

Glial Fibrillary Acidic Protein Level Is Associated with in vivo Detected Cumulative Neurodegenerative Burden



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Background

- In vivo biomarkers enable detection of mixed neurodegenerative pathologies and support precision medicine in clinical practice.
- Plasma neurofilament light chain (NfL) and Glial Fibrillary Acidic Protein (GFAP) reflect neurodegeneration severity and progression, but their relationship to co-existing Alzheimer’s disease (AD), alpha-synucleinopathy (aSyn), 4-repeat tauopathies (4RT) and small vessel disease (SVD) is unclear.

Objective

- We aimed to evaluate the impact of identified co-pathology on plasma NfL and GFAP levels.

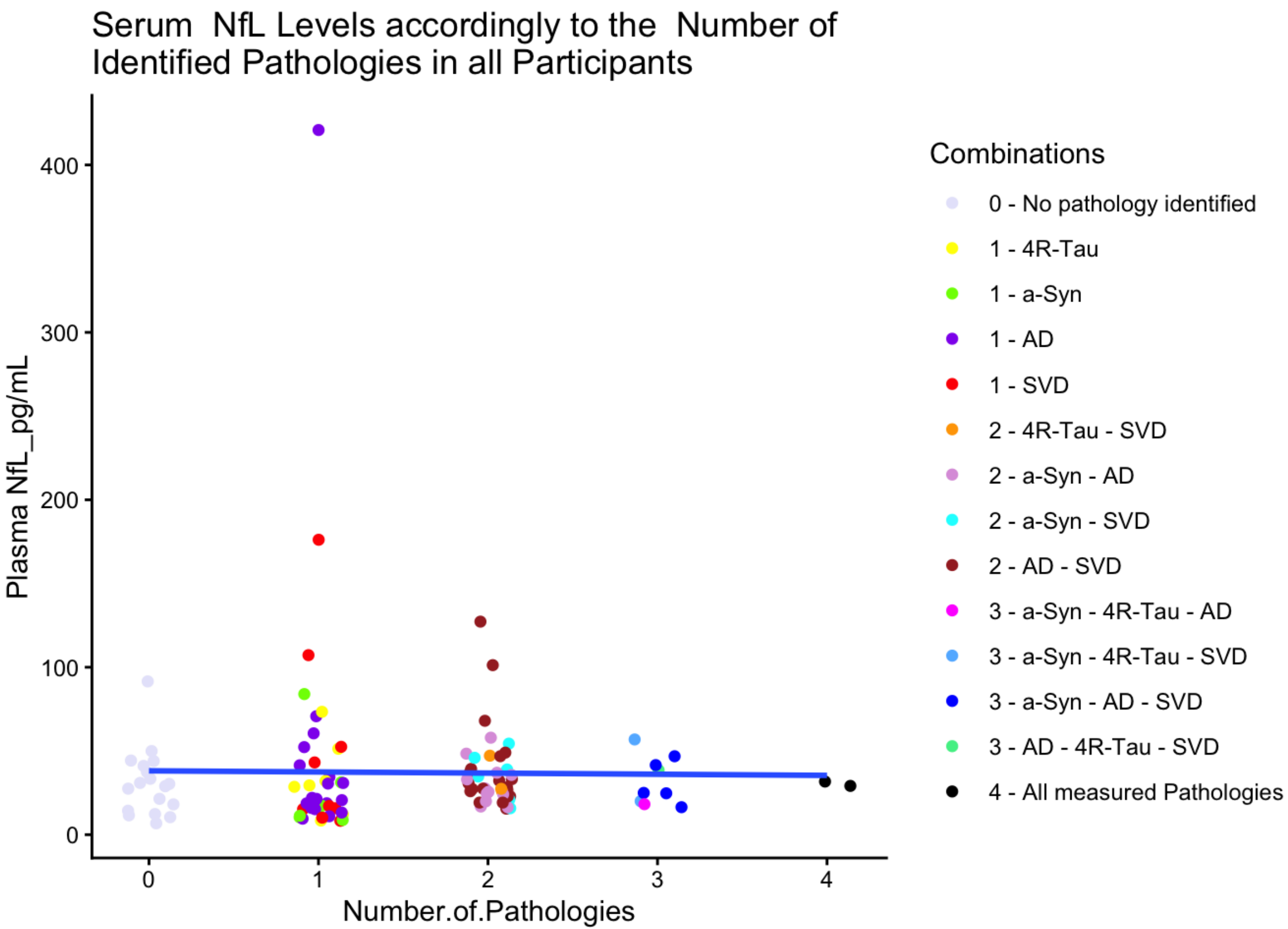
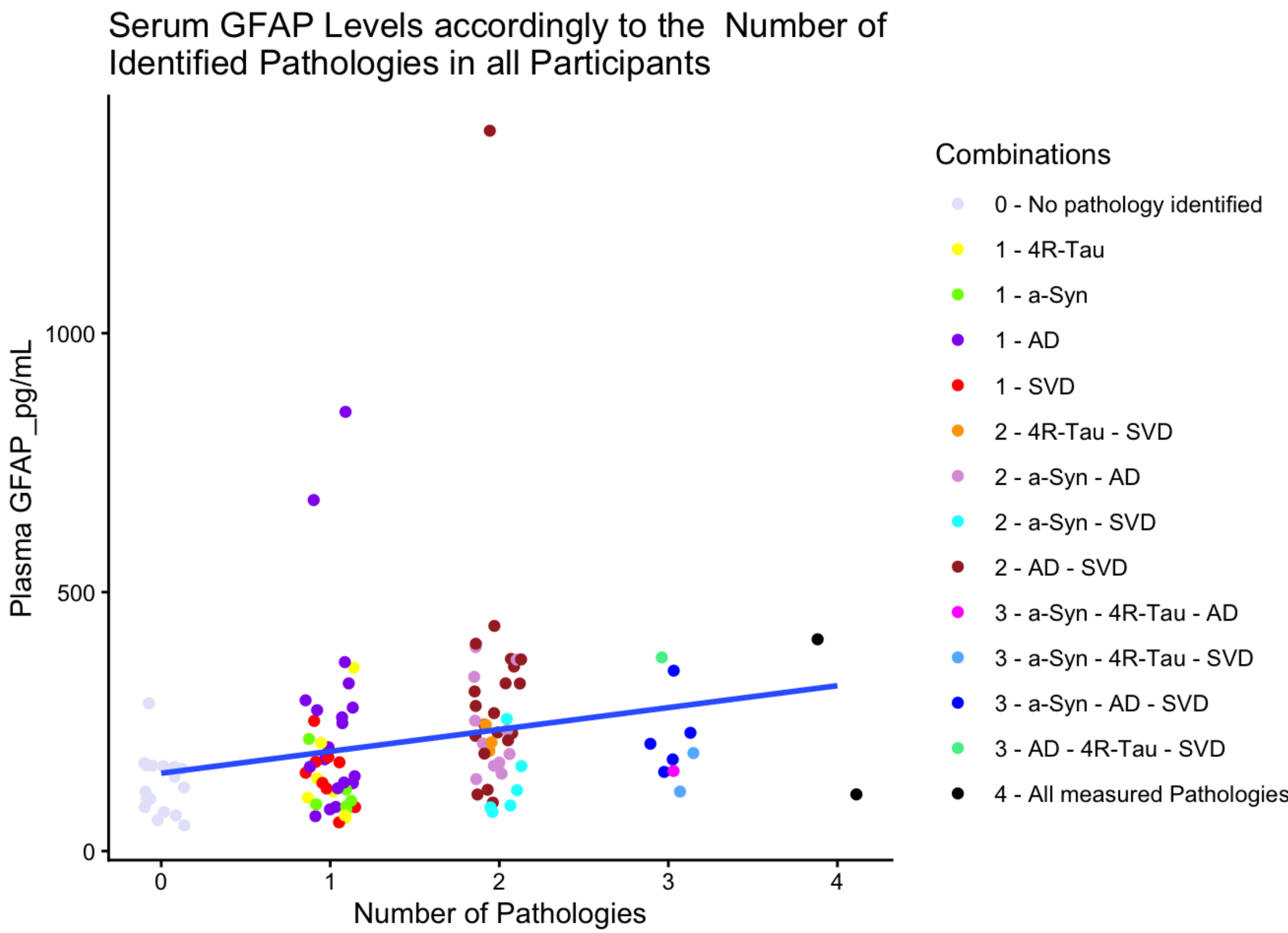
Methods

- Participants were recruited from an ongoing multi-center biomarker research program from four Toronto Dementia Research Alliance-affiliated memory clinics (November 2023-December 2025).
- Baseline assessments included clinical evaluation, MRI, and biospecimen collection (blood, and skin biopsy)
- Plasma GFAP, NfL, and phosphorylated-tau217 (pTau217) levels were measured using Simoa.
- AD status was defined by PET amyloid or plasma p-Tau217.
- Seed Amplification Assays (SAAs) were used to assess for aSyn and 4RT presence in skin biopsies.
- SVD was defined as Fazekas score ≥ 2 .
- Linear models were used to assess for associations between co-pathology burden and GFAP and NfL levels, controlling for age.

Results

- We included 111 participants,
 - 58 (52.3%) males.
 - Mean age was 71.8 $\pm$ 9.9;
- Dementia: 50 (45.0%); Mild Cognitive Impairment 56 (50.5%); and Subjective Cognitive Impairment 5 (4.5%).
- Pathology counts were:
 - Zero in 18 (6.2%).
 - One in 41 (36.9%).
 - Two in 41 (36.9%).
 - Three in 9 (8.1%).
 - Four in 2 (1.8%).

- Mean GFAP was 210.9 $\pm$ 166.6 pg/mL.
- Mean NfL was 37.3 $\pm$ 44.6 pg/mL.
- Models: Each additional pathology was associated with:
 - An increase of **GFAP of 33.2 pg/mL** (CI95%: 7.7 to 58.7; p value = 0.011).
 - **No association** with NfL (-2.2; CI95%: -6.4 to 2.0; p value = 0.29).



Conclusion

- In this real-world, multicentric cohort, increasing co-pathology burden was associated with higher plasma GFAP but not NfL.
- Our results suggests a prominent role for neuroinflammation across neurodegenerative diseases and increasing with the number of co-pathologies.