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WJCCM mainly publishes articles reporting research results and findings obtained in the field of critical care medicine and covering a wide range of topics including acute kidney failure, acute respiratory distress syndrome and mechanical ventilation, application of bronchofiberscopy in critically ill patients, cardiopulmonary cerebral resuscitation, coagulant dysfunction, continuous renal replacement therapy, fluid resuscitation and tissue perfusion, hemodynamic monitoring and circulatory support, ICU management and treatment control, sedation and analgesia, severe infection, etc.

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Recovery after acute kidney injury requiring kidney replacement therapy in patients with left ventricular assist device: A meta-analysis

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Abstract

BACKGROUND

Acute kidney injury (AKI) is a common and severe complication after left ventricular assist device (LVAD) implantation with an incidence of 37%; 13% of which require kidney replacement therapy (KRT). Severe AKI requiring KRT (AKI-KRT) in LVAD patients is associated with high short and long-term mortality compared with AKI without KRT. While kidney function recovery is associated with better outcomes, its incidence is unclear among LVAD patients with severe AKI requiring KRT.

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AIM

To identify studies evaluating the recovery rates from severe AKI-KRT after LVAD placement, which is defined by regained kidney function resulting in the discontinuation of KRT. Random-effects and generic inverse variance method of DerSimonian-Laird were used to combine the effect estimates obtained from individual studies.

METHODS

A total of 268 patients from 14 cohort studies that reported severe AKI-KRT after LVAD were included. Follow-up time ranged anywhere from two weeks of LVAD implantation to 12 mo. Kidney recovery occurred in 78% of enrollees at the time of hospital discharge or within 30 d. Overall, the pooled estimated AKI recovery rate among patients with severe AKI-KRT was 50.5% (95%CI: 34.0%-67.0%) at 12 mo follow up. Majority (85%) of patients used continuous-flow LVAD. While the data on pulsatile-flow LVAD was limited, subgroup analysis of continuous-flow LVAD demonstrated that pooled estimated AKI recovery rate among patients with severe AKI-KRT was 52.1% (95%CI: 36.8%-67.0%). Meta-regression analysis did not show a significant association between study year and AKI recovery rate ($P = 0.08$). There was no publication bias as assessed by the funnel plot and Egger's regression asymmetry test in all analyses.

RESULTS

A total of 268 patients from 14 cohort studies that reported severe AKI-KRT after LVAD were included. Follow-up time ranged anywhere from two weeks of LVAD implantation to 12 mo. Kidney recovery occurred in 78% of enrollees at the time of hospital discharge or within 30 d. Overall, the pooled estimated AKI recovery rate among patients with severe AKI-KRT was 50.5% (95%CI: 34.0%-67.0%) at 12 mo follow up. Majority (85%) of patients used continuous-flow LVAD. While the data on pulsatile-flow LVAD was limited, subgroup analysis of continuous-flow LVAD demonstrated that pooled estimated AKI recovery rate among patients with severe AKI-KRT was 52.1% (95%CI: 36.8%-67.0%). Meta-regression analysis did not show a significant association between study year and AKI recovery rate ($P = 0.08$). There was no publication bias as assessed by the funnel plot and Egger's regression asymmetry test in all analyses.

CONCLUSION

Recovery from severe AKI-KRT after LVAD occurs approximately 50.5%, and it has not significantly changed over the years despite advances in medicine.

Key Words: Acute kidney injury; Kidney recovery; Kidney replacement therapy; Left ventricular assist devices

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Core Tip: Left ventricular assist devices (LVAD) are mechanical support tools that augment cardiac output and improve kidney perfusion. Acute Kidney Injury (AKI) is a common complication after LVAD implantation. High short- and long-term mortality is associated with severe AKI requiring Kidney replacement therapy (KRT) in LVAD patients compared with those without KRT. While kidney function recovery is associated with better outcomes, the recovery rate is unclear among LVAD patients with severe AKI requiring KRT. To investigate this further, we conducted the current systematic review and meta-analysis evaluating kidney recovery rate after AKI-KRT among LVAD patients. We report that the pooled estimated AKI recovery rate among patients with severe AKI-KRT was 50.5% (95%CI: 34.0%-67.0%) at 12 mo follow up.

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INTRODUCTION

Heart transplantation remains the treatment of choice for patients with severe end-stage heart failure. Deteriorating kidney function is commonly noted among advanced heart failure patients secondary to cardiorenal physiology and is associated with unfavorable outcomes[1-4]. Left ventricular assist devices (LVAD) are mechanical support tools that augment cardiac output by unloading the left ventricle and improving kidney perfusion. LVAD is used as a bridge to transplantation for patients on the transplant list or destination therapy for individuals who are not ideal transplant candidates[5].

Even though kidney perfusion improves in most patients, acute kidney injury (AKI) is a common and severe complication following LVAD implantation with an incidence of 37%[6]. About one-third of them (13%) sustain severe AKI post LVAD placement needing kidney replacement therapy (KRT)[6]. As reported in previous studies, severe AKI-KRT in LVAD patients is associated with high short and long-term mortality compared to those without KRT[7]. Risk factors associated with increased risk of AKI post LVAD insertion include older age, use of intra-aortic balloon pump (IABP), lower mean total protein and albumin levels, post-implantation shock, elevated central venous pressure > 16 mmHg, longer cardiopulmonary bypass times, postoperative right ventricular failure and preexisting chronic kidney disease before implantation[8-10].

Kidney recovery is defined as independence from KRT in AKI-KRT patients within fourteen d of the initial injury [11]. In a study by Grinstein *et al*[12], early kidney improvement is defined as an increase in eGFR $\geq 15\%$ within one week of LVAD implantation. In a recent prospective, multicenter assessment, serial evaluation, and subsequent sequelae (ASSESS-AKI) cohort study by Bhatraju *et al*[13] evaluating the incidence and progression of chronic kidney disease (CKD) and dialysis in patients who sustained AKI episodes as compared to patients without AKI, a 2- and 3-fold higher risk of major kidney adverse effects were reported among those with resolving and non-resolving AKI, respectively, as compared to patients without AKI. Additionally, patients with non-resolving AKI had higher De Novo and progressive CKD rates than no AKI and resolving AKI.

Early improvement in kidney function in patients with AKI after LVAD placement is associated with decreased length of stay and fewer complications [14]. Kidney recovery is associated with a favorable prognosis in estimating postoperative kidney function in adults and children undergoing LVAD placement [15]. While recovery of kidney function is associated with better outcomes, kidney recovery rates among LVAD patients with severe AKI-KRT are unknown. We, therefore, conducted the current meta-analysis to report the incidence of kidney recovery among patients needing KRT post LVAD implantation at 30 d or at the time of discharge and up to 12 mo.

MATERIALS AND METHODS

Search strategy

This manuscript follows the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis)[16] statement and MOOSE (Meta-analysis of Observational Studies in Epidemiology)[17] guidelines. A systematic search was conducted through the Ovid MEDLINE, EMBASE, and Cochrane Library from database inception to January 2020 using the following search terms: ('left ventricular assist device' OR 'lvad' OR 'ventricular assist device') AND ('acute kidney failure' OR 'acute kidney injury' OR 'renal replacement therapy' OR dialysis). The detailed search strategy for each database is summarized in [Supplementary material](#). No language restrictions were applied.

Inclusion criteria

The following inclusion criteria determined the eligibility of each article, including: (1) The nature of the study is observational or conference abstract; (2) Study population consisted of patients with LVAD; and (3) The rates of kidney recovery after AKI episode among patients after LVAD placement is considered one of the outcomes of

interest. Exclusion criteria consisted of pediatric patients, case series, and studies that did not mention outcomes of interest. Study eligibility was independently evaluated by two investigators (Kovvuru K and Kanduri SR). Any disagreements were resolved by mutual consensus. The quality of each study was appraised using the Newcastle–Ottawa quality scale[18], which assesses six components, including: (1) Representativeness of the subjects; (2) Ascertainment of the exposure; (3) Demonstration of the outcome of interest was not present at the start of the study; (4) Assessment of outcome; (5) Follow-up duration period was long enough for an outcome to occur; and (6) Adequate follow-up duration.

Review process and data extraction

The titles and abstracts of all identified studies were screened (Kovvuru K and Kanduri SR) before a full-text review. The full-text of the screened articles was reviewed to determine their eligibility. We created a standardized data collection form to extract the relevant information from the included studies, including the first author's name, year of publication, country of origin, study design, sample size, AKI definition, number of patients with AKI, rate of kidney recovery, duration of follow up. Kidney recovery was defined as independence from dialysis after an episode of severe AKI.

Measurements

The rates of kidney recovery among patients with severe AKI-KRT and kidney recovery rates among the subgroup of patients with continuous-flow devices entered the meta-analysis. The results were reported in percentage along with 95% confidence interval (CI). A Forest plot of each analysis was created. Results were presented in percentage for categorical data and in mean \pm SD or median (interquartile range) for continuous data.

Evaluation of publication bias

Publication bias was evaluated by funnel plot (if the total number of studies was > 10 [18] and Egger's regression intercept. An intercept P value of less than 0.05 was considered significant for potential publication bias.

Statistical analysis

All statistical analyses were performed by the Comprehensive Meta-analysis version 3 software (Eaglewood, NJ, United States). Statistical heterogeneity of the included studies was assessed using Cochran's Q-test and I^2 statistics. An I^2 value of $\leq 25\%$ represents insignificant heterogeneity, 25%-50% represents low heterogeneity, 50%-75% represents moderate heterogeneity, and $> 75\%$ represents high heterogeneity. For analyses with $I^2 > 50\%$, the results were analyzed by the random-effects model to minimize the heterogeneity and external variance[20]. A P value of less than 0.05 represents statistical significance.

RESULTS

Study characteristics

A total of 14 studies[7,8,21-31], consisting of 268 subjects, were included in the current meta-analysis. Figure 1 provides a flowchart of the literature search and study selection for this analysis. Included studies were published from 2000 to 2019. The study designs included retrospective and prospective cohort studies. The total duration of follow-up was anywhere from 2 wk to 12 mo. Table 1 illustrates study characteristics and kidney recovery rates among patients included in this systematic review.

Asleh *et al*[30] reported among patients requiring KRT after LVAD placement, one-third had kidney recovery, one-third required outpatient hemodialysis, and one-third of the patients died before hospital discharge. In study by Borgi *et al*[7] patients with post LVAD AKI were more likely to suffer longer hospital stay (32.4 *vs* 18.7; $P = 0.05$), right ventricular (RV) failure (25% *vs* 5.6%; $P = 0.01$) and a higher mortality rate as compared to non-AKI groups at 30-day (17.9% *vs* 0%; $P < 0.001$), 180-day (28.6% *vs* 2.8%; $P < 0.001$), and 360- day (28.6% *vs* 6.9%; $P = 0.012$), respectively. In a study by Demirozu *et al*[21], patients with sustained clinical recovery after LVAD eventually had kidney recovery. Muslem *et al*[32] evaluated long-term mortality after LVAD placement and reported that severe AKI (*i.e.*, stages 2 and 3) was associated with

Table 1 Study characteristics and outcomes included in the systematic review

Study	Year	Country	Patients	AKI definition	No of patients with AKI	Rate of kidney recovery
Kaltenmaier <i>et al</i> [31]	2000	Germany	LVAD-implantation during 1988-1995; Pulsatile Berlin Heart System HeartMate 2000, Novacor.	KRT	55	3/55 = 6%; Kidney recovery at hospital discharge
Demirozu <i>et al</i> [21]	2011	United States	LVAD implantation during 2003-2009; Continuous HeartMate II	KRT	15	10/15 = 67%; Kidney recovery at 7 mo
Hasin <i>et al</i> [8]	2012	United States	LVAD from 2007 to 2010; Continuous HeartMate II	KRT	8	2/8 = 25%; Kidney recovery at 6 mo
Popov <i>et al</i> [22]	2012	United Kingdom	Patient with end-stage heart failure underwent LVAD implantation-2007-2011; Continuous Heart Ware	KRT	12	10/12 = 83%; Kidney recovery post-op/
Borgi <i>et al</i> [7]	2013	United States	End-stage heart failure LVAD during 2006-2011; Continuous HeartMate II; Heart Ware	AKI (KDIGO); KRT	28; 9	17/28 = 60%; Kidney recovery one month; 4/9 = 44.5%; Kidney recovery after KRT--one month
Sumida <i>et al</i> [23]	2014	Japan	LVAD implantation during 2011-2013; LVAD type not specified	AKI; KDIGO; KRT	11; 6	11/11 = 100%; Kidney recovery at Hospital discharge; 4/6 = 66.6%; Kidney recovery after KRT at hospital discharge
Deschika <i>et al</i> [24]	2016	Germany	LVAD recipients with pre-operative biventricular impairment who received an additionally RVAD	KRT	9	9/9 = 100%; Kidney recovery at hospital discharge
Shebab <i>et al</i> [25]	2016	Australia	Dilated cardiomyopathy and severe biventricular failure -underwent dual HVAD implantation as a bridge to transplant during 2011-2014; Continuous Heart Ware	KRT	4	3/4 = 75%; Kidney recovery at post-op
Nadziakiewicz <i>et al</i> [26]	2016	Portland	Patients with end-stage heart failure underwent LVAD implantation during 2007-2014; Continuous Heart ware, HeartMate II	KRT	7	5/7 = 72%; Kidney recovery after KRT- 2 weeks
Raichlin <i>et al</i> [27]	2016	United States	End-stage heart failure with preexisting kidney dysfunction underwent LVAD implantation - 2009-2014; Continuous HeartMate II	KRT	15	6/15 = 40%; Kidney recovery after KRT -one month
Muslem <i>et al</i> [32]	2018	Netherlands, United States	LVAD implantation during 2004-2015; Continuous Heart ware, HeartMate II	KRT	23	14/23 = 61%; Kidney recovery after KRT at one year
Schmack <i>et al</i> [28]	2018	Germany	End-stage heart failure patients underwent LVAD from 2010 to 2017; Continuous Heart Ware	KRT	32	5/32 = 16%; Kidney recovery one-month post-KRT
Shebab <i>et al</i> [29]	2018	Australia	LVAD implantation as a bridge to transplant from 2007 to 2016; Continuous Heart Ware	KRT	19	15/19 = 79%; Kidney recovery after KRT Post-op
Asleh <i>et al</i> [30]	2019	United States	LVAD implantation during 2007-2017; ContinuousHeartMate II; HeartMate III; Heart Ware	KRT	54	18/54 = 33%; Kidney recovery at hospital discharge

AKI: Acute kidney injury; KDIGO: Kidney Disease Improving Global Outcomes; N/A: Not available; KRT: Kidney replacement therapy; LVAD: Left ventricular assist device.

higher mortality (hazard ratio 2.2, [95%CI: 1.1 to 4.5], $P = 0.027$) at one year. Schmack *et al*[28] reported higher pre-operative blood urea nitrogen (BUN) and low albumin levels as strong predictors of the need for kidney replacement therapy post LVAD implantation.

Additionally, they reported a negative association between postoperative hemodialysis and short-term survival. Sumida *et al*[23] reported plasma NGAL levels perioperatively could help predict severe AKI-KRT, while lower NGAL levels were associated with kidney recovery in patients after LVAD implantation.

Rates of Kidney Recovery from severe Acute Kidney Injury after LVAD

78.5% of patients had kidney recovery occurred at the time of hospital discharge or within 30 d. Overall, the pooled estimated rates of AKI recovery among patients with severe AKI-KRT was 50.5% (95%CI: 34.0%-67.0%) (Figure 2) and did not significantly change over the years despite advances in medicine. Meta-regression analysis did not

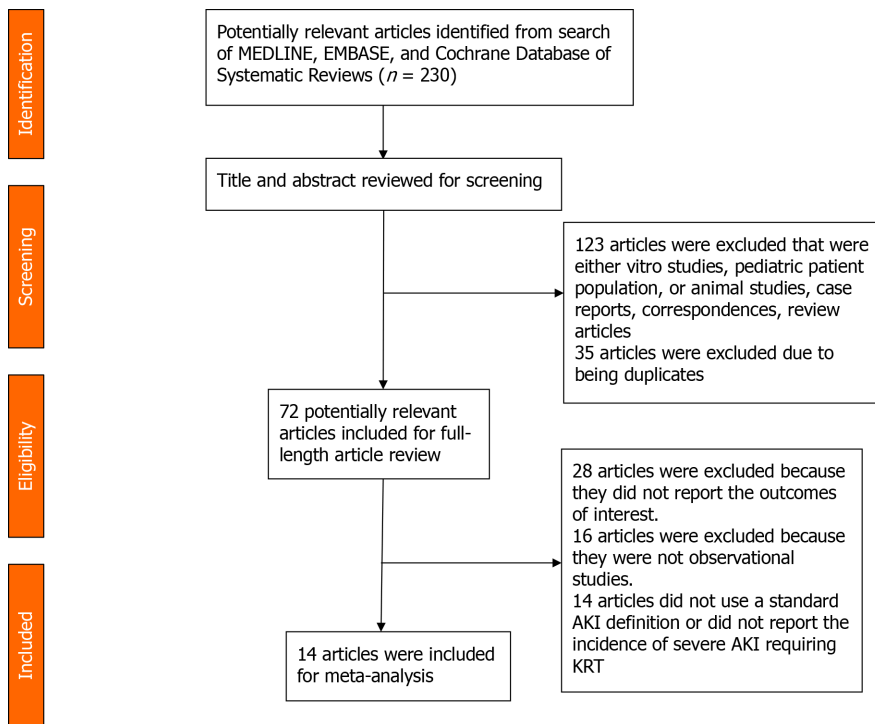


Figure 1 This picture provides a flowchart of the literature search and study selection for this analysis.

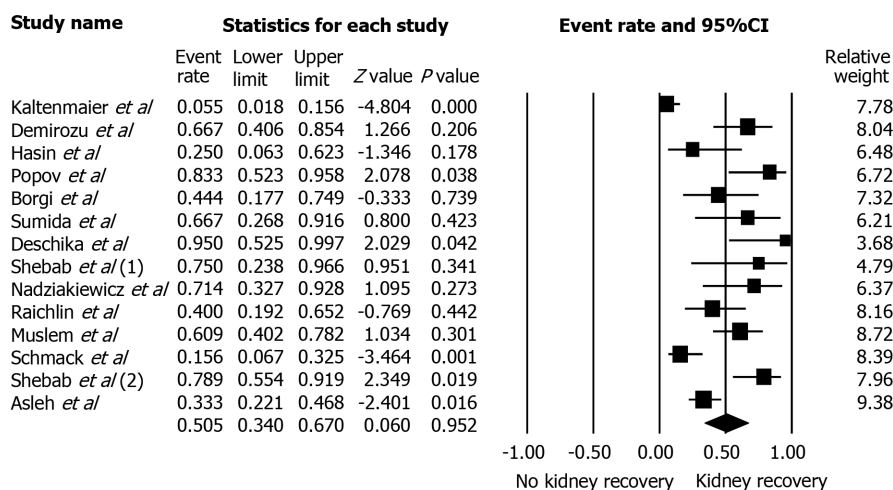


Figure 2 Kidney recovery of acute kidney injury kidney replacement therapy after left ventricular assist device placement.

demonstrate a significant association between study year and AKI recovery rate ($P = 0.08$).

Rates of kidney recovery from severe AKI among continuous flow LVAD

The data on pulsatile-flow LVAD were limited, as the majority (85%) of patients used continuous-flow LVAD. Subgroup analysis of continuous-flow LVAD demonstrated the pooled estimated rates of AKI recovery among patients with severe AKI-KRT was 52.1% (95%CI: 36.8%-67.0%) (Figure 3).

Evaluation for publication bias

Funnel plots (Figure 4) and Egger's regression asymmetry tests were performed to assess publication bias in analysis evaluating the rate of AKI recovery. No significant publication bias in the meta-analysis evaluating rates of AKI recovery among patients with AKI ($P = 0.17$) was evident.

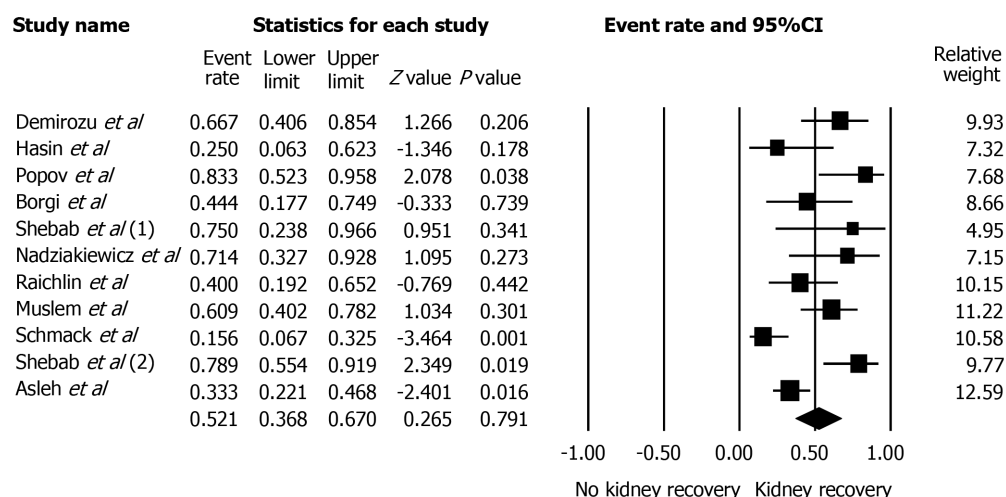


Figure 3 Subgroup analysis of kidney recovery of acute kidney injury kidney replacement therapy after continuous-flow left ventricular assist device.

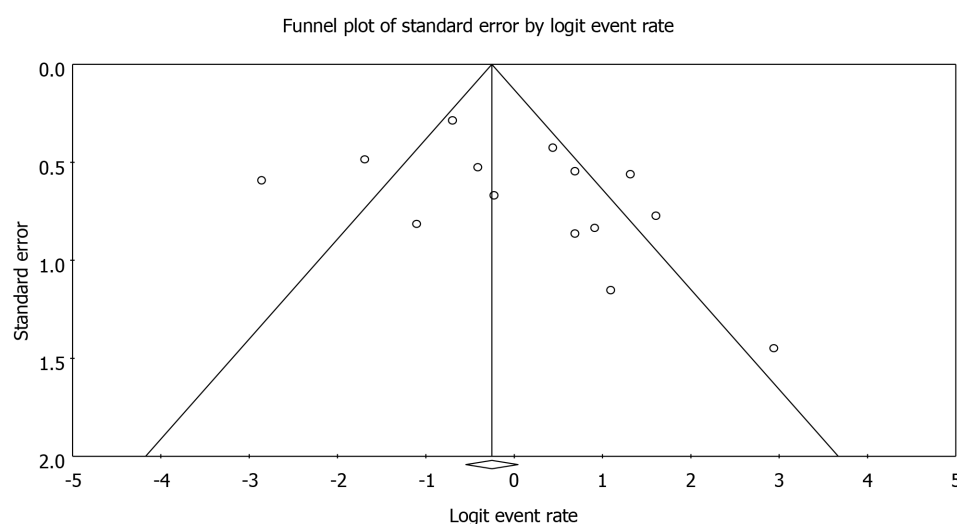


Figure 4 Funnel Plot of kidney recovery of acute kidney injury kidney replacement therapy after left ventricular assist device placement.

DISCUSSION

Our analysis included 14 cohort studies that defined severe AKI as needing KRT (AKI-KRT). Kidney recovery occurred in 78.5% of patients at the time of hospital discharge or within 30 d of LVAD implantation. The initial improvement in kidney function could be secondary to hemodynamic stabilization, cardiac output optimization, and reduction in kidney venous pressures. The subsequent rise in cardiac output facilitates kidney perfusions and glomerular filtration rates (GFR) [33].

In our analysis, kidney function recovery occurred in about half of individuals with AKI-KRT. Even though 70% had initial kidney recovery within 30 d of LVAD initiation, kidney recovery rates when followed for up to 12 mo were only 50%. This observation is consistent with previous studies demonstrating a sustained and gradual decline in GFR at long-term follow-up. As evidenced by Brisco *et al* [34], even though half of the patients had initial improvement in GFR after one month of LVAD implantation, a significant decline in GFR was noted at one year. Similar findings were also reported by Hasin *et al* [8] with initial improvement in GFR at one month followed by an eventual decline at 3 and 6 mo, respectively.

The potential mechanisms for the eventual decline in kidney functions are multifactorial. Chronic hemolysis is caused by shear stress leading to red blood cell breakdown and pigment nephropathy [35]. Subsequent development of right ventricular failure after LVAD placement could contribute to a decline in kidney functions. Additionally, GFR could be overestimated post LVAD implantation

secondary to reduced creatinine generation from sarcopenia and volume overload. Cystatin-based calculations of kidney clearances can be used to provide better insight into kidney functions [36].

Lack of pulsatility among continuous flow devices could lead to structural changes in the arterial system, perpetuating aortic wall stiffness. Animal studies demonstrated periarteritis and subsequent inflammation with continuous-flow devices, potentiating increased AKI risk[37]. However, the previous metaanalysis reported almost similar AKI rates among patients with continuous and pulsatile flow devices[6]. Subgroup analysis on continuous-flow LVAD revealed pooled incidence of kidney recovery after AKI episode leading to KRT independence was 52%. Given limited data, we could not analyze kidney recovery among AKI-KRT with pulsatile flow LVAD. However, we hypothesize that recovery rates after AKI-KRT among patients with pulsatile flow LVAD could be similar to continuous flow devices given similar AKI rates.

Another interesting observation in our analysis is pooled incidence of kidney recovery from KRT is 50%, which is reassuring compared to kidney recovery rates of other cohorts like hematopoietic stem cell transplant (HSCT). The pooled estimated kidney recovery rates after severe AKI-KRT at 100 d among the HSCT cohort are as low as 10%[38]. This difference could be secondary to multiple factors as patients after HSCT are much sicker from underlying terminal cancer and exposed to high-dose chemotherapy or radiation. However, the HSCT cohort was followed for only 100 d, and unclear if long-term follow-up would generate encouraging results.

Few measures to enhance kidney recovery during the post-AKI/acute kidney disease (AKD) phase include medication reconciliation, avoidance of nephrotoxic drugs, avoiding supra therapeutic vancomycin levels, and contrast agents. Meticulous care should be taken to minimize hypotension during dialysis sessions[39]. Adequate catheter care education should be provided to patients and families at discharge and as an outpatient. Patients should be well informed of blood pressure goals, diuretics, bodyweight targets, and sick day protocol during the recovery period. The severity of kidney disease should be considered while managing AKI patients after LVAD, especially those requiring KRT[40]. An algorithmic approach should be protocolized in implementing diagnostic and therapeutic interventions to facilitate rapid and complete kidney function recovery.

Our study has few strengths. This is the first study analyzing kidney recovery rates after severe AKI-KRT among patients with LVAD implantation. We report that about half of the patients, when followed closely, have dialysis independence after LVAD. To mention few limitations, the cohort studies included in our analysis might not identify a causal relationship between patients with AKI-KRT and kidney recovery rates. However, they report associations between the two variables. The overall analysis showed significant statistical heterogeneity questioning the validity of included studies. However, we found similar rates of kidney recovery in the subgroup analysis. Additionally, we do not have the mean GFR of patients before LVAD insertion and after kidney recovery from KRT. Lastly, data on AKI recovery impact on outcomes among patients after LVAD insertion were not reported.

CONCLUSION

In conclusion, recovery from severe AKI-KRT after LVAD occurs in approximately 50.5%. Recovery of kidney functions is associated with improved kidney function, fewer complications, and better outcomes than patients with non-resolving AKI. Hence, adequate measures should be taken to facilitate diagnostic and therapeutic approaches aiming for early and complete kidney recovery.

ARTICLE HIGHLIGHTS

Research background

Acute kidney injury (AKI) is a common (37%) and severe complication after left ventricular assist device (LVAD) implantation, and 13% require kidney replacement therapy (KRT). Severe AKI requiring KRT in LVAD patients is associated with high short-term and long-term mortality compared with those without KRT.

Research motivation

While recovery of kidney function is associated with better outcomes, the recovery

rates of kidney function among LVAD patients with severe AKI-KRT are unclear.

Research objectives

To demonstrate the rates of kidney recovery among patients with AKI-KRT after LVAD implantation.

Research methods

Eligible articles were searched through Ovid MEDLINE, EMBASE, and the Cochrane Library. The inclusion criteria included adult patients with recovery from severe AKI-KRT after LVAD placement, which is defined by regained kidney function resulting in discontinuation of KRT.

Research results

A total of 268 patients from 14 cohort studies with severe AKI-KRT after LVAD were enrolled. Follow-up time ranges from 2 wk of LVAD implantation up to 12 mo. 78.5% of kidney recovery occurred at the time of hospital discharge or within 30 d. The majority (85%) of patients used continuous-flow LVAD. Overall, the pooled estimated AKI recovery rates among patients with severe AKI-KRT were 50.5% (95%CI: 34.0%-67.0%). While the data on pulsatile-flow LVAD was limited, subgroup analysis of continuous-flow LVAD demonstrated the pooled estimated AKI recovery rates among patients with severe AKI-KRT was 52.1% (95%CI: 36.8%-67.0%). Meta-regression analysis did not show a significant association between study year and AKI recovery rate ($P = 0.08$). There was no publication bias as assessed by the funnel plot and Egger's regression asymmetry test in all analyses.

Research conclusions

Recovery from severe AKI-KRT after LVAD occurs approximately 50.5%, and it has not significantly changed over the years despite advances in medicine.

Research perspectives

Our study results offer a perspective of rates of kidney recovery after AKI-KRT among patients with LVAD implantation. As recovery of kidney functions is associated with improved outcomes compared to those with no AKI recovery, we suggest a meticulous approach to monitoring patients post AKI and acute kidney disease in achieving early and complete kidney recovery.

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