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# New strategies for evaluating the quality of kidney grafts from elderly donors

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A B S T R A C T

The increased demand for kidney transplantation and organ shortage resulted in the increased use of kidneys from suboptimal donors. Therefore, identification of kidneys that can be accepted without significantly compromising the outcome of allograft or recipient has become critical. A robust assessment of organ quality is of particular importance especially in kidneys from elderly donors in whom morphological and functional changes associated with aging and diseases are obvious. A number of predictive tools have been developed to help with evaluating the suitability of a deceased-donor kidney for transplantation. Among those, Kidney Donor Profile Index and zero hour graft biopsy in elderly donors have been already implemented in several transplant programs. This review captures the recent literature on this subject and discusses approaches for evaluating the quality of kidney grafts from elderly donors.



## 1. Introduction

The increased waiting list for kidney transplantation and organ shortage resulted in the increased use of kidneys from suboptimal, marginal donors. There are gross differences in acceptance criteria of such kidneys among centers and countries. Therefore it has become important to develop tools for identification of kidneys that can be accepted without significantly compromising the outcome of allograft or recipient. A robust assessment of organ quality is of particular importance especially in kidneys from elderly donors in whom morphological and functional changes associated with aging and diseases are obvious. Risks of delayed graft function and limited function of marginal grafts need to be balanced against patients survival benefit [1].

An inappropriate discard of donor kidneys has serious consequences for wait-listed patients. The percentage of kidneys recovered but not transplanted remains over 40% in the United States. Major determinants of discard rates are pretransplant biopsy findings and parameters of machine pump perfusion [2]. According to other evidence, 18% of all donated kidneys and 45% of ECD kidneys in the United States in 2011 were not allocated for transplantation despite the fact that such kidneys could have been transplanted with good outcomes [3,4]. Nevertheless, decision making tools used to discard a kidney have not been clearly shown to have impact on graft outcome. Broad difference in discard rates observed between centers may be a result of the subjective nature of organ assessment as well as conflicting evidence regarding the value of appraisal tools [5].

A number of predictive tools have been developed to assist the transplant team in evaluating the suitability of a deceased-donor kidney for transplantation. These include stratification of donors according to clinical parameters, clinical donor risk scores, histological donor biopsy scores, machine perfusion characteristics, donor biomarkers, molecular diagnostic tools etc. However, the evidence supporting the use of these methods and their predictive ability is lacking as most have not been validated outside the original study population. Beside the dichotomous Expanded Criteria Donor (ECD) classification [6], none of the scoring systems have been accepted by transplant community for routine use in clinical practice [7].

This review briefly summarizes recent approaches for evaluating the quality of kidney grafts from elderly donors.

## 2. Clinical Scoring Systems

The concept of Expanded Criteria Donor was introduced in 2002. ECD kidneys were defined as those with relative risk of graft loss greater than 1.70 when compared to a standard donor and included all donors 60 years and older and those aged between 50 to 59 years who meet at least two of the following conditions: serum creatinine >1.5 mg/dL (132.5 μmol/L), cerebrovascular accident as a cause of death or a history of hypertension [6]. These three criteria together with donor age were considered as surrogate markers of reduced nephron mass.

ECD classification was introduced to predict increased risk of graft failure and has led in fact to increased discard rate of ECD kidneys. This tool dichotomously separated kidneys into expanded and standard criteria donors (SCD) based on their age, patient history and cause of death [8]. Clearly, this selection formed a heterogeneous ECD cohort with an unequal risk of delayed graft function (DGF). In contrary, many recipients of SCD kidneys develop DGF and have worse graft

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survival despite an uneventful surgery and acceptable length of cold ischemia [9].

Weaknesses of ECD classification are so obvious that several other scoring systems were developed. These systems include more donor and recipient's characteristics to predict allograft function and survival. Unfortunately, some of them were generated only from the registry data and were not further validated in multicenter trials.

Nyberg et al. [10] used five donor variables (age, history of hypertension, creatinine clearance, cause of death and HLA mismatch) to generate a deceased donor score (DDS) ranging from 0 to 39 points. Donor score above 20 points identified marginal kidneys with worse renal function and graft survival. Superiority of DDS over ECD classification in prediction of DGF and graft survival was validated in Spanish study [11]. Schold et al. [12] developed the donor risk score (DRS) based on donor characteristics (donor race, age, cause of death, history of hypertension, diabetes), donor–recipient matches (CMV, HLA-A, HLA-B, HLA-DR) and cold ischemia time and found its impact on short- and long- term graft survival. Irish et al. [13] established a nomogram for identifying patients at risk for DGF based on sixteen donor (donor age, serum creatinine, history of hypertension, cause of death, donor after cardiac death) and recipient risk factors (peak PRA, race, gender, history of diabetes mellitus, previous transplant, pretransplant dialysis, pretransplant transfusion, combined transplantation, HLA mismatch and cold ischemia time). This nomogram has been recently used for patient enrollement in the clinical trial with eculizumab (NCT01919346) to better assess the risk of DGF which is the outcome of the study.

Predictive value of these scoring systems has been shown in populations from which they were initially derived. Moore et al. evaluated predictive power of above mentioned preoperative donor quality scores [10,12–14] in a separate representative population of 217 patients and suggested that of donor scoring systems, Schold's donor risk score [12] is the early indicator closely associated with subsequent graft function development [15]. Similarly, Gourishankar et al. validated four preoperative clinical scoring systems (DDS, DRS, KDRI and DGF nomogram) in prediction of early and late graft outcome [16].

Nowadays, there is an urgent need to use a simple and validated scoring system in international clinical trials with DGF as a study endpoint, where population is derived from recipients of ECD kidney grafts. Without generally accepted criteria, outcomes of such studies would vary among centers with different kidney graft allocation/acceptance policy. Clinical scoring systems mentioned in this review are summarized in Table 1.

## 3. Kidney Donor Risk Index (KDRI) and Kidney Donor Profile Index (KDPI)

Disappointment from dichotomous rigidity of ECD classification, limited applicability of above mentioned clinical scoring systems and need for a more comprehensive risk index that would capture donor and transplant characteristics led to development of continuous kidney donor risk index (KDRI) for deceased donor kidneys [17]. Originally, by analysis of almost 70,000, solitary, deceased donor kidney recipients, Rao et al. divided study population into quintiles based on their KDRI. The decreasing trend in graft survival with increasing KDRI was apparent. Transplants of kidneys in the highest KDRI quintile (>1.45) had an adjusted 5-year graft survival of 63%, compared with 82% and 79% in the two lowest KDRI quintiles (<0.79 and 0.79–0.96, respectively). Median lifetime of the kidneys in the highest KDRI quintile (>1.45) was 7.5 years compared with 13.6 years for those in the lowest quintile (<0.79). So KDRI, by assessing multiple donor and transplant characteristics, calculates the profile of a renal graft and provides an estimate of posttransplant outcome [17].

Rao's KDRI included 14 donor and transplant factors, each found to be independently associated with graft failure or death: donor age, race, history of hypertension, history of diabetes, serum creatinine, cerebrovascular cause of death, height, weight, donation after cardiac death, hepatitis C virus status, human leukocyte antigen-B and DR mismatch, cold ischemia time, and double or *en bloc* transplant. The KDRI reflected the rate of graft failure relative to that of an "ideal reference" donor (i.e. 40-year-old non-African American race origin, brain dead donor with cause of death other than cerebrovascular event with serum creatinine 1.0 mg/dL, normotensive, without diabetes, with height 170 cm and weight over 80 kg, HCV negative). The reference transplant was characterized by two mismatches at the HLA-B locus and one mismatch at the HLA-DR locus with 20 hours of cold ischemia time.

A new allocation policy based on the Kidney Donor Risk Index (KDRI) and Kidney Donor Profile Index (KDPI) [18] was implemented by the end of 2014 in the United States. The original KDRI combined 14 donor and transplant factors to estimate the relative risk of graft failure after kidney transplant from a particular deceased donor compared to the reference donor [19]. Since some transplant factors are generally not known at the time offer is made, the donor-only KDRI version, based on 10 donor factors, was implemented. The risk of graft failure was compared to the graft failure rate of median kidney graft recovered previous year [20] not to a reference donor as defined by Rao et al. [19]. No predictive ability is lost by using a donor-only version of the KDRI ($c = 0.596$) compared to a full version of the KDRI ($c = 0.601$).

The Kidney Donor Profile Index (KDPI) is an additional numerical score, which results from ranking KDRI from the 1st to the 100th percentile, with reference to a given Organ Procurement and Transplantation Network (OPTN) donor cohort. It is a number currently reported during the allocation process as a tool to aid clinicians in deciding whether to accept an offer of a deceased donor kidney [21]. For example, a donor with a KDPI of 80% has higher expected risk of graft failure than 80% of all kidney donors recovered last year [17].

### 3.1. Pros and cons of KDPI

KDPI is an improvement over the ECD classification in several ways; it incorporates 10 donor factors (instead of 4 in the ECD definition), it is a continuous "score" instead of a binary indicator. It also illuminates the fact that not all ECDs are alike, some ECD kidneys have reasonably good estimated quality and some SCD kidneys actually have lower estimated quality than some ECDs.

Limitation of the KDPI is its relatively low predictive power (*c*-statistics = 0.60). It is a tool not precise enough to differentiate with high confidence the quality of kidney donors with only slight differences in KDPI. In addition, the KDPI does not include all donor factors potentially associated with kidney graft outcomes, as donor biopsy findings, because donor kidney biopsies are not routinely performed in all cases. Since the KDPI is a donor-level measure, it is not specific to either kidney [17].

### 3.2. Validation of KDRI

Han el al. validated prognostic value of KDRI in clinical practice on 362 cases of deceased donor kidney transplantation and confirmed its better predictive value for short-term outcomes than ECD classification or histologic score [22]. The KDRI strongly correlated with renal function at 1 year ($R^2 = 0.230$, $p < 0.001$), and higher KDRI was associated with a higher risk of graft failure (HR 2.63, 95% CI 1.01–6.87). Contrary to KDRI, graft survival rates were not significantly different between ECD and SCD nor associated with higher histologic score [22].

### 3.3. Use of KDPI in clinical practice

Transition in the allocation system from the ECD criteria to KDPI was proposed in a good faith to increase utilization of marginal kidneys and decrease the discard rates. KDPI scoring system was never meant to be utilized as a discriminatory tool to determine acceptance/rejection of a particular kidney offer, but only to better characterize potential donor organs. However, the use of KDPI in the allocation policy has the