

Outcomes of COVID-19 patients treated with continuous positive airway pressure outside ICU

Supplementary material

Study Design

This was a multicentre, retrospective observational study performed in six hospitals of the eastern Piedmont region, Northern Italy i.e., “Maggiore della Carità” University hospital in Novara, “SS. Antonio Biagio e Cesare Arrigo”, hospital in Alessandria, “S. Andrea” hospital in Vercelli, “VCO ASL” in Domodossola, “Nuovo Ospedale degli Infermi” hospital in Biella. One centre i.e., “Maggiore della Carità” University hospital in Novara, enrolled patients prospectively n=138 patients, as the protocol for the data collection, has been approved on the 07th June 2019 (CE 64/19) for a study, monitoring patients treated with CPAP outside ICU.

All the participating centres obtained ethics committee approval for the present research project (CE 87/20; CE 112/20, CE 111/20, CE 110/20, ASO.RianGen.20.02, AslVC.RianGen.20.01). Informed consent was obtained for all the patients prospectively enrolled and for those still in the hospital after ethics committee protocol approval, while for the others, ethics committee waived the need for informed consent. Local investigators were responsible for ensuring data integrity and validity.

Criteria for intubation

Criteria for intubation were cardiac or respiratory arrest; inability to protect the airway; coma or psychomotor agitation; unmanageable secretions or uncontrolled vomiting; life threatening arrhythmias or electrocardiographic signs of ischemia; hemodynamic instability defined as systolic arterial pressure < 90 mmHg despite adequate filling or use of vasoactive agents; intolerance to all interfaces; dyspnoea during noninvasive continuous positive airway pressure (CPAP), respiratory rate >30 breaths/min; peripheral oxygen saturation (SpO₂) below 92% during CPAP, acidosis with a pH < 7.35.

CPAP

CPAP was delivered through helmets (Intersurgical, Mirandola (MO), Italy; Dimar, Medolla, MO, Italy) and face masks (Intersurgical, Mirandola, MO, Italy; Dimar, Medolla, MO, Italy; Fisher&Paykel, Auckland, New Zealand; ResMed, San Diego, CA, USA; Philips Respironics, Murrysville, PA, USA) via Boussignac systems or via flow-meters (typically 30-50 l/min depending on the interface chosen) with a scale that allowed the clinician to regulate oxygen and air flow separately to set inspiratory oxygen fraction (FiO_2). Bacterial and viral filter was applied to the expiratory port. CPAP was set between 10 and 12 cmH₂O according to patient's needs, tolerance and any side-effects. CPAP pressure could be increased up to 15 cmH₂O. CPAP was delivered on an as-needed basis. When respiratory parameters improved, CPAP support was gradually reduced with a progressive increase of time off CPAP, until discontinuation.

Respiratory intermediate care unit organization

Nurse to patient ratios varied from a maximum of 1:6 both during day and night to a minimum of 1:8 and 1:12, respectively during days and nights. In three hospitals, medical staff treating CPAP COVID-19 patients was an ad-hoc mixed team, mainly internists, pneumologists, emergency physicians, cardiologists, anaesthesiologists/ICU physicians, while in the other three hospitals the medical team was the same as before COVID-19 pandemic. CPAP was prescribed mainly by anaesthesiologists actively working with the ad-hoc COVID-19 ward team, but also by pneumologists and emergency doctors or by consulting anaesthesiologists. Personnel was adequately trained for NIV; those who were not, received a short-organized training during pandemic. Ward monitoring included SpO₂, non-invasive blood pressure, ECG applied continuously or at a defined time point depending on the severity of the patient. Blood gas analysis was performed when clinically relevant. Patients received daily visit from the consulting physician who prescribed CPAP if not present in the ad-hoc ward team.

Statistical analysis

Fine and Gray model included as adjustment age, gender, comorbidities i.e., Charlson comorbidity index and hypertension, LDH, C-reactive protein levels and lymphocyte count. The model was further adjusted by centre. The adjustment variables were selected on the base of their clinical relevance. Multiple imputation procedures were applied to account for missing data.

Figure 1S Study flow chart

COVID-19, coronavirus disease 19; iMV, invasive mechanical ventilation; ICU, intensive care unit; NIV, noninvasive ventilation; CPAP, noninvasive continuous positive airway pressure.

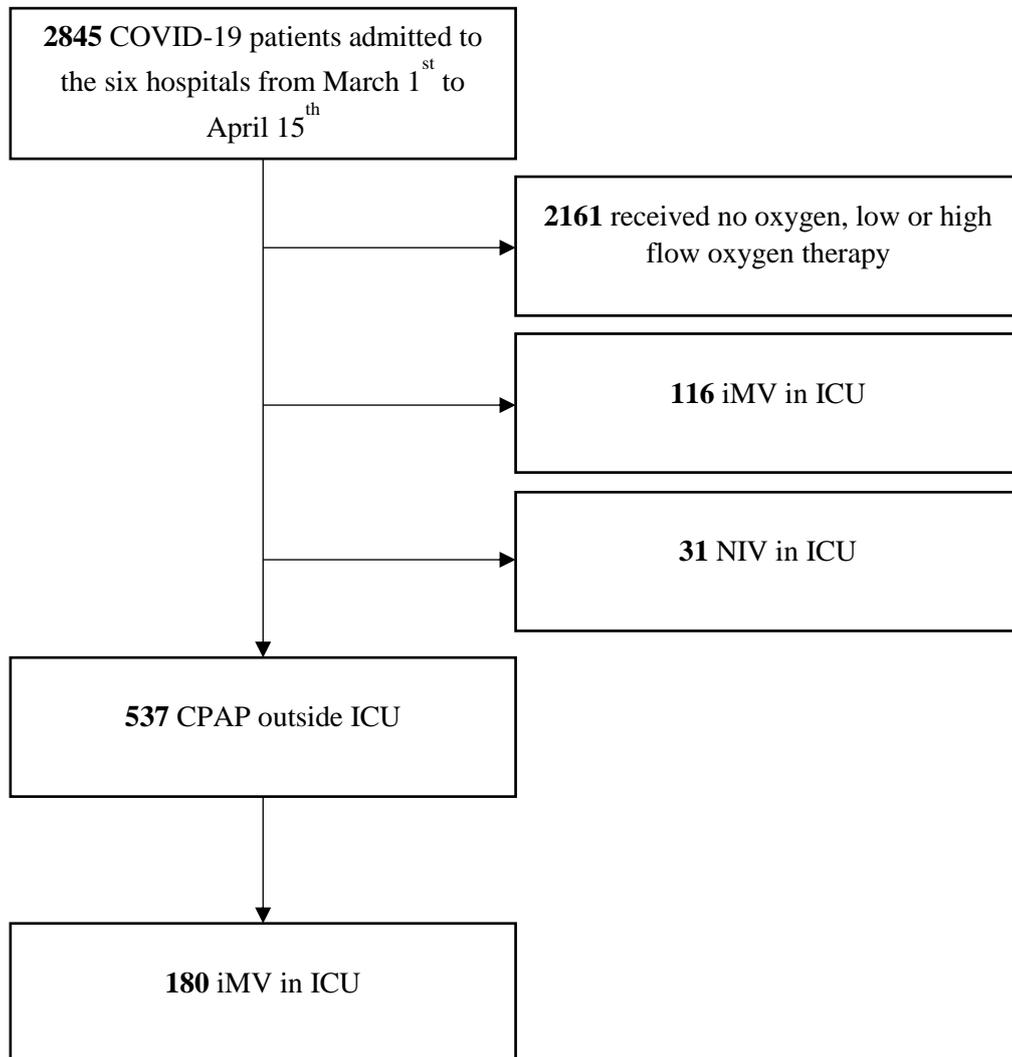
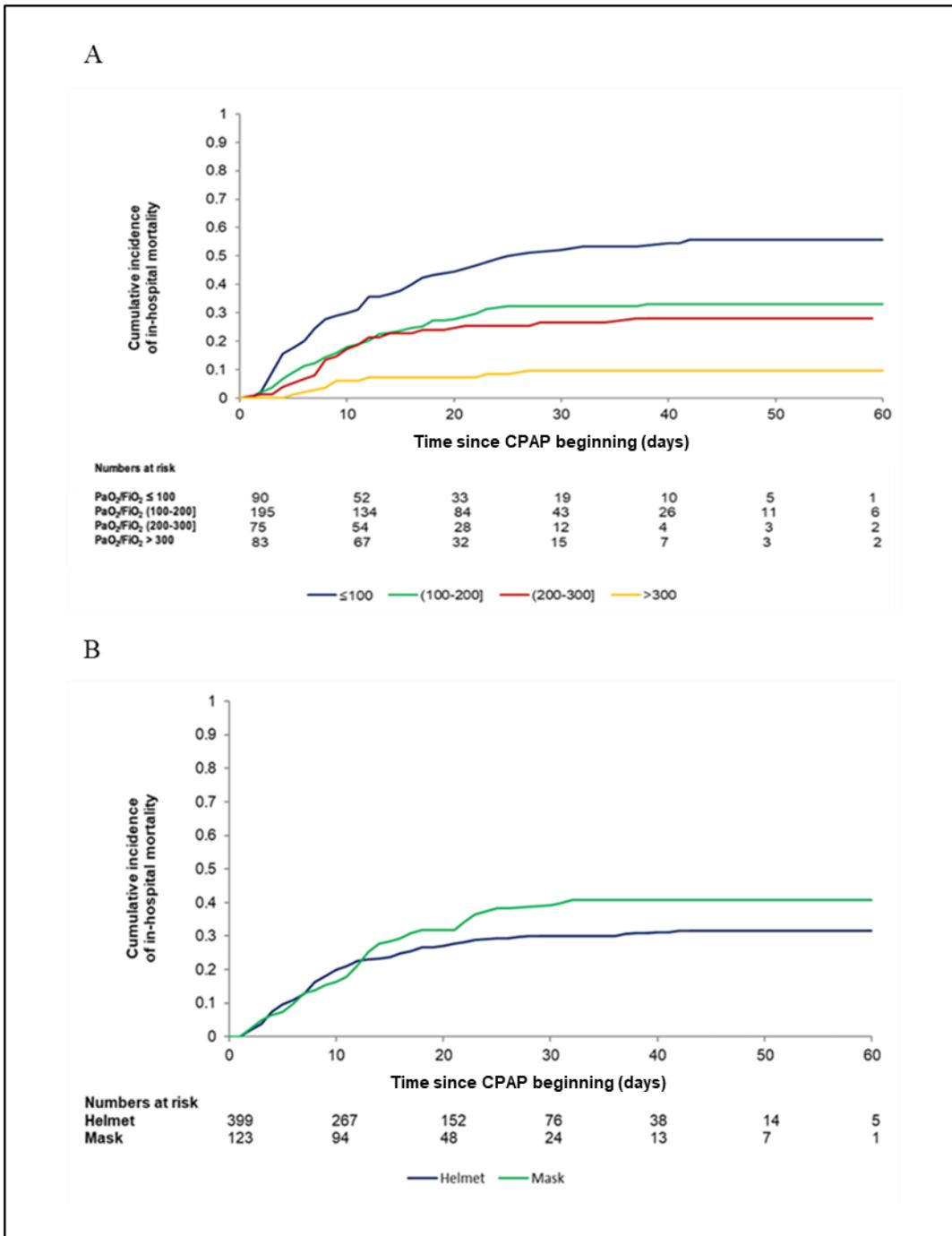


Figure 2S Cumulative incidence of in-hospital mortality stratified by PaO₂/FiO₂ levels (Panel A) and interface applied (Panel B).



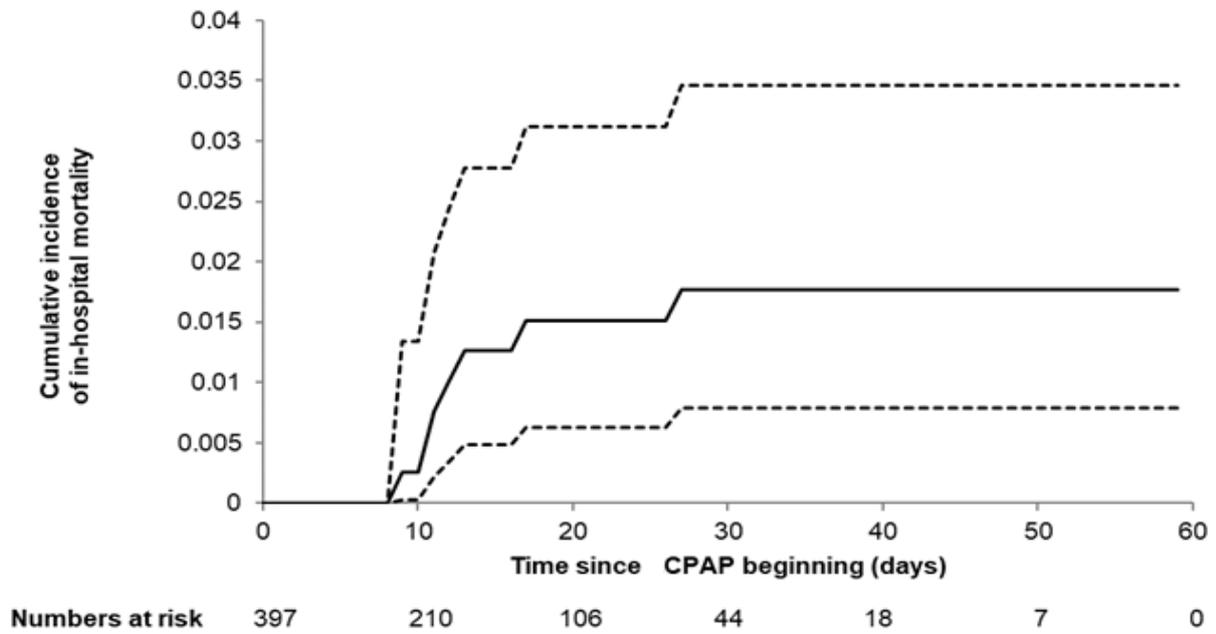
PaO₂/FiO₂

Cumulative incidence at 60 days – PaO₂/FiO₂ ≤ 100: 0.558 (0.448-0.654).
 Cumulative incidence at 60 days – PaO₂/FiO₂ (100-200]: 0.329 (0.264-0.395).
 Cumulative incidence at 60 days – PaO₂/FiO₂ (200-300]: 0.280 (0.183-0.385).
 Cumulative incidence at 60 days – PaO₂/FiO₂ > 300: 0.100 (0.045-0.172).
 P-value Grey's test for equality of CIF < 0.0001

CPAP device

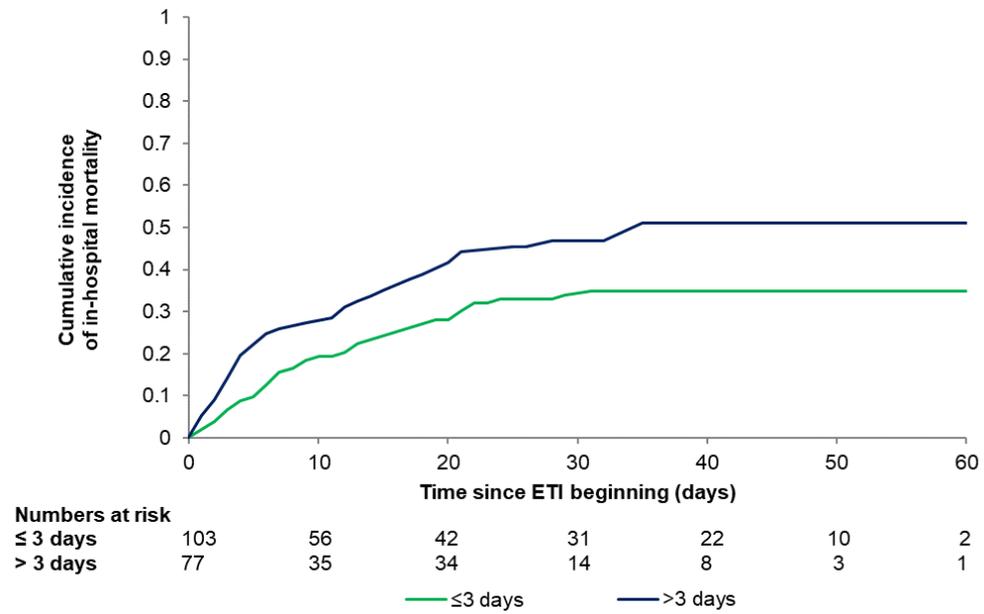
Cumulative incidence at 60 days – CPAP Helmet: 0.315 (0.270-0.361).
 Cumulative incidence at 60 days – CPAP Mask: 0.407 (0.320-0.493).
 P-value Grey's test for equality of CIF 0.0938

Figure 3S Cumulative incidence of in-hospital mortality in full treatment patients not requiring invasive mechanical ventilation



Curves and corresponding 95% confidence intervals (dashed lines).
 Cumulative incidence at 60 days 0.018 (0.008-0.035).
 CPAP, noninvasive continuous positive airway pressure

Figure 4S Cumulative incidence of in-hospital mortality stratified by number of CPAP days among patients undergoing endotracheal intubation (median)



Cumulative incidence at 60 days – CPAP days ≤ 3 : 0.350 (0.259-0.441).
 Cumulative incidence at 60 days – CPAP days > 3 : 0.510 (0.393-0.615).
 P-value Grey’s test for equality of CIF 0.0256

Table 1S Number of observations for each variable

	Overall (n= 537)
Characteristic, number of observations	
Age	537
Male	537
Body mass index	239
White blood cell count	533
Lymphocyte count	529
Creatinine	531
Aspartate-aminotransferase	335
Alanine-aminotransferase	503
C-reactive protein	509
Ferritin	223
Lactate dehydrogenase	454
D-dimer	192
Charlson Comorbidity index	537
Chronic arterial hypertension	537
Diabetes	537
Ischaemic heart disease	537
CPAP	537
Hospital length of stay	537

CPAP, noninvasive continuous positive airway pressure

Table 2S General characteristics of patients stratified according to PaO₂/FiO₂ value

	PaO₂/FiO₂ > 300	300 ≥ PaO₂/FiO₂ < 200	200 ≥ PaO₂/FiO₂ >100	PaO₂/FiO₂ ≤ 100
	177 (33)	75 (14)	195 (36)	90 (17)
Characteristics				
Age, years ^a	69 (59-76)	66 (59-73)	68 (60-75)	72 (65-79)
Male, n (%)	128 (72)	53 (71)	146 (75)	64 (71)
Body mass index, kg/m ²	28 (25-31)	27 (25-31)	28 (25-31)	28 (23-31)
White blood cell count, x10 ³ /μL ^a	6.7 (5.1-8.9)	6.7 (5.4-9.3)	6.8 (4.7-9.0)	8.1 (5.5-11.3)
Lymphocyte count, x10 ³ /μL ^a	0.9 (0.6-1.2)	0.8 (0.6-1.2)	0.9 (0.6-1.1)	0.7 (0.5-1.0)
Creatinine, mg/dL ^a	1.0 (0.8-1.2)	0.9 (0.7-1.2)	0.9 (0.8-1.3)	1.1 (0.8-1.6)
Aspartate-aminotransferase, U/L	40 (26-59)	38 (27-48)	42 (30-61)	43 (33-70)
Alanine-aminotransferase, U/L	34 (21-51)	31 (22-50)	33 (23-50)	34 (21-51)
C-reactive protein, mg/dL	13 (7-20)	10 (4-15)	11 (6-18)	13 (7-20)
Ferritin, ng/mL ^a	802 (430-1545)	1177 (600-1879)	1143 (621-1679)	1222 (931-1697)
Lactate dehydrogenase, U/L	575 (446-732)	544 (422-759)	597 (383-840)	510 (405-754)
D-dimer, μgFEU/L	931 (525-1730)	1294 (522-1990)	897 (549-2008)	987 (483-2190)
Charlson comorbidity index	1 (0-2)	1 (0-2)	1 (0-2)	1 (0-2)
Chronic arterial hypertension, n (%)	88 (50)	31 (41)	103 (53)	56 (62)
Diabetes, n (%)	44 (25)	14 (19)	55 (28)	25 (28)
Ischaemic heart disease, n (%)	23 (13)	11 (15)	20 (10)	12 (13)
CPAP, days ^a	6 (3-9)	5 (3-9)	4 (1-9)	1 (1-6)
Hospital length of stay, days	14 (6-27)	16 (10-27)	17 (8-30)	14 (6-27)

e range) or number (percentage). p values were calculated by Mann-Whitney U test or χ^2 test, as appropriate

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CPAP, noninvasive continuous positive airway pressure; FEU, fibrinogen-equivalent unit. ^aKruskal-Wallis $p < 0.05$

Table 3S General characteristics of patients according to CPAP interface applied

	Helmet (n=399)	Mask (n=123)	Mask and Helmet (n=15)
Characteristics			
Age, years	68 (58-74)	71 (64-78)*	75 (71-82)
Male, n (%)	292 (73)	86 (70)	13 (87)
Body mass index, kg/m ²	28 (25-31)	28 (25-30)	28 (27-29)
White blood cell count, x10 ³ /μL	6.7 (5.1-9.0)	8.0 (5.1-10.5)†	7.1 (4.5-10.6)
Lymphocyte count, x10 ³ /μL	0.8 (0.6-1.2)	0.7 (0.5-1.0)§	0.6 (0.5-0.8)
Creatinine, mg/dL	0.9 (0.8-1.2)	1.0 (0.8-1.4)	1.0 (0.8-1.3)
Aspartate-aminotransferase, U/L	41 (29-54)	46 (30-70)	59 (30-89)
Alanine-aminotransferase, U/L	32 (22-50)	31 (23-47)	38 (26-82)
C-reactive protein, mg/dL	11 (5-17)	12 (8-18)	11 (6-23)
Ferritin, ng/mL	1053 (572-1662)	1012 (480-1310)	1434 (518-1697)
Lactate dehydrogenase, U/L	616 (450-808)	448 (318-606)°	470 (314-482)
D-dimer, μgFEU/L	1050 (579-1951)	677 (426-1603)‡	1320 (1169-2576)
Charlson comorbidity index	1 (0-2)	1 (0-2)	1 (0-2)
Chronic arterial hypertension, n (%)	207 (52)	58 (47)	13 (87)
Diabetes, n (%)	106 (27)	25 (20)	7 (47)
Ischaemic heart disease, n (%)	45 (11)	20 (16)	1 (7)
CPAP, days	4 (2-8)	3 (1-9)	7 (2-13)
Hospital length of stay, days	16 (9-27)	17 (11-27)	13 (8-35)

Values are median (interquartile range) or number (percentage).

CPAP, noninvasive continuous positive airway pressure; ICU, intensive care unit; FEU, fibrinogen-equivalent unit

Helmet vs. mask: * p =0.030, † p=0.002, § p=0.001, °p<0.0001, ‡ p=0.032.

Table 4S Number of observations for each variable

	Full treatment (n=397)	Do-not-intubate (n=140)
Characteristic, number of observations		
Age	397	140
Male	397	140
Body mass index	196	43
White blood cell count	395	138
Lymphocyte count	392	137
Creatinine	394	137
Aspartate-aminotransferase	248	87
Alanine-aminotransferase	371	132
C-reactive protein	377	132
Ferritin	180	43
Lactate dehydrogenase	345	109
D-dimer	150	42
Charlson Comorbidity index	397	140
Chronic arterial hypertension	397	140
Diabetes	397	140
Ischaemic heart disease	397	140
Cancer	397	140
CPAP	397	140
Hospital length of stay	397	140

CPAP, noninvasive continuous positive airway pressure

Table 5S Arterial blood gas analysis at baseline and after CPAP outset

	Overall (n=537)	Full treatment (n=397)	Do not intubate (n=140)
ABG before CPAP^a			
pH	7.47 (7.43-7.49)	7.47 (7.44-7.49) [†]	7.46 (7.42-7.48)
PaCO ₂ , mmHg	35 (31-38)	35 (31-38)	34 (31-37)
PaO ₂ , mmHg	60 (49-73)	60 (51-73) [†]	54 (46-68)
SpO ₂ , %	91 (86-95)	92 (87-95) [†]	90 (83-93)
HCO ₃ ⁻ , mmol/L	25 (23-27)	26 (23-28) [†]	24 (22-26)
Lactate, mmol/L	1.2 (0.9-1.7)	1.2 (0.9-1.6)	1.2 (1.0-1.7)
FiO ₂ , %	50 (50-100)	50 (50-100)	50 (50-100)
PaO ₂ /FiO ₂ , mmHg	108 (71-157)	115 (73-158)	94 (66-146)
SpO ₂ /FiO ₂ , %	164 (95-194)	171 (96-194)	161 (94-190)
Respiratory Rate, breaths/min	27 (22-32)	26 (22-32)	28 (24-32)
ABG after CPAP^b			
pH	7.45 (7.42-7.48)	7.45 (7.42-7.48) ^{**}	7.43 (7.40-7.46) [*]
PaCO ₂ , mmHg	36 (33-40)	36 (33-40) [*]	36 (32-41) [*]
PaO ₂ , mmHg	85 (60-132)	87 (62-135) [*]	75 (56-126) [*]
SpO ₂ , %	96 (91-98)	96 (92-98) ^{**}	94 (90-98) [*]
HCO ₃ ⁻ , mmol/L	26 (23-28)	26 (24-28) [†]	25 (21-28)
Lactate, mmol/L	1.2 (0.9-1.6)	1.1 (0.8-1.6) ^{**}	1.4 (1.0-1.7)
FiO ₂ , %	50 (50-60)	50 (50-60) [*]	50 (50-60) [*]
PaO ₂ /FiO ₂ , mmHg	157 (109-255)	162 (109-259) [*]	148 (105-232) [*]
SpO ₂ /FiO ₂ , %	176 (153-196)	176 (152-196) [*]	180 (157-196) [*]
Respiratory Rate, breaths/min	24 (20-28)	24 (20-28) [*]	25 (21-28) [*]
CPAP, cmH ₂ O	10 (10-12)	10 (10-12)	10 (10-12)

ABG, arterial blood gas analysis; CPAP, noninvasive continuous positive airway pressure; PaCO₂, arterial partial pressure of carbon dioxide; PaO₂, arterial partial pressure of oxygen; SpO₂, peripheral oxygen saturation; HCO₃⁻, bicarbonate; FiO₂, inspired oxygen fraction; PaO₂/FiO₂, arterial partial pressure of oxygen to inspired oxygen fraction ratio; SpO₂/FiO₂, peripheral oxygen saturation to inspired oxygen fraction ratio

^aArterial blood gas analysis performed before CPAP initiation

^bFirst arterial blood gas analysis performed 2-24 hours after CPAP outset

[†]Mann Whitney U test p < 0.01 full treatment vs. do not intubate

^{*}Wilcoxon signed-rank test p < 0.01 ABG before CPAP vs. ABG after CPAP

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	Overall (n= 537)	Full treatment (n=397)	Do not intubate (n=140)
ABG before CPAP^a			
pH	492	370	122
PaCO ₂	493	371	122
PaO ₂	497	374	123
SpO ₂	535	395	140
HCO ₃ ⁻	484	365	119
Lactate	434	329	105
FiO ₂	409	307	102
PaO ₂ /FiO ₂	383	290	93
SpO ₂ /FiO ₂	408	306	102
Respiratory Rate	351	258	93
ABG after CPAP^b			
pH	462	353	109
PaCO ₂	462	352	110
PaO ₂	466	356	110
SpO ₂	534	395	139
HCO ₃ ⁻	456	347	109
Lactate	392	299	93
FiO ₂	499	376	102
PaO ₂ /FiO ₂	443	344	99
SpO ₂ /FiO ₂	499	376	123
Respiratory Rate	348	257	91
CPAP	454	344	110

Abbreviations: ABG, arterial blood gas analysis; CPAP, noninvasive continuous positive airway pressure; PaCO₂, arterial partial pressure of carbon dioxide; PaO₂, arterial partial pressure of oxygen; SpO₂, peripheral oxygen saturation; HCO₃⁻, bicarbonate; FiO₂, inspired oxygen fraction; PaO₂/FiO₂, arterial partial pressure of oxygen to inspired oxygen fraction ratio; SpO₂/FiO₂, peripheral oxygen saturation to inspired oxygen fraction ratio

^aArterial blood gas analysis performed before CPAP initiation

^bFirst arterial blood gas analysis performed 2-24 hours after CPAP outset

Table 7S Fine and Gray model for the association between CPAP treatment duration and mortality after the application of multiple imputation procedure.

	sHR	95%CI
CPAP, days	1.060	(1.001-1.121)
Male	1.229	(0.668-2.261)
Age	1.037	(1.002-1.073)
Hypertension, yes vs. no	1.075	(0.671-1.722)
Charlson index	1.260	(1.049-1.515)
Lactate dehydrogenase, U/L	1.000	(0.999-1.001)
C-reactive protein, mg/dL	0.996	(0.963-1.030)
Lymphocytes, x10 ³ /mL	1.323	(0.854-2.049)

Abbreviations: CPAP, continuous positive airway pressure; sHR, sub-distribution hazard ratio; 95% CI; 95% confidence interval. Sub-distribution hazard ratio and 95% corresponding confidence interval deriving from the multivariate Fine and Gray models. Estimates are further adjusted by center. N:180