

Time-dependent associations of GFAP and interferon- α with cognitive and functional outcomes after ischemic stroke: a prospective cohort study

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Abstract

Blood biomarkers after ischemic stroke are commonly evaluated at a single sampling time and against a single outcome, although their concentrations and clinical associations may change during the acute-to-subacute phase. We prospectively studied 218 patients with acute ischemic stroke and measured plasma glial fibrillary acidic protein (GFAP), neurofilament light chain, interleukin-6, ubiquitin C-terminal hydrolase L1, and interferon- α (IFN- α) at admission, 24 hours, and day 7. At 3 months, 116 patients (53.2%) met education-adjusted criteria for post-stroke cognitive impairment (PSCI), and 51 (23.4%) had poor functional outcome (modified Rankin Scale [mRS] 3–6). GFAP showed the most consistent association with PSCI across sampling times (AUC 0.683, 0.680, and 0.683; all FDR $q < 0.001$). Admission GFAP remained associated with PSCI after clinical adjustment (OR 1.87 per ln-unit increase, 95% CI 1.27–2.75) and with lower 3-month Montreal Cognitive Assessment (MoCA) scores after adjustment for baseline cognition, but was not associated with poor functional outcome (adjusted OR 0.86, 95% CI 0.58–1.28). In contrast, day-7 IFN- α was independently associated with poor functional outcome (adjusted OR 1.97, 95% CI 1.43–2.70), and this association remained essentially unchanged after accounting for pulmonary infection. Paired within-patient comparisons showed greater discrimination of admission GFAP for cognitive than functional outcome, whereas delayed IFN- α showed greater discrimination for functional outcome. These findings indicate that the prognostic information carried by circulating biomarkers after stroke depends on both sampling time and the clinical outcome assessed, supporting the use of serial sampling and outcome-specific analyses in future biomarker studies of post-stroke recovery.

Introduction

Post-stroke cognitive impairment (PSCI) affects approximately one-third to one-half of stroke survivors within the first year and is associated with reduced functional independence, poorer rehabilitation participation, and worse long-term outcomes [1, 2]. The burden is particularly substantial in China, which has the largest number of people living with stroke worldwide [3]. Identifying patients at increased risk of cognitive impairment during the acute admission, when rehabilitation and follow-up plans are established, is therefore an important clinical priority.

Acute-phase risk stratification relies mainly on demographic and clinical characteristics, including age, stroke severity, and educational level, together with neuroimaging measures of infarct burden and cerebral small-vessel disease (CSVD) [4]. These measures are clinically informative but do not fully account for the marked interindividual variation in cognitive recovery. Blood-based biomarkers may provide complementary information by capturing tissue injury and inflammatory responses that are not directly represented by routine clinical assessment.

Glial fibrillary acidic protein (GFAP), released with astrocytic injury and reactive astrogliosis, and neurofilament light chain (NfL), a marker of neuroaxonal damage, have been widely investigated after acute ischemic stroke (AIS) and are associated with neurological injury and functional outcome [5, 6].

Their relation to post-stroke cognition is less consistent. Some studies identified both GFAP and NfL as independent predictors of PSCI and reported improved prediction when they were combined [7], whereas other analyses suggested substantial overlap between their prognostic signals [8]. Ubiquitin C-terminal hydrolase L1 (UCHL1) is another circulating marker of neuronal injury and may reflect brain tissue damage after AIS, but its association with subsequent cognitive impairment remains uncertain [9].

Biomarker interpretation is further complicated by time. Circulating concentrations evolve after stroke [8, 10, 11], so a value measured at admission may not represent the same biological phase as a value measured several days later. This temporal dimension also applies to inflammatory biomarkers. Elevated plasma interleukin-6 (IL-6) measured months after stroke, rather than at the acute admission, has been associated with later PSCI [12]. Type I interferons, including interferon- α (IFN- α) and interferon- β , are involved in innate immune activation and vascular inflammation [13]. Their activation and pathogenic role have been investigated in AIS animal models [14–16]; however, type I interferons as circulating markers of cognitive or functional recovery after AIS have rarely been examined.

Heterogeneity across published biomarker studies may therefore reflect three related design choices: which markers are measured, when blood is sampled, and which clinical outcome is modeled. Most studies examine one or two preselected markers at a single time point, limiting direct comparison of their relative performance and temporal behavior. In addition, cognitive and functional outcomes after stroke are related but not interchangeable. Parallel analysis of both endpoints within the same patients can help distinguish biomarker associations that are preferentially related to cognition from those that mainly reflect global stroke severity.

We therefore systematically compared plasma GFAP, NfL, IL-6, UCHL1, and IFN- α at admission, 24 hours, and day 7 in a prospective AIS cohort. Fifteen biomarker-time combinations were evaluated against two 3-month outcomes: education-adjusted PSCI and poor functional outcome. We examined temporal differences in biomarker discrimination, their independent and incremental value beyond clinical variables, their relationship to cognitive recovery, and whether the same biomarkers showed different associations with cognitive and functional outcomes.

Methods

Study design and participants

This single-center prospective observational cohort enrolled consecutive patients with acute ischemic stroke admitted to the Department of Neurology, Jiangsu University Affiliated Kunshan Hospital, between April 2025 and March 2026. Eligible patients were 18 years or older, had ischemic stroke confirmed by clinical assessment and neuroimaging, and presented within 24 hours of symptom onset. Exclusion criteria were pre-stroke modified Rankin Scale (mRS) score of 3 or higher, pre-existing dementia or cognitive impairment, severe aphasia or impaired consciousness precluding cognitive testing, major pre-existing neurological or psychiatric disease, active malignancy, active systemic inflammatory or

infectious disease at admission, and traumatic disease. Of 276 patients screened, 218 with complete biomarker and 3-month outcome data comprised the analytic cohort.

The study was approved by the institutional ethics committee (reference 2022-06-022-K01), registered at the Chinese Clinical Trial Registry (ChiCTR2300069479), and conducted in accordance with the Declaration of Helsinki [17]. Written informed consent was obtained from all participants or their legal representatives.

Clinical and neuroimaging assessment

Demographic characteristics, educational level, vascular risk factors, and stroke etiology according to the TOAST classification (Adams et al., 1993) were recorded at admission. Stroke severity was quantified with the National Institutes of Health Stroke Scale (NIHSS). Computed tomography or magnetic resonance imaging was used to categorize infarct extent (focal/small, regional/medium, or large/massive), mass effect, hemorrhagic transformation, and malignant edema. CSVD burden was characterized by white-matter hyperintensity severity (Fazekas score, dichotomized at 2 or higher), at least two lacunes of presumed vascular origin, and cerebral microbleeds on susceptibility-weighted imaging. Pulmonary infection developing during hospitalization was recorded as a post-stroke complication. Diagnosis and treatment followed published guidelines [18, 19].

Biomarker measurement

Venous blood was collected at T1 (admission), T2 (24 hours after admission), and T3 (day 7) into EDTA-containing tubes and centrifuged at $2,000 \times g$ for 10 minutes at 4°C. Plasma was aliquoted, snap-frozen, and stored at -80°C until analysis. GFAP, NfL, IL-6, UCHL1, and IFN- α were quantified using the AST-Dx90 single-molecule immunoassay platform (Astrabio, Suzhou, China) with the corresponding reagent kits according to the manufacturer's instructions. Samples were measured in duplicate, and laboratory personnel were blinded to clinical data. Biomarker concentrations were natural-log transformed for regression analyses because of marked right skew. Dose-response was also examined by biomarker quartiles, and the linear-in-log specification was compared with a restricted cubic spline on the raw scale (Supplementary Table S1 and Supplementary Figure S1).

Outcomes

Cognition was assessed using the Beijing version of the Montreal Cognitive Assessment (MoCA) [20] at admission and 3 months. Because 155 of 218 participants (71.1%) had fewer than 12 years of formal education, the primary cognitive outcome used the education correction specified by the MoCA scoring instructions: one point was added for participants with 12 or fewer years of education, and PSCI was defined as an education-adjusted 3-month MoCA score below 26. This definition classified 116 patients (53.2%) as impaired, compared with 135 (61.9%) using the unadjusted threshold. One participant with a

raw score of 30 received an uncapped adjusted score of 31; this did not alter the binary PSCI classification.

Functional outcome was assessed with the mRS at 3 months; poor functional outcome was defined as mRS 3–6. Depressive symptoms were assessed with the Hamilton Depression Rating Scale (HAMD) at admission and 3 months.

Statistics and reproducibility

Continuous variables are summarized as median (interquartile range) and were compared with the Mann–Whitney U test; categorical variables are presented as n (%) and were compared with the χ^2 test. All tests were two-sided.

The analysis followed four stages. First, each of the five biomarkers at each of three sampling times was evaluated in a separate logistic model for PSCI (15 biomarker-time combinations); *P* values were corrected across these 15 tests using the Benjamini–Hochberg false-discovery rate (FDR) procedure. Second, the leading cognitive marker and sampling time were evaluated in multivariable clinical models. Third, the same biomarker panel was screened against poor functional outcome using the identical procedure. Fourth, biomarker discrimination was compared directly between the cognitive and functional endpoints.

Clinical adjustment models differed by endpoint: age, admission NIHSS, and admission HAMD were included for PSCI, whereas age, admission NIHSS, and infarct extent were included for functional outcome. An extended cognitive model comprised age, sex, admission NIHSS, education, and admission MoCA. Discrimination was quantified by the area under the receiver-operating-characteristic curve (AUC). Nested-model AUCs were compared with the DeLong method [21], and incremental model fit was assessed using likelihood-ratio tests.

To determine whether biomarker discrimination differed between cognitive and functional outcomes, AUCs for the same biomarker were compared within patients using paired bootstrap resampling (4,000 resamples). Cross-endpoint comparisons were performed for the biomarkers selected from the cognitive and functional screens, with Holm adjustment across the two AUC comparisons; corresponding clinically adjusted biomarker–outcome associations were FDR-corrected across the four tests. To evaluate endpoint dependence across the biomarker panel as a whole, outcome labels were permuted within patients 2,000 times, and the observed maximum absolute Δ AUC and sum of squared Δ AUC values across all 15 biomarker–time combinations were compared with their permutation distributions. The complete set of 15 cross-endpoint AUC comparisons was considered exploratory, and corrected using the Benjamini–Hochberg FDR procedure. Because the two endpoints contained 116 and 51 events, respectively, a sensitivity analysis repeated the cognitive AUC analysis after randomly down-sampling PSCI cases to 51 across 500 replicates.

Cognitive recovery was evaluated by modeling 3-month MoCA (raw score without being adjusted for education) with admission MoCA as a covariate, together with age, sex, admission NIHSS, and education, rather than analyzing an arithmetic change score. *P* values for the 15 biomarker–time combinations in the cognitive-recovery analysis were corrected using the Benjamini–Hochberg procedure.

As a sensitivity analysis, the cognitive analyses were repeated using an unadjusted MoCA threshold of < 26; incremental discrimination of the combined GFAP–NfL model was also assessed.

Because pulmonary infection could influence circulating inflammatory biomarkers and was associated with functional outcome, post hoc sensitivity analyses examined its potential influence on the principal biomarker associations. Pulmonary infection was added to the endpoint-specific clinical adjustment models; analyses were then repeated after excluding patients who developed pulmonary infection. Biomarker-by-infection interaction terms were additionally tested for the principal GFAP and IFN- α associations.

Statistical analyses were performed in SPSS version 26.0 (IBM Corp., Armonk, NY, USA) and Python version 3.14.6; *P* < 0.05 was considered statistically significant after the prespecified multiplicity adjustment where applicable.

Results

Cohort characteristics

Among 218 patients, 116 (53.2%) met the education-adjusted definition of PSCI at 3 months and 51 (23.4%) had poor functional outcome. Patients with PSCI were older (median 68 versus 60 years, *P* < 0.001) and had more severe strokes (admission NIHSS 6 versus 2, *P* < 0.001). Cardioembolic stroke, larger infarct extent, mass effect, hemorrhagic transformation, malignant edema, pulmonary infection, and moderate-to-severe white-matter hyperintensities were also more frequent among patients with PSCI (Table 1).

Table 1

Baseline characteristics, serial plasma biomarkers, and 3-month outcomes by cognitive status.

Variable	Non-PSCI (n = 102)	PSCI (n = 116)	P value
Demographics and medical history			
Age, years	62 (52–72)	68 (61–78)	< 0.001
Male, n (%)	73 (71.6)	83 (71.6)	1.000
Education, n (%)			0.658
<i>No formal education</i>	3 (2.9)	6 (5.2)	
<i>3–5 years</i>	30 (29.4)	40 (34.5)	
<i>6–11 years</i>	37 (36.3)	39 (33.6)	
<i>≥ 12 years</i>	32 (31.4)	31 (26.7)	
TOAST subtype, n (%)			0.021
<i>Large-artery atherosclerosis</i>	42 (41.2)	45 (38.8)	
<i>Cardioembolism</i>	21 (20.6)	43 (37.1)	
<i>Small-vessel occlusion</i>	35 (34.3)	28 (24.1)	
<i>Other/undetermined</i>	4 (3.9)	0 (0.0)	
Hypertension, n (%)	24 (23.5)	26 (22.4)	0.973
Diabetes mellitus, n (%)	73 (71.6)	76 (65.5)	0.416
Dyslipidaemia, n (%)	35 (34.3)	23 (19.8)	0.024
Prior stroke/TIA, n (%)	26 (25.5)	23 (19.8)	0.403
Smoking, n (%)	48 (47.1)	37 (31.9)	0.031
Admission clinical and imaging			
Admission NIHSS	2 (1–4)	6 (3–10)	< 0.001
Infarct extent, n (%)			0.003
<i>Focal/small</i>	70 (68.6)	56 (48.3)	
<i>Regional/medium</i>	20 (19.6)	27 (23.3)	
<i>Large/massive</i>	12 (11.8)	33 (28.4)	
Note: Data are median (IQR) or n (%). PSCI defined as education-adjusted 3-month MoCA < 26. NIHSS, National Institutes of Health Stroke Scale; TOAST, Trial of Org 10172 in Acute Stroke Treatment; GFAP, glial fibrillary acidic protein; NfL, neurofilament light chain; IL-6, interleukin-6; UCHL1, ubiquitin C-terminal hydrolase L1; IFN- α , interferon- α ; MoCA, Montreal Cognitive Assessment; HAMD, Hamilton Depression Rating Scale; mRS, modified Rankin Scale.			

Variable	Non-PSCI (n = 102)	PSCI (n = 116)	P value
Demographics and medical history			
Mass effect (mild or greater), n (%)	1 (1.0)	12 (10.3)	0.009
Hemorrhagic transformation, n (%)	4 (3.9)	21 (18.1)	0.002
Malignant edema, n (%)	1 (1.0)	13 (11.2)	0.005
Pulmonary infection, n (%)	7 (6.9)	21 (18.1)	0.023
Fazekas score ≥ 2 , n (%)	42 (41.2)	65 (56.0)	0.040
Old lacunes ≥ 2 , n (%)	42 (41.2)	64 (55.2)	0.054
Cerebral microbleeds, n (%)	29 (28.4)	30 (25.9)	0.785
Treatment, n (%)			0.004
<i>Intravenous thrombolysis</i>	40 (39.2)	37 (31.9)	
<i>Endovascular therapy</i>	3 (2.9)	19 (16.4)	
<i>Conservative/medical</i>	59 (57.8)	60 (51.7)	
Plasma biomarkers			
GFAP T1 (pg/mL)	10.84 (6.30–17.43)	19.34 (10.42–29.41)	< 0.001
GFAP T2 (pg/mL)	14.11 (7.74–23.52)	23.54 (12.84–87.11)	< 0.001
GFAP T3 (pg/mL)	15.43 (8.04–29.03)	28.41 (15.54–145.60)	< 0.001
NfL T1 (pg/mL)	33.31 (17.60–64.59)	58.77 (29.70–111.68)	0.001
NfL T2 (pg/mL)	29.36 (17.27–62.84)	49.70 (24.32–94.71)	< 0.001
NfL T3 (pg/mL)	47.41 (26.41–89.69)	80.27 (35.51–136.90)	0.007
IL-6 T1 (pg/mL)	1.77 (1.00–6.04)	3.65 (1.24–9.09)	0.014
IL-6 T2 (pg/mL)	1.78 (0.97–4.88)	2.83 (1.33–6.28)	0.030
IL-6 T3 (pg/mL)	1.73 (0.83–5.53)	4.02 (1.42–7.31)	0.008
Note: Data are median (IQR) or n (%). PSCI defined as education-adjusted 3-month MoCA < 26. NIHSS, National Institutes of Health Stroke Scale; TOAST, Trial of Org 10172 in Acute Stroke Treatment; GFAP, glial fibrillary acidic protein; NfL, neurofilament light chain; IL-6, interleukin-6; UCHL1, ubiquitin C-terminal hydrolase L1; IFN-α, interferon-α; MoCA, Montreal Cognitive Assessment; HAMD, Hamilton Depression Rating Scale; mRS, modified Rankin Scale.			

Variable	Non-PSCI (n = 102)	PSCI (n = 116)	P value
Demographics and medical history			
UCHL1 T1 (pg/mL)	37.15 (20.94–65.41)	29.84 (14.89–65.06)	0.283
UCHL1 T2 (pg/mL)	32.97 (17.35–54.77)	29.48 (18.02–60.08)	0.973
UCHL1 T3 (pg/mL)	29.44 (14.99–54.54)	32.57 (15.86–57.85)	0.575
IFN-α T1 (pg/mL)	8.38 (4.91–25.52)	11.34 (4.72–51.01)	0.133
IFN-α T2 (pg/mL)	8.52 (4.78–37.45)	14.13 (4.79–51.55)	0.066
IFN-α T3 (pg/mL)	8.61 (4.68–30.04)	22.04 (5.64–56.04)	0.011
D-dimer (mg/L)	0.29 (0.16–0.69)	0.46 (0.22–0.92)	0.015
Admission neuropsychological assessment			
MoCA	23 (21–25)	20 (19–22)	< 0.001
HAMD	7 (5–8)	8 (7–9)	< 0.001
Outcomes at 3 months			
MoCA (raw)	27 (26–28)	22 (20–23)	< 0.001
MoCA (education-adjusted)	27 (26–28)	23 (21–24)	< 0.001
HAMD	6 (4–7)	7 (6–8)	< 0.001
NIHSS	2 (1–5)	7 (5–14)	< 0.001
mRS	1 (0–2)	2 (1–3)	< 0.001
Poor outcome (mRS 3–6), n (%)	13 (12.7)	38 (32.8)	< 0.001
Note: Data are median (IQR) or n (%). PSCI defined as education-adjusted 3-month MoCA < 26. NIHSS, National Institutes of Health Stroke Scale; TOAST, Trial of Org 10172 in Acute Stroke Treatment; GFAP, glial fibrillary acidic protein; NfL, neurofilament light chain; IL-6, interleukin-6; UCHL1, ubiquitin C-terminal hydrolase L1; IFN-α, interferon-α; MoCA, Montreal Cognitive Assessment; HAMD, Hamilton Depression Rating Scale; mRS, modified Rankin Scale.			

GFAP is consistently associated with cognitive outcome across sampling times

Across the 15 biomarker-time combinations, GFAP showed the most consistent association with PSCI. Discrimination was similar at admission, 24 hours, and day 7 (AUC 0.683, 0.680, and 0.683, respectively; all $q < 0.001$). NfL showed weaker associations at admission and 24 hours (AUC 0.625 and 0.638), IFN-α

was associated with PSCI only at T3 after FDR correction (AUC 0.600), and neither IL-6 nor UCHL1 showed a corrected association at any sampling time (Table 2; Fig. 1A).

Table 2
Association of each plasma biomarker with 3-month PSCI by sampling time.

Marker	OR per ln-unit	95% CI	<i>P</i>	<i>q</i> (FDR)	AUC
T1 – admission					
GFAP	2.056	1.47–2.88	< 0.001	< 0.001	0.683
NfL	1.309	1.05–1.63	0.015	0.037	0.625
IL-6	1.164	0.99–1.37	0.061	0.084	0.597
IFN- α	1.178	1.00–1.38	0.045	0.082	0.559
UCHL1	0.925	0.76–1.13	0.443	0.511	0.542
T2 – 24 hours					
GFAP	1.767	1.39–2.25	< 0.001	< 0.001	0.680
NfL	1.390	1.09–1.78	0.009	0.026	0.638
IL-6	1.184	1.00–1.40	0.052	0.082	0.585
IFN- α	1.221	1.02–1.47	0.032	0.069	0.572
UCHL1	1.008	0.82–1.24	0.939	0.939	0.499
T3 – day 7					
GFAP	1.617	1.30–2.01	< 0.001	< 0.001	0.683
NfL	1.244	0.98–1.58	0.073	0.091	0.605
IL-6	1.167	1.00–1.37	0.055	0.082	0.605
IFN- α	1.328	1.09–1.61	0.004	0.016	0.600
UCHL1	1.036	0.85–1.26	0.725	0.777	0.522
Note: Odds ratios per natural-log unit. <i>q</i> , Benjamini–Hochberg false-discovery rate across all fifteen marker–time-point combinations.					

Admission GFAP remains associated with cognitive outcome after clinical adjustment

Because GFAP discriminated PSCI similarly at all three sampling times, admission was prioritized for detailed analysis on clinical and statistical grounds. Adding GFAP to the cognitive clinical model improved model fit most strongly at admission (likelihood-ratio $\chi^2 = 11.70$, $P < 0.001$), compared with 24

hours and T3 ($\chi^2 = 5.93$ and 5.97 , respectively; both $P = 0.015$), and the admission sample is available at the time initial rehabilitation decisions are made.

Admission GFAP remained independently associated with PSCI after adjustment for age, admission NIHSS, and HAMD (OR 1.87 per ln-unit, 95% CI 1.27–2.75; $P = 0.001$), yielding a model AUC of 0.822. In the extended model, admission MoCA was the strongest predictor (OR 0.61 per point, $P < 0.001$), but GFAP remained independently associated with PSCI in the extended model (OR 2.14, 95% CI 1.40–3.25; $P < 0.001$), and the model AUC increased to 0.870 (Table 3; Fig. 2).

The incremental gain in discrimination from GFAP was modest. Adding admission GFAP to the clinical model increased AUC from 0.808 to 0.822 (difference 0.013, 95% CI – 0.015 to 0.042; $P = 0.365$). Thus, GFAP added statistically independent information without materially improving patient ranking beyond the clinical model.

Admission GFAP was also associated with subsequent cognitive performance. After adjustment for admission MoCA, age, sex, admission NIHSS, and education, higher admission GFAP was associated with a lower 3-month MoCA score ($\beta = -0.468$ points per ln-unit, 95% CI – 0.764 to – 0.173; $P = 0.002$; $q = 0.025$), whereas admission GFAP was not associated with admission MoCA ($\beta = -0.123$; $P = 0.456$).

Table 3
Multivariable models for 3-month PSCI including admission GFAP.

Variable	OR	95% CI	P	Model AUC
Model 1 – Clinical				
Age, per year	1.042	1.017–1.069	0.001	0.808
Admission NIHSS, per point	1.174	1.092–1.263	< 0.001	
Admission HAMD, per point	1.477	1.229–1.776	< 0.001	
Model 2 – GFAP-T1 alone				
ln GFAP-T1, per ln-unit	2.056	1.466–2.883	< 0.001	0.683
Model 3 – Clinical + GFAP-T1				
Age, per year	1.037	1.010–1.064	0.006	0.822
Admission NIHSS, per point	1.160	1.077–1.249	< 0.001	
Admission HAMD, per point	1.493	1.235–1.804	< 0.001	
ln GFAP-T1, per ln-unit	1.870	1.273–2.747	0.001	
Model 4 – Extended clinical				
Age, per year	1.052	1.023–1.083	< 0.001	0.851
Female sex	0.612	0.283–1.324	0.213	
Admission NIHSS, per point	1.173	1.093–1.260	< 0.001	
Education, per category	1.096	0.734–1.637	0.654	
Admission MoCA, per point	0.628	0.535–0.738	< 0.001	
Model 5 – Extended + GFAP-T1				
Age, per year	1.048	1.017–1.079	0.002	0.870
Female sex	0.563	0.249–1.274	0.168	
Admission NIHSS, per point	1.175	1.092–1.264	< 0.001	
Education, per category	1.090	0.717–1.658	0.685	
Admission MoCA, per point	0.606	0.512–0.718	< 0.001	
ln GFAP-T1, per ln-unit	2.136	1.404–3.249	< 0.001	

Admission GFAP is not associated with poor functional outcome

Admission GFAP, the leading cognitive marker, was not associated with poor functional outcome (unadjusted AUC 0.542; OR 1.13, 95% CI 0.85–1.50; $P = 0.416$). After adjustment for age, admission NIHSS, and infarct extent, the association remained null (OR 0.86, 95% CI 0.58–1.28; $P = 0.465$), and adding GFAP did not improve the functional clinical model. Thus, the admission GFAP signal observed for cognition was not reproduced for global disability.

Delayed IFN- α is independently associated with poor functional outcome

The functional-outcome screen showed a different temporal pattern. At T3, GFAP and IFN- α each had an AUC of 0.743; IFN- α at 24 hours also discriminated poor outcome (AUC 0.737). At admission, IL-6 was the only biomarker associated with poor functional outcome after FDR correction (AUC 0.686), whereas admission GFAP was uninformative (AUC 0.542) (Fig. 1B; Supplementary Table S2).

In the multivariable model containing age, admission NIHSS, infarct extent, GFAP-T3, and IFN- α -T3, IFN- α remained independently associated with poor functional outcome (OR 1.97, 95% CI 1.43–2.70; $P < 0.001$), whereas GFAP-T3 did not (OR 1.09, 95% CI 0.77–1.54; $P = 0.615$). The combined model had an AUC of 0.896 (Table 4; Fig. 3). These results indicate that the late functional association of GFAP was largely accounted for by clinical measures of stroke burden, whereas IFN- α contributed additional information.

Table 4
Models for poor functional outcome using day-7 biomarkers.

Variable	OR	95% CI	P	Model AUC
Biomarker model – GFAP + IFN-α at T3				
ln GFAP-T3	1.819	1.42–2.33	< 0.001	0.813
ln IFN- α -T3	2.006	1.50–2.68	< 0.001	
Clinical model				
Age, per year	1.018	0.99–1.05	0.231	0.865
Admission NIHSS, per point	1.104	1.05–1.16	< 0.001	
Infarct extent, per category	3.410	2.12–5.48	< 0.001	
Clinical + GFAP + IFN-α at T3				
Age, per year	1.016	0.99–1.05	0.300	0.896
Admission NIHSS, per point	1.097	1.03–1.17	0.004	
Infarct extent, per category	3.065	1.81–5.20	< 0.001	
ln GFAP-T3	1.092	0.77–1.54	0.615	
ln IFN- α -T3	1.967	1.43–2.70	< 0.001	

Association of delayed IFN- α with functional outcome is robust to pulmonary infection Pulmonary infection occurred in 28 patients (12.8%) and was more frequent among patients with poor functional outcome (29.4% versus 7.8%). Because infection can activate type-I interferon responses and is itself associated with adverse stroke outcome, we examined whether pulmonary infection could account for the association between IFN- α and functional outcome. Adding pulmonary infection to the clinical model had little effect on the association of IFN- α with poor outcome: the adjusted OR for T3 IFN- α changed from 1.97 to 1.94, while that for 24-hour IFN- α remained 1.91. Among the 190 patients without pulmonary infection, the associations remained significant and were slightly stronger (T3: OR 2.14, 95% CI 1.50–3.06, $P < 0.001$; 24 hours: OR 2.07, $P < 0.001$). There was no statistical evidence that the association differed according to infection status (interaction $P = 0.157$).

The association between admission GFAP and PSCI was similarly unaffected by pulmonary infection. The adjusted OR changed from 1.87 to 1.85 after inclusion of pulmonary infection and remained 1.86 among patients without infection, with no evidence of interaction ($P = 0.885$). Full sensitivity analyses for all biomarker–time combinations are provided in Supplementary Table S3.

Biomarker associations differ between cognitive and functional outcomes

The two leading biomarkers showed contrasting associations with the two outcomes. Admission GFAP remained associated with PSCI after clinical adjustment (OR 1.87, 95% CI 1.27–2.75; $q = 0.003$) but was not associated with poor functional outcome (OR 0.86, 95% CI 0.58–1.28; $q = 0.465$). Conversely, T3 IFN- α was independently associated with poor functional outcome (OR 1.97, 95% CI 1.43–2.70; $q < 0.001$) but not significantly with PSCI (OR 1.24, 95% CI 0.99–1.55; $q = 0.083$). In paired comparisons within the same patients, admission GFAP discriminated cognitive outcome better than functional outcome ($\Delta\text{AUC} + 0.141$, 95% CI + 0.028 to + 0.251; Holm-adjusted $P = 0.018$), whereas T3 IFN- α showed greater discrimination for functional outcome ($\Delta\text{AUC} - 0.142$, 95% CI - 0.237 to - 0.040; Holm-adjusted $P = 0.016$) (Table 5).

Endpoint dependence was also evident at the panel level. In permutation analyses across all 15 biomarker–time combinations, both the maximum absolute difference in AUC ($P = 0.026$) and the overall sum of squared AUC differences ($P = 0.016$) exceeded the corresponding null distributions. The complete exploratory comparison of all 15 biomarker–time combinations is provided in Supplementary Table S4.

The temporal profiles were consistent with these cross-endpoint differences. GFAP discrimination for cognitive outcome remained essentially unchanged from admission to T3 (AUC 0.683, 0.680, and 0.683), whereas its discrimination for poor functional outcome increased from 0.542 at admission to 0.700 at 24 hours and 0.743 at T3. IFN- α showed little discrimination for either endpoint at admission but became one of the strongest markers of poor functional outcome at 24 hours (AUC 0.737) and T3 (AUC 0.743) (Fig. 1A–C).

The findings were also robust to the unequal number of outcome events. After repeatedly down-sampling PSCI cases from 116 to 51 to match the number of poor functional outcomes, the mean admission GFAP AUC for cognition remained 0.682 (95% empirical interval 0.622–0.743), compared with the observed AUC of 0.542 for functional outcome.

Table 5
Cross-endpoint comparison of admission GFAP and T3 IFN- α for 3-month cognitive and functional outcomes.

Biomarker	Cognitive outcome, adjusted OR	Functional outcome, adjusted OR	ΔAUC cognition - function	Holm-adjusted P
GFAP T1	1.87 (1.27–2.75), $q = 0.003$	0.86 (0.58–1.28), $q = 0.465$	+ 0.141 (+ 0.028 to + 0.251)	0.018
IFN- α T3	1.24 (0.99–1.55), $q = 0.083$	1.97 (1.43–2.70), $q < 0.001$	- 0.142 (- 0.237 to - 0.040)	0.016
Note: Adjusted ORs were derived from endpoint-specific clinical models. ΔAUC was estimated by paired bootstrap within the same patients; q values for adjusted ORs reflect Benjamini–Hochberg correction across the four selected marker–outcome associations; P values for ΔAUC reflect Holm correction across the two selected cross-endpoint comparisons.				

Sensitivity analyses

Using an unadjusted MoCA threshold of 26 classified 135 patients (61.9%) as impaired but did not change the direction of the main findings. Under this definition, the incremental discrimination from the combination of GFAP and NfL was larger and reached significance at T2 ($\Delta\text{AUC} + 0.050$, 95% CI 0.007–0.092; $P = 0.022$). Quartile analyses showed a monotonic increase in PSCI across GFAP concentrations at all three sampling times, whereas NfL tended to plateau at higher concentrations (Supplementary Table S1); representative dose-response patterns are illustrated in Supplementary Fig. S1.

Discussion

In this prospective AIS cohort, five plasma biomarkers were measured at three time points and evaluated against cognitive and functional outcomes at 3 months. The main finding was that biomarker associations depended on both sampling time and outcome. GFAP showed the most consistent association with PSCI across the acute-to-subacute period, and admission GFAP remained associated with cognition after adjustment for clinical variables and baseline cognitive performance. In contrast, admission GFAP was not associated with poor functional outcome. Delayed IFN- α showed a contrasting pattern: its plasma concentration at day 7 was independently associated with poor functional outcome but was not independently associated with PSCI after clinical adjustment. The paired cross-endpoint analysis and panel-level permutation test support the interpretation that these differences are not explained simply by comparing separate patient groups or by unequal event counts.

Plasma GFAP showed relatively stable discrimination for cognitive outcome in AIS patients from admission to day 7, whereas its discrimination for functional outcome was poor at admission, consistent with previous studies from two different regions of China [22, 23]. A study from Italy similarly reported that serum GFAP correlated with stroke severity as assessed by NIHSS but was not associated with mRS during the first 3 months after ischemic stroke [10]. However, our findings and previous studies highlight the importance of sampling time when interpreting the prognostic value of circulating biomarkers. In our cohort, the discrimination of GFAP alone for poor functional outcome increased markedly over time, with AUCs rising from 0.542 at admission to 0.700 at 24 hours and 0.743 at day 7. Despite this increase, the association between day-7 GFAP and poor functional outcome (mRS 3–6) was no longer independent after adjustment for NIHSS and infarct extent. This observation is line with reports that the relationship between circulating GFAP and cerebral infarct volume becomes more evident 5 days after ischemic stroke rather than within the first 24 hours [11]. Thus, later GFAP concentrations may increasingly reflect overall brain lesion burden, which could account for the attenuation of its independent association with functional outcome. Distinct temporal kinetics have also been reported for other circulating markers, including NfL, UCHL1 and IL-6 [8, 10–12]. Such differences may help explain why studies using different sampling windows have reached inconsistent conclusions regarding biomarker prognostic value. Biomarker measurements obtained at different stages after stroke should therefore not be assumed to represent the same biological phase.

The cross-endpoint analysis also helps separate biomarker associations with cognition from associations with global stroke severity. A biomarker that simply tracks infarct burden would be expected to associate with both cognition and disability. Admission GFAP did not show this pattern: it remained associated with PSCI after clinical adjustment, was unrelated to poor functional outcome, and was not associated with cognition at admission while predicting the 3-month MoCA score. These findings support a preferential relation between early astroglial injury and subsequent cognitive outcome, although they do not establish biological specificity or causality.

The IFN- α findings extend this temporal pattern to innate immune activation. IFN- α showed little prognostic information at admission but became strongly associated with poor functional outcome from 24 hours onward, and the day-7 association remained independent of age, NIHSS, infarct extent, and GFAP. Experimental and transcriptomic studies support dynamic activation of type-I interferon pathways after cerebral ischemia, including interferon-responsive microglial states and signaling linked to secondary neuroinflammation [14–16]. However, the human study has rarely investigated the pathogenic role of type-I interferon in AIS. Because type-I interferon responses can also be induced by infection, pulmonary infection represented an important alternative explanation for the delayed IFN- α signal [24]. However, adjustment for pulmonary infection produced almost no attenuation of the IFN- α association, and the association remained strong among patients who did not develop pulmonary infection. These findings argue against pulmonary infection as the principal explanation for the delayed IFN- α signal. Nevertheless, they do not establish a causal role for IFN- α in secondary brain injury; the marker may also reflect other components of the evolving systemic, vascular, or neuroimmune response after stroke.

From a clinical-prediction perspective, admission GFAP added only a small increment in AUC beyond age, NIHSS, and HAMD, and baseline MoCA remained the strongest individual predictor. GFAP should therefore not be interpreted as a stand-alone replacement for cognitive assessment. Its value in this cohort lies in providing independent biological information and in its association with 3-month cognition after accounting for baseline MoCA. This distinction is important: a biomarker may be informative about disease biology or recovery without producing a large improvement in patient-level discrimination.

Strengths and limitations

Strengths of this study include prospective enrollment, serial sampling of biomarkers representing several injury pathways, parallel assessment of cognitive and functional outcomes in the same patients, education-adjusted PSCI classification, and formal cross-endpoint comparison with multiplicity correction and sensitivity analysis for unequal event counts.

Several limitations should be considered. The study was conducted at a single center and lacks external validation. PSCI was defined using a screening instrument rather than formal domain-specific neuropsychological testing, and follow-up was limited to 3 months. Infarct location and strategic network involvement were not incorporated into the principal models. The precise timing of pulmonary infection relative to serial biomarker sampling was not incorporated into the analysis. Finally, only 51

patients had poor functional outcome, limiting the precision of multivariable functional models. These findings therefore require replication in larger, multicenter cohorts with standardized serial sampling and longer cognitive follow-up.

Conclusions

Plasma biomarker associations after acute ischemic stroke were both time-dependent and outcome-dependent. Admission GFAP was preferentially associated with 3-month cognitive outcome and subsequent cognitive performance, whereas delayed IFN- α was more strongly associated with global functional outcome. Biomarker studies after stroke should therefore prespecify and report sampling windows and evaluate candidate markers across clinically distinct outcomes rather than assuming that a single measurement has the same prognostic meaning throughout the post-stroke course.

Declarations

Conflicts of interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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Data availability

The data associated with the paper are not publicly available due to patient confidentiality and institutional regulations but can be provided from the corresponding author upon reasonable request and subject to approval by the Ethics Committee.

Ethical approval for studies involving human participants

All procedures performed in this study involving human participants received ethical approval from the independent ethics committee at Jiangsu University Affiliated Kunshan Hospital (Reference number: 2022-06-022-K01), as described in the appropriate section of the manuscript, and have been conducted in accordance with the 1964 Helsinki Declaration and its later amendments.

Informed consent

Written informed consent was obtained from all participants or their legal representatives prior to inclusion in the study and for publication of their data, as described in the appropriate section of the manuscript.

Authors' Contributions

Conceptualization: Y.Z., Y.L.; Investigation (patient recruitment/data collection): W.M., X.Q., S.W., C.Y., F.S., Y.W., Z.M.; Data analysis: W.M., Y.L.; Supervision: Y.Z.; Project administration: X.Q.; Funding acquisition: Y.Z., Y.L; All authors contributed to drafting the manuscript; Y.L. critically revised the manuscript. All authors read and approved the final version.

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Declaration of generative AI and AI-assisted technologies

During preparation of this manuscript, Claude (Anthropic) and ChatGPT (OpenAI) were used to assist with language editing and structural refinement. After using these tools, the author(s) reviewed and edited the content and take full responsibility for the content of the published work.

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Figures

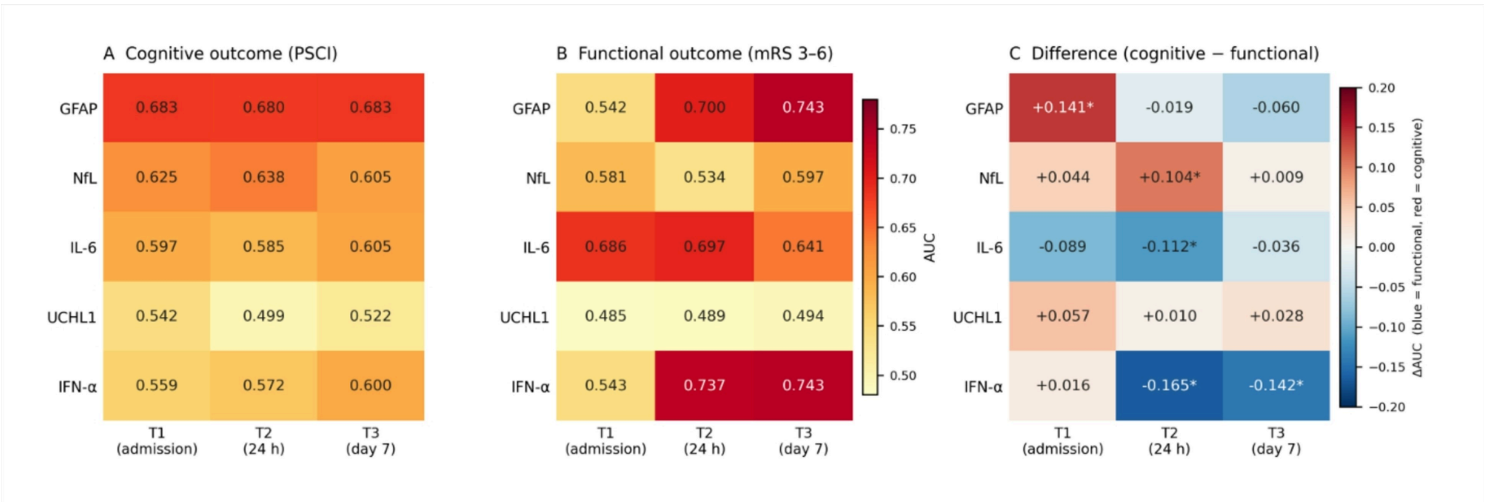


Figure 1

Time-dependent discrimination of plasma biomarkers for cognitive and functional outcomes after ischemic stroke. (A) Area under the receiver-operating-characteristic curve (AUC) for each biomarker—GFAP, NfL, IL-6, UCHL1, and IFN-α—for discrimination of post-stroke cognitive impairment (PSCI), defined as education-adjusted 3-month MoCA <26, at T1 (admission), T2 (24 hours), and T3 (day 7). (B) Corresponding AUCs for poor functional outcome, defined as 3-month modified Rankin Scale (mRS) 3–6. (C) Within-patient difference in AUC between cognitive and functional outcomes ($\Delta AUC = AUC \text{ for PSCI} - AUC \text{ for poor functional outcome}$). Positive values indicate greater discrimination for cognitive outcome

and negative values greater discrimination for functional outcome. Asterisks indicate nominal $P<0.05$ from paired bootstrap comparison of the two AUCs; multiplicity-adjusted inference for the selected cross-endpoint comparisons is reported in Table 5. GFAP, glial fibrillary acidic protein; NfL, neurofilament light chain; IL-6, interleukin-6; UCHL1, ubiquitin C-terminal hydrolase L1; IFN- α , interferon- α .

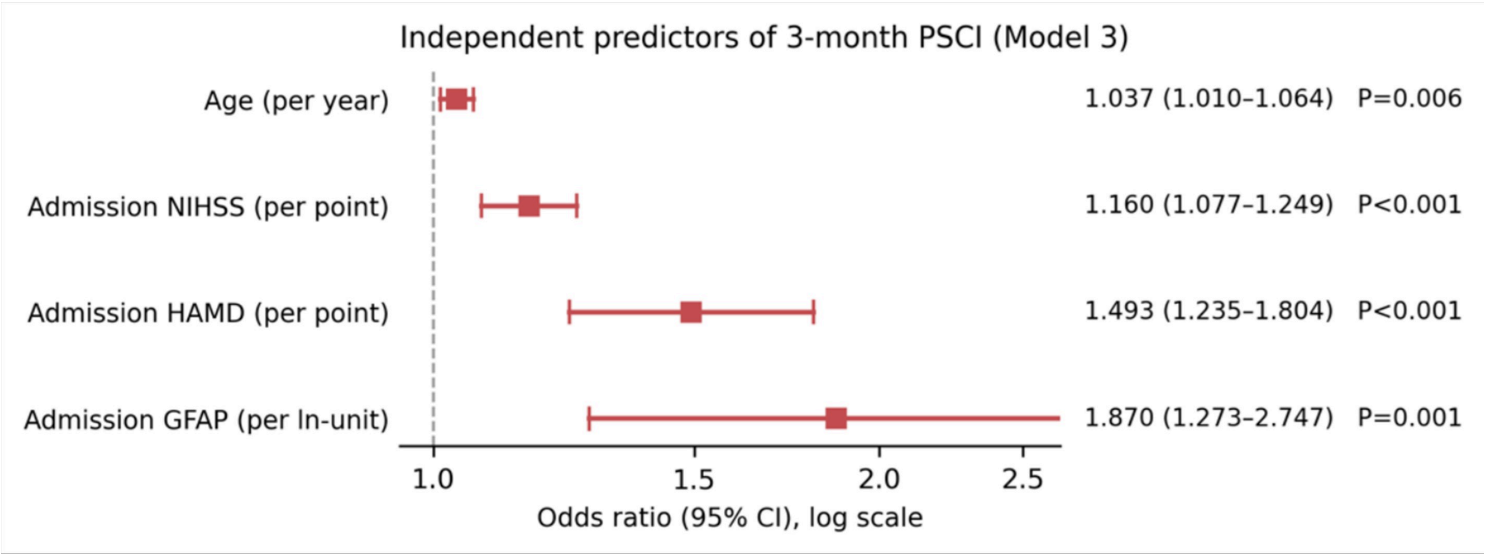


Figure 2

Independent associations of admission GFAP and clinical variables with 3-month post-stroke cognitive impairment. Forest plot showing adjusted odds ratios (ORs) and 95% confidence intervals from the multivariable logistic regression model including age, admission NIHSS, admission HAMD, and admission plasma GFAP. PSCI was defined as education-adjusted 3-month MoCA <26. ORs are expressed per 1-year increase in age, per 1-point increase in NIHSS or HAMD, and per natural-log-unit increase in GFAP concentration. Squares indicate adjusted ORs and horizontal lines indicate 95% confidence intervals; the vertical reference line denotes OR=1. GFAP, glial fibrillary acidic protein; NIHSS, National Institutes of Health Stroke Scale; HAMD, Hamilton Depression Rating Scale; PSCI, post-stroke cognitive impairment.

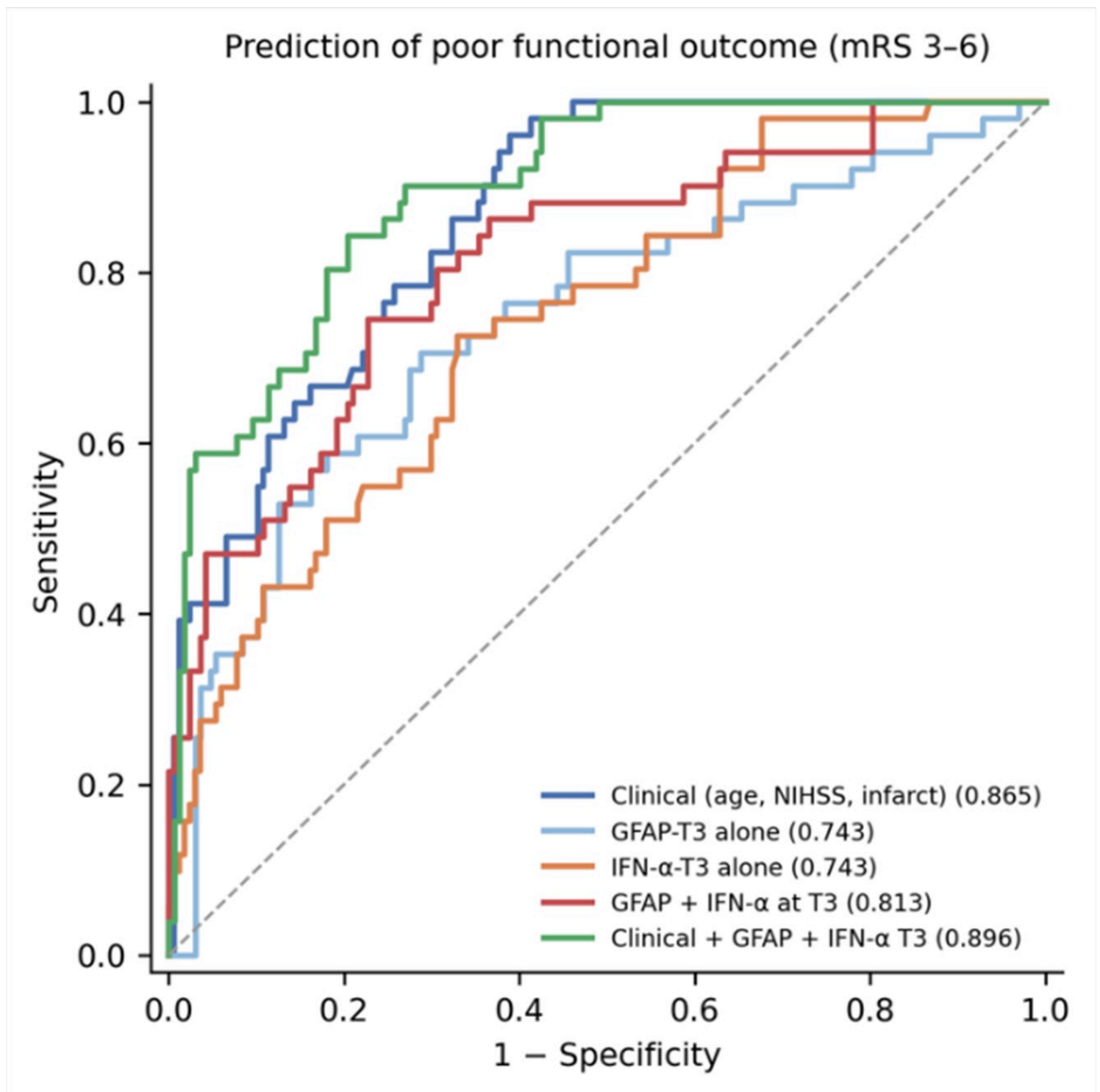


Figure 3

Discrimination of clinical and T3 biomarker models for poor functional outcome. Receiver-operating-characteristic curves for prediction of poor functional outcome, defined as 3-month mRS 3–6. Curves show the clinical model comprising age, admission NIHSS, and infarct extent (AUC 0.865); T3 GFAP alone (AUC 0.743); T3 IFN- α alone (AUC 0.743); the biomarker model containing T3 GFAP and IFN- α (AUC 0.813); and the combined clinical plus T3 GFAP and IFN- α model (AUC 0.896). The diagonal dashed line represents discrimination expected by chance (AUC 0.50). T3 denotes day 7. GFAP, glial fibrillary acidic

protein; IFN- α , interferon- α ; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale.

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