Delirium in Adults With COVID-19–related ARDS: Comparison With Other Etiologies

Author(s):
Raphael Bernard-Valnet, MD, PhD; Eva Favre, RN, MScN; Adriano Bernini, PhD; Mauro Oddo, MD; Jean-Daniel Chiche, MD, PhD; Renaud A. Du Pasquier, MD; Andrea Rossetti, MD, FAES on behalf of CORO-NEURO-ICU study group

Corresponding Author:
Raphael Bernard-Valnet, raphael.bernard-valnet@chuv.ch

Affiliation Information for All Authors: 1. Neurology service, Department of Clinical Neurosciences, Lausanne University Hospital (Centre Hospitalier Universitaire Vaudois) and University of Lausanne, Lausanne, Switzerland 2. Department of Intensive Care Medicine, Lausanne University Hospital (Centre Hospitalier Universitaire Vaudois) and University of Lausanne, Lausanne, Switzerland 3. Neuroscience Critical Care Research Group, Department of Intensive Care Medicine, Lausanne University Hospital (Centre Hospitalier Universitaire Vaudois) and University of Lausanne, Lausanne, Switzerland 4. Medical direction, Lausanne University Hospital (Centre Hospitalier Universitaire Vaudois) and University of Lausanne, Lausanne, Switzerland

Equal Author Contribution:

Contributions:
Raphael Bernard-Valnet: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
Eva Favre: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design
Adriano Bernini: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data
Mauro Oddo: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design
Jean-Daniel Chiche: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design
Renaud A. Du Pasquier: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design
Andrea Rossetti: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design; Analysis or interpretation of data

Neurology® Published Ahead of Print articles have been peer reviewed and accepted for publication. This manuscript will be published in its final form after copyediting, page composition, and review of proofs. Errors that could affect the content may be corrected during these processes.

Copyright © 2022 American Academy of Neurology. Unauthorized reproduction of this article is prohibited
Abstract

Background and objectives: Neurological complications have been associated with COVID-19, including delirium. Such complications have been reported to be frequent among ICU admitted patients. We hypothesized that the rate of neurological complications would be higher in COVID-19 associated acute respiratory distress syndrome (ARDS) than those who develop ARDS from a different cause.

Methods: We conducted a retrospective cohort study in the adult intensive care unit (ICU) of our hospital, including all consecutive patients fulfilling Berlin criteria for ARDS hospitalized between December 2017 and June 2021, stratifying exposure between COVID-19 or not. The primary outcome was delirium onset during ICU stay, defined by the confusion assessment method (CAM-ICU). Exploratory outcomes included development of neurological complications of the central (stroke, hemorrhage, vasculitis) or critical illness weakness, and 30 and 180 days all-cause mortality.
Results: 311 patients were included in the study (253 with COVID-19 and 58 with other causes); CAM-ICU was assessed in 231 (74.3% in COVID-19 vs. 74.1% in non-COVID-19). The proportion of patients developing delirium was similar in patients with COVID-19 and controls in univariate comparison (69.1% vs 60.5%, \( P=0.246 \)). Yet, COVID-19 patients had higher body mass index, lower ICU severity, longer mechanical ventilation, and higher sedation doses (propofol, dexmedetomidine). After adjusting for these factors in COVID-19 patients in a multivariable analysis, the risk of delirium remained comparable across groups (adjusted odds ratio (OR) (95% CI): 0.86 (0.35-2.1)). Similarly, COVID-19 related ARDS had no impact on all-cause mortality at 30 days (adjusted OR: 0.87 (0.39-1.92)) and 180 days (adjusted OR: 0.67 (0.33-1.35)). Finally, neurological complications affecting the central nervous system (adjusted OR: 1.15 (0.25-5.29)) and critical illness weakness (adjusted OR: 2.99 (0.97-9.1)) were not higher in the COVID-19 group.

Discussion: Compared to other etiologies, patients with COVID-19 did not have higher incidence of delirium and other neurological complications, after accounting for underlying disease severity in ARDS patients. Management of COVID-19 associated ARDS needed longer invasive ventilation and higher sedation, which could explain higher rates of delirium in uncontrolled studies.

Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) manifests primarily as respiratory symptoms. It had been estimated that up to 17% of hospitalized patients during the first epidemic waves required invasive ventilation, mostly due to development of an acute respiratory distress syndrome (ARDS)\(^1\). Histological examinations of autopsy studies revealed that SARS-CoV-2 causes diffuse alveolar damage with severe endothelial injury and capillary microthrombi\(^2\). In addition to pulmonary involvement, it has been suggested that SARS-CoV-2 triggers an hyperinflammatory and prothrombotic state that could induce multiorgan involvement\(^3\).

Neurological complications in patients with COVID-19 have been reported since the beginning of the pandemic, and encompass ICU-related conditions such as neuro-myopathy or delirium (also termed in several publications as encephalopathy)\(^4\), thromboembolic manifestations (ischemic stroke),\(^5\) or para-infectious complications (such as encephalitis, Guillain-Barré syndrome)\(^6,7\). In this context, delirium is the most frequently reported neurological complication, with a frequency of up to 80% of COVID-19 patients admitted to the intensive care unit (ICU)\(^8-10\), which represents a high proportion compared to other ICU-related conditions\(^11,12\). Delirium is associated with mid- and long-term neurocognitive dysfunction\(^13,14\) that may account for some of the deficits observed after COVID-19. While it seems that SARS-CoV-2 does not directly infect the central nervous system\(^15\), some studies suggest that
inflammation, hypoxia\textsuperscript{16} and microvascular damage may affect the blood-brain interface and induce brain dysfunction\textsuperscript{17,18}. In addition to biological mechanisms, some changes in the ICU standard of care (i.e. pain management, sedation/analgesia choice, delirium prevention, early mobilization, family engagement) in the context of bed shortage could impact the delirium rate\textsuperscript{19,20}. Yet, this increase could also be influenced by the dramatic increase of the number of patients with severe respiratory failure requiring special management during the COVID-19 pandemic, including longer invasive ventilation support and high doses of continuous sedative/analgesic drugs infusions\textsuperscript{21}.

To our knowledge, very little attention has been directed to compare the risk of neurological complications between COVID-19 ARDS patients as compared to other etiologies. Our study aimed to investigate whether delirium and other neurological complications are more frequent in ICU patients developing ARDS related to COVID-19 compared with ARDS from other etiologies, taking into account disease severity.
Material and methods:

Design, setting and participants. We conducted a retrospective cohort study at the Lausanne University Hospital (Centre Hospitalier Universitaire Vaudois - CHUV), considering COVID-19 as exposure and occurrence of delirium as outcome. All consecutive adults (≥18 years old) admitted at the CHUV ICU for more than 24h for severe respiratory distress between December 2017 and June 2021 were screened for ARDS. All patients fulfilling Berlin ARDS criteria were included. Patients who did not consent to clinical research, were unable to consent, or had suffered from severe prior cognitive impairment (as mentioned in their charts) were excluded.

Data related to the ICU stay were extracted directly from patients’ electronic medical records (MetaVision, iMDSofT, Tel Aviv, Israel). Data collected included demographics (age, gender), weight, BMI, simplified acute physiology score II (SAPS II) on admission, comorbidities at admission (chronic obstructive pulmonary disease (COPD), stroke (or transient ischemic attack), mild cognitive impairment, heart failure, chronic kidney disease, hypertension, atrial fibrillation, active smoking, diabetes, coronary disease), PaO$_2$/FiO$_2$ ratio on admission, worst PaO$_2$/FiO$_2$ ratio, severity of ARDS (according to Berlin ARDS criteria), CAM-ICU (which was only routinely assessed during the ICU stay), total dose (including boluses and continuous infusions) of fentanyl, propofol, midazolam, dexmedetomidine, clonidine, quetiapine, cisatracurium or haloperidol, coma duration (defined as the number of days with a Richmond Agitation-Sedation Score (RASS) at -5 or -4), steroids use, duration of mechanical ventilation, and neurological complications. We also retrieved C-reactive protein (CRP) and D-dimers levels as biomarkers of inflammation and thrombosis. Data on survival were extracted from the Swiss federal death registry, allowing to consider death after discharge of our hospital.

Standard Protocol Approvals, Registrations, and Patient Consents. This study has been approved by the local ethic committee (CER-VD) in the frame of the CORO-NEURO study (authorization n° 2020-01123). We obtained a consent waiver for deceased patients.

Management of analgesia and sedation. These parameters were standardized according to a local nurse-led protocol in line with current recommendations. Prescribed drug doses were tailored to the level of sedation required and defined by the RASS. Analgesia was provided using continuous infusion of fentanyl (1-1.5 µg/kg/h). Preemptive boluses of analgesic drugs could be administered before painful procedures. Patients were sedated with propofol (2-4 mg/kg/h) as a first-line treatment; midazolam (0.05-0.15 mg/kg/h) was administrated as second-line. When clinically required, a neuromuscular blockade agent (cisatracurium) was administrated in addition to analgesia and sedation.

Care organization during COVID-19. To cope with the influx of intensive care patients during the pandemic, healthcare professionals usually working in other acute care units were requisitioned. They were less familiar with the recommended practices of analgesia and sedation in ICU units but were...
coached by the ICU staff. Family/friends visitations were strictly prohibited between March 2020 and June 2020 except for end-of-life situations. After June 2020, visitations were restricted to one relative, one hour per day.

**Outcome variables.** The primary outcome was delirium, assessed through the CAM-ICU routinely performed by nurses twice a day in patients with RASS $\geq -2$. Patients were considered delirious if they had at least one positive CAM-ICU, as in previous studies $^{8,27,28}$. We also analysed delirium length by analyzing the number of days with at least one positive CAM-ICU. Yet, these data were censored when the patients were discharged from ICU. Patients were considered as still delirious at discharge if they had at least one positive CAM-ICU in the last 48h before discharge without 2 consecutive negative assessment.

Patients for whom a CAM-ICU assessment could not be performed were excluded from the analysis of the primary outcome (delirium), but included in analyses of exploratory outcomes, i.e. survival at day 30 and at 180, occurrence of complications of the central nervous system (such as stroke, vasculitis) or critical illness weakness during acute hospital stay.

Central nervous system and critical illness weakness were assessed clinically (by critical care or neurology specialists) and reported in the patients’ charts. However, there was no standardized screening for critical illness weakness.

**Statistical analysis.** We aimed to test the hypothesis that incidence of delirium and neurological complication is higher in COVID-19 associated ARDS than in ARDS from other causes. The rate of delirium was recently estimated at 59% in critically-ill patients without COVID-19 in our hospital $^{27}$. Conversely, previous studies $^{8,9}$ available at the initiation of this project, reported delirium rates over 80% in COVID-19 patients. We originally estimated a 2-sided $\alpha$ level of .05 and power of 80% to detect an absolute increase of 22% in the delirium incidence in COVID-19 patients; assuming an incidence of 60% in the control group and a 4:1 inclusion ratio (COVID-19:non-COVID-19), at least 180 patients including 144 with COVID-19 versus 36 without COVID-19 were to be enrolled.

Continuous variables are reported as median (interquartile range, IQR – 25-75%) and categorical variables as numbers and percentages. Comparison across groups were performed using *Chi-square tests* for categorical variables and *Student t test* for continuous variables (when equal variance assumption was violated, *Welch t test* was used). $P$ values reported were 2-sided, and statistical significance was set at $P = 0.05$.

For the analysis of primary and exploratory outcomes, stepwise binomial logistic regressions were performed. We included in the model the independent variables that were found to be significantly different between groups in the univariate analysis and that were considered as relevant for their plausible implication on the outcome (we did not include coma length, as this variable was not considered independent from analgosedation and delirium). We also analyzed survival in a time-
dependent manner using a Cox model including the same parameters. To analyze variables associated with delirium, we also ran a binomial logistic regression including demographics, SAPS II, duration of mechanical ventilation, tracheostomy, worst PaO2/FiO2 ratio, highest C-reactive protein (CRP) during ICU stay, use of steroids, benzodiazepines or other sedative agents.

Statistical analyses were performed using SPSS 27 software (IBM, Armonk, USA). Prism 9.0 (GraphPad software, San Diego, USA) was used for graphical representations.

Our report follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

**Data availability.** Anonymized data would be made available upon reasonable request from qualified and non-commercial entities.

**Results**

390 patients were admitted to the ICU at CHUV between 1st December 2017 and 31st May 2021 for severe acute respiratory distress. Of these, 382 fulfilled Berlin ARDS criteria and 311 were included for analysis (Figure 1).

In our center, the density of ARDS drastically increased during the COVID-19 pandemic, rising from a median incidence of 1 (IQR 0-2) case per month for ARDS from other etiologies, to 16 (IQR 4-26) (Figure 2). In non-COVID-19 patients, pneumonia was the main cause (86.2%).

Baseline and clinical characteristics of the overall cohort (311 patients) are illustrated in Table 1. The median age did not differ between groups (66 vs 66 year old, \(P=0.155\)). Similarly, except for COPD (20.7 vs 9.1%, \(P=0.012\)), the comorbidities at admission were equally distributed among groups especially mild cognitive impairment (4.7 vs 3.4%, \(P=0.668\)) and history of stroke (or TIA) (5.9 vs 3.4, \(P=0.454\)).

The vast majority of patients in both groups developed a severe ARDS (93.3% vs 98.8%, \(P=0.332\)) and there was no differences in worst PaO2/FiO2 ratio (59.1 vs 57.7 mmHg, \(P=0.295\)). However, compared with controls, COVID-19 patients had a significantly lower SAPSII (46 vs 41, \(P=0.030\)) and higher BMI (28.7 vs 25.1, \(P=0.03\)). Overall, COVID-19 patients needed longer mechanical ventilation (11.6 vs 7.1 days, \(P=0.027\)), required higher total doses of analgo-sedation (propofol and fentanyl) and the duration in coma (10 vs 4 days, \(P=0.001\)) and of ICU stay (15 vs 11 days, \(P=0.049\)) were longer (Table 1). Overall use of neuromuscular blocking agents was also higher in the COVID-19 group (5.6 vs 3.9 mg/kg, \(P=0.032\)). Neither the proportion of patients receiving benzodiazepine-based sedation (70% vs 72.4%, \(P=0.712\)) nor its total dose (Table 1) were different between groups. Non-COVID-19
patients had higher CRP levels (24 vs 48 mg/L, \( P<0.001 \)). Only 13 non-COVID ARDS had D-Dimers assessed during their ICU stay. When measured, D-Dimers were comparable in the 2 groups.

The primary outcome (delirium) could be assessed in 231 subjects, and the proportion of patients with impossibility to assess delirium was similar between the two groups (25.7 vs 25.9 %, \( P=0.949 \)). Reasons which prevented delirium evaluation are summarized in Figure 1. Of note, there were no patients with recent (<30 days) acute brain injury on admission (including subjects with coma after traumatic brain injury, ischaemic/haemorrhagic stroke, cardiac arrest, status epilepticus) evaluated for the primary outcome in both groups. Clinical characteristics of assessed patients did not differ from the whole cohort (eTable 1). The incidence of delirium was higher in patients with ARDS related to COVID-19 (69.1%) than from other causes (60.5%), but it was not statistically significant (unadjusted OR (95% CI): 1.47 (0.74-2.91), \( P=0.246 \)), even after adjusting for SAPSII, BMI, duration of mechanical ventilation, doses of propofol and dexmedetomidine, and steroids use (adjusted OR (95% CI): 0.86 (0.35-2.1), \( P=0.747 \) (Table 2).

The overall duration of delirium in the ICU was also similar between groups (median (IQR): 3 (2-5) vs 3 (2-5) days, \( p=0.396 \) – Data not shown). 43 (22.9%) COVID-19 patients and 9 (20.9%) non-COVID ones were considered as still delirious at discharge from ICU (\( p=0.843 \)).

We analyzed the factors independently associated with a higher risk of developing delirium assessed by CAM-ICU in our sample (231 patients). SAPSII, length of invasive ventilation and use of sedative drugs were associated with higher risk to develop delirium (Figure 3). Of note, benzodiazepine use (i.e. midazolam) did not lead to higher delirium rate (OR (95% CI): 1.57 (0.77-3.21), \( P=0.208 \)), whereas steroids had a protective role (OR (95% CI): 0.34 (0.15-0.75), \( P=0.008 \)).

Given, the low number of patients (eTable 1) with mild cognitive impairment, we did not assessed it as a risk factor for delirium. However, all 9 patients with mild cognitive impairment developed delirium during their ICU stay.

On the whole cohort of 311 patients, complications involving the central nervous system (CNS) were relatively uncommon in both groups (Table 2), occurring in 3 control subjects (5.2%, 2 ischemic strokes, 1 subarachnoid hemorrhage) and 14 COVID-19 patients (5.5%, 9 ischemic stokes, 2 hemorrhagic strokes, 2 subarachnoid hemorrhages and 1 CNS vasculitis). The overall risk of CNS complications was not increased in individuals with COVID-19 (unadjusted OR(95% CI): 1.07 (0.30-3.86), adjusted OR(95% CI): 1.15 (0.25-5.29), \( P=0.857 \)). Risk factors usually associated with cerebrovascular events are depicted in eTable 2.

Despite no systematic evaluation, critical illness weakness tended to be more frequent in patients with COVID-19 than non-COVID-19 counterparts (unadjusted OR(95% CI): 2.87 (1.18-6.99), adjusted OR(95% CI): 2.99 (0.97-9.1)).
All-cause mortality did not differ between groups at 30 (unadjusted OR(95% CI): 0.58 (0.30-1.08), adjusted OR(95% CI): 0.87 (0.39-1.92)) and 180 days (unadjusted OR(95% CI): 0.55 (0.30-0.98), adjusted OR(95% CI): 0.67 (0.33-1.35)) after admission (Table 2). Similar results were found analyzing survival in a time-dependent manner using a Cox model adjusted for the above mentioned variables (unadjusted hazard ratio : 0.65 (95% CI: 0.4-1.02), adjusted hazard ratio : 0.81 (95% CI: 0.48-1.38)) (Figure 4).
Discussion

This study represents, to the best of our knowledge, the first attempt to compare the advent of delirium and neurological complications between two populations of ARDS related or not to COVID-19. Our results suggest that patients with COVID-19 ARDS were not more prone to develop this type of acute brain dysfunction than individuals with ARDS from other etiologies after adjustment for variables known to associated with delirium. Similarly, they were not at higher risk of developing neurological complications (either from the central nervous system or critical illness weakness ), or of all-cause mortality.

Even if the incidence of delirium was comparable across groups, it is of importance to note the striking difference between the management of ARDS related to COVID-19 and ARDS related to other etiologies substantiating the need for adjustments in the analyses of these two groups. COVID-19 ARDS patients stayed longer on mechanical ventilation and requested higher dose of sedative/analgesic drugs. Similarly, COVID-19 patients were comatose for a longer duration, as previously illustrated. These parameters have been shown in our study and in two other cohorts of ICU-admitted COVID-19 patients to be independently associated with the development of delirium. Thus, differences in the management of COVID-19 ARDS could explain variations in the delirium incidence, ranging from 55% to 84% and reaching 69% in our cohort. It is also possible that these differences could reflect the use of benzodiazepines, which have been shown to predispose for delirium. Indeed, the two studies with higher level of delirium report higher proportions of benzodiazepine use (86.4% and 78.4% against 70% in our cohort and 64% in another one). Yet, in our analysis benzodiazepines use was not significantly associated with higher delirium. While the tendency may not have resulted significant in view of the relatively limited sample size, this might also reflect the application of our local analgo-sedation protocol recommending limitation of benzodiazepine use. However, we were not able ascertain the level of compliance to this protocol during COVID-19 pandemic.

There was no difference between groups for delirium in the univariate analysis, suggesting that other key factors may account for delirium development, such as hypoxia, initial illness severity, or systemic inflammation (given the protective effect of steroids), as outlined in Figure. 4.

SARS-CoV-2 has been initially suggested to directly attack the CNS, especially the brainstem. However, subsequent studies failed to demonstrate any invasive SARS-CoV-2 infection within the CNS. It was also proposed that SARS-CoV-2 affects the brain by indirect mechanisms, such as inflammation, hypoxia or development of a prothrombotic state. We previously demonstrated, among other groups, that COVID-19 patients with delirium exhibit higher level of IL-8 and CCL2 in the CSF correlating with peripheral inflammation. This was associated to signs of blood-brain barrier dysfunction and strong glial (astrocytes and microglia) activation. However, these features
are not unique to COVID-19 patients: even if the pathophysiology of delirium is still poorly understood, it has been suggested that peripheral inflammation (notably IL-1β) could lead to blood-brain barrier dysfunction and induce a glial reactivity that in turn produces cytokines like IL-8 and CCL2. This neuroinflammation would subsequently trigger a reduction in the cerebral metabolism, thus leading to delirium. These findings are substantiated by our results that do not show a higher rate of delirium in ARDS associated to COVID-19 after adjusting for confounders. Use of steroids was strongly and inversely associated with delirium, further supporting a role for peripheral and CNS inflammation in the development of delirium. Indeed, in COVID-19 patients, high dose steroids have been shown to exert a beneficial effect on encephalopathy.

It has also been proposed that COVID-19 could induce a prothrombotic state and trigger cerebral ischemic and hemorrhagic consequences. With a small number of neurological complications, we could not demonstrate differences compared to ARDS from other causes. The early use of anticoagulation to prevent arterial and venous complications in the context of prothrombotic state might explain this observation.

Conversely, the rate of critical illness weakness was higher in patients suffering of COVID-19, but it was mainly explained by the longer time on invasive ventilation and the higher use of steroids and neuromuscular blocking agents, which are well-recognized risk factors for this entity. Yet, we have to acknowledge that incidence of critical illness weakness was low in our cohort. As there was no standardized evaluation, we may hypothesize that only the most severe forms were reported. However, the evaluation and reporting have been similar between the two groups.

Regarding mortality, median SAPS II was higher in non-COVID-19 patients (median (IQR): 46 (37-63) than in COVID-19 ones (median (IQR): 41 (34-49)), resulting in an estimated ICU mortality of 36% and 26%, respectively. This might partially explain the lower survival in non-COVID-19 patients that was not significant in multivariable analyses correcting for SAPS II. Nevertheless, our delirium rate seems congruent with other centers.

Our study has several limitations. First, its retrospective design and the relatively limited patient sample size may have reduced the sensitivity to detect smaller differences in delirium incidence. Our sample assumption was based on two single-center studies reporting a high delirium incidence in this population. Differences between groups could have been missed because of the lack of statistical power. Furthermore, information regarding the pre-existing comorbidities that could favor delirium was limited; major cognitive disorders was an exclusion criteria, and was only assessed retrospectively on patients’ charts. Indeed, premorbid frailty including advanced age, dementia, alcohol abuse, vision/hearing loss are known to play a role in development of delirium. Similarly, we were not able to assess important factors that could have affected delirium prevention, including early mobilization, physical restraints use, or visit from family/friends. While this last parameter has been shown to
play a role in delirium prevention, family visits were strongly limited for COVID-19 patients but not for ARDS of the pre-COVID era. Furthermore, we only had limited information of delirium type (hypo- vs hyperactive) and the compliance to prescribed sedation levels. We were also not able to reliably compare delirium duration, for the sake of data quality we limited our analysis to the ICU stay (as CAM assessments were not routinely performed outside the ICU), and many patients were discharged still delirious. Around 25% of the ARDS cohort patients could not be assessed for delirium (the vast majority died in coma), but the proportion was nearly identical across the two groups, strengthening the internal validity of the study. The overall proportion of patients with delirium that seems comparable to the largest study to date suggests generalizability of our results. Yet, contrary to many other centers, the Lausanne University Hospital was not significantly affected by sedative drugs shortage. This might partially explain some discrepancies in delirium rate to other studies performed in centers strongly affected by beds and drugs shortages. Finally, COVID-19 patients included in this analysis were infected with the alpha or delta variant of SARS-CoV-2 but not the highly contagious, but less severe, omicron variant.

To conclude, this first controlled study comparing ARDS due to COVID-19 and other causes suggests that the risk of neurological complications of these patients is similar, including development of delirium. Given the long term impact of ICU stay and delirium on cognition, and the massive increase in ARDS patients over this last two years due to the pandemic, COVID-19 neurological sequelae should be evaluated in large, prospective, long-term assessments.

SDC -- http://links.lww.com/WNL/C270

References


### Appendix 2 – Coinvestigators

<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
<th>Participation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nawfel Ben Hamouda</td>
<td>Department of Intensive Care Medicine, Lausanne University Hospital (Centre Hospitalier Universitaire Vaudois) and University of Lausanne, Lausanne, Switzerland</td>
<td>Data collection</td>
</tr>
<tr>
<td>Lise Piquilloud Imboden</td>
<td>Department of Intensive Care Medicine, Lausanne University Hospital (Centre Hospitalier Universitaire Vaudois) and University of Lausanne, Lausanne, Switzerland</td>
<td>Data collection</td>
</tr>
<tr>
<td>Beatrice Pizzarotti</td>
<td>Neurology service, Department of Clinical Neurosciences, Lausanne University Hospital (Centre Hospitalier Universitaire Vaudois) and University of Lausanne, Lausanne, Switzerland</td>
<td>Data collection</td>
</tr>
</tbody>
</table>

### Figures Legend

**Figure 1 - Study Flow Chart.**

Legend: ARDS: acute respiratory distress syndrome, ICU: Intensive care unit
Figure 2 - Monthly incidence of ARDS.
Number of patients admitted for acute respiratory distress in the ICU per month between December 2017 and May 2021. Patients associated with COVID-19 associated ARDS are depicted in green and ARDS from other cause in red.

Figure 3 – Forest plot of independent factors associated with delirium.
In patients assessed for delirium with CAM-ICU (COVID: 188, non-COVID: 43), a binomial logistic regression assessed the impact on delirium of the following parameters: Age, Gender, SAPS II, length of invasive ventilation, tracheotomy, worst PaO2/FiO2, sedative infusion, benzodiazepine use, worst C-reactive protein (CRP) level and use of steroids. For all continuous variables (age, SAPSII, length of invasive ventilation, worst PaO2/FiO2, worst C-reactive protein (CRP)) comparisons shown in parentheses correspond to the 75th vs 25th percentile values for these variables. Statistically significant differences are highlighted in bold.

1 No infusion of sedative drugs (including propofol, dexmedetominidine or midazolam)
2 Use of non-benzodiazepine sedative drugs (propofol, dexametomidine) or no sedative drugs

Legend: SAPS II: Simplified Acute Physiology Score II, CRP: C-reactive protein, PaO2: oxygen partial pressure, FiO2: inspired oxygen fraction
Figure 4 – Survival during the first year after admission to ICU for ARDS. Hazard ratio (HR) provided has been calculated from a cox model adjusted for: SAPSII, BMI, length of mechanical ventilation, propofol dose, dexmedetominidine dose, steroids use. Unadjusted HR: 0.65 (0.4-1.02).

Table 1 - Demographic and clinical characteristics of patients with ARDS
*assessed in 13/58 patients.

<table>
<thead>
<tr>
<th>Age in year, median (IQR)</th>
<th>Non-COVID-19 (n=58)</th>
<th>COVID-19 (n=253)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, Female, n (%)</td>
<td>66 (50-75)</td>
<td>66 (59-73.5)</td>
<td>0.155*</td>
</tr>
</tbody>
</table>

Simplified Acute Physiology Score II at admission, median (IQR)

BMI at admission, in kg/m², median (IQR)

ARDS

Cause of ARDS

Respiratory support

Copyright © 2022 American Academy of Neurology. Unauthorized reproduction of this article is prohibited
Table 2 - Outcome variables.
Variables included in the multivariable analysis are: SAPSII, BMI, COPD, length of mechanical ventilation, propofol dose, dexmedetomidine dose, steroids use for Delirium and All-cause mortality; SAPSII, BMI, length of mechanical ventilation, hypertension, active smoking, diabetes for CNS complication; SAPSII, BMI, length of mechanical ventilation, propofol dose, dexmedetomidine dose, steroids use, cisatracurium dose for critical illness weakness
Statistically significant values are highlighted in bold.

<table>
<thead>
<tr>
<th>Primary outcome</th>
<th>Non-COVID-19 (n=43)</th>
<th>COVID-19 (n=188)</th>
<th>Between group differences Unadjusted odds ratio (95% CI)</th>
<th>Adjusted odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delirium</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Positive at least once during ICU stay, n (%)</td>
<td>26 (60.5)</td>
<td>130 (69.1)</td>
<td>1.47 (0.74-2.91)</td>
<td>0.86 (0.35-2.1)</td>
</tr>
<tr>
<td>Exploratory Outcomes</td>
<td>Non-COVID-19 (n=58)</td>
<td>COVID-19 (n=253)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurological complications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Central nervous system, n (%)</td>
<td>3 (5.2)</td>
<td>14 (5.5)</td>
<td>1.07 (0.30-3.86)</td>
<td>1.15 (0.25-5.29)</td>
</tr>
<tr>
<td>- Critical illness weakness, n (%)</td>
<td>6 (10.3)</td>
<td>63 (24.9)</td>
<td>2.87 (1.18-6.99)</td>
<td>2.99 (0.97-9.1)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- 30 days after admission, n (%)</td>
<td>18 (31)</td>
<td>52 (20.6)</td>
<td>0.58 (0.30-1.08)</td>
<td>0.87 (0.39-1.92)</td>
</tr>
<tr>
<td>- 180 days after admission, n (%)</td>
<td>25 (43.1)</td>
<td>74 (29.2)</td>
<td>0.55 (0.30-0.98)</td>
<td>0.67 (0.33-1.35)</td>
</tr>
</tbody>
</table>
Delirium in Adults With COVID-19–related ARDS: Comparison With Other Etiologies

Neurology published online August 25, 2022
DOI 10.1212/WNL.0000000000201162

This information is current as of August 25, 2022

<table>
<thead>
<tr>
<th>Updated Information &amp; Services</th>
<th>including high resolution figures, can be found at:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><a href="http://n.neurology.org/content/early/2022/08/25/WNL.0000000000201162.full">http://n.neurology.org/content/early/2022/08/25/WNL.0000000000201162.full</a></td>
</tr>
<tr>
<td>Subspecialty Collections</td>
<td>This article, along with others on similar topics, appears in the following collection(s):</td>
</tr>
<tr>
<td></td>
<td>All CBMRT/Null Hypothesis</td>
</tr>
<tr>
<td></td>
<td><a href="http://n.neurology.org/cgi/collection/all_cbmrt_null_hypothesis">http://n.neurology.org/cgi/collection/all_cbmrt_null_hypothesis</a></td>
</tr>
<tr>
<td></td>
<td>COVID-19</td>
</tr>
<tr>
<td></td>
<td><a href="http://n.neurology.org/cgi/collection/covid_19">http://n.neurology.org/cgi/collection/covid_19</a></td>
</tr>
<tr>
<td></td>
<td>Delirium</td>
</tr>
<tr>
<td></td>
<td><a href="http://n.neurology.org/cgi/collection/delirium">http://n.neurology.org/cgi/collection/delirium</a></td>
</tr>
<tr>
<td>Permissions &amp; Licensing</td>
<td>Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:</td>
</tr>
<tr>
<td></td>
<td><a href="http://www.neurology.org/about/about_the_journal#permissions">http://www.neurology.org/about/about_the_journal#permissions</a></td>
</tr>
<tr>
<td>Reprints</td>
<td>Information about ordering reprints can be found online:</td>
</tr>
<tr>
<td></td>
<td><a href="http://n.neurology.org/subscribers/advertise">http://n.neurology.org/subscribers/advertise</a></td>
</tr>
</tbody>
</table>