MGH 1811

MASSACHUSETTS GENERAL HOSPITAL

VE RI TAS

HARVARD MEDICAL SCHOOL

COVID-19: A Case for Network Physiology

Kathryn A. Hibbert

26 July, 2022

34yo M develops viral symptoms after exposure to a sick family member and is diagnosed with SARS-CoV-2

Day 10

Admitted to the ICU with hypoxemic respiratory failure and severe ARDS (acute respiratory distress syndrome)

Day 75

Discharged from the ICU after course complicated by:

- Pulmonary embolism
- Renal failure
- Ischemic bowel
- ECMO and prolonged mechanical ventilation

Month 8-9

Returns to clinic with persistent cognitive impairment, shortness of breath, and difficulty with a “normal” level of physical activity

What Have Been Our Successes

- **Survival**
- Better understanding of disease process and manifestations
- Development of *some* therapeutic interventions
- **Vaccines!!**

What have been our failures?

- Accurate identification of patients who will become critically ill
- Precise intervention based on disease and host dynamics
- Understanding of post-acute sequelae of COVID-19 and their etiology
- Prophylactic treatment of susceptible hosts

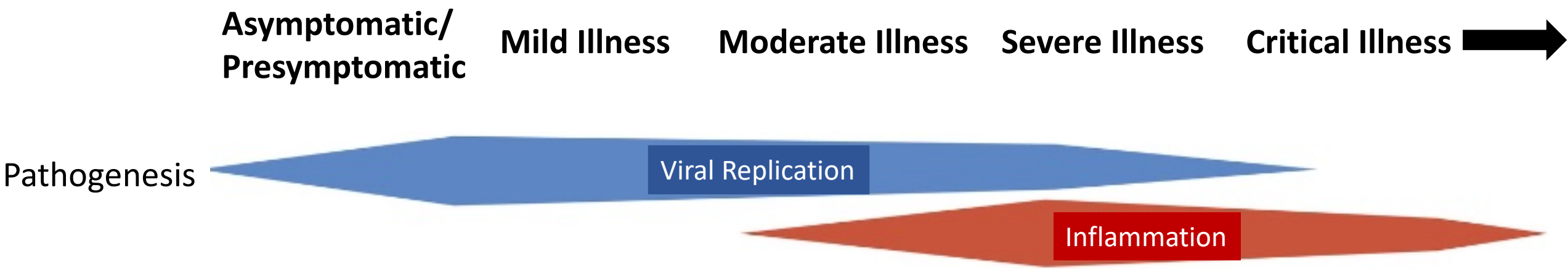
Sources of Heterogeneity and Complexity in COVID-19

Temporal Heterogeneity

Heterogeneity of Severity

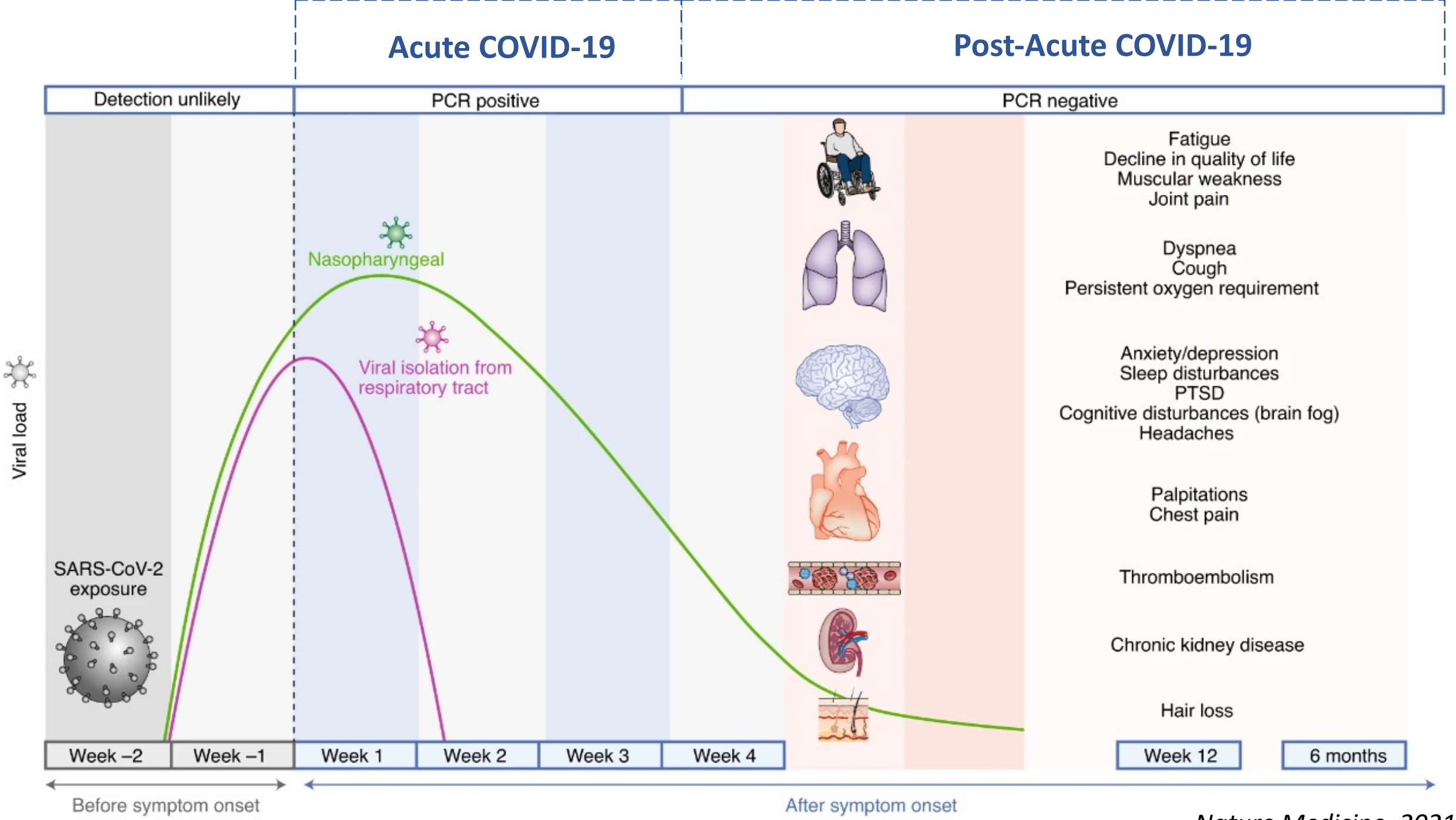
Heterogeneity of Recovery

Temporal Heterogeneity in COVID-19



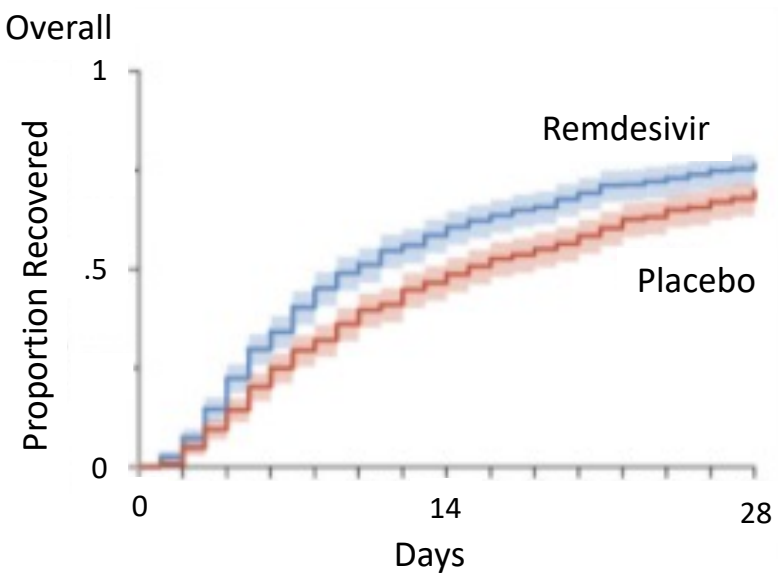
- Pathogenesis is not constant throughout illness and at any time point is due to a balance between direct viral effects and inflammatory host response
- Intervention therefore should not be focused on the same target throughout illness

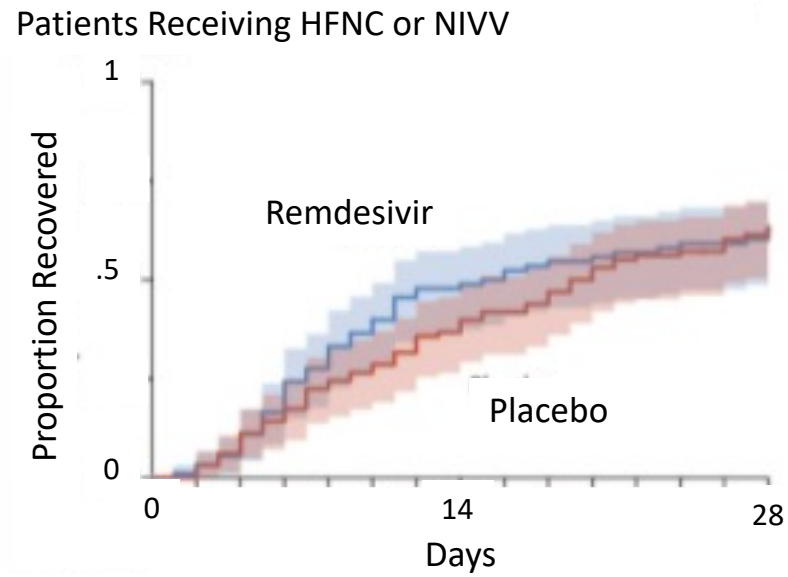
NEJM 2020

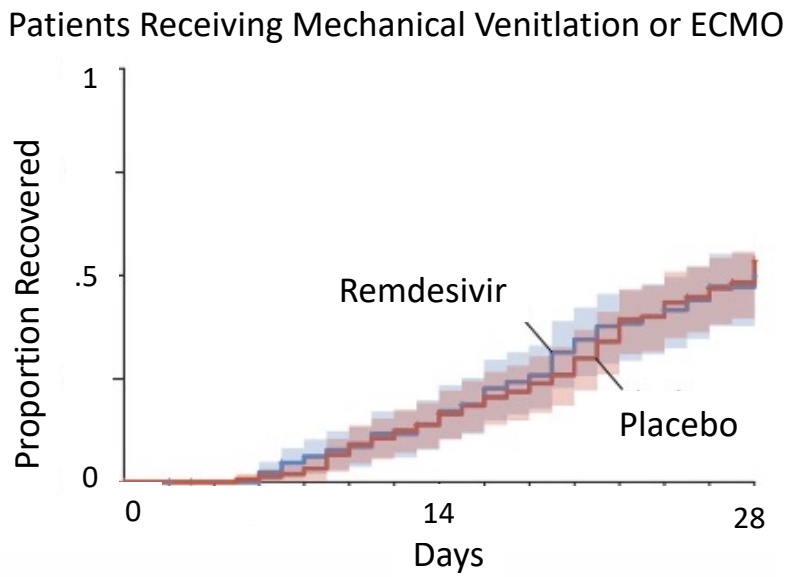


Nature Medicine, 2021

Remdesivir for COVID-19: ACTT-1 Trial





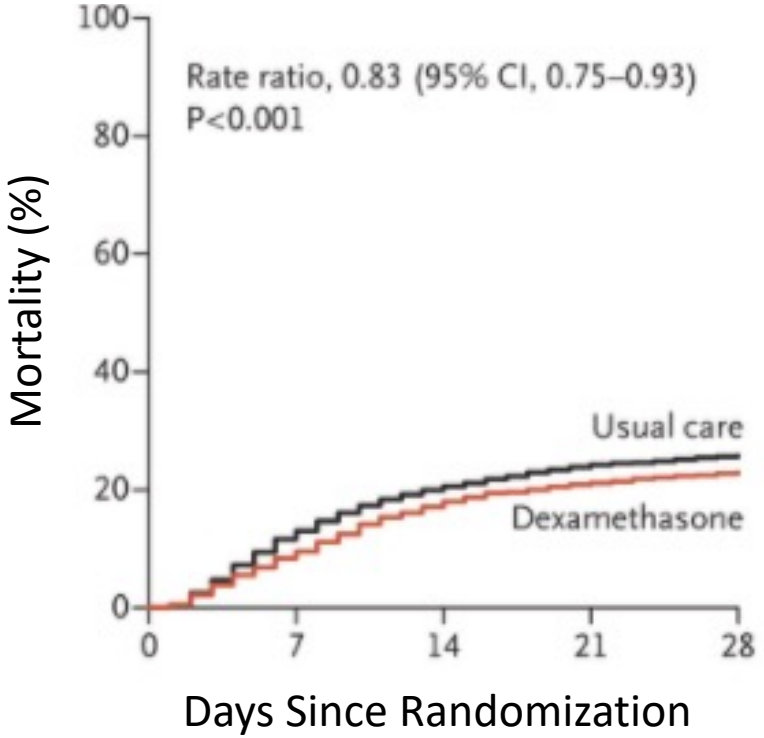


- 1062 patients randomized to remdesivir v placebo
- Shortened time to recovery but not in patients with more severe disease

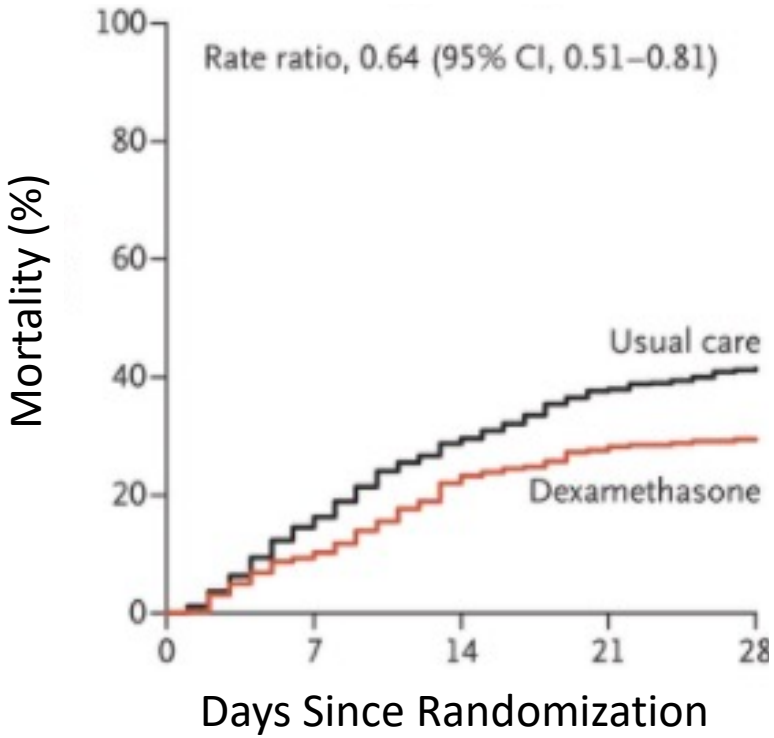
Beigel, et al. N Engl J Med 2020

Dexamethasone in COVID-19

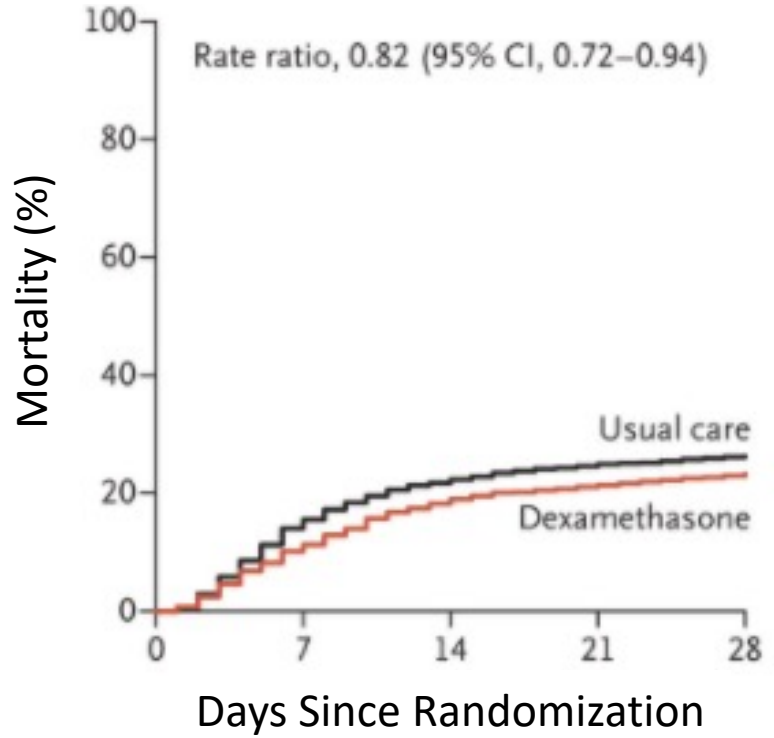
All Participants (N= 6425)



Invasive Mechanical Ventilation (N=1007)



Oxygen Only (N=3883)



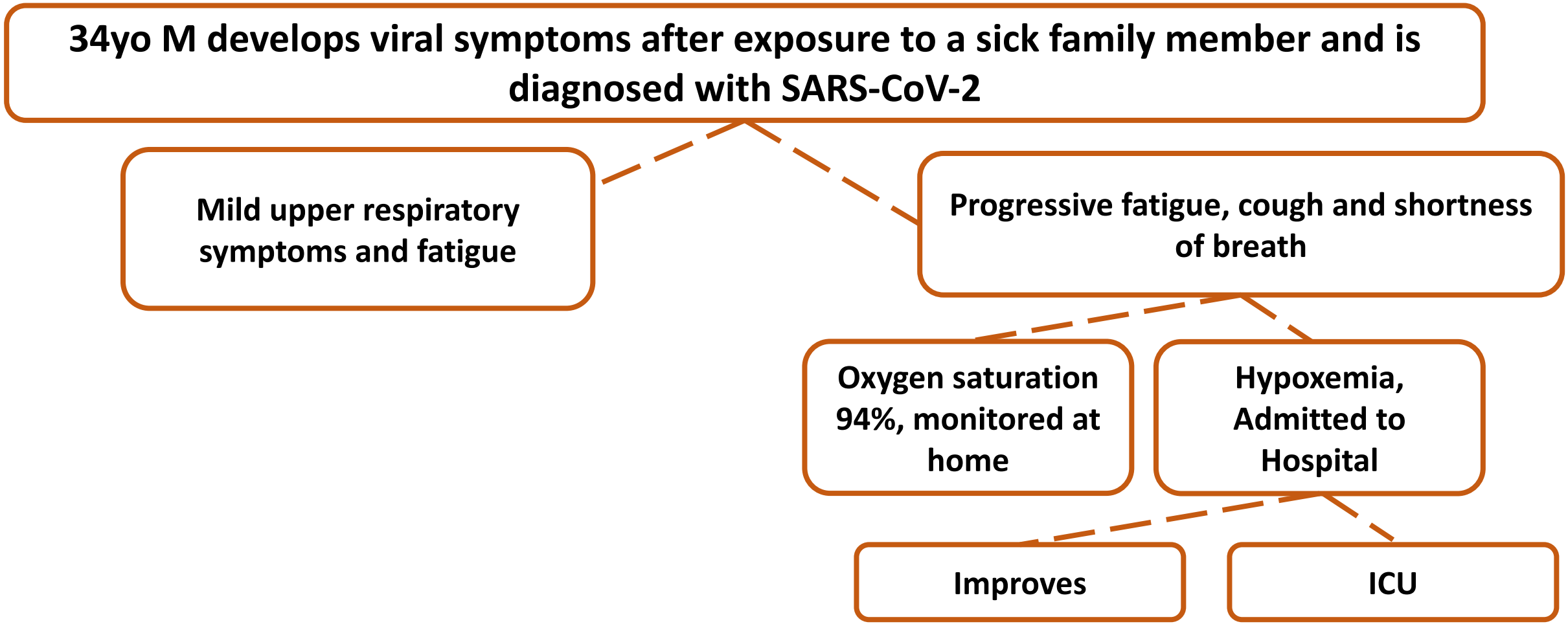
- Pragmatic platform trial of steroids in COVID-19
- Benefit largest in the sickest patients (on oxygen and mechanically ventilated)

N Engl J Med 2020

Assessing Point-In-Time Disease State

- Very limited diagnostic options including
  - PCR testing
  - Viral cycle threshold
  - Systemic markers of inflammation
- Difficult to assess organ-level information
- Limited and time-delayed ability to quantify response to treatment

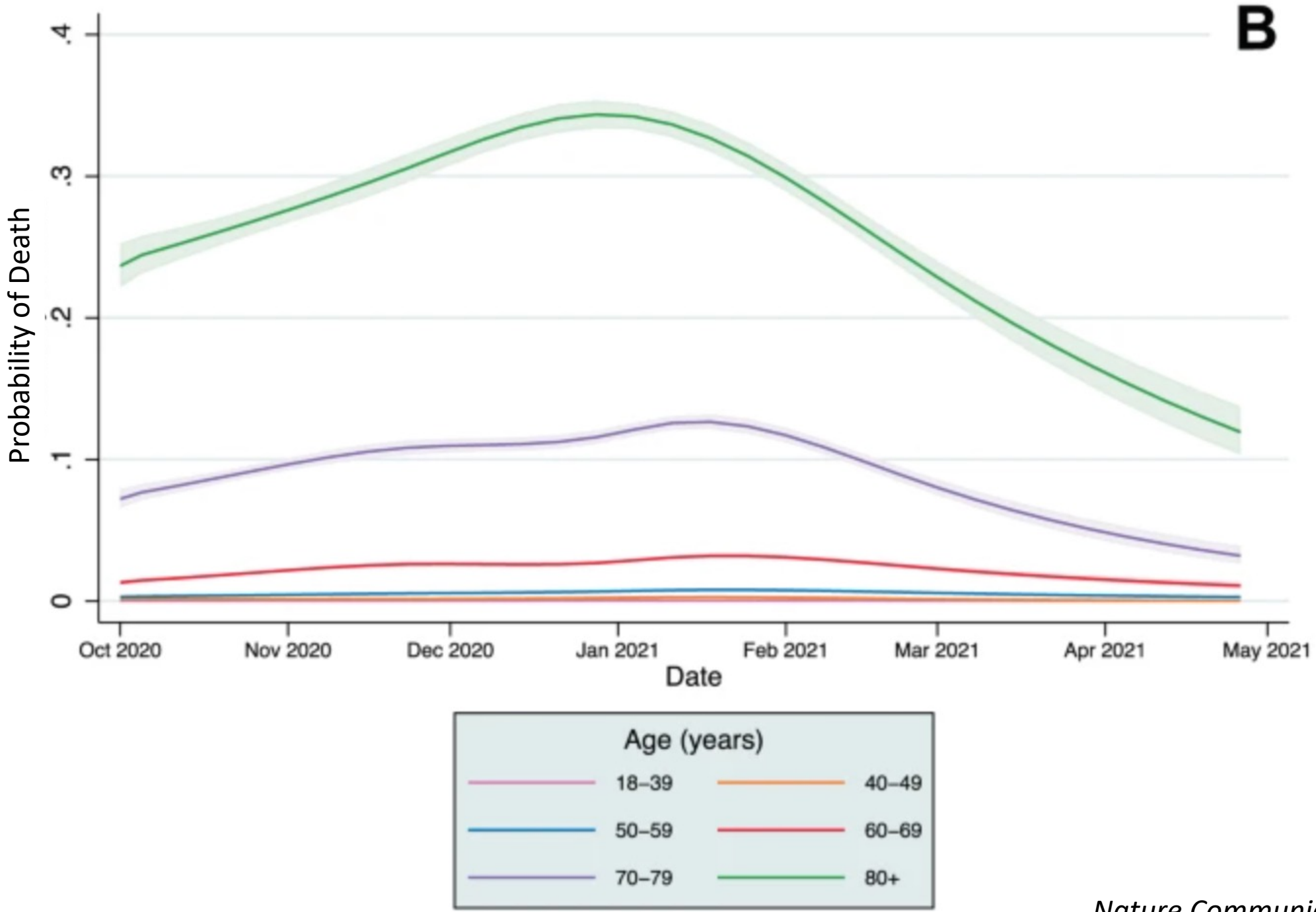
Heterogeneity of Severity in COVID-19



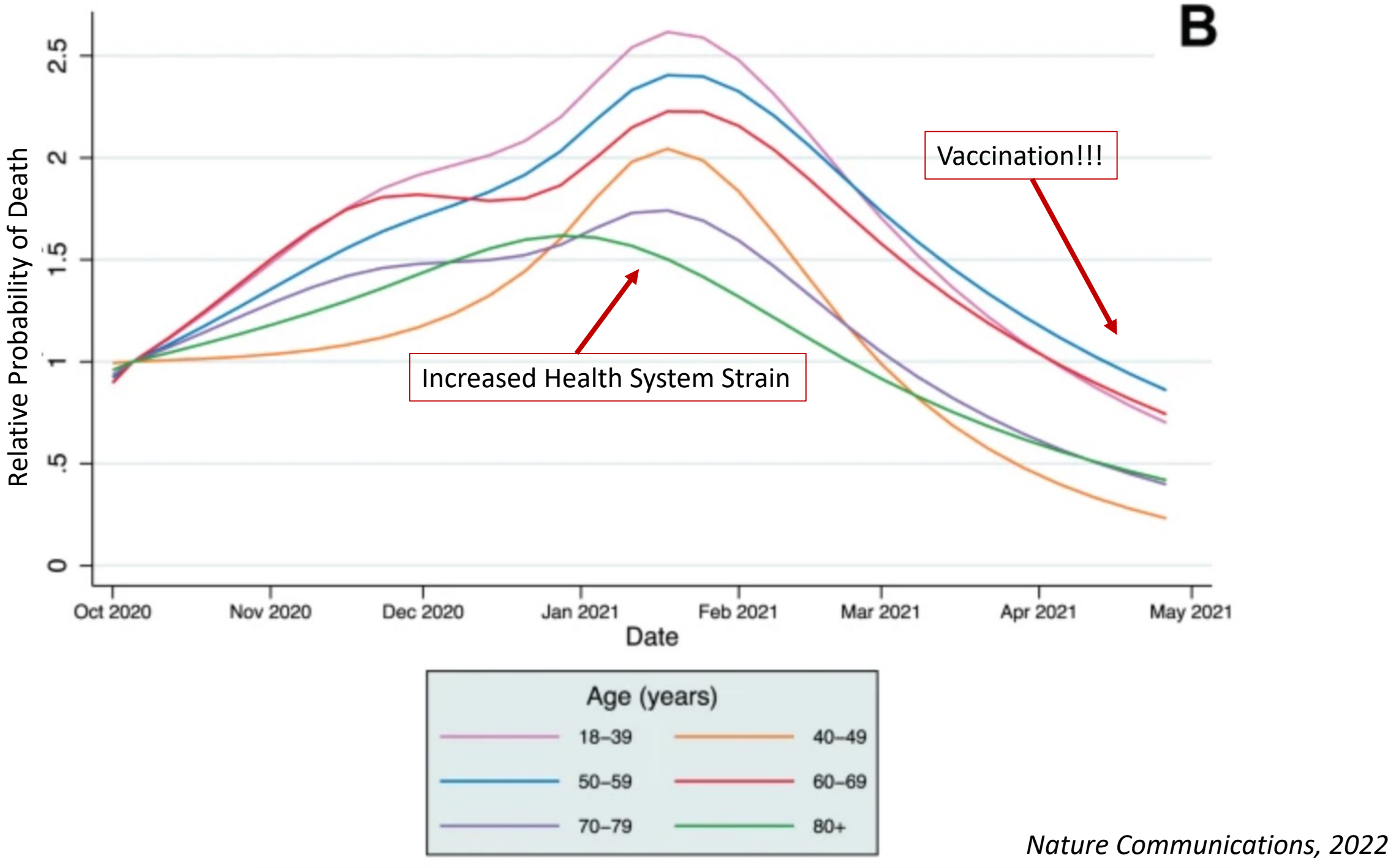
Age group rate ratios compared to ages 18 to 29 years[1]

Rate compared to 18-29 years old[1]	0-4 years old	5-17 years old	18-29 years old	30-39 years old	40-49 years old	50-64 years old	65-74 years old	75-84 years old	85+ years old
Cases[2]	<1x	1x	Reference group	1x	1x	1x	1x	1x	1x
Hospitalization[3]	1x	<1x	Reference group	2x	2x	3x	5x	8x	10x
Death[4]	<1x	<1x	Reference group	4x	10x	25x	60x	140x	330x

CDC.Gov, accessed July 2022

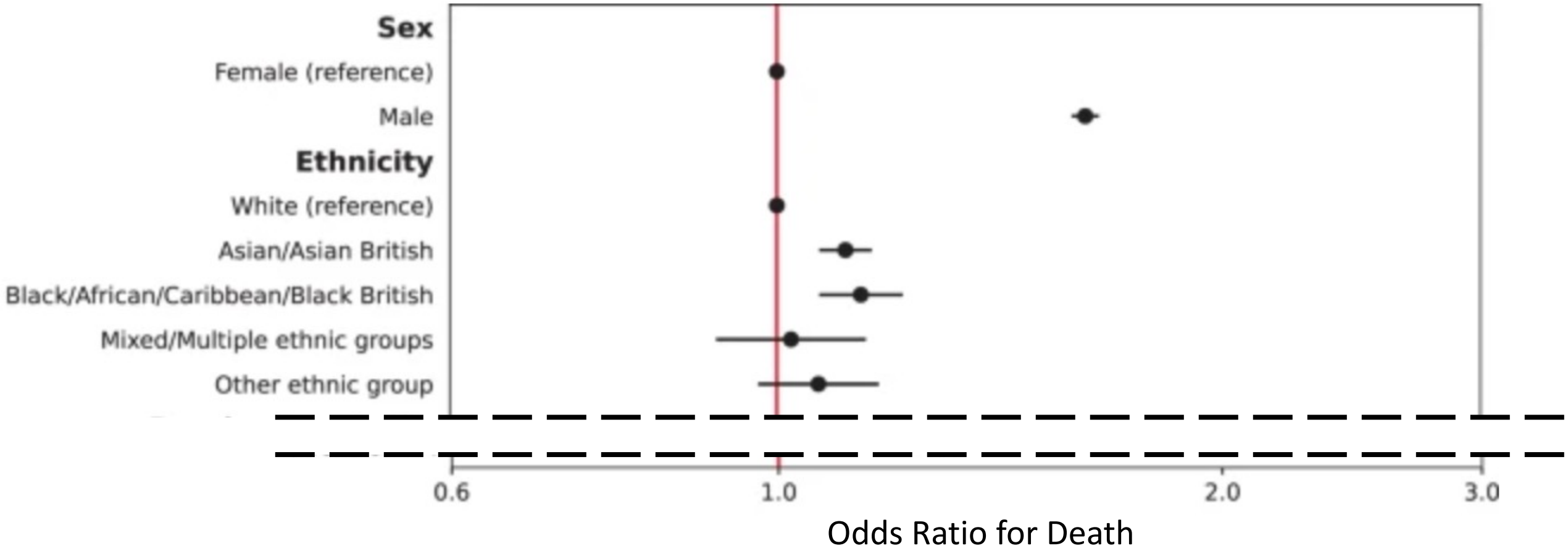


Nature Communications, 2022



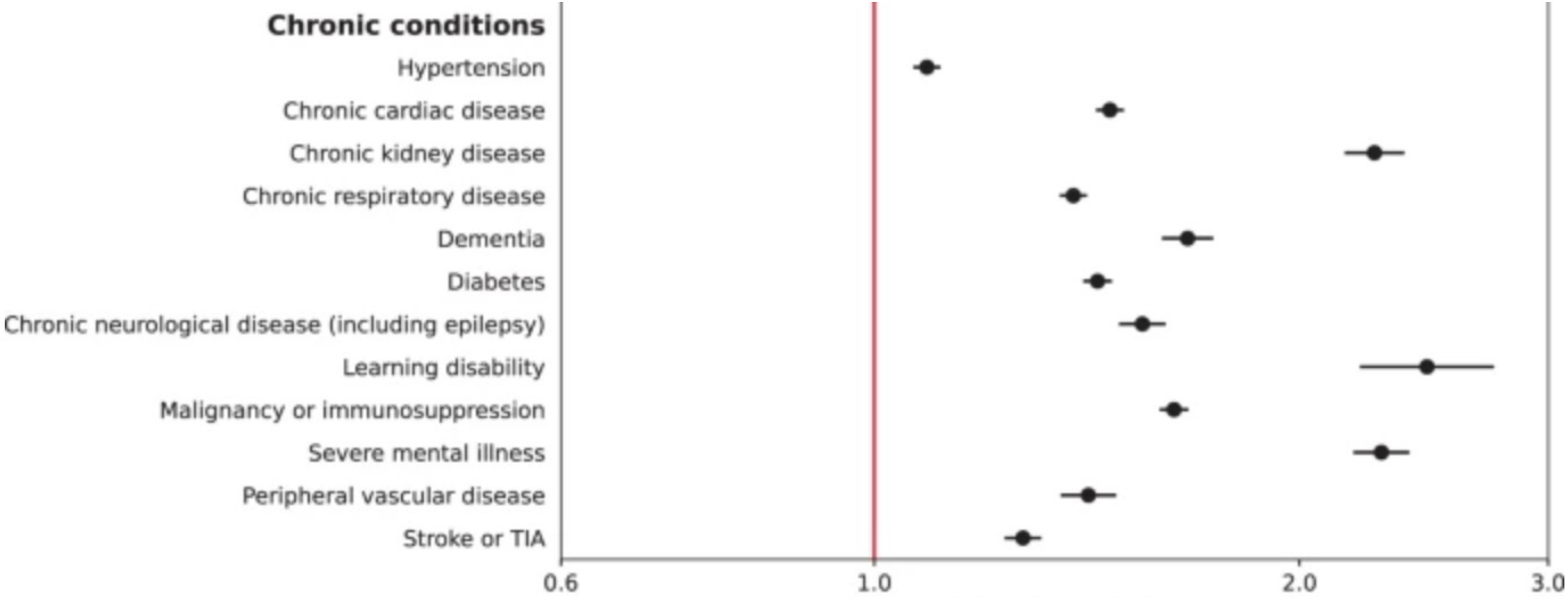
Nature Communications, 2022

Adjusted Odds Ratio for Death within 28 Days



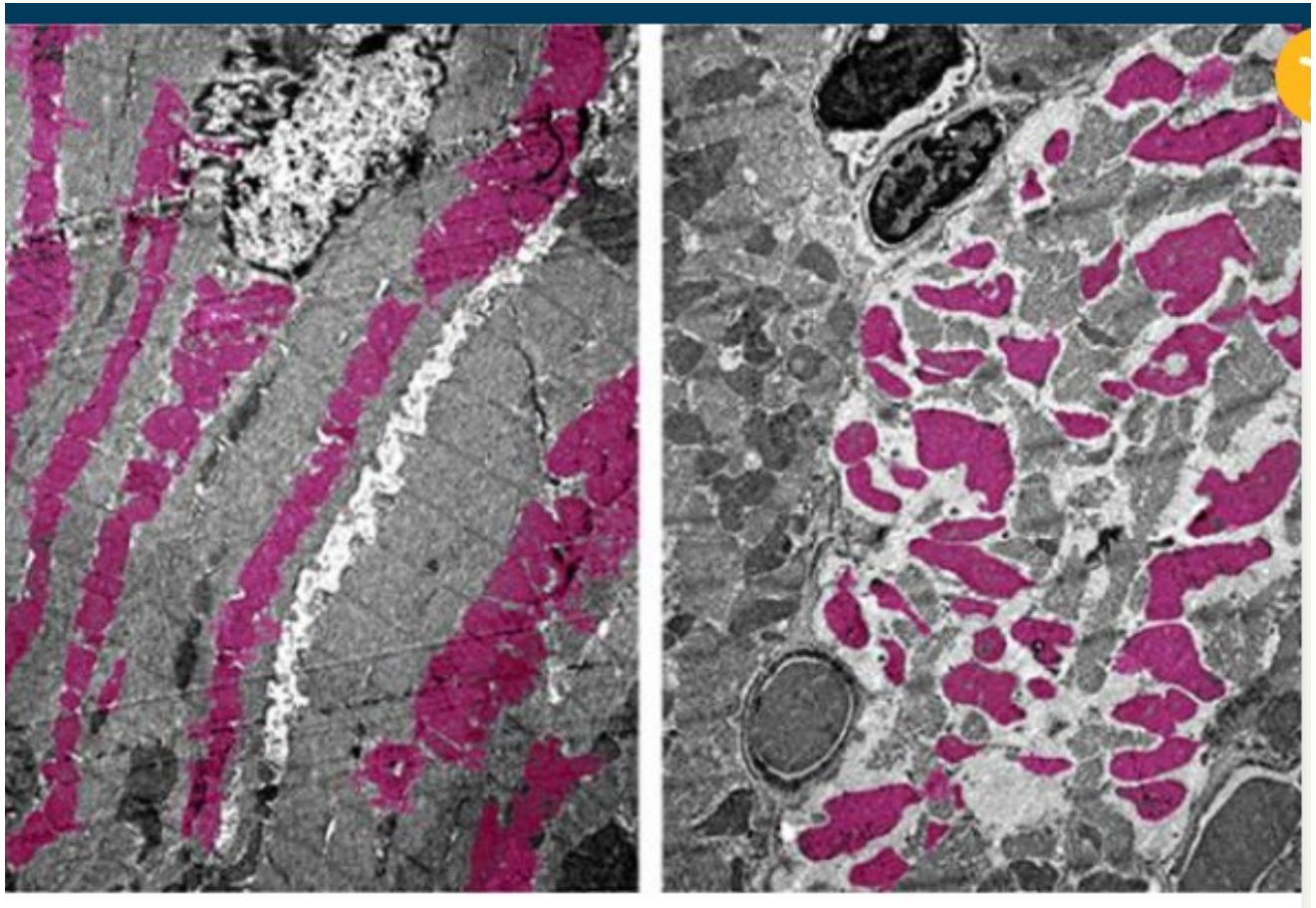
Nature Communications, 2022

Adjusted Odds Ratio for Death within 28 Days



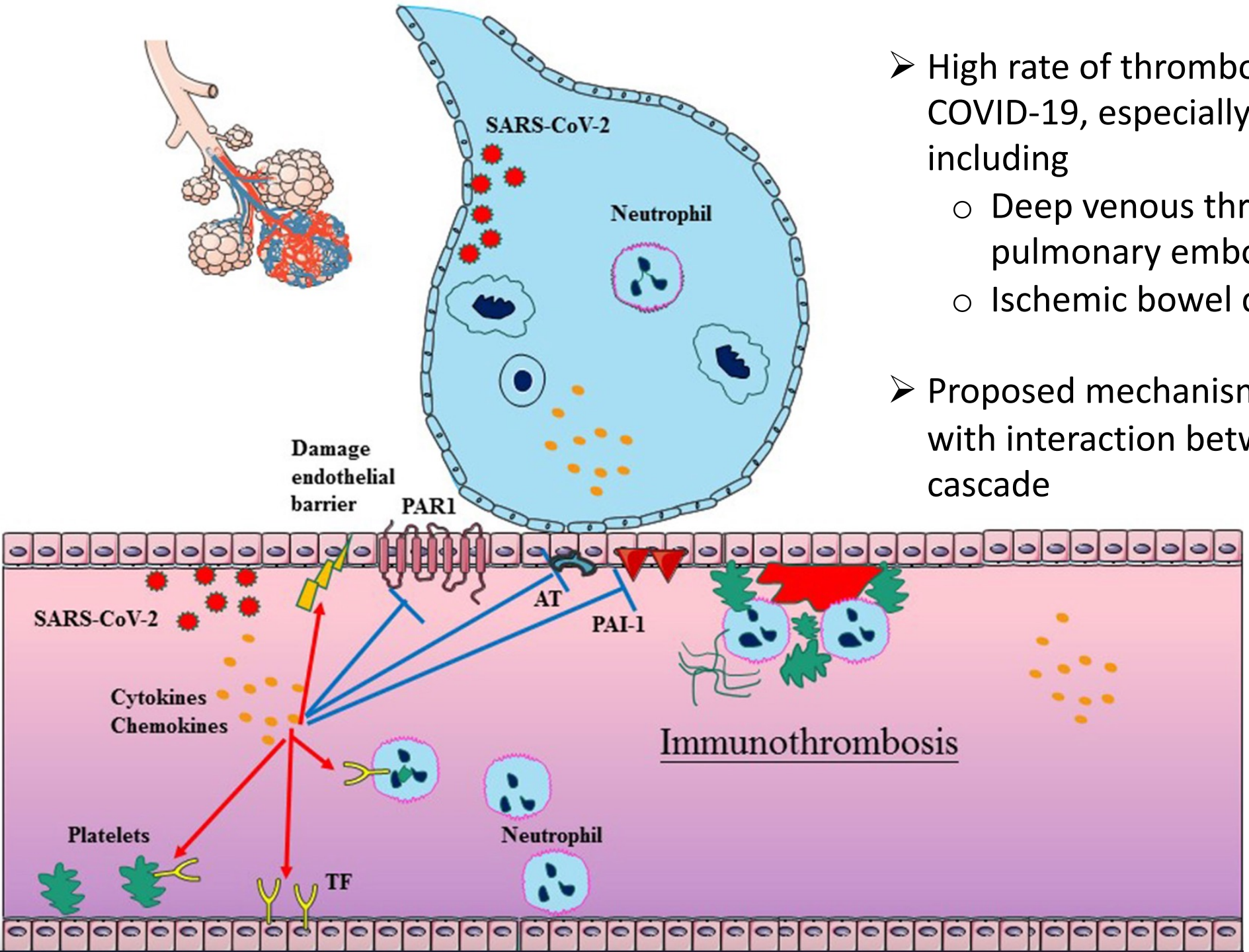
Nature Communications, 2022

Multisystem Illness In Critical COVID-19



Myocardium of health uninfected mouse (left) and mouse infected with SARS-CoV-2 (right) with mitochondria seen in pink

- Primary manifestation of COVID-19 is respiratory
  - Upper respiratory systems in mild illness
  - Pneumonia and ARDS in severe illness
- Multiple organ failure is common in severe disease
- Direct tissue infection ? documented in humans and animal models → unclear significance/truth

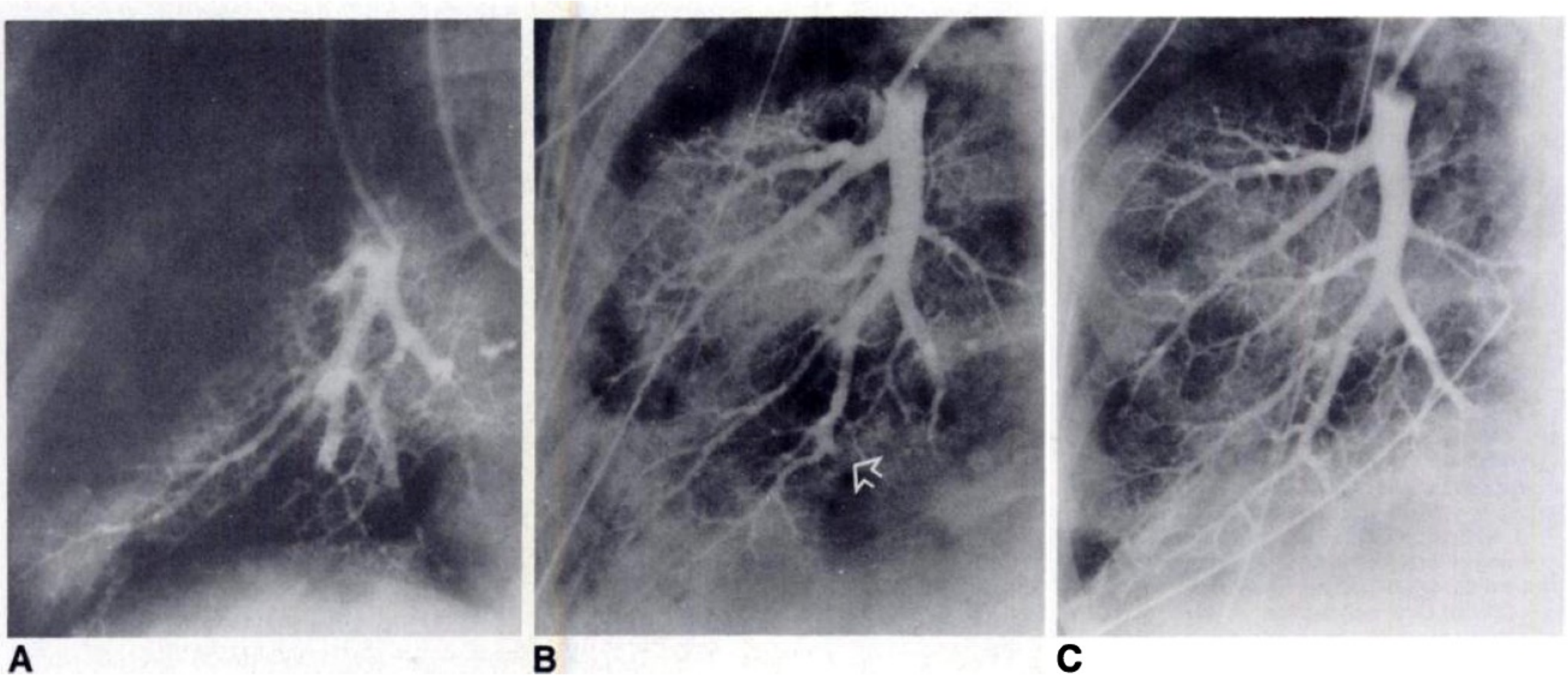


- High rate of thrombotic complications in COVID-19, especially critical COVID-19 including
  - Deep venous thromboembolism and pulmonary embolism
  - Ischemic bowel due to thrombosis

- Proposed mechanism of immunothrombosis with interaction between virus and clotting cascade

Frontiers Immunology, 2021

Pulmonary Vascular Pathology in ARDS

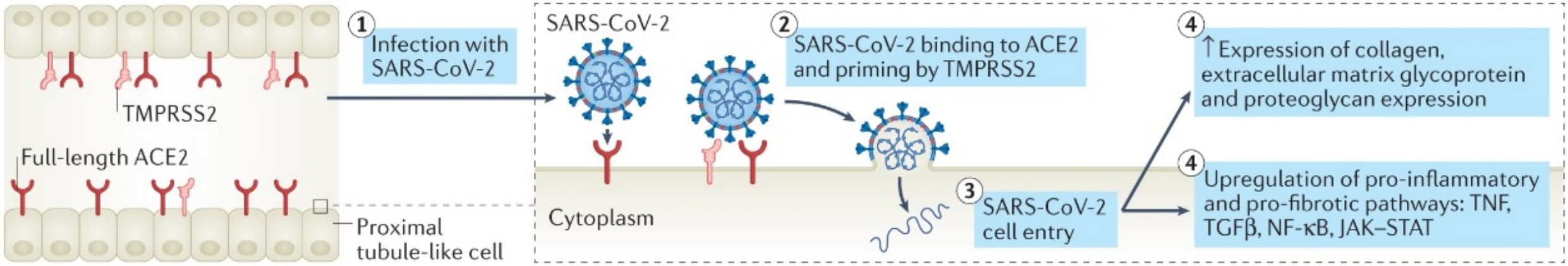


Balloon Occlusion Pulmonary Angiography in ARDS (A) and after 48 hours (B) and 96 hours (C) of thrombolytic infusion

Greene et. al., AJR, 1987

Fig. 1: Direct SARS-CoV-2 infection in human kidney organoids.

From: Potential SARS-CoV-2 kidney infection and paths to injury



- Unable to assess direct infection *in vivo*
- Multiple organ failure is common in non-COVID ARDS (up to 50% of patients)
- Additional organ failures (essentially) always associated with increased risk of mortality

Nature Reviews Nephrology, 2021

Predicting and Assessing Disease Severity

- "Risk Factors" are not predictive on an individual level
- Wait for organ failure (e.g. hypoxemia) to assign severity
- Is not specific to uncontrolled viral replication or dysregulated host response
- Limited ability to model on a population level

Why Does Understanding Severity Trajectory Matter?

- More accurate identification of risk factors within at-risk groups
- Study design and enrichment
- Capacity planning in strained times
- Potential for early intervention
- Allocation of scarce resources to those most likely to benefit

Heterogeneity of Recovery in COVID-19

34yo M develops viral symptoms after exposure to a sick family member and is diagnosed with SARS-CoV-2. He is hospitalized with COVID-19 pneumonia.

Remains in the hospital 2 days, goes home and feels return to normal in 2 weeks

Remains in the hospital 2 weeks, oxygen levels are slow to return to normal

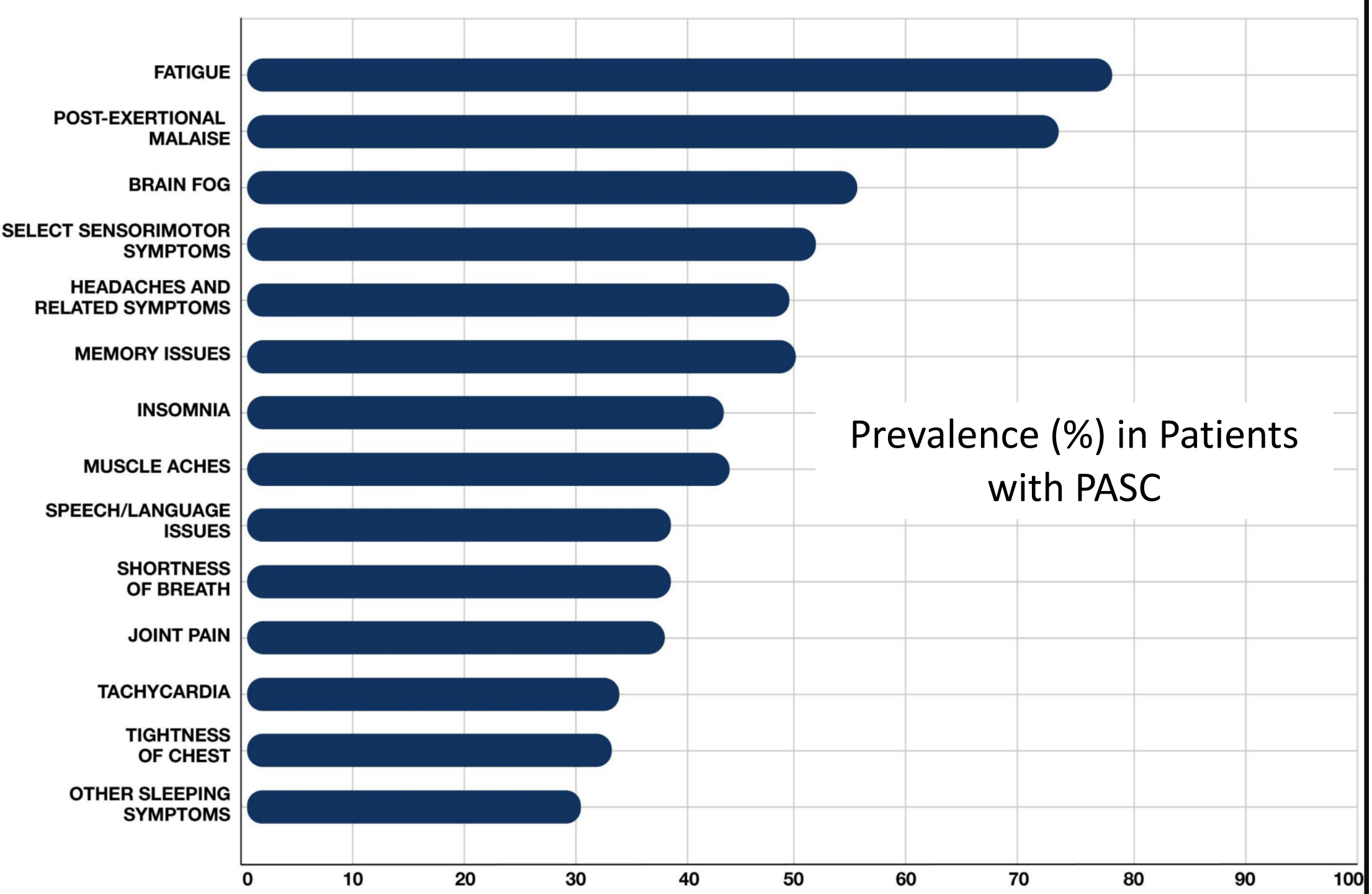
Feels return to normal in 4 weeks

Persistent shortness of breath

Slowly Improves

Presents for Evaluation

- Recovery depends on viral dynamics and resolution of inflammation
- Host factors are complex and may include immunosufficiency, autoimmune axes, and comorbidities (e.g. chronic lung disease)



Front Microbiol, 2021

Challenges in Studying PASC

- Unclear specificity to COVID-19 infection
- Difficult to assess background rates of symptoms in similar non-COVID infected population
- Few definitive physiologic tests to identify pathophysiology of non-specific (and often non-localized) symptoms

34yo M develops viral symptoms after exposure to a sick family member and is diagnosed with SARS-CoV-2

Goals:

- Accurately predict his risk of becoming seriously ill
- Assess his infection-inflammation axis and intervene appropriately prior to serious illness
- Bring him in to the hospital earlier if he is worsening at home

34yo M develops viral symptoms after exposure to a sick family member and is diagnosed with SARS-CoV-2

Day 10

Admitted to the ICU with hypoxemic respiratory failure and severe ARDS (acute respiratory distress syndrome)

Goals:

- Dynamically evaluate his risk of additional organ failures and complications (*e.g.* thrombosis)?
- Shorten his length of stay in the ICU with more precise therapeutics?
- Rapidly assess his response to therapeutic intervention?

Goals:

- Intervene once he has serious illness to prevent long term functional limitation

- Better understand the pathophysiology of long-term symptoms

Day 75

Discharged from the ICU after course complicated by:
- **Pulmonary embolism**
- **Renal failure**
- **Ischemic bowel**
- **ECMO and prolonged mechanical ventilation**

Month 8-9

Returns to clinic with persistent cognitive impairment, shortness of breath, and difficulty with a "normal" level of physical activity

Looking Ahead