Delirium in Patients with Severe COVID-19: Preliminary Results of the MAPA Longitudinal Study

Delirium em Doentes com COVID-19 Grave: Resultados Preliminares do Estudo Longitudinal MAPA

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Palavras-chave: COVID-19; Delírio; Fatores de Risco; Neuropsiquiatria; Qualidade de Vida

Dear Editor,

We have read a letter published in Acta Médica Portuguesa[1] about delirium in older patients with COVID-19, emphasizing the importance of early detection and therapeutic intervention, in the light of the associated adverse outcomes. Regarding severe COVID-19, the literature indicates that around 65% of patients develop delirium.[2] Several reasons that justify such a high risk have been identified, including direct central nervous system invasion and the effect of sedation or prolonged invasive mechanical ventilation (IMV).[3] However, there are still limited data available on the post-discharge clinical picture of these patients.

We hereby present preliminary data of a longitudinal study focused on predictors and outcomes associated with delirium in patients with severe COVID-19, and which are part of a larger ongoing project: MAPA-Mental health in critically ill patients with COVID-19.

COVID-19 survivors admitted between March and May 2020 (first wave) to the Intensive Care Medicine Department of Centro Hospitalar Universitário São João, were included. Participants were evaluated by telephone in follow-up appointments (median = 106 days), for cognition, depressive and anxiety symptoms, as well as health-related quality of life. Sociodemographic and clinical data (including delirium assessed through clinical observation) were obtained from the hospital's electronic health records and clinical interview.

The sample included 59 patients. None had previous history of cognitive impairment or dementia. Delirium was registered in 49.2% patients, who were significantly older, were more likely to have nosocomial infection, had difficult weaning from IMV, were more likely to have been deeply sedated (propofol, fentanyl and/or midazolam) and require IMV. They also stayed longer in the hospital and after discharge were more likely to report impairments in terms of mobility, self-care and everyday activities (Table 1). Variables that showed statistically significant associations with delirium in the bivariate analyses (age, nosocomial infection, difficult weaning from IMV and deep sedation), or those which are reported in the literature as risk factors for delirium (namely, comorbidities), were selected to enter the logistic regression analysis. In the final model, only age was predictive of an increased risk of delirium (OR = 1.063, 95% CI: 1.006 - 1.125, p = 0.013), while comorbidities (OR = 0.819, 95% CI: 0.600 - 1.117, p = 0.207), nosocomial infection (OR = 1.614, 95% CI: 0.223 - 11.661, p = 0.635), difficult weaning from IMV (OR = 1.313, 95% CI: 0.318 - 5.416, p = 0.706) and deep sedation (OR = 3.561, 95% CI: 0.397 - 31.948, p = 0.257) did not increase the likelihood of developing delirium.

These findings are not only in line with results from previous studies conducted with critically ill non-COVID patients,[4] but also with earlier research on COVID-19,[5] specially concerning the association of delirium with advanced age. We also provide data on health-related effects of severe COVID-19, showing significant differences among those who have also developed delirium.

Through this preliminary analysis, we expect to contribute to the growing understanding of delirium in patients with COVID-19, highlighting distinctive factors and implications for health that are associated with delirium. Such features should draw our attention towards identifying high-risk patients who should be targeted for early routine screening and preventive interventions during hospitalization, and encourage the implementation of follow-up approaches, in order to minimize the associated adverse consequences.

AUTHORS CONTRIBUTION

SM: 1) Contribution to the conception/design of the work, acquisition and analysis of data; 2) Drafting the work and revising it critically for important intellectual content; 3) Final approval of the version to be published and 4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

ARF: 1) Contribution to the conception/design of the work and analysis of data; 2) Drafting the work and revising it critically for important intellectual content; 3) Final approval of the version to be published and 4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

JF, TV, LFontes, IC: 1) Contribution to the acquisition and analysis of data; 2) Revising it critically for important intellectual content; 3) Final approval of the version to be published and 4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

JAP, LFernandes: 1) Contribution to the conception/design of the work and analysis of data; 2) Revising it critically for important intellectual content; 3) Final approval of the version to be published and 4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki

Table 1 – Sample characteristics and bivariate analysis

Baseline characteristics	Overall (n = 59)	Delirium (n = 29)	No delirium (n = 30)	*p*-value
Age (years), median (min. - max.)	65 (24 - 81)	72 (30 - 80)	62 (24 - 81)	**0.010**(1)
Male, n (%)	39 (66.1)	18 (62.1)	21 (70.0)	0.520(2)
Education (years), median (min. - max.)	6 (2 - 19)	4 (2 - 19)	6.5 (2 - 17)	0.357(1)
Married, n (%)	37 (62.7)	17 (58.6)	20 (66.7)	0.295(3)
Past psychiatric history, n (%)	25 (42.4)	11 (37.9)	14 (46.7)	0.497(2)
Total number of comorbidities, median (min. - max.)	4 (0 - 11)	4 (0 - 7)	4 (0 - 11)	0.975(1)
Medication (daily), median (min. - max.)	4 (0 - 16)	4 (0 - 11)	4 (0 - 16)	0.771(1)
Hospital clinical data				
Acute illness severity, median (min. - max.)				
APACHE-II score	16 (5 - 36)	17 (6 - 36)	15 (5 - 34)	0.188(1)
SAPS-II score	35 (7 - 77)	41 (10 - 75)	33 (7 - 77)	0.414(1)
Nosocomial infection, n (%)	40 (67.8)	24 (82.8)	16 (53.3)	**0.016**(2)
Difficult weaning from IMV, n (%)	28 (47.5)	18 (62.1)	10 (33.3)	**0.027**(2)
Deep sedation, n (%)	44 (75.0)	26 (89.7)	18 (60.0)	**0.009**(2)
Invasive mechanical ventilation, n (%)	44 (75.0)	26 (89.7)	18 (60.0)	**0.009**(2)
Post-hospital discharge				
Hospital LoS, median (min. - max.)	48 (9 - 255)	67 (13 - 55)	36.5 (9 - 156)	**0.014**(1)
Cognitive impairment (6CIT), n (%)	10 (16.9)	5 (17.2)	5 (16.7)	1.000(4)
Depression (PHQ-9), n (%)	17 (28.8)	7 (24.1)	10 (33.3)	0.436(2)
Anxiety (GAD-7), n (%)	14 (23.7)	4 (13.8)	10 (33.3)	0.078(2)
Health-related quality of life (EQ-5D-5L), n (%) (problems in the following domains)				
Mobility	37 (62.7)	22 (75.9)	15 (50.0)	**0.044**(2)
Self-care	17 (28.8)	14 (48.3)	3 (10.0)	**0.001**(2)
Everyday activities	39 (66.1)	23 (79.3)	16 (53.3)	**0.035**(2)
Pain/discomfort	41 (69.5)	21 (72.4)	20 (66.7)	0.632(2)
Depression/anxiety	35 (59.3)	18 (62.1)	17 (56.7)	0.673(2)

min.- max.: minimum - maximum; APACHE-II: Acute Physiology and Chronic Health Evaluation II; SAPS-II: The Simplified Acute Physiology score; IMV: invasive mechanical ventilation; LoS: length of stay; 6CIT: Six-item Cognitive Impairment test; PHQ-9: Patient Health Questionnaire; GAD-7: General Anxiety Disorder scale: EQ-5D-5L: EuroQol 5-Dimension 5-Level questionnaire; **(1)**: Mann-Whitney test; **(2)**: Chi-square independent test; **(3)**: Chi-square's exact test; **(4)**: Fisher's exact test

Declaration of the World Medical Association updated in 2013. This project was approved by the Ethics Committee for Health of the CHUSJ/FMUP (Ref. nº 218/2020, 05/06/20 – CES, CHUSJ/FMUP).

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

The authors have declared that no competing interests exist. Exploratory results have been presented as poster presentation at the 34th European College of Neuropsychopharmacology (ECNP) Congress Hybrid, 5 Oct 2021.

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