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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JLi, IP, SE, and CG contacted trialists for clarification on their data and invited researchers to provide unpublished data.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]))

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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) Usual care (CPAP)+APP	48 31								The rate of tracheal intubation	The rate of ICU mortality, the length of stay, and the rate of Healthcare Workers infected by SARS-CoV2													
Altinay, 2021	Turkey	ICU	Non RCT, single center, retrospective	Usual care (NRM) Usual care (NRM)+APP	23 25	18 hours/day intermittently		72·6±10·1 62·4±10·9	9 (39·1) 11 (44·0)	26·6±3·1 25·1±2·5	167.6 (159.5-213.5) 175.7 (156.8-193.2)		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													
Barker, 2021	UK	ICU	Non RCT, single center, retrospective	Usual care (NIV) Usual care (NIV)+APP	10 10	As long as possible		64±10 59±6	6 (60·0) 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													
Fazzini, 2021	UK	General ward	Non RCT, single center, prospective	Usual care (HFNC/Facemask/ CPAP)+APP<1h Usual care (HFNC/Facemask/ CPAP)+APP>1h	12 34	As long as tolerated		56 (30-79) 56 (22-77)					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													
Ferrando, 2020	Spain	ICU	Non RCT, multicenter, prospective	Usual care (HFNC) Usual care (HFNC)+APP	144 55	>16 hours/day regardless of the number of sessions		63 (55-71) 60 (54-70)	104 (72·7) 41 (75·9)	27·3 (25·1-29·4) 26·8 (24·8-31·2)	$ \begin{array}{r} 111 \cdot 0 \\ (83 \cdot 0 - 144 \cdot 0) \\ 125 \cdot 0 \\ (99 \cdot 0 - 187 \cdot 0) \end{array} $		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													
Jagan, 2020	USA		Non RCT, single center, retrospective	APP<1h or <5 occasions per day and for <= 1 continuous hour overnight APP>=1h or >=5	65	>= 1 continuous		$65{\cdot}8\pm16{\cdot}3$	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													
			renospective	occasions per day and for >= 1 continuous hour overnight	40	occasions per day and for >= 1 continuous hour overnight		$56{\cdot}0\pm14{\cdot}4$	20 (50.0)	31.3 (26.4-37.5)				lengen of swy, and anonalge apposition													
Padrão, 2020	Brazil	ED	Non RCT, single center, retrospective	Usual care (Nasal cannula/Venturi mask/NRM) Usual care (Nasal cannula/Venturi	109	At least 4 hours in their first session		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													
				mask/NRM) +APP	57	and then twice daily		51·8±13	40 (70)					in RR, SpO2, S/F, ROX index													
Lauffrage 2021	France	ICU	Non RCT,	Usual care (COT/HFNC/NIV /CPAP)	339	D . A 1		62 (53–69)	255 (75·2)	28 (25-32)	138 (98-196)		Intubation at day	Intubation at day 28, intubation until ICU discharge,													
Jouffroy, 2021 Franc	France	ICU multice retrospo	multicenter, retrospective	Non RCT, multicenter, retrospective	Non RCT, multicenter, retrospective	Non RCT, multicenter, retrospective	Non RCT, multicenter, retrospective	Non RCT, multicenter, retrospective	Non RCT, multicenter, retrospective	Non RCT, multicenter, retrospective	Non RCT, multicenter, retrospective	Non RCT, ICU multicenter, retrospective	ICU multicenter, retrospective	ICU Multicenter, retrospective	ICU Non RCT, retrospective	Non RCT, U multicenter, retrospective	Usual care (COT/HFNC/CPA P)+APP	40	Between 3 and 6 hours per session t wice daily physiotherapy.		59.5 (56-64)	36 (90.0)	28.5 (26-31)	90 (71-125)		10	day-28 mortality

Author, year	Country	Enrolment location	Study design	Interventions	Population	Targeting duration of APP	Actual duration of APP (hours)	Age (years)	Sex (Male, %)	BMI (kg/m²)	Baseline P/F or S/F*	Use of corticosteroid s (n, %)	Primary outcomes	Secondary outcomes
Loureiro- Amigo, 2021	Spain	Non-ICU	Non RCT, multicenter,	Usual care	103	APP was used at least		70·8 (60·6-74·2) 66·6	71 (68.9)		400 (241·7-438·1)* 409·5	62 (60·2)	Death during hospitalization	None
			renospective	Usual care+APP	60	one day		(59-2-72-4)	43 (/1./)		(306.3-438.1)*	52 (86.7)		
Meredith, 2021	USA	ICU	Non RCT, single center, retrospective	Usual care Usual care + APP	87 26								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
Ni. 2020	China	ICU	Non RCT, single center.	Usual care	35			64±12	21 (60.0)		128±60	22 (62·9)	Oxygenation improvement (cumulative mean	Lung lesion absorption, NEWS2, time to clinical improvement, rate of intubation
,			prospective	Usual care+APP	20	At least 4 hours per day for 10 days		60±12	12 (60.0)		147±51		difference of S/F, ROX index, and Borg scale)	avoidance, death, time to virus shredding, length of hospital stay, and adverse events
Pierucci, 2021	Italy	Intermediate	Non RCT, single center,	Usual care (HFNC/CPAP/NIV)	16			70 ± 15	10 (62)		179±18		The proportion of patients on prolonged	Improvement in oxygenation, hospital length of
		care unit	retrospective	(HFNC/CPAP/NIV)+APP	16	As long as possible		59 ± 11	13 (81)		226±74		discharged home	stay, and o-month survivar
Perez-Nieto,	Mexico-	ED, Intermediate	Non RCT, multicenter,	Usual care (Nasal cannula/NRM/HFNC)	322		T (1 12 (9	55·8±14·5	230 (71·4)			69 (21.4)	Intubation for	Death during in-hospital follow-up, factors associated with intubation amongst patients in
2021	Ecuador	ICU	retrospective	Usual care (Nasal cannula/NRM/HFNC) +APP	505	At least 2 continuous hours	Total: 12 (8- 24)	$53{\cdot}4\pm\!13{\cdot}9$	370 (73·3)			84 (16.6)	mechanical ventilation	the APP group
			Non RCT,	Usual care (COT/HFNC/NIV)	15	A minimum of 2		57·5±12·2	9 (60.0)			13 (86.7)		ROX index at 30 min from the start of the intervention, ROX
Sryma, 2021	India		single center, prospective	Usual care (COT/HFNC/NIV)+APP	30	hours per session with a target of duration of 8 hours per day		50·9±10·1	29 (96.7)			26 (86.7)	The rate of intubation	index at 12 h, days to the recovery of hypoxia (defined as room air SpO2 >93%), and mortality
Vianello, 2021	Italv	Intermediate	Non RCT, single center.	Usual care (HFNC)	43			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
,	2	care unit	prospective	Usual care (HFNC)+APP	50	At least 2 consecutive hours		67 (36-89)	33 (66.0)	26.9 (20.8-41.5)	107·2 (6·8-300·0)	50 (100.0)		of hospital stay
Prud'homme			Non RCT,	Usual care (COT/HFNC)	48	At least 3 hours each		61±18	31 (64.6)	28±5	299±45*	28 (58.3)	Upgrading of oxygen	
2021	France	Non-ICU	multicenter, retrospective	Usual care (COT/HFNC)+APP	48	day during 3 consecutive days		62±11	37 (77.1)	27±5	279±84*	28 (58·3)	delivery method on day 14	Death at day 14
		Intermediate	Non RCT,	Usual care (HFNC/CPAP)	11		Daily: 3h	71±10		28±5	95±92			
Simioli, 2021	Italy	care unit	single center, retrospective	Usual care (HFNC/CPAP)+APP	18		Daily: >10h	61±14		28±2	96·5±35			
Tonelli, 2021	Italy	ICU	Non RCT, multicenter.	Usual care (HFNC/NIV)	76			70 (33-80)	55 (73)	28 (20-37)	153 (84-232)	55 (73)	Endotracheal intubation	Time to intubation, mortality, non invasive respiratory support-free-days (i.e. days spent without HENC, NIV, CPAP, or invasive
,21	,		retrospective	Usual Care (HFNC/NIV)+APP	38	At least 3 hours per session with 1-4 sessions per day		61 (32-75)	25 (66)	26 (19-36)	141 (73-223)	25 (66)	rate	mechanical ventilation at 1-month), tracheostomy, length of RICU and hospital stay
Zang, 2020	China	ICU	Non RCT, single center,	Usual care (Face mask)	37			66·14±9·19	26 (70.3)					
			prospective	Usual care (Face mask)+APP	23		13·43±8·04	62·65±10·83	13 (56.5)					

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

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; SpO₂, pulse oxygen saturation.

Table S2. Comorbidities of the included RCTs.

Author, year	Interventions	Population	Hypertension	COPD	Chronic kidney disease (r, θ')	Severe liver disease $(n, 0/2)$	Diabetes	Cancer
	COT (Poom air/Negel connule/Magk/HENC)	124	(11, 70)	(11, 70)	(11, 70)	(11, 70)	(11, 70) 20 (20, 1)	(11, 70)
Appex,	$COT (D = \frac{1}{2} D = \frac{1}{2}$	154	$02(40^{-}3)$	14(10.4)			39 (29-1)	9(0.7)
Unpublished	COT (Room air/Nasal cannula/Mask/HFNC) +APP	159	/6 (4/·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)
God 2021	NRM	15	3 (20.0)	3 (20.0)			6 (33·3)	
Odu, 2021	NRM+APP	15	4 (26.7)	5 (33·3)			7 (46.7)	
I	Standard care (Face mask/NRM)	30	9 (30.0)				19 (63.3)	
Jayakumar, 2021	Standard care (Nasal Prongs/Face mask/NRM/HFNC/NIV) +APP	30	13 (43.3)				13 (43.3)	
I-h 2021	Usual care (Room air/ nasal cannula)	15						
Johnson, 2021	Usual care (Room air/nasal cannula)+APP	15						
Whenet 2021	Usual care (Nasal cannula)	17	9 (52.9)	0 (0)	1 (5.9)		3 (17.6)	
Kilarat, 2021	Usual care (Nasal cannula) +APP	10	3 (30.0)	0 (0)	0 (0)		2 (20.0)	
D / 2021	HFNC/NIV	39	21 (55)	4 (10)	2 (5.1)	1 (3)	11 (28.2)	1 (3)
Rosen, 2021	HFNC/NIV+APP	36	17 (47)	2 (6)	3 (8.3)	0 (0)	14 (38.9)	4 (11)
T 1 2021	Usual care (Room air/ nasal cannula/HFNC/NIV)	13			2 (15.4)		5 (38.5)	
Taylor, 2021	Usual care (Nasal cannula/HFNC/NIV) +APP	27			7 (25.9)		10 (37.0)	
Harris,	Usual care (Nasal cannula/NRM/HFNC/NIV)	30	3 (10.0)	0 (0)		0 (0)	10 (33.3)	0 (0)
Unpublished	Usual care (Nasal cannula/NRM/HFNC/NIV) +APP	31	6 (19·4)	0 (0)		1 (3.2)	14 (45.2)	0 (0)
Fralick,	Standard care (Nasal cannula/ venturi mask/HFNC)	122	42 (34.4)	15 (12.3)			31 (25.4)	
Unpublished	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, %)
	Usual care (CPAP)	48				•	· · · · · · ·	
Alsharif, 2021	Usual care (CPAP)+APP	31						
A 14:	Usual care (NRM)	23	15 (65.2)	0 (0)	1 (4·3)		6 (26.1)	2 (8.7)
Altinay, 2021	Usual care (NRM)+APP	25	10 (40.0)	2 (8.0)	0 (0)		10 (40.0)	0 (0)
Barker 2021	Usual care (NIV)	10						
Darker, 2021	Usual care (NIV)+APP	10						
Fazzini, 2021	Usual care (HFNC/Facemask/CPAP)+APP<1h	12						
Fazzini, 2021	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)
54gan, 2020	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)
	Usual care (Nasal cannula/Venturi mask/NRM)	109	62 (57)				36 (33.0)	6 (6)
Padrão, 2020	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)	
Journoy, 2021	Usual care (COT/HFNC/CPAP)+APP	40	13 (32.5)	3 (7.5)	2 (5.0)		11 (27.5)	
Loureiro-Amigo,	Usual care	103	64 (62.1)	16 (15.5)			38 (36.9)	
2021	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	10 (27.5)				12 (25.0)	
Prud'homme, 2021	Usual care (COT/HFNC)	48	18 (37.5)				12 (25.0)	
	Usual care (UUT/HFNC)+APP	48	15 (31-3)				/ (14·6)	
Simioli, 2021	Usual care (HFNC/CPAP)	11						
	Usual care (HFNC/CPAP)+APP	18	60 (70)	11 (15)	8 (10)		14 (19)	8 (11)
Tonelli, 2021	Usual care (HFINC/INIV)	/0	00 (79)	6 (16)	δ (10) 2 (6)		14 (18)	8 (11)
	Usual care (FINU/NIV)+APP	30 27	32 (04) 17 (45-0)	0(10)	2 (0)		0 (24,2)	4 (11)
Zang, 2020	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.

Risk ratio for intubation (random effects model)



Figure S3. Funnel plot of mortality for included RCTs.

Risk ratio for mortality (random effects model)



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

Risk ratio for need for escalation of respiratory support (random effects model)



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

Risk ratio for ICU admission (random effects model)



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

Risk ratio for ICU length of stay (random effects model)



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

Risk ratio for Hospital length of stay (random effects model)

		Selection	on		Comparal	oility		Outcome		
Author, year	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	Quality [#]
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 1 or 2 stars in 'Comparability' domain AND 2 or 3 stars in 'Outcome' domain; Fair - 2 stars in 'Selection' domain AND 1 or 2 stars in 'Comparability' domain OR 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.

Risk ratio for intubation (random effects model)



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

Risk ratio for intubation (random effects model)

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

			No of p	articipants			Certainty assessme	ent		No of	oatients	Effect (Randon	n effects model)	
Outcome	No of studies	Study design	APP	Control	Risk of bias	Imprecision	Inconsistency	Indirectness	Publication bias	APP	Control	Relative risk (95% CI)	Absolute effect (95% CI)	Certainty
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)	-	$\oplus \oplus \bigcirc \bigcirc$ Low
Subgroup: Advanced respiratory support	3	RCT	605	604	Not serious ^a	High ^d	Moderatei	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	Moderatei	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	Moderateg	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.









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

		APP	C	ontrol			Weight	Weight
Study	Events	Total	Events	Total	Risk Ratio	RR [95%–Cl]	(fixed)	(random)
Alsharif, 2021	2	31	12	48	<u> </u>	0.26 [0.06; 1.08]	2.3%	3.0%
Altinay, 2021	8	25	19	23		0.39 [0.21; 0.71]	4.9%	7.5%
Barker, 2021	6	10	5	10	÷ 🛌	1.20 [0.54; 2.67]	1.2%	6.0%
Fazzini, 2021	10	34	10	12		0.35 [0.20; 0.63]	3.6%	7.7%
Ferrando, 2020	22	55	60	144		0.96 [0.66; 1.40]	8.2%	9.4%
Jagan, 2020	4	40	18	65		0.36 [0.13; 0.99]	3.4%	4.7%
Jouffroy, 2021	16	40	240	339		0.57 [0.38; 0.83]	12.5%	9.3%
Meredith, 2021	3	26	14	87		0.72 [0.22; 2.30]	1.6%	4.0%
Ni, 2020	0	20	1	35		0.58 [0.02; 13.53]	0.3%	0.8%
Padrao, 2020	33	57	53	109		1.19 [0.89; 1.60]	9.0%	10.0%
Perez-Nieto, 2021	119	505	130	322		0.58 [0.48; 0.72]	39.2%	10.6%
Pierucci, 2021	2	16	3	16		0.67 [0.13; 3.47]	0.7%	2.4%
Prudhomme, 2021	7	48	8	48		0.88 [0.34; 2.22]	2.0%	5.2%
Simioli, 2021	1	18	2	11		0.31 [0.03; 2.99]	0.6%	1.4%
Sryma, 2021	2	30	5	15		0.20 [0.04; 0.91]	1.6%	2.7%
Tonelli, 2021	7	38	30	76		0.47 [0.23; 0.96]	4.9%	6.6%
Vianello, 2021	4	50	12	43		0.29 [0.10; 0.82]	3.2%	4.5%
Zang, 2020	8	23	4	37	\$ 	3.22 [1.09; 9.49]	0.8%	4.3%
Fixed effect model		1066		1 4 40	*	0.65 [0.57; 0.73]	100.0%	
Random effects model					<u></u>	0.62 [0.47; 0.83]		100.0%
Heterogeneity: $I^2 = 65\%$, χ	$\frac{2}{17} = 48.5$	1 (p < (0.01)	Г		1		
				0.0	0.1 0.5 1 2 102	20		

Favours APP Favours control

B Mortality

		APP	Co	ontrol			Weight	Weight
Study	Events	Total	Events	Total	Risk Ratio	RR [95%-CI]	(fixed)	(random)
Alsharif, 2021	1	31	5	48		0.31 [0.04; 2.53]	1.1%	0.5%
Altinay, 2021	9	25	16	23		0.52 [0.29; 0.93]	4.9%	6.4%
Barker, 2021	1	10	4	10		0.25 [0.03; 1.86]	1.2%	0.6%
Fazzini, 2021	9	34	5	12		0.64 [0.27; 1.52]	2.2%	2.9%
Ferrando, 2020	8	55	17	144	<u>;</u>	1.23 [0.56; 2.69]	2.7%	3.6%
Jagan, 2020	0	40	16	65		0.05 [0.00; 0.79]	3.7%	0.3%
Jouffroy, 2021	4	40	96	339		0.35 [0.14; 0.91]	5.9%	2.5%
Loureigo, 2021	26	60	64	103)	0.70 [0.50; 0.97]	13.8%	20.9%
Padrao, 2020	6	57	22	109		0.52 [0.22; 1.21]	4.4%	3.1%
Perez-Nieto, 2021	100	505	120	322		0.53 [0.42; 0.67]	42.8%	43.7%
Pierucci, 2021	0	16	3	16		0.14 [0.01; 2.55]	1.0%	0.3%
Prudhomme, 2021	4	48	6	48		0.67 [0.20; 2.21]	1.8%	1.5%
Simioli, 2021	0	18	3	11		0.09 [0.01; 1.57]	1.3%	0.3%
Sryma, 2021	2	30	4	15		0.25 [0.05; 1.21]	1.6%	0.9%
Tonelli, 2021	5	38	17	76		0.59 [0.23; 1.47]	3.3%	2.6%
Vianello, 2021	2	50	7	43		0.25 [0.05; 1.12]	2.2%	1.0%
Zang, 2020	10	23	28	37		0.57 [0.35; 0.95]	6.3%	8.9%
Fixed effect model		1080		1421	÷	0.53 [0.45; 0.61]	100.0%	
Random effects model						0.56 [0.48; 0.65]		100.0%
Heterogeneity: $I^2 = 0\%$, χ^2_{10}	$_{0} = 15.49$	(<i>p</i> = 0.	49)	Г]		
				0.00	01 0.51 23	3		
					Favours APP Fav	ours control		

Figure S14. Subgroup analysis of mortality for included RCTs

		APP	C	ontrol				Weight	Weight
Study	Events	Total	Events	Total	Risk Ratio	RR [95%	%–CI]	(fixed)	(random)
Advanced respiratory s	upport								
Ehrmann, 2021	117	564	132	557		0.88 [0.70;	1.09]	97.6%	90.6%
Rosen, 2021	6	36	3	39		2.17 [0.58;	8.03]	2.1%	7.8%
Harris, unpublished	1	5	0	8		4.64 [0.23; 9	94.58]	0.3%	1.5%
Fixed effect model		605		604	\$	0.91 [0.74;	1.13]	100.0%	_
Random effects model					\rightarrow	1.23 [0.54;	2.80]	_	100.0%
Heterogeneity: $I^2 = 32\%$, χ_2^2	= 2.92 (p = 0.2	3)						
Conventional oxygen th	erapy								
Gad, 2021	3	15	3	15		1.00 [0.24;	4.18]	35.0%	37.5%
Jayakumar, 2021	2	27	2	30		1 11 [0 17;	7.35]	22.1%	22.0%
Johnson, 2021	2	15	0	15		— 5.00 [0 . 26; 9	95.88]	5.8%	9.2%
Kharat, 2021	0	10	0	17				0.0%	0.0%
Taylor, 2021	0	27	0	13				0.0%	0.0%
Appex, unpublished	2	159	2	134		0.84 [0.12;	5.90]	25.3%	20.8%
Fralick, unpublished	1	126	1	122		0.97 [0.06; 1	5.31]	11.8%	10.5%
Harris, unpublished	0	26	0	22				0.0%	0.0%
Fixed effect model		405		368	\sim	1.21 [0.51;	2.87]	100.0%	_
Random effects model					\sim	1.14 [0.47;	2.75]	_	100.0%
Heterogeneity: $I^2 = 0\%$, $\chi_4^2 =$	= 1.1 (p =	= 0.89)							
						1			
				0.0	05 051 2 10	100			
				Fa	avours APP Favours contro)I			

A. Mortality (Advanced vs. Conventional respiratory support)

Test for subgroup differences (fixed effect): $\chi_1^2 = 0.40$, df = 1 (p = 0.53) Test for subgroup differences (random effects): $\chi_1^2 = 0.02$, df = 1 (p = 0.90)

B. Mortality (ICU vs. Non ICU)

		APP	Co	ontrol			Weight	Weight
Study	Events	Total	Events	Total	Risk Ratio	RR [95%–Cl]	(fixed)	(random)
ICU								
Ehrmann, 2021	110	538	122	533		0.89 [0.71; 1.12]	96.1%	95.9%
Gad, 2021	3	15	3	15		1.00 [0.24; 4.18]	2.4%	2.4%
Jayakumar, 2021	3	30	2	30		1 50 [0 27; 8 34]	1.6%	1.7%
Fixed effect model		583		578	\$	0.91 [0.72; 1.13]	100.0%	_
Random effects model					\$	0.90 [0.72; 1.13]	_	100.0%
Heterogeneity: $I^2 = 0\%$, χ^2_2	= 0.36 (p	= 0.83	3)					
Non ICU								
Ehrmann, 2021	7	26	10	24		0.65 [0.29; 1.42]	71.3%	72.4%
Johnson, 2021	2	15	0	15		- 5.00 [0.26; 95.88]	3.4%	5.2%
Kharat, 2021	0	10	0	17			0.0%	0.0%
Taylor, 2021	0	27	0	13			0.0%	0.0%
Appex, unpublished	2	159	2	134		0.84 [0.12; 5.90]	14.9%	11.9%
Fralick, unpublished	1	126	1	122		0.97 [0.06; 15.31]	7.0%	5.9%
Harris, unpublished	1	31	0	30		- 2.90 [0.12; 68.58]	3.5%	4.5%
Fixed effect model		394		355	$ \rightarrow $	0.93 [0.48; 1.78]	100.0%	_
Random effects model					$ \rightarrow $	0.81 [0.41; 1.59]	—	100.0%
Heterogeneity: $I^2 = 0\%$, χ_4^2	= 2.42 (p	= 0.66	6)					
				0.	05 051 2 10	100		
				0.		100		

Test for subgroup differences (fixed effect): $\chi_1^2 = 0.00$, df = 1 (p = 0.95) Test for subgroup differences (random effects): $\chi_1^2 = 0.08$, df = 1 (p = 0.77)



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





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.

Study	Events	APP Total	Co Events	ontrol Total	Risk Ratio	RR [95%–CI]	Weight (fixed)	Weight (random)
Ehrmann, 2021 Kharat, 2021 Taylor, 2021 Appex, unpublished Fralick, unpublished	117 0 2 1	564 10 27 159 126	132 0 0 2 1	557 17 13 134 122		0.88 [0.70; 1.09] 0.84 [0.12; 5.90] 0.97 [0.06; 15.31]	97.7% 0.0% 0.0% 1.6% 0.7%	98.1% 0.0% 0.0% 1.2% 0.6%
Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$, c_2^2	= 0.01 (p	886 = 1.00)	843 0.0	05 0.5 1 2 10 2 Favours APP Favours contro	0.88 [0.70; 1.09] 0.88 [0.70; 1.09] 0.88 [0.70; 1.09]	100.0%	 100.0%

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

Study	Events	APP Total	Co Events	ontrol Total	Risk Ratio	RR [95%-CI]	Weight (fixed)	Weight (random)
Alsharif, 2021	1	31	5	48		0.31 [0.04; 2.53]	1.3%	0.5%
Altinay, 2021	9	25	16	23		0.52 [0.29; 0.93]	5.4%	6.6%
Barker, 2021	1	10	4	10		0.25 [0.03; 1.86]	1.3%	0.6%
Fazzini, 2021	9	34	5	12		0.64 [0.27; 1.52]	2.4%	3.0%
Ferrando, 2020	8	55	17	144	<u>t</u>	1.23 [0.56; 2.69]	3.0%	3.7%
Jouffroy, 2021	4	40	96	339		0.35 [0.14; 0.91]	6.6%	2.6%
Loureigo, 2021	26	60	64	103		0.70 [0.50; 0.97]	15.2%	21.5%
Padrao, 2020	6	57	22	109		0.52 [0.22; 1.21]	4.9%	3.2%
Perez-Nieto, 2021	100	505	120	322		0.53 [0.42; 0.67]	47.4%	44.9%
Prudhomme, 2021	4	48	6	48	<u>t</u> +	0.67 [0.20; 2.21]	1.9%	1.6%
Tonelli, 2021	5	38	17	76		0.59 [0.23; 1.47]	3.7%	2.7%
Zang, 2020	10	23	28	37		0.57 [0.35; 0.95]	6.9%	9.1%
Fixed effect model		926		1271	\$	0.57 [0.49; 0.66]	100.0%	
Random effects model					\$	0.58 [0.50; 0.68]		100.0%
Heterogeneity: $I^2 = 0\%$, c_{11}^2	1 = 7.76 (<i>j</i>	b = 0.7	3)	I				
				0.0	01 0.5 1 23	3		
					Favours APP Fav	ours control		

Figure S20. Secondary outcomes for included RCTs

Study	Events	APP Total	Co Events	ontrol Total	Risk Ratio	RR [95%–CI]	Weight (fixed)	Weight (random)
Ehrmann, 2021	205	564	243	557		0.83 [0.72; 0.96]	78.5%	32.3%
Jayakumar, 2021	20	30	13	30		1.54 [0.95; 2.49]	4.2%	17.7%
Johnson, 2021	12	15	7	15	-	1.71 [0.94; 3.12]	2.2%	14.0%
Kharat, 2021	0	10	1	17		0.56 [0.02; 12.43]	0.4%	0.8%
Appex, unpublished	16	159	18	134		0.75 [0.40; 1.41]	6.3%	13.0%
Fralick, unpublished	18	126	17	122		1.03 [0.55; 1.90]	5.5%	13.5%
Harris, unpublished	7	31	9	30		0.75 [0.32; 1.76]	2.9%	8.6%
Fixed effect model		935		905	4	0.88 [0.78; 1.01]	100.0%	
Random effects model	•			_	�	1.03 [0.77; 1.37]	—	100.0%
Heterogeneity: $I^2 = 46\%$, χ	$\frac{2}{6} = 11.10$	(p = 0.	09)	1	1 1 1 1	I		
				0.0	1 0.1 0.5 1 2 10	0 20		
					Favours APP Favours of	control		

A Need for escalation of respiratory support

B Need for ICU admission

		APP	Co	ontrol			Weight	Weight
Study	Events	Total	Events	Total	Risk Ratio	RR [95%–Cl]	(fixed)	(random)
Ehrmann, 2021	6	26	10	24		0.55 [0.24; 1.29]	24.6%	20.3%
Johnson, 2021	5	15	2	15		2 50 [0.57; 10.93]	4.7%	6.7%
Kharat, 2021	0	10	0	17			0.0%	0.0%
Taylor, 2021	8	27	6	13		0.64 [0.28; 1.47]	19.2%	21.3%
Appex, unpublished	9	159	6	134		1.26 [0.46; 3.46]	15.4%	14.3%
Harris, unpublished	10	31	15	30		0.65 [0.35; 1.20]	36.1%	37.4%
Fixed effect model		268		233		0.81 [0.55; 1.18]	100.0%	
Random effects model					\rightarrow	0.75 [0.51; 1.10]	_	100.0%
Heterogeneity: $I^2 = 10\%$, χ	$\chi_4^2 = 4.44$ (p = 0.3	5)	I				
				0	1 0.2 0.5 1 2 5 3 Favours APP Favours control	20		

C ICU length of stay

Ctudy.	Total	Moon	APP	Total	C	ontrol	Mod	n Difforo			0.50/ 011	Weight	Weight
Sludy	Total	wear	30	Total	wear	30	Mea	In Differen	ice	MD [:	5%-CI]	(lixeu)	(ranuoni)
Ehrmann, 2021	360	11.71	11.07	394	11.92	9.55			-	-0.21 [-1.0	69; 1 . 27]	42.9%	42.9%
Gad, 2021	15	8.00	3.00	15	7.00	2.00				1.00 [-0.8	32; 2.82]	28.3%	28.3%
Jayakumar, 2021	30	11.53	6.92	30	9.97	5.69				1.56 [-1.0	65; 4.77]	9.2%	9.2%
Rosen, 2021	36	11.13	17.12	39	16.03	17.50		+		-4.90 [-12.]	74; 2.93]	1.5%	1.5%
Harris, unpublished	31	2.60	4.90	30	3.60	4.20		_	-	–1.00 [–3.	29; 1.29]	18.0%	18.0%
Fixed effect model	472			508					\downarrow	0.08 [-0.8	9; 1.05]	100.0%	_
Random effects model									\diamond	0.08 [-0.8	9; 1.05]		100.0%
Heterogeneity: $I^2 = 8\%$, χ_4^2	= 4.35	(p = 0.3)	36)							-			
						_	15 –10	-5	0 5				
							F	avours AP	P Favours	s control			

D Hospital length of stay

			APP		С	ontrol			Weight	Weight
Study	Total	Mean	SD	Total	Mean	SD	Mean Difference	MD [95%–CI]	(fixed)	(random)
Ehrmann, 2021	564	16.40	10.50	557	16.50	9.70	#	-0.10 [-1.28; 1.08]	35.6%	33.1%
Gad, 2021	15	28.00	5.00	15	26.00	5.00		2.00 [-1.58; 5.58]	3.9%	6.1%
Johnson, 2021	15	6.58	6.30	15	4.24	1.33	- <u> </u>	2.34 [-0.92; 5.60]	4.7%	7.2%
Kharat, 2021	10	9.70	3.09	17	11.00	5.84		-1.30 [-4.67; 2.07]	4.4%	6.8%
Rosen, 2021	36	17.29	8.51	39	23.94	20.74		-6.65 [-13.73; 0.43]	1.0%	1.7%
Taylor, 2021	27	10.17	13.93	13	6.49	5.90		3.68 [-2.47; 9.84]	1.3%	2.2%
Appex, unpublished	159	4.84	5.36	134	3.67	3.71		1.17 [0.13; 2.22]	45.8%	37.7%
Harris, unpublished	31	12.90	8.50	30	13.10	6.90		-0.20 [-4.08; 3.68]	3.3%	5.2%
Fixed effect model	857			820			-	0.61 [-0.10; 1.31]	100.0%	_
Random effects model							\$	0.57 [-0.35; 1.49]		100.0%
Heterogeneity: $I^2 = 34\%$, χ	$\frac{2}{7} = 10.5$	57 (p =	0.16)							
						-	5 -10 -5 0 5 10			
							Favours APP Favours cont	o		

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)

		APP	Co	ontrol			Weight	Weight
Study	Events	Total	Events	Total	Risk Ratio	RR [95%–CI]	(fixed)	(random)
Advanced respiratory s	upport							
Ehrmann, 2021	205	564	243	557	-	0.83 [0.72; 0.96]	99.7%	92.7%
Harris, unpublished	2	5	1	8		- 3.20 [0.38; 26.78]	0.3%	7.3%
Fixed effect model		569		565	\$	0.84 [0.73; 0.97]	100.0%	_
Random effects model						1.06 [0.39; 2.89]	_	100.0%
Heterogeneity: $I^2 = 35\%$, χ^2	² ₁ = 1.53 (p = 0.2	2)					
Conventional oxygen th	nerapy							
Jayakumar, 2021	2	27	13	30		0.17 [0.04; 0.69]	18.7%	8.1%
Johnson, 2021	12	15	7	15		1.71 [0.94; 3.12]	10.6%	25.9%
Kharat, 2021	0	10	1	17		0.56 [0.02; 12.43]	1.7%	1.9%
Appex, unpublished	16	159	18	134		0.75 [0.40; 1.41]	29.6%	24.4%
Fralick, unpublished	18	126	17	122		1.03 [0.55; 1.90]	26.2%	25.2%
Harris, unpublished	5	26	8	22		0.53 [0.20; 1.38]	13.1%	14.5%
Fixed effect model		363		340	<	0.78 [0.57; 1.08]	100.0%	_
Random effects model					\diamond	0.77 [0.43; 1.39]	_	100.0%
Heterogeneity: $I^2 = 57\%$, χ^2	$\frac{2}{5} = 11.66$	(p = 0.	04)					
	~			Г				
				0.0	1 0.1 0.51 2 10	50		

Favours APP Favours control

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

		APP	C	ontrol			Weight	Weight
Study	Events	Total	Events	Total	Risk Ratio	RR [95%–CI]	(fixed)	(random)
ICU								
Ehrmann, 2021	201	538	238	533		0.84 [0.72; 0.97]	94.8%	65.8%
Jayakumar, 2021	20	30	13	30	-	1.54 [0.95; 2.49]	5.2%	34.2%
Fixed effect model		568		563	4	0.87 [0.76; 1.00]	100.0%	
Random effects model					\diamond	1.08 [0.60; 1.96]	_	100.0%
Heterogeneity: $I^2 = 82\%$, χ	² ₁ = 5.65 (p = 0.0)2)					
Non ICU								
Ehrmann, 2021	4	26	5	24		0.74 [0.22; 2.43]	8.8%	8.9%
Johnson, 2021	12	15	7	15		1.71 [0.94; 3.12]	11.8%	25.6%
Kharat, 2021	0	10	1	17	· · · · · ·	0.56 [0.02; 12.43]	1.9%	1.5%
Appex, unpublished	16	159	18	134		0.75 [0.40; 1.41]	32.9%	23.8%
Fralick, unpublished	18	126	17	122		1.03 [0.55; 1.90]	29.1%	24.7%
Harris, unpublished	7	31	9	30		0.75 [0.32; 1.76]	15.4%	15.5%
Fixed effect model		367		342	\$	0.94 [0.68; 1.30]	100.0%	
Random effects model						1.00 [0.69; 1.44]	_	100.0%
Heterogeneity: $I^2 = 0\%$, χ_5^2	= 4.74 (p	= 0.45	5)	Г				
				0.0	1 0.1 0.5 1 2	10		
					Favours APP Favou	rs control		

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

Study	Events	APP Total	Co Events	ntrol Total	Risk Ratio	RR [95%-CI]	Weight (fixed)	Weight (random)
Advanced respiratory s Ehrmann, 2021 Rosen, 2021 Harris, unpublished Fixed effect model Random effects model Heterogeneity: $l^2 = 51\%$, c	support 47 10 4 $\frac{2}{2} = 4.04$ (228 36 5 269 <i>p</i> = 0.1	75 8 8 3)	218 39 8 265	+ + & &	0.60 [0.44; 0.82] 1.35 [0.60; 3.05] 0.82 [0.55; 1.21] 0.68 [0.52; 0.89] 0.77 [0.53; 1.11]	84.1% 8.4% 7.5% 100.0%	47.9% 13.8% 38.3% 100.0%
Conventional oxygen the Johnson, 2021 Kharat, 2021 Taylor, 2021 Appex, unpublished Harris, unpublished Fixed effect model Random effects model Heterogeneity: $l^2 = 4\%$, c_3^2	herapy 5 0 8 9 6 = 3.12 (p	15 10 27 159 26 237	2 0 6 7 7	15 17 13 134 22 201	0.5 1 2 5 burs APP Favours control	 2.50 [0.57; 10.93] 0.64 [0.28; 1.47] 1.26 [0.46; 3.46] 0.73 [0.29; 1.84] 0.99 [0.60; 1.62] 0.91 [0.56; 1.50] 	8.3% 0.0% 33.5% 26.9% 31.3% 100.0%	12.2% 0.0% 34.8% 24.7% 28.3% 100.0%

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

Study	Events	APP Total	Co Events	ontrol Total	Risk Ratio	RR [95%-CI]	Weight (fixed)	Weight (random)
Ehrmann, 2021	6	26	10	24		0.55 [0.24; 1.29]	25.8%	21.7%
Kharat, 2021	0	10	0	17			0.0%	0.0%
Taylor, 2021	8	27	6	13		0.64 [0.28; 1.47]	20.1%	22.8%
Appex, unpublished	9	159	6	134		1.26 [0.46; 3.46]	16.2%	15.4%
Harris, unpublished	10	31	15	30		0.65 [0.35; 1.20]	37.9%	40.1%
Fixed effect model		253		218		0.72 [0.48; 1.07]	100.0%	
Random effects model	/			r		0.69 [0.47; 1.03]		100.0%
Heterogeneity: $I^2 = 0\%$, c_3^2	= 1.72 (p	= 0.63	5)			I		
				0. F	1 0.2 0.5 1 2 5 Favours APP Favours contro	20 ol		

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

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

Study	Total	Mean	APP SD	Total	C Mean	ontrol SD	Mean Difference	MD [95%–CI]	Weight (fixed)	Weight (random)
Advanced respiratory s	suppo	rt								
Ehrmann, 2021	360	11.71	11.07	394	11.92	9.55		-0.21 [-1.69; 1.27]	75.2%	75.2%
Rosen, 2021	36	11.13	17.12	39	16.03	17.50		-4.90 [-12.74; 2.93]	2.7%	2.7%
Harris, unpublished	5	5.00	2.20	8	6.10	2.80		-1.10 [-3.84; 1.64]	22.1%	22.1%
Fixed effect model	401			441			\triangleleft	-0.53 [-1.82; 0.75]	100.0%	—
Random effects model							\Rightarrow	-0.53 [-1.82; 0.75]	_	100.0%
Heterogeneity: $I^2 = 0\%$, χ^2_2	= 1.54	(p = 0.4)	46)							
Conventional oxygen tl	herapy	/								
Gad, 2021	15	8.00	3.00	15	7.00	2.00		1.00 [-0.82; 2.82]	56.7%	56.7%
Jayakumar, 2021	27	11.53	6.92	30	9.97	5.69		1 56 [–1 75, 4 87]	17.2%	17.2%
Harris, unpublished	26	2.30	5.10	22	2.60	4.40		-0.30 [-2.99; 2.39]	26.1%	26.1%
Fixed effect model	68			67			\diamond	0.76 [-0.62; 2.13]	100.0%	_
Random effects model							\diamond	0.76 [-0.62; 2.13]		100.0%
Heterogeneity: $I^2 = 0\%$, χ^2_2	= 0.89	(p = 0.6	64)							
						I				
						-1	5 –10 –5 0 5	5		
							Favours APP Favours	s control		

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

Study	Total	Mean	APP SD	Total	Co Mean	ntrol SD	Mean Difference	MD [95%–CI]	Weight (fixed)	Weight (random)
ICU Ehrmann, 2021 Gad, 2021	538 15	11.84	11.12	533	12.10	9.57		-0.26 [-1.50; 0.98]	62.0% 28.7%	62.0% 28.7%
Javakumar. 2021	30	11.53	6.92	30	9.97	5.69		1.56 [-1.65; 4.77]	9.3%	9.3%
Fixed effect model	583			578			\sim	0.27 [-0.71; 1.25]	100.0%	
Random effects model								0.34 [-0.77; 1.45]	_	100.0%
Heterogeneity: $I^2 = 0\%$, χ^2_2	= 1.94	(p = 0.3)	38)							
Non ICU										
Ehrmann, 2021	26	4.23	2.10	24	5.21	6.02		-0.98 [-3.52; 1.56]	44.8%	44.8%
Harris, unpublished	31	2.60	4.90	30	3.60	4.20		–1.00 [–3.29; 1.29]	55.2%	55.2%
Fixed effect model	57			54				-0.99 [-2.69; 0.71]	100.0%	—
Random effects model								-0.99 [-2.69; 0.71]		100.0%
Heterogeneity: $I^2 = 0\%$, χ_1^2	= 0 (p	= 0.99)						-		
								I		
						_	4 -2 0 2 4	6		

Favours APP Favours control

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

Weight APP Control Weight Mean Difference MD [95%-CI] (fixed) (random) Study **Total Mean** SD Total Mean SD Advanced respiratory support Ehrmann, 2021 564 16.40 10.50 557 16.50 9.70 -0.10 [-1.28; 1.08] 89.0% 82.8% Rosen, 2021 36 17.29 8.51 39 23.94 20.74 -6.65 [-13.73; 0.43] 2.5% 4.0% Harris, unpublished 5 13.00 3.50 8 13.80 3.30 -0.80 [-4.63; 3.03] 8.5% 13.1% Fixed effect model 605 604 -0.32 [-1.44; 0.79] 100.0% Random effects model -0.35 [-1.53; 0.83] 100.0% Heterogeneity: $I^2 = 39\%$, $\chi^2_2 = 3.26$ (p = 0.20) Conventional oxygen therapy Gad, 2021 15 28.00 5.00 15 26.00 2.00 [-1.58; 5.58] 9.4% 5.00 6.3% Johnson, 2021 15 6.58 6.30 15 4.24 1.33 2.34 [-0.92; 5.60] 7.5% 11.2% Kharat, 2021 10 9.70 3.09 17 11.00 5.84 -1.30 [-4.67; 2.07] 7.0% 10.5% 3.68 [-2.47; 9.84] 1.17 [0.13; 2.22] Taylor, 2021 27 10.17 13.93 13 6.49 5.90 2.1% 3.4% Appex, unpublished 159 4.84 5.36 134 3.67 3.71 - 1 73.6% 60.0% 0.00 [-4.81; 4.81] 1.15 [0.26; 2.05] Harris, unpublished 26 12.80 9.20 22 12.80 3.5% 5.4% 7.80 Fixed effect model 216 \diamond 252 100.0% Random effects model \diamond 1.15 [0.26; 2.05] 100.0% Heterogeneity: $I^2 = 0\%$, $\chi_5^2 = 3.63$ (p = 0.60) Г -10 0 10 -15 -5 5 Favours APP Favours control

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

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

Study	Total	Mean	APP SD	Total	Co Mean	ntrol SD	Mean Difference	MD [95%–CI]	Weight (fixed)	Weight (random)
ICU Ehrmann, 2021 Gad, 2021 Fixed effect model Random effects model	538 15 553	16.50 28.00	10.56 5.00	533 15 548	16.74 26.00	9.75 5.00		-0.24 [-1.46; 0.98] 2.00 [-1.58; 5.58] -0.01 [-1.16; 1.14] 0.22 [-1.55; 2.00]	89.6% 10.4% 100.0%	82.9% 17.1% 100.0%
Heterogeneity: $I^2 = 26\%$, χ^2	² ₁ = 1.3	5 (<i>p</i> = 0	.25)					0[10010,0
Ehrmann. 2021	26	13.31	7.71	24	10.47	5.85		2.84 [-0.94: 6.62]	5.5%	9.1%
Johnson, 2021	15	6.58	6.30	15	4.24	1.33		2.34 [-0.92; 5.60]	7.4%	11.8%
Kharat, 2021	10	9.70	3.09	17	11.00	5.84		-1.30 [-4.67; 2.07]	7.0%	11.1%
Taylor, 2021	27	10.17	13.93	13	6.49	5.90		3.68 [-2.47; 9.84]	2.1%	3.6%
Appex, unpublished	159	4.84	5.36	134	3.67	3.71		1 17 [0 13; 2 22]	72.7%	55.8%
Harris, unpublished	31	12.90	8.50	30	13.10	6.90		-0.20 [-4.08; 3.68]	5.3%	8.6%
Fixed effect model	268			233			\diamond	1.16 [0.27; 2.05]	100.0%	
Random effects model								1.16 [0.27; 2.05]		100.0%
Heterogeneity: $I^2 = 0\%$, χ_5^2	= 4.43	(p = 0.4	49)			Fa	-5 0 5 1	ר ו 0		



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

Study	Events	APP Total	Co Events	ontrol Total	Risk Ratio	RR [95%-Cl]	Weight (fixed)	Weight (random)
Pierucci, 2021 Brudhoroma, 2021	6	16	3	16 49		2.00 [0.60: 6.64]	5.0% 41 5%	17.3%
Vianello, 2021	9	50	16	43		0.48 [0.24; 0.98]	28.5%	24.7%
Zang, 2020	23	23	19	37	-	1.92 [1.41; 2.62]	25.0%	30.2%
Fixed effect model		137		144	\$	0.96 [0.74; 1.25]	100.0%	
Handom effects model Heterogeneity: $l^2 = 87\%$. χ	2 5 = 23.33	$(\rho < 0)$.01)	I		ן 1.00 (0.48; 2.09) ר	_	100.0%
				0.	1 0.2 0.5 1 2 5 1 Favours APP Favours contro	D I		

C Need for ICU admission

		APP	C	ontrol			Weight	Weight
Study	Events	Total	Events	Total	Risk Ratio	RR [95%–CI]	(fixed)	(random)
Fazzini, 2021	14	34	10	12	— — • i i	0.49 [0.31; 0.79]	16.1%	29.0%
Jagan, 2020	11	40	26	65	— — • +	0.69 [0.38; 1.23]	21.6%	25.2%
Padrao, 2020	47	57	79	109		1.14 [0.96; 1.34]	59.1%	38.9%
Pierucci, 2021	2	16	3	16 ·		- 0.67 [0.13; 3.47]	3.3%	6.9%
Fixed effect model		147		202		0.92 [0.78; 1.09]	100.0%	_
Random effects model Heterogeneity: $I^2 = 76\%$, χ^2	; = 12.58	(p < 0	.01}	Г		0.76 [0.47; 1.22]		100.0%
	,			0.1	0.5 1 2	5		
					Favours APP Favours	control		

D ICU length of stay

			APP		c	ontrol			Weight	Weight
Study	Total	Mean	SD	Total	Mean	SD	Mean Difference	MD [95%-CI]	(fixed)	(random)
Altinay, 2021	25	8.79	9 .80	23	8.00	5.93	÷	0.79 [-3.75; 5.33]	30.4%	28.4%
Barker, 2021	10	29.00	19.00	10	9.00	7.00		20.00 [7.45; 32.55]	4.0%	15.2%
Fazzini, 2021	14	23.71	94.97	10	18.77	19.09		4.94 [-46.20; 56.07]	0.2%	1.6%
Ferrando, 2020	55	11.17	10.33	144	11.52	13.44	+	-0.34 [-3.85; 3.16]	51.1%	30.0%
Tonelli, 2021	38	15.25	16.95	76	14.67	17.05		0.59 [-6.03; 7.20]	14.3%	24.8%
Fixed effect model	142			263				0.96 [-1.55; 3.46]	100.0%	
Random effects model								3.38 [-3.29; 10.05]		100.0%
Heterogeneity: $I^2 = 58\%$, χ_z^2	$\frac{2}{4} = 9.4^{\circ}$	$1 (\rho = 0)$.05)					1		
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Study	Total	Mean	APP SD	Total	Mean	Control SD	Mean Difference	MD [95%–CI]	Weight (fixed)	Weight (random)
Fazzini, 2021	34	13.33	17.05	12	24.69	24.81	#	-11.36 [-26.52; 3.80]	2.1%	12.5%
Jagan, 2020	40	11.13	7.86	65	16.10	8.92		-4.97 [-8.23; -1.71]	44.8%	21.9%
Loureigo, 2021	60	15.58	11.04	103	11.50	9.92		4.08 [0.69; 7.47]	41.5%	21.9%
Ni, 2020	20	39.16	17.85	35	35.00	10.38	+	4.16 [-4.39; 12.70]	6.5%	18.0%
Tonelli, 2021	38	21.33	28.17	76	24.00	31.13	+	-2.67 [-14.03: 8.70]	3.7%	15.6%
Vianello, 2021	50	51.05	145.83	43	119.42	653.08		-68.37 [-267.71; 130.97]	0.0%	0.2%
Zang, 2020	23	13.56	18.58	37	44.45	54.09	-	-30.89 [-49.90; -11.88]	1.3%	9. 9 %
Fixed effect model	265			371				-1.01 [-3.20; 1.17]	100.0%	
Random effects model Heterogeneity: $l^2 = 78\%$, γ	$r_{e}^{2} = 27.5$	53 (p <	0.01)					-4.46 [-12.45; 3.53]		100.0%
	•		·			-3	0 –200 –100 0 100 Favours APP Favours o	200 control		

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, %)
Annual Handlich al	COT (Room air/Nasal cannula/Mask/HFNC)	134							28 (20.9)
Appex, Unpublished	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)			
Enimann, 2021	HFNC+APP	564	8 (1.4)	15 (2.7)	26 (4.6)	3 (0.5)			
Gad 2021	NRM	15							
Gau, 2021	NRM+APP	15							
	Standard care (Face mask/NRM)	30	0 (0)	0 (0)					0 (0)
Jayakumar, 2021	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							
Johnson, 2021	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)
Kharat, 2021	Usual care (Nasal cannula) +APP	10	0 (0)	0 (0)	0 (0)	0 (0)	6 (60.0)	0 (0)	6 (60.0)
Destin 2021	HFNC/NIV	39	9 (23.1)	0 (0)	0 (0)	1 (2.6)			
Kosen, 2021	HFNC/NIV+APP	36	2 (5.6)	1 (2.8)	0 (0)	2 (5.6)			
Texter 2021	Usual care (Room air/ nasal cannula/HFNC/NIV)	13	0 (0)		0 (0)	0 (0)			
Taylor, 2021	Usual care (Nasal cannula/HFNC/NIV)+APP	27	0 (0)		0 (0)	0 (0)			
Harrie Uppublished	Usual care (Nasal cannula/NRM/HFNC/NIV)	30	0 (0)	0 (0)	0 (0)	0 (0)	1 (3.3)		
marins, emptionshed	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							
ranek, Onpublished	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 inclu	ded non-RCTs.
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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, %)
41.1 .: 6 2021	Usual care (CPAP)	48							
Alsharif, 2021	Usual care (CPAP)+APP	31							
Altinav 2021	Usual care (NRM)	23							
Annay, 2021	Usual care (NRM)+APP	25							
Barker 2021	Usual care (NIV)	10							
Durker, 2021	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							
5ugun, 2020	APP>=1h orn >=5 occasions per day and for >= 1 continuous hour overnight	40							
D 1 7 2020	Usual care (Nasal cannula/Venturi mask/NRM)	109				0 (0%)			
Padrao, 2020	Usual care (Nasal cannula/Venturi mask/NRM) +APP	57				0 (0%)	3 (5·3)		
Lauffrage 2021	Usual care (COT/HFNC/NIV/CPAP)	339							
Journoy, 2021	Usual care (COT/HFNC/CPAP)+APP	40							
Loureiro-Amigo 2021	Usual care	103							
Louivio Tinigo, 2021	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 (Nasal compute/NPM/HENC)	222							
Perez-Nieto 2021	Usual care (Nasal compula/NRM/HFNC)	322							
10102 11000, 2021	+APP	505							
	Usual care (COT/HFNC/NIV)	15					0 (0%)	0 (0%)	
Sryma, 2021	Usual care (COT/HFNC/NIV)+APP	30					2 (6.6)	2 (6.7)	
Min 11, 2021	Usual care (HFNC)	43							
vianello, 2021	Usual care (HFNC)+APP	50							
Brudhamma 2021	Usual care (COT/HFNC)	48							
Flue nomine, 2021	Usual care (COT/HFNC)+APP	48							
Simioli, 2021	Usual care (HFNC/CPAP)	11							
51111011, 2021	Usual care (HFNC/CPAP)+APP	18							
Tonelli, 2021	Usual care (HFNC/NIV)	76							
101011, 2021	Usual care (HFNC/NIV)+APP	38							
Zang, 2020	Usual care (Face mask) Usual care (Face mask)+APP	37 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) Usual care (Room air/Nasal cannula/Mask/HFNC)+APP	134 159	Up to four 1-2h daily sessions, and up to 12h nightly		54 (43-63) 52 (39-62)	80 (59·7) 96 (60·4)		402 (311-457)* 396 (308-457)*		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/d eath)	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
Ehrmann, 2021	USA, Mexico, Canada, Ireland, France, Spain	ICU, intermediate care unit, ED, General ward	RCT, multicenter	Usual care (HFNC) Usual care (HFNC)+APP	557	As long and as frequently as possible	Daily: 0 (0-0) Daily: 5-0 (1-6 - 8-8)	60·7 ±14·0 61·5 ±13·3	366 (65·7) 380 (67·4)	29·7± 4·6 29·7± 4·6	117·3 ±37·2 119·3 ±43·3	492 (88·3) 494 (87·6)	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
Gad, 2021	Egypt	ICU	RCT, single center	Usual care (NRM) Usual care (NRM)+APP	15 15	1-2 hours each session, 3 hours apart during waking hours for the first 3 days		46·0 (33-51) 49·0 (38-62)	8 (53·3) 9 (60·0)		$ \begin{array}{c} 111 \cdot 0 \\ (97 \cdot 0 - 175 \cdot 0) \\ 126 \cdot 0 \\ (88 \cdot 0 - 164 \cdot 0) \end{array} $		Improvement of oxygenation and avoidance of intubation within the first 3 days of critical care admission		ICU stay and hospital stay
Jayakumar, 2021	India	ICU	RCT, multicenter	Usual care (Nasal cannula/Face mask/NRM/HFNC/N IV) Usual care (Nasal cannula/Face mask/NRM/HFNC/N IV)+APP	30 30	At least 6 hours a day		57·3±12·1 54·8±11·1	25 (83·3) 25 (83·3)	25·8±2·6 28·2±5·7	185·6±126·1 201·4±118·8	30 (100·0) 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
Johnson, 2021	USA	General ward	RCT, single center	Usual care (Room air/ nasal cannula) Usual care (Room air/nasal cannula)+APP	15 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) 52 (40-65)	8 (53·3) 8 (53·3)	29·3 (24·4-32·9) 32·9 (27·5-39·4)			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
Kharat, 2021	Switzerla nd	General ward	RCT, single center	Usual care (Nasal cannula) Usual care (Nasal cannula)+APP	17 10	Self-proning for 12 hours per day and alternate body position every 4 hours	Total: 0·11±0·48 Total: 4·9 ± 3·6	60±11 54±14	11 (64·7) 6 (60·0)	27·3±4·2 29·7±5·3	336 (303-388)* 318 (284-341)*		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 davs
Rosén, 2021	Sweden	ICU, general ward	RCT, multicenter	Usual care (HFNC/NIV) Usual care (HFNC/NIV)+APP	39 36	At least 16 hours per day	Daily: 3·4 (1·8- 8·4) Daily: 9·0 (4·4- 10·6)	65 (55-70) 66 (53-74)	32 (82·1) 23 (63·9)	29 (27-33) 28 (25-30)	115.5 (93.75-129.75) 115.5 (86.25-130.5)		Intubation within 30 days after enrolment	30	Duration of APP, use of NIV, time to NIV for patients included with HENO, use of vasopressors/inotropes, CRRT, ECMO, ventilator-free days, days

															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	RCT, single	Usual care (Room air/ nasal cannula/HFNC/NIV)	13			60 (54-63)	10 (76-9)	31 (28-38)		9 (69·2)	Outcomes relative to successful	Until discharge/d	S/F, time on S/F <315, receipt of intensive care, oxygen flow >61/min_intubation_hospital length
14,101, 2021	0011	ward	center	Usual care (Nasal cannula/HFNC/NIV) +APP	27			56 (45-66)	17 (63.0)	29 (26-39)		19 (70·4)	implementation of a future definitive RCT	eath	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	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 proming; 28-day Mortality; Length of stay in ICU and hospital; Duration of invasive mechanical ventilation; Displacement of devices; Adverse
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 overniebt	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.