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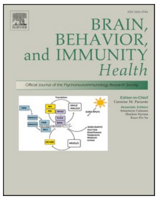

Vascular inflammation in neuropsychiatric long COVID

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ABSTRACT

The role of vascular inflammation in neuropsychiatric Long COVID (LC) is suspected but not well understood. This study evaluated whether vascular inflammation is present in individuals with neuropsychiatric LC and how it relates to cognitive and mental health symptoms. This cross-sectional, case-control study included individuals with acute COVID-19 (AC), neuropsychiatric LC, and recovered controls. Participants were enrolled from the COVID Mind Study and the Yale IMPACT Study (hospitalized), and an independent cohort from the Johns Hopkins University (JHU) Long COVID Study. Fifty individuals with neuropsychiatric LC (new symptoms a median of 368 days post-COVID), 28 with AC, and 29 recovered controls (>3 months post-COVID) were evaluated. All underwent blood sampling and neuropsychiatric testing. The JHU cohort included 114 individuals with late LC (median 1065 days post-COVID illness associated with LC onset) and 31 recovered controls (median 852 days). Fourteen plasma biomarkers of vascular inflammation were measured. ANCOVA was used to compare groups, adjusting for comorbidities. Non-hospitalized participants completed the Global Neuropsychological Assessment, GAD-7, and PHQ-9. LC and recovered groups were demographically similar, while AC participants had higher obesity and hypertension rates. LC participants had elevated circulating biomarkers of endothelial, leukocyte, and platelet adhesion (sL-selectin, ADAMTS13, sP-selectin, sICAM-1) compared to recovered controls. Coagulation markers (D-dimer, fibrinogen) did not differ. Most biomarkers were highest in AC and lower in LC; however, fetuin, sL-selectin, and α-2 macroglobulin were higher in LC than AC. In LC, higher sP-selectin correlated with lower fluency and verbal learning. Lower α1-acid glycoprotein levels were strongly associated with poorer verbal memory, verbal learning, fluency, depression, and anxiety. In the JHU cohort, late LC and recovered controls showed no differences in biomarkers or demographics, suggesting normalization over time. Persistent dysregulation at the intersection of inflammation, platelet adhesion, and endothelial dysfunction is strongly linked to neuropsychiatric Long COVID. Elevated markers of endothelial adhesion in LC suggest distinct pathophysiology from AC. These biomarkers correlate with lower fluency and verbal learning, linking vascular dysfunction to brain function. This study underscores the critical need for longitudinal, within-person investigations to elucidate how vascular inflammation evolves over time.

1. Introduction

LC is a pressing public health issue that patients, providers, and researchers are eager to understand. It affects over 18 million Americans, including 8.6% of women and 5.1% of men (Fang et al., 2024). Despite the prevalence and disabling effects of neuropsychiatric LC, the mechanisms remain poorly understood and treatment options limited (Tak, 2023). Early in the pandemic, individuals with acute COVID-19 (AC) were found to have an increased risk of macro- and microvascular complications (Siddiqi et al., 2021). Biomarkers of platelet and endothelial cell are highly elevated in individuals with AC, including increased fibrinogen, D-dimer, and von Willebrand factor (Goshua et al., 2020, 2021). Thromboinflammation in AC involves coagulopathy, thrombocytopathy, and endotheliopathy (Gu et al., 2021/03). Microvascular injury, fibrinogen leakage, and congestion have been linked to neurologic complications including stroke, seizure, and encephalopathy (Lee et al., 2020).

LC symptoms and biomarkers fluctuate over time, with patterns varying between individuals. Many individuals with Long COVID improve over time, but rates of full recovery are difficult to capture and data beyond 24 months remain limited (Demko et al., 2024; Yeung et al., 2025/03; Hurt et al., 2024/01). One 3-year study found those who did recover still had poorer physical and mental health compared to controls (Gottlieb et al., 2025). Proposed hypotheses for symptom improvement

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over time include waning acute inflammation, tissue healing, and waning autoreactivity against SARS-CoV-2. Both antibody and immune response to SARS-CoV-2 have been shown to decline over time (García-Abellán et al., 2021).

Neuropsychiatric Long COVID (LC) involves new or worsening neuropsychiatric symptoms lasting more than 3 months. Common symptoms include "brain fog," cognitive dysfunction, headache, dizziness, dysautonomia, neuropathy, sleep disturbances, and fatigue, anxiety, or depression (Taquet et al., 2021a). Cognitive testing shows impairments in attention, executive function, memory, and fluency (Serrano Del Pueblo et al., 2024; Braga et al., 2022; Nicotra et al., 2023). A variety of subjective and objective testing instruments have been used; however, it is clear cognitive dysfunction has a negative impact on quality of life (Braga et al., 2023). Preliminary studies show benefit from cognitive rehabilitation (Braga et al., 2023; Contreras-Briceño et al., 2021).

Prior to the emergence of Long COVID, neurologic and psychiatric conditions had already been linked to systemic inflammation. Mental health changes are common in central nervous system diseases including MS, Parkinson's, stroke, and Alzheimer's (Menculini et al., 2021). In recent years, growing evidence has linked several mental health conditions to systemic inflammation. Major depression has been linked to elevated IL-6, TNF-α, and CRP (Réus et al., 2023/12). In depression, increased TSPO PET uptake in the cingulate and temporal lobes, along with elevated CSF cytokines, point to microglial activation (Enache et al., 2019). These findings suggest that both systemic and neuroinflammation, particularly involving microglial activation, may play a role in the development of depressive symptoms. Psychiatric symptoms, including depression and anxiety, have also been shown to increase following COVID-19 (Taquet et al., 2021a). COVID-19 has been associated with a 2.1-fold increased risk of a first-time psychiatric diagnosis within 6 months, even in those without prior history (Taquet et al., 2021a, 2021b).

A recent study found that individuals with Long COVID show increased blood–brain barrier permeability more than two years post-infection, which correlates with poorer motor function and may serve as a biomarker of neuropsychiatric complications (Rubin et al., 2025). Additionally, other studies have linked microvascular dysfunction to fatigue and exercise intolerance in LC (Prasannan et al., 2022; Leitner et al., 2024). Whether vascular inflammation from AC contributes to LC pathophysiology is a critical question. We hypothesized that microvascular and endothelial dysfunction contributes to both cognitive and mental health symptoms in Long COVID. We compared biomarkers of coagulation, immune, and vascular inflammation across individuals with AC, LC, and recovered controls. Our findings suggest persistent activation of these processes may be due to endothelial and microvascular dysfunction and underlie both cognitive and mental health symptoms in LC. We are the first to report vascular inflammation biomarkers spanning >3 years from acute COVID-19 to late LC.

2. Methods

2.1. Study design & participants

Three groups were prospectively enrolled in the longitudinal, outpatient-based COVID Mind Study at Yale: (1) 28 individuals with acute COVID-19 (AC) hospitalized and enrolled through the Yale IMPACT Study; (2) 50 individuals with neuropsychiatric Long COVID (LC) were carefully selected; and (3) 29 recovered controls with no LC symptoms >3 months post-COVID. AC participants were recruited during hospitalization at Yale-New Haven Hospital with acute COVID-19 ($\leq$30 days from symptom onset) and at least one neurologic symptom. Neuropsychiatric LC is defined by onset of new, self-reported neuropsychiatric symptoms (cognitive dysfunction, headache, etc) after confirmed COVID-19 lasting >3 months assessed during screening, enrollment, and with a formal survey. LC participants were recruited from the Yale NeuroCOVID Clinic and the community. Recovered participants reported no residual symptoms on formal surveys and were recruited from the community. All LC and control participants underwent clinical assessment (surveys, chart review) and blood collection. A validation cohort included 114 individuals with late LC (>24 months post-COVID) and 31 recovered controls from Johns Hopkins University (JHU), who also underwent detailed clinical assessment and blood collection. Exclusion criteria for LC and recovered controls included age <18, pregnancy, major and/or pre-existing neurologic illness, major and/or pre-existing psychiatric disorder, anticoagulant use, and prior cognitive dysfunction or impairment. AC participants had no history of dementia, thrombotic events, or coagulopathy during hospitalization. SARS-CoV-2 infection was confirmed by PCR or rapid antigen testing between March 2020 and October 2023.

All studies were approved by the Yale IRB (HIC #1502015318 and #2000032207) and the Johns Hopkins IRB (IRB00375493). Written or verbal consent was obtained from all participants. Anonymized data may be made available by reasonable request from any qualified investigator. This study followed STROBE reporting guidelines.

2.2. Cognitive and mental health assessments

Participants with LC, recovered controls, and the JHU cohort completed cognitive and mental health assessments. AC participants did not undergo cognitive testing. Cognitive performance was assessed using four subtests from the Global Neuropsychological Assessment (GNA): (1) immediate story recall for verbal learning; (2) delayed recall for verbal memory; (3) Perceptual Comparison for processing speed (total correct minus errors); and (4) verbal fluency (animal naming). Higher scores reflect better performance. Mental health symptoms were assessed using the Generalized Anxiety Disorder-7 (GAD-7) and the Patient Health Questionnaire-9 (PHQ-9), which measure anxiety and depressive symptoms, respectively. Total scores were used in analyses.

2.3. Laboratory methods

Soluble biomarkers were measured in frozen EDTA plasma by Eve Technologies (Calgary, Alberta) using two multiplex bead-based ELISA arrays that included the following analytes: α1-acid glycoprotein (AGP), α-2 macroglobulin, ADAMTS13, C-reactive protein (CRP), D-dimer, fetuin A, fibrinogen, haptoglobin, platelet factor 4 (PF4), serum amyloid protein (SAP), serum amyloid A (SAA), soluble L-selectin (sL-selectin), sP-selectin, and sVCAM-1. Samples (100 μL) were run in duplicate at two concentrations with quality control in each session. For each analyte, the concentration with the fewest out-of-range values was used. All biomarkers were detectable, except seven SAA values in the AC group exceeded the upper limit, for which the maximum value was assigned. The samples were run in one batch to minimize inter assay variability.

In the JHU cohort, the same arrays were used to analyze frozen ACD plasma. Due to differences in plasma tubes and potential batch effects, Yale and JHU values were not directly comparable; thus, a separate recovered control group was used at JHU.

2.4. Statistical analysis

Kruskal-Wallis and Fisher's exact tests were used to compare demographic features across all three groups and between LC and recovered controls. The Benjamini-Hochberg procedure was applied to each biomarker comparison across groups to adjust for multiple comparisons; all biomarkers remained significant and were included in analyses. Biomarkers were assessed for normality. Fibrinogen, sL-selectin, SAP, and ADAMTS13 were normally distributed; the rest were log-transformed. Confounder analysis identified age, BMI, and type 2 diabetes as significant covariates. ANCOVA was used to compare biomarker levels across groups, adjusting for these covariates. The Benjamini-Hochberg procedure was applied to resulting p-values. Adjusted F-values were derived using residual error and degrees of freedom to calculate final p-values. Linear regression was used in the LC group to assess associations between three key biomarkers and time since acute COVID-19. To evaluate relationships between biomarkers and cognitive/mental health measures, Pearson correlations were conducted in the total sample and by group. Partial correlations were then used to adjust for age, BMI, and type 2 diabetes. A Benjamini-Hochberg correction was applied to all resulting p-values. All analyses were performed in R.

To further evaluate the relationship between mental health scores and five key biomarkers, the PHQ-9 and GAD-7 were dichotomized into established severity ranges. PHQ-9: Minimal/None (0–4), Mild (5–9), Moderate (10–14), Moderately Severe (15–19), and Severe (20–27). GAD-7: Minimal (0-4), Mild (5-9), Moderate (10-14), and Severe (>15). Ordinal logistic regression analyses investigated the relationship between five key circulating vascular biomarkers (sP-selectin, ICAM-1, Fetuin, AGP, ADAMTS) and increasing severity of depressive (PHQ-9) and anxiety (GAD-7) symptoms. Each estimate reflects the change in odds of being in a higher symptom category per doubling of biomarker concentration ($\log_2$ scale), adjusted for age and BMI. Receiver operating characteristic (ROC) analyses were performed to evaluate the ability of vascular biomarkers to discriminate cognitive impairment across domains (learning, memory, processing speed, and fluency). Separate multivariable logistic regression models were constructed for each biomarker (α1-acid glycoprotein, fetuin, sP-selectin), adjusting for age and BMI. Predicted probabilities from each model were used to generate ROC curves, and model discrimination was quantified using the area under the curve (AUC).

Primary analyses were replicated in an independent validation cohort from Johns Hopkins University using the same analytic pipeline to assess robustness and generalizability.

3. Results

LC participants (n = 50) and recovered controls (n = 29) were enrolled in The COVID Mind Study at Yale. Samples from 28 participants enrolled in the IMPACT Study during AC were selected matching for age and sex. In the LC group, the most frequently reported symptoms were fatigue (82%), poor concentration (74%), post-exertional malaise (74%), word finding difficulty (72%), poor memory (72%), and anxiety (62%) (Fig. 1). The LC and recovered control groups were similar demographically, in terms of age, sex, race, vascular risk factors, and medication history (Table 1). The LC group was a mean of 50 years (SD 13), 70% female (n = 35), and 82% white (n = 41), while the AC group was a mean of 49 years (SD 10), 61% female (n = 17), and 54% white (n = 15). The recovered control group was a mean of 43 years (SD 15), 72% female (n = 21), and 69% white (n = 20). No participant in the recovered control group was hospitalized for AC compared to 18% in the LC group and 100% in the AC group. In the LC group, study visits were performed a median of 368 days [IQR 293-645] after AC, which is similar to 445 days [IQR 322 – 619] in the recovered control group. A higher proportion of the recovered control group were vaccinated prior to infection (control: 62%) compared to the LC and AC groups (LC: 20% vs. AC: 0%; $p < 0.001$) due to vaccine availability at the time of recruitment.

Rates of vascular risk factors were similar between the LC and recovered control groups: smoking (LC: 4% vs. control: 10%; p = 0.55), hyperlipidemia (LC: 20% vs. control: 7%; p = 0.19), diabetes (LC: 12% vs. control: 0%; p = 0.08), pre-existing cardiovascular disease (LC: 2% vs. control: 0%; p = 0.99), and history of alcoholism (LC: 4% vs. control: 10%; p = 0.35). The AC group did have a higher BMI (AC group: 34% vs. LC: 29% vs. control: 25%; p = 0.008) and prevalence of hypertension (AC group: 36% vs. LC: 22% vs. control: 7%; p = 0.03) compared to the LC and recovered control groups. No participants in the LC or recovered control group were taking an anticoagulant and there were similar rates of aspirin/antiplatelet use in these groups (LC: 20% vs. control: 7%; p = 0.19). Data on anticoagulant and antiplatelet use was not available for the AC group.

3.1. *Group differences in coagulation, inflammation and vascular biomarkers*

The three participant groups differed across many of the 14 biomarkers (Fig. 2). Biomarkers were measured at a median of 8 days [IQR 5-9] during AC and 378 days [IQR 296 – 669] after COVID-19 in LC. Each of these biomarkers has several functions in coagulation and vascular and immune health. We classified them according to the hypothesized role in LC. As expected, values were highest in the AC group and were lower in the LC and recovered control groups in 10 biomarkers. The acute phase proteins, AGP (p = 0.0005), CRP ($p < 0.0001$), and haptoglobin (p = 0.0003), were markedly elevated in AC compared to LC. In the AC group, D-dimer ($p < 0.0001$) was highly elevated, as expected.

Biomarkers of endotheliopathy and platelet activation were markedly elevated in AC compared to LC, including ADAMS13 (p = 0.001), PF4 (p = 0.0001), sP-selectin ($p < 0.0001$), and sVCAM-1 ($p < 0.0001$). Immune recruitment and inflammatory markers sICAM-1 (p = 0.052) and SAP (p = 0.51) are similar in the AC and LC groups. Lastly, three

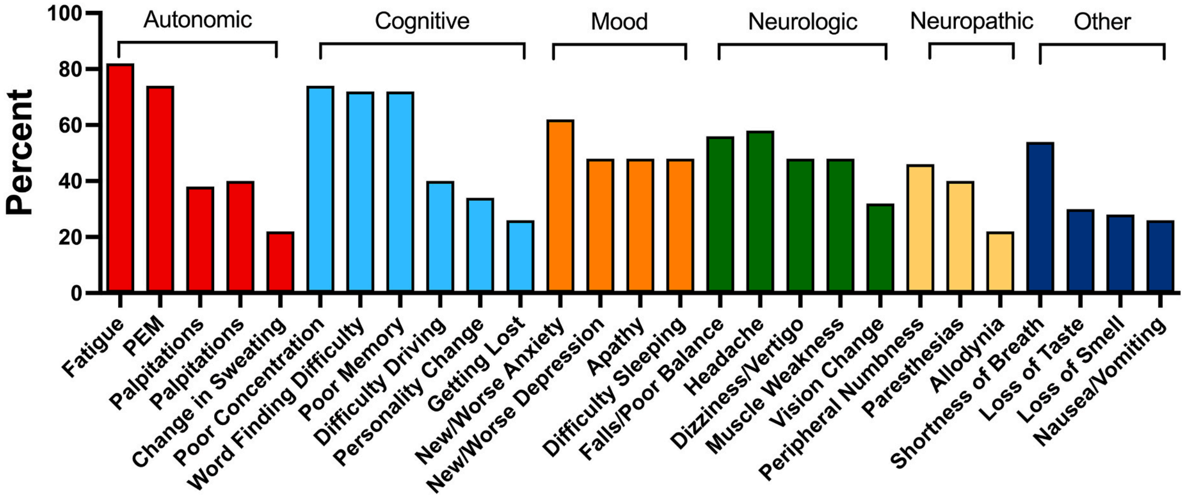

Fig. 1. Neuropsychiatric Long COVID Symptoms. Frequency of Long COVID symptoms in the Yale neuropsychiatric Long COVID group. PEM = post-exertional malaise.

Table 1
Demographics and clinical characteristics of study participants.

	Acute COVID-19 N = 28 Mean (SD) Median [IQR] N (%)	Neuropsychiatric Long COVID N = 50 Mean (SD) Median [IQR] N (%)	Controls N = 29 Mean (SD) Median [IQR] N (%)	P-Value Between 3 Groups
Age (years)	49 (10)	50 (13)	43 (15)	0.06
Female Sex	17 (61%)	35 (70%)	21 (72%)	0.62
BMI (kg/m^2)	34 (8)	29 (7)	26 (11)	0.008**
Race				0.10
Asian	0 (0%)	0 (0%)	2 (7%)	
Black	8 (29%)	7 (14%)	4 (14%)	
White	15 (54%)	41 (82%)	20 (69%)	
Other/Mixed	0 (0%)	2 (4%)	3 (10%)	
Ethnicity				
Hispanic	5 (18%)	7 (14%)	5 (17%)	0.84
Hospitalized for Acute COVID-19	28 (100%)	9 (18%)	0 (0%)	<0.0001***
Days Since Onset of Acute COVID-19	8 [5-9]	368 [293-645]	445 [322-619]	0.54 (2 groups)
Education (years)	-	16 (3)	17 (4)	0.33
Vaccination Status				0.0007**
None	33 (100%)	9 (18%)	3 (10%)	
Prior to infection	0 (0%)	10 (20%)	18 (62 %	
After infection	0 (0%)	31 (62%)	8 (28%)	
Vascular Risk Factors				
Smoking History				0.55
Never	-	33 (66%)	17 (59%)	
Current	-	2 (4%)	3 (10%)	
Former	-	15 (30%)	9 (31%)	
Hypertension	10 (36%)	11 (22)	2 (7)	0.03[a]
Diabetes	7 (25%)	6 (12)	0 (0)	0.08
Hemoglobin A1c	6.6 [5.5 – 7.4]	-	-	
Obesity (BMI >30)	17 (61%)	13 (36%)	8 (28%)	0.03[a]
Hyperlipidemia	-	10 (20%)	2 (7%)	0.19
Cardiac Disease	3 (11%)	1 (2%)	0 (0%)	0.11
Excessive Alcohol	-	2 (4%)	3 (10%)	0.35
Pre-Morbid Mental Health History[a]				
Severe Depression or Anxiety Episode	-	7 (14%)	5 (17%)	0.75
Alcohol or Drug Addiction	-	3 (6%)	3 (10%)	0.66
Medications				
Aspirin/Anti-Platelet	-	10 (20%)	2 (7%)	0.19
Anti-Coagulant	-	0 (0%)	0 (0%)	-
Statin	-	8 (16%)	2 (7%)	0.31
Anti-Hypertensive	-	9 (18%)	2 (7%)	0.31
Anti-Depressant	-	12 (24%)	8 (28%)	0.43

[a] This is lifetime mental health history. Participants were excluded if they were currently experiencing a severe episode of depression or anxiety, or if they were abusing alcohol or drugs. Additionally, individuals with any major psychiatric diagnosis (schizophrenia, psychosis, bipolar disorder, etc) were not enrolled.

biomarkers were higher in LC group compared to the AC group: fetuin ($p < 0.0001$), sL-selectin ($p = 0.002$), and α-2 macroglobulin ($p < 0.0001$).

Strikingly, there were several differences in biomarker levels between the LC and recovered control groups. Acute phase proteins AGP ($p = 0.0005$) and C-reactive protein ($p = 0.04$) were elevated in LC compared to recovered controls (Fig. 2). Biomarkers associated with atherosclerosis were elevated in the LC group, including SAP ($p = 0.0005$) and fetuin ($p = 0.001$). Biomarkers of leukocyte endothelial adhesion and endothelial inflammation were elevated in LC compared to recovered controls, including sL-selectin ($p = 0.01$), ADAMTS13 ($p < 0.0001$), sP-selectin ($p = 0.0001$), and sICAM-1 ($p = 0.03$). Levels of fetuin-A, ADAMTS13, and sP-selectin significantly declined as time since AC increased in the Yale LC cohort (Fig. 3). No other biomarker showed a relationship to time since AC. Importantly, there was no evidence of coagulopathy in LC. D-dimer ($p = 0.15$) and fibrinogen ($p = 0.33$) were similar in the LC and recovered control groups.

3.2. *Associations between biomarkers, cognition, and mental health symptoms*

Compared to recovered controls, the LC group demonstrated poorer verbal memory (Cohen's $d = 0.61$; $p = 0.02$) and processing speed (Cohen's $d = 0.67$; $p = 0.03$) and demonstrated a trend towards lower fluency (Cohen's $d = 0.47$; $p = 0.09$) compared to the recovered control group (sTable 2). There was no difference in verbal learning between groups (Cohen's $d = 0.38$; $p = 0.13$). In terms of mental health, the LC group reported higher anxiety ($p = 0.0004$) and depression ($p < 0.000001$) compared to the recovered control group.

The relationship between the biomarkers and cognitive and mental health endpoints (after adjusting for confounders: age, BMI, and diabetes) was investigated to better understand the clinical relevance of the elevated biomarkers (Fig. 4). In the total sample, higher sP-selectin was associated with poorer fluency ($p = 0.00005$), processing speed ($p = 0.0008$), verbal learning ($p = 0.002$) and verbal memory ($p = 0.004$) as well as greater anxiety ($p = 0.02$) and depressive symptoms ($p = 0.001$) (Fig. 4a–c). Fig. 4e demonstrates a trend toward higher odds of severe depression with increasing sP-selectin, with a 1.57-fold increase in odds per doubling of sP-selectin ($p = 0.079$). Higher levels of fetuin were related to poorer fluency ($R = -0.27$; $p = 0.04$). Higher levels of fetuin (atherosclerosis) and ADAMS13 (endotheliopathy) were also both associated with greater anxiety (p's $= 0.01$) and depressive symptoms (p's < 0.05). Doubling of ADAMTS was associated with a smaller 1.27-fold increase in the odds of severe depression ($p = 0.54$).

Among the LC group only, higher levels of sP-selectin were associated with poorer fluency ($R = -0.53$; $p = 0.002$) and verbal learning ($R = -0.42$; $p = 0.02$) (Fig. 4b). There was a strong relationship between fluency and sP-selectin in both the LC group and whole cohort (Fig. 4d). In Fig. 5c, AUC values ranging from 0.72 to 0.75 indicate a modest, but consistent ability of sP-selectin to discriminate cognitive impairment across domains in LC. Lower levels of AGP were associated with poorer verbal learning ($R = 0.47$; $p = 0.009$) and memory ($R = 0.56$; $p = 0.001$) as well as fluency ($R = 0.50$; $p = 0.005$). Fig. 5a demonstrates AGP also demonstrates consistent discriminatory performance across cognitive domains in Long COVID, with AUC values ranging from 0.71 to 0.79. Conversely, lower levels of AGP were associated with greater anxiety ($R = -0.38$; $p = 0.04$) and depressive symptoms ($R = -0.41$; $p = 0.03$). Lower levels of fetuin were also associated with poorer fluency ($R = -0.36$; $p = 0.05$). In Fig. 5b, AUC values ranging from 0.76 to 0.81 indicate strong discriminatory performance of fetuin for cognitive impairment across domains in Long COVID. Interestingly, there are several notable associations in the recovered control group. Lower processing speed was associated with higher CRP and sP-selectin. Anxiety and depression symptoms were higher in those with higher ADAMTS13 and sICAM-1.

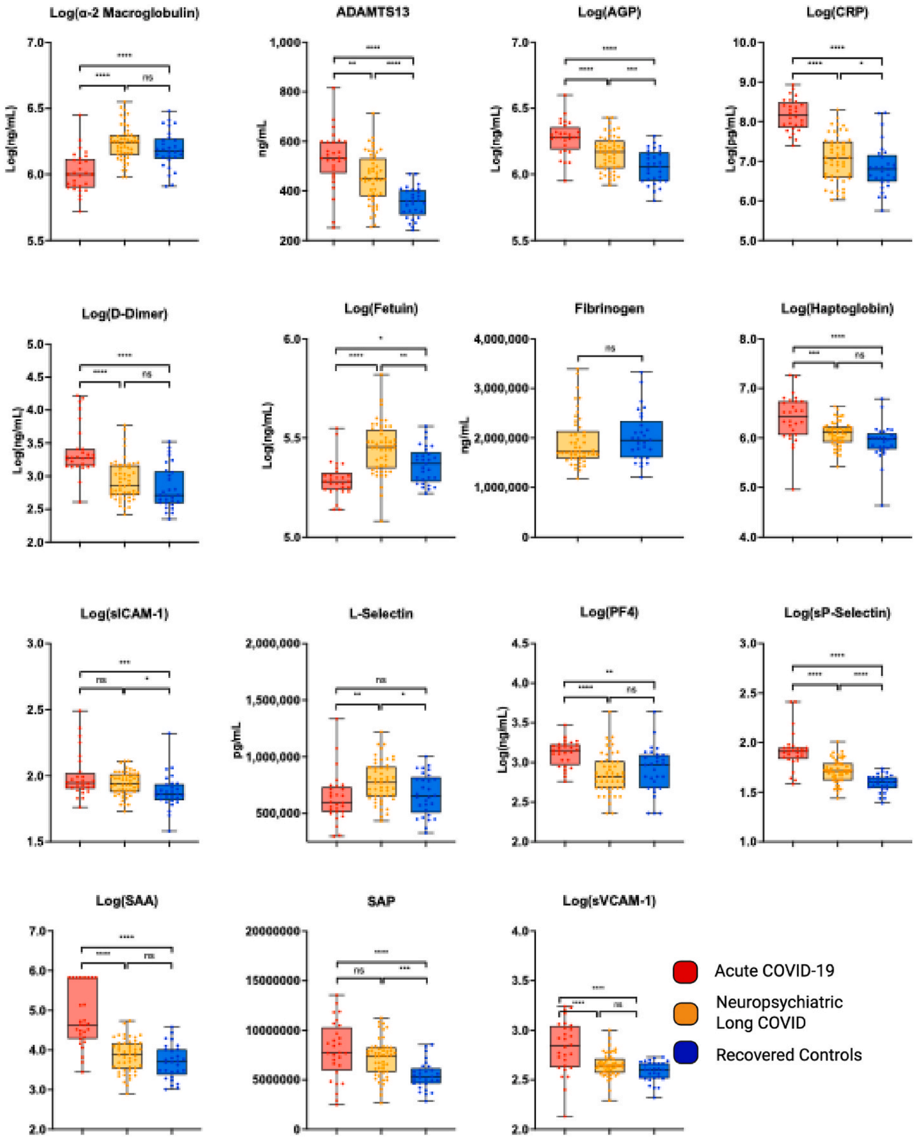

Fig. 2. Plasma Vascular Inflammatory Biomarkers. Detailed results from the vascular dysfunction, inflammation and coagulation biomarkers in the serum are reported in acute COVID-19 (red; n = 28), neuropsychiatric Long COVID (orange; n = 50), and recovered control group (blue; n = 29). All results have been adjusted for multiple comparisons as well as age, BMI, and diabetes. Several biomarkers have numerous functions related to vascular and immune function. Here we provided a broad classification. (ns, $p > 0.05$, *$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$, ****$p \leq 0.0001$). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

3.3. *JHU independent cohort*

Late LC participants (n = 114) and recovered controls (n = 31) were enrolled at JHU. The late LC group was a median of 1065 days [IQR 761-1309] from SARS-CoV-2 infection. Fatigue (95.5%), poor memory (90.2%), poor concentration (81.3%), headache (80.4%), post-exertional malaise (78.6%), and word finding difficulty (77.7%), were the most frequently reported symptoms in the LC group (sTable 3). The late LC and recovered control groups were similar demographically, in terms of age, sex, race/ethnicity, and vascular risk factors (sTable 3). Notably, there were higher rates of aspirin/antiplatelet (late: 30% vs. control: 13%; p = 0.07) and anti-hypertensive use (late: 45% vs. control: 20%; p = 0.02) in the late LC group compared to recovered controls. There were no differences between groups across all 14 biomarkers (sTable4). There were notably higher levels of in depression, anxiety, and PTSD symptoms in the late LC group (sTable 5).

Here we demonstrate that inflammation and coagulation are dysregulated in Long COVID, and because endothelial cells are key regulators of these processes, the persistent elevation of endothelial-enriched biomarkers suggests ongoing endothelial dysfunction in LC.

4. Discussion

Long COVID currently affects almost 18 million Americans and relatively little is known about the underlying pathophysiology and the long-term health implications (Fang et al., 2024). The syndrome has a large impact on quality of life and functional capacity (Braga et al., 2022). Our study aimed at understanding neuropsychiatric symptoms after COVID-19 (LC). We observed elevations in blood biomarkers related to systemic inflammation, leukocyte adhesion, and coagulation dysfunction in LC patients compared to individuals who fully recovered from COVID-19. Endothelial cells are central regulators of these processes, and our findings uniquely demonstrate that persistent vascular dysfunction correlates with specific neuropsychiatric symptoms in Long COVID. We provide novel, clinically relevant evidence that individuals with neuropsychiatric Long COVID exhibit ongoing endothelial

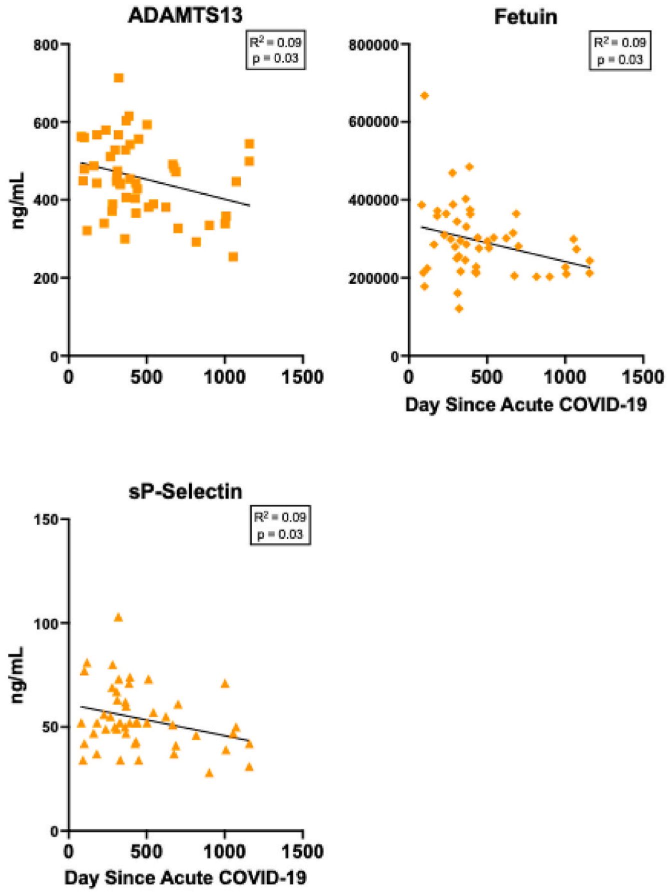

Fig. 3. Key Vascular Biomarkers in Relation to Acute COVID-19 illness. In the Long COVID group, three key endothelial biomarkers demonstrated significant decline as time since AC increased.

dysfunction, reflected by elevated endothelial-enriched biomarkers and dysregulated inflammation and coagulation.

Our findings are in alignment with other neurologic and mental health conditions. Cognitive impairment is a hallmark of classical cerebral small vessel disease, which is driven, in large part, by underlying microvascular endothelial cell dysfunction. Individuals with cerebral small vessel disease are also at an increased risk of depression (Quick et al., 2021/04; Wei et al., 2024). The presence of mental health symptoms in LC is not unexpected, given such symptoms are common in many diseases affecting the brain. Growing evidence has demonstrated systemic inflammation in individuals with mental health conditions such as depression and anxiety (Réus et al., 2023/12; Enache et al., 2019).

Two biomarker patterns emerged across the Yale cohort (Fig. 2; sTable 1). The most common pattern followed a gradient from highest levels in AC to moderate in LC to lowest in recovered controls. AGP, CRP, haptoglobin, SAA, SAP, ADAMTS13, sP-selectin, and sVCAM-1 all followed this gradient pattern. AGP is intricately involved in the inflammatory cascade and regulates the binding of pathogens and modulates the leukocyte attack sequence (Ceciliani and Lecchi, 2019). Typically, it increases in response to tissue injury, cancer, or infection. CRP is an acute phase protein during the infectious/inflammatory cascade. It is a biomarker of both acute and chronic inflammation and has been directly linked to cardiovascular disease (Luan and Yao, 2018; Amezcua-Castillo et al., 2023). The LC group was also characterized by elevation of markers that facilitate enhanced leukocyte adhesion to the endothelium. ADAMTS13 is a plasma protease that cleaves circulating ultra-large von Willebrand factor (vWF) to prevent microvascular platelet clumping. vWF is a glycoprotein involved in platelet and subendothelial collagen adhesion in the vessel wall (Lenting et al., 2015). Elevated ADAMTS13 suggests endothelial activation to reduce platelet aggregation due to ultra-large vWF monomers. sP-selectin promotes leukocyte and platelet adhesion to the endothelium (Ferroni et al., 2009/01). sICAM-1 is an adhesion receptor that is highly expressed on the endothelium and regulates endothelial leukocyte adhesion. Beyond the vasculature, sICAM-1 has also been identified to play a role in immune cell effector functions, pathogen and dead cell clearance, and T-cell activation (Bui et al., 2020).

Of particular interest was the marked elevation of biomarkers in LC as compared to AC and the recovered control groups. Elevations in sL-selectin, fetuin, and α-2 macroglobulin in LC suggests a distinct pathophysiology from the pattern of resolving AC. sL-Selectin is predominately located on leukocytes and mediates adhesion, chemotaxis, and transendothelial migration (TEM) on the vessel wall (Ivetic et al., 2019). Fetuin is a liver-derived negative acute-phase protein that typically decreases during inflammation (Li et al., 2011). Higher levels are associated with increased risk of type 2 diabetes, stroke, and heart attack (Lorant et al., 2011). Its biological significance is likely context-dependent, reflecting complex interactions influenced by metabolic status. α-2 Macroglobulin is a protease inhibitor that has numerous other functions including binding circuiting hormones and cytokines, facilitating neutrophil adhesion and migration, inhibiting complement and activating the procoagulant function of factor VIII and von Willebrand glycoprotein (Vandooren and Itoh, 2021; Switzer et al., 1983). It was previously shown to be low in AC and normalize with recovery as we demonstrated here (Akbasheva et al., 2023). Lastly, it is important to note that we found no evidence of coagulopathy (D-dimer, fibrinogen) in the LC group compared to recovered controls, which aligns with the clinically observed lack of clotting pathology in individuals with LC.

Chronic vascular inflammation, particularly in the context of cerebral small vessel disease, is strongly associated with and predictive of cognitive decline (Zanon Zotin et al., 2021; Evans et al., 2021; Mekhora et al., 2024/12; Tian et al., 2022). Vascular inflammation and injury during acute COVID-19 are increasingly recognized as drivers of brain dysfunction, particularly through endothelial dysfunction, blood–brain barrier disruption, and both acute and progressive vascular damage (Mun and Hinman, 2022/02). Here we demonstrate the correlation of several vascular inflammatory biomarkers with in both the Long COVID and control cohorts. Fetuin and two other biomarkers demonstrate key associations with cognitive and mental health endpoints in the LC group and whole cohort. Elevated sP-selectin was associated with poorer verbal learning and fluency. These are both defining clinical characteristics of LC “brain fog.” Participants with LC describe word finding difficulty, loosing track of their thoughts while speaking, and difficulty recalling conversations and tasks. One possible explanation is that microvascular endotheliopathy negatively affects cognitive function through dysregulated inflammation, coagulation, and blood brain barrier permeability (Rubin et al., 2025; Galea, 2021/11). Interestingly, higher levels of AGP (a marker of general, systemic inflammation) in the LC group were associated with poorer verbal learning and memory, and fluency as well as worse depression and anxiety. These biomarkers are clinically relevant to the LC syndrome. Lastly, the correlations observed in the recovered group are not unprecedented, as several neuroimaging studies using PET, functional MRI, and structural MRI have demonstrated lasting brain changes in individuals who have fully recovered from COVID-19 (Huang et al., 2022; Thapaliya et al., 2025; Douaud et al., 2022/04). These findings highlight the strong need to understand the short- and long-term impacts of COVID-19 vascular inflammation on the brain, both in Long COVID and in the general population. It is unclear if the vascular abnormalities are a primary driver of Long COVID or secondary consequence of systemic inflammation.

From a pathophysiology perspective, our overall findings align with LC in two ways. First, lower concentrations of AGP stimulate mononuclear cell proliferation, particularly T-cells (Hochepied et al.,

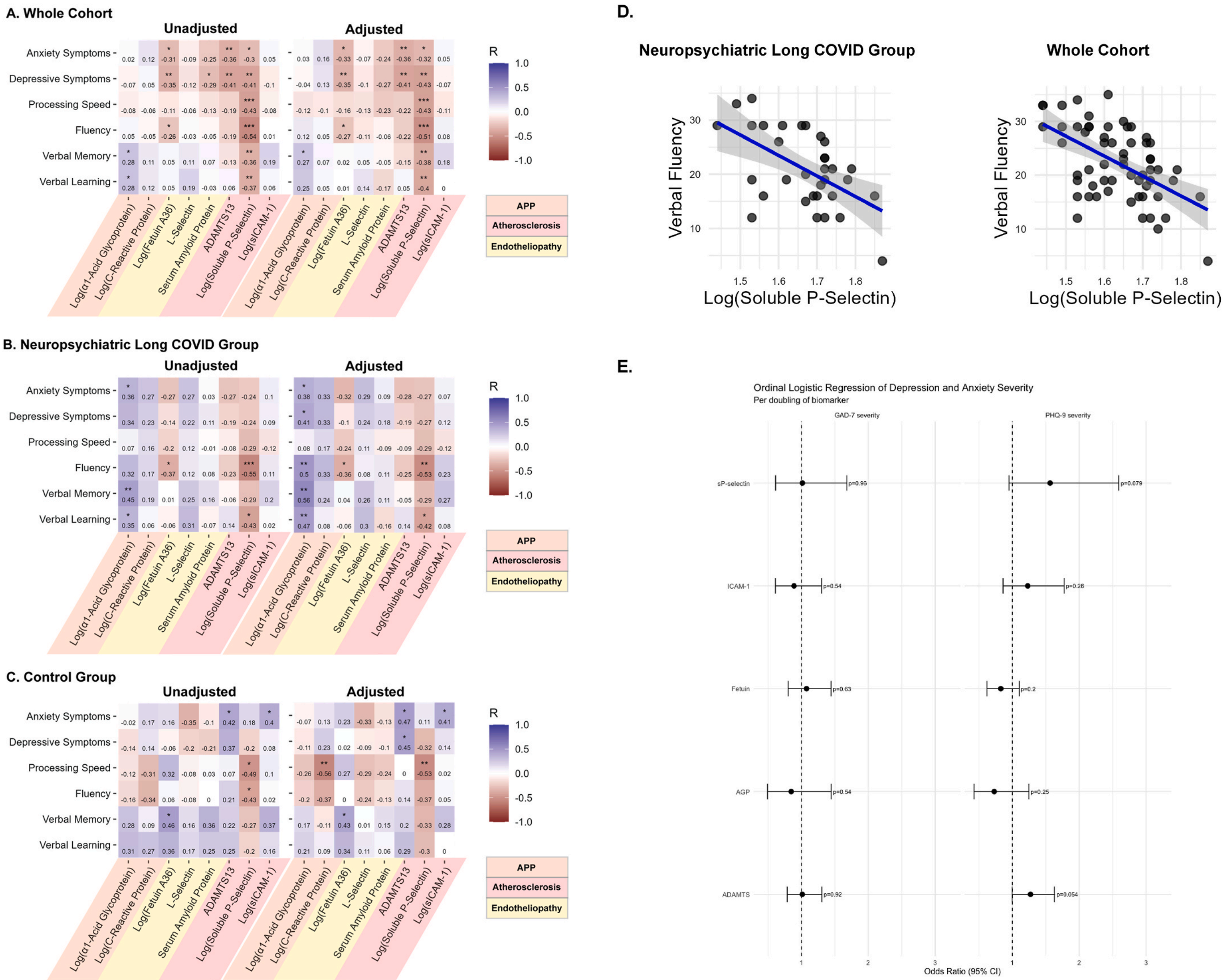

Fig. 4. **Associations between Vascular Biomarkers and Neuropsychiatric Outcomes.** Results are presented both unadjusted (left) and adjusted for age, BMI, and diabetes (right). Detailed results comparing correlations between cognitive and mental health assessments are reported in A) the whole cohort (n = 62); B) only the neuropsychiatric Long COVID group (n = 33); C) only the recovered control group (n = 29). The significance is reported in each comparison box (empty = ns, $p>0.05$, *$p\leq 0.05$, **$p\leq 0.01$, ***$p\leq 0.001$, ****$p\leq 0.0001$). The Pearson's correlation coefficient is reported in each comparison box ($-1 < r < 1$). The color of the box reflects the strength of the correlation (right hand legend) with a positive correlation closer to 1 (dark blue) and a negative correlation closer to −1 (dark pink). D) A detailed the relationship between sP-selectin and fluency in neuropsychiatric Long COVID (left) and the whole cohort. The blue line is the best fit line, and the gray area is the standard error. E) Ordinal logistic regression models demonstrate the association between key vascular biomarkers and symptom severity for depression (PHQ-9) and anxiety (GAD-7). Points represent odds ratios and error bars denote 95% confidence intervals for the odds of being in a higher symptom severity category per doubling of biomarker levels ($\log_2$-transformed), adjusted for age and BMI. P-values are shown for each association. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

2003/02). In LC, there is T-cell immune dysregulation with increased frequencies of $CD4^+$ T cells that are poised to migrate to inflamed tissues and exhausted SARS-CoV-2-specific $CD8^+$ T cells (Yin et al., 2024/02). Second, lower levels of AGP inhibit platelet aggregation and enhance neutrophil aggregation (Hochepied et al., 2003/02). In AC, AGP was shown to regulate SARS-CoV-2 infected neutrophil netosis (Mestriner et al., 2022/11). Neutrophil netosis is the process of forming neutrophil extracellular traps made up of chromatin and bactericidal proteins, and it is triggered by oxidative stress, pathogens, antibodies and immune complexes, and cytokines (Vorobjeva and Chernyak, 2020; Azzouz and Palaniyar, 2024). Lower AGP levels may be a symptom of excessive platelet and neutrophil aggregation. There is new evidence that both oxidative stress and neutrophil netosis are persistently elevated in LC and intimately related to one another and the endothelium (Shafqat et al., 2023; Stufano et al., 2023; Vlaming-van Eijk et al., 2024/10; Al-Hakeim et al., 2023/02). A psychiatry study demonstrated increased oxidative toxicity and lowered antioxidant defense related to both increased depression and anxiety scores (Al-Hakeim et al., 2023/02). They provided a compelling evidence that results that LC mental health symptoms likely have a neuroimmune and neuro-oxidative origin. They key question is why oxidative stress and netosis continue in LC beyond the acute illness, and whether this plays a role in triggering endothelial activation and increasing vascular permeability. In summary, here lower AGP may reflect dysregulated immune and platelet–neutrophil interactions, potentially driven by persistent oxidative stress and NETosis, which may perpetuate endothelial activation in Long COVID.

Timing of study visits in Long COVID course appeared to be a key factor distinguishing between the Yale and JHU cohorts. We described groups at three different time points in their illness: 1) acute COVID-19; 2) early LC (Yale; median 383 days); 3) late LC (JHU; median 1065

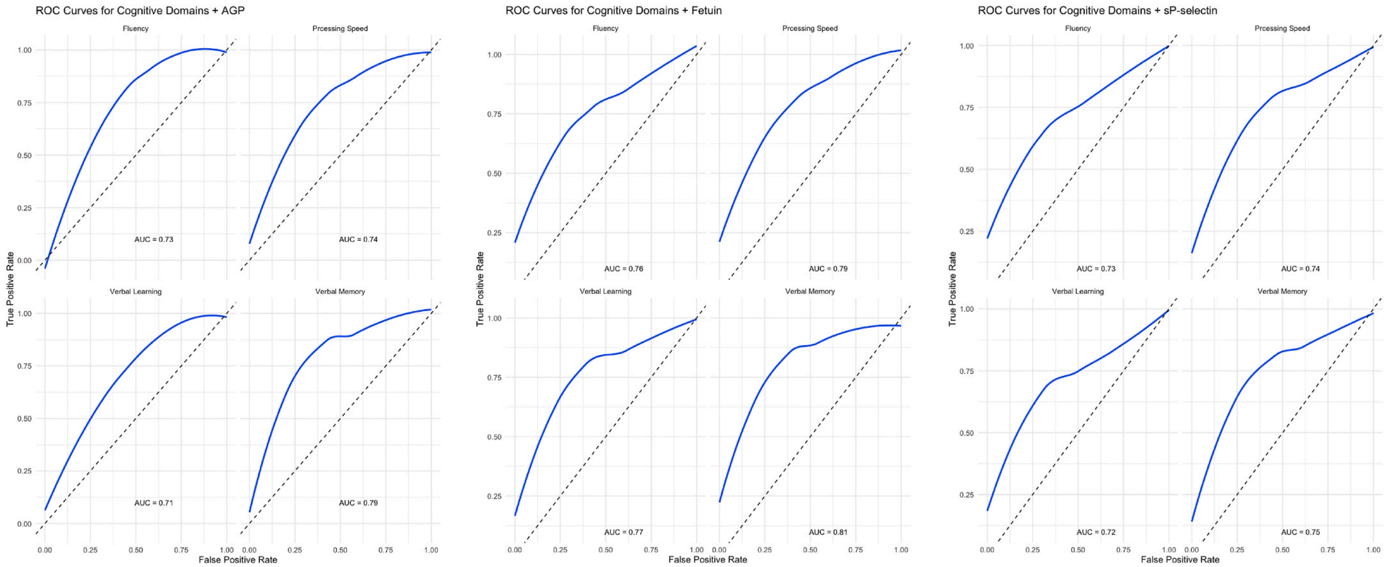

Fig. 5. Predictive performance of vascular biomarkers for cognitive impairment across domains. Receiver operating characteristic (ROC) curves depicting the performance of multivariable logistic regression models incorporating age, body mass index (BMI), and individual biomarkers to predict impairment across cognitive domains (learning, memory, processing speed, and fluency). Biomarkers were selected based on associations identified in Fig. 4A–C and are presented as separate panels: (A) α1-acid glycoprotein, (B) fetuin, and (C) sP-selectin. Curves were smoothed using LOESS (span = 1). The dashed diagonal line represents chance discrimination (AUC = 0.5). Area under the curve (AUC) values are displayed for each domain.

days). During acute COVID-19, vascular inflammatory biomarkers are elevated across the board. The JHU cohort did not replicate the Yale cohort findings. There are three key differences between the cohorts, including timing of study visit in LC course, differences in cognitive outcomes, and higher rates of aspirin and anti-hypertensive use in the JHU cohort. Despite the differences, both Yale and JHU LC groups had high rates of anxiety and depression. Comparing the cohorts raises two potential hypotheses: 1) abnormalities of the vascular endothelial function and cognitive function may improve over time, and 2) aspirin and/or anti-hypertensives may confer an anti-inflammatory treatment effect. These findings highlight the limitations of cross-sectional analyses and the critical need for longitudinal, within-person studies, which we are actively pursuing.

Here we demonstrate that inflammation and coagulation are dysregulated in Long COVID, and because endothelial cells are key regulators of these processes, the persistent elevation of endothelial-enriched biomarkers suggests ongoing endothelial dysfunction in LC. Our findings support a model where endotheliopathy in the brain may have a significant impact on small vessel function, namely regulation of immune cell and platelet recruitment and activation. We propose further study into oxidative stress, vascular regulation, and innate immunity processes, like netosis, as possible primary or secondary mechanisms. Identifying relevant biomarkers may allow stratification of LC patients for targeted treatment and clinical trials. We are continuing to study the participants longitudinally and look forward to reporting on additional findings. Future studies will need to further investigate this line of inquiry using both a multi-modal and longitudinal approach.

There are several limitations of our study. We did not have complete vascular risk factor data on the AC group. There were differences in illness severity and vaccination status between Yale groups. Viral strain was not systematically accounted for and may vary with recruitment period and cohort. Participants were required to wait >30 days after a vaccination prior to enrollment. Otherwise, vaccination status was not systematically accounted for and may have influenced biomarker profiles and clinical outcomes, either attenuating or amplifying observed associations. Finally, limited sample sizes in all cohorts may mask significant differences.

In conclusions, this study provides novel, integrative evidence that the health and function of the vascular endothelium is associated with LC. We identified a novel and distinct vascular inflammatory signature in Long COVID, characterized by elevations in endothelial adhesion–related biomarkers (α-2 macroglobulin, sL-selectin), suggesting a mechanism of endothelial activation rather than residual post-acute inflammation. Additionally, we showed that specific biomarkers (fetuin, sP-selectin, AGP) directly correlate with cognitive and mental health outcomes, underscoring their clinical and translational relevance. While the cross-sectional design limits causal inference, these findings provide a critical mechanistic link between endothelial dysfunction and neuropsychiatric symptomatology. Ongoing longitudinal work in this cohort is designed to define biomarker trajectories over time and identify therapeutic targets in Long COVID focused on vascular health and endothelial dysfunction.

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CRediT authorship contribution statement

Lindsay S. McAlpine: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Eran F. Shorer:** Formal analysis, Methodology, Software, Writing – review & editing. **Jennifer Chiarella:** Data curation, Project administration. **Allison Nelson:** Data curation, Project administration, Supervision. **Rebecca Veenhuis:** Data curation, Investigation, Methodology, Project administration, Supervision, Writing – review & editing. **Alba Azola:** Data curation, Project administration, Supervision, Writing – review & editing. **Alfred Lee:** Methodology, Validation, Writing – review & editing. **Richard Pierce:** Validation, Writing – review & editing. **Shelli Farhadian:** Funding acquisition, Methodology, Resources, Supervision, Validation, Writing – original draft. **Leah H. Rubin:** Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing. **Serena S. Spudich:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review

& editing.

Declaration of competing interest

All authors declare that they have no competing financial or non-financial interests related to the work described in this manuscript. The authors report no relevant financial relationships, personal relationships, intellectual property interests, consultancies, advisory roles, employment, honoraria, stock ownership, paid expert testimony, grants, or other funding sources that could be perceived as influencing the results or interpretation of the study.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2026.101247.

Data availability

Data will be made available on request.

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