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Concordance between the updated Elecsys CSF immunoassays and amyloid PET for the diagnosis of Alzheimer's disease: findings from the Apollo study

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Introduction

- According to the recent diagnostic criteria for Alzheimer's disease (AD), three cerebrospinal fluid (CSF) biomarkers play a crucial role in the timely and accurate diagnosis of the disease: β-amyloid(1–42) ($Aβ_{42}$), tau phosphorylated at a threonine residue at position 181 ($pTau_{181}$) and total tau (tTau).[1,2]
- Elecsys® β-Amyloid(1–42; $Aβ_{42}$) CSF II, Elecsys Phospho-Tau (181P; pTau) CSF and Elecsys Total-Tau (tTau) CSF immunoassays (Roche Diagnostics International Ltd, Rotkreuz, Switzerland) are electrochemiluminescence immunoassays that use a quantitative sandwich principle to detect these biomarkers, which are indicative of amyloid pathology.[3]
- The original cutoff values for the Elecsys CSF immunoassays and their ratios, pTau/$Aβ_{42}$ and tTau/$Aβ_{42}$, were determined in *frozen* samples collected under the BioFINDER-1 study and their performance was validated in *frozen* samples from the Alzheimer's Disease Neuroimaging Initiative (ADNI) study.[4]
- Since the initial clinical validation, all three CSF immunoassays have been updated, and a new pre-analytical procedure has been established.[5] The cutoff values were adjusted via a bridging study.[3]

Objective

- The aim of the present study was to assess amyloid positron emission tomography (PET) concordance of pTau/$Aβ_{42}$, tTau/$Aβ_{42}$ and $Aβ_{42}$ with the adjusted cutoff values in *fresh* CSF samples collected using the new routine-use pre-analytical procedure and measured with the updated Elecsys CSF immunoassays.

Methods

- Apollo, a small prospective study, supported the verification of the clinical performance of the updated Elecsys CSF $Aβ_{42}$, pTau and tTau immunoassays and their adjusted cutoffs for measuring fresh CSF samples collected using the new routine-use pre-analytical procedure.[5]
- Participants with subjective cognitive decline (SCD) or mild cognitive impairment (MCI) were recruited from cohort C or C2 of the Swedish BioFINDER-2 study (eligibility criteria previously described).[6]
  - To be eligible for the Apollo study, participants were required to have available CSF biomarker test results measured via the Elecsys CSF assays, as well as a time-matched amyloid PET scan. Fresh CSF samples used for measurements must have been collected using the new routine-use pre-analytical procedure.
- The main study objective was to demonstrate concordance of the Elecsys CSF pTau/$Aβ_{42}$ and tTau/$Aβ_{42}$ ratios with amyloid PET visual read status.
  - Classification cutoff values were: pTau/$Aβ_{42}$ >0.023, tTau/$Aβ_{42}$ >0.28 and $Aβ_{42}$ ≤1,030 pg/mL.
  - Amyloid PET results were assessed by the majority vote of three blinded independent expert readers.
  - The performance of pTau/$Aβ_{42}$, tTau/$Aβ_{42}$ and $Aβ_{42}$ was assessed against pre-specified acceptance criteria.
  - An exploratory analysis investigated the stability of frozen CSF samples after storage at −20°C for 1–13 weeks.

Results

- A total of 108 participants were initially enrolled in the Apollo study, of whom 16 were excluded due to missing biomarker measurements in fresh CSF samples and one was excluded during the monitoring process due to not fulfilling the inclusion criterion for cohort C/C2 (Mini-Mental State Examination ≥24).
- The primary analysis population included 40 amyloid PET-positive and 51 amyloid PET-negative participants. The demographic and clinical characteristics of this population are shown in **Table 1**.
- Of the 91 participants who were enrolled at baseline or at the 2-year follow-up visit of the BioFINDER-2 study, 67 (73.6%) were from cohort C and 24 (26.4%) from cohort C2.
- In all participants, the mean (standard deviation) distribution for $Aβ_{42}$, pTau and tTau was 1,125 (±580), 22.3 (±10.7) and 250 (±103) pg/mL, respectively.

Table 1. Demographic and clinical characteristics of the primary analysis population*.

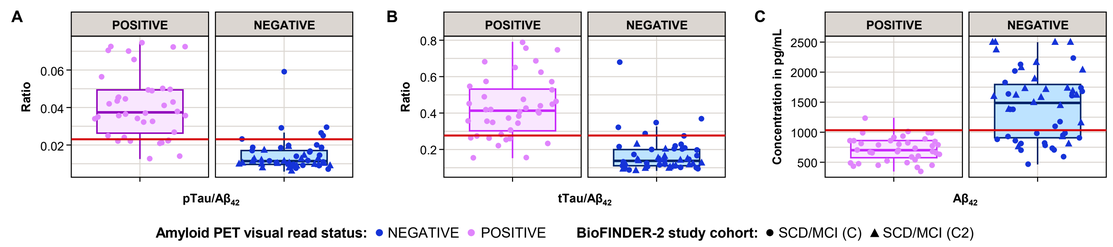
	Amyloid PET-positive (n=40)	Amyloid PET-negative (n=51)	All (N=91)
Age, mean years (min–max)	72.9 (55.0–90.0)	68.2 (43.0–85.0)	70.3 (43.0–90.0)
Gender, n (%)			
Female	15 (37.5)	23 (45.1)	38 (41.8)
Male	25 (62.5)	28 (54.9)	53 (58.2)
SCD/MCI, n (%)			
SCD	15 (37.5)	26 (51.0)	41 (45.1)
MCI	20 (50.0)	11 (21.6)	31 (34.1)
No sub-classification available†	5 (12.5)	14 (27.5)	19 (20.9)
MMSE, mean (min–max)	28.2 (25.0–30.0)	28.7 (24.0–30.0)	28.5 (24.0–30.0)
Visit during the BioFINDER-2 study, n (%)			
Baseline visit	30 (75.0)	31 (60.8)	61 (67.0)
Follow-up after 2 years	10 (25.0)	20 (39.2)	30 (33.0)

*Primary analysis population included eligible participants who met the criteria of having CSF biomarker test measurements and an amyloid PET visual read.
†For 19 participants classified as SCD/MCI, details of sub-classification into SCD or MCI were not available to Roche.
MMSE, Mini-Mental State Examination.

Results (cont.)

- The primary analysis demonstrated that the pTau/$Aβ_{42}$ and tTau/$Aβ_{42}$ ratios can distinguish amyloid PET-positive from amyloid PET-negative participants with high accuracy (pTau/$Aβ_{42}$: positive percent agreement [PPA]=0.80, negative percent agreement [NPA]=0.88; tTau/$Aβ_{42}$: PPA=0.78, NPA=0.90) (**Figure 1, Table 2**).
- The performance of the pTau/$Aβ_{42}$ and tTau/$Aβ_{42}$ ratios, and $Aβ_{42}$ alone, met the pre-specified acceptance criteria for all three biomarkers (**Table 2**).
- CSF biomarker status, determined by the pTau/$Aβ_{42}$ and tTau/$Aβ_{42}$ ratios and $Aβ_{42}$ alone in fresh CSF, showed good concordance with amyloid PET visual read status (**Table 3**).

Figure 1. Distribution of (A) pTau/$Aβ_{42}$, (B) tTau/$Aβ_{42}$ and (C) $Aβ_{42}$ by amyloid PET visual read status.*



*Red lines indicate the respective cutoffs (pTau/$Aβ_{42}$ >0.023; tTau/$Aβ_{42}$ >0.28; $Aβ_{42}$ ≤1,030 pg/mL).

Table 2. Testing of pre-specified acceptance criteria for pTau/$Aβ_{42}$, tTau/$Aβ_{42}$ and $Aβ_{42}$.

Performance measure	Point estimate (95% CI)	Acceptance criteria	Testing result
pTau/$Aβ_{42}$			
PPA	0.80 (0.65–0.90)	PPA >0.75 & LCL >0.60	Successful
NPA	0.88 (0.77–0.95)	NPA >0.75 & LCL >0.60	Successful
tTau/$Aβ_{42}$			
PPA	0.78 (0.63–0.88)	PPA >0.75 & LCL >0.60	Successful
NPA	0.90 (0.79–0.96)	NPA >0.75 & LCL >0.60	Successful
$Aβ_{42}$			
PPA	0.98 (0.87–1.00)	PPA >0.75 & LCL >0.60	Successful
LR-	0.04 (0.01–0.27)	UCL <1	Successful

CI, confidence interval; LCL, lower confidence limit; LR-, negative likelihood ratio; UCL, upper confidence limit.

Table 3. Concordance of pTau/$Aβ_{42}$, tTau/$Aβ_{42}$ and $Aβ_{42}$ with amyloid PET visual read status.

	pTau/$Aβ_{42}$		tTau/$Aβ_{42}$		$Aβ_{42}$	
	Amyloid PET-positive	Amyloid PET-negative	Amyloid PET-positive	Amyloid PET-negative	Amyloid PET-positive	Amyloid PET-negative
CSF-positive, n (%)	32 (35.2)	6 (6.6)	31 (34.1)	5 (5.5)	39 (42.9)	18 (19.8)
CSF-negative, n (%)	8 (8.8)	45 (49.5)	9 (9.9)	46 (50.5)	1 (1.1)	33 (36.3)

- Exploratory analysis: of the 91 fresh CSF samples included in this study, 33 (36.0%) had available CSF results from frozen samples stored at −20°C for 1–13 weeks.
  - The concentration recoveries for pTau, tTau and $Aβ_{42}$ were within 100 ± 10% in all samples stored at −20°C for 1–8 weeks (n=6), indicating sample stability under these conditions.
  - For samples stored at −20°C for >8–13 weeks (n=27), the concentration recoveries varied. Recoveries for pTau and tTau were within 100 ± 10%; however, the concentration recovery of $Aβ_{42}$ for six of the samples was slightly below 90%.

Limitations

- Participants with AD dementia, who are part of the intended use population, were not enrolled in the present verification study.
- The sample size was small and thus point estimate confidence intervals for PPA and NPA were quite broad.

Conclusions

- CSF biomarker status as determined by pTau/$Aβ_{42}$, tTau/$Aβ_{42}$ or $Aβ_{42}$ alone, using pre-specified cutoff values, showed good concordance with amyloid PET visual read status and the acceptance criteria were met.
- CSF pTau/$Aβ_{42}$ and tTau/$Aβ_{42}$ ratios can be used to identify amyloid PET positivity with high diagnostic accuracy.
- The new routine-use pre-analytical procedure, along with the adjusted cutoffs for the updated CSF immunoassays, are recommended for use in clinical practice.
- As a conservative approach, CSF samples can be stored at −20°C for up to 8 weeks before testing, as good stability is maintained under such conditions.

Disclosures

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- H.S., E.M. and S.M. are full-time employees of Roche Diagnostics GmbH, Penzberg, Germany, and shareholders of F. Hoffmann-La Roche; M.F.J., M.G., R.N. and E.S. have no conflicts of interest; S.G. is an employee of TRIGA-S GmbH contracted by Roche Diagnostics GmbH, Penzberg, Germany; M.C. is a full-time employee of Roche Diagnostics International Ltd, Rotkreuz, Switzerland, and a shareholder of F. Hoffmann-La Roche.
- ELECSYS is a trademark of Roche. Elecsys β-Amyloid(1–42) CSF II, Elecsys Phospho-Tau (181P) CSF and Elecsys Total-Tau CSF assays are approved for clinical use.

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