Supplementary Online Content

Lilien TA, Groeneveld NS, van Etten-Jamaludin F, et al. Association of arterial hyperoxia with outcomes in critically ill children: a systematic review and meta-analysis. *JAMA Netw Open*. 2022;5(1):e2142105. doi:10.1001/jamanetworkopen.2021.42105

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Search strategy

Database	**MEDLINE (OVID)**	
Searched from	**1946 to February 01, 2021**	
#	**Searches**	**Results**
1	Intensive Care Units, Pediatric/	8127
2	(Critical Illness/ or Critical Care/) and (exp Child/ or Pediatrics/)	7984
3	(PICU or PICUs or pediatric ICU* or paediatric ICU* or pediatric intensive care or paediatric intensive care).ti,ab,kf,kw.	11908
4	(critical* adj3 child*).ti,ab,kw,kf.	5910
5	1 or 2 or 3 or 4	22680
6	Hyperoxia/	3829
7	(hyperoxi* or hyperoxemi* or hyperoxaemi* or PAO2 or PO2 or FIO2).ti,ab,kw,kf.	38728
8	((high or increased or elevated or supraphysiol*) adj3 oxygen adj3 (concentra* or tension* or pressure* or level*)).ti,ab,kw,kf.	5801
9	(oxygen adj3 (supplement* or therap* or suppl* or administra* or inspir*)).ti,ab,kw,kf.	35694
10	(arteria* adj3 oxygen adj3 (concentra* or tension* or pressure* or level*)).ti,ab,kw,kf.	6743
11	6 or 7 or 8 or 9 or 10	77518
12	5 and 11	621
Database	**EMBASE (OVID)**	
Searched from	**1947 to February 01, 2021**	
#	**Searches**	**Results**
1	pediatric intensive care unit/	7209
2	(critically ill patient/ or critical illness/ or intensive care/) and (exp child/ or pediatrics/)	25652
3	(PICU or PICUs or pediatric ICU* or paediatric ICU* or pediatric intensive care or paediatric intensive care).ti,ab,kw.	21148
4	(critical* adj3 child*).ti,ab,kw.	8673
5	1 or 2 or 3 or 4	44904
6	hyperoxia/	10441
7	(hyperoxi* or hyperoxemi* or hyperoxaemi* or PAO2 or PO2 or FIO2).ti,ab,kw.	60208
8	((high or increased or elevated or supraphysiol*) adj3 oxygen adj3 (concentra* or tension* or pressure* or level*)).ti,ab,kw.	7937
9	(oxygen adj3 (supplement* or therap* or suppl* or administra* or inspir*)).ti,ab,kw.	51850
10	(arteria* adj3 oxygen adj3 (concentra* or tension* or pressure* or level*)).ti,ab,kw.	9189
11	6 or 7 or 8 or 9 or 10	115973
12	5 and 11	1505
Database	**Cochrane Central Register of Controlled Trials**	
Searched from	**Inception to February 2021**	
#	**Searches**	**Results**
1	(PICU or PICUs or pediatric ICU* or paediatric ICU* or pediatric intensive care or paediatric intensive care):ti,ab,kw	2601
2	MeSH descriptor: [Intensive Care Units, Pediatric] explode all trees	1054
3	#1 or #2	3322
4	MeSH descriptor: [Critical Illness] explode all trees	2303
5	MeSH descriptor: [Critical Care] this term only	1738
6	MeSH descriptor: [Child] explode all trees	56347
7	(#4 or #5) and #6	226
8	#3 or #7	3396

#	Searches	Results
9	MeSH descriptor: [Hyperoxia] explode all trees	204
10	(hyperoxi* or hyperoxemi* or hyperoxaemi* or PAO2 or PO2 or FIO2):ti,ab,kw	5963
11	((high or increased or elevated or supraphysiol*) near/3 oxygen near/3 (concentra* or tension* or pressure* or level*)):ti,ab,kw	397
12	(oxygen near/3 (supplement* or therap* or suppl* or administra* or inspir*)):ti,ab,kw	9619
13	(arteria* near/3 oxygen near/3 (concentra* or tension* or pressure* or level*)):ti,ab,kw	2261
14	#9 or #10 or #11 or #12 or #13	15171
15	#8 and #14 in Trials	338

eTable 2. Newcastle-Ottawa-Score for quality of cohort studies.

	Selection				Comparability	Outcome			
Study	Representativeness of cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome of interest	Comparability of cohorts	Assessment of outcome	Adequate duration of follow-up	Adequate follow-up of cohort	Total score
Bennett et al,[1] 2013	A*	A*	A*	A*	B*	B*	A*	A*	8
Cashen et al,[2] 2018	B*	A*	A*	A*	B*	A*	A*	B*	8
Del Castillo et al,[3] 2012	B*	A*	A*	A*	-	A*	A*	B*	7
Ferguson et al,[4] 2012	A*	A*	A*	A*	A* B*	A*	A*	A*	9
Guerra-Wallace et al,[5] 2013	A*	A*	A*	A*	-	A*	A*	A*	7
Ketharanathan et al,[6] 2020	A*	A*	A*	A*	-	A*	A*	A*	7
Kraft et al,[7] 2017	B*	A*	A*	A*	A*B*	A*	A*	B*	9
López-Herce et al,[8] 2014	A*	A*	A*	A*	-	A*	A*	A*	7
Numa et al,[9] 2018	A*	A*	A*	A*	A*	A*	A*	A*	8
Pelletier et al,[10] 2020	A*	A*	A*	A*	A*	A*	A*	A*	8
Peters et al,[11] 2018	NA	NA	NA	NA	NA	NA	NA	NA	NA
Raman et al,[12] 2016	B*	A*	A*	A*	A*B*	A*	A*	A*	9
Ramgopal et al,[13] 2019	A*	A*	A*	A*	A*	A*	A*	A*	8

Study	Representativeness of cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome of interest	Comparability of cohorts	Assessment of outcome	Adequate duration of follow-up	Adequate follow-up of cohort	Total score
Ramgopal et al,[14] 2020	A*	A*	A*	A*	A*	A*	A*	A*	8
Sznycer-Taub et al,[15] 2016	A*	A*	A*	A*	-	A*	A*	A*	7
Van Zellem et al,[16] 2015	A*	A*	A*	A*	B*	A*	A*	A*	8

Comparability of cohorts: A for severity of disease score, B for age.

eTable 3. Overview of all assessed outcomes in this review that were reported in included studies.

Study \ Outcome	28-day mortality	In-PICU mortality	In-hospital mortality	6-month mortality	Incidence of IMV	Duration of IMV	Duration of respiratory support	Incidence of AKI	Incidence of organ support	Duration of organ support	Length of stay PICU	Length of stay hospital	Neurological outcome (PCPC)	Long-term functional score	Long-term lung function
Bennett et al,[1] 2013			■		Not reported by any study		Not reported by any study		■		■	■	■	Not reported by any study	Not reported by any study
Cashen et al,[2] 2018			■					■		■	■	■			
Del Castillo et al,[3] 2012			■												
Ferguson et al,[4] 2012			■					■	■						
Guerra-Wallace et al,[5] 2013				■											
Ketharanathan et al,[6] 2020		■													
Kraft et al,[7] 2017			■								■	■			
López-Herce et al,[8] 2014			■										■		
Numa et al,[9] 2018		■													
Pelletier et al,[10] 2020			■												
Peters et al,[11] 2018		■				■				■	■				
Raman et al,[12] 2016	a	a	a	a											
Ramgopal et al,[13] 2019			■												
Ramgopal et al,[14] 2020			■												
Sznycer-Taub et al,[15] 2016	b		■						■		■	■			
Van Zellem et al,[16] 2015			■												

eTable 3. Organ support was defined as extra corporeal membrane oxygenation or continuous venovenous hemodialysis. a, Raman et al did not specify at what time point mortality was assessed; b, Sznycer-Taub et al.[15] assessed mortality at day 30 and not precisely at day 28; PICU, pediatric intensive care unit; IMV, invasive mechanical ventilation; AKI, acute kidney injury; PCPC, pediatric cerebral performance category.

eTable 4. Other secondary outcomes found in included studies.

Outcome	Hyperoxia (Liberal)[a]	Normoxia (Conservative)[a]	Odds Ratio (95% CI)	*P*-value
Duration of IMV (days)				
Peters et al,[11] 2018; median [IQR]	3 [2-6]	3 [2-6]	NA	1.0
Incidence of AKI				
Cashen et al,[2] 2018; N (Total)	117 (331)	54 (153)	1.00 (0.67-1.50)	0.99
Ferguson et al,[4] 2012; N (Total)	16 (207)	93 (1220)	1.02 (0.58-1.76)	0.96
Incidence of organ support				
Bennet et al,[1] 2013; N (Total)	11 (87)	4 (66)	2.24 (0.68-7.39)	0.184
Ferguson et al,[4] 2012; N (Total)	9 (207)	36 (1220)	1.49 (0.71-3.15)	0.29
Sznycer-Taub et al,[15] 2016; N (Total)	32 (73)	3 (20)	4.42 (1.19-16.42)	**0.026**
Duration of organ support (days)				
Cashen et al,[2] 2018; median [IQR]	4.7 [2.5-8.0]	5.9 [3.1-10.5]	NA	**0.009**
Peters et al,[11] 2018; median [IQR]	0 [0]	0 [0]	NA	NA
Length of stay PICU (days)				
Bennet et al,[1] 2013; median [IQR]	5 [1-16]	6 [2-12.5]	NA	NA
Cashen et al,[2] 2018; median [IQR]	25.0 [12.8-48.2]	30.5 [15.6-54.0]	NA	**0.045**
Kraft et al,[7] 2017; mean ±SD	24.5 ±15.9	30.7 ±25.2	NA	**0.039**
Peters et al,[11] 2018; median [IQR]	6 [4-11]	5 [4-8]	NA	0.292
Sznycer-Taub et al,[15] 2016; median [IQR]	21 [14-42]	28.5 [20-52]	NA	0.08
Length of stay hospital (days)				
Bennet et al,[1] 2013; median [IQR]	9 [1-29]	7 [3-17]	NA	NA
Cashen et al,[2] 2018; median [IQR]	33.2 [13.4-67.5]	39.1 [19.7-64.8]	NA	0.231
Kraft et al,[7] 2017; mean ±SD	43.3 ±30.2	58.9 ±46.9	NA	**0.0003**
Sznycer-Taub et al,[15] 2016; median [IQR]	28 [18-63]	48 [31-64]	NA	0.09
Neurological outcome (PCPC)				
Bennett et al,[1] 2013; ≤2[b] N (Total)	30 (87)	37 (88)	1.02 (0.46-2.27)[c]	0.96

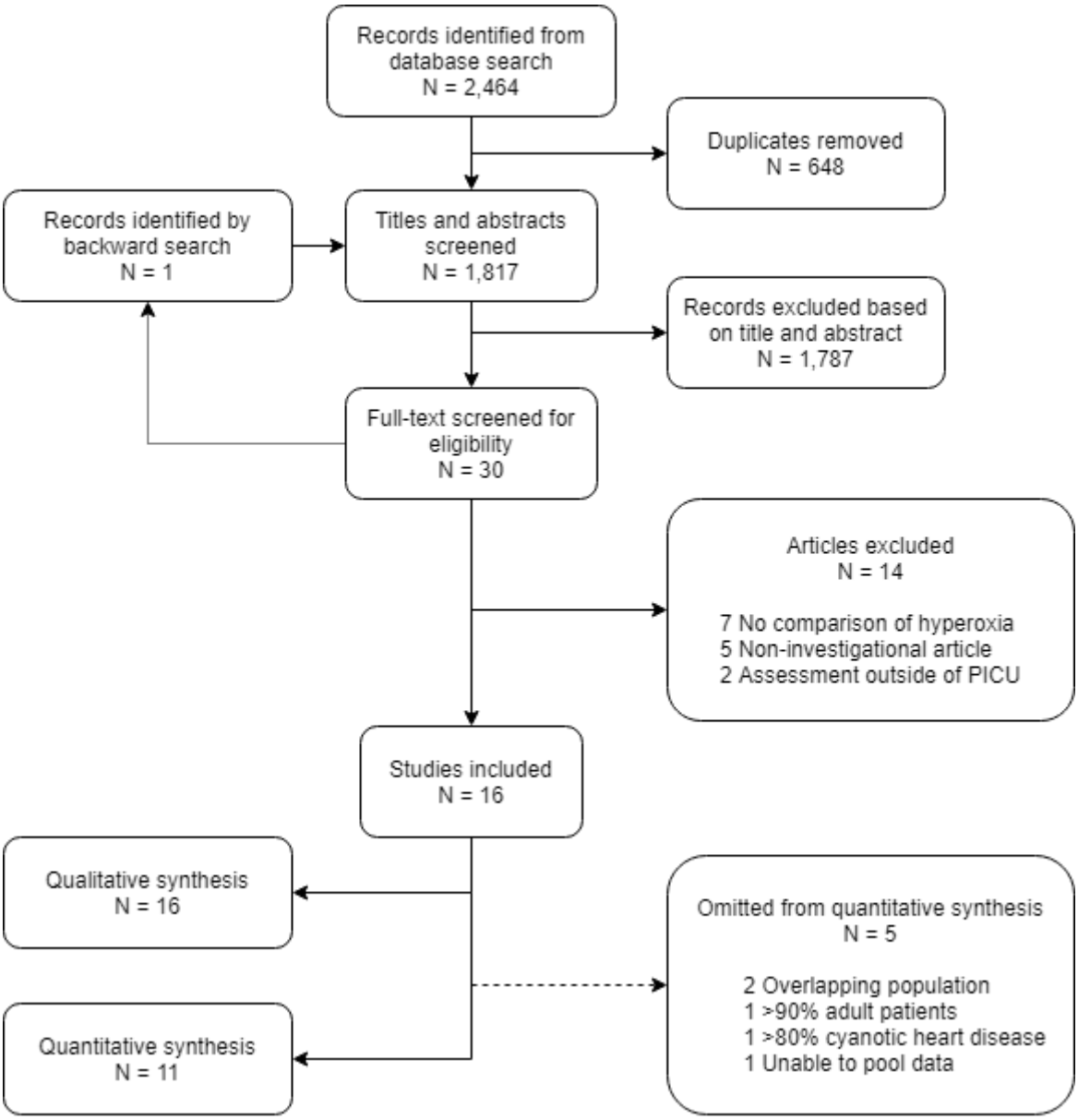
Outcome	Hyperoxia (Liberal)[a]	Normoxia (Conservative)[a]	Odds Ratio (95% CI)	*P*-value
Neurological outcome (PCPC)				
López-Herce et al,[8] 2014; >2 %	16.7[d]	33.3[d]	0.400 (0.103-1.553)	0.186

eTable 4. a, Liberal or Conservative oxygenation applies to Peters et al[11]; b, Or no change if pre-admission PCPC was above 2; c, Adjusted odds ratio; d, PaO2 1h after cardiac arrest. PICU, pediatric intensive care unit; CI, confidence interval; IQR, interquartile range; NA, not available; SD, standard deviation; IMV, invasive mechanical ventilation; AKI, acute kidney injury; PCPC, pediatric cognitive performance category.

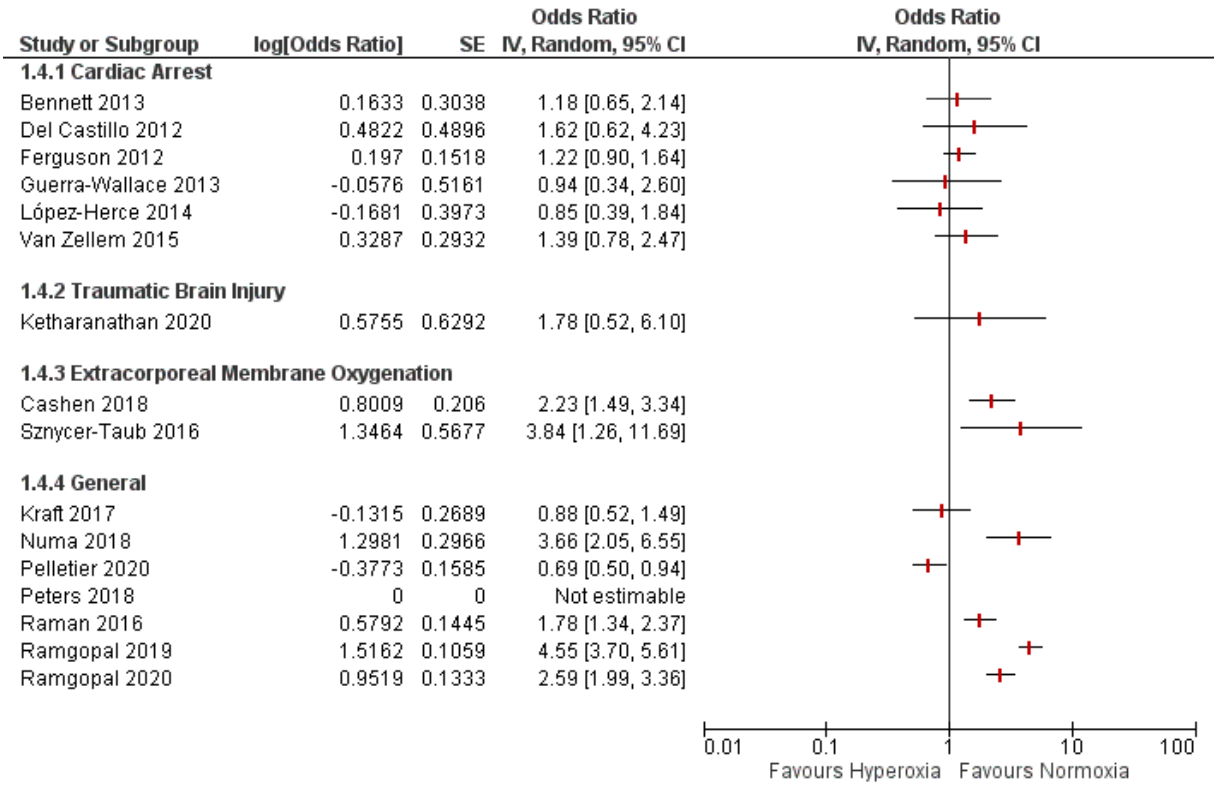
eTable 5. *P* curve summary of statistics.

		Full Curve		Half Curve		Evidential Value	
	$P_{Binomial}$	z_{Full}	P_{Full}	z_{Half}	P_{Half}	Present	Absent
Right-Skewness Test	0.125	-5.424	0	-5.059	0	Yes	No
Flatness Test	1.000	3.728	1	4.231	1		

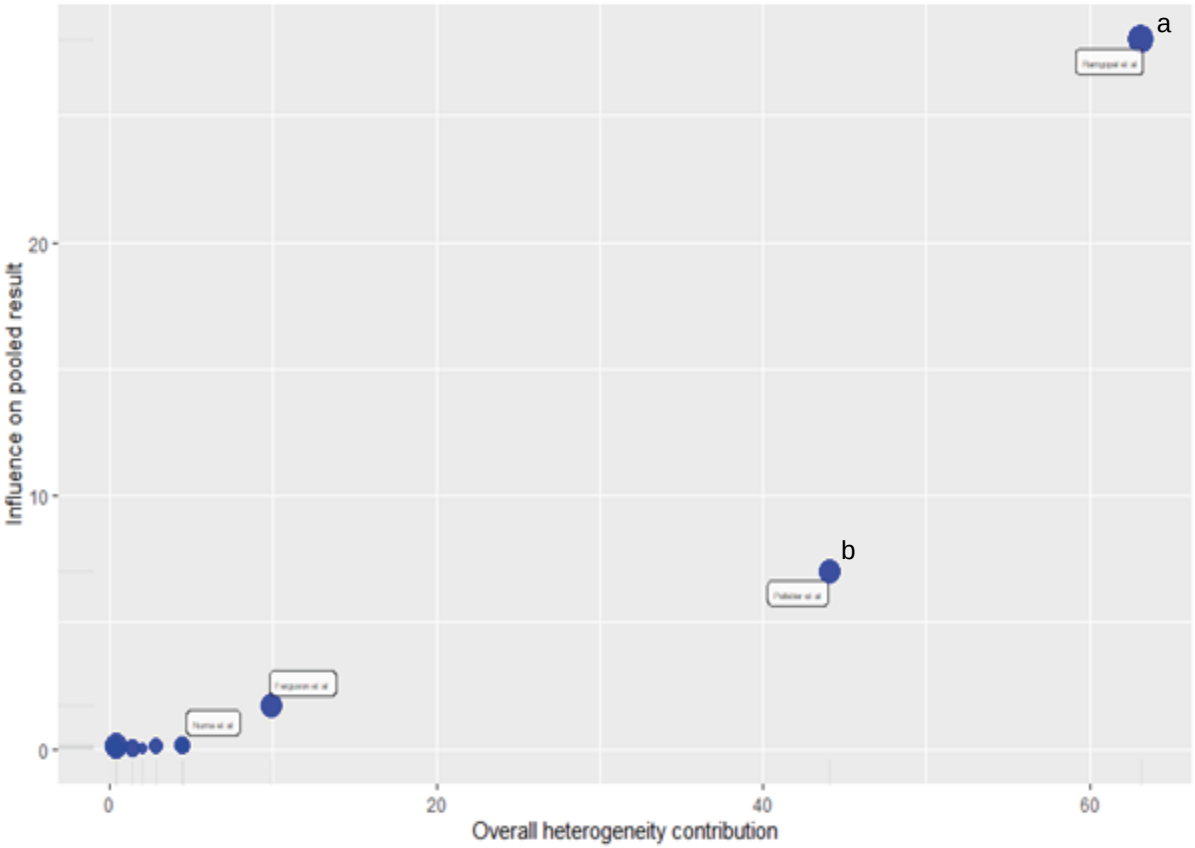
eFigure 1. PRISMA Flowchart of study screening process



eFigure 2. Forest Plot of Hyperoxia (categorical) and Mortality, longest follow-up, stratified by Case mix

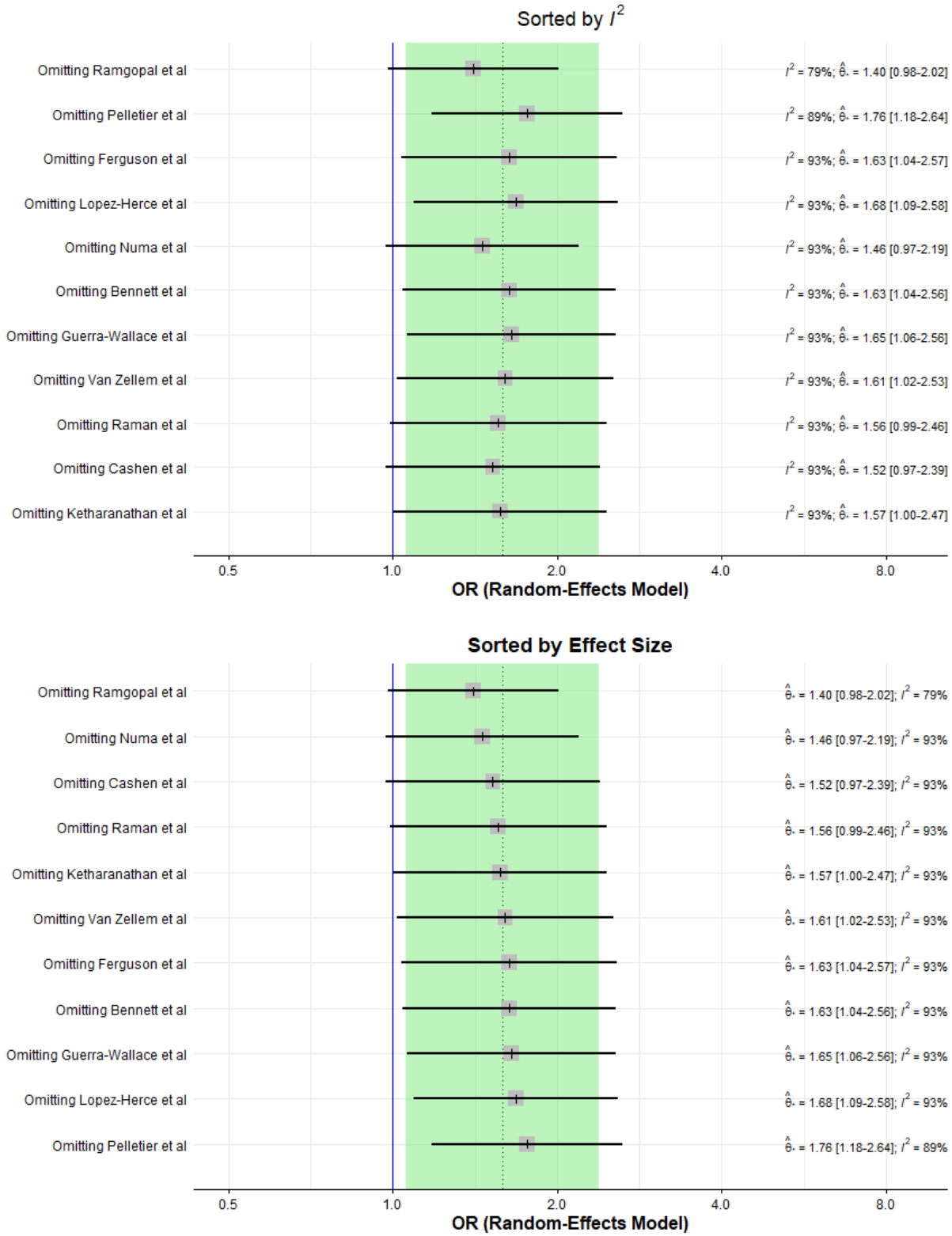


eFigure 3 Bajaut plot of the contribution to the overall heterogeneity and pooled effect estimate of each study



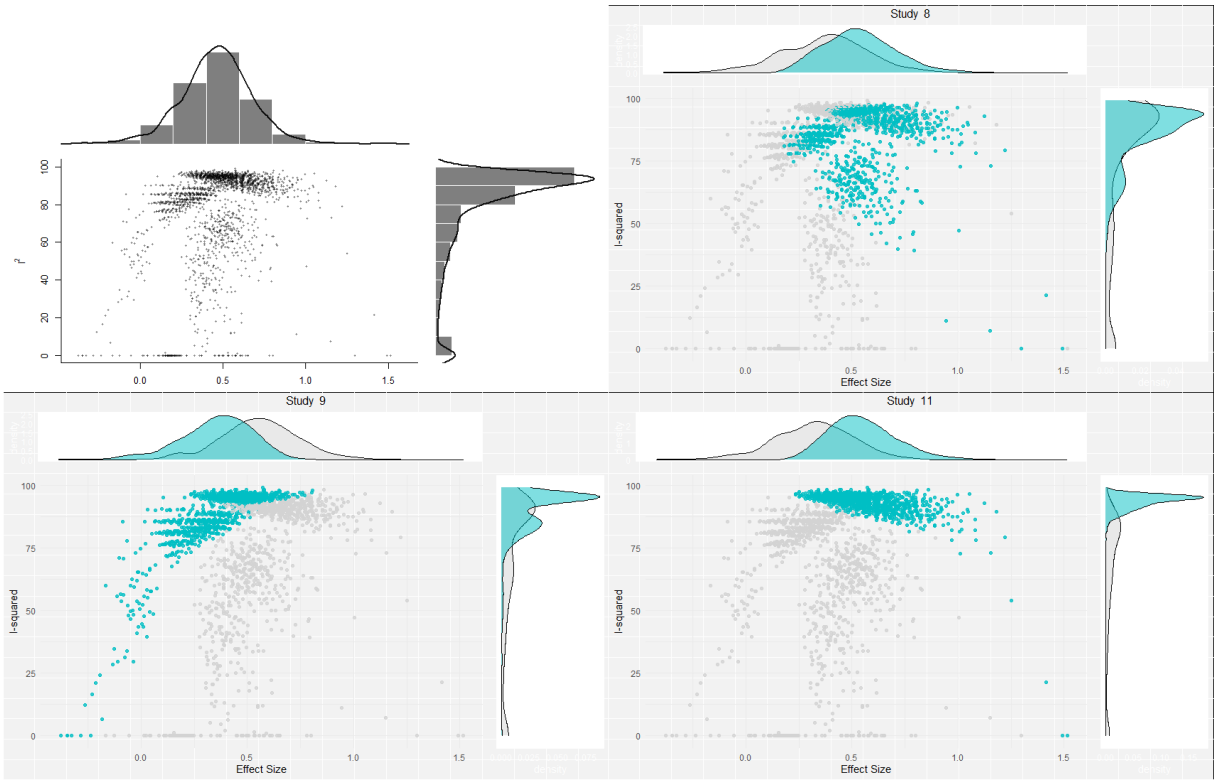
eFigure 3. a, Ramgopal et al.[14]; b, Pelletier et al.[10]

eFigure 4 Leave-One-Out plots sorted by the effect on overall heterogeneity and the pooled effect estimate



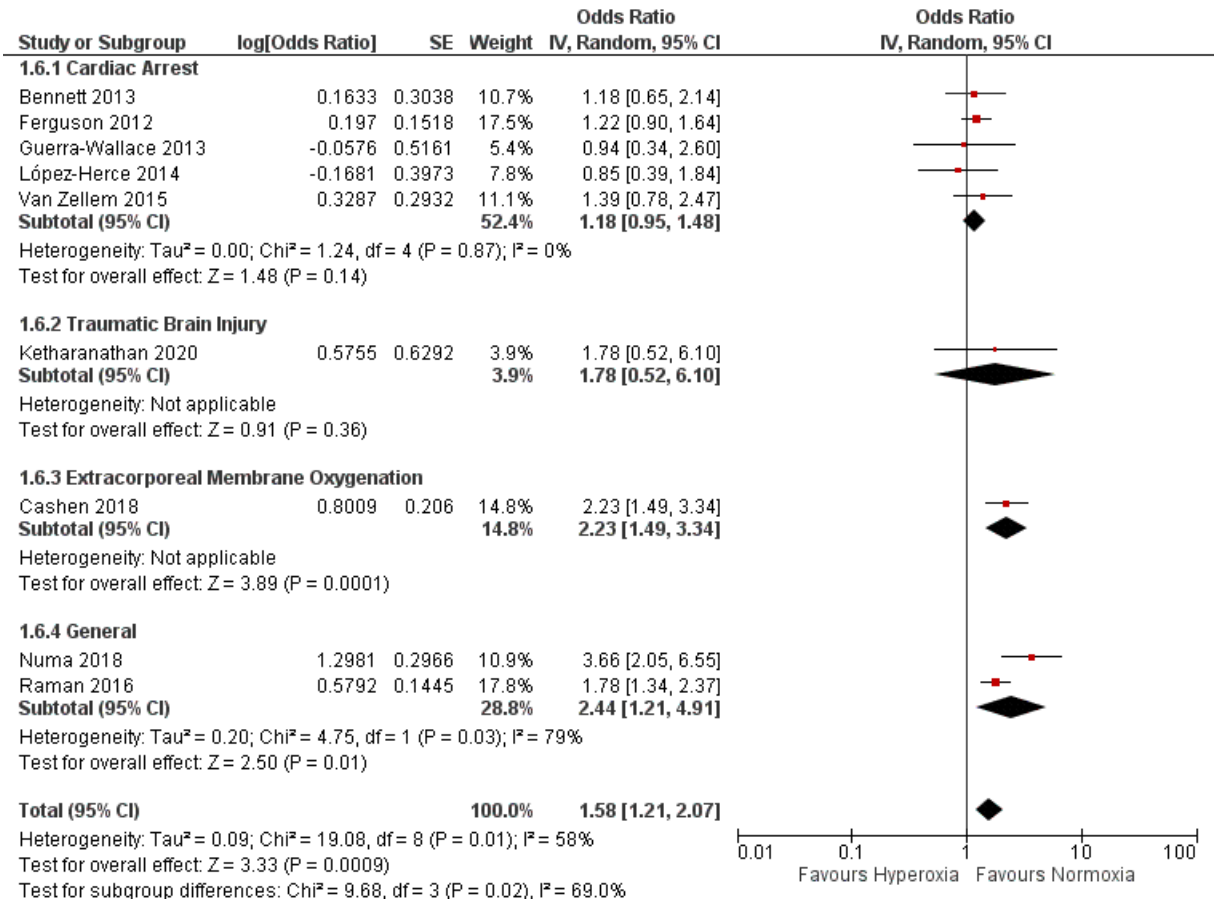
OR, odds ratio.

eFigure 5. GOSH plot of all subsets of studies with the overall heterogeneity and estimated pooled effect size and the three outlying studies based on the GOSH plot

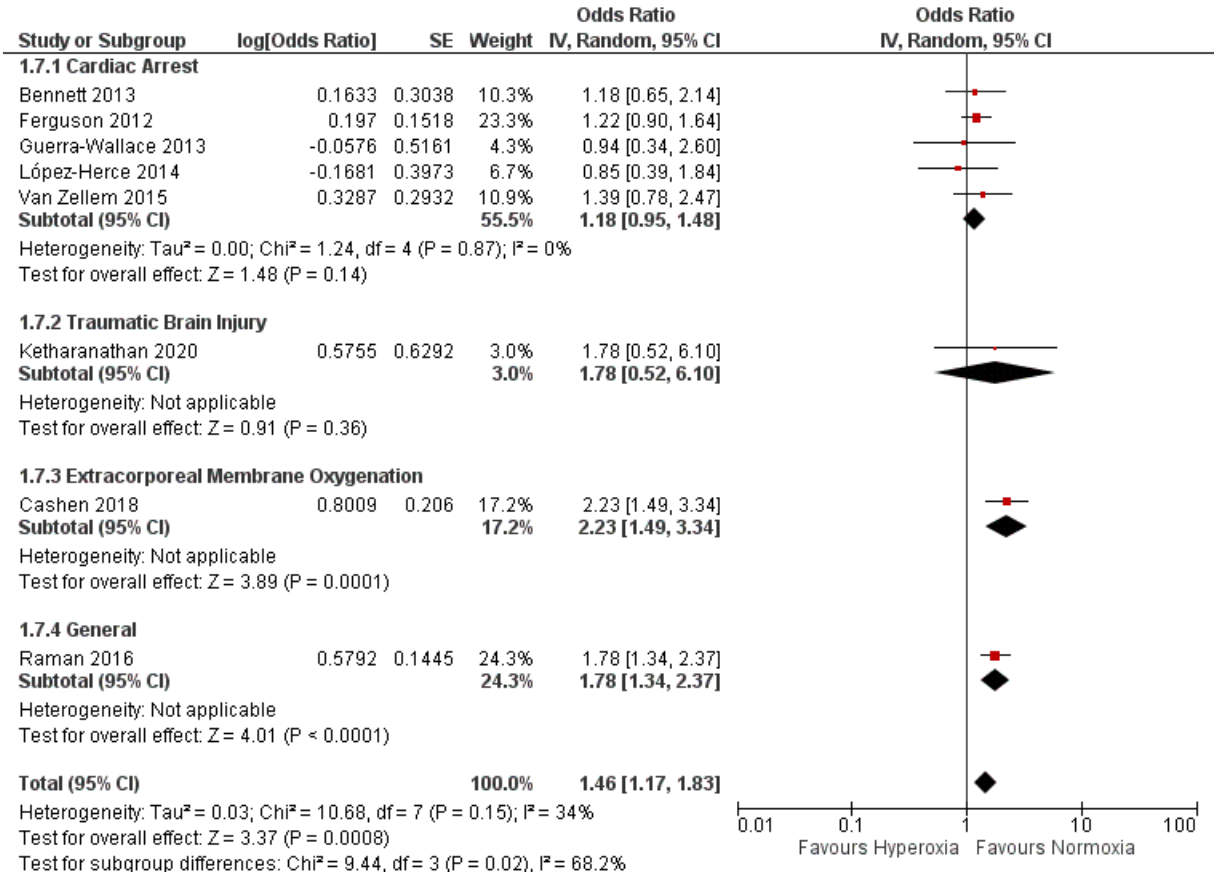


eFigure 5. Top left, GOSH-plot of all simulated subsets of studies; Study 8 (top right), Numa et al.[9]; Study 9 (bottom left), Pelletier et al[10]; Study 11 (bottom right), Ramgopal et al.[13]; GOSH, Graphic Display of Heterogeneity.

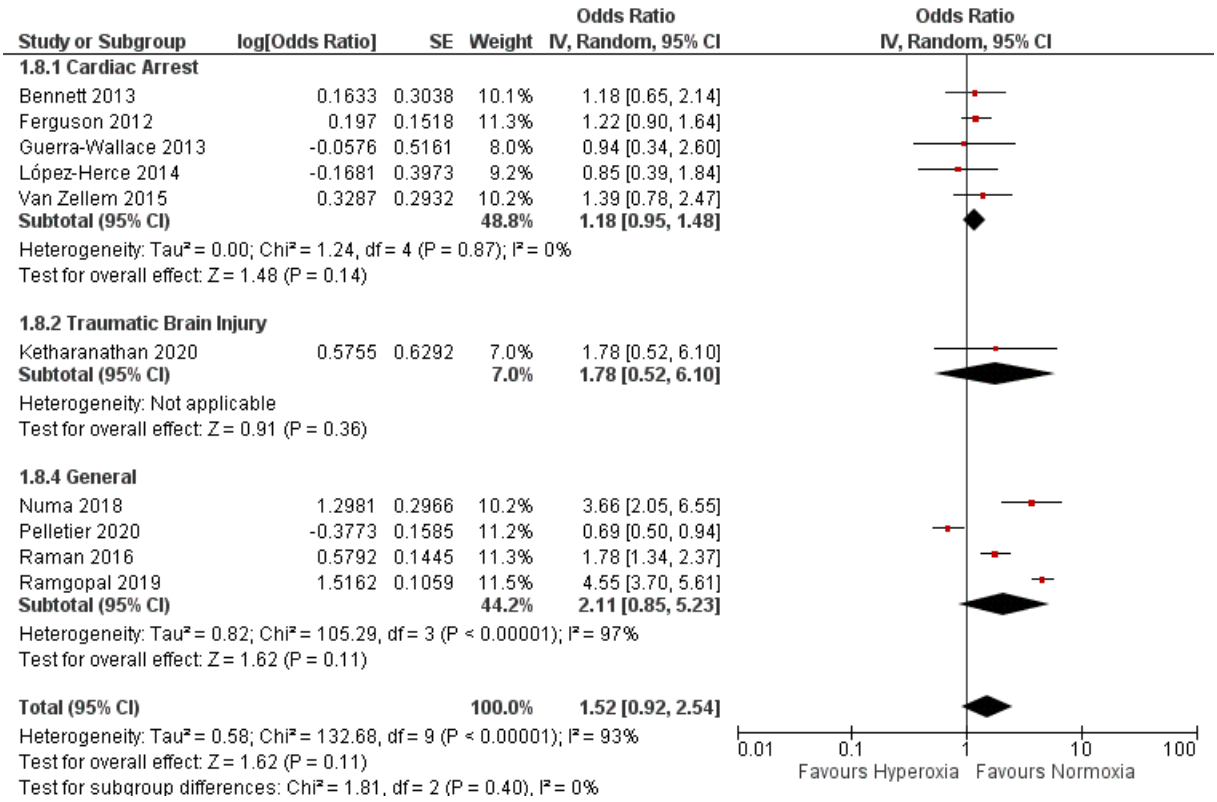
eFigure 6. Sensitivity analysis 1: excluding pronounced outliers



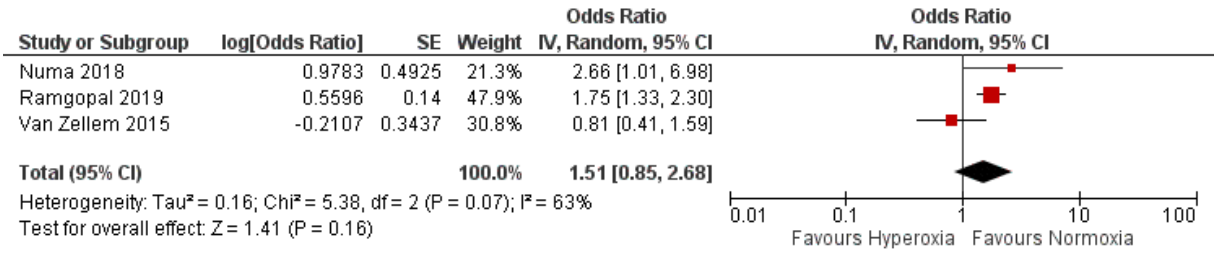
eFigure 7. Sensitivity analysis 2: excluding pronounced and potential outliers



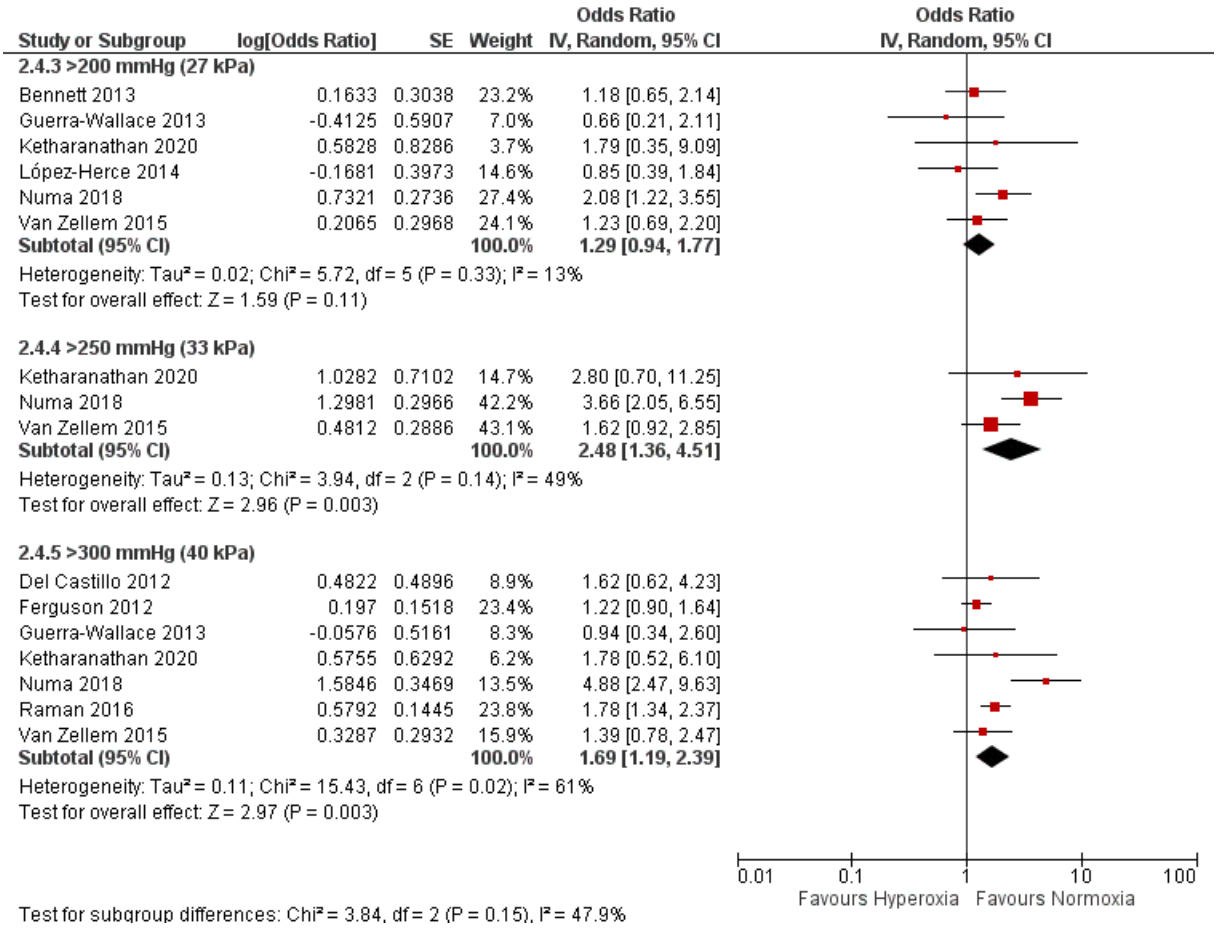
eFigure 8. Sensitivity analysis 3: excluding studies with only patients on ECMO support



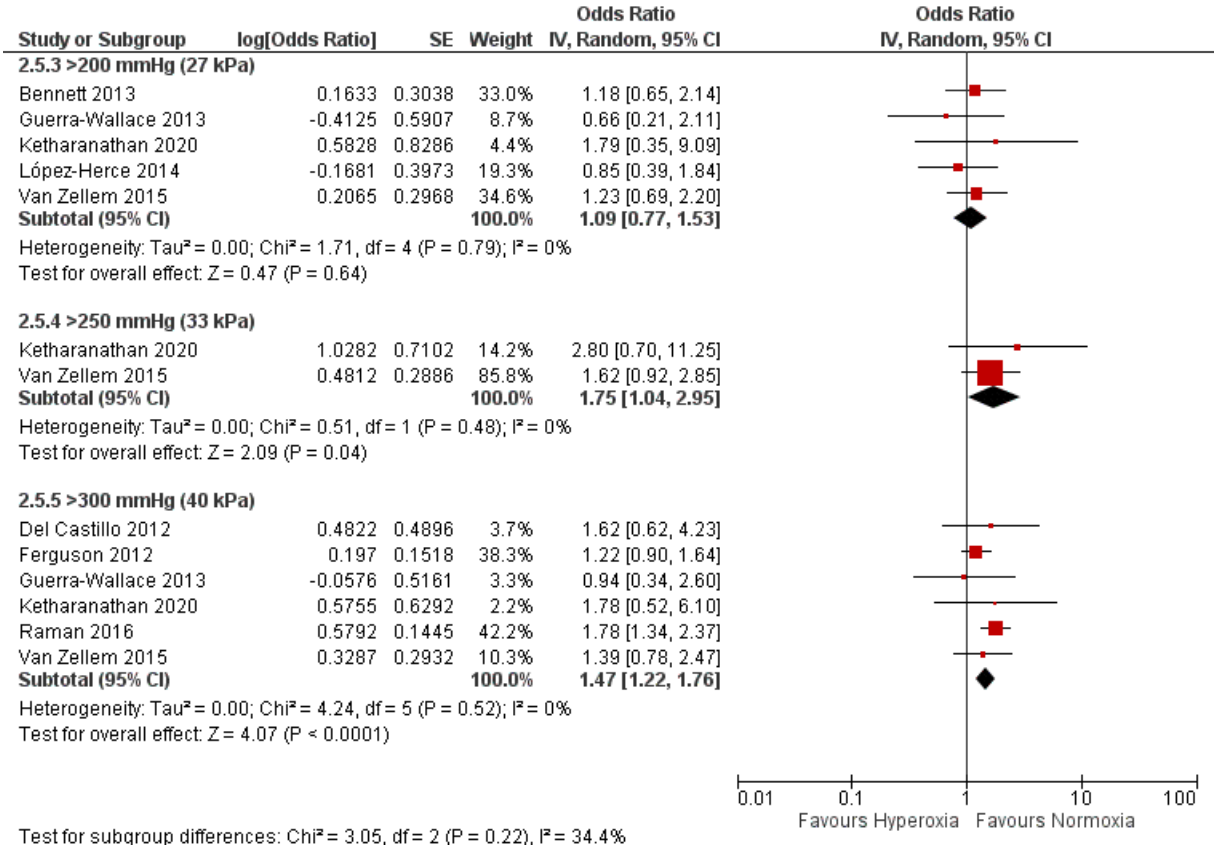
eFigure 9. Sensitivity analysis 4: including only studies with adjusted odds ratio for mortality



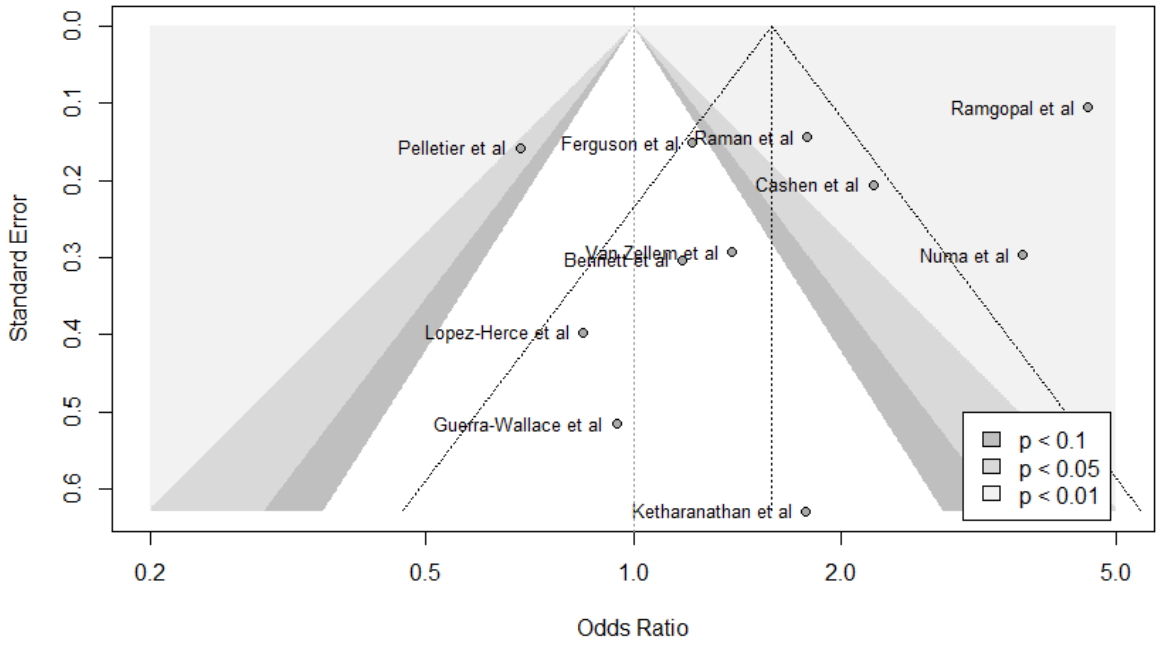
eFigure 10. Random-Effects Meta-analysis of Hyperoxia (Categorical) and Mortality, Longest Follow-up, Stratified by the Threshold of Hyperoxia With Exclusion of Pronounced Outlying Studies and Those Including Only Patients on ECMO Support (Subtotals)



eFigure 11. Random-Effects Meta-analysis of Hyperoxia (Categorical) and Mortality, Longest Follow-up, Stratified by the Threshold of Hyperoxia With Exclusion of Pronounced and Potential Outlying Studies and Those Including Only Patients on ECMO Support (Subtotals)



eFigure 12. Funnel plot of included studies in the main quantitative synthesis



eReferences

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