Impact of reduced creatinine clearance on early heart transplantation outcomes: a propensity score adjusted analysis

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Heart transplantation (HTx) remains the unsurpassed standard of care for end-stage congestive heart failure (HF). HTx outcomes are benchmarks against which key outcome metrics of alternative lines of advanced HF management are compared to. Postoperative renal failure in non-renal solid organ transplant recipients leads to a fourfold increase in mortality [1]. Many perioperative factors converge to adversely affect renal function. These include preoperative renal dysfunction, suboptimal hemodynamics, and calcineurin inhibitor therapy [1]. Moreover, multiple comorbidities common to HTx candidates, such as hypertension and diabetes mellitus, act in concert to compromise renal function. Renal dysfunction is common among HTx candidates [2]. A consensus as to the degree of renal dysfunction that presents an absolute contraindication to isolated HTx is lacking, as evidenced by diverse worldwide institutional practices [3]. The introduction of combined heart and kidney transplantations has further challenged the contemporary indications for HTx, adding an entirely new layer of complexity to the process of patient selection [3]. Precise definition of the impact of renal dysfunction on post-HTx outcomes is, therefore, paramount to optimizing patient selection. A continuously increasing organ demand is contrasted by limited donor availability [4]. Patients who require dialysis in the acute postoperative period have been found to have a substantial increase in mortality that may reach 60-70% [5]. The occurrence of acute renal failure in close proximity to a cardiac surgical procedure is a major adverse event. No single strategy designed to prevent renal injury after cardiac surgery has been found to be unequivocally effective [5].

We aimed to evaluate the independent effect of reduced functional renal reserve, quantified by pretransplant creatinine clearance, on 6-month survival and the requirement for acute renal replacement therapy (RRT) among patients undergoing isolated HTx. Data on all heart transplantations performed in Croatia from January 1, 2008 to November 1, 2014 were retrieved from two institutional electronic databases. Ethical standards in line with the Declaration of Helsinki were adhered to. The local Institutional Review Boards approved the study. Written informed consent was waived due to the study's retrospective nature.

During the study period 220 HTx were performed in Croatia. After harvesting data from electronic databases, individual medical records of HTx recipients were reviewed for

demographic, clinical, and laboratory data. Four patients were found to have missing data and were excluded. Accumulated donor variables included age and gender. Creatinine clearance (CrCl) values most proximal to the HTx procedure were used for estimating kidney function. CrCl was calculated using the Cockcroft-Gault formula. The primary end-point was 6-month posttransplant mortality. Secondary outcome measures were RRT within 30 days of Htx, stroke, resternotomy, incidence of postoperative mechanical circulatory assistance (MCS) and prolonged mechanical ventilation. Patients were dichotomized according to a CrCl cut-off value of 50 ml/min (Group A: CrCl≤50 ml/min; Group B: CrCl>50 ml/min). Propensity scores (PS) were calculated via logistic regression as the predicted probability of each patient's group membership. The variables included in the PS adjustment were recipient age and gender, preoperative atrial fibrillation, smoking history, organ ischemic time, duration of cardiopulmonary bypass (CPB), body mass index, preoperative MCS and reoperation. We then incorporated the PS into a binary logistic regression model, thereby adjusting for the confounders.

Sixty-three (29%) were found to have a CrCl≤50 ml/min. Patient characteristics are summarized in Table 1. Briefly, patients aggregated in Group A (CrCl≤50 ml/min) were older (56±11 vs. 49±12 years, P<0.001), and also had longer donor organ ischemic times (197±65 vs. 162±62 min, P<0.001). Dilated cardiomyopathy (CMP) was the most common pathology among patients with preserved preoperative renal functional reserve, followed by ischemic disease. Conversely, among patients with a CrCl≤50 ml/min ischemic CMP was the more prevalent pathology. The inter-group differences in the incidences of various cardiac pathologies antedating HTx were not statistically significant (Table 1).

Six-month survival in the entire cohort was 83% (179/216). The overall incidence of posttransplant RRT was 15% (33/216). Acute postprocedural RRT (within 30 days of the index procedure) was required more commonly in patients with depressed pretransplant CrCl (16/63 (25%) vs. 17/153 (11%); OR 2.72 (1.28-5.82); P=0.012). The occurrence of dialysis-dependent renal failure led to a potent increase in mortality (20/33 (61%) vs. 17/183 (9%); OR 15.02 [95% CI 6.37-35.44]; P <0.001). Of the 13 patients requiring acute RRT that were alive at 6 month follow-up, 12 recovered their renal function, while one patient remained dialysis dependent. Among patients with a CrCl≤50 ml/min 6-

month mortality was higher than in patients with preserved renal function (18/63 (29%) vs. 19/153 (12%); unadjusted odds ratio (OR) 2.82 [95% CI 1.36-5.84]; *P*=0.009). No differences were observed in the incidence of stroke, resternotomy, postoperative MCS or prolonged mechanical ventilation (Table 2).

A PS was determined by entering 9 covariates into a logistic regression model with CrCl as the dependent variable. All variables found to be statistically significantly different between the two studied cohorts on univariate analysis were included into the PS adjustment process. Additionally, we also included variables previously shown to exert an impact on outcome (recipient gender, reoperation, body mass index).

Patients with a CrCl≤50 ml/min had increased 6-month mortality on the PS adjusted analysis (OR 2.44 [95% CI 1.09-5.49]; *P*=0.030). Similarly, the incidence of RRT remained higher among Group A patients after PS adjustment (OR 3.36 [95% CI 1.43-7.92]; *P*=0.005).

The expanding gap between organ demand and availability underscores the impetus for optimizing transplant recipient selection [6]. Controversial data on the impact of pre-HTx renal dysfunction on outcomes have been published [7,8,9,10]. Overall, renal dysfunction among HTx candidates (CrCl≤50 ml/min) was not uncommon in our practice. We have shown that the incidence of perioperative RRT was significantly increased among patients with reduced pre-HTx renal functional reserve. The profound negative impact of perioperative RRT on survival has been substantiated by our results. Most survivors who required dialysis in the acute postoperative period, however, recovered their renal function and were not dependent on RRT at 6-month follow-up.

Survival was reduced in patients with reduced preoperative CrCl in our study. This effect remained significant after PS adjustment. These findings have important clinical implications as the proportion of high-risk patients enrolled into contemporary HTx programs is rising. In summary, the strength of the relationship between pretransplant CrCl and the risk of acute renal failure mandating dialysis and death from any cause suggests that CrCl remains a valid prognostic marker among HTx candidates in the current era.

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Table 1. Patient demographic and clinical data

Patient characteristics	***Group A (CrCl≤50 ml/min), n=63***	***Group B (CrCl>50 ml/min), n=153***	***P***
Recipient age (years)	56±11	49±12	<0.001
Male recipients (n/%)	48 (76)	125 (82)	0.355
Body mass index (kg/m^2)	25±4	26±5	0.257
Donor age (years)	39±11	39±12	0.875
Male donors (n/%)	46 (73)	100 (65)	0.338
PVR (dyn·s·cm−5)	213±107	188±96	0.145
Hyperlipidemia (n/%)	22 (35)	55 (36)	1.0
Hypertension (n/%)	28 (44)	62 (41)	0.650
Diabetes mellitus (n/%)	18 (29)	34 (22)	0.382
Smoking history (n/%)	10 (16)	45 (29)	0.040
Atrial fibrillation (n/%)	23 (37)	39 (25)	0.041
Creatinine clearance (mL/min)	39±8	75±18	<0.001
Reoperation (n/%)	18 (29)	34 (22)	0.382
Preoperative MCS (n/%)	6 (10)	17 (11)	0.813
Organ ischemic time (min)	197±65	162±62	<0.001
CPB time (min)	175±62	158±56	0.060
Pretransplant cardiac pathology			
Dilated CMP	30 (48)	88 (58)	0.229
Ischemic CMP	31 (49)	53 (35)	0.065
Valvular CMP	0 (0)	2 (1)	1.0

Restrictive CMP	1 (2)	3 (2)	1.0
Hypertrophic obstructive CMP	0 (0)	2 (1)	1.0
Left ventricular non-compaction CMP	0 (0)	2 (1)	1.0
Grown-up congenital disease	0 (0)	1 (1)	1.0
ARVD	1 (2)	2 (1)	1.0

CrCl = creatinine clearance, PVR = pulmonary vascular resistance, MCS = mechanical circulatory assistance, CPB = cardiopulmonary bypass, CMP = cardiomyopathy, ARVD = arrhythmogenic right ventricular dysplasia.

Table 2. Analysis of perioperative outcomes

Table 2A. Primary and secondary study outcomes on univariate analysis				
	Group A (CrCl ≤ 50 mL/min), n=63	*Group B (CrCl>50 ml/min), n=153*	*Crude OR (95% CI)*	*P*
6-month mortality (n/%)	18 (29)	19 (12)	2.82 (1.36-5.84)	0.009
RRT (n/%)	16 (25)	17 (11)	2.72 (1.28-5.82)	0.012
Stroke (n/%)	2 (3)	5 (3)	0.97 (0.18-5.14)	1.0
Resternotomy (n/%)	15 (24)	24 (16)	1.68 (0.81-3.47)	0.175
Postoperative MCS (n/%)	7 (11)	11 (7)	1.61 (0.60-4.37)	0.417
Prolonged mechanical ventilation (n/%)	22 (35)	38 (25)	1.62 (0.86-3.06)	0.137

Table 2B. Primary and secondary study outcomes after propensity score adjustment		
	PS adjusted OR (95% CI)	*P*
6-month mortality (n/%)	2.44 (1.09-5.49)	0.030
RRT (n/%)	3.36 (1.43-7.92)	0.005

CrCl = creatinine clearance, OR = odds ratio, CI = confidence interval, RRT = renal replacement therapy, MCS = mechanical circulatory assistance, PS = propensity score