Emergency Care Journal

Official Journal of the Academy of Emergency Medicine and Care (AcEMC)

eISSN 2282-2054
https://www.pagepressjournals.org/index.php/ecj/index

Emerg Care J 2024 [Online ahead of print]

To cite this Article:
Giannone A, Piazza I, Preti C, et al. **Outcomes of bailout use of continuous positive airway pressure in patients with severe COVID-19 respiratory failure.** *Emerg Care J* doi: 10.4081/ecj.2024.12225

Outcomes of bailout use of continuous positive airway pressure in patients with severe COVID-19 respiratory failure

Alberto Giannone,[1] Isabelle Piazza,[1,2] Carlo Preti,[1,2] Eleonora M. Pisano,[1,2] Arianna Ghirardi,[3] Alberto Benetti,[4] Stefano Fagiuoli,[5] Ferdinando L. Lorini,[6] Marco Rizzi,[7] Fabiano di Marco,[2,8] Roberto Cosentini[1]

[1]Emergency department, ASST Papa Giovanni XXIII, Bergamo; [2]Università degli Studi di Milano, Milan; [3]FROM Research foundation, ASST Papa Giovanni XXIII, Bergamo; [4]Unit of Internal Medicine, ASST Papa Giovanni XXIII, Bergamo; [5]Unit of Gastroenterology, Hepatology and Transplantation, ASST Papa Giovanni XXIII, Bergamo; [6]Intensive Care Unit, ASST Papa Giovanni XXIII, Bergamo; [7]Unit of Infectious Disease, ASST Papa Giovanni XXIII, Bergamo; [8]Unit of Pulmonary Medicine, ASST Papa Giovanni XXIII, Bergamo, Italy

Correspondence: Roberto Cosentini, Emergency department – EAS, ASST Papa Giovanni XXIII, Piazza OMS 1, 24127 Bergamo, Italy.

Tel.: +39.035.2674540 - Fax: +39.035.2674936
E-mail: rcosentini@asst-pg23.it

Key words: emergency department, COVID-19, CPAP, respiratory failure, outcome.

Contributions: AGir, article's draft, conception and design; IP article's draft, conception and design, analysis and interpretation of data; CP, EP, article's draft; AGhir analysis and interpretation of data; AB, SF, FL, MR, FDM, critical revision for important intellectual content; RC: conception and design; critical revision for important intellectual content. All the authors approved the final version of the paper agreed to be accountable for all aspects of the work.

Conflict of interest: the authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Funding: none

Ethical statements: this retrospective, observational study was approved by the local Ethical Committee (N. 37/2020). In the view of the urgent need to treat critical patients, and to avoid paper contamination, local Ethical Committee authorized data collection from clinical record review and their publication after the study period.

Informed consent: all patients participating in this study signed a written informed consent form for participating in this study.

Patient consent for publication: written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

Availability of data and materials: all data generated or analyzed during this study are included in this published article.

Abstract

During the first wave of the Coronavirus-19 (COVID-19) pandemic, due to an overflow of patients in the ICU, continuous positive airway pressure (CPAP) was used as a last resort to mechanical ventilation. The purpose of this study is to evaluate prognostic factors in COVID-19 severe respiratory failure patients treated with helmet CPAP. We reviewed the medical records of COVID-19 respiratory failure patients treated with H-CPAP at the Emergency Department from February 23rd to March 14th, 2020. A total of 202 (40%) patients admitted for respiratory failure due to COVID-19 pneumonia were considered. 129 (64%) patients received H-CPAP, while 73 (36%) required endotracheal intubation and invasive mechanical ventilation despite initial H-CPAP. 99 patients (49%) died. The mortality rate in the IMV group was 37%, compared to 56% in the group that received only H-CPAP ($p= 0.004$). The age and comorbidities of patients in the two groups differed significantly ($p < 0.001$). Age and PaO_2/FiO_2 were identified as the only independent risk factors for death. Identifying these independent predictors of mortality in patients with acute respiratory insufficiency may help clinicians optimize treatment escalation.

Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The World Health Organization (WHO) declared the outbreak of the pandemic on March 11th 2020.[1] In the context of this infection, the proportion of patients admitted with severe acute hypoxemic respiratory failure ranged widely and was reported to be between 6.1% and 41% of all hospitalizations.[2] Among them, 30-88% of patients needed mechanical ventilation. Death rates in the Intensive Care Unit (ICU) varied from 16 to 78%.[3]

Due to the overwhelming number of patients requiring respiratory support and the lack of ICU beds, the majority of patients admitted were treated with non-invasive ventilation despite evidence of severe respiratory failure.[4,5] Some studies report that 11-62% of patients admitted to the ICU were treated with Non-Invasive Respiratory Support (NIRS), breathing support administered through a face mask, nasal mask, or a helmet without the need for endotracheal intubation or High Flow Nasal Cannula (HFNC) during the first outbreak.[5,6]

The Papa Giovanni XXIII Hospital in Bergamo was one of the most severely affected hospitals worldwide at the beginning of the COVID-19 pandemic with thousands of patients admitted in a short period of time. The overflow of patients necessitated a reorganization of the Emergency Department (ED) and the hospital as a whole, which greatly increased its capacity. In particular, the number of ICU beds increased from 16 to 92 during the first outbreak due to the high prevalence of critically ill patients requiring intensive care resources. Nonetheless, due to the overload of the ICU, continuous positive airway pressure (CPAP), non-invasive ventilation that applies a single level of positive airway pressure throughout the whole respiratory cycle, was used as a bailout alternative to mechanical ventilation to treat patients with COVID-19 respiratory failure. In this case, the interface used was the helmet, which is widely available in the Italian EDs.

The role of NIRS in COVID-19 pneumonia is uncertain: some authors recommend its use only in selected patients, while others indicate NIRS or HFNC as a first-line therapy, claiming their potential role in preventing endotracheal intubation (ETI) and Invasive Mechanical Ventilation (IMV).[7-10] At the time of the initial COVID-19 outbreak, *i.e.* when data collection started, there was uncertainty about the selection criteria, risk stratification, timing, defined indications, duration, and success or failure criteria for CPAP in this clinical setting. This depends on the fact that the majority of initially available studies were observational retrospective monocentric experiences, whereas only a few were

prospective.[11-21] Only one randomized clinical trial (RCT) was initially published as a preview in August 2021.[22]

Our study aims to assess prognostic factors in patients with acute respiratory failure due to COVID-19 pneumonia treated with helmet-CPAP (H-CPAP) in ED or during the hospitalization with a minimum 28-day follow-up with the intent to discriminate between patients who need early invasive mechanical ventilation (IMV) and patients who could improve with H-CPAP alone.

Materials and Methods

Study design and setting

This is a retrospective observational study. All consecutive patients admitted to the ED for respiratory failure due to COVID-19 pneumonia and treated with H-CPAP during hospitalization in the Papa Giovanni XXIII hospital from the beginning of the pandemic on 23 February 2020 to 14 March 2020 were analyzed. Exclusion criteria were no need for respiratory support and contraindication to noninvasive ventilation.

Patients without signs of respiratory failure, such as oxygen saturation (SpO_2) < 94% at rest (without supplemental oxygen) or a decrease in SpO2 more than 5% while walking for 30 meters were discharged from ED and not included in the analysis. Follow-up was censored on 11 April 2020, so that every patient had a minimum observation of 28 days.

Patients' data were extracted from electronic medical records.

At admission to ED, blood gas analysis, blood test, nasal swab, and chest X-ray were performed. Diagnosis was based upon clinical, and radiological criteria and a PCR-RT test nasal swab positivity, according to updated international and institutional guidelines.

Indication of H-CPAP was an arterial partial pressure of oxygen (PaO_2) < 60 mmHg or a respiratory rate (RR) > 30 breaths after a trial, performed immediately on presentation to the ED, with the non-rebreather mask with an oxygen flow of 15 Liters for 15 min. Indication of BiPAP modality (NIPPV) was a respiratory acidosis at admission or during H-CPAP or other oxygen therapy or clinical signs of respiratory distress. Due to limited healthcare resources compared to the patients' inflows, IMV was considered only in case of persistent hypoxemia despite H-CPAP treatment, or even after hypoxemia correction by H-CPAP in patients who had worsening tachypnoea, pH, or level of consciousness. Patient comorbidities, age, and ICU bed saturation were also taken into account.

The study was approved by the local Ethical Committee (N. 37/2020). In the view of the urgent need to treat critical patients, and to avoid paper contamination, local Ethical Committee authorized data collection from clinical record review and their publication after the study period.

Outcome analysis

The primary outcome was 28-day mortality which was analyzed according to the presence of comorbidities, and clinical and ventilatory parameters at presentation. Finally, 28 days was modeled as the dependent variable in a multivariable logistic regression analysis.

Statistical analysis

Continuous variables were expressed as mean and standard deviation (SD) or as the median and interquartile range (IQR) and compared by T student or Wilcoxon-Mann-Whitney test according to the distribution of data that was visually inspected. Categorical variables were expressed as absolute counts and percentages and were compared by chi-square or Fisher exact test as appropriate. 28-day survival rates were estimated by Kaplan-Meier curves. A multivariate logistic regression model was used to identify predictors of death at 28 days. The variables that resulted significantly associated with death at 28 days at univariate comparison were considered as potential covariates which were finally selected by the LASSO method. For all tests, a p-value < 0.05 was considered significant.

Statistical analysis was performed using STATA software, release 16 (StataCorp LP, College Station TX, USA).

Results

Demographic, clinical characteristics, and blood gas parameters at admission

Two hundred-two out of 509 consecutive patients (39.7%) admitted to our ED with a diagnosis of COVID-19 pneumonia were treated with H-CPAP and therefore included in the study. One hundred-fifty-three (75.7%) patients were male, with a median age of 66.5 (IQR 56.0-75.0) years, median body mass index (BMI) of 27.5 (25.0-31.0), and 51 patients (36.4 %) were active smokers. The most common comorbidities were: hypertension (57%), diabetes (22.7%), previous myocardial infarction (15.7%), and vascular disease (15.1%). At admission 112 patients (58.3%) were already on antihypertensive therapy, 12 patients (6.3%) on steroids, 30 (15.5%) on oral hypoglycemic

medications, 19 (9.8%) on insulin, 22 (11.5%) on oral anticoagulation therapy and 55 (28.6%) on antiplatelet medications. Median CCI was 3.0 (2.0-5.0) (Table 1).

Table 1 shows the most common comorbidities and medications in the study population, with hypertension, diabetes, and previous myocardial infarction as the most common past illnesses.

At the admission median heart rate (HR) was 86 (76-97) bpm, systolic blood pressure (SBP) was 127 (114-142) mmHg, respiratory rate (RR) was 24 (18-30) bpm and 123 patients (65.4%) were febrile. The arterial blood gas analysis (ABG) records showed a median pH of 7.47 (7.44-7.5), with a PaO2/FiO2 ratio of 194 (105-252) (Table 2).

Drugs and ventilatory therapy in ED

During the first 24 hours, 22 (11.2%) patients received low-flow oxygen through a nasal cannula, 17 (8.6%) Venturi masks, 36 (18.3%) non-rebreather masks, 99 (50.3%) H-CPAP, 7 (3%) BiPAP modality (NIPPV), 6 (3.6%) IMV and 10 (5%) did not receive any respiratory support.

All the 202 patients included in the study received respiratory support by H-CPAP in the ED or during hospitalization: 37.6% on the first day after ED admission, and 88% within the 4th day (Figure 1). The median time elapsed before starting H-CPAP was 1 day (IQR 0-3) (Table 2).

Antiviral therapy was administered to 173 (91.1%), hydroxychloroquine to 165 (87.8%), steroids to 23 (12.2%), antibiotics to 183 (96.3%), and IL-6 inhibitors to 15 (8%) patients (Table 2).

Outcome according to demographic and comorbidities associated variables

In the overall population included in the study, the primary outcome (28-day mortality) occurred in 99 (49%) patients, ranging from 10.9% among patients younger than 56 years of age (6/55 patients) to 93.5% in those aged 76 years or older (43/46 patients). Indeed, median age was significantly higher in non-survivors than in survivors (74 ± 5.5 years versus 58 ± 7.5, $p < 0.001$) (Table 1).

The primary outcome was significantly affected by comorbidities such as hypertension, chronic kidney disease, previous myocardial infarction, vascular disease ($p < 0.001$), diabetes mellitus ($p = 0.001$), active hematologic malignancy ($p = 0.015$) and chronic obstructive pulmonary disease (COPD) ($p = 0.024$).

According to the CCI, the mortality rate ranged from 5% among patients with CCI = 0 (1/20 patients) to 69.8% in those with CCI ≥ 3 (88/126 patients). In the non-survivors group, 1 (1%) patient scored 0, and 88 (91.7%) had a score equal to three or higher ($p < 0.001$). (Table 1, Table 2)

The use of antihypertensives, insulin, and antiplatelet drugs was associated with 28-day mortality, as well as flu vaccination.

Outcome according to clinical and ventilation parameters

Hypoxemia at presentation was a predictor of mortality: PaO2/FiO2 mean ratio was 228 in the survivors group and 145 in the non-survivors group ($p < 0.001$). Fifty-four (65%) of the non-survivors had a PaO2/FiO2 ratio < 200 ($p = 0.001$) (Table 2).

The median oxygen saturation was 90% (85-94%) vs 92% (89-95%) and serum lactate levels were 1.63 (1.23-2.23) vs 1.3 (0.96-1.58) in nonsurvivors as compared with survivors. ($p=0.02$ an $p < 0.001$, respectively) (Table 2).

The overall 28-day mortality rate of patients needing ventilatory support on the first day after hospitalization was 64.4%. Mortality rate was higher in the first period followed by a progressive reduction in the subsequent weeks of hospitalization, as shown by the Kaplan-Meier 28-day survival curve (Figure 2A) and the distribution of non-survivors over time (Figure 2B).

Antivirals and IL-6 inhibitors were associated with a lower mortality ($p = 0.017$ and 0.029, respectively; Table 2).

Independent predictors of mortality

Six predictors of 28-day mortality were included in the multivariable analysis: severity of respiratory failure expressed as PaO2/ FiO2 ratio, age, hypertension, diabetes, coronary heart disease on medical history, or antiplatelet therapy (Table 3). The multivariate logistic regression model revealed that the severity of respiratory failure and age were the only predictors of 28-day mortality.

Comparison between H-CPAP-only group vs H-CPAP+IMV group

Among 202 patients supported by H-CPAP, 73 (36.1%) underwent intubation and mechanical ventilation (Table 4). The 28-day mortality rate was 35.6% (26/73) in patients who had undergone intubation after the H-CPAP trial and 56.6% (73/129) in the H-CPAP-only group (p=0.004; Table 4).

No statistical differences in the respiratory failure severity at presentation were observed in the two groups. However, patients who underwent endotracheal intubation were younger and healthier: median age was 71 years (IQR 61-79) in the H-CPAP group vs 60 years (IQR 54-67) in the IMV group (p<0.001); median CCI scores were 4.0 (IQR 2.0-6.0) in the H-CPAP group and 2.0 (1.0-4.0) in the IMV group (p<0.001; Table 4).

Discussion

During the first ten days of the pandemic, the admission rate of patients presenting to the Bergamo ED with COVID-19 infection increased progressively from 20 per day on February 29th to 150 on March 6th. During the first pandemic outbreak in Bergamo, the majority of the patients who presented to the ED had severe respiratory failure. Respiratory support was started in almost 40% of the cases within the first day after ED admission and in 88% within the 4th day (Figure 1). These patients were admitted at a critical stage of the disease, indeed the overall 28-day-mortality rate of patients requiring ventilatory support on the first day after admission was very high. As shown in another study conducted in our ED by Duca *et al.*,[8] the prevalence of critically ill patients needing ventilatory support on first evaluation was very high (31% of all admissions of patients with COVID-19 pneumonia). The role of CPAP in pneumonia dates back to 2010[23,24] when an RCT showed that oxygenation was significantly improved with the use of H-CPAP compared with conventional oxygen treatment. A second clinical RCT demonstrated that the use of CPAP in patients with pneumonia significantly reduced the need for intubation.[25] In the COVID-19 era, CPAP has been empirically used for the treatment of severe hypoxemia refractory to standard oxygen therapy caused by lung atelectasis (second clinical phase of COVID-19 pulmonary infection)[17,26] Kofod *et al*. recently observed, in a smaller sample of patients, that CPAP seems to have a positive effect on oxygenation and respiratory rate in most patients with severe respiratory failure caused by COVID-19.[18]

Ramirez *et al.* confirmed that NIRS and physiotherapy are a viable treatment option for patients with severe COVID-19 and severe comorbidities.[19] Elderly patients with high oxygen requirements and a ceiling for treatment outside the ICU were found to have a poor prognosis in both studies.

In a systematic review and meta-analysis, Cammarota *et al.* showed that the overall in-hospital mortality of patients receiving NIRS outside the ICU was 36%. A quarter of the patients failed NIRS and required intubation, with a higher rate of in-hospital mortality. The authors concluded that delivering NIRS outside the ICU was a feasible strategy to cope with the massive demand for ventilatory assistance.[27]

The first evidence of a positive clinical effect of the application of CPAP in COVID-19 adult hospitalized patients with acute respiratory failure is found in the Recovery-Respiratory Support trial. For the first time, this study showed that CPAP, compared with conventional oxygen therapy, reduced the composite outcome of intubation or death within 30 days in patients with COVID-19 pneumonia. No beneficial effect was observed, compared with conventional oxygen therapy, with the use of HFNC.[22] The same data about the inefficacy of HFNC in severe respiratory distress in COVID-19 patients was demonstrated by Grieco *et al*.[14]

In our population, due to the rapid saturation of ICU ventilated beds, H-CPAP was used extensively in very critical patients. This treatment allowed stabilization in 35 (17.3%) patients, 73 (36.1%) patients needed escalation to IMV while 64 (31.6%) patients died during H-CPAP treatment. Significant heterogeneity in demographic and clinical characteristics was observed when comparing these three subgroups of patients. This is due to the mismatch between healthcare resources and the high demand for intensive care, resulting in a selection bias in the choice of patients eligible for ICU beds. In this resource-limited environment, clinicians were forced to select patients who were younger and healthier to optimize the inadequate resources available at the time. A similar scenario was predicted by Lee Daugherty et al. in a visionary review titled “Too Many Patients. A Framework to Guide Statewide Allocation of Scarce Mechanical Ventilation During Disasters”, published in 2019, before the COVID pandemic.[28]

Another interesting data emerged from our analysis concerns the mortality rate among intubated patients (35.6%), which is similar to those previously reported in other studies related to critically ill COVID-19 patients who underwent early IMV. This suggests that, in limited resource settings, the treatment with H-CPAP may be a useful bridge treatment for severe acute respiratory failure needing IMV. Not surprisingly, younger patients and those with fewer comorbidities were more likely to undergo IMV after an initial trial of H-PAP. Interestingly this subset of patients had a better outcome as compared to those treated with H-CPAP only despite a similar PaO_2/FiO_2. These results confirm that an initial trial of H-PAP does not compromise the efficacy of a rescue IMV and that the

allocation of mechanical ventilation based on age and comorbidities is a reasonable criterion in a setting characterized by limited resources.

Furthermore, our data suggests that the treatment with H-CPAP can be an important rescue therapy for patients affected by severe acute respiratory failure who do not respond to standard oxygen therapy and are ineligible for invasive care. As other studies have shown, H-CPAP may improve survival.[29]

The best respiratory support for patients with severe COVID-19 pneumonia on admission to the hospital remains uncertain. The ideal treatment has rarely been applicable in the real world, where hospitals have been overwhelmed by the surge of the epidemic. As a result, the only feasible therapeutic approach was a compromise between the excessive demand and the lack of resources. In addition, the availability of resources tended to change significantly within a few weeks. This was due to political decisions (e.g. lockdown). To understand the conflicting results of different studies, this scenario should be kept in mind. Therefore, the results of this study may not be fully generalizable, as they should be contextualized within the specific setting of the first wave in the city of Bergamo and northern Italy during a well-defined period.

In conclusion, this preliminary experience of treatment of critical patients with COVID-19-related respiratory failure shows that an H-CPAP trial is feasible and may allow patient stabilization.

Limitations

The limits of our study are mostly related to its observational and retrospective methodology. Furthermore, data were retrieved within a very dynamic period in terms of disease epidemiology and treatment protocols. Therefore we should be very cautious in considering these observations in the treatment of contemporary patients with COVID-19 pneumonia-related respiratory insufficiency. As the data source is based on a chart review of patients presenting to the ED we have consistent numbers of missing data restricting the possibility of adjusting for relevant covariates.

Conclusions

This study aims to identify predictors of mortality in patients with acute respiratory failure caused by COVID-19 pneumonia treated with helmet CPAP in a scenario of a public health emergency with a lack of intensive care resources.

In such an extreme scenario, treatment of patients with severe acute respiratory failure with H-CPAP was used as a bridge for those with an indication of IMV until an ICU bed would be available. Moreover, H-CPAP might be contemplated as a rescue therapy for those who were not responders to standard oxygen therapy and not eligible for IMV, also identified as "do-not-intubate" (DNI).

The multivariate logistic regression model revealed that the severity of respiratory failure and age were predictors of 28 mortality.

The identification of these independent predictors of mortality in patients with acute respiratory insufficiency might be helpful to guide clinicians to optimize treatment escalation. However further studies are necessary to prove the therapeutic effect of H-CPAP in patients with acute respiratory failure in COVID-19 pneumonia and the prognostic variables need clinical validation.

References

1. World Health Organization Director - General's opening remarks at the media briefing on COVID-19: 2020. Published March 11, 2020. Accessed May 2, 202). Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-COVID-19—11-march-2020
2. Chen N, Zhou M, Dong X. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507-13.
3. Piva S, Filippini M, Turla F, et al. Clinical presentation and initial management critically ill patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in Brescia, Italy. J Crit Care 2020;58:29-33.
4. World Health Organization, Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected. (Interim Guidance. 2020. Accessed May 2, 2020). Available from: https://iris.who.int/handle/10665/330893
5. ARDS Definition Task Force; Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA 2012;307:2526-33.
6. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054-62.

1. Brusasco C, Corradi F, Di Domenico A, et al. CPAP-Covid-19 study group; collaborators of the Galliera CPAP-COVID-19 study group are. Continuous positive airway pressure in COVID-19 patients with moderate-to-severe respiratory failure. Eur Respir J 2021;57:2002524.

2. Duca A, Memaj I, Zanardi F, et al. Severity of respiratory failure and outcome of patients needing a ventilatory support in the Emergency Department during Italian novel coronavirus SARS-CoV2 outbreak: Preliminary data on the role of Helmet CPAP and Non-Invasive Positive Pressure Ventilation. EClinicalMedicine 2020;24:100419.

3. Oranger M, Gonzalez-Bermejo J, Dacosta-Noble P, et al. Continuous positive airway pressure to avoid intubation in SARS-CoV-2 pneumonia: a two-period retrospective case-control study. Eur Respir J 2020;56:2001692.

4. Grasselli G, Greco M, Zanella A, et al. Risk Factors Associated With Mortality Among Patients With COVID-19 in Intensive Care Units in Lombardy, Italy. JAMA Intern Med 2020;180:1345-55. Erratum in: JAMA Intern Med 2021;181:1021.

5. Alhazzani W, Møller MH, Arabi YM, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). Intensive Care Med 2020;46:854-87.

6. Rali AS, Howard C, Miller R, et al. Helmet CPAP revisited in COVID-19 pneumonia: A case series. Can J Respir Ther 2020;56:32-4.

7. Lucchini A, Giani M, Isgrò S, et al. The "helmet bundle" in COVID-19 patients undergoing non invasive ventilation. Intensive Crit Care Nurs 2020;58:102859.

8. Grieco DL, Menga LS, Cesarano M, et al. Effect of Helmet Noninvasive Ventilation vs High-Flow Nasal Oxygen on Days Free of Respiratory Support in Patients With COVID-19 and Moderate to Severe Hypoxemic Respiratory Failure: The HENIVOT Randomized Clinical Trial. JAMA 2021;325:1731-43.

9. Amirfarzan H, Cereda M, Gaulton TG, et al. Use of Helmet CPAP in COVID-19 - A practical review. Pulmonology 2021;27:413-22.

10. Rauseo M, Mirabella L, Caporusso RR, et al. SARS-CoV-2 pneumonia succesfully treated with cpap and cycles of tripod position: a case report. BMC Anesthesiol 2021;21:9.

11. Ing RJ, Bills C, Merritt G, et al. Role of Helmet-Delivered Noninvasive Pressure Support Ventilation in COVID-19 Patients. J Cardiothorac Vasc Anesth 2020;34:2575-9.

18. Kofod LM, Nielsen Jeschke K, Kristensen MT, et al. COVID-19 and acute respiratory failure treated with CPAP. Eur Clin Respir J 2021;8:1910191.

19. Ramirez GA, Bozzolo EP, Gobbi A, et al. Outcomes of noninvasive ventilation as the ceiling of treatment in patients with COVID-19. Panminerva Med 2022;64:506-16.

20. Menzella F, Barbieri C, Fontana M, et al. Effectiveness of noninvasive ventilation in COVID-19 related-acute respiratory distress syndrome. Clin Respir J 2021;15:779-87.

21. De Vita N, Scotti L, Cammarota G, et al. Predictors of intubation in COVID-19 patients treated with out-of-ICU continuous positive airway pressure. Pulmonology 2022;28:173-80.

22. Perkins GD, Couper K, Connolly B, et al. RECOVERY-Respiratory Support: respiratory strategies for patients with suspected or proven COVID-19 respiratory failure; continuous positive airway pressure, high-flow nasal oxygen, and standard care: a structured summary of a study protocol for a randomised controlled trial. Trials 2020;21:687.

23. Cosentini R, Brambilla AM, Aliberti S, et al. Helmet continuous positive airway pressure vs oxygen therapy to improve oxygenation in community-acquired pneumonia: a randomized, controlled trial. Chest 2010;138:114-20.

24. Bellani G, Patroniti N, Greco M, et al. The use of helmets to deliver non-invasive continuous positive airway pressure in hypoxemic acute respiratory failure. Minerva Anestesiol 2008;74:651-6.

25. Brambilla AM, Aliberti S, Prina E, et al. Helmet CPAP vs. oxygen therapy in severe hypoxemic respiratory failure due to pneumonia. Intensive Care Med 2014;40:942-9.

26. Gattinoni L, Chiumello D, Caironi P, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes? Intensive Care Med 2020;46:1099-102.

27. Cammarota G, Esposito T, Azzolina D, et al. Noninvasive respiratory support outside the intensive care unit for acute respiratory failure related to coronavirus-19 disease: a systematic review and meta-analysis. Crit Care 2021;25:268.

28. Daugherty Biddison EL, Faden R, Gwon HS, et al. Too Many Patients…A Framework to Guide Statewide Allocation of Scarce Mechanical Ventilation During Disasters. Chest 2019;155:848-54.

29. Coppadoro A, Benini A, Fruscio R, et al. Helmet CPAP to treat hypoxic pneumonia outside the ICU: an observational study during the COVID-19 outbreak. Crit Care 2021;25:80.

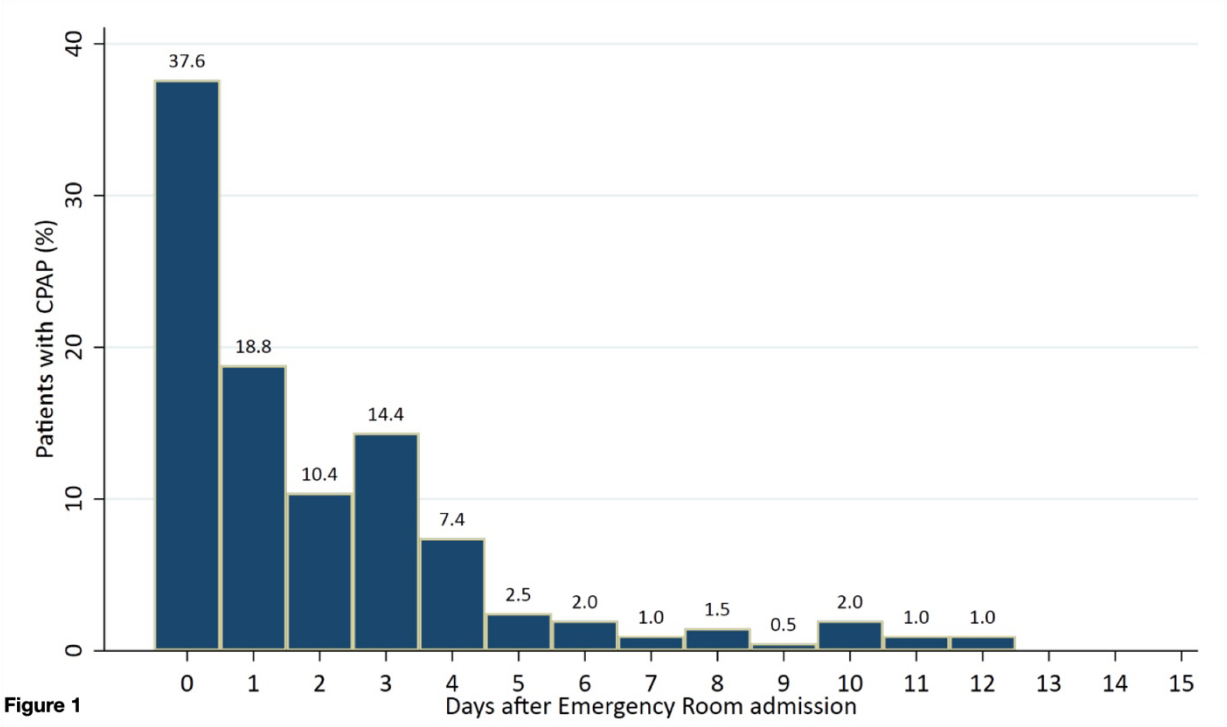

Figure 1. Proportion of patients undergoing CPAP over time

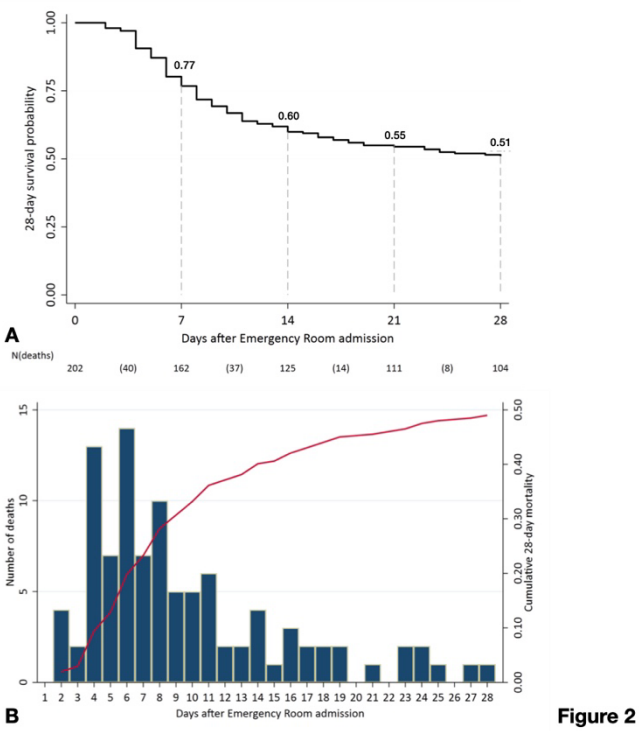

Figure 2. A) Kaplan-Meier, 28-day survival curve; **B)** Distribution of non-survivors over time

Table 1. Demographic and clinical characteristics by death. Angiotensin-Converting-Enzym Inhibitor (ACE-Inhibitor), Angiotensin II receptor blocker (ARB), Body Mass Index (BMI), Charlson Comorbidity Index (CCI), Chronic Obstructive Pulmonary Disease (COPD), Invasive Mechanical Ventilation (IMV), Interquartile Range (IQR).

	Total	**28-DAY MORTALITY**		**p-value**
	N=202	**Survivors (N=103)**	**Non-survivors (N=99)**	
Male gender - *n (%)*	153 (75.7)	73 (70.9)	80 (80.8)	0.100
Age - *y median (IQR)*	66.5 (56.0-75.0)	58.0 (51.0-66.0)	74.0 (68.0-79.0)	**<0.001**
≤ 56 – n (%)	55 (27.2)	49 (47.6)	6 (6.1)	**<0.001**
57-67 – *n (%)*	49 (24.3)	31 (30.1)	18 (18.2)	
68-75 – *n (%)*	52 (25.7)	20 (19.4)	32 (32.3)	

≥ 76 – *n (%)*	46 (22.8)	3 (2.9)	43 (43.4)	
BMI - *median (IQR)*	27.5 (25.0-31.0)	27.8 (25.0-31.2)	27.5 (25.0-30.8)	0.63
≥ 30 – *n (%)*	49 (28.2)	25 (27.2)	24 (29.3)	0.76
Current/former smokers – *n (%)*	51 (36.4)	21 (30.0)	30 (42.9)	0.11
Comorbidities – *n (%)*				
Hypertension	114 (57.0)	42 (40.8)	72 (74.2)	**<0.001**
Diabetes	45 (22.7)	14 (13.6)	31 (32.6)	**0.001**
Chronic Kidney Failure	14 (7.1)	0 (0.0)	14 (14.7)	**<0.001**
COPD	14 (7.1)	3 (2.9)	11 (11.6)	**0.024**
Long-term oxygen therapy	4 (2.0)	2 (1.9)	2 (2.1)	1.00
Active solid neoplasm	12 (6.1)	4 (3.9)	8 (8.4)	0.24
Active hematologic malignancy	9 (4.5)	1 (1.0)	8 (8.4)	**0.015**
Cerebrovascular disease	10 (5.1)	4 (3.9)	6 (6.3)	0.43
Previous Myocardial Infarction	31 (15.7)	6 (5.8)	25 (26.6)	**<0.001**
Chronic heart failure	14 (7.0)	4 (3.9)	10 (10.4)	0.096
Vasculopathy	30 (15.1)	7 (6.8)	23 (24.0)	**<0.001**
Rheumatic pathology	16 (8.1)	8 (7.8)	8 (8.4)	0.87
Immunosuppression	20 (10.1)	6 (5.8)	14 (14.6)	**0.040**
CCI score - *median (IQR)*	3.0 (2.0-5.0)	2.0 (1.0-3.0)	5.0 (3.0-6.0)	**<0.001**
CCI=0 – n (%)	20 (10.1)	19 (18.4)	1 (1.0)	**<0.001**
CCI=1-2 – n (%)	53 (26.6)	46 (44.7)	7 (7.3)	
CCI=3+ – n (%)	126 (63.3)	38 (36.9)	88 (91.7)	
Home therapies – *n (%)*				
Antihypertensives	112 (58.3)	45 (44.6)	67 (73.6)	**<0.001**
ACE-inhibitors	33 (17.0)	6 (5.9)	27 (29.3)	**<0.001**
ARBs	36 (18.6)	16 (15.7)	20 (21.7)	0.28
Other antihypertensives	85 (43.6)	33 (32.4)	52 (55.9)	**<0.001**
Steroids	12 (6.3)	6 (5.9)	6 (6.7)	0.81

Oral antidiabetics	30 (15.5)	11 (10.8)	19 (20.9)	0.053
Insulin	19 (9.8)	4 (3.9)	15 (16.5)	**0.006**
Oral anticoagulation therapy	22 (11.5)	8 (7.8)	14 (15.7)	0.089
Antiplatelets	55 (28.6)	10 (9.8)	45 (50.0)	**<0.001**
Flu vaccine – *n (%)*	60 (47.2)	20 (29.9)	40 (66.7)	**<0.001**

Table 2. Clinical characteristics, blood gas analysis at presentation and in-hospital treatments. Continuous Positive Airway Pressure (CPAP), Invasive Mechanical Ventilation (IMV), Fraction of Inspired Oxygen (FiO2), Inspiratory Positive Airway Pressure (IPAP), Heart rate (HR), Interquartile Range (IQR), Non Invasive Positive Pressure Ventilation (NIPPV), Arterial partial pressure of Oxygen (PaO2), Arterial Partial Pressure of Carbon Dioxide (PaCO2), Positive End-Expiratory Pressure (PEEP), Respiratory Rate (RR), Arterial Saturation of Oxygen (SaO2), Systolic Blood Pressure (SBP).

	Total	**28-DAY MORTALITY**		**p-value**
	N=202	**Survivors (N=103)**	**Non-survivors (N=99)**	
At entry in Emergency Room				
AVPU – *no. (%)*				
A (alert)	185 (93.4)	95 (94.1)	90 (92.8)	0.16
V (verbal)	5 (2.5)	4 (4.0)	1 (1.0)	
P (pain)	2 (1.0)	1 (1.0)	1 (1.0)	
U (unresponsive)	6 (3.0)	1 (1.0)	5 (5.2)	
HR, *bpm* **-** *median (IQR)*	86.0 (76.0-97.0)	90.0 (80.0-100.0)	84.0 (74.0-92.0)	**0.002**
SBP, *mmHg* **-** *median (IQR)*	127.0 (114.0-142.0)	126.0 (110.0-139.5)	130.0 (118.0-146.0)	0.067
RR, *acts/min* **-** *median (IQR)*	24.0 (18.0-30.0)	23.5 (18.0-30.0)	25.0 (18.0-30.0)	1.00
Fever – *no. (%)*	123 (65.4)	70 (73.7)	53 (57.0)	**0.016**
pH - *median (IQR)*	7.47 (7.44-7.50)	7.48 (7.45-7.50)	7.46 (7.42-7.50)	**0.039**
FiO2	0.34 (0.21-0.70)	0.21 (0.21-0.60)	0.60 (0.21-0.70)	**0.012**

PaO_2/FiO_2 - *median (IQR)*	194.3 (105.0-252.4)	228.6 (152.5-261.9)	145.0 (91.4-223.8)	**<0.001**
<200 – no. (%)	87 (52.4)	33 (39.8)	54 (65.1)	**0.001**
$SatO_2$, % - *median (IQR)*	91.0 (86.5-94.0)	92.0 (89.0-95.0)	90.0 (85.0-94.0)	**0.020**
$PaCO_2$, *mmHg - median (IQR)*	32.0 (29.0-35.0)	32.0 (29.0-36.0)	33.0 (29.0-35.0)	0.87
HCO_3^-, *mmol/L - median (IQR)*	24.1 (22.0-25.9)	24.5 (23.0-26.8)	23.7 (22.0-25.0)	**0.041**
Lac, *mmol/L - median (IQR)*	1.42 (1.05-1.94)	1.30 (0.96-1.58)	1.63 (1.23-2.23)	**<0.001**
In the first 24h				
Oxygen and ventilatory support – *no. (%)*				
Low flow oxygen cannula	22 (11.2)	15 (14.9)	7 (7.3)	0.092
Venturi mask	17 (8.6)	14 (13.9)	3 (3.1)	**0.010**
Non-rebreather mask	36 (18.3)	23 (22.8)	13 (13.5)	0.094
CPAP	99 (50.3)	35 (34.7)	64 (66.7)	**<0.001**
NIPPV	6 (3.0)	4 (4.0)	2 (2.1)	0.68
IMV	7 (3.6)	6 (5.9)	1 (1.0)	0.12
FiO_2 - *median (IQR)*	60.0 (50.0-70.0)	60.0 (40.0-70.0)	60.0 (60.0-70.0)	0.13
PEEP, *cmH_2O - median (IQR)*	15.0 (12.0-16.0)	14.0 (11.0-16.0)	15.0 (12.0-15.0)	0.25
IPAP, *cmH_2O -median (IQR)*	26.5 (22.0-28.0)	27.0 (22.0-28.0)	26.0 (26.0-26.0)	0.77
Therapies				
Antiviral – *no. (%)*	173 (91.1)	93 (95.9)	80 (86.0)	**0.017**
Hydroxychloroquine – *no. (%)*	165 (87.8)	89 (91.8)	76 (83.5)	0.085
Steroid – *no. (%)*	23 (12.2)	15 (15.5)	8 (8.7)	0.15
Antibiotics – *no. (%)*	183 (96.3)	95 (96.9)	88 (95.7)	0.64
IL-6 Inhibitors – *no. (%)*	15 (8.0)	12 (12.5)	3 (3.3)	**0.029**

Table 3. Predictors of 28-mortality in patients treated with helmet CPAP estimated by a multivariable logistic regression model. Acute myocardial infarction (AMI), Confidence interval (CI), Odds ratio (OR).

	OR (95% CI)	**p-value**
Age, *for 1-unit increase*	1.13 (1.07 - 1.19)	**<0.001**
PaO2/FiO2 < 200	2.51 (1.07 - 5.91)	**0.035**
Antiplatelets	2.64 (0.91 - 7.7)	0.076
Hypertension	2.17 (0.93 - 5.04)	0.071
Previous AMI	1.99 (0.52 - 7.66)	0.317
Diabetes	1.44 (0.52 - 3.98)	0.477

Table 4. Demographic and clinical characteristics of intubated/non-intubated patients. Angiotensin-Converting-Enzym Inhibitor (ACE-Inhibitor), Angiotensin II receptor blocker (ARB), Body Mass Index (BMI), Charlson Comorbidity Index (CCI), Chronic Obstructive Pulmonary Disease (COPD), Invasive Mechanical Ventilation (IMV), Interquartile Range (IQR).

	No IMV (N=129)	IMV **(N=73)**	**p-value**
Male gender - *n (%)*	97 (75.2)	56 (76.7)	0.81
Age - *y median (IQR)*	71.0 (61.0-79.0)	60.0 (54.0-67.0)	**<0.001**
≤ 56 – *n (%)*	25 (19.4)	30 (41.1)	**<0.001**

57-67 – *n (%)*	24 (18.6)	25 (34.2)	
68-75 – *n (%)*	38 (29.5)	14 (19.2)	
≥ 76 – *n (%)*	42 (32.6)	4 (5.5)	
BMI - *median (IQR)*	27.5 (25.0-29.4)	28.3 (25.0-31.2)	0.23
≥ 30 – *n (%)*	26 (23.9)	23 (35.4)	0.10
Current/former smokers – *n (%)*	42 (42.9)	9 (21.4)	**0.016**
PaO_2/FiO_2 - *median (IQR)*	200.7 (115.2-257.1)	178.9 (91.7-240.0)	0.12
Comorbidities – *n (%)*			
Hypertension	77 (60.6)	37 (50.7)	0.17
Diabetes	34 (27.2)	11 (15.1)	**0.049**
Chronic Kidney Failure	10 (8.0)	4 (5.5)	0.58
COPD	11 (8.8)	3 (4.1)	0.26
Long-term oxygen therapy	3 (2.4)	1 (1.4)	1.00
Active solid neoplasm	9 (7.2)	3 (4.1)	0.54
Active hematologic malignancy	7 (5.6)	2 (2.7)	0.49
Cerebrovascular disease	6 (4.8)	4 (5.5)	0.83
Previous Myocardial Infarction	22 (17.7)	9 (12.3)	0.31
Chronic heart failure	11 (8.7)	3 (4.1)	0.26
Vasculopathy	23 (18.3)	7 (9.6)	**0.01**
Rheumatic pathology	11 (8.8)	5 (6.8)	0.63
Immunosuppression	13 (10.3)	7 (9.6)	0.87
CCI score - *median (IQR)*	4.0 (2.0-6.0)	2.0 (1.0-4.0)	**<0.001**
CCI=0 – n (%)	12 (9.5)	8 (11.0)	**<0.001**
CCI=1-2 – n (%)	20 (15.9)	33 (45.2)	

CCI=3+ – n (%)	94 (74.6)	32 (43.8)	
Home therapies – *n (%)*			
Antihypertensives	76 (62.8)	36 (50.7)	0.10
ACE-inhibitors	24 (19.7)	9 (12.5)	0.20
ARBs	21 (17.2)	15 (20.8)	0.53
Other antihypertensives	62 (50.4)	23 (31.9)	**0.012**
Steroids	8 (6.6)	4 (5.7)	0.81
Oral antidiabetics	22 (18.0)	8 (11.3)	0.21
Insulin	15 (12.3)	4 (5.6)	0.21
Oral anticoagulation therapy	17 (14.0)	5 (7.1)	0.15
Antiplatelets	42 (34.7)	13 (18.3)	**0.015**
Flu vaccine – *n (%)*	44 (49.4)	16 (42.1)	0.45
Main outcome, n (%)			
Death	73 (56.6)	26 (35.6)	**0.004**