Session 2: Acute Inflammation – Part 1

Abstract 2: Clinical Rebound of COVID-19 Following Nirmatrelvir/Ritonavir Is Not Associated With Delayed Immune Response or Severe Disease

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Clinical, Virologic, & Immunologic Evaluation of Rebound COVID-19 After Nirmatrelvir-Ritonavir

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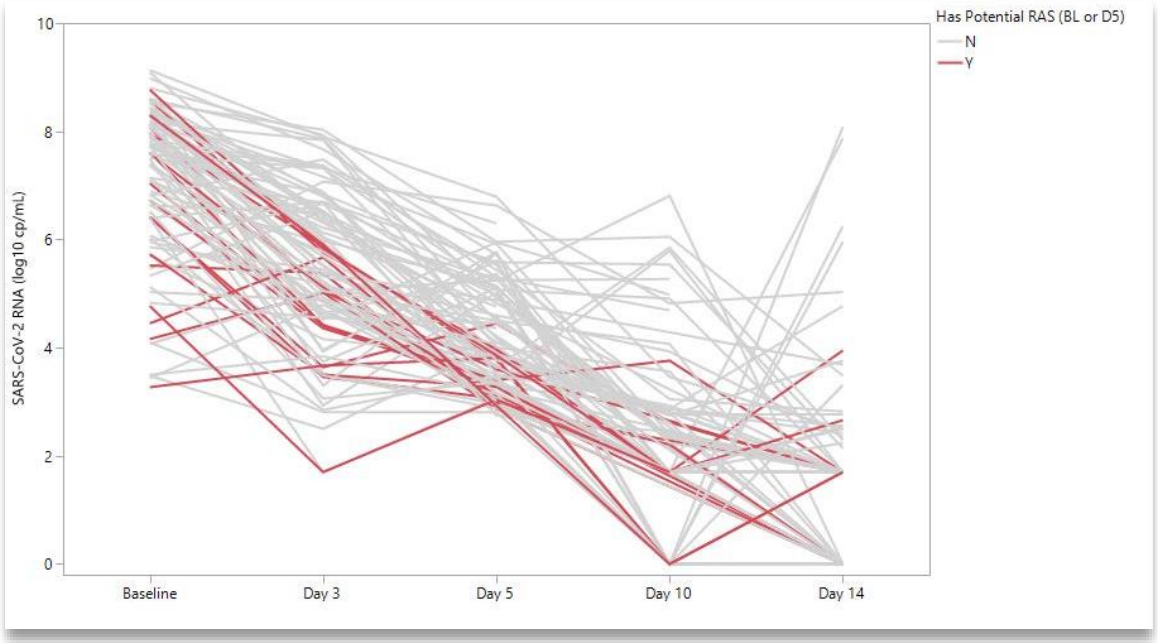
Background

- December 2021: Nirmatrelvir-ritonavir (NMV-r/Paxlovid) granted EUA by the FDA, first SARS-CoV-2 protease inhibitor to be made available
- Reduced risk of hospitalization and death by COVID-19 in unvaccinated high risk adults (0.72% vs. 6.53% treated with placebo)
- Several patients (in both placebo and NMV-r groups) demonstrated viral rebound at day 10-14
- Multiple reports of patients experiencing symptomatic rebound, culminating in a CDC Health Advisory



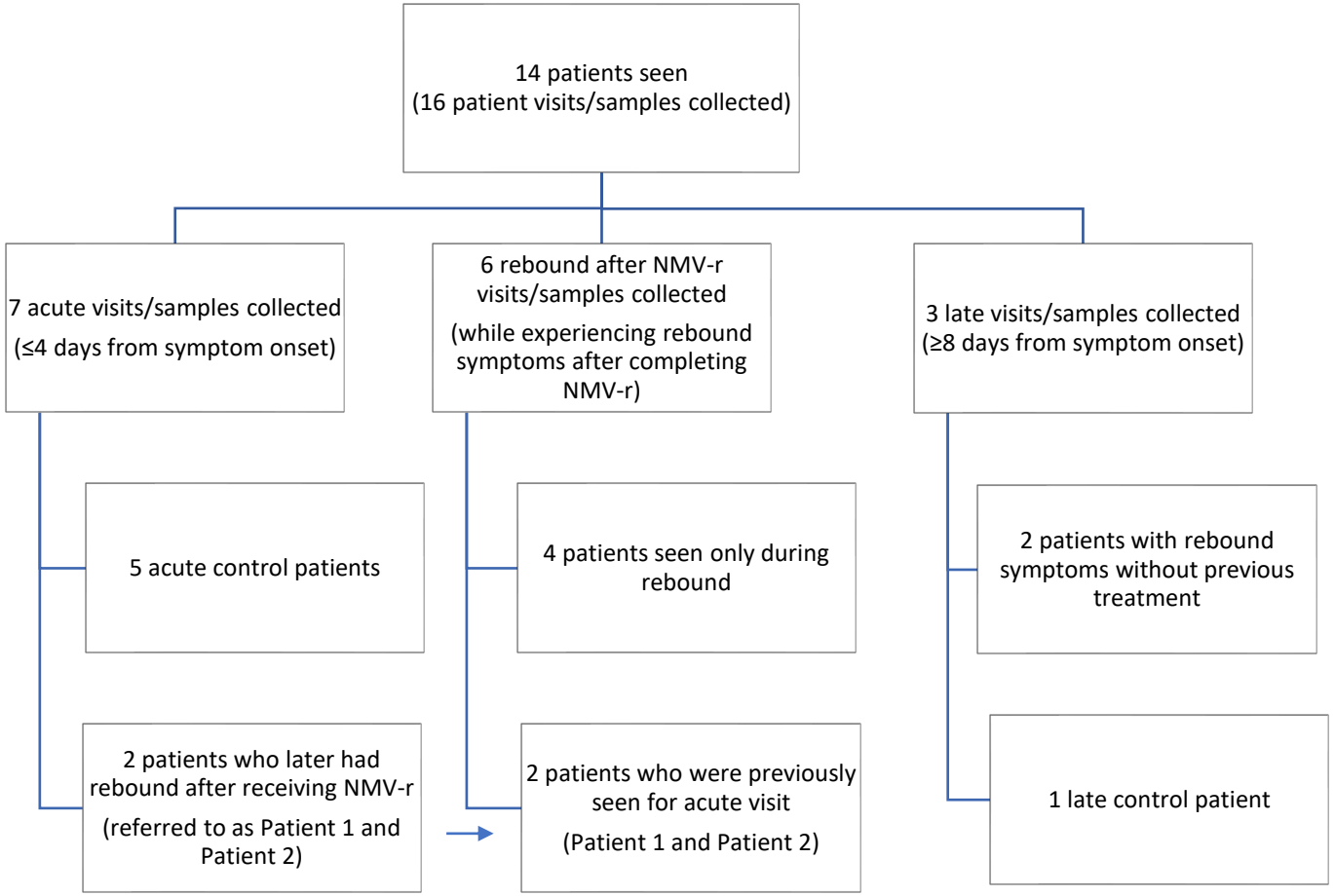
Graphic from EUA CDER Review

- Emergency Use Authorization (EUA) for Paxlovid (nirmatrelvir tablets co-packaged with ritonavir tablets) Center for Drug Evaluation and Research (CDER) Review. Center for Drug Evaluation and Research (CDER), **2021**
- Hammond J, Leister-Tebbe H, Gardner A, et al. Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19. N Engl J Med **2022**; 386(15): 1397-408.
- Charness M, Gupta K, Stack G, et al. Rapid Relapse of Symptomatic Omicron SARS-CoV- 2 Infection Following Early Suppression with Nirmatrelvir/Ritonavir. Research Square preprint, **2022**.
- Gupta K, Strymish J, Stack G, Charness M. Rapid Relapse of Symptomatic SARS-CoV-2 Infection Following Early Suppression with Nirmatrelvir/Ritonavir. medRxiv Preprint **2022**.
- Ranganath N, O'Horo JC, Challener DW, et al. Rebound Phenomenon after Nirmatrelvir/Ritonavir Treatment of Coronavirus Disease-2019 in High-Risk Persons. Clin Infect Dis **2022**.
- Carlin AF, Clark AE, Chaillon A, et al. Virologic and Immunologic Characterization of COVID-19 Recrudescence after Nirmatrelvir/Ritonavir Treatment. Clinical Infectious Diseases **2022** (accepted manuscript).

Questions

- Etiology?
  - Immune evasion because of early viral suppression?
- Risk of severe disease?
- Viral transmissibility?
- Role of NMV-r resistance?

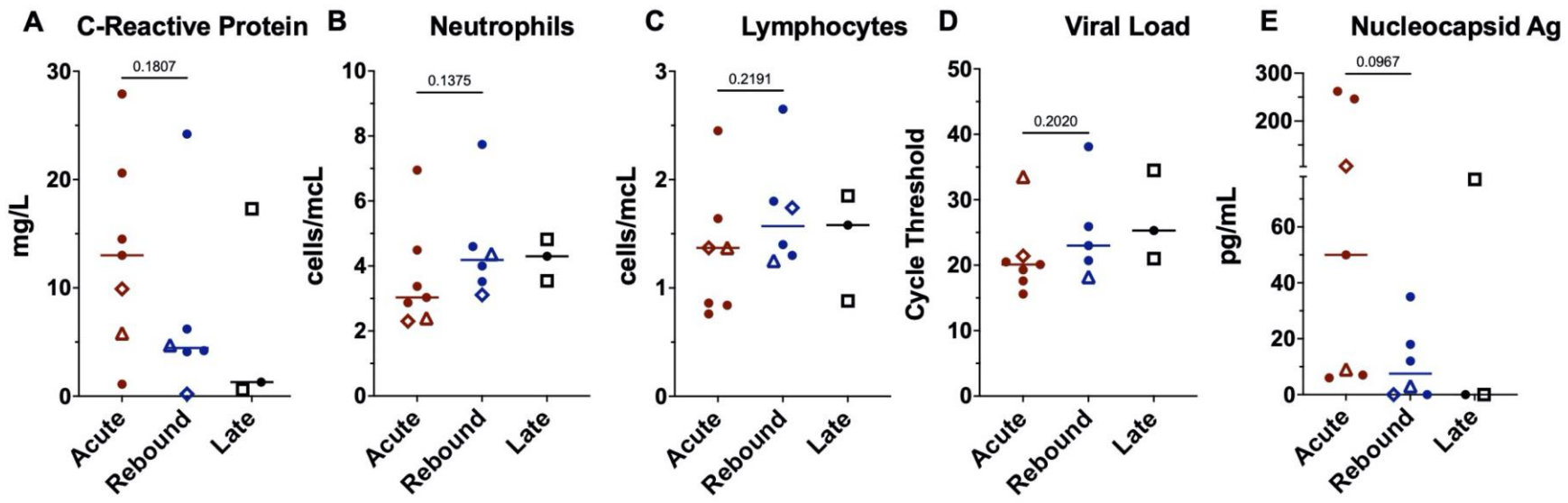
Study Participants



Clinical Evaluation (I)

- NMV-r started between 1-4 days after initial symptom onset
- Median time to symptom recurrence was 12.5 days after initial symptom onset in NMV-r rebound group
  - 6.5 days after completing NMV-r
- Rebound symptom severity:
  - Milder: 6 (2/2 in rebound without treatment)
  - Similar: 1
  - Worse: 1
- No rebound patients required additional treatment or hospitalization

Clinical Evaluation (II)



Clinical Evaluation – Conclusions

- Rebound symptoms occurred after starting NMV-r on a range of days of illness (1 to 4); no clear impact of delayed start
- Symptoms returned on a range of days
  - 11-15 days in NMV-r rebound group
  - 9-20 in rebound without treatment group

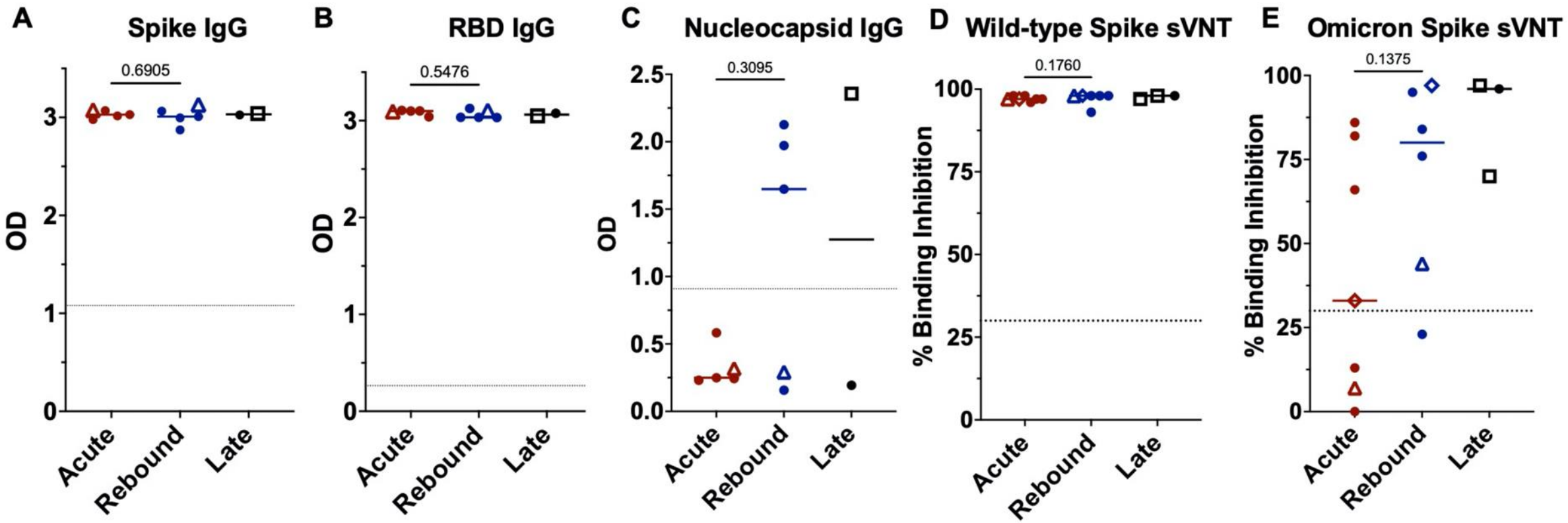
- Most with improved symptoms
- No evidence of progression to severe disease
- Decreased CRP in rebound vs acute

Virologic Evaluation

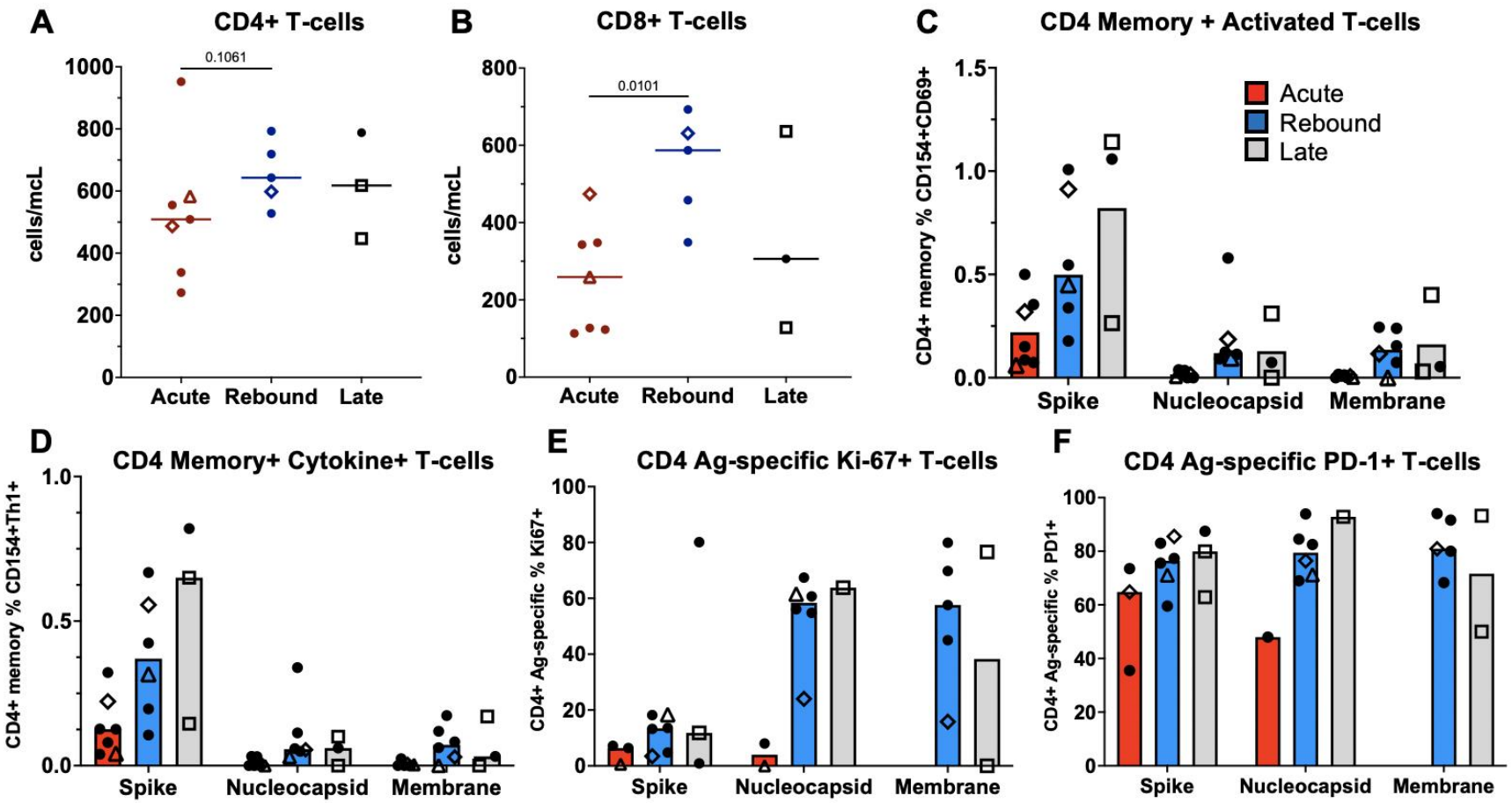
- SARS-CoV-2 from nasal swabs cultured with on Vero E6 cells
- Infectious replication-competent virus isolated from 1/8 rebound patients
  - From patient on a TNF-α inhibitor
- Isolated from 5/8 after adding polybrene
- No subsequent transmissions from our rebound cases
- No resistance mutations identified by sequencing including 1 longitudinal sample

- Boucau J, Uddin R, Marino C, et al. Characterization of virologic rebound following nirmatrelvir-ritonavir treatment for COVID-19. Clin Infect Dis **2022**.
- Davis HE, Morgan JR, Yarmusha ML. Polybrene increases retrovirus gene transfer efficiency by enhancing receptor-independent virus adsorption on target cell membranes. Biophysical Chemistry **2002**; (97): 159-72.

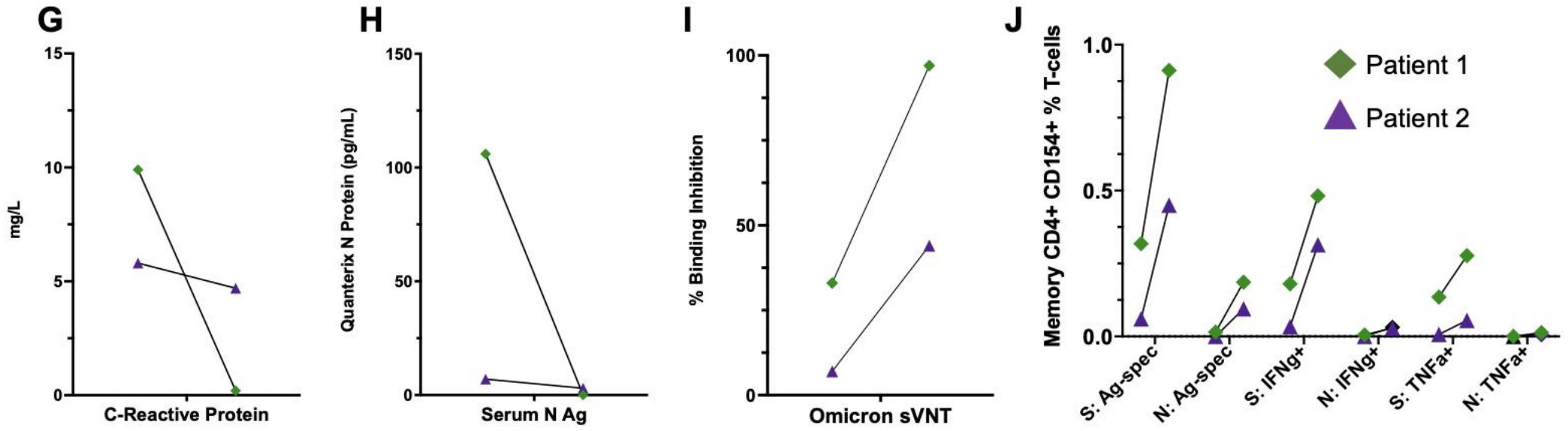
Immunologic Evaluation – Antibody levels and sVNT



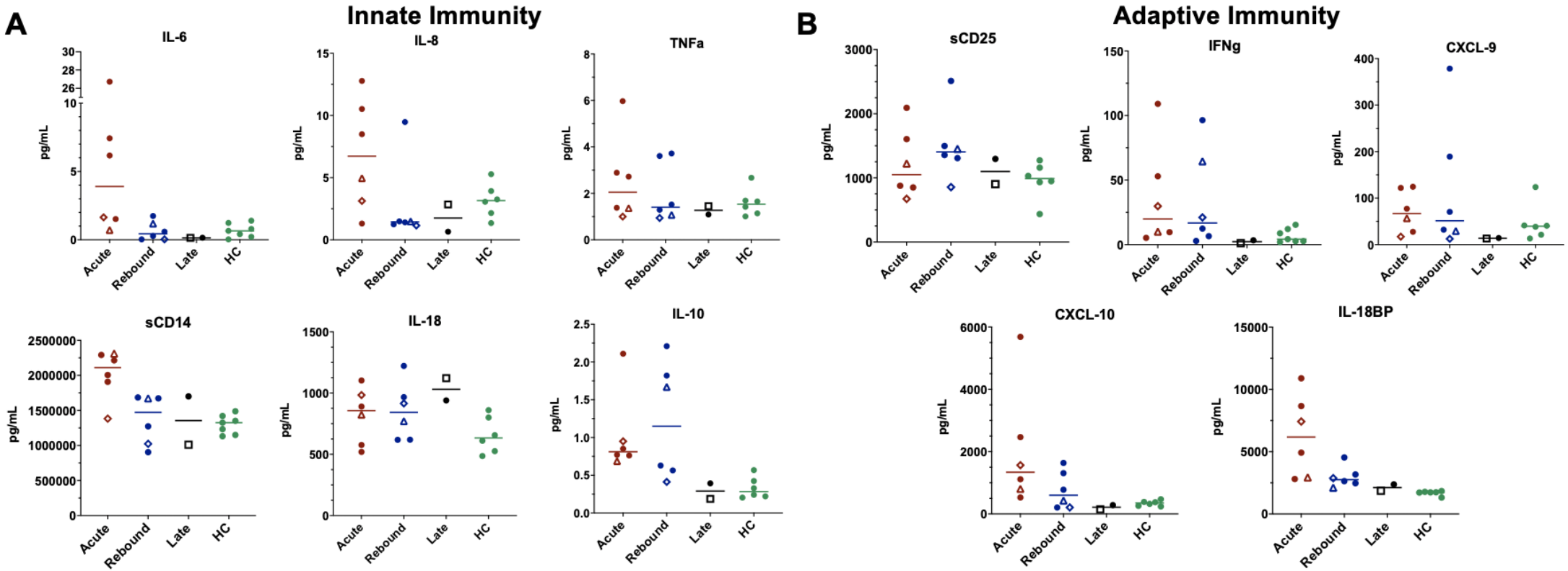
Immunologic Evaluation – T cell responses



Immunologic Evaluation – Longitudinal Patients



Immunologic Evaluation – Biomarkers



Key Findings

- Clinical: Most patients had improved symptoms at rebound; no patients developed severe disease or required additional treatment

- Virologic:
  - No viral resistance mutations identified
  - Infectious replication-competent virus isolated from 1/8 rebound patients, 5/8 after adding polybrene; ?potential of transmission

- Immunologic: Adaptive immunity against SARS-CoV-2 appeared intact

Conclusions & Next Steps

- Pathogenesis of rebound may be caused by a more robust immune response rather than uncontrolled viral replication
- Immunocompromised patients who cannot rely on adaptive immune responses may require prolonged or additional therapies
- Further detailed evaluation in larger cohorts is required to assess the incidence as well as the clinical and epidemiologic implications of rebound COVID-19