

Interest of α -synuclein Seed Amplification Assay (SAA) in patients with dementia with Lewy bodies difficult to diagnose

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Introduction : Dementia with Lewy Bodies (DLB) is characterized by the accumulation of misfolded α -synuclein aggregates within diseased neurons. The α -synuclein Real-Time Quaking-Induced Conversion (RT-QuIC) seeding amplification assay (SAA) offers excellent sensitivity and specificity for diagnosing DLB. However, RT-QuIC has rarely been tested in clinically challenging scenarios, such as prodromal (early-stage) phases or cases with highly uncertain diagnostic features. The aim of our study is to assess whether α -synuclein RT-QuIC can aid in challenging DLB diagnoses.

Patients and methods : A total of 116 patients were enrolled and categorized into 2 groups: a “difficult” group (n=82) with patients presenting diagnostic uncertainty (no clinical diagnosis due to a complete absence of DLB core symptoms (n=26) (based on McKeith’s 2017 criteria for dementia and 2020 criteria for prodromal DLB), and multiple suspected diagnoses including DLB (n=17)) and a “simple” group (n=39) with Alzheimer disease (AD) patients.

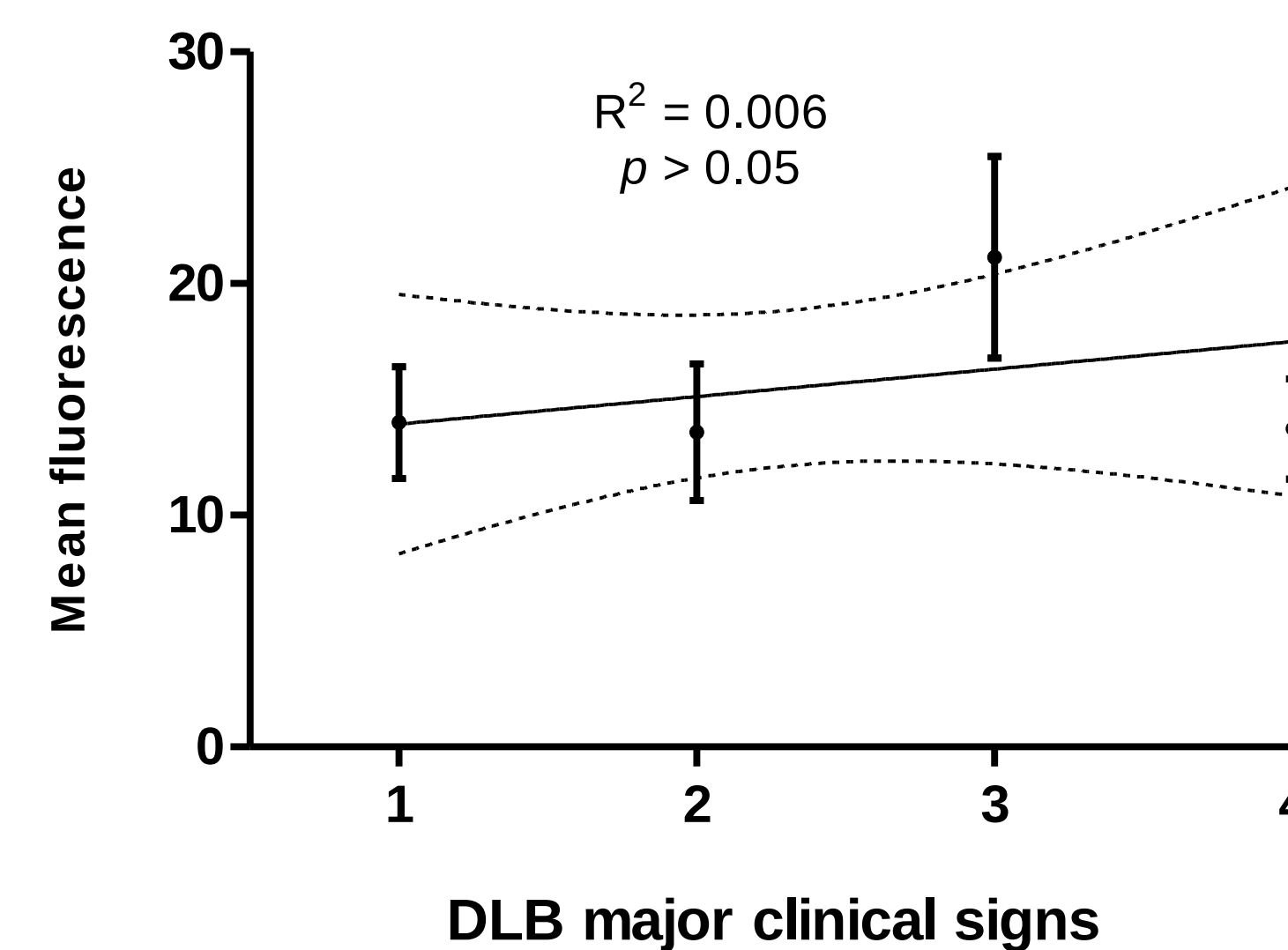
Technique for SAA (α -synuclein RT-QuIC): CSF was combined with a reaction mixture containing recombinant protein and Thioflavin T (ThT) dye, which enables detection of a fluorescent signal during fibril formation. The mixture is heated at 42°C, in the context of quaking, for at least 120 hours. This operation is performed simultaneously in 4 wells for each patient. An SAA result was defined as positive if a fluorescent signal was detected in ≥ 1 out of 4 wells.

Results :

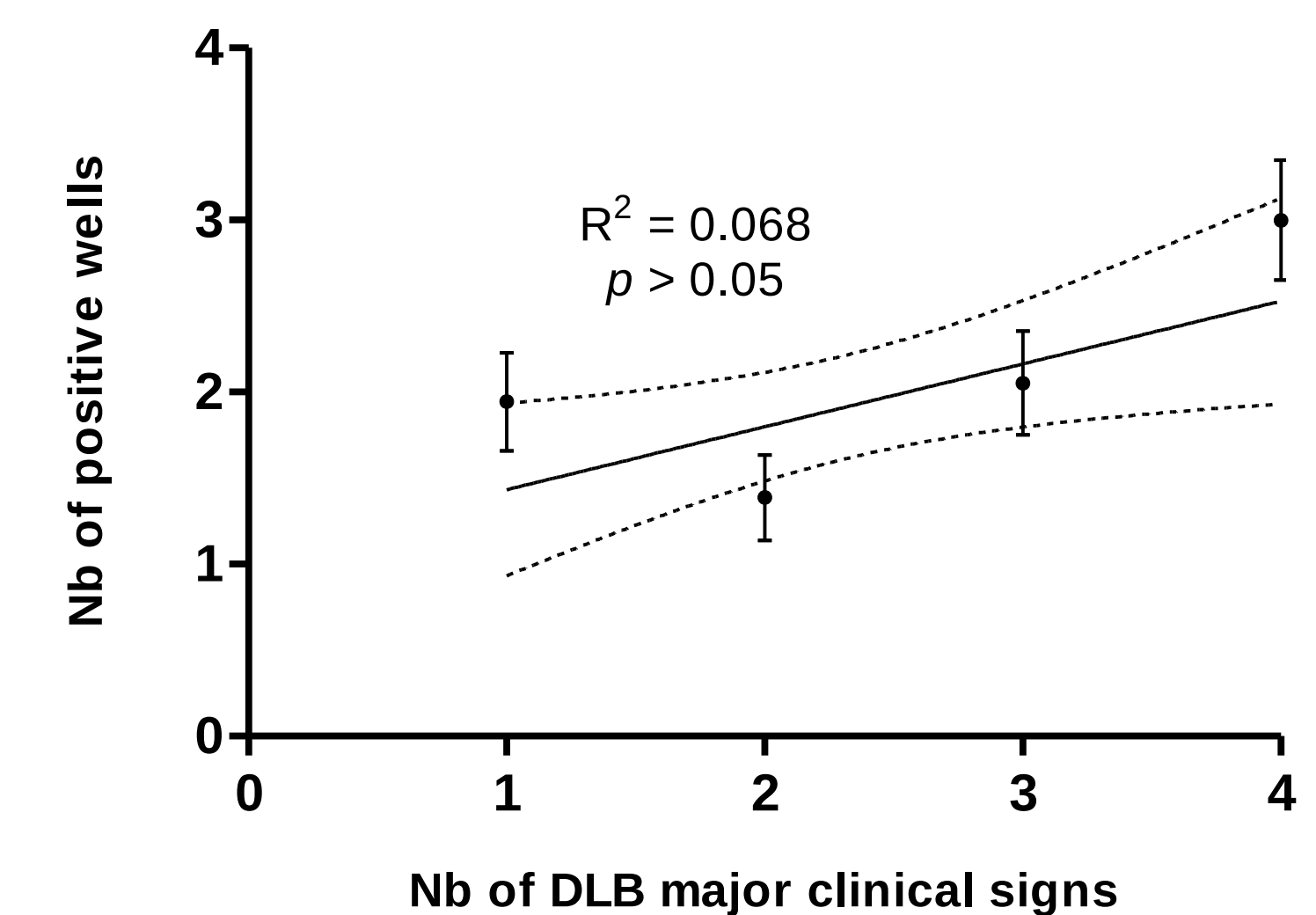
	1 well	2 wells	3 wells	4 wells
Sensitivity	76,83%	60,98%	36,59%	17,07%
Specificity	67,65%	82,35%	91,18%	97,06%
Positive predictive value	85,14%	89,29%	90,91%	93,33%
Negative predictive value	54,76%	46,67%	37,35%	32,67%

69% of patients with AD had at least one of the four symptoms included in the major diagnostic criteria for DLB

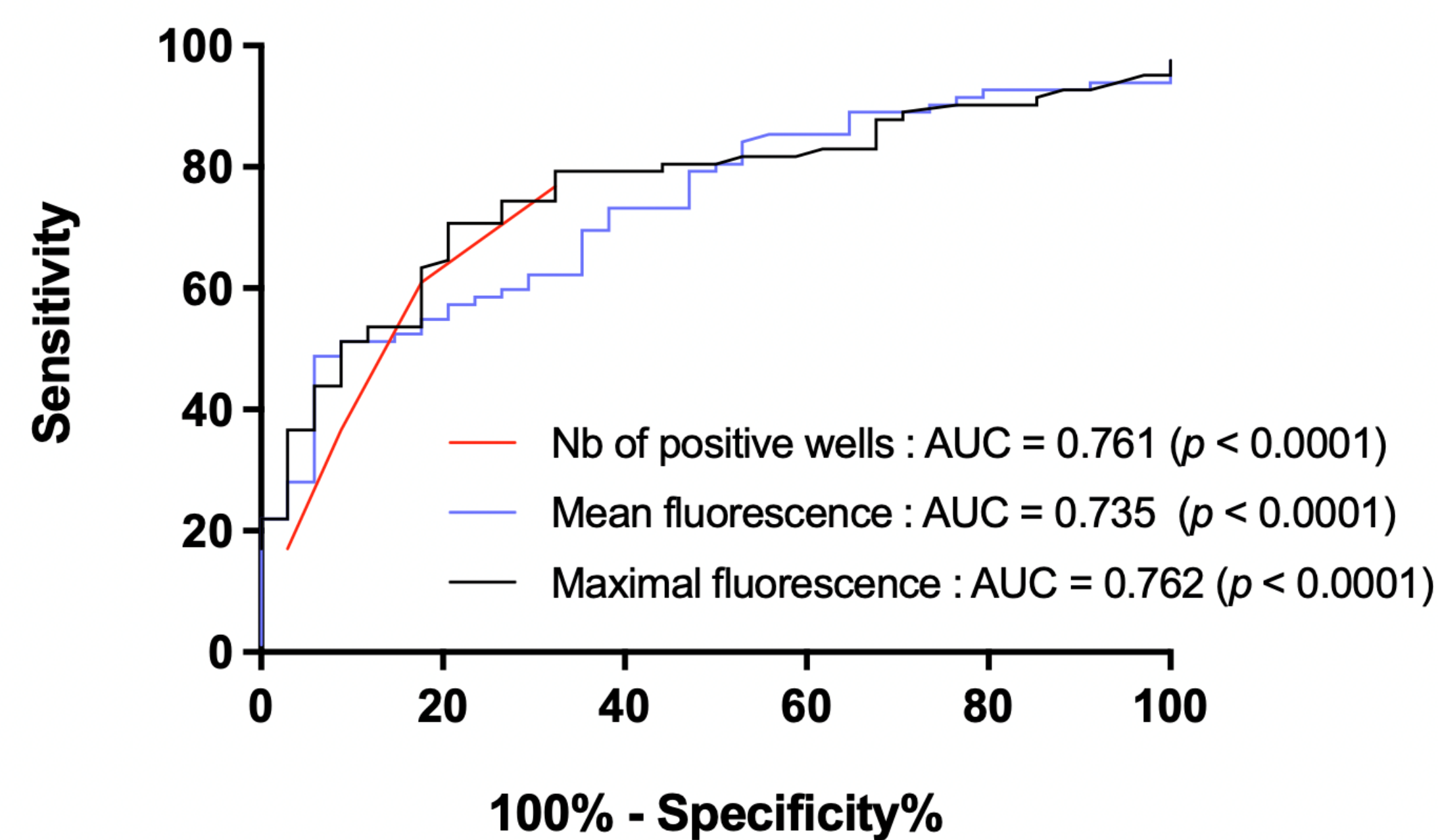
Correlation between DLB major clinical signs and mean fluorescence



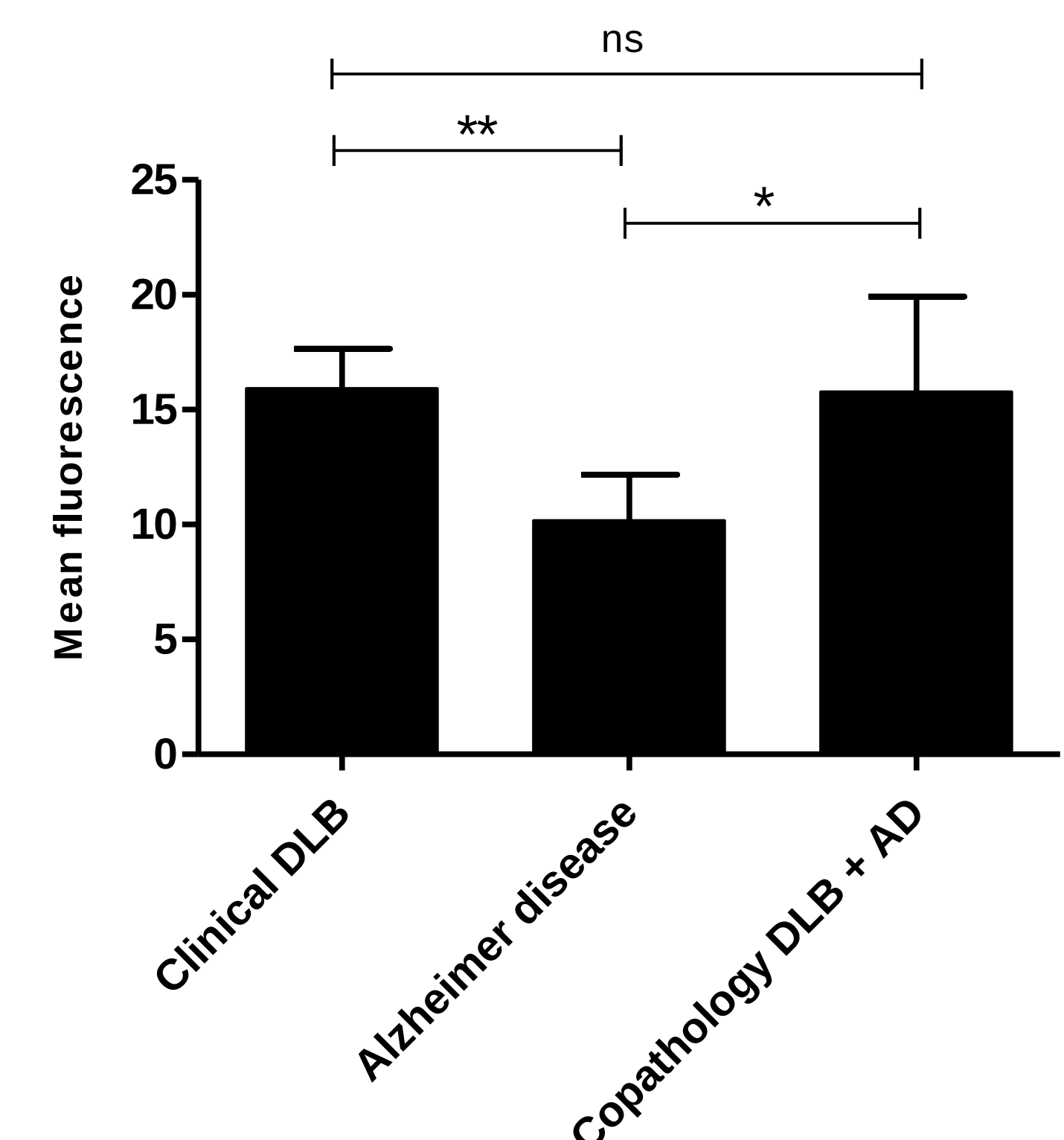
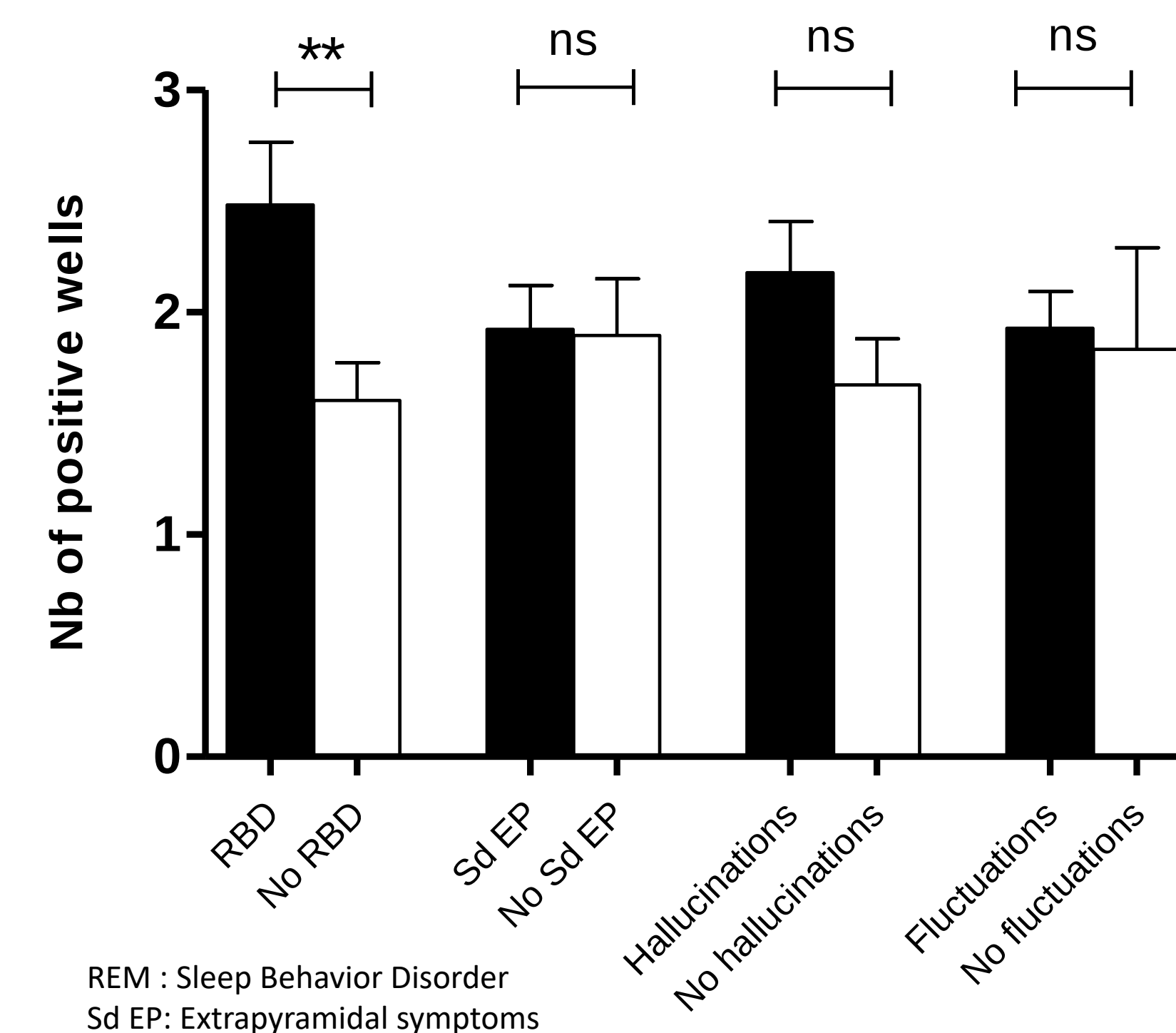
Correlation between the number of DLB major clinical signs and the number of positive wells



Comparison of diagnostic tests ROC curves



Number of positive wells based on major LBD clinical signs



Conclusion :

The SAA has excellent sensitivity in simple clinical diagnoses. In complex cases, its sensitivity is lower, but can help to identify DLB diagnoses, particularly if the patient does not show any core clinical signs of DLB, or when multiple diagnoses are suspected.