The Effectiveness of Levosimendan on Veno-Arterial Extracorporeal Membrane Oxygenation Management and Outcome: A Systematic Review and Meta-Analysis

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Supplementary Material

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Supplementary material

Tables

Figures

Literature search

Search tools
Boolean operator, Subject heading tools/thesauri were used in addition to combining search terms manually.

Table S1 Literature search results

Database	Search strategy	Number of hits
MEDLINE	**MeSH:** ("Simendan"[Mesh]) AND "Extracorporeal Membrane Oxygenation"[Mesh] - Using ECMO, ECLS, or extracorporeal life support yielded Extracorporeal Membrane Oxygenation - No MeSH term for mechanical circulatory support	13
	Levosimendan AND ECMO - Search details: ("simendan"[MeSH Terms] OR "simendan"[All Fields] OR "levosimendan"[All Fields]) AND ("extracorporeal membrane oxygenation"[MeSH Terms] OR ("extracorporeal"[All Fields] AND "membrane"[All Fields] AND "oxygenation"[All Fields]) OR "extracorporeal membrane oxygenation"[All Fields] OR "ecmo"[All Fields])	27
	Levosimendan AND "extracorporeal membrane oxygenation" - Search details: ("simendan"[MeSH Terms] OR "simendan"[All Fields] OR "levosimendan"[All Fields]) AND "extracorporeal membrane oxygenation"[All Fields]	(same as above)
	Levosimendan AND ECLS - Search details: ("simendan"[MeSH Terms] OR "simendan"[All Fields] OR "levosimendan"[All Fields]) AND ECLS[All Fields]	4
	Levosimendan AND "extracorporeal life support" - Search details: ("simendan"[MeSH Terms] OR "simendan"[All Fields] OR "levosimendan"[All Fields]) AND "extracorporeal life support"[All Fields]	8
	Levosimendan AND MCS - Search details: ("simendan"[MeSH Terms] OR "simendan"[All Fields] OR "levosimendan"[All Fields]) AND MCS[All Fields]	2
	Levosimendan AND "mechanical circulatory support"	

	- Search details: ("simendan"[MeSH Terms] OR "simendan"[All Fields] OR "levosimendan"[All Fields]) AND "mechanical circulatory support"[All Fields]	17
EMBASE	**Levosimendan AND ECMO** - Search details: ('levosimendan'/exp OR levosimendan) AND ecmo	93
	Levosimendan AND "extracorporeal membrane oxygenation" - Search details: ('levosimendan'/exp OR levosimendan) AND 'extracorporeal membrane oxygenation'	94
	Levosimendan AND ECLS - Search details: ('levosimendan'/exp OR levosimendan) AND ecls	15
	Levosimendan AND "extracorporeal life support" - Search details: ('levosimendan'/exp OR levosimendan) AND 'extracorporeal life support'	29
	Levosimendan AND MCS - Search details: ('levosimendan'/exp OR levosimendan) AND mcs	8
	Levosimendan AND "mechanical circulatory support" - Search details: ('levosimendan'/exp OR levosimendan) AND 'mechanical circulatory support'	93
CENTRAL (Cochrane Library)	Levosimendan AND ECMO Levosimendan AND "extracorporeal membrane oxygenation" Levosimendan AND ECLS Levosimendan AND "extracorporeal life support" Levosimendan AND MCS Levosimendan AND "mechanical circulatory support"	3 2 1 2 0 1
ProQuest Public Health	Levosimendan AND ECMO Levosimendan AND "extracorporeal membrane oxygenation" Levosimendan AND ECLS Levosimendan AND "extracorporeal life support" Levosimendan AND MCS Levosimendan AND "mechanical circulatory support"	28 41 41 4 3 30
ScienceDirect	Levosimendan AND ECMO Levosimendan AND 'extracorporeal membrane oxygenation' Levosimendan AND ECLS Levosimendan AND 'extracorporeal life support'	58 75 12 18 9

	Levosimendan AND MCS Levosimendan AND 'mechanical circulatory support'	54
Scopus	Levosimendan AND ECMO Levosimendan AND "extracorporeal membrane oxygenation" Levosimendan AND ECLS Levosimendan AND "extracorporeal life support" Levosimendan AND MCS Levosimendan AND "mechanical circulatory support	40 83 5 16 7 62
Web of Science	Levosimendan AND ECMO Levosimendan AND "extracorporeal membrane oxygenation" Levosimendan AND ECLS Levosimendan AND "extracorporeal life support" Levosimendan AND MCS Levosimendan AND "mechanical circulatory support"	12 32 4 7 2 25
clinicaltrials.gov (U.S. NIH)	Levosimendan AND ECMO Levosimendan AND "extracorporeal membrane oxygenation" Levosimendan AND ECLS Levosimendan AND "extracorporeal life support" Levosimendan AND MCS Levosimendan AND "mechanical circulatory support"	2 1 0 1 0 0
ISRCTN Registry	Levosimendan	5
Open Grey	Levosimendan	5
Total		1,094
Updated search*		122
Grand total		1,216

**Literature search was updated on June 30, 2020 resulted in 122 studies. Three databases were used (MEDLINE [17 studies], EMBASE [101 studies], CENTRAL [4 studies]) with similar search terms mentioned above.*

Table S2 Data extraction table template

Title	-
Citation	- Authors: - Publication year:
Study characteristics	- Main country of investigation: - Number of study sites: - Study design: - Study duration: - Follow-up:
Patients characteristics	- Total number: - Setting: - Inclusion/diagnostic criteria: - Exclusion criteria: - Mean/median age: - Gender: M - Co-morbidities: - Sample size calculation: - Indication for ECMO: - ECMO duration:
Intervention	- Total number: - Specific intervention: - Intervention details: - Weaning protocol:
Comparator	- Total number: - Specific intervention: - Intervention details (sufficient for replication, if feasible):
Outcomes	- Outcomes of interest and time points: outcome definition (with diagnostic criteria if relevant) - O_1: - O_2: - O_3: - Safety:
Results	Outcomes of interest:

Intervention Vs. Comparator	- O_1: - O_2: - O_3: - Safety:
Key conclusion	
Limitations/Risk of bias	
Comments	
Abbreviations	

Table S3 Excluded studies

No.	Study	Reason for exclusion
1	Marzorati C, Erba L, Cortinovis B, *et al.* Levosimendan infusion during ECMO weaning: Effect on endothelial function and haemodynamics. *Appl Cardiopulm Pathophysiol*.2013;17(2):170-171.[#] **Or** Marzorati C, Erba L, Cortinovis B, *et al.* Levosimendan infusion during ECMO weaning: effect on endothelial function and haemodynamics. Applied Cardiopulmonary Pathophysiology, 2014; 17 (2): 170 – 171.	Poster of a published study (included in the meta-analysis)*
2	Jacky A, Rudiger A, Spahn DR, Bettex DA. Success of ECLS weaning with levosimendan. *Intensive Care Med Exp*.2016; 4(Suppl 1).	Poster of a published study (included in the meta-analysis)[&]
3	Levosimendan Efficacy for Veno-arterial ECMO Weaning: a Retrospective Study. (ClinicalTrials.gov Identifier: NCT03346824) - University Hospital, Strasbourg, France.	Ongoing trial. Last updated on 28 February 2018. Possibly published as a poster.[$]
4	Říha H, Syrovátka P, Kramář P, *et al.* Levosimendan in patients with mechanical circulatory support. *Kardiologicka Rev*.2013;15(2):104-106. https://www.kardiologickarevue.cz/en/journals/cardiology-review/2013-2/levosimendan-in-patients-with-mechanical-circulatory-support-40607?hl=cs (English e-copy)	Review article.
5	Herpain A, Bouchez S, Girardis M, *et al.* Use of Levosimendan in Intensive Care Unit Settings: An Opinion Paper. *J Cardiovasc Pharmacol*. 2019;73(1):3-14	Review article.
6	Cui WW, Ramsay JG. Pharmacologic approaches to weaning from cardiopulmonary bypass and extracorporeal membrane oxygenation. *Best Pract Res Clin Anaesthesiol*. 2015;29(2):257-270.	Review article.
7	Essandoh M, Hsu KS, Whitson B, Andritsos M. Levosimendan for ECLS Weaning: A Strategy in Need of Validation. *J Cardiothorac Vasc Anesth*. 2018;32(5):2120-2122.	Editorial paper.
8	Ranjan A, Bhudia N, McGovern I, *et al.* Levosimendan: Use, cost-effectiveness and outcome in a tertiary cardiothoracic centre. *Crit Care.*2015;19(Suppl 1):P152.	On levosimendan usage of a center. Not on ECMO weaning.
9	Trethowan BA, Agelaki M, Kaul S. One year retrospective review of use of levosimendan in a tertiary referral heart and lung centre in patients undergoing mechanical circulatory support. *Intensive Care Med*.2011;37(Suppl 1):S65.	Retrospective study on levosimendan use. Not on ECMO weaning.
10	Zotzmann V, Rilinger J, Lang CN, *et al.* Epinephrine, inodilator, or no inotrope in venoarterial extracorporeal membrane oxygenation implantation: a single-center experience. *Crit Care*. 2019;23(1):320. Published 2019 Sep 18. doi:10.1186/s13054-019-2605-4. (PubMed citation) **Or** Zotzmann V, Lang C, Wengenmayer T, *et al*. Early inotropic therapy in patients after venoarterial extracorporeal membrane oxygenation implantation-a single center experience. *Crit Care.*2019;23(Suppl 2)	Not on ECMO weaning.
11	Krumnikl JJ, Toller WG, Prenner G, *et al.* Beneficial outcome after prostaglandin-induced post-partum cardiac arrest using levosimendan and extracorporeal membrane oxygenation. *Acta Anaesthesiol Scand*.2006;50(6):768-770.	Not on ECMO weaning.

12	Frigerio M, Verde A, Ammirati E, *et al.* Repeated levosimendan infusions in patients with refractory heart failure. *Eur J Heart Fail*.2013;12(Suppl 1):S277.	Not on ECMO weaning.
13	Sponga S, Ivanitskaia E, Potapov E, Krabatsch T, Hetzer R, Lehmkuhl H. Preoperative treatment with levosimendan in candidates for mechanical circulatory support. *ASAIO J*. 2012;58(1):6-11. (PubMed citation). Other citations: *J Heart Lung Transpl*.2011;30:4(Suppl 1):S216. *G Ital Cardiol*.2011;12:12(Suppl 3):e113.	Not on ECMO weaning.
14	Pappalardo F, Pieri M, Arnaez Corada B, *et al.* Timing and Strategy for Weaning From Venoarterial ECMO are Complex Issues. *J Cardiothorac Vasc Anesth*. 2015;29(4):906-911.	Not on levosimendan use.
15	Seiler F, Trudzinski FC, Hörsch SI, *et al.* Weaning from prolonged veno-venous extracorporeal membrane oxygenation (ECMO) after transfer to a specialized center: a retrospective study. *J Artif Organs*. 2018;21(3):300-307.	Not on levosimendan use.
16	Aso S, Matsui H, Fushimi K, Yasunaga H. In-hospital mortality and successful weaning from venoarterial extracorporeal membrane oxygenation: analysis of 5,263 patients using a national inpatient database in Japan. *Crit Care*. 2016;20:80. Published 2016 Apr 5. doi:10.1186/s13054-016-1261-1.	Not on levosimendan use.
17	Reusch, F., Scheid, M., Beckmann, A., Gassel, A.M., Krian, A. Pulmonary embolism of rare coincidence under employment of extracorporeal-membrane-oxygenation system (ECMO). Z *Herz Thorax Gefasschir*. 2008;22(1):pp.32-35.	Case report not on ECMO weaning.
18	TCTAP C-148 Revascularization of Chronic Total Occlusion to Facilitate Weaning from Extracorporeal Membrane Oxygenation in Patients with Cardiogenic Shock. Ying-Chang. *J Am Coll Cardiol*.2018;71(16):S217-S218.	Case report not on levosimendan use.
19	Broman LM, Malfertheiner MV, Montisci A, Pappalardo F. Weaning from veno-venous extracorporeal membrane oxygenation: how I do it. *J Thorac Dis*. 2018;10(Suppl 5):S692-S697.	Review article on VV-ECMO in PICU.
20	Hauffe T, Krüger B, Bettex D, Rudiger A. Shock Management for Cardio-surgical Intensive Care Unit Patient: The Silver Days. *Card Fail Rev*. 2016;2(1):56-62.	Review article. Not on ECMO weaning.
	Updated literature search	
21	Caetano F, Templeman V, Remmington C, Passariello M, Trimlett R, Price S. The use of levosimendan on weaning from venous-arterial extracorporeal mechanical oxygenation support: Results of a tertiary centre. *Intensive Care Med. Exp.* 2019; 7(Suppl 3):000108.	Confusing statements.^
22	Burgos LM, Seoane L, Furmento JF, *et al*. Effects of levosimendan on weaning and survival in adult cardiogenic shock patients with veno-arterial extracorporeal membrane oxygenation: systematic review and meta-analysis [published online ahead of print, 2020 May 24]. *Perfusion*. 2020;267659120918473. doi:10.1177/0267659120918473.	Systematic review and meta-analysis.
23	Silvestri EG, Pino JE, Donath E, Ghumman W. Use of Levosimendan as a Strategy to Wean off Veno-Arterial ECMO in Cardiogenic Shock; A Systematic Review and Metanalysis. *J. Card. Fail.* 2019;25(8):S171. (Poster)	Systematic review and meta-analysis.
24	Vally S, Ferdynus C, Persichini R, Braunberger E, Pinto HL, Bouchet B, Martinet O, Aujoulat T, Allyn J, Allou N. Impact of levosimendan on peripheral venoarterial extracorporeal membrane oxygenation weaning in intensive care unit. Ann. Intensive Care 2019;9(Suppl 1).	Poster of a published study (included in the meta-analysis).§

25	Cholley B, Levy B, Fellahi JL, *et al.* Levosimendan in the light of the results of the recent randomized controlled trials: an expert opinion paper. *Crit Care*. 2019;23(1):385.	Opinion paper.
26	van Diepen S, Mehta RH, Leimberger JD, *et al.* Levosimendan in patients with reduced left ventricular function undergoing isolated coronary or valve surgery. *J Thorac Cardiovasc Surg*. 2020;159(6):2302-2309.e6.	Not on ECMO.
27	Morosin M., Garda R., Zaleska-Kociecka M., Piotrowska K., Banya W., Guha K., Patel B., Sundeep K. Safety and efficacy of levosimendan in a cardiothoracic ICU - 5 year data. *J. Cardiothorac. Vasc. Anesth.* 2019;33(Suppl 2):S162-S163.	Levosimendan indications.
28	Pfeffer TJ, List M, Ricke-Hoch M, Sieweke JT, Schaefer A, Bauersachs J, Hilfker-Kleiner D. Treatment of cardiogenic shock complicating peripartum cardiomyopathy with the calcium sensitizer, levosimendan-data from the german PPCM registry. *Eur. J. Heart Fail.* 2019;21(Suppl 1):435.	Not on ECMO.
29	Dutton J, Morosin M, Fernandez Garda R, Garcia Saez D, Simon A, Zych B, Kaul S, Aw TC, Lees N, Hurtado Doce A. Levosimendan for primary graft failure treatment after orthotopic heart transplantation. *Eur. J. Heart Fail.* 2019;21(Suppl 1): 262-263.	Not on ECMO alone.
30	Ajello V, Buioni D, Farinaccio A, Colella D, Pisano C, Nardi P, Greci M, Ruvolo G. ECH-MO-simendan", successful and rapid approach in acute heart failure with cardiac hemochromatosis. *Artif. Organs* 2020;44(3):E109-E110.	Not on ECMO weaning.
31	Zhuravel S.V., Aleksandrova V.E., Utkina I.I., Kuznetsova N.K., Tarabrin E.A. Levosimendan in lung transplant recipients on VA-ECMO. *Russian Journal of Transplantology and Artificial Organs*. 2020;22(1):118-122.	Not on ECMO weaning.
32	Baker A, Caetano F, Price S, Uddin S, Trimlett R, Arachchillage D. A case of peripartum cardiomyopathy supported by VA-ECMO. *J Intensive Care Soc*. 2019;20(2 Suppl):1-253.	Not on ECMO weaning.
33	Ferro B., Tofani R., Gargani L., Borelli G., Roncucci P. A case of intracoronary and endovenous levosimendan as a rescue therapy for refractory cardiac arrest. *Intensive Care Med. Exp*. 2019;7(Suppl 3)	Not on ECMO weaning.

ECMO, extracorporeal membrane oxygenation; PICU, pediatric intensive care unit; VV, veno-venous.

[#]From EMBASE database cited in 2 differents years (i.e. 2013 and 2014). Marzorati C, Erba L, Cortinovis B, *et al.* Levosimendan infusion during ECMO weaning: Effect on endothelial function and haemodynamics. *Appl Cardiopulm Pathophysiol*.2014;17(2):170-171.

Sangalli F, Avalli L, Laratta M, et al.* Effects of Levosimendan on Endothelial Function and Hemodynamics During Weaning From Veno-Arterial Extracorporeal Life Support. *J Cardiothorac Vasc Anesth*. 2016;30(6):1449-1453.

[&]Jacky A, Rudiger A, Krüger B, *et al.* Comparison of Levosimendan and Milrinone for ECLS Weaning in Patients After Cardiac Surgery-A Retrospective Before-and-After Study. *J Cardiothorac Vasc Anesth*. 2018;32(5):2112-2119.

[$]Same site and sample size for a poster included in the meta-analysis: Haffner G, Ajob G, Cristinar M, *et al.* Levosimendan for weaning veno-arterial ECMO (VA ECMO). *Crit Care*.2018;22(Suppl 1):P128.

[^]In one statement "The first LV infusion was started ±7 days……" and in another statement "The infusion ran for ±23 hrs…". Both statements are not clear and confusing i.e. does the sign ± means average? Or mean (±SD)? Interpretation was attempted but consensus could not be reached. Thus, the decision was to exclude this paper from our analysis.

[§]Vally S, Ferdynus C, Persichini R, *et al.* Impact of levosimendan on weaning from peripheral venoarterial extracorporeal membrane oxygenation in intensive care unit. *Ann Intensive Care*. 2019;9(1):24. Published 2019 Feb 1. doi:10.1186/s13613-019-0503-1.

Table S4 Case report summary

Case description	Management	Outcomes
▪ 43-year-old man ▪ History of pulmonary HTN and mild RV dysfunction ▪ Underwent BSSLTx ▪ Early post-op developed severe grade 3 PGD ▪ PGD was associated with increased PAP (67/36/53 mmHg), RV dilatation, severely decreased CI (1.5 L/min/m^2), and distant organ hypoperfusion	▪ **ECMO indication**: persistence of severe reperfusion injury, falling cardiac output, diuretic-unresponsive oliguria, and severe gas exchange impairment ▪ **ECMO effect**: arterial oxygenation and reduction of pulmonary arterial flow improved ▪ **Issue**: no rapid recovery of cardiac function; vasoactive support added ▪ **Post-op D4**: improvement; weaning from ECMO attempted ▪ **Weaning issue**: recurrence of pulmonary HTN (mean PAP 35 - 45 mmHg) with borderline gas exchange and increase in PVR ▪ **TEE during weaning on D4**: RV dilatation, increased systolic RV pressure (i.e. TRPG ~ 40 mmHg), leftward interventricular septum displacement, and mild pericardial effusion. LV dysfunction with reduced LV filling ▪ **Vasoactive agents**: pulmonary vasodilator agents and inhaled NO were ineffective in reducing RV afterload, improving RV contractility and restoring hemodynamics ▪ **Levosimendan**: started at 0.05 to 0.15 mcg/kg/min for 24 hr, without LD on top of ongoing treatment (dobutamine, NE, milrinone, and inhaled NO) ▪ **Effect within 24 hr**: gradual reduction in PAP and PVR; moderate reduction in PCWP (from 16 to 13 mmHg). Another 0.1 mcg/kg/min 24 hr-infusion of levosimendan was administered, and vasoactive treatment was decreased	▪ Improvement in EF of both RV and LV, in the presence of adequate gas exchange, allowed for reducing ECMO support ▪ Reduction in right chambers dilation and stabilization of RV mechanical efficiency led to ECMO weaning and decannulation ~24 hours after the second infusion ▪ TEE: improvement of RV FAC and lengthening of TAPSE ▪ Renal function was restored, and peripheral and splanchnic hypoperfusion were resolved (i.e. no lactic acidosis) ▪ Dobutamine and NE were withdrawn (post-op D6) ▪ MV was weaned off and followed by NIV with helmet for several days (Post-op D8) ▪ ICU discharge with no signs of organ dysfunction (post-op D16)

BSSLTx, bilateral sequential single lung transplantation; CI, cardiac index; D, day; ECMO, extracorporeal membrane oxygenation; EF, ejection fraction; FAC, fractional area change; hr, hour(s); HTN, hypertension; LD, loading dose; LV, Left ventricular; MV, mechanical ventilation; NE, norepinephrine; NIV, non-invasive ventilation; NO, nitric oxide; PAP, pulmonary arterial pressure; PGD, primary graft dysfunction; post-op, post operation/operative; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; TEE, transesophageal echocardiography; TRPG, tricuspid regurgitation pressure gradient. Reference: Feltracco P, Carollo C, Ori C. Levosimendan in lung transplant recipients with difficult weaning from ECMO. Minerva Anestesiol. 2015;81(1):92-93.

Table S5 ROBIN-I risk of bias assessment - ECMO weaning

Study	Pre-intervention bias			At intervention bias				Overall risk of bias*
	Confounding	Selection of participants	Classification of interventions	Deviation from intended interventions	Missing data	Measurement of outcomes	Selection of the reported result	
Affronti *et al*[34] 2013	Serious	Serious	Moderate	Low	No information	Moderate	Moderate	Serious
Distelmaier *et al*[35] 2016	Moderate	Moderate	Moderate	Low	No information	Moderate	Moderate	Serious
Haffner *et al*[36] 2018	Critical	Moderate	Moderate	No information	No information	No information	No information	Critical
Jacky et *al*[37] 2018	Serious	Moderate	Moderate	Low	No information	Moderate	Moderate	Serious
Sangalli *et al*[38] 2016	Serious	Moderate	Moderate	Low	No information	Moderate	Moderate	Serious
Vally *et al*[39] 2019	Moderate	Moderate	Low	Low	No information	Moderate	Moderate	Moderate
Zipfel *et al*[40] 2018	Critical	Moderate	Serious	No information	No information	No information	No information	Critical

**Overall risk of bias: Low if study is comparable to a well-performed randomized trial; Moderate if study provides sound evidence for a non-randomized study but cannot be considered to be comparable to a well-performed randomized trial; Serious if the study has some important problems; Critical if the study is problematic.*

Table S6 ROBIN-I risk of bias assessment - mortality

Study	Pre-intervention bias			At intervention bias				Overall risk of bias*
	Confounding	Selection of participants	Classification of interventions	Deviation from intended interventions	Missing data	Measurement of outcomes	Selection of the reported result	
Affronti *et al*[34] 2013	Serious	Serious	Moderate	Low	No information	Low	Low	Serious
Distelmaier *et al*[35] 2016	Moderate	Moderate	Moderate	Low	No information	Low	Low	Moderate
Haffner *et al*[36] 2018	Critical	Moderate	Serious	No information	No information	Low	Low	Critical
Jacky *et al*[37] 2018	Serious	Moderate	Moderate	Low	No information	Low	Low	Serious
Sangalli *et al*[38] 2016	Serious	Moderate	Moderate	Low	No information	Low	Low	serious
Vally *et al*[39] 2019	Moderate	Moderate	Low	Low	No information	Low	Low	Moderate
Zipfel *et al*[40] 2018	Critical	Moderate	Serious	No information	No information	Low	Low	Critical

**Overall risk of bias: Low if study is comparable to a well-performed randomized trial; Moderate if study provides sound evidence for a non-randomized study but cannot be considered to be comparable to a well-performed randomized trial; Serious if the study has some important problems; Critical if the study is problematic.*

Sensitivity analysis – VA-ECMO weaning

Table S7 Sensitivity analysis for VA-ECMO weaning

Author	Heterogeneity	Overall effect	
Affronti *et al*[34] 2013	$Tau^2 = 0.29$; $Chi^2 = 10.10$, df = 5 (P = 0.07); $I^2 = 50\%$	Z = 2.99 (P = 0.003)	moderate heterogeneity
Distelmaier *et al*[35] 2016	$Tau^2 = 0.52$; $Chi^2 = 10.80$, df = 5 (P = 0.06); $I^2 = 54\%$	Z = 2.89 (P = 0.004)	moderate heterogeneity
Sangalli *et al*[38] 2016	$Tau^2 = 0.07$; $Chi^2 = 6.18$, df = 5 (P = 0.29); $I^2 = 19\%$	Z = 3.79 (P = 0.0002)	not be important
Jacky *et al*[37] 2018	$Tau^2 = 0.40$; $Chi^2 = 11.71$, df = 5 (P = 0.04); $I^2 = 57\%$	Z = 2.92 (P = 0.003)	moderate heterogeneity
Zipfel *et al*[40] 2018	$Tau^2 = 0.44$; $Chi^2 = 10.94$, df = 5 (P = 0.05); $I^2 = 54\%$	Z = 2.60 (P = 0.009)	moderate heterogeneity
Haffner *et al*[36] 2018	$Tau^2 = 0.21$; $Chi^2 = 8.21$, df = 5 (P = 0.15); $I^2 = 39\%$	Z = 3.91 (P < 0.0001)	moderate heterogeneity
Vally *et al*[39] 2019	$Tau^2 = 0.53$; $Chi^2 = 11.70$, df = 5 (P = 0.04); $I^2 = 57\%$	Z = 2.66 (P = 0.008)	moderate heterogeneity

Sensitivity analysis was carried out by removing each study

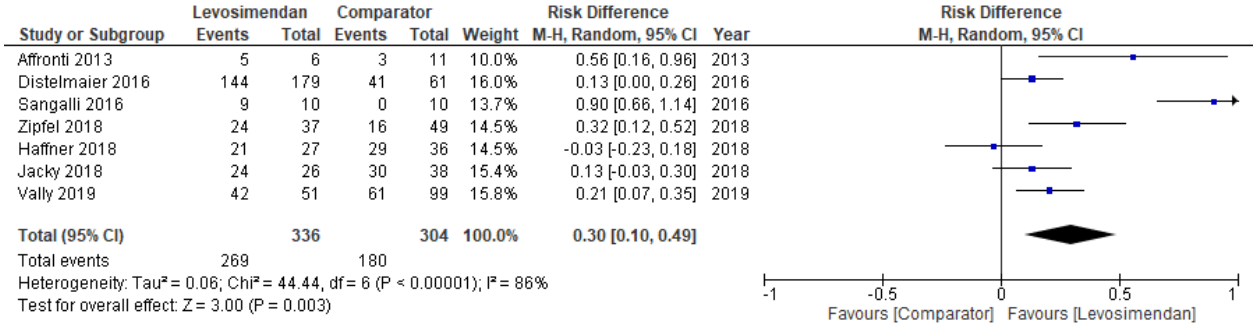

Figure S1 Risk difference – VA-ECMO weaning

The risk difference is the difference between the observed risks (proportions of individuals with the outcome of interest) in the two groups; here it was reported as 30% i.e. the estimated difference in the probability of experiencing weaning between levosimendan and the comparators.

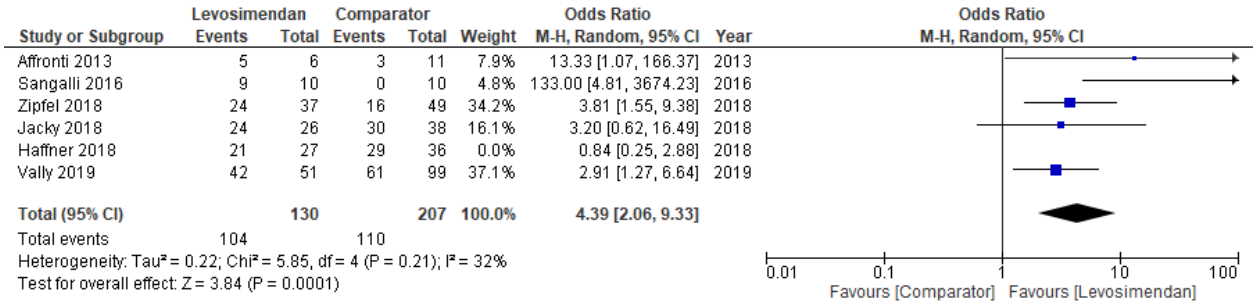

Figure S2 Odds ratio without Haffner *et al.* study

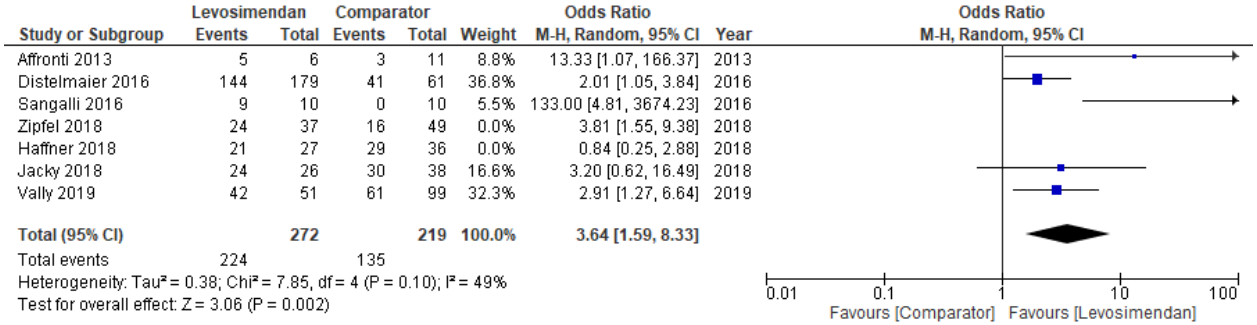

Figure S3 Odds ratio without Haffner *et al.* and Zipfel *et al.* studies

The heterogeneity improved further when studies by Sangalli et al (2016) and Haffner et al. (2018) were removed from the studies.

Table S8 Rates of outcomes in levosimendan and comparators groups

First author	Levo	Comparator	NNT	Levo	Comparator	NNT
	ECMO (%)			Mortality (%)		
Jacky *et al*[37] 2018	92.0	79.0	7.7	34.6	40.0	18.5
Affronti *et al*[34] 2013	83.3	27.3	1.8	33.0	63.6	3.3
Sangalli *et al*[38] 2016	90.0	0	1.1	-	-	-
Zipfel *et al*[40] 2018	64.8	32.6	3.1	48.7	77.6	3.5
Haffner *et al*[36] 2018	24.0	80.6	1.8	33.3	36.1	35.7
Vally *et al*[39] 2019	82.4	61.6	4.8	21.6	50.5	3.5
Distelmaier *et al*[35] 2016	80.4	67.2	7.6	62.0	73.8	8.5
	P value = 0.073		5	*P* value = 0.041		5

Using Mann-Whitney test

Sensitivity analysis – Mortality

Table S9 Sensitivity analysis for mortality

Author	Heterogeneity	Overall effect	
Affronti *et al*[34] 2013	Tau² = 0.10; Chi² = 6.02, df = 4 (P = 0.20); I² = 34%	Z = 3.08 (P = 0.002)	moderate heterogeneity
Distelmaier *et al*[35] 2016	Tau² = 0.11; Chi² = 5.53, df = 4 (P = 0.24); I² = 28%	Z = 3.02 (P = 0.003)	might not be important
Jacky *et al*[37] 2018	Tau² = 0.06; Chi² = 5.08, df = 4 (P = 0.28); I² = 21%	Z = 3.61 (P = 0.0003)	might not be important
Zipfel *et al*[40] 2018	Tau² = 0.05; Chi² = 4.79, df = 4 (P = 0.31); I² = 16%	Z = 2.83 (P = 0.005)	might not be important
Haffner *et al*[36] 2018	Tau² = 0.03; Chi² = 4.56, df = 4 (P = 0.34); I² = 12%	Z = 3.92 (P < 0.0001)	might not be important
Vally *et al*[39] 2019	Tau² = 0.00; Chi² = 3.80, df = 4 (P = 0.43); I² = 0%	Z = 2.82 (P = 0.005)	might not be important

Sensitivity analysis was carried out by removing each study

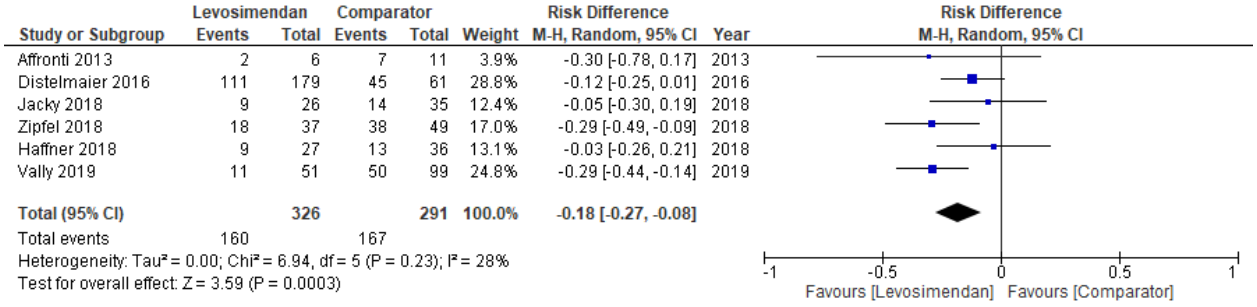

Figure S4 Risk difference – Mortality

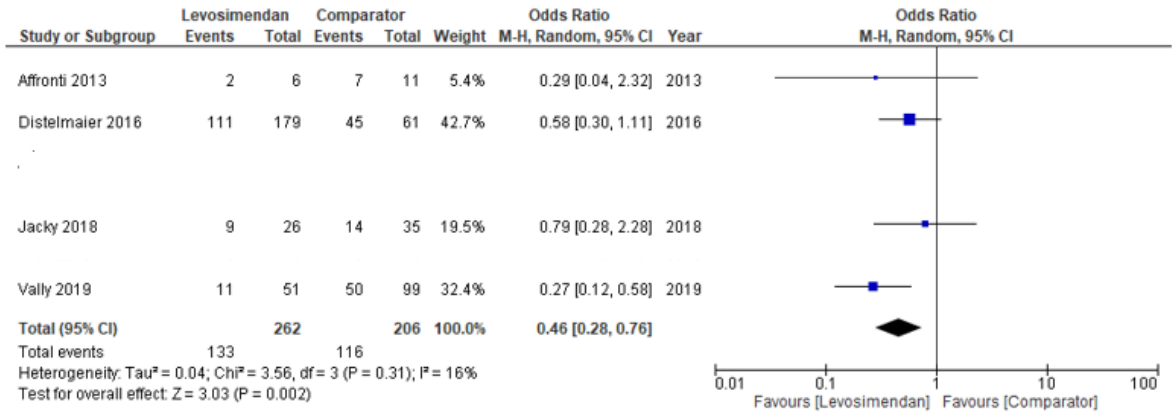

Figure S5 Odds ratio without Haffner *et al.* and Zipfel *et al.* studies

By removing the study by Haffner et al. (2018), Zipfel et al. (2018) and Vally et al. (2019) the heterogeneity improved further.