0930

Persistent immune dysregulation and metabolic alterations following SARS-CoV-2 infection

Silvia Lucena Lage[1], Katherine Bricker-Holt[1], Joseph M. Rocco[1], Adam Rupert[2], Eduardo P. Amaral[1], Gabriel Rosenfeld[1], Thomas Dalhuisen[3], Avery Eun[3], Emily Fehrman[3], Jeffrey N. Martin[3], Steven G. Deeks[3], Timothy J. Henrich[3], Michael J. Peluso[3], Irini Sereti[1]

[1]National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA, [2] AIDS Monitoring Laboratory, Frederick, MD, USA , [3]University of California, San Francisco, San Francisco, CA, USA.

BACKGROUND

- SARS-CoV-2 infection can lead to medical comorbidities (eg, autoimmunity, vascular complications) as well as Long COVID (LC), a multisystem disease encompassing a wide range of symptoms.
- The biological drivers of these conditions and the long-term immunologic impact of COVID-19 are incompletely understood.

METHODS

- We analyzed blood samples from individuals from the pre-Omicron era who had their first COVID-19 episode 4-months prior to sampling [COVID, N=96, San Francisco-based Long-term Impact of Infection with Novel Coronavirus (LIINC) cohort (NCT04362150)] and contemporaneous SARS-CoV-2-naïve controls [No COVID: NC, N=30], from the Longitudinal Study of COVID-19 Sequalae and Immunity (RECON_19) cohort (NCT044411147)], matched for age, gender, and race.
- The post-COVID participants included those who had WHO-defined LC (LC, N=58) or had fully recovered (RC, N=38).
- We performed an in-depth immunometabolic screen with multidimensional flow cytometry and plasma measurements of inflammatory biomarkers and metabolites.

RESULTS

- Sustained caspase-1/4/5 activity (p=0.0026) and mitochondrial superoxide production (p=0.005) were observed in monocytes post-COVID.

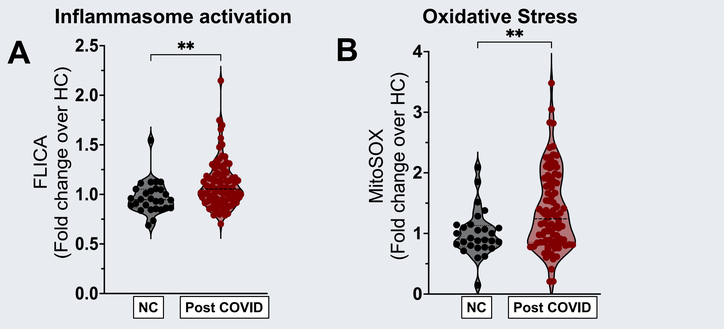


Figure 1. Measures of inflammasome activity and oxidative stress in monocytes from participants with and without prior COVID-19. (**A**) Geometric mean fluorescence intensity (gMFI) of FLICA (fluorochrome inhibitor of caspase-1/4/5) within circulating monocytes from SARS-CoV-2-naïve controls (NC, n=28) and COVID-19 participants (n=92). (**B**) Levels of mitochondrial superoxide (MitoSOX) in monocytes from NC (n=28) and COVID-19 (n=92). gMFIdata are expressed as median of the fold change (gMFI of each sample over the gMFI mean of the NC group) . Bars represent median ± quartiles. Statistical analysis was performed using a two-sided Mann-Whitney test (**, *P* < 0.005).

RESULTS

- Enrichment in HLA-DRlo/p16INK4alo immature monocytes, increased plasma arachidonic acid (p<0.0001) and decreased plasma tryptophan levels (p<0.0001), were also found post-COVID.

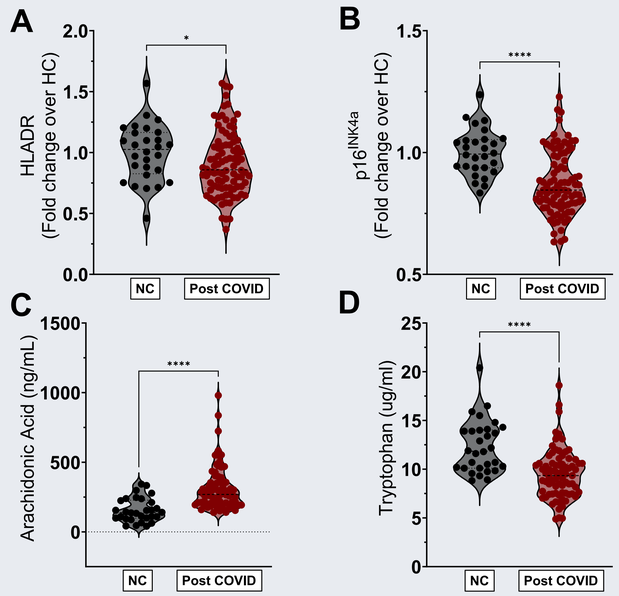


Figure 2. Phenotypic changes in circulating monocytes and altered plasma inflammatory markers post-COVID-19. Geometric mean fluorescence intensity (gMFI) expression of HLA-DR (A) and p16INK4a (B) on circulating monocytes from NC and COVID-19 individuals. gMFIdata are expressed as median of the fold change (gMFI of each sample over the gMFI mean of the NC group). Cellular levels of arachidonic acid (AA) (C) and Tryptophan (D). Bars represent median ± quartiles. Statistical analysis was performed using a two-sided Mann-Whitney test (*, P < 0.05,****, P < 0.0001).

- A distinct subset of senescent effector CD8 T-cells (CD57lo/ p16INK4ahi) was observed in those who developed Long COVID (LC).

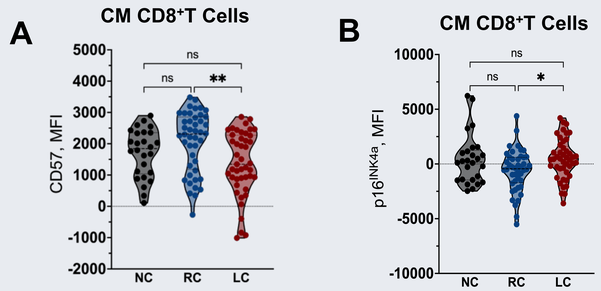


Figure 3. Immune phenotyping of PBMCs following COVID-19 infection. Geometric mean fluorescence intensity (gMFI) expression of CD57 (A) and p16INK4a (B) in central memory (CM) CD8 T cells from SARS-CoV-2-naïve controls (NC), recovered COVID-19 (RC), and Long COVID (LC) patients. Bars represent median ± quartiles. Statistical analysis was performed using a Kruskal-Wallis test (*, P < 0.05, **, P < 0.005).

RESULTS

- Unique immunometabolic profiles were found in No COVID vs COVID groups.

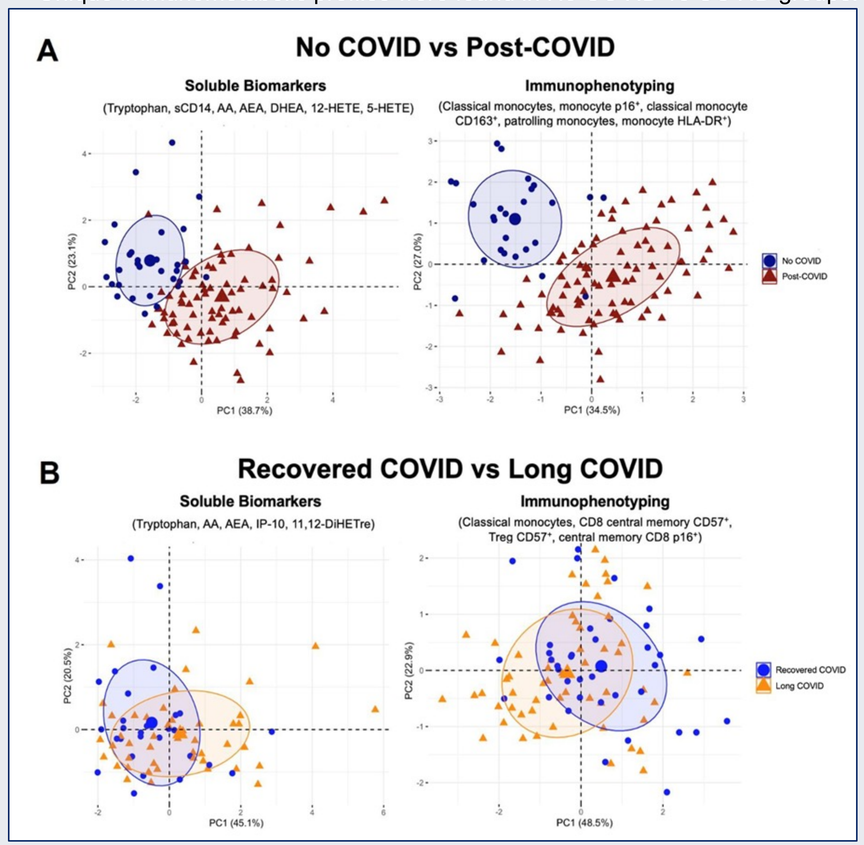


Figure 4. Principal component analysis highlights unique immune profiles in No COVID vs Post-COVID groups. Principle component analysis (PCA) was performed incorporating the most differentiating soluble biomarkers and immunophenotyping markers selected by Elastinet regression models. PCAs were generated in R (version 4.3.2) using the FactoMineR and factoextra packages. (A) PCA comparing No COVID to post-COVID patients. (B) PCA comparing recovered COVID-19 and Long COVID patients. AA, arachidonic acid; AEA, arachidonoylethanolamide; DHEA, dehydroepiandrosterone; 5,12-HETE, 5,12-hydroxyeicosatetraenoic acids; IP-10, interferon gamma-induced protein 10; 11,12-DiHETre, dihydroxyeicosatrienoic acids.

CONCLUSIONS

- SARS-CoV-2 infection can have a profound and sustained immunometabolic effect, which could contribute to post-acute morbidity.
- A combination of disjointed innate and adaptive immune recovery with metabolic alterations may contribute to LC.
- Our data could guide evaluation of treatments targeting inflammasome, oxidative stress, metabolic, and senescence pathways involved in persistent LC symptoms.

Acknowledgement: *This work was supported by the Intramural Research Program of the National Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health (NIH). LIINC is supported by the PolyBio Research Foundation.*

Disclaimer: *The views expressed in this work are those of the author(s) and do not reflect the official policy of the U.S. Army, the Department of Defense or the U.S. Government.*