Original Paper

Outcomes of Moderate-to-Severe Acute Kidney Injury following Left Ventricular Assist Device Implantation

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Keywords

Renal function · Left ventricular assist device · End-stage heart failure

Abstract

Background: Although acute kidney injury (AKI) is a common complication following cardiac surgery, less is known about the occurrence and consequences of moderate/severe AKI following left ventricular assist device (LVAD) implantation. **Methods:** All patients who had an LVAD implanted at our center from 2008 to 2016 were reviewed to determine the incidence of, and risk factors for, moderate/severe (stage 2/3) AKI and to compare postoperative complications and mortality rates between those with and those without moderate/severe AKI. **Results:** Of 246 patients, 68 (28%) developed moderate/severe AKI. A multivariable logistic regression comprising body mass index and prior sternotomy had fair predictive ability (area under the curve = 0.71). A 1-unit increase in body mass index increased the risk of moderate/severe AKI by 7% (odds ratio = 1.07; 95% confidence interval: 1.03–1.11); a prior sternotomy increased the risk more than 3-fold (odds ratio = 3.4; 95% confidence interval: 1.84–6.43). The group of patients with moderate/severe AKI had higher rates of respiratory failure and death than the group of patients with mild/no AKI. Patients with moderate/severe AKI were at 3.2 (95% confidence interval: 1.2–8.2) times the risk of 30-day mortality compared to those with-

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out. Even after adjusting for age and Interagency Registry for Mechanically Assisted Circulatory Support profile, those with moderate/severe AKI had 1.75 (95% confidence interval: 1.03–3.0) times the risk of 1-year mortality compared to those without. **Discussion:** Risk-stratifying patients prior to LVAD placement in regard to AKI development may be a step toward improving surgical outcomes.

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Introduction

Left ventricular assist devices (LVADs) have become an increasingly common therapy for patients with end-stage heart failure as a bridge to cardiac transplantation or as destination therapy [1]. However, this treatment modality is not without complications. One potential complication, acute kidney injury (AKI), has been associated with increased mortality in the setting of cardiac surgery [e.g., 2], including LVAD implantation [3–5]. Important clinical aspects that are less known are the rates, predictors, and consequences of *moderate/severe* AKI after LVAD placement. Predictors of AKI, as well as moderate/severe AKI, are poorly defined for LVAD recipients, as previous studies have offered varying results and suggestions for treatment and preventative measures. The accuracy of these results may be further diminished as many LVAD recipients have heart failure-related renal dysfunction (i.e., cardiorenal syndrome [CRS]), which in some studies has been shown to improve following LVAD placement [6–8].

Hence, this study, with one of the largest LVAD/AKI databases to date, aimed to determine the incidence, predictors, and subsequent postoperative consequences of moderate/severe AKI following LVAD placement in a cohort of dialysis-independent patients. We hope to better define the risk factors and implications of moderate/severe AKI, which may result in stronger, clarified preventative measures, thereby lowering comorbidity and mortality among LVAD recipients.

Methods

We retrospectively reviewed the medical records on consecutive patients undergoing LVAD implantation at our high-volume center from June 2008 to May 2016. We used the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines to classify AKI stages [9] and defined moderate/severe AKI as stage 2 or 3 AKI. To eliminate confounding, patients having required dialysis prior to surgery were excluded from the analyses. The pre- and intraoperative variables considered are in Table 1. Right heart failure was defined according to the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) as signs and symptoms of persistent right ventricular dysfunction following LVAD implantation. Right heart failure was categorized based on the duration of inotropes (0–7 days on inotropes = mild; 8–14 days = moderate; >14 days = severe) or the need for a right ventricular assist device (acute severe) [10]. Respiratory failure was defined as the need for mechanical ventilation following initial extubation.

Statistical Analysis

We used Wilcoxon rank-sum and χ^2 tests to assess differences in demographics between those who developed moderate AKI and those who did not. Preoperative and intraoperative variables having significant relations to AKI were considered jointly in a multivariable logistic regression model constructed via stepwise selection, with the optimal model chosen by Akaike's corrected information criterion. Wilcoxon rank-sum, χ^2 , and Fisher's exact tests were used to assess group differences in postoperative outcomes. Finally, we assessed the effect of moderate/severe AKI on the competing risks of transplantation and mortality from hazard ratios obtained via the Fine and Gray method [11]. We repeated the analysis after adjusting for age and INTERMACS profile. For simplicity, we refer to "mortality" and "survival" when we truly mean "transplant-free mortality" and "transplant-free survival." Continuous variables are reported as median (quarter 1, quarter 3). Categorical variables are reported as frequencies (percentages). All analyses were performed in SAS version 9.4 (SAS Institute, Cary, NC, USA).

Table 1. Baseline characteristics

Variable	Stage 2/3 AKI (n = 68)	Stage 1/no AKI (n = 178)	p value
Male	58 (85.3%)	140 (78.7%)	0.24
Age, years	61 [52.5, 66.5]	58.5 [47, 66]	0.25
Body mass index	31.8 [27.8, 38.5]	28.1 [24.2, 33.6]	<0.001
Race			0.36
African American	16 (23.5%)	43 (24.2%)	
Caucasian	51 (75.0%)	125 (70.2%)	
Other	1 (1.5%)	10 (5.6%)	
INTERMACS profile			0.08
1	11 (16.2%)	31 (17.4%)	
2	20 (29.4%)	67 (37.6%)	
3	24 (35.3%)	66 (37.1%)	
4	13 (19.1%)	14 (7.9%)	
MELD score ¹	13.5 [11, 16]	131 [10, 17]	0.6
HeartMate risk score ¹	1.9 [1.5, 2.6]	1.8 [1.3, 2.2]	0.1
Diabetes	33 (48.5%)	68 (38.2%)	0.14
Chronic obstructive pulmonary disease	7 (10.3%)	17 (9.6%)	0.86
Destination therapy ¹⁰	36 (53.7%)	82 (48.5%)	0.47
Ischemic cardiomyopathy ¹	13 (19.1%)	15 (8.5%)	0.02
Type of LVAD			1
HeartMate II	63 (92.7%)	163 (91.6%)	
HeartMate 3	1 (1.5%)	5 (2.8%)	
HeartWare	4 (5.9%)	10 (5.6%)	
Prior sternotomy	34 (50.0%)	49 (27.5%)	<0.001
Central venous pressure, mm Hg ³	15 [8, 18]	14 [10, 19]	0.81
Medication (in past year)			
ACE inhibitor	38 (55.9%)	99 (55.6%)	0.97
Aldosterone	45 (66.2%)	105 (59.0%)	0.3
Amiodarone ¹	33 (48.5%)	63 (35.6%)	0.06
Angiotensin receptor blocker ¹	9 (13.2%)	19 (10.7%)	0.58
Antiplatelet	49 (72.1%)	112 (62.9%)	0.18
Beta blocker	57 (83.8%)	153 (86.0%)	0.67
Warfarin ¹	26 (38.2%)	64 (36.2%)	0.76
Preoperative creatinine clearance, mL/min	69.1 [54.2, 97.7]	72.3 [47.8, 92.9]	0.54
Preoperative serum creatinine, mg/dL	1.5 [1.3, 1.7]	1.4 [1.1, 1.8]	0.045
eGFR, mL/min/1.73 m ²	50.8 [42.3, 59.0]	57.4 [41.2, 72.4]	0.05
Chronic kidney disease stage (per eGFR)			0.03
1	4 (5.9%)	23 (12.9%)	
2	11 (16.2%)	55 (30.9%)	
3a	27 (39.7%)	43 (24.2%)	
3b	20 (29.4%)	42 (23.6%)	
4 or 5	6 (8.8%)	15 (8.4%)	
Preoperative BUN, mg/dL ⁵⁵	27 [18, 41]	25.5 [20, 34]	0.68
Preoperative systolic blood pressure, mm Hg ²	108 [96, 125.5]	101.5 [92, 112]	0.007
Preoperative diastolic blood pressure, mm Hg ²	72 [63, 76]	66 [57, 75]	0.03
Preoperative length of stay, days	5.5 [2, 11]	6 [2, 11]	0.55
Heart rate, bpm	82 [74.5, 95.5]	86 [77, 98]	0.23
Intraoperative variables			
Cross clamp use ³	6 (8.8%)	13 (7.4%)	0.72
Cardiopulmonary bypass time, min ¹¹	79.5 [62, 113]	78 [60, 98]	0.37
Volume ultrafiltrated, mL ¹⁵	1,600 [0, 3,000]	1,800 [0, 3,000]	0.64
Nadir hematocrit, % ²	26 [23.8, 29.5]	27 [24.0, 30]	0.28

Values denote n (%) or median [quarter 1, quarter 3]. Superscripts indicate the number of missing values. INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; MELD, Model for End-Stage Liver Disease; LVAD, left ventricular assist device; eGFR, estimated glomerular filtration rate; BUN, blood urea nitrogen.

Table 2. Prediction model for postoperative moderate acute kidney injury

	Estimate	Standard error	χ^2	p value
Intercept	−3.03	0.61	24.34	<0.0001
Body mass index	0.07	0.02	13.88	0.0002
Prior sternotomy (yes vs. no)	0.62	0.16	15.07	0.0001

Results

Postoperative AKI Risk Factors

There were 246 patients who met the criteria for our study, i.e., they underwent LVAD implantation from June 2008 to May 2016 and had not been on dialysis prior to surgery. Most ($n = 226$; 92%) were implanted with a HeartMate II (Abbott, St. Paul, MN, USA) device. Of the study cohort, 68 patients (28%) developed moderate/severe AKI. The development of AKI was not associated with age or gender (Table 1). Interestingly, we found no associations between surgical risk scores and AKI outcomes (INTERMACS profile, $p = 0.08$; Model for End-Stage Liver Disease [MELD] score, $p = 0.60$; HeartMate Risk Score [HMRS], $p = 0.10$). Those who developed moderate/severe AKI had a greater body mass index (BMI; $p < 0.001$), slightly higher preoperative serum creatinine levels ($p = 0.045$), and approximately twice the rates of ischemic cardiomyopathy ($p = 0.02$) and prior sternotomy ($p < 0.001$) than those who did not.

Multivariable Analysis

When considering multivariable models for the prediction of moderate/severe AKI following LVAD placement, the optimal model utilized BMI and prior sternotomy (Table 2), yielding an area under the curve of 0.71, indicating fair predictive ability. For every 1-unit increase in BMI, the risk of developing moderate/severe AKI increased by 7% (odds ratio = 1.07; 95% confidence interval [CI]: 1.03–1.11). Those who had undergone prior sternotomy were at >3 times the risk of developing moderate/severe AKI (odds ratio = 3.44; 95% CI: 1.84–6.43).

Comorbidities and Mortality

Those who developed moderate/severe AKI were more likely to develop right heart failure and respiratory failure; however, the incidence rates of stroke, thrombus, and driveline infection did not differ significantly (Table 3). Patients with moderate/severe AKI were at >3 times the risk of 30-day mortality compared to those with mild or no AKI (hazard ratio = 3.2; 95% CI: 1.24–8.17). Additionally, the hazard ratio for moderate AKI from the 1-year mortality model neared statistical significance (hazard ratio = 1.69; 95% CI: 0.99–2.89; $p = 0.056$) and reached significance after adjustment for age and INTERMACS profile (Fig. 1; hazard ratio 0 1.75; 95% CI: 1.03–3.0; $p = 0.04$).

Discussion

The present cohort showed an overall incidence of 28% of moderate/severe AKI following LVAD implantation, which is comparable to the previously published findings of Muslem et al. [5], who broke down their AKI results by KDIGO stage. Our study identified increased BMI and prior sternotomy as significant risk factors for developing AKI following LVAD placement. Preoperative serum creatinine and ischemic cardiomyopathy were also associated with postoperative moderate/severe AKI in bivariate analyses. Those who developed moderate/

Table 3. Surgical outcomes

Variable	Moderate/ severe AKI (n = 68)	Mild/ no AKI (n = 178)	p value
Exploratory operation for bleeding	14 (20.6%)	25 (14.0%)	0.21
Right heart failure (n = 240)			0.07
None/mild	44 (65.7%)	148 (85.6%)	
Moderate	10 (14.9%)	11 (6.4%)	
Severe	6 (9.0%)	6 (3.5%)	
Acute severe	7 (10.5%)	8 (4.6%)	
Gastrointestinal bleed	9 (13.2%)	18 (10.1%)	0.48
Pump thrombus	7 (10.3%)	22 (12.4%)	0.65
Driveline infection	3 (4.4%)	15 (8.4%)	0.41
Respiratory failure	24 (35.3%)	35 (19.7%)	0.01
Stroke	9 (13.2%)	23 (12.9%)	0.95
Postoperative length of stay, days	14 [10, 23]	14 [11, 20]	0.95
Deceased at 30 days ^a	9 (13.2%)	8 (4.5%)	0.02
Deceased at 1 year ^a	21 (30.9%)	37 (20.8%)	0.056

Values denote n (%) or median [quarter 1, quarter 3]. ^a These p values were calculated from competing risk models.

Fig. 1. Cumulative incidence functions for the effect of moderate/severe acute kidney injury on 1-year mortality following left ventricular assist device implantation. Adjusted for age and Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profile.

severe AKI had worse survival rates at 30 days than those with stage 1 or no AKI. Patients with moderate/severe AKI also had significantly worse 1-year survival rates after adjusting for age and INTERMACS profile [5]. Along with an increased mortality rate, postoperative AKI was associated with higher postoperative rates of respiratory failure.

A clinical increase in creatinine following cardiothoracic surgery may indicate either structural kidney damage or temporarily decreased perfusion [12]. Many studies have sought to identify risk factors for AKI development in the postoperative setting [3, 4, 7, 13–15]. Alba et al. [13] found significant relations between postoperative AKI and cardiopulmonary bypass (CPB) time, reoperation following placement, and blood loss during the procedure. Conversely, Naik et al. [3] found diabetes mellitus to be the only predictor of postoperative AKI, with

existing cerebrovascular disease and preoperative hematocrit trending toward significance, while Borgi et al. [4] found preoperative intubation and increased central venous pressure to be predictors. A study of heart transplant recipients also revealed CPB time, reoperation following the procedure, and blood loss-related transfusions to be risk factors for postoperative AKI [15]. We did not find an association between postoperative AKI and CPB duration, central venous pressure, diabetes mellitus, or bleeding. However, as supported by our data, Tjahjono et al. [15] reported a trend of increased AKI risk with prior sternotomy. Those who have undergone a prior sternotomy tend to have excess scar tissue that the surgeon must cut through during surgery. As such, these patients typically have higher bleeding rates and longer CPB times than those who have not had a prior sternotomy. Additionally, the condition for which the prior sternotomy was performed may also play a role in current outcomes, although this role may be more difficult to pinpoint as the condition varies per individual. Finally, AKI was positively associated with BMI in our cohort. Associations between BMI and renal complications and higher creatinine have been well documented [16, 17].

While some patients with high preoperative creatinine develop AKI postoperatively [18], others with CRS may have improvements in renal function following LVAD placement [7, 14, 19–21]. Many studies note these transient renal functional improvements, with return to baseline dysfunction after 1 or more years [6, 7]. Kirklin et al. [20] found that the improvement remained up to 2 years following device placement, and their group expressed the need for LVAD placement prior to worsening CRS. Prevention of CRS should be the clinical goal, because once initiated, CRS cannot be readily aborted and is not completely reversible [22]. These reports emphasize the capacity of correcting reversible CRS, though the long-term impact of LVAD as destination therapy in these patients is not completely understood [18]. As renal dysfunction associated with heart failure may improve with device placement, it is difficult to assess the risk of moderate/severe AKI without an optimal laboratory tool for prediction and/or assessment [23]. Identifying biomarkers that confirm cardiac surgery-associated AKI, such as urine neutrophil gelatinase-associated lipocalin, have been evaluated, but to date the results have been unreliable in predicting clinical outcomes [24]. Recently, preoperative estimated glomerular filtration rate and proteinuria were identified as predictors of postoperative renal dysfunction necessitating renal replacement therapy in continuous-flow LVAD recipients [25]. Recent evidence from a single center showed intravenous inotropic therapy to be noninferior to LVAD placement for end-stage heart failure patients with respect to mortality and the need for renal perfusion [26]. The success of this therapy may be due to the correction of reversible kidney injury secondary to poor perfusion, though long-term studies have not yet been completed [19, 24].

Several studies have indicated AKI as a predictor of postoperative mortality for both short-term [4] and long-term [4, 5, 27] intervals. Borgi et al. [4] reported that patients with postoperative AKI experienced significantly longer hospital stays and higher rates of ventilator-dependent respiratory failure and right ventricular failure, as well as increased mortality rates at 30 days, 6 months, and 1 year. In one retrospective analysis, the risk of long-term mortality was reported to increase 3-fold in a 1-year period for patients who developed AKI following LVAD placement [27]. Originally, Chertow et al. [28] had shown that increased baseline (preoperative) creatinine correlated directly with an increased incidence of acute renal failure following cardiac surgery. Kirklin et al. [20] reported that increased preoperative renal dysfunction, quantified by blood urea nitrogen and estimated glomerular filtration rate, was associated with increased postoperative mortality, particularly in the first 3 months. We also found, similar to Chertow et al. [28], that preoperative serum creatinine was higher in those who developed moderate AKI ($p = 0.045$), which subsequently increased the risk of mortality, consistent with the previous literature [20, 25]. This increased preoperative creatinine may be an indicator of baseline renal dysfunction of some degree, though various

biomarkers and ratios (such as urine albumin and the urine albumin creatinine ratio) may prove more reliable [28, 29]. Although higher BMI has been associated with renal complications and AKI, it is conversely not associated with mortality (or may even be protective, in some cases, when compared to the underweight population) [3, 15–17].

As our findings are from a retrospective cohort at a single center with the vast majority of patients receiving a HeartMate II device, our results may not be widely generalizable. Our choice to consider moderate/severe AKI (i.e., KDIGO stages 2 and 3) instead of all AKI stages is novel and prompted by what is generally believed to be clinically significant; however, it also potentially limits the generalizability of our findings. As the data had not originally been recorded with the intent to perform research, several potentially interesting variables (proteinuria, hypertension, cardiovascular disease, stroke, etc.) were not available for analysis.

In conclusion, we found that those who developed moderate/severe AKI following LVAD implantation had poor surgical outcomes, including increased mortality rates. Strategies, including risk stratification, should be implemented to reduce the occurrence of moderate/severe AKI following LVAD placement. In our study, we identified BMI and previous sternotomy as significant risk factors for moderate/severe AKI development.

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Statement of Ethics

The protocol for data collection was approved by the Institutional Review Board of the Baylor University Medical Center (Dallas, TX, USA), and informed consent was waived.

Disclosure Statement

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