SIGNIFICANCE OF ELEVATED SARS-COV-2 ANTIGEN LEVELS DURING EARLY HOSPITALIZATION

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BACKGROUND

- The Therapeutics for Inpatients with COVID-19 (TICO) trial platform within the NIH- Accelerating COVID-19 Therapeutic Intervention and Vaccines (ACTIV) conducted randomized, placebo-controlled trials of novel neutralizing monoclonal antibodies (mAb).
- Patients hospitalized with COVID-19 were randomized to standard of care (SoC) plus placebo or SoC plus mAb[bamlanivimab[1,2], sotrovimab[3], ambarvimab-romlusevimab[3], or tixagevimab-cilgavimab[4]] in the TICO platform trial. None of the mAbs differed from placebo in the time to sustained recovery through day 90.
- Baseline plasma nucleocapsid antigen (plasma Ag) levels are associated with poor outcomes in those with COVID-19 [5,6].
- Combining these cohorts, we assessed if early changes in plasma antigen were associated with clinical outcomes.

METHODS

Study population:

- TICO/ACTIV-3 enrolled 2,254 patients between 8/5/2020 to 9/30/2021.
- Remdesivir was provided as part of SoC unless contraindicated.
- Included participants had samples collected on Days 0, 1, 3, 5.
- Participants (n=2149) had samples at baseline and one or more at Days 1, 3, or 5 and were followed for 90 days.
- Primary outcome was sustained recovery defined as return to home for 14 consecutive days.
- Secondary outcomes included all cause mortality at 90 Days and Pulmonary Ordinal Scale at Day 7.

Sample Analysis:

- Level of plasma antigen was quantified using Quanterix SARS-CoV-2 Protein Antigen assay (lower limit of detection 3 ng/L).
- Level of anti-spike antibody was evaluated using the GenScript SARS-CoV-2 cPass Surrogate Virus Neutralization assay (positive is > 30% binding inhibition).

Statistical Analysis:

- First, we examined longitudinal differences in trajectories of plasma Ag between subpopulations using linear mixed models with a random intercept for each participant and a subpopulation fixed effect for each follow-up visit (Day 0, 1, 3 and 5). Contrasts in trajectories were made comparing the subpopulation and their complemental subpopulation with their respective geometric mean plasma Ag levels plotted over time. An example of chronic kidney disease is shown in **Figure 1.** Differences between the two subpopulations at each follow-up visit (Day 0, 1, 3, 5) were calculated as a ratio of geometric means. A pooled ratio of geometric means was used to compare average differences across days 0, 1, 3, 5 reflecting an average difference across days 0, 1, 3, and 5. **(Figure 2)**
- Next, we defined a subgroup with plasma Ag values in the top quartile at baseline and again at day 5, and examined which baseline factors were associated with being in the persistently high Ag trajectory subgroup using logistic regression. **(Table 2)**
- Finally, we examined the association between being in the top quartile for plasma Ag over time and clinical outcomes using a proportional odds model for the pulmonary ordinal scale, a Cox proportional hazards model for mortality through Day 90, and a Fine-gray competing risk model for sustained recovery through Day 90.(**Table 2**)

Key points:

- High plasma Ag over 5 days is associated with:
  1). Worse clinical outcomes
  2). Comorbidities and features of acute COVID-19
- Association of persistent high plasma Ag with worse outcomes suggests a pathogenic role of ongoing viral replication in hospitalized patients with COVID-19
- Serial measurements of plasma Ag may be useful to identify patients that could potentially benefit from antiviral therapies

RESULTS

Table 1: Baseline Characteristics	n= 2,149
Age, median (IQR)	57 (46-68)
Female sex, n (%)	903 (42.0)
Comorbidities, n (%)	
Cardiovascular disease	1,034 (48.1)
Chronic lung disease	326 (15.2)
Diabetes	618 (28.8)
Immunosuppression	188 (8.7)
HIV	36 (1.7)
Obesity	1,151 (53.7)
Renal Impairment	208 (9.7)
Any comorbidity	1,395 (64.9)
COVID-19 vaccination status, n (%)	
Fully vaccinated	190 (8.8)
Partially vaccinated	195 (9.1)
Not vaccinated	1,178 (54.8)
Concomitant Medications, n (%)	
Corticosteroids	1,465 (68.2)
Remdesivir	1,296 (60.3)
Symptom duration, median (IQR)	8 (6-10)
Pulmonary ordinal scale, n (%)	
No supplemental oxygen	553 (25.7)
<4L oxygen per minute	816 (38)
≥4L oxygen per minute	582 (27.1)
HFNO* or NIV^	198 (9.2)
Delta# , n(%)	658 (50.3)
N antigen ≥ 100 ng/L, n (%)	899 (41.9)

Figure 1

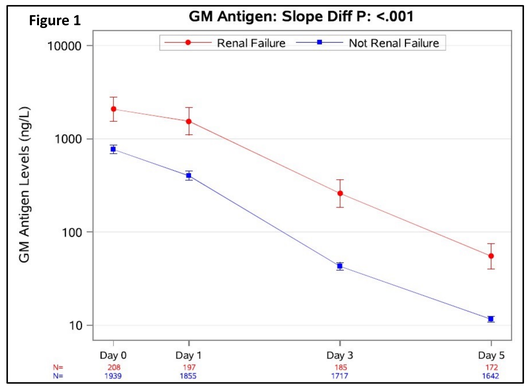


Figure 1: Geometric mean of plasma antigen levels over Days 0 - 5 in patients with and without renal failure.

Table 2: Baseline factors and clinical outcomes among those who had high plasma nucleocapsid Ag levels at Days 0 and 5. This represents 13.9% of the total cohort.
Those in this group had a higher hazard for worse outcome at day 7 and all cause mortality.

⁺ Odds ratio
*High flow nasal oxygen
^ non-invasive ventilation
# Hazard ratio
$ Recovery

Figure 2

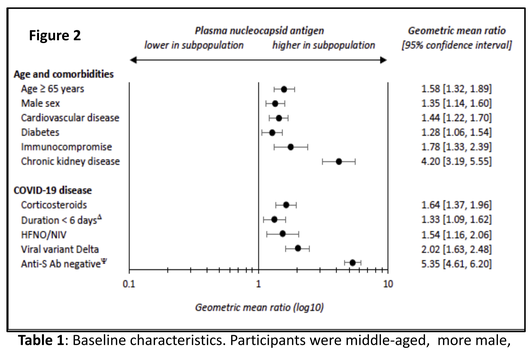


Figure 2: Forest Plot depicting the geometric mean ratio (log10) of plasma Ag and baseline clinical factors associated with COVID-19 disease.
^Δ symptoms prior to baseline (Day 0 of study)
^Ψ Anti-spike antibody negative

Table 1: Baseline characteristics. Participants were middle-aged, more male, had multiple co-morbidities, slightly over half were not vaccinated, most were on no or <4 liters of oxygen/minute, and half of samples tested were delta.
- High flow nasal oxygen
^ non-invasive ventilation
# total with samples able to be tested (n= 1149)

CONCLUSIONS

- Persistently high levels of plasma Ag over the first 5 days were associated with elevated risk for death and reduced recovery.
- This group includes those with chronic kidney disease, use of oxygen for COVID-19, and those who were negative for anti-spike antibody.
- Persistently high plasma Ag among hospitalized patients requiring low-flow oxygen was associated with high risk for poor outcomes, potentially identifying those patients that would benefit from additional treatment.

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Table 2: Association of having a plasma Ag measurement in the top quartile at Days 0 and 5, baseline factors, and clinical outcomes.	
Association with baseline factors	**(OR⁺, 95% CI)**
Anti- spike Ab positive	0.15 (0.10, 0.20)
Chronic kidney disease	4.05 (2.79, 5.86)
Pulmonary Ordinal Scale	
No oxygen	[reference]
<4L oxygen per minute	2.24 (1.52, 3.37)
≥ 4L oxygen per minute	4.88 (3.29, 7.35)
HFNO* or NIV^	5.27 (3.11, 8.95)
Association with clinical outcomes	
Pulmonary ordinal scale, Day 7 **(HR#, 95% CI)**	6.3 (5.0 to 7.9)
Day 90 all cause mortality **(HR, 95% CI)**	4.4 (3.2 to 5.9)
Sustained Recovery through Day 90 **(RRR$, 95% CI)**	0.85 (0.75 to 0.96)

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