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Early View

Original article

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

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

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Take-home message: Our study describes characteristics and in-hospital mortality of the largest population of COVID-19 patients treated with CPAP outside ICU. Treatment duration for patients failing CPAP prior to intubation represents a risk factor for mortality.

Abstract

Aim We aim at characterizing a large population of Coronavirus 19 (COVID-19) patients with moderate-to-severe hypoxemic acute respiratory failure (ARF) receiving CPAP outside intensive care unit (ICU), and ascertaining whether the duration of CPAP application increased the risk of mortality for patients requiring intubation.

Methods In this retrospective, multicentre cohort study, we included COVID-19 adult patients, treated with CPAP outside ICU for hypoxemic ARF from March 1st to April 15th, 2020. We collected demographic and clinical data, including CPAP therapeutic goal, hospital length of stay (LOS), and 60-day in-hospital mortality.

Results The study includes 537 patients with a median age of 69 (IQR, 60-76) years. Males were 391 (73%). According to predefined CPAP therapeutic goal, 397 (74%) patients were included in full treatment subgroup, and 140 (26%) in the do-not intubate (DNI) subgroup. Median CPAP duration was 4 (IQR, 1-8) days, while hospital LOS 16 (IQR, 9-27) days. Sixty-day in-hospital mortality was overall 34% (95%CI, 0.304-0.384), and 21% (95%CI, 0.169-0.249) and 73% (95%CI, 0.648-0.787) for full treatment and DNI subgroups, respectively. In the full treatment subgroup, in-hospital mortality was 42% (95%CI, 0.345-0.488) for 180 (45%) CPAP failures requiring intubation, while 2% (95%CI, 0.008-0.035) for the remaining 217 (55%) patients who succeeded. Delaying intubation was associated with increased mortality [HR, 1.093 (95%CI, 1.010-1.184)].

Conclusions We described a large population of COVID-19 patients treated with CPAP outside ICU. Intubation delay represents a risk factor for mortality. Further investigation is needed for early identification of CPAP failures.

Introduction

Noninvasive ventilation (NIV) administered as bi-level positive airway pressure (BiPAP) or continuous positive airway pressure (CPAP) is commonly used in various critical care settings across a variety of aetiologies of acute respiratory failure (ARF). For hypercapnic ARF, mainly consequent to chronic obstructive pulmonary disease exacerbation, BiPAP can be used at an early stage to prevent intubation, at a later stage as alternative to first-line endotracheal intubation, or as a mean to facilitate weaning [1]. For hypoxemic ARF, recommendations strongly support the use of both BiPAP and CPAP in patients with episodes of cardiogenic pulmonary edema [2,1], while fewer data suggest their use in immunosuppressed [3,1] and in post-operative [4,1] patients. In patients with *de novo* hypoxemic ARF evidences and recommendations on the use of NIV are still to be determined [1]. Moreover, the application of NIV in patients with acute respiratory distress syndrome (ARDS) complicating viral pneumonia is controversial [5].

During coronavirus disease 2019 (COVID-19) pandemic, Piedmont together with Lombardy, Emilia-Romagna and Veneto was one of the most affected Italian regions. Due to the exceptional demand on intensive care unit (ICU) resources, hospitals increased the number of ICU beds and converted many general wards in respiratory intermediate care units (RICU) to treat patients with severe pneumonia and ARDS-needing respiratory support and monitoring. Indeed, NIV in patients with different therapeutic indications i.e., full-treatment and do-not-intubate [6] has been shown to be successfully applicable also outside the ICU [7,8], when appropriate monitored setting and trained personnel are employed.

Data on NIV during COVID-19 pandemic, so far, consider predominantly patients admitted to the ICU [9,10,11,12,13]. The rate of patients receiving NIV at ICU admission ranges from 11%, as reported by an Italian multicentre investigation [10], to 56% according to a Chinese single centre study [11]. Exposure to noninvasive forms of respiratory support might have been even more diffuse outside ICU, though only data from two monocentre studies are presently available, accounting overall for 40 patients, 38 treated with CPAP [14] and two with NIV or high flow oxygen therapy [15].

We designed this retrospective multicentre study to describe the clinical characteristics of patients with laboratory-confirmed COVID-19 treated with CPAP outside ICU, to assess 60-day in-hospital mortality, and hospital length of stay (LOS), and to ascertain whether the duration CPAP application prior to CPAP failure affects outcome in patients requiring endotracheal intubation.

Methods

Study Design

This is a multicentre, retrospective observational study performed in six hospitals from the area of Eastern Piedmont in Northern Italy. All the participating centres obtained ethic committee approval. More details on study design and ethics approval are provided in the supplementary material.

Patient enrolment and data collection

All patients admitted to one of the participating hospitals from March 1st to April 15th 2020 with hypoxemic ARF secondary to confirmed SARS-CoV-2. Inclusion criteria were: 1) age ≥18 years, 2) respiratory distress and partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 200 mmHg during Venturi mask oxygen therapy, 3) CPAP initiation outside ICU. Patients who received post-extubation CPAP were excluded.

Patients were classified according to predefined CPAP therapeutic goal applied by the medical team, in two subgroups [6]: 1) full treatment, i.e. patients scheduled to receive intubation in the case of CPAP failure; and 2) do-not-intubate (DNI), when CPAP was ceiling of treatment. In case patient changed the therapeutic goal during hospital stay, the last CPAP goal has been considered. The therapeutic goal of CPAP was collegially discussed within the multidisciplinary teams, with the patients and with the families, taking into account comorbidities [16], quality of life and patient wishes. Possible discrepancies between patients and relatives were solved through additional discussions between patient, relatives, and the medical team.

Demographic characteristics, body mass index (BMI), blood sample exams performed at hospital entrance (white blood cell count, lymphocytes count, creatinine, alanine transaminase, aspartate transaminase, lactate dehydrogenase, C-reactive protein, D-dimer, ferritin), arterial blood gas (ABG) values obtained prior to CPAP initiation and 2 to 24 hours after; and coexisting comorbidities were also recorded. Charlson Comorbidity Index (CCI)[17] was also computed on the first day of hospital admission. This index contemplates 17 categories of comorbidity recorded via anamnesis. Age is not included as comorbidity in the CCI version adopted. Finally, we collected data about the clinical

outcomes such as duration of CPAP use, hospital length of stay (LOS), intubation and hospital mortality. For patients still in the hospital on May 15th (n=32), the outcomes have been censored on that day.

CPAP and RICU organization

Details on CPAP setting, schedule, RICU organization and criteria for intubation are described in the supplementary material.

Statistical analysis

Descriptive statistics are used to summarize the main demographic characteristics and the results of laboratory findings of all patients included in the study. Categorical variables are reported as absolute frequencies and percentages, while numerical variables as median and interquartile range (IQR). The frequency and percentage of missing values for all variables is also reported. Mann Whitney U test is used to assess the difference between two independent samples, while Wilcoxon signed-rank test for repeated measurements. Chi-square statistic is used for testing relationships of categorical variables.

Curves of cumulative incidence of in-hospital mortality are drawn to describe mortality along 60 days, either overall and stratified for treatment goal, and in the full treatment subgroup separately for patients succeeding CPAP or receiving intubation.

In order to avoid immortal time bias, in the survival analysis of patients receiving intubation, observation period started at the day of intubation. In the other analyses, observation period started at the day of CPAP initiation. Since discharge must be considered an informative censoring [18], cumulative incidence was calculated using methods accounting for competing risk. To evaluate the cumulative incidence of in-hospital mortality for patients not undergoing intubation, all full treatment subjects are considered, and intubation is treated as a competing event allowing to account for the contribution of the time spent by intubated patients on CPAP. The Gray's test is used to assess the difference between cumulative incidence functions. Fine and Gray multivariate competing risk model is adopted to calculate the sub-distribution hazard ratios (sHR) and the corresponding 95% confidence intervals (95%CI) for the association between CPAP duration and in-hospital mortality risk in intubated patients, considering discharge as competing event. In the main analyses, missing data are managed by listwise deletion. We

also carried out a secondary analysis using multiple imputation to evaluate the impact of missing values on the association estimates. Missing imputation is performed using the Expectation-Maximization algorithm (500 imputations) and considering the "missing at random" mechanism. More details about the model are provided in the supplementary material.

All hypothesis tests are two-tailed and a significance level of 0.05 is considered. All statistical analysis was performed using STATA (Stata Statistical Software: Release 15. College Station, TX, USA: StataCorp LLC), SAS (version 9.4; SAS Institute Cary, NC, USA) and R (version 3.5.1).

Results

From March 1st to April 15th, a total of 2845 patients with confirmed COVID-19 were admitted to the six hospitals of the eastern Piedmont (Figure 1s). Of these, 326 (11%) patients were treated in ICU, 31 (1%) and 295 (10%) with noninvasive and invasive mechanical ventilation, respectively. CPAP was applied to 537 (22%) patients in RICU.

Table 1 shows the demographic and clinical patients' characteristics. The number of observations for each variable is displayed in table 1s. The median age was 69 (IQR, 60-76) years, and BMI 28 (IQR, 25-31) kg/m^2. Males were 391 (73%). Laboratory values at hospital entrance are also summarized in table 1. Median white blood cell count was 6.9 (IQR, 5.1-9.5) x 10^3/μL, with lymphopenia, i.e., 0.8 (0.6–1.1) x 10^3/μL. Median values of creatinine, aspartate-aminotransferase, alanine-aminotransferase were in the normal range, while C-reactive protein, ferritin, lactate dehydrogenase and D-dimer were all above the normal range. CCI median value was 1 (IQR, 0-2), chronic arterial hypertension was present in 278 (52%) patients, diabetes in 138 (26%) patients, and ischaemic heart disease in 66 (12%) patients.

The most common interface was the helmet, in 399 (74%) patients, while face masks were used in 123 patients (23%); 15 patients (3%) alternated both interfaces. Median CPAP duration was 4 (IQR, 1-8) days. Overall cumulative 60-day in-hospital mortality was 34% (cumulative incidence, 0.344, 95%CI, 0.304-0.384), as depicted in Figure 1A, while hospital LOS was 16 (IQR, 9-27) days.

Demographic and clinical patients' characteristics stratified by PaO_2/FiO_2 performed 2 to 24 hours after CPAP initiation and interface applied, are provided in the supplementary material in table 2s and 3s, respectively. Overall cumulative 60-day in-hospital mortality stratified according to PaO_2/FiO_2 and interface applied is also depicted in Figure 2s A and B, in the supplementary material. As expected, mortality seemed to increase in patients with lower PaO_2/FiO_2, while was not different between patients treated with helmet (cumulative incidence, 0.315, 95%CI, 0.270-0.361) or face mask (cumulative incidence, 0.407, 95%CI, 0.320-0.493), p= 0.094.

When dividing patients according to the therapeutic goal (table 2), patients in the full treatment subgroup were younger [median, 66 (IQR, 57-72) years] compared to DNI [median, 79 (IQR, 72-84) year]. DNI subgroup had higher D-dimer values than full treatment patients [median, 1351 (IQR, 637-3518)

µgFEU/L vs. 897 (IQR, 496-1665) µgFEU/L] (p=0.02), and greater CCI [median, 2 (IQR, 1-3) vs. median, 0 (IQR, 0-1)] (p<0.0001). The number of observations for each variable is displayed in table 4s.

Table 5s shows ABGs and table 6s the number of observations for each variable. While the first ABG indicated in table 5s was performed 1-day (IQR, 0-3 days) after hospital admission, the second was performed 2 to 24 hours after CPAP initiation.

Before starting CPAP, patients presented a PaO_2/FiO_2 of 108 (IQR, 71-157) mmHg and a respiratory rate of 27 (IQR, 22-32) breaths/min. Soon after CPAP, PaO_2/FiO_2 raised to 157 (IQR, 109-255) mmHg and respiratory rate decreased to 24 (IQR, 20-28) breaths/min with median CPAP of 10 (IQR, 10-12) cmH_2O, and FiO_2 of 50% (IQR, 50-60%). Median CPAP duration was 4 days for both subgroups, while hospital LOS was 19 (IQR, 11-30) days for full treatment and 11 (IQR, 6-20) days for DNI subgroup.

Figure 1B depicts 60-day in-hospital mortality for full-treatment [21% (cumulative incidence 0.208, 95%CI, 0.169-0.249)] and DNI [73% (cumulative incidence 0.731, 95%CI, 0.648-0.787)], (p < 0.0001). Within the full treatment subgroup, 60-day in-hospital mortality was 42% (cumulative incidence 0.418, 95%CI, 0.345-0.488) for patients receiving intubation (Figure 2), and 2% (cumulative incidence 0.018, 95%CI, 0.008-0.035) for patients succeeding CPAP (Figure 3s).

CPAP duration was 2 days (IQR, 1-3 days) in patients who survived and 3 days (IQR. 1-5 days) in patients who died (p=0.061). Table 3 shows that duration of CPAP application was an independent predictor of mortality for patients requiring intubation. The model, adjusting for age, gender, comorbidities, LDH, C-reactive protein values, and lymphocyte count, indicates a 9.3% [HR, 1.094 (95%CI, 1.010-1.184)] increase of the risk of death for each day of treatment. The association between duration of CPAP and mortality does not substantially change in the secondary analysis using multiple imputation [HR, 1.060 (95%CI, 1.001-1.121)], as presented in Table 7s. 60-day in-hospital mortality was significantly higher in patients subjected to CPAP for more than 3 days (cumulative incidence 0.510, 95%CI, 0.393-0.615) as compared to those receiving CPAP for 3 days or less (cumulative incidence 0.350, 95%CI, 0.259-0.441), as shown in Figure 4s.

Discussion

This multicentre retrospective observational study on 537 patients hypoxemic ARF secondary to laboratory-confirmed COVID-19 infection, shows that CPAP applied to different therapeutic goals i.e., candidate to intubation in the case of CPAP failure and do-not-intubate in which CPAP is considered the ceiling of treatment, is feasible outside ICU. Treatment duration for patients failing CPAP prior to intubation represents a risk factor for mortality.

CPAP can be delivered both in ICU and outside ICU. Grasselli et al. [10], found that 11% of the patients entering ICU needed NIV, while early data from China revealed a higher percentage i.e., 41.7% [13], 43.3% [19], 56% [11], 62%[15]. In keeping with data by Grasselli et al. [10], as CPAP was delivered to 31 out of 326 patients (9.5%) entering ICU.

Data on the use of CPAP in COVID-19 patients treated outside ICU are scarce. Two over 28 patients (7%) received NIV or HFNC outside ICU in a single centre study in Wuhan [15]. Oranger et al., treated 38 patients with CPAP in a respiratory ward [14]. Although the study included a limited patients' number, CPAP resulted to be feasible and the authors also suggest a potential benefit for both full treatment and DNI patients, as opposed to those treated with oxygen only [14].

As far as mortality concerns, we showed an overall cumulative 60-day in-hospital mortality of 34% in patients with moderate to severe forms of ARF COVID-19-related needing CPAP. The rate of mortality observed in our study, is not divergent from those reported in several prior studies [9,10,15,12,13] for ICU patients, predominantly intubated, which varied from 17% [13] to 67% [9].

Lastly, our study includes 26% of DNI patients, for whom CPAP was considered ceiling of treatment. Rate of DNI patients reported in our study is similar to 15% observed in a small cohort of patients treated outside ICU during COVID-19 pandemic [14], i.e., as well as to 30% reported by a large Italian multicentre observational study in patients with pneumonia non-COVID-19 related, treated with NIV outside ICU [20]. In our study, 60-day in-hospital mortality for DNI patients was 73%.

A major concern when treating patients with hypoxemic ARF with NIV, is related to NIV-failure rate that might occur in up 50% of the cases with consequent recourse to intubation [21]. Undue prolongation

of NIV may worsen lung injury resulting in the so-called patient self-inflicted lung injury [22], while the direct consequence of NIV failure is delaying intubation and adequate treatment with invasive ventilation [23,1]. Our data confirm that intubation delay for those requiring afterward invasive ventilation is associated with increased risk for mortality. In other pandemics, such as influenza, H1N1, and severe acute respiratory syndrome (SARS), NIV failure ranges from 10 to more than 70% [24], reaching 90% with middle east respiratory syndrome [25]. In our study, CPAP failure rate was 45%, which indicates that effective treatment occurred in more than half of patients, who avoided invasive ventilation through an endotracheal tube, which is a life-saving procedure, but it is also prone to several side-effects and complications [26].

Limitations

The study has several limitations. First, we were not able to compare our population with an historical control. Second, most of data have been retrospectively derived from the medical records. According to the retrospective nature of the study, formal criteria to start CPAP treatment were not defined a priori, and the time span between CPAP initiation and control ABG was relatively long. Third, definitions of full treatment and DNI patients, although internationally accepted [6], are influenced by patients, families, and clinicians thinking and might be influenced by cultural, religious and geographical factors. Fourth, due to the diversity of interfaces and devices used in our study, the actual applied pressure could somewhat differ from the preset value [27]. Fifth, due to the number of missing data among many important variables such as D-Dimer and respiratory rate, we were not able introduce them in the model that explore the correlation between CPAP duration and mortality. Lastly, because of the exceptionality of pandemic outbreak, our results are not generalizable to other conditions.

Conclusions

To the best of our knowledge, this is the largest retrospective cohort study on patients with COVID-19 treated with CPAP outside ICU. We show that CPAP is feasible outside ICU with overall in-hospital mortality similar to that reported in other studies treating critically ill ICU patients. In-hospital mortality is closely related to the therapeutic goal, patients having DNI order being affected by much higher mortality. Intubation delay is confirmed to be an independent risk factor for mortality. Further studies

are necessary to ascertain the potential infective risk related to CPAP treatment outside ICU among healthcare workers.

Table 1 General characteristics of patients with CPAP outside ICU

	Overall (n=537)
Characteristics	
Age, years	69 (60-76)
Male, n (%)	391 (73)
Body mass index, kg/m^2	28 (25-31)
White blood cell count, $x10^3/\mu L$	6.9 (5.1-9.5)
Lymphocyte count, $x10^3/\mu L$	0.8 (0.6-1.1)
Creatinine, mg/dL	1.0 (0.8-1.3)
Aspartate-aminotransferase, U/L	41 (29-59)
Alanine-aminotransferase, U/L	31 (22-50)
C-reactive protein, mg/dL	11 (6-17)
Ferritin, ng/mL	1053 (565-1643)
Lactate dehydrogenase, U/L	560 (410-786)
D-dimer, μgFEU/L	954 (526-1874)
Charlson comorbidity index	1 (0-2)
Chronic arterial hypertension, n (%)	278 (52)
Diabetes, n (%)	138 (26)
Ischaemic heart disease, n (%)	66 (12)
CPAP, days	4 (1-8)
Hospital length of stay, days	16 (9-27)

Values are median (interquartile range) or number (percentage).
CPAP, noninvasive continuous positive airway pressure; ICU, intensive care unit;
FEU, fibrinogen-equivalent unit

Table 2 General characteristics of patients stratified according to CPAP therapeutic goal

	Full treatment (n=397)	Do not intubate (n=140)	p value
Characteristics			
Age, years	66 (57-72)	79 (72-84)	< 0.0001
Male, n (%)	293 (74)	98 (70)	0.22
Body mass index, kg/m^2	28 (25-31)	28 (25-31)	0.74
White blood cell count, $x10^3/\mu L$	6.8 (5.1-9.1)	7.1 (5.0-10.6)	0.47
Lymphocyte count, $x10^3/\mu L$	0.8 (0.6-1.1)	0.7 (0.5-1.1)	0.04
Creatinine, mg/dL	0.9 (0.8-1.2)	1.2 (0.9-1.5)	< 0.0001
Aspartate-aminotransferase, U/L	42 (31-59)	39 (26-60)	0.36
Alanine-aminotransferase, U/L	34 (24-53)	25 (19-39)	< 0.0001
C-reactive protein, mg/dL	11 (6-17)	12 (7-18)	0.26
Ferritin, ng/mL	1068 (600-1674)	817 (411-1389)	0.08
Lactate dehydrogenase, U/L	575 (415-786)	538 (393-760)	0.47
D-dimer, μgFEU/L	897 (496-1665)	1351 (637-3518)	0.02
Charlson comorbidity index	0 (0-1)	2 (1-3)	< 0.0001
Chronic arterial hypertension, n (%)	199 (50)	79 (56)	0.12
Diabetes, n (%)	94 (24)	44 (31)	0.047
Ischaemic heart disease, n (%)	37 (9)	29 (21)	0.001
CPAP, days	4 (2-9)	4 (1-8)	0.33
Hospital length of stay, days	19 (11-30)	11 (6-20)	< 0.0001

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

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

Table 3 Fine and Gray model for the association between CPAP duration and mortality

	sHR	95%CI
CPAP, days	1.094	(1.010-1.184)
Male	1.596	(0.814-3.129)
Age	1.023	(0.985-1.064)
Hypertension, yes vs. no	1.224	(0.729-2.056)
Charlson index	1.392	(1.145-1.693)
Lactate dehydrogenase, U/L	1.001	(1.000-1.002)
C-reactive protein, mg/dL	0.983	(0.947-1.020)
Lymphocytes, $x10^3$/mL	1.269	(0.699-2.302)

CPAP, noninvasive 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:146

Figure legends

Fig. 1 Cumulative incidence of in-hospital mortality in the overall patients (Panel A) and stratified by treatment (Panel B) i.e., DNI and full treatment patients in grey and in black lines, respectively. Curves and corresponding 95% confidence intervals (dashed lines).

CPAP, noninvasive continuous positive airway pressure; DNI, do not intubate.

Fig. 2 Cumulative incidence of in-hospital mortality in patients requiring invasive mechanical ventilation. Curve and corresponding 95% confidence interval (dashed lines).

ETI, endo-tracheal intubation.

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Reference List

1. Rochwerg B, Brochard L, Elliott MW, Hess D, Hill NS, Nava S, Navalesi PMOT, Antonelli M, Brozek J, Conti G, Ferrer M, Guntupalli K, Jaber S, Keenan S, Mancebo J, Mehta S, Raoof S Members Of The Task Force. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. Eur Respir J 2017; 50:

2. Masip J, Roque M, Sanchez B, Fernandez R, Subirana M, Exposito JA. Noninvasive ventilation in acute cardiogenic pulmonary edema: systematic review and meta-analysis. JAMA 2005; 294: 3124-3130.

3. Lemiale V, Mokart D, Resche-Rigon M, Pene F, Mayaux J, Faucher E, Nyunga M, Girault C, Perez P, Guitton C, Ekpe K, Kouatchet A, Theodose I, Benoit D, Canet E, Barbier F, Rabbat A, Bruneel F, Vincent F, Klouche K, Loay K, Mariotte E, Bouadma L, Moreau AS, Seguin A, Meert AP, Reignier J, Papazian L, Mehzari I, Cohen Y, Schenck M, Hamidfar R, Darmon M, Demoule A, Chevret S, Azoulay E. Effect of Noninvasive Ventilation vs Oxygen Therapy on Mortality Among Immunocompromised Patients With Acute Respiratory Failure: A Randomized Clinical Trial. JAMA 2015; 314: 1711-1719.

4. Jaber S, Lescot T, Futier E, Paugam-Burtz C, Seguin P, Ferrandiere M, Lasocki S, Mimoz O, Hengy B, Sannini A, Pottecher J, Abback PS, Riu B, Belafia F, Constantin JM, Masseret E, Beaussier M, Verzilli D, De JA, Chanques G, Brochard L, Molinari N. Effect of Noninvasive Ventilation on Tracheal Reintubation Among Patients With Hypoxemic Respiratory Failure Following Abdominal Surgery: A Randomized Clinical Trial. JAMA 2016; 315: 1345-1353.

5. Namendys-Silva SA, Hernandez-Garay M, Rivero-Sigarroa E. Non-invasive ventilation for critically ill patients with pandemic H1N1 2009 influenza A virus infection. Crit Care 2010; 14: 407-

6. Curtis JR, Cook DJ, Sinuff T, White DB, Hill N, Keenan SP, Benditt JO, Kacmarek R, Kirchhoff KT, Levy MM. Noninvasive positive pressure ventilation in critical and palliative care settings: understanding the goals of therapy. Crit Care Med 2007; 35: 932-939.

7. Cabrini L, Moizo E, Nicelli E, Licini G, Turi S, Landoni G, Silvani P, Zangrillo A. Noninvasive ventilation outside the intensive care unit from the patient point of view: a pilot study. Respir Care 2012; 57: 704-709.

8. Cabrini L, Esquinas A, Pasin L, Nardelli P, Frati E, Pintaudi M, Matos P, Landoni G, Zangrillo A. An international survey on noninvasive ventilation use for acute respiratory failure in general non-monitored wards. Respir Care 2015; 60: 586-592.

9. Arentz M, Yim E, Klaff L, Lokhandwala S, Riedo FX, Chong M, Lee M. Characteristics and Outcomes of 21 Critically Ill Patients With COVID-19 in Washington State. JAMA 2020;

10. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, Cereda D, Coluccello A, Foti G, Fumagalli R, Iotti G, Latronico N, Lorini L, Merler S, Natalini G, Piatti A, Ranieri MV, Scandroglio AM, Storti E, Cecconi M, Pesenti A, Nailescu A, Corona A, Zangrillo A, Protti A, Albertin A, Forastieri MA, Lombardo A, Pezzi A, Benini A, Scandroglio AM, Malara A, Castelli A, Coluccello A, Micucci A, Pesenti A, Sala A, Alborghetti A, Antonini B, Capra C, Troiano C, Roscitano C, Radrizzani D, Chiumello D, Coppini D, Guzzon D, Costantini E, Malpetti E, Zoia E, Catena E, Agosteo E, Barbara E, Beretta E, Boselli E, Storti E, Harizay F, Della MF, Lorini FL, Donato SF, Marino F, Mojoli F, Rasulo F, Grasselli G, Casella G, De FG, Castelli G, Aldegheri G, Gallioli G, Lotti G, Albano G, Landoni G, Marino G, Vitale G, Battista PG, Evasi G,

Citerio G, Foti G, Natalini G, Merli G, Sforzini I, Bianciardi L, Carnevale L, Grazioli L, Cabrini L, Guatteri L, Salvi L, Dei PM, Galletti M, Gemma M, Ranucci M, Riccio M, Borelli M, Zambon M, Subert M, Cecconi M, Mazzoni MG, Raimondi M, Panigada M, Belliato M, Bronzini N, Latronico N, Petrucci N, Belgiorno N, Tagliabue P, Cortellazzi P, Gnesin P, Grosso P, Gritti P, Perazzo P, Severgnini P, Ruggeri P, Sebastiano P, Covello RD, Fernandez-Olmos R, Fumagalli R, Keim R, Rona R, Valsecchi R, Cattaneo S, Colombo S, Cirri S, Bonazzi S, Greco S, Muttini S, Langer T, Alaimo V, Viola U. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. JAMA 2020;

11. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T, Wang Y, Pan S, Zou X, Yuan S, Shang Y. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020;

12. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, Barnaby DP, Becker LB, Chelico JD, Cohen SL, Cookingham J, Coppa K, Diefenbach MA, Dominello AJ, Duer-Hefele J, Falzon L, Gitlin J, Hajizadeh N, Harvin TG, Hirschwerk DA, Kim EJ, Kozel ZM, Marrast LM, Mogavero JN, Osorio GA, Qiu M, Zanos TP. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA 2020;

13. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA 2020;

14. Oranger M, Gonzalez-Bermejo J, Dacosta-Noble P, Llontop C, Guerder A, Trosini-Desert V, Faure M, Raux M, Decavele M, Demoule A, Morelot-Panzini C, Similowski T. Continuous

positive airway pressure to avoid intubation in SARS-CoV-2 pneumonia: a two-period retrospective case-control study. Eur Respir J 2020;

15. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395: 497-506.

16. Gristina GR, Orsi L, Carlucci A, Causarano IR, Formica M, Romano M. [Part I. End-stage chronic organ failures: a position paper on shared care planning. The Integrated Care Pathway]. Recenti Prog Med 2014; 105: 9-24.

17. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987; 40: 373-383.

18. Resche-Rigon M, Azoulay E, Chevret S. Evaluating mortality in intensive care units: contribution of competing risks analyses. Crit Care 2006; 10: R5-

19. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020; 382: 1708-1720.

20. Brambilla AM, Prina E, Ferrari G, Bozzano V, Ferrari R, Groff P, Petrelli G, Scala R, Causin F, Noto P, Bresciani E, Voza A, Aliberti S, Cosentini R. Non-invasive positive pressure ventilation in pneumonia outside Intensive Care Unit: An Italian multicenter observational study. Eur J Intern Med 2019; 59: 21-26.

21. Frat JP, Thille AW, Mercat A, Girault C, Ragot S, Perbet S, Prat G, Boulain T, Morawiec E, Cottereau A, Devaquet J, Nseir S, Razazi K, Mira JP, Argaud L, Chakarian JC, Ricard JD, Wittebole X, Chevalier S, Herbland A, Fartoukh M, Constantin JM, Tonnelier JM, Pierrot M, Mathonnet A, Beduneau G, Deletage-Metreau C, Richard JC, Brochard L, Robert R. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. N Engl J Med 2015; 372: 2185-2196.

22. Brochard L, Slutsky A, Pesenti A. Mechanical Ventilation to Minimize Progression of Lung Injury in Acute Respiratory Failure. Am J Respir Crit Care Med 2017; 195: 438-442.

23. Brochard L, Lefebvre JC, Cordioli RL, Akoumianaki E, Richard JC. Noninvasive ventilation for patients with hypoxemic acute respiratory failure. Semin Respir Crit Care Med 2014; 35: 492-500.

24. Esquinas AM, Egbert PS, Scala R, Gay P, Soroksky A, Girault C, Han F, Hui DS, Papadakos PJ, Ambrosino N. Noninvasive mechanical ventilation in high-risk pulmonary infections: a clinical review. Eur Respir Rev 2014; 23: 427-438.

25. Alraddadi BM, Qushmaq I, Al-Hameed FM, Mandourah Y, Almekhlafi GA, Jose J, Al-Omari A, Kharaba A, Almotairi A, Al KK, Shalhoub S, Abdulmomen A, Mady A, Solaiman O, Al-Aithan AM, Al-Raddadi R, Ragab A, Balkhy HH, Al HA, Sadat M, Tlayjeh H, Merson L, Hayden FG, Fowler RA, Arabi YM. Noninvasive ventilation in critically ill patients with the Middle East respiratory syndrome. Influenza Other Respir Viruses 2019; 13: 382-390.

26. Esteban A, Frutos-Vivar F, Muriel A, Ferguson ND, Penuelas O, Abraira V, Raymondos K, Rios F, Nin N, Apezteguia C, Violi DA, Thille AW, Brochard L, Gonzalez M, Villagomez AJ, Hurtado J, Davies AR, Du B, Maggiore SM, Pelosi P, Soto L, Tomicic V, D'Empaire G, Matamis D, Abroug F, Moreno RP, Soares MA, Arabi Y, Sandi F, Jibaja M, Amin P, Koh Y, Kuiper MA,

Bulow HH, Zeggwagh AA, Anzueto A. Evolution of mortality over time in patients receiving mechanical ventilation. Am J Respir Crit Care Med 2013; 188: 220-230.

27. Vargas F, Thille A, Lyazidi A, Campo FR, Brochard L. Helmet with specific settings versus facemask for noninvasive ventilation. Crit Care Med 2009; 37: 1921-1928.

FIGURE 1

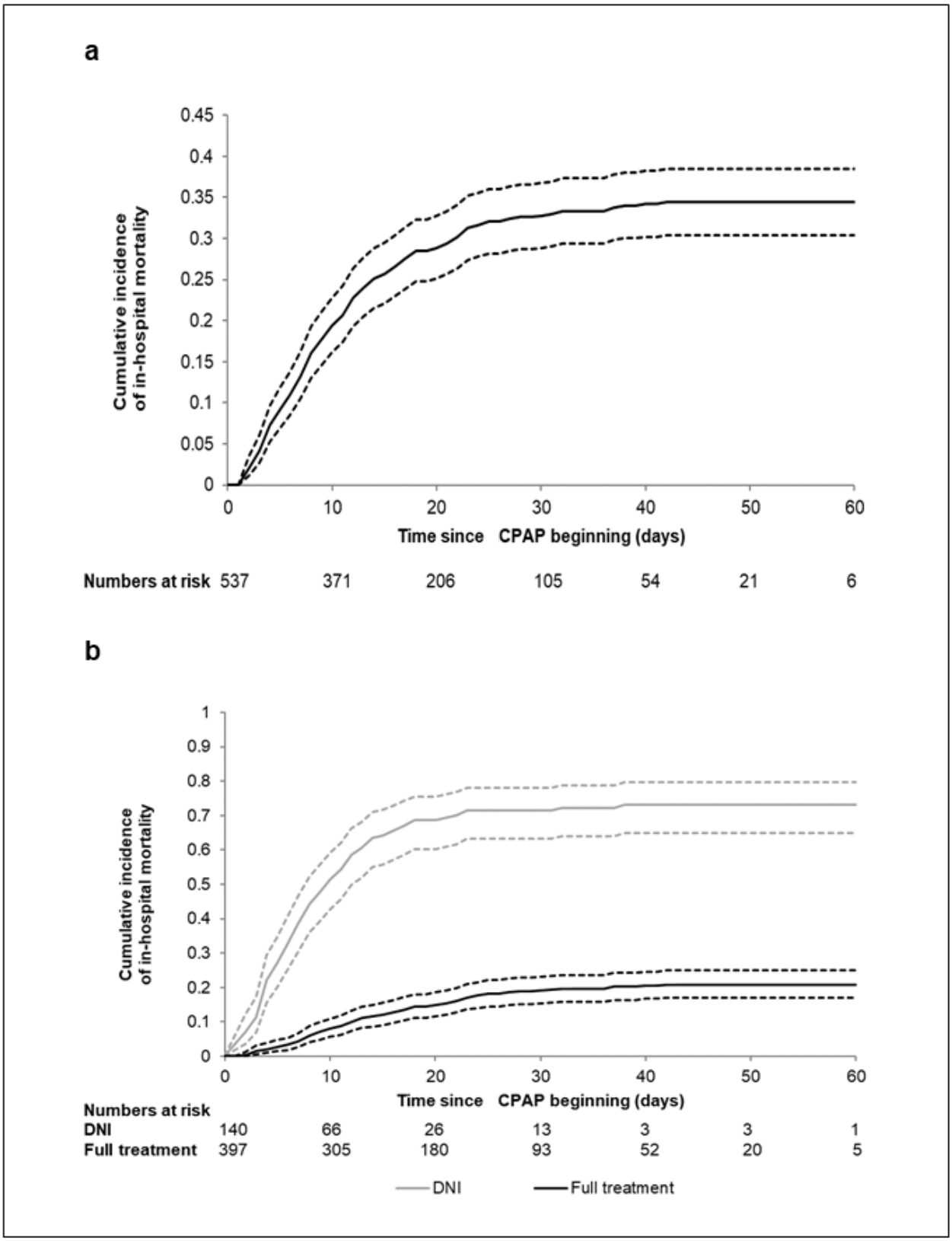
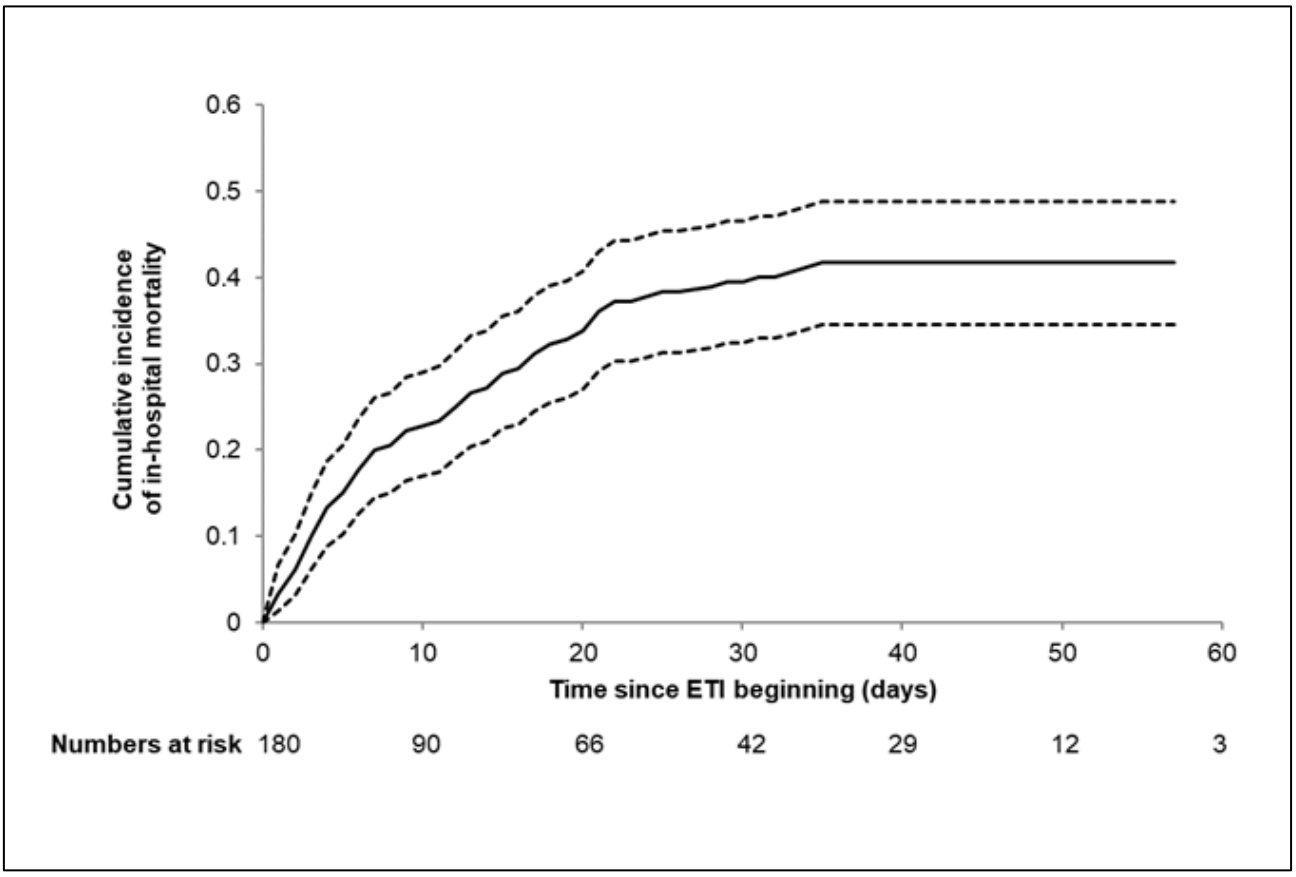

a
Cumulative incidence of in-hospital mortality
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
0
10
20
30
40
50
60
Time since CPAP beginning (days)
Numbers at risk 537 371 206 105 54 21 6
b
Cumulative incidence of in-hospital mortality
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
10
20
30
40
50
60
Time since CPAP beginning (days)
Numbers at risk
DNI 140 66 26 13 3 3 1
Full treatment 397 305 180 93 52 20 5
DNI
Full treatment

FIGURE 2


Cumulative incidence of in-hospital mortality
0.6
0.5
0.4
0.3
0.2
0.1
0
0
10
20
30
40
50
60
Time since ETI beginning (days)
Numbers at risk 180 90 66 42 29 12 3

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 (SpO_2) 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 cmH_2O according to patient's needs, tolerance and any side-effects. CPAP pressure could be increased up to 15 cmH_2O. 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 SpO_2, 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.

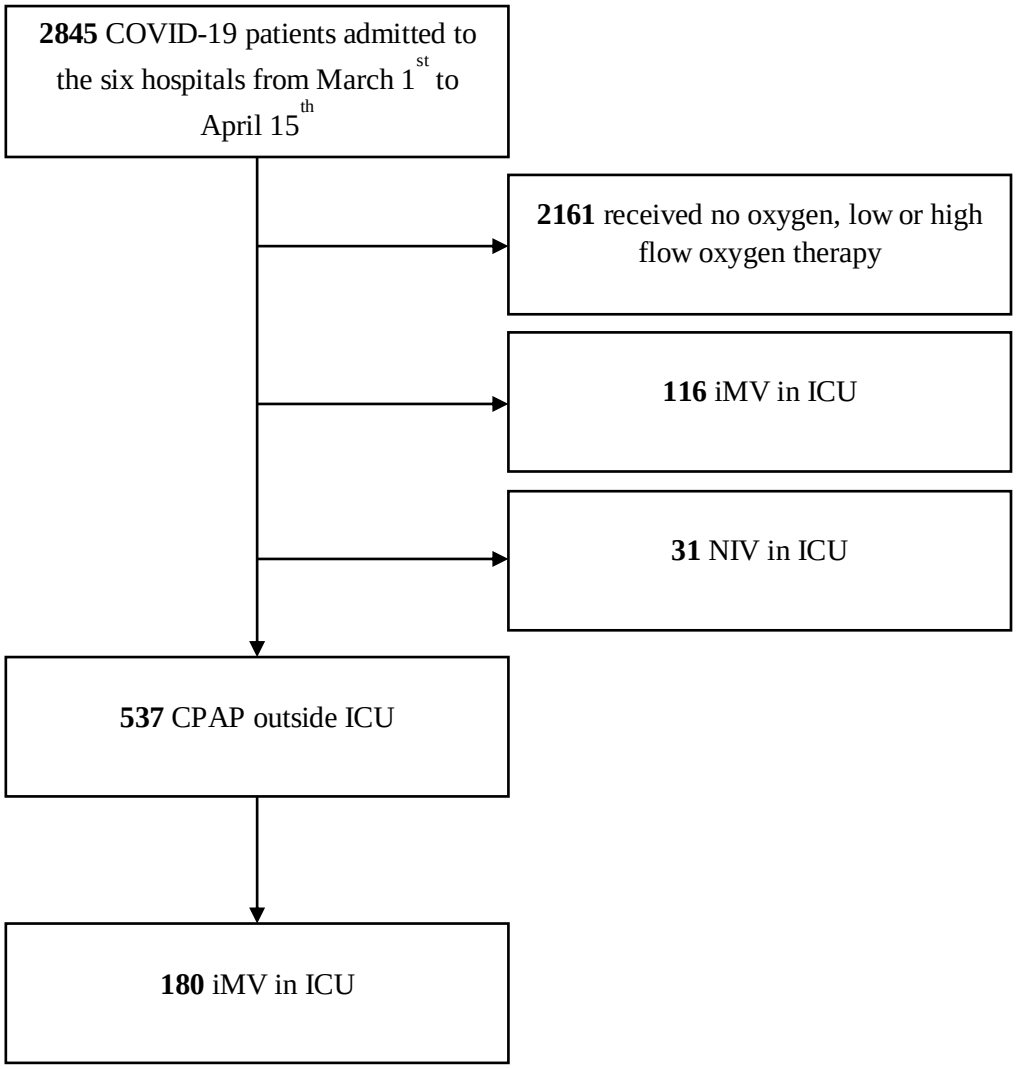
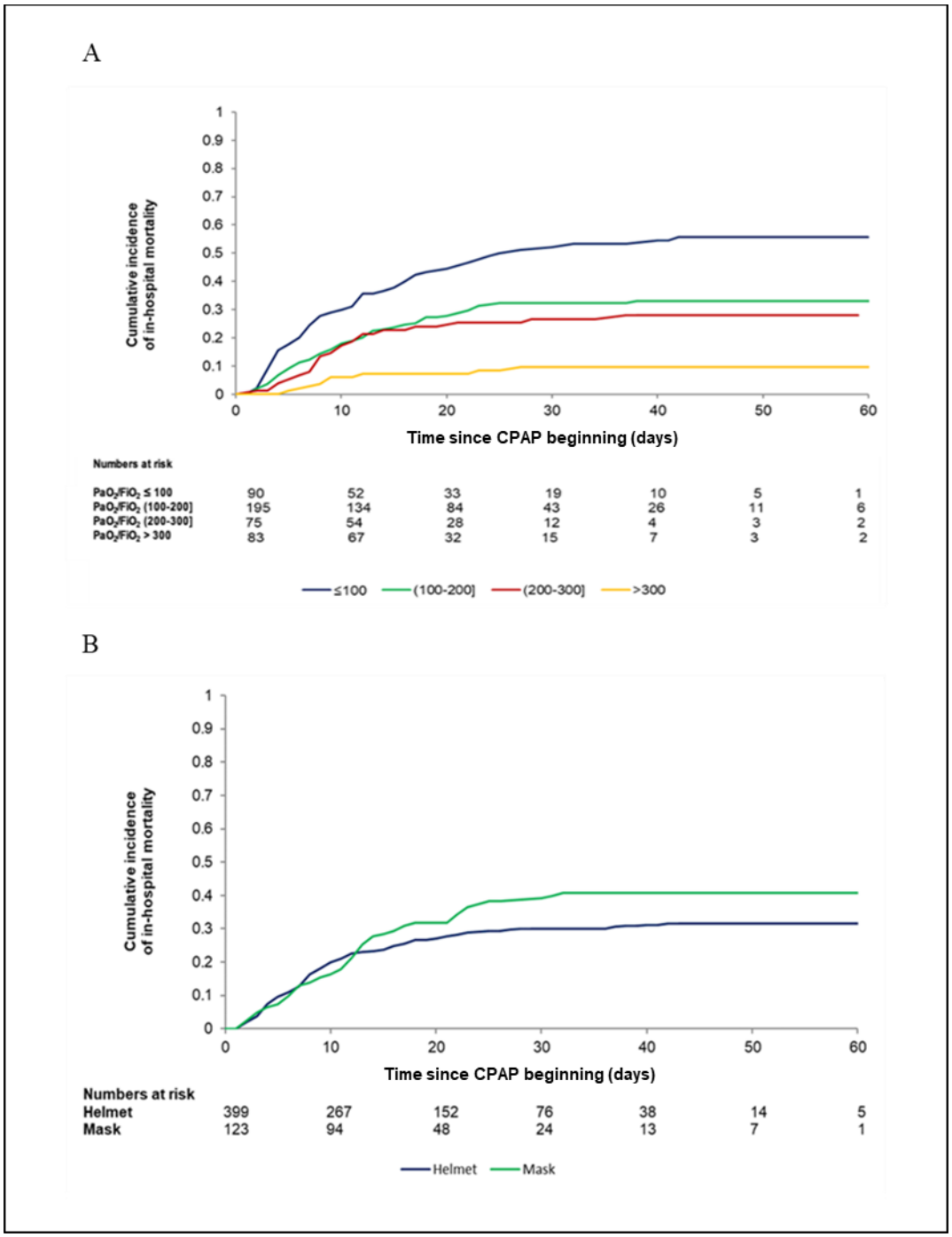


Figure 2S Cumulative incidence of in-hospital mortality stratified by PaO_2/FiO_2 levels (Panel A) and interface applied (Panel B).



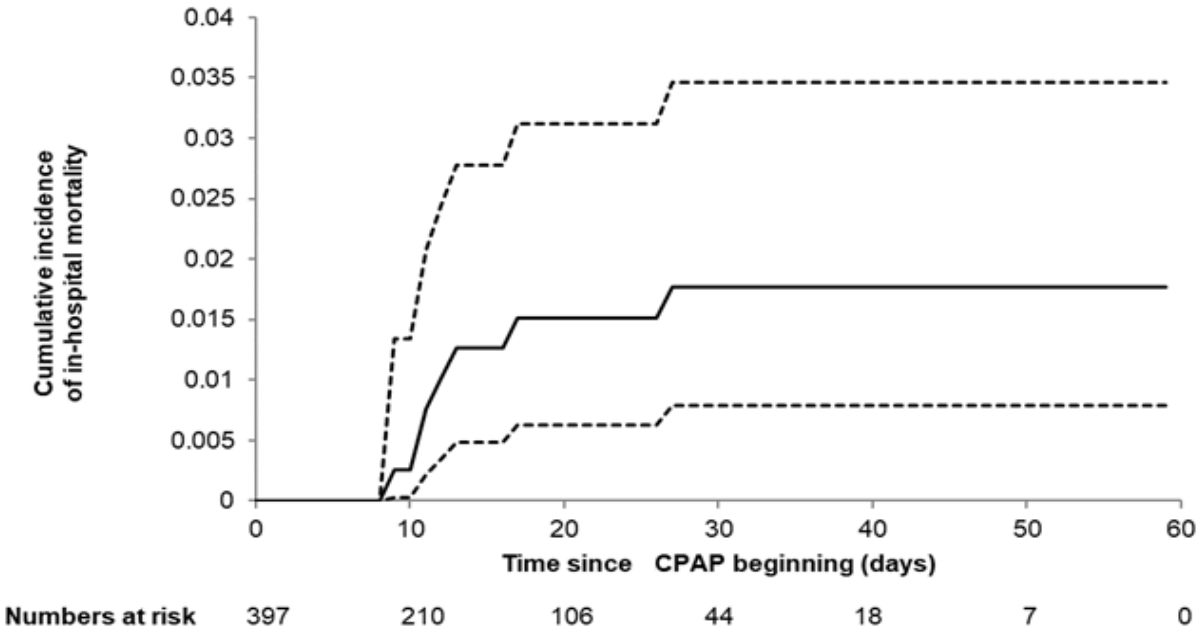
PaO_2/FiO_2

Cumulative incidence at 60 days – $PaO_2/FiO_2 \leq 100$: 0.558 (0.448-0.654).
Cumulative incidence at 60 days – PaO_2/FiO_2 (100-200]: 0329 (0.264-0.395).
Cumulative incidence at 60 days – PaO_2/FiO_2 (200-300]: 0.280 (0.183-0.385).
Cumulative incidence at 60 days – $PaO_2/FiO_2 > 300$: 0.100 (0.045-0.172).
P-value Grey's test for equality of CIF <0.0001

CPAP device

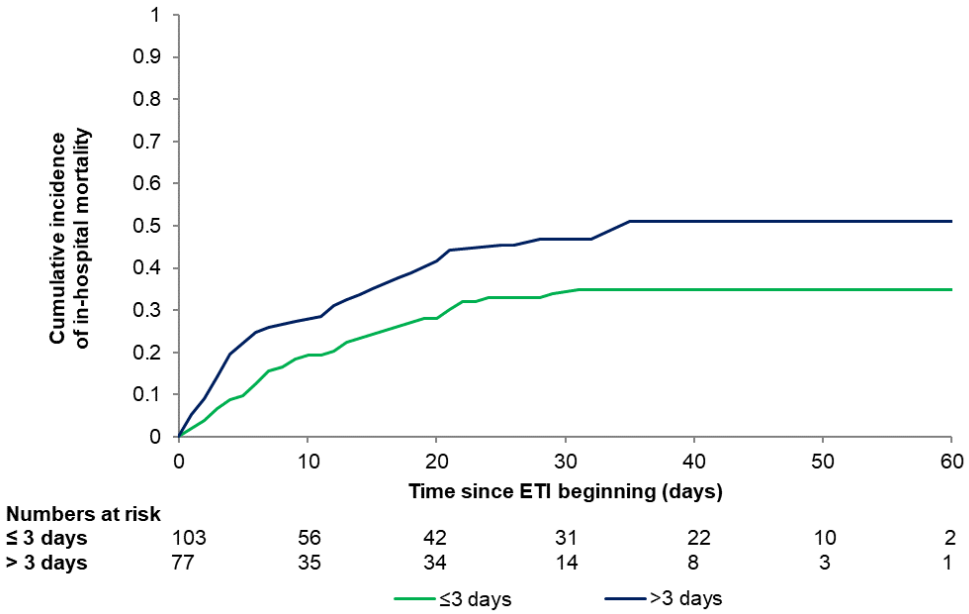
Cumulative incidence at 60 days – CPAP Helmet: 0.315 (0.270-0.361).
Cumulative incidence at 60 days – CPAP Mask: 0.407 (0.320-0.493).
P-value Grey's test for equality of CIF 0.0938

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 PaO_2/FiO_2 value

	$PaO_2/FiO_2 > 300$	$300 \geq PaO_2/FiO_2 < 200$	$200 \geq PaO_2/FiO_2 > 100$	$PaO_2/FiO_2 \leq 100$
	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, $x10^3/\mu L$ [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, $x10^3/\mu L$ [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)

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

CPAP, noninvasive continuous positive airway pressure; FEU, fibrinogen-equivalent unit. [a]Kruskal-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, $x10^3/\mu L$	6.7 (5.1-9.0)	8.0 (5.1-10.5)†	7.1 (4.5-10.6)
Lymphocyte count, $x10^3/\mu L$	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)
$HCO3^-$, 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)[*]
$HCO3^-$, 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_2O	10 (10-12)	10 (10-12)	10 (10-12)

ABG, arterial blood gas analysis; CPAP, noninvasive continuous positive airway pressure; $PaCO_2$, arterial partial pressure of carbon dioxide; PaO_2, arterial partial pressure of oxygen; SpO_2, peripheral oxygen saturation; HCO^{3-}, bicarbonate; FiO_2, inspired oxygen fraction; PaO_2/FiO_2, arterial partial pressure of oxygen to inspired oxygen fraction ratio; SpO_2/FiO_2, peripheral oxygen saturation to inspired oxygen fraction ratio

[a]Arterial blood gas analysis performed before CPAP initiation

[b]First 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

Table 6S Number of observations for each variable

	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
$HCO3^-$	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
$HCO3^-$	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; $PaCO_2$, arterial partial pressure of carbon dioxide; PaO_2, arterial partial pressure of oxygen; SpO_2, peripheral oxygen saturation; HCO^{3-}, bicarbonate; FiO_2, inspired oxygen fraction; PaO_2/FiO_2, arterial partial pressure of oxygen to inspired oxygen fraction ratio; SpO_2/FiO_2, peripheral oxygen saturation to inspired oxygen fraction ratio

[a]Arterial blood gas analysis performed before CPAP initiation

[b]First 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