Delirium is common in patients hospitalized with COVID-19

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Dear Editor,

Delirium is a clinical syndrome with acute disturbances in attention, awareness and cognition, and is a common and severe complication to somatic illness. Several aspects of COVID-19 are known risk factors of delirium, such as hypoxia, inflammation, heavy sedation and mechanical ventilation and it was from the start of the outbreak hypothesized that COVID-19 patients could be at increased risk of delirium [1]. Early case reports informed that delirium could be the first sign of COVID-19 [2] and later published studies report that up to 12–25% of COVID-19 patients can have delirium already at hospital admission [3, 4]. An Italian study of 57 patients with dementia showed that delirium was the first sign of COVID-19 in 37% of the patients. Fever, dyspnea and other typical symptoms of COVID-19 appeared 24–96 h after delirium onset, and the authors suggest that delirium could be a prodromal sign of COVID-19 [5]. Delirium in COVID-19 is associated with increased mortality [4, 6–8] and the small amount of existing available data also suggest functional impairments after hospital discharge [9].

There are now several studies published on delirium prevalence in COVID-19 and it varies from 11% [8] up to 84 [10], depending on study population. As expected is delirium most common in severe cases of COVID 19[10] and in patients with co-morbidities, especially dementia [8].

In this cohort study, we report the occurrence of delirium among all COVID-19 patients admitted to Oslo University Hospital (OUH), Norway over an 8-week period from the start of the pandemic.

Methods

All patients above 18 years hospitalized at OUH with confirmed COVID-19 until May 1 2020 were consecutively included. They were enrolled in a COVID-19 quality registry ("COVID-19 OUH"), approved by the data protection officer at OUH (Ref 20/08,822). Informed consent was waived in accordance with the data protection officer. Delirium was diagnosed according to the DSM-5 criteria by two experienced delirium researchers (LOW and BEN), using all available data, including results of delirium screening tools and after scrutinizing all sections of the case notes. This included information on previous medical history, dementia status and medication use. All sections of the case notes were scrutinized for key words suggestive of delirium, i.e., inattention, hallucinations, agitation, novel prescriptions of antipsychotics and, most importantly, a description of an acute change in mental status. Each of the two experts first classified the patients independently, and in cases of initial disagreement, they discussed the patient until a consensus was reached. Both hyper- and hypoactive episodes of delirium were recorded. Data were analyzed using SPSS version 26.

Patient and Public involvement: the quality registry was established when the first patient was admitted, and lack of time made it impossible to involve patients in the planning.

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Results

186 patients above 18 years were admitted to Oslo University Hospital with confirmed COVID-19 between March 6 and May 1 2020. 18 patients were excluded from the study (14 patients were admitted with conditions non related to COVID-19 (e.g., child delivery or elective procedures) and in four patients were delirium status impossible to determine due to continuous sedation and mechanical ventilation until death or final date of follow–up (May 6 2020)).

Of the 168 patients included in this study, 10% were delirious upon admission and an additional 19% developed delirium during the hospital stay. Patients with delirium were older and had more polypharmacy and co–morbidities. At admission, they had significantly lower oxygen saturation and a trend towards lower systolic blood pressure and higher body temperature. Significantly more patients with delirium had a quick Sequential Organ Failure Assessment (qSOFA) score ≥ 2 and a Glasgow Coma Scale (GCS) < 15. National Early Warning Score 2 (NEWS2) was also higher (Table 1). 41 patients were treated in the Intensive Care Unit (ICU) and of these, 30 (73%) developed delirium. All 25 patients requiring mechanical ventilation developed delirium. In 14 (56%) of these, extubation was postponed because of delirium and four patients (16%)

Table 1 Demographics and Clinical Characteristics of the first 168 patients admitted for COVID-19 at Oslo University Hospital, Norway

Characteristics	All, $n = 168$	No delirium, $n = 120$ (71%)	Delirium, $n = 48$ (29%)	p values[a]
Demographics				
Age, median (IQR), y	58 (48–73)	54 (46–67)	67 (56–85)	<0.001
Sex, male, n (%)	101 (60)	66 (56)	32 (71)	0.07
Number of medications, n (%)				
0	53 (32)	43 (36)	10 (21)	
1–4	74 (44)	55 (46)	19 (40)	
5–6	15 (9)	7 (6)	8 (17)	
7 or more	26 (16)	15 (13)	10 (23)	
Polypharmacy (≥ 5 medications)	41 (24)	22 (18)	19 (40)	0.004
CCI, median (IQR)	1 (0–2)	0.5 (0–1)	1 (0–2)	0.16
CFS (in those above 65 years), median (IQR), $n = 57$	3 (3–5)	3 (3–4)	4 (3–6)	0.13
Clinical (at admission)				
Delirium at admission[b]	15 (10)			
RF/min, median (IQR)[c]	23 (20–28)	22 (20–28)	24 (19–32)	0.19
SpO2 (%), median (IQR)[d]	94 (92–97)	96 (93–98)	92 (87–94)	<0.001
Temperature (C), median (IQR	37.2 (36.5–38.2)	37.1 (36.5–38.1)	37.7 (36.8–38.4)	0.07
HR/min, median (IQR)[e]	90 (76–101)	90 (75–102)	87 (77–101)	0.91
Systolic BP, median (IQR)	127 (115–141)	129 (117–142)	121 (101–140)	0.06
qSOFA ≥ 2, n (%)[f]	21 (13)	6 (5)	15 (33)	<0.001
GCS < 15, n (%)[g]	15 (9)	3 (3)	12 (25)	<0.001
NEWS2, median (IQR)[h]	5 (3–7)	4 (2–6)	8 (6–10)	<0.001
Clinical (highest during stay)				
NEWS2, median (IQR)[i]	9 (5–12)	6 (4–10)	13 (11–15)	<0.001

IQR Interquartile Range, *CCI* Charlson Comorbidity Index, *CFS* Clinical Frailty Scale, *NEWS2* National Early Warning Score 2, *RF* Respiratory Frequency, *HR* Heart Rate, *qSOFA* quick Sepsis–related Organ Failure Assessment, *GCS* Glasgow Coma Scale

[a]Mann–Whitney test for continuous variables and Chi Square tests for categorical variables

[b]15 patients were intubated before they came to the hospital and delirium status at admission could not be assessed

[c]RF at admission missing in four patients

[d]SpO2 at admission missing in two patients

[e]HR at admission missing in one patient

[f]qSOFA at admission missing in five patients

[g]GCS at admission missing in one patient

[h]NEWS at admission is missing in nine patients

[i]Highest NEWS during stay is missing in five patients

had to be re-intubated. Ten out of 13 patients (77%) never on mechanical ventilation that died, experienced delirium in the terminal phase of palliative care.

Discussion

This study reports prevalence of delirium at a University Hospital over an 8 weeks period at the onset of the pandemic. Our results show that delirium is common, in particular in the ICU. All patients who were mechanically ventilated developed delirium. Long-term sedation using high dose opioids and benzodiazepines is likely to have been a contributing factor. The patients admitted to our hospital were rather young (median age 58 years) and none were admitted from nursing homes. Age, frailty and especially dementia are important risk factors for delirium, and we expect delirium rates to be even higher in a more frail population, i.e., in nursing homes.

The findings from our study adds to the existing evidence that delirium is a highly relevant condition in COVID-19 patients for several reasons. (1) Delirium can be an early symptom of COVID-19, as also reported by others [2, 3, 5, 6]. (2) Delirium can make it difficult to deliver optimal care for patients with COVID-19, and we found that extubation had to be postponed in many delirious patients. People with delirium often misinterpret or misunderstand information about necessary procedures. Many are terrified and some have paranoid delusions, and understandably does not always co-operate to treatment, such as ventilatory support. Our findings are in line with a recently published French study of 150 ICU-patients with COVID-19 showing that agitation led to prolonged sedation in 70% of the patients and 8% of the patients (all delirious) experienced accidental extubation [10]. (3) Reports from delirium survivors confirm that delirium can be an extremely distressful experience [11, 12]. This is particularly worrisome since delirium is common in the terminal phase, as was seen in our study. There are no effective pharmacological treatment options, and non-pharmacological interventions are highly recommended. However, such interventions can be especially hard to implement in COVID-19 patients, and mandatory infection control measures (isolation, use of facemask and protective clothes, restriction of visits of family members) may trigger delirium [13]. A recently published study of risk factors for delirium in ICU-patients with COVID-19 found that involvement of family members was the only measure that significantly protected against delirium [14]. This finding highlights that, despite obvious challenges, health care workers should prioritize non–pharmacological interventions also in COVID-19 patients.

A limitation of this study was that for many patients, the delirium diagnosis was chart–based. Such a method is known to have reduced sensitivity compared with bedside delirium assessments and some episodes of delirium might therefore have been missed [15]. On the other hand, there is also a risk that a chart–based evaluation inflates delirium rates since all notions of abnormal behavior ("inattentive", "confused", "disoriented") could potentially be interpreted as delirium. The latter is most likely to occur in ICU patients where we found delirium to be very common. However, the French ICU study, with prospective bed side evaluation of delirium, reported even higher delirium prevalence in the ICU than ours [10].

Our study shows that delirium is very common in COVID-19 patients, especially in the ICU. As delirium is associated with long-term cognitive impairment after critical illness we strongly recommend that cognitive assessments are included in the follow–up of COVID-19 survivors.

Declarations

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