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Supplementary appendix

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Awake Prone Positioning for Non-intubated Patients with COVID-19 Related Acute Hypoxaemic Respiratory Failure: A Systematic Review and Meta-Analysis

Supplementary appendix

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1.1 Authors' contribution

JLi, JGL, CG and SE designed the meta-analysis project.
Two independent groups of investigators (JLi, WT, JLuo on one hand and YP, IP on the other hand) performed literature search, screening, and data extraction.
JLi, IP, SE, and CG contacted trialists for clarification on their data and invited researchers to provide unpublished data.
MIE, DLV, AK, and BM participated in the resolution of discrepancies on data extraction.
JLi, JLuo, YP, IP, WT, and ET had full access to the data and verified the data.
JLuo and ET conducted data analysis.
All authors significantly contributed to the conduct of the meta-analysis.
JLi, JLuo, YP, IP, WT, MIE, DLV, AK, BM, ET, JGL, CG and SE attended bi-monthly web meetings.
JLi drafted the manuscript, all authors reviewed the manuscript for important intellectual content, and approved the final manuscript.
JLi, JLuo, YP, IP, and WT equally contributed to the overall project described in this article.
SE and JLi were responsible for the decision to submit the manuscript.

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2.1 Search strategy

(((((((prone position[MeSH Terms]) OR ("prone positioning"[Title/Abstract])) OR ("Prone Positions"[Title/Abstract])))) OR (PPV[Title/Abstract])) OR ("awake prone position"[Title/Abstract])) OR ("awake prone positioning"[Title/Abstract]))) AND ((((((((((("Oxygen inhalation therapy"[MeSH Terms]) OR ("Oxygen Inhalation"[Title/Abstract])) OR ("Oxygen therapy"[Title/Abstract])) OR ("Respiratory therapy"[Title/Abstract])) OR ("Non-intubated"[Title/Abstract])) OR ("Oxygen support"[Title/Abstract])) OR ("Oxygen supply"[Title/Abstract])) OR (awake[Title/Abstract])) OR ("spontaneous breath"[Title/Abstract])) OR (spontaneously breath[Title/Abstract])) OR ((((HFNC[Title/Abstract]) OR ("high-flow nasal cannula"[Title/Abstract])) OR ("high-flow nasal oxygen"[Title/Abstract])) OR ("high-flow oxygen"[Title/Abstract]))) OR ((((((Noninvasive Ventilation[MeSH Terms]) OR (NIV[Title/Abstract])) OR (NIPPV[Title/Abstract])) OR ("Non-Invasive Ventilation"[Title/Abstract])) OR ("Non invasive Ventilation"[MeSH Terms])) OR (NPPV[Title/Abstract]))) OR ((prone position[MeSH Terms]) OR ("prone positioning”[Title/Abstract]) OR ("Prone Positions”[Title/Abstract]) OR ("awake prone position”[Title/Abstract]) OR ("awake prone positioning”[Title/Abstract])) AND ((COVID-19[MeSH Terms]) OR (SARS-CoV-2[MeSH Terms]))

2.2 Reference list for the included non-RCTs

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Table S1. Demographic details of the included non-RCTs.

Author, year	Country	Enrolment location	Study design	Interventions	Population	Targeting duration of APP	Actual duration of APP (hours)	Age (years)	Sex (Male, %)	BMI (kg/m^2)	Baseline P/F or S/F*	Use of corticosteroids (n, %)	Primary outcomes	Secondary outcomes
Alsharif, 2021	Kingdom of Saudi Arabia		Non RCT, single center, prospective	Usual care (CPAP)	48								The rate of tracheal intubation	The rate of ICU mortality, the length of stay, and the rate of Healthcare Workers infected by SARS-CoV2
				Usual care (CPAP)+APP	31									
Altinay, 2021	Turkey	ICU	Non RCT, single center, retrospective	Usual care (NRM)	23			72·6±10·1	9 (39·1)	26·6±3·1	167·6 (159·5-213·5)		The rate of tracheal intubation	Ventilation free days, length of ICU stay, mortality at 28 days of ICU stay, post intensive care hospitalization or home discharge
				Usual care (NRM)+APP	25	18 hours/day intermittently		62·4±10·9	11 (44·0)	25·1±2·5	175·7 (156·8-193·2)			
Barker, 2021	UK	ICU	Non RCT, single center, retrospective	Usual care (NIV)	10			64±10	6 (60·0)				S/F, recorded after each APP	Admission ISARIC COVID-19 4C mortality score, ICU length of stay, escalation to IMV, and 28-day mortality
				Usual care (NIV)+APP	10	As long as possible		59±6	6 (60·0)					
Fazzini, 2021	UK	General ward	Non RCT, single center, prospective	Usual care (HFNC/Facemask/ CPAP)+APP<1h	12	As long as tolerated		56 (30-79)					Change in P/F and S/F	Change in respiratory rate, work of breathing, shortness of breath, ICU admission, endotracheal intubation, hospital length of stay, 90-day mortality
				Usual care (HFNC/Facemask/ CPAP)+APP>1h	34			56 (22-77)						
Ferrando, 2020	Spain	ICU	Non RCT, multicenter, prospective	Usual care (HFNC)	144	>16 hours/day regardless of the number of sessions		63 (55-71)	104 (72·7)	27·3 (25·1-29·4)	111·0 (83·0-144·0)		Need for invasive mechanical ventilation	Time from onset of symptoms and from hospital admission to initiation of respiratory support, ICU length of stay, and ICU mortality
				Usual care (HFNC)+APP	55			60 (54-70)	41 (75·9)	26·8 (24·8-31·2)	125·0 (99·0-187·0)			
Jagan, 2020	USA		Non RCT, single center, retrospective	APP<1h or <5 occasions per day and for <= 1 continuous hour overnight	65			65·8 ± 16·3	37 (56·9)	28·0 (24·9-34·4)			The need for intubation	Mortality, time to intubation, and changes in S/F, need for ICU admission, ICU length of stay, hospital length of stay, and discharge disposition
				APP>=1h or >=5 occasions per day and for >= 1 continuous hour overnight	40	>= 1 continuous hour or >= 5 occasions per day and for >= 1 continuous hour overnight		56·0 ± 14·4	20 (50·0)	31·3 (26·4-37·5)				
Padrão, 2020	Brazil	ED	Non RCT, single center, retrospective	Usual care (Nasal cannula/Venturi mask/NRM)	109	At least 4 hours in their first session and then twice daily		61·4 ±13·6	72 (66)			4 (3·7)	Endotracheal intubation up to 15 days	6-point clinical outcome ordinal scale, mechanical ventilation-free days, admission to ICU, and need of hemodialysis and of vasoactive drugs, improvement in RR, SpO2, S/F, ROX index
				Usual care (Nasal cannula/Venturi mask/NRM) +APP	57			51·8±13	40 (70)					
Jouffroy, 2021	France	ICU	Non RCT, multicenter, retrospective	Usual care (COT/HFNC/NIV /CPAP)	339	Between 3 and 6 hours per session t wice daily physiotherapy.		62 (53–69)	255 (75·2)	28 (25-32)	138 (98-196)		Intubation at day 10	Intubation at day 28, intubation until ICU discharge, day-28 mortality
				Usual care (COT/HFNC/CPA P)+APP	40			59·5 (56–64)	36 (90·0)	28·5 (26-31)	90 (71-125)			

Table S1. Demographic details of the included non-RCTs. (Continued)

Author, year	Country	Enrolment location	Study design	Interventions	Population	Targeting duration of APP	Actual duration of APP (hours)	Age (years)	Sex (Male, %)	BMI (kg/m^2)	Baseline P/F or S/F*	Use of corticosteroids (n, %)	Primary outcomes	Secondary outcomes
Loureiro-Amigo, 2021	Spain	Non-ICU	Non RCT, multicenter, retrospective	Usual care	103	APP was used at least one day		70·8 (60·6-74·2)	71 (68·9)		400 (241·7-438·1)*	62 (60·2)	Death during hospitalization	None
				Usual care+APP	60			66·6 (59·2-72·4)	43 (71·7)		409·5 (306·3-438·1)*	52 (86·7)		
Meredith, 2021	USA	ICU	Non RCT, single center, retrospective	Usual care	87								Rate of intubation	Time to mechanical ventilation in days, amount of respiratory support required (defined as: oxygen requirement, nasal cannula, HFNC, NIPPV, and mechanical ventilation), time at this maximal therapy in days, and number of deaths
				Usual care + APP	26									
Ni, 2020	China	ICU	Non RCT, single center, prospective	Usual care	35	At least 4 hours per day for 10 days		64±12	21 (60·0)		128±60	22 (62·9)	Oxygenation improvement (cumulative mean difference of S/F, ROX index, and Borg scale)	Lung lesion absorption, NEWS2, time to clinical improvement, rate of intubation avoidance, death, time to virus shredding, length of hospital stay, and adverse events
				Usual care+APP	20			60±12	12 (60·0)		147±51			
Pierucci, 2021	Italy	Intermediate care unit	Non RCT, single center, retrospective	Usual care (HFNC/CPAP/NIV)	16	As long as possible		70 ± 15	10 (62)		179±18		The proportion of patients on prolonged prone position and discharged home	Improvement in oxygenation, hospital length of stay, and 6-month survival·
				Usual care (HFNC/CPAP/NIV)+APP	16			59 ± 11	13 (81)		226±74			
Perez-Nieto, 2021	Mexico-Ecuador	ED, Intermediate care unit, ICU	Non RCT, multicenter, retrospective	Usual care (Nasal cannula/NRM/HFNC)	322	At least 2 continuous hours	Total: 12 (8-24)	55·8±14·5	230 (71·4)			69 (21·4)	Intubation for mechanical ventilation	Death during in-hospital follow-up, factors associated with intubation amongst patients in the APP group
				Usual care (Nasal cannula/NRM/HFNC) +APP	505			53·4 ±13·9	370 (73·3)			84 (16·6)		
Sryma, 2021	India		Non RCT, single center, prospective	Usual care (COT/HFNC/NIV)	15	A minimum of 2 hours per session with a target of duration of 8 hours per day		57·5±12·2	9 (60·0)			13 (86·7)	The rate of intubation	ROX index at 30 min from the start of the intervention, ROX index at 12 h, days to the recovery of hypoxia (defined as room air SpO2 >93%), and mortality
				Usual care (COT/HFNC/NIV)+APP	30			50·9±10·1	29 (96·7)			26 (86·7)		
Vianello, 2021	Italy	Intermediate care unit	Non RCT, single center, prospective	Usual care (HFNC)	43	At least 2 consecutive hours		69 (37-86)	26 (60·5)	28·3 (22·9-33·3)	92·4 (52·4-240·9)	43 (100·0)	Rate of intubation	Rate of escalation of respiratory support, i·e·, NIV or ETI; In-hospital mortality rate; Length of hospital stay
				Usual care (HFNC)+APP	50			67 (36-89)	33 (66·0)	26·9 (20·8-41·5)	107·2 (6·8-300·0)	50 (100·0)		
Prud'homme, 2021	France	Non-ICU	Non RCT, multicenter, retrospective	Usual care (COT/HFNC)	48	At least 3 hours each day during 3 consecutive days		61±18	31 (64·6)	28±5	299±45*	28 (58·3)	Upgrading of oxygen delivery method on day 14	Death at day 14
				Usual care (COT/HFNC)+APP	48			62±11	37 (77·1)	27±5	279±84*	28 (58·3)		
Simioli, 2021	Italy	Intermediate care unit	Non RCT, single center, retrospective	Usual care (HFNC/CPAP)	11		Daily: 3h	71±10		28±5	95±92			
				Usual care (HFNC/CPAP)+APP	18		Daily: >10h	61±14		28±2	96·5±35			
Tonelli, 2021	Italy	ICU	Non RCT, multicenter, retrospective	Usual care (HFNC/NIV)	76	At least 3 hours per session with 1-4 sessions per day		70 (33-80)	55 (73)	28 (20-37)	153 (84-232)	55 (73)	Endotracheal intubation rate	Time to intubation, mortality, non invasive respiratory support-free-days (i.e. days spent without HFNC, NIV, CPAP, or invasive mechanical ventilation at 1-month), tracheostomy, length of RICU and hospital stay
				Usual Care (HFNC/NIV)+APP	38			61 (32-75)	25 (66)	26 (19-36)	141 (73-223)	25 (66)		
Zang, 2020	China	ICU	Non RCT, single center, prospective	Usual care (Face mask)	37			66·14±9·19	26 (70·3)					
				Usual care (Face mask)+APP	23		13·43±8·04	62·65±10·83	13 (56·5)					

Data was presented as mean±SD or median (IQR). Missing data was presented as blank. * Data was shown at S/F. APP, awake prone positioning; BMI, body mass index; COT, conventional oxygen therapy; CPAP, continuous positive airway pressure; ED, emergency department; ETI, endotracheal intubation; HFNC, high flow nasal cannula; HFNO, high-flow nasal oxygen therapy; ICU, intensive care unit; IMV, invasive mechanical ventilation; NEWS2, National Early Warning Score 2; NIPPV, non-invasive positive pressure ventilation; NIV, non-invasive ventilation; NRM, non-rebreather mask; P/F, ratio of partial pressure of arterial oxygen to fraction of inhaled oxygen; RICU, respiratory intensive care unit; RR, respiratory rate; S/F, ratio of pulse oxygen saturation to fraction of inhaled oxygen; SpO_2, pulse oxygen saturation.

Table S2. Comorbidities of the included RCTs.

Author, year	Interventions	Population	Hypertension (n, %)	COPD (n, %)	Chronic kidney disease (n, %)	Severe liver disease (n, %)	Diabetes (n, %)	Cancer (n, %)
Appex, Unpublished	COT (Room air/Nasal cannula/Mask/HFNC)	134	62 (46·3)	14 (10·4)			39 (29·1)	9 (6·7)
	COT (Room air/Nasal cannula/Mask/HFNC) +APP	159	76 (47·8)	16 (10·1)			45 (28·3)	6 (3·8)
Ehrmann, 2021	HFNC	557			35 (6)	6 (1)	173 (31)	31 (6)
	HFNC+APP	564			45 (8)	8 (1)	176 (31)	45 (8)
Gad, 2021	NRM	15	3 (20·0)	3 (20·0)			6 (33·3)	
	NRM+APP	15	4 (26·7)	5 (33·3)			7 (46·7)	
Jayakumar, 2021	Standard care (Face mask/NRM)	30	9 (30·0)				19 (63·3)	
	Standard care (Nasal Prongs/Face mask/NRM/HFNC/NIV) +APP	30	13 (43·3)				13 (43·3)	
Johnson, 2021	Usual care (Room air/ nasal cannula)	15						
	Usual care (Room air/nasal cannula)+APP	15						
Kharat, 2021	Usual care (Nasal cannula)	17	9 (52·9)	0 (0)	1 (5·9)		3 (17·6)	
	Usual care (Nasal cannula) +APP	10	3 (30·0)	0 (0)	0 (0)		2 (20·0)	
Rosén, 2021	HFNC/NIV	39	21 (55)	4 (10)	2 (5·1)	1 (3)	11 (28·2)	1 (3)
	HFNC/NIV+APP	36	17 (47)	2 (6)	3 (8·3)	0 (0)	14 (38·9)	4 (11)
Taylor, 2021	Usual care (Room air/ nasal cannula/HFNC/NIV)	13			2 (15·4)		5 (38·5)	
	Usual care (Nasal cannula/HFNC/NIV) +APP	27			7 (25·9)		10 (37·0)	
Harris, Unpublished	Usual care (Nasal cannula/NRM/HFNC/NIV)	30	3 (10·0)	0 (0)		0 (0)	10 (33·3)	0 (0)
	Usual care (Nasal cannula/NRM/HFNC/NIV) +APP	31	6 (19·4)	0 (0)		1 (3·2)	14 (45·2)	0 (0)
Fralick, Unpublished	Standard care (Nasal cannula/ venturi mask/HFNC)	122	42 (34·4)	15 (12·3)			31 (25·4)	
	Standard care (Nasal cannula/ venturi mask/HFNC) +APP	126	56 (44·4)	12 (9·5)			36 (28·6)	

Missing data was presented as blank. APP, awake prone positioning; COPD, chronic obstructive pulmonary disease; COT, conventional oxygen therapy; HFNC, high-flow nasal cannula; NIV, non-invasive ventilation; NRM, non-rebreather mask; RCT, randomised controlled trial.

Table S3. Comorbidities of the included non-RCTs.

Author, year	Interventions	Population	Hypertension (n, %)	COPD (n, %)	Chronic kidney disease (n, %)	Severe liver disease (N, %)	Diabetes (n, %)	Cancer (n, %)
Alsharif, 2021	Usual care (CPAP)	48						
	Usual care (CPAP)+APP	31						
Altinay, 2021	Usual care (NRM)	23	15 (65·2)	0 (0)	1 (4·3)		6 (26·1)	2 (8·7)
	Usual care (NRM)+APP	25	10 (40·0)	2 (8·0)	0 (0)		10 (40·0)	0 (0)
Barker, 2021	Usual care (NIV)	10						
	Usual care (NIV)+APP	10						
Fazzini, 2021	Usual care (HFNC/Facemask/CPAP)+APP<1h	12						
	Usual care (HFNC/Facemask/CPAP)+APP>1h	34						
Ferrando, 2020	Usual care (HFNC)	144	60 (41·7)	6 (4·2)	14 (9·7)		23 (16·0)	9 (6·3)
	Usual care (HFNC)+APP	55	20 (36·4)	4 (7·3)	4 (7·3)		9 (16·4)	3 (5·5)
Jagan, 2020	APP<1h or <5 occasions per day and for <= 1 continuous hour overnight	65	36 (55·4)	11 (16·9)	15 (23·1)		25 (38·5)	6 (9·2)
	APP>=1h orn >=5 occasions per day and for >= 1 continuous hour overnight	40	24 (60)	5 (12·5)	5 (12·5)		18 (45·0)	3 (7·5)
Padrão, 2020	Usual care (Nasal cannula/Venturi mask/NRM)	109	62 (57)				36 (33·0)	6 (6)
	Usual care (Nasal cannula/Venturi mask/NRM) +APP	57	27 (47)				22 (38·6)	1 (2)
Jouffroy, 2021	Usual care (COT/HFNC/NIV/CPAP)	339	175 (51·6)	17 (5·0)	63 (18·6)		103 (30·4)	
	Usual care (COT/HFNC/CPAP)+APP	40	13 (32·5)	3 (7·5)	2 (5·0)		11 (27·5)	
Loureiro-Amigo, 2021	Usual care	103	64 (62·1)	16 (15·5)			38 (36·9)	
	Usual care+APP	60	35 (58·3)	5 (8·3)			19 (31·7)	
Meredith, 2020	Non-self proning	87						
	Self-proning	26						
Ni, 2021	Usual care	35	10 (28·6)	3 (8·6)			7 (20·0)	
	Usual care+APP	20	7 (41·2)	3 (15·)			5 (25)	
Pierucci, 2021	Usual care (HFNC/CPAP/NIV)	16	11 (68·8)		6 (37·5)		4 (25·0)	
	Usual care (HFNC/CPAP/NIV)+APP	16	5 (31·2)	0 (0)	5 (31·2)		3 (18·8)	
Perez-Nieto, 2021	Usual care (Nasal cannula/NRM/HFNC)	322	119 (37)		12 (3·7)	3 (0·9)	121 (37·6)	8 (2·5)
	Usual care (Nasal cannula/NRM/HFNC) +APP	505	166 (32·9)		23 (4·6)	2 (0·4)	194 (38·4)	2 (0·4)
Sryma, 2021	Usual care (COT/HFNC/NIV)	15	7 (46·7)				9 (60·0)	
	Usual care (COT/HFNC/NIV)+APP	30	12 (40·0)				11 (36·7)	
Vianello, 2021	Usual care (HFNC)	43						
	Usual care (HFNC)+APP	50						
Prud'homme, 2021	Usual care (COT/HFNC)	48	18 (37·5)				12 (25·0)	
	Usual care (COT/HFNC)+APP	48	15 (31·3)				7 (14·6)	
Simioli, 2021	Usual care (HFNC/CPAP)	11						
	Usual care (HFNC/CPAP)+APP	18						
Tonelli, 2021	Usual care (HFNC/NIV)	76	60 (79)	11 (15)	8 (10)		14 (18)	8 (11)
	Usual care (HFNC/NIV)+APP	38	32 (84)	6 (16)	2 (6)		8 (23)	4 (11)
Zang, 2020	Usual care (Face mask)	37	17 (45·9)				9 (24·3)	
	Usual care (Face mask)+APP	23	6 (26·1)				3 (13·0)	

Missing data was presented as blank. APP, awake prone positioning; COPD, chronic obstructive pulmonary disease; COT, conventional oxygen therapy; CPAP, continuous positive airway pressure; HFNC, high-flow nasal cannula; NIV, non-invasive ventilation; NRM, non-rebreather mask; RCT, randomised controlled trial.

Figure S1. Assessment on risk of bias for included RCTs.

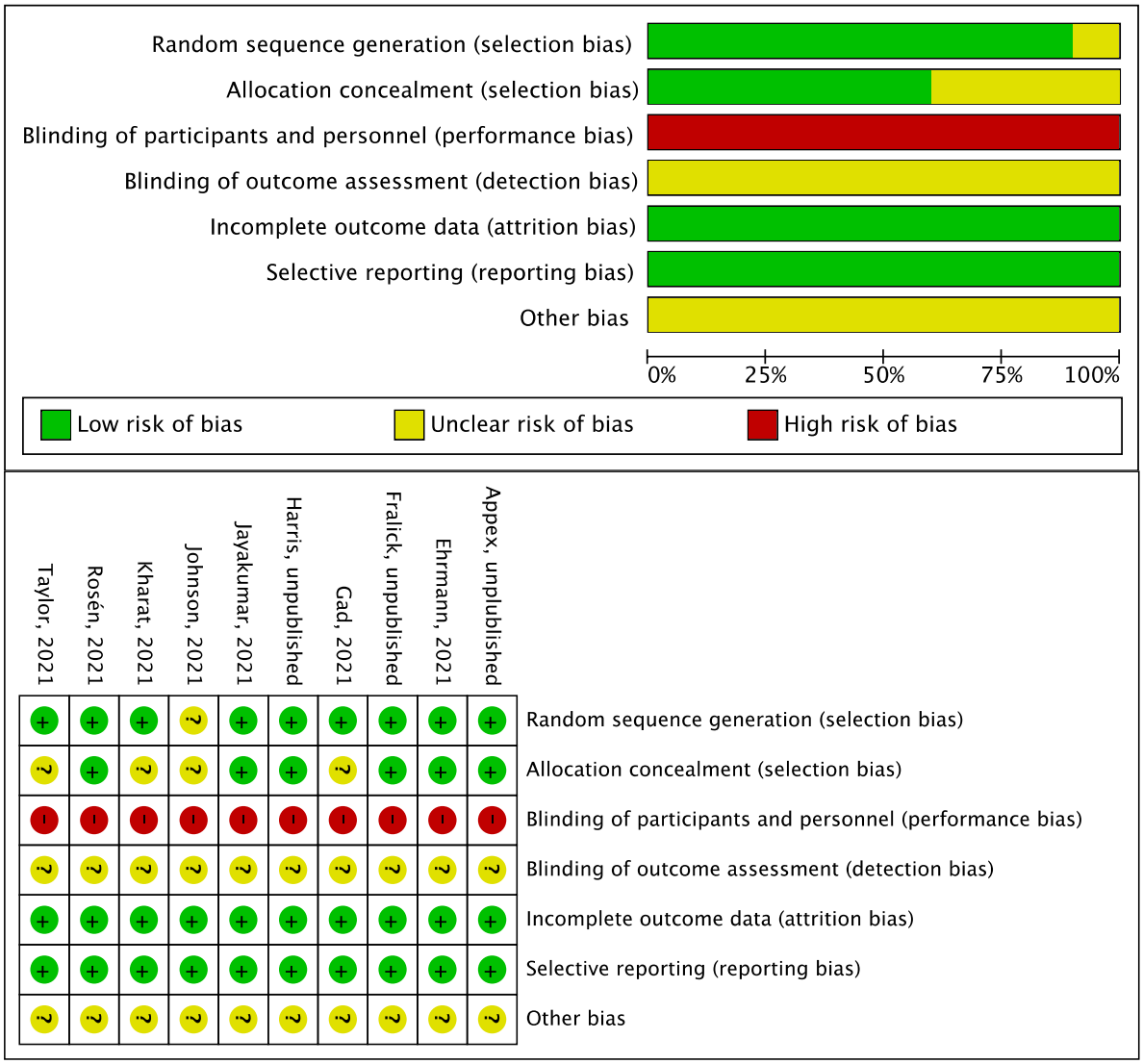


Figure S2. Funnel plot of intubation for included RCTs.

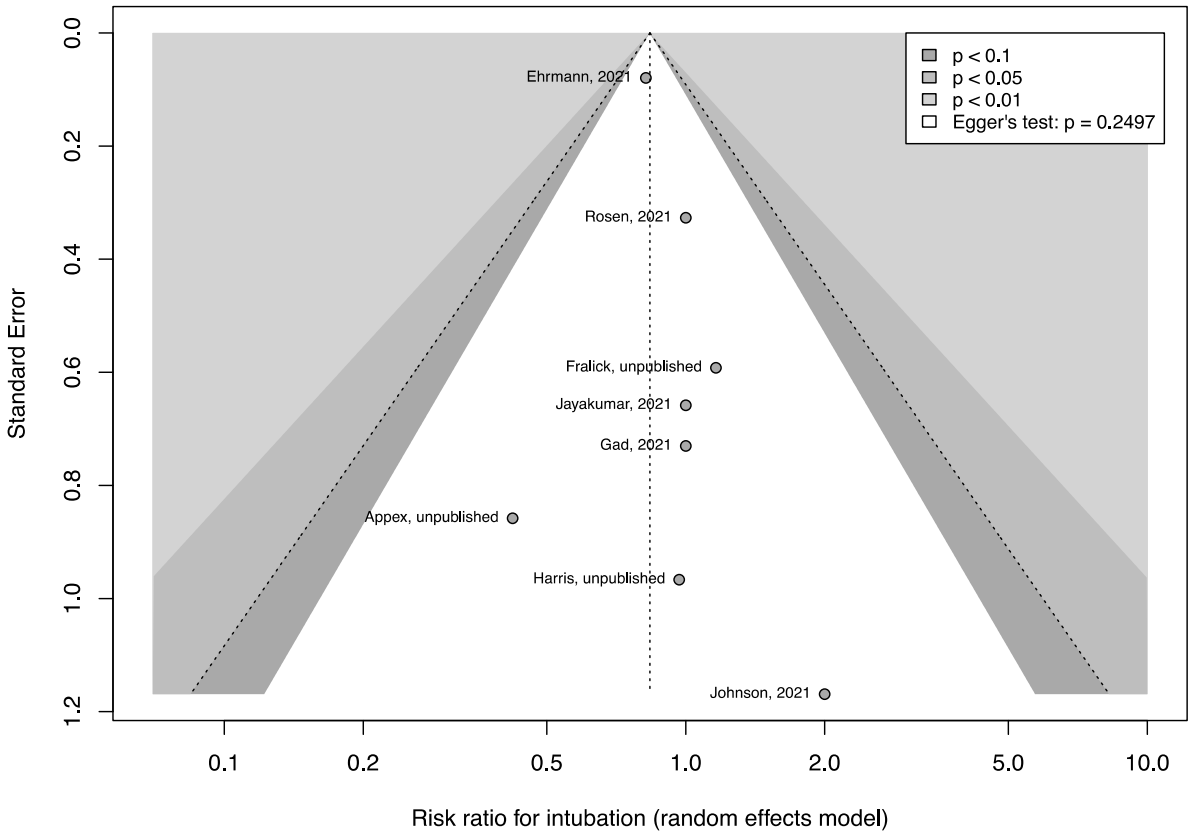


Figure S3. Funnel plot of mortality for included RCTs.

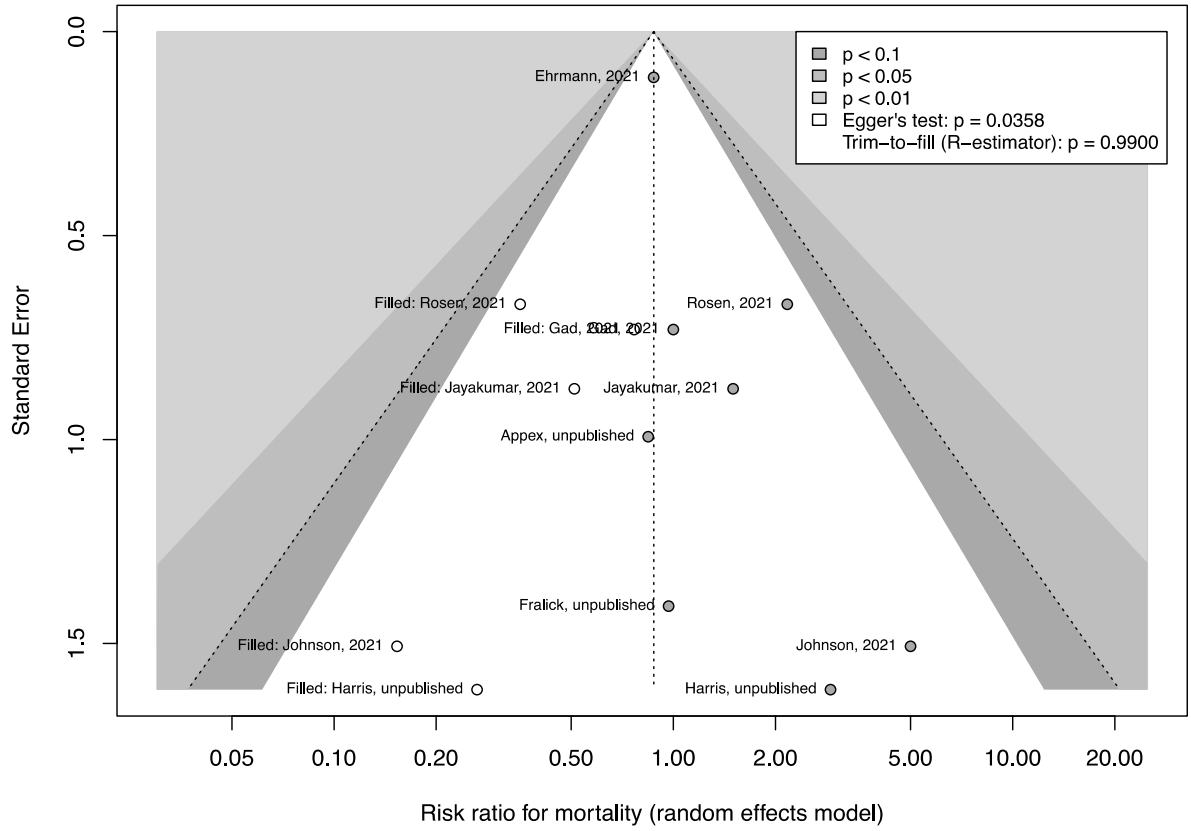


Figure S4. Funnel plot of need for escalation of respiratory support for included RCTs.

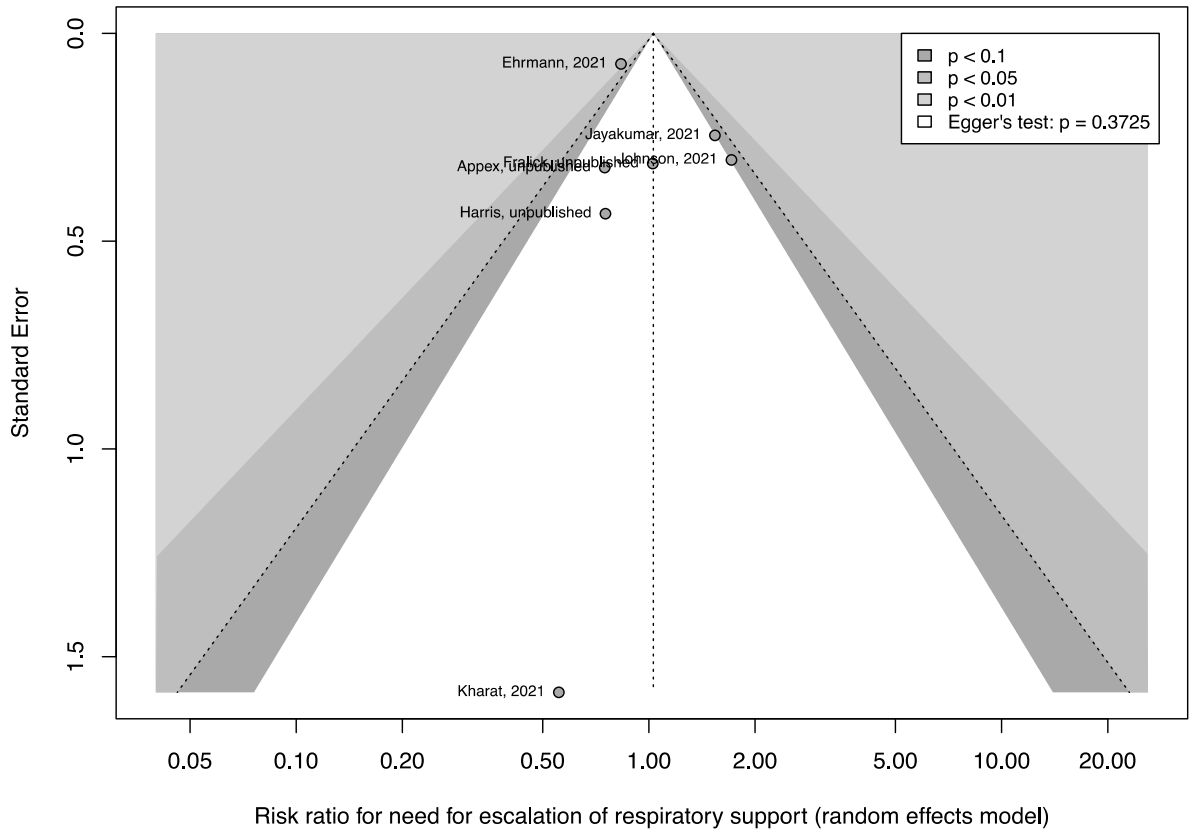


Figure S5. Funnel plot of need for ICU admission for included RCTs.

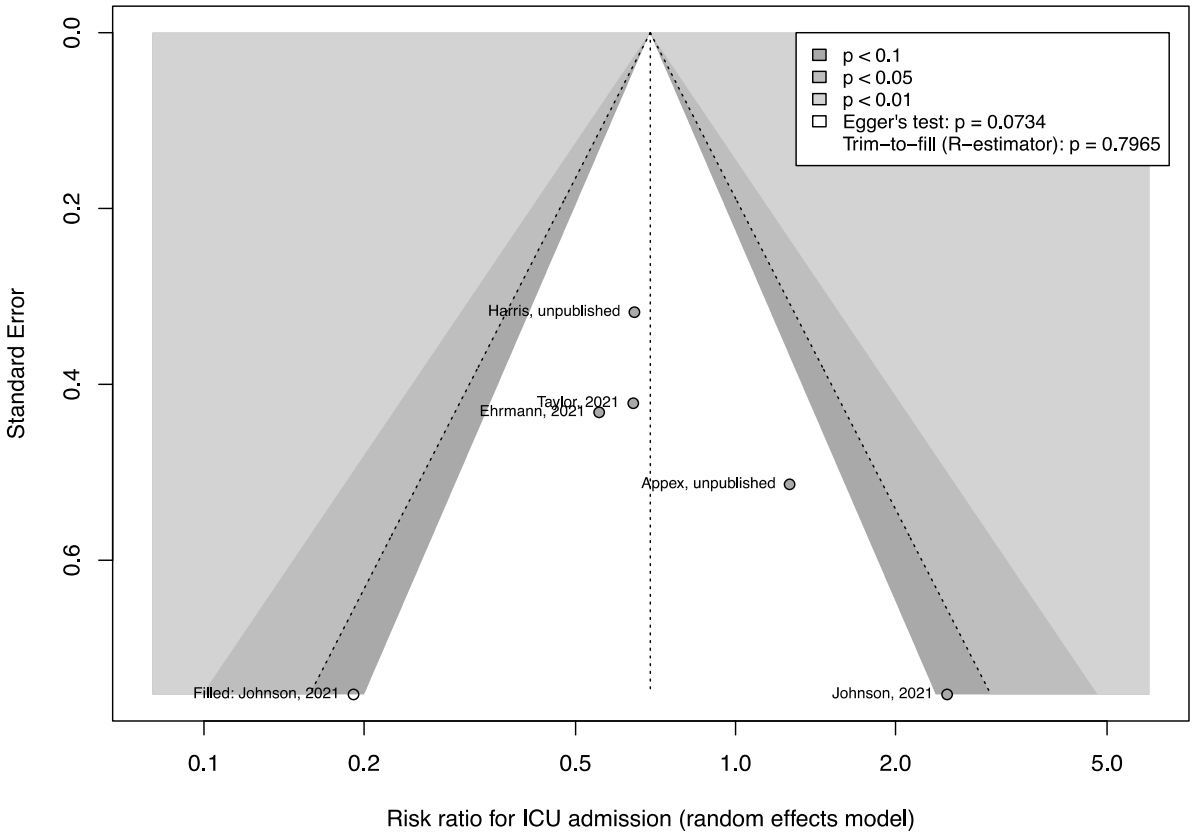


Figure S6. Funnel plot of ICU length of stay for included RCTs.

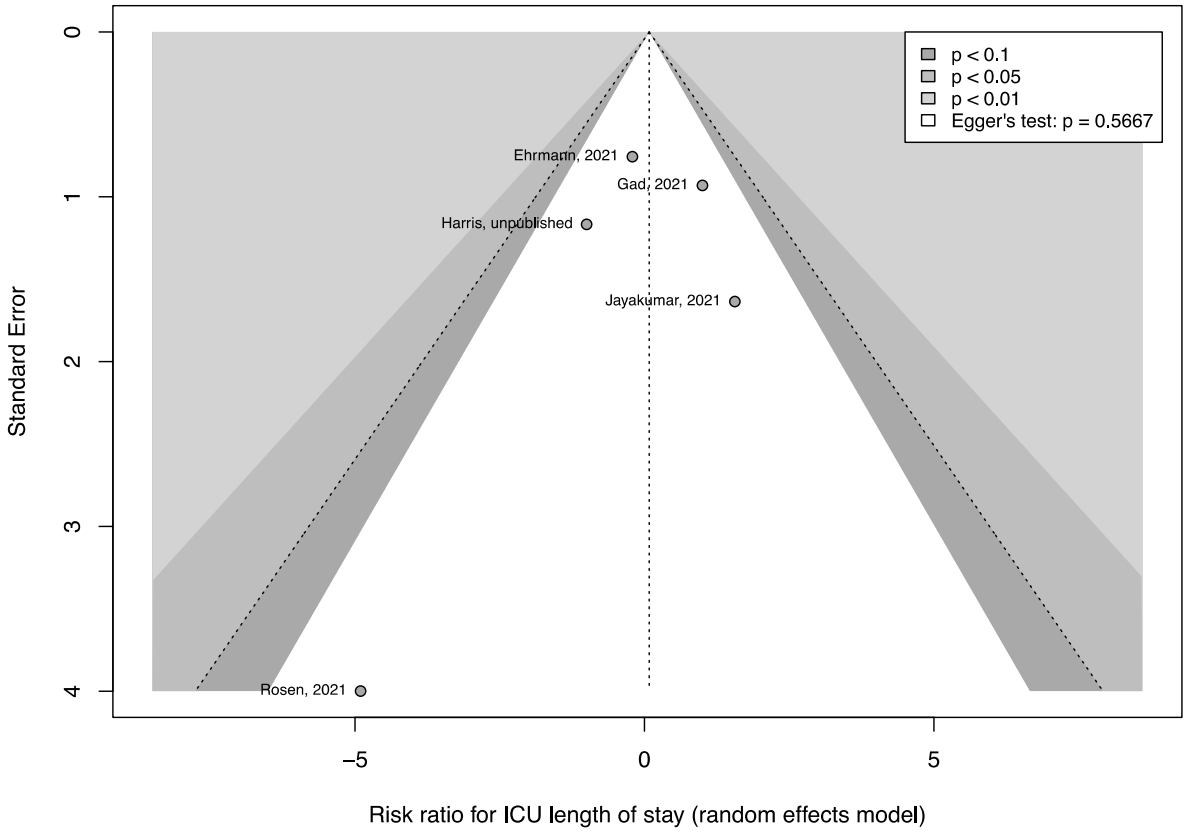


Figure S7. Funnel plot of hospital length of stay for included RCTs.

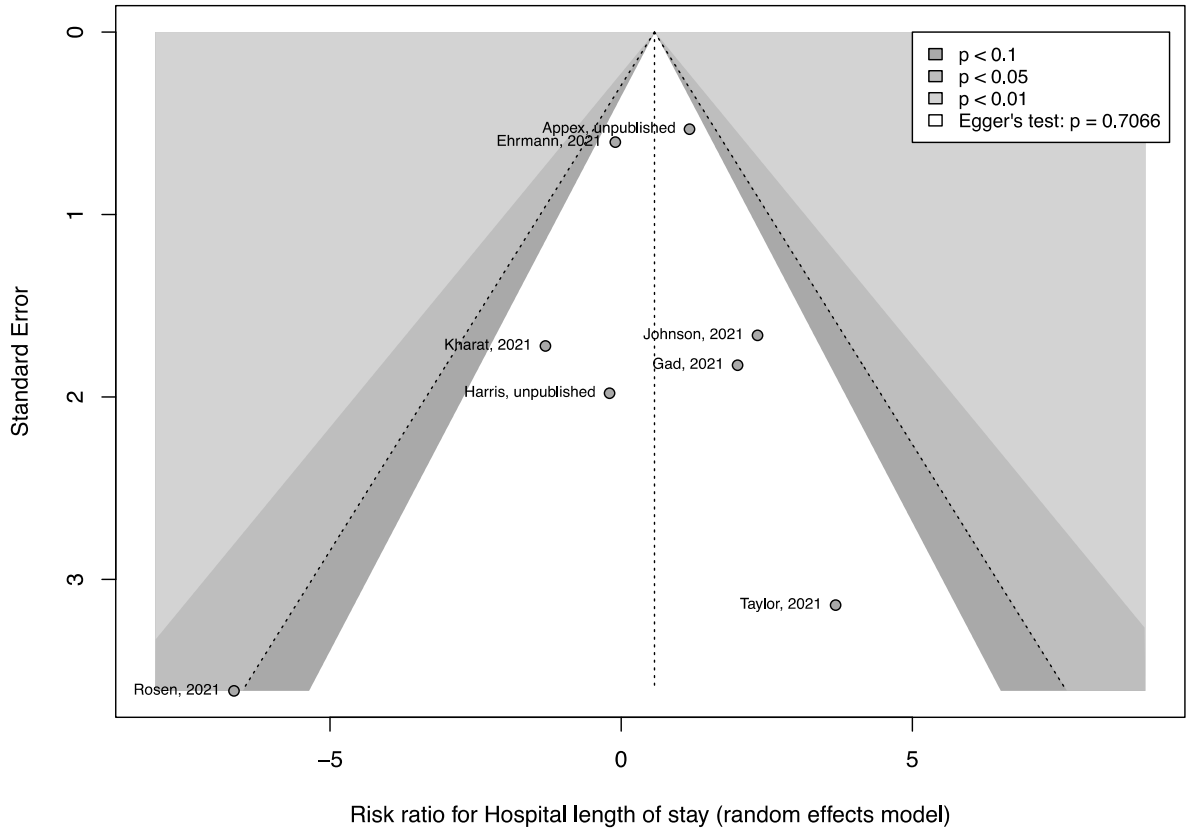


Table S4. Assessment on risk of bias for included non-RCTs using Newcastle-Ottawa Scale.

Author, year	Selection				Comparability		Outcome			Quality[#]
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study	Controls for age, sex, and marital status	Controls of other factors	Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	
Alsharif, 2021			*	*	MD	MD	*	*	*	MD
Altinay, 2021			*	*		*	*	*	*	Fair
Barker, 2021			*	*	*		*	*	*	Fair
Fazzini, 2021			*	*	*	*	*	*	*	Fair
Ferrando, 2020			*	*	*		*	*	*	Fair
Jagan, 2020			*	*		*	*	*	*	Fair
Padrão, 2020			*	*			*	*	*	Poor
Jouffroy, 2021			*	*	*		*	*	*	Fair
Loureiro-Amigo, 2021			*	*	*		*	*	*	Fair
Meredith, 2020			*	*	MD	MD	*	*	*	MD
Ni, 2021			*	*	*	*	*	*	*	Fair
Pierucci, 2021			*	*			*	*	*	Poor
Perez-Nieto, 2021			*	*			*	*	*	Poor
Sryma, 2021			*	*		*	*	*	*	Fair
Vianello, 2021			*	*	*		*	*	*	Fair
Prud'homme, 2021			*	*	*	*	*	*	*	Fair
Simioli, 2021			*	*	*	*	*	*	*	Fair
Tonelli, 2021			*	*			*	*	*	Poor
Zang, 2020			*	*	*		*	*	*	Fair

MD, missing data. [#]The quality (good, fair, and poor) was defined based on the following criteria: Good - 3 or 4 stars in 'Selection' domain AND 1or 2 stars in 'Comparability' domain AND 2 or 3 stars in 'Outcome' domain; Fair - 2 stars in 'Selection' domain AND 1or 2 stars in 'Comparability' domain AND 2 or 3 stars in 'Outcome' domain; Poor - 0 or 1 star in 'Selection' domain OR 0 star in 'Comparability' domain OR 0 or 1 star in 'Outcome' domain. RCT, randomised controlled trial.

Figure S8. Funnel plot of intubation for included non-RCTs.

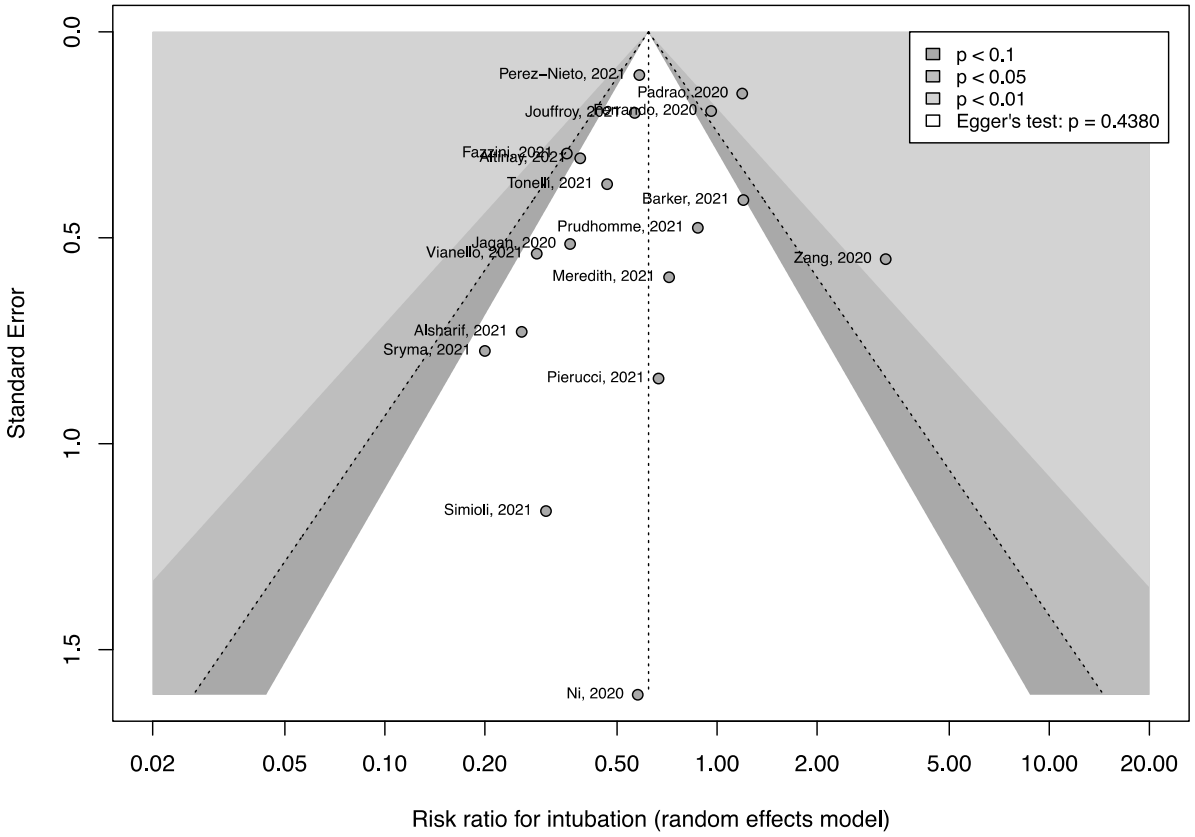


Figure S9. Funnel plot of mortality for included non-RCTs.

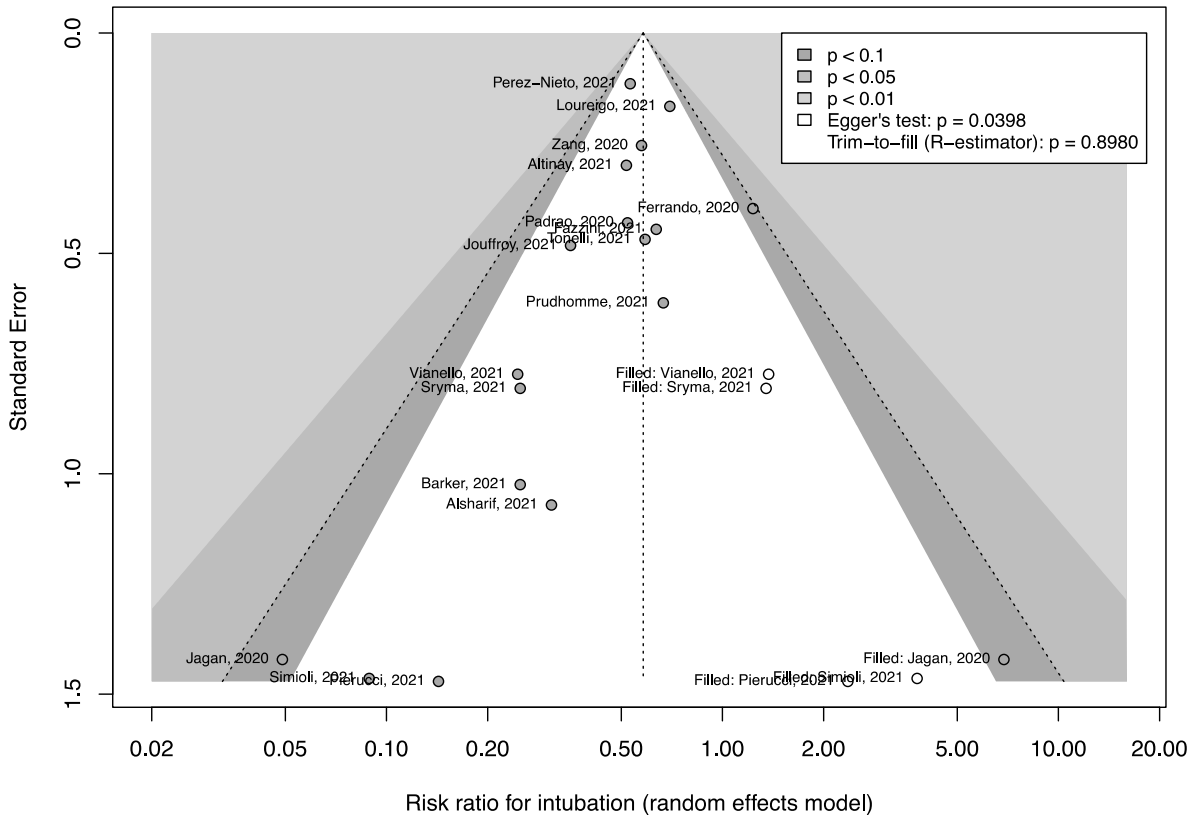


Table S5. Grading of recommendations, assessment, development and evaluations (GRADE).

Outcome	No of studies	Study design	No of participants		Certainty assessment					No of patients		Effect (Random effects model)		Certainty
			APP	Control	Risk of bias	Imprecision	Inconsistency	Indirectness	Publication bias	APP	Control	Relative risk (95% CI)	Absolute effect (95% CI)	
Risk of intubation	10	RCT	1013	972	Not serious[a]	Low[b]	Low[h]	Low	Low[j]	216/976 (22.1%)	255/942 (27.1%)	0.84 (0.72-0.97)	-	⊕⊕⊕⊕ High
Subgroup: Advanced respiratory support	3	RCT	605	604	Not serious[a]	Low[c]	Low[h]	Low		198/605 (32.7%)	237/604 (39.2%)	0.83 (0.71-0.97)	-	⊕⊕⊕⊕ High
Subgroup: Conventional oxygen therapy	8	RCT	405	368	Not serious[a]	High[d]	Low[h]	Low		16/368 (4.3%)	18/338 (5.3%)	0.87 (0.45-1.69)	-	⊕⊕⊕◯ Moderate
Subgroup: ICU	3	RCT	583	578	Not serious[a]	Low[c]	Low[h]	Low		189/583 (32.4%)	226/578 (39.1%)	0.83 (0.71-0.97)	-	⊕⊕⊕⊕ High
Subgroup: Non ICU	7	RCT	394	355	Not serious[a]	High[d]	Low[h]	Low		15/357 (4.2%)	16/325 (4.9%)	0.88 (0.44-1.76)	-	⊕⊕⊕◯ Moderate
Mortality	10	RCT	1013	972	Not serious[a]	High[d]	Low[h]	Low	High[k]	135/976 (13.8%)	143/942 (15.2%)	1.0 (0.70-1.44)	-	⊕⊕◯◯ Low
Subgroup: Advanced respiratory support	3	RCT	605	604	Not serious[a]	High[d]	Moderate[i]	Low		124/605 (20.5%)	135/604 (22.4%)	1.23 (0.54-2.80)	-	⊕⊕◯◯ Low
Subgroup: Conventional oxygen therapy	8	RCT	405	368	Not serious[a]	High[d]	Low[h]	Low		10/342 (2.9%)	8/316 (2.5%)	1.14 (0.47-2.75)	-	⊕⊕◯◯ Low
Subgroup: ICU	3	RCT	583	578	Not serious[a]	High[e]	Low[h]	Low		116/583 (19.9%)	127/578 (22.0%)	0.90 (0.72-1.13)	-	⊕⊕◯◯ Low
Subgroup: Non ICU	7	RCT	394	355	Not serious[a]	Low[f]	Low[h]	Low		13/357 (3.6%)	13/325 (4.0%)	0.81 (0.41-1.59)	-	⊕⊕⊕◯ Moderate
Need for escalation of respiratory support	7	RCT	935	905	Not serious[a]	High[d]	Moderate[i]	Low	Low[j]	278/935 (29.7%)	308/905 (34.0%)	1.03 (0.77-1.37)	-	⊕⊕◯◯ Low
Need for ICU admission	6	RCT	268	233	Not serious[a]	Moderate[g]	Low[h]	Low	Low[k]	38/258 (14.7%)	39/216 (18.1%)	0.75 (0.51-1.10)	-	⊕⊕⊕⊕ High
ICU length of stay	5	RCT	472	508	Not serious[a]	High[e]	Low[h]	Low	Low[j]	472	508	-	0.08 days longer (-0.89-1.05)	⊕⊕◯◯ Low
Hospital length of stay	8	RCT	857	820	Not serious[a]	High[e]	Moderate[i]	Low	Low[j]	857	820	-	0.57 days longer (-0.35-1.49)	⊕⊕◯◯ Low

a. According to Figure S1 Assessment of risk of bias for RCTs, 1 study did not mention random sequence generation, 4 studies did not mention allocation concealment, and all studies lacked blinding due to the nature of prone positioning in awake patients and did not mention the blinding of outcome assessment.

b. Although the 95% CI of relative risk was close to a relative risk of 1.0 (no effect), the largest plausible effect suggested that APP might reduce the relative risk of intubation by as much as 28% especially when considering the overall risk of intubation of 40% or more in hypoxemic patients with COVID-19. In addition, trial sequential analysis supported the true positive conclusion by reaching the optimal information size.

c. Although the 95% CI of relative risk was close to a relative risk of 1.0 (no effect), the largest plausible effect suggested that APP might reduce the relative risk of intubation by as much as 29% especially when considering the overall risk of intubation of 40% or more in hypoxemic patients with COVID-19. In addition, trial sequential analysis did not indicated futility although the optimal information size was not reached but very close already.

d. The 95% CI of relative risk was wide and overlapped a relative risk of 1.0 (no effect). Trial sequential analysis indicated that the optimal information size was not reached.

e. The 95% CI of relative risk overlapped a relative risk of 1.0 (no effect). Trial sequential analysis indicated that the optimal information size was not reached.

f. Although the 95% CI of relative risk overlapped a relative risk of 1.0 (no effect), trial sequential analysis indicated that the optimal information size was reached.

g. The 95% CI of relative risk overlapped a relative risk of 1.0 (no effect). Although the optimal information size was not reached, but trial sequential analysis indicated futility in the pooled effect estimate.

h. Confidence intervals of each study overlapped and no statistical heterogeneity was found.

i. $I^2 = 32\%$ although heterogeneity test showed p-value > 0.05.

j. According to Figure S4 Funnel plot for RCTs, Egger's test showed symmetry.

k. According to Figure S5 Funnel plot for RCTs, Egger's test showed symmetry.

APP, awake prone positioning; CI, confidence interval; ICU, intensive care unit; RCT, randomized controlled trial.

Figure S10. Trial sequential analysis of intubation for included RCTs.

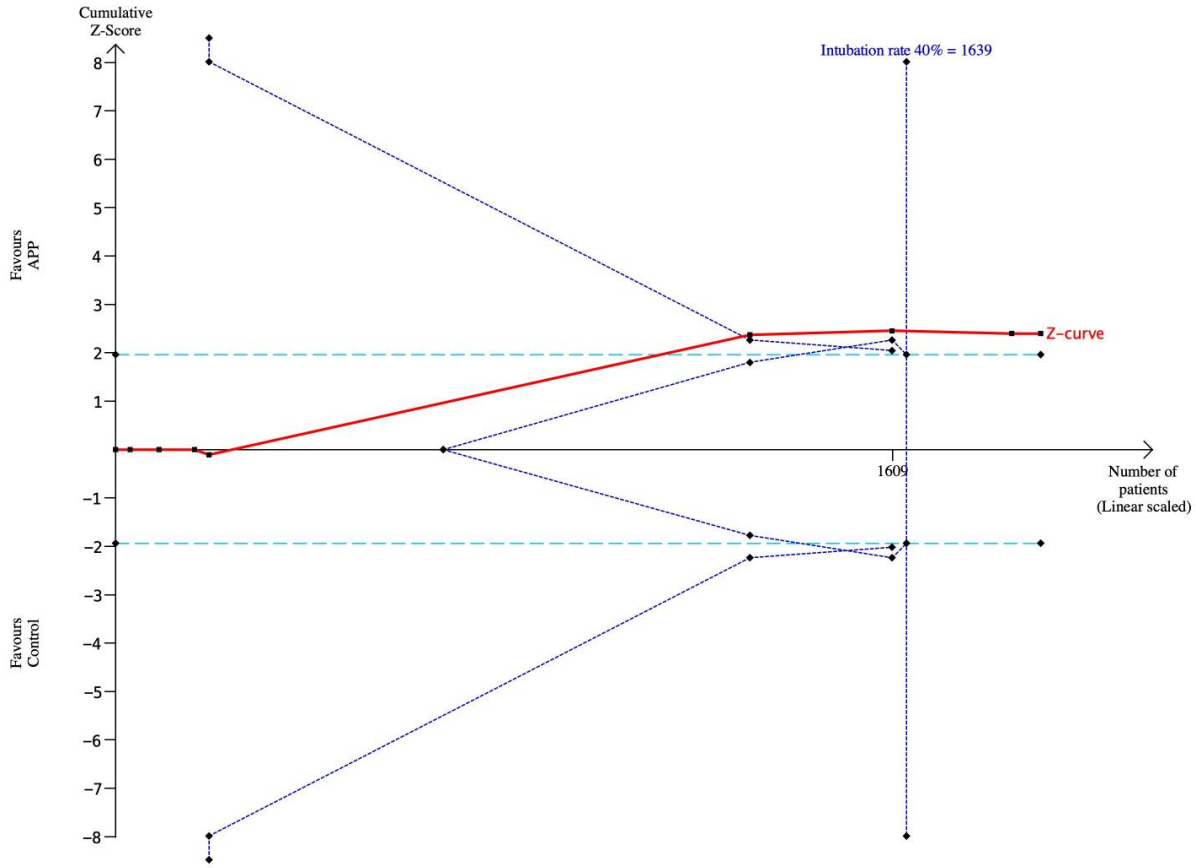
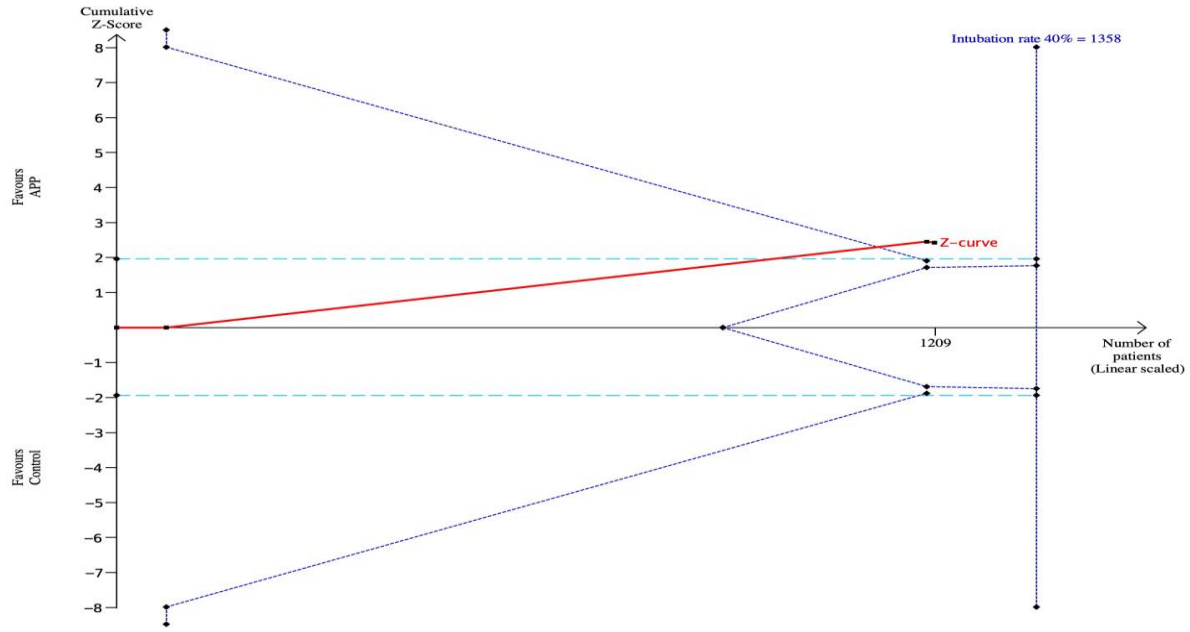


Figure S11. Trial sequential analysis of intubation in subgroups of advanced respiratory support and conventional oxygen therapy for included RCTs.

A. Advanced respiratory support



B. Conventional oxygen therapy

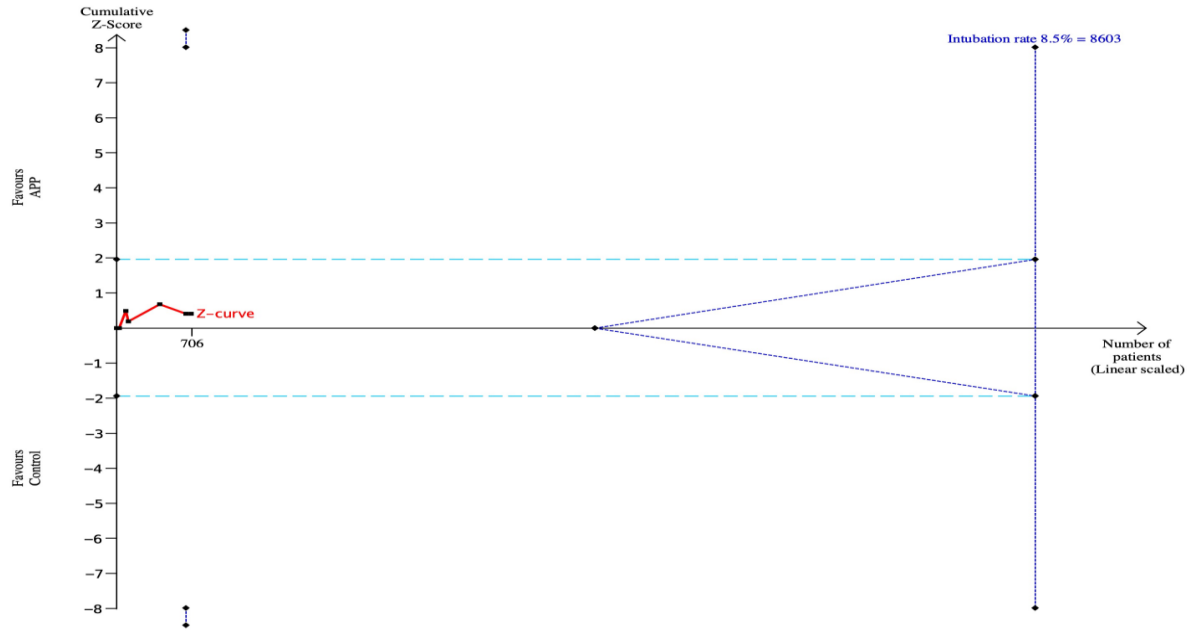


Figure S12. Trial sequential analysis of intubation in subgroups of ICU and non-ICU for included RCTs.

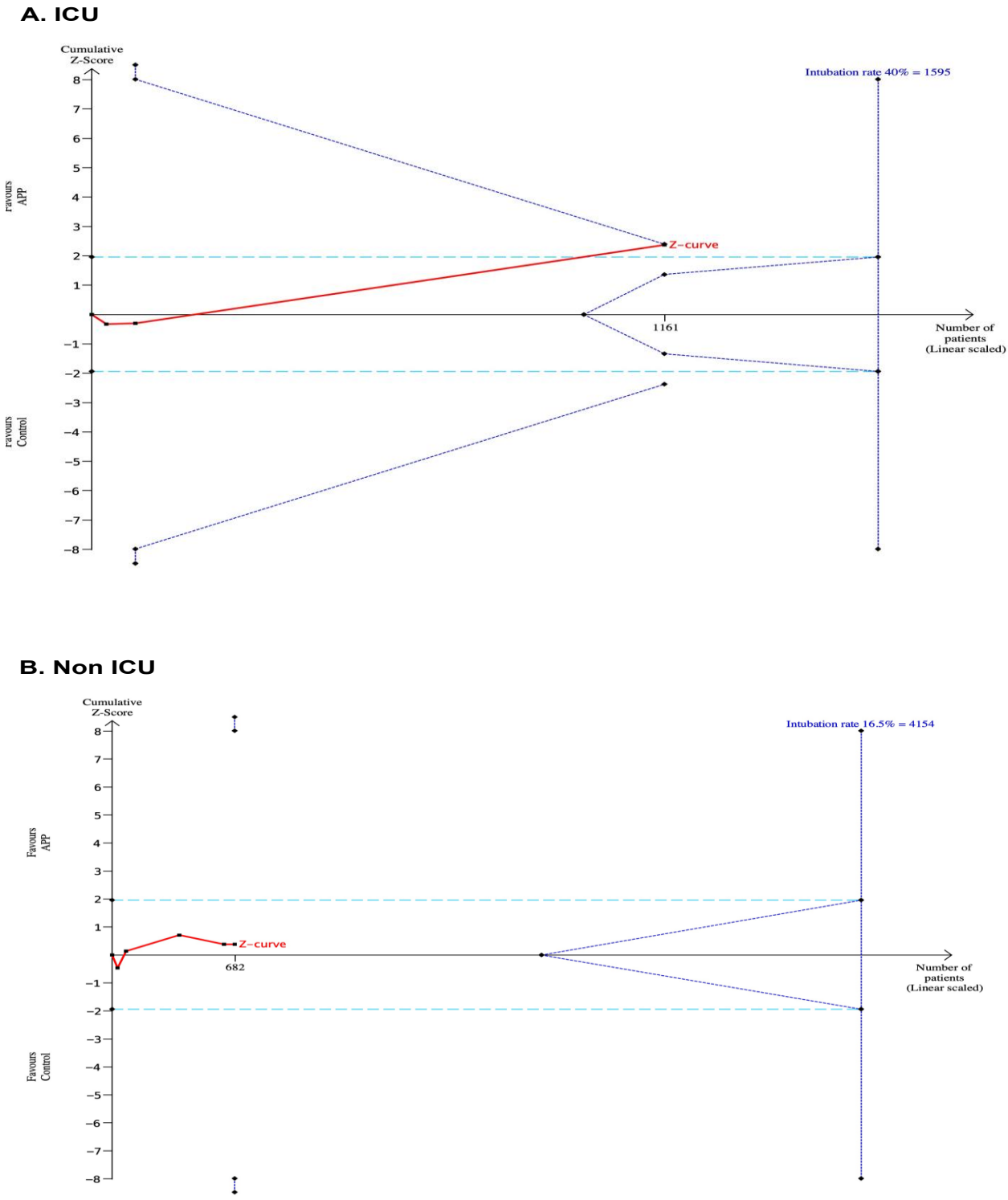
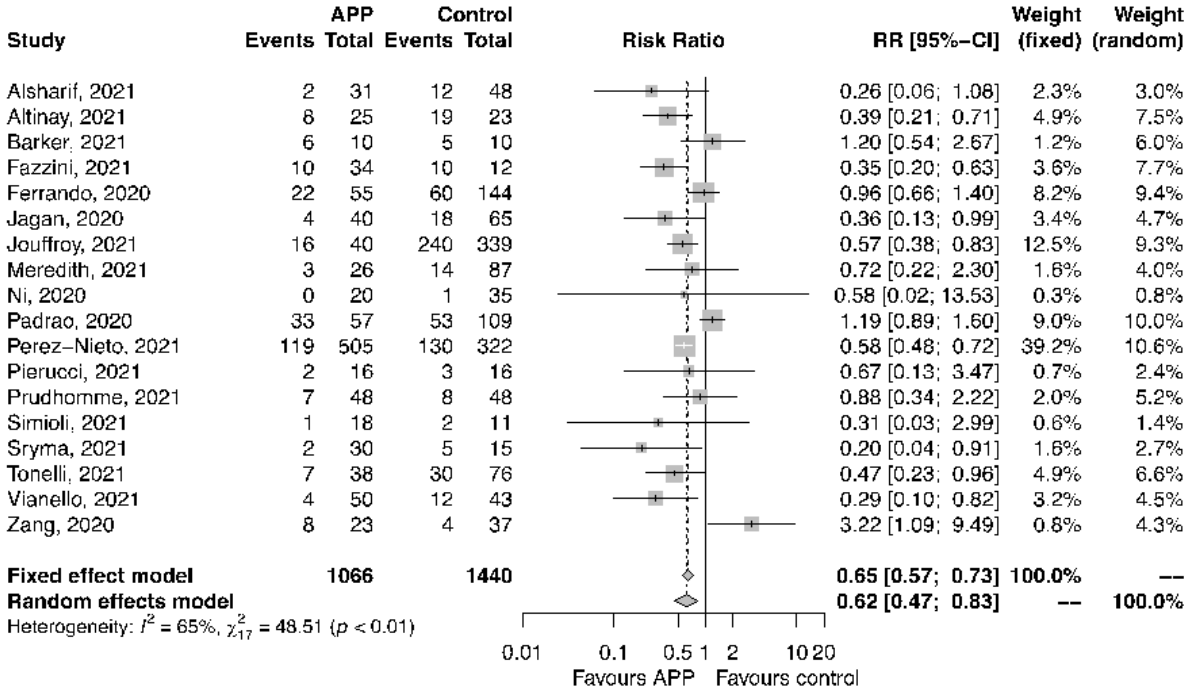


Figure S13. Intubation and mortality for Non-RCTs.

A Intubation



B Mortality

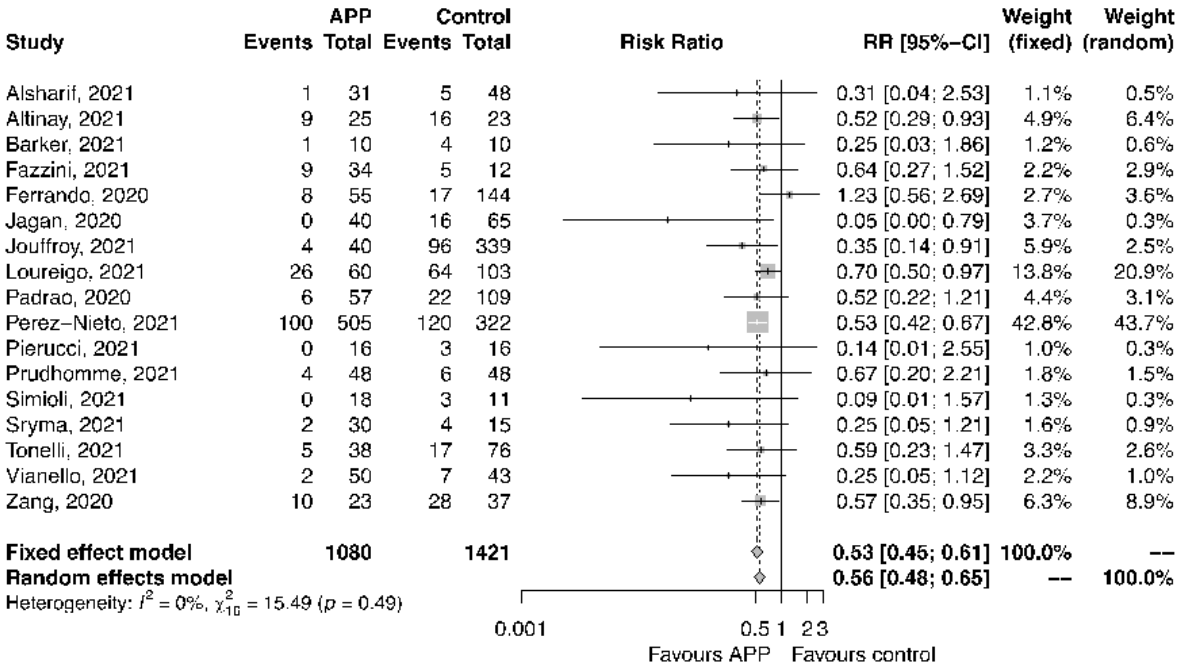
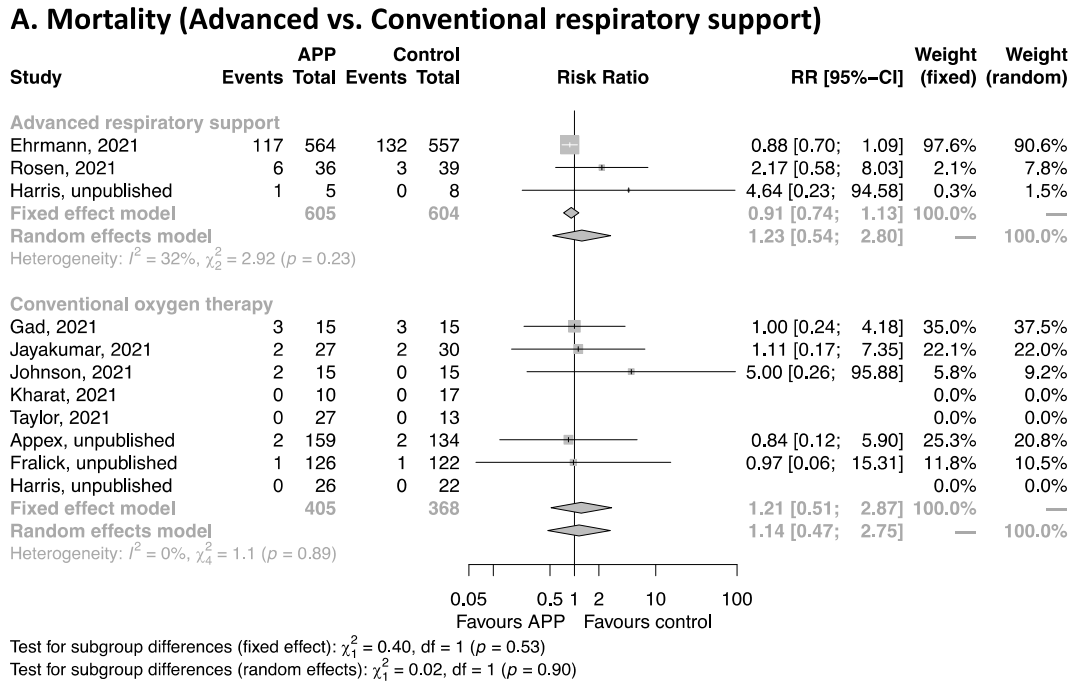


Figure S14. Subgroup analysis of mortality for included RCTs



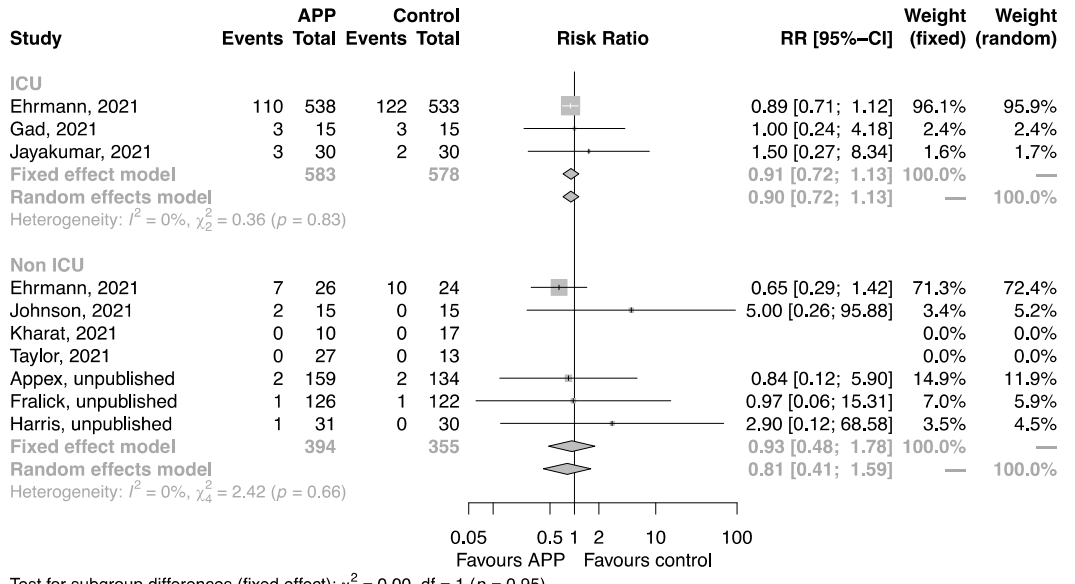


Figure S15. Trial sequential analysis of mortality for included RCTs.

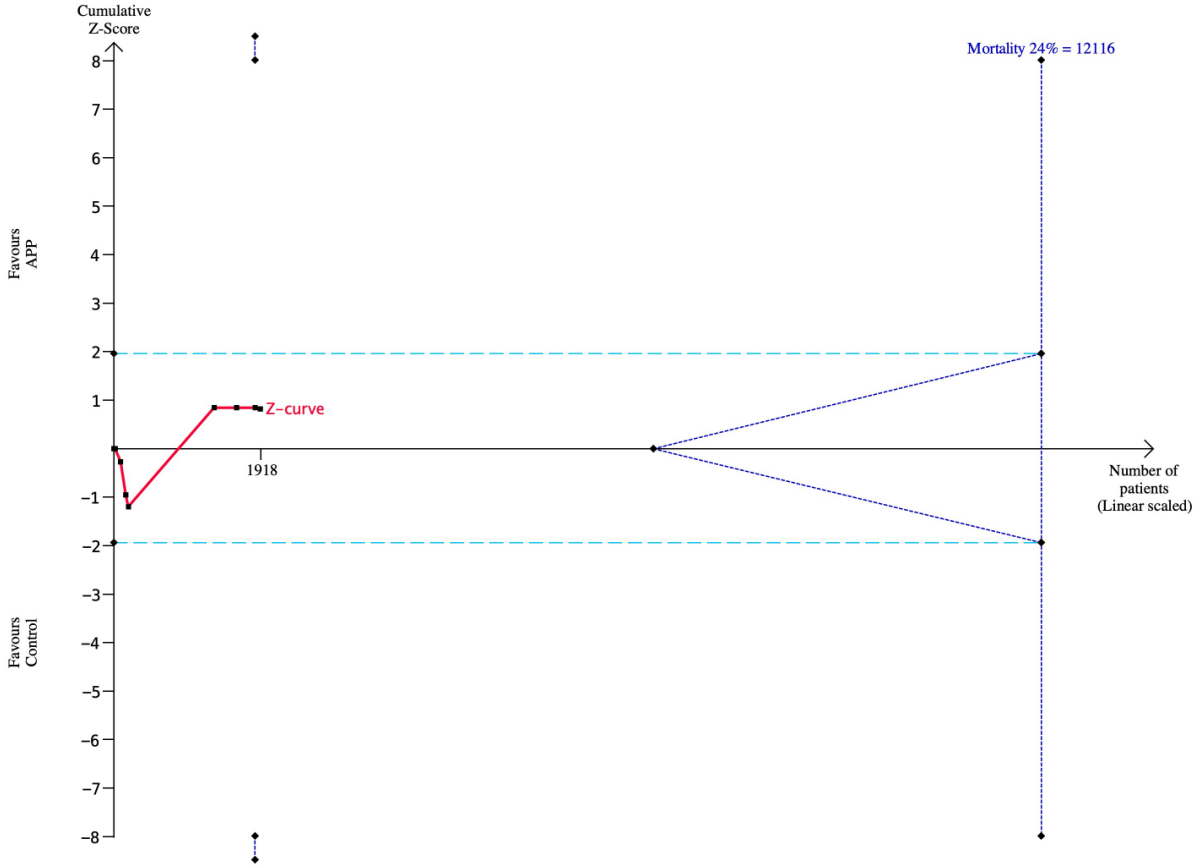
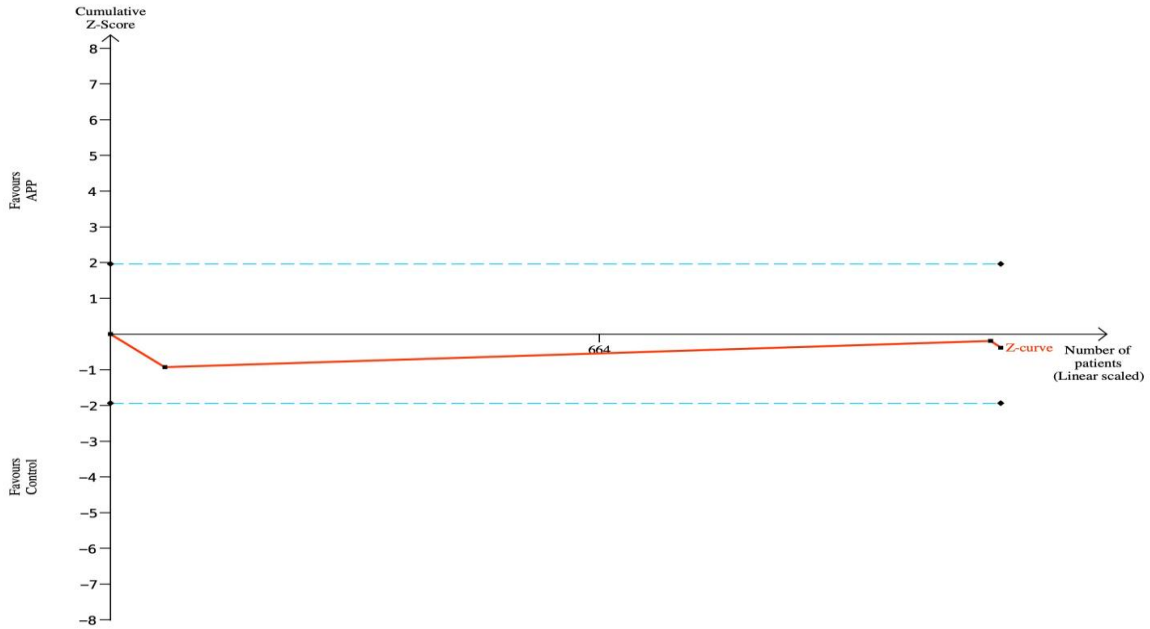


Figure S16. Trial sequential analysis of mortality in subgroups of advanced respiratory support and conventional oxygen therapy for included RCTs.

A. Advanced respiratory support



B. Conventional oxygen therapy

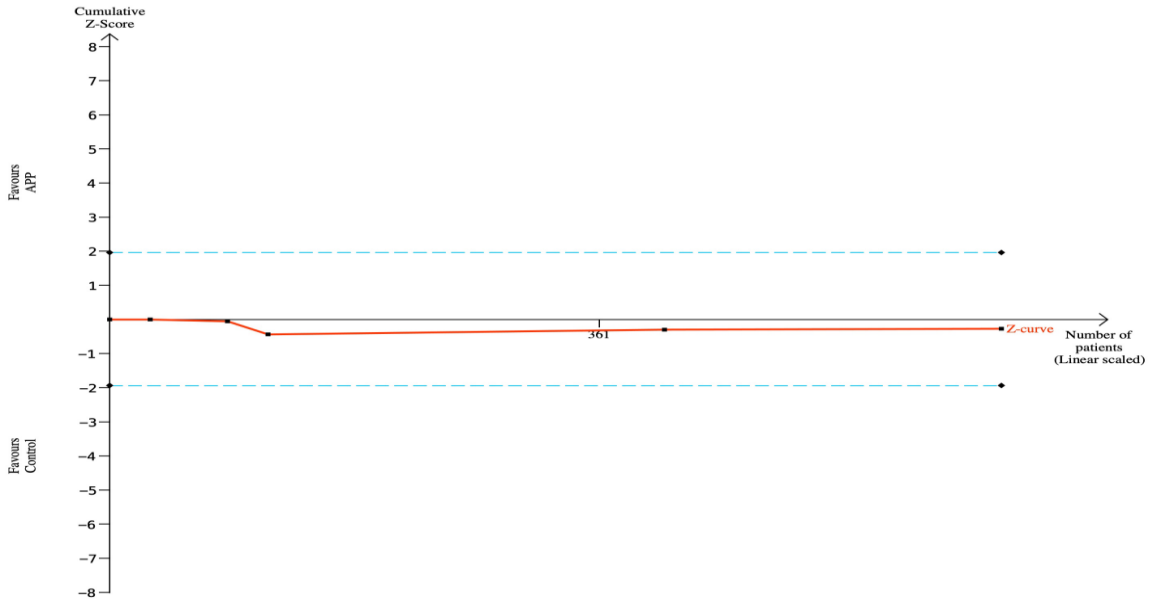


Figure S17. Trial sequential analysis of mortality in subgroups of ICU and non-ICU for included RCTs.

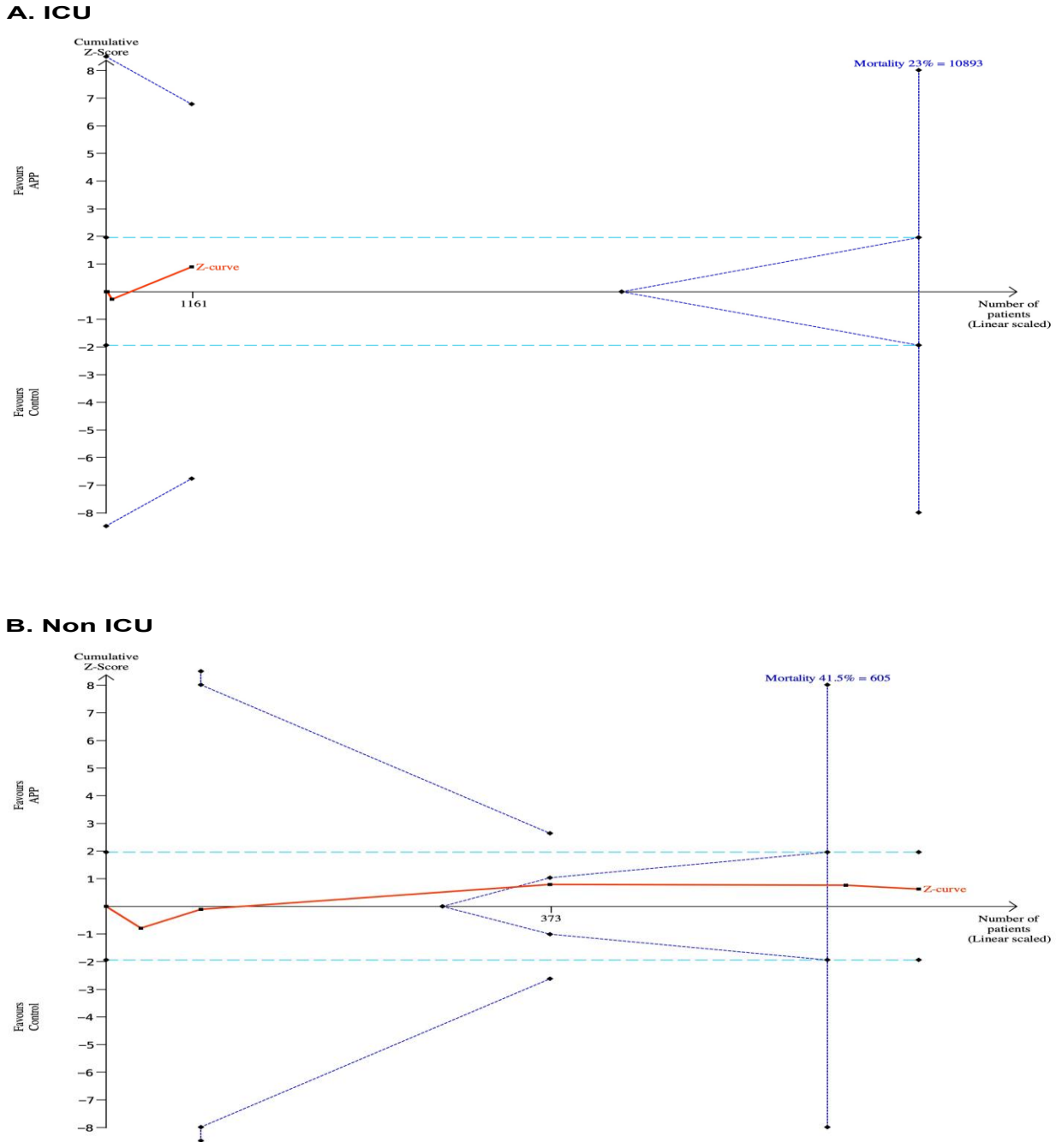


Figure S18. Meta-analysis of mortality for RCTs after exclusion of studies with small-study effects by trim-and-fill.

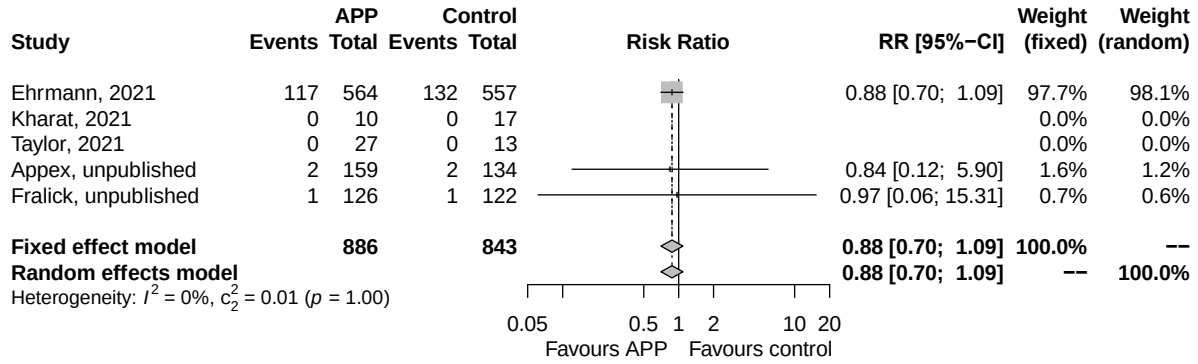


Figure S19. Meta-analysis of mortality for non-RCTs after exclusion of studies with small-study effects by trim-and-fill.

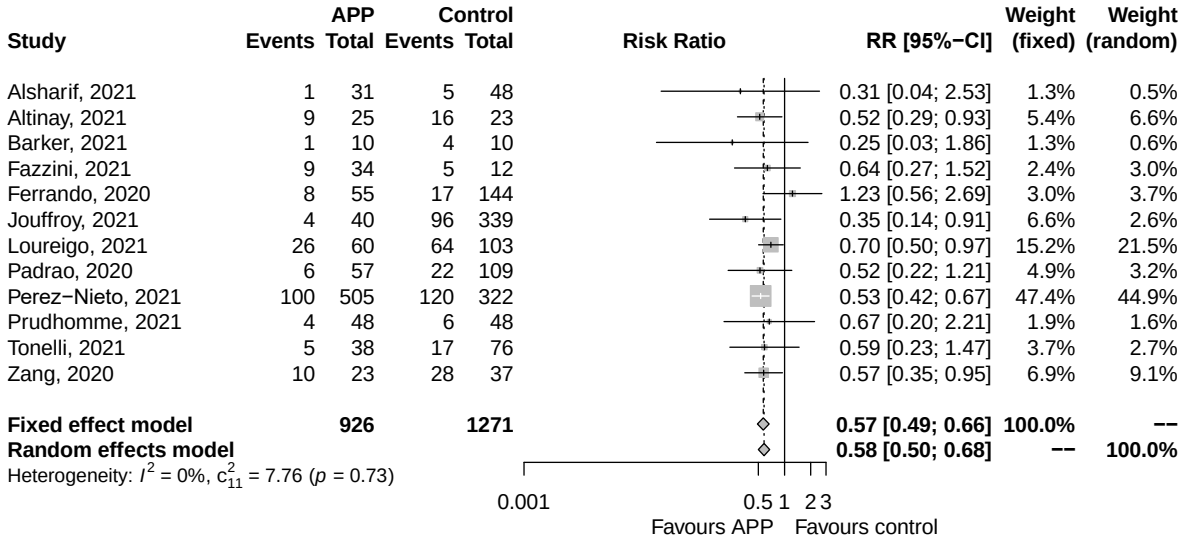
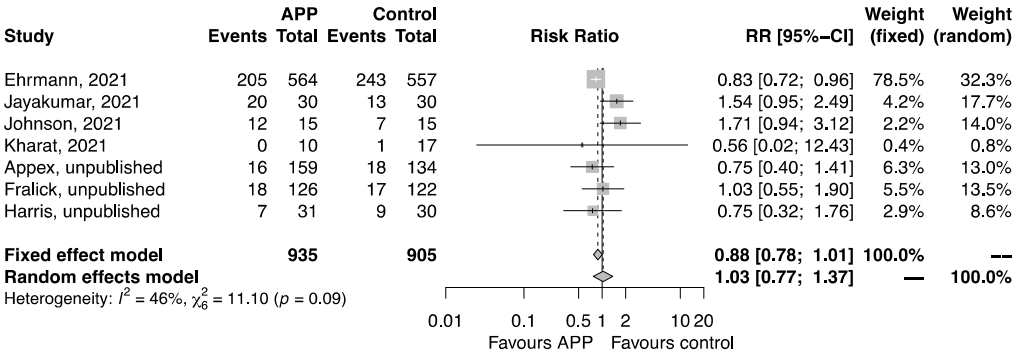
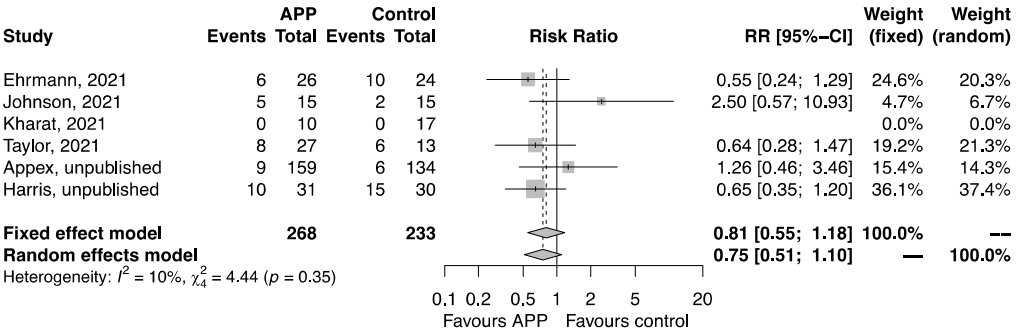


Figure S20. Secondary outcomes for included RCTs

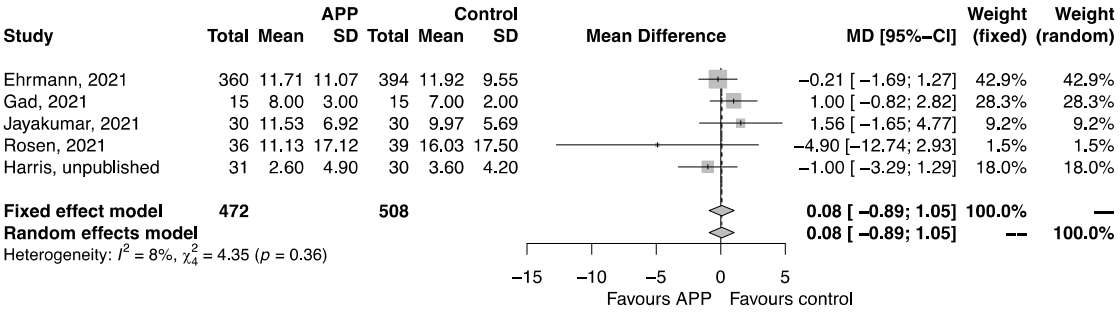
A Need for escalation of respiratory support



B Need for ICU admission



C ICU length of stay



D Hospital length of stay

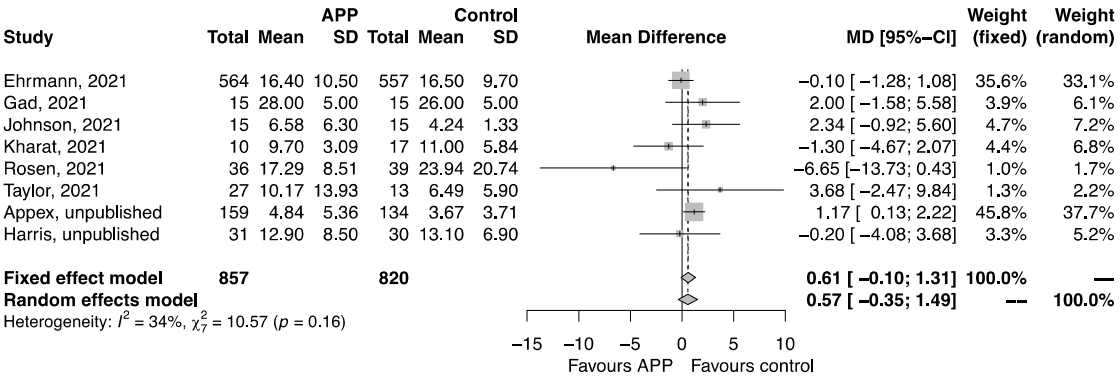
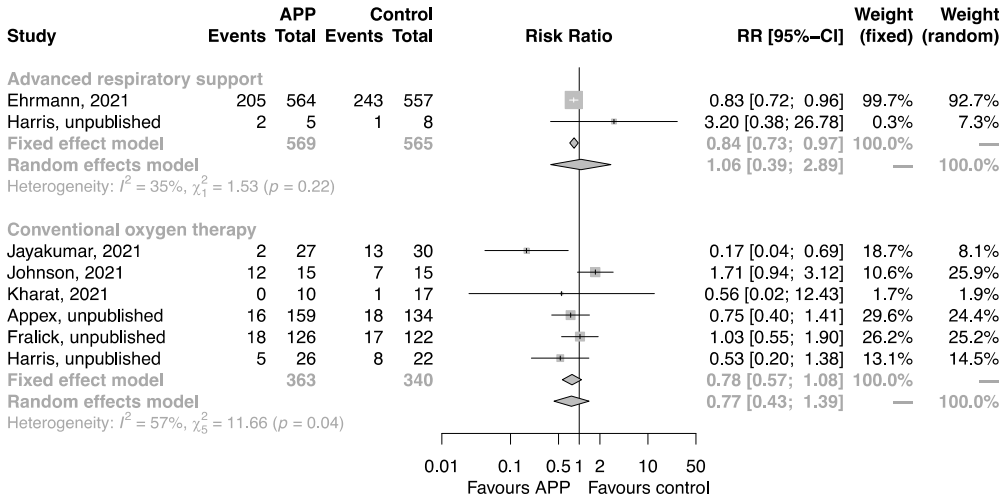


Figure S21. Subgroup analysis of need for escalation of respiratory support for included RCTs

A. Need for escalation of respiratory support (Advanced vs. Conventional respiratory support)



B. Need for escalation of respiratory support (ICU vs. Non ICU)

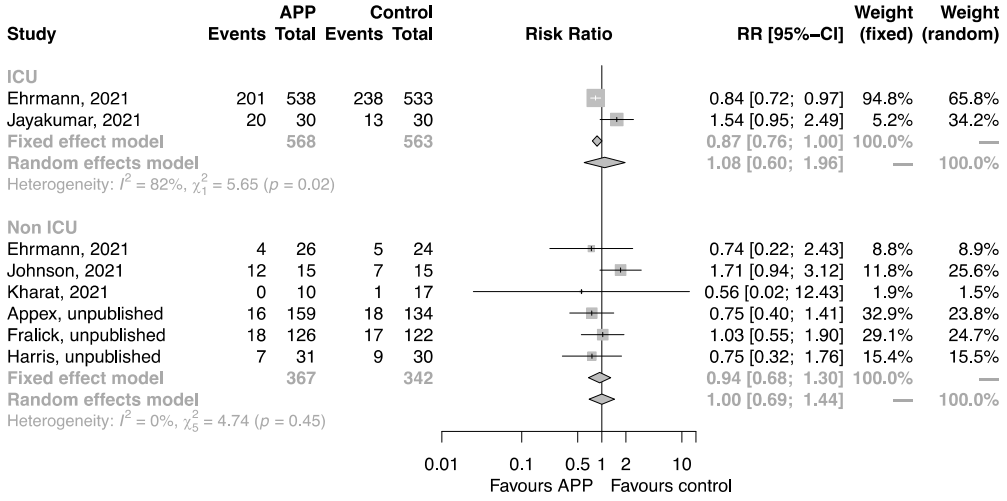


Figure S22. Subgroup analysis of need for ICU admission for included RCTs

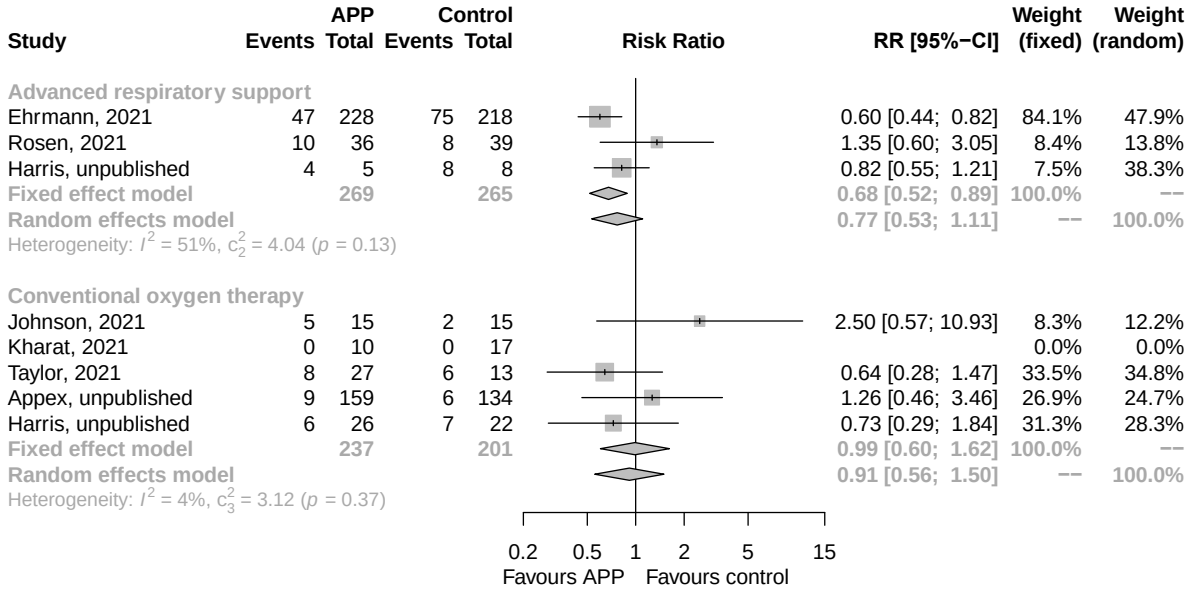


Figure S23. Meta-analysis of need for ICU admission for RCTs after exclusion of studies with small-study effects by trim-and-fill.

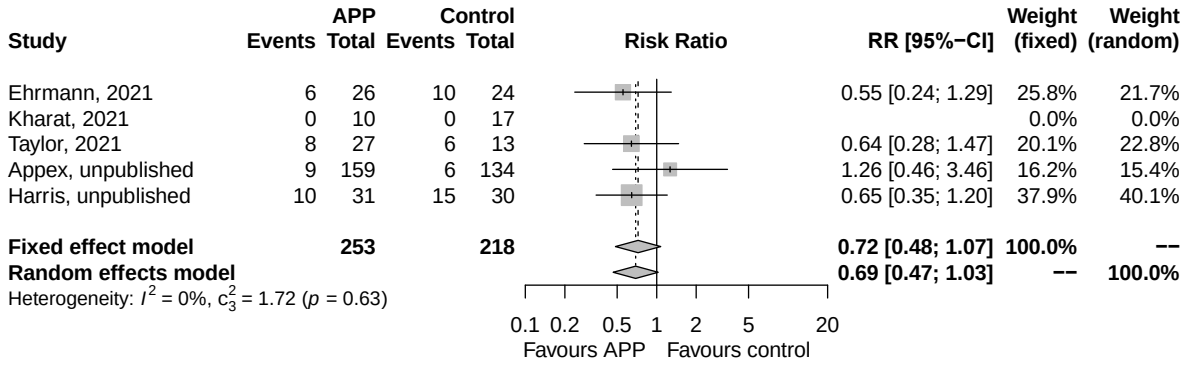
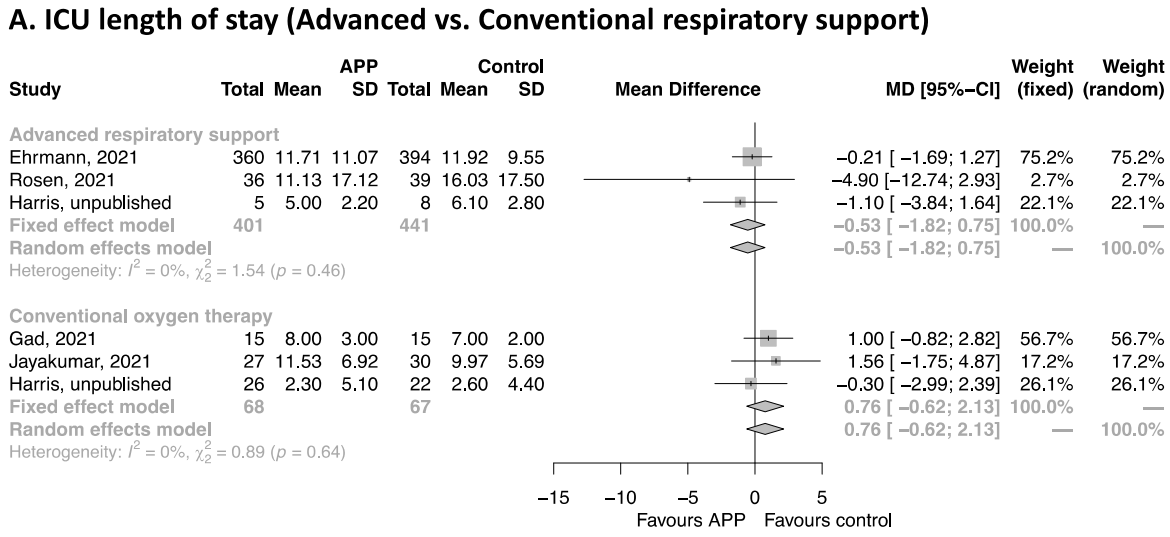


Figure S24. Subgroup analysis of ICU length of stay for included RCTs



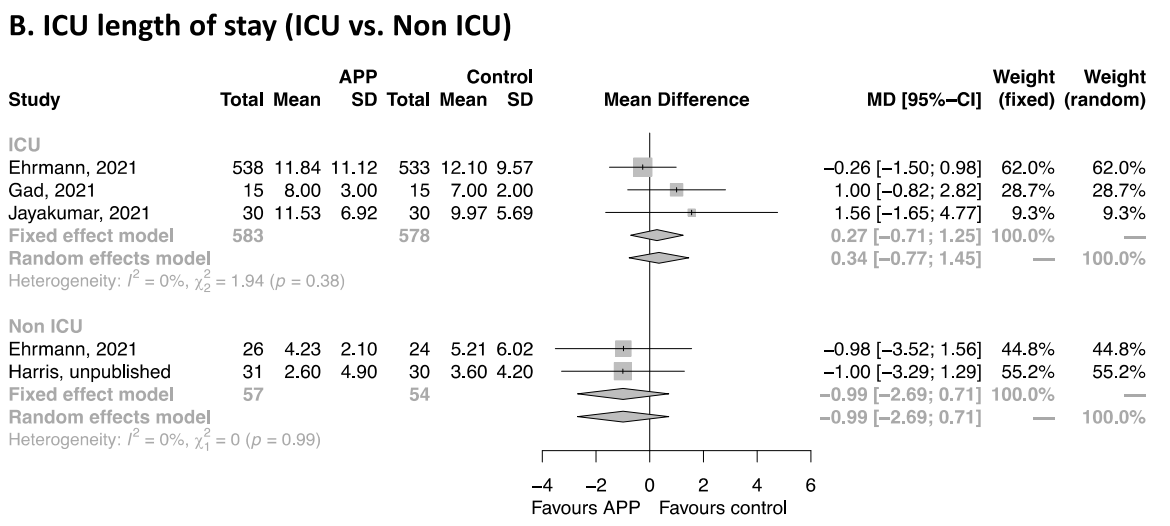
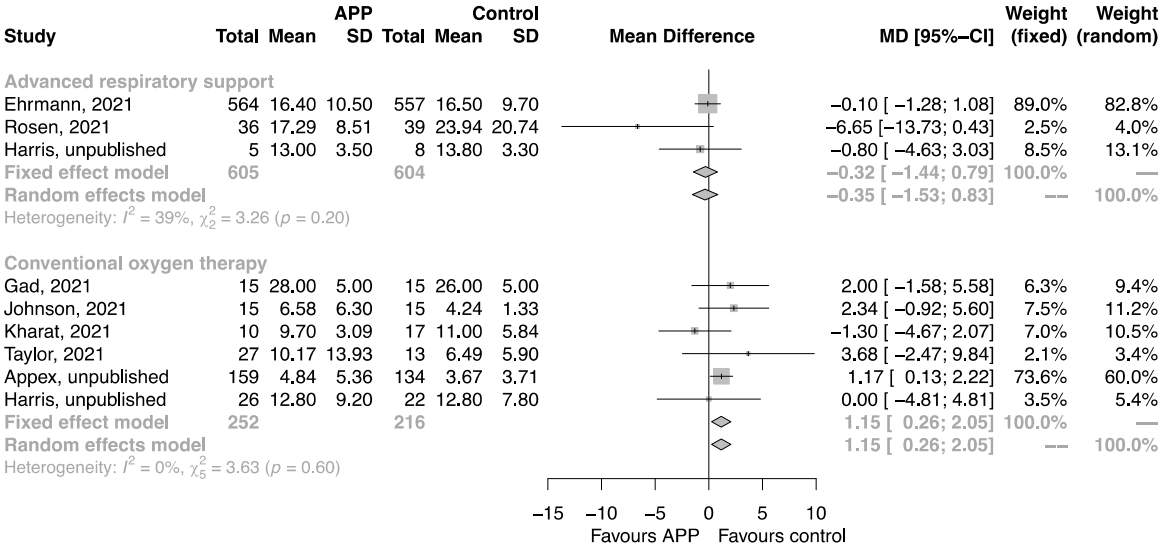


Figure S25. Subgroup analysis of hospital length of stay for included RCTs

A. Hospital length of stay (Advanced vs. Conventional respiratory support)



B. Hospital length of stay (ICU vs. Non ICU)

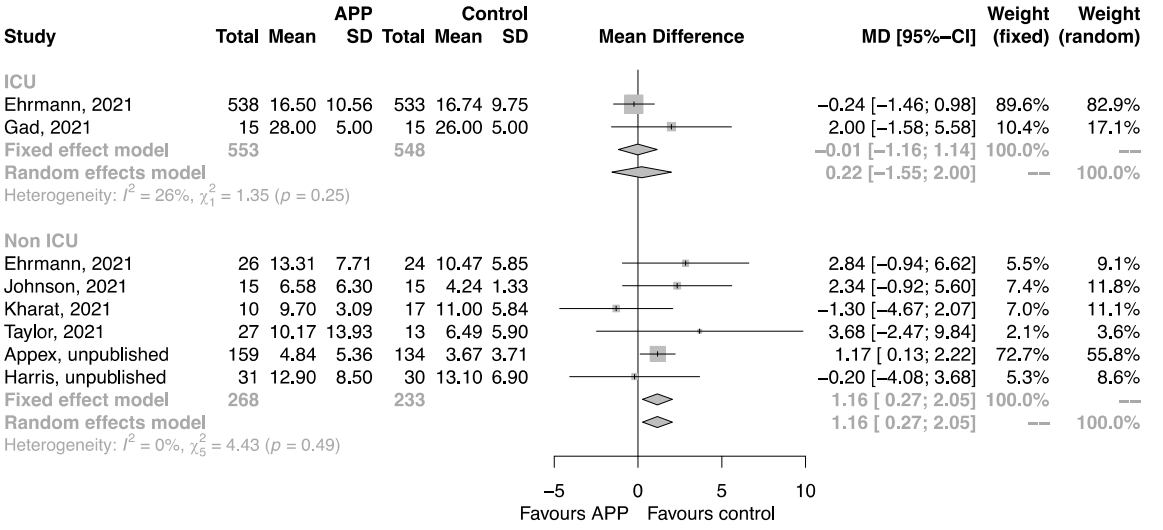


Figure S26. Trial sequential analysis of need for escalation of respiratory support for included RCTs.

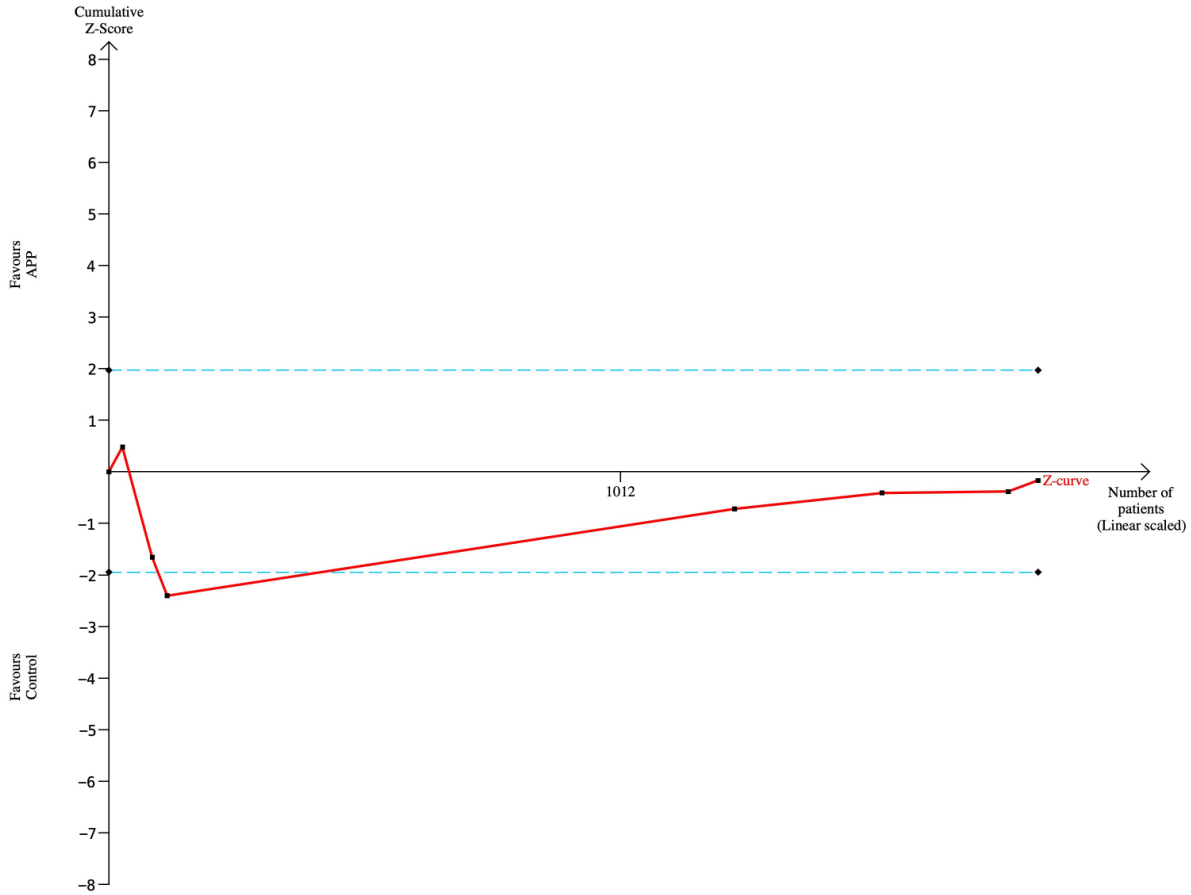


Figure S27. Trial sequential analysis of need for ICU admission for included RCTs.

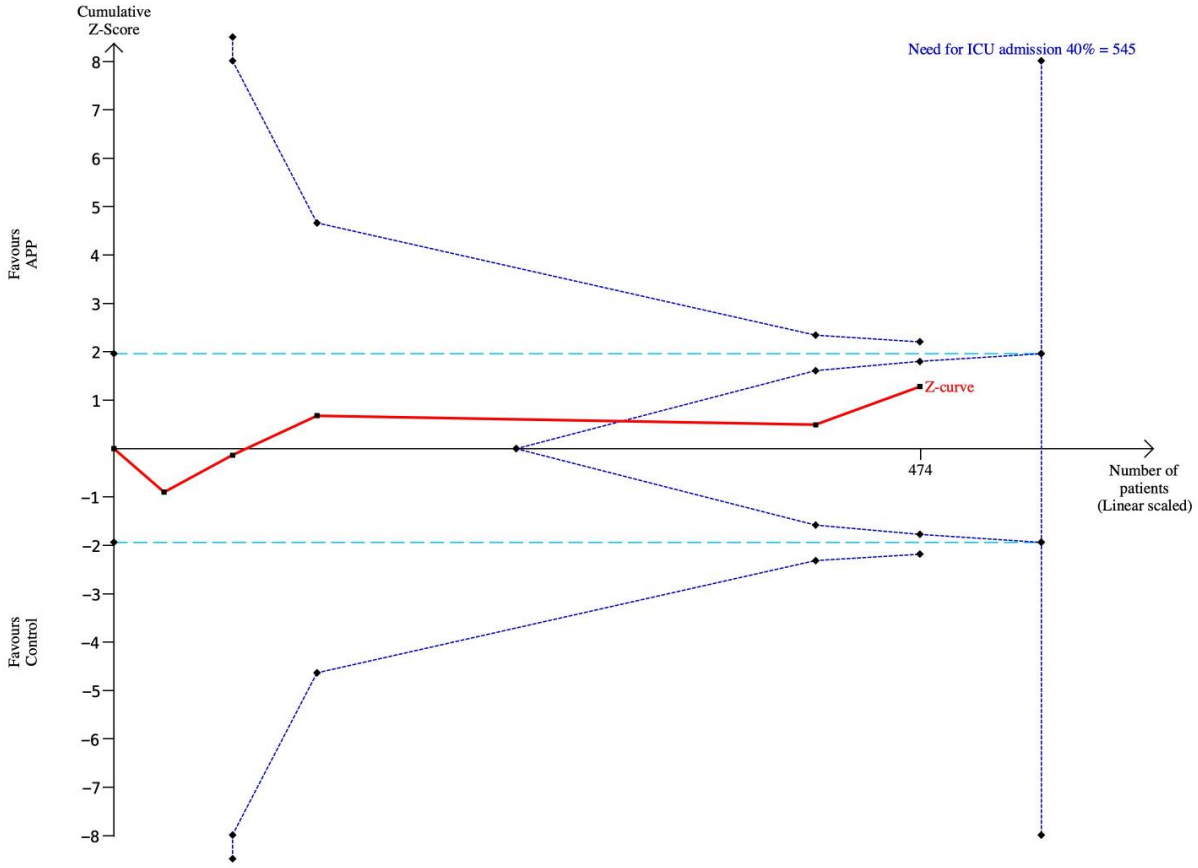


Figure S28. Trial sequential analysis of ICU length of stay for included RCTs.

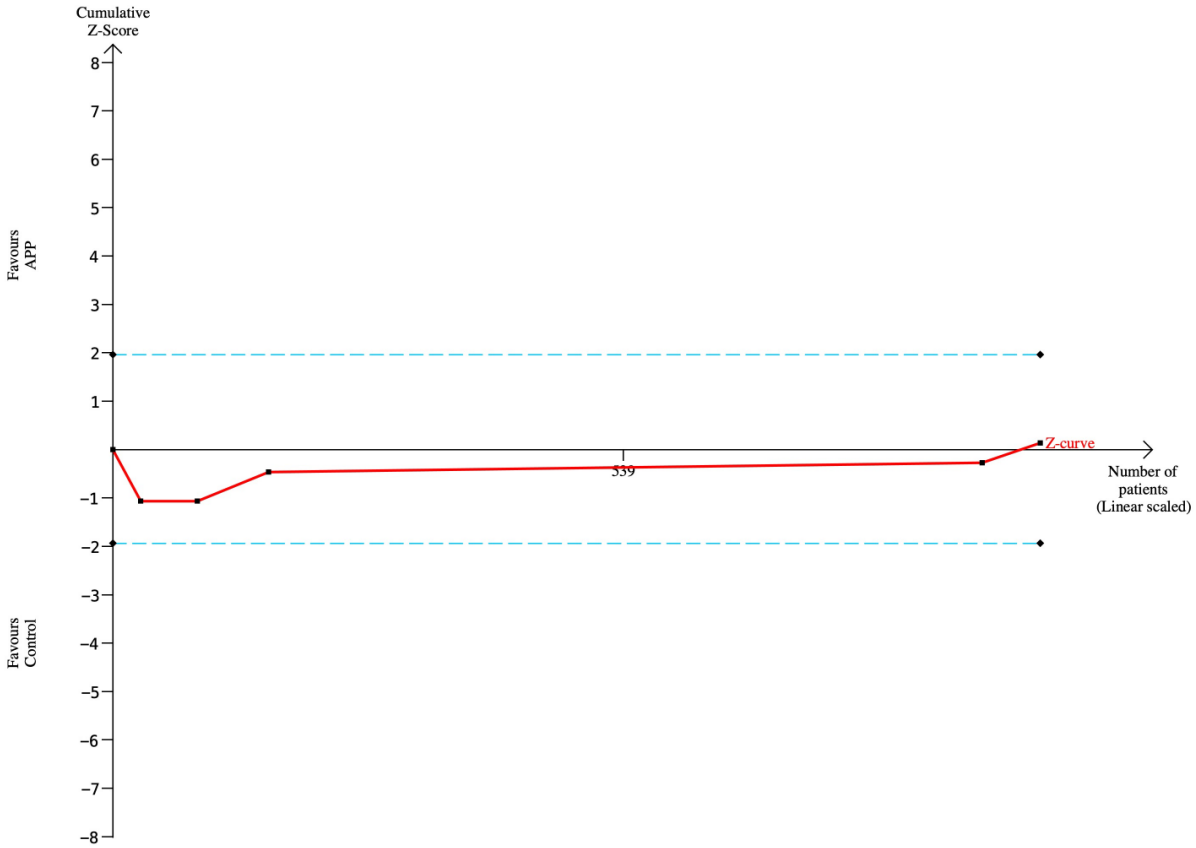


Figure S29. Trial sequential analysis of hospital length of stay for included RCTs.

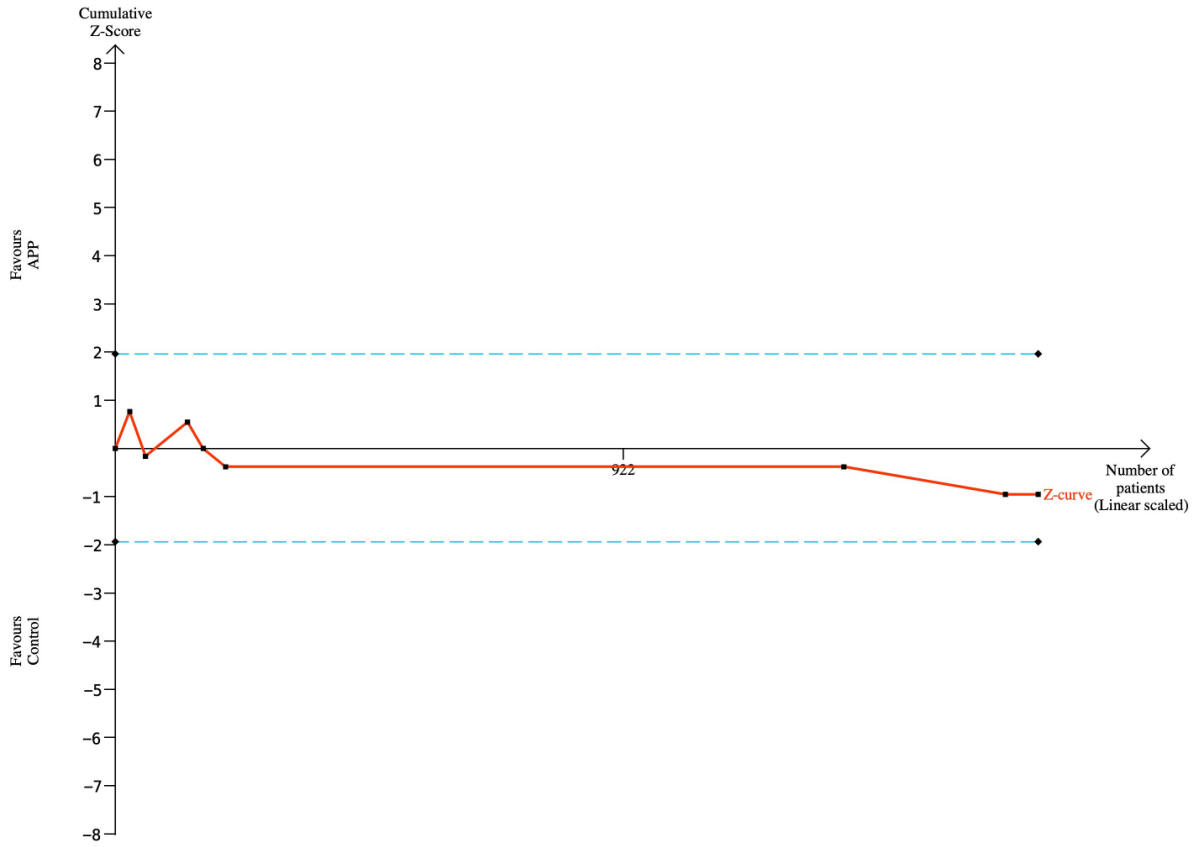
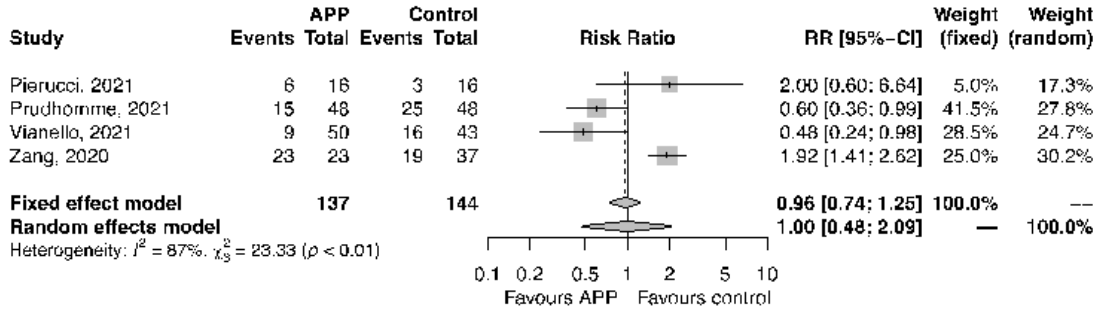
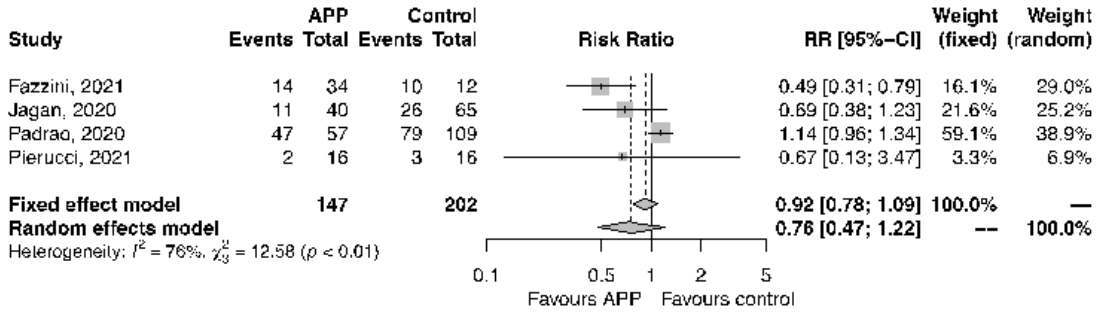


Figure S30. Secondary outcomes for non-RCTs.

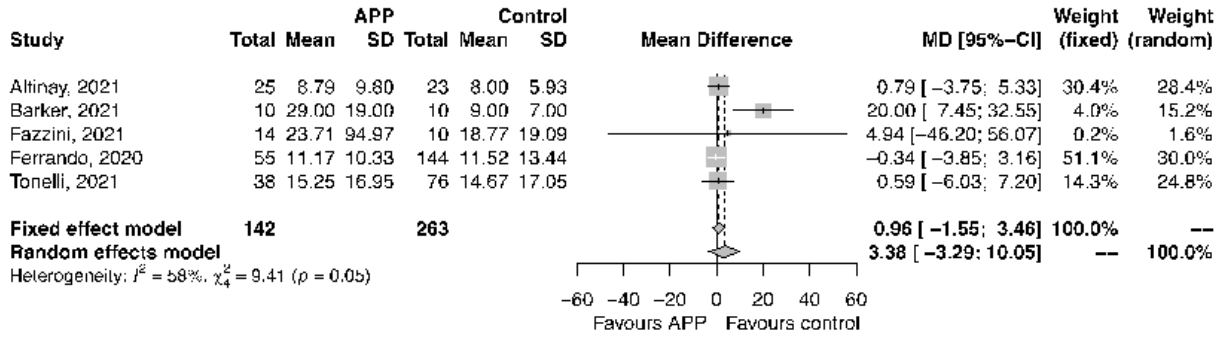
A Need for escalation of respiratory support



C Need for ICU admission



D ICU length of stay



F Hospital length of stay

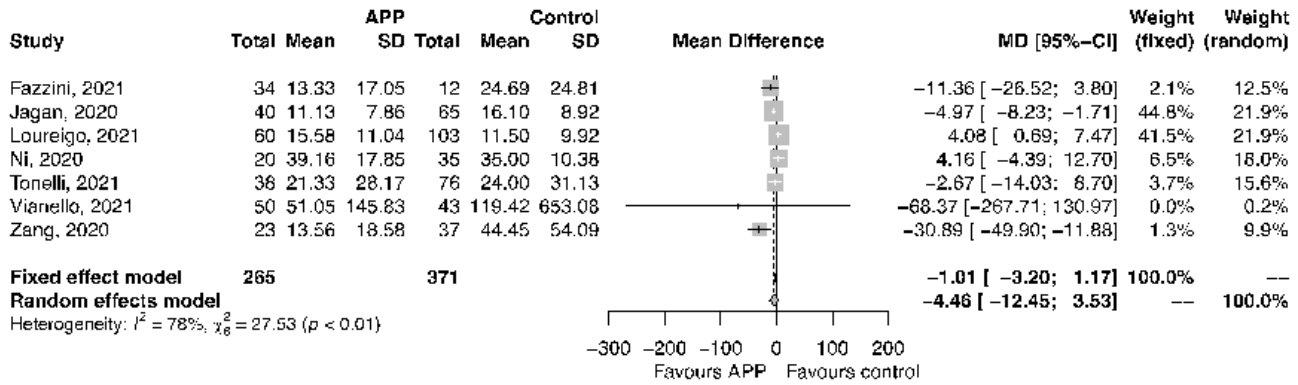


Table S6. Adverse events of the included RCTs.

Author, year	Interventions	Population	Skin breakdown (n, %)	Vomiting (n, %)	Central or arterial line dislodgement (n, %)	Cardiac arrest at any time (n, %)	Back pain (n, %)	Bloating sensation (n, %)	Discomfort (n, %)
Appex, Unpublished	COT (Room air/Nasal cannula/Mask/HFNC)	134							28 (20·9)
	COT (Room air/Nasal cannula/Mask/HFNC)+APP	159							14 (8·8)
Ehrmann, 2021	HFNC	557	10 (1·8)	18 (3·2)	17 (3·1)	1 (0·2)			
	HFNC+APP	564	8 (1·4)	15 (2·7)	26 (4·6)	3 (0·5)			
Gad, 2021	NRM	15							
	NRM+APP	15							
Jayakumar, 2021	Standard care (Face mask/NRM)	30	0 (0)	0 (0)					0 (0)
	Standard care (Nasal Prongs/Face mask/NRM/HFNC/NIV) +APP	30	0 (0)	0 (0)					2 (6·7)
Johnson, 2021	Usual care (Room air/ nasal cannula)	15							
	Usual care (Room air/nasal cannula)+APP	15							
Kharat, 2021	Usual care (Nasal cannula)	17	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Usual care (Nasal cannula) +APP	10	0 (0)	0 (0)	0 (0)	0 (0)	6 (60·0)	0 (0)	6 (60·0)
Rosén, 2021	HFNC/NIV	39	9 (23·1)	0 (0)	0 (0)	1 (2·6)			
	HFNC/NIV+APP	36	2 (5·6)	1 (2·8)	0 (0)	2 (5·6)			
Taylor, 2021	Usual care (Room air/ nasal cannula/HFNC/NIV)	13	0 (0)		0 (0)	0 (0)			
	Usual care (Nasal cannula/HFNC/NIV)+APP	27	0 (0)		0 (0)	0 (0)			
Harris, Unpublished	Usual care (Nasal cannula/NRM/HFNC/NIV)	30	0 (0)	0 (0)	0 (0)	0 (0)	1 (3·3)		
	Usual care (Nasal cannula/NRM/HFNC/NIV)+APP	31	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)		
Fralick, Unpublished	Standard care (Nasal cannula/ venturi mask/HFNC)	122							
	Standard care (Nasal cannula/ venturi mask/HFNC)+APP	126							

Missing data was presented as blank. APP, awake prone positioning; COT, conventional oxygen therapy; HFNC, high-flow nasal cannula; NIV, non-invasive ventilation; NRM, non-rebreather mask; RCT, randomised controlled trial.

Table S7. Adverse events of the included non-RCTs.

Author, year	Interventions	Population	Skin breakdown (n, %)	Vomiting (n, %)	Central or arterial line dislodgement (n, %)	Cardiac arrest at any time (n, %)	Back pain (n, %)	Bloating sensation (n, %)	Discomfort (n, %)
Alsharif, 2021	Usual care (CPAP)	48							
	Usual care (CPAP)+APP	31							
Altinay, 2021	Usual care (NRM)	23							
	Usual care (NRM)+APP	25							
Barker, 2021	Usual care (NIV)	10							
	Usual care (NIV)+APP	10							
Fazzini, 2021	Usual care (HFNC/Facemask/CPAP)+APP<1h	12							
	Usual care (HFNC/Facemask/CPAP)+APP>1h	34							
Ferrando, 2020	Usual care (HFNC)	144							
	Usual care (HFNC)+APP	55							
Jagan, 2020	APP<1h or <5 occasions per day and for <= 1 continuous hour overnight	65							
	APP>=1h orn >=5 occasions per day and for >= 1 continuous hour overnight	40							
Padrão, 2020	Usual care (Nasal cannula/Venturi mask/NRM)	109				0 (0%)			
	Usual care (Nasal cannula/Venturi mask/NRM) +APP	57				0 (0%)	3 (5·3)		
Jouffroy, 2021	Usual care (COT/HFNC/NIV/CPAP)	339							
	Usual care (COT/HFNC/CPAP)+APP	40							
Loureiro-Amigo, 2021	Usual care	103							
	Usual care+APP	60							
Meredith, 2020	Non-self proning	87							
	Self-proning	26							
Ni, 2021	Usual care	35	0 (0%)						
	Usual care+APP	20	0 (0%)						
Pierucci, 2021	Usual care (HFNC/CPAP/NIV)	16							
	Usual care (HFNC/CPAP/NIV)+APP	16							
Perez-Nieto, 2021	Usual care (Nasal cannula/NRM/HFNC)	322							
	Usual care (Nasal cannula/NRM/HFNC) +APP	505							
Sryma, 2021	Usual care (COT/HFNC/NIV)	15					0 (0%)	0 (0%)	
	Usual care (COT/HFNC/NIV)+APP	30					2 (6·6)	2 (6·7)	
Vianello, 2021	Usual care (HFNC)	43							
	Usual care (HFNC)+APP	50							
Prud'homme, 2021	Usual care (COT/HFNC)	48							
	Usual care (COT/HFNC)+APP	48							
Simioli, 2021	Usual care (HFNC/CPAP)	11							
	Usual care (HFNC/CPAP)+APP	18							
Tonelli, 2021	Usual care (HFNC/NIV)	76							
	Usual care (HFNC/NIV)+APP	38							
Zang, 2020	Usual care (Face mask)	37							
	Usual care (Face mask)+APP	23							

Missing data was presented as blank. APP, awake prone positioning; COT, conventional oxygen therapy; CPAP, continuous positive airway pressure; HFNC, high-flow nasal cannula; NIV, non-invasive ventilation; NRM, non-rebreather mask; RCT, randomised controlled trial.

Table S8. Demographical details of the induced RCTs.

Author, year	Country	Enrolment location	Study design	Interventions	Population	Targeting duration of APP	Actual duration of APP (hours)	Age (years)	Sex (Male, %)	BMI (kg/m^2)	Baseline P/F or S/F*	Use of corticosteroids (n, %)	Primary outcomes	Follow up (days)	Secondary outcomes
APPEX-19, Unpublished	USA	General ward	RCT, multicenter	Usual care (Room air/Nasal cannula/Mask/HFNC)	134	Up to four 1-2h daily sessions, and up to 12h nightly		54 (43-63)	80 (59·7)		402 (311-457)*		Progression of ARF, composite outcome of either respiratory deterioration (progression to NRB/HFNC/NIV/IMV or requiring increase in O2 ≥2L/min compared to baseline) or admission to the ICU	14 (or until discharge/death)	Respiratory deterioration, admission to the ICU, receipt of IMV, hospital mortality, diagnosis of ARDS, median self-reported dyspnea (Borg), safety outcomes, and compliance with APP
				Usual care (Room air/Nasal cannula/Mask/HFNC)+APP	159			52 (39-62)	96 (60·4)		396 (308-457)*				
Ehrmann, 2021	USA, Mexico, Canada, Ireland, France, Spain	ICU, intermediate care unit, ED, General ward	RCT, multicenter	Usual care (HFNC)	557	As long and as frequently as possible	Daily: 0 (0-0)	60·7 ±14·0	366 (65·7)	29·7± 4·6	117·3 ±37·2	492 (88·3)	Treatment failure within 28 days of enrolment, defined as intubation or death	28	Intubation, mortality, use of NIV, length of hospital stay, time to HFNC weaning in patients with treatment success, duration of invasive mechanical ventilation among intubated patients surviving to day 28, mortality in invasively mechanically ventilated patients, predefined safety outcomes, and physiological response to APP, including the ratio of S/F to respiratory rate, known as the ROX index
				Usual care (HFNC)+APP	564		Daily: 5·0 (1·6 - 8·8)	61·5 ±13·3	380 (67·4)	29·7± 4·6	119·3 ±43·3	494 (87·6)			
Gad, 2021	Egypt	ICU	RCT, single center	Usual care (NRM)	15	1-2 hours each session, 3 hours apart during waking hours for the first 3 days		46·0 (33-51)	8 (53·3)		111·0 (97·0-175·0)		Improvement of oxygenation and avoidance of intubation within the first 3 days of critical care admission		ICU stay and hospital stay
				Usual care (NRM)+APP	15			49·0 (38-62)	9 (60·0)		126·0 (88·0-164·0)				
Jayakumar, 2021	India	ICU	RCT, multicenter	Usual care (Nasal cannula/Face mask/NRM/HFNC/NIV)	30	At least 6 hours a day		57·3±12·1	25 (83·3)	25·8±2·6	185·6±126·1	30 (100·0)	The proportion of patients adhering to the protocol	Until discharge	Proportion of patients requiring escalation of respiratory support, number of hours prone and maximum hours of continuous prone positioning in a day, length of stay in ICU, ICU mortality, adverse events
				Usual care (Nasal cannula/Face mask/NRM/HFNC/NIV)+APP	30			54·8±11·1	25 (83·3)	28·2±5·7	201·4±118·8	30(100·0)			
Johnson, 2021	USA	General ward	RCT, single center	Usual care (Room air/ nasal cannula)	15	Every 4 hours with a duration of 1-2 hours or as long as tolerated	Total: 1·6 (0·2-3·1)	62 (49-75)	8 (53·3)	29·3 (24·4-32·9)			The change in P/F at 72 hours after admission	28	The change of P/F at 48 hours; need for endotracheal intubation; ICU transfer; escalation in oxygen delivery system; length of stay; ventilator-free days; in-hospital mortality
				Usual care (Room air/nasal cannula)+APP	15			52 (40-65)	8 (53·3)	32·9 (27·5-39·4)					
Kharat, 2021	Switzerland	General ward	RCT, single center	Usual care (Nasal cannula)	17	Self-proning for 12 hours per day and alternate body position every 4 hours	Total: 0·11±0·48	60±11	11 (64·7)	27·3±4·2	336 (303-388)*		Oxygen needs assessed by nasal cannula oxygen flow at 24 hours	28	S/F ratio at 24 h, respiratory and heart rate at 24 h, patient trajectory (transfer to critical care unit) and potential intervention-related adverse effects as defined by neck pain, position-related discomfort and gastro-oesophageal reflux, intubation, death at 28 days
				Usual care (Nasal cannula)+APP	10		Total: 4·9 ± 3·6	54±14	6 (60·0)	29·7±5·3	318 (284-341)*				
Rosén, 2021	Sweden	ICU, general ward	RCT, multicenter	Usual care (HFNC/NIV)	39	At least 16 hours per day	Daily: 3·4 (1·8-8·4)	65 (55-70)	32 (82·1)	29 (27-33)	115·5 (93·75-129·75)		Intubation within 30 days after enrolment	30	Duration of APP, use of NIV, time to NIV for patients included with HFNO, use of vasopressors/inotropes, CRRT, ECMO, ventilator-free days, days
				Usual care (HFNC/NIV)+APP	36		Daily: 9·0 (4·4-10·6)	66 (53-74)	23 (63·9)	28 (25-30)	115·5 (86·25-130·5)				

														free of NIV/HFNO, hospital and ICU length of stay, 30-day mortality, WHO-ordinal scale for clinical improvement at day 7 and 30, adverse events
Taylor, 2021	USA	General ward	RCT, single center	Usual care (Room air/ nasal cannula/HFNC/NIV) Usual care (Nasal cannula/HFNC/NIV) +APP	13 27			60 (54-63) 56 (45-66)	10 (76·9) 17 (63·0)	31 (28-38) 29 (26-39)		9 (69·2) 19 (70·4)	Outcomes relative to successful implementation of a future definitive RCT	Until discharge/death	S/F, time on S/F <315, receipt of intensive care, oxygen flow >6L/min, intubation, hospital length of stay, hospital mortality at 48 hours, safety outcomes
Harris, Unpublished	Qatar	General ward	RCT, multicenter	Usual care (Nasal cannula/NRM/HFNC /NIV) Usual care (Nasal cannula/NRM/HFNC /NIV)+APP	30 31	At least 3 hours and up to 16 hours per day		40 (36-45) 41 (35-50)	25 (83·3) 29 (93·5)	27·2±4·6 28·4±3·7	196 (182-240)* 196 (165-245)*	30 (100·0) 31 (100·0)	Escalation of respiratory support within the 30 days of the study	30	Incidence of intubation within 30 days of enrolment; Use of NP, HM, NRB, NIV and IMV in each group in 1st 3 days of study; Physiological response to prone averaged over days 1-3; PF or SF ratio and ROX index at baseline, 1 hour after first prone and daily for 4 days; Length of time tolerating proning; 28-day Mortality; Length of stay in ICU and hospital; Duration of invasive mechanical ventilation; Displacement of devices; Adverse events
Fralick, Unpublished	Canada, USA	General ward	RCT, multicenter	Usual care (Nasal cannula/ venturi mask/HFNC) Usual care (Nasal cannula/ venturi mask/HFNC)+APP	122 126	Four times per day (up to 2 hours for each session) and encouraged to sleep in prone position overnight	Total: 0 (0-2) [first 72 hrs]; 0 (0-0) [From 72 hours to 7 days] Total: 6 (1.5-12.8) [first 72 hrs]; 0 (0-12) [From 72 hours to 7 days]	54 (44-62) 59.5 (45-68)	82 (65.1) 77 (63.1)		305 (267-339)* 303 (261-336)*	119 (97.5) 117 (92.9)	A composite of in-hospital death, mechanical ventilation, or worsening respiratory failure defined as requiring at least 60% FiO2 for more than 24 hours	30	The components of the composite analyzed individually; time spent in prone position; change in S/F; time to recovery (defined as being on room air for at least 24 hours); time-to-discharge from hospital and the rate of serious adverse events

Data was presented as mean±SD or median (IQR). Missing data was presented as blank * Data was shown at S/F. APP, awake prone positioning; ARDS, acute respiratory distress syndrome; ARF, acute respiratory failure; BMI, body mass index; COT, conventional oxygen therapy; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; ED, emergency department; HFNC, high flow nasal cannula; HM, Hudson mask; ICU, intensive care unit; IMV, invasive mechanical ventilation; NIV, non-invasive ventilation; NP, nasal prongs, NRM, non-rebreather mask; P/F, ratio of partial pressure of arterial oxygen to fraction of inhaled oxygen; RCT, randomized controlled trial; S/F, ratio of pulse oxygen saturation to fraction of inhaled oxygen.