Incidence and impact of acute kidney injury on patients with implantable left ventricular assist devices: a Meta-analysis

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ABSTRACT

Background: We aimed to evaluate the acute kidney injury (AKI) incidence and its associated risk of mortality in patients with implantable left ventricular assist devices (LVAD).

Methods: A systematic literature search in Ovid MEDLINE, EMBASE, and Cochrane Databases was conducted through January 2020 to identify studies that provided data on the AKI incidence and AKI-associated mortality risk in adult patients with implantable LVADs. Pooled effect estimates were examined using random-effects, generic inverse variance method of DerSimonian-Laird.

Results: Fifty-six cohort studies with 63,663 LVAD patients were enrolled in this meta-analysis. The pooled incidence of reported AKI was 24.9% (95% CI: 20.1%–30.4%) but rose to 36.9% (95% CI: 31.1%–43.1%) when applying the standard definition of AKI per RIFLE, AKIN, and KDIGO criteria. The pooled incidence of severe AKI requiring renal replacement therapy (RRT) was 12.6% (95% CI: 10.5%–15.0%). AKI incidence did not differ significantly between types of LVAD (p = .35) or indication for LVAD use (p = .62). While meta-regression analysis did not demonstrate a significant association between study year and overall AKI incidence (p = .55), the study year was negatively correlated with the incidence of severe AKI requiring RRT (slope = −0.068, p < .001). The pooled odds ratios (ORs) of mortality at 30 days and one year in AKI patients were 3.66 (95% CI, 2.00–6.70) and 2.22 (95% CI, 1.62–3.04), respectively. The pooled ORs of mortality at 30 days and one year in severe AKI patients requiring RRT were 7.52 (95% CI, 4.58–12.33) and 5.41 (95% CI, 3.63–8.06), respectively.

Conclusion: We found that more than one-third of LVAD patients develop AKI based on standard definitions, and 13% develop severe AKI requiring RRT. There has been a potential improvement in the incidence of severe AKI requiring RRT for LVAD patients. AKI in LVAD patients was associated with increased 30-day and 1 year mortality.

Introduction

Implantable left ventricular assist devices (LVADs) are increasingly utilized as a bridge to heart transplantation or destination therapy for patients with end-stage heart failure [1–7]. The use of LVADs is shown to be associated with reduced mortality in patients on heart transplantation waiting lists, and they improve quality of life and functional status in advanced heart failure patients [8]. LVADs alleviate the cardiovascular load on a failing heart and have shown notable advantages in treating patients with advanced heart failure, providing prolonged survival and improvement in the quality of

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life [9,10]. Clinical outcomes after LVAD implantation have significantly improved over the past decade, with 1 year and 2 year survival of 83% and 73%, respectively [11, 12]. In the United States, the number of LVAD implantations rose, from only 459 implants in 2008 to a total of 2,118 implants in 2017 [11].

Despite the LVAD benefits mentioned above, several studies have reported persistent adverse complications following LVAD implantation, such as bleeding, cardiac arrhythmias, hypertension, sepsis, disabling stroke, and acute kidney injury (AKI) [8,13]. Post-implantation AKI has been associated with negative impacts on patient outcomes, including right ventricular failure, arrhythmia, and reduced survival [14,15]. The reported AKI incidence among LAVD patients widely ranged from 4–70%. This variability is likely due to the use of non-standardized AKI definitions in previous studies [15–70]. Furthermore, the mortality associated with AKI and current trends of AKI occurrence in LVAD patients are unclear [18,21,22,24,26,40,44,46,52,54,57,63,65].

This systematic review and meta-analysis were conducted to summarize the AKI incidence and mortality risk among adult patients with LVADs.

Methods

The protocol for this meta-analysis is registered with PROSPERO (no. CRD42020134592). The meta-analyses were conducted in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [71].

Search strategy

Two investigators (CT and PL) independently searched for published clinical trials or observational studies indexed in MEDLINE, EMBASE and the Cochrane databases from inception to January 2020 using a search strategy (S1 in online Supplementary Data 1) that included the terms “left ventricular assist device”, “LVAD”, “ventricular assist device”, “acute kidney failure”, “acute kidney injury” and “renal replacement therapy”. No language restrictions were applied in this systematic review and meta-analysis. A manual search for additional pertinent studies and review articles using references from the retrieved articles was also completed.

Study eligibility criteria

Two main criteria were used for study inclusion. First, the study had to report the incidence of AKI or severe AKI requiring renal replacement therapy (RRT), and AKI associated mortality risk in adult patients with LVADs aged at least 18 years. Second, the study had to include data assessing AKI incidence or mortality risk with 95% confidence intervals (CIs) (or sufficient raw data for the calculation). Patients were excluded if they only used a temporary, short-term, non-implantable LVAD during a hospitalization. Study eligibility was independently determined by two investigators (CT and PL). Differences were resolved by mutual consensus.

A standardized data collection form was used to obtain the following information from each study: title, name of the first author, year of study, year of publication, country of origin, number of participants, demographic data of participants, the method used to diagnose the outcomes of interest (AKI incidence and associated mortality), the average duration of follow-up, adjusted and unadjusted risk ratios and their corresponding 95% CI, and list of confounders that were adjusted for in the multivariate analyses. To ensure accuracy, both investigators independently performed this data extraction process. Any data discrepancy was resolved by referring back to the original articles. The Newcastle-Ottawa quality assessment scale was utilized to appraise the quality of observational studies [72].

Statistical analysis

The meta-analysis of combined data was performed using a random-effects, generic inverse variance method of DerSimonian and Laird [73]. We assessed the overall incidence of AKI, which was defined by the consensus definitions provided by the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) [74], Acute Kidney Injury Network (AKIN) [75], and Kidney Disease: Improving Global Outcomes (KDIGO) [76] classifications. We did not impute missing values for any outcomes in our analyses. A random-effect model was used to pool AKI incidence and AKI-associated mortality risk due to the possibility of between-study variance. Heterogeneity among included studies was statistically evaluated by the Cochrane’s Q test and the I² statistic. Heterogeneity was considered insignificant when I² of ≤25%, low when I² of 26–50%, moderate when I² of 51–75%, and high when I² of ≥75% [77]. Per Cochrane, publication bias was assessed using a funnel plot. Funnel plot asymmetry was further confirmed with Egger’s test if there were >10 available studies [78]. All analysis was performed using The Comprehensive Meta-Analysis software version 3.3.070 (Biostat Inc, New Jersey, USA). The data underlying the results presented in the study are
Results

Our search approach identified a total of 1,665 potentially eligible articles. We initially excluded 846 articles because they were case reports, correspondences, review articles, or studies involving in-vitro, animal, or pediatric patients. Six hundred fifty-eight duplicated articles were additionally excluded. After the review of 161 full-length articles, we subsequently excluded 67 articles because the data on AKI incidence and its associated mortality was not available, 28 articles because they were not observational studies or clinical trials, and 10 articles because they investigated AKI in short-term LVAD use, not implantable LVAD [79–88]. Therefore, 56 cohort studies [15–70] with a total of 63,663 adult patients were included in this meta-analysis. Figure 1 demonstrates by flowchart the systematic review of the literature. Table 1 shows the characteristics of the included studies. The kappa for systematic searches, selection of studies and data extraction were 1.00, 0.91 and 0.98, respectively.

Incidence of AKI in LVAD patients

Fifty-six studies [15–70] evaluated AKI incidence in LVAD patients. The pooled incidence of reported AKI was 24.9% (95%CI: 20.1%–30.4%, $I^2 = 99\%$, Supplementary Figure S1), and the pooled incidence of severe AKI requiring RRT was 12.6% (95%CI: 10.5%–15.0%, $I^2 = 95\%$, Figure 2). Using standard AKI definitions (RIFLE, AKIN, and KDIGO criteria), the pooled incidence of AKI was 36.9% (95%CI: 31.1%–43.1%, $I^2 = 97\%$, Figure 3).

AKI incidence did not differ significantly between types of LVAD (pulsatile vs. continuous flow) ($p = .35$) or indication of LVAD use (bridge to transplant vs.
| Study           | Year | Country | Patients                                                                 | Number | LVAD type                        | AKI definition                                                                 | AKI and/or RRT incidence |
|-----------------|------|---------|--------------------------------------------------------------------------|--------|----------------------------------|--------------------------------------------------------------------------------|--------------------------|
| Kaltenmaier et al. [40] | 2000 | Germany | Patient underwent LVAD implantation during 1988–1995 Mean age: 41.7 F: 22% Bridge to transplant: 71.8% | 227    | Pulsatile Berlin Heart System HeartMate 2000, Novacor | RRT                                                                     | RRT 55/227 (24.2%)          |
| Frazier et al. [35]          | 2001 | USA     | Cardiac transplant candidate underwent LVAD implantation Median age: 55 F: 17.1% Bridge to transplant: 100% | 280    | Pulsatile HeartMate Vented Electric LVAS (VE LVAS) | SCr ≥ 2.2 mg/dL or BUN value ≥50 mg/dL                                          | AKI 158/280 (56.4%)        |
| Haddad et al. [37]           | 2004 | Canada  | Patients underwent LVAS as a bridge to cardiac transplant during 1991–2003 Mean age: 43.8 F: 31.4% | 54     | Pulsatile Thoratec VAD, Novacor   | RRT                                                                     | RRT 4/54 (7.4%)            |
| Deng et al. [32]             | 2005 | USA     | Patients underwent LVAD implantation during 2002–2004 from Mechanical Circulatory Support Device (MCSD) database LVAD only: 82.2% LVAD + RVAD : 15.3% Bridge to transplant : 78.3% Destination therapy : 11.9% | 655    | Continuous and Pulsatile (90%) | Not specified                                                               | AKI 85/655 (13%)          |
| Topkara et al. [65]           | 2005 | USA     | Patients underwent LVAD implantation during 1996–2004                    | 201    | Pulsatile Thoratec HeartMate     | RRT                                                                     | RRT 65/201 (32.3%)         |
| Feller et al. [34]           | 2007 | USA     | Patients underwent LVAD implantation during 2002–2005 Mean age: 54.1 F: 26% Bridge to transplant: 77.8% Destination therapy: 22.2% ICM: 48.1% | 27     | Continuous (51.9%) and Pulsatile (48.1%) Jarvik 2000, HeartMate XVE, Novacor | RRT                                                                     | RRT 6/27 (22.2%)           |
| Miller et al. [43]            | 2007 | USA     | Patient with end-stage heart failure on a waiting list for heart transplant underwent LVAD from 2005 to 2006 Mean age : 50.1 F: 21% ICM: 49/133 (37%) | 133    | Continuous HeartMate II         | RRT                                                                     | RRT 18/133 (13.5%)         |
| Sandner et al. [52]           | 2008 | Austria | Patients with end-stage heart failure underwent LVAD implantation as bridge to transplant during 1994–2007 | 92     | Continuous (68.5%) and Pulsatile (31.5%) MicroMed DeBakey, HeartWare, Terumo DuraHeart | RRT : Total 33/92 (35.9%) Continuous LVAD 24/63 (38.1%) Pulsatile LVAD 9/29 (31.0%) | RRT Total 33/92 (35.9%) Continuous LVAD 24/63 (38.1%) Pulsatile LVAD 9/29 (31.0%) |
| Pagani et al. [48]            | 2009 | USA     | Patient with end-stage heart failure on a waiting list for heart transplant underwent LVAD from 2005 to 2008 Bridge to transplant :100% Age: 50 F: 24% ICM: 43% | 281    | Continuous HeartMate II         | RRT                                                                     | RRT 30/281 (10.7%)         |

(continued)
| Study          | Year  | Country          | Patients                                                                 | Number | LVAD type                                                                 | AKI definition                                                                 | AKI and/or RRT incidence |
|---------------|-------|------------------|--------------------------------------------------------------------------|--------|---------------------------------------------------------------------------|--------------------------------------------------------------------------------|--------------------------|
| Alba et al.   | 2009  | Canada           | Patients with end-stage heart failure underwent LVAD during 2001–2007    | 53     | Continuous and Pulsatile Abiomed BVSS00, Thoratec, Novacor, VE HeartMate, HeartMate II, Novacor | RIFLE criteria                                                            | AKI: 24/53 (45.28%) RRT: 15/53 (28.3%) |
| Slaughter et al. | 2009  | USA              | Patients with end-stage heart failure underwent LVAD implantation        | 200    | Continuous (67%) and Pulsatile (33%) HeartMate II, HeartMate XVE           | RRT                                                                             | RRT: 35/200 (17.5%)     |
| Genovese et al. | 2010  | USA              | Patients underwent LAVD or bi-VAD from 1996 to 2008                      | 163    | Continuous (18%), pulsatile (54%), BiVAD (27.6%)                          | INTERMACS criteria: RRT or an increase in Scr ≥ 3 times baseline or Scr ≥ 5 mg/dL sustained for over 48 hours | AKI: 22/163 (13.5%)    |
| Demirozu et al. | 2011  | USA              | Patients underwent LVAD implantation during 2003–2009                  | 107    | Continuous HeartMate II                                                   | RRT                                                                             | RRT: 15/107 (14.0%) New RRT after LVAD: 10/102 (9.8%)                     |
| John et al.   | 2011  | USA              | Patients underwent HeartMate II implantation as a bridge to transplant after FDA approval during 2008–2010 from the INTERMACS registry | 1496   | Continuous HeartMate II                                                   | INTERMACS criteria: RRT or an increase in Scr ≥ 3 times baseline or Scr ≥ 5 mg/dL sustained for over 48 hours | AKI: 129/1496 (8.6%)   |
| Starling et al. | 2011  | USA              | Patient underwent LVAD implantation as a bridge to transplant in 2008  | 338    | 169 Continuous HeartMate II, HeartMate XVE, Implantable VAD               | INTERMACS criteria: RRT or an increase in Scr ≥ 3 times baseline or Scr ≥ 5 mg/dL sustained for over 48 hours | HM II                   |
| Strueber et al. | 2011  | Germany, Australia, United Kingdom, USA, Austria | Patients with end-stage heart failure underwent LVAD implantation as a bridge to transplant during 2006–2008 | 50     | Continuous HeartWare                                                      | INTERMACS criteria: RRT or an increase in Scr ≥ 3 times baseline or Scr ≥ 5 mg/dL sustained for over 48 hours | AKI: 21/169 (12.4%) AKI: 5/50 (10%) |
| Park et al.   | 2012  | USA              | Patient underwent LVAD implantation during 2005–2009                   | 414    | Continuous HeartMate II                                                   | RRT                                                                             | RRT: 51/414 (12.3%)     |
| Study                | Year | Country      | Patients Description                                                                 | Number | LVAD type                  | AKI definition                                                                 | AKI and/or RRT incidence |
|---------------------|------|--------------|--------------------------------------------------------------------------------------|--------|---------------------------|--------------------------------------------------------------------------------|--------------------------|
| Aaronson et al. [16]| 2008 | USA          | Patient with end-stage heart failure underwent LVAD bridging to heart transplant during 2008–2010  
Mean age: 52.4  
F: 24.9% | Continuous  
HeartWare | INTERMACS criteria:  
RRT or an increase in SCr  
≥3 times baseline or SCr  
≥ 5 mg/dl sustained for over 48 hours | AKI  
12/140 (8.6%) |
| Arnaoutakis et al. [23]| 2012 | USA          | Patients underwent LVAD bridging to orthotropic heart transplant during 2005–2010 from UNOS database  
Mean age: 52  
F: 18.1%  
Idiopathic cardiomyopathy: 50.7%  
Ischemic: 41.2%  
Patients underwent LVAD from 2007 to 2010  
Mean age: 63  
F: 19%  
CKD: 54%  
Mean GFRs: 40 ml/min/1.73 m² ischemic: 55%  
Bridge to transplant: 32%  
Destination therapy: 68% | 1312 | Continuous  
HeartMate II | RRT | RRT  
106/1312 (8.1%) |
| Hasin et al. [38]   | 2012 | USA          | Patient with end-stage heart failure underwent LVAD implantation during 2007–2011  
Mean age: 51  
F: 15%  
ICM: 23.5%  
Preop IABP: 2.9%  
Ischemic: 41.2%  
Bridge to transplant: 53.9%  
Destination therapy: 25.3% | 34 | Continuous  
HeartWare | RRT | RRT  
12/34 (35.3%) |
| Popov et al. [50]   | 2012 | United Kingdom | Patient with end-stage heart failure underwent LVAD implantation during 2007–2011  
Mean age: 52  
F: 24.2%  
ICM: 29.1%  
Idiopathic: 46.3%  
Bridge to transplant: 53.9%  
Destination therapy: 25.3% | 182 | Continuous and Pulsatile  
HeartMate XVE, HeartMate II | RRT | RRT  
32/182 (17.6%) |
| Yuan et al. [69]    | 2012 | USA          | Patients with end-stage heart failure underwent LVAD during 2000–2012  
Mean age: 50  
F: 24.2%  
ICM: 29.1%  
Idiopathic: 46.3%  
Bridge to transplant: 53.9%  
Destination therapy: 25.3% | 488 | Continuous and Pulsatile  
HeartMate XVE, HeartMate II  
HeartWare, VentAssist,  
DuraHeart, Novacor, CorAide,  
Lionheart, Incor, DeBakey  
LVAD alone 166/443 (37.9%)  
LVAD + RVAD 33/45 (73.3%) | Not specified | AKI  
199/488 (40.8%)  
LVAD alone 166/443 (37.9%)  
LVAD + RVAD 33/45 (73.3%) |
| Aissaoui et al. [20]| 2013 | Germany      | Patients undergone LVAD implantation during 2001–2011  
LAVD + RVAD: 45/488 (9.2%) | 100 | Continuous  
HeartMate II, HeartWare | RIFLE criteria | AKI  
28/100 (28%)  
RRT  
9/100 (9%) |

(continued)
| Study            | Year | Country         | Patients                                                                 | Number | LVAD type          | AKI definition   | AKI and/or RRT incidence |
|------------------|------|-----------------|---------------------------------------------------------------------------|--------|--------------------|-------------------|--------------------------|
| Lok et al. [42]  | 2013 | The Netherlands | End-stage heart failure patients who underwent LVAD placement as a bridge to transplantation during 2006–2011 | 85     | Continuous         | RRT               | RRT: 9/85 (10.6%)        |
|                  |      |                 | Mean age: 45                                                              |        | HeartMate II       |                   |                          |
|                  |      |                 | F: 27%                                                                    |        |                   |                   |                          |
|                  |      |                 | NICM: 71%                                                                 |        |                   |                   |                          |
|                  |      |                 | ICM: 28%                                                                  |        |                   |                   |                          |
|                  |      |                 | 2006–2011                                                                 |        |                   |                   |                          |
| Ono et al. [47]  | 2012 | USA             | Patient underwent LVAD implantation                                         | 15     | Continuous         | RIFLE criteria    | AKI 1/15 (6.7%)          |
| Slaughter et al. | 2013 | USA             | Patients underwent LVAD implantation as a bridge to transplant in 2008     | 332    | Continuous         | INTERMACS criteria: | AKI: 32/332 (9.6%)       |
|                  |      |                 | Mean age: 52.5                                                             |        | HeartWare          | RRT or an increase in SCr ≥ 3 times baseline or SCr ≥ 5 mg/dL sustained for over 48 hours | |
|                  |      |                 | F: 28.4%                                                                   |        |                   |                   |                          |
|                  |      |                 | NICM: 70.45%                                                               |        |                   |                   |                          |
|                  |      |                 | ICM: 29.5%                                                                 |        |                   |                   |                          |
|                  |      |                 | Bridge to transplant: 68.2%                                                 |        |                   |                   |                          |
| Tsiouris et al.  | 2013 | USA             | Patients underwent LVAD implantation during 2006–2011                      | 88     | Continuous         | Not specified     | AKI: 22/88 (25%)         |
|                  |      |                 | Mean age: 52.5                                                             |        | HeartMate II, HeartWare |                   | RRT 6/88 (6.8%)          |
|                  |      |                 | F: 21.7%                                                                   |        |                   |                   |                          |
|                  |      |                 | NICM: 70.45%                                                               |        |                   |                   |                          |
|                  |      |                 | ICM: 29.5%                                                                 |        |                   |                   |                          |
|                  |      |                 | Bridge to transplant: 39.3%                                                 |        |                   |                   |                          |
| Brisco et al.    | 2014 | USA             | Patients underwent LVAD or LVAD + RVAD implantation from INTERMACS database during 2006–2011 | 3363   | Continuous (79.3%) and Pulsatile (20.7%) | Decrease in eGFR ≥ 25% | AKI: 336/3363 (10%)      |
|                  |      |                 | Mean Age: 54.5                                                             |        |                   |                   |                          |
|                  |      |                 | F: 21.7%                                                                   |        |                   |                   |                          |
|                  |      |                 | NICM: 70.45%                                                               |        |                   |                   |                          |
|                  |      |                 | ICM: 29.5%                                                                 |        |                   |                   |                          |
|                  |      |                 | Bridge to transplant: 39.3%                                                 |        |                   |                   |                          |
|                  |      |                 | Destination therapy: 17.7%                                                  |        |                   |                   |                          |
|                  |      |                 | LVAD alone: 92.1%                                                          |        |                   |                   |                          |
| Strueber et al.  | 2014 | Europe and Australia | Patients underwent LVAD implantation from ReVOLVE registry from 2009 to 2012 | 254    | Continuous         | INTERMACS criteria: | 10/254 (3.9%)           |
|                  |      |                 | Mean age: 41.5                                                             |        | HeartWare          | RRT or an increase in SCr ≥ 3 times baseline or SCr ≥ 5 mg/dL sustained for over 48 hours | |
|                  |      |                 | F: 19.3%                                                                   |        |                   |                   |                          |
|                  |      |                 | NICM: 15.2%                                                                |        |                   |                   |                          |
|                  |      |                 | ICM: 64.5%                                                                 |        |                   |                   |                          |
| Naik et al. [46] | 2014 | USA             | Patients underwent LVAD during 2008–2012                                    | 157    | Pulsatile (3.2%)   | RIFLE criteria or AKN criteria | RIFLE AKI 44/157 (28.02%) |
|                  |      |                 | Bridge to transplant: 47.78%                                                |        | HeartMate XVE      | Continuous HeartMate II, Heartware, | AKN AKI 67/157 (42.7%) |
|                  |      |                 | Destination therapy: 51.59%                                                 |        | Continuous         |                   | RRT 11/157 (7.0%)        |
|                  |      |                 |                                                                            |        | HeartWare          |                   |                          |
| Sumida et al.    | 2014 | Japan           | Patients underwent LVAD implantation during 2011–2013                       | 31     | Not specified      | KDIGO criteria    | AKI 17/31 (54.8%)        |
|                  |      |                 | Mean age: 41.5                                                             |        |                   |                   | RRT 6/31 (19.4%)         |
|                  |      |                 | F: 19.3%                                                                   |        |                   |                   |                          |
|                  |      |                 | NICM: 15.2%                                                                |        |                   |                   |                          |
|                  |      |                 | ICM: 64.5%                                                                 |        |                   |                   |                          |

(continued)
| Study                  | Year | Country | Patients                                                                 | Number | LVAD type | AKI definition     | AKI and/or RRT incidence |
|-----------------------|------|---------|--------------------------------------------------------------------------|--------|------------|--------------------|--------------------------|
| Schechter et al. [53] |      |         | Patients underwent LVAD implantation from 2003 to 2012                   |        |            | All: 12/60 (20%)   |                          |
|                       |      |         | Primary implantation: 50% Replacement: 50%                              |        |            | Primary implantation: 3/30 (10%) Replacement: 9/30 (30%) |                          |
| Go et al. [36]        | 2015 | USA     | Patients underwent LVAD implantation during 2006–2014                   | 200    | Continuous | RIFLE criteria     | AKI 74/200 (37.5%)       |
|                       |      |         | Mean age: 54.3 F: 24% Chronic renal insufficiency: 40.5 Bridge to transplant: 49.5% Definitive treatment: 50.5% |        | HeartMate II, HeartWare |                          |                          |
| Topkara et al. [64]   | 2015 | USA     | Patients underwent LVAD implantation during 2004–2015                   | 389    | Continuous | RRT                | Any RRT 44/389 (11.3%) New RRT after LVAD 38/383 (9.9%) |
|                       |      |         | Mean age: 60.3 F: 20.1% ICM: 45.8% Bridge to transplant: 64% IABP: 27.5% |        | HeartMate II, HeartWare |                          |                          |
| Deschka et al. [33]   | 2016 | Germany | LVAD recipients with pre-operative biventricular impairment who received an additionally RVAD after a failed weaning attempt from cardiopulmonary bypass due to acute RV failure | 25     | Not specified | RRT                | RRT 9/25 (36%)           |
|                       |      |         | Age: 55.4 F: 20% ICM: 56% DCM: 40% Destination therapy: 36% Bridge to transplant: 64% |        |            |                          |                          |
| Nadziakiewicz et al. [45] | 2016 | Poland  | Patients with end-stage heart failure underwent LVAD implantation during 2007–2014 | 44     | Pulsatile (54.5%) Polvad MEV Continuous Heartware, HeartMate II | RRT                 | RRT 7/44 (15.9%)         |
|                       |      |         | ICM: 36.6%                                                              |        |            |                          |                          |
| Raichlin et al. [51]  | 2016 | USA     | End-stage heart failure Patients with preexisting renal dysfunction underwent LVAD implantation during 2009–2014 | 165    | Continuous | RRT                | RRT : 15/165 (9.1%)       |
|                       |      |         | Age: 55.6 F: 19% Bridge to transplant: 50% ICM: 51% Mean Baseline GFR: 64.1 |        | HeartMate II |                          |                          |
| Shehab et al. [55]    | 2016 | Australia | Patients with dilated cardiomyopathy and severe biventricular failure who underwent dual HVAD implantation as a bridge to transplant during 2011–2014 | 13     | Continuous | INTERMACS criteria: RRT or an increase in Scr ≥ 3 times baseline or Scr ≥ 5 mg/dL sustained for over 48 hours | AKI 4/13 (30.7%)         |
|                       |      |         | Mean age: 45.6 F: 23%                                                   |        | HeartWare |                          |                          |

(continued)
| Study            | Year | Country     | Patients                                                                 | Number | LVAD type | AKI definition                  | AKI and/or RRT incidence |
|------------------|------|-------------|---------------------------------------------------------------------------|--------|-----------|----------------------------------|--------------------------|
| Abbas et al. [17]| 2017 | USA         | Patients underwent LVAD from the National Inpatient Sample (NIS) 2009–2011 database | 4869   | Not specified | ICD-9 codes and procedure code | AKI 1985/4869 (40.8%) RRT 277/4869 (5.7%) |
|                  |      |             | Mean age: 56 F: 22.2%                                                    |        |           |                                  |                          |
|                  |      |             | Chronic renal failure: 38%                                                |        |           |                                  |                          |
| Verma et al. [67]| 2017 | USA         | Patients with end-stage heart failure underwent LVAD placement during 2010–2013 | 169    | Continuous | Increase in Scr of 0.3 mg/dL in 48 hours or 1.5 times from baseline in the seven days, or the need for RRT. | AKI 70/169 (47.3%) RRT 6/169 (3.5%) |
|                  |      |             | Mean age: 57.8 F: 23.7%                                                  |        |           |                                  |                          |
|                  |      |             | CKD: 43.8%                                                              |        |           |                                  |                          |
|                  |      |             | Bridge to transplant: 23.67%                                             |        |           |                                  |                          |
| Anjum et al. [22]| 2018 | USA         | Patients underwent LVAD during 2003–2016                                 | 520    | Continuous | RIFLE criteria                    | AKI 75/520 (14.4%)       |
|                  |      |             | Mean age: 54.7 F: 21.9%                                                  |        |           |                                  |                          |
|                  |      |             | Bridge to transplant: 53.3%                                               |        |           |                                  |                          |
| Briasoulis et al. [27] | 2018 | USA         | Patients underwent LVAD during 2009–2014 from the National Inpatient Sample (NIS) database | 3572   | Continuous | ICD9, procedure codes            | RRT 228/3572 (6.4%)     |
|                  |      |             | Mean age: 55.42 F: 23.63%                                                |        |           |                                  |                          |
|                  |      |             | Chronic renal failure: 37.79%                                             |        |           |                                  |                          |
| Catino et al. [29]| 2018 | USA         | Patients with chronic heart failure underwent LVAD implantation during 2008–2014 | 81     | Continuous | INTERMACS criteria: RRT or an increase in Scr ≥ 3 times baseline or Scr ≥ 5 mg/dL sustained for over 48 hours | AKI 9/81 (11.1%) RRT 3/81 (3.7%) |
|                  |      |             | Mean age: 52.8 F: 21%                                                    |        |           |                                  |                          |
|                  |      |             | Bridge to transplant: 76.5%                                               |        |           |                                  |                          |
|                  |      |             | ICM: 40.7%                                                               |        |           |                                  |                          |
| Critsinelis et al. [30] | 2018 | USA         | Patients underwent LVAD implantation during 2004–2016                    | 524    | Continuous | RIFLE criteria                    | AKI 75/524 (14.3%)      |
|                  |      |             | Mean age: 54.7 F: 21.9%                                                  |        |           |                                  |                          |
|                  |      |             | Bridge to transplant: 76.5%                                               |        |           |                                  |                          |
|                  |      |             | ICM: 45.6%                                                               |        |           |                                  |                          |
| Kurihara et al. [41] | 2018 | USA         | Patients underwent LVAD implantation during 2003–2016                    | 526    | Continuous | RIFLE criteria                    | AKI 75/526 (14.3%)      |
|                  |      |             | Mean age: 54.7 F: 21.9%                                                  |        |           |                                  |                          |
|                  |      |             | Bridge to transplant: 283/526 (52.6%)                                    |        |           |                                  |                          |
|                  |      |             | CM: 45.4%                                                                |        |           |                                  |                          |
|                  |      |             | Bridge to transplant: 155/241 (64.32%)                                   |        |           |                                  |                          |
| Muslem et al. [44] | 2018 | The Netherlands, USA | Patients underwent LVAD implantation during 2004–2015                       | 241    | Continuous | KDIGO criteria                    | AKI 169/241 (70.1%) RRT 23/241 (9.5%) |
|                  |      |             | Mean age: 52.4 F: 24%                                                    |        |           |                                  |                          |
|                  |      |             | ICM: 34.4%                                                               |        |           |                                  |                          |
|                  |      |             | Bridge to transplant: 155/241 (64.32%)                                   |        |           |                                  |                          |
| Schmack et al. [54] | 2018 | Germany     | Symptomatic end-stage heart failure patients underwent LVAD from 2010 to 2017 | 68     | Continuous | RRT                               | RRT 32/68 (47.1%) RRT 11/68 (17.0%) |
| Shehab et al. [56] | 2018 | Australia   | Patients underwent VAD implantation as a bridge to transplant from 2007 to 2016 | 112    | Continuous | RRT                               | RRT 11/112 (17.0%)      |
|                  |      |             | Bridge to transplant: 100%                                               |        |           |                                  |                          |
| Study            | Year  | Country | Patients                                                                                       | Number | LVAD type                                      | AKI definition | AKI and/or RRT incidence |
|------------------|-------|---------|------------------------------------------------------------------------------------------------|--------|-----------------------------------------------|----------------|--------------------------|
| Baxter et al. [25] | 2019 | USA     | Patients underwent LVAD during 2008–2016                                                        | 202    | Continuous HeartMate II (90%), HeartMate III (3.3%), HeartWare (6.0%) | KDIGO criteria | AKI stage 2 and 3 66/202 (32.7%) |
| Silver et al. [57]  | 2019 | USA     | Patients with end-stage heart failure who were ineligible for transplantation underwent LVAD implantation during 2008–2013 from the national inpatient sample database | 8362   | Not specified                                 | ICD-9 codes    | AKI 4186/8362 (50.1%)   |
| Walther et al. [68]  | 2019 | USA     | Patient with end-stage heart failure underwent LVAD implantation during 2006–2015 from the national inpatient sample database | 24140  | Not specified                                 | ICD-9-CM, procedure codes | AKI 13534/24140 (56.1%) |
| Zhigalov et al. [70] | 2019 | Germany| Patient underwent LVAD implantation from 2007 to 2018                                            | 124    | Continuous HeartMate II (60%), HeartMate III (27%), HeartWare (13%) | RRT            | RRT 1568/24140 (6.5%)   |
| Adegbala et al. [18] | 2019 | USA     | Patients underwent LVAD implantation from 2012 to 2014 from National readmission database        | 3957   | Not specified                                 | RRT            | RRT 178/3957 (4.5%)     |
| Asleh et al. [24]  | 2019 | USA     | Patients underwent LVAD implantation during 2007–2017                                            | 354    | Continuous HeartMate II (80%), HeartMate III (2%) HeartWare (18%)    | RRT            | RRT 54/354 (15.3%)      |
| Ahmed et al. [19]  | 2020 | USA     | Patients underwent LVAD implantation during 2009–2014 from the National Inpatient Sample database | 3511   | Not specified                                 | ICD9 codes, procedure codes | AKI 1996/3511 (56.9%) |

**Abbreviations.** AKI: acute kidney injury; AKIN: Acute Kidney Injury Network; CKD: chronic kidney disease; F: female; ICD: International Classification of Diseases; ICM: ischemic cardiomyopathy; KDIGO: Kidney Disease: Improving Global Outcomes; LVAD: left ventricular assist device; RVAD: right ventricular assist device; RRT: renal replacement therapy; SCr: serum creatinine; USA: Unites States of America; RIFLE: Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease.
destination therapy) \((p = 0.62)\). While meta-regression analysis did not demonstrate a significant association between study year and overall AKI incidence \((p = .55)\) (Supplementary Figure S2), the study year was negatively correlated with the incidence of severe AKI requiring RRT (slope = \(-0.068\), \(p < .001\), Figure 4).

### Mortality associated with AKI in LVAD patients

Thirteen studies \([18,21,22,24,26,40,44,46,52,54,57,63,65]\) evaluated mortality associated with AKI in LVAD patients, as shown in Table 2. The pooled odds ratio (OR) of 30-day mortality was 3.66 (95% CI, 2.00–6.70, \(I^2 = 71\%\), Supplementary Figure S3) and the pooled OR of 1-year mortality was 2.22 (95% CI, 1.62–3.04, \(I^2 = 0\%\), Supplementary Figure S4) in LVAD patients with AKI, compared with no AKI. The pooled OR of 30-day mortality was 7.52 (95% CI, 4.58–12.33, \(I^2 = 73\%\), Supplementary Figure S5) and the pooled OR of 1-year mortality was 5.41 (95% CI, 3.63–8.06, \(I^2 = 0\%\), Supplementary Figure S6) in LVAD patients with severe AKI requiring RRT, compared with no RRT.

### Publication bias evaluation

Using funnel plots (Supplementary Figure S7–10) and Egger’s regression asymmetry tests, there was no significant publication bias found in this meta-analysis \((p\text{-values} = .78, .25, .53, \text{and} .59, \text{respectively})\).
| Group by AKI definition | Study name | Statistics for each study | Event rate and 95% CI | Relative weight |
|------------------------|------------|---------------------------|-----------------------|----------------|
|                       |            | Event rate | Lower limit | Upper limit | Z-Value | p-Value |                         |              |
| AKIN                  | Naik et al | 0.427      | 0.352      | 0.505      | -1.829  | 0.067    |                         | 100.00       |
| AKIN                  |            | 0.427      | 0.352      | 0.505      | -1.829  | 0.067    |                         | 31.08        |
| KDIGO                | Sumida et al | 0.548    | 0.374      | 0.711      | 0.538   | 0.591    |                         | 34.51        |
| KDIGO                | Muslem et al | 0.701    | 0.640      | 0.756      | 6.063   | 0.000    |                         | 34.42        |
| KDIGO                | Baxter et al | 0.327    | 0.266      | 0.394      | -4.820  | 0.000    |                         | 14.34        |
| KDIGO                |            | 0.526      | 0.260      | 0.779      | 0.180   | 0.857    |                         | 15.23        |
| RIFLE                 | Alba et al | 0.453      | 0.325      | 0.587      | -0.686  | 0.493    |                         | 4.50         |
| RIFLE                 | Borgi et al | 0.280    | 0.201      | 0.376      | -4.241  | 0.000    |                         | 16.30        |
| RIFLE                 | Ono et al | 0.067      | 0.009      | 0.352      | -2.550  | 0.011    |                         | 16.54        |
| RIFLE                 | Go et al | 0.370      | 0.306      | 0.439      | -3.634  | 0.000    |                         | 16.54        |
| RIFLE                 | Anjum et al | 0.144    | 0.117      | 0.177      | -14.265 | 0.000    |                         | 16.55        |
| RIFLE                 | Critsinelis et al | 0.143 | 0.116    | 0.176      | -14.346 | 0.000    |                         |              |
| RIFLE                 | Kurihara et al | 0.143    | 0.115      | 0.175      | -14.386 | 0.000    |                         |              |
| RIFLE                 |            | 0.220      | 0.146      | 0.318      | -4.950  | 0.000    |                         |              |
| Overall               |            | 0.369      | 0.311      | 0.431      | -4.041  | 0.000    |                         |              |

Figure 3. Forest plots of the included studies evaluating the incidence of AKI using standard AKI definitions (RIFLE, AKIN, and KDIGO criteria) among LVAD patients. A diamond data marker represents the overall rate from the individual studies (square data marker) and 95% CI.

Figure 4. Meta-regression analysis demonstrated a significant negative correlation between the incidence of severe AKI requiring RRT and study year (slope = −0.068, p < .001)
Discussion

This meta-analysis supports that AKI is a common complication after LVAD implantation. The pooled incidence of post-LVAD AKI (using standard AKI definitions) and severe AKI requiring RRT was 37% and 13%, respectively. We found no significant difference in AKI...
incidence after adjusting for LVAD indication (bridging vs. destination therapy). Moreover, our analysis did not show any difference in AKI incidence between pulsatile and continuous flow LVAD devices. It was also noted that the incidence of AKI was higher (37% vs. 25%) when using standard AKI criteria, such as RIFLE, AKIN, and KDIGO. This may indicate that defining AKI using consensus criteria may improve the sensitivity of detecting AKI in LVAD patients. This meta-analysis further identified that AKI incidence remained constant over time, while the need for RRT due to AKI decreased significantly in more recent studies.

The mechanisms of AKI among LVAD patients are complex and can be multifactorial [5,89,90]. Mechanical stress on red blood cells traveling through the LVAD leads to constant low-level hemolysis, potentially resulting in pigment nephropathy [5]. These patients also tend to have acquired von Willebrand disease, as the von Willebrand factor multimers suffer fragmentation when passing through the LVAD pump, leading to subsequent increased risk of AKI due to decreased effective blood volume secondary to bleeding from arteriovenous malformations or severe epistaxis [5,8]. An additional concern is, the development of right heart failure following LVAD implantation, which is observed in approximately 20–50% of patients [14,91–94]. This right heart failure could further potentiate renal venous congestion, compromised net effective renal perfusion pressure and decrease GFR [95,96]. Hemodynamic instability in the immediate post-operative period could exacerbate kidney ischemia and lead to acute tubular necrosis. Accelerated thrombogenicity secondary to the LVAD pump and blood stasis may trigger renal microemboli, as evidenced by the presence of kidney infarctions [97]. Yet another proposed hypothesis for the development of worsening kidney function in LVAD patients is that the continuous flow of the LVAD might lead to a proliferation of afferent arteriolar smooth muscle cells and periarteriolaris, which causes an eventual decline in eGFR [98]. However, in our study, the incidence of AKI was similar between pulsatile-flow and continuous-flow LVADs, suggesting that the lack of pulsatility from continuous-flow LVADs might not be the cause of associated AKI. On the other hand, currently only a limited amount of pulsatility can be generated by LVADs using periodic speed steps, and it is considerably smaller in both flow increase and rate than what is found with natural pulsatile circulation [99]. Given the ongoing efforts to advance LVAD technology, future studies are needed to evaluate whether or not improvements in pulsatile-flow LVADs can reduce the incidence of post-LVAD implantation AKI.

The findings from our study demonstrated that LVAD patients who developed AKI had greater odds of 30-day and 1-year mortality. The pooled odds ratios were even higher in patients with severe AKI requiring RRT. It is emphasized that even an occurrence of AKI following LVAD implantation has long-lasting negative clinical impacts, especially if dialysis is required [40, 100]. Post-implantation AKI is associated with right ventricular failure and arrhythmias, both of which are, in turn, associated with increased mortality [28]. Our study shows that LVAD patients with severe AKI requiring RRT are associated with 7.5-fold and 5.4-fold increased risks of 30-day and 1-year mortality, respectively. While the findings of our study suggested no significant changes in overall AKI incidence over the study years, the incidence of severe AKI requiring RRT appeared to decrease over study year significantly. This finding suggests potential improvements in the prevention, mitigation, and clinical management of severe AKI in LVAD patients. Interventions proposed to mitigate the incidence and severity of post-LVAD implantation AKI include maintenance of high mean arterial pressures (MAP) and coronary perfusion rates [96], inotropic support when needed, frequent monitoring of MAP via audible doppler ultrasound in combination with calibrated blood pressure measurement devices, and maintaining central venous pressures between 8 and 12 mm Hg via diuretics or extracorporeal ultrafiltration. Avoiding nephrotoxic medications postoperatively until hemodynamic stability is achieved has also been recommended. In patients with severe right heart failure, right ventricular assist devices may help decrease right-sided venous congestion and improve renal perfusion [96]. Future studies are required to assess whether these measures can significantly help to reduce AKI incidence or promote AKI recovery among LVAD patients, to improve patient survival rates ultimately.

Our systematic and meta-analysis is subject to certain limitations. First, all studies were observational in design, making them susceptible to potential selection bias. The potential sources of this heterogeneity included differences in variation in baseline characteristics (e.g., age, sex, ethnicity, and underlying chronic kidney disease), LVAD types, indications for LVAD, and outcome ascertainment. Second, the incidence of AKI is predisposed to several confounding factors. Our meta-analysis had a high degree of heterogeneities. However, we performed subgroup analyses after applying standardized AKI definitions and conducted meta-regression analyses assessing the effects of the study year, LVAD types (pulsatile vs. continuous flow), and indications for LVAD implantation (bridge to transplant
were limited [104, 106]. Furthermore, future studies using artificial intelligence to predict AKI among LVAD patients are needed [107].

In conclusion, AKI is a common complication among LVAD patients. There have been some potential improvements in the incidence rates of severe AKI requiring RRT in LVAD patients, AKI, while on LVAD, is associated with increased 30-day and 1-year mortality.

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No potential conflict of interest was reported by the author(s).

Authors’ contributions
All authors had access to the data, reviewed, and approved the final manuscript.

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