SARS-CoV-2 Antibody Levels Associate with Neutrophil Activation

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Background

- In Coronavirus Disease 2019 (COVID-19) neutrophilia and a hyperactive neutrophil response has been associated with worse outcomes as activated neutrophils provoke endothelial injury, coagulation, and progression to ARDS[1,2,3].
- COVID-19 induces an altered and exuberant antibody response, with titers and subclasses of antibodies correlating with disease severity[4].
- Neutrophils respond to IgG and IgA antibody complexes, leading to a variety of effector functions such as phagocytosis, degranulation, and NETosis[5,6]
- Here we query associations between the endogenous SARS-CoV-2 antibody response and neutrophil activation in COVID-19.

Methods

- Baseline plasma samples from 57 patients hospitalized on oxygen with COVID-19 treated in a phase II study evaluating the safety and efficacy of fostamatinib, a spleen tyrosine kinase inhibitor, were obtained. We subsequently performed:

1. Quantitative measurements of SARS-CoV-2 specific antibodies using a luciferase-based immunoprecipitation system assay
2. Quantitative measurements of neutrophil specific biomarkers using Luminex technology
3. Neutrophil extracellular traps (NETs) as measured by myeloperoxidase-DNA (MPO-DNA) complexes by ELISA.

- Absolute neutrophil count (ANC) and immature granulocyte count (IGC) were measured from complete blood counts (CBC).

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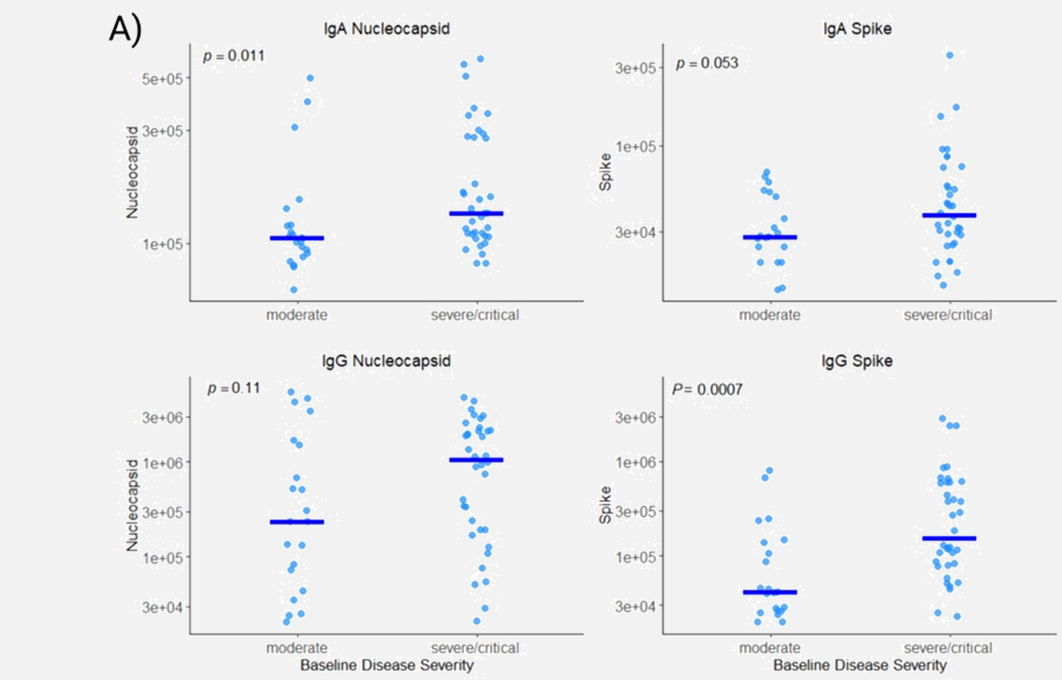

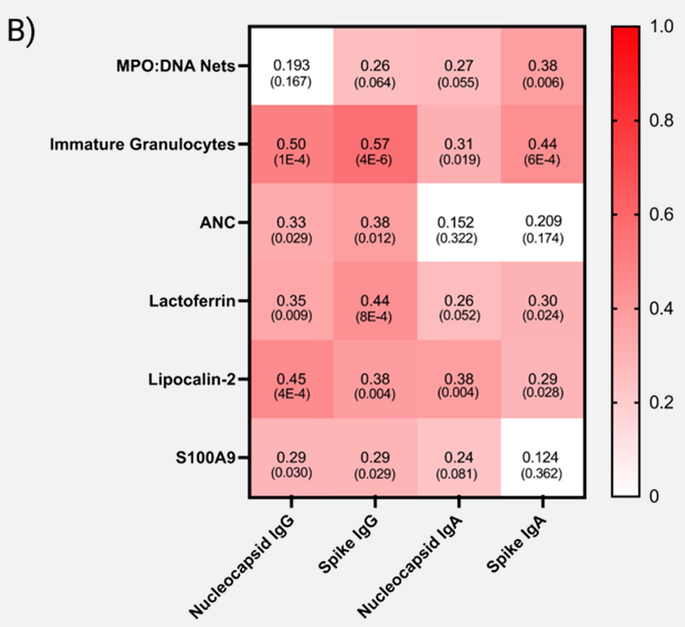

Figure 1A) Levels of anti-Spike and anti-Nucleocapsid IgA and IgG levels measured in the serum of 57 unvaccinated hospitalized COVID-19 patients. Moderate illness represents ordinal scale 5 requiring low flow oxygen, while severe/critical patients represent ordinal scale 6 and 7, requiring high flow oxygen, non-invasive or mechanical ventilation, respectively. P values are compared by a Wilcoxon ranked sum test.

Figure 1B) Heatmap showing Spearman correlations between levels of anti-Spike and anti-Nucleocapsid IgA and IgG and markers of neutrophil activation. P values for individual correlations are represented in parentheses. MPO (myeloperoxidase), ANC (absolute neutrophil count), S100A9 (S100 calcium binding protein A9).

Results

- Severe COVID-19 was associated with higher levels of nucleocapsid-IgA as well as spike-IgG compared to moderate disease
- Levels of IgG-spike and IgG-nucleocapsid both had significant correlations with Absolute Neutrophil Count
- All four antibody titers showed strong correlations with Immature Granulocyte count, evidence of emergency granulopoiesis and altered neutrophil populations
- S100A9, a component of calprotectin, lactoferrin and lipocalin-2, components of primary and secondary granules correlated strongly with antibody titers
- Circulating NETs levels demonstrated a significant correlation with spike IgA levels, and its correlations with IgG-spike and IgA-nucleocapsid additionally approached significance

Conclusion

- Higher anti-spike and anti-nucleocapsid IgG and IgA levels associated with more severe COVID-19 illness.
- Endogenous SARS-CoV-2 specific antibody levels associate with markers of emergency granulopoiesis and neutrophil hyperactivation
- Circulating NETs levels, which have been previously been associated with disease severity and thrombotic markers, correlated with antibody levels[7]
- Targeting antibody mediated neutrophil activation may prove beneficial to treatment of SARS-CoV-2 [8]

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