ORIGINAL ARTICLE

Association between primary graft dysfunction and acute kidney injury after orthotopic heart transplantation – a retrospective, observational cohort study

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SUMMARY

Acute kidney injury (AKI) and primary graft dysfunction (PGD) are serious complications after heart transplantation (HT). The relationship between AKI and PGD is poorly understood. We sought to examine the incidence of AKI and identify risk factors associated with AKI. We hypothesized that PGD is one of the risk factors independently associated with post-HT AKI. We gathered data for all adult patients who underwent HT between 2009 and 2014. AKI was defined by the KDIGO criteria. PGD was categorized using ISHLT criteria. We assessed univariable and multivariable logistic regression to identify risk factors independently associated with post-HT AKI. Out of 316 patients, postoperative AKI occurred in 273 (86%) patients: 188 (68%) stage I, 44 (16%) stage II, and 41 (15%) stage III. Stage II/III AKI was associated with increased risk of mortality at 1 year. There was significant association between severe PGD and stage II/III AKI (P = 0.001, OR 3.63, 95% CI: 1.69–7.94). Other clinical factors significantly associated with stage II/III AKI included longer donor brain death duration and lower recipient baseline creatinine. We found that stage II/III AKI is common and independently associated with severe PGD. Another potentially modifiable risk factor is donor brain death duration.

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Introduction

Acute kidney injury (AKI) following cardiac surgery remains a frequent and serious complication associated with high morbidity and mortality rates [1,2]. According to the latest report of the International Society of Heart and Lung Transplantation (ISHLT), AKI following orthotopic heart transplantation (HT) occurs at a rate of 25% at 1 year and 51% at 5 years, and end-stage renal disease (ESRD) requiring long-term dialysis occurred at rates of 1.7% and 3% at 1 and 5 years, respectively [3]. AKI after HT is associated with significant morbidity and with increased early and late mortality [4-7]. The pathophysiology of AKI occurring in the immediate postoperative period following HT is complex and multifactorial. Some of the risk factors

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described in the literature include recipient age, pre-existing kidney dysfunction, recipient diabetes mellitus, preoperative right heart hemodynamics, previous cardiac surgery, graft ischemic time, transfusion of blood products and nephrotoxic drugs [4-8]. Moreover, across a variety of clinical settings, heart performance and kidney injury are closely interconnected beyond hemodynamic factors, through humoral and cell-mediated pathways, and distant organ damage leading to "organ crosstalk." This bidirectional hemodynamic and non-hemodynamic relationship between the heart and kidney has been described as the cardiorenal syndrome (CRS). CRS can account for AKI in HT recipients because of both long-standing congestive heart failure before transplantation leading to progressive chronic kidney disease (CRS type 2) and early graft failure after HT resulting in abrupt worsening of kidney function (CRS type 1) [9,10]. Early graft failure after HT is described as primary graft dysfunction (PGD) and occurs at an incidence ranging from 2.5% to 30% depending on the definition used and the stringency of criteria [11,12]. The relationship between early graft failure and AKI after HT has not been described.

In this single-institution, retrospective study of HT procedures, we sought to examine the incidence and risk factors associated with AKI. We hypothesize that PGD is one of the risk factors independently associated with AKI after HT.

Materials and methods

The study was approved by the Duke University Institutional Review Board as a retrospective, observational cohort study. We conducted review of medical records from consecutive patients over 18 years of age who underwent HT from January 1, 2009, to December 31, 2014. Detailed demographic, clinical, and intraoperative echocardiographic data were collected from quality controlled, prospectively entered databases as well as hospital medical records. Patients supported on veno-arterial extracorporeal membrane oxygenation (VA-ECMO) at the time of HT and patients who underwent an additional organ transplantation (liver, kidney, lung) concurrently with HT were excluded. Donor characteristics and additional recipient information were obtained from the United Network for Organ Sharing (UNOS)/Organ Procurement and Transplantation Network (OPTN) registry. The data listed in the UNOS registry include pre- and post-transplant variables captured and entered by transplant centers into an online database at the time of listing, transplantation, and follow-up. The UNOS registry Standard Transplant Analysis and Research files provide de-identified data, which are publicly available. The UNOS data were matched to the Duke University Medical Center patient list based on recipient date of transplant, age, and gender as previously described by our group [11].

Donor procurement, preservation method for donor hearts, and surgical technique for implantation have been previously described by our group [11]. Anesthesia and cardiopulmonary bypass (CPB) were conducted according to institutional protocol. Intraoperative hemodynamic assessment was performed in all patients using a pulmonary artery catheter, and right atrial, right ventricular (RV), pulmonary artery pressures, and cardiac index were recorded.

All patients have received the same immunosuppression protocol over the study period. Intraoperatively, all patients have received methylprednisolone 1000 mg and induction therapy with basiliximab 20 mg postreperfusion. Maintenance therapy in the early postoperative therapy included triple-drug therapy with (i) steroids, (ii) calcineurin inhibitors (tacrolimus 1 mg every 12 h titrated to a trough goal level 10–15 ng/ml or cyclosporine 1.5 to 5 mg/kg every 12 h titrated to a trough goal level of 300 ng/ml), and (iii) antiproliferative agents (mycophenolate mofetil 1500 mg twice daily adjusted to maintain a white blood count of at least 3500/μl or azathioprine 2 mg/kg daily adjusted to maintain a white blood count of at least 3500/μl).

Serum creatinine (SCr) was measured in the Duke Clinical Pathology Laboratory. Preoperative SCr values were recorded before HT, on the day that was closest to the day of surgery and for the first 10 days postoperatively per institutional protocol [13].

The primary outcome was AKI, ascertained and categorized according to the Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guidelines with modification because of the absence of urine output data [14]. Postoperative AKI was defined using preoperative SCr values (baseline) that were collected prior to surgery and all available SCr values that were measured for the first 10 days postoperatively or until discharge, whichever occurred first. The presence of postoperative AKI was ascertained when there was postoperative SCr rise ≥50% in the first 10 postoperative days, or 0.3 mg/dl increase detected using a rolling 48-hour window across the 10 days postoperative period. A staging characterization of postoperative AKI was also generated as follows: (1) stage I—risk: those with 1.5- to 1.9-fold increase in SCr (i.e., 50-90% increase) or greater than 0.3 mg/dl increase; (2) stage II—injury:

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those with 2.0- to 2.9-fold rise of SCr (i.e., 100–200% increase) within 10 days; (3) stage III—failure: those with ≥3.0-fold rise of SCr (i.e., ≥200% increase) within 10 days or ≥4 mg/dl increase in a rolling 48-hour window.

The clinical risk factors for postoperative AKI included recipient preoperative and intraoperative characteristics, donor characteristics, and PGD after HT. PGD was diagnosed in the first 24 h after completion of transplantation and was defined according to the presence of either left ventricle PGD (PGD-LV) or right ventricle PGD (PGD-RV) using criteria established by the ISHLT consensus statement [15]. PGD-RV was defined as mechanical support with right VAD implantation. PGD-LV was defined as either (1) mechanical support with left VAD implantation or VA-ECMO, or (2) LV EF 45% or less by intraoperative post-CPB TEE and (a) placement of IABP at the time of transplantation, or (b) the need for high-dose inotropic support in the immediate post-HT period defined as an inotrope score >10. Inotrope score was calculated using the formula recommended by the ISHLT consensus statement: inotrope score = dopamine (×1) + dobutamine (×1) + milrinone (×15) + epinephrine (×100) + norepinephrine (×100) with each drug dosed in mcg/kg/min [15]. As previously published [11], because PGD without VAD may be considered a less severe form of PGD, we have performed the analysis using two levels of PGD severity: (1)PGD without VAD and (2)PGD with VAD.

Statistical analysis

For the primary analysis, we have combined the patients in two groups of AKI severity: none/stage I AKI and stage II/III AKI. Data are reported as median with first and third quartiles or mean and standard deviation for continuous variables, or as count with percent for categorical variables. We conducted univariable comparisons of clinical and demographic variables between the none/stage I and stage II/III AKI groups using Wilcoxon rank sum or t-tests for continuous variables and chi-square or Fisher's exact tests for categorical variables.

We constructed a multivariable logistic regression model via backward selection based on Akaike information criterion (AIC). Clinical and demographic variables were included in the selection set if they were nonmissing for more than 90% of the cohort, and did not produce model collinearity. Model fit was evaluated with the Hosmer–Lemeshow goodness-of-fit test, and model performance was evaluated with c-index.

One-year mortality was summarized in our cohort. The Kaplan–Meier method was used to describe the unadjusted prognostic significance of postoperative AKI with respect to event-free survival. Differences between survival curves were compared using the log-rank test.

Results

A total of 325 adult patients underwent HT during the study period. Of these, 9 patients were excluded (5 multi-organ transplant, 2 VA-ECMO prior to HT, and 2 incomplete medical records) resulting in 316 patients constituting the study cohort. Recipient and donor characteristics are presented in Table 1.

Postoperative AKI occurred in 273 (86%) of patients, of which 188 (68%) had stage I AKI, 44 (16%) had stage II AKI, and 41 (15%) had stage III AKI. Thirty-two patients required in-hospital renal replacement therapy (RRT). Of these, 6 patients died in-hospital and 14 were discharged, receiving chronic RRT. Renal function data are presented in Table 2.

Overall, PGD occurred in 99 patients (31%); PGD without VAD which occurred in 60 (19%) patients and PGD with VAD occurred in 39 (12%) patients.

In the univariable analysis, we found 3 significant differences between the two AKI outcome groups: Patients who developed stage II/III AKI were more likely to have PGD requiring VAD (22.35% vs 8.66%, $P = 0.001$) when compared with patients with none/stage I AKI. The patients who developed stage II/III AKI were also more likely to have had cardiac surgery prior to HT (69.41% vs 57.14%, $P = 0.04$) and to have received organs from recipients with a longer donor brain death duration (defined as time from declaration of donor brain death to placement of the aortic cross-clamp during organ prelevation) (34.18 h of interquartile range (IQR) [29.27, 41.70] vs 31.43 h IQR [27.02, 38.15], $P = 0.008$) when compared with patients with none/stage I AKI.

In building the multivariable model, we excluded body mass index percent change donor to recipient and preoperative right heart catheterization hemodynamic measures because of the degree of missing data (11-12%) for these variables, as well as nonischemic cardiomyopathy because of a high level of collinearity with ischemic cardiomyopathy. The final multivariable model, selected for optimal AIC, consisted of effects for PGD, donor brain death duration, recipient gender, pretransplant SCr, and donor race. Factors independently associated with the development of stage II/III AKI included PGD requiring VAD ($P = 0.001$, OR 3.63,

Table 1. Baseline patient characteristics for the study cohort

	Total (*N* = 316)
Donor characteristics	
Race (AA)	78 (24.68%)
Gender (M)	235 (74.37%)
Recipient–donor gender mismatch	68 (21.52%)
Diabetes	21 (6.67%)
Hypertension	73 (23.40%)
Pulmonary infection	181 (57.28%)
Prerecovery thyroxine (T4)	256 (81.27%)
BMI % change donor to recipient	16.09 [6.99, 24.51]
Age (years)	36.0 [26.0, 46.0]
Ischemic time (hours)	2.97 [2.46, 3.50]
Donor brain death duration (hours)	32.31 [27.52, 38.61]
LV ejection fraction (%)	60.0 [55.0, 65.0]
Recipient characteristics	
Any PGD	99 (31.33%)
Type of PGD	
None	217 (68.67%)
PGD without VAD	60 (18.99%)
PGD with VAD	39 (12.34%)
Pretransplantation amiodarone	130 (41.27%)
Gender (M)	235 (74.37%)
Race (AA)	89 (28.16%)
Diabetes	118 (38.31%)
Ischemic cardiomyopathy	133 (42.09%)
Nonischemic cardiomyopathy	168 (53.16%)
Previous cardiac surgery	191 (60.44%)
LVAD pretransplantation	104 (33.02%)
Inotropes dependence pretransplantation	132 (41.77%)
Age (years)	58.0 [48.0, 63.5]
Preoperative RAP	10.00 [6.0, 16.0]
Preoperative PVR	2.60 [1.83, 3.53]
Preoperative PSP	43.0 [35.0, 52.0]
Preoperative PDP	20.5 [15.0, 26.0]
Preoperative creatinine	1.30 [1.00, 1.60]
Post-transplantation CVP	12.0 [9.0, 16.0]

Values are presented as numeric median (q1, q3) or as number (N) and percentage (%) of population.

RAP, PVR, PSP, and PDP obtained from the last right heart catheterization before heart transplant.

AA, African American; BMI, body mass index; CVP, central venous pressure; LV, left ventricle; LVAD, left ventricular assist device; M, male; PDP, pulmonary diastolic pressure; PGD, primary graft dysfunction; PSP, pulmonary systolic pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RV, right ventricle; VAD, ventricular assist device.

95% CI: 1.69–7.94), donor brain death duration (P = 0.017, OR 1.33/10 h, 95%CI: 1.06–1.70), recipient pretransplant SCr (P = 0.013, OR 1.28, 95% CI: 1.06–1.56 per 0.3 unit decrease), and recipient male gender (P = 0.023, OR 2.16, 95% CI:1.14–4.33; Fig. 1). The C-index for the final multivariable model was 0.67, and we found no evidence of model miss-fit (P = 0.48). The optimal AIC model also included PGD not requiring VAD and donor race.

Median follow-up time in the study cohort was 4.25 years, IQR [2.78, 6.1]. We compared the incidence of postoperative AKI with event-free survival over the follow-up period between none/stage I AKI and stage II/III AKI groups. During the first year after transplantation, there was a significant difference in survival distribution between the two groups (log-rank P = 0.02), with stage II/III AKI being associated with increased risk of mortality (Fig. 2); however, over the entire follow-up period, there was no difference in mortality between the two groups (log-rank P = 0.67).

Discussion

In this single-center, retrospective study on 316 patients undergoing HT, we have found that PGD requiring VAD is one of the risk factors associated with the development of stage II/III AKI after HT. Other variables independently associated with stage II/III AKI were longer donor brain death duration, lower recipient pretransplant SCr, and recipient male gender. During the first year after transplantation, there was a significant difference in survival distribution between patients with none/stage I AKI and stage II/III AKI, with stage II/III AKI being associated with increased risk of mortality.

Although several risk factors for the development of AKI have been identified in patients undergoing HT, no studies have investigated the relationship of PGD. Romeo et al found that older age, elevated SCr, and elevated pulmonary vascular resistance were independently associated with development of stage III AKI [6]. Garcia-Gigorro et al found that development of post-HT complications such as cardiac tamponade, acute RV failure, and major bleeding, as well as a higher logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) was independently associated with the development of AKI [5]. Findings from the current study, which is the first to include PGD, contrast with these previous studies, potentially highlighting the significance of this variable as a risk factor.

We found PGD requiring VAD to be an independent risk factor for the development of stage II/III AKI. This may be a manifestation of an acute CRS syndrome [9] as humoral and hemodynamic changes described in PGD are similar to those mediating the pathophysiology of AKI. Low cardiac output, which does not meet the

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Table 2. Renal function data

Renal function descriptor	Total	No PGD	PGD with VAD	PGD without VAD
AKI by RIFLE (*n*/%)*	189 (60.38%)	119 (54.84%)	36 (62.07%)	34 (89.47%)
AKI by KDIGO (*n*/%)	273 (86.39%)	186 (85.71%)	49 (81.67%)	38 (97.44%)
AKI stage (by KDIGO)				
Stage I	188 (68.86%)	135 (72.58%)	34 (69.39%)	19 (50.00%)
Stage II	44 (16.11%)	25 (13.44%)	8 (16.33%)	11 (28.95%)
Stage III	41 (15.02%)	26 (13.98%)	7 (14.29%)	8 (21.05%)
Preoperative creatinine, mg/dl (mean/SD)*	1.37 (0.46)	1.38 (0.47)	1.25 (0.35)	1.50 (0.51)
Peak postoperative serum creatinine, mg/dl (mean/SD)	2.55 (1.60)	2.45 (1.57)	2.41 (1.73)	3.24 (1.40)
Percent change in creatinine (mean/SD)*	193.69% (126.39%)	187.28% (126.63%)	195.46% (136.85%)	226.32% (104.28%)
In-hospital RRT (*n*/%)	32 (10.13%)	15 (6.91%)	7 (11.67%)	10 (25.64%)
Dialysis at discharge (*n*/%)	14 (4.43%)	5 (2.30%)	2 (3.33%)	7 (17.95%)

AKI, acute kidney injury; KDIGO, Kidney Disease Improving Global Outcomes classification; PGD, primary graft dysfunction; RIFLE, Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease classification; RRT, renal replacement therapy; SD, standard deviation; VAD, ventricular assist device.

*Preoperative creatinine missing for 2 patients. Results in missing RIFLE and percent change values.

metabolic needs, and elevated central venous filling pressure seen in patients with PGD contribute to decreased renal blood flow, increased interstitial pressure, and renal hypoxia [16]. PGD is also accompanied by a cascading pro-inflammatory response, supported by the elevation in several inflammatory markers, such as tumor necrosis factor-α, interleukin-6, neutrophils, and procalcitonin [17]. The presence of temporary VAD for circulatory support in patients with severe PGD may also contribute to the heightened inflammatory response through high levels of shear stress and presence of foreign materials. Immediate postoperative increase in interleukin-6 and interleukin-8 levels following VAD implantation has been described in patients with advanced heart failure and was associated with worse outcomes [18]. The exaggerated inflammatory response in diseased states can induce structural and functional damage in distant organs (i.e., kidney) with cell apoptosis, and renal tubular epithelium and vascular endothelium alterations [9]. We did not find an association between PGD not requiring VAD and AKI. However, a higher percentage of the patients with PGD not requiring VAD and AKI required in-hospital RRT or dialysis at discharge when compared with patients with PGD requiring VAD and AKI (in-hospital RRT 25.64% vs 11.67%, dialysis at discharge 17.95% vs 3.33%). While the small number of events in the outcomes mentioned above precludes us from further investigating these findings, another concern is the potential bias related to deceased patients in the PGD with VAD group.

While the association between PGD and the occurrence of AKI we observed is not causative, it is interesting to speculate on their interaction. As prolonged ischemia time is one of the known risk factors for early graft dysfunction, there are several initiatives in the transplant field oriented toward decreasing the cold ischemia time, such as ex-vivo perfusion. It will be interesting to see whether interventions that reduce the incidence of PGD are associated with changes in the occurrence of AKI.

We have also found that a longer donor brain death duration was independently associated with development of stage II/III AKI. Donor brain death is associated with pathophysiological changes in the recipient such as rapid release of catecholamines and activation of multiple pro-inflammatory mediators [19,20]. While this finding could be related to the deterioration of cardiac function in the donor in the time period between brain death and heart retrieval, in our study population we did not find an independent association between this time interval and the development of PGD [11]. Some

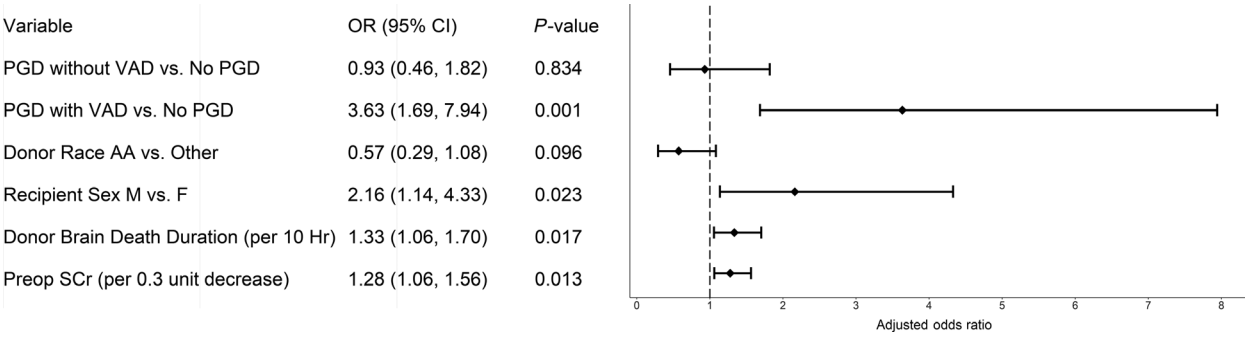

Figure 1 Final multivariable model for the development of stage II/III AKI. AA, African American; AKI, acute kidney injury; CI, confidence interval; F, female gender; M, male gender; OR, odds ratio; Preop, preoperative; PGD, primary graft dysfunction; SCr, serum creatinine; VAD, ventricular assist device.

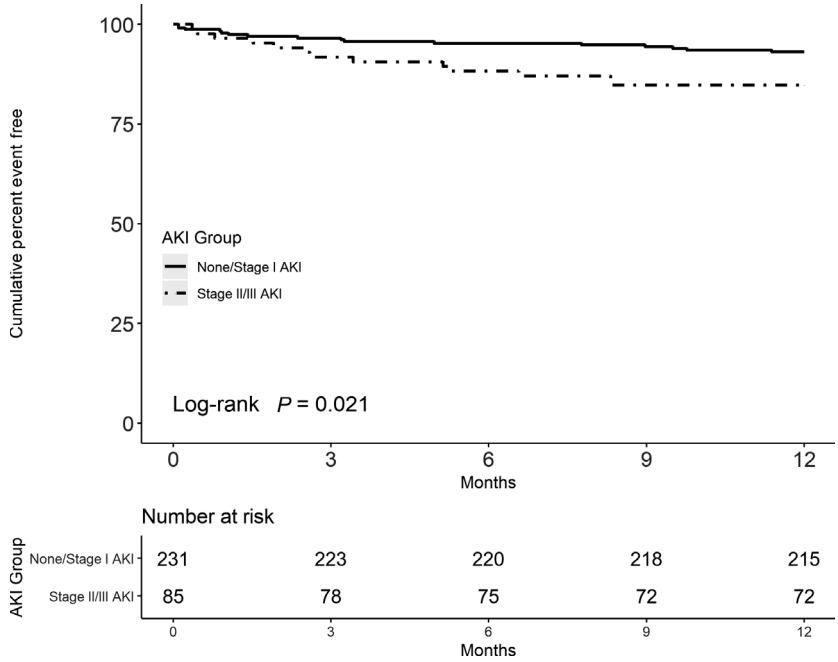

Figure 2 Kaplan–Meier plots for 1-year survival for the two groups (none/stage I AKI and stage II/III AKI). AKI, acute kidney injury.

studies have suggested that longer donor brain death duration may have an impact on outcomes in patients undergoing HT being associated with increased long-term mortality [21,22]. However, large recent UNOS registry analyses have shown that longer donor brain death duration was not associated with worse survival for both the HT population and patients undergoing lung transplantation [23,24]. While we do not have an explanation for this finding, we think that it requires further research as donor management seems to be widely variable; in our study cohort donor, brain death duration ranged from 11.2 to 107.1 h.

We have also observed that patients with lower baseline SCr were at increased risk of developing stage II/III AKI. We speculate that this finding is an artifact generated by the dichotomization of the outcome groups in none/stage I AKI and stage II/III AKI and definition of stage II and III AKI, which requires doubling or tripling of the baseline SCr. It is also possible that lower baseline SCr identifies patients with a poorer nutrition status and therefore at higher risk for perioperative complications.

There are several limitations to our study. While most variables have been extracted by individual chart review, other variables have been obtained from already established databases which can introduce unknown biases. In addition, data for donors were obtained from UNOS, which is dependent on adequate data collection at the time of donor management and cannot be

queried for accuracy. Additionally, this study is retrospective in nature and uncontrolled biases may have been introduced by decision-making at the time of transplantation with regard to treatment of graft dysfunction or RRT. This is a single-center study, and therefore, our findings may reflect our unique patient population and standards of care specific to our institution. Conversely, although we do not have available granular data regarding certain aspects of perioperative care (e.g., patient-level immunosuppressive treatment data), our single-center study, which includes a large number of patients with data related to PGD, spans a relatively short study period which ensures a uniform process of care.

In conclusion, we found that AKI after HT is common and more advanced stages of AKI are associated with increased risk of mortality in the first year after HT. Some of the risk factors associated with AKI may be modifiable, such as PGD and donor brain death duration.

Authorship

AN, AK, MC and MSS: conceived the research design and drafted the original version of the manuscript. AN, AK and JL: were involved in data acquisition. MC: analyzed the data. CP, JS, SM, MP, CM and MS: reviewed and edited the manuscript.

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Conflict of Interest

The authors have declared no conflicts of interest.

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