NIH RADx® Tech

Long COVID Associates with Slow Viral Clearance and Viral Rebound During Acute SARS-CoV-2 Infection

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BACKGROUND

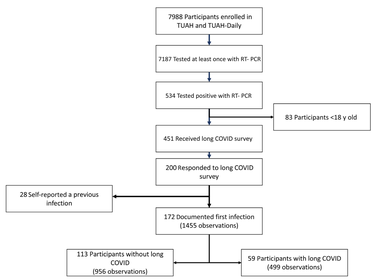
- Millions of people around the globe have experienced long COVID, yet the mechanisms underlying its pathobiology remain unclear.
- Prior work suggests that SARS-CoV-2 and antibody response kinetics during acute infection may be linked to the subsequent development of long COVID. However, prior studies were limited by infrequent sampling during acute infection and small cohort sizes.

OBJECTIVE

- To determine whether the rate of viral clearance from the upper respiratory tract during acute infection associates with subsequent development of long COVID.
- To determine whether viral rebound during acute infection associates with subsequent development of long COVID.

METHODS

- Our study included participants from 2 longitudinal cohort studies: the Test Us at Home (TUAH) and the TUAH-Daily studies, which enrolled between October 2021 and February 2022.
- Eligible participants for TUAH and TUAH-Daily were >2 years old, living in an area with high SARS-CoV-2 transmission rates, and did not have COVID-19 symptoms or SARS-CoV-2 infection at the time of enrollment.
- 7,187 TUAH and TUAH-Daily participants self-collected anterior nasal swabs for SARS-CoV-2 antigen and RT-PCR testing per the schedule below.
- In August 2023, participants ≥18 years old with ≥1 positive PCR test during the original study period were asked whether they had symptoms lasting 3 months or longer that were not present prior to COVID-19.



Study Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
TUAH-Daily	x	x	x	x	x	x	x	x	x	x					
TUAH	x		x		x		x		x		x		x		x

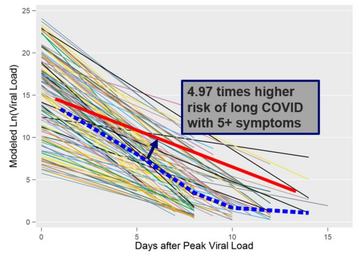
Figure 1. (Left) CONSORT flow diagram of study. (Right) TUAH and TUAH-Daily testing schedule.

- Slower viral clearance during acute SARS-CoV-2 infection associates with subsequent development of long COVID, especially in people with more symptoms and in women.
- Viral rebound during acute SARS-CoV-2 infection associates with long COVID as well.

RESULTS

Table 1. Participant characteristics.

Characteristic, no. (%)	Long COVID (n=59)	No Long COVID (n=113)
Age ≥ 45	18 (31%)	21 (19%)
Female sex	46 (78%)	82 (73%)
BMI >25	42 (71%)	66 (58%)
1+ comorbidities	25 (42%)	40 (35%)
Not vaccinated before acute COVID-19	7 (12%)	23 (20%)
Hospitalized for acute COVID-19	0 (0%)	1 (1%)
Omicron variant	44 (79%)	92 (84%)



	Slope of Viral Clearance: β (95% CI)	
Number of Long COVID Symptoms	Unadjusted Relative Risk	Adjusted Relative Risk
No Long Covid (reference group)	1	1
1-2 symptoms	0.59 (0.21-1.69)	0.65 (0.22-1.97)
3-4 symptoms	1.49 (0.55-4.01)	2.44 (0.88-6.82)
5+ symptoms	4.39 (1.27-15.23)	4.97 (1.90-12.98)

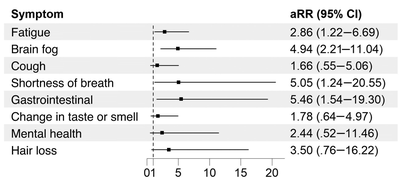


Figure 2. (Top left) The slope of viral clearance was calculated using a mixed effects model with random intercepts and slopes, clustered at the participant level. Modeled slopes of viral clearance for each participant are shown by day after peak viral load. Red line shows one unit-increase in slope from modeled slope in those without long COVID (blue dotted line). (Top right) Each unit-increase in slope was associated with 2.44 times higher risk of 3-4 long COVID symptoms and 4.97 times higher risk of having 5+ long COVID symptoms after adjusting for maximum number of acute symptoms, age, and variant. (Bottom) Association of specific long COVID symptoms with slope of viral clearance. Relative risk is adjusted for maximum number of acute symptoms, age, and variant. Significant associations were found with fatigue, brain fog, shortness of breath, and GI symptoms.

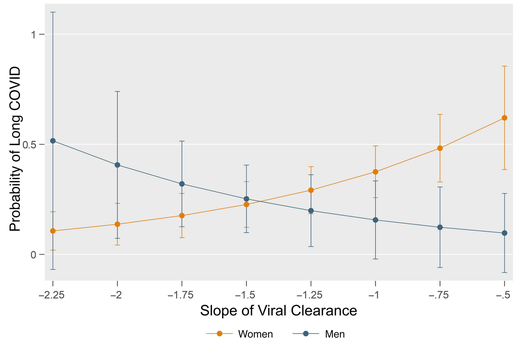
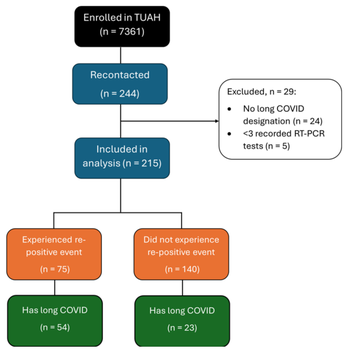


Figure 3. Probability of long COVID by viral clearance slope and sex. Data from females shown in orange, males in blue. Whiskers show 95% confidence intervals. As the slope of viral clearance increases, the probability of long COVID increases among females (p <0.001) but not males (p=0.10).



Subsequent long COVID was associated with viral rebound during acute infection (OR: 13.1, 95% CI: [6.79, 26.2]).

After adjustment for other symptoms and covariates, certain post-acute symptoms and symptom clusters associated with viral rebound during acute infection.
- Constitutional/general symptoms (OR 8.7 [3.2, 26.6])
- Respiratory symptoms (OR 3.9 [1.52, 10.7])

Figure 4. (Left) CONSORT flow diagram of viral rebound analysis. 215 participants who completed the original TUAH or TUAH-Daily study with 3+ RT-PCR test days and who responded to the long COVID survey were included. Viral rebound is defined as having a re-positive RT-PCR test after a negative RT-PCR test. (Right) Results of analysis. Viral rebound during acute infection was associated with long COVID and with certain long COVID symptoms.

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