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High diagnostic performance of the random-access Sysmex HISCL™ pTau-217, Aβ42 and Aβ40 plasma assays for detecting amyloid pathology across the Alzheimer's disease clinical continuum.

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BACKGROUND

Alzheimer's disease (AD) blood biomarkers are now being implemented in clinical and trial settings; particularly phosphorylated tau-217 (pTau-217) and amyloid-beta (Aβ)42 and Aβ40. Robust assays on fully automated random-access instruments are required to increase accessibility and scalability of the blood testing and advance its clinical uptake.

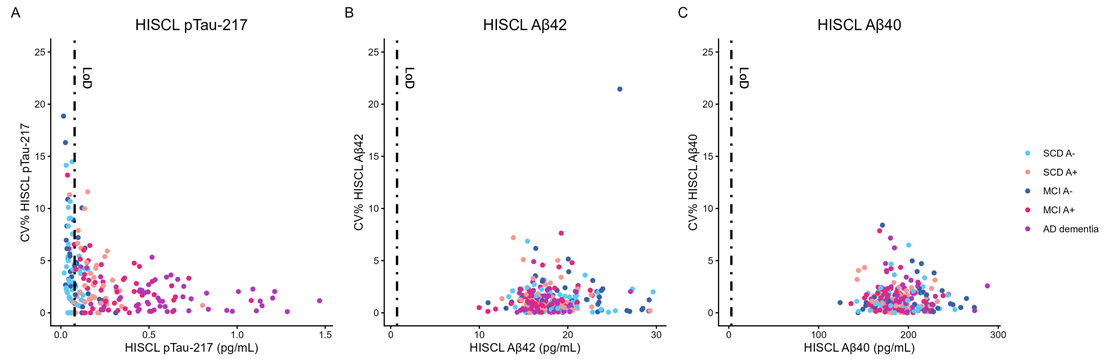
AIM

To analytically and clinically validate the Sysmex HISCL™ 5000 / 800 pTau-217, Aβ42 and Aβ40 assays for their potential to detect amyloid pathology across the clinical AD continuum.

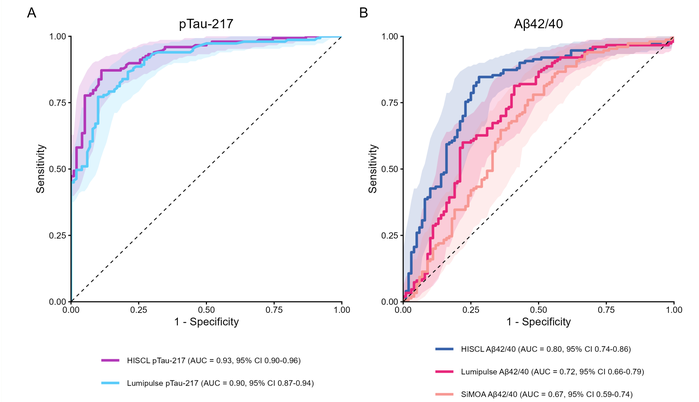
METHODS

- Analytical sensitivity, precision, parallelism, linearity and recovery of the HISCL™ assays pTau217, Aβ42 and Aβ40 were assessed in-house.
- Then, we selected plasma samples from the Amsterdam Dementia biobank from individuals with subjective cognitive decline (SCD; 50 amyloid status (Aβ) - and 50 Aβ + based on cerebrospinal fluid biomarker testing), mild cognitive impairment (MCI; 50 Aβ-, 50 Aβ+) and AD dementia (50 Aβ+). Groups were age and sex matched (mean ± SD age 66 ± 5.6 years; 40% female).
- Plasma samples were measured with HISCL™-5000 (pTau-217, Aβ42 and Aβ40), Lumipulse (pTau-217, Aβ42 and Aβ40) and Simoa (Aβ42 and Aβ40).

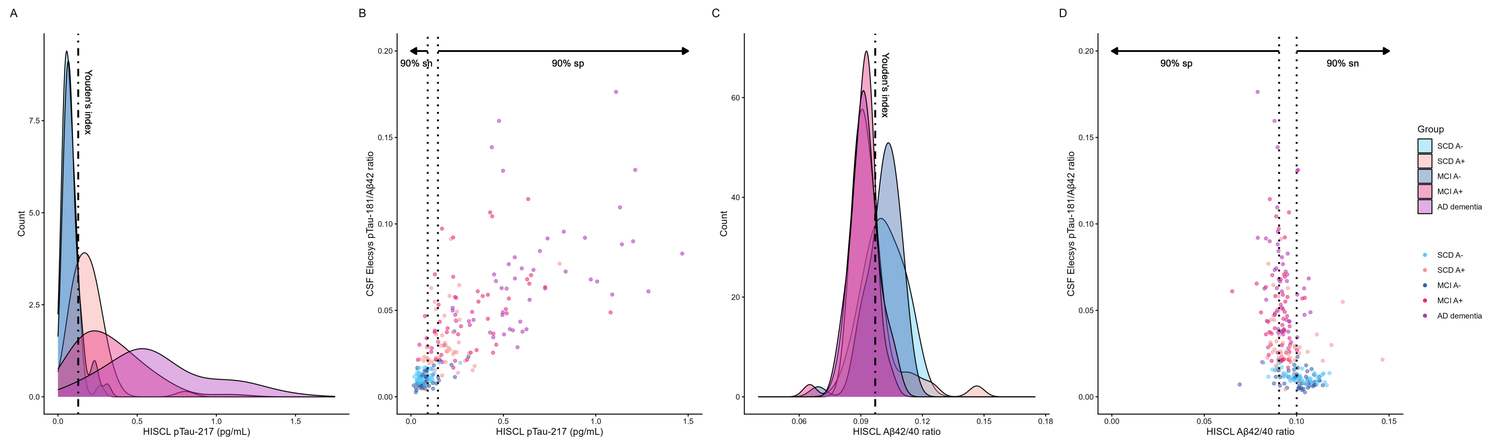
RESULTS



In these **precision plots**, coefficient of variation (CV) of duplicate measurements is plotted against the concentrations measured in the 250 clinical samples. Data points are color-coded for CSF-based amyloid status (Aβ- = blue, Aβ+ = red). The vertical lines represent the Limits of Detection (LoD) of the assays, which are 0.078 pg/mL for pTau217 (**A**), 0.71 pg/mL for Aβ42 (**B**) and 2.84 pg/mL for Aβ40 (**C**). pTau-217 concentrations were measured below the LoD in 63 samples (26%). All Aβ42 and Aβ40 concentrations were measured above their respective LoDs. Average CV was 2.9 ± 3.1% for pTau217, 1.4 ± 1.8% for Aβ42 and 1.4 ± 1.4% for Aβ40. In addition to the data presented in these plots: parallelism, linearity and recovery of all three assays were within acceptable limits.



ROC-AUC curves to detect CSF Aβ+ across the clinical continuum are presented. HISCL plasma pTau-217 performed significantly better than Lumipulse pTau-217 (**A**; ΔAUC = 0.03, DeLong's p = 0.02). HISCL Aβ42/40 performed significantly better than both Lumipulse Aβ42/40 and Simoa Aβ42/40 (**B**; ΔAUC 0.08 and ΔAUC = 0.14; DeLong's p ≤ 0.02).



Data distribution of HISCL pTau-217 **(A, B)** and Aβ42/40 **(C, D)** values measured across the AD clinical continuum, and in comparison to CSF pTau181/Aβ42 values is presented.

Cutoffs pTau-217:
Youden's = 0.128 pg/mL
(87.2% sensitivity, 88.8% specificity);
90%Sensitivity = <0.099 pg/mL,
90%Specificty = >0.146 pg/mL
(intermediate range = 12.1%).

Cutoffs Aβ42/40:
Youden's = 0.097
(84.7% sensitivity, 72.0% specificity).
90% Sensitivity = >0.100,
90% Specificity = <0.091
(intermediate range = 39%).

CONCLUSION

The Sysmex HISCL™-5000 / 800 pTau-217, Aβ42 and Aβ40 assays show strong analytical sensitivity and precision. HISCL pTau-217 and Aβ42/40 had strong diagnostic performance to detect AD across the clinical continuum, with significantly higher ROC-AUCs than obtained for Lumipulse and Simoa. These data qualify the HISCL™-5000 / 800 pTau-217 and Aβ42 and Aβ40 assays as reliable clinical-grade assays for implementation in clinics and trials.

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