

Plasma TDP43 biomarkers for distinguishing autopsy-confirmed LATE from non-TDP43 cases

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BACKGROUND

Definitive diagnosis of limbic-predominant age-related TDP43 encephalopathy (LATE) is currently only possible at post-mortem. Biofluid biomarkers are urgently needed for *in vivo* detection.

AIM

To assess the diagnostic performance of NULISA plasma TDP43 and pTDP43-409 in discriminating between autopsy-confirmed LATE and non-TDP43 cases.

METHODS

Participants:

- N = 82 from Sydney Brain Bank, Victorian Brain Bank and NSW Brain Tissue Resource Centre.

Post-mortem disease classifications:

- “LATE”: participants with LATE.
- “non-TDP43”: participants without LATE or other TDP-43 proteinopathies (e.g., FTLT-TDP or ALS), including individuals with no neuropathological abnormalities.

Plasma assay:

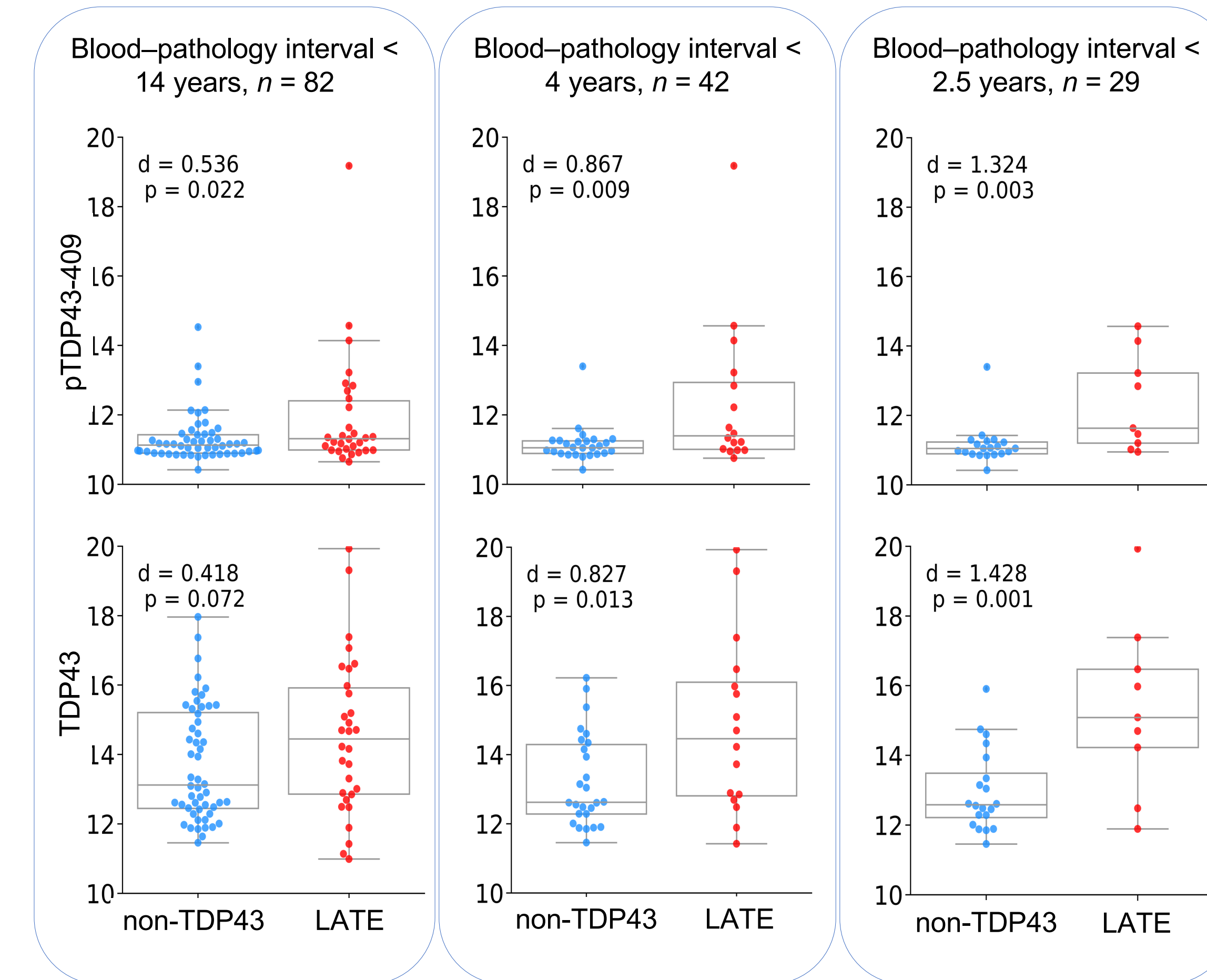
- Alamar NULISAseq CNS panel
 - Total TDP43 or TARDBP
 - Phosphorylated TDP43 at serine 409 (pTDP43-409)

Diagnostic performance

- Evaluated using area under the ROC curve (AUC)

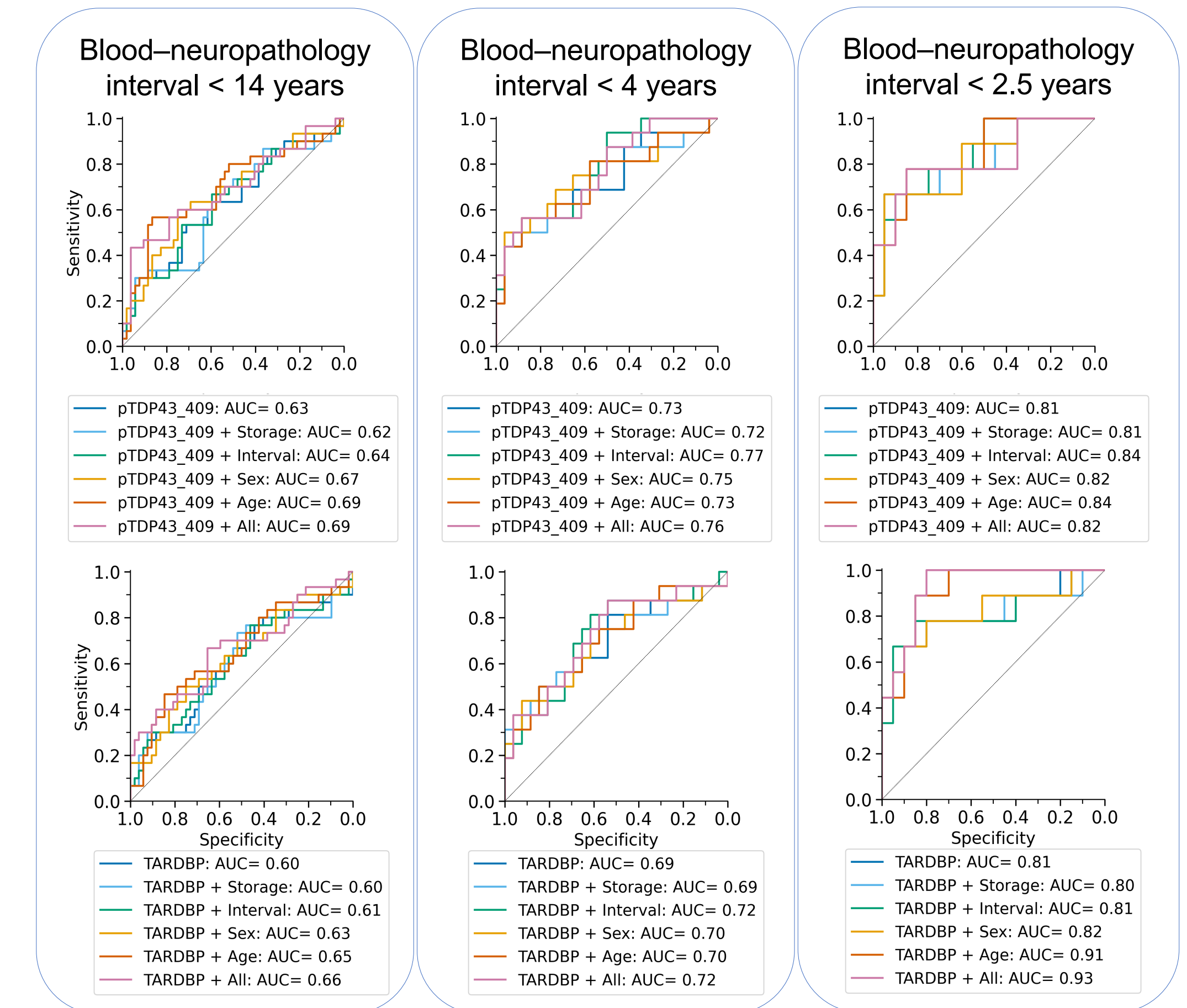
RESULTS

- Plasma TDP43 and pTDP43-409 levels were higher in LATE compared with non-TDP43 cases.
- Progressive tightening of the blood–neuropathology interval led to improved separation between LATE and non-TDP43 groups for both biomarkers.



Plasma TDP43 and pTDP43-409 levels stratified by blood–neuropathology interval. Plots show plasma pTDP43-409 (top row) and total TDP43 (bottom row) in non-TDP43 and LATE participants across progressively stricter blood–neuropathology intervals: full cohort (left), ≤ 4 years (middle), and ≤ 2.5 years (right). Cohen's *d* effect sizes and *p* values for group comparisons are shown within each panel.

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ROC curves showing discrimination of LATE vs non-TDP43 cases, using plasma pTDP43-409 and TDP43, across blood–neuropathology intervals. Models include biomarker alone and with covariates (blood storage duration, blood–pathology interval, sex, age, and all covariates). Diagnostic performance improves with shorter blood–neuropathology intervals, with highest AUCs in the ≤ 2.5 -year subset.

CONCLUSION

- Reduced diagnostic performance with long blood–neuropathology intervals likely reflects temporal mismatch rather than intrinsic biomarker limitations.
- Plasma TDP43 biomarkers show promise for *in vivo* detection of LATE. However, larger studies using more contemporaneously collected plasma, with shorter storage duration, are needed to confirm diagnostic performance.