



SCIENTIFIC LETTER

Changes in the stress hormone cortisol during intensive care unit stay as a predictor of objective cognition at discharge



Cambios en la hormona del estrés cortisol durante la estancia en la unidad de cuidados intensivos como predictor de la cognición objetiva al alta

Dysregulation of the hypothalamic–pituitary–adrenal axis is a well-documented phenomenon in critically ill patients, and cortisol, its end product, plays a crucial role in the physiological response to stress.¹ Experiencing critical illness requiring admission to an intensive care unit (ICU) can be a stressful, even traumatic, experience, especially for patients requiring invasive mechanical ventilation (IMV).² Brain dysfunction is also common during and after ICU stay,³ but its biological mechanisms remain unclear. A recent study identified that systemic inflammation and endogenous anticoagulant activity are associated with delirium in critically ill patients.⁴ However, this study did not measure the stress hormone cortisol, which previous research has shown to be associated with brain dysfunction.¹ Importantly, cortisol has already been observed to be higher in critically ill patients who develop delirium, regardless of inflammatory status, but no relationship with subjective cognition has been found.⁵ To date, no study has specifically explored the relationship between cortisol and objective cognition (OC) in critically ill patients. A prospective observational pilot study was conducted to explore whether cortisol, measured in hair (cumulative pre-ICU stress) and blood (acute ICU stress), and OC are related in ICU survivors.

Between November 2018 and February 2020, a convenience sample of 26 adult patients with >24 h of IMV in a medical-surgical ICU was recruited. Patients with a history of neuropsychiatric disease, including previous cognitive impairment, or with severe alopecia were excluded. Written

informed consent was obtained from all patients or from an authorized surrogate, such as a family member. If consent was initially obtained from an authorized surrogate, for example in the case of a deeply sedated or delirious patient, we ratified the patients' consent once they were mentally competent, defined by having a normal mental status and being free of delirium according to the Richmond Agitation-Sedation Scale (RASS=0)⁶ and the Confusion Assessment Method for the ICU-7 (CAM-ICU-7 ≤ 2).⁷ Patients whose authorized surrogates refused to participate, those who did not sign the informed consent, or those who refused to participate despite prior consent from their authorized surrogates were also excluded. Cortisol was determined in a hair sample (pre-ICU cumulative stress) and in a blood sample (basal acute ICU stress), obtained 24–48 h after ICU admission. Cortisol was also measured in a second blood sample obtained at ICU discharge to analyze the rate of change of acute stress during their ICU stay according to the formula: (basal blood cortisol–blood cortisol at discharge)/basal blood cortisol. OC was assessed with the Montreal Cognitive Assessment (MoCA) test at discharge if the patient was mentally competent, defined as RASS=0 and CAM-ICU-7 ≤ 2.⁸ The association between the different cortisol measures and OC at discharge was analyzed by age-adjusted partial correlations and linear regressions. Ethical approval was obtained from the local ethics committee (2018/542) and the study was registered at clinicaltrials.gov (NCT03736135).

Of the 26 patients included, four (15.38%) died during their ICU stay and three (11.54%) were unable to complete the MoCA test due to altered mental status (RASS ≠ 0) or delirium (CAM-ICU-7 > 2). Data from 19 (73.08%) patients were analyzed. One (5.26%) patient received corticosteroid treatment during their ICU stay and 15 (78.95%) had altered OC at discharge (MoCA score < 26 points) (Table 1). The rate of change of blood cortisol during ICU stay proved to be the only significant predictor of MoCA performance at discharge, as shown by both age-adjusted partial correlations ($r = -0.530$, $p = 0.024$) and linear regression analyses ($B = -1.638$, $p = 0.024$). No significant associations were observed between hair cortisol or blood cortisol, whether measured at admission or discharge, and MoCA scores at discharge (Tables S1–S5, Supplementary material). Given the potential impact of corticosteroid treatment on cortisol level and adrenal function,¹ the

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Table 1 Patient characteristics (n = 19).

Median (range) is reported unless otherwise specified	
Sociodemographic data	
Female sex, n (%)	4 (21.05)
Age, years	64.16 (21.88–75.22)
Education, years	10 (0–17)
Clinical data	
Diagnosis at ICU admission, n (%)	
Septic shock	8 (42.11)
Pneumonia	3 (15.79)
Intestinal perforation	3 (15.79)
Multiple trauma	3 (15.79)
Asthmatic crisis	1 (5.26)
Hemorrhagic shock	1 (5.26)
CCI at ICU admission	4 (0–8)
APACHE II at ICU admission	20 (11–29)
Days on IMV	5 (1–24)
Delirium during ICU stay, n (%)	7 (36.84)
Corticosteroid treatment, n (%)	1 (5.26)
Length of ICU stay, days	9 (2–30)
Length of hospital stay (including ICU stay), days	26 (7–174)
Stress hormone response	
Hair cortisol (cumulative pre-ICU stress), pg/mg (n = 17)	142.92 (10.67–899.51)
Blood cortisol at ICU admission (basal acute stress), mcg/dL	14.2 (0.69–86)
Blood cortisol at ICU discharge, mcg/dL	15.4 (2.24–46.2)
Rate of cortisol (or acute stress) change during ICU stay ^a	0.09 (–0.92 to 10.81)
Objective cognition (OC) at ICU discharge	
MoCA total score	19 (8–29)
MoCA score <26 points (OC impairment), n (%)	15 (78.95)

APACHE-II, Acute Physiology and Chronic Health Evaluation II; CCI, Charlson Comorbidity Index; ICU, intensive care unit; IMV, invasive mechanical ventilation; MoCA, Montreal Cognitive Assessment; OC, objective cognition.

^a Calculated according to the formula: (basal blood cortisol–blood cortisol at discharge)/basal blood cortisol.

analyses were repeated after excluding the patient receiving corticosteroid treatment during their ICU stay. The results remained consistent (Tables S6–S10, [Supplementary material](#)), further reinforcing the robustness of the findings.

This study explored the relationship between cortisol and OC in survivors of critical illness requiring IMV. The results show that a reduction in the blood level of cortisol, the stress hormone, during the ICU stay was associated with better OC at discharge, highlighting the role of cortisol dynamics on cognitive outcomes in ICU survivors. This finding complements previous research that identified that systemic inflammation and endogenous anticoagulant activity during ICU stay are associated with brain dysfunction, primarily delirium, in critically ill patients.⁴ It also complements other research that has shown that elevated cortisol levels during ICU stay is associated with delirium, independent of inflam-

matory status, but not with subjective cognition.⁵ In the present study, the rate of change of blood cortisol during ICU stay proved to be the only biological measure significantly associated with OC at discharge. This is a novel contribution, as previous investigations had mainly focused on delirium or subjective cognition, and not on OC.^{4,5} Importantly, no significant associations were observed between hair cortisol (reflecting cumulative pre-ICU stress) or blood cortisol measured at admission or discharge (reflecting acute ICU stress) and OC. These results suggest that it is the rate of change in blood cortisol (or cortisol dynamics) during the ICU stay that may have a more immediate and influential impact on OC at discharge, rather than prior chronic stress (or hair cortisol) or isolated measures of acute stress (or blood cortisol) taken at ICU admission or discharge. The main limitation of the study is the small sample size, which may affect the generalizability of the results. Although the analyses were adjusted for age –a key predictor of OC– other important factors, such as medical comorbidities, illness severity, duration of IMV, duration of delirium, and analgo-sedation, among others, could not be taken into account,³ as the limited sample size restricted the number of independent variables that could be included in the models to no more than two. In addition, the use of the MoCA test, while valuable, has inherent limitations, as it is primarily a screening tool and may not fully capture the breadth or depth of OC impairment.⁸

In conclusion, this pilot study highlights the potential of cortisol dynamics during ICU stay as a biomarker to stratify the risk of OC deterioration in survivors of critical illness requiring IMV. A decrease in blood cortisol level during ICU stay could indicate a lower risk of OC deterioration at discharge, whereas an increase could signal a higher risk. This finding also suggests the potential for targeted interventions, such as pharmacological modulation of the hypothalamic–pituitary–adrenal axis, to mitigate the impact of critical illness on brain function. Larger, well-powered studies controlling for more demographic and clinical variables are needed to validate these results and explore additional therapeutic strategies, such as early cognitive stimulation and stress reduction techniques, to reduce brain dysfunction during and after ICU stay.^{9,10}

CRedit authorship contribution statement

Conceptualization: L.B., J.L.A., S.F.G.; Data curation: G.N.V., S.F.G.; Formal analysis: G.N.V., J.L.A., S.F.G.; Funding acquisition: S.F.G.; Investigation: G.N.V., M.G.G., S.F.G.; Methodology: G.N.V., J.L.A., S.F.G.; Project administration: S.F.G.; Resources: L.B., J.L.A., S.F.G.; Supervision: S.F.G.; Validation: G.N.V., J.L.A., S.F.G.; Visualization: G.N.V., M.G.G.; Writing – original draft: G.N.V.; and Writing – review & editing: G.N.V., M.G.G., L.B., J.L.A., S.F.G.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimen-

tation and with the Declaration of Helsinki of 1964 and its subsequent revisions.

Declaration of Generative AI and AI-assisted technologies in the writing process

No form of Generative AI or AI-assisted technologies were used in the conduct of the study or in the production of the text.

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Declaration of competing interest

The authors declare that they have no conflict of interest.

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Declaration of competing interest

The authors declare that they have no conflict of interest.

Data availability

The data sets used and/or analyzed during the present study are available to the corresponding author, M.G.G. (mrgodoy@tauli.cat), upon reasonable request.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.medine.2025.502166>.

References

1. Cuesta JM, Singer M. The stress response and critical illness: a review. *Crit Care Med*. 2012;40:3283–9, <http://dx.doi.org/10.1097/CCM.0b013e31826567eb>.
2. Navarra-Ventura G, Godoy-González M, Gomà G, Jodar M, Sarlabous L, Santos-Pulpón V, et al. Occurrence, co-occurrence and persistence of symptoms of depression and post-traumatic stress disorder in survivors of COVID-19 critical illness. *Eur J Psychotraumatol*. 2024;15:2363654, <http://dx.doi.org/10.1080/2008066.2024.2363654>.
3. Ramnarain D, Pouwels S, Fernández-Gonzalo S, Navarra-Ventura G, Balanzá-Martínez V. Delirium-related psychiatric and neurocognitive impairment and the association with post-intensive care syndrome—a narrative review. *Acta Psychiatr Scand*. 2023;147:460–74, <http://dx.doi.org/10.1111/acps.13534>.
4. Brummel NE, Hughes CG, McNeil JB, Pandharipande PP, Thompson JL, Orun OM, et al. Systemic inflammation and delirium during critical illness. *Intensive Care Med*. 2024;50:687–96, <http://dx.doi.org/10.1007/s00134-024-07388-6>.
5. van den Boogaard M, Kox M, Quinn KL, van Achterberg T, van der Hoeven JG, Schoonhoven L, et al. Biomarkers associated with delirium in critically ill patients and their relation with long-term subjective cognitive dysfunction; indications for different pathways governing delirium in inflamed and noninflamed patients. *Crit Care*. 2011;15:R297, <http://dx.doi.org/10.1186/cc10598>.
6. Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O'Neal PV, Keane KA, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med*. 2002;166:1338–44, <http://dx.doi.org/10.1164/rccm.2107138>.
7. Khan BA, Perkins AJ, Gao S, Hui SL, Campbell NL, Farber MO, et al. The confusion assessment method for the ICU-7 delirium severity scale: a novel delirium severity instrument for use in the ICU. *Crit Care Med*. 2017;45:851–7, <http://dx.doi.org/10.1097/CCM.0000000000002368>.
8. Needham DM, Sepulveda KA, Dinglas VD, Chessare CM, Friedman LA, Bingham CO, et al. Core outcome measures for clinical research in acute respiratory failure survivors. An international modified Delphi consensus study. *Am J Respir Crit Care Med*. 2017;196:1122–30, <http://dx.doi.org/10.1164/rccm.201702-0372OC>.
9. Navarra-Ventura G, Gomà G, de Haro C, Jodar M, Sarlabous L, Hernando D, et al. Virtual reality-based early neurocognitive stimulation in critically ill patients: a pilot randomized clinical trial. *J Pers Med*. 2021;11:1260, <http://dx.doi.org/10.3390/jpm11121260>.
10. Martí-Hereu L, Navarra-Ventura G, Navas-Pérez AM, Fernández-Gonzalo S, Pérez-López F, de Haro-López C, et al. Usage of immersive virtual reality as a relaxation method in an intensive care unit. *Enferm Intensiva (Engl Ed)*. 2024;35:107–13, <http://dx.doi.org/10.1016/j.enfie.2023.08.005>.

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