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Blessing and a curse of outpatient management of delayed graft function

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Abstract

Delayed graft function (DGF) is a common complication occurring most often after deceased donor kidney transplant with several donor characteristics as well as immunologic factors that lead to its development post-transplant. These patients require dialysis and close kidney function monitoring until sufficient allograft function is achieved. This has resulted in limited options for DGF management, either prolonged hospitalization until graft function improves to the point where dialysis is no longer needed or discharge back to their home dialysis unit with periodic follow up in the transplant clinic. DGF is associated with a higher risk for acute rejection, premature graft failure, and 30-d readmission; therefore, these patients need close monitoring, immunosuppression management, and prompt allograft biopsy if prolonged DGF is observed. This may not occur if these patients are discharged back to their home dialysis unit. To address this issue, the University of Wisconsin-Madison created a clinic in 2011 specialized in outpatient DGF management. This clinic was able to successfully reduce hospital length of stay without an increase in 30-d readmission, graft loss, and patient death.

Key words: Delayed graft function; Kidney transplantation; Immunosuppression; Acute rejection; Kidney donor profile index; Kidney donor risk index; Dialysis

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Core tip: Delayed graft function (DGF), traditionally defined as needing dialysis within seven days following kidney transplant, occurs most often after deceased donor kidney transplantation. Both donor characteristics, as well as immunologic factors, influence the development of DGF. Historically, outpatient management has been difficult, often leading to increased length of stay (LOS), however, the DGF clinic at University of Wisconsin - Madison which was established in 2011 has shown that it is possible to

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provide high-quality outpatient DGF management without increasing LOS, 30-d readmission, or acute rejection rates.

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APPROACH TO MANAGING DELAYED GRAFT FUNCTION

Delayed graft function (DGF) is most often defined as the need for dialysis within the first seven days following kidney transplantation. However, this definition is subject to center level variation^[1]. It is more commonly seen after deceased donor kidney transplantation with an estimated incidence of 30%^[1,2].

Certain factors are associated with the development of DGF including the cause of donor death, donor age, kidney donor profile index (KDPI), cold ischemia time (CIT), and higher serum creatinine at the time of death^[3]. KDPI is a numerical measure of overall kidney quality in deceased donor (DD) kidneys. It is derived by first calculating kidney donor risk index (KDRI) which incorporates several donor characteristics including age, height, weight, cause of death, history of diabetes, history of hypertension, ethnicity, Hepatitis C status, serum creatinine, and donation after circulatory death (DCD) status. Lower KDRI and KDPI scores are associated with increased donor quality and expected longevity whereas higher scores (> 85%) are associated with increased risk for DGF as well as decreased graft survival and longevity^[4,5]. Longer CIT, over 20 h, is also associated with a higher incidence of DGF^[6]. There is a higher risk of developing DGF following DCD kidney transplantation due to the presence of warm ischemia and reduced perfusion during procurement^[7].

DGF is a costly complication and often leads to prolonged hospitalization. DGF recovery is most often seen within 7 to 10 d^[8], however, it can take up to three to four weeks for DGF to completely resolve to the point where dialysis is no longer needed. Managing DGF poses a unique challenge for health care providers who are tasked with reducing hospital stay while at the same time ensuring these patients are receiving close monitoring of kidney function. Traditionally DGF management has been limited to either prolonged length of stay (LOS) until allograft recovery has been achieved or discharge back to their home dialysis center with regular follow up in the clinic. These patients are often medically complex with fluctuating volume status, so care must be taken to prevent inappropriate dialysis during DGF recovery. They are at high risk for readmission within the first 30 d after transplantation^[9]. Those with DGF are also at higher risk for acute rejection which can lead to premature graft failure and is associated with decreased 1, 3, and 5-year graft survival^[3,10,11]. Therefore, not only is optimizing immunosuppression critical but prompt diagnosis with renal allograft biopsy, if prolonged DGF is observed, is also important. These opportunities may be missed if patients are not followed closely in the transplant clinic.

Because outpatient DGF management has been challenging due to the need for ongoing dialysis and close monitoring of kidney function, the transplant clinic is the ideal setting for DGF follow-up. However, this can be difficult for patients and family members who do not reside near the transplant center. In order to address this need for consistent outpatient DGF management, the University of Wisconsin Hospital created an outpatient clinic in July 2011 which specializes in DGF management. This multidisciplinary clinic consists of transplant nephrology physicians, experienced advanced practice providers (APPs) specialized in kidney transplantation, social workers, and pharmacists. DGF discharge planning frequently is initiated upon consultation to transplant nephrology when DGF is suspected. These patients are then either discharged home (if local) or to a nearby hotel with a support person along with a scheduled clinic visit within 1-3 d of discharge. Majority of these patients are required to follow up in the DGF clinic 3 d per week. Each clinic visit day begins with labs which are usually completed in the outpatient labs at the hospital. These include complete metabolic panel, complete blood count, should be urinalysis, urine protein-creatinine ratio, beta-2-microglobulin, tacrolimus drug level. Patients then proceed to the clinic where height, weight, and vital signs are obtained. They then undergo assessment and physical exam by either an APP or physician. If dialysis is deemed

necessary, an appointment is then scheduled for dialysis in the hospital inpatient dialysis unit that same day. Prior to leaving clinic, a follow-up appointment is scheduled and a new medication list is provided to the patient. DGF clinic follow up continues until adequate graft function is achieved. During dialysis, all patients go through the same standard isolation precaution of contact or airborne isolation or no isolation. If no improvement in graft function is noted within 7 to 14 d after transplantation, a kidney transplant biopsy is scheduled. Donor-specific antibodies (DSA) are monitored on all patients at the time of a kidney biopsy. Also, DSA are monitored on all patients, based on the immunological risk as described previously^[12]. In the near future, we are also planning to monitor DGF and perform biopsy based on the new biomarkers, along with the banking of the tissue, serum and urine sample^[13].

To assess the impact of this clinic on outpatient DGF management, Muth *et al*^[14] conducted a retrospective review of 697 DD performed from July 2009 to July 2014. Patients were divided into three groups, no DGF, and DGF before and after implementation of the DGF clinic. Baseline characteristics of the three groups were similar. They compared LOS, 30-d readmission, acute rejection, and patient/graft survival. What they found was a significant decrease in LOS post-DGF clinic compared pre-DGF clinic^[14]. DGF clinic patients were less likely to develop acute rejection, while 30-d readmission, graft loss and patient death did not differ significantly between pre and post-DGF clinic^[14]. These findings suggest outpatient DGF management can successfully reduce LOS without increasing adverse outcomes or compromising patient care. To achieve this, we needed a dedicated multidisciplinary team as well as a motivated patient with their support person to navigate DGF, because often times, the patient is overwhelmed due to the frequent nature of clinic visits as well as being away from home. In summary, our experience with intensive multidisciplinary outpatient management of DGF has been effective in closely monitoring and supporting patients in their DGF recovery, and limiting adverse events. Based on our experience, we recommend a transplant center to weigh the cost-benefit of this complex patient. Centers with a high volume of DGF may benefit from establishing a DGF clinic.

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Histological and clinical evaluation of marginal donor kidneys before transplantation: Which is best?

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Abstract

Organ shortage represents one of the major limitations to the development of kidney transplantation. To increase the donor pool and to answer the ever increasing kidney request, physicians are recurring to marginal kidneys as kidneys from older donors, from hypertensive or diabetic donors and from non-heart beating donors. These kidneys are known to have frequently a worse outcome in the recipients. To date major problem is to evaluate such kidneys in order to use or to discard them before transplantation. The use of such kidneys create other relevant question as whether to use them as single or dual transplant and to allocate them fairly according transplant programs. The pre-transplant histological evaluation, the clinical evaluation of the donor or both the criteria joined has been used and according the time each criterion prevailed over the others. Aim of this review has been to examine the advantages and the drawbacks of any criterion and how they have changed with time. To date any criterion has several limitations and several authors have argued for the development of new guidelines in the field of the kidney evaluation for transplantation. Several authors argue that the use of omic technologies should improve the organ evaluation and studies are ongoing to evaluate these technologies either in the donor urine or in the biopsies taken before transplantation.

Key words: Kidney evaluation; Pre-transplant biopsies; Kidney donor evaluation; Kidney risk profile index; Omic technologies; Deceased donor score; Donor risk score

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Core tip: With the extension of donor pool to high risk donors, the kidney pre-transplant

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evaluation became mandatory. Different criteria have been used, each of them with advantages and limitations. Probably the use of pre-transplant kidney biopsies in those kidneys coming from donors with the highest profile index seem to give the better results. These could be improved applying omic technologies either to donor urine or to pre-transplant biopsies. However the application of omic technologies is time consuming and not everywhere applicable. Several studies on these technologies are to date ongoing, but their results are yet not known.

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INTRODUCTION

To date, organ shortage represents one of the major limitations to the development of kidney transplantation.

To increase the donor pool many transplant programs accept kidneys from the so-called extended criteria donors (ECDs)^[1,2]. Kidneys from the ECD pool are known to have worse outcomes in recipients with a higher rate of delayed graft function (DGF), primary non function (PNF), and reduced function of the allograft and reduced graft survival^[3]. The main challenge is to evaluate such kidneys before transplantation either for a better and fair allocation or for discarding the kidney in the case of a very poor evaluation of the offered kidney.

Several factors related to the donors are known to influence the post-transplant outcomes. **Figure 1** identifies which donor, procurement and graft characteristics principally influence the outcomes. They may be divided into clinical and histological factors and factors related to the donor and related to the offered kidney and to the procurement management.

Historically, the evaluation of the kidneys from ECDs has been made histologically by the so-called zero-time biopsy^[4], by clinical evaluation of the donor by different kidney allocation scores or by a combination of histological and clinical parameters.

Additionally, it should be highlighted that the need of a clear evaluation of the “so called” marginal donors became a must with the increased use of such kidneys. With time the experience documented that several kidneys from ECD pool performed well, while other kidneys labeled as standard criteria donors (SCD) did not perform well. Hence, the opportunity of a safe evaluation also for SCD. De facto the recent kidney donor risk index (KDRI) automatically offers the evaluation for any kidney.

The aim of this review is to describe the aforementioned evaluation criteria of ECD kidneys and to describe how they have changed with time.

SELECTION CRITERIA OF THE ARTICLES INCLUDED IN THIS REVIEW AND THEIR DRAWBACKS

The criteria to evaluate the kidneys have been histological, clinical and mixed histological-clinical. We have searched for all the papers concerning these points. The main studies concerning the most important scoring systems are shown on **Table 1**. With the exception of the two single centre studies as Maryland Aggregate Pathology Index (MAPI) and the Irish nomogram, all the studies considered included a large number of patients with the limitation to be retrospective in the attempt to validate the original findings. Clearly, in this review are also included articles documenting the drawbacks of the different scoring systems and these articles may include a limited number of patients. Similarly, the studies evaluating the omics on the renal biopsies or on the donor urine have a limited number of patients.

HISTOLOGICAL EVALUATION OF DONOR KIDNEYS

By 1999, Karpinski *et al*^[5] considering that kidneys from high risk donors had worse outcomes in the recipient after transplantation tried to establish which donor or

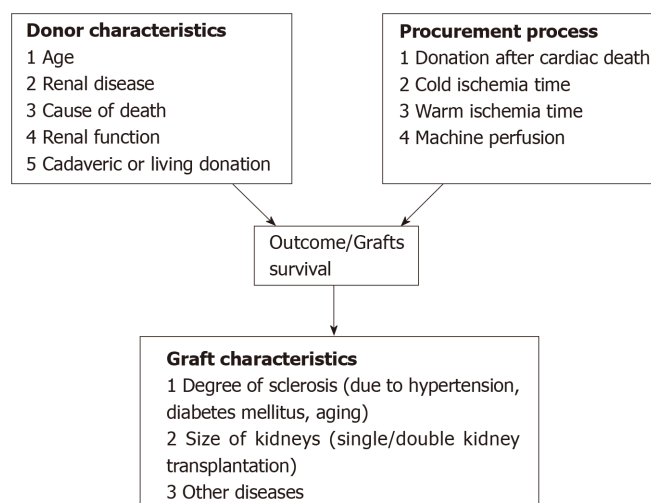


Figure 1 Main donor, procurement and graft related factors influencing the post-transplant outcomes.

kidney variables were most relevant to these poor outcomes. For high donor risk, they considered donation after cardiac death donors, donors over 55 years of age, donors with a history of hypertension or diabetes, and donors with abnormal kidney anatomy or abnormal renal function^[6]. The study found that a low calculated creatinine clearance (CrCl) and donor kidney pathology were the main predictors of worse outcomes

In particular, the donor renal pathology was scored 0-3 in each of four distinct aspects: Glomerulosclerosis, interstitial fibrosis, tubular atrophy and vascular disease (Table 2). Previous studies have documented the relevance of pre-implantation histological findings on recipient outcomes^[7-9]. None of these studies had been concordant, and the study of Karpinski *et al.*^[5] may be considered a pioneering study documenting the relevance of the pathology score over the transplant outcomes.

Since the study of Karpinski *et al.*^[5], several studies have documented the relevance of the pathology score of donor kidneys over the outcomes, while other studies did not find a similar usefulness of the pathology score.

One of the most important studies in favor of the pathology score has been the study of Remuzzi *et al.*^[10]. According to this study, the pathology score allows transplant kidneys with a score up to 3 to be used as single kidneys, while kidneys with a score from 4 to 6 are better allocated as dual transplants and kidneys with a score of 7 or higher should be discarded.

Additionally, the study documents the importance of the pre-transplant renal biopsy for donors over 60 years when comparing the renal outcomes with and without biopsy (Figure 2).

In a different study, Mancilla *et al.*^[11] suggested the utility of zero-time biopsy in the case of living donor kidneys, particularly for donors with borderline renal function or with a history of familial renal disorders^[12,13]. In a study from Kayler *et al.*^[14] a correlation of histological findings on pre-implantation biopsy with kidney graft survival was also found but was restricted to vascular lesions, while glomerulosclerosis and low-grade interstitial fibrosis did not have statistical significance.

Based on 371 pre-transplant biopsies and correlating the findings with post-transplant outcomes, Munivenkatappa *et al.*^[15] developed the MAPI. In the study, glomerulosclerosis, glomerular size and periglomerular fibrosis in addition to vascular pathology and arteriolar hyalinosis were considered in developing the MAPI score (Table 3). The authors found that the five-year actuarial graft survival rate was related to the MAPI scoring (Figure 3) and that the MAPI score at the multivariate analysis correlated with the risk of graft failure better than any other clinical parameter (Table 4). This study suddenly received several comments, which brought up several unanswered questions about the relevance of pre-transplant biopsies in predicting post-transplant outcomes. Many of these questions were raised by Nickeleit^[16].

One point that is not clarified is whether wedge specimens or needle biopsies should be used. This issue is well described in a further paper^[17] that considers wedge biopsies to be safer and superior to core biopsies in finding significant findings.

Another point is whether frozen or paraffinized sections should be used, even if the original MAPI score found paraffinized sections to be more reliable.

Table 1 Descriptive table of selected clinical scoring system

Score	Authors	Variables included in risk score	Score grades	Outcome
Expanded criteria donor	Port <i>et al</i> ^[58] , 2002	Donor age	SCD	Relative risk of graft failure compared to SCD
		Cerebrovascular accident as cause of death	ECD	RR>1.7
		Serum creatinine> 1.5mg/dL		
		History of hypertension		
Deceased donor score	Nyberg <i>et al</i> ^[65] , 2003	Age		5-year graft survival
		History of hypertension	A (0-9 points)	Grade A 82%
		Creatinine clearance	B (10-19 points)	Grade B 79%
		HLA mismatch	C (20-29 points)	Grade C 72%
		Cause of death	D (30-39 points)	Grade D 65%
Donor risk score (DRS)	Schold <i>et al</i> ^[67] , 2005	Donor risk factors		5-year graft survival
		Race	I	Grade I 76.7%
		Age	II	Grade II 73.6%
		History of hypertension	III	Grade III 66.3%
		History of diabetes	IV	Grade IV 54.8%
		Cause of death	V	Grade V 47.6%
		History of hypertension		
		History of diabetes		
		Cause of death		
		HLA-Dr mismatch		
		CMV mismatch		
		Cold ischemia time		
DGF nomogram	Irish <i>et al</i> ^[70] , 2003	Donor risk factors	Continuous point score	Delayed graft function
		Age		
		Serum creatinine		
		History of hypertension		
		Cause of death		
		Donor after cardiac death		
		Recipient risk factors		
		Peak PRA		
		Race		
		Gender		
		History of diabetes mellitus		
		Previous transplant		
		Pretransplant dialysis		
		Pretransplant transfusions		
		Combined transplantation		
		HLA mismatch		
		Cold ischemia time		
KDRI	Rao <i>et al</i> ^[71] , 2009	Donor risk factors	KDRI quintile	5-year graft survival
		Age	0.45-0.79	82%
		Race	0.80-0.96	79%
		Height	0.97-1.15	NA
		Weight	1.16-1.45	NA
		History of hypertension	>1.45	63%
		History of diabetes		
		Cause of death		
		Serum creatinine		
		Hepatitis C		
		Donation after cardiac death		
		HLA-B mismatch		

Donor-only KDRI	OPTN ^[72] , 2014	HLA-DR mismatch	
		Cold ischemia time	
		Double or <i>en bloc</i> transplant	
		Donor risk factors	5-year graft survival
		Age	<0.6
		Race	0.61-0.79
		Height	0.80-0.99
		Weight	1.00-1.19
		History of hypertension	1.20-1.59
		History of diabetes	1.60-1.99
		Cause of death	>1.99
		Serum creatinine	
		Hepatitis C	
		Donation after cardiac death	

ECD: Expanded criteria donor; KDRI: Kidney donor risk index; OPTN: The Organ Procurement and Transplantation Network; SCD: Standard criteria donor.

Additionally, it should be better defined when zero-time biopsies should be taken: before or after reperfusion. Biopsy time is relevant in detecting the complement activation that is predictive of early antibody mediated rejection^[18].

An important point, not well considered by the MAPI score is how the lesions should be scored and whether the Banff criterion is appropriate^[19]. This point is relevant for comparing zero-time biopsies with subsequent post-transplant biopsies. Nickeleit^[16]'s conclusions were that much remains to be determined about zero-time biopsies and that consensus guidelines remain to be defined.

Recommendations on these points have been given by two German workshops and described by Pisarski *et al*^[20] in 2016. The German recommendations advocate a detailed assessment of the findings and do not agree with the recommendations of the Interpretation Biopsy Banff Working Group^[21], whose approach is adopted for a general pathologist, without specific training in the field.

The issue of an expert pathologist was addressed in 2012 in a study of the pre-implantation biopsies in the Organ Procurement Organization (OPOS) that found a lack of concordance among OPOS pathologists^[22]. The lack of a correlation between the findings of on-call pathologists and the lack of association between their findings and the transplant outcomes is highlighted by two papers^[23,24] that advocate for specific training in renal pathology to optimize the histological evaluation of donor kidneys. It could also be argued that a renal pathologist "per se" could not be expert enough in evaluating such biopsies. Probably a specific training should be the best solution.

By 2011, Mueller *et al*^[25], reviewing several studies on histopathology-based variables at zero-time biopsies, highlighted the limitations due to sampling errors, confounding clinical variables, and inter-observer variability^[26,27] and advocated for a validated approach for the analysis of pathology findings. In particular, they advocate for the use of omic technologies such as proteomics, transcriptomics and metabolomics that could have the potential to improve the significance of the histological findings. Table 5 highlights the principal studies that were conducted until 2011^[28,39].

A study from Krol *et al*^[40], documented that the apoptosis of tubular epithelial cells in pre-implantation biopsies is related to DGF. Their findings were confirmed by another study^[41] that found a relationship between high *BAX/BCL2* expression in pre-implantation biopsies and DGF, confirming that apoptosis-related gene expression levels are predictors of DGF.

A recent study^[42] confirmed that zero-time biopsies in ECDs showed a significant increase in the transcripts of *MCP-1*, *RANTES*, *TGF beta* and *IL 10*, documenting a higher gene expression of inflammatory cytokines in ECDs that could predict the post-transplant outcome.

In recent years, several studies, often retrospective, and several reviews and meta-analyses did not confirm the utility of zero-time biopsy in allocating or discarding ECD kidneys. Wang *et al*^[43] reviewed 47 studies published between 1994 and 2014, where each study included pre-transplant biopsies format least 50 donors and compared the histological findings with post-transplant outcomes. Overall, 15 scoring systems were proposed by the studies, but none were able to correlate with post-transplant outcomes.

Table 2 Histological score according Karpinski

Histological score	
Glomerular score	0 = no globally sclerosed glomeruli 1 = < 20% global glomerulosclerosis 2 = 20-50% global glomerulosclerosis 3 = > 50% global glomerulosclerosis
Tubular score	0 = absent 1 = < 20% of tubules affected 2 = 20-50% of tubules affected 3 = > 50% of tubules affected
Interstitial score	0 = absent 1 = < 20% of cortical parenchyma replaced by fibrous connective tissue 2 = 20-50% of cortical parenchyma replaced by fibrous connective tissue 3 = > 50% of cortical parenchyma replaced by fibrous connective tissue
Vascular score	0 = absent 1 = increased wall thickness but to a degree that is less than the diameter of the lumen 2 = wall thickness that is equal or slightly greater than the diameter of the lumen 3 = wall thickness that far exceeds the diameter of the lumen, with extreme narrowing

Naesens^[44] reviewed the problems and the utility of zero-time biopsy and highlighted that the major problems were the wedge *vs* core needle biopsy^[45,46]; frozen *vs* paraffin-embedded tissue^[47,48]; pathologist's experience^[23,24]; different composite histological scoring such as the Pirani score^[49], Chronic Allograft Damage Index (CADI)^[50], and Donor Score^[23]; and the lack of utilizing hard clinical end-points in evaluating graft and recipient outcomes. The author concluded that zero-time biopsies are not useful for assigning or discarding kidneys or improving dual kidney transplantation programs. The author recognizes that the molecular phenotype in pre-transplant biopsies could be useful in donor selection and in peri-transplant management even if the time required could make such a procedure difficult^[51-54].

Two recent Italian studies on the utility of pre-implantation biopsy in allocating ECD kidneys^[4,55] concluded that histological evaluation was not superior to donor clinical evaluation in allocating ECD kidneys either as a single kidney or as a dual kidney transplant. The authors concluded that, according to their experience, the histological score poorly evaluates the donor kidney quality. Accordingly, the use of histological criteria to assign as single or dual kidneys does not seem to offer advantages over the evaluation made on clinical basis.

A Banff Pre-implantation Biopsy Working Group has been established to develop guidelines for the interpretation of pre-implantation renal biopsies^[56]. The last working group meeting stated that to date, histological parameters are poorly correlated with post-transplant outcomes and that remain significant limitations in understanding the role of pre-implantation biopsies.

Recently, Carpenter *et al*^[57] from Columbia University examined their experience and compared procurement biopsies with reperfusion paraffin-embedded biopsies and with post-transplant biopsies. All the findings were then correlated with allograft failures and patient deaths. No agreement has been found between frozen procurement biopsies and paraffin-embedded biopsies, and frozen procurement biopsies were poorly correlated with post-transplant biopsies and the hard end-point considered.

COMBINED CLINICAL AND HISTOLOGICAL EVALUATION OF DONOR KIDNEYS

A different approach to evaluating ECD kidneys has been to combine histological findings with clinical donor-related parameters. The latter have been identified since the publication of the study by Port *et al*^[58]. In a study in 2001, Verran *et al*^[59] found that the combination of abnormal biopsy findings with donor age and donor cardiovascular disease and hypertension was associated with poor outcomes.

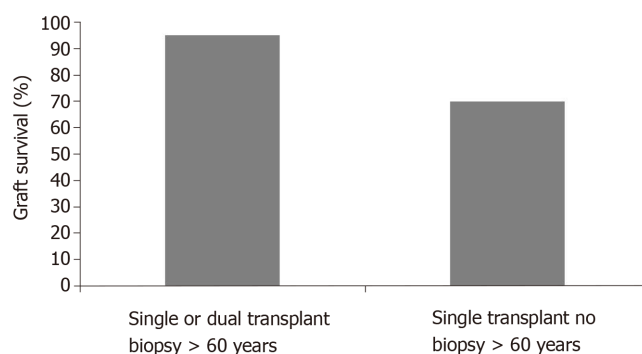


Figure 2 36 month graft survival for donors over 60 years according pre-transplant biopsy.

In an Italian study^[60], donor kidneys were assigned with good results according to donor renal function [estimated glomerular filtration rate (eGFR) under or over 50 mL/min] and the previously mentioned Karpinski score.

The largest study that evaluated the predictive value of clinical and histological findings taken together was conducted by Anglicheau *et al.*^[61]. The authors, evaluating 313 kidney transplants from donors aged >50 years, developed the so-called Anglicheau score. The best predictive parameters were a history of hypertension in the donor, serum creatinine levels under or over 1.5 mg/dL and glomerulosclerosis less than or over 10%. These parameters in the multivariate analysis significantly correlated with renal function at 1 year post-transplantation.

A different study^[62] recognizes the utility of zero-time biopsy, but, as none of the histological variables and scores provided a good prediction of post-transplant outcomes, the histological findings need to be integrated with all the known donor-related clinical parameters.

Finally, a very recent Spanish study^[63] highlights the utility of evaluating the pre-transplant donor biopsies in the donor with the highest kidney donor profile index (KDPI) that is based on several deceased donor variables.

CLINICAL EVALUATION OF DONOR KIDNEYS

In an attempt to improve the evaluation of the donor kidneys, principally in the US, where the donor kidney evaluation is strictly connected with their discard or their allocation to different recipients according to national programs, several clinical donor quality scoring systems have been performed.

The first one was the characterization and a better definition of ECDs. According to the report of the Kidney Working Group^[1], kidneys belonging to the ECD were kidneys with a relative risk of graft failure of 1.7 with respect to standard kidneys. These kidneys are characterized by a donor age older than 59 years with two of the following characteristics: cerebrovascular accident as cause of death, history of hypertension or creatinine over 1.5 mg/dL^[2].

Nyberg *et al.*^[64] evaluated 241 consecutive cadaveric renal transplants and gave a score based on recognized clinical factors responsible for DGF. These factors were age, cause of death, history of hypertension, diabetes mellitus, creatinine clearance and presence in the donor of renal artery stenosis. A scoring system was developed from these seven donor variables, allowing stratification of cadaver kidneys into four classes (grades A, B, C, D). Univariate and multivariate analyses were performed, and a significant decline in early renal function was observed with an increase in the score. Additionally, the multivariate analysis had a better prognostic value with respect to each single variable considered in the univariate analysis.

Later, Nyberg *et al.*^[65], in an attempt to validate his scoring system, applied the analysis to a wider population, including 34324 transplant patients from the UNOS registry in the period between 1994 and 1999. This study allowed us to evaluate the feasibility of the score on a larger follow-up. The study allowed the recognition of five clinical variables as predictive of a poorer outcome [age, cause of death, history of hypertension, creatinine clearance and human leukocyte antigen (HLA) mismatch]. This score was called the Deceased Donor Score or Nyberg score and was able to predict renal function at 12 mo and graft survival at 6 years (Figure 4).

A further study by the same author^[66] also confirmed these data for kidneys

Table 3 Maryland Aggregate Pathology Index scoring system for pre-transplant kidney biopsies

	HR (95%CI)	P value	MAPI points	
			Absent	Present
Arteriolar hyalinosis	3.93 (2.02-7.64)	<0.0001	0	4
PGF (any)	4.09 (1.65-10.14)	0.002	0	3
Scar (any)	2.58 (1.24-5.38)	0.01	0	3
GS > 15%	1.87 (1.17-2.99)	0.009	0	2
WLR interlobular arteries > 0.5	2.05 (1.21-3.47)	0.008	0	2

MAPI: Maryland Aggregate Pathology Index; WLR: Wall to lumen ratio; CI: Confidence interval.

receiving machine reperfusion.

To further improve clinical factors able to evaluate kidney status and to predict outcomes after transplantation, Schold *et al*^[67] studied different clinical variables that were applied to transplants included in the National Scientific Transplant Registry from 1996 to 2002.

The variables were age, race, and history of hypertension, diabetes mellitus, and cause of death, cold ischemia time, HLA mismatch, and immunological status and CMV status. This was called the Donor Risk Score and allowed for the calculation of the multivariate estimates for graft loss by donor grade (Figure 5).

A further study^[68] compared the different clinical risk scores and documented that the Donor Risk Score was better associated with subsequent allograft function.

ECD-KDRI-KDPI

As already mentioned, by 2002, in an attempt to improve the utilization of marginal deceased donor kidneys, the concept of ECD *vs* SCD was introduced^[1,2]. With time this dichotomy (SCD/ECD) demonstrated several drawbacks. Indeed, the experience documented that several kidneys labeled as ECD performed well, while other kidneys labeled as SCD did not perform well^[69]. To improve these limitations other different scoring systems have been attempted. The donor score of Nyberg and the donor risk score of Schold have been described. Additionally, Irish *et al*^[70] applied a nomogram aimed at predicting the risk of DGF based on 16 donor and recipient risk factors. Moore *et al*^[68] documented that Schold's donor risk score is the scoring system that best predicts graft outcomes, but the need still remains for a simple and validated system that applies to the entire donor population viewed as a continuum and not in a dichotomous fashion.

In 2009, Rao *et al*^[71] analyzed 69440 deceased donor adult transplants registered in the Scientific Registry of Transplant Recipients (SRTR) and proposed a new continuous KDRI for deceased donor kidneys combining donor and transplant variables.

Rao's KDRI included 14 donor and transplant factors, each associated with shorter graft survival. Table 6 shows the mentioned risk factors.

The KDRI is a continuous spectrum for any kind of donor (ECD and SCD) and allows for dividing the donor population into quintiles based on their KDRI. By the end of 2014, the KDRI was implemented by the OPTN^[72]. Indeed, as some transplant factors are not known at the time of transplant, the donor-only KDRI based on 10 donor factors has been implemented.

All the mentioned donor scoring systems are shown in Table 1^[73]. Woodside *et al*^[74] examined the SRTR data from 2002 to 2010, and applying the KDRI, they found that kidneys belonging to the same KDRI quintile had similar outcomes independently of their belonging to ECD or SCD. However, ECD kidneys had a higher discard rate.

The use of the KDRI was further validated by several studies. Jun *et al*^[75] examined the use of the KDRI in donors with acute kidney injury (AKI) and found a good correlation between KDRI quintiles and graft outcomes.

A different study^[76] documented that the KDRI was a good prognostic tool for graft outcomes in deceased donor kidney transplantation with a short cold ischemia time. In this study, the KDRI correlated with renal function at 1 year, and a high KDRI was associated with a high risk of graft failure.

Recently, a Spanish study validated the usefulness of the KDRI in a European population^[77]. The study evaluated 144 renal transplants. All kidneys transplanted

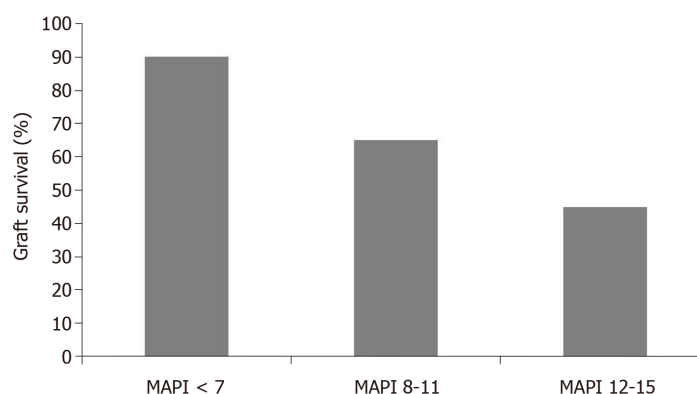


Figure 3 Five years graft survival for the study population according low, intermediate and high Maryland Aggregate Pathology Index score ranges. MAPI: Maryland Aggregate Pathology Index.

were evaluated by the KDRI and biopsied. The aims of the study were to verify the concordance between the KDRI and the histological findings and to validate the prognostic value of the KDRI for transplant outcomes. The study concluded that there was a poor concordance between the KDRI and histological score and that the KDRI had a good prognostic value.

Strictly connected with the KDRI is the KDPI. The KDPI represents the relative risk of graft failure in the case of a particular deceased donor compared to a reference donor. The KDPI was introduced in 2014 in the US^[78] and is derived by ranking the KDRI on a scale of 0-100% with reference to a donor cohort in the OPTN. It is useful and is represented by a number that helps in deciding the allocation of a specific organ^[79]. The KDRI and KDPI are strictly related.

These scoring systems have advantages over the ECD system because they represent a continuum, are based on 10 donor factors and represent a measure of donor quality.

Limitations of the KDRI and KDPI are represented by the fact that they do not include all of the donors' factors that could impact the graft outcome. Additionally, the KDPI is a measure of the donor and is not specific for each kidney taken individually.

The KDPI is useful for introducing the concept of the so-called longevity matching. The concept consists of allocating kidneys with a higher KDPI to patients on dialysis with a lower life expectancy. A retrospective study^[80] documented those patients older than 50 years or with a long waiting list time who were transplanted with kidneys with a high KDPI had a better survival than similar patients remaining on dialysis. This is particularly evident for patients older than 70 years^[81]. Notwithstanding, a German study^[82] reporting the experience of transplanting kidneys with a high KDPI observed that poor kidney quality, even when matching donors and recipients is the main factor responsible for poor outcomes. Several studies have evaluated the utility of the KDPI even outside of the US.

In a retrospective study, Lehner *et al*^[83] evaluated the utility of the KDPI in almost 1000 European kidney transplants. The study found rather good outcomes in the case of donors with a very high KDPI. A Spanish study^[84] evaluated the KDPI score on 389 transplants. The study documented that only the KDPI correlated with the risk of graft failure. This study also documented the utility of the KDPI measure in a cohort of European patients.

To further improve the KDPI, a retrospective study^[85] was conducted in the US. The study evaluated the KDPI in adult transplant recipients in the OPTN/UNOS database from 2000 to 2015. This study, while validating the usefulness of the KDPI, found that terminal serum creatinine of the donor (one of the components of the KDPI) is not a useful variable.

Another European study^[86] analyzed 1,305 kidney transplants. The study retrospectively applied the KDPI in 889 deceased donors and the living donor kidney profile index (LKDPI) in 416 living donors using the LKDPI realized by a US study for living donation^[87]. The European study was able to validate both the KDPI and LKDPI.

A major concern is what to do with donor kidneys with very a high KDPI (>80%).

In the US, the discard rate of these kidneys is approximately 50%. However, the allocation of kidneys with a KDPI higher than 80% in patients older than 60 years results in a lower patient mortality compared to patients who remain on the waiting list^[88]. Indeed, several kidneys with a KDPI higher than 80% are viable. A recent

Table 4 Cox Multivariate analysis showing association of Maryland Aggregate Pathology Index score and clinical parameters to risk of graft failure

	HR (95%CI)	P value
MAPI	1.21 (1.05-1.40)	0.008
Donor age	1.03 (1.00-1.07)	0.096
Cold ischemia (h)	3.66 (0.77-17.40)	0.102
Donor history of hypertension	1.62 (0.67-3.97)	0.287
Donor terminal creatinine > 1.5 mg/dL	1.34 (0.43-4.18)	0.611
CVA as cause of donor death	0.98 (0.35-2.73)	0.973

CVA: Cerebrovascular accident; MAPI: Maryland Aggregate Pathology Index.

study^[89] evaluated the 1-year eGFR and graft failure for kidneys transplanted with a KDPI higher than 80%. The discard of such kidneys had been decided with the help of a pre-Tx kidney biopsy, renal resistance and kidney injury biomarker levels. The 1-year eGFR was low but satisfying. The authors request the use of new biological tools for a proper evaluation of these kidneys.

An Italian multicenter study tried to reduce the discard rate of kidneys with a KDPI higher than 80% using pre-transplant kidney biopsy for these kidneys^[90]. The discard rate was reduced from 50% to 15%-37% according to the KDPI. The 1-year eGFR was lower for these marginal kidneys, but the graft survival was similar to that of standard kidneys. The study highlighted the utility of pre-transplant biopsy for kidneys with a very high KDPI.

Finally, a recently raised relevant question is whether the KDPI may be universally applied in allocating marginal kidneys or whether it is UNOS specific. A recent study from Ruggerenti *et al*^[91] documented the allocation and good graft survival of 37 renal transplants with donors with a KDPI between 96% and 100% after a pre-transplant biopsy. These kidneys should have been discarded according to the UNOS criteria^[92]. Similar findings have come from a previous study by Ekser *et al*^[93]. The 5-year graft survival was 91%, and the mean KDPI was 97%. More than 80% of these kidneys should have been discarded according to the UNOS^[94].

The question of UNOS specificity of the KDPI is examined in a recent study by Ruggerenti *et al*^[95]. According to the author, the difference in ethnicity may only partially explain the different results and the different discard rates of UNOS and several European studies^[96]. The author highlights the usefulness of pre-transplant biopsy for kidneys of donors with a very high KDPI.

In conclusion, the KDRI/KDPI represents an easy scoring system that could facilitate the decision to discard organs or allocate them in the best way.

According to several studies, the KDPI may also be applicable to European patients, even though this point is to date debated.

Based on the KDPI, the UNOS is implementing new allocation systems such as "longevity matching". Each candidate willing to participate in the "longevity matching" will receive an "estimated post-transplant survival score" (EPTS) and will receive a graft according to the matching KDPI/EPTS.

The allocation of kidneys with the highest KDPI is debated. Often, these kidneys are discarded^[97], but the use of pre-transplant biopsy may allow allocation of many of these kidneys, thus reducing the discard rate^[98].

MACHINE PERFUSION AND PERFUSATE BIOMARKERS

Hypothermic machine perfusion is increasingly used in deceased donor kidney transplantation, but the question still remains on how efficient are MP in assessing the quality of an organ?

One study evaluating the reasons for discarding 12536 ECD kidneys found that 15% of perfused kidneys were discarded partly based on high renovascular resistance (RR)^[99]. In a prospective study by Jochmans *et al*^[100] RR values of 302 MP kidneys were evaluated. The study conclusions were that RR as a standalone quality assessment tool cannot be used to predict the graft outcomes.

More recently, Parikh *et al*^[101] in a prospective observational cohort study examined the association between pump parameters and graft outcomes. They found an association between 1 h perfusate flow and DGF but with a border line value.

In conclusion, according the currently available data, there is a weak correlation

Table 5 Studies on molecular markers measured in 0-h biopsies (up to 2011)

Ref.	Pats	f/u	Findings/timing of biopsy-technology
Hoffmann <i>et al</i> ^[28] , 2002	24	1 h	IRI injury ass w increased adhesion, chemotaxis, apoptosis, monocyte recruitment/activation transcripts. Post-reperfusion/RT-PCR
Hauser <i>et al</i> ^[29] , 2004	36	1	Increased Communication, apoptosis, inflammation
Kainzet <i>al</i> ^[30] , 2004	10	1	DD kidneys distinctly different transcripts in the TI but not in the G compartment compared to LD. End of CIT/microarrays
Avihingsanon <i>et al</i> ^[31] , 2005	75	6	15 selected genes associated with outcomes, included DGF, REJ and 6 mofunction. Post-reperfusion/RT-PCR
Kainzet <i>al</i> ^[32] , 2007	31	12	Increased immunity, signal transduction, oxidative stress response associated with lower 1-year function
Park <i>et al</i> ^[33] , 2007	15	12	Increased inflammation and immune response at 1-year in uncomplicated grafts
Mas <i>et al</i> ^[34] , 2008	33	3	Increased immunity, inflammation and apoptosis genes associated with DGF. End of CIT/microarrays
Mueller <i>et al</i> ^[35] , 2008	87	12	Increased acute phase, complement, chemochines and reduced metabolism, transporters in DD versus LD, transcriptome identifies risk for DGF better than clinical ± histological markers. Post-reperfusion/ microarrays
Perco <i>et al</i> ^[36] , 2009	82	12	Increased immunity/ defense, communication, apoptosis in damaged kidneys, CADI score + clinic explained 14%, 3 biomarkers 28% of 1-year creatinine variability. End of CIT/ microarrays
Naesens <i>et al</i> ^[37] , 2009	28	36	Complement genes differ between LD and DD and are associated with early and late function. End of CIT and post-transplant/ microarrays
Bodonyi-Kovacs <i>et al</i> ^[38] , 2010	75	48	Pre-selected genes associated with 2-year graft function. Post-reperfusion/RT-PCR
Cravedi <i>et al</i> ^[39] , 2010	49	12	LDvs DD differ by inflammation, donor age and ITGB2 prognostic for 1-year function. Post-reperfusion/RT-PCR

f/u: Follow up in months; IRI: Ischemia-reperfusion injury; DD: Deceased donor; LD: Living donor; IGF: Immediate graft function; DGF: Delayed graft function; REJ: Rejection; CIT: Cold ischemia time; TI: Tubulointerstitial; G: Glomerular.

between perfusion parameters and graft outcomes and additional studies are needed.

FUTURE PERSPECTIVES AND EMERGING TECHNOLOGIES

All the scoring systems, either histological or clinical, need to be improved with the help of new tools. Indeed, several cited studies advocate for newest approach in the evaluation of donor kidneys. Nicleleit^[16] stated that new consensus guidelines remain to be defined on zero-time biopsies. Mueller *et al*^[25] highlighting the confounding variables, advocate for the use of omic technologies in the evaluation of kidney biopsies. This point is also highlighted by the Banff Pre-Implantation Biopsy Working Group^[56]. The usefulness of biomarkers in the evaluation of donor kidneys has also

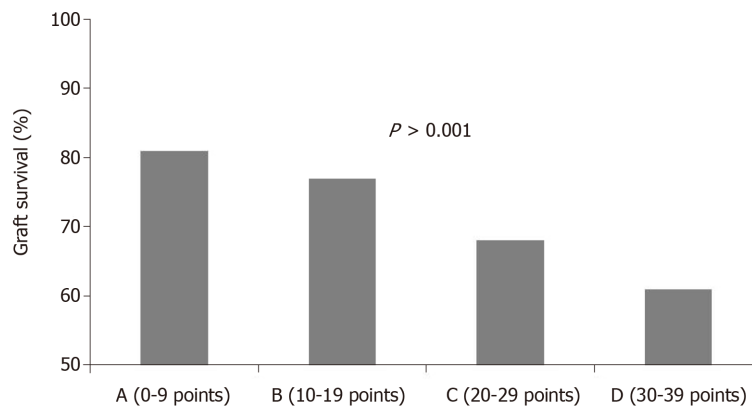


Figure 4 Grade of deceased donor kidney score significantly influenced graft survival at 6 years after transplantation.

been highlighted by another recent study^[90].

There are a number of emerging technologies to examine an organ at molecular level ranging from proteomics to metabolomics to transcription studies.

The most important study on proteomics is the study of Reese *et al*^[102] who examined the association between four different biomarkers and the post-transplant renal function. All the urine injury biomarkers strongly associated with donor AKI, but resulted of limited value in predicting DGF or early graft function

By using transcription analysis, Scian *et al*^[103] validated a set of three genes (*CCL5*, *CXCR4* and *ITGB2*) that was up regulated in kidneys with a low eGFR post-transplantation.

Gustafson *et al*^[104] still by transcription analysis found a set of 13 genes (Table 7) associated with allograft loss at two or three years after transplantation.

By metabolomics studies, Guy *et al*^[105] found in the perfusate of the hypothermic machine significant lower levels of gluconate, glucose, inosine and leucine in kidneys with DGF.

Finally, a novel technique able to recondition the kidney and to restore normal function prior to transplantation is the *ex vivo* normothermic perfusion. Phase I studies in ECD documented its safety and feasibility in clinical practice^[106].

Some studies are ongoing, but their results are to date unknown.

An important study aims to evaluate the relevance of molecular biomarkers of aging in the blood of donors. This study (Senesce Test) has been completed, but no results are available yet (NCT02335333)^[107]. Another NIH study coordinated by Yale University is testing biomarkers characteristic of renal injury in the urine of the donor and in the perfusion media (NCT01848249)^[108].

The PREDICTION study aims to evaluate the improvement in viability of marginal kidneys treated by pulsatile perfusion^[109].

CONCLUSION

The increase in the demand of kidneys for transplantation may only be satisfied with the increase in the use of marginal donors as kidneys from aged donors or with the use of donation after cardiac death donors.

Such kidneys need to be carefully evaluated either to be discarded or for a fair allocation.

The histological evaluation met several drawbacks as the time of the biopsy (pre or post reperfusion, the type of biopsy (wedge versus core biopsy), the pathologist involved in the evaluation (pathologist on-call or trained pathologist in this field).

Additionally, the difficulty of obtaining adequate histological analysis from pre implantation biopsies and the risk/benefit considerations to prolong cold ischemia time waiting for chronic histological abnormalities that often show poor correlation with clinical outcomes represents the most relevant drawback. All these drawbacks led to give more importance to the clinical evaluation of the donor. The KDRI/KDPI is an easily applicable scoring system, but this system also has its drawbacks especially in the evaluation of donors with the highest KDPI.

In the US, the use of KDPI led to a very high discard rate of the marginal donor kidneys, while other studies documented that several of these kidneys might be

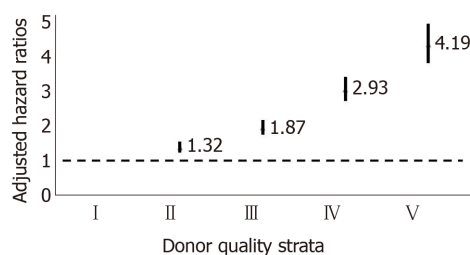


Figure 5 Multivariate estimates for graft loss by donor grade (Hazard ratio expressed as mean +/- confidence interval).

usefully transplanted.

Overall, is not easy to establish how many centers have taken part to the different scoring system as many of them are retrospective studies.

The elaboration of the Port scoring of standard criteria donors versus expanded criteria donors has been done comparing retrospectively 24756 SCD versus 4312 ECD from almost all the UNOS centers.

The MAPI has been done in a single center considering 371 transplants.

The Nyberg deceased donor score was made in three steps. In a first step 241 transplants were enrolled in two centers. Then in the attempt to give more strength to the scoring system, this was evaluated retrospectively on 34324 UNOS kidney transplants and in a third phase on 48952 UNOS kidney transplants.

The Donor risk score of Schold was evaluated retrospectively on 45850 data from SRTR.

The DGF nomogram of Irish was evaluated in a single center in UK on 217 prospective transplant patients.

Finally the KDRI of Rao was retrospectively evaluated on 69440 patients from SRTR. Subsequently the scoring was evaluated prospectively in different countries.

A hope for the future seems to come from the use of biomarkers. However, to date the use of urine biomarkers offers discordant results and does not provide sufficient power to be used in the kidney evaluation.

According recent studies, the use of pre-implantation biopsy has been shown to have its major utility in the evaluation of kidneys with a very high KDPI.

A very recent study from Moeckli *et al*^[110] helps in clarifying what's new in the current and emerging techniques of kidney evaluation. In particular the study concerns the use of omics and states that the most promising is transcriptome profile, also according the already cited studies.

Waiting for the advent of omics it seems that the best strategy in evaluating kidneys for transplantation is the clinical one. In the case of a very high KDRI pretransplant biopsy may be useful in allocating or not the kidneys

Table 6 Donor and transplant factors and corresponding hazard ratios for graft failure

	Hazard ratio	95%CI	P value
Donor parameter			
Age	1.013	1.011-1.015	< 0.0001
Afro American race	1.20	1.13-1.27	< 0.0001
Serum creatinine	1.25	1.17-1.23	< 0.0001
Hypertensive	1.13	1.08-1.19	< 0.0001
Diabetic	1.14	1.04-1.24	0.0040
Cause of Death	1.09	1.04-1.14	0.0002
Height	0.96	0.94-0.97	< 0.0001
Weight	0.98	0.97-0.99	0.0003
Donation after cardiac death	1.14	1.02-1.28	0.0246
HCV positive	1.27	1.13-1.43	< 0.0001
Transplant parameter			
HLA-DR mismatch	0.88	0.84-0.92	< 0.0001
Cold ischemia time	1.005	1.003-1.008	< 0.0001
En bloc transplant	0.70	0.57-0.84	0.0002
Double kidney transplant	0.86	0.75-1.00	0.0494

HLA:Human leukocyte antigen; HCV:Hepatitis C virus.

Table 7 Genes included in the study

ID	Symbol	Gene description	CADI-12 correlation	P value
3954887	CHCHD 10	Coiled-coil-helix-coiled-coil-helix domain containing 10	0.404	2.85×10^{-5}
4019160	KLHL 13	Kelch-like family member 13 (Drosophila)	0.369	1.49×10^{-4}
3326826	FJX1	Four jointed box 1 (Drosophila)	0.367	1.60×10^{-4}
3120343	MET	Met proto-oncogene (hepatocyte growth factor receptor)	0.352	3.01×10^{-4}
2864449	SERUNC5	Seine incorporator 5	0.318	0.0012
2567583	RNF149	Ring finger protein 149	0.280	0.0046
2879105	SPRY4	Sprout homolog 4 (Drosophila)	0.270	0.0062
3776504	TGIF1	TGFB-induced factor homeobox 1	0.244	0.0140
2898441	KAAG1	Kidney associated antigen 1	0.240	0.0154
3361971	ST5	Suppression of tumorigenicity 5	0.232	0.0197
2459352	WNT9A	Wingless-type MMTV integration site family member 9A	0.212	0.0332
3021696	ASB15	Ankrin repeat and SOCS box-containing 15	-0.263	0.0079
3193339	RXRA	Retinoid X receptor alpha	-0.300	0.0023

CADI-12: Chronic allograft damage index at 12 mo.

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Pancreatic transplantation: Brief review of the current evidence

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Abstract

Kidney transplantation is the treatment of choice for management of end-stage renal disease. However, in diabetic patients, the underlying metabolic disturbance will persist and even may get worse after isolated kidney transplantation. Pancreatic transplantation in humans was first introduced in 1966. The initial outcome was disappointing. However, this was changed after the improvement of surgical techniques together with better patient selection and the availability of potent and better-tolerated immune-suppression like cyclosporine and induction antibodies. Combined kidney and pancreas transplantation will not only solve the problem of organ failure, but it will also stabilise or even reverse the metabolic complications of diabetes. Combined kidney and pancreas transplantation have the best long term outcome in diabetic cases with renal failure. Nevertheless, at the cost of an initial increase in morbidity and risk of mortality. Other transplantation options include pancreas after kidney transplantation and islet cell transplantation. We aim by this work to explore various options which can be offered to a diabetic patient with advanced chronic kidney disease. Our work will provide a simplified, yet up-to-date information regarding the different management options for those diabetic chronic kidney failure patients.

Key words: Combined kidney pancreas transplantation; Renal transplantation; Diabetic kidney disease; Diabetes mellitus

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Core tip: Kidney transplantation is the treatment of choice for end-stage renal disease. Combined kidney-pancreas transplantation provides the patients with the highest long term survival. There are different surgical approaches for combined kidney-pancreas transplantation with recognised advantages and limitations of each technique. Islet cell transplantation is a minimally invasive treatment option but carries a risk of sensitisation to a wide range of human leukocyte antigen antigens.

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INTRODUCTION

Diabetes mellitus (DM) is the leading cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD) worldwide^[1]. Successful pancreas transplantation provides optimisation of glucose metabolism for diabetic patients^[2]. The current management options for diabetic patients with advanced CKD are summarised in [Figure 1](#).

Pancreas transplant alone (PTA) is another option for managing diabetic patients with normal renal function. Moreover, transplantation of the islets of Langerhans is a promising alternative to whole pancreas transplantation which can provide adequate glycemic control without exposing the recipient to major surgical interventions^[2].

DIABETIC ELIGIBILITY CRITERIA FOR TRANSPLANTATION

Diabetes is classified into two main subtypes, type 1 and type 2, based on the American Diabetes Association classification system. The discrimination between the two types of DM may be difficult in many cases^[3]. [Table 1](#) summaries the main characteristics of type 1 and type 2 DM in children and adolescents^[4].

Pancreas transplantation is offered primarily to type 1 diabetic CKD patients, an approach that was supported by the fact of absence of endogenous insulin and normal insulin sensitivity. However, some cases with insulin-dependent type 2 diabetes in the United States have been accepted on simultaneous pancreas-kidney (SPK) waiting list if their body mass index (BMI) is less than 30 kg/m², requiring insulin, but < 1.5 U/kg per day. About 6% only of SPK waiting list cases are type 2 DM^[2]. The plan for transplan-tation modality is simplified in [Figure 2](#).

MANAGEMENT OPTIONS FOR DIABETIC PATIENTS WITH ADVANCED CKD

In advanced CKD, Preemptive kidney transplantation from a living donor will offer the patient the highest patient survival rate at five years reaching up to 91% (compared to 84% for non-extended-criteria donor transplant, and 70% for extended-criteria donor transplants)^[5]. Nevertheless, this management option will not usually solve diabetes-related medical condition (as DM control may be impaired if steroids were used post kidney transplantation either as maintenance therapy or for treatment of rejection episodes)^[1,2].

In the United Kingdom, the national five-year patient survival is 88% for SPK recipients, and 78% for pancreas only transplant recipients. Pancreas allograft survival rate at five years is 75% for SPK recipients and 45% pancreas-only transplants^[6].

A retrospective analysis of long-term survival of 18549 patients with type 1 DM in the United States has demonstrated that the patient survival at eight years for SPK recipients was similar to living-donor kidney recipients (about 72%) while the survival for cadaveric kidney recipients was only 55%^[7]. SPK is associated with significantly elevated early mortality risk most probably secondary to the surgical procedure itself, and the related complications, which result in prolonged and recurrent hospitalisation is the first few months post-transplantation^[1,7]. On the other

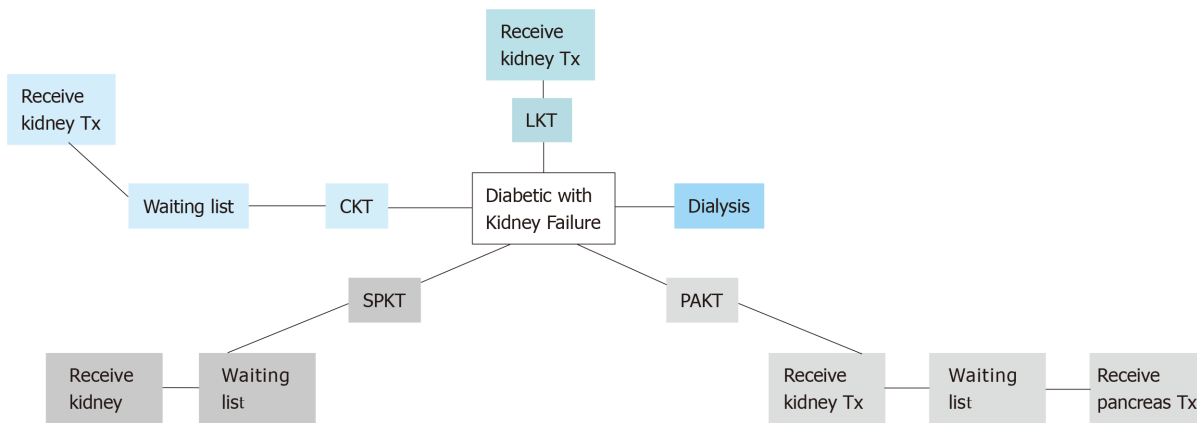


Figure 1 Options for diabetic patients with kidney failure. LKT: Living kidney transplantation. CKT: Deceased kidney transplantation; SPKT: Simultaneous pancreas and kidney transplantation; PAKT: Pancreas after kidney transplantation.

hand, the long-term outcome for SPK is better than any other transplantation option in diabetic patients^[1,7]. Recent data regarding kidney allograft survival with various types of kidney pancreas transplantation are summarized in [Table 2](#)^[8].

The kidney outcomes for pancreas after kidney (PAK) were from the time of pancreas transplant, which may explain the lower survival rates compared to those of SPK recipients^[8]. The maintenance of a functioning pancreas allograft was associated with the favourable long-term outcome with SPK most probably secondary to stabilisation or even improvement of most of the DM associated systemic complications as illustrated in [Table 3](#).

Data collected from 20,854 pancreas transplant recipients between 1996 and 2012 by the United Network for Organ Sharing (UNOS) was analysed for patient and graft survival^[16]. The best graft survival outcome was observed in recipient ranged between 40-49 years old. Additionally, the study documented an inverse relationship between recipient age and patient survival, with reduced patient survival in those who are older than 50 years^[16].

SURGICAL IMPLANTATION TECHNIQUES

In SPK operation, the kidney is usually transplanted into the left iliac fossa by the traditional approach using the iliac vessels for vascular anastomosis^[2]. There are several options for pancreatic implantation reflecting the fact that there is no standard optimal technique, each surgical option has its advantages as well as disadvantages. One of the challenges is the exocrine and endocrine drainage of the pancreatic allograft^[2]. The various pancreatic implantations techniques are simplified in [Figure 3](#)^[2,3,17,18], while the possible complications of pancreatic transplantation were summarized in [Table 4](#)^[19].

PRETRANSPLANT ASSESSMENT

The patient evaluation should follow the local protocol for transplant candidate. This includes detailed medical, surgical, and psychosocial history; a meticulous physical examination; and laboratory evaluation. However, the pretransplant workup should be very strict to identify any possible undiagnosed condition related to DM that will negatively affect the outcome. Particular attention should be given for assessing cardiovascular status and the presence of peripheral vascular disease^[20].

Pancreatic transplantation is associated with an increased risk of mortality in the early post-operative period, and the most frequent cause of death is of cardiovascular event^[20]. There is no universally standardised cardiovascular screening protocol for asymptomatic CKD patients^[21]. Some of the internationally published protocols are illustrated in [Figure 4](#)^[21].

The initial cardiac assessment could be suggested by myocardial perfusion imaging (MPI) together with exercise-based (+/- dobutamine) stress test, and results should be interpreted by an expert cardiologist^[21]. Myocardial perfusion studies provide valuable information regarding functional capacity, the extent of myocardial viability, and the extent of stress-induced ischemia as well as the degree of stress defect

Table 1 Comparison of criteria of type 1 and type 2 diabetes mellitus^[4]

	Type 1 diabetes	Type 2 diabetes
Prevalence	Common, increasing	Increasing
Age at presentation	Throughout childhood	Puberty
Onset	Typically, acute severe	Insidious to severe
Ketosis at onset	Common	5% to 10% ¹
Affected relative	5% to 10%	75% to 90%
Female: male	1:1	Approximately 2:1
Inheritance	Polygenic	Polygenic
HLA-DR3/4	Strong association	No association
Ethnicity	Most common in non- Hispanic white	All ²
Insulin secretion	Decreased/absent	Variable
Insulin sensitivity	Normal when controlled	Decreased
Insulin dependence	Permanent	Variable
Obese or overweight	20% to 25% overweight ³	> 80% obese
Acanthosis nigricans	12% ⁴	50% to 90% ⁴
Pancreatic antibodies	Yes ⁵	No ⁶

¹Reported frequency of ketonuria or ketoacidosis at time of diagnosis of type 2 diabetes mellitus (T2DM) varies widely.

²In North America, T2DM predominates in native America, African-American, Hispanic, Canadian First Nation, Pacific Islander, and Asian-American youth.

³With increased prevalence of childhood overweight, 20% to 25% of newly diagnosed with type 1 diabetes mellitus (T1DM) are overweight, which is higher than the prevalence of overweight in a similar population without T1DM. However, the prevalence of obesity is not increased among children and adolescents with T1DM. Recent weight loss is common at presentation of children with T1DM, including among those who are overweight or obese.

⁴These frequencies of acanthosis nigricans are based on a registry study in the United States. Populations with lower rates of obesity or difference ethnic mixes may have different results.

⁵Autoantibodies to insulin (IAA), islet cell cytoplasm (ICA), glutamic acid decarboxylase (GAD), tyrosine phosphatase (insulinoma associated) antibody (IA-2 and IA-2 β), or zinc channel antibody (ZnT8) are present at diagnosis in 85% to 89% of patients with T1DM.

⁶One study reported that 9.8% of youth with phenotypic T2DM have pancreatic antibodies to IA-2 and/or GAD. HLA: Human leukocyte antigen.

reversibility^[21]. Some studies demonstrated an increased risk of cardiovascular events among patients who fail to complete exercise stress test regardless of the presence of negative test results^[21].

The decisions regarding coronary catheterisation and revascularisation should be considered based on cardiologist recommendations. Patients with significant coronary pathology that is not amenable to revascularisation are not candidates for pancreatic transplantation^[20].

SUGGESTED POST-OPERATIVE FOLLOW UP PLAN

Following successful transplantation BTS recommends reviewing the recipients in clinic twice to three times per week for the first month, weekly visits for the next two months, monthly for another three months, then every 2-3 months later on^[22]. The clinic visit should include a detailed history of any new symptoms, careful medical examination and appropriate laboratory investigations (including immune-suppressant drug levels if possible). The patient care should involve a multidisciplinary team including a pharmacist, social worker, dietician, and psychologist^[22].

Meticulous pancreatic donor and recipient selection criteria together with the modern immune suppression protocols have steadily decreased the incidence of pancreatic rejection to range between 10% to 20% in the first year post-transplant^[2]. The majority of the early complications of the transplantation can be attributed to surgical and technical failures rather than an immunological injury. Complications include anastomotic leak, vascular thrombosis of the graft, graft pancreatitis, and infection^[2,23].

ACUTE REJECTION

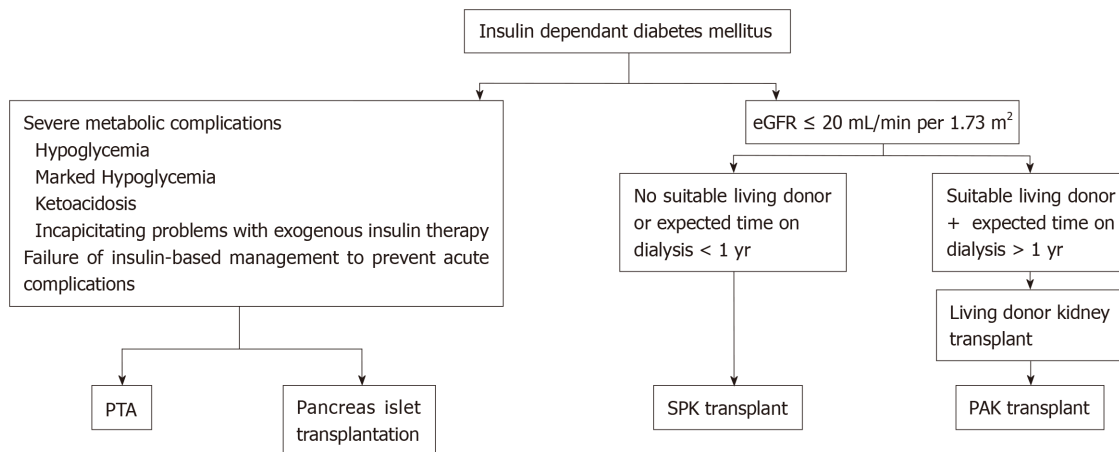


Figure 2 Algorithm for clinical decision making for diabetic patients. KTA: Kidney transplant alone; SPK: Simultaneous pancreas-kidney; PAK: Pancreas after kidney; PTA: Pancreas transplant alone.

Most cases of pancreas allograft rejection are asymptomatic, so we should keep a high index of suspicion to detect allograft rejection early enough to allow early initiation of the proper therapy. The islet cells are spared in the initial phase of rejection, and hyperglycaemia is a late finding^[2]. We should start our workup once allograft dysfunction is suspected (*e.g.*, elevated serum amylase and/or lipase)^[2,24]. A recommended approach for evaluation of pancreatic allograft dysfunction is illustrated in Figure 5^[24].

Maintenance immunosuppressive therapy for pancreatic transplantation is similar for that used for kidney transplantation. Most centres use a combination of a calcineurin inhibitor (predominantly tacrolimus), an antimetabolite (mycophenolate mofetil or mycophenolate sodium), and low-dose corticosteroids^[2,20]. Induction therapy with lymphocyte-depleting agents (*e.g.*, antithymocyte globulin and alemtuzumab) allows early steroid withdrawal and steroid free regimens which are adopted by some centres^[2].

ISLET CELL TRANSPLANTATION

Islet transplantation is an evolving and promising therapeutic option for management of type 1 DM. Successful isolation of islet cells from the whole pancreas is followed by infusion of the cells to the portal vein of the recipient via a percutaneous catheter as illustrated in Figure 6^[25].

Keeping in mind that the major mass of the pancreas is formed of exocrine gland with only scattered clusters of endocrine cells, separation of islet cells from exocrine part will not only allow transplantation via minimally invasive technique (infusion of islets isolated from cadaveric pancreas via the portal vein), but it will also avoid vascular and allograft duodenal anastomoses, hence avoiding an essential source of surgical complications^[2].

On the other hand, this therapeutic option is facing significant challenges that include: Achieving insulin independence necessitates transplantation of an adequate islet mass, which requires isolation from multiple donors (typically 2 to 4 donors), thus islet cell recipients are exposed to numerous human leukocyte antigen (HLA) mismatches which may jeopardize the possibility of future transplantation due to sensitization and formation of donor-specific antibodies^[2,23]; The patient would require lifelong immune suppression even if received islet cell transplantation alone^[2,23]; Despite the satisfactory short-term outcome of this technique (about 80% of the cases remained insulin independent after two years), the long-term outcome is still disappointing^[2]; In the case of advanced CKD in addition to DM, Islet cell transplantation alone is not a valid option in the management of such medical condition.

CONCLUSION

There is no individual management plan for diabetic patients with advanced CKD; instead, we have different management options that depend on the patient comorbidities as well as personal preferences. Nevertheless, each option has its

Table 2 Kidney transplant graft failure rates associated with simultaneous pancreas-kidney and pancreas after kidney^[8]

Type of the allograft	1 yr	5 yr	10 yr
SPK	3.1%	16.5%	37.7%
PAK (deceased donor)	3.3%	21.2%	51.2%
PAK (living donor)	3.0%	13.7%	37.0%

SPK: Simultaneous pancreas-kidney; PAK: Pancreas after kidney.

limitations and possible complications. The best management plan for diabetic patient approaching ESRD is SPK which will offer the best long-term survival, in addition to the better quality of life and regression of most of DM complications. However, this approach is associated with early increased risk of morbidity and mortality. PTA and islet cell transplantation are possible options for managing diabetic patients. However, they are not suitable alone for patients with concomitant advanced CKD. The pretransplant workup for SPK is more stringent compared to kidney transplantation alone to minimise the risk of early postoperative morbidity and mortality and to achieve long-term patient and graft survival. Islet cell transplantation carries the risk of sensitisation against a group of HLA antigens, which makes the patients less likely to get a compatible kidney allograft in the future. PAK is not recommended above the age of 50 as it is negatively affecting the survival of patients older than 50 years. Additionally, it may result in loss of kidney allograft as a complication of this major intervention.

Table 3 Sample of studies evaluating the effect of pancreatic transplantation on the complications of diabetes mellitus

Ref.	Patient cohorts	Outcomes of interest	Time after transplant (yr)	Results
Cardiovascular disease				
Fiorina <i>et al</i> ^[9] , 2000	SPK (<i>n</i> = 42) <i>vs</i> KTA (<i>n</i> = 26) <i>vs</i> type 1 diabetes (<i>n</i> = 20)	Left ventricular systolic and diastolic function assessed by radionuclideventriculography	4 yr	Left ventricular ejection fraction was higher in SPK recipients than in KTA recipients [75.7 (SD 1.8%) <i>vs</i> 65.3% (2.8%); <i>P</i> = 0.02] and type 1 diabetes controls (75.7 (1.8%) <i>vs</i> 61.2 (3.7%); <i>P</i> = 0.004).
Biesenbach <i>et al</i> ^[10] , 2005	SPK (<i>n</i> = 12) <i>vs</i> KTA (<i>n</i> = 10)	Composite endpoint of myocardial infarction, stroke, and amputation	10 yr	Lower incidence of myocardial infarction (16% <i>vs</i> 50%), stroke (16% <i>vs</i> 40%), and amputations (16% <i>vs</i> 30%) in SPK <i>vs</i> KTA recipients (<i>P</i> < 0.05 for composite endpoint of all three events)
Diabetic nephropathy				
Fioretto <i>et al</i> ^[11] , 1998	PTA: Pre-transplant <i>vs</i> post-transplant (<i>n</i> = 8)	Native kidney biopsy: structural morphology before and after transplant	10 yr	Improvement in glomerular basement membrane thickening, tubular basement membrane thickening, and mesangial expansion after transplantation compared with before
Boggi <i>et al</i> ^[12] , 2011	PTA: Pre-transplant <i>vs</i> post-transplant (<i>n</i> = 71)	Proteinuria and estimated GFR (eGFR)	Up to 4 yr	Overall, proteinuria decreased from 1.36 (SD 2.72) g/d pre-transplant to 0.29 (0.51) g/d post-transplant (<i>P</i> < 0.01) eGFR decreased by about 20% from 94 (39) mL/min per 1.73m ² to 75 (22) mL/min per 1.73 m ² (<i>P</i> < 0.01)
Diabetic neuropathy				
Havrdova <i>et al</i> ^[13] , 2016	SPK: Pre-transplant <i>vs</i> post-transplant (<i>n</i> = 12)	Epidermal nerve fiber density on skin biopsy, autonomic function tests, and nerve conduction studies	Up to 8 yr	No improvement in epidermal nerve fiber density or functional deficits on autonomic function tests
Boggi <i>et al</i> ^[12] , 2011	PTA: Pre-transplant <i>vs</i> post-transplant (<i>n</i> = 71)	Clinical neurologic examination (vibration threshold), nerve conduction studies, and autonomic function tests (lying-to-standing test)	Up to 4 yr	Significant improvement in mean vibration thresholds, nerve conduction studies, and autonomic function tests after PTA compared with before
Diabetic retinopathy				
Boggi <i>et al</i> ^[12] , 2011	PTA: Pre-transplant <i>vs</i> post-transplant (<i>n</i> = 71)	Visual acuity scores and fundoscopic examination	Up to 4 yr	Before transplantation, 7.5% of patients had no retinopathy and remained lesion-free at 4 yr. Of the 29.5% with non-proliferative retinopathy, 75% improved and 25% remained unchanged. In the remainder with proliferative retinopathy, lesions remained stable in 82% and progressed in 18%

Giannarelli <i>et al</i> ^[14] , 2006	PTA (<i>n</i> = 33) <i>vs</i> type 1 diabetes (<i>n</i> = 35)	Visual acuity scores, fundoscopic examination, and angiography in selected cases	Up to 30 mo	Before transplant, 9% of patients with PTA and 6% of those with type1 diabetes had no retinopathy, 24% and 29% had non-proliferative retinopathy, and 67% and 66% had proliferative retinopathy. Overall, the percentage of patients with improved or stabilized retinopathy was significantly higher in the PTA group (<i>P</i> < 0.01)
Koznarova <i>et al</i> ^[15] , 2000	SPK (<i>n</i> = 43) <i>Vs</i> KTA (<i>n</i> = 45)	Visual acuity scores and fundoscopic examination	3 yr	In the SPK group, fundoscopic findings at the end of follow-up had improved, stabilized, or deteriorated in 21.3%, 61.7%, and 17.0%, respectively. In the KTA group these figures were 6.1 %, 48.8%, and 45.1% (<i>P</i> < 0.001)

KTA: Kidney transplant alone; SPK: Simultaneous pancreas-kidney; PAK: Pancreas after kidney.

Table 4 Complications of pancreatic transplantation^[19]

Complications		
Early complications		
Allograft parenchymal complications		Acute pancreatitis
		Necrotizing pancreatitis
		Fistulous tracts
Infection and abscesses		
Enteric complications		Anastomosis leakage at duodeno-enterostomy
		Ileus Colonic infection.
Vascular complications		Venous or arterial graft thrombosis
		Acute bleeding
Late complications		
Allograft parenchymal complications		Rejection
		Pseudocyst formation
		Post-transplant lymphoproliferative disease
Enteric complications		Small bowel obstruction
		Colonic infection
Vascular complications		Arterial or venous pseudoaneurysms

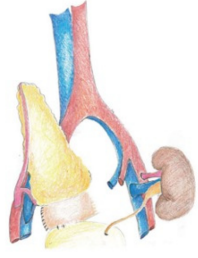
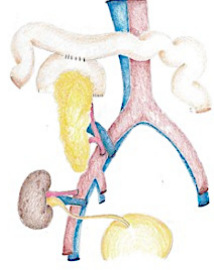
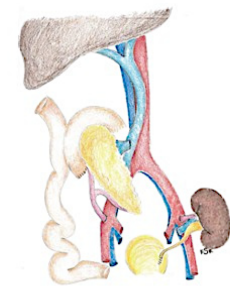
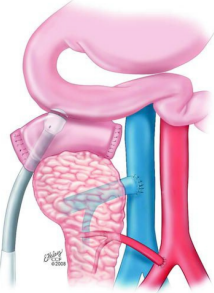
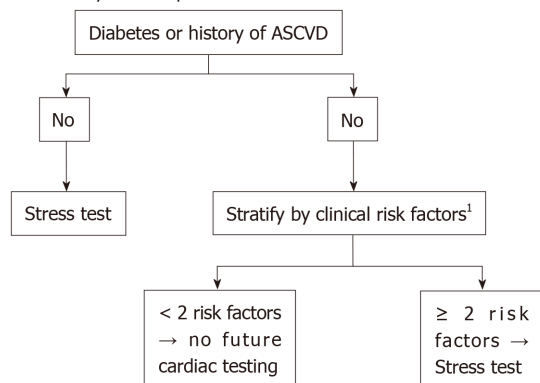
Procedure	Advantages	Disadvantages
Bladder exocrine drainage and systemic venous endocrine drainage ^[17] 	Pancreatic dysfunction can be detected early by changes of urinary amylase Easily accessible for biopsy Reduced rate of infection due to the relative sterility of the lower urinary tract Technical considerations (Bladder vasculature promote healing, bladder mobilisation permits tension-free, multi-layer anastomosis, Control of anastomotic leakage can be achieved by bladder catheter)	Fluid and electrolyte imbalance Metabolic acidosis Urologic complications (cystitis, haematuria, urethritis, balanitis and urethral stricture) Lower urinary tract infection and stone formation Reflux pancreatitis Enteric conversion if indicated will expose the patient to another major surgery
Enteric exocrine drainage and systemic venous endocrine drainage ^[17] 	More physiologic approach Avoid urologic complications Avoid the future risk of enteric conversion	Higher incidence of pancreatitis, leakage of pancreatic enzymes, and peripancreatic fluid collections More risk of anastomotic leakage, peritonitis, intra-abdominal collection and sepsis Inability to measure exocrine secretions for early detection of graft dysfunction Allograft biopsy is more challenging Occasional need for diverting Roux en y limb
Enteric exocrine drainage and portal venous endocrine drainage ^[17] 	Same advantages mentioned above in addition to: Avoid the risk of postprandial hypoglycaemia Better lipoprotein metabolism	Same points as mentioned above in addition to: Higher risk of vascular thrombosis
Duodenal exocrine drainage and systemic venous endocrine drainage ^[18] 	A modification of enteric exocrine drainage with systemic venous endocrine drainage with additional benefits in the form of: Improved accessibility for biopsy via endoscopy ^[3,16] It expands the options for exocrine drainage sites, especially in cases of pancreas retransplantation ^[16]	Same disadvantages mentioned above with enteric exocrine drainage and systemic venous endocrine drainage except for relatively easily accessible allograft

Figure 3 Various pancreatic implantation techniques.

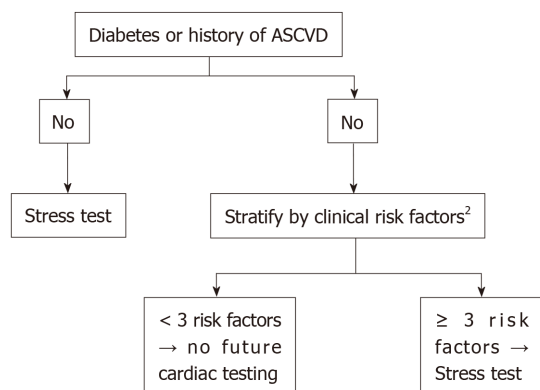
KDOQI

All should undergo cardiac testing

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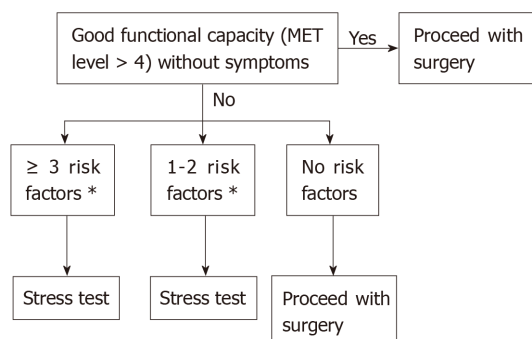
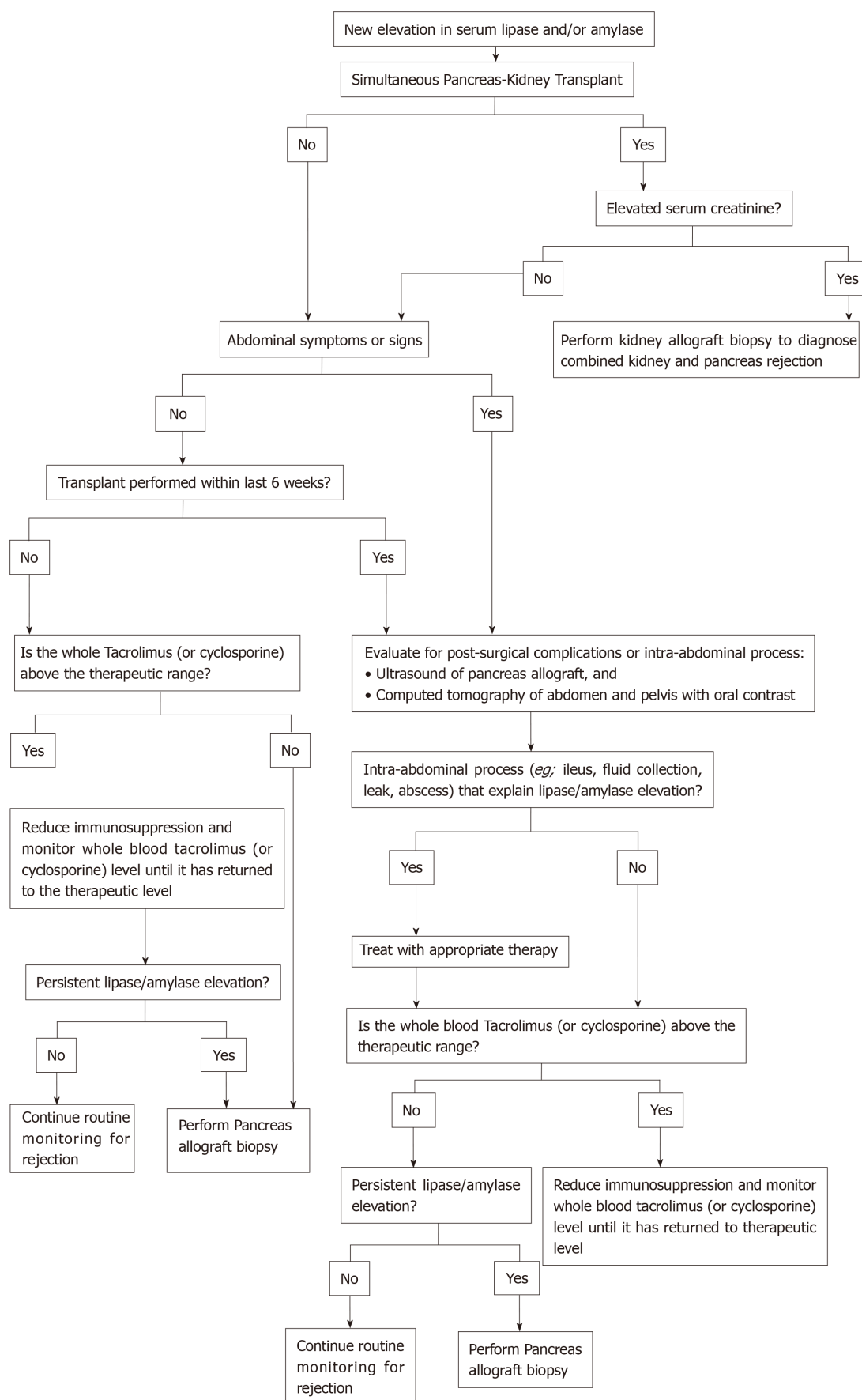


Figure 4 Outlines of preoperative cardiac risk assessment guidelines.¹Hypertension, age (> 45 for men or > 55 for women), cigarette smoking, left ventricular hypertrophy, dyslipidemia, family history of coronary disease. ²Hypertension, left ventricular hypertrophy, dyslipidemia, age > 60, > one year on dialysis. ³Ischemic heart disease, cerebrovascular disease, renal insufficiency, diabetes. KDOQI: Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines; AST: American Society of Transplantation; Lisbon: Report of the Lisbon Conference on the Care of the Kidney Transplant Recipient; ACC/AHA: American College of Cardiology/American Heart Association.

Figure 5 Algorithm for evaluation of pancreatic allograft dysfunction^[24].

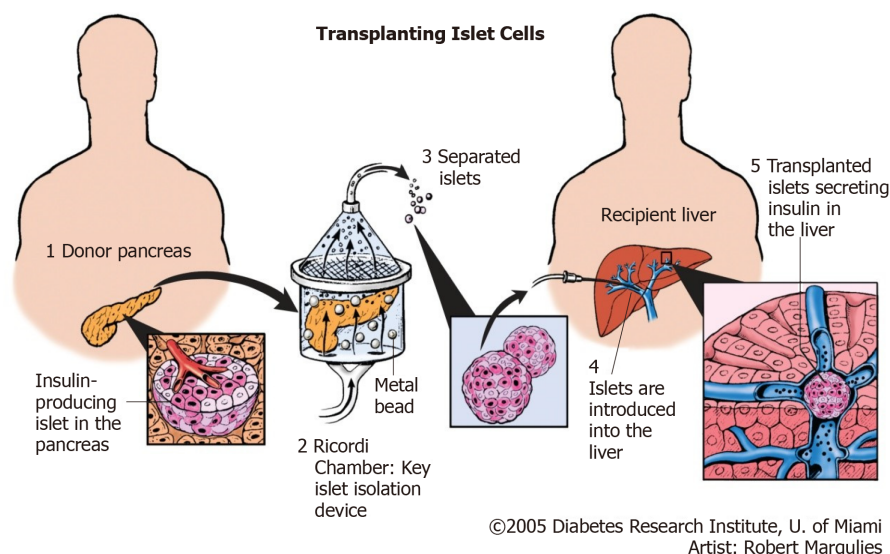


Figure 6 Principles of islet cell transplantation^[25].

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