Immune Status and SARS-CoV-2 Viral Dynamics

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Background

- Severe disease from SARS-CoV-2 infection disproportionately affects immunocompromised individuals
- Case reports and series showed prolonged viral shedding and evolution in severely immunocompromised individuals
- The immunocompromise status represents a broad range of severity. It is unknown how the severity of the immunocompromise affect viral shedding and viremia

Methods

- ACTIV-2/A5401: A multicenter Phase 2/3 adaptive platform trial to evaluate COVID-19 therapeutics in non-hospitalized adults
- Eligibility
  - Non-hospitalized
  - Adult ≥18 years
  - Documented SARS-CoV-2 infection
  - ≤10 days of COVID-19 symptoms
  - Ongoing symptoms within 24-48 hours before enrollment
- Immunocompromise categorization

None	• Not having any of the immunocompromised conditions. Benign tumor; skin tumor treated with resection; skin conditions requiring topical treatment only • Gestational diabetes • Arthritis (not inflammatory)
Mild	• Diabetes mellitus (excluding pre-diabetes) • Cirrhosis\Kidney disease (excluding acute kidney injury) • Autoimmune disease, not receiving immunosuppressants/corticosteroids • HIV infection
Moderate	• Autoimmune disease on immunosuppressants/corticosteroids* • Solid malignant tumor • Receiving strong immunosuppressants regardless of medical history*
Severe	• Solid organ transplant (SOT) • Hematopoietic stem cell transplant (HSCT) • ≥3 types of concurrent immunosuppressants (high dose corticosteroid, antimetabolites, calcineurin inhibitors etc.) • Lymphoma and leukemia • B cell deficiency (congenital or acquired)

*, except on B-cell inhibitors, which will be categorzied as Severe.

- Nasal (day 0, 3, 7, 14, 28) and plasma (day 0, 7) SARS-CoV-2 RNA
  - Limit of detection (LoD) of 1.4 $\log_{10}$ copies/mL (imputed to 0.7 if below LoD)
  - Lower limit of quantification (LLoQ) of 2.0 $\log_{10}$ copies/mL (imputed to 1.7 if below LLoQ and above LoD)
- SARS-CoV-2 serostatus: Bio-Plex platform or Roche platform
- Statistics: Associations between immunocompromise and nasal RNA were compared with linear regression, and plasma RNA detectability with modified poisson regression with robust variance
  - Models were adjusted for age, sex, BMI (≤ 35 vs > 35 kg/m²), smoking, symptom duration at day 0, COVID-19 vaccination status

Conclusions

- In primarily unvaccinated persons with acute COVID-19, nasal SARS-CoV-2 burden is greater in those with moderate/severe immunocompromise.
- Risk of prolonged plasma viremia may be increased with all degrees of immunocompromise.

Results

Table 1. Baseline characteristics

	Immunocompromise Levels			
	None (N=1956)	Mild (N=383)	Moderate/Severe (N=194)	P-value
Age (years), median (Q1, Q3)	43 (34, 55)	54 (45, 62)	57 (47, 64)	<0.001
Sex, n (%)				
Female	1028 (53)	162 (42)	125 (64)	<0.001
Male	928 (47)	221 (58)	69 (36)	
Smoking Status, n (%)				
Current/Former	562 (29)	124 (33)	65 (34)	0.002
Never	1388 (71)	257 (67)	128 (66)	
Not Reported	6	2	1	
Symptom Duration at Study Entry (days), median (Q1, Q3)	6 (4, 7)	6 (4, 7)	6 (4, 7)	0.18
COVID-19 Vaccination, n(%)	85 (4)	23 (6)	8 (4)	0.35
SARS-CoV-2 Serostatus, n (%)				0.002
Negative	650 (56)	104 (46)	60 (67)	
Positive	510 (44)	121 (54)	30 (33)	
Not Reported	796	158	104	

- At entry, median nasal RNA in non-immunocompromised, mild and moderate/severe group was 4.49, 4.69 and 5.50 $\log_{10}$ copies/mL, respectively.
- 25% (581/2351) had detectable plasma RNA.

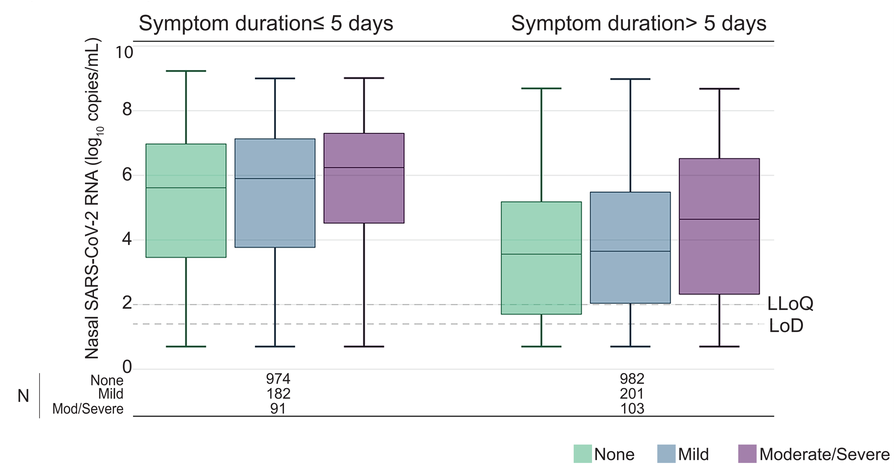


Figure 1. Distribution of Nasal RNA by immunocompromised status stratified by symptom duration at study entry.

Table 2. Day 0 SARS-CoV-2 RNA and immunocompromise levels.

Day 0 AN Swab SARS-CoV-2 RNA levels ($\log_{10}$copies/mL)				
Model		**Diff. in means**	**95% CI**	**P**
Unadjusted	Mild vs. None [ref]	0.18	-0.10, 0.47	0.21
(N=2533)	Moderate/Severe vs. None [ref]	0.73	0.35, 1.11	**<0.001**
Adjusted	Mild vs. None [ref]	0.16	-0.10, 0.43	0.23
(N=2438)	Moderate/Severe vs. None [ref]	0.47	0.12, 0.83	**0.009**
Day 0 Plasma SARS-CoV-2 RNA (detectable vs undetectable)				
Model		**Risk Ratio**	**95% CI**	**P**
Unadjusted	Mild vs. None [ref]	1.20	1.00, 1.45	0.054
(N=2351)	Moderate/Severe vs. None [ref]	1.29	1.02, 1.63	**0.036**
Adjusted	Mild vs. None [ref]	1.15	0.95, 1.39	0.14
(N=2256)	Moderate/Severe vs. None [ref]	1.18	0.93, 1.51	0.18

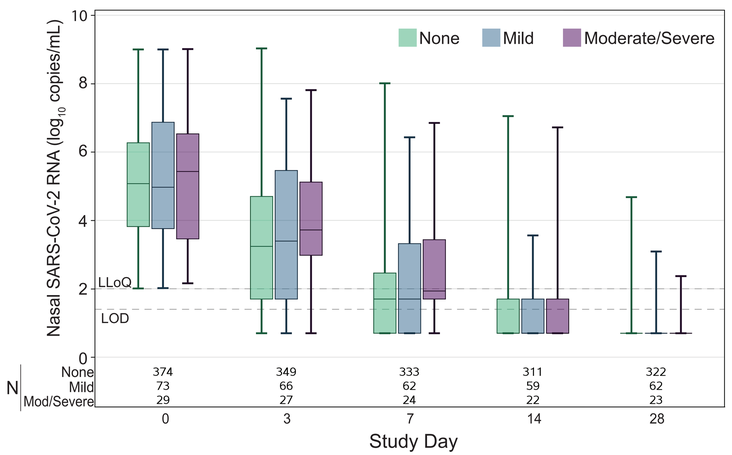


Figure 2. Nasal RNA over time by immunocompromise status among participants on placebo with day 0 SARS-CoV-2 RNA≥LLoQ . LOD, level of detection; LLoQ, lower level of quantification.

Table 3. Day 0 and day 7 SARS-CoV-2 plasma RNA detectability in participants on placebo.

	Immunocompromised Status		
	None (N=334)	Mild (N=52)	Moderate/Severe (N=26)
Day 0, n (%)			
Detectable	70 (22)	8 (16)	4 (15)
Undetectable	251 (78)	42 (84)	22 (85)
Day 7, n (%)			
Detectable	8 (3)	5 (11)	2 (9)
Undetectable	273 (97)	39 (89)	21 (91)

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