Supplemental Data File

Supplemental Table 1. Clinical sites

Institution	Number of Sites	Location
Denver Health	1	Denver, Colorado
Emory University	3	Atlanta, Georgia
New York University	2	New York, New York
University of Arizona	1	Tucson, Arizona
University of California	1	Irvine, California
University of Nebraska Medical Center	1	Omaha, Nebraska
University of Southern California	3	Los Angeles, California
University of Washington	3	Seattle, Washington

Supplemental Table 1.a. Secondary and exploratory hypotheses about clinical manifestations

1. Patient characteristics such as race/ethnicity, age, gender, co-morbidities, and outpatient medications are associated with increased risk for viral SARI (such as COVID-19 and influenza in patients admitted with lower respiratory viral infection syndrome).
2. Patient characteristics (demographics, comorbidities, and molecular profiles during the course of illness) can impact clinical interventions to modify risk and severity of organ failure (e.g., acute respiratory distress syndrome (ARDS), AKI, shock/cardiovascular, delirium/myopathy), hospital and ICU length of stay, and death in patients with viral SARI.
3. Early initiation of invasive mechanical ventilation is associated with improved survival in viral SARI.
4. Greater time from onset of symptoms to admission is associated with poor outcomes, including critical illness and death, in viral SARI.
5. Distinct clinical sub-phenotypes of viral SARI caused by specific viral pathogens exist and are associated with differing clinical outcomes
6. Patient characteristics (demographics, comorbidities, and molecular profiles) interact with clinical interventions to modify risk of poor long-term outcomes (e.g., chronic respiratory failure, end-stage renal disease, impaired cognition and mobility, death) in patients with viral SARI.
7. Outcomes in patients during epidemics/pandemics of viral SARI are associated with measures of hospital and ICU stress.

Supplemental Table 1.b. Secondary and exploratory hypotheses about adaptive immunity, virology and co-Infections

1. Early development of a humoral immune response to viral infection in patients with SARI (e.g., anti-SARS-CoV-2) is associated with better clinical outcomes.
2. Time to development of a humoral immune response to viral infection in SARI patients (e.g., anti-SARS-CoV-2) is associated with severity of illness.
3. Viral genomic evolution based upon sequencing of prospectively collected respiratory specimens is associated with differing immune responses and clinical outcomes in SARI patients.
4. Outcomes in patients with viral SARI (e.g., COVID-19) are associated with administration of anti-viral therapy.
5. Outcomes in patients with viral SARI (e.g., COVID-19) are associated with administration of immune-modulating therapy.
6. Outcomes in patients with viral SARI (e.g., COVID-19) are associated with the presence of co-infections (viral or bacterial) on admission (e.g., influenza, RSV, *Streptococcus pneumoniae*, *Staphylococcus aureus*)
7. Patients with viral SARI (e.g., COVID-19) are at risk for a unique spectrum of nosocomial infections compared with other non-viral SARI admissions and the specific nosocomial infections differ between underlying cause of viral SARI.
8. Viral RNA load in respiratory specimens at hospital admission is associated with outcomes in patients with severe viral SARI (e.g., SARS-CoV-2, influenza A and B).

Supplemental Table 1.c. Secondary and exploratory hypotheses about molecular markers specific to SARS-CoV-2

1. Circulating inflammatory markers and/or MAS/HLH on ICU admission are associated with more severe organ dysfunction (ARDS, AKI, shock, DIC)
2. Elevation in markers of the Renin-Angiotensin System is associated with more severe respiratory failure
3. Dysregulation of inflammation, innate immunity, adaptive immunity, endothelial injury, and apoptosis is associated with risk for poor outcomes in COVID-19 (e.g., Ang1/Ang2/Tie2, FAS/FASL, IL17/Th17, IL-2/IL2R, TNF/TNFR1, IL1B/IL1RA, sCD14)

*MAS = Macrophage activation syndrome; HLH = Hemophagocytic lymphohistiocytosis; ARDS = Acute respiratory distress syndrome; AKI = Acute kidney injury; DIC = Disseminated intravascular coagulation; Ang = Angiopoietin; Tie2 = Tyrosine kinase receptor; FAS = FS-7-associated surface antigen; FASL = FAS ligand; IL = Interleukin; R = receptor; TNF = Tumor necrosis factor; A = antigen; s = Soluble; CD = Cluster of differentiation

Supplemental Table 2. Timeline of biological specimen collection

Samples	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Blood/DNA	X					
Blood/RNA	X	X	X	X	X	X
Blood/Plasma	X	X	X	X	X	X
Blood/PBMC	X	X	X	X	X	X
Urine	X	X	X	X	X	X
NP or Oral Swab	X	X	X	X	X	X
LRT Specimen	X	X	X	X	X	X

Visit 1: <24 hours of hospital presentation, Visit 2: 48-72 hours after study enrollment, Visit 3: 7-14 days after study enrollment, Visit 4: Hospital discharge, Visit 5: 30 days after hospital discharge, Visit 6: 60-90 days after hospital discharge.

PBMC: peripheral blood mononuclear cells; NP: nasopharyngeal; LRT: lower respiratory tract, includes bronchoalveolar lavage or endotracheal aspirate in patients requiring mechanical ventilation.

Swabs and stool may occur across the sampling period. Urine will be collected only if a patient has an indwelling foley catheter.

Supplemental Table 3. Volume and aliquots of specimens collected

Biological Sample	Timing of Sample Collection	Volume	Collection Container	Aliquots
DNA, blood	V1	Collected from 4 mL EDTA tube after processing for plasma	EDTA tube (purple top)	1
RNA, blood	V1-V6	3 mL	Paxgene Blood RNA tube (blue top)	1
Plasma	V1-V6	4 mL	EDTA tube (purple top)	4/each 0.5 mL of plasma
PBMC	V1-V6	8 mL	Cell preparation tube (CPT), variable top	2 aliquots of PBMCs 6/each 0.5 mL aliquot of plasma
Urine	V1-V6	50 mL	Sterile cup	6/each 0.5 mL of urine 4/each 10 mL of urine
NP or Oral Swab	V1-V6	Swab or Saliva	Sterile container	1
LRT Specimen	V1-V6	2 mL	Sterile cup	2

Visit 1 <24 hours of hospital presentation (V1), V2: 48-72 hours after study enrollment, V3: 7-14 days after study enrollment, V4: Hospital Discharge, V5: 30 days after hospital discharge, V6: 60-90 days after hospital discharge.
PBMC – peripheral blood mononuclear cells; NP – nasopharyngeal; LRT – lower respiratory tract, includes bronchoalveolar lavage or endotracheal aspirate in patients requiring mechanical ventilation
Conjunctival or rectal swabs and stool collection may occur across the sampling period.

Supplemental Table 4. SARI-PREP Persons Under Investigation ("At-Risk") Patient Data Collection

Element	Values	Timing
Demographic		
Age in years	18-90, >90	Admit
Sex	M, F, other	Admit
Race/Ethnicity	Standard	Admit
Zipcode	Value	Admit
Week of admission	Date of Monday, a Mo-Su week	Admit
Comorbidities		
Smoking	Active, former, no	Admit
Diabetes	Yes/no	Admit
Hypertension	Yes/no	Admit
Cardiovascular disease	Yes/no	Admit
Chronic obstructive pulmonary disease	Yes/no	Admit
Asthma	Yes/no	Admit
Other chronic pulmonary disease	Yes/no	Admit
Liver disease	Yes/no	Admit
Kidney disease	Yes/no	Admit
Malignancy	Yes/no	Admit
Immunosuppressive therapy	Yes/no	Admit
Non-iatrogenic immunodeficiency	Yes/no	Admit
Hospital Events		
Admission type	Acute care, ICU	Admit
Diagnoses	ICD	Discharge
LOS	Days	Discharge
Discharge Status	Alive/ Dead	Discharge