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Levosimendan for VA-ECMO weaning: the silver lining

Inadequate end-organ tissue perfusion characterizes circulatory compromise, such as cardiogenic shock, that leads to ischaemia and multiorgan failure with a high mortality rate. Temporary mechanical circulatory support devices, namely, venoarterial extracorporeal membrane oxygenation (VA-ECMO), restore haemodynamic stability, improve tissue perfusion, allow time for the myocardium to recover,[1] and bridge patients to heart transplantation or durable mechanical circulatory support.[2] The prolonged use of VA-ECMO is associated with complications such as thrombo-embolic events, bleeding, limb ischaemia, brain or lung injury, and infection.[1,2] Early weaning is encouraged, because decreasing weaning failure may reduce VA-ECMO-related morbidity and mortality.[2] Successful weaning is still one of the main challenges following myocardial recovery.[1] Levosimendan improves myocardial contractility without affecting the intracellular calcium or increasing oxygen consumption and the related serious arrhythmias. Levosimendan can unload the ventricles due to the vasodilatory effect induced by the relaxation of the smooth muscles of the systemic, coronary, and pulmonary vessels.[1–3] Therefore, levosimendan may have a beneficial effect in facilitating VA-ECMO weaning.[1,2]

We read, with great interest, the published rationale and design of an ongoing trial (WEANILEVO; NCT04158674) to evaluate the use of levosimendan before VA-ECMO weaning in a prospective, randomized, and double-blind design.[2] The awaited study will address the limitations and heterogeneous aspects of the currently available observational studies on this subject matter presented in recent meta-analyses.[1,4,5] Examples of limitations include the observational nature of the studies, inconsistency in the VA-ECMO weaning definition, and the protocols used across the studies; variability in levosimendan dose and time of administration; and the absence of details about inotropes or intra-aortic balloon pump use.[1,3] We published a systematic review and meta-analysis of seven observational studies (n = 630) evaluating levosimendan use in VA-EMCO weaning in critically ill patients. Weaning success rates ranged from 65.0% to 92.0% in the levosimendan group compared with 27.0% to 88.0% in the comparator group (OR 2.89, 95% CI 1.53–5.46; $P_{\text{overall effect}}$ = 0.001, I^2 = 49%). The mortality rates with levosimendan use ranged from 20.0% to 62.0% as compared with 36.0% to 77.0% in the other group (OR 0.46, 95% CI 0.30–0.71; $P_{\text{overall effect}}$ = 0.0004, I^2 = 20%).[1] Findings were consistent with that of the meta-analyses of four (n = 471) and five studies (n = 557) by Silvestri *et al*.[4] and Burgos *et al*.,[5] respectively, who investigated a similar clinical question. Levosimendan improved haemodynamic and echocardiographic parameters as well.[1]

Since the publication of our meta-analysis, two retrospective cohort studies that investigated levosimendan effectiveness in VA-ECMO weaning in patients with circulatory compromise have been published without outcome advantages with levosimendan use.[6,7] Guilherme *et al*. conducted their single-centre study between January 2012 and December 2018, which enrolled 200 adult patients with refractory cardiogenic shock who were admitted to the cardiothoracic intensive care unit. Levosimendan was administered initially at a dose of 0.1 μg/kg/min for 1 h and then as a continuous infusion of 0.1 to 0.2 μg/kg/min for 24 h. Another inotropic support was permitted, and the timings of its and levosimendan's administration were at the discretion of treating physicians. The weaning failure rate was 28.3% in the levosimendan group as compared with 29.9% in the control group (OR 0.92; 95% CI 0.46–1.85). After matching, the corresponding findings were 29.1% and 35.4% (OR 0.69; 95% CI 0.25–1.88), respectively. There was no statistically significant difference between the groups in terms of the 28 day mortality rate (44.2% vs. 37.5%) (OR 0.69; 95% CI 0.39–2.51). After matching, the 28 day and 6 month mortality rates were slightly lower in the levosimendan group [41.0% vs. 41.6% (OR 1.08; 95% CI 0.42–2.81) and 50.0% vs. 54.3% (OR 0.79; 95% CI 0.30–2.07), respectively].[6] Alonso-Fernandez-Gatta *et al*. recruited 123 adults with refractory cardiogenic shock of various aetiologies from 2013 to May 2020. Initial levosimendan rate was 0.05 μg/kg/min with a target of 0.1 μg/kg/min. The timing of administration was according to the treating physician's criteria. The removal of VA-ECMO was attempted at least 24 h of the infusion. Successful weaning rate was numerically higher in the levosimendan group (60.9% vs. 44.0%, P = 0.169). The survival rates at discharge and longer follow-up (20.6 months) were numerically higher in the levosimendan group [(52.2% vs. 36.0%, P = 0.116) and (47.8% vs. 32.0%, P = 0.124)], respectively.[7] The two studies shared common

Table 1 Key characteristics and outcomes

Parameters	Alonso-Fernandez-Gatta *et al.*[7]	Guilherme *et al.*[6]	Kaddoura *et al.*[1]
Study characteristics			
Study design	Retrospective analysis	Observational retrospective	Meta-analysis of 7 observational trials
Publication year(s)	2020	2020	2020 Range: 2013–2019
Recruitment period	2013–2020	2012–2018	2010–2017
Duration	7 years	7 years	Range: 1–7 years
Setting	ICU (mixed)	ICU (CT)	Operating room, ICU (including CT, mixed)
Sample size	123	200	630 Range: 10 – 240
Patient characteristics			
Age (years)	61.6 ± 10	53 ± 13.5	Range: 53–65
Male sex	73.2%	64.5%	Range: 50.0–78.0%
Co-morbidities	HTN (56.1%), DM (30.9%), cardiopathy (46.3%), dyslipidaemia (46.3%)	HTN (31.0%), DM (18.0%), CAD (44.0%), HF (51.0%)	HTN (43.0–70.0%), DM (23.0–40.0%) CAD (29.0–69.0%), HF (23.0–25.0%)
Outcomes			
VA-ECMO weaning success/failure *Levosimendan vs. control*	**Successful weaning** 60.9% vs. 44.0% ($P = 0.169$) OR: NR	**Weaning failure** (after matching) 29.1% vs. 35.4% OR: 0.69 (95% CI 0.25–1.88)	**Successful weaning** Range: 65.0–92.0% vs. 27.0–88.0% Pooled results: OR: 2.89 (95% CI 1.53–5.46; $P = 0.001$)
Mortality/survival *Levosimendan vs. control*	**Survival rate** At discharge: 52.2% vs. 36.0% ($P = 0.116$) At follow-up: 47.8% vs. 32.0% ($P = 0.124$) OR: NR	**28 day mortality** (after matching) 41.0% vs. 41.6% OR: 1.08 (95% CI 0.42–2.81) **6 month mortality** (after matching) 50.0% vs. 54.3% OR: 0.79 (95% CI 0.30–2.0)	**Mortality** Range: 20.0–62.0% vs. 36.0–77.0% Pooled results: OR: 0.46 (95% CI 0.30–0.71; $P = 0.0004$)

CAD, coronary artery disease; CI, confidence interval; CT, cardiothoracic; DM, diabetes mellitus; HF, heart failure; HTN, hypertension; ICU, intensive care unit; NR, not reported; OR, odds ratio; VA-ECMO, venoarterial extracorporeal membrane oxygenation.

Figure 1 Pooled data of the new studies.[6,7]

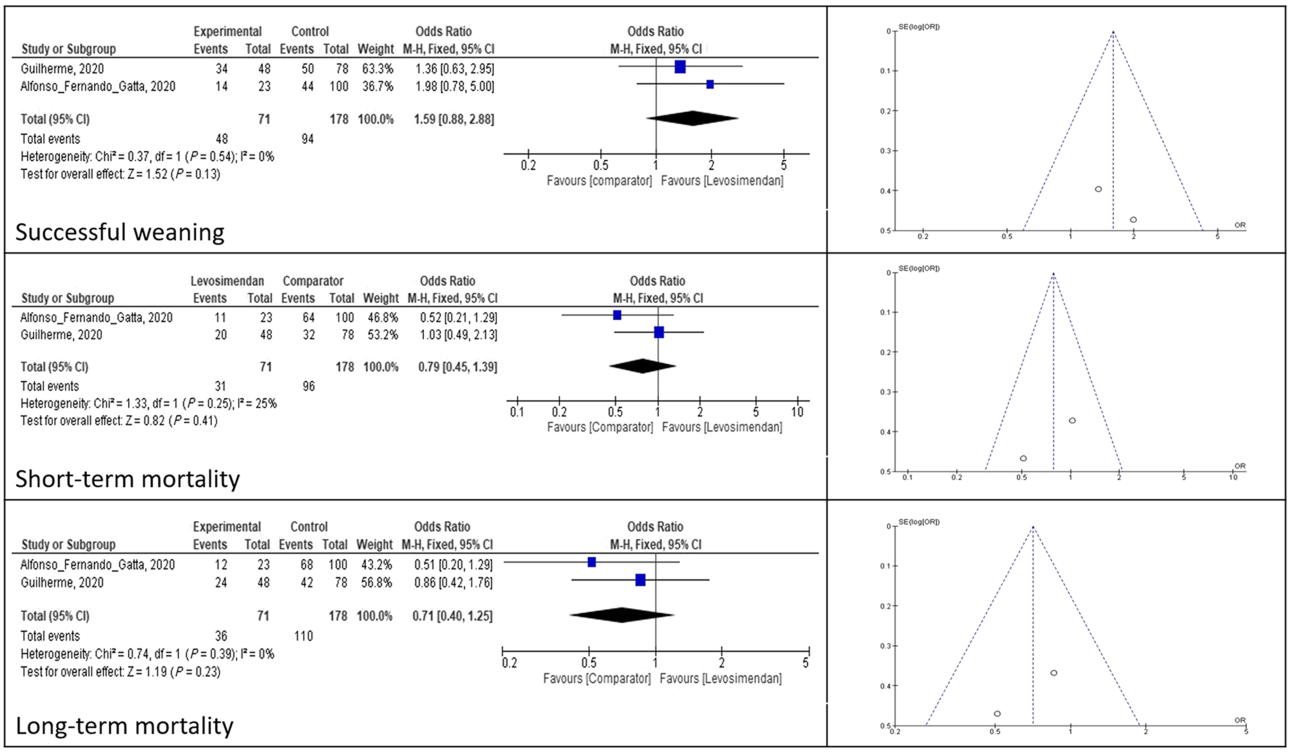

Figure 2 Addition of new studies to the previous meta-analysis.[1]

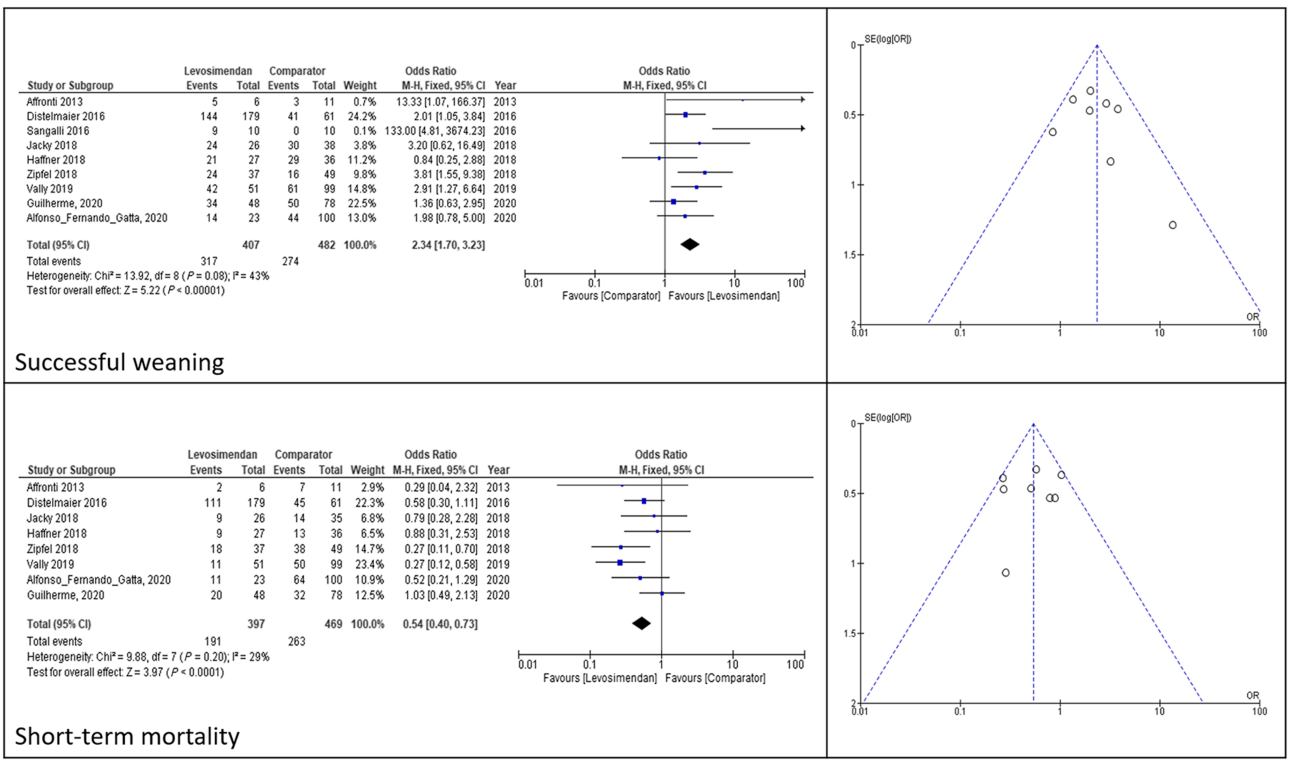

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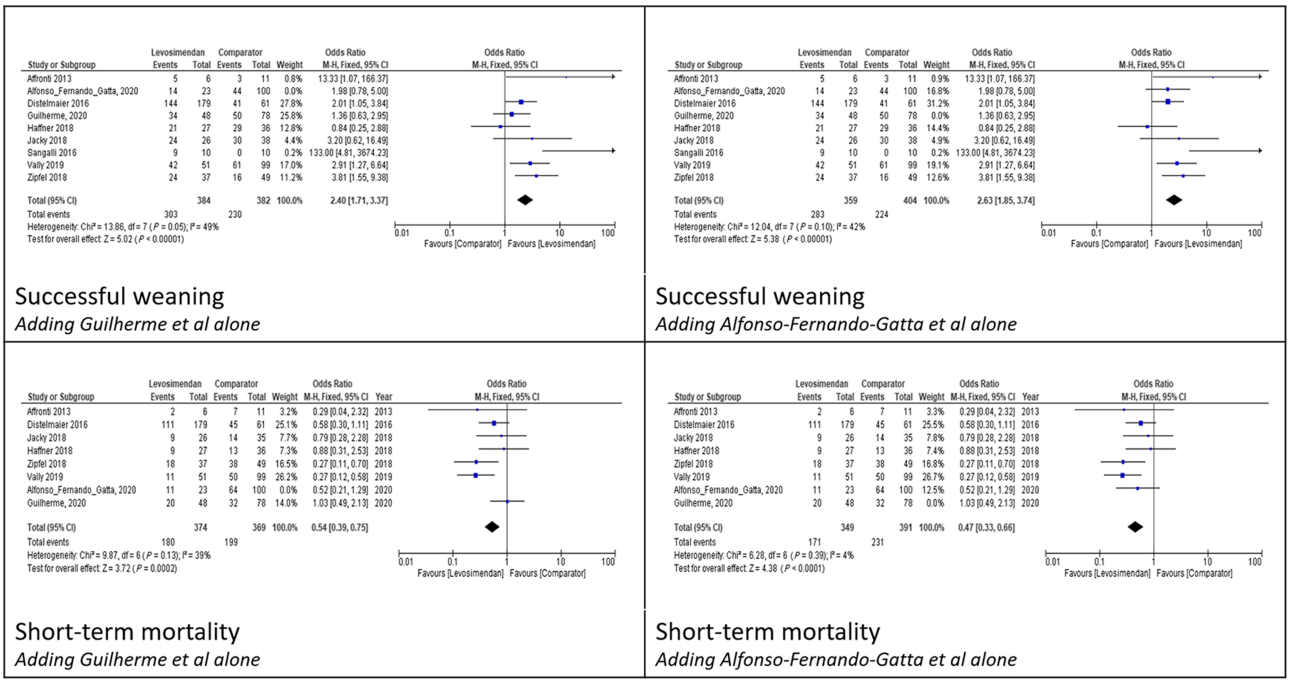
Figure 3 Sensitivity analysis.



limitations. Key characteristics and outcomes of the two published studies,[6,7] along with the aggregate data of our meta-analysis,[1] are presented in *Table 1*.

To study the changes in effect estimates, we pooled the data of the two studies together[6,7] and then with the pooled data of our published meta-analysis.[1] The pooled data of the two studies did not show significant difference between the groups in terms of weaning success (OR 1.59, 95% CI 0.88–2.88; $P_{\text{overall effect}} = 0.13$, $I^2 = 0\%$), short-term mortality (OR 0.79, 95% CI 0.45–1.39; $P_{\text{overall effect}} = 0.41$, $I^2 = 25\%$), or long-term mortality (OR 0.71, 95% CI 0.40–1.25; $P_{\text{overall effect}} = 0.23$, $I^2 = 0\%$). The funnel plots indicated potential threat to publication bias (*Figure 1*). When the findings of the two studies were pooled with those of the seven studies included in the published meta-analysis,[1] successful weaning rate was significantly higher (OR 2.34, 95% CI 1.70–3.23; $P_{\text{overall effect}} < 0.00001$, $I^2 = 43\%$), and short-term mortality rate was significantly lower (OR 0.54, 95% CI 0.40–0.73; $P_{\text{overall effect}} < 0.0001$, $I^2 = 29\%$) with levosimendan use. The respective funnel plots demonstrated reasonable symmetry and less threat to publication bias (*Figure 2*). Sensitivity analysis by adding one study at a time showed comparable results for successful weaning {[(OR 2.40, 95% CI 1.71–3.37; $P_{\text{overall effect}} < 0.00001$, $I^2 = 49\%$) by adding Guilherme *et al*.] and [(OR 2.63, 95% CI 1.85–3.74; $P_{\text{overall effect}} = 0.00001$, $I^2 = 42\%$) by adding Alfonso-Fernando-Gatta *et al*.]}. Similarly, sensitivity analysis for the short-term mortality produced comparable results {[(OR 0.54, 95% CI 0.39–0.75; $P_{\text{overall effect}} = 0.0002$, $I^2 = 39\%$) with Guilherme *et al*.] and [(OR 0.47, 95% CI 0.33–0.66; $P_{\text{overall effect}} < 0.0001$, $I^2 = 4\%$) with Alfonso-Fernando-Gatta *et al*.]} (*Figure 3*).

Although the new analysis confirms that levosimendan may be an effective option to facilitate weaning from VA-ECMO and reduce mortality risk, the conclusion must be interpreted with caution given the potential limitations of the currently available studies. In addition to the published design of the ongoing WEANILEVO trial (NCT04158674),[2] another randomized trial (LEVOECMO; NCT04728932) is currently registered. The findings of both studies will be awaited to support the conclusion of the current pooled data.

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