PREDICTORS OF LONG COVID IN ADULTS WITH UNTREATED MILD-TO-MODERATE COVID-19

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BACKGROUND

- Risk factors for and mechanisms of Long COVID remain poorly defined.
- We studied associations with Long COVID in the ACTIV-2/A5401 trial.

METHODS

- Non-hospitalized adults with COVID-19 randomized to placebo within 10 days of symptom onset were analyzed.
- Long COVID was defined as self-reporting overall COVID-19 symptoms as present in the preceding 4 weeks in the Long Term (LT) diary at study week 24, which also assessed 27 individual symptoms.
- Demographics, clinical and biomarker variables at day 0 (body mass index, smoking, COVID-19 vaccination, comorbidities, symptom score summed across 13 acute symptoms each graded as absent[0]/mild[1]/moderate[2]/severe[3], anterior nasal viral RNA levels, serostatus by anti-Spike and anti-nucleocapsid antibody), and inflammatory/coagulation markers at days 0 and 28 were evaluated as predictors of Long COVID using Modified Poisson regression models. Effect modification by sex was evaluated via interaction terms with demographics, clinical and inflammatory/coagulation markers.

RESULTS

- 545/699 (78%) of participants who received placebo January-August 2021 completed LT diary at week 24 (Table 1).
- 74/545 (14%) had Long COVID, including 55/287 (19%) women and 19/258 (7%) men (Table 1).
- Symptoms reported by ≥40% with Long COVID were fatigue, musculoskeletal pain, difficulty concentrating/thinking, muscle weakness, cough, breathing difficulties; most were mild (Fig 1).

Table 1. Baseline Characteristics by Long COVID Status

	Absent (n=471)	Present (n=74)	Total (n=545)
Age (years): median (IQR)	43 (34, 54)	47 (38, 56)	44 (35, 54)
Sex			
Female	232 (49%)	55 (74%)	287 (53%)
Male	239 (51%)	19 (26%)	258 (47%)
Cis-gender	467 (99%)	74 (100%)	541 (99%)
Race			
Black or African American	61 (13%)	9 (12%)	70 (13%)
White	381 (81%)	56 (76%)	437 (80%)
Hispanic/Latino ethnicity	255 (54%)	33 (45%)	288 (53%)
Country of Enrollment			
US	387 (85%)	68 (15%)	455 (83%)
Non-US	84 (93%)	6 (7%)	90 (17%)
Body Mass Index [kg/m²]: median (IQR)	29 (26, 34)	31 (26, 35)	29 (26, 34)
Cigarettes Smoking Status (Current)	96 (20%)	17 (23%)	113 (21%)
History of COVID Vaccine Prior to Entry	71 (15%)	12 (16%)	83 (15%)
Reporting ≥1 high-risk co-morbidity	269 (57%)	48 (65%)	317 (58%)
Total Symptom Score at Day 0: median (IQR)	10 (7, 16)	12 (9, 18)	11 (7, 16)
COVID-19 Anterior Nasal (AN) RNA (log10 copies/mL) at Day 0: median (IQR)	3.6 (1.7, 5.4)	4.3 (1.7, 6.0)	3.7 (1.7, 5.5)
Anti-N or Anti-S Serostatus at Day 0			
Positive	231 (52%)	35 (51%)	266 (52%)
Negative	216 (48%)	33 (49%)	249 (48%)

Female sex, US enrollment, higher symptom burden at study entry, and higher day 28 fibrinogen and CRP levels were associated with an increased risk of Long COVID.

Associations with female sex were not explained by coagulation and inflammatory biomarkers or clinical variables.

- Female sex, US enrollment and higher symptom score at day 0 were significant predictors of Long COVID in multivariable analyses (Fig 2).
- The association of symptom score at day 0 with Long COVID appeared different in women than men, p for interaction=0.048 (Fig 3).
- Nasal viral RNA and serostatus at day 0 were not significant predictors of Long COVID.
- Higher fibrinogen and CRP levels at day 28 were also associated with increased risk of Long COVID (Fig 4). There was no association between day 0 biomarker levels and Long COVID.
- The univariable association of fibrinogen levels on Long COVID differed by sex at day 28 but not at day 0 (Fig 5).

Figure 1. Severity of 13 Acute Symptoms and 14 Long COVID Related Symptoms on LT Diary at Week 24 by Long COVID Status

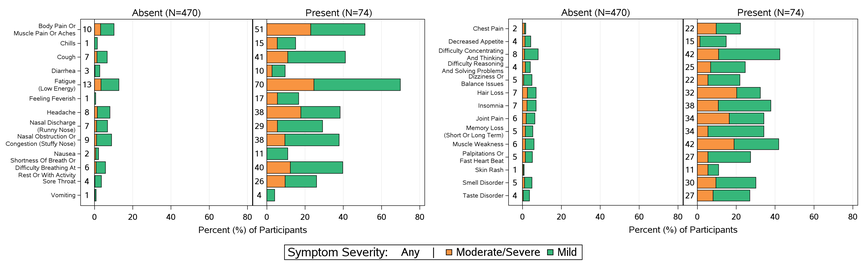
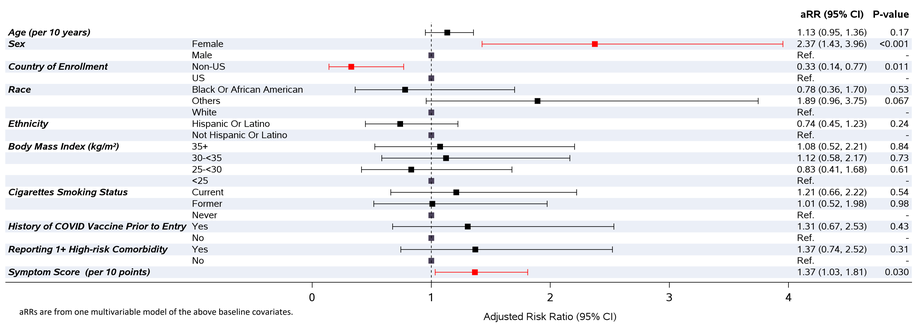


Figure 2. Adjusted Risk Ratios of Long COVID for Baseline Characteristics



aRRs are from one multivariable model of the above baseline covariates.

Figure 3. Observed Risk of Long COVID by Symptom Score (SS) at Day 0 – Overall and by Sex (bubble size proportional to number of participants with each value of SS)

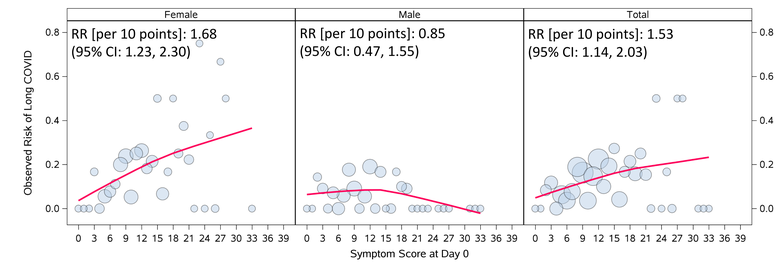
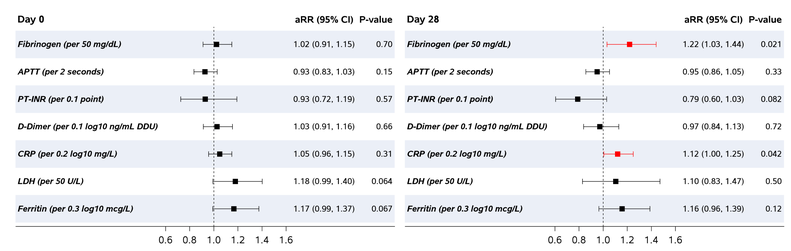
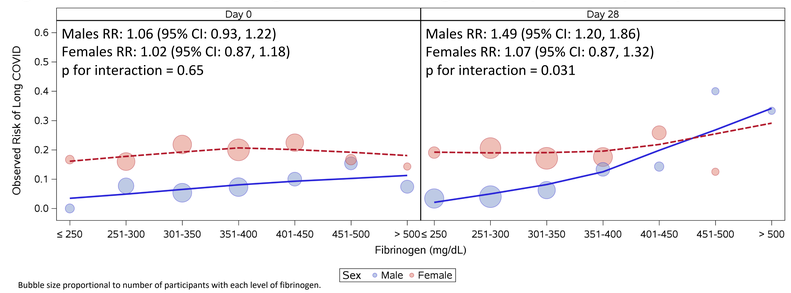


Figure 4. Adjusted Risk Ratios of Long COVID for each Biomarker at Day 0 and Day 28



aRRs are from separate multivariable models, each adjusted for Pre-COVID baseline covariates.

Figure 5. Observed Risk of Long COVID for Fibrinogen on Day 0 and Day 28 By Sex



Bubble size proportional to number of participants with each level of fibrinogen.

CONCLUSIONS

- In untreated adults with mild-to-moderate COVID-19, female sex, US enrollment, and higher CRP and fibrinogen at day 28 were associated with increased risk of Long COVID.
- The association of female sex with risk for Long COVID persisted in all models and was not explained by variables analyzed in this study.
- There was some evidence that symptom burden and fibrinogen associations may differ by sex.
- Additional studies are needed to understand mechanisms underlying associations between Long COVID and sex.

ADDITIONAL KEY INFORMATION

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More information about ACTIV-2 can be found at www.riseabovecovid.org

Trial Registration: ClinicalTrials.gov Identifier: NCT04518410