Vascular Inflammation in Neuropsychiatric Post-Acute Sequelae of COVID-19

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Background

- Biomarkers of platelet and endothelial dysfunction are elevated in patients with acute COVID-19 and predict mortality in critically ill patients.[1,2]
- Biomarkers of coagulopathy and endothelial dysfunction are elevated 60 days after COVID and correlate inversely with a 6-min walk test.[3] Evidence of 'microclotting' on blood testing after COVID-19 has unclear clinical implications.[4]
- It is unknown if vascular inflammation persists in individuals with neuropsychiatric Post-COVID-19 Conditions (N-PCC). We investigated for vascular inflammation in 3 groups: individuals with acute COVID-19, N-PCC, and post-COVID-19 controls with no PCC.

Methods

- Participants with N-PCC (new or worsening neuropsychiatric symptoms >3 months after COVID-19) and post-COVID-19 controls with no PCC underwent a cross-sectional clinical assessment (surveys, chart review) and blood collection
- Participants with acute COVID-19 were enrolled while hospitalized due to COVID-19. Individuals with dementia or an acute thrombotic event were excluded.
- Plasma samples were tested via multiplex bead-based ELISA for the following analytes: α1-acid glycoprotein (AGP), α2 macroglobulin, ADAMTS13, C-reactive protein (CRP), D-dimer, Fetuin A36, fibrinogen, haptoglobin, L-selectin, platelet factor 4 (PF4), serum amyloid protein (SAP) A, serum amyloid A (SAA), soluble intercellular adhesion molecule-1 (sICAM-1), soluble platelet selectin (sP-Selectin), and soluble vascular cell adhesion molecule-1 (sVCAM-1) (Eve Technologies).
- Non-parametric multiple Mann-Whitney testing was used with a False Discovery Rate adjustment to address for multiple comparisons. Kruskal-Wallis and Fisher's exact tests were used to compare demographics.
- Exclusion Criteria: <18 years old, pregnant, and history of dementia, stroke, or other major neurologic/psychiatric illness.

Results

- The acute COVID-19, N-PCC, and control groups were similar demographically, in terms of age, gender, race, and most vascular risk factors (Table 1).
- The acute COVID-19 and N-PCC groups had higher BMI (p=0.008), more hypertension (p=0.03), and were enrolled prior to widespread vaccine availability (p=0.0007).
- We found no evidence of coagulopathy in the N-PCC group.
- All acute phase proteins were elevated in acute COVID-19 and two remain persistently elevated in N-PCC, AGP (p=0.001) and haptoglobin (p=0.01).
- Markers of leukocyte adhesion to the endothelium and endothelial dysfunction were persistently elevated in N-PCC compared to controls, including L-selectin, ADAMTS13, sP-selectin, sICAM-1, and sVCAM-1.
- sICAM-1 (endothelial adhesion) and SAP (vascular remodeling) remained elevated in the N-PCC group at acute COVID-19 levels.
- Three markers were higher in N-PCC group compared to the acute COVID-19 group, including Fetuin A36 (vascular calcification), L-selectin (endothelial adhesion), and α2 macroglobulin (endothelial adhesion) suggesting a distinct pathophysiology from acute COVID-19.

In individuals with neuropsychiatric Post-COVID-19 Conditions (N-PCC), we report persistent elevation of markers related to leukocyte adhesion to the endothelium, endothelial dysfunction, vascular calcification, and vascular remodeling

Figure 1. Results Detailed results from vascular inflammatory markers in the serum are reported in acute COVID-19 (red), N-PCC (orange), and control groups (blue) (ns $p>0.05$, * $p\leq0.05$, ** $p\leq0.01$, *** $p\leq0.001$, **** $p\leq0.0001$)

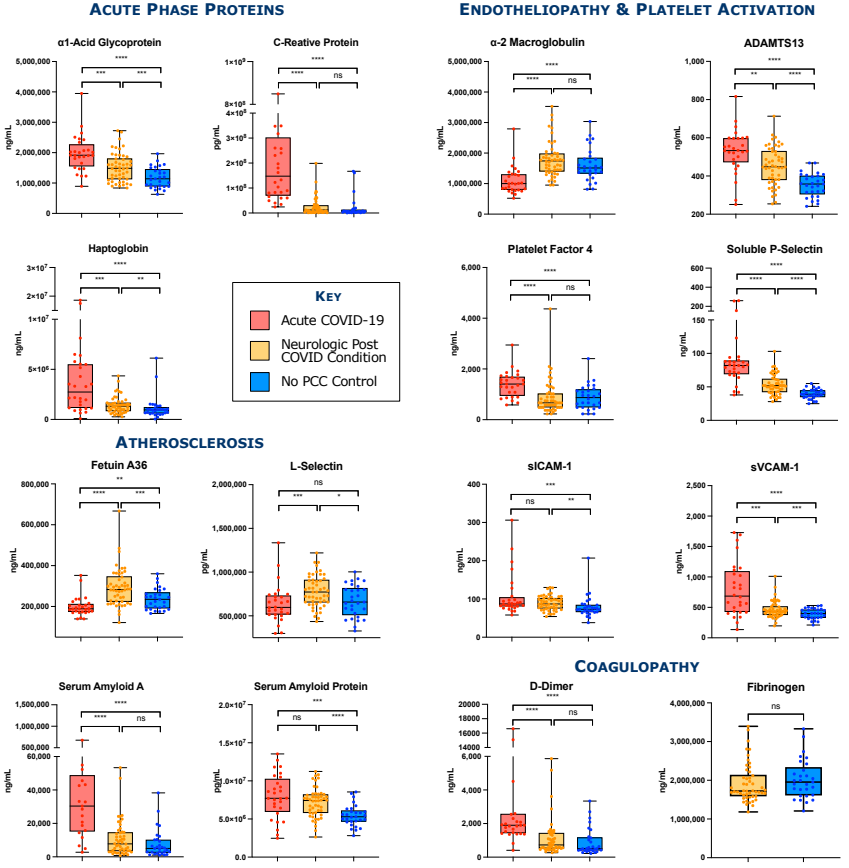
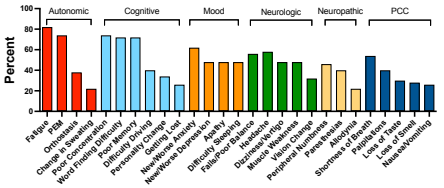


TABLE 1. DEMOGRAPHICS	Acute COVID-19 N = 28 Median [IQR] N (%)	N-PCC N = 50 Median [IQR] N (%)	Control N = 29 Median [IQR] N (%)	P-Value
Age (years)	49 [43 – 54]	49 [40 – 62]	41 [31 – 55]	0.06
Female Gender	17 (61%)	35 (70%)	21 (72%)	0.62
BMI (25kg/m2)	34 [27 – 39]	29 [25 – 31]	25 [22 – 32]	0.008**
Race				0.1
Asian	0 (0%)	0 (0%)	2 (7%)	
Black	8 (29%)	7 (14%)	4 (14%)	
White	15 (54%)	41 (82%)	20 (69%)	
Mixed/Other	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 Acute COVID-19	8 [5 – 9]	378 [296 – 669]	445 [322 – 619]	0.54
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*
Diabetes	-	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*
Hyperlipidemia	-	10 (20%)	2 (7%)	0.19
Cardiac Disease	3 (21%)	1 (2%)	0 (0%)	0.11
Excessive Alcohol	-	2 (4%)	3 (10%)	0.35
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	-	16 (32%)	7 (24%)	0.61

Figure 2. Symptoms

Prevalence of PCC symptoms in the N-PCC group.



Conclusions

- In the N-PCC group, there is persistent elevation of markers related to leukocyte adhesion to the endothelium, endothelial dysfunction, and vascular remodeling.
- Several markers were higher in the N-PCC group compared to the acute COVID-19 group suggesting a distinct pathophysiology from acute COVID-19.
- There is no evidence of an ongoing coagulopathy.
- Further studies will longitudinally investigate endothelial adhesion and dysfunction in individuals with N-PCC.

We have no relevant disclosures

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Citations:

[1] PMID: 32619411; PMCID: PMC7326446.
[2] PMID: 33477776; PMCID: PMC7832393.
[3] PMID: 34375505; PMCID: PMC8420256.
[4] PMID: 35195253; PMCID: PMC8883497.

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