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Cognitive Reserve and Cluster Analysis: New Pieces in the Puzzle of Cognitive Impairment after ICU?

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To the Editor:

Critically ill patients, especially those who develop delirium or require invasive mechanical ventilation (IMV) during hospital admission, are prone to develop long-term cognitive sequelae (1). Ventilator-associated brain injury is a new research priority (2), and the question of cognitive dysfunction in ICU patients has been debated at length by experts from the NIH. Palakshappa and colleagues (3) identified major gaps in the current knowledge of the factors underlying brain dysfunction in patients with acute respiratory distress syndrome, stressing that aspects such as the implementation of assessment measures of its real-life impact on patients and the development of innovative statistical analyses should be included in the scientific agenda.

Cognitive reserve, that is, the brain's ability to maintain normal cognitive function despite the presence of brain pathology or injury, has emerged as a potential protective factor for brain dysfunction in several clinical populations (4) and has recently been associated with better cognitive performance in both the short and the long term after ICU discharge (5–8). However, the impact of cognitive reserve on long-term cognitive outcomes has not been studied using innovative statistical approaches. As critically ill patients present a particularly heterogeneous profile, unsupervised machine learning methods that

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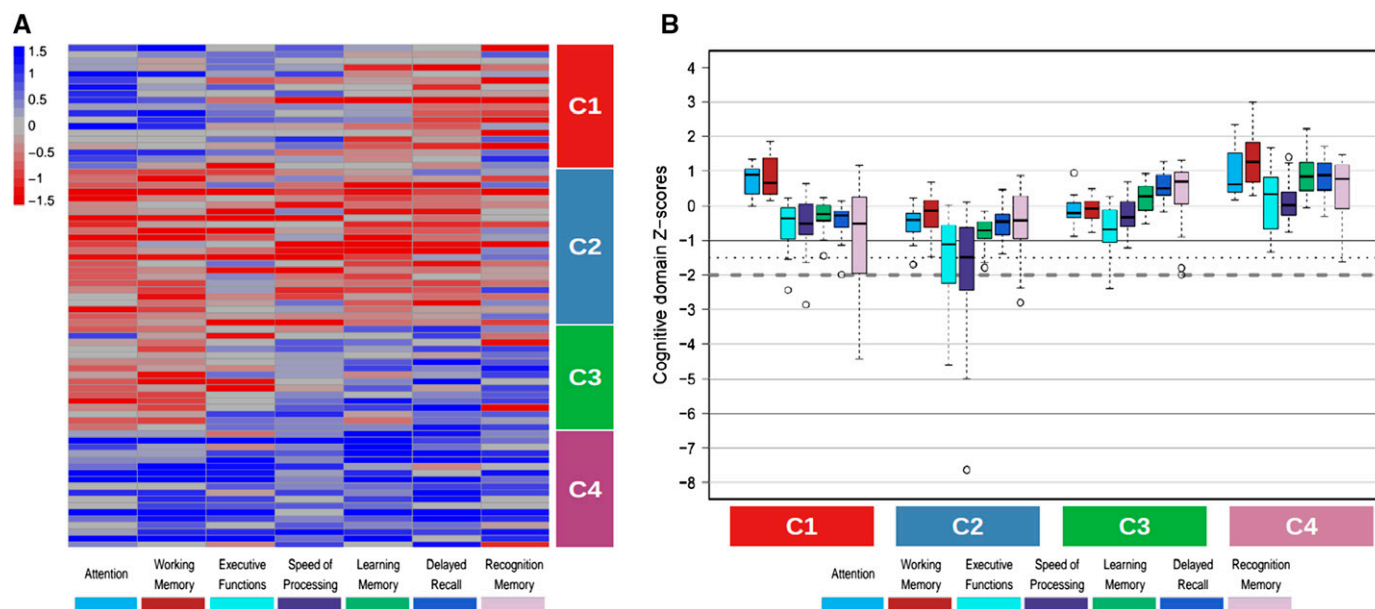


Figure 1. Cluster analysis on cognitive domain scores and derived cognitive patterns. (A) Heatmap showing the results of the clustering analysis conducted on 77 critically ill patients with coronavirus disease (COVID-19) according to their post-ICU cognitive performance. Heatmap cells represent standardized (centered and scaled) values of cognitive domain scores, where red indicates high, blue represents low, and color intensity expresses more extreme values (see legend). Color intensities were saturated approximately to the 5th and 95th percentiles of the overall value distribution. Clusters of patients and variables were derived from a procedure that consisted in three steps: 1) estimation of pairwise patients' dissimilarities by unsupervised random forest; 2) application of Kruskal's nonmetric multidimensional scaling to the resulting dissimilarity matrix; and 3) analysis of the components derived from Kruskal's nonmetric multidimensional scaling using the Mclust algorithm. This clustering procedure was conducted on the cognitive domain indices. No demographic or clinical variables were included in the clustering algorithm. (B) Boxplots showing the cognitive domain profiles in each of the clusters. The dotted line indicates the score for moderate impairment. The dashed line indicates the score for severe impairment.

allow patient clustering according to their long-term phenotype may help improve the conventional classification of cognitive impairment in ICU survivors (5).

In this study, we aimed to explore the role of cognitive reserve in a cohort of ICU survivors with coronavirus disease (COVID-19) who were classified by cluster analysis according to their cognitive performance one year after ICU discharge.

Some of the results of these studies have been previously reported in abstract form (9, 10).

Methods

A cross-sectional observational study was proposed to explore the role of cognitive reserve in long-term cognitive outcomes in a cohort of ICU survivors with COVID-19 recruited between March 2020 and January 2021 (review board reference 2020/577; ClinicalTrials.gov identifier NCT 04422444). Patients ≥ 18 years of age with diagnoses of COVID-19 who were admitted to the ICU for ≥ 24 hours with or without IMV and who provided written informed consent were included. Exclusion criteria were previous neurological disease, history of severe psychiatric disorder, preexisting cognitive impairment or dementia, substance or alcohol abuse, intelligence quotient ≤ 70 , inability to speak or understand Spanish, and refusal to participate. Demographic and clinical data were collected retrospectively by reviewing medical records. The presence of delirium was estimated on the basis of three criteria: a medical report of delirium, the presence of an episode of agitation, and/or prescription of antipsychotic and/or neuroleptic treatment during admission. Disease severity was measured using the Acute Physiology and Chronic Health Evaluation II and

degree of comorbidity using the Charlson Comorbidity Index.

Cognitive reserve was assessed after ICU discharge using the Cognitive Reserve Questionnaire (range, 0–25) (11). One year after ICU discharge, two trained neuropsychologists also assessed long-term cognitive state administering a comprehensive neuropsychological battery (Digit Span Forward and Backward and Spatial Score Forward and Backward from the Wechsler Adult Intelligence Scale, third edition, Rey Auditory Verbal Learning Test, 10/36 Spatial Recall Test, Stroop Color and Word Test, Trail Making Test, and phonetic verbal fluency). Raw scores were transformed into z-scores (mean, 0; SD, ± 1) using the normative population data provided for each cognitive test, correcting the effects of age and education. Seven cognitive indexes were calculated: attention, working memory, learning memory, delayed recall, memory recognition, processing speed, and executive functions (6).

A clustering procedure based on well-established statistical and machine learning methods (12) was conducted on cognitive domain indices to classify patients according to their cognitive performance 12 months after ICU discharge. No demographic or clinical variables were included in the clustering algorithm. Associations between the derived patient clusters and clinical and demographic variables were assessed using nonparametric methods (Fisher exact test, Kruskal-Wallis test, and Mann-Whitney *U* test).

Results

Among a cohort of 150 ICU survivors with COVID-19 (8), 77 were analyzed (median age, 60.44 yr [range, 33.13–79.59 yr]; 29.9%

Table 1. Differences in Sociodemographic and Clinical Characteristics among the Cognitive Clusters

	All Patients (n = 77 [100.0%])	C1 (n = 19 [24.7%])	C2 (n = 24 [31.2%])	C3 (n = 16 [20.8%])	C4 (n = 18 [23.4%])	P Value
Age ^{*†‡}	60.4 (33.1–79.6)	67.8 (43.0–80.0)	61.0 (37.1–76.0)	52.5 (33.1–74.7)	64.3 (46.7–70.7)	0.0186
Female sex	23 (29.9)	6 (31.6)	9 (37.5)	6 (37.5)	2 (11.1)	0.2130
Cognitive Reserve Questionnaire raw score ^{‡§}	11 (0–21)	14 (0–21)	9 (2–17)	12 (4–19)	12.5 (6–21)	0.0270
CCI ^{*†‡}	2 (0–5)	3 (0–5)	2 (0–5)	1 (0–4)	2 (0–4)	0.0099
APACHE II score	8 (2–3)	10 (3–32)	8.5 (2–20)	6.5 (2–18)	8 (3–14)	0.1697
Need for IMV	47 (61.0)	12 (63.2)	14 (58.3)	10 (62.5)	11 (61.1)	>0.9999
Length of IMV						
No IMV	30 (39.0)	7 (36.8)	10 (41.7)	6 (37.5)	7 (38.9)	0.9960
1–15 d	22 (28.6)	5 (26.3)	6 (25.0)	5 (31.2)	6 (33.3)	
>15 d	25 (32.5)	7 (36.8)	8 (33.3)	5 (31.2)	5 (27.8)	
Length of ICU stay, d	11 (2–74)	9 (2–49)	12 (3–57)	13 (4–74)	8 (3–65)	0.7567
Presence of delirium during ICU stay	32 (41.6)	6 (31.6)	13 (54.2)	7 (43.8)	6 (33.3)	0.4204

Definition of abbreviations: APACHE II = Acute Physiology and Chronic Health Evaluation II; CCI = Charlson Comorbidity Index; IMV = invasive mechanical ventilation.

Cells show medians and ranges (continuous variables) and absolute frequencies and percentages (categorical variables) within each cluster and in the overall series. Statistical significance was assessed using the Kruskal-Wallis (continuous) or Fisher test for contingency tables (categorical variables).

*Significant difference between C1 and C3.

†Significant difference between C2 and C3.

‡Significant difference between C3 and C4.

§Significant difference between C1 and C2.

||Significant difference between C2 and C4.

¶Significant difference between C1 and C4.

women; and 61.04% receiving IMV). The cluster analysis classified patients into four groups: C1, C2, C3, and C4 (Figure 1A).

Cognitive reserve was significantly higher in C1, C3, and C4 than in C2. C2 included patients with greater impairments than C1, C3, or C4 in nearly all the cognitive domains, with particularly pronounced deficits in processing speed and executive functions (Figure 1B). In contrast, C3 and C4 presented the most preserved cognitive profile. C3 patients were younger and had fewer comorbidities than their C1, C2, and C4 counterparts. No significant differences in age and degree of comorbidity were found among C1, C2, and C4, although higher disease severity was observed in C1. No differences between clusters were found in sex, days of ICU stay, need for IMV, and presence of delirium (Table 1).

Discussion

Cognitive reserve has a positive impact on long-term cognitive performance in ICU survivors with COVID-19, including those who are inherently vulnerable. Higher cognitive reserve appears to mitigate cognitive alterations compatible with frontal-subcortical dysfunction in critically ill patients with COVID-19, offering a protective effect against long-term cognitive decline, even in older patients with multiple comorbidities (Charlson Comorbidity Index ≥ 3) and more severe illness. Our results support the scientific findings recorded to date suggesting a relationship between a higher degree of cognitive reserve and improved cognitive and functional status in survivors of critical illness due either to COVID-19 or to other pathologies (5–8). In addition, these findings expand our knowledge of the possible impact of cognitive reserve on subgroups of ICU survivors with increased vulnerability to long-term cognitive impairment.

A key limitation of this study is the lack of standardized clinical tools (e.g., Confusion Assessment Method for the ICU) for detecting

delirium. Further research exploring cognitive reserve in specific ICU populations (e.g., sepsis, acute respiratory distress syndrome) could advance the detection of critically ill patients at increased risk of developing post-ICU cognitive dysfunction while also leading to a better understanding of patient needs during the course of their ICU journeys. Cognitive reserve is built on factors such as education, occupational complexity, social engagement, and leisure activities, and as such it can be considered a neuropsychological construct with a real impact on patients' daily lives. Thus, this more comprehensive approach to long-term cognitive impairment, together with the use of innovative statistical analyses, may not only broaden our knowledge of the pathophysiological mechanisms underlying post-ICU cognitive impairment but also help identify new preventive and therapeutic targets for enhancing cognitive reserve in these patients, such as lifelong learning, social interaction, and cognitive stimulation. ■

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Anandamide Is a Potential Blood Biomarker of Hermansky-Pudlak Syndrome Pulmonary Fibrosis

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To the Editor:

Hermansky-Pudlak syndrome (HPS) is a rare disorder caused by biallelic mutations in 1 of 11 genes; 3 of the genetic subtypes lead to fatal adult-onset pulmonary fibrosis (PF) with no effective treatment (1). HPS-1 is the most common and severe form, with universal development of progressive PF by middle age (2, 3). PF in HPS-1 advances rapidly, with end-stage disease occurring approximately 3 years after clinical diagnosis (4). Although the development of PF is inevitable in patients with HPS-1, there are individual differences in the age of onset and the rate of disease progression. This variability underscores the need for blood biomarkers capable of detecting subclinical PF and predicting the onset of clinical disease. Such biomarkers are crucial for identifying patients at risk of disease progression. They could be instrumental in facilitating early therapeutic interventions, potentially delaying or even preventing the onset of PF in HPS.

The endocannabinoids anandamide (AEA) and 2-arachidonoylglycerol are synthesized and used on demand by multiple cell types in tissues and blood to modulate the cannabinoid receptors that serve autocrine or paracrine functions. Endocannabinoids act through cannabinoid receptor 1 (CB₁R) and promote fibrosis in various peripheral organs, including the lung. Consequently, peripheral CB₁R antagonism has emerged as a

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