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Clinical paper

Exposure to severe hyperoxemia worsens survival and neurological outcome in patients supported by veno-arterial extracorporeal membrane oxygenation: A meta-analysis

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Abstract

Background: Veno-arterial Extracorporeal Membrane Oxygenation (VA-ECMO) is a rescue treatment in refractory cardiogenic shock (CS) or refractory cardiac arrest (CA). Exposure to hyperoxemia is common during VA-ECMO, and its impact on patient's outcome remains unclear.

Methods: We conducted a systematic review (PubMed and Scopus) and meta-analysis investigating the effects of exposure to severe hyperoxemia on mortality and poor neurological outcome in patients supported by VA-ECMO. When both adjusted and unadjusted Odds Ratio (OR) were provided, we used the adjusted one. Results are reported as OR and 95% confidence interval (CI). Subgroup analyses were conducted according to VA-ECMO indication and hyperoxemia thresholds.

Results: Data from 10 observational studies were included. Nine studies reported data on mortality ($n = 5$ refractory CA, $n = 4$ CS), and 4 on neurological outcome. As compared to normal oxygenation levels, exposure to severe hyperoxemia was associated with higher mortality (nine studies; OR: 1.80 [1.16–2.78]; $p = 0.009$; $I^2 = 83\%$; low certainty of evidence) and worse neurological outcome (four studies; OR: 1.97 [1.30–2.96]; $p = 0.001$; $I^2 = 0\%$; low certainty of evidence). Magnitude and effect of these findings remained valid in subgroup analyses conducted according to different hyperoxemia thresholds (>200 or >300 mmHg) and VA-ECMO indication, although the association with mortality remained uncertain in the refractory CA population ($p = 0.13$). Analysis restricted to studies providing adjusted OR data confirmed an increased likelihood of poorer neurological outcome (three studies; OR: 2.11 [1.32–3.38]; $p = 0.002$) in patients exposed to severe hyperoxemia but did not suggest higher mortality (five studies; OR: 1.68 [0.89–3.18]; $p = 0.11$).

Conclusions: Severe hyperoxemia exposure after initiation of VA-ECMO may be associated with an almost doubled increased probability of poor neurological outcome and mortality. Clinical efforts should be made to avoid severe hyperoxemia during VA-ECMO support.

Keywords: Hyperoxia, Normoxia, Extracorporeal cardiopulmonary resuscitation, Cardiogenic shock, Mortality, Poor neurological outcome

Introduction

In the last decade, Extracorporeal Membrane Oxygenation (ECMO) became increasingly available for the cardiopulmonary support of critically ill patients, and its indications are becoming wider.[1] The Veno-Arterial (VA) configuration of ECMO offers support for refractory cardiogenic shock (CS). In the last two decades, according to the Extracorporeal Life Support Organization (ELSO) registry, over 15.000 adults have been supported by VA ECMO for refractory CS (survival rate to hospital discharge 40%).[2] Moreover, use of VA ECMO has been recently extended to the so-called extracorporeal cardiopulmonary resuscitation (eCPR) in patients suffering from refractory cardiac arrest (CA).[3–5]

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Despite increasing clinical expertise and technological advances in both circuits and cannulae reducing risks of bleeding and thrombosis,[6] rescue VA ECMO can be provided only by specialized centers and it is still burdened by high mortality and morbidity,[7] with reduced quality-of-life and high risk of psychological impairment in survivors.[8] Among others, neurological complications contribute to these poor outcomes in patients supported by VA ECMO.[9]

There is uncertainty regarding the role of hyperoxemia on the outcome of patients admitted to the intensive care unit (ICU).[10,11] It has been suggested that hyperoxemia may be harmful in different clinical scenarios such as myocardial infarction, stroke, traumatic brain injury, sepsis and post-cardiac resuscitation.[12,13] Conversely, recent studies raised concerns about the potential for worse outcomes induced by restrictive oxygenation strategy.[14–16] The EXACT trial conducted in unconscious adults with return of spontaneous circulation after CA found higher mortality when targeting an oxygen saturation of 90–94% as compared to standard treatment (98–100%, $p = 0.05$).[17]

There is growing literature on the effects of hyperoxemia on mortality in patients supported by VA ECMO, but the findings are somewhat conflicting.[18,19] Moreover, there is lack of a universally accepted approach for the definition of hyperoxemia.[20] Therefore, we aimed at investigating the effects of exposure to hyperoxemia on mortality and neurological outcomes in patients supported by VA ECMO for CS and/or e-CPR.

Methods

We conducted a systematic search on two databases (PubMed and SCOPUS) to identify the relevant articles on the 14th April 2023. Our study is reported in accordance with the PRISMA statement,[21] and a PECOS approach was adopted (Additional File). We included prospective and retrospective observational studies evaluating effects of exposure to severe hyperoxemia [according to values of arterial partial pressure of oxygen, (PaO_2] after VA ECMO cannulation in adult patients rescued for CS and/or eCPR. We evaluated two primary endpoints: mortality and poor neurological outcome. There was no date restriction and only articles published in English were considered. Pediatric studies were excluded. The PRISMA Checklist is available as Additional File.

The protocol of our study was registered in PROSPERO (CRD42023401477). For our search process both on PubMed and Scopus Databases, we combined the findings of two groups of search terms: 1)"hyperox*" OR"oxygen tension" OR"oxygen partial pressure" OR"saturation", and 2)"extracorporeal membrane oxygenation" OR"ECMO" OR"extracorporeal cardiopulmonary resuscitation" OR"eCPR" OR"extracorporeal life support" OR"ECLS" for the second group. Two pairs of assessors screened independently findings according to PECOS criteria. Articles categorized as included, excluded and dubious were subsequently cross-checked by two other authors. Full texts of articles identified as potentially relevant were assessed against eligibility criteria by three authors. Discordances were resolved by the senior author. We contacted the corresponding authors of the articles judged of potential interest to gather further data if needed. Two authors entered data into a predesigned collection form. Two authors explored references of the included full-texts to identify further studies of interest.

Analysis of outcomes

The co-primary outcomes were: all-cause mortality and neurological outcome, at the longest follow-up reported. For the neurological outcome analysis, we considered only studies referring to the cerebral performance category (CPC) scale or to the modified Rankin scale (mRS; good outcomes CPC = 1–2 and/or mRS = 0–3). We compared patients classified as with normal oxygenation values to those with severe hyperoxia. We planned analyses of subgroups according to the cut-off used to define hyperoxemia ($PaO_2 \geq 200$ mmHg or $\geq$300 mmHg) or to the indication for VA ECMO support (CS vs e-CPR). However, we admit that the analysis according to indication for ECMO was not clearly specified in the above-mentioned registration protocol, though we intended to perform such sub-analysis from the beginning. We planned four sensitivity analyses:

- including adjusted Odds ratio (OR) only,
- with *"leave-one-out at time"* approach,
- including studies with slightly different PECOS criteria,
- excluding studies at high-risk of bias.

We conducted one post-hoc analysis pooling studies that used identical timing of PaO_2 assessment to define hyperoxemia.

Quality assessment and grade of evidence

Methodological design quality of the included studies was evaluated using the Newcastle-Ottawa scale (NOS),[22] which appraises quality in three domains: selection, comparability and outcome. Studies may score a maximum of 9 points (high-risk 1–3 points, intermediate-risk 4–5 points, or low-risk of bias 6–9 points). Grade of evidence was performed according to the recommendations of the Grading of Recommendations Assessment, Development and Evaluation working group using GRADEpro software.[23]

Statistical analysis

Variables of interest were dichotomous and collected as event/total or Odds Ratio (OR). Whenever available we used adjusted OR from the included studies. For the studies providing adjusted OR, we provide the variables included in the multivariate or multiregression models for each study in the Additional File. Analysis was conducted with inverse variance approach using random-effect model with 95% Confidence interval (CI). Values are reported as OR, and two-tailed $p < 0.05$ was considered significant. Statistical heterogeneity was assessed using the X2 test. Heterogeneity was likely if $p \leq 0.10$. Quantification of heterogeneity was performed with I^2 and values of 0–24.9%, 25–49.9%, 50–74.9% and >75% were considered as none, low, moderate and high heterogeneity respectively. Publication bias was investigated inspecting the funnel plot. Meta-analysis was performed using review manager (Revman, Version 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Trial sequential analysis was not feasible due to use of data in OR.[24]

Results

Study selection

The overall literature search produced 1649 titles, which were appraised against PECOS criteria. As shown in the PRISMA flow-

chart (Additional File), 21 findings were potentially relevant, but after appraisal of full-texts we excluded 10 studies (n = 5 paediatric population, n = 5 no PaO_2 data according to PECOS criteria, i.e. data in PaO_2 tertiles). For the latter articles, we received no answer from corresponding and/or the senior authors after multiple email attempts. One study was excluded[25] due to overlap of population with another. Therefore, we included 10 studies,[18,19,26–33] all published in the 2019–2023 period.

One of the included studies reported neurological outcome as "acute brain injury" (composite outcome including also seizures) and not according to CPC/mRS. Hence, for the neurological outcome endpoint, it was used only in the sensitivity analysis.[26]

Study characteristics are shown in Table 1 and we provide separately the baseline characteristics of the populations in the included studies (Additional File). In total, five studies,[18,26,28,29,32] provided adjusted OR values for mortality and neurological outcome correcting for different confounders. Another study provided the adjusted OR for the neurological outcome only.[30] Variables used for the statistical adjustment are listed in Additional File.

Overall, we analyzed data on outcome on 10,063 patients regarding mortality; of these 31.5% exposed to severe hyperoxemia (n = 3174) and the remaining to normal PaO2 values (n = 6889, 68.5%), whilst data on 4483 patients exposed to mild/moderate hyperoxemia were not included. Regarding the neurological outcome, we included data on 1321 patients (41.9% exposed to severe hyperoxemia, n = 553). A summary of all the analyses is shown in Table 2.

Mortality

Nine studies reported data on mortality (n = 5 eCPR, n = 4 CS). Based on PaO_2, two studies[31,32] defined hyperoxemia using a cut-off of 200 mmHg, while the remaining seven[18,19,26–30] used 300 mmHg. As shown in Fig. 1, mortality was significantly associated with exposure to hyperoxemia with OR 1.80 [1.16–2.78] (p = 0.009; I^2 = 83%). The analysis did not show subgroup differences (p = 0.93; I^2 = 0%) according to the cut-off for the definition of hyperoxemia, with ORs for mortality 1.84 ([1.07–3.17]; p = 0.03; I^2 = 87%) when using a cut-off of 300 mmHg, and 1.78 ([1.12–2.83]; p = 0.01; I^2 = 0%) when considering a cut-off of 200 mmHg.

The other subgroup analysis included data for five studies in patients supported by eCPR[26–28,30,32] and the remaining four with CS as indication for VA ECMO.[18,19,29,31] As shown in Fig. 2, the analysis did not show subgroup differences (p = 0.82; I^2 = 0%) according to the indication; however, mortality was significantly associated with exposure to hyperoxemia in the CS group (OR 1.78 [1.13–2.81]; p = 0.01; I^2 = 64%), but this association was not significant in the eCPR (OR 2.00 [0.82–4.88], p = 0.13; I^2 = 89%). Inspection of funnel plots did not suggest publication bias (Additional File).

Table 1 – Characteristics of the included studies reporting outcome(s) of interest. We report the design of the study, the type and the number of patients included, the cut-off for severe hyperoxemia used and the timing of assessment, the outcome(s) reported. VA, venoarterial, VV venovenous; eCPR, extracorporeal cardiopulmonary resuscitation; CS, cardiogenic shock; OR, Odds Ratio.

Article Design	Setting (n)	Cut-off of PaO_2 Timeframe	Outcome(s) of interest Measure effect used
M.D. Moussa et al., Critical Care, 2022 Multi-center, retrospective	CS (430)	≥300 Within 48 h after ICU admission	28-d Mortality Adjusted OR
P. Ross et al., Australian Crit Care, 2020 Single-center, retrospective	CS (30)	≥300 Within 72 h after ICU admission	In-hospital Mortality Unadjusted OR
W-T-Chang et al., Critical Care Medicine, 2019 Single-center, retrospective	eCPR (291)	≥300 Within 24 h after ECMO initiation	Neurological outcome at hospital discharge Unadjusted OR
M. Halter et al., Am J Emerg Medicine, 2019 Single-center, retrospective	eCPR (66)	≥300 PaO_2 at 24 h after ECMO initiation	28-d Mortality Unadjusted OR
M. Nishihara et al., J Emerg Medicine, 2022 Multi-center, prospective	eCPR (453)	≥300 PaO_2 at 24 h after ECMO initiation	30-d Mortality (Unadjusted OR) 30-d Neurological Outcome (Adjusted OR)
M. Kashiura et al., BMC Cardiovasc Dis, 2022 Multi-center, retrospective	eCPR (847)	≥300 Initial PaO_2 after ECMO initiation	30-d Mortality 30-d Neurological Outcome Adjusted OR
M. Kobayashi et al., Frontiers in Medicine, 2022 Single-center, retrospective	eCPR (110)	≥200 PaO_2 at 24 h after ECMO initiation	30-d Survival 30-d Neurological outcome Adjusted OR
Chenglong Li et al., Critical Care, 2022 Single-center, retrospective	CS (340)	≥300 PaO_2 at 24 h after ECMO initiation	In-hospital mortality Unadjusted OR
B.L. Shou et al., J Heart Lung Transplant, 2022 Multi-center, retrospective	eCPR (3125)	≥300 PaO_2 at 24 h after ECMO initiation	In-hospital mortality Adjusted OR
J.C. Jentzer et al., Circulation: Heart Failure, 2023 Multi-center, retrospective	CS (9959)	≥300 PaO_2 at 24 h after ECMO initiation	In-hospital mortality Adjusted OR

Table 2 – Summary of the results of the analyses. Results are presented in Odds Ratio (OR) with 95% confidence Interval (95% CI), both for the overall analysis and for the subgroups analyses. We also report the data of the analyses conducted with studies providing adjusted OR. CA, cardiac arrest; CS: cardiogenic shock; PaO_2, partial arterial pressure of oxygen.

Outcome	Studies included	Odds Ratio [95% CI]	*p* value	I^2
Mortality	**9**	**1.80 [1.16–2.78]**	**0.009**	**83%**
Subgroup cut-off 300 mmHg	7	1.86 [1.15–3.01]	0.03	87%
Subgroup cut-off 200 mmHg	2	1.78 [1.12–2.83]	0.01	0%
Subgroup CS as indication	4	1.78 [1.13–2.81]	0.01	64%
Subgroup CA as indication	5	2.00 [0.82–4.88]	0.13	89%
Adjusted OR only	5	1.68 [0.89–3.18]	0.11	89%
Poor Neurological Outcome (all CA)	**4**	**2.01 [1.32–3.06]**	**0.001**	**0%**
Subgroup cut-off 300 mmHg	3	2.01 [1.32–3.06]	0.001	0%
Adjusted OR only	3	2.11 [1.32–3.38]	0.002	0%

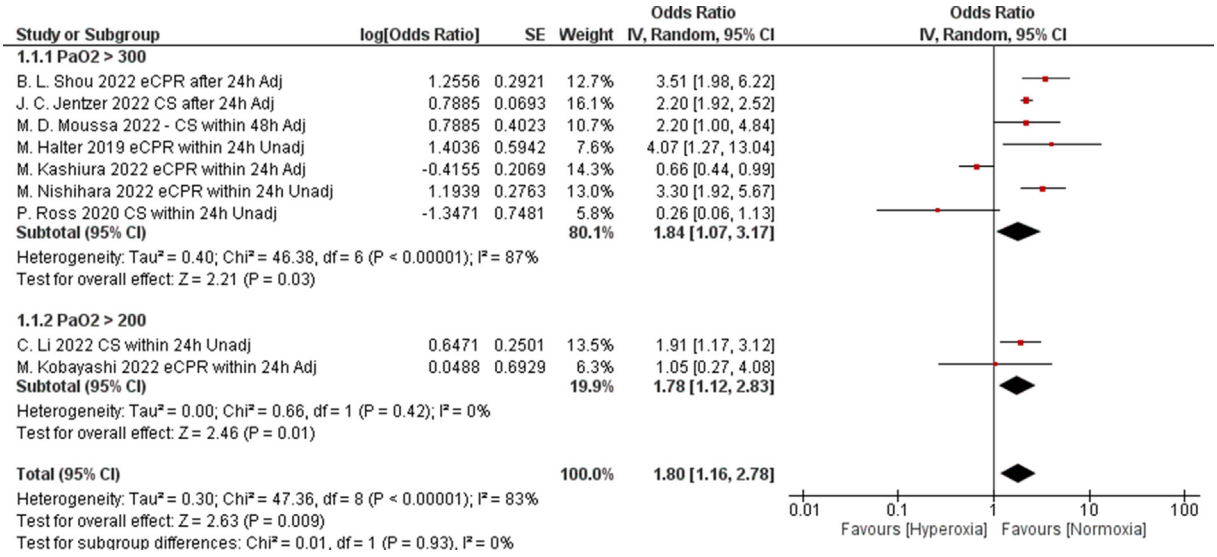

Fig. 1 – Forest plot of mortality in patients supported by Veno-Arterial Extracorporeal Membrane Oxygenation according to exposure to hyperoxemia or normoxemia. Subgroup analysis is conducted according to the PaO_2 cut-offs used to define hyperoxemia. Results are reported in Odds Ratio with Inverse Variance (IV) method and 95% Confidence Interval (CI). Adj, adjusted Odds Ratio; CS, cardiogenic shock; eCPR, extracorporeal cardiopulmonary resuscitation; SE, Standard Error; Unadj, unadjusted Odds Ratio.

Neurological outcome

Four studies reported data on neurological outcome, all of them being performed in the context of refractory CA using cut-off of $PaO_2 \geq 300$ mmHg[28,30,33] or ≥200 mmHg.[32] As shown in Fig. 3, we found a significant association between poor neurological outcome and exposure to hyperoxemia (OR 1.97 [1.30–2.96], $p = 0.001$; $I^2 = 0\%$), with no subgroup differences ($p = 0.58$; $I^2 = 0\%$). In particular, the subgroup of studies using 300 mmHg as cut-off had an OR for poor neurological outcome of 2.01 [1.32–3.06], $p = 0.001$; $I^2 = 0\%$). Inspection of funnel plots suggested no publication bias (Additional File).

Risk of bias and Grade of evidence

All but one of the included studies were at low risk of bias, scoring between 7 and 9 points in the NOS scale. The only study with intermediate risk of bias scored 5 points (Additional File).[31] GRADE of evidence resulted in a low certainty of evidence for both outcomes (Table 3), due to the observational design of the included studies.

Sensitivity analyses

Four types of sensitivity analyses were planned. The first was conducted including data only from studies that provided adjusted ORs only, thereby including five studies reporting mortality[18,26,28–29,32] and three describing neurological outcome.[28,30,32] In this analysis, we confirmed that hyperoxemia was associated with increased likelihood of poor neurological outcome (OR 2.11 [1.32–3.38], $p = 0.002$; $I^2 = 0\%$), but not of mortality (OR 1.68 [0.89–3.18], $p = 0.11$; $I^2 = 89\%$).

The association between hyperoxemia and mortality was confirmed in most of the nine analyses conducted excluding one study at time. In particular, when removing the study by Jentzer et al.[29] the findings were not significant ($p = 0.09$), whilst removing Shou

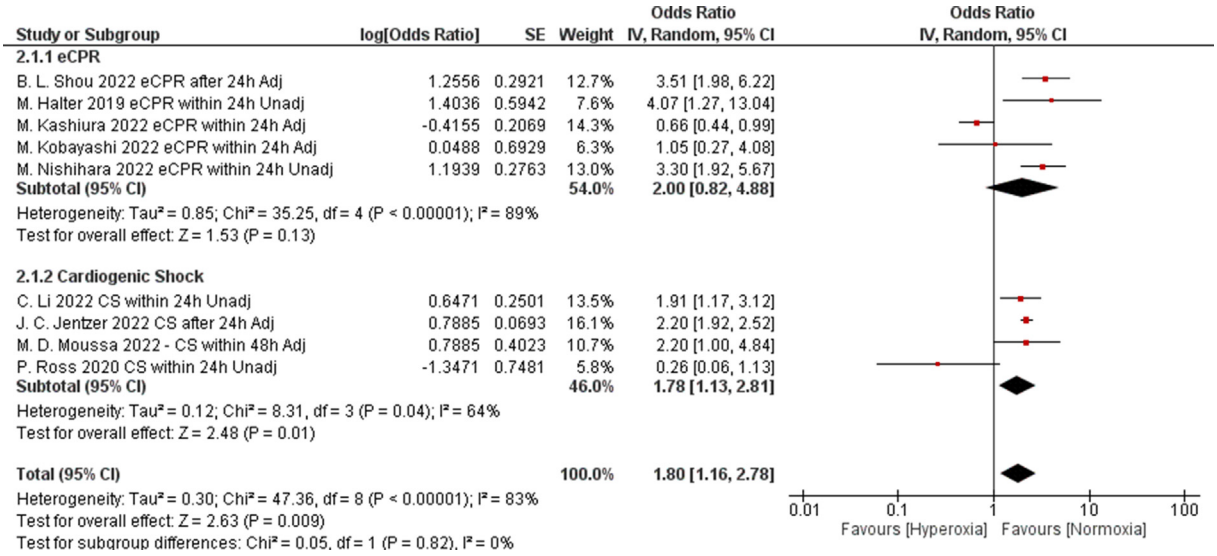

Fig. 2 – Forest plot of mortality in patients supported by Veno-Arterial Extracorporeal Membrane Oxygenation according to exposure to hyperoxemia or normoxemia. Subgroup analysis is conducted according to the indication for starting extracorporeal support. Results are reported in Odds Ratio with Inverse Variance (IV) method and 95% Confidence Interval (CI). Adj, adjusted Odds Ratio; CS, cardiogenic shock; eCPR, extracorporeal cardiopulmonary resuscitation; SE, Standard Error; Unadj, unadjusted Odds Ratio.

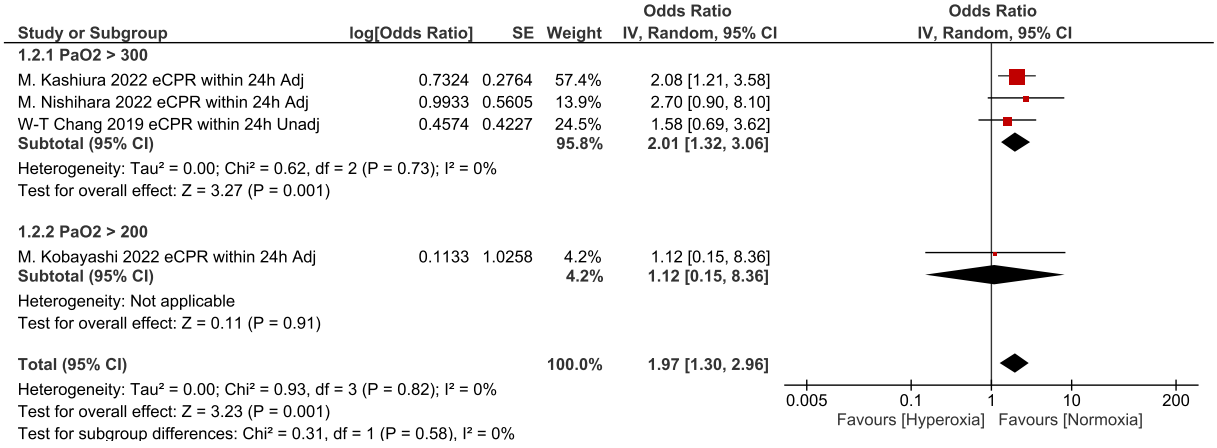

Fig. 3 – Forest plot of poor neurological outcome in patients supported by Veno-Arterial Extracorporeal Membrane Oxygenation (for extracorporeal cardiopulmonary resuscitation, eCPR) according to exposure to hyperoxemia or normoxemia. Subgroup analysis is conducted according to the PaO_2 cut-offs used to define hyperoxemia. Results are reported in Odds Ratio with Inverse Variance (IV) method and 95% Confidence Interval (CI). Adj, adjusted Odds Ratio; SE, Standard Error; Unadj, unadjusted Odds Ratio.

et al.[26] or Nishihara et al.[30] the association was borderline ($p = 0.05$). For the poor neurological outcome, the results of four analyses with *"leave-one-out at time"* approach confirmed the significant association with hyperoxemia three times, and yielded a not significant result when removing Kashiura et al.[28] ($p = 0.06$).

As mentioned, Shou et al.[26] did not report neurological outcome according CPC/mRS. Another study[34] was excluded as classified patients according to the duration of hyperoxemia and not to exposure. After the inclusion of one or both of these studies, the overall association between exposure to hyperoxemia and worse neurological outcome remained significant.

Only the study of Li et al.[31] conducted in the CS population and using a PaO_2 cut-off of 200 mmHg had intermediate risk of bias. When removing this study, mortality remained significantly associated with hyperoxemia ($p = 0.01$), but its association was lost in the subgroup with CS.

Post-hoc analysis

We performed one post-hoc analysis after we noted that the majority of the included studies divided groups according to PaO_2 values obtained at the same timepoint (24 hours after initiation of VA ECMO support). Such analysis included six studies, and confirmed a significant association between hyperoxemia and mortality, with even

Table 3 – Grade of the Evidence. Question: Does the exposure to hyperoxemia during the first 72 hours after veno-arterial extracorporeal membrane oxygenation (VA-ECMO) initiation affect outcomes? Setting: VA ECMO initiated for cardiogenic shock or extracorporeal membrane oxygenation. CI: confidence interval; OR: odds ratio.

CERTAINTY ASSESSMENT							SUMMARY OF FINDINGS		
							Effect		Certainty
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative (95% CI)	Absolute (95% CI)	
MORTALITY									
9	Observational studies	Not serious	Not serious[a]	Not serious	Not serious	None	**OR 1.80** (1.16–2.78)	**2 fewer per 1.000** (from 3 fewer to 1 fewer)	⊕⊕○○ Low
POOR NEUROLOGICAL OUTCOME									
4	Observational studies	Not serious	Not serious	Not serious	Not serious	None	**OR 1.97** (1.30–2.96)	**2 fewer per 1.000** (from 3 fewer to 1 fewer)	⊕⊕○○ Low

greater OR 2.43 (1.92–3.07); $p < 0.0001$) and lower statistical heterogeneity ($I^2 = 28\%$).

Discussion

The main finding of our study is that exposure to hyperoxemia after initiation of VA ECMO is significantly associated with almost doubled incidence of mortality or poor neurological outcome (ORs 1.80 and 1.97, respectively). Notably, the magnitude and the direction of findings were confirmed in the subgroup analyses according to the indication for starting VA ECMO (CS or eCPR) or to the cut-off used to define hyperoxemia (200 vs. 300 mmHg), although in the subgroup of eCPR patients this association failed to reach statistical significance.

Some considerations strengthen our results: (1) findings were confirmed in most of the sensitivity analyses; (2) the analysis pooled a large amount of data (over 10,000 patients for mortality, over 1300 for neurological outcome); (3) the post-hoc analysis of studies using the same timepoint (24 hours after initiation) showed even greater OR for mortality (2.43) with lower heterogeneity. Moreover, harmful effects of hyperoxemia have been also suggested for pediatric populations of critically ill patients supported by VA ECMO.[35] It should be also considered that further five adult VA ECMO studies could not be included in our meta-analysis for a different approach in data reporting, and all of them suggest negative impact of high PaO_2. Three of these studies were conducted in the eCPR population. Bonnemain et al.[36] found significantly higher mean PaO_2 values over the first 24 hours in non-survivors (306 mmHg vs. 164 mmHg); Hong et al.[37] found that patients in the highest PaO_2 tertile (>160 mmHg) had significantly higher mortality. Tonna et al.[38] found that those with higher PaO_2 values within 24 hours had higher mortality (OR = 1.45, $p < 0.001$). Similarly, the other two studies (unselected VA ECMO populations) showed significant association between higher PaO_2 values and mortality.[39,40] However, when we restricted our analysis to adjusted ORs only, the analysis did not confirm the findings of the primary analyses (OR = 1.68, $p = 0.11$). We think that, despite the GRADE suggests low certainty of evidence (observational studies), the sample size and the quality of the data suggests discrete robustness of our findings. In truth, a higher level of evidence may only come from randomized controlled trials (RCTs), but randomizing critically ill patients to severe hyperoxemia would be unethical.[41–47] Conversely, it could be possible to perform a RCT assessing whether exposure to mild hyperoxemia could be advantageous.

We conducted subgroup analyses according to the cut-off used for the definition of hyperoxemia. Whilst most studies used 300 mmHg,[18,19,25–30] others have been more conservative (200 mmHg),[31,32] or sporadically used a higher threshold (400 mmHg).[28] In our study, the association between mortality and exposure to hyperoxemia was confirmed in both subgroup analyses (200 and 300 mmHg). The presence of most studies using the same cut-off (>300 mmHg) had the value of reducing the clinical heterogeneity of our findings; however, this leaves uncertainty whether a lower degree of hyperoxemia (>200 mmHg) could be harmful. Interestingly, a recent sub-analysis from a RCT in patients resuscitated after CA confirmed a "U-shape" effect of PaO_2 levels on mortality. Indeed, the authors identified 197 mmHg as the best cut-off for predicting an increase in mortality,[47] a value very close to the 200 mmHg cut-off used by some included studies. Moreover, in a population undergoing eCPR, Chang et al.[33] identified the PaO_2 range of 77–220 mmHg (OR = 2.29) as the best interval for favorable neurological outcome, again suggesting that 200 mmHg may be the most likely correct threshold of severe hyperoxemia. More data would be certainly desirable to guide clinicians dealing with VA ECMO in the adjustment of the fraction of oxygen at the gas-blender (FbO_2).

We also analyzed subgroups according to the indication for starting VA ECMO support, namely CA or CS. In this case the subgroup analysis was conducted for mortality only, as studies on CS did not report neurological outcome. These subgroup analyses point in the same direction, although the association between mortality and exposure to hyperoxemia was not confirmed in the eCPR population (OR = 2.00; $p = 0.13$). Our results provide further support to the recent European Resuscitation Council guidelines that suggest avoidance of hyperoxemia after return of spontaneous circulation and to target oxygen saturation 94–98% in the post-resuscitation period.[46] Further, another large meta-analysis suggested, both

worse survival and neurological outcome in CA patients experiencing severe hyperoxemia.[43]

Our meta-analysis represents the first attempt to pool data on the impact of hyperoxemia episodes after VA ECMO cannulation in patients experiencing CA or CS. Our results suggest that clinical efforts should be made to avoid severe hyperoxemia. While it is difficult to clearly define a PaO_2 threshold, it seems reasonable to avoid prolonged exposure to values above 200 mmHg and specially to keep the PaO_2 below 300 mmHg. A simple action that could be practically suggested is to avoid high FbO_2 at the time of cannulation unless concomitant severe respiratory failure is present. Two ongoing large RCTs on VA ECMO patients (BLENDER-NCT03841084[45]; ECMOxy-NCT04990349[48]) are studying different targets of post-oxygenator saturations achieved modifying the FbO_2; however, these studies are not targeting high levels of PaO_2 and will not provide meaningful data on exposure to severe hyperoxemia.

Limitations

Our meta-analysis has some limitations. First, pooling results from observational studies we obtained a low certainty of evidence. Moreover, even if the risk of bias in the included studies was in most cases deemed low, this should not be misunderstood and considered as equal high-quality evidence. Nonetheless, we analyzed a large pool of data and sensitivity analyses mostly supported the primary results. It should be considered that observational studies on this specific topic probably remain the only available and ethical approach to understand whether severe hyperoxemia may be harmful. As mentioned, at least five studies that could not be included, provided additional evidence on the harmful effects of hyperoxemia.[36–40] Second, we could not evaluate the impact of the duration of exposure to severe hyperoxemia nor if a very early exposure (i.e. <6 hours) is more harmful than exposure at later period. Notably, six studies referred to the exposure to hyperoxemia at 24 hours after cannulation, and the analysis of these studies only showed greater OR for mortality (2.43). Third, several factors may act as potential confounders on hyperoxemia. In this regard, the peripheral cannulation and the underlying cardiac contractility may determine differences in PaO_2 according to the site of sampling. Not all studies confirmed whether they used the right radial artery for arterial blood gas sampling. Fourth, as most results were reported as OR, a trial sequential analysis to assess robustness of results was not feasible.[24] Fifth, we carefully avoided the overlap between data from two studies reporting data on the mortality outcome from the ELSO Registry.[26,29] However, we cannot exclude that some of the other included studies provided data that marginally contributed to Registry itself. If this had happened, it is possible that some degree of patient's overlap has took place.

Conclusions

The exposure to hyperoxemia after the initiation of VA-ECMO for cardiogenic shock or cardiac arrest may be associated with increased probability of poor neurological outcome and mortality. Despite the limitations due to retrospective data, clinical efforts should be made to avoid severe hyperoxemia during VA-ECMO support. However, the effects of the duration of the exposure to high levels of PaO_2 remain uncertain.

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Funding

No authors received funding for undertaking this project.

Authors' contributions

The systematic search was conducted by three authors (ST, LLV, FS). Two pairs of assessors screened independently titles of the systematic search according to the PECOS criteria (AC and CL). Articles categorized as included and dubious were subsequently cross-checked by two other authors (ST and LLV). Two authors downloaded the full texts of the articles identified as potentially relevant (ST, FS). These articles were assessed against eligibility criteria by three authors (ST, SR, and GL), and discordances were resolved discussing with the senior author (FS). Two authors entered information of the included studies into a pre-designed data collection form (AC and CL). Three authors (MV, SR and GL) explored the references of the included studies to identify further studies of interest. All the authors conducted also an independent search on Medline to check for further evidence. Analyses (primary and sensitivity) were conducted by three authors (ST, MV and FS) and cross-checked by two authors (AC and CL). Grade of evidence was performed by two authors (LLV and FS), and subsequently discussed with other three authors (MV, SR and GL). Two authors wrote the draft of the manuscript (ST and FS), which was critically revised by all the other authors. The final version of the manuscript has been read and approved by all the authors listed.

CRediT authorship contribution statement

Stefano Tigano: Visualization, Formal analysis, Data curation, Conceptualization. **Alessandro Caruso:** Visualization, Investigation, Data curation. **Calogero Liotta:** Visualization, Investigation, Data curation. **Luigi La Via:** Visualization, Formal analysis, Data curation. **Maria Vargas:** Visualization, Validation, Methodology. **Stefano Romagnoli:** Visualization, Formal analysis, Data curation, Conceptualization. **Giovanni Landoni:** Writing – review & editing, Validation, Supervision. **Filippo Sanfilippo:** Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Formal analysis.

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.

Appendix A. Supplementary material

Supplementary material to this article can be found online at https://doi.org/10.1016/j.resuscitation.2023.110071.

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