High diagnostic performance of the random-access Sysmex HISCL™-5000 pTau217, 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 tau217 (pTau217) 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 pTau217, 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 three HISCL™ assays (pTau217, Aβ42 and Aβ40) were assessed in-house.

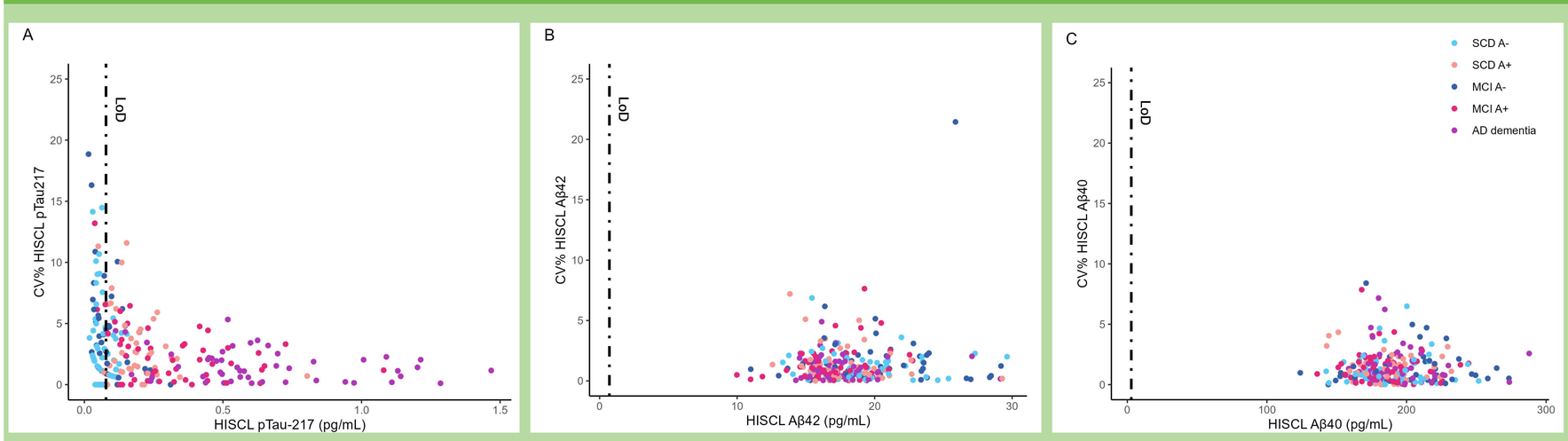
We selected plasma samples from the Amsterdam Dementia biobank from individuals with subjective cognitive decline (SCD; 50 amyloid status (Aβ) negative and 50 Aβ positive based on cerebrospinal fluid biomarker testing), mild cognitive impairment (MCI; 50 Aβ-, 50 Aβ+) and AD dementia (50 Aβ+). Groups were age and sex matched (mean ± SD age 66 ± 5.6 years; 40% female).

Plasma samples were measured with HISCL-5000 (pTau217, Aβ42 and Aβ40), Lumipulse (pTau217, Aβ42 and Aβ40) and Simoa (Aβ42 and Aβ40).

CONCLUSION

- The Sysmex HISCL™-5000/800 pTau217, Aβ42 and Aβ40 have strong analytical sensitivity and precision.
- HISCL pTau217 (and equally pTau217/Aβ42) had strong diagnostic performance to detect AD across the clinical continuum. Lumipulse pTau217 and pTau217Aβ42 had similar performance to detect AD.
- HISCL Aβ42/40 had a higher diagnostic performance than Lumipulse and Simoa Aβ42/40 to detect AD.

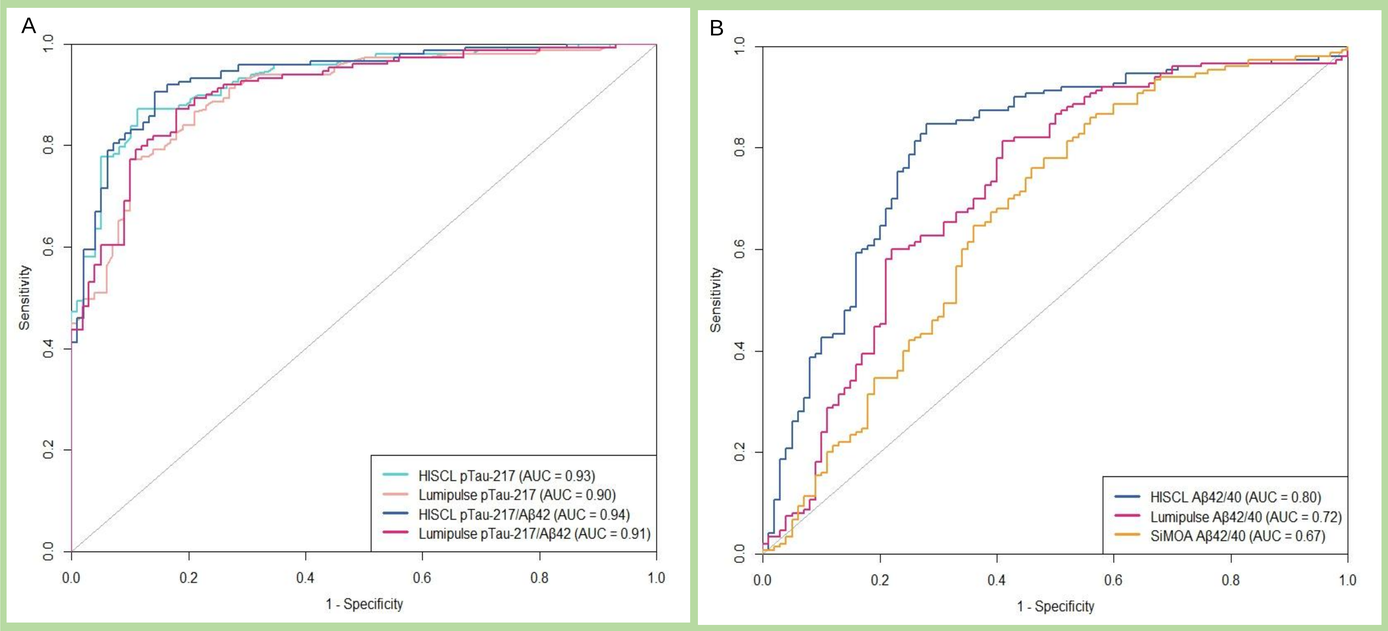
Analytical sensitivity and precision results of HISCL™ pTau217, Aβ42 and Aβ40



*In these **precision plots**, coefficient of variation (CV) of duplicate measurements is plotted against the concentrations as measured in the 250 clinical samples. The data points are color-coded for the CSF-based amyloid status (negative = blue, positive = red). The vertical lines represent the Limits of Detection (LoD) of the three 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).*

All samples were measured above the lower limit of detection of the Aβ42 and Aβ40 assays, and 74% of the samples were measured above the lower limit of detection of the pTau217 assays. Average ± SD CV was 3.3 ± 6.0% for pTau217, 1.4 ± 1.8% for Aβ42 and 1.4 ± 1.4% for Aβ40.

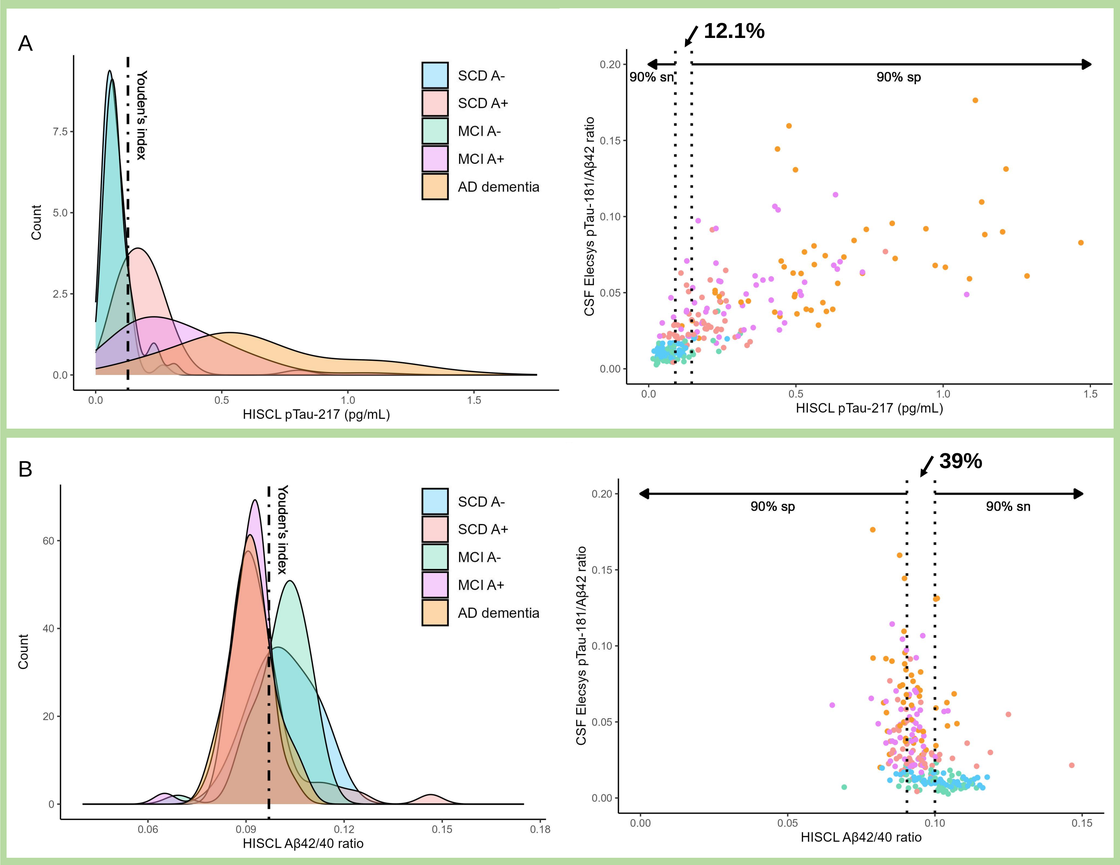
Comparison of diagnostic accuracy for AD for HISCL™ versus Lumipulse and Simoa



A) HISCL pTau217 AUC to detect AD across the clinical continuum was 0.93 (95%CI: 0.90 – 0.96), which was slightly better than AUC obtained with Lumipulse (DeLong's p = 0.02).

B) HISCL Aβ42/40 AUC to detect AD across the clinical continuum was 0.80 (95%CI: 0.74 – 0.86), which was higher than AUCs obtained with Lumipulse and Simoa (both: DeLong's p ≤ 0.02).

Cutoffs establishment for HISCL™ assays to identify AD



A) Data distribution of HISCL pTau217 levels as measured across the AD clinical continuum and in comparison to CSF pTau181/Aβ42 values are presented. The Youden's cutoff of 0.128 pg/mL resulted in 87.2% sensitivity and 88.8% specificity.

Cutoffs set at <0.099 pg/mL to achieve 90% sensitivity and at >0.146 pg/mL to achieve 90% specificity resulted in ***12.1%*** values falling in the intermediate range, PPV of 93% and NPV of 85%.

B) Data distribution of HISCL Aβ42/40 levels as measured across the AD clinical continuum and in comparison to CSF pTau181/Aβ42 values are presented. The Youden's cutoff of 0.097 resulted in 84.7% sensitivity and 72.0% specificity.

Cutoffs set at >0.100 to achieve 90% sensitivity and at <0.091 to achieve 90% specificity resulted in ***39%*** values in the intermediate range, PPV of 86% and NPV of 79%.

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