

Plasma Neurofilament Light Chain To Support Delirium Diagnosis In Hospitalised Older Adults

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Background

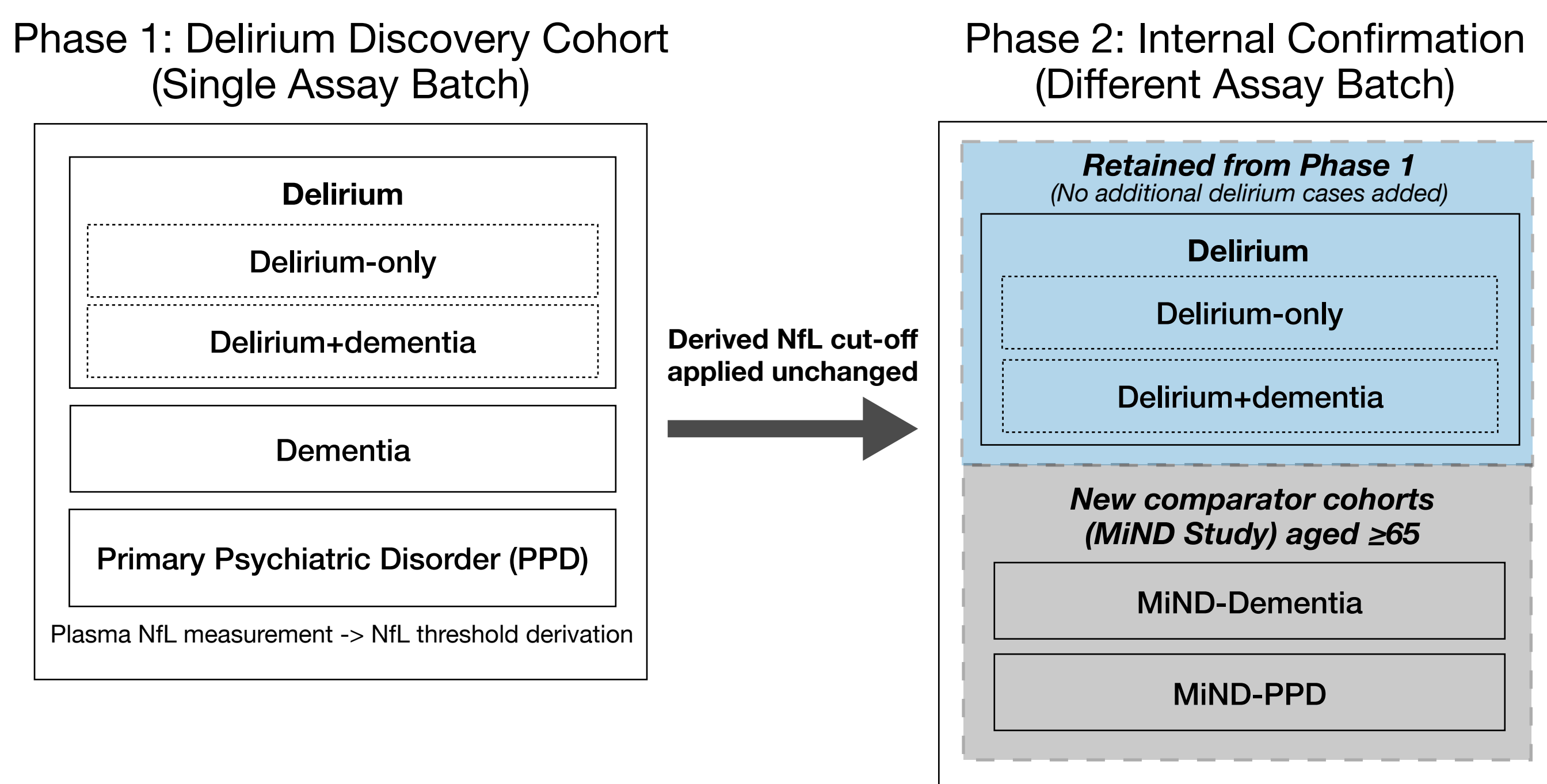
Delirium is common among hospitalised older adults yet frequently missed or misattributed to dementia and primary psychiatric disorders (PPD) due to overlapping features. Plasma neurofilament light chain (NfL) can be elevated in perioperative and intensive care patients with delirium, but its utility in general hospital inpatients with delirium remains unclear. We examined whether plasma NfL and glial fibrillary acidic protein (GFAP) can distinguish delirium from dementia and PPD in a population of general hospital inpatients.

Research Question

Can plasma NfL and/or GFAP screen for delirium in the acute hospital setting?

Methods

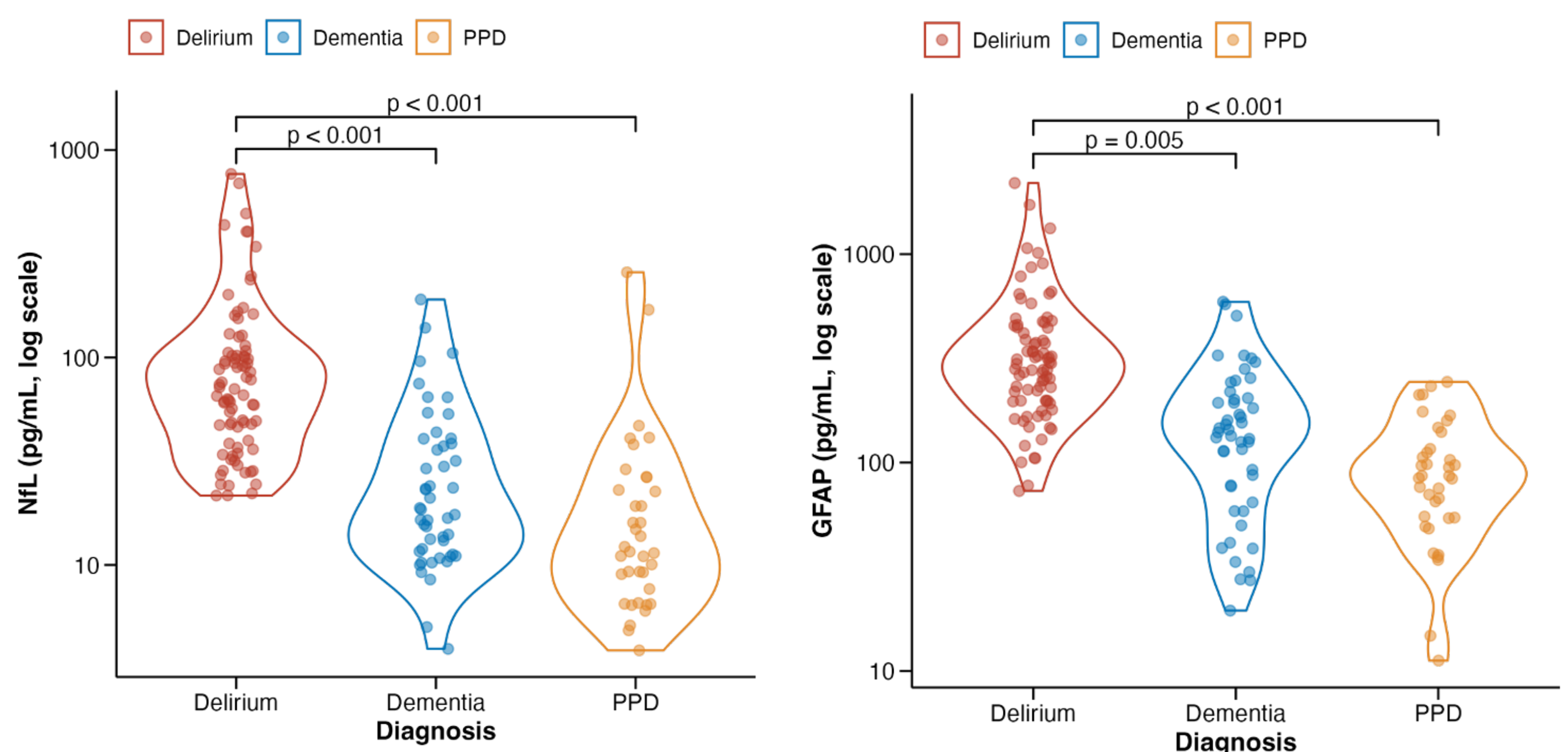
In Phase 1 (Delirium Discovery Cohort), we measured plasma NfL and GFAP using Simoa in hospitalised patients with delirium and compared them with dementia and PPD groups to derive an optimal NfL threshold. Phase 2 tested this threshold's performance by pairing the Phase 1 delirium group with internal independent dementia and PPD groups (MiND-Dementia & MiND-PPD).



Results

Characteristics: In Phase 1, the delirium group was significantly older than both the dementia and PPD groups. After adjusting for age, sex, and eGFR, plasma NfL was higher in delirium than in dementia ($\beta = 0.70$ [0.27, 1.15], $p < 0.001$) and PPD ($\beta = 1.08$ [0.60, 1.60], $p < 0.001$). Plasma GFAP showed the same pattern (dementia $\beta = 0.48$ [0.14, 0.85], $p = 0.005$; PPD $\beta = 0.93$ [0.59, 1.33], $p < 0.001$).

Mean (SD); n (%)	Phase 1: Delirium Discovery Cohort			Phase 2: MiND	
Characteristic	Delirium N = 82	Dementia N = 49	PPD N = 37	Dementia N = 36	PPD N = 34
Age (years)	83 (10)	64 (9)	63 (10)	71 (5)	74 (6)
Sex: Females	39 (48%)	22 (45%)	19 (51%)	11 (31%)	17 (50%)
eGFR	61 (25)	80 (14)	80 (16)	76 (11)	69 (13)
Weight (kg)	69 (16)	73 (19)	76 (19)	N/A	N/A
NfL (pg/mL)	113 (137)	33 (36)	27 (48)	18 (15)	23 (9)
GFAP (pg/mL)	435 (541)	168 (132)	98 (60)	190 (113)	185 (85)



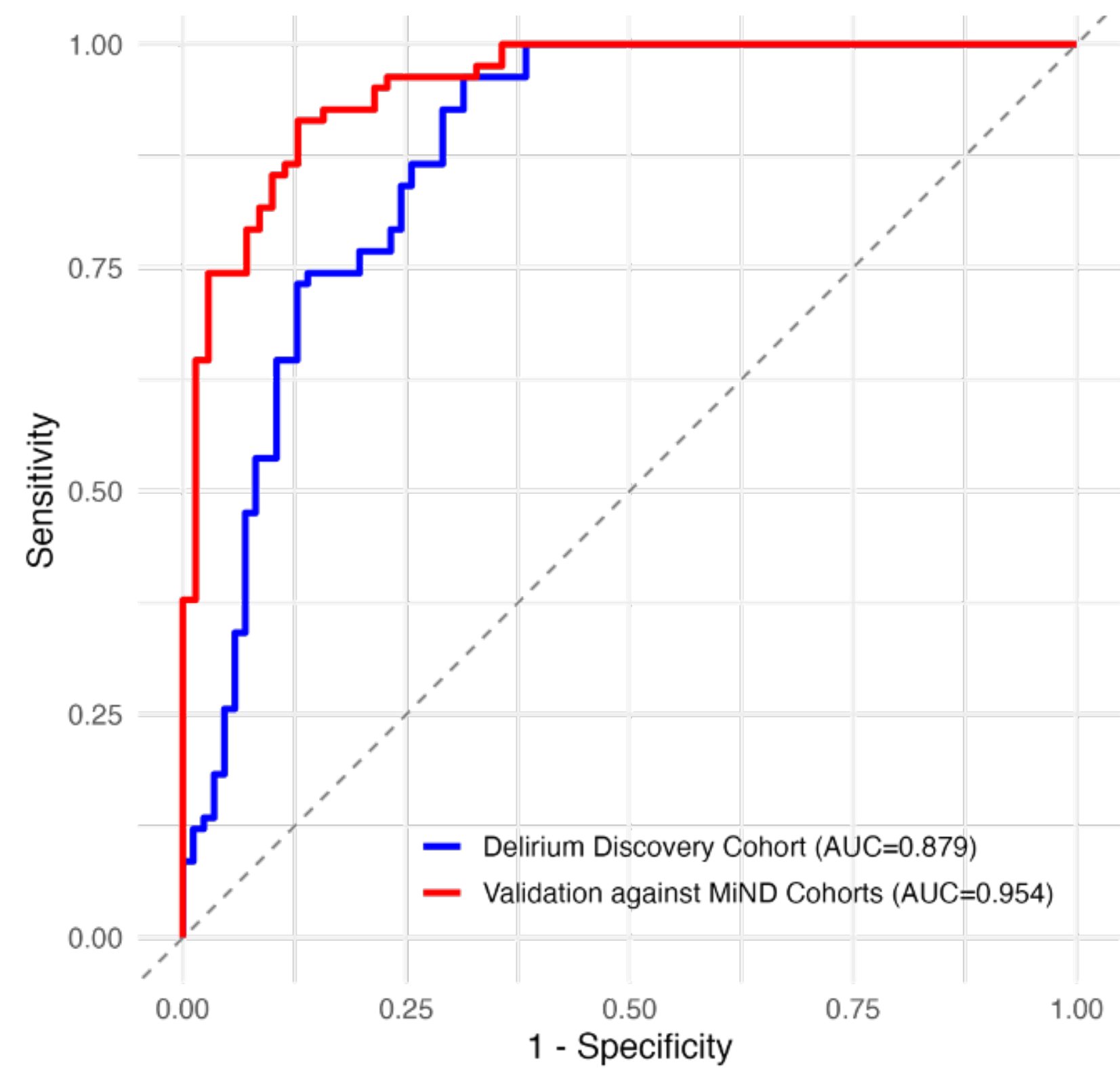
Figures 1-2. Distribution of plasma NfL (left) and GFAP (right) concentrations across diagnostic groups. Violin plots with individual data points overlaid.
P-values derived from bootstrapped GLM adjusting for age, sex and eGFR.

Delirium with and without dementia: Within the delirium group, plasma NfL was higher in delirium-only than in delirium with comorbid dementia ($\beta = 0.35$ [0.05, 0.66], $p = 0.022$).

Diagnostic accuracy: Plasma NfL showed strong discrimination (AUC 0.88). An optimal threshold of 24.1 pg/mL yielded 96% sensitivity and 69% specificity. GFAP performed slightly lower (AUC 0.86), and combining the two biomarkers did not meaningfully improve accuracy (AUC 0.90). In Phase 2, the same NfL threshold maintained strong performance against independent MiND comparator cohorts (AUC 0.95).

Biomarker	AUC	Sens	Spec	PPV	NPV	Accuracy
NfL (Phase 1)	0.88 [0.83, 0.93]	96%	69%	75%	95%	82%
GFAP (Phase 1)	0.86 [0.81, 0.92]	87%	71%	74%	85%	79%
NfL + GFAP (Phase 1)	0.90 [0.85, 0.95]	90%	79%	80%	89%	85%
NfL (Phase 2, validation)	0.95 [0.92, 0.98]	96%	77%	83%	94%	88%

Figure 3. ROC curves for plasma NfL discriminating delirium from dementia and PPD (Phase 1 = blue, Phase 2 = red)



Clinical takeaway
In a patient with acute confusion, a markedly elevated plasma NfL supports delirium, even against a background of dementia or PPD.

Conclusions

Plasma NfL shows promise as a biomarker for delirium in hospitalised patients, distinguishing it from dementia and PPD presentations with high sensitivity. Larger multicentre studies are needed to refine cut-offs, evaluate temporal dynamics, and determine integration into acute hospital delirium management pathways. The availability of a blood marker to aid in the identification of delirium would have significant health, economic and social benefits.



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