. Rosell, J. M. Berian, and I. Pascual, "Complications of kidney transplantation with grafts from expanded criteria donors," *World Journal of Urology*, 2012.

[22] A. Collini, C. de Bartolomeis, G. Ruggieri, R. Barni, M. Bernini, and M. Carmellini, "Long-term outcome of renal transplantation from marginal donors," *Transplantation Proceedings*, vol. 38, no. 10, pp. 3398–3399, 2006.

[23] P. di Cocco, G. Orlando, V. Rizza et al., "Kidney transplantation from older donors," *Transplantation Proceedings*, vol. 43, no. 4, pp. 1033–1035, 2011.

[24] F. Ferrer, A. Mota, R. Alves et al., "Renal transplantation with expanded criteria donors: the experience of one Portuguese center," *Transplantation Proceedings*, vol. 41, no. 3, pp. 791–793, 2009.

[25] S. M. Fraser, R. Rajasundaram, A. Aldouri et al., "Acceptable outcome after kidney transplantation using "expanded criteria donor" grafts," *Transplantation*, vol. 89, no. 1, pp. 88–96, 2010.

[26] L. Resende, J. Guerra, A. Santana, C. Mil-Homens, F. Abreu, and A. G. da Costa, "Impact of donor age on renal allograft function and survival," *Transplantation Proceedings*, vol. 41, no. 3, pp. 794–796, 2009.

[27] B. Nardo, R. Bertelli, G. Cavallari et al., "Analysis of 80 dual-kidney transplantations: a multicenter experience," *Transplantation Proceedings*, vol. 43, no. 5, pp. 1559–1565, 2011.

[28] K. Noppakun, F. G. Cosio, P. G. Dean, S. J. Taler, R. Wauters, and J. P. Grande, "Living donor age and kidney transplant outcomes," *American Journal of Transplantation*, vol. 11, no. 6, pp. 1279–1286, 2011.

[29] P. de Rosa, M. Santangelo, A. Ferrara et al., "Suboptimal kidney: the experience of a single transplant unit," *Transplantation Proceedings*, vol. 36, no. 3, pp. 488–490, 2004.

[30] D. Dahmane, V. Audard, C. Hiesse et al., "Retrospective follow-up of transplantation of kidneys from 'marginal' donors," *Kidney International*, vol. 69, no. 3, pp. 546–552, 2006.

[31] H. Basar, A. Soran, R. Shapiro et al., "Renal transplantation in recipients over the age of 60: the impact of donor age," *Transplantation*, vol. 67, no. 8, pp. 1191–1193, 1999.

[32] J. R. Weinstein and S. Anderson, "The aging kidney: physiological changes," *Advances in Chronic Kidney Disease*, vol. 17, no. 4, pp. 302–307, 2010.

[33] A. J. Bleyer, L. R. Shemanski, G. L. Burke, K. J. Hansen, and R. G. Appel, "Tobacco, hypertension, and vascular disease: risk factors for renal functional decline in an older population," *Kidney International*, vol. 57, no. 5, pp. 2072–2079, 2000.

[34] C. S. Fox, M. G. Larson, E. P. Leip, B. Culleton, P. W. F. Wilson, and D. Levy, "Predictors of new-onset kidney disease in a community-based population," *Journal of the American Medical Association*, vol. 291, no. 7, pp. 844–850, 2004.

[35] R. D. Lindeman, J. D. Tobin, and N. W. Shock, "Association between blood pressure and the rate of decline in renal function with age," *Kidney International*, vol. 26, no. 6, pp. 861–868, 1984.

[36] I. H. de Boer, R. Katz, L. F. Fried et al., "Obesity and change in estimated GFR among older adults," *American Journal of Kidney Diseases*, vol. 54, no. 6, pp. 1043–1051, 2009.

[37] M. C. Foster, S. Hwang, M. G. Larson et al., "Overweight, obesity, and the development of stage 3 CKD: the Framingham Heart Study," *American Journal of Kidney Diseases*, vol. 52, no. 1, pp. 39–48, 2008.

[38] G. Sarno, G. Muscogiuri, and P. de Rosa, "New-onset diabetes after kidney transplantation: prevalence, risk factors, and management," *Transplantation*, vol. 93, no. 12, pp. 1189–1195, 2012.

[39] D. F. Davies and N. W. Shock, "Age changes in glomerular filtration rate, effective renal plasma flow, and tubular excretory capacity in adult males," *The Journal of Clinical Investigation*, vol. 29, no. 5, pp. 496–507, 1950.

[40] J. W. Rowe, R. Andres, J. D. Tobin, A. H. Norris, and N. W. Shock, "The effect of age on creatinine clearance in men: a cross sectional and longitudinal study," *Journals of Gerontology*, vol. 31, no. 2, pp. 155–163, 1976.

[41] N. K. Hollenberg, D. F. Adams, H. S. Solomon, A. Rashid, H. L. Abrams, and J. P. Merrill, "Senescence and the renal vasculature in normal man," *Circulation Research*, vol. 34, no. 3, pp. 309–316, 1974.

[42] W. K. Bolton, F. R. Benton, J. G. Maclay, and B. C. Sturgill, "Spontaneous glomerular sclerosis in aging Sprague Dawley rats. I. Lesions associated with mesangial IgM deposits," *American Journal of Pathology*, vol. 85, no. 2, pp. 277–300, 1976.

[43] C. A. Jones, M. E. Francis, M. S. Eberhardt et al., "Microalbuminuria in the US population: third National Health and Nutrition Examination Survey," *American Journal of Kidney Diseases*, vol. 39, no. 3, pp. 445–459, 2002.

[44] S. A. Emamian, M. B. Nielsen, J. F. Pedersen, and L. Ytte, "Kidney dimensions at sonography: correlation with age, sex, and habitus in 665 adult volunteers," *American Journal of Roentgenology*, vol. 160, no. 1, pp. 83–86, 1993.

[45] H. Tauchi, K. Tsuboi, and J. Okutomi, "Age changes in the human kidney of the different races," *Gerontologia*, vol. 17, no. 2, pp. 87–97, 1971.

[46] R. Schmitt and L. G. Cantley, "The impact of aging on kidney repair," *American Journal of Physiology*, vol. 294, no. 6, pp. F1265–F1272, 2008.

[47] J. C. Tan, B. Workeneh, S. Busque, K. Blouch, G. Derby, and B. D. Myers, "Glomerular function, structure, and number in renal allografts from older deceased donors," *Journal of the American Society of Nephrology*, vol. 20, no. 1, pp. 181–188, 2009.

[48] A. Asderakis, P. Dyer, T. Augustine, J. Worthington, B. Campbell, and R. W. G. Johnson, "Effect of cold ischemic time and hla matching in kidneys coming from "young" and "old" donors: do not leave for tomorrow what you can do tonight," *Transplantation*, vol. 72, no. 4, pp. 674–678, 2001.

[49] U. Frei, J. Noeldeke, V. Machold-Fabrizii et al., "Prospective age-matching in elderly kidney transplant recipients—a 5-year analysis of the Eurotransplant Senior Program," *American Journal of Transplantation*, vol. 8, no. 1, pp. 50–57, 2008.

[50] F. Moreso, D. Serón, S. Gil-Vernet et al., "Donor age and delayed graft function as predictors of renal allograft survival in rejection-free patients," *Nephrology Dialysis Transplantation*, vol. 14, no. 4, pp. 930–935, 1999.

[51] A. K. Salahudeen, N. Haider, and W. May, "Cold ischemia and the reduced long-term survival of cadaveric renal allografts," *Kidney International*, vol. 65, no. 2, pp. 713–718, 2004.

[52] M. D. Doshi, N. Garg, P. P. Reese, and C. R. Parikh, "Recipient risk factors associated with delayed graft function: a paired kidney analysis," *Transplantation*, vol. 91, no. 6, pp. 666–671, 2011.

[53] A. O. Ojo, R. A. Wolfe, P. J. Held, F. K. Port, and R. L. Schmouder, "Delayed graft function: risk factors and implications for renal allograft survival," *Transplantation*, vol. 63, no. 7, pp. 968–974, 1997.

[54] G. Opelz and B. Döhler, "Multicenter analysis of kidney preservation," *Transplantation*, vol. 83, no. 3, pp. 247–253, 2007.

[55] V. Tandon, J. F. Botha, J. Banks, A. R. Pontin, M. D. Pascoe, and D. Kahn, "A tale of two kidneys—how long can a kidney transplant wait?" *Clinical Transplantation*, vol. 14, no. 3, pp. 189–192, 2000.

[56] L. K. Kayler, J. Magliocca, I. Zendejas, T. R. Srinivas, and J. D. Schold, "Impact of cold ischemia time on graft survival among ecd transplant recipients: a paired kidney analysis," *American Journal of Transplantation*, vol. 11, no. 12, pp. 2647–2656, 2011.

[57] M. Naesens, D. R. J. Kuypers, and M. Sarwal, "Calcineurin inhibitor nephrotoxicity," *Clinical Journal of the American Society of Nephrology*, vol. 4, no. 2, pp. 481–508, 2009.

[58] L. Furian, N. Baldan, G. Margani et al., "Calcineurin inhibitor-free immunosuppression in dual kidney transplantation from elderly donors," *Clinical Transplantation*, vol. 21, no. 1, pp. 57–62, 2007.

[59] C. Legendre, Y. Brault, J. M. Morales et al., "Factors influencing glomerular filtration rate in renal transplantation after cyclosporine withdrawal using sirolimus-based therapy: a multivariate analysis of results at five years," *Clinical Transplantation*, vol. 21, no. 3, pp. 330–336, 2007.

[60] A. Reutzel-Selke, A. Jurisch, C. Denecke et al., "Donor age intensifies the early immune response after transplantation," *Kidney International*, vol. 71, no. 7, pp. 629–636, 2007.

[61] R. S. Sung, L. L. Christensen, A. B. Leichtman et al., "Determinants of discard of expanded criteria donor kidneys: impact of biopsy and machine perfusion," *American Journal of Transplantation*, vol. 8, no. 4, pp. 783–792, 2008.

[62] G. Remuzzi, P. Cravedi, A. Perna et al., "Long-term outcome of renal transplantation from older donors," *The New England Journal of Medicine*, vol. 354, no. 4, pp. 343–352, 2006.

[63] G. Remuzzi, J. Grinyò, P. Ruggenenti et al., "Early experience with dual kidney transplantation in adults using expanded donor criteria. Double Kidney Transplant Group (DKG)," *Journal of the American Society of Nephrology*, vol. 10, no. 12, pp. 2591–2598, 1999.

[64] H. Meier-Kriesche, A. O. Ojo, D. M. Cibrik et al., "Relationship of recipient age and development of chronic allograft failure," *Transplantation*, vol. 70, no. 2, pp. 306–310, 2000.

[65] J. D. Pirsch, A. M. D'Alessandro, H. W. Sollinger et al., "The effect of donor age, recipient age, and HLA match on immunologic graft survival in cadaver renal transplant recipients," *Transplantation*, vol. 53, no. 1, pp. 55–59, 1992.

[66] H. M. Kauffman, M. A. McBride, C. S. Cors, A. M. Roza, and J. J. Wynn, "Early mortality rates in older kidney recipients with comorbid risk factors," *Transplantation*, vol. 83, no. 4, pp. 404–410, 2007.

[67] G. Gavazzi and K. Krause, "Ageing and infection," *Lancet Infectious Diseases*, vol. 2, no. 11, pp. 659–666, 2002.

[68] P. N. A. Martins, J. Pratschke, A. Pascher et al., "Age and immune response in organ transplantation," *Transplantation*, vol. 79, no. 2, pp. 127–132, 2005.

[69] H.-U. Meier-Kriesche, A. O. Ojo, J. A. Hanson, and B. Kaplan, "Exponentially increased risk of infectious death in older renal transplant recipients," *Kidney International*, vol. 59, no. 4, pp. 1539–1543, 2001.

[70] R. Yancik and L. A. G. Ries, "Aging and cancer in America: demographic and epidemiologic perspectives," *Hematology/Oncology Clinics of North America*, vol. 14, no. 1, pp. 17–23, 2000.

[71] B. L. Kasiske, J. J. Snyder, D. T. Gilbertson, and C. Wang, "Cancer after kidney transplantation in the United States," *American Journal of Transplantation*, vol. 4, no. 6, pp. 905–913, 2004.

[72] B. L. Kasiske, C. B. Cangro, S. Hariharan et al., "The evaluation of renal transplant candidates: clinical practice guidelines," *American Journal of Transplantation*, vol. 1, supplement 2, pp. 5–95, 2001.

[73] J. M. A. Smits, G. G. Persijn, H. C. van Houwelingen, F. H. J. Claas, and U. Frei, "Evaluation of the Eurotransplant Senior Program. The results of the first year," *American Journal of Transplantation*, vol. 2, no. 7, pp. 664–670, 2002.

[74] L. Fritsche, J. Hörstrup, K. Budde et al., "Old-for-old kidney allocation allows successful expansion of the donor and recipient pool," *American Journal of Transplantation*, vol. 3, no. 11, pp. 1434–1439, 2003.

[75] W. H. Lim, S. Chang, S. Chadban et al., "Donor-recipient age matching improves years of graft function in deceased-donor kidney transplantation," *Nephrology Dialysis Transplantation*, vol. 25, no. 9, pp. 3082–3089, 2010.

[76] C. Moers, J. M. Smits, M. H. Maathuis et al., "Machine perfusion or cold storage in deceased-donor kidney transplantation," *The New England Journal of Medicine*, vol. 360, no. 1, pp. 7–19, 2009.

[77] J. Treckmann, C. Moers, J. M. Smits et al., "Machine perfusion versus cold storage for preservation of kidneys from expanded criteria donors after brain death," *Transplant International*, vol. 24, no. 6, pp. 548–554, 2011.

[78] P. M. Buchanan, K. L. Lentine, T. E. Burroughs, M. A. Schnitzler, and P. R. Salvalaggio, "Association of lower costs of pulsatile machine perfusion in renal transplantation from expanded criteria donors," *American Journal of Transplantation*, vol. 8, no. 11, pp. 2391–2401, 2008.

[79] R. Snanoudj, M. Rabant, M. O. Timsit et al., "Donor-estimated GFR as an appropriate criterion for allocation of ECD kidneys into single or dual kidney transplantation," *American Journal of Transplantation*, vol. 9, no. 11, pp. 2542–2551, 2009.

[80] G. A. Knoll, "Kidney transplantation in the older adult," *American Journal of Kidney Diseases*, vol. 61, no. 5, pp. 790–797, 2013.

[81] V. Fabrizii, J. Kovarik, M. Bodingbauer, R. Kramar, W. H. Hörl, and W. C. Winkelmayer, "Long-term patient and graft survival in the Eurotransplant Senior Program: a single-center experience," *Transplantation*, vol. 80, no. 5, pp. 582–589, 2005.

[82] G. P. Segoloni, M. Messina, G. Squiccimarro et al., "Preferential allocation of marginal kidney allografts to elderly recipients combined with modified immunosuppression gives good results," *Transplantation*, vol. 80, no. 7, pp. 953–958, 2005.

[83] J. O. M. Pestana, J. M. Grinyo, Y. Vanrenterghem et al., "Three-year outcomes from BENEFIT-EXT: a phase III study of belatacept versus cyclosporine in recipients of extended criteria donor kidneys," *American Journal of Transplantation*, vol. 12, no. 3, pp. 630–639, 2012.