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# Different strategies in left ventricle unloading during venoarterial extracorporeal membrane oxygenation: A network meta-analysis

Han Zhang [1], Tianlong Wang [1], Jing Wang, Gang Liu, Shujie Yan, Yuan Teng, Jian Wang, Bingyang Ji [*]

*Department of Cardiopulmonary Bypass, National Center for Cardiovascular Disease, Chinese Academy of Medical Sciences & Peking Union Medical College, National Clinical Research Center for Cardiovascular Diseases, Fuwai Hospital, Beijing, China*

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ABSTRACT

*Background:* Left ventricular (LV) overload is a frequent complication during VA-ECMO associated with poor outcomes. Many strategies of LV unloading have been documented but lack of evidence shows which is better. We conducted a network meta-analysis to compare different LV unloading strategies.

*Methods:* We searched databases for all published studies on LV unloading strategies during VA-ECMO. The pre-defined primary outcome was all-cause mortality.

*Results:* 45 observational studies (34235 patients) were included. The Surface Under the Cumulative Ranking values (SUCRA) demonstrated that compared to no unloading strategy (15.4 %), IABP (73.8 %), pLVAD (60.8 %), atrial septostomy (51.2 %), catheter venting (48.8 %) were all associated with decreased all-cause mortality, in which IABP and pLVAD existed statistical significance. For secondary outcomes, no unloading group had the shortest VA-ECMO duration, ICU and hospital length of stay, and the lower risk of complications compared with unloading strategies. IABP was associated with reducing VA-ECMO duration, ICU and hospital length of stay, and the risk of complications (except for hemolysis as the second best) compared with other unloading strategies.

*Conclusions:* LV unloading strategies during VA-ECMO were associated with improved survival compared to no unloading, but the tendency to increase the risk of various complications deserves more consideration.

## 1. Introduction

Venoarterial extracorporeal membrane oxygenation (VA-ECMO) is the primary mechanical circulatory support for the initial management in cardiogenic shock or cardiac arrest over the past decades [1]. With the development of ECMO, increasing attention is given to the potential impact of VA-ECMO, including left ventricular (LV) dilation. Peripheral cannulation during VA-ECMO causes retrograde blood flow to the ascending aorta and resistance of LV ejection, thus increasing afterload on the heart and raising myocardial oxygen demand in the already failing ventricle, further leading to reduced stroke volume, LV distention, and complications such as myocardial ischemia, arrhythmias, pulmonary edema, and LV thrombus formation, all of which may impair myocardial recovery and worsen prognosis [2–4]. Therefore, LV unloading was the key point in the VA-ECMO management.

Various LV unloading strategies have been employed, including pharmacological approach, intra-aortic balloon pump (IABP), percutaneous left ventricular assist device (pLVAD, mainly as Impella pump), surgically LV cannulation, and percutaneous atrial septostomy [5–7]. Recent clinical studies and meta-analyses have shown that LV decompression during VA-ECMO is associated with a reduced risk of mortality [3,8–10]. However, each strategy is associated with its risks. Several studies have revealed the association between mechanical circulatory support devices and significant adverse events including bleeding or

*Abbreviations:* CI, Confidence intervals; IABP, Intra-aortic balloon pump; LA, Left atrium; LV, Left ventricular; NMA, Network meta-analysis; NOS, Newcastle-Ottawa Scale; OR, Odds ratio; pLVAD, Percutaneous left ventricular assist device; pRVAD, Percutaneous right ventricular assist device; RRT, Renal replacement therapy; SMD, Standardized mean difference; SUCRA, the Surface Under the Cumulative Ranking values; VA-ECMO, Venoarterial extracorporeal membrane oxygenation.

* Corresponding author at: Department of Cardiopulmonary Bypass, National Center for Cardiovascular Disease and Fuwai Hospital, No. 167 Beilishi Road, Xicheng District, 10010 Beijing, China.

*E-mail address:* jibingyang@fuwai.com (B. Ji).

[1] These authors contributed equally.

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thrombosis [11–13]. There is no consensus or recommendation on the optimal choice of LV unloading strategies during VA-ECMO. High-quality randomized controlled studies about this question are lacking and the results of observational studies remain controversial. Hence, we conducted a network meta-analysis (NMA) to evaluate the clinical outcomes of different LV unloading strategies during VA-ECMO, thus investigating the efficacy and safety of each LV unloading strategy.

## 2. Materials and methods

This NMA was performed in accordance with the PRISMA extension statement for NMA [14]. The PRISMA 2020 checklist [15] of this study is included in **Supplemental Material 1**. The protocol was registered with the PROSPERO (International Prospective Register of Systematic Reviews, CRD42024517760).

### 2.1. Search strategy

A systematic search was performed independently using MEDLINE, EMBASE, Scopus and Cochrane Library. All English articles published before 1 MARCH 2024 were selected. The search terms included: "VA-ECMO", "venoarterial extracorporeal membrane oxygenation", "ECPR", "left ventricle", "LV", "LA", "unloading", "decompression", "venting", "IABP", "Impella", "pLVAD", "atrial septostomy", "catheter", "cannula", "vasodilators". The search strategy was shown in **Supplemental Material 2**. Additionally, snowball searches for reference lists of published systematic reviews and meta-analyses were reviewed. Three authors independently screened study titles and abstracts for potential eligibility, assessed their validity, and reviewed full texts included in the analysis. Disagreement between authors was assessed and resolved through a process of discussion or a senior reviewer, who will be consulted.

### 2.2. Eligibility criteria

#### 2.2.1. Patients

Adult patients receiving VA-ECMO treatment for any reason.

#### 2.2.2. Comparator

VA-ECMO without LV unloading strategies.

#### 2.2.3. Intervention

VA-ECMO with LV unloading strategies. Each LV unloading strategy is considered as a separate intervention, and patients receive only one type of unloading strategies during VA-ECMO support. We defined the types of LV unloading strategies according to the published articles, as follows: (1) intra-aortic balloon pump (IABP); (2) percutaneous left ventricular assist device (pLVAD); (3) atrial septostomy; (4) catheter venting including pulmonary artery cannula, left atrial cannula, surgical left ventricular cannula [16,17].

#### 2.2.4. Outcomes

Primary outcomes: all-cause mortality.

Secondary outcomes: in-hospital complications after VA-ECMO initiation, VA-ECMO duration, ICU length of stay, hospital length of stay.

#### 2.2.5. Study selection

All published clinical studies investigating the effects of VA-ECMO with and without LV unloading strategy support or with at least two different LV unloading strategies were evaluated for inclusion in this meta-analysis.

### 2.3. Data extraction

Two reviewers independently extracted and recorded all data with a standardized form including the following general information.

***Study characteristics:*** year of publication, title, authors, contact address, country.

***Methods:*** study design and statistical analysis methods.

***Patient characteristics:*** overall numbers of patients, number of patients in each intervention, sex, age, BMI, surgery types and preoperative comorbidities.

***VA-ECMO and unloading characteristics:*** VA-ECMO duration, the cannulation site, type of unloading.

***Primary and secondary outcomes:*** Considering that studies presented in-hospital mortality, 2-week mortality, 30-day mortality and 90-day mortality. All-cause mortality included all of the above. In-hospital complications after VA-ECMO initiation included limb ischemia, bleeding, cerebrovascular accident, infection, hemolysis and renal replacement therapy (RRT).

Percentages were extracted for categorical variables. Means with standard deviations or medians with interquartile ranges were extracted for continuous outcomes. Under the assumption of a normal distribution, we transformed the interquartile range into standard deviations according to the Cochrane Handbook for Systematic Reviews of Interventions (Part 2, Chapter 7.7.3.5). If the standard deviation was zero, the lowest standard deviation of another group within the study was used in the meta-analysis.

### 2.4. Risk of bias

Quality assessment of observational studies included in this report was done with the Newcastle-Ottawa Scale (NOS) tool by three authors independently [18]. Additionally, funnel plots were produced to assess reporting bias.

### 2.5. Network meta-analysis

A NMA can provide reliable evidence for the comparison of direct and indirect multiple interventions. A design-by-treatment interaction model designed by processing was adopted for network element analysis. The results were reported as standardized mean difference (SMD) or odds ratio (OR) with 95 % confidence intervals (CI). The Surface Under the Cumulative Ranking values (SUCRA) were calculated to hierarchically rank each unloading strategy based on the probability of being the best for a given outcome, and unloading strategies were ranked from best to worst based on progressively lower SUCRA [19].

#### 2.5.1. Transitivity analysis

As an extension of clinical and methodological homogeneity to comparisons across groups of studies, transitivity refers to the validity of indirect comparisons of a treatment network. To meet the transitivity assumption, we evaluated the included studies by comparing the characteristics of the population, intervention, and study design.

#### 2.5.2. Heterogeneity analysis

The homogeneity of direct evidence was assessed using $I^2$.

#### 2.5.3. Consistency analysis

We checked the evidence of consistency between direct and indirect analyses using node splitting analysis [20]. If $p < 0.05$, inconsistency was considered to exist between direct and indirect analyses.

#### 2.5.4. Sensitivity analysis

Sensitivity analysis was conducted by excluding studies with less than 20 patients per arm.

### 2.6. Statistics

Data processing was conducted using Review Manager (version 5.3). NMA was performed using the package "netmeta" in R (version 4.2.2).

### 2.7. Certainty assessment

The quality of each NMA estimate was rated based on the four-step approach suggested by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group [21]. We rated the certainty of the directed and indirect evidence as high, moderate, low, or very low, based on study limitations, publication bias, inconsistency, indirectness, and imprecision. The final quality of the NMA effect estimates was based on a combination of direct and indirect evidence quality ratings.

## 3. Results

### 3.1. Search results

A cumulative of 4576 potentially relevant records were obtained: 4565 from the database and 11 from snowball searches. A total of 1080 were excluded after duplicate removal and 3386 were excluded during screening based on title and abstract and 110 studies met the criteria for full-text review. The final meta-analysis included 34,235 patients across 45 observational studies (Fig. 1) [1,3,8–10,22–61]. The patients were divided into 5 treatment groups according to LV unloading strategies: IABP (n = 7166), pLVAD (n = 4078), atrial septostomy (n = 130), catheter venting (n = 83), and VA-ECMO without unloading strategies (n = 22645). For the comparison between IABP and no unloading, 22 studies were found; for the comparison between pLVAD and no unloading, 12 studies were included; for the comparison between atrial septostomy and no unloading, 3 studies were found; for the comparison between catheter venting and no unloading, 1 study was found; for the comparison between IABP and pLVAD, 10 studies were found; for the comparison between pLVAD and catheter venting, 2 studies were found; for the comparison between IABP and atrial septostomy, 1 study was included. A summary of the included studies is shown in Supplemental Material 3.

### 3.2. Preliminary analysis

The pooled mortality of the included studies was 58 % (95 % CI: 55 %, 62 %). The pooled mortality was the highest in no unloading group (63 %; 95 % CI: 56 %, 70 %) and the lowest in IABP group (53 %; 95 % CI: 47 %, 60 %). All LV unloading strategies existed lower pooled mortality compared to no unloading group (Supplemental Material 4).

### 3.3. Network meta-analysis

#### 3.3.1. All-cause mortality

All studies reported the results of mortality (Supplemental Material 5). All results for the mortality are shown in Table 1. The direct and NMA results both revealed a decreasing trend for mortality in all unloading groups when compared to no unloading group. In the direct results, statistical significance was observed for comparison of IABP vs. no unloading (OR, 0.78; 95 % CI: 0.66, 0.93). In the NMA results, statistical significance was found for comparisons of IABP vs. no unloading (OR, 0.77; 95 % CI: 0.66, 0.90) and pLVAD vs. no unloading (OR, 0.81; 95 % CI: 0.66, 0.99). When all interventions were ranked according to SUCRA (Fig. 2), IABP showed the highest probability of being the best treatment in reducing mortality (73.8 %), followed by pLVAD (60.8 %), atrial septostomy (51.2 %), catheter venting (48.8 %), no unloading (15.4 %).

### 3.4. Secondary outcomes

#### 3.4.1. VA-ECMO duration

A total of 26 studies included relevant data on the VA-ECMO duration. Supplemental Material 5 shows the qualified network diagram of the VA-ECMO duration for 5 groups, namely, IABP, pLVAD, atrial septostomy, catheter venting, and no unloading. All results for the VA-ECMO duration are shown in Supplementary Material 6. In the direct results, statistical significance was observed for comparisons of

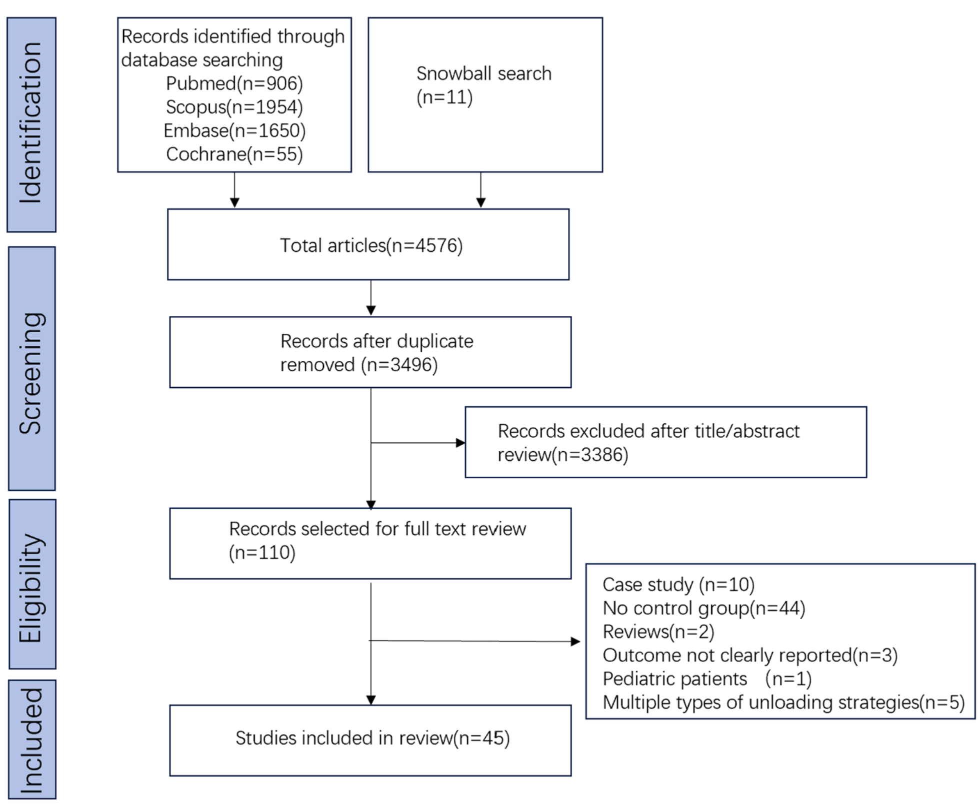


**Fig. 1.** Article retrieval flow chat.

**Table 1**
Network and direct comparison results for mortality.

| | | | | |
|---|---|---|---|---|
| **IABP** | 0.90 (0.70, 1.16) | 0.92 (0.23, 3.66) | – | **0.78 (0.66, 0.93)** |
| 0.95 (0.77,1.17) | **pLVAD** | – | 0.64 (0.30, 1.37) | 0.92 (0.73, 1.17) |
| 0.91 (0.53,1.55) | 0.95 (0.55,1.66) | **Atrial septostomy** | – | 0.85 (0.48, 1.50) |
| 0.89 (0.45,1.76) | 0.94 (0.49,1.81) | 0.99 (0.42,2.30) | **Catheter venting** | 0.27 (0.07, 1.02) |
| **0.77 (0.66,0.90)** | **0.81 (0.66,0.99)** | 0.85 (0.50,1.43) | 0.86 (0.44,1.68) | **No unloading** |

**Note:** Comparisons between left ventricle unloading strategies in VA-ECMO should be read from left to right, and the results are all comparisons between treatments defined on the top left and treatments defined on the bottom right. The table is divided into lower left and upper right sections with left ventricle unloading strategies as the dividing line. The lower left part represents the network comparison results, and the upper right part represents the direct comparison results. For comparison results, when odd ratio (OR) < 1, treatment on the left tended to positive effect, when OR > 1, treatment on the lower right tended to positive effect. Significant results are in bold and underline, and "-" means that the results are not available. IABP, intra-aortic balloon pump; pLVAD, percutaneous left ventricular assist device.

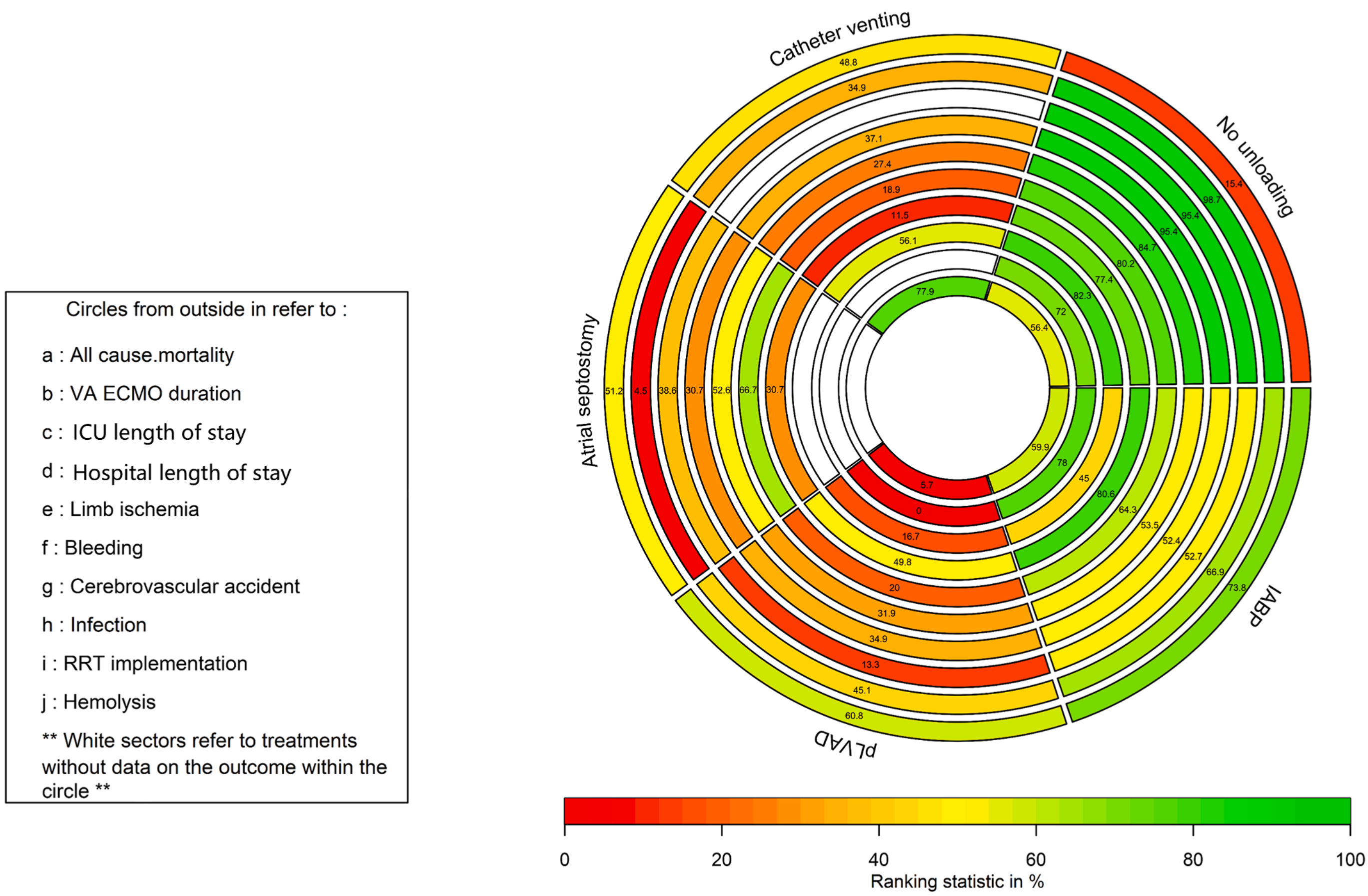


**Fig. 2.** The ranking plot based on the Surface Under the Cumulative Ranking (SUCRA) values of different strategies of left ventricular unloading during VA-ECMO support for all outcomes. **Note:** For one outcome, the closer the SUCRA value of one unloading strategy is to 100%, the higher the likelihood that this strategy is in the top rank of the positive effect. RRT, renal replacement therapy; IABP, intra-aortic balloon pump; pLVAD, percutaneous left ventricular assist device; VA-ECMO, venoarterial extracorporeal membrane oxygenation; SUCRA, Surface Under the Cumulative Ranking values.

IABP vs. no unloading (SMD, 0.19; 95 % CI: 0.01, 0.36), pLVAD vs. no unloading (SMD, 0.51; 95 % CI: 0.29, 0.74), and atrial septostomy vs. no unloading (SMD, 1.10; 95 % CI: 0.76, 1.45). In the NMA results, statistical significance was observed for comparisons of IABP vs. no unloading (SMD, 0.28; 95 % CI: 0.13, 0.43), pLVAD vs. no unloading (SMD, 0.41; 95 % CI: 0.22, 0.59), IABP vs. atrial septostomy (SMD, −0.68; 95 % CI: −1.02, −0.34), and pLVAD vs. atrial septostomy (SMD, −0.55; 95 % CI: −0.91, −0.20). When all interventions were ranked according to SUCRA (Fig. 2), no unloading (98.7 %) was associated with the lowest length of VA-ECMO duration, followed by IABP (66.9 %), pLVAD (45.1 %), catheter venting (34.9 %), and atrial septostomy (4.5 %) was associated with the highest VA-ECMO duration.

### 3.4.2. ICU length of stay

A total of 10 studies included relevant data on the ICU length of stay. Supplemental Material 5 shows the qualified network diagram of the ICU length of stay for 4 groups, namely, IABP, pLVAD, atrial septostomy, and no unloading. All results for the ICU length of stay are shown in Supplementary Material 6. In the direct results, statistical significance was observed for comparisons of pLVAD vs. no unloading (SMD, 1.75; 95 % CI: 0.49, 3.02). In the NMA results, statistical significance was observed for comparisons of pLVAD vs. no unloading (SMD, 1.23; 95 % CI: 0.17, 2.30). When all interventions were ranked according to SUCRA (Fig. 2), no unloading (95.4 %) was associated with the lowest ICU length of stay, followed by IABP (52.7 %), atrial septostomy (38.6 %), and pLVAD (13.3 %) was associated with the highest ICU length of stay.

### 3.4.3. Hospital length of stay

A total of 15 studies included relevant data on the hospital length of stay. Supplemental Material 5 shows the qualified network diagram of the hospital length of stay for 5 groups, namely, IABP, pLVAD, atrial septostomy, catheter venting, and no unloading. All results for the hospital length of stay are shown in **Supplementary Material 6**. In the direct results, statistical significance was observed for comparisons of pLVAD vs. no unloading (SMD, 0.52; 95 % CI: 0.05, 1.00), and atrial septostomy vs. no unloading (SMD, 0.59; 95 % CI: 0.10, 1.07). In the NMA results, statistical significance was observed for comparisons of pLVAD vs. no unloading (SMD, 0.48; 95 % CI: 0.09, 0.87), and atrial septostomy vs. no unloading (SMD, 0.52; 95 % CI: 0.08, 0.96). When all interventions were ranked according to SUCRA (Fig. 2), no unloading (95.4 %) was associated with the lowest hospital length of stay, followed by IABP (52.4 %), catheter venting (37.1 %), and pLVAD (34.9 %), and atrial septostomy (30.7 %) was associated with the highest hospital length of stay.

#### *3.4.4. Limb ischemia*

A total of 20 studies included relevant data on the limb ischemia. **Supplemental Material 5** shows the qualified network diagram of the limb ischemia for 5 groups, namely, IABP, pLVAD, atrial septostomy, catheter venting, and no unloading. All results for the limb ischemia are shown in **Supplementary Material 6**. In the direct results, statistical significance was observed for comparisons of IABP vs. no unloading (OR, 1.24; 95 % CI: 1.03, 1.49), and pLVAD vs. no unloading (OR, 1.38; 95 % CI: 1.06, 1.78). In the NMA results, statistical significance was observed for comparisons of IABP vs. no unloading (OR, 1.22; 95 % CI: 1.02, 1.47), and pLVAD vs. no unloading (OR, 1.41, 95 % CI, 1.09, 1.81). When all interventions were ranked according to SUCRA (Fig. 2), no unloading (84.7 %) was associated with the lowest risk of limb ischemia, followed by IABP (53.5 %), atrial septostomy (52.6 %), and pLVAD (31.9 %), and catheter venting (27.4 %) was associated with the highest risk of limb ischemia.

#### *3.4.5. Bleeding*

A total of 27 studies included relevant data on the bleeding. **Supplemental Material 5** shows the qualified network diagram of the bleeding for 5 groups, namely, IABP, pLVAD, atrial septostomy, catheter venting, and no unloading. All results for the bleeding are shown in **Supplementary Material 6**. In the direct results, statistical significance was observed for comparisons of IABP vs. pLVAD (OR, 0.50; 95 % CI: 0.33, 0.76), and pLVAD vs. no unloading (OR, 1.90; 95 % CI: 1.35, 2.66). In the NMA results, statistical significance was observed for comparisons of IABP vs. pLVAD (OR, 0.54; 95 % CI: 0.38, 0.77), and pLVAD vs. no unloading (OR, 2.08; 95 % CI: 1.52, 2.86). When all interventions were ranked according to SUCRA (Fig. 2), no unloading (80.2 %) was associated with the lowest risk of bleeding, followed by atrial septostomy (66.7 %), IABP (64.3 %), and pLVAD (20 %), and catheter venting (18.9 %) was associated with the highest risk of bleeding.

#### *3.4.6. Cerebrovascular accident*

A total of 24 studies included relevant data on the cerebrovascular accident. **Supplemental Material 5** shows the qualified network diagram of the cerebrovascular accident for 5 groups, namely, IABP, pLVAD, atrial septostomy, catheter venting, and no unloading. All results for the cerebrovascular accident are shown in **Supplementary Material 6**. In the direct results, statistical significance was observed for comparison pLVAD vs. catheter venting (OR, 0.26; 95 % CI: 0.09, 0.69). In the NMA results, statistical significance was observed for comparisons of IABP vs. catheter venting (OR, 0.22; 95 % CI: 0.08, 0.62), and pLVAD vs. catheter venting (OR, 0.26; 95 % CI: 0.09, 0.69). When all interventions were ranked according to SUCRA (Fig. 2), IABP (80.6 %) was associated with the lowest risk of cerebrovascular accident, followed by no unloading (77.4 %), pLVAD (49.8 %), and atrial septostomy (30.7 %), and catheter venting (11.5 %) was associated with the highest risk of cerebrovascular accident.

#### *3.4.7. Infection*

A total of 12 studies included relevant data on the infection. **Supplemental Material 5** shows the qualified network diagram of the infection for 4 groups, namely, IABP, pLVAD, catheter venting, and no unloading. All results for the infection are shown in **Supplementary Material 6**. In the direct results, statistical significance was observed for the comparison of pLVAD vs. no unloading (OR, 1.54; 95 % CI: 1.05, 2.25). In the NMA results, statistical significance was observed for comparison of pLVAD vs. no unloading (OR, 1.54; 95 % CI: 1.06, 2.23). When all interventions were ranked according to SUCRA (Fig. 2), no unloading (82.3 %) was associated with the lowest risk of infection, followed by catheter venting (56.1 %), and IABP (45 %), and pLVAD (16.7 %) was associated with the highest risk of infection.

#### *3.4.8. Renal replacement therapy implementation*

A total of 27 studies included relevant data on the renal replacement therapy (RRT) implementation. **Supplemental Material 5** shows the qualified network diagram of the RRT implementation for 3 groups, namely, IABP, pLVAD, and no unloading. All results for the RRT implementation are shown in **Supplementary Material 6**. In the direct results, statistical significance was observed for comparisons of IABP vs. pLVAD (OR, 0.66; 95 % CI: 0.59, 0.74), and pLVAD vs. no unloading (OR, 1.51; 95 % CI: 1.38, 1.64). In the NMA results, statistical significance was observed for comparisons of IABP vs. pLVAD (OR, 0.66; 95 % CI: 0.59, 0.73), pLVAD vs. no unloading (OR, 1.51; 95 % CI: 1.39, 1.65). When all interventions were ranked according to SUCRA (Fig. 2), IABP (78 %) was associated with the lowest risk of RRT implementation, followed by no unloading (72 %), and pLVAD (0 %) was associated with the highest risk of RRT implementation.

#### *3.4.9. Hemolysis*

A total of 10 studies included relevant data on the hemolysis. **Supplemental Material 5** shows the qualified network diagram of the hemolysis for 4 groups, namely, IABP, pLVAD, catheter venting, and no unloading. All results for the hemolysis are shown in **Supplementary Material 6**. In the direct results, statistical significance was observed for comparison of pLVAD vs. no unloading (OR, 2.36; 95 % CI: 1.06, 5.23). In the NMA results, statistical significance was observed for the comparison of pLVAD vs. no unloading (OR, 2.36; 95 % CI: 1.06, 5.23). When all interventions were ranked according to SUCRA (Fig. 2), Catheter venting (77.9 %) was associated with the lowest risk of hemolysis, followed by IABP (59.9 %), no unloading (56.4 %), and pLVAD (5.7 %) was associated with the highest risk of hemolysis.

### *3.5. Publication bias*

Funnel plots for NMA analysis are provided in **Supplementary Material 7**. No evidence of publication bias was found according to funnel plot asymmetry and the Egger's regression test values were over 0.05 for all outcomes, except for infection ($p = 0.005$).

### *3.6. Quality assessment*

Quality assessment was conducted for the outcome of the all-cause mortality (**Supplementary Material 8**). The quality of observational studies was determined according to the NOS tool and quality scores all varied from 7 to 9, except for 2 studies with a quality score of 6 [24,46].

### *3.7. Transitivity, heterogeneity, consistency and sensitivity analysis*

We analyzed the distribution of baseline variables in the included studies between different unloading strategies to assess transitivity. The difference between baseline variables was small in most comparison groups (**Supplemental Material 9**). Gender difference was found in the comparisons for IABP vs. no unloading; pLVAD vs. no unloading. **Supplemental Material 10** shows the results of the heterogeneity analysis and consistency analysis. The sensitivity analysis was conducted by excluding studies with less than 20 patients (**Supplemental Material 11**). No changes in SURCA ratings for all outcomes were found in sensitivity analysis results, except for ICU and hospital length of stay.

### *3.8. Certainty of evidence assessment*

Contribution plot revealed that direct evidence accounted for most of the sources of NMA analysis results in this study (**Supplemental Material 12**). Due to all of the included studies were observational designs; consequently, the level of evidence for all results in this study was of low quality (**Supplemental Material 13**).

## 4. Discussion

To the best of our knowledge, this study displayed the largest and most comprehensive meta-analysis comparing different LV unloading strategies during VA-ECMO support, including 45 studies containing data on 34,235 patients. The results demonstrated that all unloading treatments existed a decreased trend in the risk of all-cause mortality when compared to no unloading strategy, in which IABP and pLVAD showed statistical significance. However, it should be noticed that all LV unloading strategies were associated with the increasing trend of the risk for various complications.

In our study, survival was inferior in no unloading group. Although VA-ECMO is an effective therapy for blood oxygenation and circulatory support in patients with cardiogenic shock, 36 % of them have significant LV distension due to retrograde aortic blood flow [4]. LV pressure overload is associated with increased myocardial oxygen consumption and mitochondrial dysfunction [62]. These negative effects contribute to the persistently high mortality rate of VA-ECMO patients without unloading. LV unloading treatments improve the mechanical performance of the heart and reduce cardiac work which may explain the better survival rate. In several previous meta-analysis studies, LV unloading was found to be associated with decreased mortality during VA-ECMO [62–65], which was similar to and further enhanced the credibility of our results. In addition, the VA-ECMO duration, ICU length of stay, and hospital length of stay were found shorter and the complication rate was lower for no unloading group in this study. One reason may be that the higher early mortality in the no unloading group, thus results in a shorter total in-hospital duration and many complications are failed to exhibit and be recorded.

Although there is reasonable evidence that an effective LV unloading strategy during VA-ECMO can prolong the survival time and improve the survival rate, it comes at the expense of an increased risk of various complications. In our study, each LV unloading strategy showed a trend toward increased risk of multiple complications. Among them, IABP and pLVAD showed statistically significant increases in the risk several of complications compared with no unloading strategy (IABP for limb ischemia, and pLVAD for limb ischemia, bleeding, infection, hemolysis and RRT implementation). Considering a large amount of clinical evidence has confirmed that the application of mechanical circulatory supporting devices (IABP, Impella, and ECMO) is related to the disorder of the kidney and the hematological and coagulation systems, the results obtained in our study are explainable [8,66]. However, it should be noticed that our findings highlighted the more adverse outcomes associated with LV unloading using pLVAD than IABP. Not only the pLVAD group caused more types of complications with statistically significant increased risk than IABP when both were compared with no unloading group, but the comparison results between IABP and pLVAD showed that IABP performed better in reducing bleeding and RRT implementation with statistical significance. The larger bore arterial access required for pLVAD placement (typically via the femoral artery) and a tendency toward higher intensity of anticoagulation may potentially increase risk of hematological and coagulation complications [67]. In addition, due to the shear forces generated by the rotary mechanism acting on red blood cells of all pump systems, hemolysis and acute renal failure frequently occur as a complication of pLVAD system [64,68]. More research is required to comprehend why pLVAD leads to more hematological and coagulation complications and find ways to reduce these complications. However, pLVAD and IABP were not inferior in all complication risks. In this study, there was no significant difference between IABP and no unloading strategy in infection, bleeding, and hemolysis and RRT application, thus further demonstrating the safety of IABP. Additionally, both IABP and pLVAD displayed no significant difference in the risk of cerebrovascular accident compared with no unloading group. It is interesting that when compared with surgical catheter venting, IABP and impella have obvious advantages in reducing the risk of cerebrovascular accident. In previous research, the use of IABP and Impella has been shown to improve cerebral blood flow and pulsatility indices, which may indicate that LV unloading strategy with mechanical circulatory supporting devices could be less harmful to cerebrovascular function [69,70]. Due to the small number of related studies included, there was poor interpretability of the evidence obtained in this study on atrial septostomy and surgical catheter venting strategies. Surgical catheter venting is conducted by percutaneous inserting catheters into the LV cavity, left atrium, or pulmonary artery and connected to the inflow cannula of the VA-ECMO circuit [50,71,72]. However, the size of the catheters limits the maximum flow due to a higher risk of hemolysis, so this approach is not commonly used [17]. Considering the medical cost and technical issues, some LV unloading strategies with mechanical circulatory supporting devices cannot be routinely implemented in some countries, therefore, surgical catheter venting may be a good choice for its simplicity and economize [73]. Atrial septostomy is also another straightforward, feasible method for LV unloading. Although our study results revealed that atrial septostomy is slightly inferior to pLVAD and IABP in reducing all-cause mortality, it had higher SURCA values in reducing complications including limb ischemia and bleeding compared to pLVAD. Various techniques such as vent placement, static balloon dilation, and stent implantation could achieve left heart decompression by the transcatheter creation of an atrial septal defect [74]. This unloading method is minimally invasive in contrast to the central venting procedure, avoiding the need for surgery under general anesthesia [48]. However, the current evidence about the safety and effectiveness of atrial septostomy is limited and controversial. The study by Delmas and colleagues reported that the mid-term persistence of interatrial shunting following percutaneous atrial septostomy could potentially increase the risk of ischemic cerebrovascular accident and right heart dilation [49]. Therefore, further research is needed to investigate the advantages of atrial septostomy as a left ventricular decompression method.

At present, some emerging LV unloading strategies during VA-ECMO deserve careful evaluation of their effectiveness and safety. Percutaneous right ventricular assist device (pRVAD), utilizing a ProTek Duo (TandemLife) MCS device to drain the pulmonary artery (PA), decreases venous return to the LV resulting in physiologic and effective LV unloading [75]. Another novel unloading approach is TandemHeart trans-septal cannula via percutaneous trans-septal left atrium (LA) drainage [76]. No clinical studies compare the outcomes of these two unloading strategies with no unloading strategy and other unloading strategies, and only a few case reports have confirmed their effectiveness. More researches are needed to focus on the effects of these technologies in the future.

## 5. Limitations

This study has several limitations. First, we had to only include available observational studies due to the lack of randomized clinical trials, leading to low quality of the evidence. The retrospective observational design of all included studies restricted the evaluation of variations in baseline characteristics, proper indications, timing of unloading, underlying etiology, and potential selection bias on the observed outcomes. However, the number of studies we have included was currently the largest among the previous meta-analyses about left ventricular unloading. Second, the timing for mortality was not uniform in the forty-five studies, thirteen studies referred to 30-day mortality, thirty studies reported in-hospital mortality, one study reported 2-week mortality and one study reported 90-day mortality. Third, the majority of the included studies had a limited sample size, which raised the probability of overstating effect sizes for the outcomes. Fourth, there existed a moderate to high level of heterogeneity for certain outcomes among the included studies. However, we used random effects model with inverse variance weighting to reduce this limitation. Fifth, other cardiovascular outcomes were not accessed, because few studies specifically reported on cardiovascular complications and the occurrence of cardiovascular complications during ECMO support was likely to be greatly influenced by primary cardiac diseases.

## 6. Conclusions

In patients treated with VA-ECMO, the implementation of any unloading strategy was associated with lower mortality compared with no unloading. However, the tendency of LV unloading strategy in increasing the risk of various complications deserves serious consideration. pLVAD and IABP have the better effect in reducing mortality, and there is no significant difference between them. Given the considerable risk of bias and low-quality evidence caused by the observational design of the included studies, further prospective randomized data is urgently required to identify the optimal LV venting strategy.

## 7. Ethics approval and consent to participate

Not applicable.

## 8. Consent for publication

All the authors consent to the publication of the manuscript and support material.

## 9. Availability of data and materials

All the data associated with this manuscript were included in the main text and supplementary materials.

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None.

## CRediT authorship contribution statement

**Han Zhang:** Writing – original draft, Methodology, Data curation, Conceptualization. **Tianlong Wang:** Writing – original draft, Methodology, Formal analysis, Conceptualization. **Jing Wang:** Methodology, Data curation. **Gang Liu:** Visualization, Data curation. **Shujie Yan:** Writing – original draft, Data curation. **Yuan Teng:** Visualization, Formal analysis. **Jian Wang:** Visualization, Formal analysis. **Bingyang Ji:** Writing – review & editing, Conceptualization.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2024.101506.

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