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Letter to the Editor

Non-linear recovery trajectories after cardiac arrest: implications for enrolment and outcome selection

Dear Editor,

Survivorship after cardiac arrest (CA) has increasingly become a central focus of post-resuscitation care. Many survivors experience difficulties across multiple, interrelated domains of recovery, which are not easily captured by global functional scales such as the Cerebral Performance Category,[1–3] and recent initiatives reflect this shift, moving beyond static neurological categories to examine longitudinal recovery trajectories, patient-reported outcomes, and multidomain support strategies.[3,4] The ENFORCER trial (NCT06395558) evaluates an internet-based educational intervention targeting anxiety, depression, and cognitive impairment in CA survivors identified through early post-discharge screening, with initial contact within two weeks.[5]

After one year of enrolment, a blinded, descriptive interim feasibility analysis—non-comparative and focused on recruitment trends, data completeness, and stability of symptom trajectories—was conducted: of 115 eligible survivors, 96 were contacted, 51 consented to screening, and 27 were randomized based on cognitive or emotional symptoms. This analysis revealed marked fluctuations in cognitive and especially emotional symptoms during the first year after CA. Fig. 1 illustrates the anxiety, depression, cognitive impairment, and quality-of-life trajectories for the 33 survivors enrolled and randomized as of March 23, 2026. Notably, four survivors showed early improvement followed by later worsening, while seven developed new symptoms in previously unaffected domains.

These early divergences and non-linear patterns suggest that relying on a single early symptom screen for enrolment may limit the ability to identify survivors who could benefit from educational interventions. This has implications for defining eligibility criteria, determining the timing of enrolment, and selecting outcomes, because early thresholds may fail to capture survivors whose emotional, cognitive, or quality-of-life impairments emerge later. Prior CA research supports this interpretation: a longitudinal study showed group-level improvements in emotional outcomes while a substantial subgroup worsened,[6] and a contemporary multicentre investigation confirmed persistent interindividual variability beyond six months.[7] Qualitative studies further describe fluctuating recovery, delayed psychological burden, and the emergence of new symptoms after an initial period of stability.[8]

In light of these considerations, the ENFORCER steering committee implemented a protocol amendment, in which eligibility criteria were expanded to include all OHCA survivors regardless of baseline HADS or TICS scores, and health-related quality of life (Short Form Heath Survey – SF-12) was elevated from a secondary to the primary outcome. This aligns the endpoint with the trial's emphasis on preventive and supportive care, particularly given the inclusion of survivors without baseline emotional or cognitive symptoms. The sample size was recalculated to detect a minimal clinically relevant difference of 4 points in SF-12, the best available estimate for a chronic disease population,[9] and the recruitment period was extended. The amendment was approved by the Ethics Committee, implemented in February 2026, and prospectively updated in the trial registry. More broadly, our experience supports the evidence that recovery after CA is a time-varying, multidomain process. Supportive trials must therefore consider eligibility, timing, and outcome selection in ways that reflect this complexity, as early symptom thresholds alone may fail to identify survivors whose needs emerge later.[10]

CRediT authorship contribution statement

Lorenzo Gamberini: Writing – original draft, Conceptualization. **Martina Masi:** Writing – review & editing, Conceptualization. **Daniele Celin:** Investigation. **Riccardo Tucci:** Investigation. **Elio Fabbri:** Visualization. **ENFORCER Network:** Data curation.

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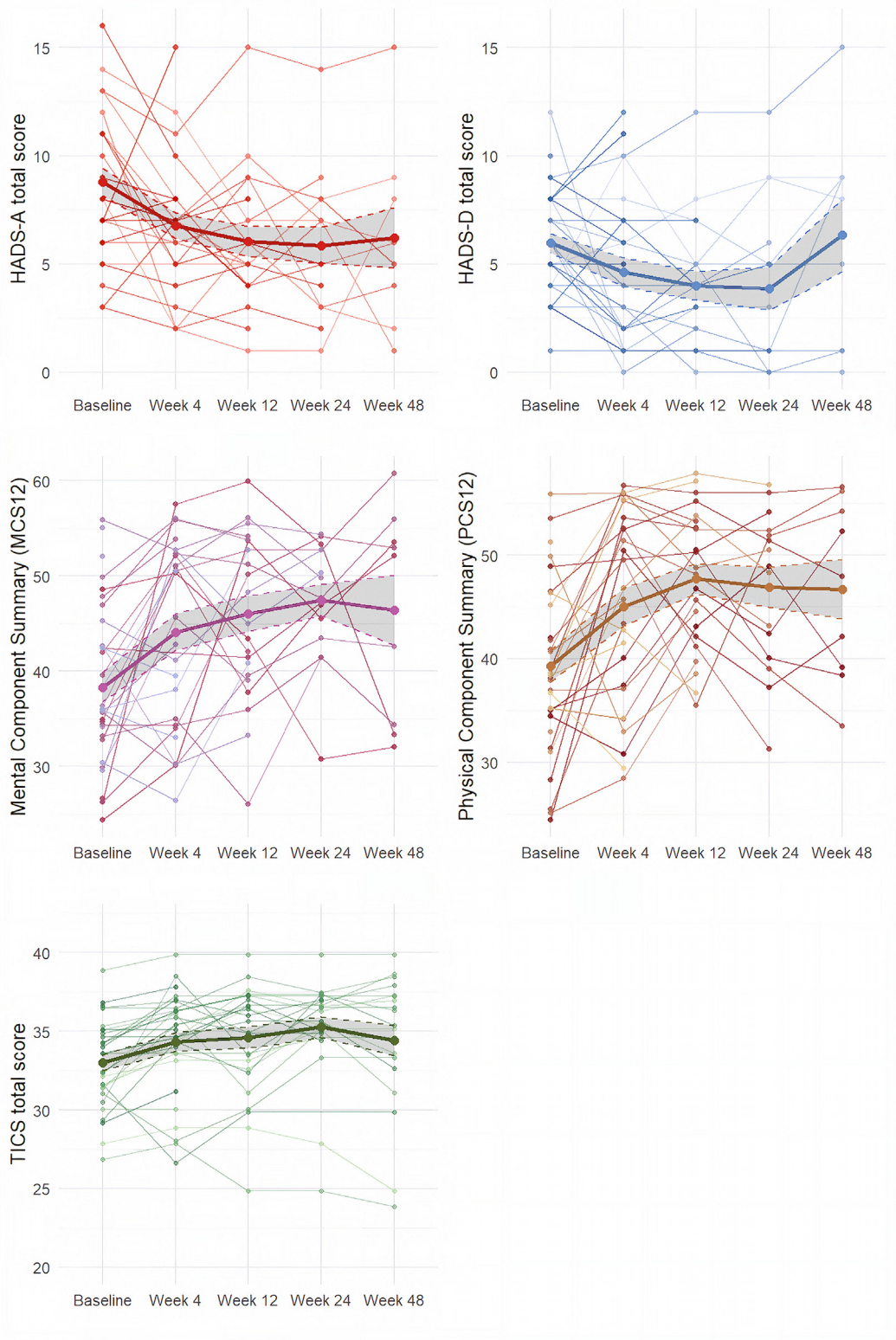

Fig. 1 – Individual and mean trajectories of anxiety, depression, quality of life, and cognitive function over 48 weeks in 33 OHCA survivors enrolled and randomized as of March 23, 2026.

Notes: Thin lines represent individual participant trajectories; bold lines represent group means. The dashed line denotes the mean trajectory; the gray band represents the standard error of the mean for the collected sample.

Abbreviations: HADS-A – Hospital Anxiety and Depression Scale, Anxiety subscale; HADS-D – Hospital Anxiety and Depression Scale, Depression subscale; MCS-12 – Mental Component Summary of the SF-12; PCS-12 – Physical Component Summary of the SF-12; TICS – Telephone Interview for Cognitive Status.

profit organization involved in the assistance and support for cardiac arrest survivors and their families. Fondazione IRC has had only a financial role and has no control over data, results publication and intellectual property of eventual results.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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