Impact of Renal Dysfunction on Outcomes after Left Ventricular Assist Device: A Systematic Review

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ABSTRACT

Background and Objectives: Renal dysfunction is a common comorbidity in patients with advanced heart failure who may benefit from left ventricular assist device (LVAD) therapy. The effect of preoperative renal dysfunction on clinical outcomes after LVAD implantation remains uncertain. We conducted a systematic review and meta-analysis to compare outcomes post-LVAD in patients with and without renal dysfunction.

Methods: PubMed, MEDLINE, and Embase databases were searched for studies comparing outcomes in patients with and without renal dysfunction who underwent LVAD implantation for advanced heart failure. The primary outcome of all-cause mortality was reported as random effects risk ratio (RR) with 95% confidence interval (CI).

Results: Our search yielded 5,229 potentially eligible studies. We included 7 studies reporting on 26,652 patients. Patients with renal dysfunction (glomerular filtration rate [GFR] <60 mL/min/1.73 m²) (n=4,630) had increased risk of all-cause mortality (RR, 2.21; 95% CI, 1.39–3.51; p<0.01) compared to patients with normal renal function (GFR >60 mL/min/1.73 m²) (n=22,019).

Conclusions: Patients with renal dysfunction have increased mortality after LVAD implantation when compared to patients with normal renal function. GFR can be used to risk stratify patients and guide decision making prior to LVAD therapy.

Keywords: Left ventricle assist device; Heart-assist devices; LVAD; Ventricular assist device; Chronic kidney disease

INTRODUCTION

Left ventricular assist devices (LVADs) are widely used as bridge-to-transplant and destination therapy (DT) in patients with advanced heart failure.1,2 These patients often have chronic kidney disease (CKD) as a major source of morbidity and mortality.3 The severity of kidney dysfunction in LVAD recipients can range from early stages of kidney disease not receiving dialysis to those with end-stage renal disease (ESRD).4
Renal dysfunction has been associated with impaired survival after LVAD implantation.\textsuperscript{5-8} Patients with ESRD at the time of LVAD implantation have an extremely poor prognosis with a median survival time of 16 days.\textsuperscript{5} Patients with higher grades of renal dysfunction have shown progressive reduction in survival.\textsuperscript{6-8} Therefore, renal dysfunction serves as an important prognostic marker in LVAD patients. This systematic review and meta-analysis provides an overview of outcomes in patients undergoing LVAD implantation with renal dysfunction as compared to patients with normal renal function.

**METHODS**

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. A comprehensive systematic search was performed up until June 8, 2020 including PubMed, Embase, Cochrane Library, ACP Journal Club, DARE, and Scopus. Both controlled vocabulary terms (i.e. MeSH) and key words were used to obtain relevant articles. The aim was to identify randomized and nonrandomized clinical studies that focused on the prognosis, mortality and morbidity of patients with kidney dysfunction who underwent LVAD. Emphasis was placed on studies that noted a history of advanced heart failure and kidney dysfunction including end stage renal disease. This study was exempt from Institutional Review Board approval as there is no protected health information included.

Keywords utilized in the initial PubMed (National Library of Medicine) MEDLINE title search were “heart-assist devices” or “ventricular assist device” or “LVAD” or “devices” and “kidney” or “dysfunction” or “kidney dysfunction” AND “chronic renal insufficiency” or “chronic kidney disease” AND “end-stage renal disease”.

**Study selection**

Studies were considered eligible if they included patients with any degree of kidney dysfunction using estimated glomerular filtration rate (GFR) and/or creatinine in patients with a minimum follow-up of 12 months post-LVAD. Our pre-specified criteria included date range from January 2000 to June 2020, only human studies, and English language articles.

Articles were excluded if the patients had primary kidney disease and prior transplanted kidneys. Case reports, abstracts, editorials, and commentaries were also excluded. Three independent reviewers (GS, MI, and CC) independently selected articles based on the predefined search criteria as well as quality assessment. Any disagreement or discrepancies were resolved by majority consensus. Reference lists from previous studies were also perused for additional articles to be appraised.

**Definitions**

The included studies used various definitions for CKD and ESRD. We defined renal dysfunction as pre-implantation GFR less than 60 mL/min/1.73 m\textsuperscript{2} or dialysis dependence. The Kidney Disease Improving Global Outcomes 2012 Clinical Practice Guidelines for CKD defines CKD as abnormalities of the kidney structure or function present for greater than 3 months with implications for health. A GFR cut-off of 60 mL/min/1.73 m\textsuperscript{2} is commonly used to classify patients with CKD.\textsuperscript{9} Bansal et al.\textsuperscript{5} defined ESRD as having received maintenance dialysis or kidney transplant for treatment of CKD.
**Statistical analysis**

The current systematic review and meta-analysis was performed by combining the results of reported incidences of the pre-determined end points. Odds ratio with 95% confidence intervals (CIs) were used to compare pooled data from the included studies and respective treatment effects for binary endpoints. Continuous variable outcomes were compared with weighted mean differences. The risk ratio (RR) was used as a summary statistic. In the present study, both fixed and random effect models were tested. The $\chi^2$ tests were used to study heterogeneity between trials. $I^2$ statistic was used to estimate the percentage of total variation across studies due to heterogeneity rather than chance. An $I^2$ value of greater than 25% was considered to represent substantial heterogeneity. If there was substantial heterogeneity, the possible clinical and methodological reasons for this were explored qualitatively. Specific analyses considering confounding factors were not possible because raw data was not available.

All p values were 2-sided. All statistical analysis was conducted with Review Manager Version 5.3 (Cochrane Collaboration, Software Update, Oxford, United Kingdom).

**RESULTS**

**Literature search**

Our search yielded 5,229 abstracts. We excluded 5,179 studies at the abstract level and selected 50 full-text articles for detailed assessment; 7 studies were ultimately included in our systematic review and meta-analysis. **Figure 1** describes the flow-chart of included studies.
Baseline characteristics of the studies

Table 1 shows the baseline characteristics of the included studies. All studies were published between 2009 and 2020. The 7 studies included 26,652 patients with 4,630 patients with renal dysfunction. The median age of the participants was 57.7 years old interquartile range (IQR; 55.9–61.8 year). The median percentage of men was 78.0 IQR (76.2–82.0). For studies that reported these selected risk factors, the median percentage of hypertension was 65.0 IQR (43.7–69.5), the median percentage of diabetes mellitus was 41.5 IQR (29.4–50.3), the median BMI average was 28.6 IQR (26.9–29.0), the median percentage of coronary heart disease was 61.5 IQR (53.8–73.0), the median percentage of chronic obstructive pulmonary disease was 18.9 IQR (13.0–21.0), the median percentage of stroke was 19.0 IQR (11.0–20.3), and the median percentage of peripheral artery disease 10.0 IQR (7.9–13.0). Racial characteristics were reported by four studies; the median percentage of white participants was 57.0 IQR (54.0–60.2) and the median percentage of black participants was 27.7 IQR (20.5–35.7). Three studies used data from national registries and four studies used data from single centers. The sample sizes ranged from 86 to 20,656 patients. Table 2 shows pooled baseline characteristics for all included studies.

LVAD outcomes in patients with renal dysfunction

The included studies all examined overall mortality outcomes of LVADs in patients with renal dysfunction based on the degree of severity determined by the level of GFR. Bansal et al. assessed LVAD outcomes in patient with ESRD. The mean dialysis time of the patients varied between trials depending on the severity of renal dysfunction. Bansal et al. investigated a national cohort using Medicare beneficiaries within 10 years (2003–2013). There were 155 patients with ESRD and 261 patients without ESRD who all underwent LVAD implantation.

Table 1. Baseline characteristics of the included studies

| Study          | Data source | Sample size | CKD status | No. of patients | Mean age (year) | Man | White | Black | HTN | DM | BMI (kg/m²) | CHD | COPD | Stroke | PAD |
|----------------|-------------|-------------|------------|----------------|----------------|-----|-------|-------|-----|----|-------------|-----|------|--------|-----|
| Bansal et al.  | USRDS       | 416         | ESRD       | 155            | 58.4±12.1      | 59.4| 59.4  | 37.4  | 98.1| 72.9| NR          | 92.9| 40.7 | 23.3   | 41.3|
|                |             |             | No ESRD    | 261            | 62.2±12.6      | 74.0| 74.0  | 20.3  | 85.1| 54.4| NR          | 90.8| 43.7 | 20.3   | 23.3|
| Kirlik et al.  | INTERMACS   | 4,974       | Severe     | 282            | 60.1±12.0      | NR  | NR    | NR    | 44.0| 24.6| NR          | NR  | 0.5  | NR     | NR  |
|                |             |             | Moderate   | 1,475          | 63.2±12.0      | NR  | NR    | NR    | 43.2| 26.6| NR          | NR  | 1.0  | NR     | NR  |
|                |             |             | Mild/none  | 3,160          | 52.8±12.0      | NR  | NR    | NR    | 27.5| 30.0| NR          | NR  | 0.8  | NR     | NR  |
| Mohamedali et al. | Single | 213         | GFR >60    | 133            | 64±11           | 76  | 57    | 34    | 67  | 51.0| 28±6        | 67  | 19   | 19     | 13  |
|                |             |             | GFR >60    | 78             | 56±14           | 82  | 45    | 46    | 65  | 36.0| 28±7        | 54  | 12   | 17     | 10  |
| Sandner et al. | Single      | 86          | GFR >60    | 40             | 58±7.6±00      | 77.5| NR    | NR    | 42.5| 35.0| 26.9±3.6    | NR  | NR   | NR     | NR  |
|                |             |             | GFR >60    | 46             | 47.3±12.7      | 91.3| NR    | NR    | 21.7| 26.1| 26.1±3.7    | NR  | NR   | NR     | NR  |
| Kilic et al.   | Single      | 238         | GFR >60 (DT)| 85            | 64±10           | 87  | 61    | NR    | 67  | 48.0| 29±6        | 66  | 21   | 11     | 11  |
|                |             |             | GFR >60 (BTT)| 47            | 54±9            | 74  | 49    | NR    | 72  | 57.0| 30±6        | 53  | 6    | 19     | 19  |
|                |             |             | GFR >60 (DT)| 54            | 57±16           | 81  | 63    | NR    | 59  | 43.0| 29±8        | 57  | 24   | 20     | 20  |
| Doshi et al.   | NIS         | 20,656      | ESRD       | 1,576          | 56.0±13.7      | 77.8| 56.9  | 19.4  | 43.9| 22.6| NR          | NR  | 10.2 | NR     | 11.5|
|                |             |             | CKD stage IV–V | 751          | 61.7±11.3      | 84.9| 54.9  | 27.7  | 39.8| 26.2| NR          | NR  | 15.1 | NR     | 7.9 |
|                |             |             | No CKD/    | 18,299         | 55.9±13.5      | 76.3| 58.7  | 20.7  | 43.4| 25.7| NR          | NR  | 18.9 | NR     | 8.6 |
|                |             |             | CKD stage I–III | 42            | 56±14           | 79  | NR    | NR    | 66  | 40.0| 29.1        | 17  | 24   | 5      |     |

Values are mean±standard deviation or number (%).

CKD = chronic kidney disease; ESRD = end stage renal disease; eGFR = estimated glomerular filtration rate; NR = not reported; GFR = glomerular filtration rate (units are mL/min/1.73 m²); HTN = hypertension; DM = diabetes mellitus; BMI = body mass index; CHD = coronary heart disease; COPD = chronic obstructive lung disease; PAD = peripheral artery disease; USRDS = United States renal data system; INTERMACS = Interagency Registry for Mechanically Assisted Circulatory Support; NIS = national inpatient sample; DT = destination therapy; BTT = bridge to transplantation.

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Patients with renal dysfunction classified as ESRD had an extremely poor prognosis with most surviving for less than 3 weeks. The median time to death was 16 days for patients with ESRD compared with 2,125 days for patients without ESRD. During a median follow-up of 762 days, 127 patients (81.9%) with ESRD and 95 patients (36.4%) without ESRD died.

Mohamedali et al.\(^5\) found patients with renal dysfunction (GFR <60 mL/min/1.73 m\(^2\)) had higher all-cause mortality than patients with normal renal function (GFR >60 mL/min/1.73 m\(^2\)) (45% vs. 27%, \(p=0.006\)). Kirklin et al.\(^7\) evaluated outcomes after LV AD implantation in a cohort of 4,917 patients. Worsening renal dysfunction was found to correlate with decreased survival with 17% mortality in patients with normal renal function (GFR >60 mL/min/1.73 m\(^2\)) compared to 25% mortality in patients with renal dysfunction (GFR <60 mL/min/1.73 m\(^2\)). The major negative survival effect was found to occur during the first 3 months.\(^7\) Sandner et al.\(^6\) report a 24% all-cause mortality in patients with normal renal function (GFR >60 mL/min/1.73 m\(^2\)) compared to 45% all-cause mortality in patients with renal dysfunction (GFR <60 mL/min/1.73 m\(^2\)) after LVAD implantation.

Kilic et al.\(^10\) reported outcomes in 238 patients with implanted LVADs as DT or bridge to transplantation (BTT) at a single institution. Patients with reduced GFR (GFR <60 mL/min/1.73 m\(^2\)) were found to have a similar survival to patients with normal GFR (GFR >60 mL/min/1.73 m\(^2\)) in both the DT and BTT cohorts.\(^10\) Doshi et al.\(^11\) compared in-hospital mortality associated with CKD using a large national database. The mortality rate in patients with CKD stage IV–V or ESRD was 38.1% compared to a 9.7% mortality rate in patients with no CKD or CKD stage I–III.\(^11\) Ajmal et al.\(^12\) reported outcomes in patients who received LVAD at a single institution based on CKD status. The mortality rate in patients with CKD was 33.3% compared to 2.3% in patients with no CKD.

Meta-analysis of the included studies revealed an increased risk of all-cause mortality in patients with renal dysfunction when compared to patients with normal renal function. This is a statistically significant increased risk of all-cause mortality in patients with renal dysfunction with a RR of 2.21 (95% CI, 1.39–3.51; \(p<0.01\)). The forest plot for all-cause mortality is shown in Figure 2 and the funnel plot is shown in Figure 3.
This is the first systematic review and meta-analysis to demonstrate the impact of renal dysfunction on outcomes in patients undergoing LV AD implantation. Our findings are derived from 7 studies reporting outcomes in 26,652 patients with varying degrees of renal function prior to LV AD implantation. Patients with renal dysfunction were found to have significantly increased risk of all-cause mortality when compared to patients with normal renal function.

Renal dysfunction has been identified as a risk factor for adverse outcomes in heart failure patients requiring advanced therapies. However, the ideal measurement of renal function and the degree of renal dysfunction that may lead to adverse outcomes in heart failure patients is not completely understood. Imamura et al. suggested serum creatinine as...
a predictor of adverse outcomes in undergoing LVAD implantation. Other studies have suggested blood urea nitrogen as a predictor of morbidity and mortality in patients with acute heart failure.\textsuperscript{15,16} GFR has also been used to assess renal function and predict adverse outcomes by several studies.\textsuperscript{15-20} The National Kidney Foundation has established a GFR of 60 mL/min/1.73 m\textsuperscript{2} as the cut-off point between mild and moderate renal dysfunction.\textsuperscript{20} This systematic review and meta-analysis incorporates studies that used GFR to divide cohorts into groups of patients with normal renal function versus patients with renal dysfunction.

The physiological relationship between renal dysfunction and poor prognosis in heart failure patients after LVAD implantation is not completely understood. In patients with end-stage heart failure, renal dysfunction can be caused by cardiorenal syndrome, pre-existing renal disease, or a combination of both. The cardiorenal syndrome describes the complex interaction between heart failure and renal dysfunction. Decreased GFR is thought to result from a reduction in cardiac output and subsequent renal perfusion.\textsuperscript{7} Studies have shown that renal failure may predispose patients to early right ventricular failure.\textsuperscript{8,22} Several studies have identified right ventricular failure as a risk factor for adverse outcomes after LVAD implantation.\textsuperscript{23-25} The poor prognosis of patients with ESRD after LVAD implantation suggests these patients may already be actively dying at the time of procedure or that the procedure expedites the process.\textsuperscript{5} The limited life expectancy of patients with irreversible end-organ failure has led to ESRD being identified as a contraindication for LVAD therapy.\textsuperscript{26}

The prognostic value of renal dysfunction in patients undergoing LVAD implantation has been demonstrated by several studies. Butler et al.\textsuperscript{16} and Sandner et al.\textsuperscript{6} both demonstrated that baseline renal dysfunction is associated with worse outcomes after LVAD implantation.\textsuperscript{27} This finding was later confirmed by Mohamedali et al.\textsuperscript{8} However, the Butler et al.\textsuperscript{16} and Sandner et al.\textsuperscript{6} studies both found that renal function improved after LVAD implantation and is associated with improved outcomes.\textsuperscript{27} Kirklin et al.\textsuperscript{7} demonstrated a progressive reduction in survival with higher grades of renal dysfunction. Bansal et al.\textsuperscript{5} demonstrated that patients with ESRD have a very poor prognosis after LVAD implantation. These studies show the importance of renal function in patient selection for LVAD therapy.

This study has important clinical implications as it provides further evidence for the use of renal dysfunction as a prognostic factor prior to LVAD therapy. Bansal et al.\textsuperscript{5} suggest that ESRD patients should be informed of the poor prognosis after LVAD implantation so that their goals and values can be incorporated into a shared decision-making process. Careful and individual consideration of renal function should be made when selecting patients for LVAD therapy.

The limitations for this systematic review and meta-analysis are influenced by the limitations of the included studies. Sandner et al.,\textsuperscript{19} Mohamedali et al.,\textsuperscript{8} Kilic et al.,\textsuperscript{20} and Ajmal et al.\textsuperscript{13} used single center retrospective study designs that are subject to limitations inherent to the study design. Kirklin et al.,\textsuperscript{7} Bansal et al.,\textsuperscript{9} and Doshi et al.\textsuperscript{11} relied on a multi-institutional registry database which introduces program variability in the application of definition and decisions regarding indications for procedures and post-operative management. The various LVADs used in each study likely influences the generalizability of the aggregate data as specific LVAD types have shown different rates of procedural complications.

In conclusion, LVAD recipients with renal dysfunction are at increased risk of adverse outcomes including all-cause mortality. GFR can be used as a risk stratification tool for
patients to determine risk of morbidity and mortality after LVAD implantation. This information can be used to support shared decision-making around LVAD placement in patients with advanced heart failure and renal dysfunction.

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