**Name of Journal:** *World Journal of Transplantation*

**Manuscript NO:** 61088

**Manuscript Type:** ORIGINAL ARTICLE

***Retrospective Cohort Study***

**Perioperative risk factors associated with delayed graft function following deceased donor kidney transplantation: A retrospective, single center study**

Mendez NV *et al*. Delayed graft function after kidney transplantation

Nicholas V Mendez, Yehuda Raveh, Joshua J Livingstone, Gaetano Ciancio, Giselle Guerra, George W Burke III, Vadim B Shatz, Fouad G Souki, Linda J Chen, Mahmoud Morsi, Jose M Figueiro, Tony M Ibrahim, Werviston L DeFaria, Ramona Nicolau-Raducu

**Nicholas V Mendez, Yehuda Raveh, Joshua J Livingstone, Vadim B Shatz, Fouad G Souki, Ramona Nicolau-Raducu,** Department of Anesthesiology, University of Miami/Jackson Memorial Hospital, Miami, FL 33136, United States

**Gaetano Ciancio, George W Burke III, Linda J Chen, Mahmoud Morsi, Jose M Figueiro, Tony M Ibrahim, Werviston L DeFaria,** Department of Surgery, Miami Transplant Institute/University of Miami/Jackson Memorial Hospital, Miami, FL 33136, United States

**Giselle Guerra,** Division of Nephrology of the Department of Medicine, University of Miami/Jackson Memorial Hospital, Miami, FL 33136, United States

**Author contributions:** Mendez NV designed research/study, wrote the paper; Raveh Y designed research/study, analyzed data, wrote the paper; Livingstone JJ designed research/study, wrote the paper; Souki FG, Shatz VB, Ciancio G, Burke III GW, Chen LJ, Morsi M, Figueiro JM, Ibrahim TM and DeFaria WL collected data; Guerra G collected data, analyzed data; Nicolau-Raducu R collected data, analyzed data, wrote the paper.

**Corresponding author: Ramona Nicolau-Raducu, MD, PhD, Associate Professor,** Department of Anesthesiology, University of Miami/Jackson Memorial Hospital, 1611 NW 12th Avenue, Miami, FL 33136, United States. rxn256@miami.edu

**Received:** November 23, 2020

**Revised:** February 5, 2021

**Accepted:** March 10, 2021

**Published online:**

**Abstract**

BACKGROUND

There is an abundant need to increase the availability of deceased donor kidney transplantation (DDKT) to address the high incidence of kidney failure. Challenges exist in the utilization of higher risk donor organs into what appears to be increasingly complex recipients; thus the identification of modifiable risk factors associated with poor outcomes is paramount.

AIM

To identify risk factors associated with delayed graft function (DGF).

METHODS

Consecutive adults undergoing DDKT between January 2016 and July 2017 were identified with a study population of 294 patients. The primary outcome was the occurrence of DGF.

RESULTS

The incidence of DGF was 27%. Under logistic regression, eight independent risk factors for DGF were identified including recipient body mass index ≥ 30 kg/m2, baseline mean arterial pressure < 110 mmHg, intraoperative phenylephrine administration, cold storage time ≥ 16 h, donation after cardiac death, donor history of coronary artery disease, donor terminal creatinine ≥ 1.9 mg/dL, and a hypothermic machine perfusion (HMP) pump resistance ≥ 0.23 mmHg/mL/min.

CONCLUSION

We delineate the association between DGF and recipient characteristics of pre-induction mean arterial pressure below 110 mmHg, metabolic syndrome, donor-specific risk factors, HMP pump parameters, and intraoperative use of phenylephrine.

**Key Words:** Delayed graft function; Outcome; Kidney transplant; Risk factors; Phenylephrine; Mean arterial pressure

Mendez NV, Raveh Y, Livingstone JJ, Ciancio G, Guerra G, Burke III GW, Shatz VB, Souki FG, Chen LJ, Morsi M, Figueiro JM, Ibrahim TM, DeFaria WL, Nicolau-Raducu R. Perioperative risk factors associated with delayed graft function following deceased donor kidney transplantation: A retrospective, single center study. *World J Transplant* 2021; In press

**Core Tip:** There is an abundant need to increase the availability of deceased donor kidney transplantation to address the high incidence of kidney failure. Challenges exist in the utilization of higher risk donor organs into what appears to be increasingly complex recipients; thus the identification of modifiable risk factors associated with poor outcomes is paramount. We delineate the association between delayed graft function and recipient characteristics of pre-induction mean arterial pressure below 110 mmHg, metabolic syndrome, donor-specific risk factors, hypothermic machine perfusion pump parameters, and intraoperative use of phenylephrine.

**INTRODUCTION**

Chronic kidney disease and end stage renal disease are leading contributors to patient morbidity, mortality, and economic burden[1,2]. Kidney transplantation is the therapy of choice, with superior survival and improved quality of life over dialysis[3,4]. Regrettably, in the United States alone nearly 5000 patients perish each year while on the wait-list due to organ shortage[5]. A common strategy to minimize the ever-increasing gap between organ supply and demand is *via* expansion of criteria for acceptable donors[6,7]. These higher-risk kidney allografts, however, frequently exhibit delayed graft function (DGF), which in turn is associated with acute rejection, chronic allograft nephropathy, shorter allograft survival, and increased costs[8-10]. A clear need exists for the identification and optimization of modifiable perioperative risk factors associated with DGF[11]. Prior studies have pointed to an association between recipients’ blood pressure and DGF, but conflicted on the clinical setting in which it contributes to DGF[12-15].

The aim of this analysis is to identify risk factors associated with DGF, with a particular focus on perioperative hemodynamic factors, since these can be more readily optimized to improve graft and patient outcomes.

**MATERIALS AND METHODS**

After approval by the institutional review board, all consecutive adult (age ≥ 18 years) patients who underwent a deceased donor kidney transplant (DDKT) at our center between January 2016 and July 2017 were identified. Recipients of multi-organ allografts were excluded, and the medical records of the remaining 313 patients were retrospectively reviewed. Recipients of *en-bloc* two kidney allografts (2 cases), or for whom hypothermic machine perfusion (HMP) pump data was not available (17 cases) were subsequently excluded, resulting in a final study population of 294 patients. The requirement for informed consent was waived by the institutional review board.

All recipients’ demographic, comorbidities, preoperative medications, and echocardiographic data within one year prior to transplant, as well as laboratory evaluation upon admission and intraoperative data were recorded. Donor data and kidney donor profile index (KDPI) were extracted from the United Network for Organ Sharing DonorNet® database. All donor kidneys were biopsied at our transplant center and placed on hypothermic machine perfusion (HMP) pumps using a DCM-100 Cassette (RM3 Renal Preservation Machine, Waters Instruments, Rochester, MN), and perfused with Belzer-MPS Machine Perfusion Solution (Trans-Med Corporation, Elk River, MN) at 4 °C, as previously described[16]. A HMP pump resistance upper limit index of 0.3 mmHg/mL/min is used at our center and as such no allografts transplanted in this study had a terminal resistance value above this cutoff.

***Study variables definition***

Cold storage time: time from donor cross-clamp until the allograft was placed on the HMP pump[17]. Total cold ischemia time: time from donor cross-clamp until the allograft was taken out of ice and placed on the surgical field, inclusive of time spent on the HMP pump. Total warm ischemia time: time from when the kidney was taken out of ice until reperfusion. HMP pump parameters are reported as terminal values at the time the kidney was removed from pump. Blood pressures measured at baseline (i.e before induction of general anesthesia), 5 min and 30 min post-reperfusion, and immediately upon arrival to either the post-anesthesia care unit (PACU) or the intensive care unit were extracted from the anesthesia record. Hypotension was defined as a decrease in mean arterial pressure (MAP) of ≥ 30 mmHg from baseline[18]. Diagnosis of postoperative pulmonary edema was based on radiographic evidence of pulmonary edema as determined by a board-certified radiologist coupled with clinical symptomatology requiring supplemental oxygen or mechanical ventilation. A postoperative adverse cardiac event was defined as the occurrence of myocardial infarction, new-onset atrial or ventricular arrhythmia, or cardiac arrest within the firstpostoperative month. Perioperative surgical complications were evaluated using the Clavien-Dindo classification grading system[19]. Occurrence of DGF, the primary study outcome, was defined as the need for dialysis within seven days after transplantation as determined by the attending transplant nephrologist[20,21]. Graft function was evaluated at one week and six months post-transplant using the estimated glomerular filtration rate (eGFR) by the Chronic Kidney Disease Epidemiology Collaboration equation[22]. Graft failure was defined as either a permanent need for dialysis or death with a functioning graft and was evaluated from the time of transplant until one year after transplantation[16].

***Intraoperative protocol***

All patients underwent ABO-compatible DDKTs under general endotracheal anesthesia with radial arterial line for hemodynamic monitoring placed after induction of general anesthesia. Our local protocol targeted a MAP ≥ 100 mmHg starting at the time of reperfusion of allograft until arrival to the postoperative unit. This hemodynamic goal was primarily achieved with crystalloid and/or colloid, reserving ephedrine or phenylephrine bolus administration for severe or refractory hypotension (MAP ≤ 65 mmHg and/or decrease in MAP of ≥ 30 mmHg from baseline) at the discretion of the anesthesia provider. Dopamine infusion was always used whenever prolonged vasopressor support was indicated. As per local protocol, all recipients received intravenous (iv) furosemide 50 mg and mannitol 12.5 g 10 min prior to, as well as 10 min after reperfusion. In recipients of a high-risk allograft, as deemed by the transplant surgeon, a furosemide infusion of 20 mg/h was initiated shortly after the second 50mg bolus dose and continued in the postoperative unit. All patients received induction immunosuppression with three immunosuppressive agents each: iv basiliximab (20 mg, 2 doses), rabbit antithymocyte globulin (1 mg/kg daily, 3 doses), and methylprednisolone (500 mg, 3 doses)[23].

Intraoperative iv heparin was selectively administered to recipients deemed high risk for graft thrombosis by the transplant surgeon. Accordingly, seven patients received intraoperative IV bolus heparin with doses ranging between 1000-3000 units. Routine postoperative thromboprophylaxis consisted of heparin 5000 units subcutaneously twice daily. Surgical drains and ureteral stents were placed at surgeon discretion and not routinely utilized.

***Statistical analysis***

Categorical variables were expressed as percentages (%) and differences between the groups were assessed with chi-square or Fisher’s exact test when appropriate. Continuous variables were expressed as median and interquartile ranges (25%-75%) and differences between the groups assessed with Wilcoxon rank-sum test. A bivariate analysis was performed to compare the groups with and without DGF regarding recipients’, donors’ and HMP pump variables, including recipient BMI, baseline MAP, donor terminal creatinine, cold ischemia time, cold storage time, and HMP pump flow rate and resistance. We subsequently determined the cut-off values for statistically significant continuous variables, using receiver operating characteristic analysis and Youden index[24]. A logistic regression model was then built for the cohort using a stepwise personality with a stopping rule P-value threshold of 0.10 for probability to enter or leave, conducted in a mixed direction, was performed to identify recipient, donor, HMP pump, and intraoperative predictors statistically associated with DGF. Clinically significant factors from Tables 1-3 were included as covariates to adjust for cofounders. Odds ratios (OR) and 95%CI were calculated. C-index was used to calculate the strength of the associations. The bootstrap method for 2500 iterations yielded bias-corrected C-index and 95%CI for the regression coefficients of the model[25]. Misclassification rates calculated the proportion of observations allocated to the incorrect group and represent the false-positive rate. Predictor’s profiler and predictor’s importance was explored for main and total effect. Main effect is the importance index that reflects the relative contribution of that factor alone and total effect is the importance index that reflects the relative contribution of that factor both alone and in combination with other factors[26]. Cochran-Armitage trend test was used to assess the association between a cut-off value of baseline MAP and intraoperative phenylephrine[27]. The statistical software used for all study calculations was JMP Pro 14.0 (SAS Institute Inc., Cary, NC, United States).

**RESULTS**

The incidence of the primary outcome DGF was 27% (79/294).

***Preoperative***

A descriptive analysis of preoperative clinical characteristics, stratified by DGF *vs* non-DGF, is shown in Table 1. Comorbidities associated with metabolic syndrome were more common in recipients with DGF when compared to non-DGF, including obesity with BMI ≥ 30 kg/m2 [47% (37/79) *vs* 28% (60/215) respectively, OR 2.3, 95%CI: 1.335-3.878, *χ*2 = 9.4, *P* = 0.002], diabetes [53% (42/79) *vs* 31% (66/215) respectively, OR 2.6, 95%CI: 1.510-4.347, χ2 = 12.5, *P* = 0.001], dyslipidemia [72% (57/79) *vs* 47% (102/215) respectively, OR 2.9, 95%CI: 1.639-5.025, *χ*2 = 14.2, *P* = 0.001], and coronary artery disease (CAD) [35% (28/79) *vs* 18% (39/215) respectively, OR 2.5, 95%CI: 1.391-4.411, *χ*2 = 9.8, *P* = 0.002]. Dialysis-associated hypotension requiring oral vasopressor therapy with midodrine was recorded in 3% (8/294) of recipients with similar incidences in DGF and non-DGF groups [3% (2/79) *vs* 3% (6/215) respectively, OR 0.90, 95%CI: 0.178-4.578, *χ*2 = 0.02, *P* = 0.90].

***Intraoperative fluid and hemodynamic management***

A descriptive analysis of intraoperative clinical characteristics, stratified by DGF *vs* non-DGF, is presented in Table 2. Administered crystalloids (type and volume), albumin, and blood products were similar in recipients with or without DGF. A clinically insignificant increase in estimated blood loss was observed in DGF recipients [150 *vs* 100 mL in non-DGF, *χ*2 = 6.5; *P* = 0.01].

In a majority of recipients (70%, 206/294) the baseline MAP was ≥ 100 mmHg. Both baseline and first postoperative MAPs were slightly lower in the DGF group compared to non-DGF [107 mmHg *vs* 112 mmHg respectively, *χ*2 = 3.1, *P* = 0.08 and 102 *vs* 105 respectively, *χ*2 = 2.9, *P* = 0.09]. A cut-off baseline MAP < 110 mmHg was statistically associated with DGF (*χ*2 = 4.6, *P* = 0.02; OR 1.8, 95%CI: 1.049-3.047]. MAPs at 5- and 30-min post-reperfusion were similar in DGF and non-DGF recipients. The targeted post-reperfusion MAP (≥ 100 mmHg) was achieved in only nearly 25% of recipients at 5 min (74/294) and 30 min (75/294) post reperfusion, and in 60% of patients (177/294) on arrival to the postoperative unit (Table 2), but similarly in recipients with or without DGF. Likewise, incidences of hypotension, with a decrease from baseline values in MAP ≥ 30 mmHg, at 5-min [24% (18/79) *vs* 26% (56/215) respectively, OR 0.83, 95%CI: 0.453-1.528, *χ*2 = 0.35, *P* = 0.55] and on arrival to the postoperative unit [9% (7/79) *vs* 9% (20/215) respectively, OR 0.94, 95%CI: 0.383-2.324, *χ*2 = 0.02, *P* = 0.90] were similar between DGF and non-DGF recipients. However, hypotension at 30 min post-reperfusion occurred more commonly in the non-DGF group 27% (57/215) *vs* 16% (13/79) in DGF group, but did not reach statistical significance (*χ*2 = 3.2; *P* = 0.07).

Phenylephrine boluses were administered to 22% (64/294) of the cohort, and were statistically associated with DGF, insofar as 32% (25/79) of recipients with DGF received phenylephrine vs 18% (39/215) in recipients who did not develop DGF (OR 2.1, 95%CI: 1.161-3.759, *χ*2 = 6.2; *P* = 0.01). An association between baseline MAP < 110 mmHg and intraoperative phenylephrine therapy was found in the Cochran-Armitage trend test (*Z* = 2.33, *P* = 0.02). Additionally, compared with untreated recipients, phenylephrine-treated recipients had lower MAPs at 5-min and 30-min post-reperfusion, and upon arrival to the PACU [103 *vs* 112 mmHg, *χ*2 = 7.9, *P* = 0.005; 87 mmHg *vs* 91 mmHg, *χ*2 = 4.1, *P* = 0.04; 87 mmHg *vs* 92 mmHg, *χ*2 = 8.2, *P* = 0.01; and 97 mmHg *vs* 106 mmHg, *χ*2 = 15.5; *P* < 0.001, respectively]. In 70 recipients (24%), the MAP 30 min post reperfusion was lower than baseline by more than 30 mmHg; 16 and 54 thereof were treated and not treated with phenylephrine, respectively. DGF occurred in 7 of the 16 (44%) and in 6 of the 54 (11%), respectively [OR 6.2, 95%CI: 1.691-22.882; *χ*2 =8.7; *P* = 0.0032]. Of the 224 recipient without a similar decrease from baseline in MAP measured 30 min post reperfusion, 48 and 176 were treated and not treated with phenylephrine, respectively; DGF occurred in 18 of the 48 (38%) and 48 of the 176 (27%), respectively [OR 1.6, 95%CI: 0.810-3.109; *χ*2 =1.8; *P* = 0.18].

***Donor data***

A descriptive analysis of donor and HMP pump data for recipients who did and did not develop DGF is presented in Table 3. Nearly half (46%) of kidney allografts used in our center were imports. A higher KDPI was recorded for imported *vs* local allografts [median 69% (42-86) *vs* 47% (23-68) respectively, *χ*2 = 22, *P* = 0.001]. Cold ischemia and cold storage times were significantly longer in DGF *vs* non-DGF allografts, [30.6 h *vs* 26.4 h (*χ*2 = 6.9; *P* =0.009); and 18.4 h *vs* 9.6 h (*χ*2 = 9.9; *P* =0.002), respectively]. Similarly, HMP flows < 150 mL/min and resistance ≥ 0.23 mmHg/mL/min were recorded for allografts that developed DGF, see Table 3.

***Postoperative and outcome data***

A descriptive analysis of postoperative characteristics in DGF and non-DGF recipients is presented in Table 4. Based on the Clavien-Dindo classification, the overall surgical complication rate in the first month postoperatively was 19% (56/294), with a higher rate in recipients with DGF than in non-DGF recipients [32% (25/79) *vs* 14% (31/215) respectively, OR 2.7, 95%CI: 1.496-5.047; *χ*2 = 11; *P* = 0.002]. Moreover, compared to non-DGF allografts, DGF was associated with significantly lower eGFR after six postoperative months, and higher incidence of 1-year graft failure [50.6 mL/min *vs* 73.3 mL/min (*χ*2 = 31.8; *P* = 0.001), and 10% *vs* 1% (OR 8, 95%CI: 2.056-30.832, *χ*2 = 12.2; *P* = 0.002), respectively]. The overall incidence of allograft failure at one year was 4% (11/294). Etiologies of graft failure were: (4) rejection, (4) thrombosis within 1st post-transplant week, (1) chronic allograft nephropathy, and (2) deaths with a functioning graft (1 sepsis, and 1 cardiac event).

Employing logistic regression, eight risk factors for DGF were identified (see Table 5): recipient BMI ≥ 30 kg/m2,; baseline MAP < 110 mmHg, intraoperative phenylephrine administration; cold storage time ≥ 16 h; donation after cardiac death, donor history of CAD, donor terminal creatinine ≥ 1.9 mg/dL, and HMP pump resistance ≥ 0.23 mmHg/mL/min. Supplementary Table 1 delineates the eight predictors in order of importance. The whole model was statistically significant in its entirety (*χ*2 = 87, *P* = 0.001), and a C-index of 0.83 was calculated for these risk factors with a bias-corrected C-index of 0.84 (95%CI: 0.76-0.88). The model’s calculated misclassification rate of 19% reflects its ability to accurately predict DGF in 81 of 100 recipients.

**DISCUSSION**

Higher-risk donor allografts provide a way to increase the deceased-donor kidney transplant pool, but have been associated with DGF. In our cohort, the incidence of DGF was 27%, which is consistent with the previously reported incidence[13,28-30]. Optimization of modifiable perioperative risk factors for the development of DGF would allow for improved transplantation outcomes, particularly improved early graft function, without shrinking the donor pool. The important role of intraoperative renal blood flow on early postoperative renal function has been known since the 1970’s[31,32], and intraoperative hemodynamic variables are the focus of several recent outcome studies[12-15].

A novel finding of this study is the identification of pre-induction MAP < 110 mmHg as an independent risk factor for the development of DGF. This observation underscores the need of the newly grafted kidney for optimal perfusion pressure that is higher than the traditional normal[33]. A complex interaction between donor’s and recipient’s comorbidities, pre-procurement ischemia, procurement and organ storage conditions, along with peri-transplant factors result in such a unique perfusion requirement of the allograft[10]. Suboptimal blood pressure has previously been explored as a potential risk factor in the development of DGF. Thomas *et al*[13] reported that half of the patients in their study with a post-reperfusion systolic BP of less than 120 mmHg experienced DGF. More recent data showed that patients with a MAP of < 80 mmHg at the time of reperfusion were 2.4 times more likely to develop DGF[12].

The optimal intraoperative hemodynamic management of recipients of renal allografts remains controversial. Since several studies reported a reduced incidence of DGF with fluid loading[14,34,35], in this study we carefully evaluated outcomes in relation to crystalloid volume, weight-based crystalloid administration, crystalloid type, colloid volume, and colloid type. Our finding of a lack of an association between fluids administered and DGF is in accord with others[12,36,37], and a recent multicenter study[38].

Vasopressors may be indicated when volume loading is insufficient to obtain optimal allograft perfusion. Reported outcomes of perioperative vasopressor use in kidney transplant are incongruous. Day *et al*[39] suggested that postoperative phenylephrine administration was associated with the development of DGF, but was not implicated in allograft function by the time of hospital discharge. A recent multicenter study identified intraoperative ephedrine use, but not phenylephrine, as an independent predictor for the development of DGF[38]. These studies, however, did not assess whether the association between vasopressor use and DGF is due to an undesirable effect of the vasopressor on the outcome, or if vasopressor use solely serves as a surrogate of suboptimal perfusion and/or volume status. In the current study, we identified the use of phenylephrine intraoperatively, but not ephedrine, as an independent risk factor for the development of DGF. Further, we performed subgroup analyses to evaluate the hemodynamic and fluid resuscitation of phenylephrine-treated and untreated recipients (Supplementary Table 2). There were no statistically significant differences in terms of volume of crystalloid administered between recipients treated and not treated with phenylephrine. Phenylephrine, however, appears to be associated with an increase in DGF in all recipients, particularly in recipients whose MAP 30 min post-reperfusion was lower than baseline by more than 30 mmHg (OR of 6.2 and 1.6, with and without similar post reperfusion hypotension, respectively). Even so, it’s unlikely that phenylephrine-induced vasoconstriction is the culprit[40], since the effect of a bolus dose is brief and the phenylephrine was administered before reperfusion in more than half of the recipients (Supplementary Table 2). Plausibly, intraoperative phenylephrine use is a surrogate of an unmeasured hemodynamic variable, *e.g.* postoperative allograft perfusion[12,13], or another clinical parameter that influences the outcome.

This study’s non-modifiable predictors of DGF (Table 5) are consistent with previously reported risk factors[7,8,17,41-46]. Of note, we found over a 5-fold increase in incidence of DGF in allografts recovered from donors with a history of CAD. This study finding of poorer transplantation outcomes in recipients with DGF, such as postoperative reintubation, increased length of stay, and reduced graft function at 6 mo (Table 4), is in agreement with previous reports[9,47]. The association of DGF with reduced graft and recipient survival is contentious; as such, our findings of an association with reduced 1-year graft survival, but not with 1-year recipient survival (Table 4) are in accord with some but not all previous studies[9,47].

The limitations of this study include: (1) Its retrospective single transplant center nature and as such the results may not be readily extrapolated to other centers with diverse practices; (2) The timing of the most recent pre-transplant dialysis was not available; (3) The hemodynamic picture of the entire perioperative period was not captured; most importantly, the postoperative period was not assessed beyond the first set of vitals upon arrival to the post-anesthesia unit; (4) The study sample size was relatively small therefore limiting the possibility of separate analysis of outcome variables other than DGF, such as graft failure, which only occurred in 3.7% (11/294) of the population; and (5) variations in individual patient adherence to immunosuppression regimens was not captured but may have contributed to graft outcomes.

**CONCLUSION**

In conclusion, this study identifies a baseline mean arterial pressure less than 110 mmHg and intraoperative phenylephrine therapy as predictive of DGF along with reaffirming other previously well-established risk factors. Further studies are needed to explore means to improve outcomes of recipients with suboptimal baseline or intraoperative blood pressure.

**ARTICLE HIGHLIGHTS**

***Research background***

There is a profound need to increase the availability of deceased donor kidney transplantation (DDKT) to address the high incidence of kidney failure. However, challenges exist in the utilization of higher risk donor organs into what appears to be increasingly complex recipients; thus the identification of modifiable risk factors associated with poor outcomes is paramount.

***Research motivation***

Higher-risk kidney allografts more frequently exhibit delayed graft function (DGF), which has previously been associated with adverse outcomes such as acute rejection, chronic allograft nephropathy, shorter allograft survival, and increased costs. Furthermore, prior studies have pointed to an association between recipients’ blood pressure and the occurrence of DGF but have conflicted on the clinical setting and unique patient characteristics that may predispose to it.

***Research objectives***

A clear need exists for the identification and optimization of modifiable perioperative risk factors associated with DGF. We aim to identify risk factors associated with DGF, with a particular focus on perioperative hemodynamic factors, since these can be more readily optimized to improve graft and patient outcomes.

***Research methods***

Consecutive adults undergoing DDKT between January 2016 and July 2017 were identified with a study population of 294 patients. All donor data and recipients’ demographic, comorbidities, preoperative medications, and echocardiographic data within one year prior to transplant, as well as laboratory evaluation upon admission and intraoperative data were recorded. The primary outcome was the occurrence of DGF.

***Research results***

The incidence of DGF was 27%. Under logistic regression, eight independent risk factors for DGF were identified including recipient body mass index ≥ 30 kg/m2, baseline mean arterial pressure < 110 mmHg, intraoperative phenylephrine administration, cold storage time ≥ 16 h, donation after cardiac death, donor history of coronary artery disease, donor terminal creatinine ≥ 1.9 mg/dL, and a hypothermic machine perfusion (HMP) pump resistance ≥ 0.23 mmHg/mL/min.

***Research conclusions***

We delineate the association between DGF and recipient characteristics of pre-induction MAP below 110 mmHg, metabolic syndrome, donor-specific risk factors, HMP pump parameters, and intraoperative use of phenylephrine.

***Research perspectives***

Future studies with larger multicenter cohorts are needed to further explore means to improve outcomes of recipients with suboptimal baseline or intraoperative blood pressure.

**REFERENCES**

1 **Collins AJ**, Foley RN, Gilbertson DT, Chen SC. The state of chronic kidney disease, ESRD, and morbidity and mortality in the first year of dialysis. *Clin J Am Soc Nephrol* 2009; **4 Suppl 1**: S5-S11 [PMID: 19996006 DOI: 10.2215/CJN.05980809]

2 **Wang V**, Vilme H, Maciejewski ML, Boulware LE. The Economic Burden of Chronic Kidney Disease and End-Stage Renal Disease. *Semin Nephrol* 2016; **36**: 319-330 [PMID: 27475662 DOI: 10.1016/j.semnephrol.2016.05.008]

3 **Wolfe RA**, Ashby VB, Milford EL, Ojo AO, Ettenger RE, Agodoa LY, Held PJ, Port FK. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. *N Engl J Med* 1999; **341**: 1725-1730 [PMID: 10580071 DOI: 10.1056/nejm199912023412303]

4 **Kaballo MA**, Canney M, O'Kelly P, Williams Y, O'Seaghdha CM, Conlon PJ. A comparative analysis of survival of patients on dialysis and after kidney transplantation. *Clin Kidney J* 2018; **11**: 389-393 [PMID: 29942504 DOI: 10.1093/ckj/sfx117]

5 **Aubert O**, Reese PP, Audry B, Bouatou Y, Raynaud M, Viglietti D, Legendre C, Glotz D, Empana JP, Jouven X, Lefaucheur C, Jacquelinet C, Loupy A. Disparities in Acceptance of Deceased Donor Kidneys Between the United States and France and Estimated Effects of Increased US Acceptance. *JAMA Intern Med* 2019 [PMID: 31449299 DOI: 10.1001/jamainternmed.2019.2322]

6 **Querard AH**, Foucher Y, Combescure C, Dantan E, Larmet D, Lorent M, Pouteau LM, Giral M, Gillaizeau F. Comparison of survival outcomes between Expanded Criteria Donor and Standard Criteria Donor kidney transplant recipients: a systematic review and meta-analysis. *Transpl Int* 2016; **29**: 403-415 [PMID: 26756928 DOI: 10.1111/tri.12736]

7 **Parikh CR**, Hall IE, Bhangoo RS, Ficek J, Abt PL, Thiessen-Philbrook H, Lin H, Bimali M, Murray PT, Rao V, Schröppel B, Doshi MD, Weng FL, Reese PP. Associations of Perfusate Biomarkers and Pump Parameters With Delayed Graft Function and Deceased Donor Kidney Allograft Function. *Am J Transplant* 2016; **16**: 1526-1539 [PMID: 26695524 DOI: 10.1111/ajt.13655]

8 **Chen G**, Wang C, Ko DS, Qiu J, Yuan X, Han M, Wang C, He X, Chen L. Comparison of outcomes of kidney transplantation from donation after brain death, donation after circulatory death, and donation after brain death followed by circulatory death donors. *Clin Transplant* 2017; **31** [PMID: 28886219 DOI: 10.1111/ctr.13110]

9 **Salazar Meira F**, Zemiacki J, Figueiredo AE, Viliano Kroth L, Saute Kochhann D, d'Avila DO, Traesel M, Saitovitch D, Poli-de-Figueiredo CE. Factors Associated With Delayed Graft Function and Their Influence on Outcomes of Kidney Transplantation. *Transplant Proc* 2016; **48**: 2267-2271 [PMID: 27742276 DOI: 10.1016/j.transproceed.2016.06.007]

10 **Siedlecki A**, Irish W, Brennan DC. Delayed graft function in the kidney transplant. *Am J Transplant* 2011; **11**: 2279-2296 [PMID: 21929642 DOI: 10.1111/j.1600-6143.2011.03754.x]

11 **Sridhar S**, Guzman-Reyes S, Gumbert SD, Ghebremichael SJ, Edwards AR, Hobeika MJ, Dar WA, Pivalizza EG. The New Kidney Donor Allocation System and Implications for Anesthesiologists. *Semin Cardiothorac Vasc Anesth* 2018; **22**: 223-228 [PMID: 28868984 DOI: 10.1177/1089253217728128]

12 **Kaufmann KB**, Baar W, Silbach K, Knörlein J, Jänigen B, Kalbhenn J, Heinrich S, Pisarski P, Buerkle H, Göbel U. Modifiable Risk Factors for Delayed Graft Function After Deceased Donor Kidney Transplantation. *Prog Transplant* 2019; **29**: 269-274 [PMID: 31167610 DOI: 10.1177/1526924819855357]

13 **Thomas MC**, Mathew TH, Russ GR, Rao MM, Moran J. Perioperative blood pressure control, delayed graft function, and acute rejection after renal transplantation. *Transplantation* 2003; **75**: 1989-1995 [PMID: 12829899 DOI: 10.1097/01.Tp.0000058747.47027.44]

14 **Snoeijs MG**, Wiermans B, Christiaans MH, van Hooff JP, Timmerman BE, Schurink GW, Buurman WA, van Heurn LW. Recipient hemodynamics during non-heart-beating donor kidney transplantation are major predictors of primary nonfunction. *Am J Transplant* 2007; **7**: 1158-1166 [PMID: 17331108 DOI: 10.1111/j.1600-6143.2007.01744.x]

15 **Tóth M**, Réti V, Gondos T. Effect of recipients' peri-operative parameters on the outcome of kidney transplantation. *Clin Transplant* 1998; **12**: 511-517 [PMID: 9850443]

16 **Ciancio G**, Gaynor JJ, Sageshima J, Chen L, Roth D, Kupin W, Guerra G, Tueros L, Zarak A, Hanson L, Ganz S, Ruiz P, O'Neill WW, Livingstone AS, Burke GW 3rd. Favorable outcomes with machine perfusion and longer pump times in kidney transplantation: a single-center, observational study. *Transplantation* 2010; **90**: 882-890 [PMID: 20703178 DOI: 10.1097/TP.0b013e3181f2c962]

17 **Paloyo S**, Sageshima J, Gaynor JJ, Chen L, Ciancio G, Burke GW. Negative impact of prolonged cold storage time before machine perfusion preservation in donation after circulatory death kidney transplantation. *Transpl Int* 2016; **29**: 1117-1125 [PMID: 27421771 DOI: 10.1111/tri.12818]

18 **Lonjaret L**, Lairez O, Minville V, Geeraerts T. Optimal perioperative management of arterial blood pressure. *Integr Blood Press Control* 2014; **7**: 49-59 [PMID: 25278775 DOI: 10.2147/IBPC.S45292]

19 **Clavien PA**, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, de Santibañes E, Pekolj J, Slankamenac K, Bassi C, Graf R, Vonlanthen R, Padbury R, Cameron JL, Makuuchi M. The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg* 2009; **250**: 187-196 [PMID: 19638912 DOI: 10.1097/SLA.0b013e3181b13ca2]

20 **Decruyenaere P**, Decruyenaere A, Peeters P, Vermassen F. A Single-Center Comparison of 22 Competing Definitions of Delayed Graft Function After Kidney Transplantation. *Ann Transplant* 2016; **21**: 152-159 [PMID: 26976295 DOI: 10.12659/aot.896117]

21 **Hall IE**, Reese PP, Doshi MD, Weng FL, Schröppel B, Asch WS, Ficek J, Thiessen-Philbrook H, Parikh CR. Delayed Graft Function Phenotypes and 12-Month Kidney Transplant Outcomes. *Transplantation* 2017; **101**: 1913-1923 [PMID: 27495761 DOI: 10.1097/TP.0000000000001409]

22 **Levey AS**, Stevens LA. Estimating GFR using the CKD Epidemiology Collaboration (CKD-EPI) creatinine equation: more accurate GFR estimates, lower CKD prevalence estimates, and better risk predictions. *Am J Kidney Dis* 2010; **55**: 622-627 [PMID: 20338463 DOI: 10.1053/j.ajkd.2010.02.337]

23 **Sageshima J**, Ciancio G, Gaynor JJ, Chen L, Guerra G, Kupin W, Roth D, Ruiz P, Burke GW. Addition of anti-CD25 to thymoglobulin for induction therapy: delayed return of peripheral blood CD25-positive population. *Clin Transplant* 2011; **25**: E132-E135 [PMID: 21083765 DOI: 10.1111/j.1399-0012.2010.01360.x]

24 **Ruopp MD**, Perkins NJ, Whitcomb BW, Schisterman EF. Youden Index and optimal cut-point estimated from observations affected by a lower limit of detection. *Biom J* 2008; **50**: 419-430 [PMID: 18435502 DOI: 10.1002/bimj.200710415]

25 **Steyerberg EW**, Harrell FE Jr. Prediction models need appropriate internal, internal-external, and external validation. *J Clin Epidemiol* 2016; **69**: 245-247 [PMID: 25981519 DOI: 10.1016/j.jclinepi.2015.04.005]

26 **Hastie T,** Tibshirani R, Friedman JH. The Elements of Statistical Learning: Data Mining, Inference, and Prediction. 2nd ed. New York: Springer-Verlag, 2009

27 **Agresti A.** Categorical data analysis. New York: Wiley, 1990

28 **Lee J**, Song SH, Lee JY, Kim DG, Lee JG, Kim BS, Kim MS, Huh KH. The recovery status from delayed graft function can predict long-term outcome after deceased donor kidney transplantation. *Sci Rep* 2017; **7**: 13725 [PMID: 29057921 DOI: 10.1038/s41598-017-14154-w]

29 **Aubert O**, Kamar N, Vernerey D, Viglietti D, Martinez F, Duong-Van-Huyen JP, Eladari D, Empana JP, Rabant M, Verine J, Rostaing L, Congy N, Guilbeau-Frugier C, Mourad G, Garrigue V, Morelon E, Giral M, Kessler M, Ladrière M, Delahousse M, Glotz D, Legendre C, Jouven X, Lefaucheur C, Loupy A. Long term outcomes of transplantation using kidneys from expanded criteria donors: prospective, population based cohort study. *BMJ* 2015; **351**: h3557 [PMID: 26232393 DOI: 10.1136/bmj.h3557]

30 **Saidi RF**, Elias N, Kawai T, Hertl M, Farrell ML, Goes N, Wong W, Hartono C, Fishman JA, Kotton CN, Tolkoff-Rubin N, Delmonico FL, Cosimi AB, Ko DS. Outcome of kidney transplantation using expanded criteria donors and donation after cardiac death kidneys: realities and costs. *Am J Transplant* 2007; **7**: 2769-2774 [PMID: 17927805 DOI: 10.1111/j.1600-6143.2007.01993.x]

31 **Anderson CB**, Etheredge EE. Human renal allograft blood flow and early renal function. *Ann Surg* 1977; **186**: 564-567 [PMID: 335986 DOI: 10.1097/00000658-197711000-00003]

32 **Hollenberg NK**, Birtch A, Rashid A, Mangel R, Briggs W, Epstein M, Murray JE, Merrill JP. Relationships between intrarenal perfusion and function: serial hemodynamic studies in the transplanted human kidney. *Medicine (Baltimore)* 1972; **51**: 95-106 [PMID: 4552153 DOI: 10.1097/00005792-197203000-00002]

33 **Forni LG**, Joannidis M. Blood pressure deficits in acute kidney injury: not all about the mean arterial pressure? *Crit Care* 2017; **21**: 102 [PMID: 28468676 DOI: 10.1186/s13054-017-1683-4]

34 **Carlier M**, Squifflet JP, Pirson Y, Decocq L, Gribomont B, Alexandre GP. Confirmation of the crucial role of the recipient's maximal hydration on early diuresis of the human cadaver renal allograft. *Transplantation* 1983; **36**: 455-456 [PMID: 6414132 DOI: 10.1097/00007890-198310000-00021]

35 **Luciani J**, Frantz P, Thibault P, Ghesquièrre F, Conseiller C, Cousin MT, Glaser P, LeGrain M, Viars P, Küss R. Early anuria prevention in human kidney transplantation. Advantage of fluid load under pulmonary arterial pressure monitoring during surgical period. *Transplantation* 1979; **28**: 308-312 [PMID: 388763 DOI: 10.1097/00007890-197910000-00008]

36 **Campos L**, Parada B, Furriel F, Castelo D, Moreira P, Mota A. Do intraoperative hemodynamic factors of the recipient influence renal graft function? *Transplant Proc* 2012; **44**: 1800-1803 [PMID: 22841277 DOI: 10.1016/j.transproceed.2012.05.042]

37 **De Gasperi A**, Narcisi S, Mazza E, Bettinelli L, Pavani M, Perrone L, Grugni C, Corti A. Perioperative fluid management in kidney transplantation: is volume overload still mandatory for graft function? *Transplant Proc* 2006; **38**: 807-809 [PMID: 16647477 DOI: 10.1016/j.transproceed.2006.01.072]

38 **Efune GE**, Zerillo J, Zhou G, Mazzeffi MA, Demaria S, Wang C; Society for the Advancement of Transplant Anesthesia Research Committee Writing Group. Intravenous Fluid Management Practices in Kidney Transplant Patients: A Multicenter Observational Cohort Pilot Study. *Semin Cardiothorac Vasc Anesth* 2020; **24**: 256-264 [PMID: 31994444 DOI: 10.1177/1089253220901665]

39 **Day KM**, Beckman RM, Machan JT, Morrissey PE. Efficacy and safety of phenylephrine in the management of low systolic blood pressure after renal transplantation. *J Am Coll Surg* 2014; **218**: 1207-1213 [PMID: 24768292 DOI: 10.1016/j.jamcollsurg.2014.01.058]

40 **Eckert RE**, Karsten AJ, Utz J, Ziegler M. Regulation of renal artery smooth muscle tone by alpha1-adrenoceptors: role of voltage-gated calcium channels and intracellular calcium stores. *Urol Res* 2000; **28**: 122-127 [PMID: 10850635 DOI: 10.1007/s002400050149]

41 **Liese J**, Bottner N, Büttner S, Reinisch A, Woeste G, Wortmann M, Hauser IA, Bechstein WO, Ulrich F. Influence of the recipient body mass index on the outcomes after kidney transplantation. *Langenbecks Arch Surg* 2018; **403**: 73-82 [PMID: 28493145 DOI: 10.1007/s00423-017-1584-7]

42 **Sood A**, Hakim DN, Hakim NS. Consequences of Recipient Obesity on Postoperative Outcomes in a Renal Transplant: A Systematic Review and Meta-Analysis. *Exp Clin Transplant* 2016; **14**: 121-128 [PMID: 27015529 DOI: 10.6002/ect.2015.0295]

43 **Jung GO**, Yoon MR, Kim SJ, Sin MJ, Kim EY, Moon JI, Kim JM, Choi GS, Kwon CH, Cho JW, Lee SK. The risk factors of delayed graft function and comparison of clinical outcomes after deceased donor kidney transplantation: single-center study. *Transplant Proc* 2010; **42**: 705-709 [PMID: 20430152 DOI: 10.1016/j.transproceed.2010.02.063]

44 **Wszola M**, Domagala P, Ostaszewska A, Gorski L, Karpeta E, Berman A, Sobol M, Durlik M, Chmura A, Kwiatkowski A. Time of Cold Storage Prior to Start of Hypothermic Machine Perfusion and Its Influence on Graft Survival. *Transplant Proc* 2019; **51**: 2514-2519 [PMID: 31473005 DOI: 10.1016/j.transproceed.2019.02.052]

45 **Guarrera JV**, Goldstein MJ, Samstein B, Henry S, Reverte C, Arrington B, Brown T, Coleman TK, Mattei G, Mendez N, Kelly J, Ratner LE. 'When good kidneys pump badly': outcomes of deceased donor renal allografts with poor pulsatile perfusion characteristics. *Transpl Int* 2010; **23**: 444-446 [PMID: 19778343 DOI: 10.1111/j.1432-2277.2009.00970.x]

46 **Ding CG**, Tian PX, Ding XM, Xiang HL, Li Y, Tian XH, Han F, Tai QH, Liu QL, Zheng J, Xue WJ. Beneficial Effect of Moderately Increasing Hypothermic Machine Perfusion Pressure on Donor after Cardiac Death Renal Transplantation. *Chin Med J (Engl)* 2018; **131**: 2676-2682 [PMID: 30425194 DOI: 10.4103/0366-6999.245274]

47 **Ditonno P**, Impedovo SV, Palazzo S, Bettocchi C, Gesualdo L, Grandaliano G, Selvaggi FP, Battaglia M. Effects of ischemia-reperfusion injury in kidney transplantation: risk factors and early and long-term outcomes in a single center. *Transplant Proc* 2013; **45**: 2641-2644 [PMID: 24034012 DOI: 10.1016/j.transproceed.2013.07.025]

**Footnotes**

**Institutional review board statement:** The study was reviewed and approved by the University of Miami Institutional Review Board, No. 20170399.

**Informed consent statement:** The requirement for informed consent was waived by the institutional review board.

**Conflict-of-interest statement:** The authors of this manuscript have no conflicts of interest to disclose and no competing financial interest.

**Data sharing statement:** Consent was not obtained but the presented data are anonymized and risk of identification is low.

**STROBE statement:** The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

**Manuscript source:** Unsolicited manuscript

**Peer-review started:** November 23, 2020

**First decision:** January 25, 2021

**Article in press:**

**Specialty type:** Transplantation

**Country/Territory of origin:** United States

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C, C, C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Cabezuelo AS, Cantarovich F, Eleftheriadis T **S-Editor:** Zhang H **L-Editor: P-Editor:**

**Table 1 Preoperative characteristics of recipients with and without delayed graft function**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **All patients** | **DGF** | **No DGF** | ***P* value** |
| ***n* = 294** | ***n* = 79** | ***n* = 215** |
| Transplant, yr, *n* (%) |  |  |  | 0.18 |
| 2016 | 175 (60) | 52 (66) | 123 (57) |
| 2017 | 119 (40) | 27 (34) | 92 (43) |
| Age, yr | 56 (44-64) | 58 (50-63) | 54 (41-64) | 0.06 |
| Male, *n* (%) | 186 (63) | 50 (63) | 136 (63) | 0.99 |
| Race, *n* (%) |  |  |  | 0.35 |
| Caucasian | 48 (16) | 8 (10) | 40 (19) |
| Afro-American | 153 (52) | 45 (57) | 108 (50) |
| Hispanic | 88 (30) | 25 (32) | 63 (29) |
| Other | 5 (2) | 1 (1) | 4 (2) |
| BMI, kg/m2 | 28 (24-32) | 29 (26-35) | 27 (24-30) | 0.001a |
| BMI ≥ 30 kg/m2 | 97 (33) | 37 (47) | 60 (28) | 0.002a |
| Redo transplant, *n* (%) | 26 (8) | 4 (5) | 22 (10) | 0.17 |
| Dialysis type, *n* (%) |  |  |  | 0.26 |
| Peritoneal | 24 (8) | 6 (8) | 18 (8) |
| Hemodialysis | 263 (90) | 73 (92) | 190 (88) |
| Pre-dialysis | 7 (2) | 0 (0) | 7 (3) |
| Duration of dialysis, mo | 67.4 (29.1-88.7) | 67.4 (52.5-92.9) | 67.1 (46.6-87.2) | 0.37 |
| Preoperative baseline laboratory |  |  |  |  |
| WBC, × 103/µL | 6.6 (5.5-8.2) | 6.8 (5.7-8.5) | 6.6 (5.4-8.1) | 0.22 |
| Hgb, g/dL | 11.1 (10.2-12.1) | 11.1 (10.2-12.9) | 11.2 (10.1-12.2) | 0.66 |
| Hct, % | 34.5 (31.0-37.6) | 34.7 (31.2-37.0) | 34.5 (30.9-37.8) | 0.97 |
| K+, mmol/L | 4.7 (4.3-5.2) | 4.9 (4.4-5.4) | 4.7 (4.3-5.1) | 0.05 |
| HCO3-, mmol/L | 26 (23-29) | 26 (23-28) | 26 (23-29) | 0.36 |
| Na+, mmol/L | 140 (138-142) | 140 (138-143) | 140 (138-142) | 0.25 |
| Creatinine, mg/dL | 8.9 (6.7-11.2) | 9.11 (7.1-11.1) | 8.9 (6.7-11.2) | 0.88 |
| Medical history, *n* (%) |  |  |  |  |
| Hypertension | 285 (97) | 77 (97) | 208 (97) | 0.75 |
| Diabetes | 108 (37) | 42 (53) | 66 (31) | 0.001a |
| Dyslipidemia | 159 (54) | 57 (72) | 102 (47) | 0.001a |
| CAD | 67 (23) | 28 (35) | 39 (18) | 0.002a |
| Smoking | 79 (27) | 19 (24) | 60 (28) | 0.51 |
| Preoperative medications, *n* (%) |  |  |  |  |
| ACEi/ARB | 99 (34) | 19 (24) | 80 (37) | 0.03a |
| CC-blocker | 134 (46) | 35 (44) | 99 (46) | 0.79 |
| Beta-blocker | 168 (57) | 47 (59) | 121 (56) | 0.62 |
| Diuretic | 33 (11) | 12 (15) | 21 (10) | 0.19 |
| Statin | 107 (36) | 43 (54) | 64 (30) | 0.001a |
| Aspirin | 94 (32) | 35 (44) | 59 (27) | 0.006a |
| Aspirin | 22 (7) | 11 (14) | 11 (5) | 0.01a |
| Midodrine | 8 (3) | 2 (3) | 6 (3) | 0.90 |
| Echocardiography |  |  |  |  |
| LV EF < 50%, *n* (%) | 8 (3) | 3 (4) | 5 (2) | 0.49 |
| DD Grade 2 or 3, *n* (%) | 44 (15) | 14 (18) | 30 (14) | 0.42 |
| LVH, *n* (%) | 183 (62) | 55 (70) | 128 (60) | 0.11 |
| RVSP, mmHg | 28 (23-34) | 27 (22-34 | 28 (23-33) | 0.91 |

Values are presented as medians with 25th and 75th percentiles, or as numbers (*n*) and percentages %. a*P* < 0.05 denotes statistical significance. 111 patients on both aspirin and clopidogrel. BMI: Body mass index; DGF: Delayed graft function; WBC: White blood cell count; Hgb: Hemoglobin; Hct: Hematocrit; K+: Potassium; NaHCO3: Sodium bicarbonate; Na+: Sodium; CAD: Coronary artery disease; ACEi: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin II receptor blocker; CC-blocker: Calcium channel blocker; LVEF: Left ventricular ejection fraction; DD: Diastolic dysfunction; LVH: Left ventricular hypertrophy; RVSP: Right ventricular systolic pressure.

**Table 2 Intraoperative characteristics for recipients with and without delayed graft function**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **All patients** | **DGF** | **No DGF** | ***P* value** |
| ***n* = 294** | ***n* = 79** | ***n* = 215** |
| Surgery time, h | 2.7 (2.0-3.9) | 2.5 (1.8-4.4) | 2.8 (2.2-3.9) | 0.03a |
| Warm ischemia time, min | 29 (24-36) | 27 (23-34) | 29 (24-36) | 0.08 |
| Fluid and electrolytes | | | | | |
| Crystalloid, L | 2.0 (1.5-2.5) | 2.0 (1.5-2.2) | 2.0 (1.5-2.5) | 0.97 |
| Plasmalyte/Isolyte, *n* (%) | 94 (32) | 23 (29) | 71 (33) | 0.82 |
| Normal saline, *n* (%) | 161 (55) | 45 (57) | 116 (54) |
| Combined, *n* (%) | 39 (13) | 11 (14) | 28 (13) |
| Weight based crystalloid (mL/kg) | 24 (19-32) | 22 (18-31) | 25 (19-33) | 0.11 |
| Albumin, grams | 25 (12.5-50) | 25 (25-50) | 25 (12.5-50) | 0.66 |
| Packed red blood cells, *n* (%) |  |  |  | 0.46 |
| None | 224 (76) | 60 (76) | 164 (76) |
| 1 unit | 39 (13) | 11 (14) | 28 (13) |
| 2 units | 25 (9) | 8 (10) | 17 (8) |
| 3+ units | 6 (2) | 0 (0) | 6 (3) |
| Fresh frozen plasma, *n* (%) |  |  |  | 0.38 |
| None | 287 (98) | 79 (100) | 208 (97) |
| 1 unit | 2 (1) | 0 (0) | 2 (1) |
| 2+ units | 5 (2) | 0 (0) | 5 (2) |
| Platelets, *n* (%) |  |  |  | 0.58 |
| None | 290 (99) | 79 (100) | 211 (98) |
| 1 unit | 4 (1) | 0 (0) | 4 (2) |
| Estimated blood loss, mL | 100 (95-200) | 150 (100-300) | 100 (50-200) | 0.01a |
| NaHCO3, mEq | 50 (50-112.5) | 50 (50-100) | 50 (50-150) | 0.76 |
| CaCl2, *n* (%) | 210 71) | 59 (75) | 151 (70) | 0.56 |
| CaCl2, g | 1 (0.75-1.5) | 1 (0.75-1.25) | 1 (0.75-1.5) | 0.65 |
| Furosemide infusion, *n* (%) | 192 (65) | 44 (56) | 148 (69) | 0.04a |
| NaHCO3, *n* (%) | 54 (18) | 11 (14) | 43 (20) | 0.31 |
| Urine output, mL | 75 (15-200) | 28 (5-80) | 100 (20-250) | < 0.0001a |
| Hemodynamics and inotropes | | | | | |
| MAP at baseline, mmHg | 109 (96-122) | 107 (95-118) | 112 (96-123) | 0.08 |
| Baseline MAP < 110 mmHg, *n* (%) | 159 (54) | 51 (65) | 108 (50) | 0.02a |
| MAP 5 min post-reperfusion, mmHg | 90 (81-100) | 91 (79-97) | 90 (82-100) | 0.45 |
| 5 min post-reperfusion MAP < 100 mmHg, *n* (%) | 220 (75) | 61 (77) | 159 (74) | 0.61 |
| Drop in MAP ≥ 30 mmHg from baseline -5 min post-reperfusion, *n* (%) | 74 (25) | 18 (24) | 56 (26) | 0.55 |
| MAP 30 min post-reperfusion, mmHg | 91 (82-100) | 92 (82-101) | 91 (83-99) | 0.85 |
| 30 min post-reperfusion MAP < 100 mmHg, *n* (%) | 218 (74) | 54 (68) | 164 (77) | 0.15 |
| Drop in MAP ≥ 30 mmHg from baseline -30 min post-reperfusion, *n* (%) | 70 (24) | 13 (16) | 57 (27) | 0.07 |
| MAP 1st post-operative, mmHg | 104 (95-113) | 102 (92-110) | 105 (96-113) | 0.09 |
| 1st post-operative MAP < 100 mmHg, *n* (%) | 117 (40) | 35 (44) | 82 (38) | 0.34 |
| Drop in MAP ≥ 30 mmHg from baseline -1st post-operative, *n* (%) | 27 (9) | 7 (9) | 20 (9) | 0.90 |
| Dopamine, *n* (%) | 5 (2) | 2 (3) | 3 (1) | 0.61 |
| Ephedrine, *n* (%) | 74 (25) | 25 (32) | 49 (23) | 0.12 |
| Ephedrine dose, mg | 10 (5-20) | 10 (5-20) | 10 (5-18) | 0.62 |
| Phenylephrine, *n* (%) | 64 (22) | 25 (32) | 39 (18) | 0.01a |
| Phenylephrine dose, mcg | 200 (100-400) | 200 (125-400) | 200 (100-400) | 0.64 |
| Phenylephrine timing: |  |  |  |  |
| None, *n* (%) | 230 (78) | 54 (68) | 176 (82) | 0.06 |
| Before reperfusion, *n* (%) | 39 (14) | 14 (18) | 25 (12) |
| After reperfusion, *n* (%) | 10 (3) | 4 (5) | 6 (3) |
| Both before and after, *n* (%) | 15 (5) | 7 (9) | 8 (4) |
| Phenylephrine and Ephedrine, *n* (%) | 37 (13) | 16 (20) | 21 (10) | 0.02a |

Values are presented as medians with 25th and 75th percentiles, or as numbers (*n*) and percentages %. a*P* < 0.05 denotes statistical significance. DGF: Delayed graft function; MAP: Mean arterial blood pressure; NaHCO3: Sodium bicarbonate; CaCl2: Calcium chloride; OR: Operating room.

**Table 3 Donor and hypothermic machine perfusion pump characteristics for recipients with and without delayed graft function**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **All patients** | **DGF** | **No DGF** | ***P* value** |
| ***n* = 294** | ***n* = 79** | ***n* = 215** |
| Donor characteristics | | | | | |
| Donor kidney |  |  |  | 0.35 |
| Left, *n* (%) | 136 (46%) | 33 (42%) | 103 (48%) |
| Right, *n* (%) | 158 (54%) | 46 (58%) | 112 (52%) |
| Donor location |  |  |  | 0.001a |
| Local, *n* (%) | 158 (54%) | 27 (34%) | 131 (61%) |
| Import, *n* (%) | 136 (46%) | 52(66%) | 84 (39%) |
| Kidney donor profile index, % | 53 (33-81) | 61 (40-85) | 49 (28-75) | 0.006a |
| Donor age, yr | 44 (32-56) | 49 (36-56) | 42 (30-55) | 0.04a |
| Donor body mass index, kg/m2 | 27 (23-31) | 28 (25-33) | 26 (23-31) | 0.009a |
| Donation after cardiac death, *n* (%) | 50 (17%) | 23 (29%) | 27 (13%) | 0.001a |
| Donor cause of death |  |  |  | 0.60 |
| Anoxia, *n* (%) | 119 (40%) | 31 (39%) | 88 (41%) |
| Head trauma, *n* (%) | 76 (26%) | 18 (23%) | 58 (27%) |
| Stroke, *n* (%) | 99 (34%) | 30 (38%) | 69 (32%) |
| Donor cardiac arrest, *n* (%) | 141 (48%) | 40 (51%) | 101 (47%) | 0.58 |
| Donor medical history |  |  |  |  |
| Hypertension, *n* (%) | 104 (35%) | 32 (41%) | 72 (33%) | 0.28 |
| Diabetes, *n* (%) | 34 (12%) | 12 (15%) | 22 (10%) | 0.24 |
| Coronary artery disease, *n* (%) | 27 (9%) | 16 (20%) | 11 (5%) | 0.001a |
| Smoking, *n* (%) | 70 (24%) | 20 (25%) | 50 (23%) | 0.73 |
| Heavy alcohol use, *n* (%) | 65 (22%) | 13 (16%) | 52 (24%) | 0.15 |
| Admit creatinine, mg/dL | 1.1 (0.9-1.4) | 1.1 (0.9-1.5) | 1.1 (0.9-1.30) | 0.20 |
| Terminal creatinine, mg/dL | 1.0 (0.7-1.6) | 1.3 (0.81-2.8) | 0.9 (0.7-1.4) | 0.001a |
| Terminal creatinine ≥ 1.9 mg/dL | 63 (21%) | 31 (39%) | 32 (15%) | 0.001a |
| Donor Biopsy: % glomerulosclerosis | 3.9 (0-8.3) | 4.6 (1.7-10) | 3.4 (0-7.6) | 0.14 |
| HMP pump characteristics | | | | | |
| Cold ischemia time | 28.5 (21.5-34.5) | 30.6 (25.8-36.4) | 26.4 (21.2-33.8) | 0.009a |
| Cold ischemia time ≥ 26 h | 172 (59%) | 58 (73%) | 114 (53%) | 0.002a |
| Cold storage time, h | 10.6 (6.8-20.6) | 18.4 (7.1-24.7) | 9.6 (6.8-18.9) | 0.002a |
| Cold storage duration ≥ 16 h | 120 (41%) | 46 (58%) | 74 (34%) | 0.001a |
| Total pump time, h | 13.3 (8.4-19.2) | 13.1 (8.2-18.9) | 13.4 (8.4-19.7) | 0.37 |
| Final pump parameters |  |  |  |  |
| Flow, mL/min | 141 (123-156) | 127 (117-148) | 142 (126-159) | 0.001a |
| Resistance, mmHg/mL/min | 0.20 (0.15-0.25) | 0.24 (0.16-0.29) | 0.19 (0.15-0.24) | 0.001a |
| Systolic pressure, mmHg | 34 (29-40) | 35 (30-40) | 33 (27-39) | 0.009a |
| Diastolic pressure, mmHg | 24 (18-29) | 26 (19-30) | 23 (18-29) | 0.09 |
| Pump flow < 150 mL/min | 190 (65%) | 65 (82%) | 125 (58%) | 0.001a |
| Pump resistance ≥ 0.23 mmHg/mL/min | 115 (39%) | 47 (59%) | 68 (32%) | 0.001a |

Values are presented as medians with 25th and 75th percentiles, or as numbers (*n*) and percentages (%).a*P* < 0.05 denotes significance. DGF: Delayed graft function; HMP: Hypothermic machine perfusion.

**Table 4 Postoperative characteristics for recipients with and without delayed graft function**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **All patients** | **DGF** | **No DGF** | ***P* value** |
| ***n* = 294** | ***n* = 79** | ***n* = 215** |
| Post-operative location, *n* (%) |  |  |  | 0.95 |
| PACU | 230 (78) | 62 (78) | 168 (78) |
| ICU | 64 (22) | 17 (22) | 47 (22) |
| Extubation in OR | 282 (96) | 74 (94) | 208 (97) | 0.24 |
| Reintubation, *n* (%) |  |  |  |  |
| Within 48 h | 4 (1) | 3 (4) | 1 (0.5) | 0.06 |
| Within 1 wk | 6 (2) | 4 (5) | 2 (1) | 0.05 |
| Pulmonary edema, *n* (%) |  |  |  |  |
| Within 48 h | 11 (4) | 5 (6) | 6 (3) | 0.16 |
| Within 1 wk | 13 (4) | 6 (8) | 7 (3) | 0.11 |
| Adverse cardiac events, *n* (%) |  |  |  |  |
| Within 48 h | 10 (3) | 2 (3) | 8 (4) | 0.62 |
| Within 1 wk | 15 (5) | 3 (4) | 12 (6) | 0.54 |
| Within 1 mo | 17 (6) | 4 (5) | 13 (6) | 0.10 |
| Clavien-Dindo at 1 mo, *n* (%)1 |  |  |  |  |
| None | 238 (81) | 54 (68) | 184 (86) | 0.002a |
| Grade I | 4 (1) | 0 (0) | 4 (2) |
| Grade II | 14 (5) | 6 (8) | 8 (4) |
| Grade IIIa | 19 (6) | 11 (14) | 8 (4) |
| Grade IIIb | 13 (4) | 4 (5) | 9 (4) |
| Grade IVa | 4 (1) | 3 (4) | 1 (0.5) |
| Grade IVb | 1 (1) | 1 (1) | 0 (0) |
| Grade V | 1 (1) | 0 (0) | 1 (0.5) |
| Total Complications | 56 (19) | 25 (32) | 31 (14) |
| Length of stay, d | 6 (5-8) | 8 (6-12) | 6 (5-7) | 0.001a |
| eGFR, 6 mo, mL/min | 65.3 (48.4-81.6) | 50.6 (36.2-71.0) | 73.3 (58.6-89.5) | 0.001a |
| eGFR < 60 mL/min at 6 mo, *n* (%) | 120 (41) | 51 (65) | 69 (32) | 0.001a |
| Graft survival at 1 yr, *n* (%)2 | 283 (96%) | 71 (90) | 212 (99) | 0.002a |
| Patient survival at 1 yr, *n* (%) | 292 (99) | 79 (100) | 213 (99) | 0.34 |

Values are presented as medians with 25th and 75th percentiles, or as numbers (*n*) and percentages %. a*P* < 0.05 denotes significance. 1Includes ultrasound evidence of 19 perinephric fluid collections not requiring intervention, and 32 perinephric fluid collections with intervention. 24 graft failure attributed to thrombosis were due to technical difficulty: two allografts had single renal arteries and two allografts had two renal arteries, only one of which underwent arterial reconstruction in which the inferior portal artery was connected to the vein in a side-to-side anastomosis. PACU: Post-anesthesia care unit; ICU: Intensive care unit; BP: Blood pressure; eGFR: Estimated glomerular filtration rate.

**Table 5 Perioperative predictors associated with delayed graft function**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **OR** | **95%CI** | ***P* value** |
| Preoperative recipient risk factor | | | |
| Recipient BMI ≥ 30 kg/m2 | 3.8 | 1.947-7.548 | 0.0001a |
| Intraoperative recipient risk factor | | | |
| Baseline MAP < 110 mmHg | 2.2 | 1.098-4.326 | 0.0260a |
| Phenylephrine usage | 2.2 | 1.040-4.820 | 0.0392a |
| Donor risk factors | | | |
| Cold storage time ≥ 16 h | 2.8 | 1.378-5.666 | 0.0044a |
| Donation after cardiac death | 4.4 | 1.872-10.225 | 0.0007a |
| Donor with history of CAD | 5.8 | 2.133-16.033 | 0.0006a |
| Terminal creatinine ≥ 1.9 mg/dL | 4.3 | 2.041-8.855 | 0.0001a |
| HMP pump risk factor | | | |
| Resistance ≥ 0.23 mmHg/mL/min | 2.2 | 1.132-4.307 | 0.0201a |

a*P* < 0.05 denotes significance. OR: Odds ratio; BMI: Body mass index; MAP: Mean arterial pressure; CAD: Coronary artery disease; HMP: Hypothermic machine perfusion pump.