Physiologic modeling of respiratory, immune and coagulation dynamics in critical COVID-19

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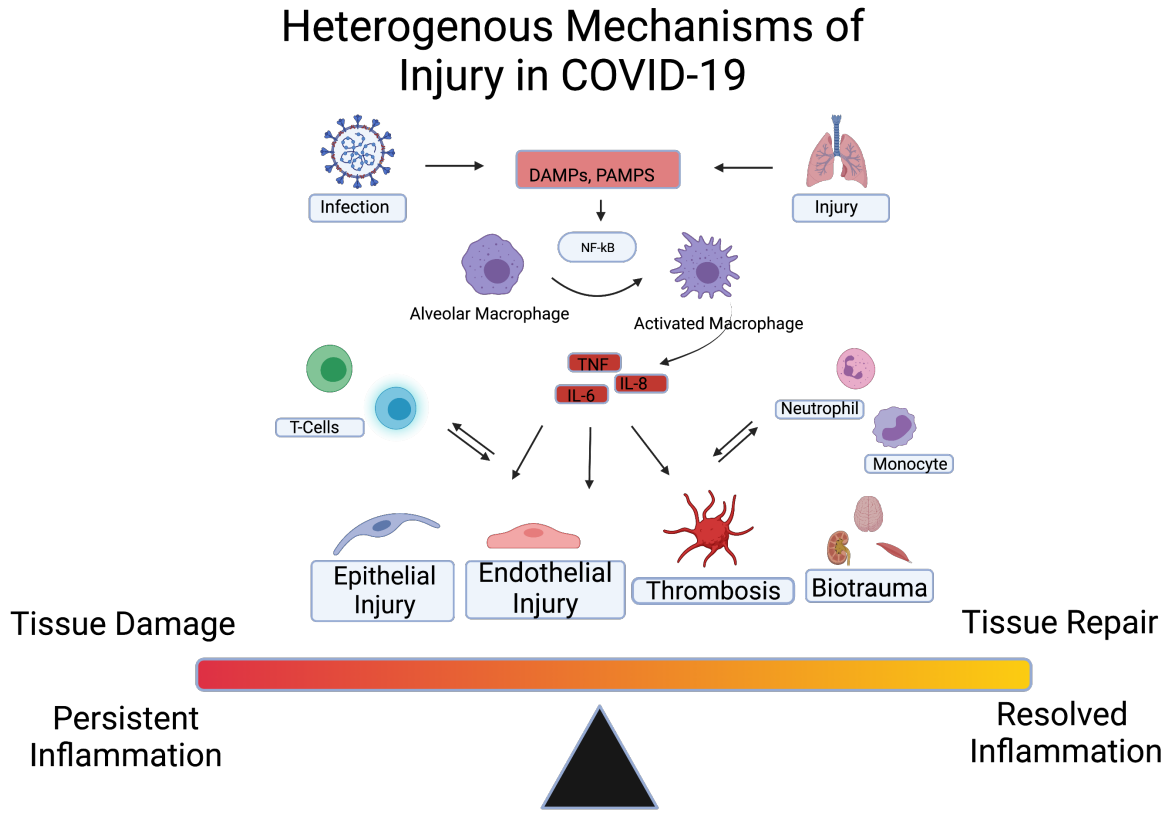
Introduction: Things I hope to convince you of

- COVID-19, like all critical illness, is a complex and heterogenous process
- Traditional approaches to clinical research are unlikely to lead to dramatic success in such a setting
- In complex systems, unstructured observations and intuitive stories will also lead to errors.
- Clinical observations must be interpreted in a structured way, using models, rigorous understanding of dynamics and network topology to be sensibly converted to therapeutic strategies



Heterogeneity in critical care

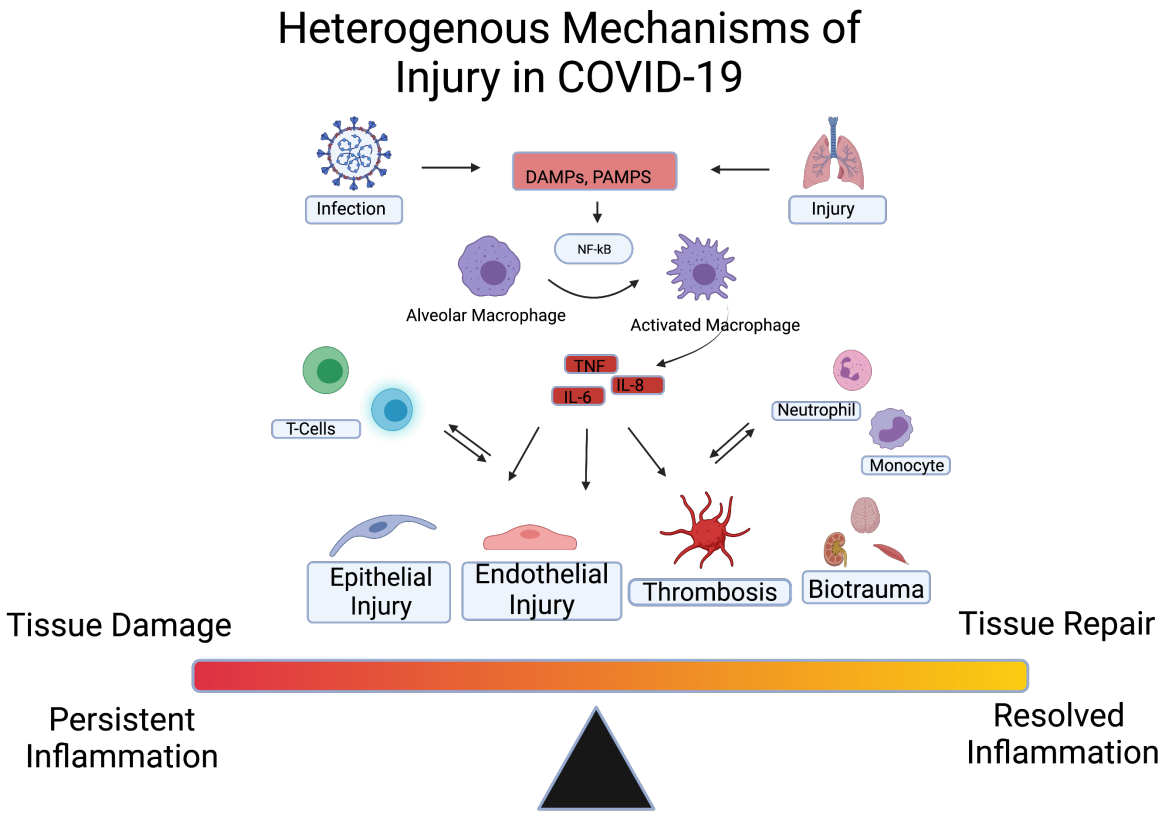
Critical illness is diagnosed by clinical features – syndromes - not biopsy, genetic or biochemical results

Sepsis

Influenza, COVID-19, necrotizing fasciitis, anthrax, staph. pneumonia, acute HIV, meningitis ,cholecystitis, cystitis

ARDS

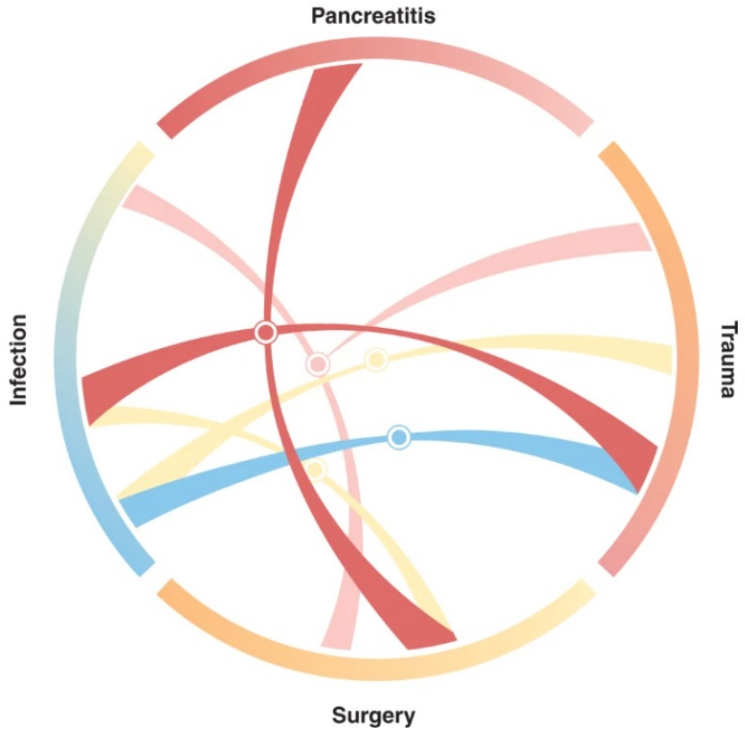
COVID-19, Influenza, pneumonia, TRALI, aspiration, chemical injury, ventilator induced injury



Critical illness syndromes may result from multiple causes, similar presentations result from diverse pathophysiologic process -> heterogeneity.

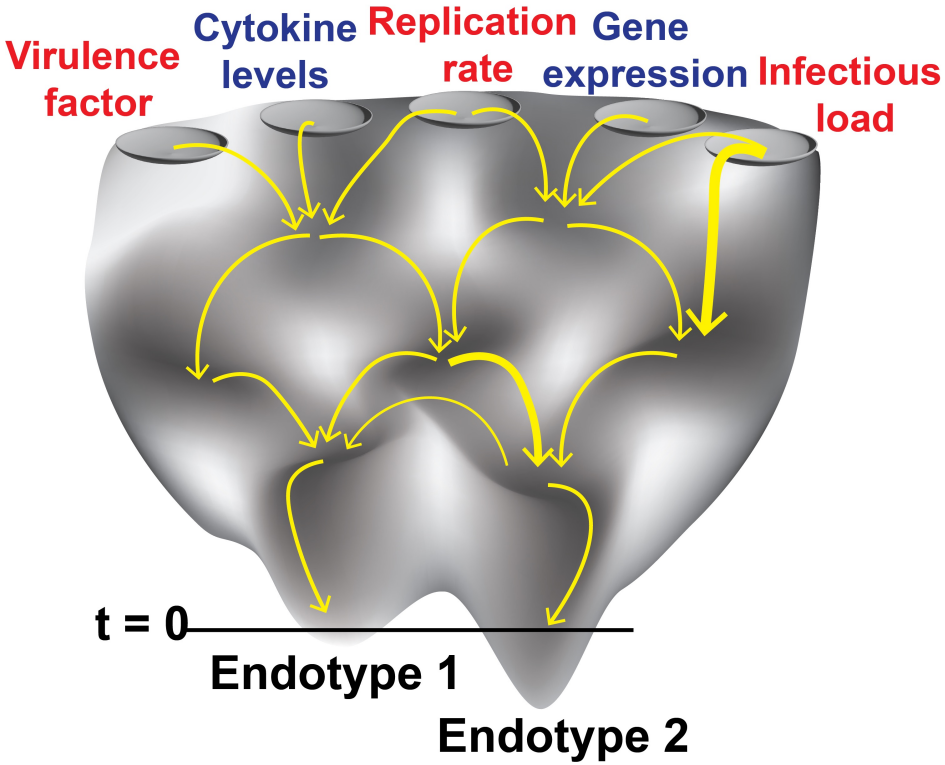
Critical care is not just *heterogenous* – it also *complex*

Heterogeneity and new models of critical illness



Heterogenous

multiple insults given rise to shared networks or pathways.



Complex

similar insults give rise to diverse outcomes

Maslove et. al, Nat. Med. 2022

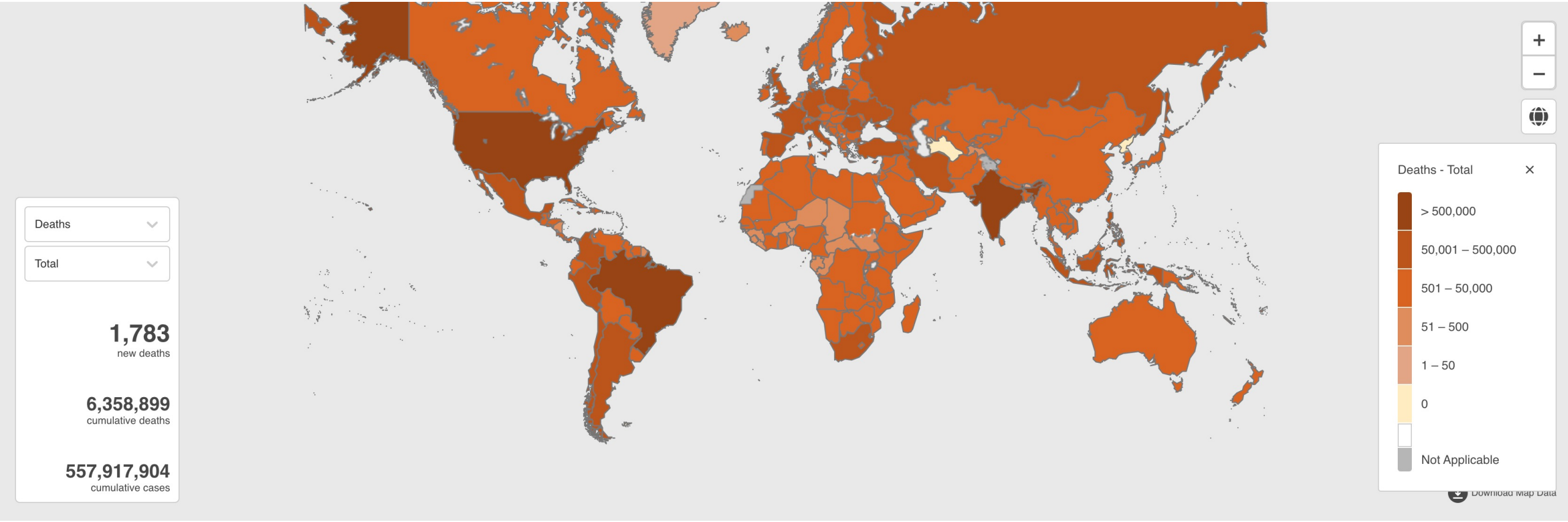
Clinical trials in critical illness: Largely negative

- nitric oxide
- surfactant/perflourocarbon
- corticosteroids
- prostaglandin E1
- lysophylline
- ibuprofen
- procysteine
- anticytokine/antiendotoxin
- ketoconazole
- streptokinase
- neutrophil elastase inhibitor
- $sPLA_2$ Inhibitor
- rhAPC
- Albuterol/salmeterol
- furosemide
- Cisatricurium
- Heparin
- IL-1 receptor antagonism

- Traditional clinical trials work best in a homogeneous environment
- Cardiology and cancer trials are designed to study common diseases with well defined pathophysiology
- Ex: PEGASUS-TIMI 54 ~20K patients comparing ticagrelor 90mg vs 60mg added to post-MI anti-platelet care
- This precision is simply unavailable in critical care

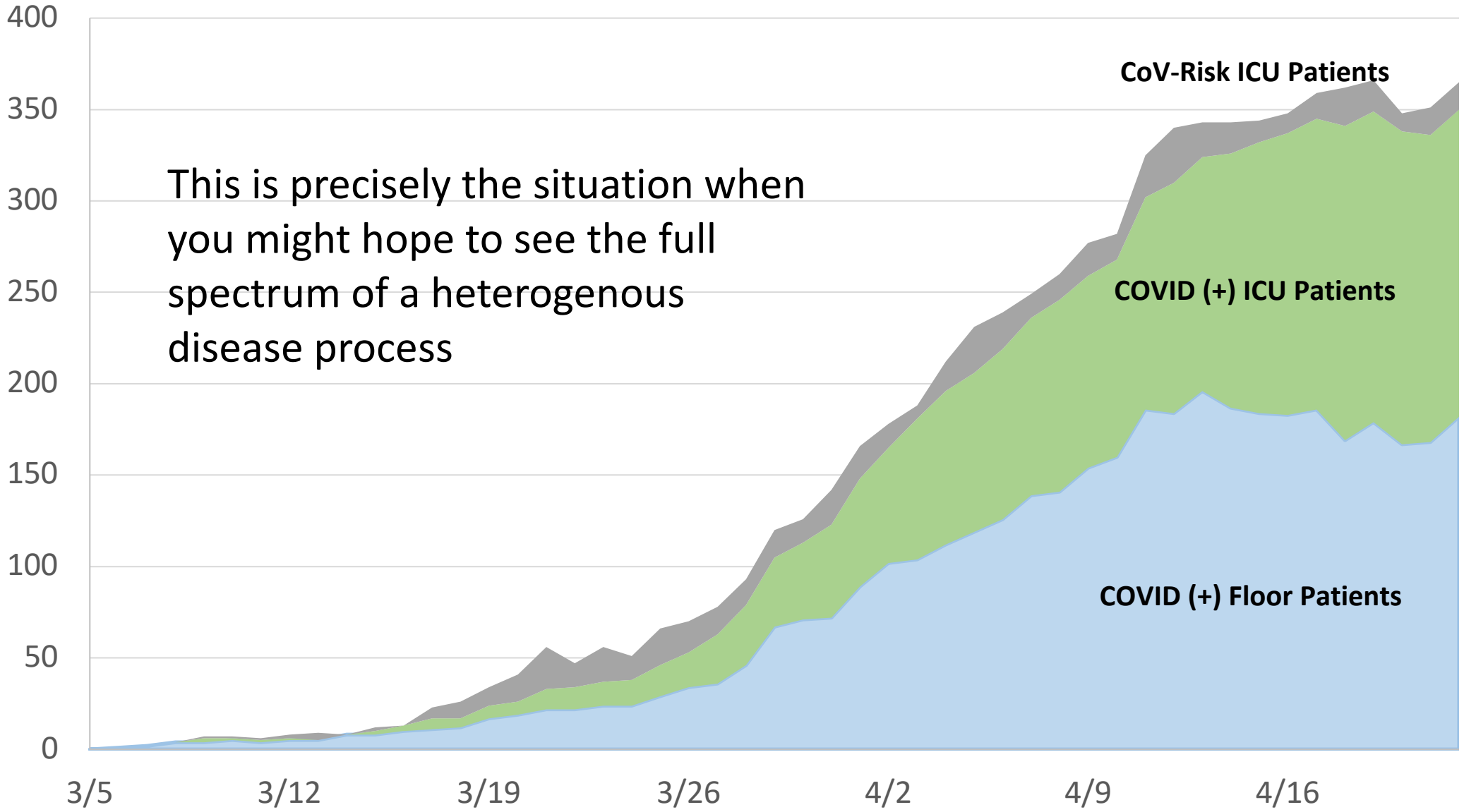
Complexity and heterogeneity are an existential challenge to traditional RCTs in critical illness

COVID-19: Global tragedy, best case scenario for critical care research



WHO COVID-19 Dashboard

MGH in mid-April 2020

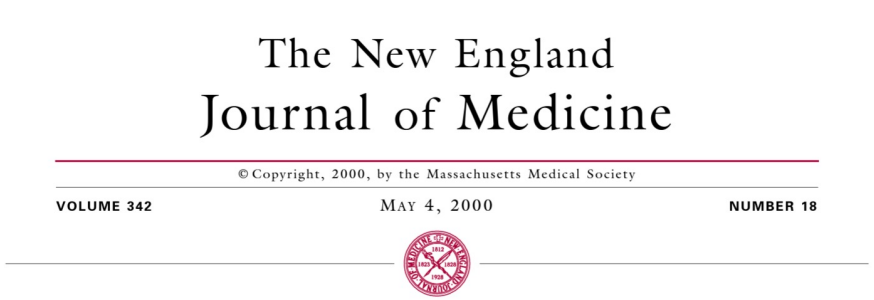


Total ICU Patients = 234, 80-90% ventilated

Normal vent. patients ~30

The scale of COVID-19 changed critical care research…

Before Covid	After Covid

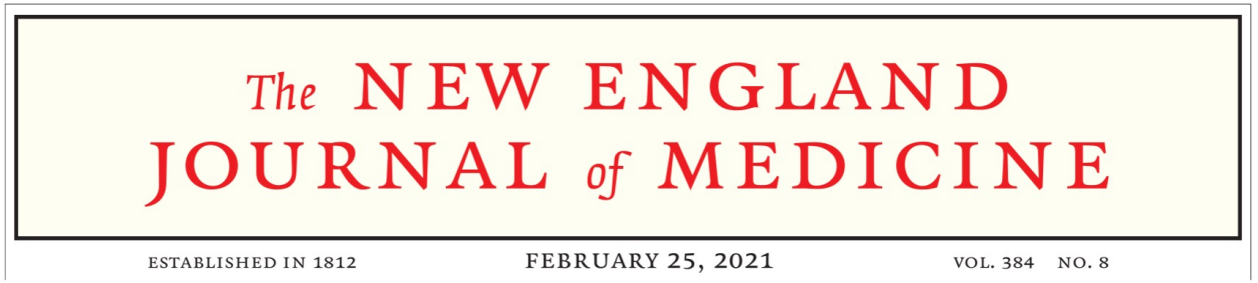


The New England
Journal of Medicine

VOLUME 342 MAY 4, 2000 NUMBER 18

VENTILATION WITH LOWER TIDAL VOLUMES AS COMPARED WITH TRADITIONAL TIDAL VOLUMES FOR ACUTE LUNG INJURY AND THE ACUTE RESPIRATORY DISTRESS SYNDROME

THE ACUTE RESPIRATORY DISTRESS SYNDROME NETWORK*



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 25, 2021 VOL. 384 NO. 8

Dexamethasone in Hospitalized Patients with Covid-19

The RECOVERY Collaborative Group*

- 3 years (1996-1999)
- 10 centers
- 861 patients
- Absolute risk reduction: 8.8%

- 1 year (2020-2021)
- 1700 centers
- 6,425 patients
- Absolute risk reduction: 2.8%

Even so, many questions persist…

Temporal heterogeneity in COVID-19

Steroids

Rate ratio not on oxygen: 0.92-1.55
Rate ratio on ventilator: 0.51-0.81

Gupta et. al. NEJM 2021

ACTIV-3 NEJM 2021

Remedesivir

Rate ratio in inpatients: 0.81 – 1.11
Hazard ratio in outpatients: 0.03 – 0.59

Solidarity Group, NEJM, 2021

Monoclonal Antibodies

Outpatient ARR: 7%
Inpatient OR: 0.56-1.29

RECOVERY Group , NEJM 2021

Gottleib et. al , NEJM 2022

Optimal treatment strategy (anti-viral vs anti-immune) varies by severity and time since infection. Time since infection is vaguely defined.

Optimal treatment strategy (anti-viral vs anti-immune) varies by severity and time since infection

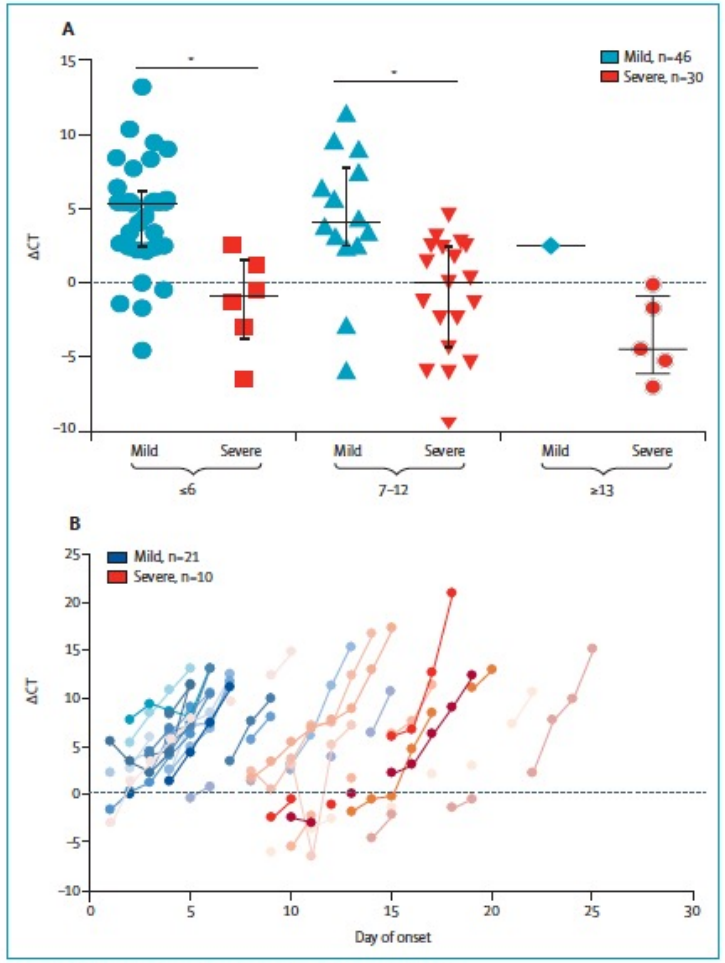


Figure: **Viral dynamics in patients with mild and severe COVID-19**
(A) ΔCT values (Ct_{sample}-Ct_{rd}) from patients with mild and severe COVID-19 at different stages of disease onset. Median, quartile 1, and quartile 3 are shown. (B) ΔCT values of serial samples from patients with mild and severe COVID-19. COVID-19=coronavirus disease 2019. *p<0·005.

<u>Broad themes are difficult to operationalize in individual patients</u>

- Mild cases tend to have rapid clearance
- Severe cases may have delayed clearance
- Of note – much higher initial viral load in severe cases
- Time since infection = time since symptom onset in trial setting

Liu et. al. Lancet Inf. Dis. 2020

Statistical approaches to understanding heterogeneity: Latent class analysis

- Now standard approach to dealing with heterogeneity
- Based on 8 biomarkers + clinical data
- Reveals hypo and hyperinflammatory groups.

May not eliminate al heterogeneity , may not be specific as to mechanism

ALVEOLI Cohort:

Number of Individuals Per Class/Subphenotype								
Number of classes	BIC	Entropy *	N_1	N_2	N_3	N_4	N_5	p-value **
2	49709.5	.87	404	145				.016
3	49383.7	.92	400	145	4			.58
4	49098.8	.94	386	129	4	30		.35
5	48955.1	.87	242	154	4	30	119	.80

Abbreviations: BIC = Bayesian Information Criterion

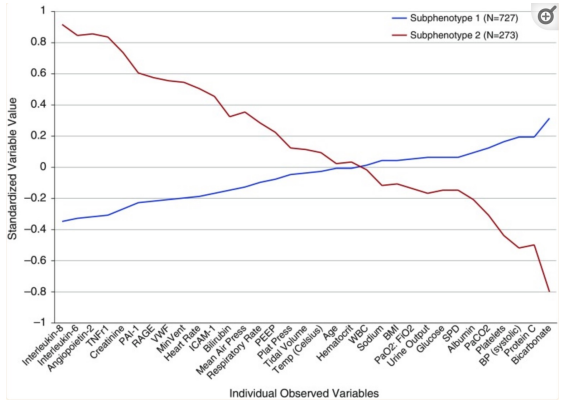


Table 3.

Clinical Outcomes by ARDS Subphenotype

	Subphenotype 1 (*n* = 727)	Subphenotype 2 (*n* = 273)	*P* Value
60-d mortality, %	21	44	<0.0001
90-d mortality, %	22	45	<0.0001
Ventilator-free days, median	19	3	<0.0001

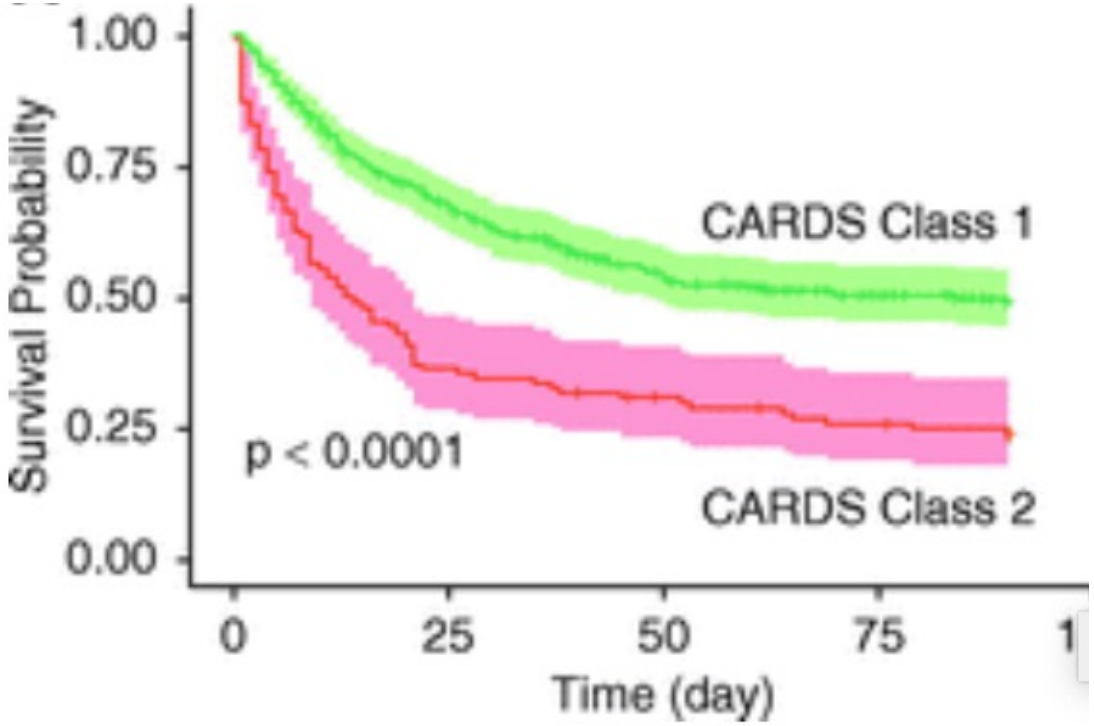
Open in a separate window

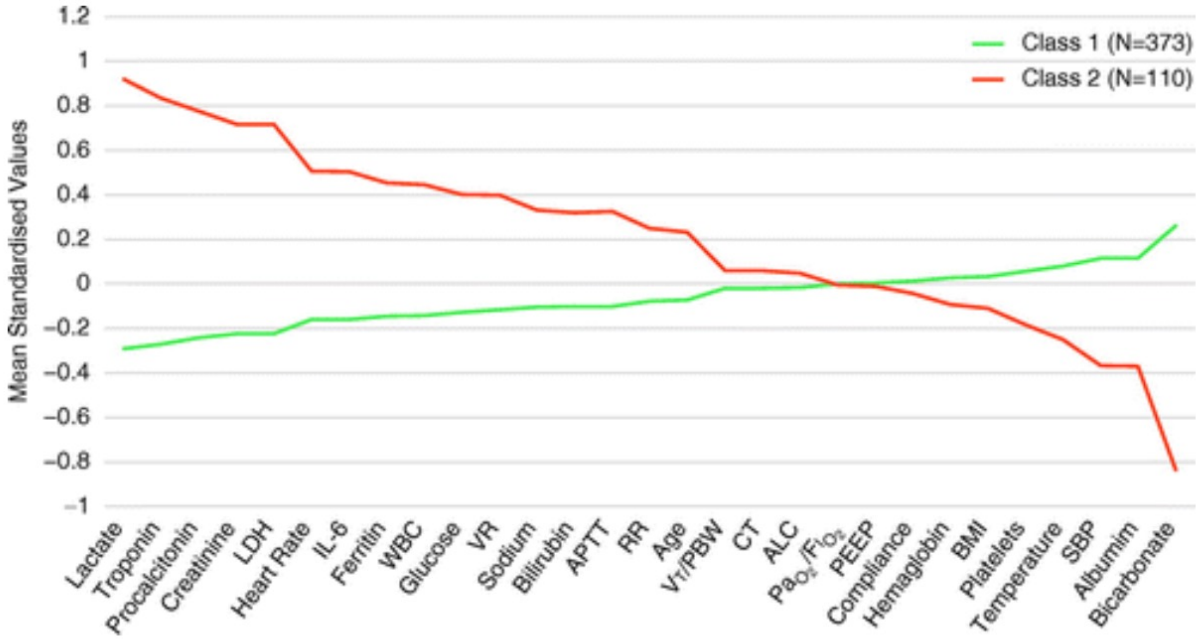
Definition of abbreviation: ARDS = acute respiratory distress syndrome.

P value represents chi-square analysis for mortality and Wilcoxon rank sum for ventilator-free days.

Calfee et. al LRM 2014, Famous et. al. AJRCCM 2017

LCA Analysis in COVID-19





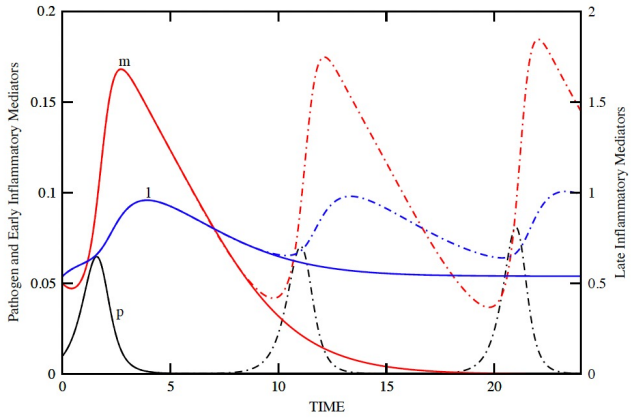
Hypo-inflammatory may be harmed by steroids, similar classes but relative size varies by cohort

Sinha et. al, AJRCCM, 2021

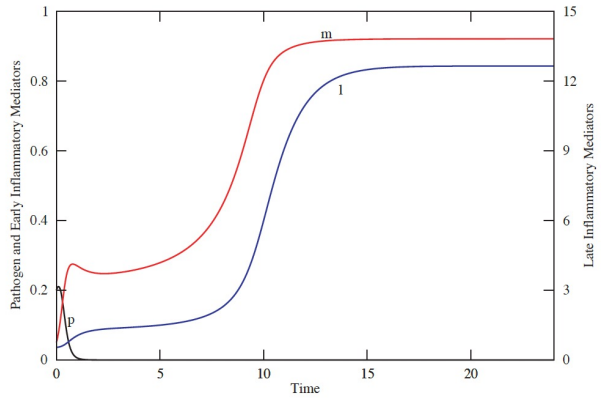
Modeling as an aid to interpretation of clinical data

- Even with huge trials and a single etiology of critical illness, heterogeneity and complexity challenge implementation of trial results to individual patients
- Biomarker studies and statistical clustering can help individualize treatment but such groups may themselves conceal heterogeneity
- LCA can only reveal groupings at time of presentation – in complex system random events, not patient or pathogen characteristics, may determine who ends up in what class.
- Clustering may only be hypothesis generating as to mechanism
- A more sophisticated approach to the interpretation of clinical data is clearly needed

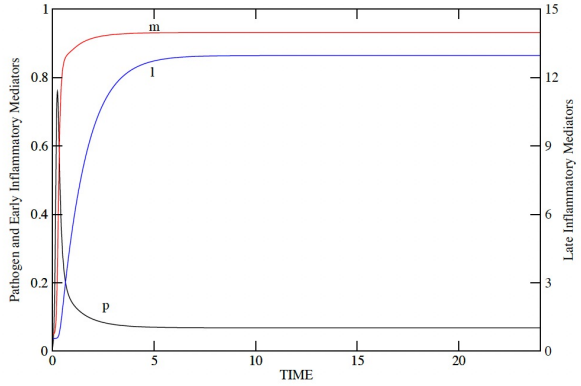
Heterogeneity and Randomness are inherent to the system – not a pathogen or patient specific phenomenon



Healthy response



Persistent, sterile inflammation



Persistent, infectious inflammation

Pathogen

Early Inflammatory Mediators (neutrophils, macrophage, TNF-α)

Late Inflammatory Mediators (IL-6)

- Simple model of predator-prey dynamics encompassing three species, p, m, l
- Depending on parameters and initial pathogen loads, multiple steady state outcomes are possible
- Simple model enables full understanding of critical points
- Small changes in pathogen load can lead to different endpoints

Kumar, J. Theo. Bio. 2004

COVID-19 ARDS

- Severe and critical COVID-19 results from a heterogeneous combination of viral-mediated injury, immune mediated injury and side effects of therapy.
- Therapy consists of a heterogenous combination of antiviral agents (protease inhibitors, nucleic acid analogues, monoclonals) , immune modulators (corticosteroids, IL-6 inhibitors, JAK inhibitors) and carefully managed supportive care (low tidal volume ventilation)
- Simple models omit clinically important detail but latent class analysis and clustering may obscure mechanism and effects of complexity

Large scale mechanistic modeling of COVID-19

Microscale lung model

Set of differential equations which govern mass balance and kinetics of process central to infection and immune response

- Number of healthy and infected epithelial and endothelial cells
- Number of free, bound and internalized viral particles
- Mass balance of ACE2 receptor
- Neutrophil and macrophage recruitment
- Formation and clearance of NETs
- Formation and degradation of interferon, pro and anti-inflammatory cytokines
- Antibody, CD8 and CD4 T-cells

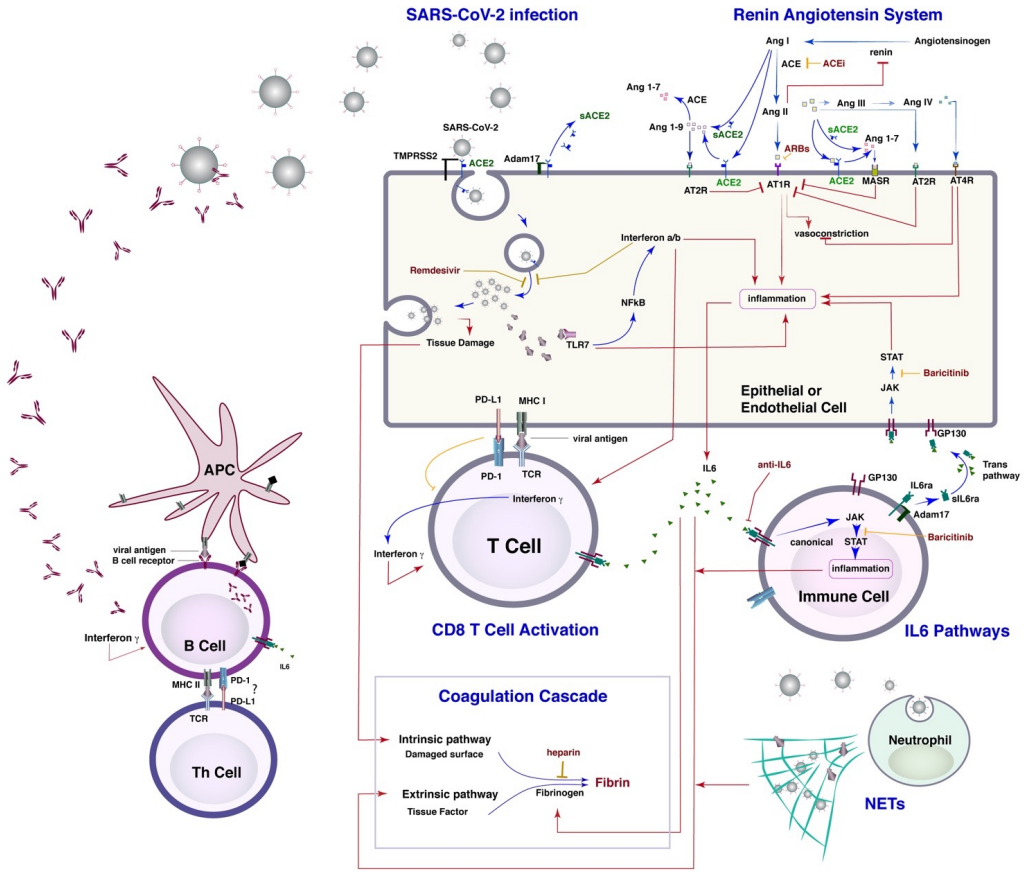
PK/PD of systemic vascular beds

Virus and thrombi originating in the lungs can disseminate to the rest of the body

- Each systemic vascular bed characterized by vascular and interstitial compartments with exchange across vessel walls
- In each compartment virus may be free, bound to endothelial ACE2 or internalized

Voutouri PNAS 2020, Subudhi E-Biomed 2021

Large scale mechanistic modeling of COVID-19



This results in a large number of parameters

Unlikely that parameters can be statistically validated given available data

Value lies in hypothesis generation - exploring phase space of model in a way that increases precision of clinical observations

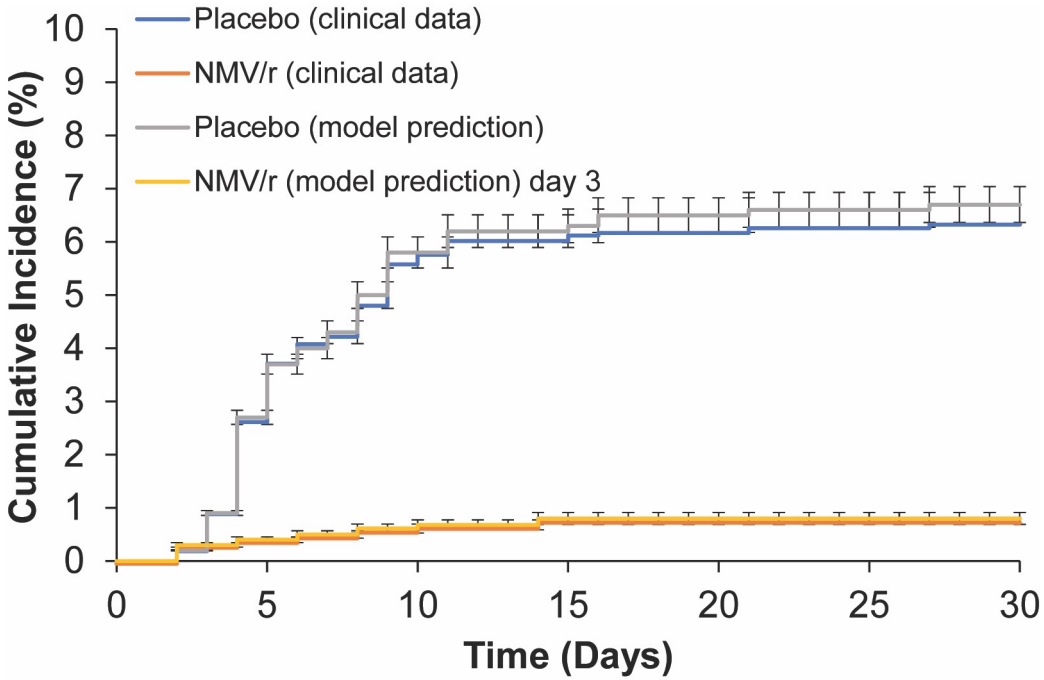
Subudhi E-Biomed 2021

Large scale mechanistic modeling of COVID-19

Anti-viral strategies

Kin	Rate of release of replicated virus	0.42x10-8 [1/h] (for 5 days) Placebo: 0.23 x10-6 [1/h]

- Model antiviral treatment by modulating the rate constant for release of replicated virus from infected cells
- We choose an effect size which is similar in magnitude to that of Paxlovid
- Agnostic as to mechanism of antiviral – we simply postulate an effective decrease in virion production on the day treatment starts
- Follow downstream effects on multiple networks– viral load, subsequently infected cells, thrombosis, cytokine release in response to infections



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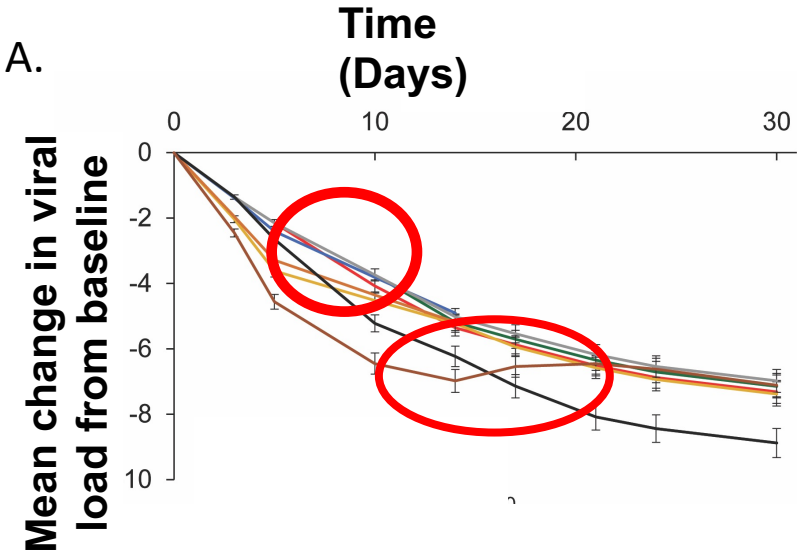

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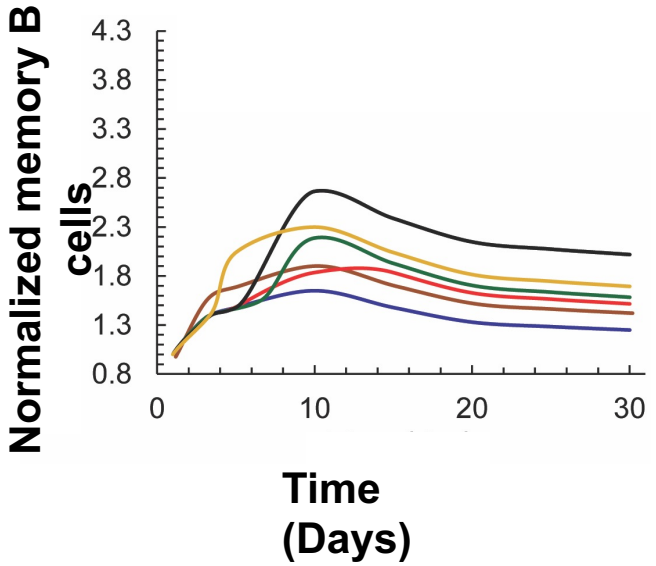

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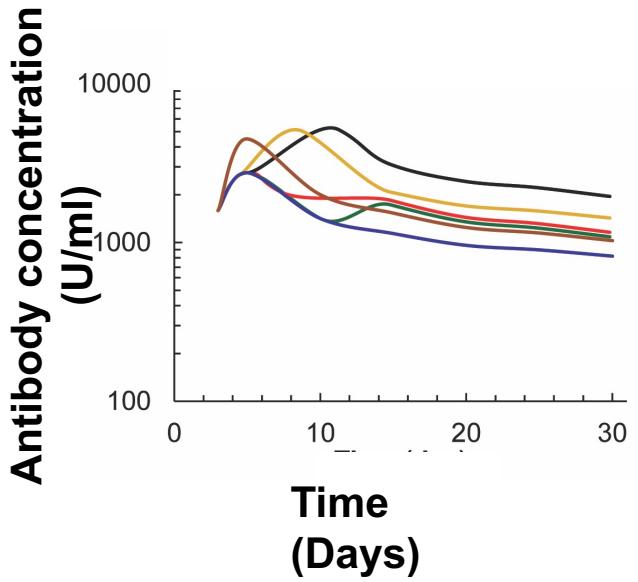


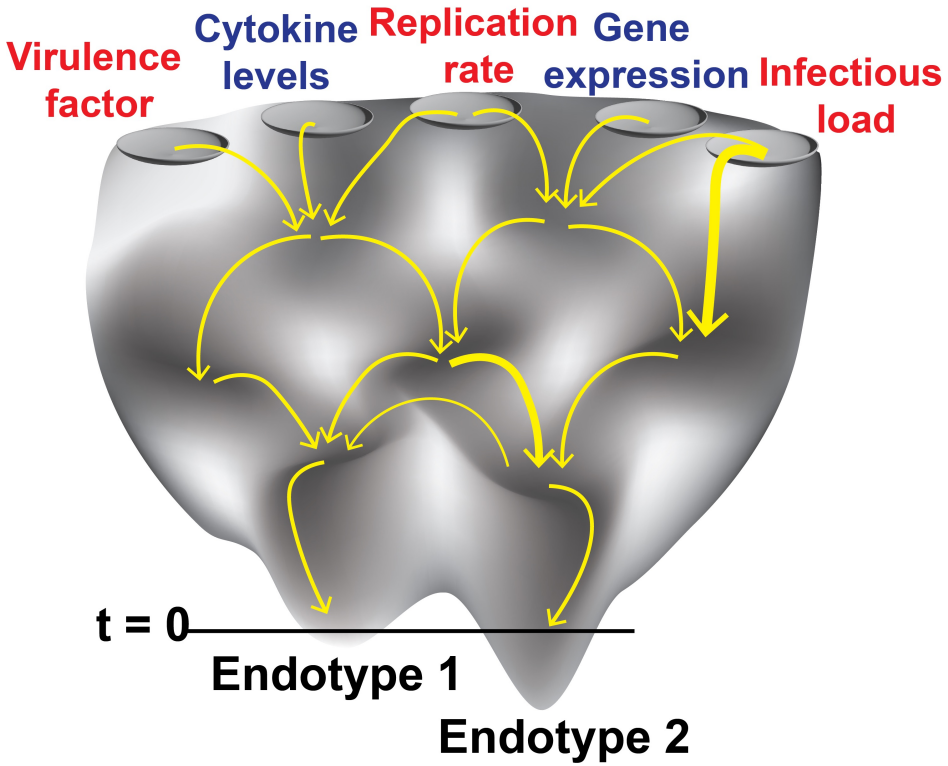
Placebo (clinical data)
NMV/r (clinical data)
Placebo (model prediction)
NMV/r (model prediction) day 0
NMV/r (model prediction) day 3
NMV/r (model prediction) day 5
NMV/r (model prediction) day 7
NMV/r (model prediction) day 10

Day 0 = first encounter with virus

- Later start results in viral load decrease similar to that seen with placebo
- Very early start results in rebound after treatment
- Early start is also associated with lower Ab and memory B cell levels in the model

Paxlovid rebound: A counter-intuitive result that may be due to complex interactions between antiviral agent, innate and adaptive immunity

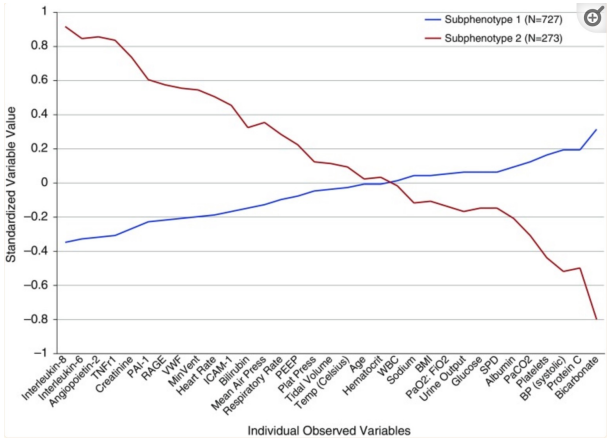
Large scale mechanistic modeling of COVID-19

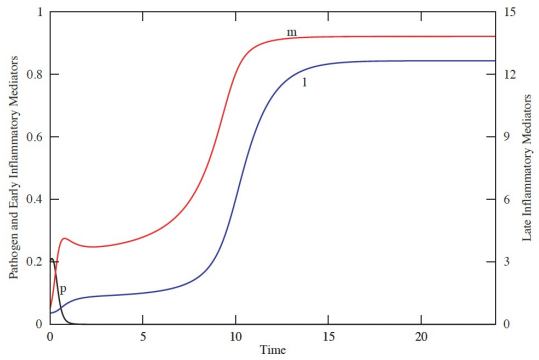


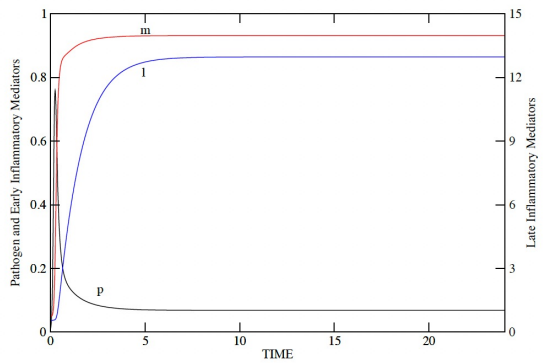
Future directions: Inflammatory injury

- The large number of physiologic networks activated during critical illness means clinicians must confront complexity
- Response to infection must neutralize pathogen while minimizing injury to healthy tissue. It is likely not possible to simultaneously optimize both functions.
- Like the glass transition or protein folding this can result in frustration and a rough ‘phase space’ or landscape.
- In such a setting, patient conditions are likely to be history dependent and non-ergodic.
- Models which explore possible outcomes can aid in the interpretation of clinical data in such a setting.

Large scale mechanistic modeling of COVID-19







Future directions: Inflammatory injury

- Further, clinical observations may mask underlying complexity
- This can lead to heterogeneity in treatment response
- Such heterogeneity can be difficult and expensive to work through in the context of a trial
- Models can suggest markers of ‘hidden states’ even when such models are not designed to fully replicate the clinical course of any particular patient. .

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