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Fluid management in adult patients undergoing venoarterial extracorporeal membrane oxygenation: A scoping review

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ABSTRACT

Background: The use of venoarterial extracorporeal membrane oxygenation (VA-ECMO) as a cardiocirculatory support has tremendously increased in critically ill patients. Although fluid therapy is an essential component of the hemodynamic management of VA-ECMO patients, the optimal fluid resuscitation strategy remains controversial. We performed a scoping review to map out the existing knowledge on fluid management in terms of fluid type, dosing and the impact of fluid balance on VA-ECMO patient outcomes.
Methods: A literature search within PubMed and EMBASE was conducted from database inception to April 2024. We included all studies involving critically ill adult patients, supported by VA-ECMO regardless of clinical indication (cardiogenic shock or extracorporeal cardiopulmonary resuscitation) with or without Renal Replacement Therapy and describing fluid resuscitation strategies or focusing on fluid type or reporting the impact of fluid balance on clinical outcomes and mortality. Details of study population, ECMO indications, fluid types, resuscitation strategies, fluid balance and outcome measures were extracted.
Results: Sixteen studies met inclusion criteria, including 14 clinical studies and two experimental animal studies. We found a lack of studies comparing restrictive and liberal approaches. No study has compared the efficacy and safety of balanced and saline solutions. The place of albumin, as an alternative fluid, should be investigated. Despite their heterogeneity, studies found a negative impact of both early and cumulative fluid overload on survival and renal outcomes.
Conclusions: The available literature on the fluid management in VA-ECMO setting is scarce. More high-quality evidence is needed regarding optimal fluid dosing, type and resuscitation endpoints in order to standardize practice and improve outcomes.

Venoarterial extracorporeal membrane oxygenation (VA-ECMO) provides support in situations of refractory cardio-circulatory failure [1]. During the initial phase of VA-ECMO support, fluid resuscitation is often required to maintain adequate ECMO blood flow. Indeed, an intravascular volume deficit of 10 % can lead to a reduction of ECMO blood flow by about 50 % [2]. This ECMO low flow state can result in hypoperfusion and organ dysfunction [2]. Intravascular volume deficit during ECMO can be attributed to native disease process or inflammatory response to extracorporeal circulation.

Regarding the underlying disease, refractory cardiogenic shock and post-cardiac arrest patients supported with VA-ECMO exhibit a systemic inflammatory response to ischemia-reperfusion injury marked by

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cytokine release with endothelial barrier dysfunction and subsequent capillary leakage [3–5].

Regarding the ECMO circuit itself, blood exposure to the non-endothelialized surface of ECMO circuit activates the contact and complement systems [6]. These features may contribute to vascular hyporeactivity and low flow state requiring fluids particularly in the early phase after ECMO implantation [6]. In addition to intravenous fluids, blood products might be required to manage ECMO-induced coagulopathy and bleeding complications [7].

Although there is a consensus that fluid therapy is an essential component of the management of critically ill patients undergoing VA-ECMO therapy, the optimal fluid resuscitation strategy remains controversial. Thus, we performed a scoping review in order to map out literature addressing these questions: what is the optimal fluid resuscitation strategy during the initial phase of VA-ECMO support in terms of fluid type and dosing and what is the impact of fluid balance on VA-ECMO patient outcomes?

1. Methods

1.1. Protocol and registration

The protocol of this review was registered at Open Science Framework (OSF) registry (identification # OSF.IO/3DRC8). We report our findings according to the Preferred Reporting Items for Systematic Reviews and Meta Analyses Extension for Scoping Reviews (PRISMA-ScR) [8] (e-Table 1).

1.2. Screening and search strategy

We performed a literature review by searching PubMed and Embase from database inception to April 30, 2024. The following keywords and MeSH terms were used: “fluid management”, “fluid balance”, “fluid overload”, “fluid responsiveness”, “crystalloid”, “colloid”, “albumin” and “extracorporeal membrane oxygenation” or “ECMO” or “extracorporeal cardiopulmonary resuscitation”. We imported search results into Zotero software where they were automatically de-duplicated. Two independent authors (AJ and QDR) assessed all articles through abstract and title screening. Potentially relevant articles were reviewed in full text and any discrepancies were resolved by a third author (NM). The search strategy is summarized in e-Table 2.

1.3. Study selection

Clinical studies were included if they fulfilled the following inclusion criteria: (1) critically ill adult patients, (2) supported with VA-ECMO regardless of clinical indication (cardiogenic shock or extracorporeal cardiopulmonary resuscitation (ECPR) with or without Renal Replacement Therapy (RRT) and (3) studies describing fluid resuscitation strategies or focusing on fluid type or reporting the impact of fluid balance on clinical outcomes and mortality. Animal studies addressing fluid management in VA-ECMO setting were also included. Book chapters, conference abstracts, editorials, letters and non-English publications were excluded from this review.

1.4. Data extraction

Extracted data included the first author’s name, year of publication, study design, sample size, ECMO modes and indications, fluid types, resuscitation strategies, fluid balance and outcome measures.

1.5. Methodological quality assessment

The United States Preventive Services Task Force rating scale was used to categorize the included clinical studies [9] (e-Table 3). The Newcastle Ottawa Scale (NOS), which includes three subscales (selection, comparability, and outcome), was used to evaluate the methodological quality of included clinical studies [10] (e-Table 4). NOS scores are categorized into three groups: very high risk of bias (0 to 3 NOS points), high risk of bias (4 to 6), and low risk of bias (7 to 9). The reporting quality of included animal studies was assessed in accordance with ARRIVE guidelines [11], which provide a checklist for evaluating the methodology and results of in vivo experiments (e-Table 5).

2. Results

2.1. Characteristics of included studies and study population

The search strategy identified 1506 non-duplicate records. After title and abstract screening, 60 were eligible for full-text review. Among them, 16 studies met inclusion criteria including 14 clinical studies and two experimental animal studies. No prospective, randomized, controlled study (level I evidence) was identified. All clinical studies were retrospective cohort studies (level II-2). The median NOS score was 8 (interquartile range IQR 7.75–8.25). The detailed quality scores are shown in e-Table 4. The selection process is illustrated in the PRISMA flow diagram (Fig. 1). Descriptive characteristics and results of all included studies are summarized in Tables 1 and 2. Half of included studies ($n = 7$ out of 14) mixed patients on VA and venovenous ECMO (VV-ECMO).

2.2. Acute fluid management during VA-ECMO

2.2.1. Liberal versus restricted fluid resuscitation strategies

There is scant evidence to guide fluid resuscitation during the acute phase of VA-ECMO support. Current ELSO guidelines provide no recommendations regarding the optimal fluid regimen and there are no clinical interventional studies comparing liberal (high-volume strategy) versus restricted strategy (near-zero fluid balance) in VA-ECMO setting [12].

We report two retrospective studies that focused on the first hours after ECMO initiation when the inflammatory process is probably highly activated. The first study retrospectively investigated data of 195 adult patients supported with VA-ECMO and found no evidence to support a liberal fluid strategy. As early as 3 h after implantation, patients with higher fluid balance above the 75th percentile had a hazard ratio of death of 6.03 when compared to average survival. The 3-h fluid balance predicted mortality with area under the curve (AUC) of 0.726 [13]. In a second study involving 101 VA-ECMO patients, the threshold of 38.8 mL/kg for the first 24 h of the ECMO run has been identified as predictive of mortality with a sensitivity of 60 %, specificity of 83 % and AUC of 0.749 (95 % CI, 0.653–0.843) [14].

Recent data from a large animal model have explored the impact of early fluid balance on renal function and organ edema in healthy pigs with VA-ECMO circulation for 10 h. The authors have compared moderate versus extensive volume therapy strategies based on the cumulative fluid administration during 10 h of ECMO run (3275 ± 263 mL vs. 5344 ± 834 mL respectively, $P < .01$). The findings showed impaired renal function and increased intestinal tissue edema in high-volume resuscitated group [15].

2.2.2. Fluid type choice in VA-ECMO setting

Crystalloids are recommended as first-line resuscitation fluids in ICU patients [16]. There is growing data supporting a protective effect of balanced solutions compared to normal saline with more favorable kidney outcomes [17]. In adult critically ill patients with sepsis, the pooled analysis of studies of interest showed that balanced solutions compared to normal saline probably resulted in a slight reduction in mortality with moderate certainty of evidence [18]. To date, no study has compared balanced and saline solutions for fluid resuscitation among adult VA-ECMO-supported patients.

Colloids can be divided into albumin and synthetic colloids such as

Table 1
Descriptive characteristics and results of clinical studies ($N = 14$).

Author (year)	Study design, Sample size, age, % male	ECMO mode, ECMO indication	Fluid management Fluid balance assessment	Outcome measures	Results	Conclusions
Fluid resuscitation strategy, fluid balance and outcomes (VA-ECMO)						
Staudacher et. 2017 [13]	Monocentric retrospective study (N = 195 patients) Mean age 58.2 ± 1.1 years, 71.8 % male	*ECMO mode:* **VA- ECMO** *ECMO indication:* Refractory cardiogenic shock; Refractory cardiac arrest IHCA ($N = 78$), OHCA ($N = 71$)	Fluid balance after 3 h (3 h FB) PFB (D1 94.7 %, D2 93.7 %, D3 92.6 %)	Mortality 75.4 %	Volume therapy D1 (S vs. NS 11,436 ± 1035 ml vs. 14,395 ± 1024 ml, $p = .012$) 3 h FB (S vs. NS 1487 ± 255 ml vs. 3612 ± 301 ml, $P < .001$) 3 h FB (4th quartile) Hazard ratio for death = 6.03; The AUC of 3 h FB for mortality prediction was 0.726	Higher fluid balance was consistently linked to poor survival. There is no evidence to support a liberal fluid therapy in VA-ECMO patients particularly in the early phase post-implantation (the first 3 h)
He et al. 2018 [29]	Monocentric retrospective study ($N = 32$ adult patients supported by VA-ECMO and concomitant CRRT) Mean age 51 years, male 69 %	*ECMO mode:* **VA-ECMO** *ECMO indication:* Cardiac ($N = 28$); Sepsis ($N = 4$)	ECMO FB at day 1, 3 and 7 (D1 FB, D3 FB, D7 FB)	Survival to hospital discharge 41 % ($N = 13$)	D3 FB (S vs. NS 210 (−125 to 625) vs. 1090 (750–1590) ml, $P < .0001$) D3 FB was independently associated with mortality (OR = 5268 (1381–20,088), $P = .015$)	The authors demonstrated that fluid balance at ECMO day 3 was an independent risk factor for mortality in adult ECMO patients requiring CRRT
Besnier et al. 2020 [14]	Monocentric retrospective study (N = 101 patients) Median age 53 (44–61) years, 68.3 % male	*ECMO mode:* **VA- ECMO** *ECMO indication:* Refractory cardiogenic shock; Refractory cardiac arrest (no-flow <5 min, low-flow <90 min, and $ETCO_2 > 10$ cm H_2O during resuscitation)	Day-1 fluid balance (D1 FB) Cumulative fluid balance (CFB) over the first 5 days	Mortality 47.5 %	D1 FB was independently associated with mortality (OR = 14.34 (1.58–129.79), $P = .02$); D1 FB > 38.8 mL/kg predicted mortality with a sensitivity of 60 % and specificity of 83 % (AUC 0.749) CFB over the first 5 days (NS vs. S 107.3 (40.5–146.2) vs. 53.0 (7.5–74.3) mL/kg, $P = .04$)	Early positive fluid balance is associated with mortality in VA-ECMO patients.

Author (year)	Study design, Sample size, age, % male	ECMO mode, ECMO indication	Fluid management Fluid balance assessment	Outcome measures	Results	Conclusions
Fluid resuscitation strategy, fluid balance and outcomes (VA-ECMO)						
Dong et al. 2023 [34]	Monocentric retrospective study ($N = 72$ adult patients) Mean age 42.6 ± 16.3 years, male 66.67 %	*ECMO mode:* **VA-ECMO** *ECMO indication: ECPR* Concomitant CRRT ($n = 48$)	Daily fluid balance DFB Cumulative fluid balance CFB (D1-D4)	Survival to ICU discharge 44.4 % (N = 32)	DFB D4 (ml/kg) (S vs. NS -11.47, 95 % CI: −18.4 to −7.9 vs. -5.08, 95 % CI: −8.5 to 11.6, $P = .046$) CFB D1-D4 (ml/kg) (S vs. NS -36.03, 95 % CI: −51.2 to −3.9 vs. -7.22, 95 % CI: −18.1 to 28.1, $P = .009$). CFB D1-D4 was significantly correlated with survival to ICU discharge (adjusted OR: 1.261, 95 % CI: 1091 to 1375, $P = .003$)	Early negative fluid balance maybe associated with survival to ICU discharge in patients receiving ECPR.
Taira et al. 2024 [35]	Retrospective multicenter cohort study (N = 959 patients) Median age 60 (49–68) years, 83.7 % male	*ECMO mode:* **VA-ECMO** *ECMO indication:* ECPR for refractory OHCA	Fluid balance in the first 24 h following ICU admission (FBD1) FB D1 = (IVF D1 + blood transfusion D1) - (urine output D1) Median FBD1 (IQR) 3673 (1777–6697) ml	In-hospital mortality 63.6 % ($N = 610$) Unfavorable neurological outcome at discharge CPC (3–5) 82 % ($N = 786$) AKI 41.5 % ($N = 391$) RRT 18.6 % ($N = 176$)	FB D1 was significantly associated with in-hospital mortality (OR 1.04, 95 % CI 1.02–1.06; $P < .001$) FB D1 was significantly associated with unfavorable neurological outcome (CPC 3–5) (OR, 1.03; 95 % CI, 1.01–1.06; $P = .005$) FB D1 was significantly associated with AKI (OR, 1.04; 95 % CI, 1.02–1.05; $P < .001$) and need of RRT (OR, 1.05; 95 % CI, 1.03–1.07; P < .001)	Excessive positive fluid balance in the first 24 h following ICU admission was associated with in-hospital mortality, unfavorable neurological outcome, incidence of AKI, and need of RRT in ECPR patients.

Author (year)	Study design, Sample size, age, % male	ECMO mode, ECMO indication	Fluid management Fluid balance assessment	Outcome measures	Results	Conclusions
Fluid resuscitation strategy, fluid balance and outcomes (Mixed population of ECMO patients)						
Schmidt et al. 2014 [27]	Monocentric retrospective study (N = 172 patients) Mean age 44 ± 15 years, 66 % male	***Mixed population*** *ECMO mode:* VA-ECMO (*N* = 115), VV-ECMO (*N* = 57) *ECMO indication:* Cardiac failure, Respiratory failure	*Resuscitation fluids:* crystalloids or 4 % albumin Day-3 fluid balance (D3 FB) PFB (*N* = 100); NFB (*N* = 72)	90-day mortality 24 % AKI 57 %; CRRT 60 % Ventilator-free days (VFD)	Median D3 FB (IQR) (S vs. NS 160 (IQR −994 - 1200) vs. 1242 (IQR 186–2587), *P* = 0.0006) CRRT (S vs. NS 53 % vs. 83 %, *P* = 0.0006) VFD (NFB vs. PFB 44 (16–54) vs. 37 (0–48), *P* = .03) 90-day mortality (NFB vs. PFB 14 % vs. 31 %, *P* = .009); Hospital mortality (NFB vs. PFB 15 % vs. 34 %, *P* = .006)	Early positive fluid balance at ECMO day 3 is an independent predictor of 90-day mortality.
Kim et al. 2018 [28]	Retrospective multicenter cohort study (N = 723 patients) CVD (mean age 58.4 ± 17.7 years, 68.2 % male) Non-CVD (mean age 55.7 ± 15.7 years, 65.3 % male)	**Mixed population** *ECMO mode*: VA-ECMO, VV-ECMO *ECMO indication:* Cardiovascular origin (CVD group) (*N* = 406); non-cardiovascular origin (non-CVD group) (*N* = 317)	*Resuscitation fluids:* Crystalloids CVD (median CFB 64.7 ml/kg; median daily FB 26.2 ml/kg/day) Non-CVD (median CFB 53.5 ml/kg, median daily FB 15.9 ml/kg/day)	90-day mortality (CVD group 51 %, non-CVD group 65.9 %) CVD [AKI (*N* = 306; 75.4 %); CRRT (*N* = 127; 31.3 %)] Non-CVD [AKI (*N* = 184; 70 %); CRRT (*N* = 92; 29 %)]	*CFB quartile groups and mortality*: CVD [(CFB Q4 vs. Q1 HR, 2.11; 95 % CI, 1.26–3.54; *P* = .004); (CFB Q3 vs. Q1 HR, 2.58; 95 % CI, 1.62–4.11; *P* < .001)] Non-CVD [(CFB Q4 vs. Q1 HR,1.69, 95 % CI, 1.05–2.72; *P* = .03); (CFB Q3 vs. Q1 HR, 1.66; 95 % CI, 1.06–2.59; *P* = .026)] *CFB threshold level associated with increased mortality risk:* CVD 82.3 ml/kg; non-CVD 189.6 ml/kg	Excessive CFB during the early phase of ECMO support increased the risk of mortality. There is a clinically significant CFB threshold level above which the risk of mortality increases.
Fong et al. 2020 [32]	Monocentric retrospective study (*N* = 123 adult patients) Median age (IQR) 55.0 (41.0–62.0) years, male 64.2 %	***Mixed population*** *ECMO mode:* VA-ECMO 36 % (*N* = 44); VV-ECMO 64 % (*N* = 79) *ECMO indication:* Pulmonary 64 % (N = 79); Cardiac 29 % (*N* = 35); ECPR 7 % (*N* = 9) Concomitant CRRT (*N* = 78)	Fluid types: normal saline, balanced solutions and gelatin. CFB (D1-D3) (D1-D7)	Hospital mortality 31.7 % (*N* = 39)	CFB D1-D3 (S vs. NS 6696 (4896–8569) ml vs. 8714 (5164–12,114) ml, *p* = .027); CFB D1-D7 (S vs. NS 9025 (4966–10,904) ml vs. 11,729 (9054–18,705) ml, *P* < .001) CFB D1-D7 was associated with increased hospital mortality (adjusted OR: 1.17, 95 % CI: 1.06–1.29, *P* = .001)	The authors demonstrated a significant association between PFB and hospital mortality in adult patients treated with ECMO.

Author (year)	Study design, Sample size, age, % male	ECMO mode, ECMO indication	Fluid management Fluid balance assessment	Outcome measures	Results	Conclusions
Fluid resuscitation strategy, fluid balance and outcomes (Mixed population of ECMO patients)						
Gunning et al. 2020 [36]	Monocentric retrospective study (N = 98 adult patients) Mean age ([FO+] 55.2 ± 19.8 vs. [FO-] 54.7 ± 12.8 years), male 67.3 %	***Mixed population*** *ECMO mode: VA-ECMO (N = 80); VV-ECMO (N = 18)* Concomitant CRRT (*N* = 48)	%FO = (Fluid in (L) - Fluid out (L)) / (ICU Admission Weight Kg) x 100 [FO+] if FA ≥ 10 % [FO-] if FA < 10 % [FO+] at 72 h (*N* = 19) [FO-] at 72 h (N = 79)	30-day mortality 60-day mortality 90-day mortality	30-day mortality ([FO+] vs. [FO-] 68.4 % vs. 35.4 %, *P* = .02) 60-day mortality ([FO+] vs. [FO-] 73.7 % vs. 48.1 %, *P* = .07) 90-day mortality ([FO+] vs. [FO-] 73.7 % vs. 50.6 %, *P* = .08) Fluid overload at 72 h was an independent predictor of 90-day mortality (adjusted OR: 2.93, 95 % CI 1.44–5.96, *P* = .003)	The authors demonstrated that ECMO patients who developed volume overload and AKI are at increased risk for mortality.
Chiu et al. 2021 [30]	Monocentric retrospective study (*N* = 152 adult patients) Mean age 50.3 ± 16.4 years, male 67.8 %	***Mixed population*** *ECMO mode:* VA-ECMO (*N* = 24); VV-ECMO (*N* = 128) *ECMO indication:* Severe ARDS	Fluid balance at 24 h after ECMO initiation (FB D1): 1327 (57–2800) ml Cumulative fluid balance at 3 days after ECMO initiation (CFB D1-D3): 1190 (−873–3935) ml	Hospital mortality 53.3 % (*N* = 81)	FB D1 (S vs. NS 846 (−160–2095) vs. 1688 (219–3668), *P* = .006 CFB D1-D3 (S vs. NS 277 (−1798 - 2384) vs. 1927 (−100–5266), *P* < .001 CFB D1-D3 was independently associated with higher hospital mortality (adjusted HR	CFB during the first 3 days of ECMO was independently associated with 90-day hospital mortality Conservative fluid strategy may prevent fluid overload in severe ARDS patients on ECMO

(*continued on next page*)

Table 1 (*continued*)

Author (year)	Study design, Sample size, age, % male	ECMO mode, ECMO indication	Fluid management Fluid balance assessment	Outcome measures	Results	Conclusions
					1.110 95 % CI 1027–1201; $P = .009$)	
Lee et al. J 2021 [31]	Monocentric retrospective study ($N = 74$ adult ARDS patients supported by ECMO) Mean age 56 years, male 45%	***Mixed population*** *ECMO mode:* VV-ECMO ($N = 65$); VA-ECMO (N = 9) *ECMO indication:* ARDS	CFB D1-D3	28-day mortality 55 % ($n = 41$)	Mean CFB D1-D3 (S vs. NS 2559 ± 3993 vs. 5844 ± 7113 ml, $P = 0.015$) use of CRRT was not statistically significantly associated with 28- day mortality (HR, 0.482; 95 % CI, 0.210–1.107; $P = .085$). CFB D1-D3 was an independent predictor of 28-day mortality (HR, 3.366; 95 %CI 1528–7417; $P = .003$	In adult ARDS patients treated with ECMO, a higher positive CFB on day 3 was found to be associated with a higher 28-day mortality risk.
Thomas et al. 2022 [33]	Monocentric retrospective study (N = 19 adult ECMO patients with concomitant CRRT) mean age 40 years, male 76 %	***Mixed population*** ECMO mode [Treatment group: VV-ECMO ($N = 16$), VA-ECMO (N = 2)]; [Control group without CRRT: VV-ECMO ($N = 17$), VA-ECMO (N = 2)] *ECMO indication:* Respiratory failure, post-cardiotomy, ECPR	Two groups: (1) Treatment group (T), ECMO support with concomitant CRRT targeting NFB (N = 18) (2) Control group (C), cohort of propensity-matched controls (ECMO support without CRRT) (N = 19)	Survival to hospital discharge AKI	After 72 h, the treatment group had a NFB of fluid balance of −3840 mL versus +425 mL in controls ($P \leq .05$) NFB (T group) was associated with higher survival to discharge (OR 2.54, 95 % CI 1.10–5.87). There was no significant difference in renal outcomes.	The use of CRRT for fluid management is effective and, when resulting in NFB, improves survival in adult ECMO patients without significant renal dysfunction.

Author (year)	Study design, Sample size, age, % male	ECMO mode, ECMO indication	Fluid management Fluid balance assessment	Outcome measures	Results	Conclusions
Fluid type						
Wengenmayer et al. 2018 [24]	Monocentric retrospective study; Whole cohort ($N = 283$), mean age 58.9 ± 14.4 years, 73.1 % male Matched cohort ($N = 192$)	*ECMO mode*: **VA-ECMO** patients with a PFB 12 h after cannulation were included. *ECMO indication:* ECPR 63.6 %	*Resuscitation fluids: (1) BC group,* balanced crystalloids alone ($N = 98$ matched patients); *(2) ALB group,* fluid resuscitation with albumin and balanced crystalloids on a 1:2 volume basis, resulting in 10 g of albumin per liter of fluid therapy ($n = 98$ matched patients)	Hospital survival 30.7 %	Hospital survival was significantly higher in the ALB group (before matching ALB vs. BC 38.4 vs. 25.7 %, $P = .026$) (after matching ALB vs. BC 43.9 vs. 27.6 %, $P = .025$) Albumin fluid resuscitation independently improves hospital survival (before matching OR 4.33 (95 % CI 2.01–9.33) (after matching OR 3.1 (95 %CI 1.15–6.38)	The authors suggest that albumin fluid resuscitation significantly improves hospital survival in VA-ECMO.
Jeon et al. 2023 [25]	Monocentric retrospective study (N = 114 patients) Mean age 67.8 ± 13.6 years, 68.4 % male	*ECMO mode:* **VA-ECMO** *ECMO indication:* Cardiogenic shock	Albumin infusion (250 ml of 5 % albumin solution for fluid resuscitation or 100 ml of 20 % albumin solution if serum albumin level < 2.6 g/dL with PFB)	Survival to discharge 48.6 % ($N = 56$)	Pre-ECMO albumin level (S vs. NS 3.6 ± 0.5 g/dL vs. 3.2 ± 0.6 g/dL, $p = .002$); Intra-ECMO albumin level (S vs. NS 3.1 ± 0.3 g/dL vs. 2.9 ± 0.4 g/dL, $P = .004$) Adjusted albumin infusion (S vs. NS 3.5 ± 2.6 g vs. 12.6 ± 18.1 g, $P < 0.001$) 30-day mortality was significantly higher in patients with a pre-ECMO albumin level ≤ 3.4 g/dL than in those with a level > 3.4 g/dL (68.9 % vs. 23.8 %, $P < .001$).	Hypoalbuminemia during ECMO was associated with higher mortality, even with higher amounts of albumin replacement, in patients with cardiogenic shock who underwent VA-ECMO.

Abbreviations: BW: Body weight, DW: Dry weight, CVVHF: continuous venovenous hemofiltration, FB: fluid balance, MV: mechanical ventilation, n.s. not significant, %FO: percent fluid overload, CRRT: Continuous renal replacement therapy, IVF: Intravenous fluid, CI: confidence interval, RC: relative change, DFB: Daily fluid balance, CFB: Cumulative fluid balance, FA: Fluid accumulation, NS: Non-survivors, S: Survivors, D1 FB: day-1 fluid-balance, AUC: area under the curve, IQR: Interquartile range, PFB: Positive fluid balance, NFB: Negative fluid balance, VFD: Ventilator-free days, Q: Quartile, ARDS: acute respiratory distress syndrome, ICU: Intensive care unit, CA: cardiac arrest, LOS: length of stay, Q1: The first quartile (or the lowest quartile), Q4: The fourth quartile (or the highest quartile).

Table 2
Descriptive characteristics and results of animal studies ($N = 2$).

Author (year)	Study design, Animal model	ECMO mode, perfusion targets	Fluid resuscitation strategy	Outcome measures	Results	Conclusions
Lescroart et al. 2023 [26]	Randomized experimental trial Domestic male pigs (Landrace) ($N = 18$) *Animal model* Phase 1 No-flow 90 s (Ischemic refractory CA (LAD ligation); Phase 2 Low flow 30 min (conventional CPR); Phase 3 ECPR (LAD reperfusion 30 min after VA-ECMO initiation)	*ECMO mode:* VA ECMO (ECPR) *Perfusion targets* MAP 65 mmHg Flow 65–70 ml/kg/min	(1) SC group: Fluids (NaCl 0.9 %) + NE ($N = 9$) (2) ALB group: Fluids (NaCl 0.9 %) + NE (N = 9) + ALB Fluids in case of decreased blood flow or cannula suction events NE (starting rate 0.2 μg/kg/min, increments 0.1 μg/kg/min, maximum dose 2 μg/kg/min)	Macrocirculatory parameters Lactate clearance Sublingual microcirculation (SDF imaging)	**IVF over 6 h** (ALB group vs. SC group (1000 (1000–2278) ml vs. 17,000 [10,000-19,000], $P < .001$) **Lactate clearance over 6 h** (ALB group vs. SC group 10.09 % (6.78–29.36) vs. 29.16 % (12.5–39.32), n.s. $P = .185$) **Microvascular parameters**, n.s.	Compared to standard care, ALB infusion was highly effective in reducing fluid loading in a porcine model of post-resuscitation syndrome after refractory cardiac arrest treated with VA ECMO.
Djordjevic et al. 2023 [15]	Retrospective subanalysis Female pigs (Landrace × Pietrain) ($N = 12$) 60.3 ± 4 kg	*ECMO mode:* VA ECMO *Perfusion targets* MAP 60–70 mmHg Flow 50 ml/kg/min/m^2 PaO_2 120–200 mmHg	MVT group: Moderate volume therapy (ratio > 2) ($N = 4$) EVT group: Extensive volume therapy (ratio < 2) ($N = 8$) Ratio = (cumulative IVF x 10 h) / (physiologic urinary output 0.05 ml/kg/min x 10 h)	Organ edema Hemodynamics, Respiratory Data, and Blood Gas Analysis	IVF (10 h ECMO) MVT vs. EVT 3275 ± 263 mL vs. 5344 ± 834 mL; $P < .01$ No significant differences were seen between the groups in regard to hemodynamic (MAP, CVP, CO, CBF) and respiratory data (PaO_2, P/F ratio) Creatinine ratio was significantly higher in EVT compared to MVT (MVT vs. EVT 1.3 ± 0.3 vs. 1.8 ± 0.5; $P = .033$ Bowel tissue showed a higher percentage of edema in EVT (MVT vs. EVT 77 ± 2 % vs. 80 ± 3 %; $P = .049$)	The authors suggest potential deterioration of renal function and intestinal mucosa function by an increase in tissue edema due to volume overload in ECMO therapy.

Abbreviations: LAD: Left anterior descending artery, ECPR: Extracorporeal cardiopulmonary resuscitation, SC: Standard care, MAP: Mean arterial pressure, ALB: Albumin, NE: norepinephrine, IVF: Intravenous fluid, MVT: Moderate volume therapy, EVT: Extensive volume therapy, n.s. not significant, CVP: central venous pressure, CO: cardiac output, CBF: cerebral blood flow, SDF: Sidestream Dark Field imaging.

Table 3
Evaluation of the evidence of structured research questions addressed in the scoping review.

Research questions	Number of trials	Intervention	Comparator	Outcomes	Conclusions	LOE
What is the optimal fluid resuscitation strategy during the critical initial phase of VA-ECMO support?	**n = 2** (VA)	–	–	Mortality	High volume resuscitation approach during the first 24 h of ECMO support could negatively impact survival[13,14]	**Low**
Which type of fluid should be used as first-line therapy in VA-ECMO patients?	Crystalloid (***n* = 0**)	–	–	–	No study has compared saline and balanced crystalloids for fluid resuscitation among adult ECMO-supported patients	**Low**
	Albumin (**n = 2**) (VA)	Albumin	Balanced crystalloids	Mortality	Albumin fluid resuscitation significantly improves hospital survival in VA-ECMO[24,25]	**Low**
What is the impact of fluid overload on VA-ECMO patient outcomes?	**n = 12** (5 VA and 7 mixed)	–	–	Mortality AKI	Fluid overload was significantly associated with mortality and poor kidney outcomes[27,28,34,35]	**Moderate**

AKI: acute kidney injury, LOE: Level of evidence.

hydroxyethyl starches (HES), dextrans and gelatins. Several studies and international guidelines recommend against the use of HES and other synthetic colloids in critically ill patients, particularly those with sepsis. HES use has been associated with renal damage and the need for RRT as well as potential detrimental effects on survival [19–21]. Concerning albumin and despite its theoretical plasma-expanding properties, anti-oxidant, anti-inflammatory and potential glycocalyx-protective effects [22], its role for fluid therapy remains controversial and recent data failed to demonstrate improved outcomes with albumin resuscitation compared to crystalloids in terms of survival and other patient-centered outcomes such as duration of mechanical ventilation, ICU length of stay, and need for RRT [23]. Thus, the latest European Society of Intensive Care Medicine guidelines suggest, with moderate evidence, using crystalloids rather than albumin for volume expansion in adult critically ill patients including those with sepsis [18].

In VA-ECMO setting, the role of albumin as a resuscitation fluid has

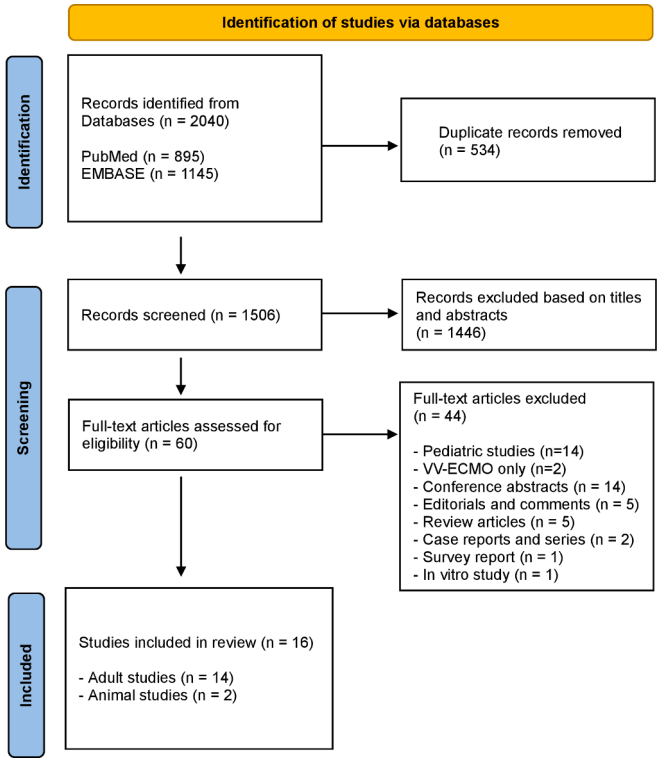

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram of study selection.

been investigated through two clinical retrospective studies and one animal study. In a retrospective registry study involving 283 ECPR patients [24], it has been reported an improved survival with albumin compared to balanced solutions (43.9 % vs. 27.6 %, respectively after propensity score matching, $P = .025$) [24]. In a second study, the impact of albumin infusion on the prognosis was retrospectively investigated in 114 VA-ECMO supported cardiogenic shock patients with hypoalbuminemia (serum albumin level < 2.6 g/dL) and positive fluid balance. It has been shown that pre-ECMO serum albumin level was an independent predictor of 30-day mortality (HR, 0.25; 95 %CI, 0.11–0.59; $P = .002$) even with higher amounts of albumin replacement [25].

In a recent randomized experimental trial comparing the effect of fluid resuscitation with albumin versus normal saline in a porcine model of ischemic refractory cardiac arrest resuscitated with VA-ECMO, the researchers found that albumin infusion was highly effective in reducing crystalloid fluid loading within the first 6 h of ECMO support (1000 [1000–2278] ml vs. 17,000 [10000–19,000] mL, $P < .001$) but there was no significant difference between the two groups in terms of lactate clearance and sublingual capillary microvascular parameters [26]. Overall, there is insufficient data to recommend albumin as a first-line therapy.

2.3. Association between fluid balance and outcomes in VA-ECMO patients

2.3.1. Fluid balance assessment methods and fluid overload definitions

In this review, three different methods of assessing fluid balance have been identified in ECMO supported critically ill patients. These methods may be listed as follows: i) net fluid balance (mL or mL/kg) (14 studies) [13] [14] [24] [27–35], ii) percent fluid overload (based on weight FO_w %) (1 study) [14], and iii) percent fluid overload (based on input/output measurements $FO_{i/o}$ %) (1 study) [36]. We have summarized fluid balance assessment methods and operational definitions of terms used in this review section in e-Table 6.

2.3.2. Fluid overload and outcomes

Most studies evaluated mortality outcome in VA-ECMO patients. Fluid overload has been associated with increased mortality for both indications (cardiogenic shock and ECPR). In a mixed population of ECMO patients, it has been shown that positive fluid balance at ECMO day 3 was an independent predictor of 90-day mortality even after adjusting for severity of illness and regardless of RRT use (OR, 4.02, 95 %CI, 1.49–10.82; $P = .006$) [27]. Similar conclusions have been reported in another retrospective multicenter cohort study including 723 ECMO patients that revealed a significantly increased risk of 90-day mortality in patients with higher cumulative fluid balance during the first 3 days after ECMO initiation in both cardiac (HR, 1.76; 95 %CI, 1.37–2.27; $p < .001$) and non-cardiac (HR, 1.46; 95 %CI, 1.17–1.83; $P < .001$) underlying conditions [28].

To date, only two recent studies have focused on the clinical outcomes of patients receiving ECPR. In the first study, higher cumulative fluid balance during the first 4 days of the ECMO run was found to be independently associated with lower ICU survival (adjusted OR: 1.261, 95 %CI: 1.091–1.375; $P = .003$) [34]. In the second study, Taira et al. [35] retrospectively analyzed the data of 959 adult patients receiving ECPR for refractory out-of-hospital cardiac arrest and they assessed the adjusted association between fluid balance in the first 24 h following ICU admission and in-hospital mortality (OR 1.04, 95 %CI 1.02–1.06; $P < .001$). The median fluid balance was 3673 mL. The highest tertile of fluid balance exhibited the highest odds ratio as a mortality predictor with a cutoff value of 5525 mL (OR, 1.97; 95 %CI, 1.39–2.81; $P < .001$) [35].

As with mortality, higher cumulative fluid balance values were found to increase significantly the risk of acute kidney injury (AKI). In a large, mixed ECMO population, AKI incidence was found to be higher in ECMO patients with highest compared to those with lowest quartiles of fluid balance in case of underlying cardiac disease (83.1 % vs. 59.3 %; $P < .001$) or without cardiac disease (83.1 % vs. 68.1 %, $P = .011$) [28]. Similarly, another study focusing on ECPR patients revealed that fluid balance was significantly associated with poor kidney outcomes such as AKI (OR, 1.04; 95 %CI, 1.02–1.05; $P < .001$) and RRT use (OR, 1.05; 95 %CI, 1.03–1.07; $P < .001$) [35].

3. Discussion

In this scoping review, we focused on fluid management in VA-ECMO patients for the two main indications: cardiogenic shock and cardiac arrest (ECPR). We analyzed a total of 14 clinical studies and 2 animal trials in order to map out the evidence regarding fluid dosing, type, safety and endpoints of fluid resuscitation in VA-ECMO setting.

First of all, we underlined the lack of studies evaluating fluid resuscitation strategies, restricted versus liberal, during the early phase of VA-ECMO therapy when the deleterious effects of ischemia–reperfusion are more pronounced. With regard to the type of crystalloid solutions, no study has compared the efficacy and safety of saline versus balanced solutions in VA-ECMO setting. The impact of fluid overload on patient-centered outcomes is the main topic investigated in most included studies in this review. Despite their heterogeneity, these studies consistently found a negative impact of fluid overload on outcomes of adult VA-ECMO patients. The research questions and the key findings are summarized in Table 3.

3.1. Fluid balance monitoring

Although the clinical relevance and prognostic significance of fluid overload are increasingly acknowledged in critically ill patients, the optimal method to assess fluid balance and the optimal definition of fluid overload are still a matter of debate. Weight-based assessment of fluid balance ($FO_{i/o}$ % = (fluid input - fluid output) / admission weight) x 100 %) [37], is the most common method used to determine fluid overload especially in critically ill children. This method is also reported

by the latest ELSO guidelines [38]. Three points are worth noting in this regard because they can impact the accuracy of fluid balance assessment. First, baseline or dry weight determination varies across studies such as ICU admission weight, the lowest recorded weight or pre-ECMO weight. Second, there are different time points and different assessment durations recorded within and across the studies such as ECMO fluid balance, peak fluid overload during ECMO and fluid overload at RRT initiation or discontinuation. Third, the fluid overload threshold in ECMO-supported patients, as in other ICU populations, is defined by a cut-off value of 10 % fluid accumulation above baseline body weight. This threshold is associated with worse outcomes and has been identified as a trigger for possible interventions, including initiation of RRT. This cut-off was also reported by the latest ELSO guidelines [38].

3.2. Fluid overload concept in ECMO setting

Unlike other ICU populations, the standardization of the definition of fluid overload such as establishing a fluid balance threshold as a prognostic factor in VA-ECMO supported patients, should take into account two critical points. First, the positive fluid balance may reflect baseline disease severity and the hyperinflammatory response to ECMO with increased capillary leakage rather than inappropriate fluid management or overresuscitation particularly during the first 24 to 48 h after cannulation to maintain adequate ECMO blood flow. This is supported by the fact that fluid loading during the acute phase is very often triggered by suction events with flow drops and hypotension. Despite potential confounding factors, including cannula misplacement or tamponade, the occurrence of suction events remains a valuable bedside marker of low intravascular volume status with insufficient venous drainage [39].

Second, as mentioned above, large amounts of fluids are almost inevitable during the initial resuscitative phase and therefore adopting a restrictive strategy or targeting a negative fluid balance, if feasible, are not necessarily associated with better outcome. However, it seems possible to implement strategies to mitigate volume overload during the late recovery and weaning phases of ECMO course by minimizing fluid creep, establishing hemodynamic monitoring to assess fluid responsiveness, and eventually considering mechanical fluid removal.

3.3. Choice of resuscitation fluid

No guideline to date has recommended a specific fluid type in VA-ECMO setting. Despite the increased use of balanced crystalloids over the last years among critically ill patients, particularly in high-risk surgical and septic patients in order to avoid the deleterious renal effects of isotonic saline [18] [40], data on the use, safety and efficacy of balanced and unbalanced resuscitative fluids in adult VA-ECMO population are lacking.

In regard to the role of albumin as a resuscitation fluid in VA-ECMO setting, two points can be highlighted: the first one is about the clinical significance of hypoalbuminemia in VA-ECMO patients. As for the other subpopulations such as surgical or septic patients, hypoalbuminemia may simply be a marker for poor prognosis rather than a therapeutic target. The second point is about the role of albumin as an adjunctive second line therapy in VA-ECMO patients with limited response to large amounts of crystalloids. This question needs to be investigated by further studies.

3.4. Renal outcomes and de-resuscitation strategies

AKI is a common complication during ECMO, affecting up to 85 % of patients. The incidence varies according to underlying condition, AKI definition and ECMO mode (VA-ECMO vs. VV-ECMO 61 % vs. 46 %). Severe AKI requiring RRT occurs in approximately 45 % of ECMO patients [41]. Renal endpoint analysis raises a number of points for discussion: (i) the role of the synergistic interplay between AKI and fluid overload in worsening outcomes of ECMO treated patients [42]; (ii) as most of the included studies, low-chloride balanced crystalloids were not widely used which may interfere with AKI prevalence [28] and finally (iii) the clinical heterogeneity of ECMO patients in terms of age, ECMO type, duration of ECMO therapy and the underlying condition. It is likely that AKI incidence would be higher with VA-ECMO than with VV-ECMO, in post-cardiotomy setting and in case of pre-existing congestive heart failure and advanced chronic kidney disease [43].

The late recovery phase of VA-ECMO support often requires goal-directed fluid removal “de-resuscitation” in order to achieve negative fluid balance. This phase starts with spontaneous or induced evacuation (diuretics or RRT). The ELSO guidelines recommend diuretics as first-line therapy to induce negative fluid balance [44] [45]. Currently, there is no evidence of benefit for the use of pre-emptive RRT in ECMO patients. In a recent consensus statement, RRT indications in ECMO patients are the same as those recommended in the general ICU population [46].

3.5. Strengths and limitations

To the best of our knowledge, this is the first review to assess the current state of fluid therapy in VA-ECMO patients. The quality of the data included in the scoping analysis and the robustness and validity of the results should be kept in mind, with limited and potentially confounded data. So, there are some limitations: First, the scarcity of the literature and the lack of prospective research are striking. Second, the high heterogeneity within and between studies related to underlying disease, pre-ECMO status and ECMO duration are noteworthy. Sicker patients received likely more fluid and despite numerous attempts at

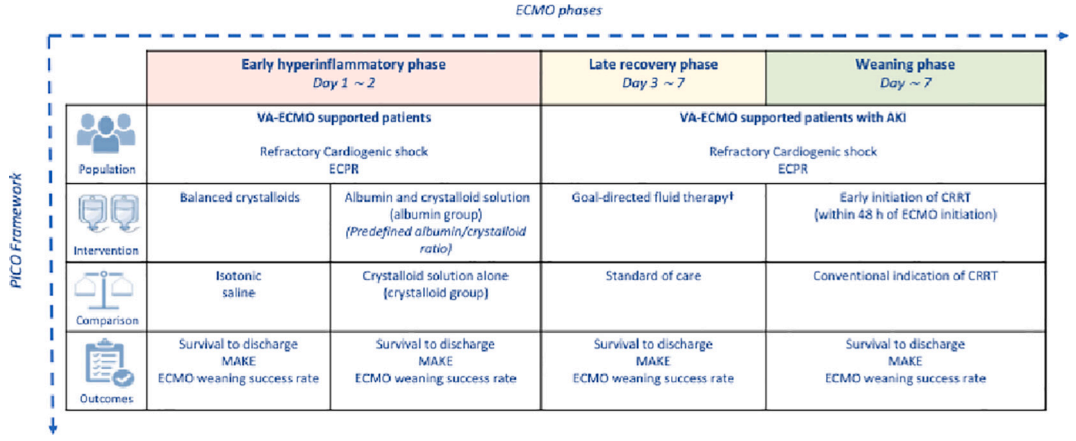

Fig. 2. Research agenda proposal for fluid therapy during veno-arterial extracorporeal membrane oxygenation.

trying to adjust for this, adequate adjustment has not been shown to be possible. Most notably, half of included studies mixed patients on VV and VA-ECMO, two populations that may be radically different in terms of age, underlying co-morbidities and precipitating diseases. Unfortunately, mixing VV and VA-ECMO is often performed in ECMO studies, regarding for instance pharmacokinetics [47], infectious [48], neurological [49] or bleeding [50] complications. Restricting our scoping review to only VA-ECMO supported patients would have led to a tiny number of "pure" studies ($n = 7$) and chose to exclude studies who focused exclusively on VV-ECMO. In addition, inclusion of animal studies within the analysis also increases heterogeneity as the animal models may demonstrate different physiology; but data were obtained on adult swine and explored areas that were insufficiently assessed in human studies (albumin and large volume of crystalloids) [15] [26]. We excluded pediatric population, despite the fact that several studies assessed these issues in children or mixed children and adults. However, differences of physiology and baseline illness preclude mixing the analysis in a single review.

Another limitation is that the impact of drainage cannula size and position during VA-ECMO setting was poorly reported in the available literature. Among included studies in our review, only 4 studies reported cannula sizes [13,14] [30] [35]. Undersized or incorrect position of the drainage cannula may limit ECMO flow leading to suction events and potentially triggering fluid resuscitation [39]. This latter point is crucial and should be taken into consideration when conducting future research. In addition to careful patient selection (indication, pre-cannulation status), technical considerations (cannula size and placement) should be assessed in order to design high-quality studies with reliable results.

3.6. Knowledge gaps and research priorities

Given the lack of evidence, this review calls for randomized trials designed specifically to answer at least three questions: First, what is the optimal fluid type during the initial phase of VA-ECMO support? Second, what is the optimal fluid resuscitation strategy (restricted versus liberal versus goal directed regimen) during VA-ECMO support? Third, what is the most accurate endpoint to guide fluid resuscitation in VA-ECMO supported patients? These trials should be conducted in homogeneous groups in relation to age, indication and severity of underlying condition. We propose a research agenda in light of data analyzed in this review (Fig. 2).

4. Conclusions

The present scoping review has highlighted the paucity of available literature focusing on the fluid management in adult VA-ECMO patients mainly constituted of retrospective studies. Despite their heterogeneity, these studies consistently found a negative impact of fluid overload on survival and renal outcomes. However, the ideal choice of crystalloid remains to be determined and yet there is no study comparing balanced versus unbalanced solutions. Large randomized controlled trials targeting specific subgroups are needed in order to standardize practice and improve outcomes.

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Ethical approval

Not required because this scoping review does not include any interaction or intervention with human subjects or include any access to identifiable private information. This review is based on data collected from publicly available materials.

CRediT authorship contribution statement

Ali Jendoubi: Writing – original draft, Methodology, Conceptualization. **Quentin de Roux:** Writing – original draft, Methodology, Conceptualization. **Solène Ribot:** Visualization. **Aurore Vanden Bulcke:** Visualization. **Camille Miard:** Visualization. **Bérénice Tiquet:** Visualization. **Bijan Ghaleh:** Visualization, Validation, Supervision. **Renaud Tissier:** Visualization, Validation, Supervision. **Matthias Kohlhauer:** Visualization, Validation, Supervision. **Nicolas Mongardon:** Writing – review & editing, Visualization, Validation, Supervision, Methodology.

Declaration of competing interest

The authors have no potential conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2024.155007.

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