The use of continuous positive airway pressure during the second and third waves of the COVID-19 pandemic

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Shareable abstract (@ERSpublications)
CPAP with high-flow output is a valid and safe option for respiratory support before intubation of patients with AHRF due to COVID-19 pneumonia. CPAP does not appear to be associated with high barotrauma risk or detrimental effect on eventual IMV. https://bit.ly/3hCqybZ

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Abstract
Background In a preliminary study during the first COVID-19 pandemic wave, we reported a high rate of success with continuous positive airway pressure (CPAP) in preventing death and invasive mechanical ventilation (IMV). That study, however, was too small to identify risk factors for mortality, barotrauma and impact on subsequent IMV. Thus, we re-evaluated the efficacy of the same CPAP protocol in a larger series of patients during second and third pandemic waves.

Methods 281 COVID-19 patients with moderate-to-severe acute hypoxaemic respiratory failure (158 full-code and 123 do-not-intubate (DNI)), were managed with high-flow CPAP early in their hospitalisation. IMV was considered after 4 days of unsuccessful CPAP.

Results The overall recovery rate from respiratory failure was 50% in the DNI and 89% in the full-code group. Among the latter, 71% recovered with CPAP-only, 3% died under CPAP and 26% were intubated after a median CPAP time of 7 days (IQR: 5–12 days). Of the patients who were intubated, 68% recovered and were discharged from the hospital within 28 days. Barotrauma occurred during CPAP in <4% of patients. Age (OR 1.128; p <0.001) and tomographic severity score (OR 1.139; p=0.006) were the only independent predictors of mortality.

Conclusions Early treatment with CPAP is a safe option for patients with acute hypoxaemic respiratory failure due to COVID-19.

Introduction
Coronavirus disease 2019 (COVID-19) has challenged the criteria for the treatment of acute hypoxic respiratory failure (AHRF). In a preliminary study [1] that we conducted between 16 March and 12 April 2020, high-flow continuous positive airway pressure (CPAP) following a standardised algorithm successfully prevented death or invasive mechanical ventilation (IMV) in 53 out of 64 (83%) patients with moderate-to-severe AHRF due to COVID-19 pneumonia. Notably, CPAP was successful even in 36 out of 53 (68%) patients with gas exchange and abnormalities on computed tomography (CT) usually considered as absolute indications for IMV in typical adult respiratory distress syndrome [2]. In other studies, the rate of success of CPAP was generally less and widely variable [1, 3–19]. However, comparisons among studies are difficult owing to differences in CPAP technique, criteria for intubation, patient-related risk factors and, possibly, virus mutations.
Our previous study included only patients of the first pandemic wave, and the sample size was too small to make the results generalisable regarding risk factors, complications and the potential impact of prior CPAP failure on eventual IMV outcome. Therefore, we report here the results of our protocol on the early use of CPAP in a larger sample of patients during the second and third COVID-19 waves. Our outcome of interest was recovery from acute respiratory failure on CPAP-only or CPAP followed by IMV within 28 days from start of CPAP treatment.

Materials and methods
We retrospectively reviewed the records of all patients admitted to the COVID-19 unit of the Galliera Hospital of Genoa between 1 September 2020 and 30 June 2021. Inclusion criteria were AHRF with CT evidence of interstitial pneumonia and positive SARS-CoV-2 nasopharyngeal swab (real-time polymerase chain reaction).

The treatment strategy was determined based on the ratio of arterial oxygen tension to inspiratory oxygen fraction ($P_{aO_2}/FIO_2$) while breathing room air, breathing frequency and presence of dyspnoea, and then adjusted following the previously published $ad hoc$ decision tree [1]. Patients with pulse oxygen saturation ($S_{pO_2}$) <95% or $P_{aO_2}/FIO_2$ <300 were given oxygen support via Ventimask. CPAP was applied in cases with one or more of the following criteria: $P_{aO_2}/FIO_2$ <200, $P_{aO_2}$ <60 mmHg, breathing frequency >30 breaths·min$^{-1}$ and dyspnoea at rest or during minimal efforts. IMV was considered after 4 days of unsuccessful CPAP, defined as $P_{aO_2}/FIO_2$ unchanged or decreased, breathing frequency still >30 breaths·min$^{-1}$, $P_{aO_2}$ <60 mmHg and arterial lactate levels >50% above pre-CPAP level, or at any time in the case of use of respiratory accessory muscles.

The choice of CPAP interface (helmet or full-face mask) depended on patient preference and anatomical characteristics. Three types of Venturi generators were available, able to generate maximal airflows of 100, 120 and 150 L·min$^{-1}$, respectively. The last one was preferred for the patients with signs of respiratory distress, i.e., very high breathing frequency and concomitant nasal flaring or sternocleidomastoid contraction during inspiration or abdominal muscles contraction during expiration [20, 21]. Positive end-expiratory pressure was set to 10 cmH$_2$O for all patients, and $FIO_2$ between 40 and 70%, depending on $P_{aO_2}$. All patients were in semi-supine or sitting positions during CPAP. CPAP weaning was started when no desaturation, tachypnoea or tachycardia were observed during CPAP interruptions for eating and $P_{aO_2}/FIO_2$ had been persistently >250 with tendency to increase for 2 consecutive days at least. During this phase, Ventimask 50% $FIO_2$ was used during daytime and CPAP overnight. When morning and evening arterial blood gas data off CPAP were comparable, CPAP was definitively withheld.

Data considered as potential predictors of survival were age, Charlson comorbidity index (CCI), times from onset of symptoms to hospital admission and to start of CPAP, C-reactive protein, procalcitonin, lymphocyte count, and treatments before and during hospitalisation. $P_{aO_2}/FIO_2$ was included as an index of AHRF severity and tomographic severity score (TSS) [22] for pneumonia extent.

Statistical analysis
Results are expressed as median with interquartile range or number with percentage. For between-groups comparisons of categorical or continuous variables, we used the Fisher exact test or the Mann–Whitney U-test as appropriate. To determine factors associated with 28-day survival, we chose variables that prior studies suggest to be likely associated with such outcome [23, 24]. Then we included these variables in a multivariate backward logistic analysis. Regression coefficient ($\beta$) and odds ratio (OR) with the corresponding 95% confidence interval (CI) were assumed as outputs of the logistic regression models. Only converged regression models that passed the Hosmer–Lemeshow goodness-of-fit test are reported. We used Kaplan–Meier product-limit estimator to compare the cumulative survival curves. The censored/uncensored patients corresponded to 28-day occurrence of death. We used the log-rank (Mantel–Cox) test with pairwise comparisons after grouping for age to evaluate the difference in survival probability. Statistical significance was assumed at two-tailed $p<0.05$. Statistical analyses were performed by using IBM SPSS (version 27.0; IBM, Armonk, NY, USA), and R statistical environment (version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria).

Results
The total number of patients admitted to hospital with COVID-19 pneumonia over the period considered was 551 (figure 1). Seven patients were directly admitted to the intensive care unit (ICU) from the emergency room, and 263 were treated by Ventimask only because of mild hypoxia (n=186) or do-not-resuscitate order (n=77) due to life-threatening comorbidities. The remaining 281 patients had moderate-to-severe AHRF and were initially treated with CPAP. Of those, 123 (44%) were do-not-intubate (DNI)
because of extreme frailty due to older age and/or CCI ≥5, whereas 158 (56%) were full-code. The recovery rate was 50% in the DNI group and 89% in the full-code group. Among the latter, 112 patients recovered with CPAP-only, five died under CPAP and 41 (26%) were intubated after a median CPAP time of 7 days (IQR 5–12). Of these, 28 (68%) recovered and were successfully discharged from the ICU by day 28. Overall, 201 (72%) patients initially treated with CPAP recovered within 28 days and were discharged from hospital after a median length of stay of 15 (IQR 11–24) days (table 1). They were younger than those who died (table 1). Compared to non-survivors, survivors had lower TSS, C-reactive protein and CCI and higher $P_aO_2/FIO_2$ before CPAP. The median time from hospital admission to CPAP start was 1 day (IQR 0–3) in all study participants, and the median duration of CPAP treatment was 6 days (IQR 4–9), without differences between survivors and non-survivors. On multiple logistic regression analysis, older age and high TSS were the only independent predictors of mortality (table 2). Compared to full-code patients, DNI patients were older (81 versus 55 yr.; p<0.001), had lower $P_aO_2/FIO_2$ before CPAP (123 versus 146; p<0.001), longer CPAP treatment (8 versus 7 days; p<0.003), higher CCI (6 versus 2; p<0.001), less steroid treatment before hospitalisation (18% versus 32%; p=0.009) and more of them were vaccinated (13% versus 2%; p=0.002). Despite these differences, DNI was not an independent predictor of mortality. The Kaplan–Meier curves (figures 2–4) showed a better 28-day survival in patients 75 years or younger, TSS ≤12 or full-code status.

The incidence of barotrauma during CPAP was 3.9%, i.e. 11 cases in 281 patients, five of whom were intubated and mechanically ventilated and only one survived. The remaining six patients were DNI and were conservatively managed with $O_2$ supplementation only; two of them were alive at day 28. The overall mortality was higher in the barotrauma group (73%; 8 out of 11 cases) compared with the non-barotrauma group (27%; 72 out of 270 cases).

**Discussion**

This observational retrospective study extends our previous report [1] showing that CPAP with high-efficiency Venturi generators is a valid option for ventilatory support in COVID-19 patients with moderate-to-severe AHRF outside the ICU.
In this study, the percentage of patients surviving on CPAP-only was less than in our preliminary study (60% versus 83%; p<0.001). Similarly, the overall survival with CPAP-only or CPAP plus IMV in this study was less than in our preliminary study (72% versus 86%; p=0.017). Since CPAP technique and decisional algorithm were identical in the two studies, the only explanations we have for the above difference in outcomes are different population-related risk factors or increased severity of second/third wave pneumonia. Indeed, the current study included a larger proportion of DNI patients who had

| Predictor                          | β      | OR (95% CI) | p-value |
|-----------------------------------|--------|-------------|---------|
| Age                               | 0.120  | 1.128 (1.057–1.203) | <0.001 |
| Charlson comorbidity index        | 0.126  | 1.134 (0.953–1.351) | 0.157  |
| Radiological TSS                  | 0.131  | 1.139 (1.039–1.250) | 0.006  |
| Time from symptoms to hospital admission | −0.003 | 0.996 (0.971–1.022) | 0.763  |
| Length of CPAP treatment          | −0.037 | 0.997 (0.988–1.046) | 0.374  |
| P_{aO2}/F_{IO2} before CPAP       | −0.003 | 0.998 (0.974–1.020) | 0.789  |
| C-reactive protein                | 0.076  | 1.079 (1.077–1.191) | 0.135  |
| Procalcitonin                     | −0.287 | 0.750 (0.519–1.084) | 0.126  |
| Lymphocyte count                  | 0.000  | 1.000 (0.999–1.001) | 0.678  |
| Previous SARS-CoV-2 vaccine       | −0.607 | 0.545 (0.130–2.292) | 0.408  |
| Home corticosteroids              | −0.606 | 0.545 (0.227–1.310) | 0.175  |
| Remdesivir                        | −0.159 | 0.853 (0.390–1.868) | 0.691  |
| Anakinra                          | −0.469 | 0.626 (0.235–1.667) | 0.348  |
| Obesity                           | 0.626  | 1.869 (0.515–6.792) | 0.342  |
| DNI                               | −0.744 | 0.475 (0.123–1.840) | 0.281  |

β: regression coefficient; OR: odds ratio; CI: confidence interval. TSS: total severity score by CT visual quantitative evaluation of lung parenchyma; CPAP: continuous positive airway pressure; P_{aO2}/F_{IO2}: arterial oxygen tension to inspiratory oxygen fraction ratio; DNI: do-not-intubate order.
expectedly lower survival rate on CPAP than full-code patients (50% versus 89%). In the latter group, CPAP-only was successful in 60%, while 20% survived after instituting IMV after CPAP. The results of multiple logistic regression analysis showed that independent risk factors for mortality in all participating were older age and higher TSS. As in our previous study [1], \(P_aO_2/F_iO_2\) was not an independent risk factor for death. An explanation for this finding is that \(P_aO_2/F_iO_2\) is an imprecise surrogate of venous admixture, being dependent on various factors, including cardiac output, \(O_2\) consumption, actual alveolar \(O_2\) pressure and nonlinear relationship with \(F_iO_2\) [25, 26]. By contrast, TSS was in the present study a risk factor for death, which may appear at variance with the lung weight not being a risk factor for CPAP failure in our previous study. To explain this inconsistency, we retrospectively measured TSS in the CT scans of the previous study and found it lower than the current one (7 (IQR 6–9) versus 11 (IQR 9–13); \(p<0.001\)), suggesting a more severe pneumonia in the second/third than in the first wave of pandemics, i.e., in the transition period between alpha and delta variants of SARS-CoV-2 in Italy (https://www.epicentro.iss.it/).

Although inferior to our previous results [1], the current ones favourably compare with most of the other reports in patients of either first or subsequent pandemic waves (table 3), particularly in DNI patients. Among the possible explanations for variability between studies are differences in CPAP techniques, or intubation criteria, or both. In our studies, the Venturi generators were adapted to guarantee flows that were presumably higher than patients’ peak inspiratory flows, and strict intubation criteria were followed including \(P_{aO_2}\), which is the most reliable measurement of patient’s oxygenation [26].

The possibility of detrimental effects of noninvasive ventilation or high-flow nasal oxygen by delaying intubation in COVID-19 patients has been recently raised [27, 28]. In these studies, the mortality was 66.5% in patients treated by IMV after failure of noninvasive ventilation [27] and 87% in very late IMV following steroid treatment [28]. The combined mortality of patients treated by IMV after CPAP failure in the present and our previous studies was 37.5%, which is also less than the 53.5% reported for primary [27] and 53% for early [28] IMV. Moreover, the length of CPAP treatment was not a risk factor for
mortality. Although the lack of details on noninvasive ventilation types and intubation criteria in the above studies does not allow explaining reasons for discrepancies, our results do not support the hypothesis that early CPAP failure might have a deleterious impact on the outcome of subsequent IMV.

Another reason of concern with noninvasive ventilation has been the incidence of barotrauma. This was 3.9% in our present study, which was less than the recently reported 6.6% with higher CPAP pressure [29], the 9.1% with bilevel positive airway pressure (BiPAP) [30] and the 13–16% with IMV in COVID-19 patients [31, 32].

The present study has strengths and limitations. The strengths are that a rigorous algorithm for patients’ inclusion and intubation criteria was followed, and the CPAP devices were adapted to guarantee high flows to patients along with prevention of infection dissemination. The major limitations are that it was a single-centre and retrospective study with no inclusion of a comparator group, but this was considered unethical owing to the excellent outcomes of our preliminary study [1]. The percentage of patients who had received SARS-CoV-2 vaccination was very small, i.e., 6.4%, because this became available in Italy only between the second and third wave, thus no inference can be made from the present results regarding its efficacy in preventing COVID-19 outcomes.

Conclusions
We confirm that use of early CPAP with high-flow output combined with an “ad hoc” algorithm to inform the decision to intubate is a valid and safe strategy for respiratory support in patients with AHRF due to COVID-19 pneumonia. The rate of CPAP success varies depending on patient-related risk factors. CPAP was associated with a small risk of barotrauma and had no apparent detrimental effect in those patients who eventually progressed to IMV.

FIGURE 3 Comparison between Kaplan–Meier cumulative survival probability curves in COVID-19 patients at 28 days after continuous positive airway pressure (CPAP) start, stratified for tomographic severity score (TSS) ≤12 or >12.
FIGURE 4 Comparison between Kaplan-Meier cumulative survival probability curves in COVID-19 patients at 28 days after continuous positive airway pressure (CPAP) start, stratified for do-not-intubate (DNI) or full-code status.

TABLE 3 Overview of studies using continuous positive airway pressure (CPAP) in COVID-19

| Reference            | Inclusion months | DNI n  | CPAP survival % | Full-code n  | CPAP survival % | IMV treatment % | IMV death % |
|----------------------|------------------|--------|-----------------|--------------|-----------------|-----------------|-------------|
| BELLANI et al. [4]   | Mar 2020         | 138 NR | 640 61          | 640 IMV      | 47              | 25              |
| Di DOMENICO et al. [5]| Feb 2020         | 27 63  | 43              | 12 63        | 22              | 27              |
| ALIBERTI et al. [6]  | Mar–Apr 2020     | 65 93  | 63              | 44 63        | 22              | 27              |
| BRADLEY et al. [7]   | NR               | 70 0   | –               | 30 0         | –               | –               |
| COPPADORO et al. [8] | Mar–Apr 2020     | 128 28 | 69              | 77 69        | 31              | 41              |
| LAWTON [9]           | Feb–May 2020     | 89 79  | 63              | 29 63        | 37              | NR              |
| De Vita et al. [10]  | Mar–Apr 2020     | NR 367 | 59              | – 59         | 41              | NR              |
| FRANCO et al. [11]   | Mar–May 2020     | NR 330 | 71              | – 71         | 25              | 32              |
| POTALVO et al. [12] | Feb–Apr 2020     | NR 71  | 80              | – 80         | 35              | 35              |
| VASCHETTO et al. [13]| Mar–Apr 2020     | 140 27 | 69              | 397 69       | 45              | 42              |
| RAMIREZ et al. [14]  | Feb–May 2020     | 38 120 | 66              | 29 66        | 34              | 37              |
| BRUSASCO et al. [1]  | Mar–Apr 2020     | 15 49  | 86              | 73 86        | 11              | 71              |
| NIGHTINGALE et al. [15]| Sep–Nov 2000   | 32 56  | 65              | 32 65        | 25              | 64              |
| MEDRINAL et al. [16] | Oct–Dec 2020     | 74 32  | 44              | 32 44        | 56              | 66              |
| SANTUS et al. [17]   | Mar 2020–Mar 2021| 51 37  | 64              | 303 64       | 32              | 66              |
| SYKES et al. [18]    | Apr 2020–Mar 2021| 98 28  | 74              | 42 74        | 26              | 100             |
| PERRINS et al. [19]  | Apr 2020–May 2021| NR 377 | 64              | – 64         | 36              | 58              |
| Present study        | Sep 2020–Jun 2021| 123 50 | 71              | 158 71       | 26              | 62              |

DNI: do-not-intubate order; IMV: invasive mechanical ventilation; NR: not reported.
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Availability of data and materials: data will be made available by the authors for global collaboration on reasonable request, within the national restrictions imposed by privacy laws and ethics.

Author contributions: C. Brusasco and F. Corradi had full access to all of the data in the study, and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: F. Corradi, C. Brusasco, A. Isirdi, F. Dazzi, and V. Brusasco. Building of the database: A. Parisini, S. Boni and G. Santori. Acquisition of data: A. Parisini, S. Boni, F. Corradi, C. Brusasco and C. Romei. Analysis and interpretation of data: all authors. Drafting of the manuscript: F. Corradi, C. Brusasco and V. Brusasco. Critical revision of the manuscript for important intellectual content and approval of the final draft: all authors. Statistical analysis: F. Corradi, C. Brusasco, G. Santori and F. Dazzi.

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