



Received: 24-09-2026
Accepted: 04-10-2026

International Journal of Advanced Multidisciplinary Research and Studies

ISSN: 2583-049X

Letter to the Editor

Comments on "Comparative Prognostic Performance of Hippocampal Volume and Plasma Biomarkers in Amyloid-Negative Subjective Cognitive Decline: A Four-Year Follow-up"

¹ Carla A Scorza, ² Fulvio A Scorza, ³ Josef Finsterer

^{1,2} Federal University of Sao Paulo (UNIFESP/EPM), São Paulo, Brazil

³ Neurology & Neurophysiology Center, Vienna, Austria

Corresponding Author: **Josef Finsterer**

Letter to the Editor

We read with interest the article by Yoon *et al.* regarding a prospective study that investigated whether "wet biomarkers" (phosphorylated tau-181, glial fibrillary acidic protein, neurofilament light chains) and MRI biomarkers (hippocampal volume) predict four-year progression or clinical conversion from subjective cognitive decline (SCD) to mild cognitive impairment (MCI) [1]. Conversion to MCI was defined as a decline of ≥ 1 point on the Mini-Mental State Examination (MMSE), while progression of cognitive decline was defined as a decline of ≥ 2 points on the MMSE [1]. The conclusion was that hippocampal atrophy predicts conversion or progression from SCD more consistently than Alzheimer's-associated plasma biomarkers [1]. While the study is noteworthy, several points warrant discussion.

A first point is that the term "subjective cognitive decline" (SCD) was not clearly defined [1]. What criteria had to be met for an individual to perceive themselves as cognitively impaired? Since cognitive decline can easily be confused with other conditions, it is essential that relevant differential diagnoses be appropriately ruled out before a participant was enrolled in the study. Differential diagnoses for SCD include depression and anxiety, chronic stress, high levels of neuroticism, somatoform disorders, fear of dementia, thyroid dysfunction, vitamin-B12 deficiency, chronic illnesses, sleep disorders, visual or auditory impairments, polypharmacy, and the use of sedatives, anticholinergics, opioids, or corticosteroids [2]. Since the results can depend heavily on the inclusion criteria, a clear definition of SCD and its explicit use in the inclusion criteria are of crucial importance.

A second point is that the MMSE has been used to assess the transition to MCI or the progression of SCD [1]. The MMSE has several disadvantages [3]. Key drawbacks include: dependence on the subject's literacy, verbal fluency, and level of education; a ceiling effect, as the test is too simple to detect subtle deficits; a strong emphasis on verbal and memory tasks, rendering it insensitive to frontal lobe or right-hemisphere dysfunction; and the fact that test performance can be affected by physical impairments such as hearing loss, visual disturbances, or fatigue [3].

A third point is that hippocampal volumetry has various disadvantages [4]. These include: a lack of specificity, as hippocampal volume loss also occurs in normal aging, depression, epilepsy, and neurodegenerative diseases; the dependence of manual segmentation on the level of anatomical expertise; the occurrence of segmentation errors (e.g., volume overestimation, failure to detect subtle structural anomalies) when using automated software tools; and confounding factors such as physiological shrinkage due to aging and overlapping pathologies.

As long as imprecise methods are used to assess cognitive performance over time, and imaging techniques prone to confounding factors are employed, the results and their interpretation may be misleading.

Declarations**Funding:** No funding was received.**Availability of Data and Material:** All data are available from the corresponding author.**Ethics Approval and Consent to Participate:** Not applicable.**Consent for Publication:** Not applicable.**Author Contribution:** JF: design, literature search, discussion, first draft, critical comments, final approval. FS and CS: literature search, discussion, critical comments, final approval.**Disclosures:** The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.**Compliance with Ethics Guidelines:** This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.**Acknowledgements:** None.**Keywords:** Subjective Cognitive Decline, Mild Cognitive Impairment, MMSE, Hippocampal Volumetry, Cerebral MRI**References**

1. Yoon B, Lee H, Hong YJ, Park KH, Kim SY, Wang MJ, *et al.* Comparative Prognostic Performance of Hippocampal Volume and Plasma Biomarkers in Amyloid-Negative Subjective Cognitive Decline: A Four-Year Follow-up. *J Clin Neurol.* 2026; 22(5):560-572. Doi: 10.3988/jcn.2025.0659
2. Jessen F, Amariglio RE, Buckley RF, Van Der Flier WM, Han Y, Molinuevo JL, *et al.* The characterisation of subjective cognitive decline. *Lancet Neurol.* Mar 2020; 19(3):271-278. Doi: 10.1016/S1474-4422(19)30368-0
3. Naugle RI, Kawczak K. Limitations of the Mini-Mental State Examination. *Cleve Clin J Med.* May 1989; 56(3):277-281. Doi: 10.3949/ccjm.56.3.277
4. Rao G, Gao H, Wang X, Zhang J, Ye M, Rao L. MRI measurements of brain hippocampus volume in relation to mild cognitive impairment and Alzheimer disease: A systematic review and meta-analysis. *Medicine (Baltimore).* Sep 8, 2023; 102(36):e34997. Doi: 10.1097/MD.00000000000034997