Whole Blood Adhesion to VCAM-1 and P-Selectin and RBC Mechanical Fragility Can be Compromised in Long COVID-19 Patients with Sickle Cell Disease

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can cause severe vascular complications associated with endothelial dysfunction and systemic inflammation. COVID19-specific IgG are detectable within a week of infection. Long-COVID has been described in patients continuing to exhibit including fatigue, dyspnea, headache, and brain fog. The recent FAIR Health study reported that 23.2% had at least one post-COVID symptom [1]. The underlying biologic mechanisms of Long-COVID remain unclear, thus treatments are limited to symptomatic relief and supportive care. Many long COVID symptoms are consistent with systemic inflammation and impaired oxygen delivery observed in individuals with sickle cell disease (SCD), in turn associated with elevated blood cell adhesion and decreased red blood cell (RBC) stability.

AIM

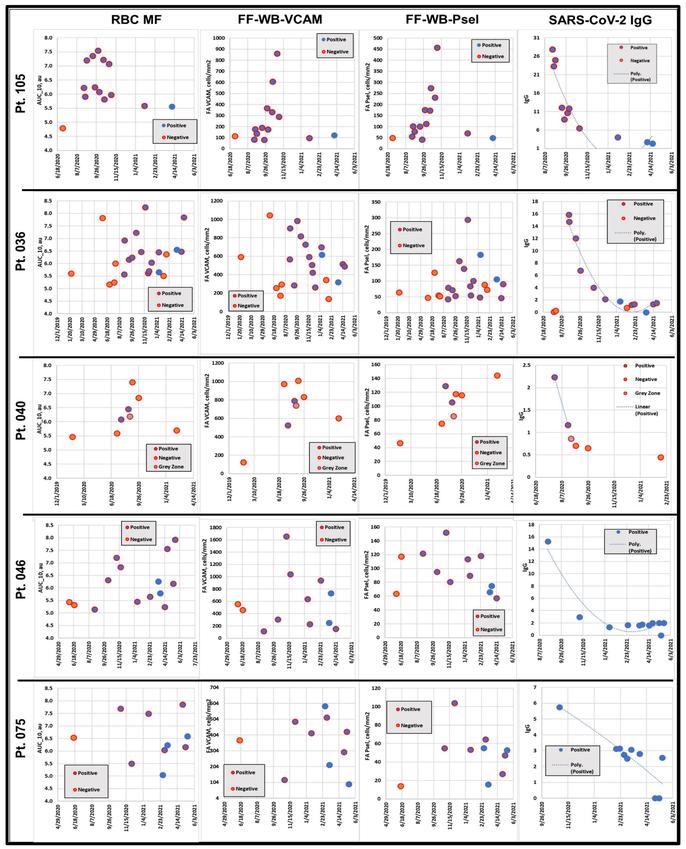
To determine if cell blood function biomarkers are associated with changes in SCD patient acute visit frequency after the resolution of COVID-19.

METHOD

- Blood samples were collected by the Foundation for Sickle Cell Disease Research from sickle cell disease (homozygous SS, n=7) subjects coming for clinic visits.
- Semiquantitative SARS-CoV-2 IgG assay was performed using DXi-800 (Beckman Coulter).
- Flow adhesion of whole blood to VCAM-1 (FA-WB-VCAM) and P-Selectin (FA-WB-Psel) were measured by counting the cells remaining adherent in a microfluidic channel after perfusion with whole blood 1:1 diluted with HBSS buffer and washed by 1 dyne/cm².
- Red blood cell mechanical fragility (RBC MF) was measured as hemolysis induced by an oscillating cylindrical magnet with periodic non-invasive probing of cell-free hemoglobin fraction.
- Study subjects were followed for 179±62 days post seroconversion.
- Fatigue assessment was extracted from the a COVID-19 symptom questionnaire administered at the point of care.
- Statistical significance was determined at p value <0.05.

RESULTS

RBC MF, FA-WB-Psel , FA-WB-VCAM and SARS-CoV-2 IgG for SCD Subjects with COVID-19-Positive Serological Status.



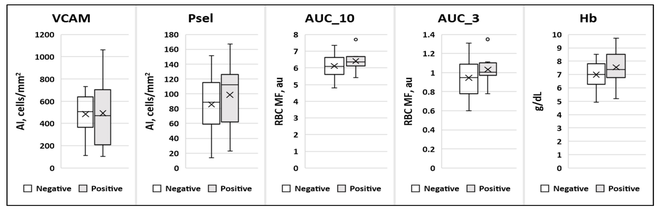
- The change of value for each biomarker was individually plotted against the date of the sample collection. Color indicated the status of Covid-19 infection based on SARS-CoV-2 IgG assay results.
- Select 5 patient data is shown

Biomarker Values Averaged Before and After Infection

	Pre- SARS-CoV-2	Post- SARS-CoV-2	p-values
Hemoglobin (g/dL)	6.8 ± 1.1	7.3 ± 1.8	0.270
RBC MF (au)	5.8 ± 0.6	6.4 ± 0.2	0.026
FA-WB-VCAM (cells/mm²)	396 ± 157	529 ± 302	0.027
FA-WB-Psel (cells/mm²)	72 ± 46	96 ± 48	0.065

- SARS-CoV-2 IgG levels varied from 0.1 to 37, with positive values being defined as IgG > 1.0. The median estimated $t_{1/2}$ of IgG was 53 days (range: 25 - 90 days).
- Hb did not change significantly before and after SARS-Cov-2 seroconversion.
- FA-WB-VCAM, FA-WB-Psel, and RBC MF were all significantly elevated after SARS-Cov-2 seroconversion.
- Following seroconversion, FA-WB-VCAM and RBC MF increased significantly and increases in FA-WB-Psel approached significance.
- These increases were highly patient-specific with potential return to pe-infection values observed in some cases at about 5-6 months after the infection.

Comparison of Cell Function Values in IgG Positive and IgG Negative Subjects



- Subject values are averaged from all measurements before and after SARS-CoV-2 seroconversion.
- Presented is the subset of SCD subjects that had both IgG positive, and IgG negative SARS-CoV-2 measurements.
- Averaged for IgG+ and IgG- conditions, combining pre- and post-infection IgG- conditions, values of patient hemoglobin (Hb), FA-WB-VCAM, FA-WB-Psel, and RBC MF cell properties lacked statistical significance (under both a paired t-test and population statistics).

CONCLUSIONS

- **Whole blood adhesion to both p-selectin and VCAM-1 as well as RBC membrane stability can be significantly impaired in convalescent SARS-Cov-2 patients, suggesting an association with Long-COVID.**
- **New and emerging treatments that modify whole blood adhesive properties and RBC membrane stability should be investigated for their potential to accelerated recovery from Long-COVID.**
- **Longer observations are required to determine if abnormal blood cell adhesive properties and RBC membrane instability are mechanisms of Long-COVID pathophysiology.**

REFERENCES

1. Health F. Detailed Study of Patients with Long-Haul COVID: An Analysis of Private Healthcare Claims [White paper]2021. Available from: https://s3.amazonaws.com/media2.fairhealth.org/whitepaper/ asset/A%20Detailed%20Study%20of%20Patients%20with%20Long-Haul%20COVID--An%20Analysis%20of%20Private%20Health care%20Claims--A%20FAIR%20Health%20White%20Paper.pdf.

DISCLOSURE

Functional Fluidics Inc is a privately held company developing methods for assessment of blood cell function. Hines, Tarasev, Gao hold stock options and are employees of, and Allen, Ferranti, and Topping are employees of Functional Fluidics Inc.

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