Kidney donor risk index assessment – analysis of current literature

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ABSTRACT

With the ongoing shortage of standard criteria donors (SCD) efforts to expand the organ pool such as use of expanded criteria donors (ECD) have intensified. Various kidney donor risk indexes have been developed to predict graft survival with various combinations of donor and recipient characteristics. Continuous kidney donor risk index (KDRI) was proposed by Rao et al. The graded impact on kidney allograft survival seems to make it more useful tool at the time of the deceased donor kidney offer than expanded and nonexpanded criteria donor classification.

Kidney transplantation is the optimal form of kidney replacement therapy. Most importantly it is beneficial to the patient by prolonging expected lifespan, improving quality of life, decreasing morbidity and limiting complications of uremia. It is also advantageous to the medical care system, being less expensive than chronic dialysis.

The increase in waiting lists for a cadaver transplant is a worldwide trend. According to a report issued in 2011 the population of patients with end stage renal disease increases by 7% annually (1).

In the USS the median time to transplant for wait-listed adult patients increased from 2.7 years in 1998 to 4.2 years in 2008. (2)

Transplantations from a live donor cover only a fraction of demand for kidneys. In an attempt to shorten the waiting lists and improve recipients’ prognosis, transplantation centers implement optimized rules for organ allocation and often collect organs from donors fulfilling expanded criteria (ECD – expanded criteria donor).

The ubiquitous acceptance of ECD kidneys does have a price, however. The disadvantages include a greater incidence of delayed graft function (DGF) and...
acute rejection, prolonged hospitalization, higher cost of treatment and unsatisfactory long-term kidney function. (3, 4, 27) The relationship between DGF and a decreased kidney-graft life is also well established. Early function of the transplanted kidney is a predictor of long-term function, while serum creatinine levels at 6 and 12 months after transplantation are an independent prognostic factor (5). The risk of losing the organ is proportional to the time of dialysis. Transplantation increases the expected lifespan twofold. (6, 7, 8, 13)

One of the key issues in modern transplantation is an objective assessment of a kidney donor to be performed before accepting the organ for transplantation. There have been various attempts at creating a numerical scale to evaluate the quality of kidneys harvested from cadaver donors (9). An adequate analysis of the donor would aid in selecting the optimal recipient. It would also be helpful in assessing the risk of potential early and late complications, choosing the immunosuppressive regimen and appropriate surveillance (such as timing of protocol biopsies).

Nyberg et al. have attempted to establish a donor risk index, taking into consideration parameters that influence the early function of a kidney-graft. They performed a retrospective analysis of 12 donor-related and 6 recipient-related risk factors, assessed during organ harvest in 250 cases. The study identified 7 factors that affected the primary end-point, eGFR (estimated glomerular filtration rate) at 30 days after transplantation. The factors regarding the donor were: cause of death, history of arterial hypertension, eGFR, age, history of diabetes, total ischaemia time and atherosclerosis of the renal arteries. Each risk factor contributed points to the scale – up to 32 in total. The influence of human leukocyte antigen (HLA) compatibility and glomerular sclerosis in time-zero biopsy were not proven to be of statistical significance. 70% of recipients with a summary risk index of 0-15 (groups A-C) had an eGFR of over 40 ml/min within a month. The risk of DGF in this group was found to be less than 25%. Transplanting a kidney from a donor with a risk index of over 15 points (group D) is, in comparison, associated with a 60% chance of DGF, longer hospitalization and higher cost of treatment (10).

It has been proven that an integrated evaluation of all 7 mentioned risk factors is a better indicator of early kidney-graft function than any single one. Consequently, the next step was to identify risk factors that would allow for a prognosis regarding long-term kidney-graft function. An analysis was performed of 34 324 patients, who received a kidney transplant between 1994 and 1999. Seven aforementioned donor-related risk factors were considered, along with 4 recipient-related ones – CMV serological status, HLA compatibility, creatinine clearance, graft survival at 6 and 12 years. The key risk factors were (in order of importance): age of donor, eGFR, duration of hypertension, HLA compatibility and cerebrovascular incident as donor’s cause of death. A single and multivariate analysis of the influence of the 5 mentioned parameters on kidney function at 6 months was performed, yielding an improved deceased-donor score (DDS). In order to simplify the index a number of risk factor were excluded. These included CMV serological status, history of diabetes and nationality (as having low prognostic importance) and time of ischaemia (as being undetermined at the time of donor qualification). More index points were indicative of a worse prognosis regarding eGFR at 6 and 12 months after transplantation, as well as 6-year kidney-graft survival. A donor index of over 20 points (a so-called marginal donor) corresponds to a donor fulfilling ECD criteria (UNOS) in regard to prognosis. Donors evaluated at 21-30 points have been labeled a moderate risk group (C). In this population a short ischaemia time has been reported to improve prognosis. For the high risk group (D) the time of ischaemia is irrelevant. Increasing the time of follow-up to 6 years has shown an statistically significant relationship for HLA compatibility between the donor and recipient and long-term kidney-graft function. The key conclusion of the improved donor index is that 40 years is the critical age of the donor. Regardless of other prognostic factors, any donor aged 40 years or less is considered to be a non-marginal one (11). A retrospective analysis of a cohort of 7209 kidney recipients in France (transplanted between 1996 and 2000) performed by Pessione et al. (12) has led to the development of a new index – the Pessione score. This tool is based solely on 3 independent donor-related risk factors: cardiovascular cause of death, history of hypertension and a serum creatinine concentration of over 150 mmol/l.

Concurrently, a German team under Schold introduced a donor risk score (DRS) – an indicator of graft survival at 1 and 5 years after transplantation. This scale included risk factors such as age, race, cause of death, history of hypertension, diabetes, CMV status, time of ischaemia and HLA mismatching. The cited assessments of the transplanted organ do not, however, take into account the influence of early surgical complications or chronic microscopic damage on graft survival (14).

Due to an increase in demand, towards the end of the XX century procedures were developed for harvesting organs from non-heart-beating and elderly donors. The share of cadavers with a history of cardiovascular disease and advanced age increased. In the beginning of the XXI century, one in four donors in Spain was aged over 60. Because function and survival of kidney-grafts from such donors was notably worse than was usual, transplantlogists were faced with a dilemma. Should they offer their patients a kidney from a marginal donor or continue dialysis, a form of kidney-replacement therapy inferior in regard to morbidity and mortality? Consequently, in 2001...
the Organ Procurement and Transplantation Network (OPTN) and United for Organ Sharing (UNOS) developed criteria for expanded criteria donors (ECD). These were introduced to aid physicians and patients in deciding whether to accept kidney-grafts from marginal donors. ECDs were defined by Port et al. as donors of an organ with a risk of dysfunction greater than 1.7 compared to a donor aged 10-39, with a serum creatinine concentration <1.5 mg/dl, a negative history of hypertension and a non-cardiovascular cause of death. The risk varies between 1.74 (for a donor aged 50-59, with a history of hypertension and an elevated creatinine level) to 2.69 (for a donor aged over 60, with a history of hypertension and a cardiovascular cause of death). It is standard practice that the recipient must consent to being transplanted an organ from an extended criteria donor. Studies reveal that the mortality of ECD kidney recipients aged over 40 is lower than those, who continue dialysis. According to reports by the Scientific Registry of Transplant Recipients (SRTR) the annual mortality of patients waiting for a kidney transplantation is 7%, while ECD kidney recipients have a survival 5 (4-11) years longer than those on the waiting list. In recent years the share of ECD kidneys increased to 17-31% of all reported donors (18, 19). Meanwhile the survival rates of recipients continue to improve. The average graft survival of ECD kidneys is 6.3 years, compared to 10.2 years for standard criteria donors (SCD). (14-17)

Extended criteria and the scoring systems developed by Nyberg and Schold are based on an arbitrary categorization of risk, hence potentially decreasing the accuracy of evaluation. In an attempt to improve the previous tools, Rao et al. have developed a continuous risk scales by eliminating categorized variables.

The indexes introduced by Rao's team, the Kidney Donor Risk Index (KDRI) and Kidney Donor Profile Index (KDPI) include the analysis of factors previously not considered. Donor-related risk factors are: age, height, weight, ethnicity, history of hypertension, diabetes, smoking, cause of death, serum creatinine concentration, HCV status, donation after circulatory death (DCD) status and incompatibility in major blood groups (17, 18). Parameters related to the transplantation procedure include: cold ischaemia time, HLA-mismatching and type of surgery (single, two kidneys or en-bloc). Factors associated with the recipient are: age, height, history of coronary disease, COPD and HCV infection. The relationship between the listed traits and graft survival has been determined by a multivariate proportional Cox hazard model. The analysis included almost 70,000 adults, first-time recipients of a single kidney in the US between 1995 and 2005. It identified 10 key clinical and demographic parameters that influenced the survival of both graft and recipient: age, height, ethnicity, history of hypertension, diabetes, cause of death, creatinine level, HCV and DCD status. Duration on hypertension and diabetes was found to be irrelevant (19). The KDRI and KDPI assess the quality of the organ donor relative to other donors. A donor with a KDPI of over 90% has a KDRI higher than 90% of the donor from which organs were harvested the year before. The lower the KDPI, the better the quality of the organ. KDRI is an estimated measurement of the risk of function loss for a particular organ donor's kidney transplanted to an average recipient, relative to an average risk donor's organ. The estimated risk of function loss for a kidney harvested from a donor with a KDRI of 1.4 is 1.4 greater than that of an average donor. The KDRI and KDPI have a number of advantages over the ECD system, when it comes to qualifying donors. Firstly, they are numerical, continuous scales, as opposed to ECD's binary nature. Furthermore, they are more precise, as they include ten factors to ECD's four. Finally they provide a more specific characteristic of the donor along with ECD's labeling of „better or worse” quality of donor. This is crucial in establishing the threshold for accepting an ECD donor for recipient from a particular transplantation center.

Rao’s KDRI estimates the risk of function loss of a kidney-graft transplanted to a „reference” donor. This is defined as a person 40 year old, non-afroamerican, 170cm tall, weighing 80kg, with a creatinine level of 1 mg/dl, 2 HLA-B mismatches, 1 HLA-DR mismatches, negative history of hypertension, diabetes and hepatitis C, a cold ischaemia time of <20h and deceased by brain death. The formula for calculating KDRI is as follows:

\[
\text{KDRI RAO} = \exp \{-0.0194 \times I(\text{Age} <18 \text{ years}) \times (\text{Age} - 18 \text{ years}) + 0.0128 \times I(\text{Age} - 40 \text{ years}) + 0.0107 \times I(\text{Age} >50 \text{ years}) + 0.179 \times I(\text{Race}=\text{African American}) + 0.126 \times I(\text{Hypertensive}) + 0.130 \times I(\text{Diabetic}) + 0.220 \times \left(\text{SCR} - 1 \text{ mg/dl}\right) - 0.209 \times I(\text{SCR} >1.5 \text{ mg/dl}) \times (\text{SCR} - 1.5 \text{ mg/dl}) + 0.0881 \times I(\text{COD} = \text{CVA}) - 0.0464 \times [\text{Height} - 170 \text{ cm}] + 0.0199 \times I(\text{Weight} <80 \text{ kg}) \times (\text{Weight} - 80 \text{ kg})/5) + 0.133 \times I(\text{DCC}) + 0.240 \times I(\text{HCV}) - 0.0766) \]

where I is equal to 1 if the condition is true and I is equal to 0 if the condition is false.

The Rao KDRI result is then normalized by a scaling factor using the following formula:

\[
\text{KDRI MEDIAN} = \text{KDRI RAO} / \text{scaling factor} \]

The scaling factor is a median value for all donors from the previous calendar year. Its value is listed in a KDRI to KDPI conversion mapping table. For example, in 2010 this was 1.24.

The KDRI MEDIAN is interpreted as a relative risk of graft function loss in an average adult recipient for this donor as compared to a median donor in the previous calendar year. When assessing long term trends or performing retrospective analyses of KDRI, the scaling factor should be omitted (taking into account only KDRI RAO) or a single scaling
The KDRI is usually between 0.5 and 3.5. Higher values are associated with relatively worse graft survival rates. The mean predictive value of KDRI is 0.6 (c=0.62). It increases notably in the extreme ranges (c=0.78), while it is lower in average ranges (c=0.58). The greater the difference between two compared values of KDRI the more plausible the estimated difference in kidney-graft survival. Utilizing the KDRI index can potentially limit the number of rejected organs, especially in cases of kidneys with a high KDRI value interpreted along with ECD criteria.

The KDPI is a derivative of KDRI determined by the KDRI to KDPI conversion mapping table. KDPI is a value ranging from 0 to 100%. A donor with a KDPI of >90% has a KDRI higher than 90% of the reference donor population for the previous calendar year in the USA. Data obtained from the reference group of donors allow for computing the scaling factor for a given year. It also allows for developing the KDRI to KDPI conversion mapping table, that shows the relationship between KDPI and any KDRI value. A donor with a KDPI of 0% has a KDRI lower than all the donors from the reference population. A donor with a KDPI of X% has a KDRI of more than (X-1)% but no more than X% of all the reference population donors. For example, a donor with a KDPI of 30% has a KDRI between 29 and 30% of all the reference population donors.

Aside from calculating the KDRI by the formula described above, that involves a donor-only version of the KDRI, Rao’s group has suggested a „full KDRI”. This value would also include the cold ischaemia time, HLA mismatches and the type of transplantation (single, double or en-bloc). These factors influence the survival rates of the kidney-graft but are unknown when the decision to accept the organ is made by the transplantation team. Because of this the full KDRI is of lesser practical importance. In theory the predictive value of the donor-only version of the KDRI (c=0.596) is very similar to that of the full KDRI (c=0.601). The survival of the kidney-graft is also determined by a number of factors related to the recipient (such as age and comorbidities), that are not taken into account by the KDRI. The strength of the relationship between the KDRI/KDPI and the estimated survival rate of the kidney-graft is influenced by these recipient-related parameters in a minor way. KDPI is, however, limited by the lack of information regarding the microscopic image of the kidney-graft, as well as any damage or visible abnormalities. Furthermore, the KDRI does not include the risk of transmitting an infectious disease or malignancy. The described indexes are not constant values. During the last 10 years the values of KDRI and KDPI have increased by 7% and 6% respectively.

A teams from Richmond and Cleveland underlines the difference in KDPI when taking the initial or final creatinine level into account. In 10% of donors the difference is over 11 points. The more stable the creatinine levels, the better the KDPI reflects the true quality of the donor. The Kidney Transplantation Committee (KTC) gathers data regarding the influence of variable creatinine levels during donor evaluation on the final KDPI value. It has not yet been determined whether this will influence the kidney-graft allocation system (24).

As was mentioned earlier the KDPI allows for estimating the survival rate of a kidney-graft. It thus helps in deciding whether to accept a kidney harvested from an ECD or wait for a possible SCD donor. KDPI has been part of DonorNet® since 2012 and it is an integral part of the new kidney allocation system (KAS) developed by the OPTN KTC, that is expected to be implemented in the US by the end of 2014. Introducing the KDPI is intended to help with “longevity matching” – a new kidney-graft allocation algorithm, that involves an estimated post-transplant score (EPTS). KDPI, as a measurement of donor quality, is supposed to help transplantologists match a particular organ and a recipient with a suitable prognosis, while taking into account the ischaemia time related to his transplantation center. A recipient with a EPTS of less than 20% should be matched with a kidney-graft from a donor with a KDPI of less than 20%. Utilizing the KDPI can help decide to transplant 2 kidney-grafts to a recipient in a case where a single organ might provide insufficient eGFR. The formula for calculating the EPTS was developed using a multivariate analysis by Cox proportional hazard model, that included 4 factors associated with patient survival after kidney transplantation: age, time of dialysis, previous transplantations and current diabetes. The calculated EPTS in a value between 0 and 100% and signifies the percentage of the recipient population with a longer expected survival rate after kidney transplantation. Every patient on the waiting list is assigned an EPTS, that is updated after every year of chronic dialysis or when the patient is diagnosed with diabetes. The new allocation system, involving the KDPI and EPTS is meant to optimize the matching of <20% KDPI donors and <20% EPTS recipients. An organ with a good estimated long-term function should be transplanted to a recipient with a suitably long expected survival rate. Matching a kidney with a good estimated long-term function and a recipient with a poor EPTS is an example of suboptimal organ use. Similarly, a young patient with a EPTS of less than 20% given a kidney-graft with a high KDPI is a bad match, as he would soon be in need of a re-transplantation. The mean kidney-graft survival for a donor with a KDPI <20% is 11.5 years, compared to 12 years for a living donor (30). Ramanathan et al, interpreting a retrospective analysis of 528 recipients, has shown that best kidney-graft survival rates are attained when the donor is 15 years younger than the recipient (28). A study of recipients in Washington has shown a statistically significant influence of KDPI on serum creatinine concentrations at 6 an 12 mon-
The new kidney allocation system, based on the donor index allows for maximal use of harvested organs and optimal recipient matching. The EPTS is only taken into account when allocating kidneys from donors with a KDPI <20%. The EPTS only sets priority in 20% cases of transplantation. A simulation performed last year by Kasiške et al. has shown that the new allocation system will improve the half-life of kidney-grafts from 8.82 to 9.07 years and increase the chance of transplantation for recipients aged 18-49, while slightly lowering the chances of transplantation for patients aged 50-64 years (29). A retrospective, single-center analysis of over 500 recipients suggests a similar one-year survival for kidney-grafts from donors with a KDPI >85% and 20-84%. The difference in prognosis are noticeable after 3 years.

The share of ECD kidneys among transplanted organs is increasing, as is the average age of patients on the waiting lists. The influence of donor-related risk factors on the recipient differs depending on the age, race, history of diabetes and ESRD cause of the recipient. The quality of the donor has a significant clinical interaction with the recipient characteristic. ECD kidneys are an appropriate option for recipients that are aged or suffer from comorbidities such as diabetes. In these cases the risk of losing the kidney-graft is lower than for younger, healthier recipients. It has been demonstrated that greater KDRI values have a lesser impact on older recipients with a history of diabetes. Conversely, the donor-related risk factors have a stronger influences on younger patients with fewer comorbidities. By definition the organ quality measured by KDPI should be constant, so additional analyses regarding other factors (such as time of ischaemia) on the survival rates of both graft and recipient are easier to perform and more predictable.

Reports show that organs fulfilling extended criteria are disqualified more often. A team from Boston has performed a retrospective analysis of the survival rates of 138 717 kidney-graft recipients, transplanted between 1995 and 2010. The analysis has demonstrated that survival of recipients is superior to those on the waiting list, regardless of the KDPI value of the transplanted organ. A common index measuring the risk of death for both recipient and a candidate for transplantation was established. It included 15 traits, with age, race and cause of ESRD being the most important. Next, groups of recipients and candidates with a similar index were compared. The study showed a significantly longer five-year survival for kidney-graft recipients of all risk groups compared to patients waiting for a transplantation. Sub-analyses show superior survival rates even for recipients with a kidney with a KDPI of 81-100% (31).

A team from the Johns Hopkins University School of Medicine has reached similar conclusions. Transplanting a kidney with a high KDPI value, compared to waiting for a “better” organ, is associated with an increased short-term and long-term mortality. The benefit is visible after 2 years. After 5 years the survival rates for recipients are superior to candidates for all KDPI values. A single-center retrospective analysis of over 500 recipients shows a similar one-years survival for kidneys with a KDPI >85% and 20-84%. The differences in survival between these groups are significant after 3 years (25). Accepting an organ with a KDPI >71% is an especially appropriate option for patients who are over 50 years old or come from a center with an average waiting time of over 33 months (32).

Kidneys with a high KDPI value (>80%) are not accepted by more than half cases in the US. The histological evaluation of a time-zero biopsy can be helpful in making a choice. Gandolfini has shown that a kidney with a greater KDPI value has better survival rates if it is also assigned a better Remmuzzi score. He concludes that a histological evaluation of an ECD kidney with a high KDPI value might be crucial in qualifying the graft for transplantation. A Remmuzzi score of over 4 points can be an indication for transplanting 2 kidney to one recipient (33, 34). The KDRI and KDPI include the donor-related factors that independently influence the overall survival of the kidney-graft harvested from a particular donor. The KDPI arranges the harvested organs according to their quality, reflecting relative risk in the population. The index should not be used as a singular tool to decide whether or not to accept a given organ. The curve of relative risk of kidney-graft survival for KDPI values between 20 and 80% is almost flat. Hence, particular KDPI values in this range do not reflect important differences in the quality of organs. The curve of kidney-graft survival increases steeply for KDPI values of over 80%. Taking into account the cited data regarding longer survival of recipients, regardless of the quality of the transplant, compared to patients on the waiting list, it is difficult to define a KDPI value of 80% as a cut-off point. The decision rests with the patients and the transplantologist. If the organ is accepted, pulsatile perfusion should be applied and ischaemia time should be shortened. The plan for monitoring the graft by biopsies and the immunosuppressive regimen should take the expected delayed graft function into account.

Woodside et al. performed a study of transplantsations from SCD and ECD donors with the same KDRI score from 2002 to 2012. They focused on donors with a KDRI between 1.4 and 2.1. This population was split into 3 groups covering the following ranges:
1.4-1.6, 1.6-1.8 and 1.8-2.0. An analysis of these groups has shown a similar number of ECD and SCD kidneys qualified for transplantation. Despite the opinion that ECD kidneys are associated with a worse prognosis, no difference in graft survival was noted within each KDRI range. That is, for organs harvested from donor with a KDRI from 1.6 to 1.8 the survival rates were not influenced by their ECD/SCD status (20).

Utilizing the KDPI/KDRI indexes for stratification of risk in organs harvested outside the US remains controversial. Bradley et al have developed a British donor risk index, based on an analysis of 7620 first-time kidney-graft recipients from years 2000-2007. The most important donor-related factors influencing graft survival were found to be: age, history of hypertension, weight, time of hospital stay and vasopressor use. The number of donors suffering from diabetes is relatively smaller in the UK, as is the percentage of ethnic minorities. The UKKDRI (United Kingdom Kidney Donor Risk Index) is equal 1 for a donor aged 40-59 years, 75kg, with no history of hypertension, a hospital stay of under 24 hours and no vasopressor use. The difference in kidney-graft survival for extreme values of the index is 40%. The formula for calculating UKKDRI includes only 5 donor traits. Since the predictive value of both indexes is similar (statistical compatibility for UKKDRI is 0.62 versus 0.63 for the USKDRI), the simplicity of the UK index is a significant advantage (26).

A kidney harvested from a particular donor should be assigned a risk index and be allocated to a recipient most likely to benefit. The kidney allocation system cannot be based solely on choosing the recipient with the longest waiting time and smallest number of HLA mismatches. It should, most importantly, take into account how the quality of a particular organ will influence a specific candidate’s survival. Such an approach may lead to an increase of kidneys accepted for transplantation. In consequence, the survival times of graft recipients should improve and the number of patients waiting for a retransplantation decrease. Estimating the donor-related risk correctly allows for decreasing the time required to accept the organ, reducing the duration of ischaemia. In the last 2 decades several risk indexes have been proposed to predict graft survival, dealing with factors related to the donor, recipient and other parameters of the transplantation procedure. Some of these were based on large populations of donor-recipient pairs and have been accepted by local organ allocation systems. As of yet none has been endorsed by international institutions a universal predictive model of graft function. The new kidney allocation system implemented in the US rates the harvested organs, based on the risk index, from 1 (worst) to 100 (best). Doubt exists as to whether KDPI, as a single parameter, is sufficient information to accept or reject an organ (38). UNOS suggests utilizing all organs with a KDPI under 85%. Who should decide if and when to accept organs rated at over 85%? Does the choice lie with the doctor, the patient or both? Questions such as these remain unanswered.

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