Frailty and cognitive-behavioral phenotype in young-onset cognitive impairment: insights from a multi-centric cohort

S. Salemme[1,2,3], F. Sciancalepore[4], P. Lorenzini[4], C. Carbone[1,2], J. Garuti[5], M. Tondelli[1,2], G. Vinceti[2], A. Chiari[2], N. Vanacore[4], G. Zamboni[1,2]

[1]Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia
[2]Neurology Unit, Azienda Ospedaliero-Universitaria di Modena
[3]International School of Advanced Studies, University of Camerino
[4]National Centre for Disease Prevention and Health Promotion, Italian National Institute of Health
[5]School of Medicine and Surgery, University of Modena and Reggio Emilia

Background & Aims

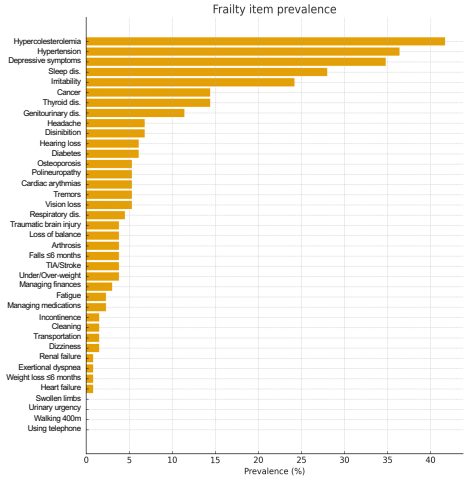
Frailty - defined as multidimensional **deficit accumulation -** predicts late-life cognitive decline and adverse outcomes. Yet most evidence derives from older cohorts and global screens; it remains unclear whether frailty relates to **specific cognitive domains** and **neuropsychiatric burden** in **young-onset MCI (<65 y)**, and how this interacts with **cognitive reserve.** In younger patients, phenotype heterogeneity complicates diagnosis and counseling; a quick, scalable **Frailty Index (FI)** may add meaningful biopsychosocial context beyond demographics and reserve.

We **aimed to** quantify (i) **frailty prevalence** among the YOMCI cohort as well as (ii) associations between **FI** (40-item; 0–40, normalized 0–1) and **global cognition**, **cognitive scores** (e.g., Benton JLO, FCSRT, Rey, Stroop, TMT, fluencies), **neuropsychiatric symptoms**, and **functional autonomy** (e.g., ADCS).

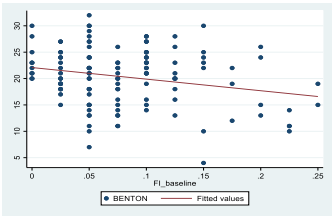
Methods

- Multicentric, consecutive, **clinic-based cohort (n= 132)** from the Cognitive Neurology Clinics of Modena & Reggio Emilia, 2019–2023; with **symptom onset < 65 y**.
- Standardized **neuropsychological battery**, including Cognitive Reserve Index questionnaire (**CRIq)** and Neuropsychiatric Inventory **(NPI)**.
- **FI** consisting of **40 items**; analyzed as **continuous**.

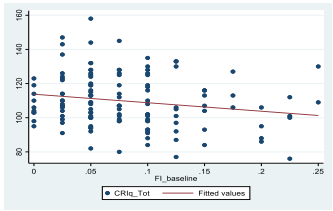
Results



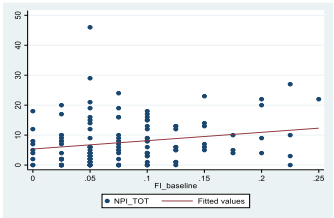
Frailty distribution:
Range: 0.03–0.24 (mean ≈0.12).
All patients below the conventional frailty threshold (0.25).



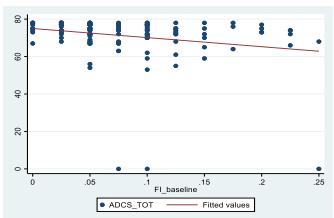
Higher FI → lower visuo-constr. abilities
(β = –22.0, 95%CI –37.5 to –6.4, p = 0.006))



Higher FI → lower cognitive reserve
(β = –49.8, 95%CI –95.0 to –4.6, p = 0.031)



Higher FI → higher neuropsychiatric burden
(β = 27.8, 95%CI 4.4 to 51.3, p = 0.020)



Higher FI → lower functional autonomy
(β = –48.6, 95%CI –84.9 to –12.3, p = 0.009)

Conclusions

- **Vascular and behavioural load despite youth:** In this young, clinic-based young-onset MCI cohort, frailty items reveal a **non-negligible vascular burden** together with **behavioural symptoms** and **sleep disturbances**. Although several individual deficits exceed 30% prevalence, the **FI distribution is low and narrow** and no participant reached the conventional frailty threshold (FI ≥ 0.25).
- **Sub-threshold frailty matters**: Even within a restricted FI range, **higher frailty** was associated with lower visuo-constructional abilities (**Benton**), increased neuropsychiatric burden (**NPI**), reduced functional autonomy (**ADCS**), and lower cognitive reserve (**CRIq**).
- **Clinical implications**: Frailty assessment provides valuable biopsychosocial context in young-onset MCI, capturing functional and behavioural vulnerabilities not explained by age alone. This highlights modifiable targets for intervention and offers **additional guidance for diagnosis, prognosis, and counselling**. These results are **hypothesis-generating** and warrant larger confirmation.

Contacts
simone.salemme@unimore.it