Delirium in Covid-19 Patients: Incidence, Risk Factors and Early Outcomes.

Jorge Humberto Mejia-Mantilla (✉ jorge.mejia@fvl.org.co)

Fundacion Valle del Lili <https://orcid.org/0000-0001-6263-8577>

Andrés Gempeler

Fundación Valle del Lili: Fundacion Valle del Lili

Leidy K Gaviria

Fundación Valle del Lili: Fundacion Valle del Lili

Pablo Amaya

Fundacion Valle del Lili

Jose Luis Aldana

Fundacion Valle del Lili

Beatriz Elena Muñoz

Fundacion Valle del Lili

Gabriel Pinilla

Icesi University: Universidad Icesi

Julian Rivillas

Icesi University: Universidad Icesi

Diego Scarpetta

Icesi University: Universidad Icesi

Cristhian Camilo Rojas Perdomo

Icesi University: Universidad Icesi

Nicolás Orozco Echeverri

Icesi University: Universidad Icesi

Alex Sotomayor

Fundación Valle del Lili: Fundacion Valle del Lili

Julián Yara

Fundación Valle del Lili: Fundacion Valle del Lili

Javier A Jimenez

Fundación Valle del Lili: Fundacion Valle del Lili

Akemi Arango

Fundación Valle del Lili: Fundacion Valle del Lili

Jorge Luis Orozco

Fundación Valle del Lili: Fundacion Valle del Lili

Research

Keywords: Covid-19, ARDS, Delirium, Post-ICU syndrome, Mechanical ventilation complications

Posted Date: July 1st, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-522962/v2>

License: This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background

Delirium is a frequent event in severely ill patients; its incidence and prevalence varies depending on several factors; Covid has been associated to high incidence of delirium leading to speculation of specific mechanisms of neurotoxicity by the SARS-CoV-2. We present the analysis of risk factors for delirium incidence and the impact of delirium in the functional outcomes.

Methods

We included patients admitted to a referral center in Cali, Colombia between April and August 2020. Patients were evaluated for demographics, severity of disease, comorbidities, clinical outcomes, delirium and survival at discharge. We evaluated the association of patient characteristics and disease factors with delirium incidence by multivariate analysis (Hosmer and Lemeshow) and the associations of delirium with functional outcome at discharge

Results

Among 333 patients, 58 (17.42%. 95% CI: 13.62–21.77%) presented delirium 16 (IQR: 11 – 20) days after symptom onset. Patients with delirium were older, reported muscular weakness more often, had a higher NEWS2 score at admission, and had more comorbidities (mainly Diabetes Mellitus II). Multivariate analysis of hospitalization events and treatments found mechanical ventilation as the only significant covariate. The association between need for mechanical ventilation and delirium development was estimated at OR = 11.72, (95%CI = 4.16–34.23). Patients who developed delirium had a higher frequency of functional impairment: mRs > 2 (70.7% vs 24.7%, $p < 0.001$) and had a prolonged ICU stay (median 13 days, IQR 8–21 vs median 5, IQR 3–10 days, $p < 0.0001$) compared to patients without delirium.

Conclusion

Our data show that premorbid functional status, the severity of respiratory dysfunction and the presence of inflammatory markers are determinant in the risk of delirium; we believe that delirium might not be specially related to SARS-CoV-2 infections, its high frequency during this pandemic could be the result of concurring factors shared between critically-ill patients and severe COVID-19 patients. Further research is granted to clarify this aspect

Introduction

The severe acute respiratory syndrome virus, SARS-CoV-2, which causes COVID-19 viral pneumonia, was first identified in late December 2019 in the Chinese city of Wuhan, Hubei province (1). It subsequently

spread rapidly around the world and was declared a pandemic by the World Health Organization (WHO) in March 2020 (2), and by the end of 2020 has infected about 79.2 millions of people in the world, with a cumulative global mortality of 3.2% approximately (2).

COVID-19 is a highly contagious pneumonia, with benign evolution in most cases, but associated with the development of severe acute respiratory distress syndrome (ARDS) in some (3). Extrapulmonary involvement has been detected as more studies with different cohorts of patients are published. One of the most important compromised systems is the nervous system, presenting with both central and peripheral neurological manifestations (3) with an incidence up to 36.4% (4). COVID-19 manifestations include transitory alterations in the state of consciousness, nerve function, or cognitive sequelae (5). Several mechanisms of neuroinfection have been proposed in animal and human studies (4, 6), for instance, a retrograde mechanism starting by the infection of the peripheral nerve terminals and propagation towards the central nervous system. In the brain a trans-synaptic spread with a vesicle-mediated secretory pathway could happen, this mechanism at the first cranial nerve can explain the anosmia and ageusia without respiratory symptoms (7, 8); the second mechanism is the spread through the blood-brain barrier, either throughout the endothelial cell with the expression of ACE2 or with the “Trojan horse mechanism” using T lymphocytes to cross the blood-brain barrier (8, 9). Other studies have postulated an aberrant immune response associated with hyperinflammation as a pathophysiological cause of brain dysregulation and the presence of neurological manifestations (10–13).

One of the most relevant problems associated with central nervous system involvement in COVID-19 patients is delirium, with a reported incidence up to 84.3% (12). Delirium is characterized by acute fluctuating disturbances in attention and cognition in a short period of time which are not explained by a pre-existing neurocognitive disorder (14). In critically ill patients, delirium is associated with worse outcomes such as increased hospital stay, increased risk of long-term neurological and neurocognitive sequelae, as well as the development of neuropsychiatric disorders or even death (15). Delirium, as well as the other neurological manifestations, has been described as a major issue in patients with ARDS due to COVID-19 pneumonia who required ICU admission and associated with the use of mechanical ventilation and sustained sedation (12).

The aim of this study is to describe the incidence of delirium in consecutive patients hospitalized due to COVID-19, and to estimate the association of delirium with other neurological manifestations, disease severity, functional outcomes and mortality at discharge.

Methods

Study Design and Participants

This was a prospective, single-center, observational study that took place at a tertiary care referral center and university hospital in Cali, Colombia. We included patients diagnosed with SARS CoV-2 infection according to the WHO criteria (2, 16) and hospitalized in the institution between April and August 2020.

SARS-CoV-2 infection was defined by detection of the virus with real-time reverse-transcription polymerase chain reaction test (RT-qPCR) in samples from upper or lower respiratory tract.

Measurements

Demographic and clinical characteristics at baseline, laboratory results (arterial blood gases, blood chemical analysis and cell count, renal function, C-reactive protein, lactate dehydrogenase, ferritin, interleukin-6, fibrinogen and coagulation parameters) and NEWS2 score at admission were measured. We recorded the presence of various neurological symptoms at presentation: headache, anosmia/hyposmia, ageusia/dysgeusia, seizures, disorientation, somnolence and loss of consciousness. In-hospital events, including admission to ICU, requirement of mechanical ventilation (MV), shock, and decision of withdrawing life-sustaining treatment, were also recorded. Shock was defined according to the guidance of WHO for the novel coronavirus disease 2019 (COVID-19) (2, 16).

The main outcome of interest was the incidence of delirium in patients with COVID-19 at any time during their hospital stay. Delirium was defined by the CAM-ICU criteria assessed routinely in ICU by medical staff (17, 18). Upon admission to general ward, all patients were assessed for delirium by study staff using the same criteria. We also measured overall mortality and score on the modified Rankin scale (mRs) at admission and discharge.

Data collection and Statistical Analysis:

Unusual or oddly-missing data was verified with primary sources. Descriptive analysis was undertaken to summarize patients' characteristics and to identify the frequency of delirium and other outcomes of interest. Continuous variables were assessed with the Shapiro-Wilk test and are described with mean and standard deviation (SD) or median and inter-quartile range (IQR), as suited. For evaluating differences between subgroups of interest, Student's t or Mann-Whitney test were used according to data distribution. Categorical variables are presented as absolute frequencies and proportions; differences between groups regarding nominal variables were assessed with the χ^2 test, or Fisher's test, as suited. All measures of frequency and of association are reported with 95% confidence intervals (95%CI); all hypotheses tests are reported with their respective p value. All analyses were conducted in RStudio version 1.3.1 software.

Factors associated with delirium were explored through the comparison of known and potential prognostic factors between patients with and without delirium. To avoid collinearity and maintain clinical interpretation and usefulness, we assessed factors identifiable at admission separately from events that occurred during hospitalization. Association of neurological symptoms and development of delirium was assessed for each neurological symptom individually and also as the presence of any neurological symptom. Given the objective of assessing an association and controlling for confounding factors, all logistic regression models used for multivariate analyses followed a purposeful variable selection process, as described by Hosmer and Lemeshow (19): all variables with $p < 0.2$ in the Wald test and those of particular clinical interest are included in an initial model which is then reduced in an iterative process where covariates are removed from the model if they are non-significant and not a confounder. Level of

significance is $\alpha = 0.1$ and confounding is considered with an estimate change greater than 20% when compared to the full model; then any variable not selected for the original model is added back, one at a time, to verify it is adequately excluded based on significance, and the previous iterative process is repeated to obtain the final model (19).

The mRs scores were compared between delirium patients and controls using the Mann-Whitney-Wilcoxon test. To assess change in mRs scores between admission and discharge for each patient, the Wilcoxon signed-rank test was used (non-parametric paired test). An mRs score >2 was used as cut-off point for dichotomization of the scale into “disability” and “no or mild disability” to compare frequency of immediate disability between groups.

Results

We included 333 patients that fulfilled selection criteria. Baseline clinical features are displayed in Table 1. Admission inflammatory markers are presented in Table 2. Treatments received during hospitalization according to the presence of delirium are displayed in Table 3. As shown, several treatments associated with severity of COVID-19 were significantly more frequent in patients with delirium. 50 patients died during hospitalization (15.0%) and they were excluded from the analysis of delirium as primary outcome. Decision to withdraw life sustaining therapies was applied in 22 non-delirium patients and 5 delirium patients (8.0 vs 8.6%, $p = 1$).

Table 1
Baseline clinical features

Characteristics	Total	Controls	Delirium
	n = 333	n = 275	n = 58
Age, <i>median(IQR)</i>	57.00 [45.00, 68.00]	56.00 [42.50, 66.00]	63.50 [57.00, 73.75]
Sex, male, <i>n(%)</i>	131 (39.3)	110 (40.0)	21 (36.2)
Obesity, <i>n(%)</i>	85 (25.5)	66 (20)	19 (32.8)
Healthcare worker, <i>n(%)</i>	17 (5.1)	15 (5.5)	2 (3.4)
Hypertension, <i>n(%)</i>	127 (38.1)	99 (36.0)	28 (48.3)
Diabetes Mellitus II, <i>n(%)</i>	65 (19.5)	43 (15.6)	22 (37.9)
Cognitive deficit/dementia, <i>n(%)</i>	6 (1.8)	4 (1.5)	2 (3.4)
Epilepsy, <i>n(%)</i>	4 (1.2)	3 (1.1)	1 (1.7)
Motor deficit, <i>n(%)</i>	3 (0.9)	2 (0.7)	1 (1.7)
mRs previous to disease, <i>n(%)</i>			
0	266 (79.9)	221 (80.4)	45 (8)
1	26 (7.8)	22 (8.0)	4 (6.9)
2	25 (7.5)	24 (8.7)	1 (1.7)
3	9 (2.7)	5 (1.8)	4 (6.9)
4	6 (1.8)	2 (0.7)	4 (6.9)
5	1 (0.3)	1 (0.4)	0 (0.0)
Upon admission:			
NEWS 2 score, <i>median (IQR)</i>	7.00 [4.00, 9.00]	7.00 [4.00, 9.00]	9.00 [7.25, 10.00]
Days since symptom onset, <i>median (IQR)</i>	7.00 [4.00, 8.00]	7.00 [4.00, 9.00]	7.00 [5.00, 7.00]
Muscle weakness, <i>n(%)</i>	84 (25.3)	60 (21.9)	24 (21)
Headache, <i>n(%)</i>	68 (20.4)	65 (23.6)	3 (5.2)
Hyposmia or anosmia, <i>n(%)</i>	31 (9.3)	29 (10.5)	2 (3.4)
Dysgeusia or ageusia, <i>n(%)</i>	34 (10.2)	31 (11.3)	3 (5.2)
Seizures, <i>n(%)</i>	2 (0.6)	1 (0.4)	1 (1.7)
Desorientation, <i>n(%)</i>	13 (3.9)	9 (3.3)	4 (6.9)

Characteristics	Total	Controls	Delirium
	n = 333	n = 275	n = 58
Glasgow Coma Scale < 14, <i>n</i> (%)	26 (7.8)	17 (6.2)	9 (15.5)
Any neurological symptom, <i>n</i> (%)	131 (39.3)	117 (42.5)	14 (20)

Table 2

Inflammatory markers at admission to hospital. N/L: Neutrophils/Lymphocytes. LDH: Lactate Dehydrogenase. ALT Alanine-transferase. PT: prothrombin time. IL-6 inter-leukine 6

Inflammatory markers	Controls	Delirium	p value
	n = 275	n = 58	
Platelet count, / μ l	240 000 [179 500, 300 000]	232 500 [171 500, 315 000]	0.984
MMean platelet volume, fl	10.10 [9.60, 10.80]	10.20 [9.50, 10.70]	0.867
Leucocyte count, / μ l	8 340 [5 730, 11 800]	8 975 [6 980, 14 195]	0.148
Neutrophil count, / μ l	6 150 [4 140, 9 580]	7 500 [5 350, 11 745]	0.012
Lymphocyte count, / μ l	1080 [790, 1575]	935 [700, 1265]	0.015
N/L index	5.71 [3.09, 11.01]	8.30 [5.24, 12.88]	0.002
C reactive protein, mg/dl	9.78 [3.81, 19.21]	15.62 [10.01, 27.13]	< 0.001
LDH, mg/dl	332.00 [242.00, 450.00]	473.00 [390.50, 588.00]	< 0.001
ALT, mg/dl	37.75 [21.12, 62.05]	33.50 [24.90, 55.90]	0.602
PT, s	13.10 [12.30, 14.20]	13.05 [12.10, 13.90]	0.432
Fibrinogen, mg/dl	539.00 [404.00, 655.00]	507.50 [421.75, 681.25]	0.862
D dimer, mg/dl	0.87 [0.51, 1.50]	1.28 [0.78, 2.59]	0.003
Ferritine, mg/dl	979.00 [484.00, 1806.00]	1177.00 [652.25, 1753.50]	0.19
IL-6,	27.05 [8.12, 86.45]	44.90 [11.20, 129.00]	0.284

Table 3

Treatments received during in-hospital stay, univariate analysis of its association with delirium. *: In the multivariate analysis, only mechanical ventilation remained significantly associated with delirium, and the regression model was consistently reduced to only mechanical ventilation, with an estimated OR: 11.72, (95%CI: 4.16–34.23). **: Calculated among intubated patients only (n of patients without delirium and mechanical ventilation)

Treatments	Delirium		p value
	No (n = 275)	Yes (n = 58)	
ICU admission, <i>n</i> (%)	163 (22)	54 (93.1)	< 0.001
Mechanical ventilation*, <i>n</i> (%)	78 (28.4)	48 (82.8)	< 0.001
Opioid administration, <i>n</i> (%)	79 (28.7)	48 (82.8)	< 0.001
Hypnotic administration, <i>n</i> (%)	80 (29.1)	48 (82.8)	< 0.001
Neuromuscular blocker, <i>n</i> (%)	78 (28.4)	48 (82.8)	< 0.001
Days of mechanical ventilation**, median [IQR]	9.00 [5.00, 13.75]	11.00 [7.00, 14.00]	0.091
Tracheostomy, <i>n</i> (%)	9 (11.5)	12 (25.0)	0.085
Shock, <i>n</i> (%)	74 (26.9)	41 (70.7)	< 0.001
Hydroxychloroquine, <i>n</i> (%)	41 (14.9)	9 (15.5)	1
Dexamethasone or Methylprednisolone, <i>n</i> (%)	213 (8)	53 (23)	0.026
Tocilizumab, <i>n</i> (%)	5 (1.8)	3 (5.2)	0.296
No-CPR order, <i>n</i> (%)	22 (8.0)	5 (8.6)	1

Delirium was detected in 58 (17.42%) patients (95% CI: 13.62% – 21.77%) and presented at a median of 16 (IQR: 11 – 20) days after symptom onset. Delirium occurred after mechanical ventilation in most patients (46/48 patients with MV). Among all the patients who exhibited delirium, 54 (93.1%) required management in the ICU. Reasons other than mechanical ventilation for ICU admission were low PaO₂/FiO₂ with signs of respiratory distress in five patients, and isolated shock in one patient. Patients with delirium were older, reported muscular weakness more often, had a higher NEWS2 score at admission, and had more comorbidities, with a higher prevalence of diabetes mellitus. Parkinson disease was present in two cases, both of which had delirium. Twenty-six patients presented with altered consciousness, as indicated by GCS < 14, and later had higher incidence of delirium (34.6%). Table 3 displays the results of multivariate analysis to identify clinical features upon admission that were associated with delirium; which main findings are the association of delirium with increasing age,

Diabetes Mellitus II, muscle pain or weakness, and COVID-19 severity as assessed by NEWS2 score. Multivariate analysis of hospitalization events and treatments was consistently reduced to a model that only included mechanical ventilation as a significant covariate (Table 4). The association between need for mechanical ventilation and delirium development was estimated at OR = 11.72, 95%CI = (4.16–34.23).

Table 4
Factors at admission associated with delirium, from multivariate analysis.

Variables	OR	95% CI
Age (per year)	1.03	1.01 ; 1.05
Sex, masculine	0.94	0.48 ; 1.79
Diabetes Mellitus II	2.47	1.24 ; 4.88
Any neurological symptom	0.47	0.23 ; 0.92
Muscle pain/weakness	2.02	1.05 ; 3.86
NEWS 2 score	1.21	1.09 ; 1.35

Delirium also affected outcomes in survivors (Table 5): patients who developed delirium had a higher frequency of functional impairment according to the mRs > 2 (70.7% vs 24.7%, $p < 0.001$) and had a prolonged ICU stay (median 13 days, IQR 8–21 vs median 5, IQR 3–10 days, $p < 0.0001$) and in-hospital stay (median 20 days, IQR 11–31 vs median 6, IQR 4–12 days, $p < 0.0001$) compared to patients without delirium.

Table 5. Comparison of the modified Rankin score before and after hospitalization for COVID-19 according to delirium status. Patients with and without delirium were not different in mRs scores at admission. Both groups of patients presented a deterioration of their functional status as evidenced by mRs change in each group after hospitalization (from Wilcoxon signed rank test), but delirium patients had a significantly worse functional outcome than controls (from Mann-Whitney-Wilcoxon test).

Modified Rankin scale score	At Hospital Admission				At Hospital Discharge			
	<u>Control, n = 275</u>		<u>Delirium, n = 58</u>		<u>Control, n = 236</u>		<u>Delirium, n = 47</u>	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
0	221	80.4	45	77.6	93	33.8	2	3.4
1	22	8	4	6.9	57	20.7	8	13.8
2	24	8.7	1	1.7	57	20.7	7	12.1
3	5	1.8	4	6.9	22	8	15	25.9
4	2	0.7	4	6.9	6	2.2	8	13.8
5	1	0.4	0	0	1	0.4	7	12.1
<i>p</i> = 0.45				<i>p</i> < 0.0001				
<i>p</i> < 0.0001				<i>p</i> < 0.0001				

Discussion

This study measured the incidence of delirium in hospitalized COVID-19 patients and explored associated risk factors. A considerable frequency of delirium (17.42%) was encountered and a significant association with patient severity, diabetes mellitus and -most notably- the need of mechanical ventilation was found. Mechanical ventilation appears to be the single most important precipitating factor for delirium development.

Previous studies that have measured delirium in COVID-19 have reported higher frequencies, mainly due to difference in patient selection (12, 24) since they included only ICU patients. Severity of COVID-19, evidenced by higher NEWS2 score and the need of ICU hospitalization, is associated to higher incidence of delirium, as reported before (24). In our patients, delirium was associated with older age, as described in previous studies in critically-ill patients, either with COVID-19 (25) or in other settings (26, 27).

Comorbidities have been reported as risk factor for delirium on previous COVID-19 series (27, 28) and in general ICU population (29, 30). In our cohort diabetes mellitus type 2 was the comorbidity with the strongest association to delirium. Other comorbidities such as obesity and arterial hypertension appeared to be associated to delirium in bivariate analysis but the trend was not maintained in multivariate analysis. Obesity, although slightly more frequent among delirium patients, was not associated to delirium either. Parkinson's disease was present in only two patients; both of them developed delirium during hospitalization. Other authors have reported delirium in patients with dementia (27, 28), in smokers (15) or in patients with a higher number of comorbidities (31). In our cohort only seven patients had a baseline cognitive deficit. Although most of them had severe disease, this condition was not associated with delirium.

Functional status before admission was poor in delirium patients, indicating a diminished physiological reserve to face the disease and the hospitalization. This decreased autonomy could be the result of a decreased cognitive status or a compromised physical capacity, both of which have been associated to delirium (25). Comorbidities and frailty are associated to the decrease in functional status, and they have recently been found to be associated with a higher incidence of delirium among elderly people suffering of COVID – 19 (25). We cannot be sure about the causes of decreased mRs in our series upon discharge and its association with delirium. Our delirium patients were older and had a higher incidence of arterial hypertension and diabetes mellitus type II, which are presumably associated with frailty and a decreased functionality (32, 33).

The association of neurological symptoms at admission and delirium has not been widely explored, Ticinesi reports an association of neuropsychiatric entities (dementia and epilepsy) with subsequent delirium (28). By contrast, we found a negative association between the presence of any neurologic symptom and the occurrence of delirium. This was particularly notable with headache at admission, which was more frequent in patients who did not develop delirium; and happened to a lesser extent with anosmia/hyposmia and dysgeusia, which were all less frequent among patients who developed delirium although no significant association was found on multivariate analysis. Interestingly, Amanat et al., in a series of 873 patients, found a high incidence of neurological manifestations both early and late in the course of disease; they report a negative association between headaches and severity of COVID-19 (34) in consonance with our finding.

Muscle weakness, by contrast, was strongly associated with a higher incidence of delirium. To our knowledge, this is the first report of such association. We speculate that muscle weakness is a sign of skeletal muscle impairment; This damage is shared by the respiratory muscles and ultimately leads to respiratory failure, later associated with need of mechanical ventilation, which, besides involving the use of opioids and hypnotics, increases the time and extent of physical dependence, routine disruption, and social isolation; all factors that increase the risk of delirium (35).

Delirium is thus more frequent among patients admitted to ICU that tend to accumulate most of the factors associated with this condition: most had mechanical ventilation and sedation for several days, and some developed shock or required tracheostomy. Mechanical ventilation as a marker of disease severity (hypoxia, inflammation, and organ failure) and a therapeutic maneuver linked to sedation, is accompanied by the greater disruption of social links, autonomy and circadian rhythm, all factors associated with delirium (35). In our series, mechanical ventilation was always accompanied by sedation based on a protocol of hypnosis with midazolam and analgesia with fentanyl, making it difficult to identify which one of these two drugs has a stronger association with delirium. The effects of these drugs are to be considered as part of the association between mechanical ventilation and delirium.

Our previous evaluation of delirium among ICU patients found a higher prevalence of delirium (29.7%) in a general population of critically ill patients with a variety of medical and surgical conditions that required ICU admission (36). That assessment included patients with a lesser severity of respiratory

failure and, perhaps, a minor inflammatory status, but the sedation used was deeper and longer than it is currently in use. Furthermore, our cohort of COVID-19 patients, also considered patients from the general ward and we used one test (CAM-ICU) applied by trained physicians to patients, when the medical staff suspected delirium. The incidence of delirium when considering only the sub-group with ICU admission was 24.9%; consistent with previously reported frequencies of delirium in ICU patients either during or before the COVID-19 pandemic (28, 36). We may have missed cases of delirium since patients underwent only one delirium assessment as part of the study and the diagnosis could be missed, although it is unlikely given that patients underwent daily routine assessments by study staff in ICU and general ward.

The severity of the SARS-CoV-2 infection has been linked to a significant inflammatory state, in the same way we found that higher serum levels of inflammatory markers such as lactic dehydrogenase, C-reactive protein, neutrophil/lymphocyte index and D dimer were associated to the development of delirium (Table 2). Other authors have linked the pathogenesis of delirium to the inflammatory state both in COVID-19 (13) and other forms of ICU admission (37).

D dimer is associated with intravascular coagulation and venous thromboembolism in COVID-19 (38) and other clinical situations (39) and it is considered a marker of disease severity (40). Our findings open the way to further study the role of micro-thrombosis in the pathogenesis of delirium, as proposed by MacLulich (37). On the other hand, it has been proposed that inflammatory mediators promote the activation of endothelial cells of the brain vasculature; consequently, they secrete soluble prostaglandins into the brain parenchyma leading to brain dysfunction activation of neural center by afferences of vagus nerve (37). Our data suggest that the presence of inflammatory mediators participates in the genesis of cognitive dysfunction in COVID – 19 patients.

Functionality of patients at discharge (mRS) was affected by delirium reflecting either the higher severity of disease or the impact of delirium in cognition and functionality after acute illness. As a consequence, less patients in the delirium group could be discharged home, and had to go to other hospices or rehabilitation units. This relationship has been already reported in COVID-19 patients (41) and has been previously recognized in other settings (35). The relationship between delirium and mortality could not be explored in this study since most deaths occurred in mechanically ventilated patients for whom delirium assessment would have occurred after extubation. Therefore, estimation of the association between death and delirium would be biased towards survival among delirium patients.

Our study has multiple strengths which comprise the inclusion of consecutive patients, high quality of the recorded data and the application of a standardized delirium assessment performed by trained physicians that employed the CAM-ICU criteria for diagnosis. It is to be noted that the study site was not overwhelmed by the influx of COVID-19 patients, and did not suffer from shortages of medications or protective equipment during the study period; an aspect to be considered for generalization of our results to other scenarios during this pandemic.

Conclusion

Delirium continues to be a common entity among critically ill patients and has been reported in a very high proportion of COVID-19 patients, suggesting that it is a characteristic of this disease. Our data show that premorbid functional status is determinant in the risk of delirium during hospitalization as well as the severity of respiratory dysfunction and the presence of inflammatory markers. Consequently, we believe that delirium might not be specifically related to SARS-CoV-2 infections, its high frequency during this pandemic could be the result of concurring factors shared between critically-ill patients and severe COVID-19 patients. The length of mechanical ventilation and hospitalization of COVID-19 patients appear to be contributing to a higher frequency of delirium. The perception of a higher incidence of delirium can be partly due to the accumulation of very severe patients in a short time period, the prolonged period of mechanical ventilation and sedation, and the difficulty to implement non-pharmacologic measures to prevent and to manage delirium in isolated patients. Special attention should be directed towards the known triggering factors of delirium to design management protocols that provide a comprehensive approach directed to the prevention of encephalopathy in COVID-19 patients during the pandemic.

Declarations

Competing interests: The authors declare not having competing interests related to this work.

Ethical Approval and Consent to participate

The study was granted approval by the Institutional Review Board/Ethics Committee (251-2020) previous to data collection. Patient data was encrypted to anonymize sensitive information.

Consent for publication: not applicable.

Funding: this work was funded by Fundación Valle del Lili.

Authors' contributions: All authors contributed to protocol design and manuscript writing; data gathering was performed by JM, LG, PA, JA, BM, GP, JR, DS, CR, NO, AS, JY and JJ. Data base design and maintenance was done by LG, Statistical analysis was performed by AG and GP

Availability of data and materials: The datasets during and/or analyzed during the current study available from the corresponding author on reasonable request.

Acknowledgements: to all the ICU and hospitalization staff devoted to Covid-19 care.

References

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The lancet*. 2020;395(10223):497-506.
2. Organization WH. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected: interim guidance, 13 March 2020. World Health Organization; 2020.

3. Desforges M, Le Coupanec A, Dubeau P, Bourgouin A, Lajoie L, Dubé M, et al. Human Coronaviruses and Other Respiratory Viruses: Underestimated Opportunistic Pathogens of the Central Nervous System? *Viruses*. 2020;12(1):14.
4. Li Y, Wang M, Zhou Y, Chang J, Xian Y, Mao L, et al. Acute Cerebrovascular Disease Following COVID-19: A Single Center, Retrospective, Observational Study. 2020.
5. Wu Y, Xu X, Chen Z, Duan J, Hashimoto K, Yang L, et al. Nervous system involvement after infection with COVID-19 and other coronaviruses. *Brain, Behavior, and Immunity*. 2020.
6. Doobay MF, Talman LS, Obr TD, Tian X, Davisson RL, Lazartigues E. Differential expression of neuronal ACE2 in transgenic mice with overexpression of the brain renin-angiotensin system. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*. 2007;292(1):R373-R81.
7. Giacomelli A, Pezzati L, Conti F, Bernacchia D, Siano M, Oreni L, et al. Self-reported <http://www.jimmunol.org/Downloaded from olfactory and taste disorders in SARS-CoV-2 patients: a cross-sectional study>. *Clin Infect Dis*. 2020.
8. Zubair AS, McAlpine LS, Gardin T, Farhadian S, Kuruvilla DE, Spudich S. Neuropathogenesis and neurologic manifestations of the coronaviruses in the age of coronavirus disease 2019: a review. *JAMA neurology*. 2020;77(8):1018-27.
9. Desforges M, Le Coupanec A, Brison É, Meessen-Pinard M, Talbot PJ. Neuroinvasive and neurotropic human respiratory coronaviruses: potential neurovirulent agents in humans. *Infectious Diseases and Nanomedicine I*. 2014:75-96.
10. Dantzer R. Neuroimmune interactions: from the brain to the immune system and vice versa. *Physiological reviews*. 2018;98(1):477-504.
11. Najjar S, Pahlajani S, De Sanctis V, Stern JN, Najjar A, Chong D. Neurovascular unit dysfunction and blood–brain barrier hyperpermeability contribute to schizophrenia neurobiology: a theoretical integration of clinical and experimental evidence. *Frontiers in psychiatry*. 2017;8:83.
12. Helms J, Kremer S, Merdji H, Clere-Jehl R, Schenck M, Kummerlen C, et al. Neurologic features in severe SARS-CoV-2 infection. *New England Journal of Medicine*. 2020;382(23):2268-70.
13. Najjar S, Najjar A, Chong DJ, Pramanik BK, Kirsch C, Kuzniecky RI, et al. Central nervous system complications associated with SARS-CoV-2 infection: integrative concepts of pathophysiology and case reports. *Journal of neuroinflammation*. 2020;17(1):1-14.
14. Slooter AJ, Otte WM, Devlin JW, Arora RC, Bleck TP, Claassen J, et al. Updated nomenclature of delirium and acute encephalopathy: statement of ten Societies. *Intensive care medicine*. 2020:1-3.

15. Girard TD, Thompson JL, Pandharipande PP, Brummel NE, Jackson JC, Patel MB, et al. Clinical phenotypes of delirium during critical illness and severity of subsequent long-term cognitive impairment: a prospective cohort study. *The Lancet Respiratory medicine*. 2018;6(3):213-22.
16. Organization WH. Clinical management of COVID-19: interim guidance, 27 May 2020. World Health Organization; 2020.
17. Ely EW, Margolin R, Francis J, May L, Truman B, Dittus R, et al. Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). *Critical care medicine*. 2001;29(7):1370-9.
18. Toro A, Escobar L, Franco JG, Díaz-Gómez J, Muñoz J, Molina F, et al. Versión en español del método para la evaluación de la confusión en cuidados intensivos, estudio piloto de validación. *Medicina intensiva*. 2010;34(1):14-21.
19. Bursac Z, Gauss CH, Williams DK, Hosmer DW. Purposeful selection of variables in logistic regression. *Source code for biology and medicine*. 2008;3(1):1-8.
20. Kissoon NR, Mandrekar JN, Fugate JE, Lanzino G, Wijedicks EF, Rabinstein AA. Positive fluid balance is associated with poor outcomes in subarachnoid hemorrhage. *Journal of Stroke and Cerebrovascular Diseases*. 2015;24(10):2245-51.
21. Zweifel C, Castellani G, Czosnyka M, Carrera E, Brady KM, Kirkpatrick PJ, et al. Continuous assessment of cerebral autoregulation with near-infrared spectroscopy in adults after subarachnoid hemorrhage. *Stroke*. 2010;41(9):1963-8.
22. Frontera JA, Claassen J, Schmidt JM, Wartenberg KE, Temes R, Connolly ES, et al. Prediction of symptomatic vasospasm after subarachnoid hemorrhage: the modified fisher scale. *Neurosurgery*. 2006;59(1):21-7.
23. Mostafa S, Bhandari S, Ritchie G, Gratton N, Wenstone R. Constipation and its implications in the critically ill patient. *British journal of anaesthesia*. 2003;91(6):815-9.
24. Khan SH, Lindroth H, Perkins AJ, Jamil Y, Wang S, Roberts S, et al. Delirium Incidence, Duration, and Severity in Critically Ill Patients With Coronavirus Disease 2019. *Critical care explorations*. 2020;2(12).
25. Emmerton D, Abdelhafiz A. Delirium in older people with COVID-19: Clinical scenario and literature review. *SN Comprehensive Clinical Medicine*. 2020:1-8.
26. O'keeffe S, Lavan J. Predicting delirium in elderly patients: development and validation of a risk-stratification model. *Age and Ageing*. 1996;25(4):317-21.
27. Garcez FB, Aliberti MJ, Poco PC, Hiratsuka M, Takahashi SdF, Coelho VA, et al. Delirium and adverse outcomes in hospitalized patients with COVID-19. *Journal of the American Geriatrics Society*.

2020;68(11):2440-6.

28. Ticinesi A, Cerundolo N, Parise A, Nouvenne A, Prati B, Guerra A, et al. Delirium in COVID-19: epidemiology and clinical correlations in a large group of patients admitted to an academic hospital. *Aging clinical and experimental research*. 2020;32(10):2159-66.
29. Dubois M-J, Bergeron N, Dumont M, Dial S, Skrobik Y. Delirium in an intensive care unit: a study of risk factors. *Intensive care medicine*. 2001;27(8):1297-304.
30. Ouimet S, Kavanagh BP, Gottfried SB, Skrobik Y. Incidence, risk factors and consequences of ICU delirium. *Intensive care medicine*. 2007;33(1):66-73.
31. Rebola P, Rozzini R, Bianchetti A, Blangiardo P, Marchegiani A, Piazzoli A, et al. Delirium in patients with SARS-CoV-2 infection: a multicenter study. *Journal of the American Geriatrics Society*. 2021;69(2):293-9.
32. Bushnell CD, Lee J, Duncan PW, Newby LK, Goldstein LB. Impact of comorbidities on ischemic stroke outcomes in women. *Stroke*. 2008;39(7):2138-40.
33. Hartley P, Adamson J, Cunningham C, Embleton G, Romero-Ortuno R. Clinical frailty and functional trajectories in hospitalized older adults: a retrospective observational study. *Geriatrics & gerontology international*. 2017;17(7):1063-8.
34. Amanat M, Rezaei N, Roozbeh M, Shojaei M, Tafakhori A, Zoghi A, et al. Neurological manifestations as the predictors of severity and mortality in hospitalized individuals with COVID-19: a multicenter prospective clinical study. *BMC neurology*. 2021;21(1):1-12.
35. Maldonado JR. Delirium pathophysiology: An updated hypothesis of the etiology of acute brain failure. *International journal of geriatric psychiatry*. 2018;33(11):1428-57.
36. Rincon HG, Granados M, Unutzer J, Gomez M, Duran R, Badiel M, et al. Prevalence, detection and treatment of anxiety, depression, and delirium in the adult critical care unit. *Psychosomatics*. 2001;42(5):391-6.
37. MacLulich AM, Ferguson KJ, Miller T, de Rooij SE, Cunningham C. Unravelling the pathophysiology of delirium: a focus on the role of aberrant stress responses. *Journal of psychosomatic research*. 2008;65(3):229-38.
38. Nauka PC, Baron SW, Assa A, Mohrmann L, Jindal S, Oran E, et al. Utility of D-dimer in predicting venous thromboembolism in non-mechanically ventilated COVID-19 survivors. *Thrombosis research*. 2021;199:82-4.
39. Ordieres-Ortega L, Demelo-Rodríguez P, Galeano-Valle F, Kremers B, Ten Cate-Hoek A, Ten Cate H. Predictive value of D-dimer testing for the diagnosis of venous thrombosis in unusual locations: a

systematic review. Thrombosis research. 2020;189:5-12.

40. Nickel CH, Kellett J, Cooksley T, Lyngholm LE, Chang S, Imfeld S, et al. The diagnoses and outcomes of emergency patients with an elevated D-dimer over the next 90 days. The American Journal of Medicine. 2021;134(2):260-6. e2.

41. Jaywant A, Vanderlind WM, Alexopoulos GS, Fridman CB, Perlis RH, Gunning FM. Frequency and profile of objective cognitive deficits in hospitalized patients recovering from COVID-19. Neuropsychopharmacology. 2021:1-6.

Figures

Figure 1

mRs score at discharge among patients with ICU admission according to presence of delirium. We excluded patients with mRs 6, since most of them were not assessed for delirium.