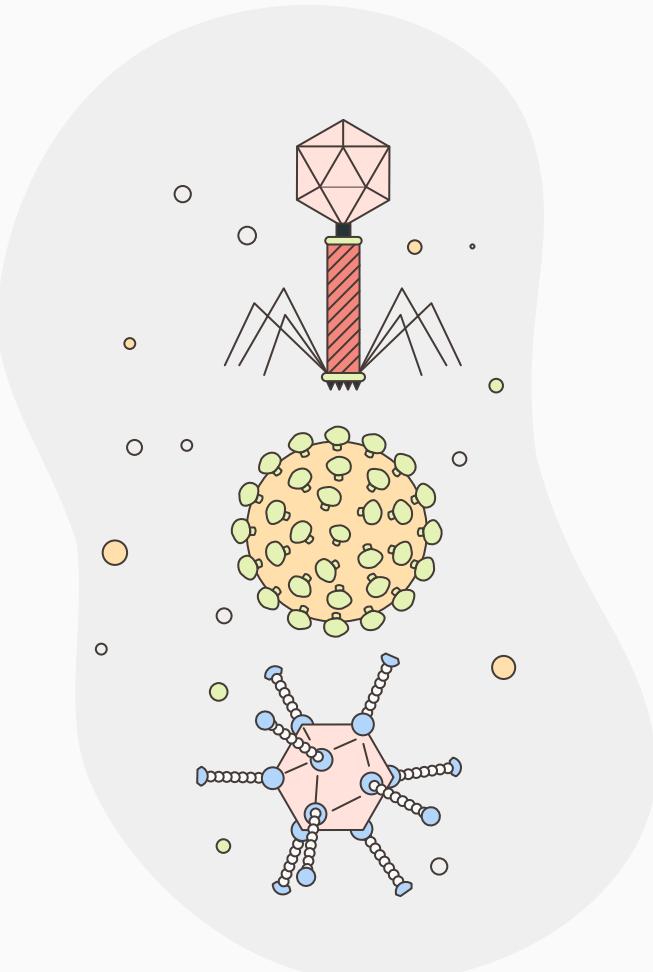


# A blood atlas of COVID-19 defines hallmarks of disease severity and specificity

By: The COvid-19 Multi-omics Blood  
ATlas (COMBAT) Consortium

**Team Noble:** Amanda Adams, Grace Tugado, Elizabeth Esquivel, Jack Rodrigue, Wai Yuen (Wylliam) Zheng



01

# Background

# Overview of COMBAT

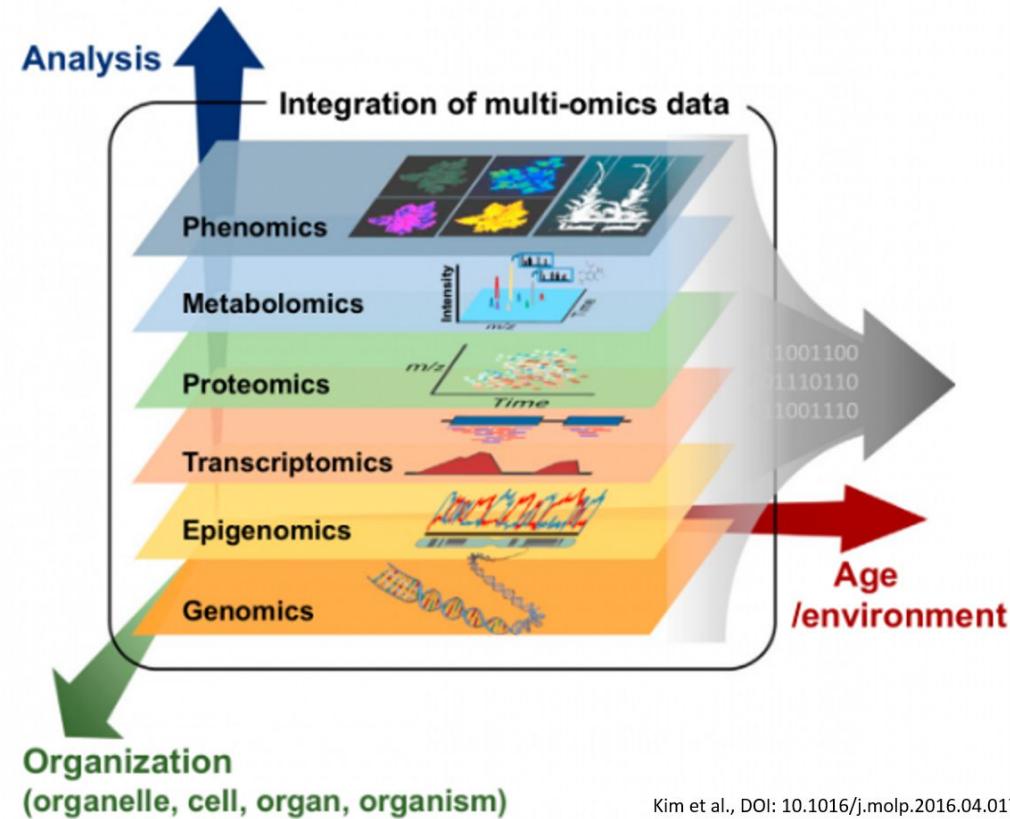
COMBAT (COVID-19 Multi-Omic Blood ATlas) Consortium, led by the University of Oxford:

<https://www.combat.ox.ac.uk/>

"We identify cells, mediators, and pathways in peripheral blood that are hallmarks of increasing COVID-19 severity; resolve shared and specific features with influenza and sepsis; and define potential biomarkers of the variable individual response to SARS-CoV-2 infection to support a future personalized medicine approach."

# Overview of Multi-omics

- Multi-omics allows for the integration of information from multiple sources using systems biology



# Motivation

*What motivates this study and makes it unique?*

**"Treatment of severe COVID-19 is currently limited by clinical heterogeneity and incomplete description of specific immune biomarkers."**

- Comprehensive nature of study allows it to be more personalized and specific
- Comparison of COVID blood atlas to those of sepsis, influenza, and healthy volunteers
  - Use of systems-based integrative analyses

**A**

# COMBAT

COVID-19 Multi-omic  
Blood ATlasIn-patient acute COVID-19  
Mild   Severe   Critical

Community COVID-19

vs

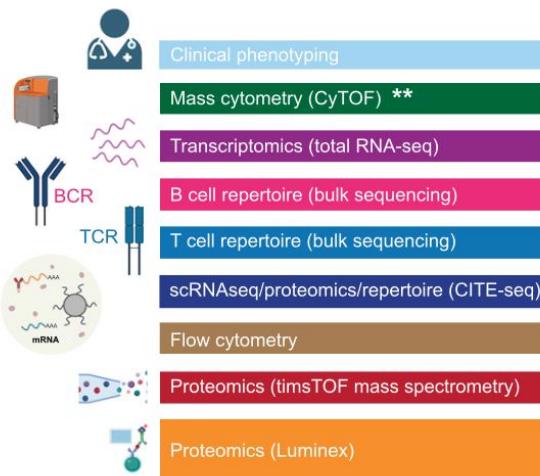
Healthy   Sepsis   Flu

Other data types

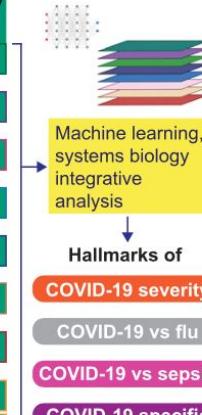
Epigenetics  
(ATAC-seq) \*\*\*Viral RNA  
(serum, swab)

Genotyping

Serology



Overall total	NUMBER OF INDIVIDUALS (SAMPLES) ASSAYED					Community COVID-19	Sepsis acute (IP)	Influenza acute (IP)	Healthy				
	COVID-19 acute in-patient (IP)*			Total									
	Mild	Severe	Critical										
126(146)	17	28	19	64(78)	13	38(44)			11				
123(143)	17	28	19	64(78)	13	36(42)			10				
76	13	26	14	53	5	12			6				
77	11	29	10	50	13	8			6				
122(138)	17	28	19	64(78)	13	23(25)	12		10				
112	17	23	18	58	13	20	11		10				
257(340)	25	49	23	97(145)	100(121)	38(52)			22				
171	25	36	19	80	21	41			29				
75				40	40		20		15				



Abbreviations used in related panels: COVID\_IP\_mild, CM; COVID\_IP\_severe, CS; COVID\_IP\_critical, CC; COVID\_community, CComm; Sepsis\_IP, Sepsis; Flu\_IP, Flu; Healthy, HV

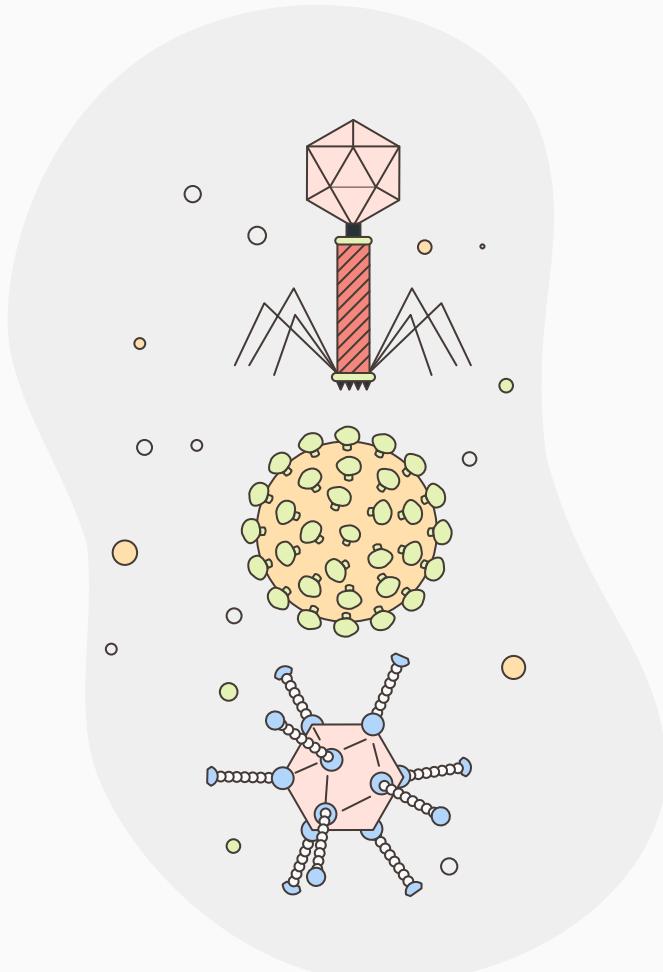
We aimed to characterize the peripheral blood response in COVID-19. To do this, we analyzed a prospective cohort of adult patients with confirmed SARS-CoV-2 presenting to clinical services at the start of the United Kingdom pandemic (February– March 2020). We recruited 116 hospitalized COVID-19 patients following informed consent at a single site (Oxford University Hospitals) through the Sepsis Immunomics study. The overall mortality rate was 23.3%. Samples were collected during the acute admission and in survivors from 28 days after discharge (convalescent samples)."

- Community cases: not admitted to hospitals

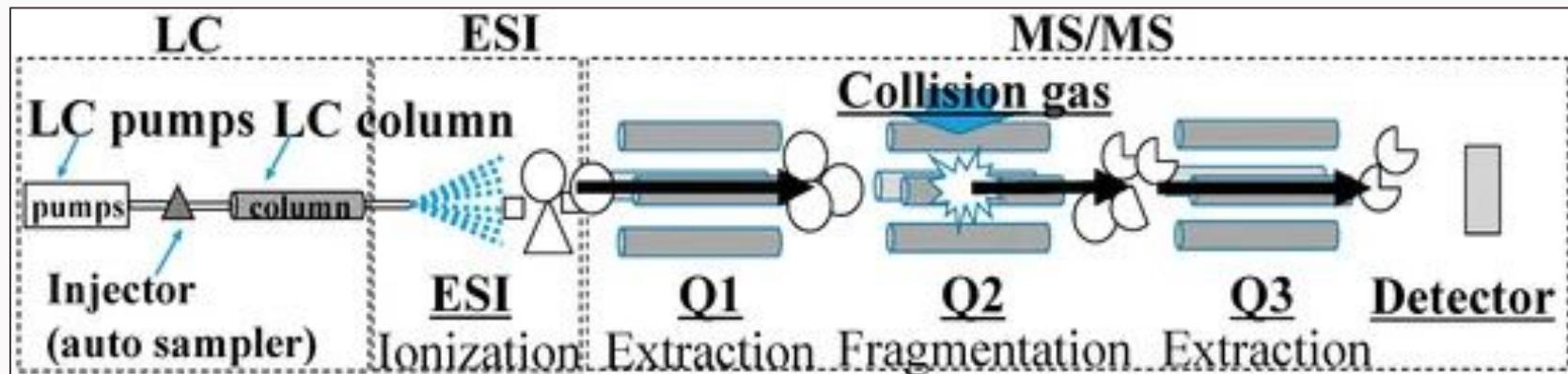
This showed severity scores and surrogate markers of illness response were highly correlated ([Data S2](#)) and that patient clusters showed broad concordance to the first-released WHO categorical criteria, namely **mild** (no requirement for supplemental oxygen), **severe** (oxygen saturation  $\text{SaO}_2 \leq 93\%$  on air but not requiring mechanical ventilation), and **critical** (requiring mechanical ventilation) ([Figure S1A](#)). This clustering persisted when we

02

# Methodology

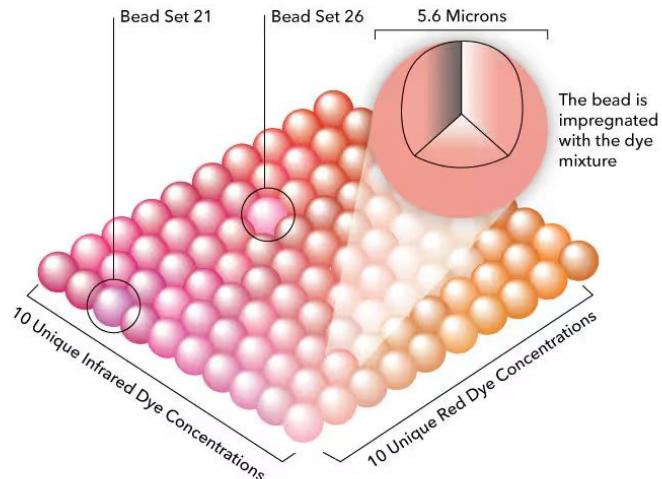


# Main Methods Used Within Study: LC-MS-MS

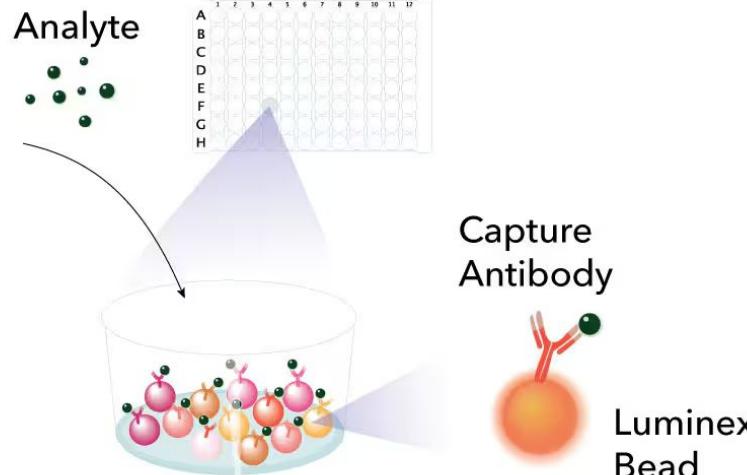


# Main Methods Used Within Study: Luminex

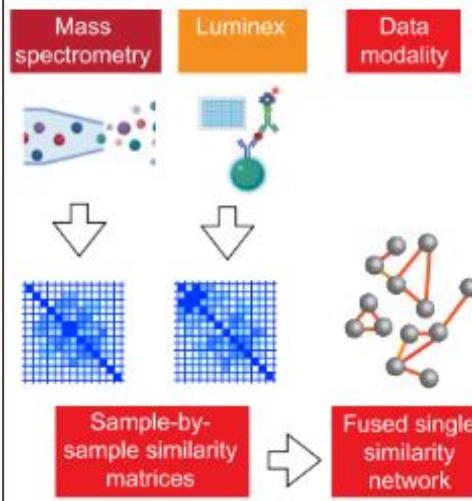
Luminex Bead Spectrum



Luminex Assay Principle

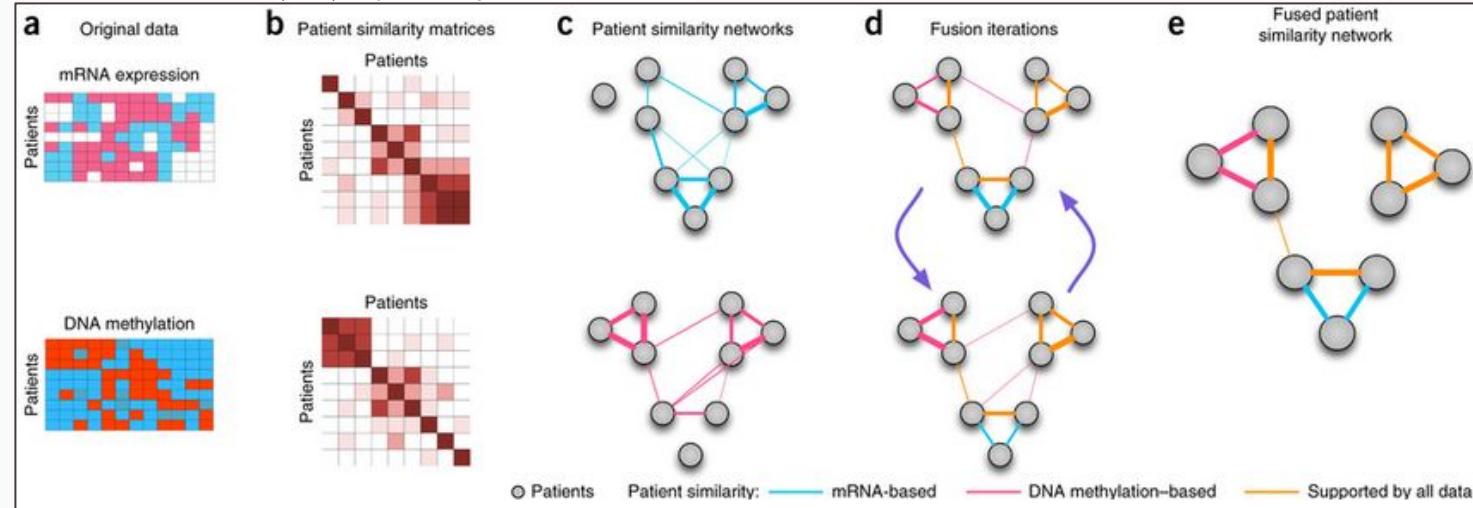


## Hospitalized COVID-19 patients



# Similarity Network Fusion

Wang, B., Mezlini, A., Demir, F. et al. Similarity network fusion for aggregating data types on a genomic scale. *Nat Methods* 11, 333–338 (2014). <https://doi.org/10.1038/nmeth.2810>



# Principal Component Analysis

$$d_1^2 + d_2^2 + d_3^2 + d_4^2 + d_5^2 + d_6^2 = \text{sum of squared distances} = \text{SS(distances)}$$

**StatQuest with Josh Starmer**

15 / 18 = 0.83 = 83%

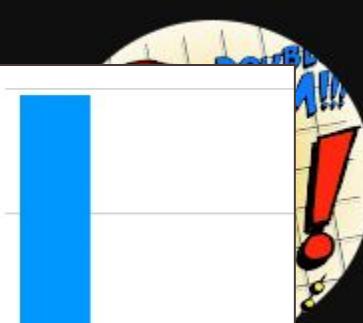
@statquest · 1.26M subscribers · 286 videos

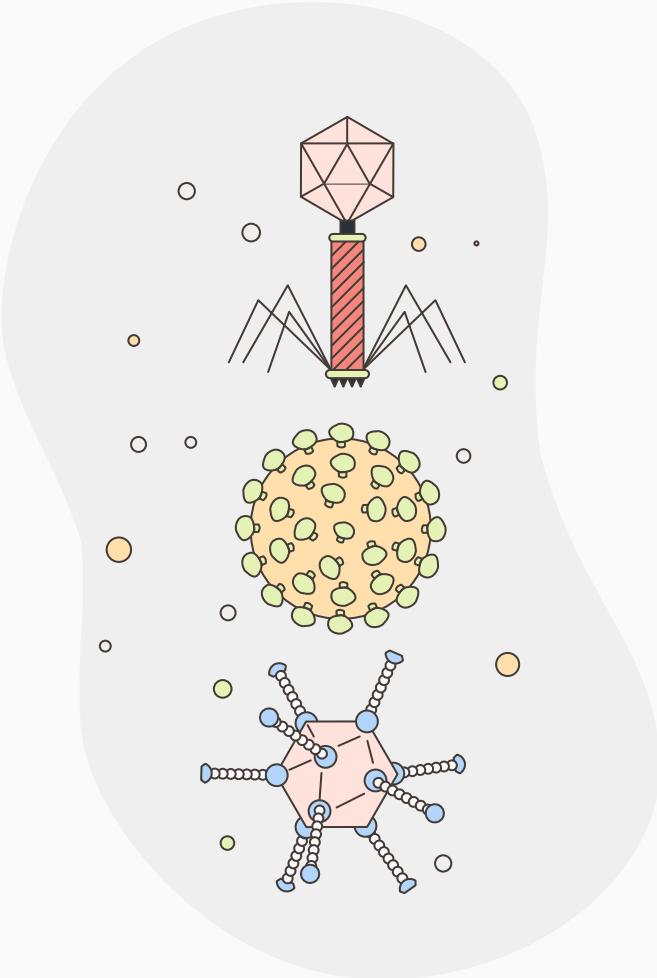
Statistics, Machine Learning and Data Science can sometimes seem like very scary topics... [...more](#)

[patreon.com/statquest](https://patreon.com/statquest) and 4 more links

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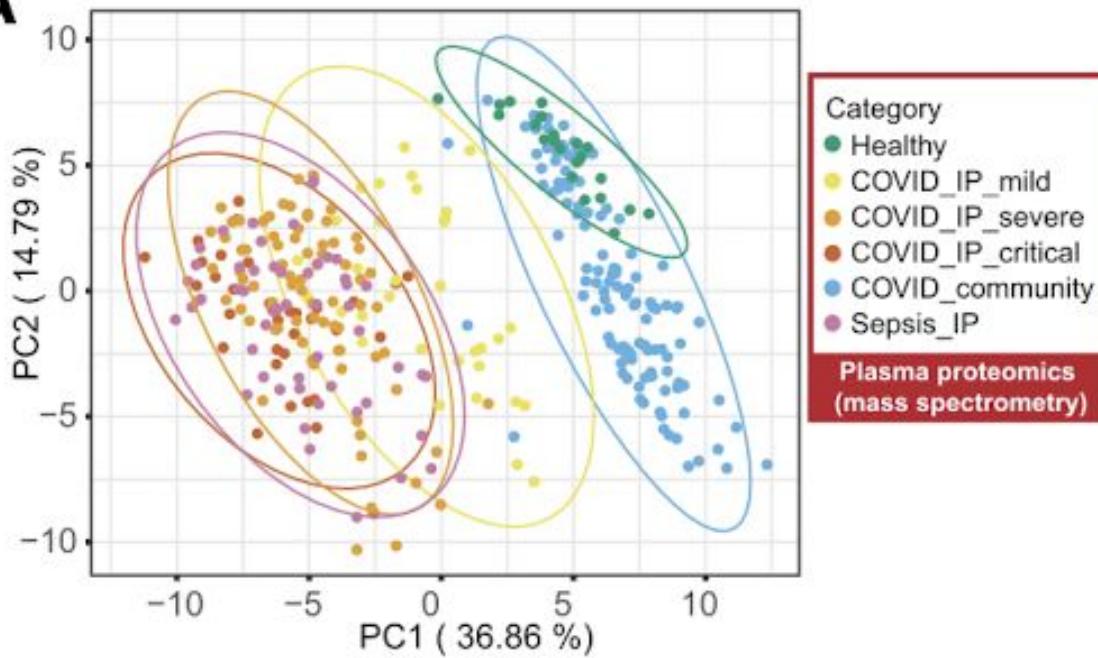


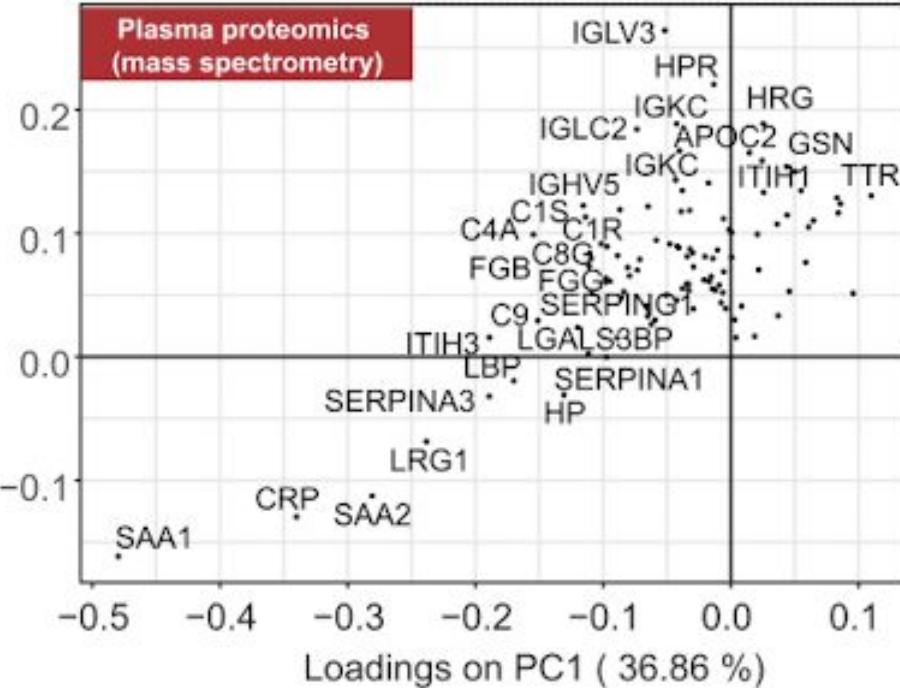


03

# Results

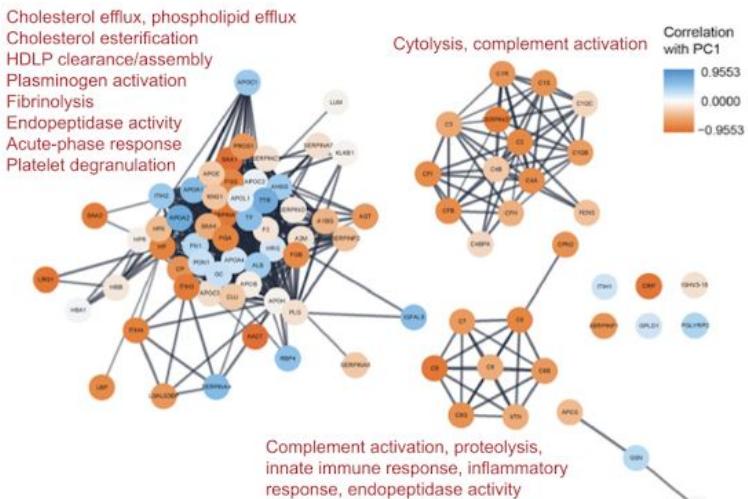
- PC1 accounts for 37% of the variability
- PC2 accounts for 15% variability

**A**

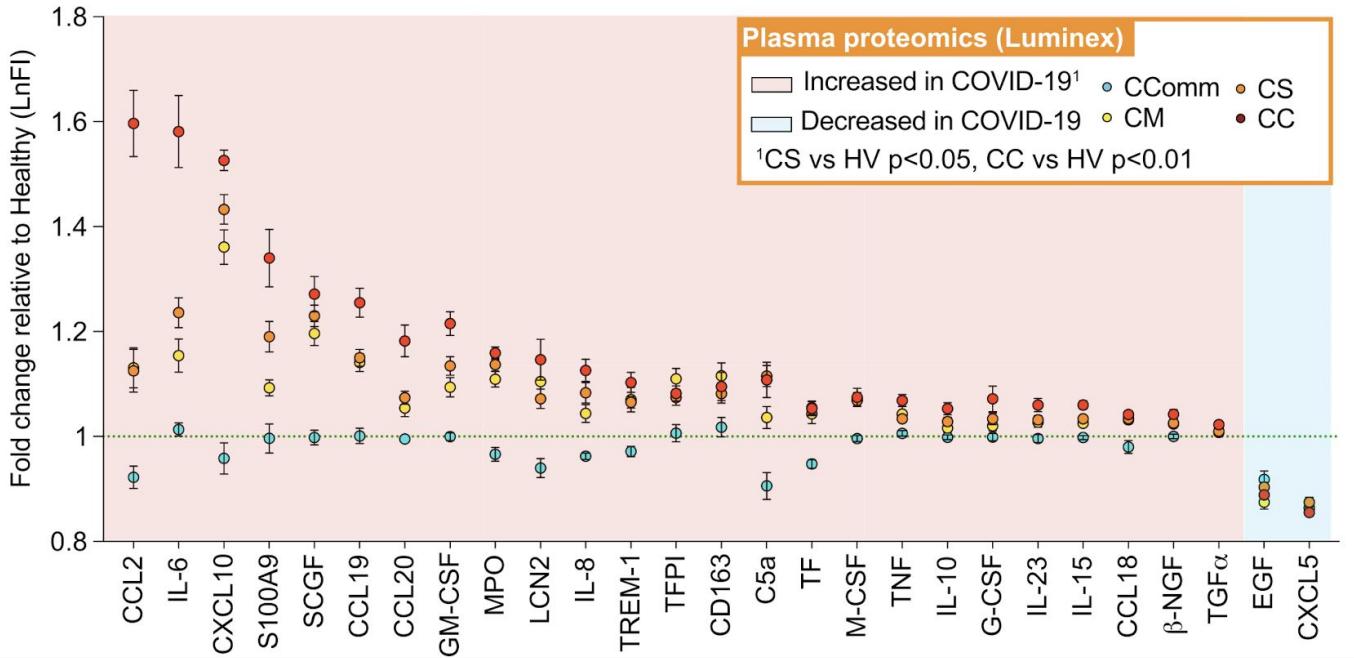


- **SAA1, SAA2, CRP, and SERPINA2:**
  - **Proteins** produced predominantly by the liver in response to inflammatory signals.
  - **SAA1** is highly increased during severe infections like COVID-19, often signaling an overactive immune response, which can lead to complications.
  - **CRP** is a key marker of inflammation. High levels are linked to worse outcomes in COVID-19, including complications like pneumonia and ARDS, and are used to monitor disease progression.
  - **SAA2**: Elevated levels indicate increased severity of inflammation and immune response, particularly in COVID-19 patients.
  - **TTR**: Functions as a transport protein for thyroxine and vitamin A; decreased levels are associated with malnutrition and poorer outcomes in critically ill patients.

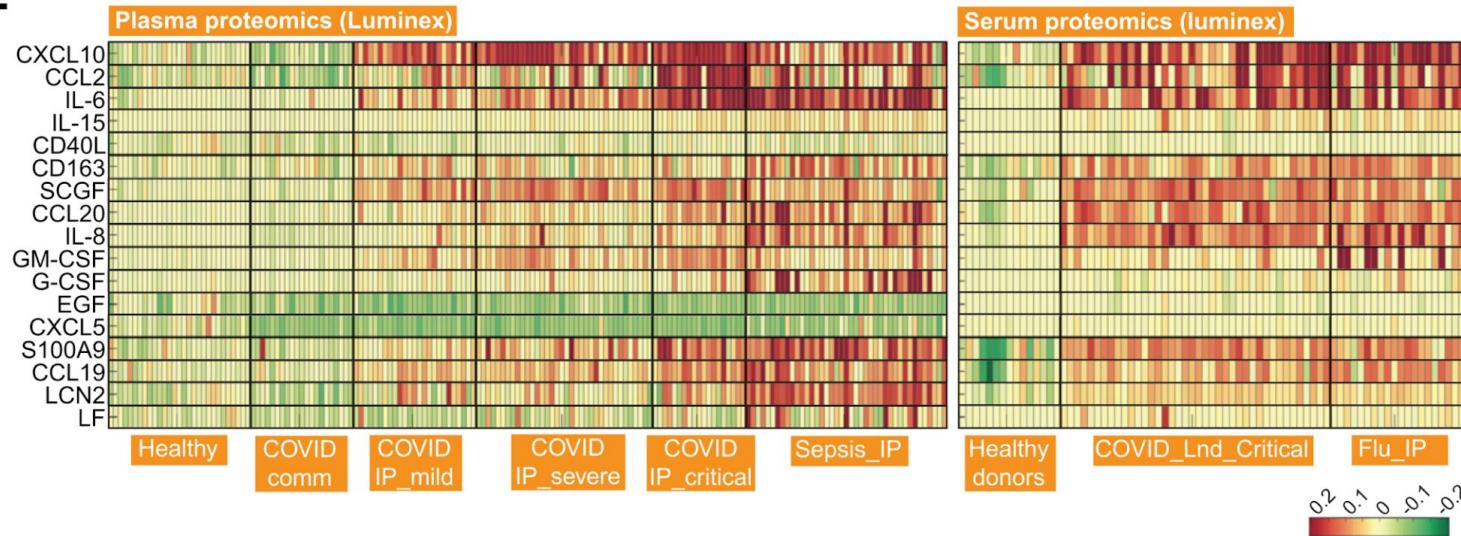
C



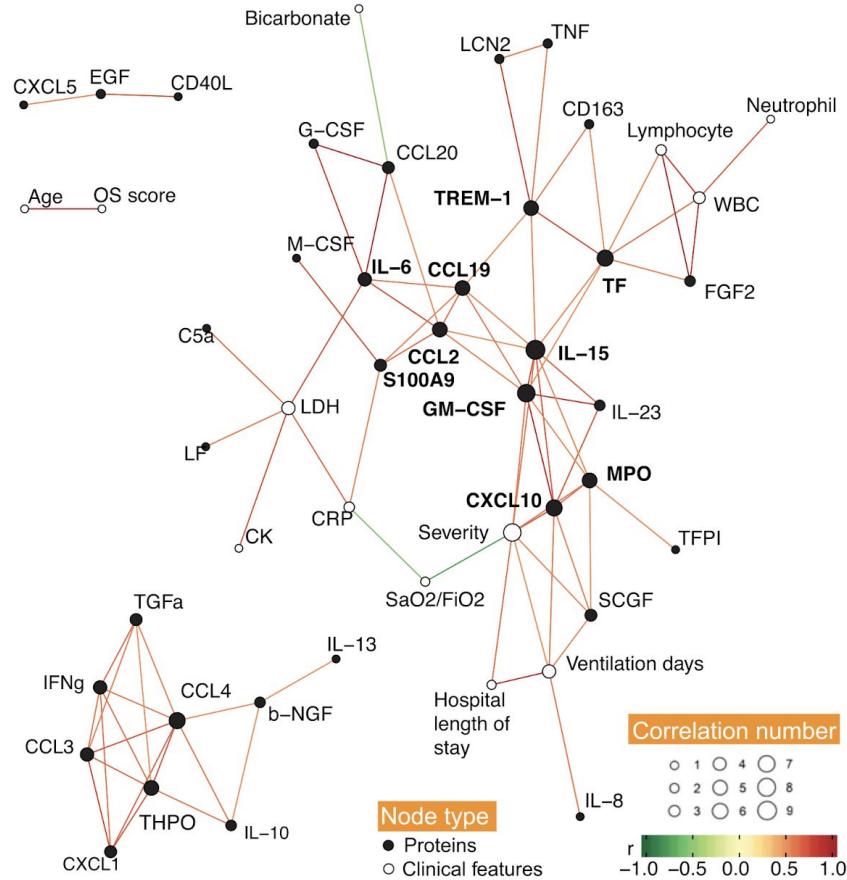
- Each cluster represents a different set of proteins & their interactions
    - Left Cluster: Lipid Metabolism & Inflammatory Response
    - Central Cluster: Fibrinolysis & Acute-Phase Response
    - Right Cluster: Complement System & Cytolysis

**D**

- Baseline  $\Rightarrow$  average protein expressions of healthy volunteers
- CComm  $\Rightarrow$  less protein expression than healthy 😞🤔🤔

**E**

- ↑ Proinflammatory Proteins ⇒ CXCL10, CCL2, IL-6
- ↓ Anti-Inflammatory Proteins ⇒ EGF, CXCL5

**F**

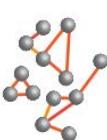
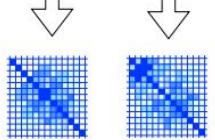
## Clinical Knowledge Graph

- Spearman Correlation
- Nodal Proteins
  - S100A9, GM-CSF, CCL2, CCL19
- Isolated networks

**G**

## Hospitalized COVID-19 patients

Mass spectrometry      Luminex      Data modality

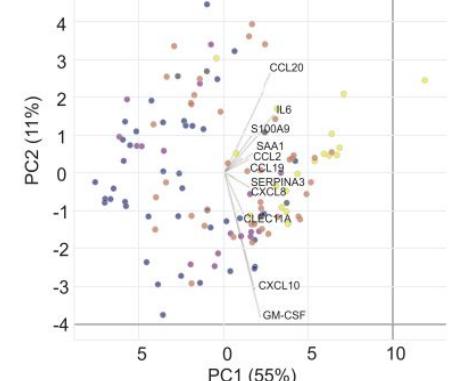
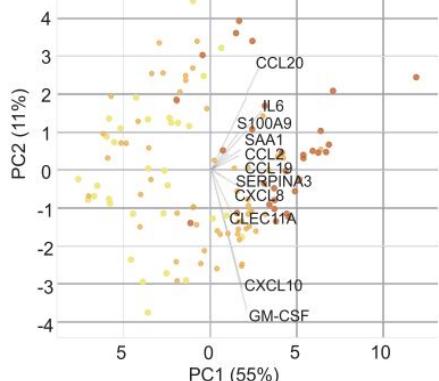
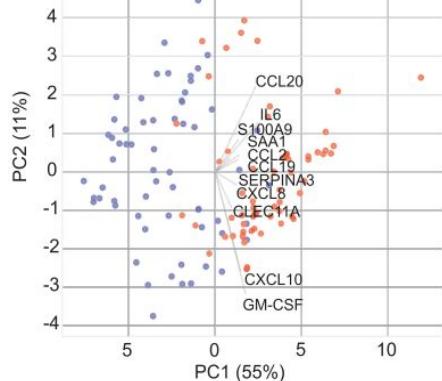


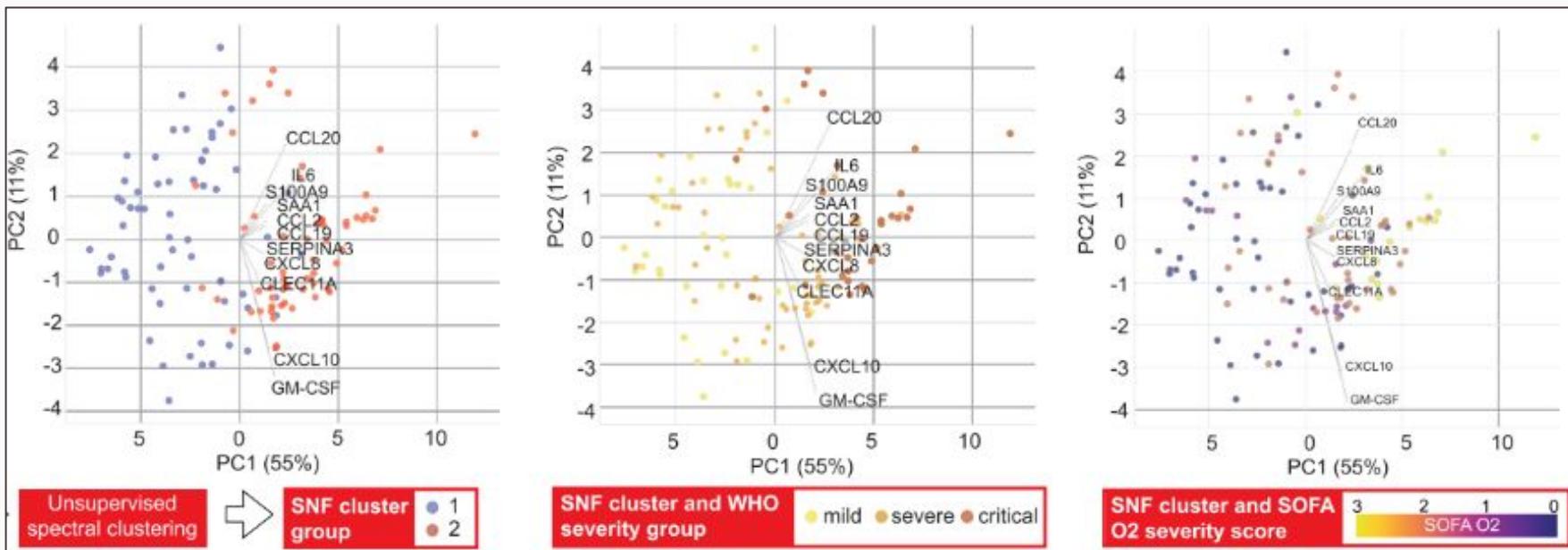
Sample-by-sample similarity matrices

Fused single similarity network

Unsupervised spectral clustering

SNF cluster group  
● 1  
● 2



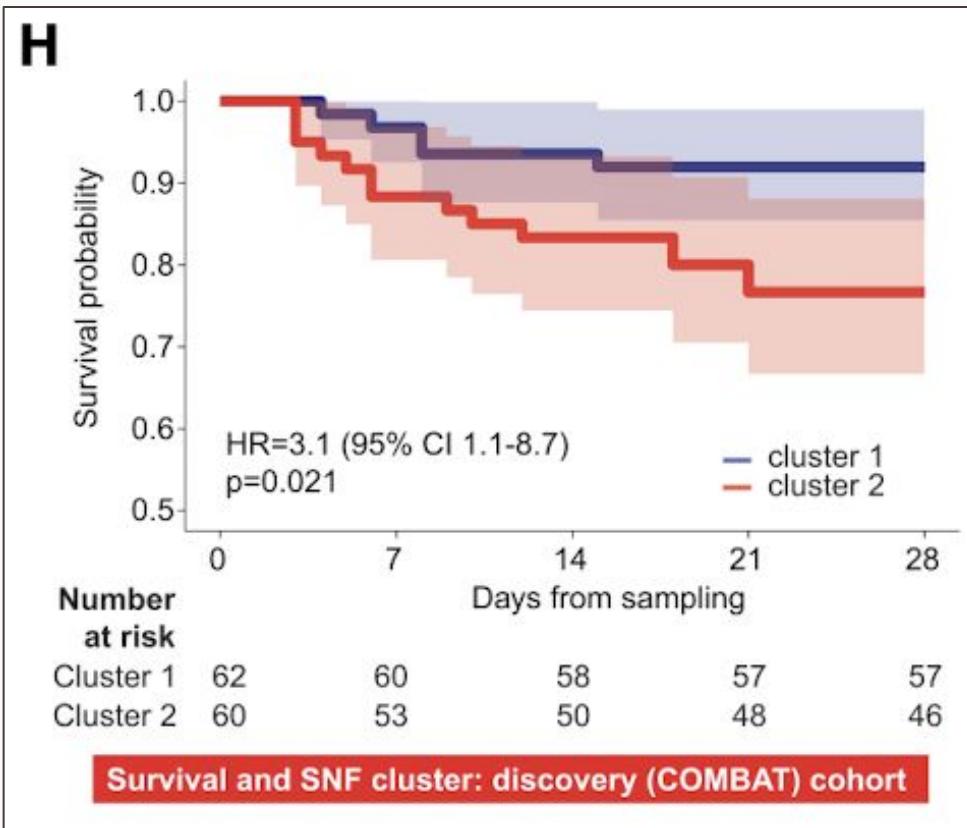


- SNF Clustering

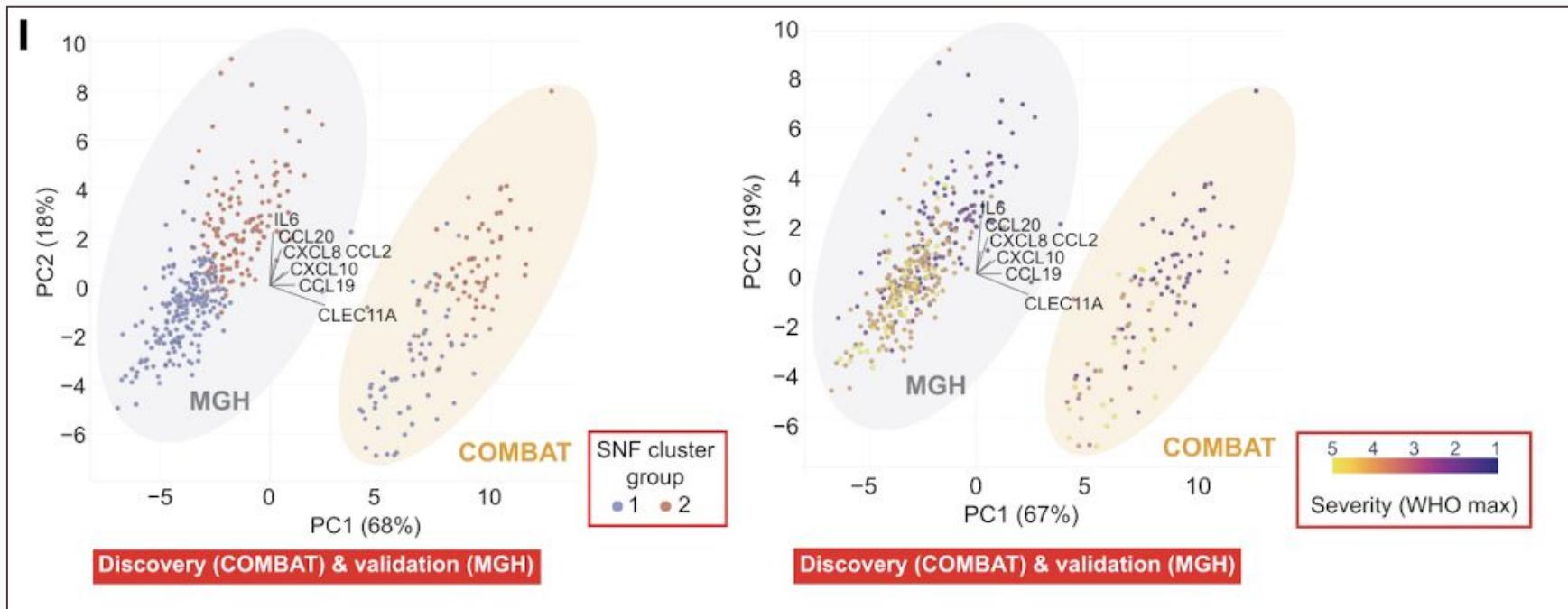
- WHO Severity Scores

- SOFA O<sub>2</sub> Severity Scores

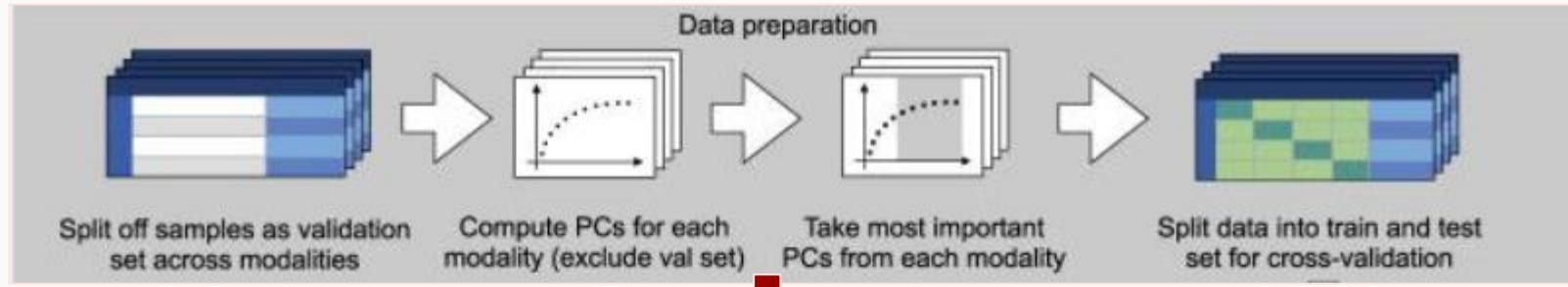
## Kaplan-Meier Survival Plot



# Validation Data

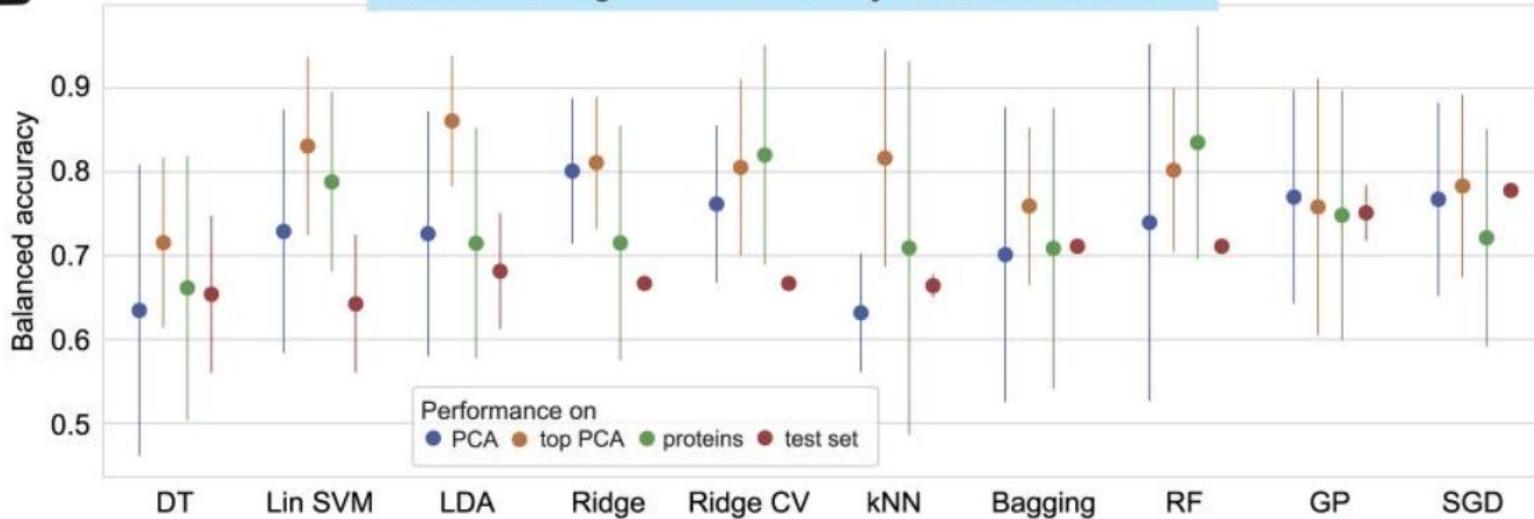


# Summary of Machine Learning Process

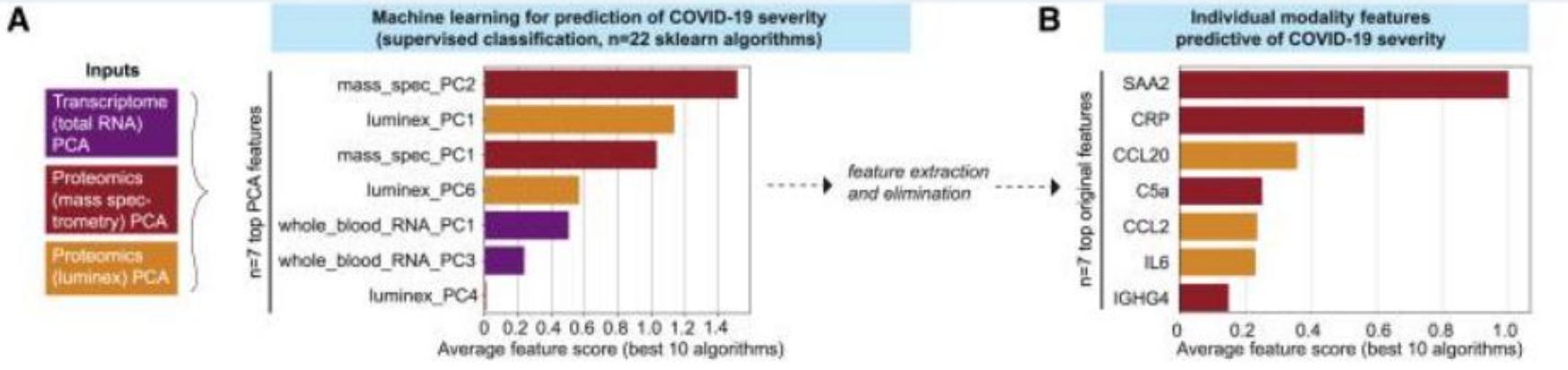
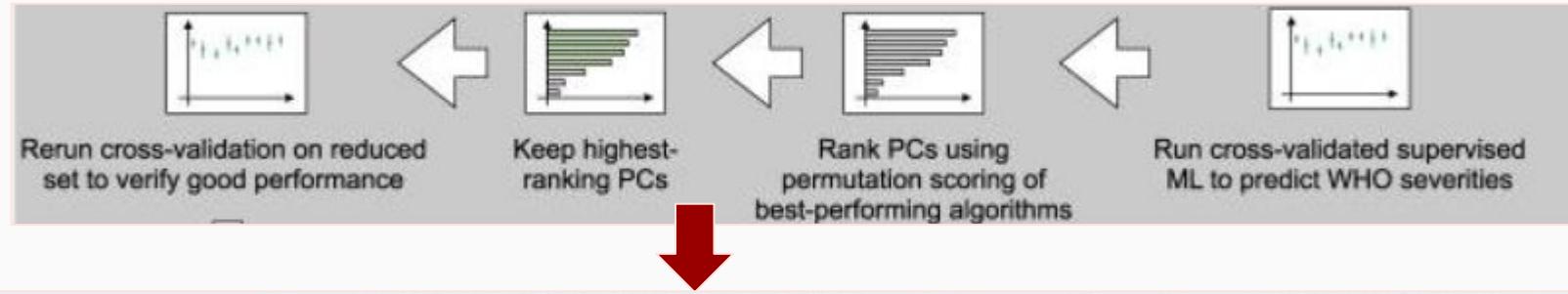


B

Machine learning: Balanced accuracy for different classifiers

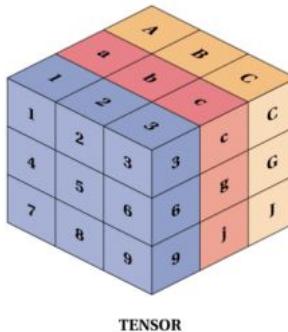


# Feature Selection (scoring and elimination) on Principal Components



# Overview of Tensor & Matrix Decomposition

(11)  $\begin{bmatrix} 5 \\ 3 \\ 7 \end{bmatrix}$  SCALAR  
 Row Vector (shape 1x3)  
 Column Vector (shape 3x1)  
 $\begin{bmatrix} 4 & 19 & 8 \\ 16 & 3 & 5 \end{bmatrix}$  MATRIX



1  $\rightarrow$

$$M_{m \times n} = U_{m \times m} \Sigma_{m \times n} V^*_{n \times n}$$

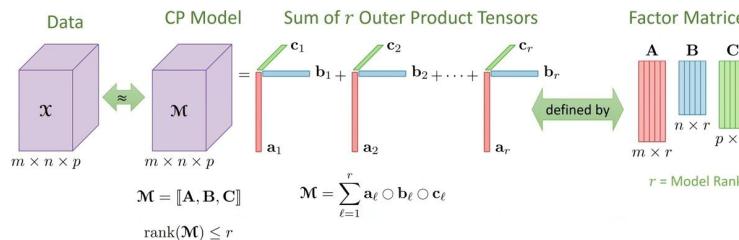
2

## Canonical Polyadic (CP) Tensor Decomposition

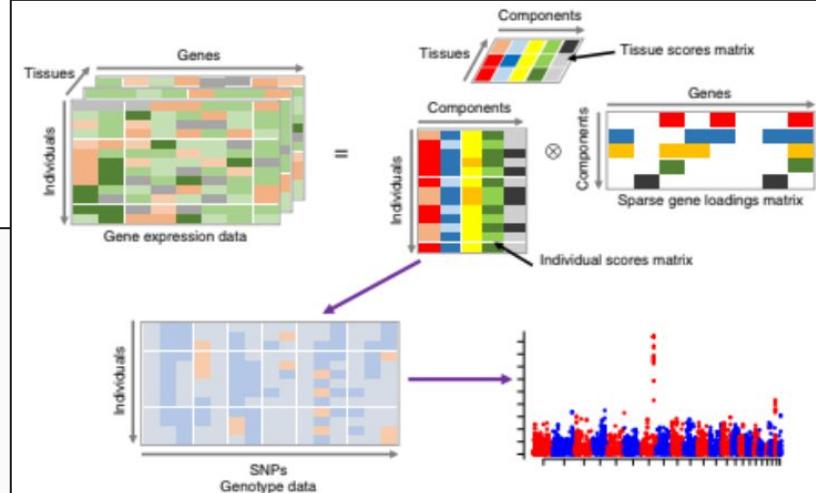
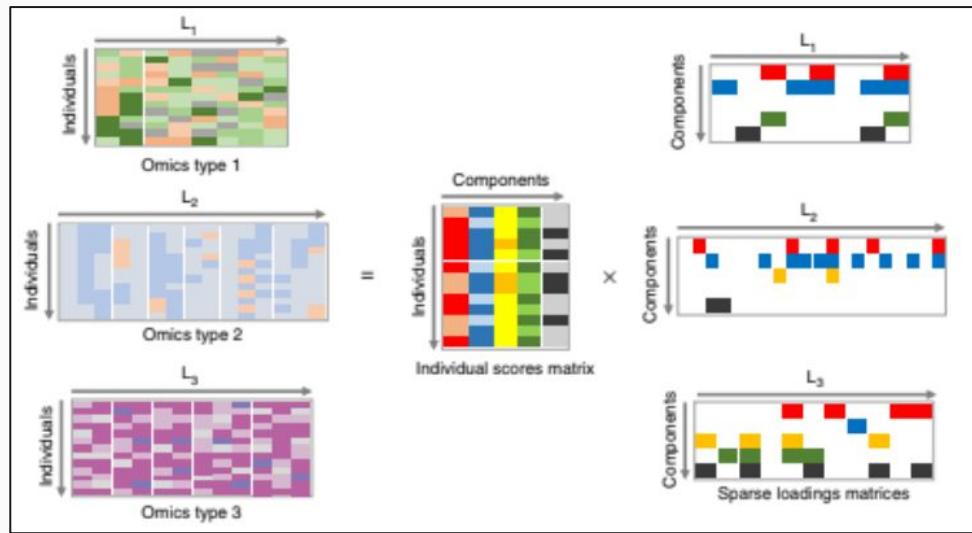


MathSci.ai

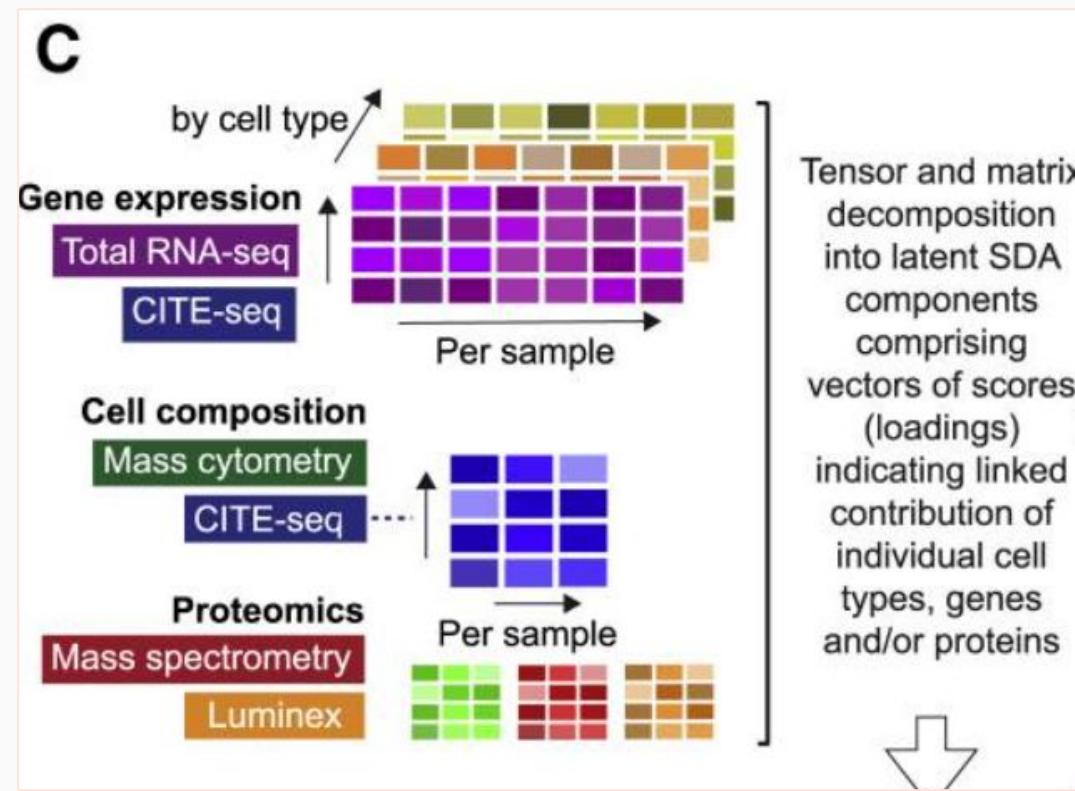
Also known as Parallel Factors (PARAFAC) or Canonical Decomposition (CANDECOMP).

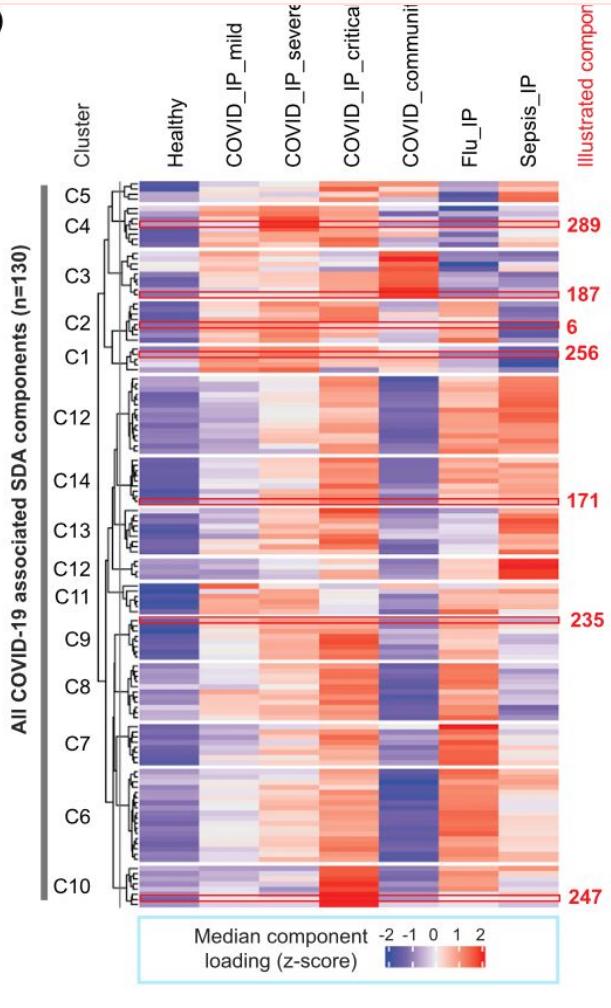


# TMD Method from Reference Paper



# Approach to TMD Across Multi-Omic Dataset

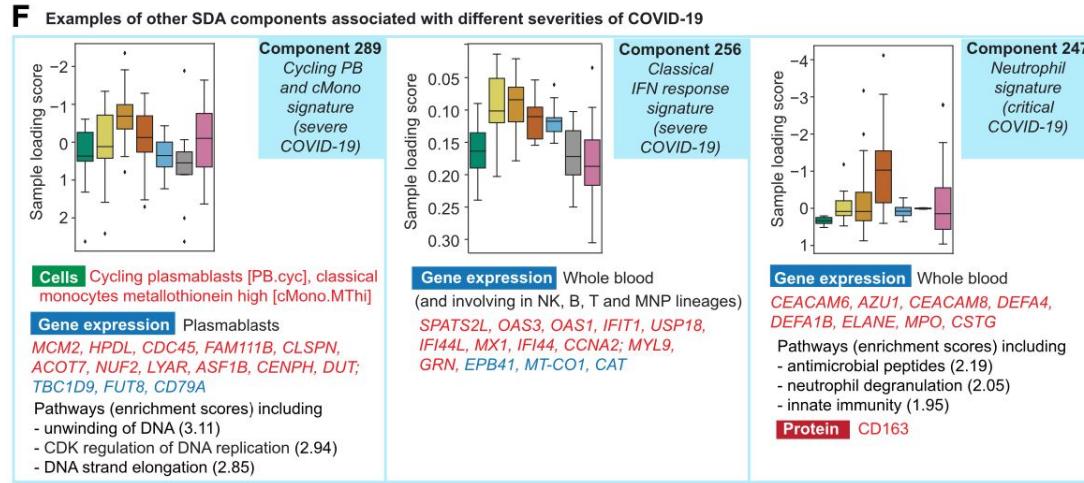
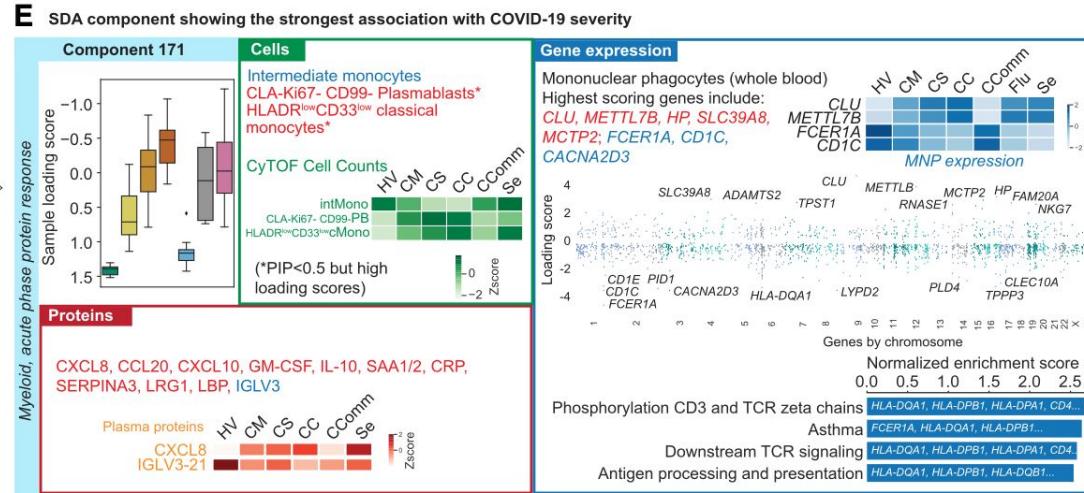
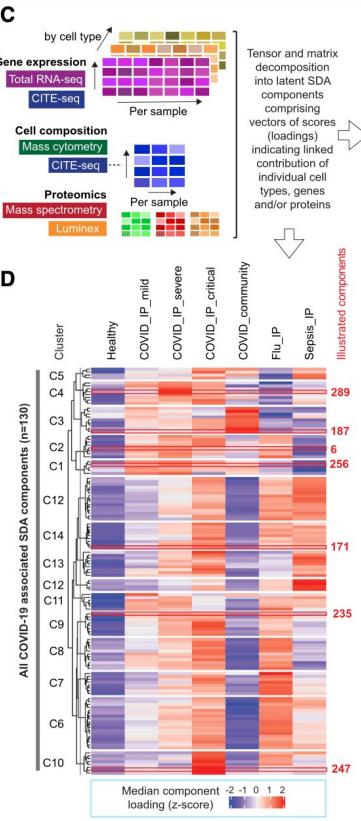


**D**

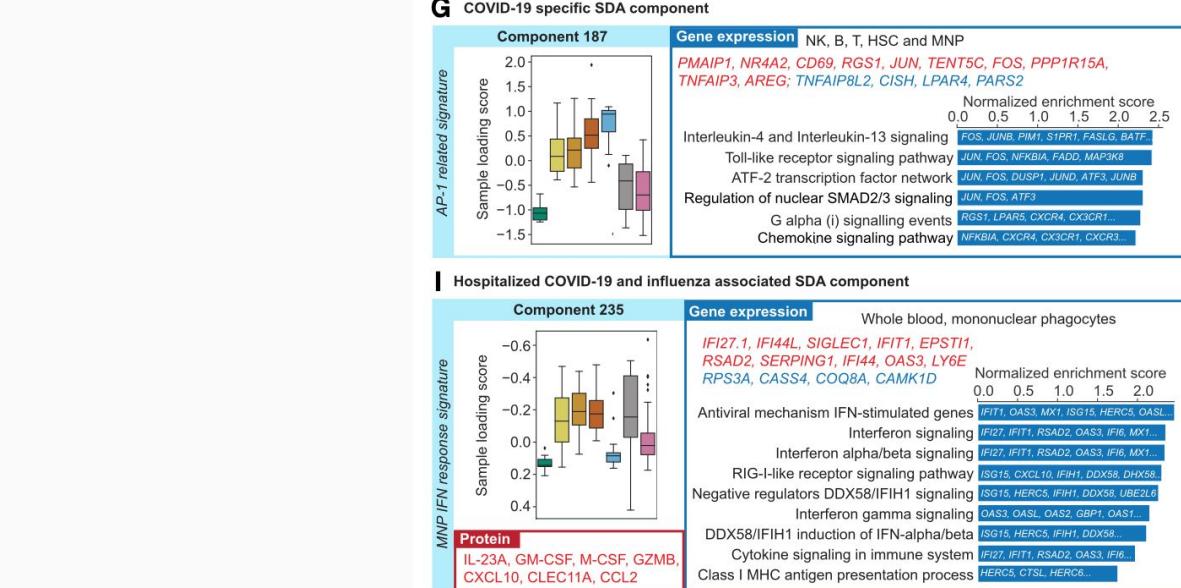
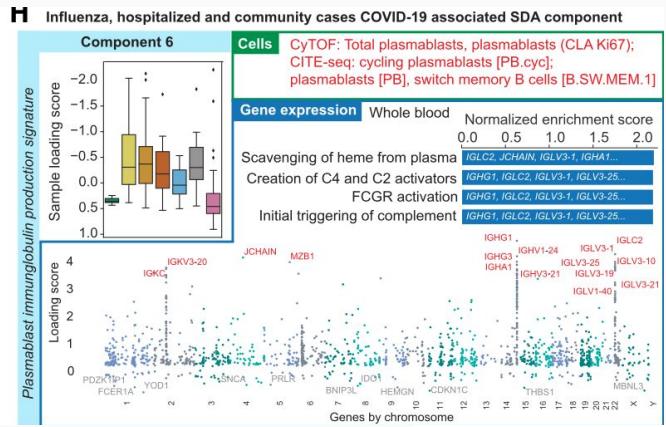
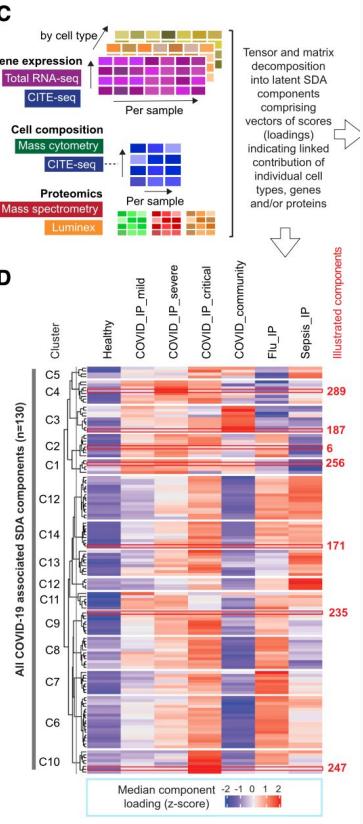
# Pairwise Contrasts & Analysis of Variance with COVID-19 Patient Groups

- Heatmap shows the loading scores for various SDA components across patient groups (for clusters C1-10)
- Z-scores show how strongly each component is associated with different patient groups
  - Red = positive associations
  - Blue = negative associations

# Figure 7



# Figure 7

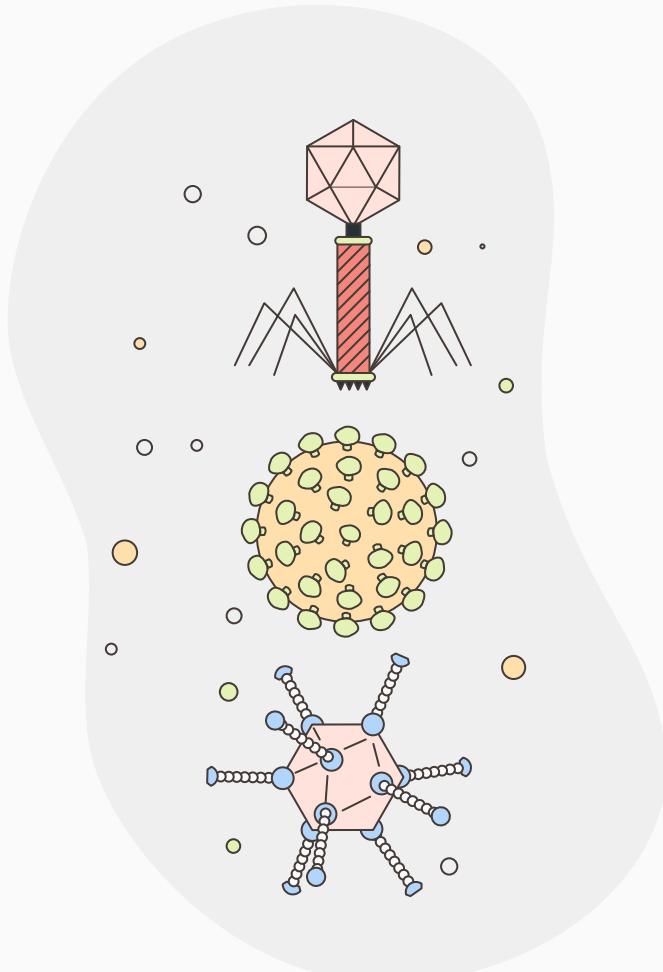


Patient source group

- Healthy
- COVID\_IP\_mild
- COVID\_IP\_severe
- COVID\_IP\_critical
- COVID\_IP\_community
- Flu\_IP
- Sepsis\_IP

04

# Discussion

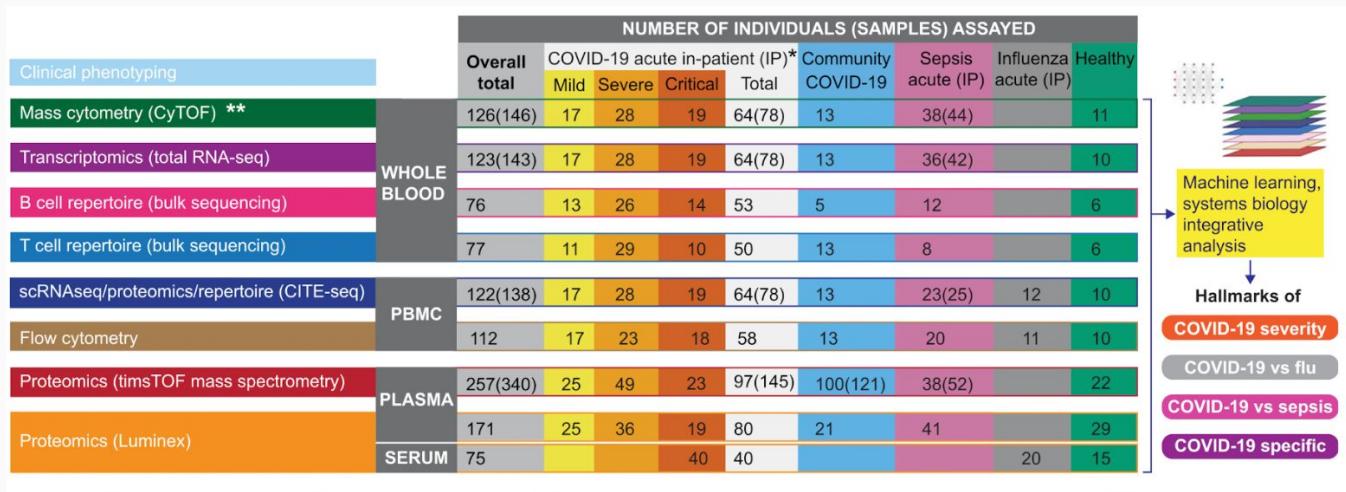


# Key Takeaway

- Mapped out correlations of proteins to disease severity
  - Defining hallmark expectation with higher severity & vice versa
- Discovered nodal / signature proteins from protein-protein interaction network
- Selected 11 signature proteins
  - Binary classification between sepsis & COVID-19
- Machine Learning Model - - - Predicting severity
  - Predictor proteins: acute phase proteins, immunoglobulin, chemokines, IL-6, complement protein C5a
  - Achieved accuracy of 75% - 80% to predict WHO category groups

# Limitations

- Selection on patients of other conditions for comparisons
- Exclusion of certain patient groups
- Drug administrations
- WHO/WHO max Score



# Applications

- Decipher relationships between signature proteins and sub-phenotypes (symptomatic parameters)
  - e.g. S100A9  $\longleftrightarrow$  C-reactive protein blood test
  - Foundation for more COVID-19 specific machine learning research
- Differentiation from some diseases
  - “Can distinguish hospitalized COVID-19 patients from sepsis”
  - Used for distinguishing cause of diseases & drug target
- A unique immune marker in COVID-19 patients was found (CD49d:CD43 ratio) that could help predict disease outcomes.

# COMBAT

COVID-19 Multi-omic  
Blood ATlas

In-patient acute COVID-19

Mild

Severe

Critical

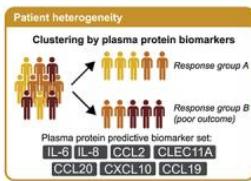
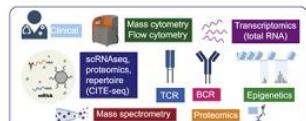
Community COVID-19

vs

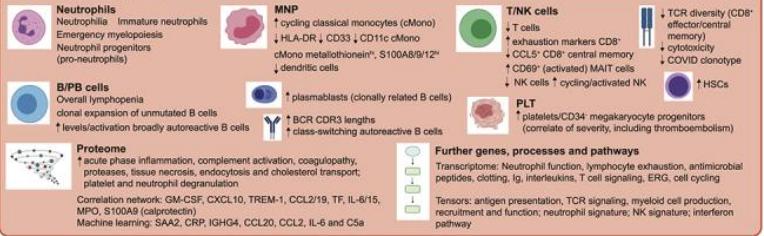
Healthy

Sepsis

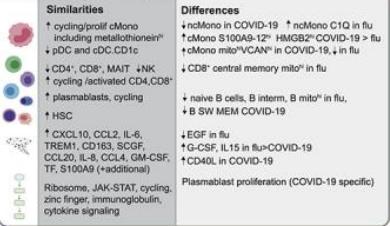
Flu



## Hallmarks of COVID-19 severity



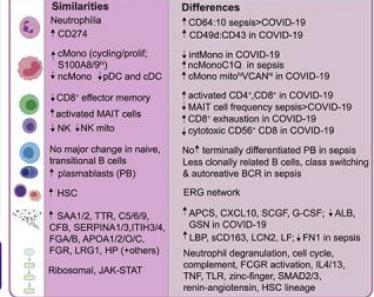
## COVID-19 vs flu (critical disease)



## COVID-19 specific (vs HV, flu and sepsis)

↑ activated CD4*, CD8* T cells	↑ AP-1/p38 MAPK
↓ non-classical monocytes	↑ CD49d:CD43 ratio neutrophils

## COVID-19 vs sepsis (severe-critical disease)



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# Thanks!

Do you have any questions?

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