

Positive predictive value of CSF biomarker testing for a clinical diagnosis of Alzheimer's disease

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PURPOSE

To examine the positive predictive value (PPV) of cerebrospinal fluid (CSF) biomarker testing for a clinical diagnosis of Alzheimer's disease (AD).

BACKGROUND

AD is a neurodegenerative illness that is defined neuropathologically by the presence of amyloid plaques and neurofibrillary tangles. The central importance of these neuropathologic findings is highlighted in recently revised 2024 criteria for the diagnosis and staging of AD, which propose that detection of AD-related neuropathologic change (ADNPC) by biomarkers is equivalent to making a diagnosis of AD biologically. While there remains ongoing debate regarding this approach to diagnosis in cognitively normal individuals, there is general consensus that testing for biomarkers indicative of ADNPC in patients with suggestive cognitive symptoms can facilitate accurate AD diagnosis.

One such biomarker test is the CSF p-tau181/Abeta-42 ratio, which we began offering at London Health Sciences Centre/St. Joseph's Health Care London (LHSC/SJHC) in November 2023 using Health Canada-approved Roche Elecsys immunoassays. An Elecsys p-tau181/Abeta-42 ratio cut-off of >0.023 as suggested by the manufacturer has been reported to have a specificity of 89-98% for ADNPC when compared to the reference standard of amyloid PET. We opted to examine the PPV of a positive CSF p-tau181/Abeta-42 ratio for a clinical diagnosis of AD, one year after test implementation at our tertiary care centre.

MATERIALS AND METHODS

We identified all patients at LHSC/SJHC who underwent Elecsys CSF AD biomarker testing (Abeta42, p-tau181, and t-tau) between November 1 2023 (test inception) and October 31 2024. Testing was performed using a Roche Cobas e 801 immunoassay analyzer. Patients with a positive p-tau181/Abeta-42 ratio (defined as a ratio of >0.023) were included in this PPV analysis.

Patients with a clinical presentation compatible with AD and no more likely alternative diagnosis were deemed to have a clinical diagnosis of AD and classified as having a true-positive result, while all other patients were deemed not to have a clinical diagnosis of AD and classified as having a false-positive result. The PPV of the p-tau181/Abeta-42 ratio was calculated as the proportion of those with positive results who were classified as true-positive.

This study was approved by the Western University Health Science Research Ethics Board.

How were patients selected for study inclusion?

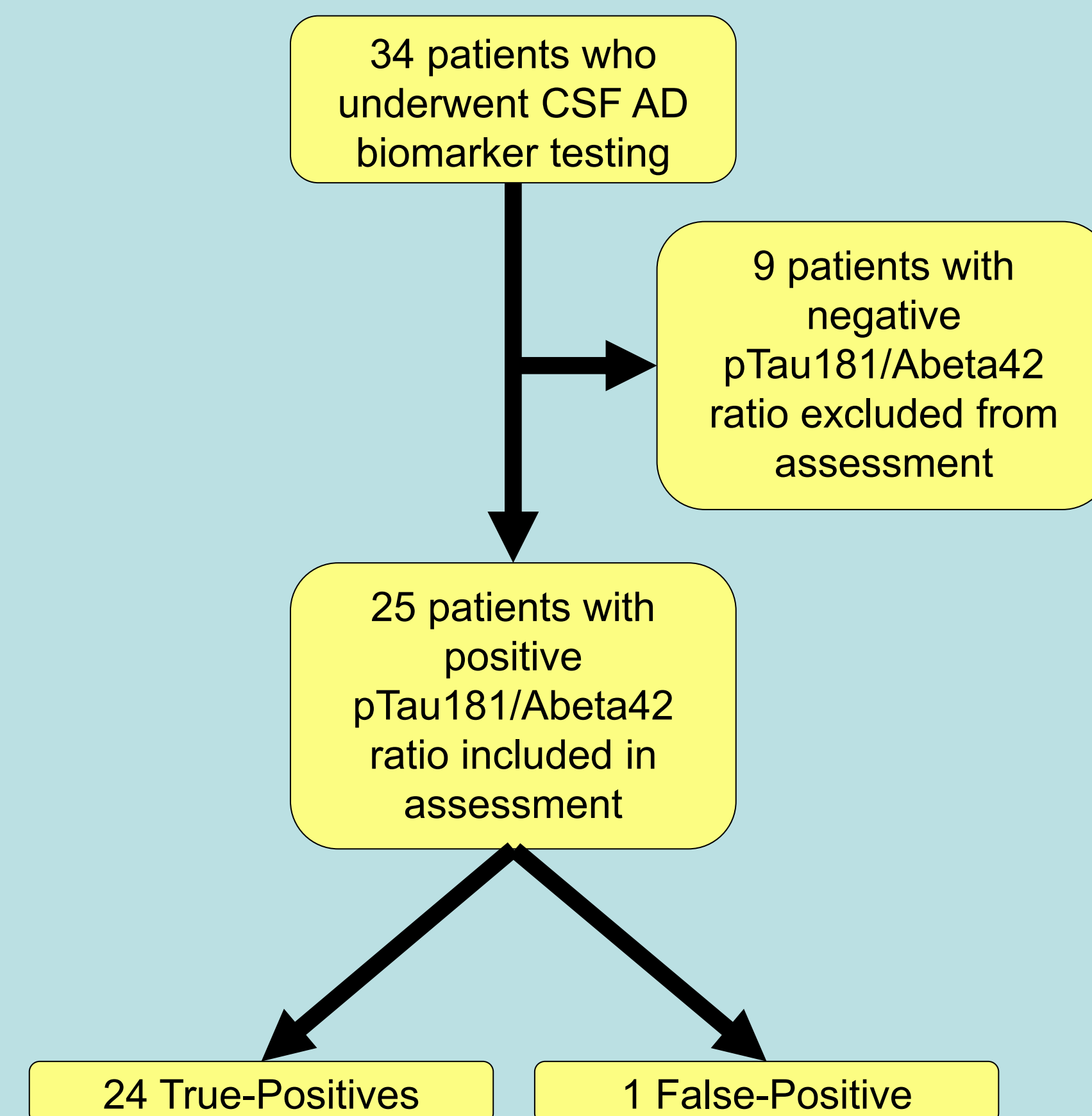


Figure 1. Flow diagram of positive p-tau181/Abeta-42 ratio results that were included in assessment.

RESULTS

Of 34 patients at LHSC/SJHC who underwent CSF AD biomarker testing over the one-year period examined, 25 (74%) had a positive p-tau181/Abeta-42 ratio and were included in study analysis (see Figure 1). The median age was 67 years (range 50-80 years) and 15/25 (60%) were male. The median MoCA score was 20 (range: 2-27).

Twenty-four were classified as true-positives, resulting in a calculated PPV of 96% (95% CI [80%, 100%] by binomial "exact" method). In 2 patients, a competing diagnostic consideration was present (semantic variant primary progressive aphasia typically associated with TAR DNA-binding protein 43 [TDP-43] pathology rather than ADNPC, 1; obstructive hydrocephalus secondary to craniopharyngioma, 1 [see Figure 2]). However, both patients presented primarily with progressive amnesic complaints and were noted to have bilateral hippocampal atrophy on MRI. In both patients, AD (typical amnesic phenotype) was therefore deemed to be the most likely etiology for their clinical symptoms, and both were classified as true-positives.

RESULTS CONT'D

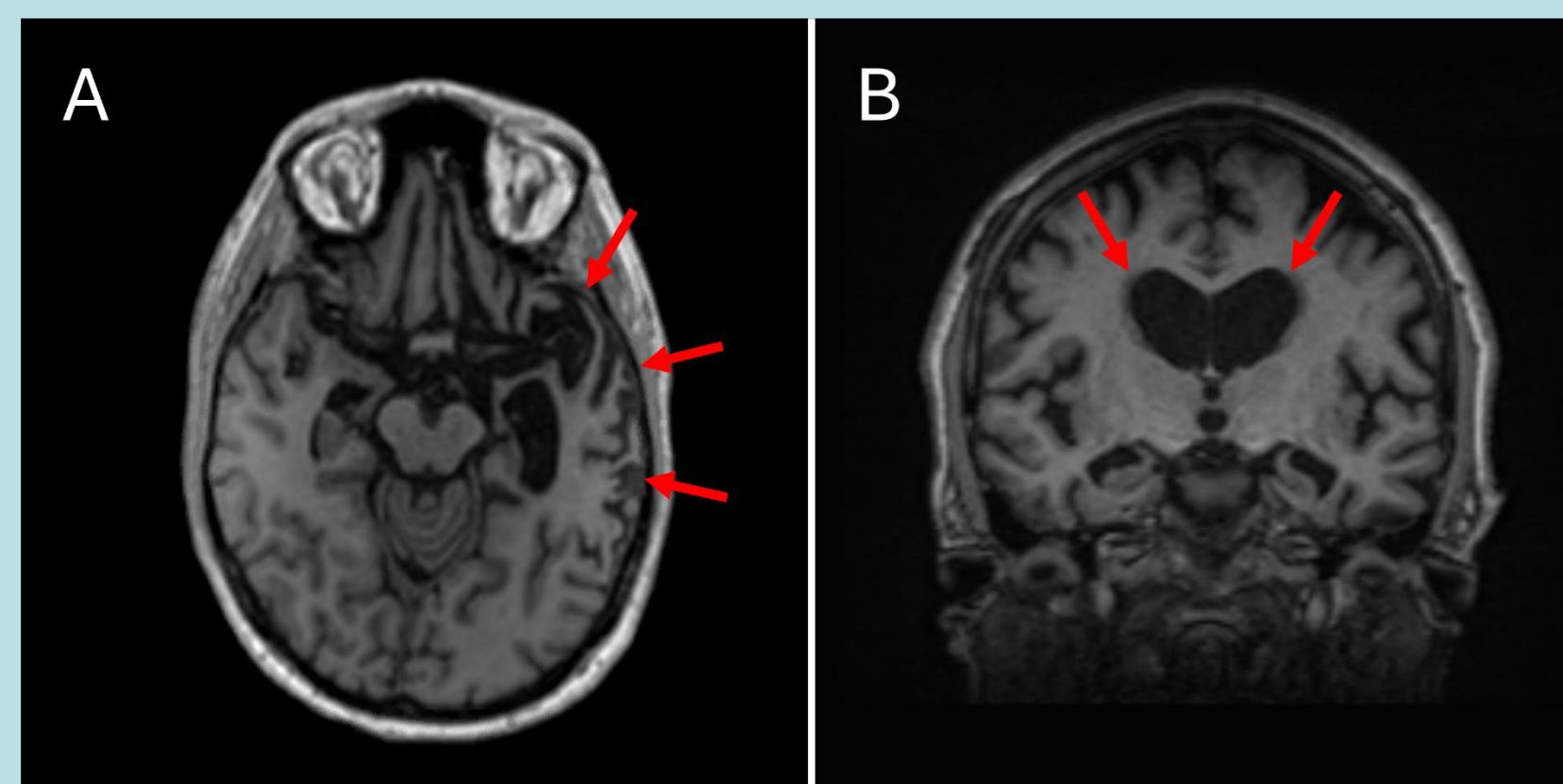


Figure 2. Neuroimaging of two patients classified as true-positives with competing diagnostic considerations

In Panel A, axial T1-weighted image shows strikingly asymmetric left temporal lobe atrophy (arrows), raising the possibility of semantic variant primary progressive aphasia (typically associated with TDP-43 pathology rather than ADNPC). In Panel B, coronal T1-weighted image MRI shows ventriculomegaly (arrows), raising the possibility of obstructive hydrocephalus secondary to craniopharyngioma (not shown) that required endoscopic third ventriculostomy.

Of 25 patients with a positive p-tau181/Abeta-42 ratio, 1 (4%) was classified as a false-positive. This patient was an 80-year-old man with progressive cognitive difficulties, behavioral changes and multiple cerebral microhemorrhages suggestive of cerebral amyloid angiopathy; however, subacute onset of symptoms and spells ultimately recognized as faciobrachial dystonic seizures (FBDS) indicated a more likely diagnosis than AD for his clinical presentation (i.e. anti-LGI1 encephalitis, confirmed on serum and CSF antibody testing by cell-based assay [CBA]) (see Figure 3). He had a modestly elevated CSF p-tau181/Abeta-42 ratio of 0.029 (normal ≤ 0.023) that was driven by an increased p-tau181 concentration (38.3 pg/mL, normal ≤ 27.0 pg/mL), while Abeta-42 concentration was normal (1304.0 pg/mL, normal >1030.0 pg/mL).

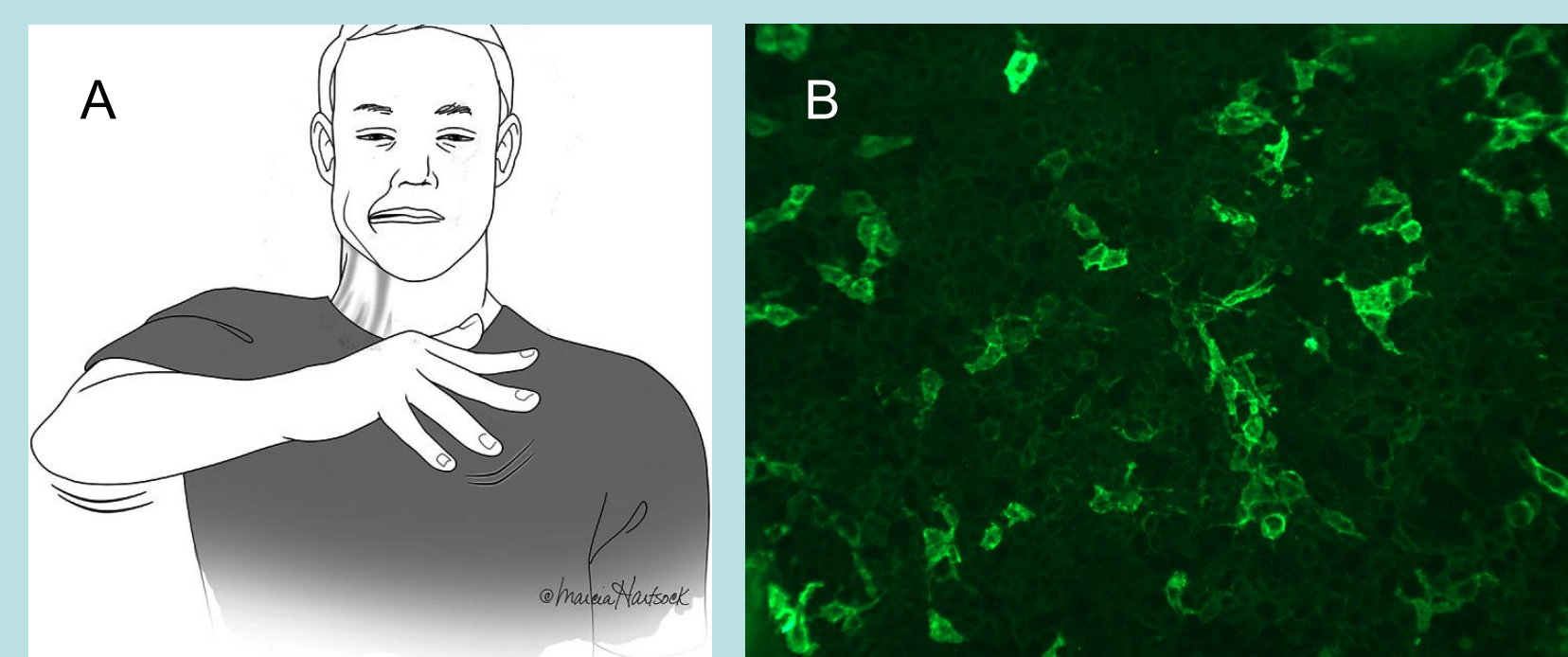


Figure 3. Representative clinical features (FBDS in panel A, as created by Marcia Hartsock, MA, CMI in PMID: 26857958) and laboratory findings (positive CBA in panel B) in anti-LGI1 encephalitis.

STUDY LIMITATIONS

Several important study limitations include:

- 1) This is a single-centre study of newly-introduced CSF AD biomarker testing performed at LHSC/SJHC, so sample size was relatively small despite identifying all patients at our institution who underwent this testing over a one-year period.
- 2) The smaller sample size limits more precise estimation of PPV in our practice setting as reflected by the wider 95% confidence interval (CI) of our calculated PPV (96%, 95% CI [80%, 100%]); while it is reassuring that all values within this CI indicate a reasonably high PPV, further studies in similar practice settings are needed to confirm the generalizability of our findings.
- 3) Test ordering at our institution is restricted to neurologists and geriatricians; such ordering restrictions may skew towards a tested population undergoing specialist assessment that has a high prevalence of AD, and could explain the high proportion of those with a positive CSF p-tau181/Abeta-42 ratio (74%) as well as the high test PPV (96%).
- 4) Clinicians were not blinded to CSF AD biomarker test results that were reported out on a clinical service-basis, but assessment of all patients by a geriatrician or neurologist specializing in cognitive impairment as well as specialist discussion in cases with competing diagnostic considerations aimed to mitigate potential bias.

CONCLUSIONS

The following conclusions are drawn from our study:

- 1) Our study indicates high PPV of a positive p-tau181/Abeta-42 ratio for a clinical diagnosis of AD at our institution.
- 2) Our findings support the use of CSF AD biomarker testing to confirm a diagnosis of AD in patients with suggestive clinical symptoms.