



Incidence and outcome of delirium during helmet CPAP treatment in COVID-19 patients

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Dear Editor,

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which may cause Acute Hypoxemic Respiratory Failure (AHRF) or Acute Respiratory Distress Syndrome (ARDS) requiring Non-Invasive Ventilation (NIV) and in particular Helmet Continuous Positive Airway Pressure (CPAP), preferred for use both as a ventilator and as a protection against viral transmission for healthcare workers.

Beyond the classical signs and symptoms of presentation as fever and cough, it is estimated that more than one-third of patients with COVID-19 develop neurologic or neuropsychiatric symptoms that seem to be associated with more severe disease [1]. Although neurologic manifestations can happen in a broad spectrum of acute infectious diseases, there are evidences suggesting that the coronavirus family is specially neurotropic, indeed many neurological complications and signs suggestive of delirium are common in the acute stage of SARS (Severe Acute Respiratory Syndrome), MERS (Middle East Respiratory Syndrome) and even COVID-19 [2]. Delirium should be recognized as a potential feature of COVID-19 and may be the only presenting symptom, especially in dementia patients [3].

In COVID-19 patients delirium has a prognostic significance, being independently associated with higher mortality rate, increased length of stay and a greater rate of admission in Intensive Care Unit (ICU) and ventilator utilisation [3–5].

Although no data are available about a direct correlation between NIV and delirium, several well-known precipitating

factors of delirium can co-exist during NIV, especially with helmet interface, as isolation, noise, contact limitation, dehydration. So much that it might be possible that prolonged CPAP could increase delirium rate.

The first aim of our study is to investigate the incidence of delirium occurring during Helmet CPAP therapy in COVID-19 patients. Moreover, we wanted to verify if there are predictable risk factors for delirium in CPAP ventilated patients and to determine if delirium increases the risk of adverse outcomes, defined as need of endotracheal intubation (ETI) and death. Secondly, we better characterize delirium's risk factors including them in a Cox proportional hazard multivariate model.

We analysed data from patients admitted to the internal medicine and infectious diseases wards of “Luigi Sacco” University Hospital of Milan from 21 February to 5 May 2020. The study is part of a prospectively conducted registry study (“REGISTRO DELLE INFEZIONI SOSPETTE E ACCERTATE COVID-19/Studio Sacco COVID-19”) which was approved by the Local Ethical Committee with the Registration Number 2020/16088.

The inclusion criteria were:

1. COVID-19 pneumoniae defined by positivity of real-time reverse transcription-polymerase chain reaction test (RT-PCR) at nose-pharyngeal swab for SARS-CoV-2 and a Chest X-Ray positive for interstitial pneumonia.
2. AHRF requiring Helmet CPAP treatment with PaO₂/FiO₂ (P/F) ≤ 200 mmHg and respiratory rate > 25/minute.

DSM-5 criteria were used for the diagnosis of delirium:

1. Presence of disorder of consciousness with reduced ability to focus, sustain, or shift attention.
2. Change in cognition that is not better accounted for by a pre-existing, established, or evolving dementia.

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3. Development of the disorder over a short period with fluctuation during the day.
4. Evidence that the disorder is caused by a direct physiologic consequence of a medical condition.

Kolmogorov–Smirnov test was used to evaluate the normality of data distribution. Qualitative data were expressed as number and percentage. Chi square or Fisher exact tests were used for group's comparison. Quantitative data were expressed as mean, standard deviation, median and range. Student *T* test and Mann–Whitney test (for non-parametric data) were used for comparison between groups. *P* value less than 0.05 was considered statistically significant. Cox proportional hazard model was used to evaluate four delirium risk factors: age, previous diagnosis of dementia or psychiatric condition, P/F soon after starting CPAP and Gr/Ly. Excel (Office program 2010) and SPSS (statistical package for social science-SPSS, Inc., Chicago, IL version 26) were used for statistical analysis.

During the observational period 1016 COVID-19 patients were admitted to our Hospital; 194 (19.1%) met the inclusion criteria. Their clinical characteristics are resumed in Table 1. Of them, 57 patients (29.3%) developed signs and symptoms of delirium during CPAP. 32 patients (56.1%) developed delirium during the first 24 h after starting CPAP and 48 (84.2%) in the first 48 h.

Patients developing delirium were older, had a higher frequency of previous diagnosis of dementia or psychiatric condition, a more compromised respiratory function as assessed by PaO₂/FiO₂ ratio (immediately after starting CPAP) and a higher neutrophile to lymphocyte ratio (NLR). No significant difference between the two groups were found with respect to comorbidity burden (Charlson Comorbidity Index—CCI), biochemical inflammation-related parameters (IL-6, CRP, D-dimer) nor the use of corticosteroids. The length of hospitalization did not differ, being approximately 20 days in both groups. Time spent in CPAP was highly variable and no statistical significance has been found between the two groups.

Twenty-seven out of 57 patients (47%) presenting delirium died, accounting for a higher mortality rate in this group. The intubation rate was lower in the delirium group than in patients that didn't develop delirium. Noticeably, delirious patients who underwent ETI were younger than non-intubated delirious ones (61.4 ± 13.4 vs 72.9 ± 12, *p* 0.02) and with a trend to a lower comorbidity burden [CCI < 4 in 5/7 (83%) of intubated patients vs 19/50 (43%) in non-intubated patients, *p* 0.06].

At Cox proportional hazard model, resumed in Table 2, age (*p* 0.04) and PaO₂/FiO₂ ratio after starting CPAP (*p* 0.02) were significantly correlated with delirium presentation, while NLR and previous diagnosis of dementia or psychiatric conditions didn't reach statistical significance.

Table 1 Clinical and biochemical characteristics of examined population

	General population	No delirium 137 70.6%	Delirium 57 29.4%	<i>P</i> value univariate	Odds ratio univariate
Age (years)	64.0 ± 14.7	60.9 ± 14.4	71.5 ± 12.7	< 0.001	
Age > 70 years	77 (36.7%)	40 (29.2%)	37 (64.9%)	< 0.0001	4.5 (2.3–8.7)
Male sex	139 (71.6%)	100 (73.0%)	39 (68.4%)	0.52	
CCI	2.66 ± 2.23	2.21 ± 1.98	3.76 ± 2.45	0.121	
Dementia or previous psychiatric condition	19 (9.8%)	9 (6.6%)	10 (17.5%)	0.024	3 (1.2–7.9)
PaO ₂ /FiO ₂ at T1	163 ± 84	173 ± 84	140 ± 81	< 0.001	
PaO ₂ /FiO ₂ at T1 < 150	99 (51%)	60 (43.7%)	39 (68.4%)	0.002	2.8 (1.5–5.3)
Time in CPAP (hours)	153.8 ± 134.4	147.7 ± 115.8	168.4 ± 171.4	0.336	
NLR	9.1 ± 9.0	7.98 ± 8.21	11.64 ± 10.23	0.011	
NLR > 8	55 (28.4%)	24 (17.5%)	31 (54.9%)	0.004	2.6 (1.4–4.9)
CRP (mg/L)	165 ± 95	157 ± 90	183 ± 104	0.088	
D-dimer	8422 ± 21,728	6493 ± 19,545	13,748 ± 26,396	0.109	
IL-6	139 ± 377	132 ± 379	161 ± 377	0.698	
Steroids therapy	19 (9.8%)	10 (7.3%)	9 (15.8%)	0.07	
Length of stay (days)	20.6 ± 14.6	20.8 ± 15.0	19.1 ± 13.0	0.52	
Deaths	59 (3.4%)	32 (23.4%)	27 (47.4%)	< 0.001	3 (1.5–5.7)
ETI	42 (21.6%)	35 (25.5%)	7 (12.3%)	0.041	

In bold the statistically significant data

T1 first data after starting CPAP, *CCI* Charlson Comorbidity Index, *NLR* neutrophile to lymphocyte ratio

Table 2 Cox proportional hazard model: age, previous diagnosis of dementia or psychiatric condition, P/F soon after starting CPAP and NLR

	<i>P</i> value multi-variate	Odds ratio multivariate
Age (years)	0.04	1.025 (1.008–1.04)
Dementia or previous psychiatric condition	0.145	1.718 (0.97–2.18)
PaO ₂ /FiO ₂ at T1	0.02	0.996 (0.992–0.998)
NLR	0.06	1.024 (0.999–1.038)

In bold the statistically significant data

The main finding of our work is that almost one third (29.3%) of a population of consecutive Helmet CPAP ventilated COVID-19 patients presented delirium; this complication was associated with a significantly higher mortality, according to the literature [3–5].

Despite many potential predisposing factors are common in CPAP ventilated patients with AHRF -as hypoxia, dehydration, isolation and noise- delirium incidence in our population seems not to differ from what reported by other studies conducted in populations in which ventilated patients were not represented [3] or constituted a minority of the studied subjects [4, 5]. Moreover, the occurrence of delirium seems not to be related to prolonged CPAP treatment, as in more than 80% of the patients it developed in the first 48 h and no correlation between time spent in CPAP and delirium onset was found.

Our data confirm that age and previous diagnosis of dementia or psychiatric condition can be considered risk factors for the development of delirium [3, 4]. Furthermore, severe respiratory impairment is associated to delirium in our cohort as PaO₂/FiO₂ ratio was statistically lower in delirious patients. This latter finding is in accordance with previous work reporting an increased risk for neuropsychiatric symptoms in patients with more severe COVID-19 disease and worst respiratory failure [1].

A significantly lower intubation rate was observed in patients who developed delirium; anyway, delirious patients were older with higher prevalence of dementia, conditions that limit ETI's indication. For this reason and for possible selection bias we can't consider this result as accurate.

The study presents some limitations. First, it is possible that patients at greater risk for delirium (i.e. elderly with severe dementia) were not ventilated, thus making possible an under-estimation of delirium occurrence when compared to non-ventilated patients. Moreover, populations in comparison found in literature were not completely comparable to ours for age, severity of illness and settings. For these reasons this data should be taken carefully. For last, our study was performed in a single center dedicated to high-complexity medical care and our results should not be generalized to different populations.

In conclusion CPAP therapy may not increase delirium occurrence, as indicated by an incidence in our cohort of non-invasive ventilated patients similar to what found in other works regarding non-ventilated COVID-19 subjects, even if further studies should be done to confirm this data. Unfortunately, COVID-19 pandemic, especially during the first wave, drastically challenged hospital organization, forcing to the use of Helmet CPAP also outside ICU or sub-intensive units, where monitoring patients is more difficult. Our study may add evidences for the recognition of patients at high risk for delirium (over 70 years; mentally ill; NLR ratio > 8; P/F < 150 mmHg after starting CPAP) needing a strict supervision and the highest intensity of care setting for at least the first 48 h.

Declarations

Conflict of Interest No conflict of interest is present as already declared in the appropriate model.

Human and animal rights statement The study is part of a prospectively conducted registry study (“REGISTRO DELLE INFEZIONI SOSPETTE E ACCERTATE COVID-19/Studio Sacco COVID-19”) which was approved by the Local Ethical Committee with the Registration Number 2020/16088.

Informed consent All participants provided informed consent prior to their participation.

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