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}/F_{IO_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}/F_{IO_2} <300 were given oxygen support *via* Ventimask. CPAP was applied in cases with one or more of the following criteria: P_{aO_2}/F_{IO_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}/F_{IO_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_2O for all patients, and F_{IO_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}/F_{IO_2} had been persistently >250 with tendency to increase for 2 consecutive days at least. During this phase, Ventimask 50% F_{IO_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}/F_{IO_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 (β) 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)

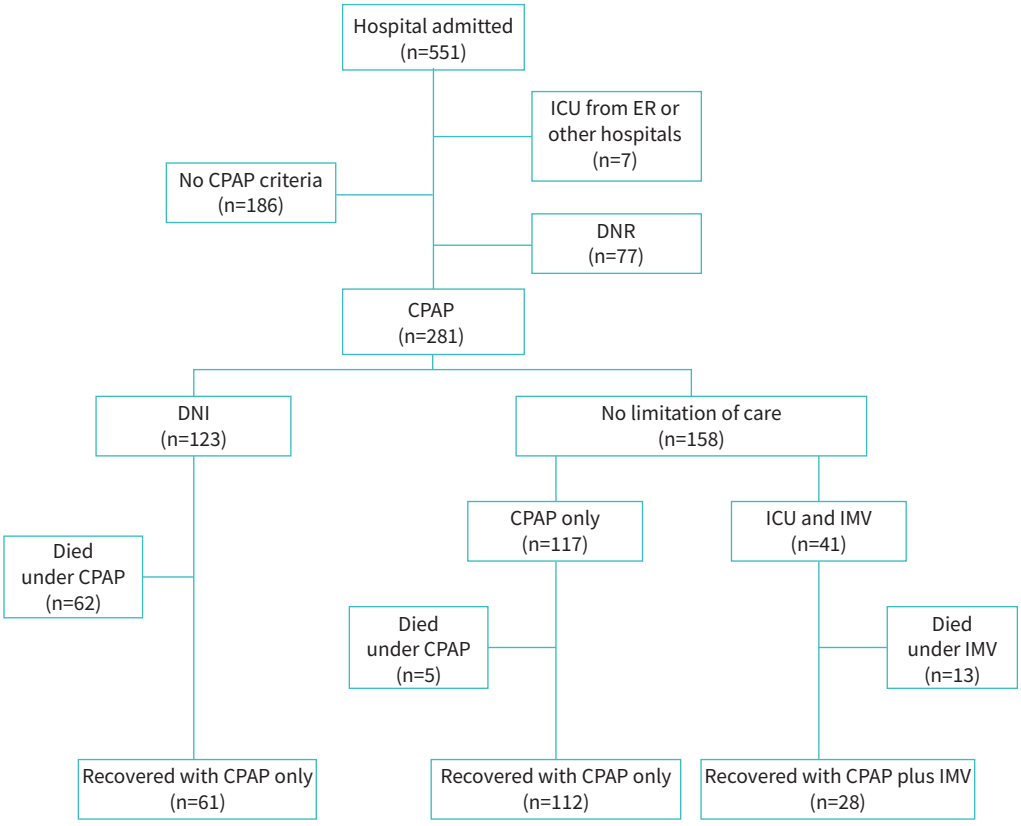

FIGURE 1 Study diagram. ICU: intensive care unit; ER: emergency room; DNI: do-not-intubate order; CPAP: continuous positive airway pressure; IMV: invasive mechanical ventilation.

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}/F_{IO_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}/F_{IO_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.

TABLE 1 Demographic and clinical characteristics of patients according to outcome

	Alive	Dead	p-value
Patients n	201	80	
Age years	61 (51–72)	80 (72–86)	<0.001
Male/female n	135/66	51/29	0.580
Time from symptoms to hospital admission days	7 (3–9)	5 (3–8)	0.456
Time from hospital admission to CPAP days	1 (0–3)	1 (0–3)	0.600
P_{aO_2}/F_{IO_2} before starting CPAP	140 (105–183)	103 (80–150)	<0.001
Radiologic TSS	11 (9–13)	13 (11–18)	<0.001
Procalcitonin ng·mL^{-1}	0.14 (0.06–0.30)	0.18 (0.07–0.31)	0.986
C-reactive protein mg·L^{-1}	8 (3–13)	11 (8–14)	0.002
Lymphocytes cells·mL^{-1}	700 (500–970)	740 (500–893)	0.920
Corticosteroids before hospital admission	56 (28)	13 (16)	0.063
Charlson Comorbidity Index	2 (1–4)	6 (4–7)	<0.001
Obesity	26 (13)	9 (11)	0.842
Previous SARS-CoV-2 vaccination	11 (5)	7 (9)	0.072
Length of hospital stay days	15 (11–24)	13 (8–22)	0.008
Face mask/helmet n	143/58	63/17	0.072
Length of CPAP treatment days	6 (5–9)	7 (3–9)	0.942
Remdesivir	130 (65)	42 (5)	0.057
Anakinra	51 (25)	16 (20)	0.438
DNI	61 (30)	62 (77)	<0.001
Full-code	140 (70)	18 (23)	<0.001

Data are median with interquartile range or number with percentage, unless otherwise stated. CPAP: continuous positive airway pressure; P_{aO_2}/F_{IO_2}: arterial oxygen tension to inspiratory oxygen fraction ratio; TSS: total severity score by CT visual quantitative evaluation of lung parenchyma; DNI: do-not-intubate order; full-code: no limitation of care.

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

TABLE 2 Multiple backward logistic regression analysis for potential predictors of survival in COVID-19 patients with acute hypoxaemic respiratory failure

Predictors	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 (0.888–1.046)	0.374
P_{aO_2}/F_{IO_2} before CPAP	−0.003	0.998 (0.974–1.020)	0.789
C-reactive protein	0.076	1.079 (0.977–1.191)	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_{aO_2}/F_{IO_2}: arterial oxygen tension to inspiratory oxygen fraction ratio; DNI: do-not-intubate order.

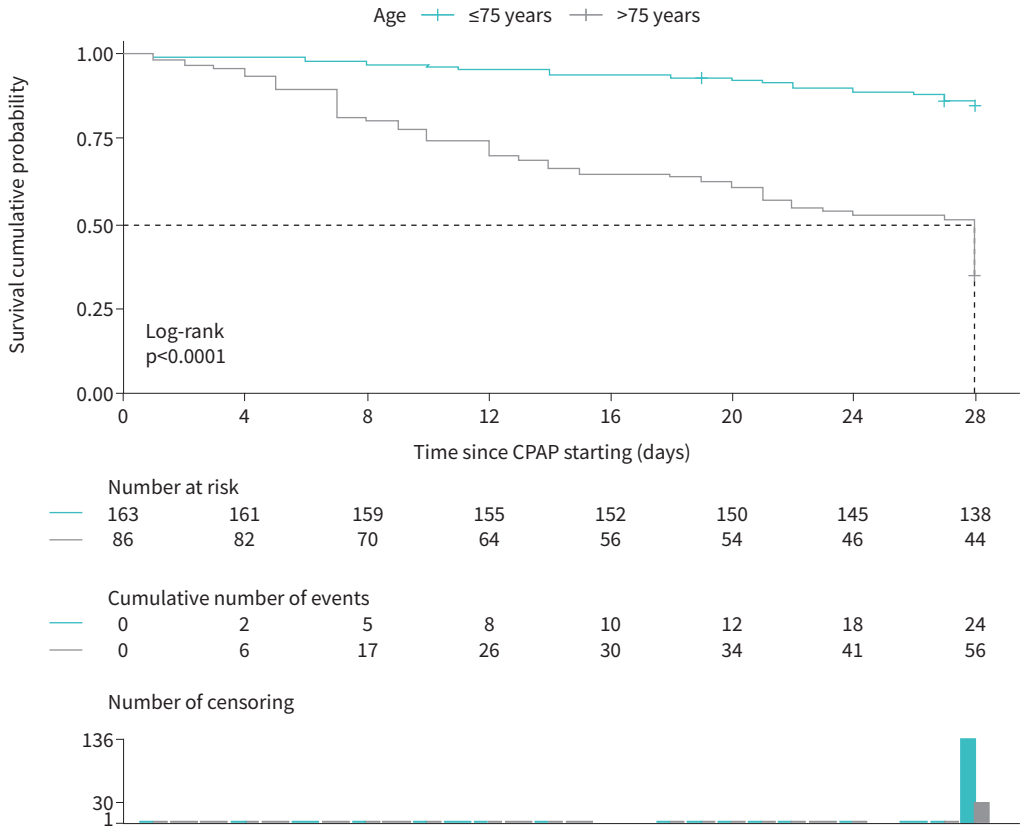

FIGURE 2 Comparison between Kaplan–Meier cumulative survival probability curves in COVID-19 patients at 28 days after continuous positive airway pressure (CPAP) start, stratified for age ⩽75 or >75 years.

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

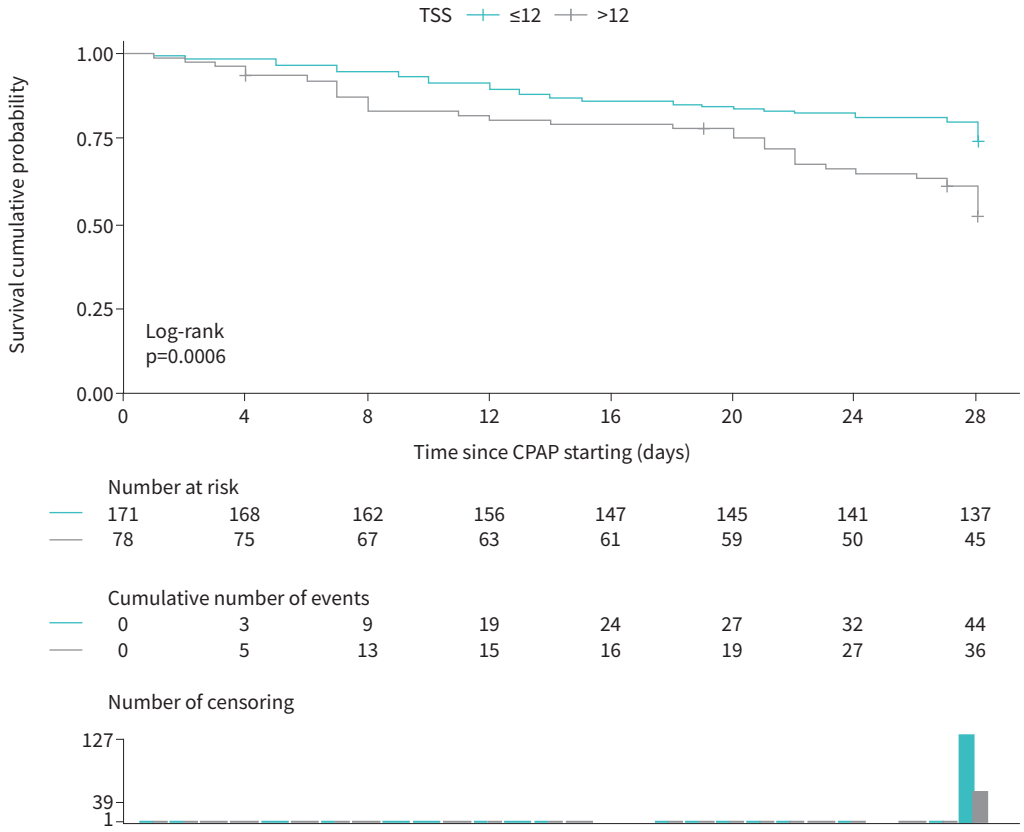

FIGURE 3 Comparison between Kaplan–Meier cumulative survival probability curves in COVID-19 patients at 28 days after continuous positive airway pressure (CPAP) start, stratified for tomographic severity score (TSS) ⩽12 or >12.

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.

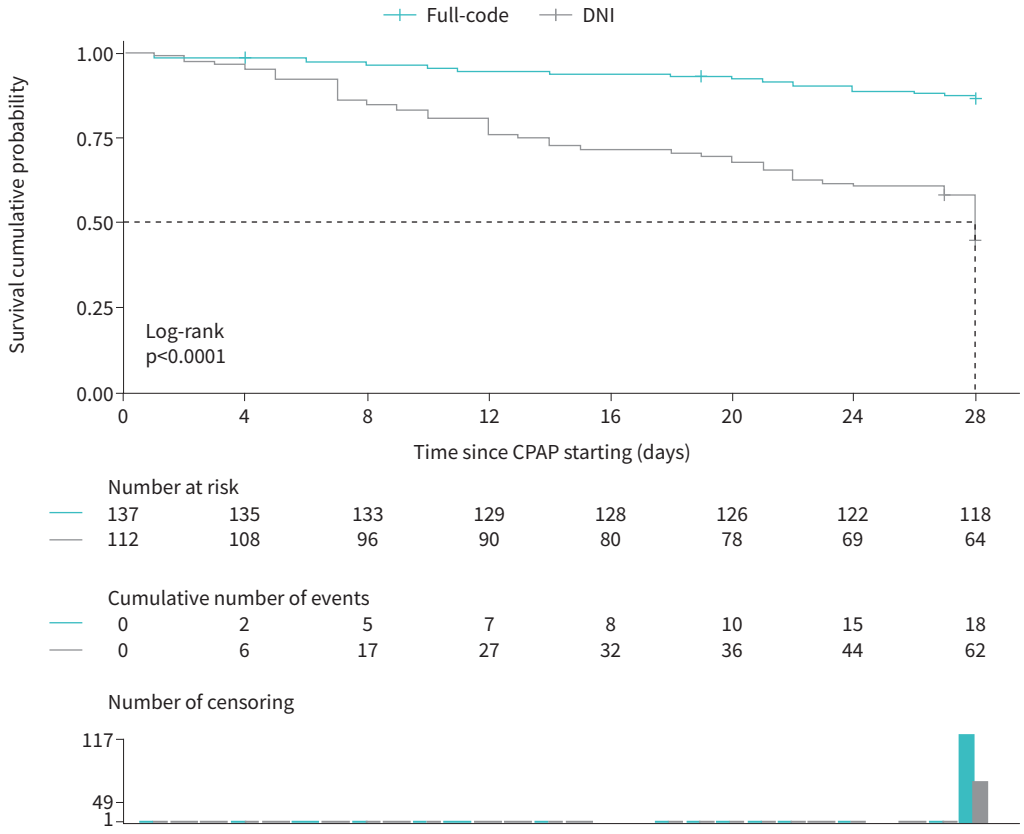

FIGURE 4 Comparison between Kaplan–Meier cumulative survival probability curves in COVID-19 patients at 28 days after continuous positive airway pressure (CPAP) start, stratified for do-not-intubate (DNI) or full-code status.

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

Reference	Inclusion months	DNI		Full-code			
		n	CPAP survival %	n	CPAP survival %	IMV treatment %	IMV death %
Bellani *et al.* [4]	Mar 2020	138	NR	640	61	47	25
Di Domenico *et al.* [5]	Feb 2020	27	12	63	43	57	47
Aliberti *et al.* [6]	Mar–Apr 2020	65	44	93	63	22	27
Bradley *et al.* [7]	NR	70	30	0	–	–	–
Coppadoro *et al.* [8]	Mar–Apr 2020	128	28	177	69	31	41
Lawton [9]	Feb–May 2020	89	29	79	63	37	NR
De Vita *et al.* [10]	Mar–Apr 2020	NR	–	367	59	41	NR
Franco *et al.* [11]	Mar–May 2020	NR	–	330	71	25	32
Potalivo *et al.* [12]	Feb–Apr 2020	NR	–	71	80	35	35
Vaschetto *et al.* [13]	Mar–Apr 2020	140	27	397	69	45	42
Ramirez *et al.* [14]	Feb-May 2020	38	29	120	66	34	37
Brusasco *et al.* [1]	Mar–Apr 2020	15	73	49	86	11	71
Nightingale *et al.* [15]	Sep–Nov 2000	32	56	56	65	25	64
Medrinal *et al.* [16]	Oct–Dec 2020	74	32	118	44	56	66
Santus *et al.* [17]	Mar 2020–Mar 2021	51	37	303	64	32	66
Sykes *et al.* [18]	Apr 2020–Mar 2021	98	28	42	74	26	100
Perkins *et al.* [19]	Apr 2020–May 2021	NR	–	377	64	36	58
Present study	Sep 2020–Jun 2021	123	50	158	71	26	32

DNI: do-not-intubate order; IMV: invasive mechanical ventilation; NR: not reported.

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Ethics approval and consent to participate: The study protocol was approved by the Institutional Ethics Committee (approval number 5/2020).

Consent for publication: The local ethics committee (Comitato etico della regione Liguria) waived written consent owing to the observational design of the study.

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.

Conflict of interest: The authors declare that they have no competing interests with the subject of the article.

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