

1 **Relationship between acute SARS-CoV-2 viral clearance with Long COVID Symptoms: a**  
2 **cohort study**

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33 **Abstract:**

34 **Introduction:** The relationship between SARS-CoV-2 viral dynamics during acute infection and  
35 the development of long COVID is largely unknown.

36 **Methods:** A total of 7361 asymptomatic community-dwelling people enrolled in the Test Us at  
37 Home parent study between October 2021 and February 2022. Participants self-collected  
38 anterior nasal swabs for SARS-CoV-2 RT-PCR testing every 24-48 hours for 10-14 days,  
39 regardless of symptom or infection status. Participants who had no history of COVID-19 at  
40 enrollment and who were subsequently found to have  $\geq 1$  positive SARS-CoV-2 RT-PCR test  
41 during the parent study were recontacted in August 2023 and asked whether they had  
42 experienced long COVID, defined as the development of new symptoms lasting 3 months or  
43 longer following SARS-CoV-2 infection. Participant's cycle threshold values were converted into  
44 viral loads, and slopes of viral clearance were modeled using post-nadir viral loads. Using a log  
45 binomial model with the modeled slopes as the exposure, we calculated the relative risk of  
46 subsequently developing long COVID with 1-2 symptoms, 3-4 symptoms, or 5+ symptoms,  
47 adjusting for age, number of symptoms, and SARS-CoV-2 variant. Adjusted relative risk (aRR)  
48 of individual long COVID symptoms based on viral clearance was also calculated.

49 **Results:** 172 participants were eligible for analyses, and 59 (34.3%) reported experiencing long  
50 COVID. The risk of long COVID with 3-4 symptoms and 5+ symptoms increased by 2.44 times  
51 (aRR: 2.44; 95% CI: 0.88-6.82) and 4.97 times (aRR: 4.97; 95% CI: 1.90-13.0) per viral load  
52 slope-unit increase, respectively. Participants who developed long COVID had significantly  
53 longer times from peak viral load to viral clearance during acute disease than those who never  
54 developed long COVID (8.65 [95% CI: 8.28-9.01] vs. 10.0 [95% CI: 9.25-10.8]). The slope of  
55 viral clearance was significantly positively associated with long COVID symptoms of fatigue  
56 (aRR: 2.86; 95% CI: 1.22-6.69), brain fog (aRR: 4.94; 95% CI: 2.21-11.0), shortness of breath  
57 (aRR: 5.05; 95% CI: 1.24-20.6), and gastrointestinal symptoms (aRR: 5.46; 95% CI: 1.54-19.3).

58 **Discussion:**

59 We observed that longer time from peak viral load to viral RNA clearance during acute COVID-  
60 19 was associated with an increased risk of developing long COVID. Further, slower clearance  
61 rates were associated with greater number of symptoms of long COVID. These findings suggest  
62 that early viral-host dynamics are mechanistically important in the subsequent development of  
63 long COVID.

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65 **Key words:**

66 COVID-19, cycle threshold, SARS-CoV-2, viral clearance, long COVID, post-acute sequelae of  
67 COVID-19 infection, PASC, viral persistence

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70 **Introduction:**

71 Long COVID, defined here as the presence of new or persistent symptoms for more than  
72 three months after COVID-19 infection that cannot be explained by an alternative diagnosis, is  
73 thought to impact between 10%-30% of patients infected with SARS-COV-2.<sup>1-3</sup> Long COVID  
74 varies widely in its manifestation and severity; common symptoms include fatigue, brain fog,  
75 and disordered sleep, and affected organ systems include cardiovascular, pulmonary, and  
76 neurologic, reviewed in Aiyegbusi et al.<sup>4</sup> Approximately one-fourth of individuals with long  
77 COVID report significant activity limitations, and long COVID has been found to have  
78 detrimental effects on quality of life.<sup>5,6</sup>

79 Currently, the mechanisms leading to long COVID remain unknown. One hypothesis is  
80 that persistence of virus or viral antigen may lead to systemic and immunologic dysfunction.<sup>7-9</sup>  
81 Specifically, studies have shown an association between long COVID and delayed clearance of  
82 viral RNA during acute COVID-19,<sup>10,11</sup> persistent SARS-CoV-2 proteins in plasma,<sup>12</sup>  
83 monocytes,<sup>13</sup> and fecal matter.<sup>14,15</sup> However, previous studies have been limited by sample size  
84 and inconsistent testing frequency.<sup>10,11</sup>

85 Using a longitudinal cohort of ambulatory participants who were first infected with SARS-  
86 CoV-2 between October 2021 and February 2022, we sought to determine if the rate of viral  
87 clearance during acute infection is associated with the risk of subsequent development of long  
88 COVID. Given that long COVID may comprise two or more mechanistically distinct syndromes,  
89 we investigated whether this association exists for some but not all long COVID symptoms.  
90 Further, we explored whether specific symptoms displayed during acute SARS-CoV-2 infection  
91 were associated with long COVID and the rate of viral clearance.

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93 **Methods:**

94 **Study Population and Data Collection:**

95 This study included participants from two longitudinal cohort studies, Test Us at Home and Test  
96 Us at Home-Daily, which were funded by the National Institutes of Health's Rapid Acceleration  
97 of Diagnostics (RADx) program. All participants provided written consent to participate, and this  
98 study was approved by the WIRB-Copernicus Group (WCG) Institutional Review Board.  
99 Participants above the age of two years from across the United States enrolled in these studies  
100 remotely between October 2021 and February 2022, and study materials were shipped to  
101 participant's homes. People were eligible to participate if they were asymptomatic on enrollment  
102 and owned a smartphone. Communities with a high prevalence of SARS-CoV-2 were targeted  
103 for enrollment, to increase the likelihood of capturing transmission and the transition from  
104 negative to positive test results. Participants were asked to complete baseline demographic  
105 surveys and weekly symptom surveys, as well as collect anterior nasal swabs for SARS-CoV-2  
106 antigen and RT-PCR testing every 48 hours over a 14-day period (Test Us at Home) or every  
107 24 hours over a 10-day period (Test Us at Home-Daily). Detailed information about the parent  
108 studies can be found elsewhere.<sup>16</sup>

109 Participants 18 years of age or older with at least one positive PCR test during the original study  
110 period were recontacted in August 2023, 18-22 months after initial SARS-CoV-2 infection. At  
111 this follow-up, participants answered a 5-minute survey on persistent symptoms (from a list of  
112 26, see Supplemental Appendix 1) and medical care utilization. Those participants who report  
113 no previous SARS-CoV-2 infection on enrollment in the original study were included in this  
114 analysis (Figure 1).

#### 115 **Measures:**

116 **SARS-CoV-2 Molecular Testing:** Every 24 to 48 hours, participants collected a bilateral  
117 anterior nasal swab, which was kept at room temperature and then mailed at room temperature  
118 within 24 hours of collection to a central laboratory, Quest Diagnostics, for Roche Cobas RT-  
119 PCR testing. Ct values for the E-gene from Roche Cobas 6800 SARS-CoV-2 RT-PCR were

120 used in analyses to quantify viral load. Viral load was calculated as  $\text{Ln}(\text{Viral Load}) = ((41.44 - \text{Ct}$   
121  $\text{Value}) / 1.06)$ , where increasing values represented increased viral load.<sup>17</sup> Peak viral load was  
122 defined as the viral load at the time of the participant's nadir Ct value.

123 **Long COVID Outcomes:** In August 2023, participants were asked: "Did you have any  
124 symptoms lasting 3 months or longer that you did not have prior to having coronavirus or  
125 COVID-19?"<sup>5</sup> Participants who answered affirmatively were categorized as having had long  
126 COVID and were then asked what symptoms they experienced from among a list of 26  
127 symptoms with a free text box to report more symptoms (Supplemental Appendix 1). We  
128 grouped long COVID symptoms by number of symptoms (1-2 long COVID symptoms, 3-4  
129 symptoms, or 5 or more symptoms). All participants were asked about their total number of  
130 SARS-CoV-2 infections to date.

131 **Survey Data from Original Study:** Number of vaccination doses, age, BMI, and comorbidities  
132 were self-reported on enrollment. Participants were asked to indicate if they had the following  
133 comorbidities: asthma, chronic kidney disease, COPD, cardiovascular disease, cancer, chronic  
134 lung disease, depression, diabetes, hypertension, immunocompromising conditions, serious  
135 mental health disorders (bipolar or schizophrenia), sickle cell disease, substance use or alcohol  
136 use disorders, or other. Participants self-reported acute symptoms (including fever, body aches,  
137 fatigue, rash, nausea, abdominal pain, diarrhea, loss of smell, runny nose, cough, headache, or  
138 other) immediately prior to each swab collection using the study app. Symptoms were  
139 categorized as upper respiratory (loss of smell, runny nose, cough), systemic (fever, body  
140 aches, fatigue, headache), or gastrointestinal symptoms (nausea, abdominal pain, diarrhea).  
141 Additionally, symptom reports were used to create a symptom score, which was the sum of  
142 symptoms the participant reported on each day. Each participant's SARS-CoV-2 variant was  
143 determined via whole genome sequencing of their positive SARS-CoV-2 sample by amplicon-

144 based next-generation sequencing on extracted RNA.<sup>18</sup> Non-sequenced positive samples  
145 (n=20) were excluded in adjusted analyses.

146 **Analyses:**

147 Demographic characteristics were tabulated and stratified between participants with and without  
148 long COVID. To calculate viral clearance, a linear mixed effects model with random slope and  
149 random intercept was used to model log viral load values during the period of viral load decline,  
150 starting from the peak viral load. To calculate a slope of recovery, participants were required to  
151 have two data points: 1) a peak viral load, and 2) one viral load of lesser value occurring after  
152 the peak viral load. Log viral load follows a linear pattern over time, which accounts for the  
153 exponential phases of viral decline during recovery.<sup>19,20</sup> Modeled slopes were calculated for  
154 each participant (Supplemental Figure 1). Using a log binomial model with the modeled slopes  
155 as the exposure, we calculated the relative risk of subsequently developing long COVID with 1-2  
156 symptoms, 3-4 symptoms, or 5+ symptoms. To assess whether the relationship between viral  
157 clearance and long COVID was consistent between men and women, we used a log binomial  
158 model with an interaction term between slope and biological sex, and nonlinear combinations of  
159 predictions were used to quantify the differences by BMI and sex and to calculate the  
160 accompanying 95% confidence intervals. We also calculated the relative risk of slope of viral  
161 clearance on each long COVID symptom that received more than 5 affirmative responses and  
162 displayed these results as a forest plot. We evaluated maximum number of symptoms during  
163 acute infection, number of infections, vaccination status, age, comorbidities, BMI, sex, and  
164 SARS-CoV-2 variant as confounders, and included variables based on a 10% change-in-  
165 estimate criterion.<sup>21</sup> Maximum symptoms, age, and variant were determined to be confounders  
166 using this criterion and included as confounders in the adjusted models. To facilitate  
167 interpretation, we also displayed slopes in terms of days to clearance, assuming intercepts (i.e.,  
168 maximum viral load) at the 25<sup>th</sup>, 50<sup>th</sup>, and 75<sup>th</sup> percentile. Estimates and 95% confidence

169 intervals were generated through the bootstrap methodology to incorporate measures of  
170 uncertainty. Clearance was defined as a Ct value  $\geq 40$  which is the limit of detection (i.e., log  
171 viral load of 3.90).

172 Lastly, we analyzed participant-reported symptoms recorded during acute infection and  
173 calculated relative risk of subsequent development of long COVID for each individual acute  
174 symptom, acute symptom category (upper respiratory, gastrointestinal, or systemic), and  
175 cumulative number of acute symptoms. Confounders were similarly determined using a 10%  
176 change-in-estimate criterion, and models were adjusted for age and variant. We conducted  
177 sensitivity analyses analyzing participants who reported just one total SARS-CoV-2 infection as  
178 of August 2023. All analyses were conducted using STATA 17.0.

## 179 **Results:**

### 180 **Participant Characteristics**

181 Of the 7988 participants enrolled in parent studies Test Us at Home and Test Us at Home Daily,  
182 451 participants tested positive for SARS-CoV-2 by RT-PCR during the parent study and were  
183 18 years or older, and thus eligible for the long COVID survey in August 2023. In total, 200  
184 participants (44.3%) responded to the long COVID survey. We limited analyses to the 172  
185 participants whose first known infection with SARS-CoV-2 occurred during the parent study  
186 period (**Figure 1**). Among 172 respondents, 59 (34.3%) reported having had long COVID, here  
187 defined as the presence of symptoms for three months or longer following COVID-19.

188 In total, 128 of the 172 (74.4%) of participants were women, and the median age was 37 (IQR,  
189 32-44). The majority of participants (62.2%) had no comorbidities, while 11.0% of participants  
190 had 2+ comorbidities (**Table 1**). Among the 59 participants with long COVID, 8 (13.6%) visited  
191 the emergency room during their SARS-CoV-2 infection, compared to just 1 participant (0.88%)  
192 without long COVID. Only one participant was hospitalized during their acute SARS-CoV-2



193 infection. As of August 2023, 71.7% of participants who never had long COVID reported having  
194 just one SARS-CoV-2 infection, while 40.7% of those with long COVID reported having just one  
195 SARS-CoV-2 infection. In our sample, 128 participants (74.4%) had their peak viral load and a  
196 prior lower viral load captured during the study period.

### 197 **Association between long COVID and Slope of Viral Clearance**

198 The slope of viral clearance was higher (i.e., flatter) among participants with 5+ long COVID  
199 symptoms compared to those with 3-4 long COVID symptoms, 1-2 long COVID symptoms, or  
200 those without long COVID (**Figure 2a, Figure 2b**). Slope of viral clearance had no association  
201 with risk of long COVID with only 1-2 symptoms (**Table 2**). However, the risk of long COVID with  
202 3-4 symptoms was 2.44 times higher (Adjusted RR (aRR): 2.44; 95% CI: 0.88-6.82) in models  
203 adjusted for age, maximum acute symptoms, and SARS-CoV-2 variant per slope-unit increase  
204 (**Table 2**). This association was strongest among participants with 5+ long COVID symptoms,  
205 where a slope-unit increase was associated with nearly five-times higher risk of long COVID  
206 with 5+ symptoms (aRR: 4.97; 95% CI: 1.90-12.98). The interaction term for biological sex was  
207 statistically significant ( $p=0.023$ ), and we observed that the relationship between slope and long  
208 COVID was not consistent between men and women. While the probability of long COVID  
209 increased as slope decreased among females, the same relationship was not observed among  
210 men (**Figure 3**).

211 For participants who never had long COVID, the time from maximum viral load to viral clearance  
212 during the first SARS-CoV-2 infection was 8.65 days (95% CI: 8.28-9.01), assuming a nadir Ct  
213 value of 24.2, which was the median among this population (**Figure 2c, Supplemental Table**  
214 **1**). Participants with long COVID had significantly longer times to viral clearance in their first  
215 SARS-CoV-2 infection than those without long COVID (No long COVID: 8.65 (95% CI: 8.28-  
216 9.01); Long COVID: 10.0 (95% CI: 9.25-10.8)). For participants with more than three long  
217 COVID symptoms, time to clearance was highest, at 11.7 days (95% CI: 10.8-12.6). For



218 participants with peak viral loads in the 25<sup>th</sup> percentile (nadir Ct value=28.6), time to clearance  
219 was lower, and ranged from 5.70 days (95% CI: 5.46-5.94) among those without long COVID to  
220 7.71 days (95% CI: 7.11-8.32) among those with more than three long COVID symptoms. For  
221 participants with peak viral loads in the 75<sup>th</sup> percentile (nadir Ct value=21.4), time to clearance  
222 was higher, and ranged from 10.5 days (95% CI: 10.0-10.9) among those without long COVID  
223 to 14.2 days (95% CI: 13.0-15.3) among those with three or more long COVID symptoms.

#### 224 **Relationship between Slope of Viral Clearance and Specific Long COVID Symptoms**

225 Slope of viral clearance was significantly positively associated with long COVID symptoms of  
226 fatigue (aRR: 2.86; 95% CI: 1.22-6.69), brain fog (aRR: 4.94; 95% CI: 2.21-11.0), shortness of  
227 breath (aRR: 5.05; 95% CI: 1.24-20.6), and gastrointestinal symptoms (aRR: 5.46; 95% CI:  
228 1.54-19.3) (**Figure 4**). In other words, for each unit increase in slope, the risk of long COVID  
229 with fatigue increased by 2.86 times. We did not observe a significant association between  
230 slope of viral clearance and long COVID symptoms of cough, change in taste or smell, mental  
231 health symptoms, or hair loss.

#### 232 **Acute COVID-19 Symptoms and Risk of long COVID**

233 Each additional symptom reported during the acute COVID-19 infection period was associated  
234 with a 21% (95% CI: 1.03-1.43) and 24% (95% CI: 1.11-1.39) increased risk of long COVID with  
235 3-4 symptoms and 5+ symptoms, respectively (**Table 3**). No acute symptoms were associated  
236 with increased risk of long COVID with 1-2 symptoms. We observed that the acute symptoms of  
237 abdominal pain (aRR: 5.41; 95% CI: 2.44-12.0), nausea (aRR: 3.01; 95% CI: 1.31-6.89), and  
238 body aches (aRR: 2.58; 95% CI: 1.26-5.30) during SARS-CoV-2 infection were the three  
239 individual symptoms most strongly associated with long COVID (Figure 5). When looking at  
240 symptom groupings, upper respiratory symptoms during acute infection, including loss of smell,  
241 runny nose, and cough, were not associated with an increased risk of long COVID, regardless  
242 of the number of symptoms. Gastrointestinal symptoms were associated with 3.91 times the risk

243 of long COVID with 5+ symptoms after adjusting for age, BMI, and variant (aRR: 3.91, 95% CI:  
244 1.72-8.92); however, gastrointestinal symptoms were not significantly associated with an  
245 increased risk of long COVID with 3-4 symptoms. Furthermore, systemic symptoms were  
246 associated with 4.16 times (95% CI: 1.63-10.6) the risk of long COVID with 3-4 symptoms and  
247 5.52 times (95% CI: 2.02-15.0) the risk of long COVID with 5+ symptoms. These results were  
248 consistent when restricting to patients who reported just one SARS-CoV-2 infection as of  
249 August 2023 (**Supplemental Table 2**).

## 250 **Discussion**

251 Using longitudinal data collected from participants during their acute SARS-CoV-2 infections, we  
252 report that longer time to clearance during acute COVID-19 is associated with an increased risk  
253 of long COVID, and this relationship is stronger with increasing numbers of long COVID  
254 symptoms. This study is unique in its ability to pair acute infection dynamics with long term  
255 outcomes of COVID-19 infection; we offer a prospective, longitudinal examination of infection  
256 trajectories and their relationship with long COVID. Our large sample size includes participants  
257 from across the United States and includes infections with both the Omicron and Delta SARS-  
258 CoV-2 variants. Further, the frequent sample collection during the acute SARS-CoV-2 infection  
259 period allowed us to model viral clearance with high granularity.

### 260 **Delayed SARS-CoV-2 Viral Clearance and Long COVID**

261 Most studies of clinical viral dynamics have occurred in hospital settings; however, nearly 81%  
262 of SARS-CoV-2 infections are mild to moderate and self-resolving.<sup>22</sup> Additionally, the majority of  
263 long COVID patients were not hospitalized for COVID-19.<sup>23</sup> Therefore, our study of adults with  
264 mild to moderate infections offers an important lens into the longitudinal course of SARS-CoV-2  
265 infections occurring outside the clinical setting. Among ambulatory outpatients with mild to  
266 moderate SARS-CoV-2 infections, Antar et al. also found that delayed time to clearance  
267 (defined as viral clearance >28 days after symptom onset) was associated with long COVID

268 with brain fog and muscle pain.<sup>10</sup> However, they did not find a statistically significant association  
269 between viral clearance and other long COVID symptoms, likely due to sample size and less  
270 frequent sampling. Our larger sample size, more frequent sampling, and inclusion of participants  
271 who went from SARS-CoV-2 negative to positive, allowed us to use a continuous measure to  
272 show that time to clearance was longer among those with long COVID than those without long  
273 COVID, rather than categorizing clearance at 28 days. Similarly, we found a strong association  
274 between viral clearance and brain fog, as well as GI symptoms and shortness of breath.  
275 Another study of participants with mild to moderate SARS-CoV-2 infections also found an  
276 association between long COVID and higher peak viral loads, as well as duration of viral  
277 shedding.<sup>11</sup> This study included primarily participants infected with non-Omicron variants, and  
278 65% of their participants were unvaccinated. Therefore, it is notable that we found that time to  
279 viral clearance had an association with long COVID in our population too, which included  
280 majority Omicron infections and vaccinated participants. Additionally, our study had >50% more  
281 participants, and we were uniquely able to document the transition from negative to positive,  
282 while Lu et al. enrolled participants within 5 days of their first positive test.

283 Our results add to evidence showing an association between delayed viral clearance  
284 and long COVID.<sup>10,11</sup> Delayed viral clearance may be related to long COVID through several  
285 mechanisms. First, delayed immune response, specifically secretory IgA, to SARS-CoV-2 may  
286 cause delayed viral clearance.<sup>24</sup> This may occur due to underlying immune dysfunction caused  
287 by autoimmune or comorbid conditions, which themselves may be associated with long  
288 COVID.<sup>25,26</sup> Furthermore, our finding is consistent with the finding that vaccination provides  
289 partial protection from long COVID.<sup>25</sup> In this case, vaccination may enable an infected individual  
290 to mount a faster or more effective immune response to clear viral RNA, and in turn this faster  
291 clearance is associated with decreased risk for long COVID.<sup>27-30</sup> Additionally, delayed viral  
292 clearance may in itself *cause* immune dysfunction through chronic immune activation, including

293 lymphocyte overstimulation, leading to inflammatory responses and potential cross-reactive  
294 immune responses.<sup>31–33</sup> Whether the immune dysfunction underlies or causes the delayed viral  
295 clearance is still unknown; however, this heightened inflammatory state may possibly delay  
296 healing from the acute infection, trigger autoimmunity, or cause organ damage, all resulting in  
297 long-term symptoms. Therefore, the speed and functionality of the immune response  
298 responsible for clearing virus from the upper respiratory tract may either directly impact long  
299 COVID risk or be associated with other dysfunction or damage related to long COVID, and  
300 result in serious implications for long-term symptom resolution.<sup>31,32</sup>

301 We also observed that the association between viral clearance and long COVID differed  
302 between men and women. It appeared the relationship between viral clearance and long COVID  
303 was stronger among women, compared to men. It is well documented that men comprised more  
304 COVID-19-related deaths and hospitalizations, compared to women, and evidence has shown  
305 higher viral loads among men compared to women.<sup>34,35</sup> However, women are more likely than  
306 men to report long COVID.<sup>1,36</sup> Men and women have been observed to have different responses  
307 to viral infection, with men having less robust innate immune responses than women.<sup>37,38</sup> This  
308 may indicate that the immune dysfunction leading to long COVID is mediated by sex-specific  
309 factors; however, this observation may also be due to the limited number of men in our study  
310 cohort. Therefore, further sex-specific analyses are necessary to further evaluate this finding.

### 311 **Association between acute symptoms and Long COVID**

312 We found that certain symptoms during acute COVID-19 infection were associated with a higher  
313 risk of long COVID than others.<sup>39,40</sup> Abdominal pain during acute COVID-19 infection was the  
314 single symptom most significantly associated with future risk of long COVID. Gastrointestinal  
315 symptoms are reported in 15-50% of acute COVID-19 infections, and SARS-CoV-2 RNA,  
316 antigen, and virions have all been identified in the GI tract of COVID-19 patients.<sup>41–43</sup> Further,  
317 previous studies have indicated that SARS-CoV-2 clearance in respiratory tissues may be more

318 rapid than clearance within gastrointestinal tissues.<sup>14</sup> Fecal shedding of RNA has been  
319 correlated with a variety of GI symptoms, including abdominal pain. It may be that abdominal  
320 pain is a crude indicator of viral dissemination outside the upper respiratory tract, and viral  
321 dissemination is associated with long COVID. However, viral RNA in the GI tract has been  
322 found in patients with and without long COVID.<sup>14</sup> The GI tract is highly immunoreactive, and it is  
323 hypothesized that prolonged exposure to SARS-CoV-2 in the GI tract may have immunological  
324 implications and contribute to many common long COVID symptoms.

### 325 **Limitations and strengths**

326 This study has several limitations. The parent study period was 14 days; therefore, duration of  
327 infection was calculated through modeled estimates, rather than observed clearance. While we  
328 classified long COVID by number of symptoms reported, we did not consider the severity of  
329 each symptom. We were also limited in our ability to perform further subgroup analyses on sex  
330 and long COVID symptoms due to sample size. Previous infections were self-reported;  
331 therefore, it is possible participants were unknowingly infected with SARS-CoV-2 prior to the  
332 infection documented during the study period. There is also the potential for recall bias for long  
333 COVID symptoms. Further, the FDA granted an EUA for Paxlovid for the treatment of  
334 individuals with mild to moderate COVID-19 at risk of developing severe COVID-19 on  
335 December 22, 2021, which occurred in the middle of our study. However, outside of long-term  
336 care settings, use of Paxlovid in January and February 2022 was very low in the United States,  
337 with less than 22 prescriptions and less than 40 prescriptions per 100,000 people <65 years old  
338 and >65 years old, respectively.<sup>44</sup> Lastly, as of December 2022, more than 50% of COVID-19  
339 cases in the United States were reinfections, and individual's cumulative exposure to the virus  
340 continues to increase with the mutation and spread of the Omicron variant.<sup>45</sup> Understanding the  
341 viral dynamics from an individual's first COVID-19 infection can form a baseline to enhance our  
342 understanding of the relationship between subsequent infections on the risk of long COVID.<sup>46</sup>

343 However, future studies are needed to explore the impact of reinfection on viral clearance and  
344 the connection with long COVID.

### 345 **Conclusion**

346 We observed that slower rates of viral RNA clearances during acute COVID-19 were associated  
347 with an increased risk of developing long COVID. Further, slower clearance rates were  
348 associated with a greater number of long COVID symptoms. These findings suggest that early  
349 viral-host dynamics are mechanistically important in the subsequent development of long  
350 COVID.

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362

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372 AA contributed to design of methodology. AS, CH, CW, JB, PS contributed to data collection  
373 and curation. CH conducted formal analysis and wrote the original draft. KL, DDM, NH, YCM,  
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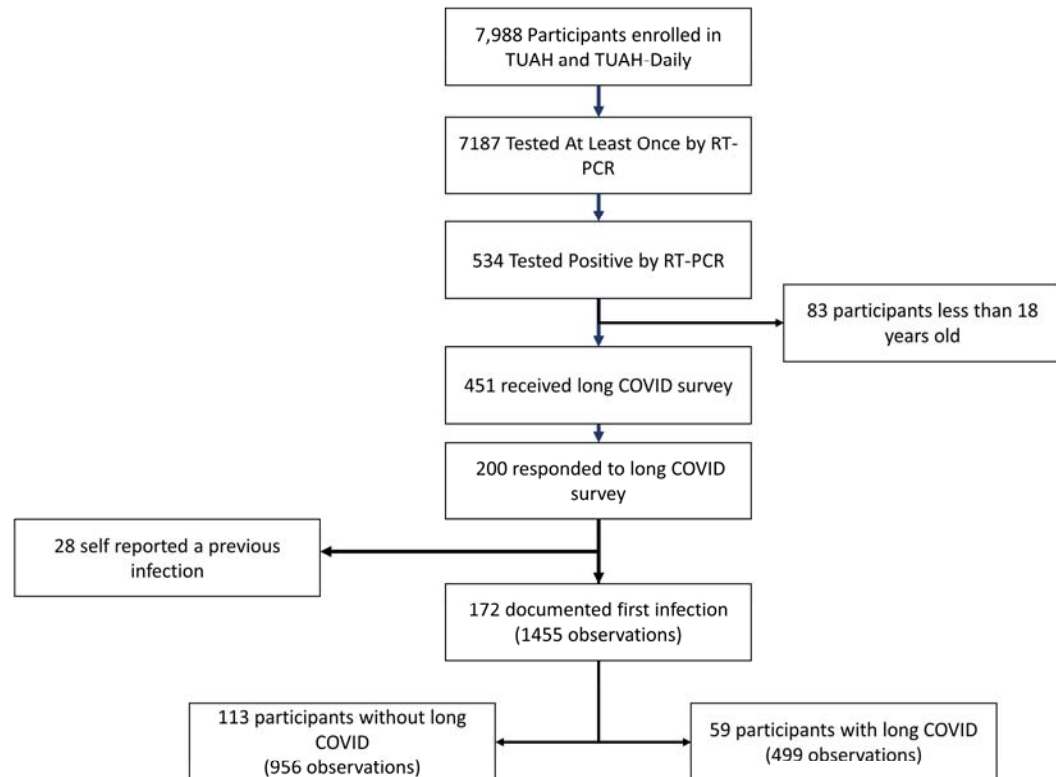
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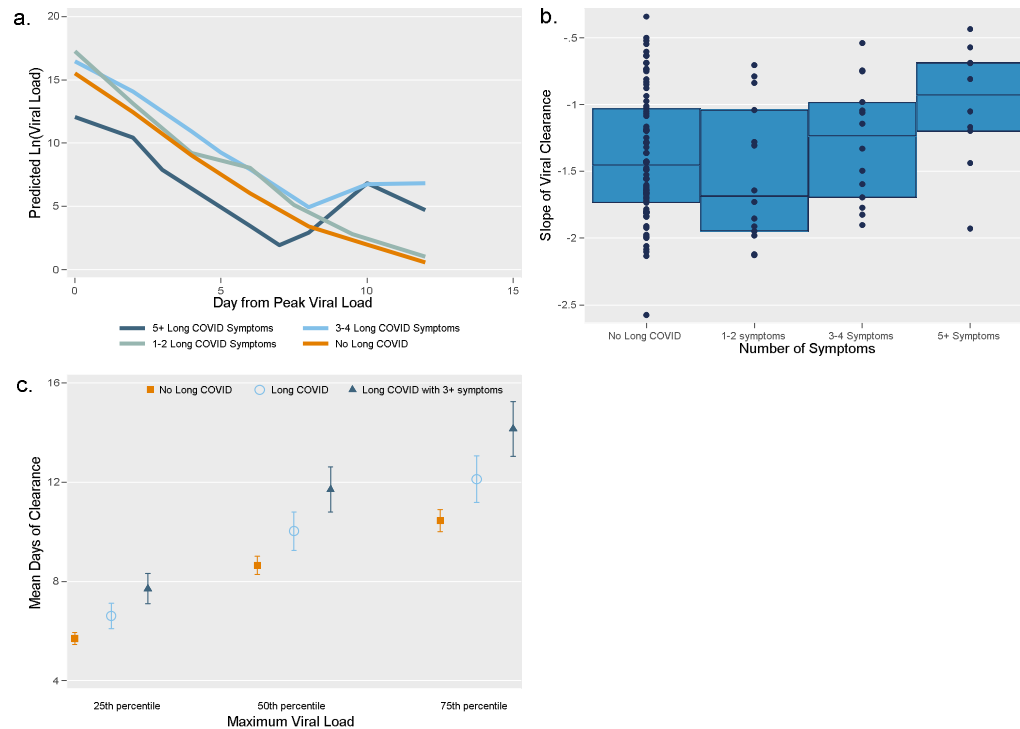
## Figures:

**Figure 1: Consort Diagram of Study Cohort**



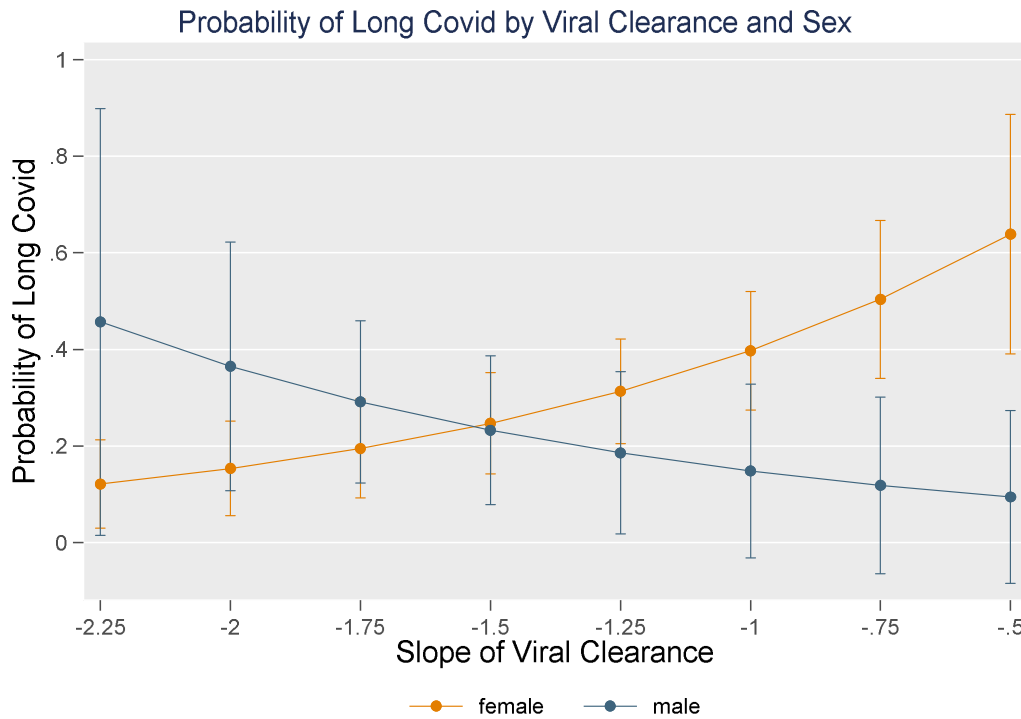
**Legend: Consort Diagram of Study Cohort.** Of the 534 participants who tested positive for SARS-CoV-2 during the parent study, 200 received the long COVID survey and responded. For these analyses, participants were excluded if they were previously infected with SARS-CoV-2; a total of 28 participants self-reported a previous infection and were excluded for this reason. 172 participants with a total of 1455 observations were included in analyses, including 113 participants (65.7%) without long COVID and 59 participants (34.3%) with long COVID.

**Figure 2: Predicted Viral Load, Slope, and Time to Clearance by Number of Long COVID Symptoms**



**Legend:** Figure 2a shows mean predicted viral load each day starting from the day of peak viral load by number of long COVID symptoms. Dark blue signifies individuals with 5+ long COVID symptoms, light blue shows individuals with 3-4 long COVID symptoms, grey indicates individuals with 1-2 long COVID symptoms, and the orange line includes individuals with no long COVID. Figure 2b displays the slope of viral clearance among participants with no long COVID, 1-2 long COVID symptoms, 3-4 long COVID symptoms, and 5+ long COVID symptoms. Higher slopes (closer to 0) are “flatter” than lower slopes (more negative). The blue boxes represent the interquartile range, and the navy line within the blue box displays the median slope for each group. Navy dots show the slope for each participant. Figure 2c shows predicted mean number of days from peak viral load to clearance calculating using the slopes of viral clearance, assuming clearance at a Ct value=40 (limit of detection). Days from peak viral load to clearance is a function of peak viral load and speed (slope) of clearance, so these estimates were calculated using maximum viral loads at the 25<sup>th</sup> percentile, 50<sup>th</sup> percentile, and 75<sup>th</sup> percentile. Participants with long COVID with 3+ symptoms are shown in dark blue triangles, those with long COVID (with any number of symptoms) are shown in light blue circles, and participants without long COVID are in orange squares. Whiskers represent 95% confidence intervals.

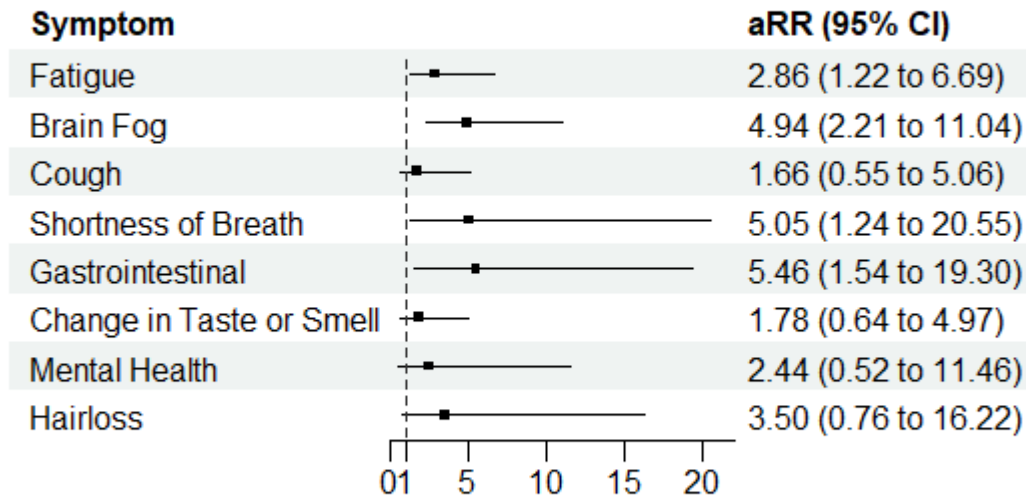
Figure 3: Probability of Long COVID by Viral Clearance and Sex



**Legend: Probability of Long COVID by Viral Clearance and Sex.** Females are displayed in orange and males are displayed in blue. Whiskers show 95% confidence intervals. As slope increases, probability of long COVID increases among females. However, there is no significant increase in probability of long COVID as slope increases among males.



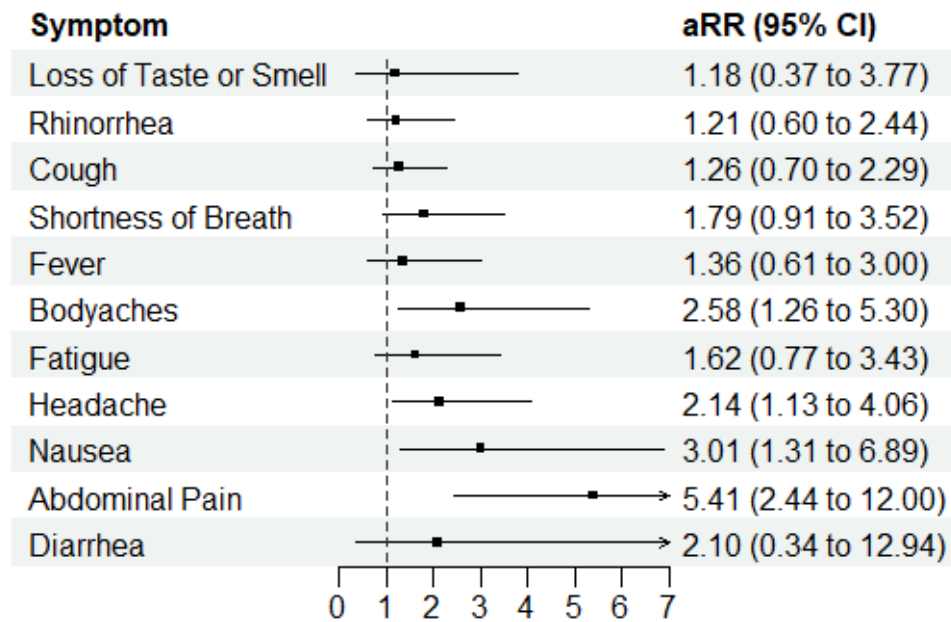
**Figure 4: Association of Specific Long COVID Symptoms with Slope of Viral Clearance**



**Legend: Association of Specific Long COVID Symptoms with Slope of Viral Clearance.**

Dotted black line shows a relative risk of 1. Black dots show the relative risk of each long COVID symptom from slope of viral clearance, adjusted for maximum number of symptoms during acute infection, age, and SARS-CoV-2 variant (Delta or Omicron). aRR: Adjusted Relative risk

**Figure 5: Association Between Acute SARS-CoV-2 Symptoms and Risk of Long COVID**



**Legend: Association Between Acute SARS-CoV-2 Symptoms and Risk of Long COVID.**

Dotted black line shows a relative risk of 1. Black dots show the adjusted relative risk of long COVID from acute SARS-CoV-2 symptoms, adjusted for age, BMI, and SARS-CoV-2 variant (Delta or Omicron). aRR: Adjusted Relative risk

**Tables:**

**Table 1: Demographics of Cohort by Long COVID Status**

		No Long COVID N=113	Long COVID N=59	P-value
Sex	Female	82 (72.6%)	46 (78.0%)	0.44
	Male	31 (27.4%)	13 (22.0%)	
Acute COVID-19 Severity	No symptoms	6 (5.3%)	0 (0.0%)	<0.001
	Managed symptoms at home	104 (92.0%)	51 (86.4%)	
	Visited the emergency department	1 (0.88%)	8 (13.6%)	
	Hospitalized	1 (0.88%)	0 (0.0%)	
	I don't remember	1 (0.88%)	0 (0.0%)	
Vaccination Doses Prior to First SARS-CoV-2 infection	Unvaccinated	23 (20.4%)	7 (11.9%)	0.14
	1 dose	4 (3.5%)	1 (1.7%)	
	2 doses	19 (16.8%)	18 (30.5%)	
	3+ doses	67 (59.3%)	33 (55.9%)	
BMI Categories	BMI <25	47 (41.6%)	17 (28.8%)	0.24
	BMI 25-30	31 (27.4%)	18 (30.5%)	
	BMI >30	35 (31.0%)	24 (40.7%)	
Number of COVID-19 infections	1	81 (71.7%)	24 (40.7%)	<0.001
	2	22 (19.5%)	28 (47.5%)	
	3	7 (6.2%)	7 (11.9%)	
	4	3 (2.7%)	0 (0.0%)	
Age Category	18-44 years	88 (77.9%)	38 (64.4%)	0.022
	45-64 years	17 (15.0%)	18 (30.5%)	
	65+ years	4 (3.5%)	0 (0.0%)	
	Missing	4 (3.5%)	3 (5.1%)	
Comorbidities <sup>a</sup>	None	73 (64.6%)	34 (57.6%)	0.66
	1 comorbidity	28 (24.8%)	18 (30.5%)	
	2+ comorbidities	12 (10.6%)	7 (11.9%)	
SARS-CoV-2 Variant	Omicron	92 (84.4%)	44 (78.6%)	0.35

Data are presented as n (%).

<sup>a</sup>Comorbidities included: asthma, chronic kidney disease, COPD, cardiovascular disease, cancer, chronic lung disease, depression, diabetes, hypertension, immunocompromising conditions, serious mental health disorders (bipolar or schizophrenia), sickle cell disease, substance use or alcohol use disorders.

**Table 2: Association of Slope of Viral Clearance with Number of Long COVID Symptoms**

Number of Long COVID Symptoms	Slope of Viral Clearance: $\beta$ (95% CI)	
	Unadjusted Relative Risk	Adjusted* Relative Risk
No Long Covid <i>(reference group)</i>	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)

**Legend: Association of Slope of Viral Clearance with Number of Long COVID Symptoms.**

Adjusted estimates are adjusted for maximum symptoms, age, and SARS-CoV-2 variant (Delta or Omicron). A unit-increase in slope was associated with a 4.97 times higher risk of having 5+ long COVID symptoms, adjusted for maximum symptoms during acute SARS-CoV-2 infection, age, and variant.

**Table 3: Association between Number of Acute COVID-19 Symptoms and Risk of Long COVID**

	Maximum symptoms reported (continuous)		Upper Respiratory Symptoms		Gastrointestinal Symptoms		Systemic Symptoms	
	Unadjusted	Adjusted*	Unadjusted	Adjusted*	Unadjusted	Adjusted*	Unadjusted	Adjusted*
<b>Long COVID with 1-2 symptoms</b>	1.05 (0.89-1.25)	1.05 (0.85-1.30)	0.64 (0.33-1.27)	0.69 (0.31-1.53)	1.93 (0.84-4.46)	1.69 (0.55-5.14)	1.12 (0.57-2.21)	1.16 (0.53-2.53)
<b>3-4 symptoms</b>	1.22 (1.06-1.40)	1.21 (1.03-1.43)	1.34 (0.57-3.16)	1.64 (0.58-4.68)	0.93 (0.24-3.56)	1.99 (0.47-8.45)	3.06 (1.28-7.29)	4.16 (1.63-10.60)
<b>5+ symptoms</b>	1.25 (1.10-1.41)	1.24 (1.11-1.39)	1.39 (0.60-3.28)	2.12 (0.87-5.23)	2.48 (1.14-5.40)	3.91 (1.72-8.92)	3.92 (1.55-9.94)	5.52 (2.02-15.04)

\*Adjusted for age, BMI, and variant (Delta or Omicron)