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# On the use of continuous positive airway pressure during the second and third waves of the Covid-19 pandemic

Claudia Brusasco, Francesco Corradi, Federico Dazzi, Alessandro Isirdi, Chiara Romei, Andrea Parisini, Silvia Boni, Gregorio Santori, Vito Brusasco, the Galliera CPAP-COVID-19 study group

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**Title page**

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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 hypoxemic respiratory failure (158 full-code and 123 do-not-intubate, DNI), were managed with high-flow CPAP early in their hospitalization. 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 hypoxemic respiratory failure due to COVID-19.

**Keywords:** acute hypoxemic respiratory failure, risk factors, do-not-intubate order, invasive mechanical ventilation, barotrauma.

## Background

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 standardized 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, 3–18] 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 generalizable 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 September 1, 2020 and June 30, 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 pressure to inspired oxygen fraction ($PaO_2/F_IO_2$) 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

($SpO_2$) <95% or $PaO_2/F_IO_2$ <300 were given oxygen support via Ventimask. CPAP was applied in cases with one or more of these criteria $PaO_2/F_IO_2$ <200, $PaO_2$ <60 mmHg, breathing frequency >30 breaths/min and dyspnoea at rest or during minimal efforts. IMV was considered after 4 days of unsuccessful CPAP, defined as $PaO_2/F_IO_2$ unchanged or decreased, breathing frequency still >30 breaths/min, $PaO_2$ <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. 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.[19, 20] PEEP was set to 10 $cmH_2O$ for all patients, and $F_IO_2$ between 40 and 70%, depending on $PaO_2$. 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 $PaO_2/F_IO_2$ 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, treatments before and during hospitalization. $PaO_2/F_IO_2$ was included as an index of AHRF severity and tomographic severity score (TSS) [21] 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.[22, 23] 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-days 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; Armonk, NY), 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 of 511 (Figure 1). Seven patients were directly admitted to intensive care unit from emergency room, 263 were treated by Ventimask only, because of mild hypoxia (n=186) or do-not-resuscitate order (77) due to life-threatening comorbidities. The remaining 281 patients had moderate-to-severe AHRF and were initially treated with CPAP. Of them, 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, 5 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 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 $PaO_2/F_IO_2$ before CPAP. The median time from hospital admission to CPAP start was in all study participants of 1 day (IQR 0-3) and the median duration of CPAP treatment was of 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 vs. 55 yr.; p<0.001), had lower $PaO_2/F_IO_2$ before CPAP (123 vs. 146; p<0.001), longer CPAP treatment (8 vs. 7 days; p=0.003), higher CCI (6 vs. 2; p<0.001), less steroid treatment before hospitalization (18% vs. 32%; p=0.009) and more of them were vaccinated (13% vs. 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 or younger, TSS ≤12 or full-code status.

The incidence of barotrauma during CPAP was 3.9%, i.e., 11 cases in 281 patients. Of them, 5 were intubated and mechanically ventilated and only one survived. The remaining 6 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 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 intensive care unit.

In this study, the percentage of patients surviving on CPAP-only was less than in our preliminary study (60% vs. 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% vs. 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 expectedly lower survival rate on CPAP than full-code patients (50% vs. 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] $PaO_2/F_IO_2$ was not an independent risk factor for death. An explanation for this finding is that $PaO_2/F_IO_2$, is an imprecise surrogate of venous admixture, being dependent on various factors, including cardiac output, $O_2$ consumption, actual alveolar $O_2$ pressure, and non-linear relationship with $F_IO_2$.[24, 25] 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 vs. 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 others' 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 $PaO_2$, which is the most reliable measurement of patient's oxygenation.[25]

The possibility of detrimental effects of non-invasive ventilation or high-flow nasal oxygen by delaying intubation in COVID-19 patients has been recently raised [26, 27]. In these studies, the mortality was 66.5% in patients treated by IMV after failure of non-invasive ventilation [26] and 87% in very late IMV following steroid treatment.[27] 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[26] and 53% for early[27] IMV. Moreover, the length of CPAP treatment was not a risk factor for mortality. Although the lack of details on non-invasive 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 non-invasive ventilation has been the incidence of barotrauma. This was in our present study of 3.9%, which was less than the recently reported 6.6% with higher CPAP pressure [28], the 9.1% with BiPAP[29] and the 13-16% with IMV in COVID-19 patients.[30, 31]

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 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 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.

Table 1. Demographic and clinical characteristics of patients according to outcome

| | Alive, n=201 | Dead, n=80 | p |
|---|---|---|---|
| Age, yr | 61 (51-72) | 80 (72-86) | <0.001 |
| Males/females, 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 |
| $PaO_2/FIO_2$ before starting CPAP | 140 (105-183) | 103 (80-150) | <0.001 |
| Radiologic TSS | 11 (9-13) | 13 (11-18) | <0.001 |
| Procalcitonin, ng/mL | 0.14 (0.06-0.30) | 0.18 (0.07-0.31) | 0.986 |
| C-reactive protein, mg/L | 8 (3-13) | 11 (8-14) | 0.002 |
| Lymphocytes, cells/mL | 700 (500-970) | 740 (500-893) | 0.920 |
| Corticosteroids before hospital admission, n | 56 (28) | 13 | 0.063 |
| Charlson Comorbity Index | 2 (1-4) | 6 (4-7) | <0.001 |
| Obesity, n | 26 (13) | 9 (11) | 0.842 |
| Previous SARS-CoV-2 vaccination, n | 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, n | 130 (65) | 42 (5) | 0.057 |
| Anakinra, n | 51 (25) | 16 (20) | 0.438 |
| DNI, n | 61(30) | 62 (77) | <0.001 |
| Full code, n | 140 (70) | 18 (23) | <0.001 |

Data are median with interquartile range or number with percentage. M: male; F: female; $PaO_2/FIO_2$: arterial oxygen tension to inspiratory oxygen fraction ratio; CPAP: continuous positive airway pressure; TSS: Total Severity Score by CT visual quantitative evaluation of lung parenchyma. DNI: do-not-intubate order; Full code: no limitation of care.

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

| Predictors | B | OR | 95%CI | p |
|---|---|---|---|---|
| Age | 0.120 | 1.128 | 1.057-1.203 | <0.001 |
| Charlson comorbidity index | 0.126 | 1.134 | 0.953-1.351 | 0.157 |
| Radiologic 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 |
| $PaO_2/FIO_2$ 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. Other abbreviations as in table 1

Table 3. Overview of studies using CPAP in COVID-19

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

IMV: invasive mechanical ventilation; NR: not reported.Other abbreviations as in table 1

**List of abbreviations:**

CPAP: continuous positive airway pressure

IMV: invasive mechanical ventilation

AHRF: acute hypoxemic respiratory failure

CT: computed tomography

$PaO_2$: arterial oxygen pressure

CCI: Charlson comorbidity index

TSS: tomographic severity score

DNI: do-not-intubate order

**Declarations:**

1. **Ethics approval and consent to participate:** The study protocol was approved by the Institutional Ethics Committee (approval number 5/2020).
2. **Consent for publication:** The local ethics committee (Comitato etico della regione Liguria) waived written consent owing to the observational design of the study.
3. **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.
4. **Competing interests:** The authors declare that they have no competing interests with the subject of the article.
5. **Funding:** none, no financial support was used for the study
6. **Author's contributions:** CB and FC had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: FC, CB, AI, FD, LG, VB. Building of the database: AP, SB, GS. Acquisition of data: AP, SB, FC, CB, CR. Analysis and interpretation of data: all authors. Drafting of the manuscript: FC, CB, VB. Critical revision of the manuscript for important intellectual content and approval of the final draft: all authors. Statistical analysis: FC, CB, GS, FD.
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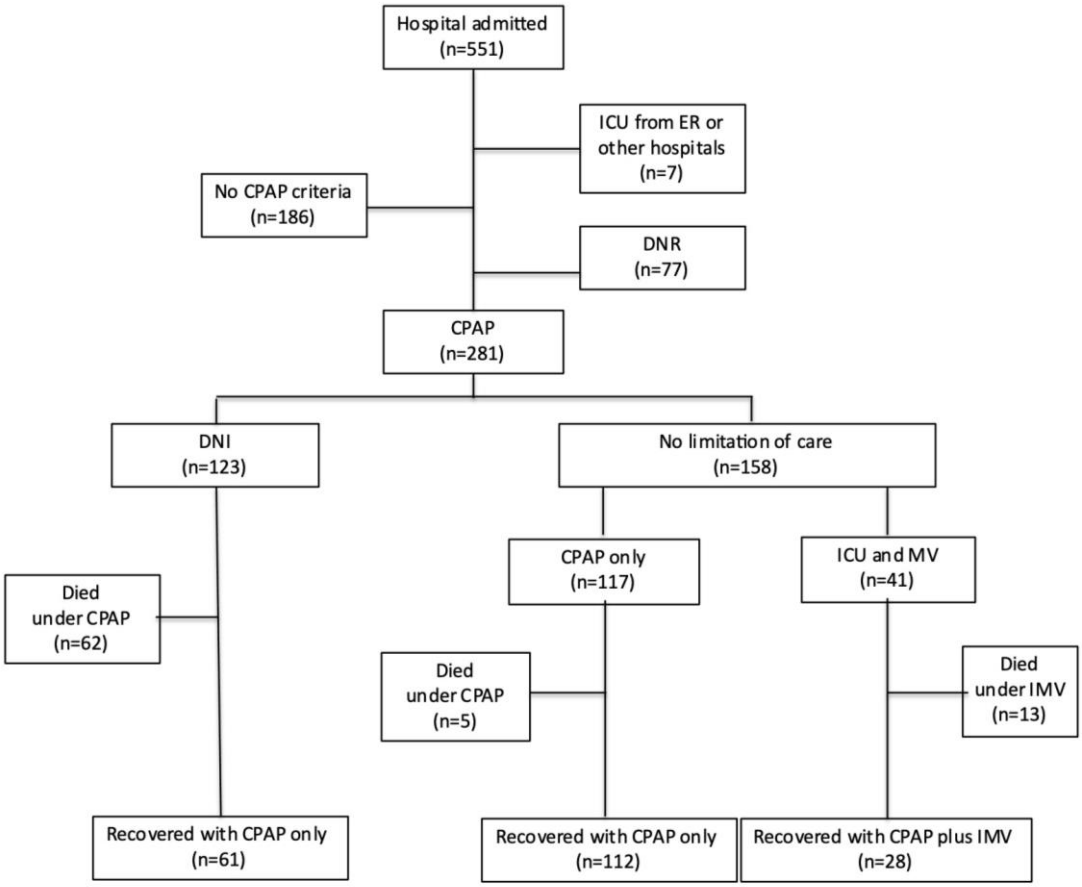
## FIGURE LEGEND

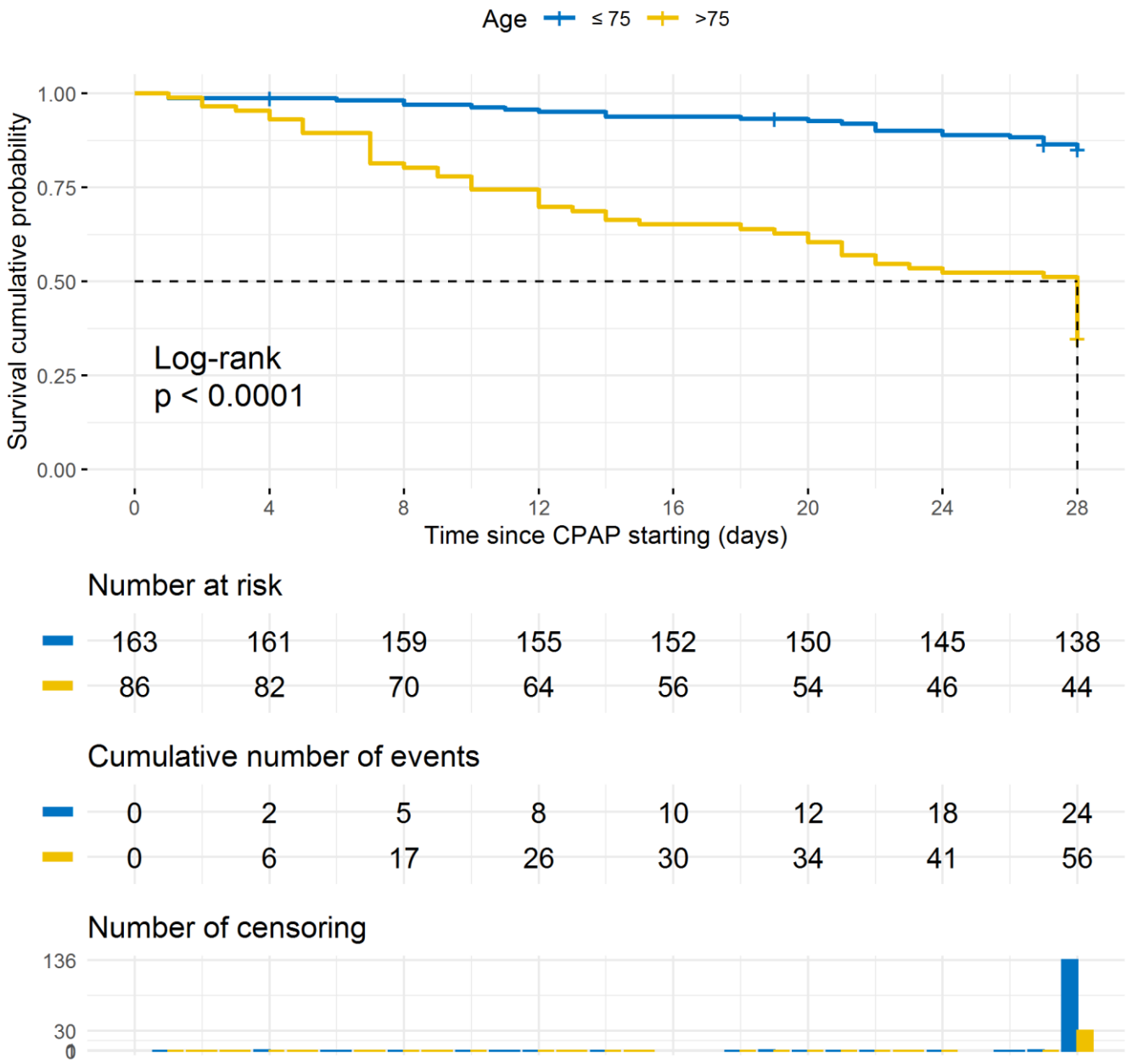
**Figure 1:** Study diagram. ICU: intensive care unit; ER: emergency room; DNI: do-not-intubate order; AP: continuous positive airway pressure; IMV: invasive mechanical ventilation.

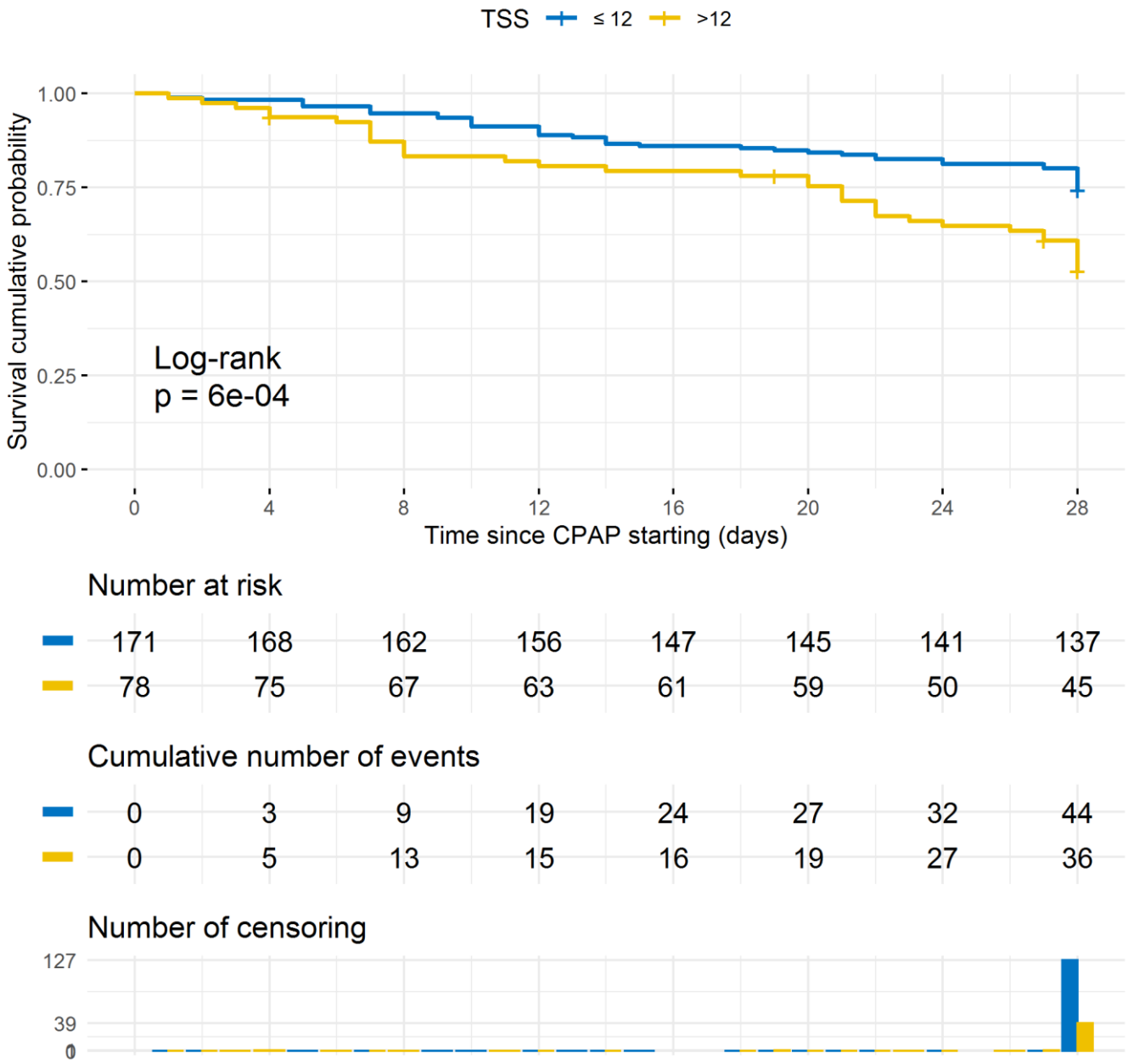
**Figure 2:** Comparison between Kaplan-Meier cumulative survival probability curves in COVID-19 patients at 28 days after CPAP start, stratified for age ≤75 or >75 years.

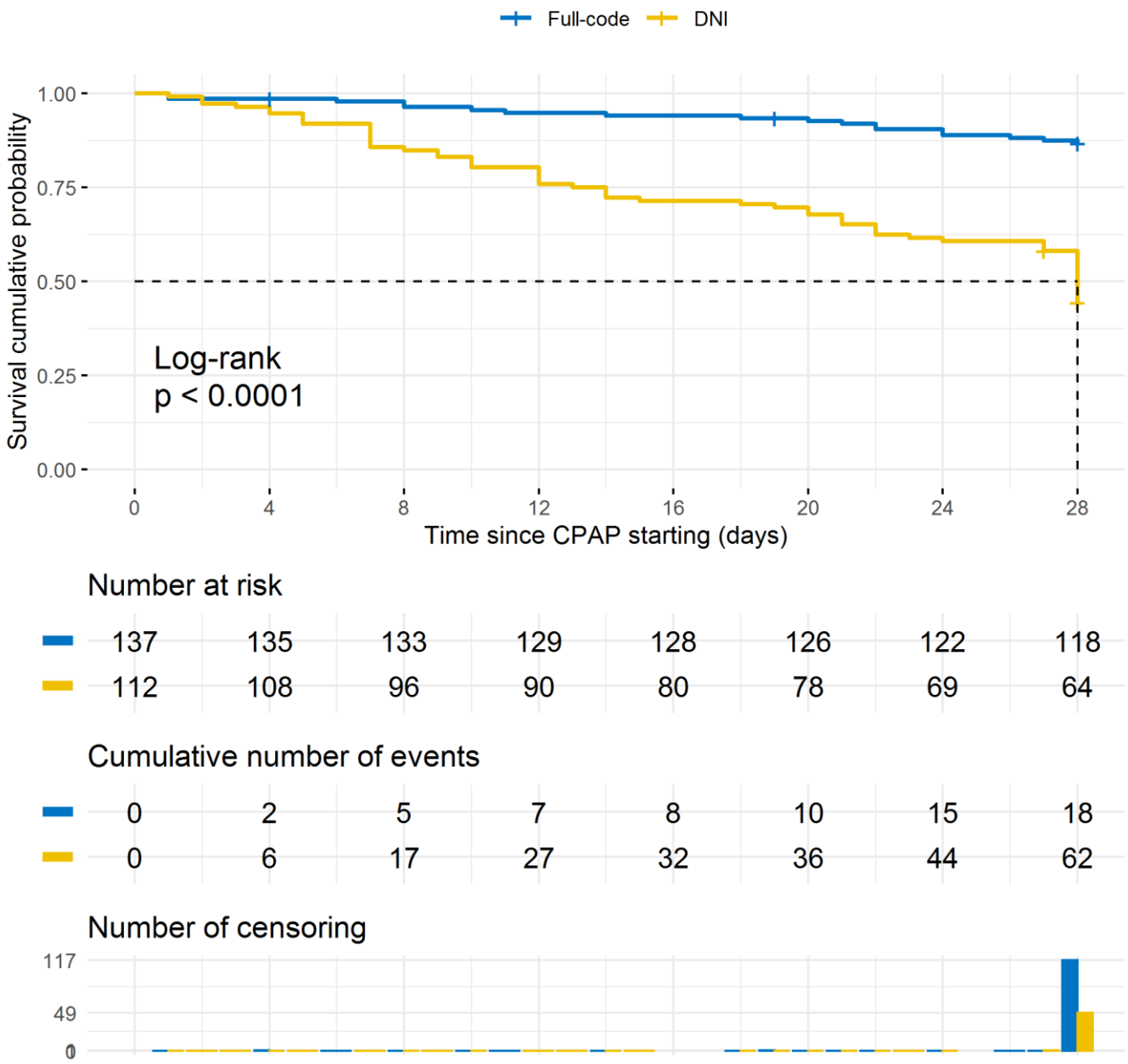
**Figure 3:** Comparison between Kaplan-Meier cumulative survival probability curves in COVID-19 patients at 28 days after CPAP start, stratified for tomographic severity score (TSS) ≤12 or >12.

**Figure 4:** Comparison between Kaplan-Meier cumulative survival probability curves in COVID-19 patients at 28 days after CPAP start, stratified for do-not-intubate (DNI) or full-code status.


Hospital admitted
(n=551)
ICU from ER or
other hospitals
(n=7)
No CPAP criteria
(n=186)
DNR
(n=77)
CPAP
(n=281)
DNI
(n=123)
No limitation of care
(n=158)
CPAP only
(n=117)
ICU and MV
(n=41)
Died
under CPAP
(n=62)
Died
under CPAP
(n=5)
Died
under IMV
(n=13)
Recovered with CPAP only
(n=61)
Recovered with CPAP only
(n=112)
Recovered with CPAP plus IMV
(n=28)


Age
≤ 75
>75
Survival cumulative probability
1.00
0.75
0.50
0.25
0.00
Log-rank
p < 0.0001
0
4
8
12
16
20
24
28
Time since CPAP starting (days)
Number at risk
163 161 159 155 152 150 145 138
86 82 70 64 56 54 46 44
Cumulative number of events
0 2 5 8 10 12 18 24
0 6 17 26 30 34 41 56
Number of censoring
136
30
0


TSS
≤ 12
>12
Survival cumulative probability
1.00
0.75
0.50
0.25
0.00
Log-rank
p = 6e-04
0
4
8
12
16
20
24
28
Time since CPAP starting (days)
Number at risk
171 168 162 156 147 145 141 137
78 75 67 63 61 59 50 45
Cumulative number of events
0 3 9 19 24 27 32 44
0 5 13 15 16 19 27 36
Number of censoring
127
39
0


Full-code
DNI
Survival cumulative probability
1.00
0.75
0.50
0.25
0.00
Log-rank
p < 0.0001
0
4
8
12
16
20
24
28
Time since CPAP starting (days)
Number at risk
137 135 133 129 128 126 122 118
112 108 96 90 80 78 69 64
Cumulative number of events
0 2 5 7 8 10 15 18
0 6 17 27 32 36 44 62
Number of censoring
117
49
0