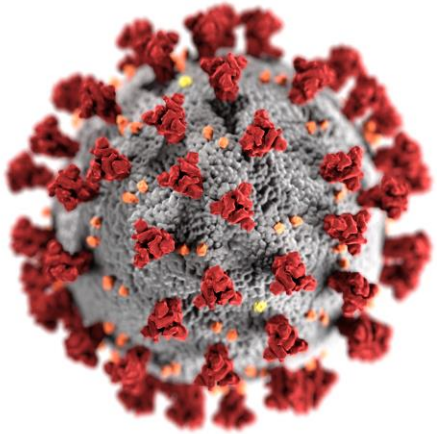
COVID 19 PANDEMIC: CLINICAL PATHOPHYSIOLOGY



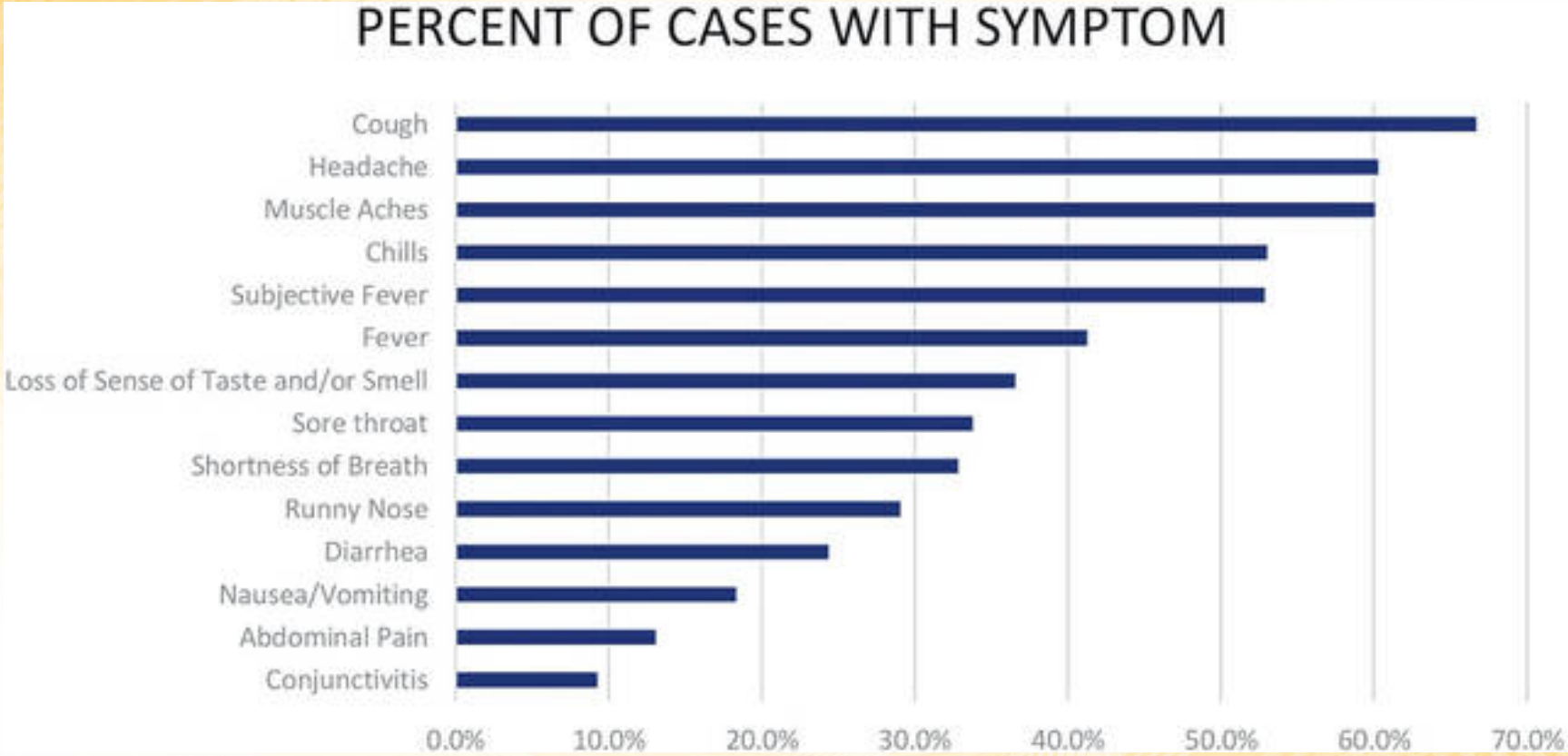
Learning Objectives

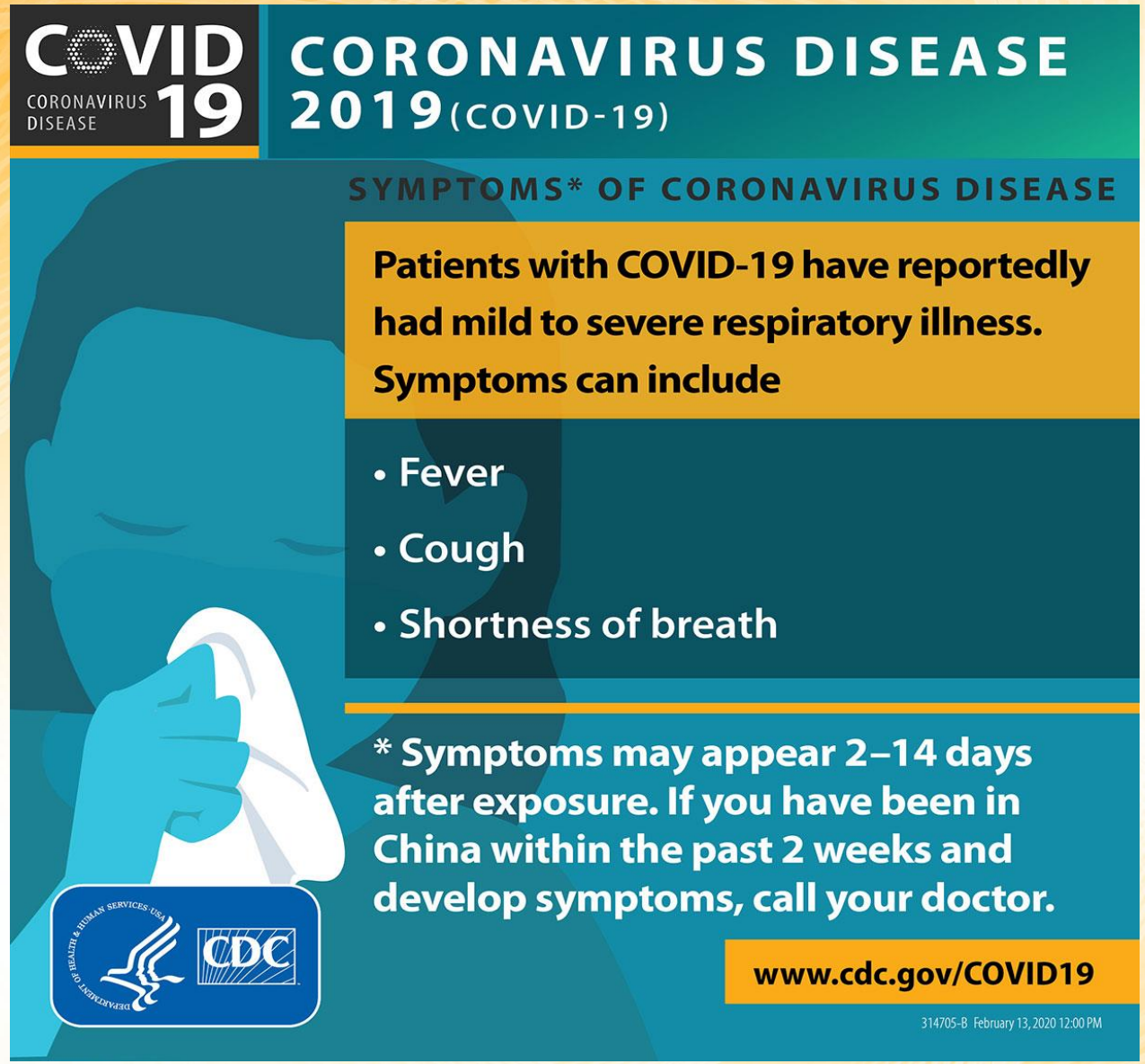
- Describe the clinical characteristics associated with COVID-19
- Review the pathophysiological responses to COVID-19
- Describe the clinical symptoms of COVID-19 salient to organ systems

Clinical Presentation of COVID-19

- Fever
- Anosmia
- Dyspnea
- Dry spasmodic cough
- Secondary symptoms
  - Headache
  - Diarrhea
  - Blueish toe/fingers
  - Confusion
  - Stroke

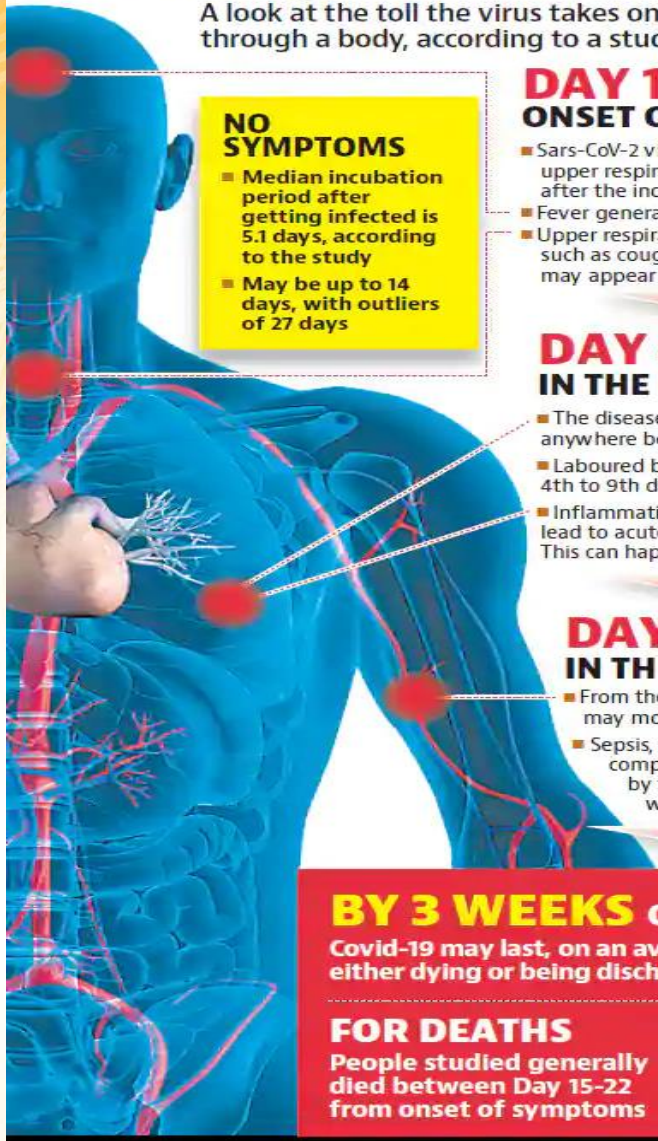
COVID-19 Symptoms




COVID 19
CORONAVIRUS DISEASE
CORONAVIRUS DISEASE 2019 (COVID-19)
SYMPTOMS* OF CORONAVIRUS DISEASE
Patients with COVID-19 have reportedly had mild to severe respiratory illness. Symptoms can include
• Fever
• Cough
• Shortness of breath
* Symptoms may appear 2–14 days after exposure. If you have been in China within the past 2 weeks and develop symptoms, call your doctor.
www.cdc.gov/COVID19
314705-B February 13, 2020 12:00 PM
DEPARTMENT OF HEALTH & HUMAN SERVICES USA
CDC

Tracking corona in humans

A look at the toll the virus takes on the body and how it progresses through a body, according to a study published in The Lancet



NO SYMPTOMS

- Median incubation period after getting infected is 5.1 days, according to the study
- May be up to 14 days, with outliers of 27 days

DAY 1-3
ONSET OF SYMPTOMS

- Sars-CoV-2 virus may start with upper respiratory symptoms after the incubation period
- Fever generally appears 1st day
- Upper respiratory symptoms such as cough and sore throat may appear by Day 3

80% patients just get these mild symptoms

DAY 4-9
IN THE LUNGS

- The disease may reach the lungs anywhere between 3 to 4 days
- Laboured breathing may start by 4th to 9th day
- Inflammation in the lungs may lead to acute respiratory distress. This can happen between Day 8-15

14% of those infected experience these severe symptoms

DAY 8-15
IN THE BLOOD

- From the lungs, the infection may move to the blood
- Sepsis, a life-threatening complication, may develop by the end of the first week, the study said

5% of those infected need ICU care

BY 3 WEEKS CRUCIAL PERIOD

Covid-19 may last, on an average, for 21 days with people either dying or being discharged by the end of the third week

FOR DEATHS

People studied generally died between Day 15-22 from onset of symptoms

FOR DISCHARGE

People were discharged between Day 18-25 from the onset of symptoms

SOURCE: A retrospective study on clinical course and risk factors for mortality in 191 adult patients from Jinyintan Hospital and Wuhan Pulmonary Hospital published in The Lancet

COVID-19

HOW DOES IT AFFECT YOU?

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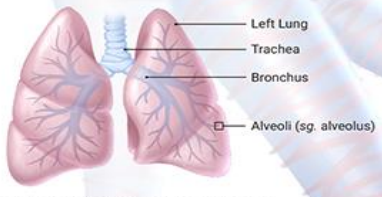
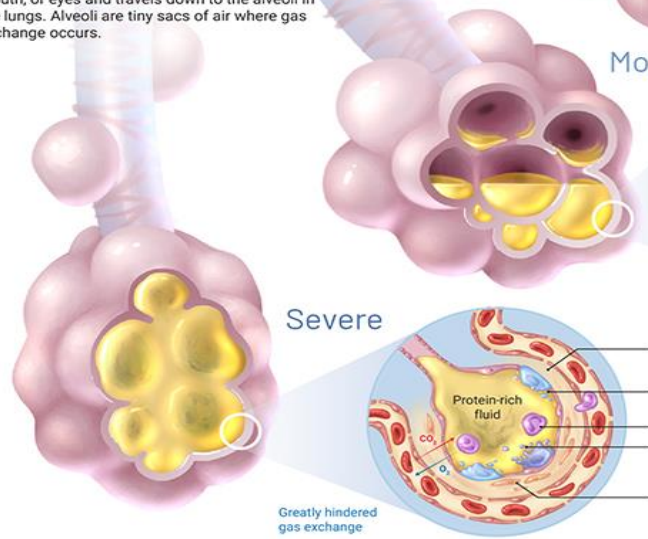
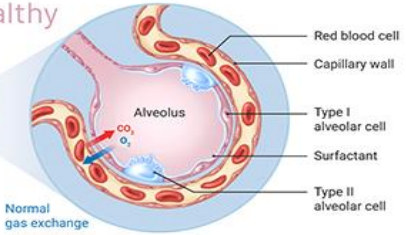
Coronavirus Disease 2019 (COVID-19) is a pandemic caused by Severe Acute Respiratory Syndrome Coronavirus 2, also called SARS-CoV-2. Despite the widespread awareness regarding COVID-19, many are still unaware about how it affects the human body.



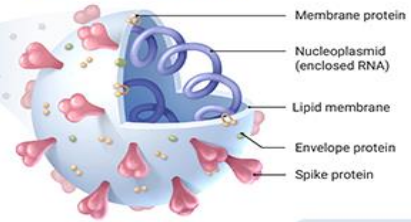
SARS-CoV-2 starts its journey in the nose, mouth, or eyes and travels down to the alveoli in the lungs. Alveoli are tiny sacs of air where gas exchange occurs.



Healthy

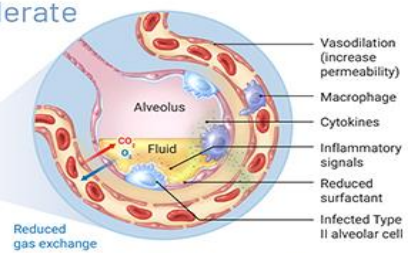


Infected



SARS-CoV-2 Structure

Moderate



Severe

Gas Exchange

Each sac of air, or alveolus, is wrapped with capillaries where red blood cells release **carbon dioxide** (CO_2) and pick up **oxygen** (O_2). Two alveolar cells facilitate gas exchange; **Type I** cells are thin enough that the oxygen passes right through, and **Type II** cells secrete **surfactant** – a substance that lines the alveolus and prevents it from collapsing.

Viral Infection

The spike proteins covering the coronavirus bind ACE2 receptors primarily on type II alveolar cells, allowing the virus to inject its RNA. The RNA "hijacks" the cell, telling it to assemble many more copies of the virus and release them into the alveolus. The host cell is destroyed in this process and the new coronaviruses infect neighbouring cells.

Impaired Gas Exchange

When the immune system attacks the area of infection it also kills healthy alveolar cells. This results in three things that hinder gas exchange:

1) Alveolar collapse due to loss of surfactant from Type II cells
2) Less oxygen enters the blood-stream due to lack of Type I cells
3) More fluid enters the alveolus

Stay Home

- Symptoms may start to show (e.g. dry cough, fever, etc.)
- Pneumonia develops
- Shortness of breath

Hospitalization

- Dangerous for high-risk individuals; secondary infections may occur

Intensive Care (ICU)

- Patients may require ventilators and life-support
- Complications unrelated to COVID-19 may occur

With proper care, patients may recover at any point during this process

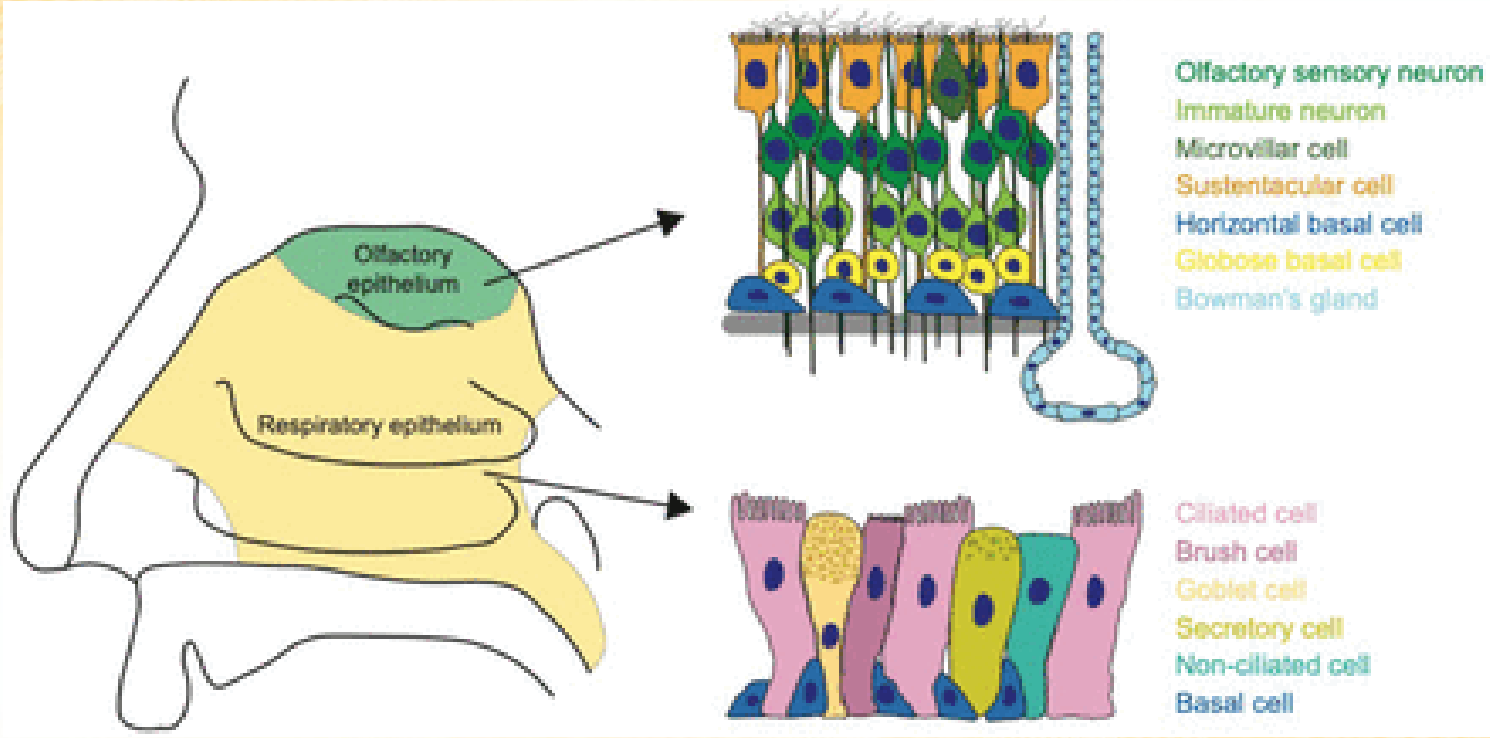
Immune Response

1. After infection, Type II cells release **inflammatory signals** that recruit **macrophages** (immune cells).
2. Macrophages release **cytokines** that cause vasodilation, which allows more immune cells to come to the site of injury and exit the capillary.
3. Fluid accumulates inside the alveolus.
4. The fluid dilutes the surfactant which triggers the onset of alveolar collapse, decreasing gas exchange and increasing the work of breathing.
5. **Neutrophils** are recruited to the site of infection and release Reactive Oxygen Species (ROS) to destroy infected cells.
6. Type I and II cells are destroyed, leading to the collapse of the alveolus and causing **Acute Respiratory Distress Syndrome** (ARDS).
7. If inflammation becomes severe, the protein-rich fluid can enter the bloodstream and travel elsewhere in the body, causing **Systemic Inflammatory Response Syndrome** (SIRS).
8. SIRS may lead to **septic shock** and **multi-organ failure**, which can have fatal consequences.

How COVID-19 Causes Smell Loss

- Temporary loss of smell, or anosmia, is the main neurological symptom and one of the earliest and most commonly reported indicators of COVID-19. Studies suggest it better predicts the disease than other well-known symptoms such as fever and cough, but the underlying mechanisms for loss of smell in patients with COVID-19 have been unclear.
- Reporting in *Science Advances* on July 24, the research team found that olfactory sensory neurons do not express the gene that encodes the ACE2 receptor protein, which SARS-CoV-2 uses to enter human cells. Instead, ACE2 is expressed in cells that provide metabolic and structural support to olfactory sensory neurons, as well as certain populations of stem cells and blood vessel cells.
- The findings suggest that infection of nonneuronal cell types may be responsible for anosmia in COVID-19 patients and help inform efforts to better understand the progression of the disease..
- A majority of COVID-19 patients experience some level of anosmia, most often temporary, according to emerging data

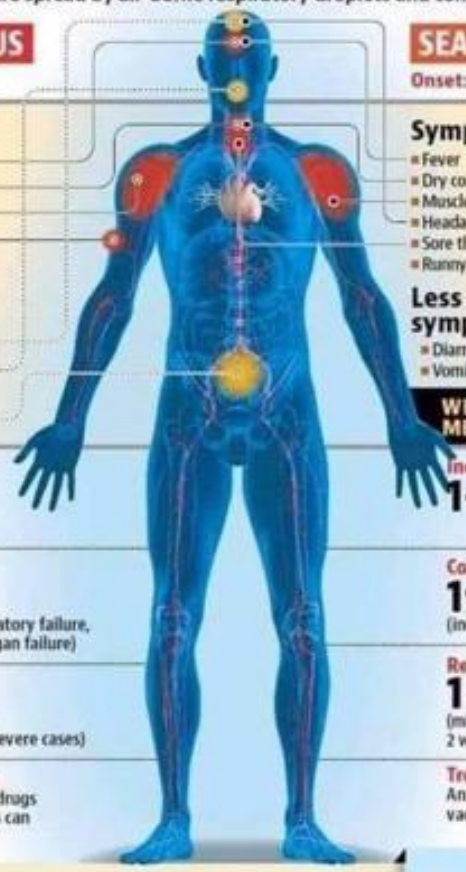
Neuron Effects of COVID-19



CORONAVIRUS, FLU, COLD?

As the number of coronavirus cases rise, some key differences set coronavirus apart from the seasonal flu and the common cold — mainly the intensity of the symptoms and the recovery period. A guide at identifying the differences in the three conditions

All three, however, are spread by air-borne respiratory droplets and contaminated surfaces



CORONAVIRUS

Onset: Sudden

Symptoms
- Fever
- Dry cough
- Muscle ache
- Fatigue

Less common symptoms
- Headache
- Coughing up blood (haemoptysis)
- Diarrhoea

Incubation: 1-14 days, may go up to 24 days

Complications: 5% cases (acute pneumonia, respiratory failure, septic shock, multiple organ failure)

Recovery: 2 weeks (mild cases); 2-6 weeks (severe cases)

Treatment or vaccine: No vaccines or anti-viral drugs available; only symptoms can be treated

SEASONAL FLU

Onset: Abrupt

Symptoms
- Fever
- Dry cough
- Muscle ache
- Fatigue
- Headache
- Sore throat
- Runny or stuffy nose

Less common symptoms
- Diarrhoea
- Vomiting

Incubation: 1-4 days

Complications: 1% cases (including pneumonia)

Recovery: 1 week (mild cases); 2 weeks (severe cases)

Treatment/vaccine: An annual seasonal flu vaccine is available

COMMON COLD

Onset: Gradual

Symptoms
- Runny or stuffy nose
- Sneezing
- Sore throat

Less common symptoms
- Low grade fever
- Muscle or body ache
- Headache
- Fatigue

Incubation: 2-3 days

Complications: Extremely rare

Recovery: 1 week for most cases; may last as long as 10 days

Treatment/vaccine: No treatment, but doctors advise treating symptoms

WHAT THIS MEANS If you have a stuffy/runny nose or are sneezing, you likely DO NOT to have coronavirus

SEVEN KINDS OF CORONA

Seven strains of corona-virus (CoV) that infect humans have been identified. These cause illness ranging from the common cold to more severe diseases such as Middle East Respiratory Syndrome (MERS-CoV)

Harmless

- Serotype 229E
- Serotype OC43
- Serotype NL63
- Serotype HUK1

These cause symptoms of the common cold, and rarely cause severe pneumonia

Dangerous

These are known to cause more severe disease. These are:

1. **Sars-CoV** which causes severe acute respiratory syndrome (Sars)
2. **Mers-CoV** was that causes Middle East respiratory syndrome (Mers)
3. **Sars-CoV2** that causes coronavirus disease (Covid-19)

The unknowns of Sars-CoV2

Sars-CoV2 is closely related (with 88% identity) to two bat-derived Sars-like coronavirses (bat-SL-CoV-2C45 and bat-SL-CoVZXC21) collected in 2018 in Zhoushan, eastern China

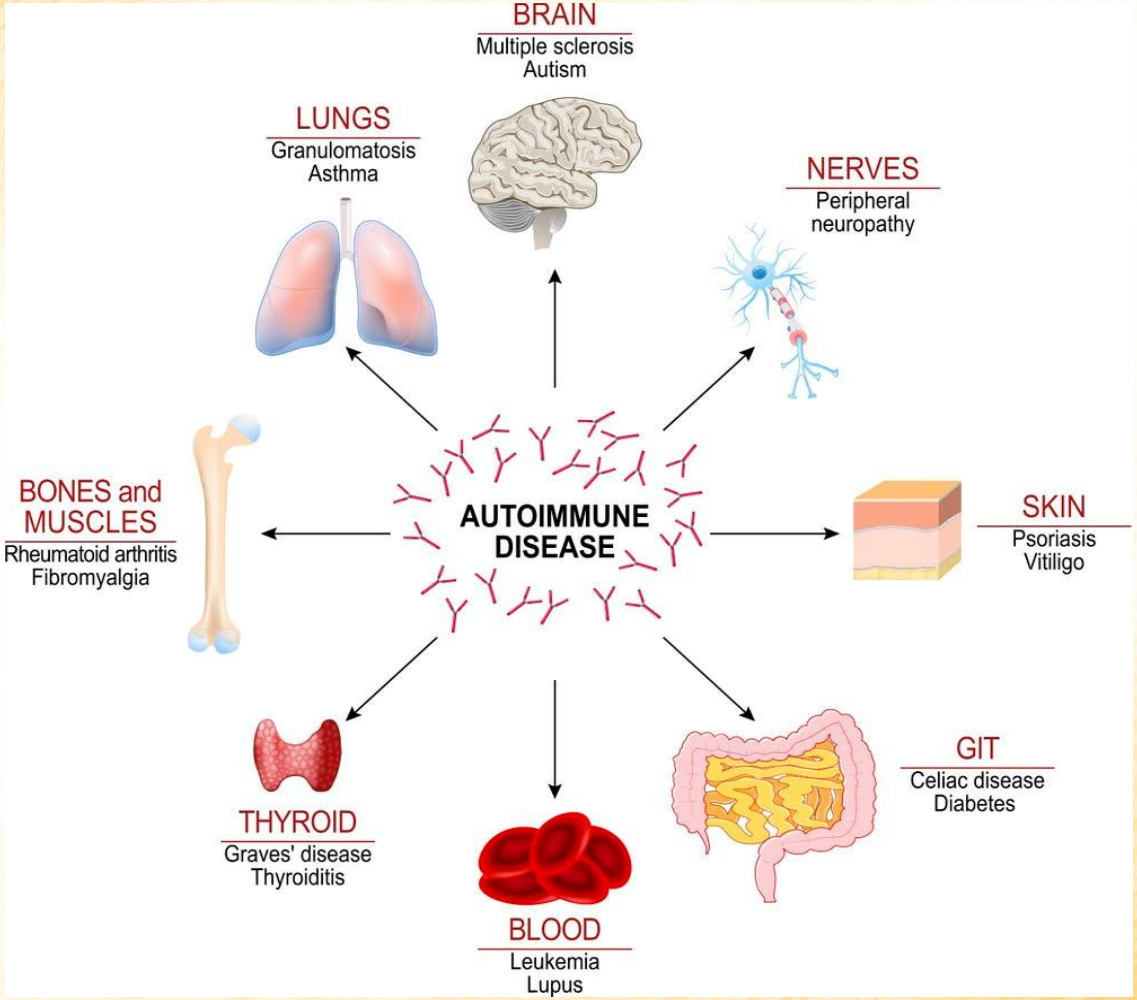
It has 79% genetic affinity with Sars-CoV, 50% with Mers-CoV

The Sars-CoV2 receptor-binding domain structure, which allows a virus to latch on to and enter a cell, is similar to Sars-CoV, despite amino acid variation at some key residues.

Little is known about **Sars-CoV2,** studies on Sars-CoV provide clues to its behaviour and ability to infect

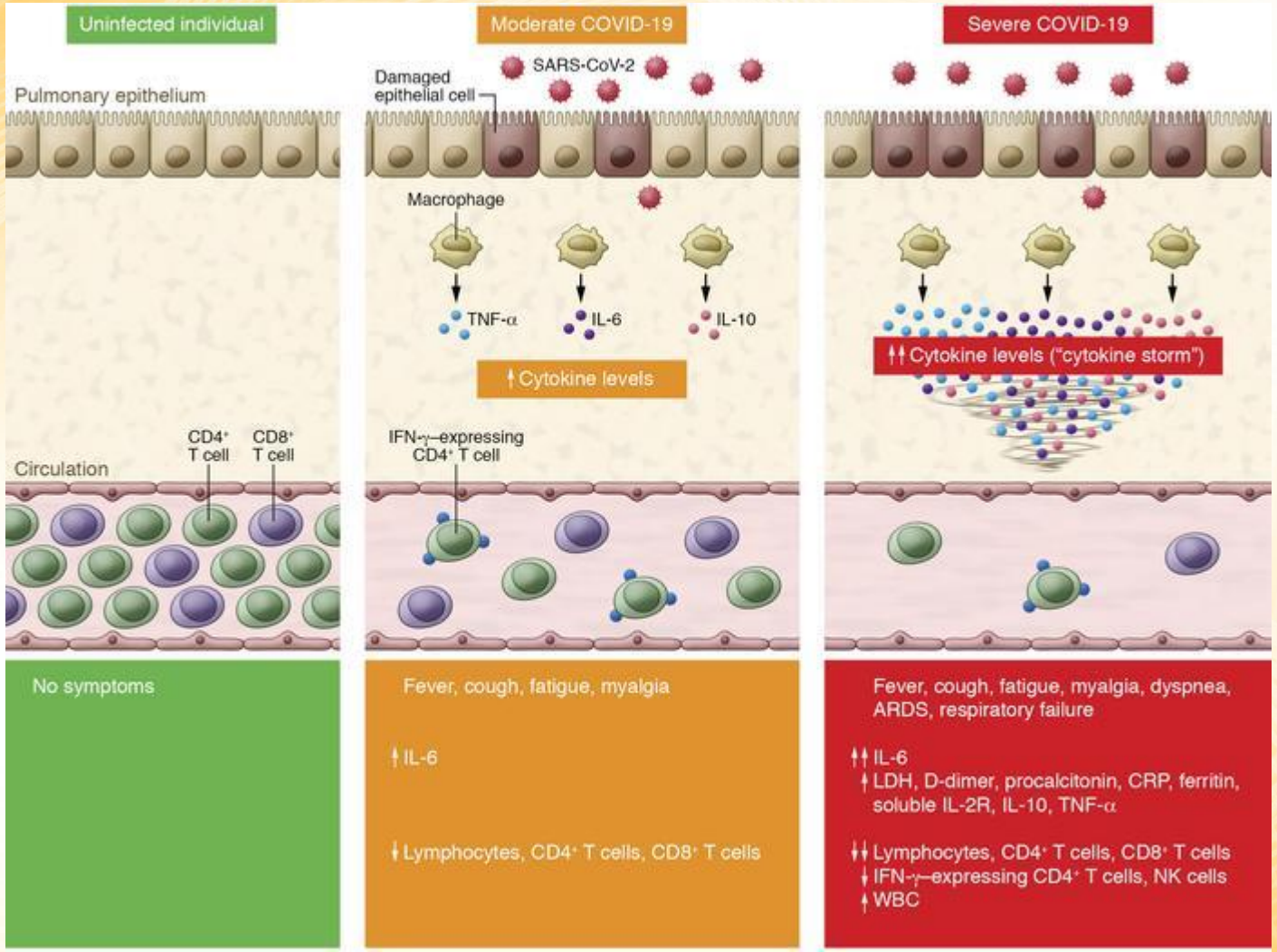
On smooth surfaces such as tables, phones etc, Sars-CoV retains its viability for 5 days at 22-25°C and relative humidity of 40-50%, which is typical for air-conditioned rooms. Though this may vary for Sars-CoV2, experts say this is a good indicator for its behaviour

An Autoimmune-like Antibody Response is Linked with Severe COVID-19



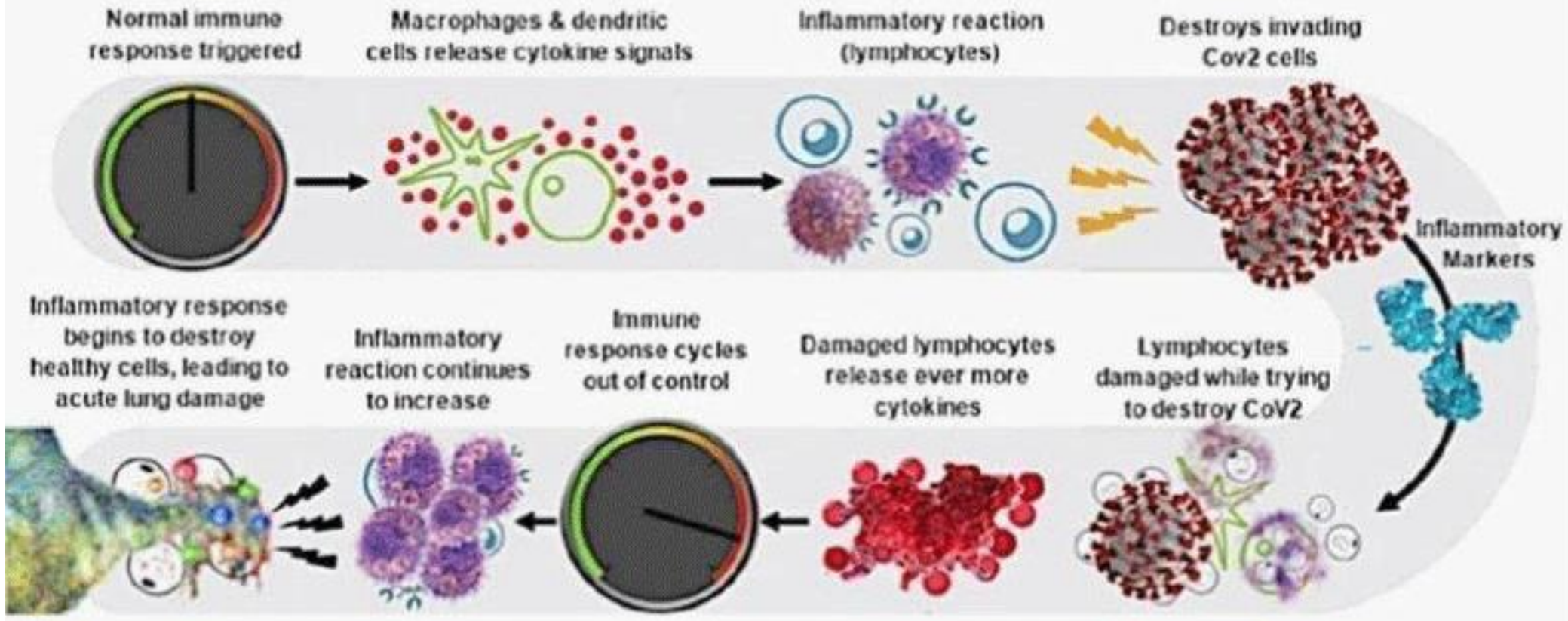
In patients with severe COVID-19 infections, evidence emerged that the inflammatory process used to fight the SARS-CoV-2 virus were, in addition to fighting the virus, potentially responsible for harming the patient. Clinical studies described so-called cytokine storms in which the immune system produced an overwhelming quantity of inflammatory molecules, antibodies triggering dangerous blood clots and inflammation of multiple organ systems, including blood vessels. All these were warning signs that in some patients, immune responses to the SARS-CoV-2 virus, which causes COVID-19, may have tipped from healing to destructive.

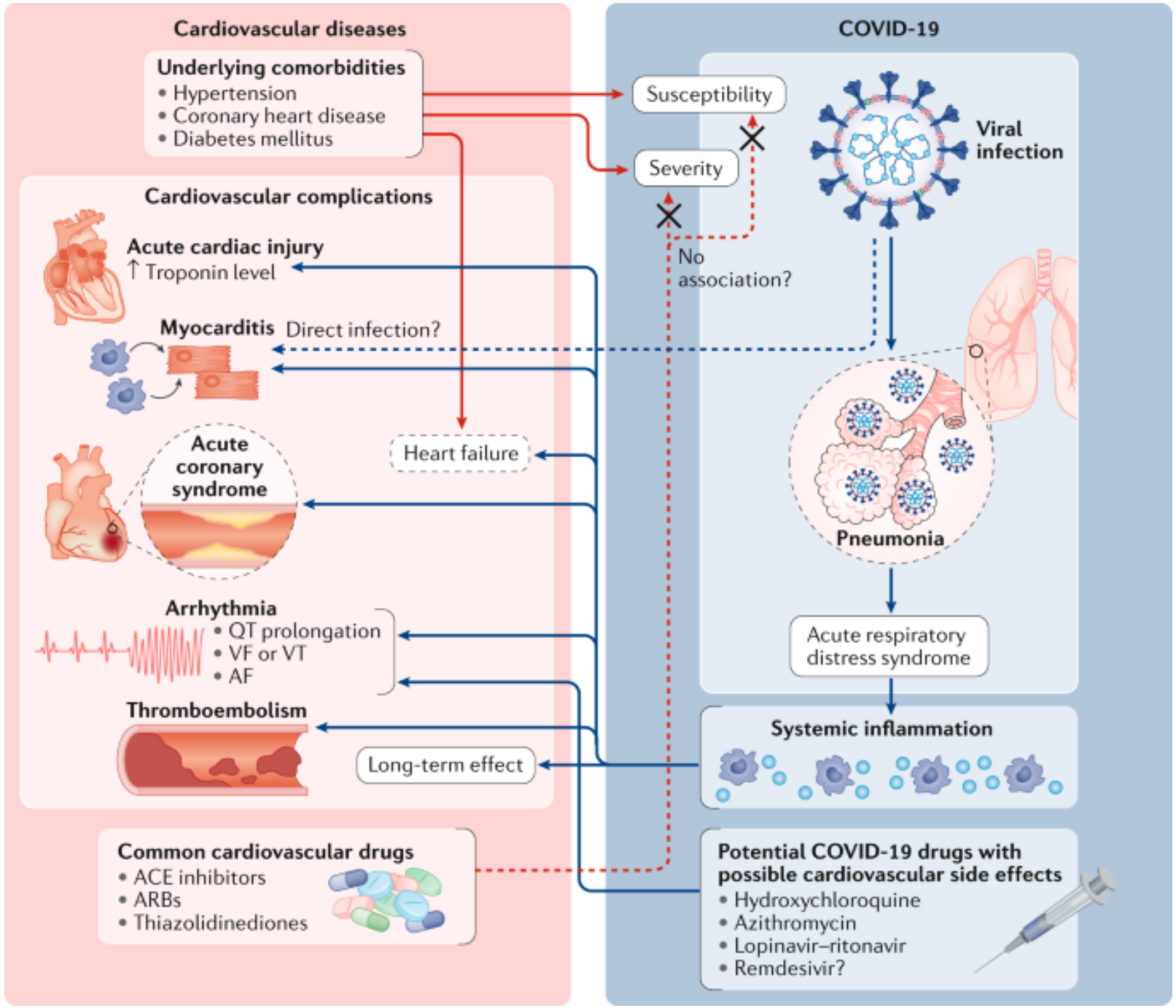
Cytokine Storm

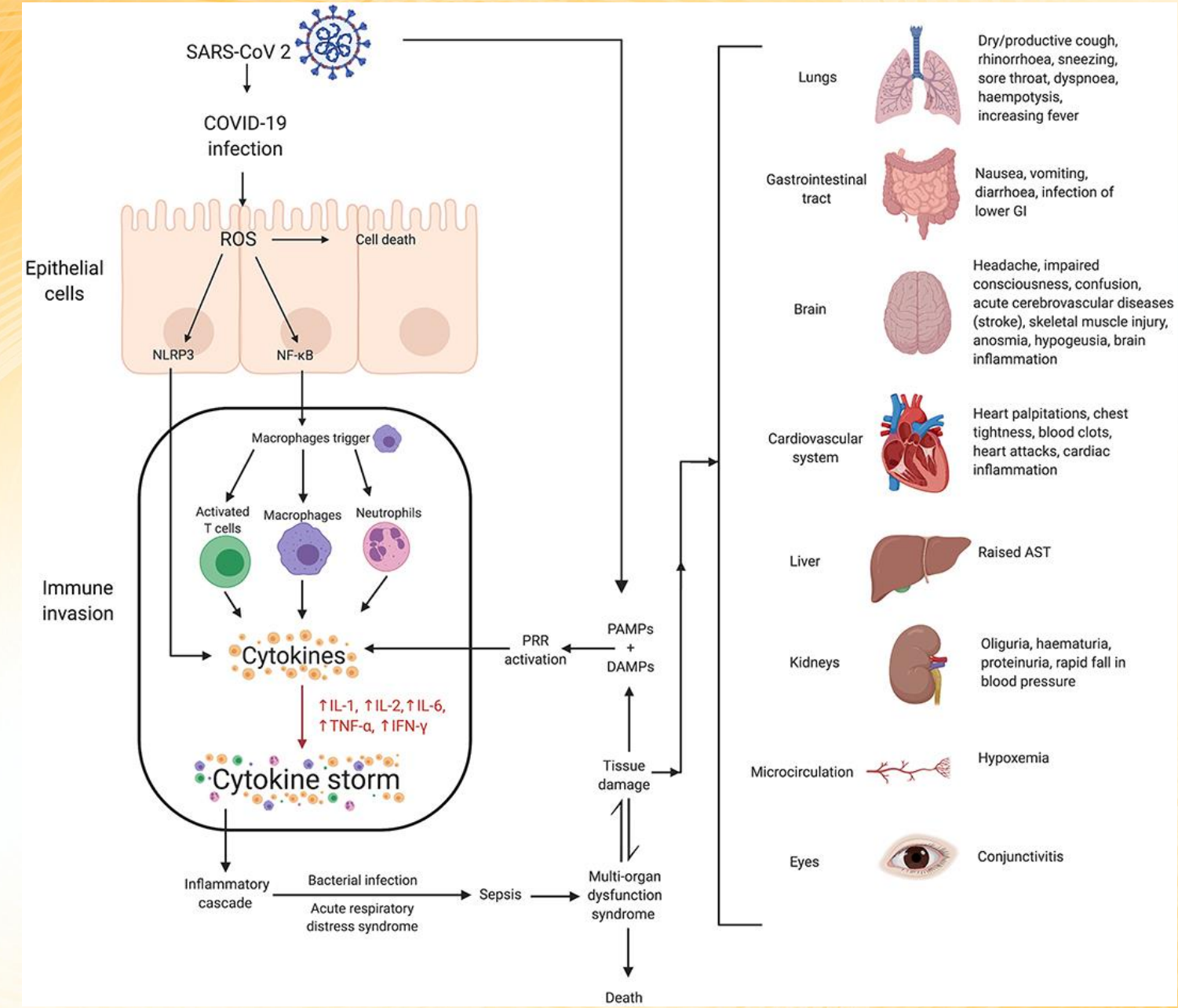


Cytokine Storms

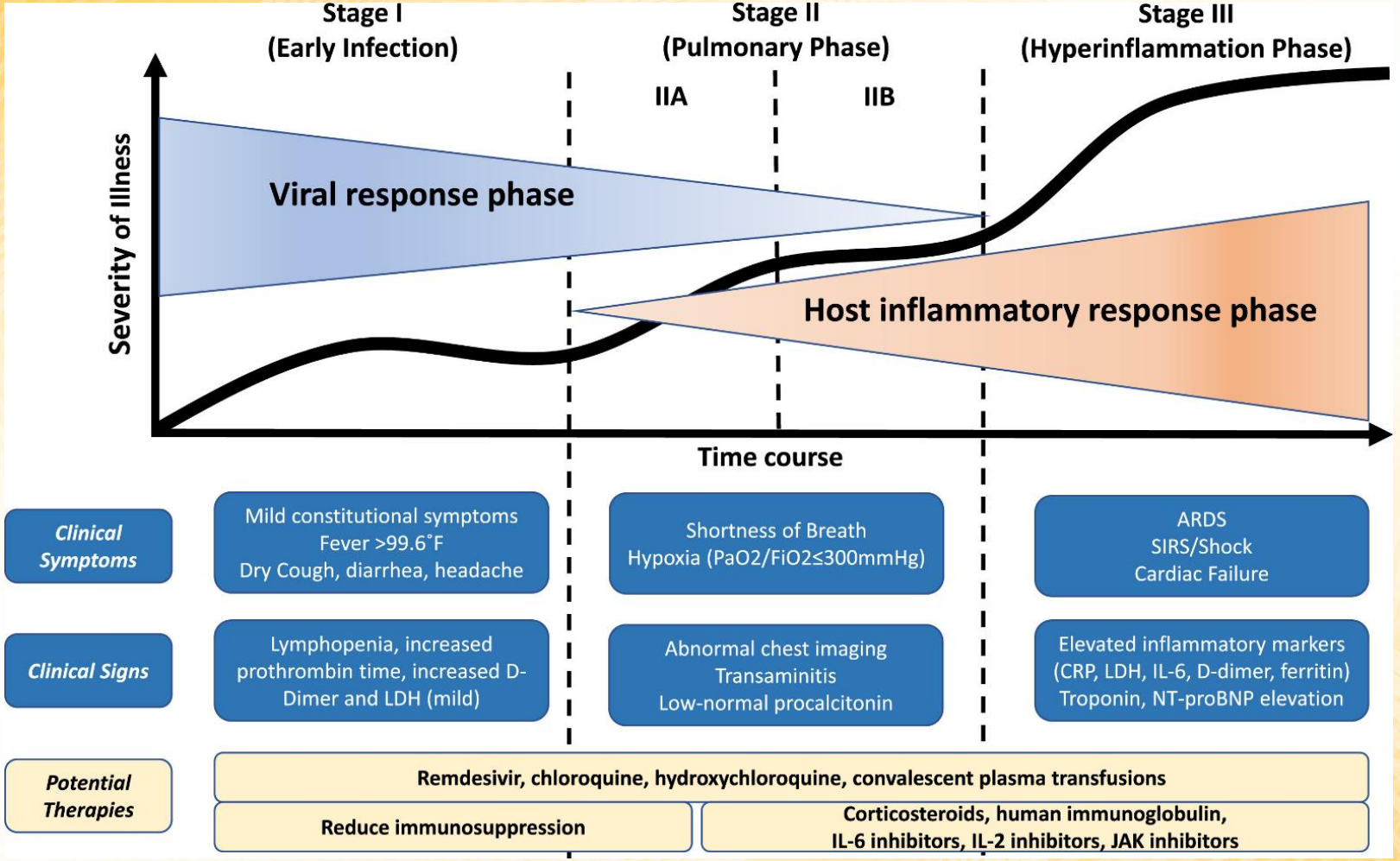
The majority of severe cases and deaths from COVID-19 result from runaway inflammatory responses within the patient's own immune systems, causing a cytokine storm that is difficult to interrupt.



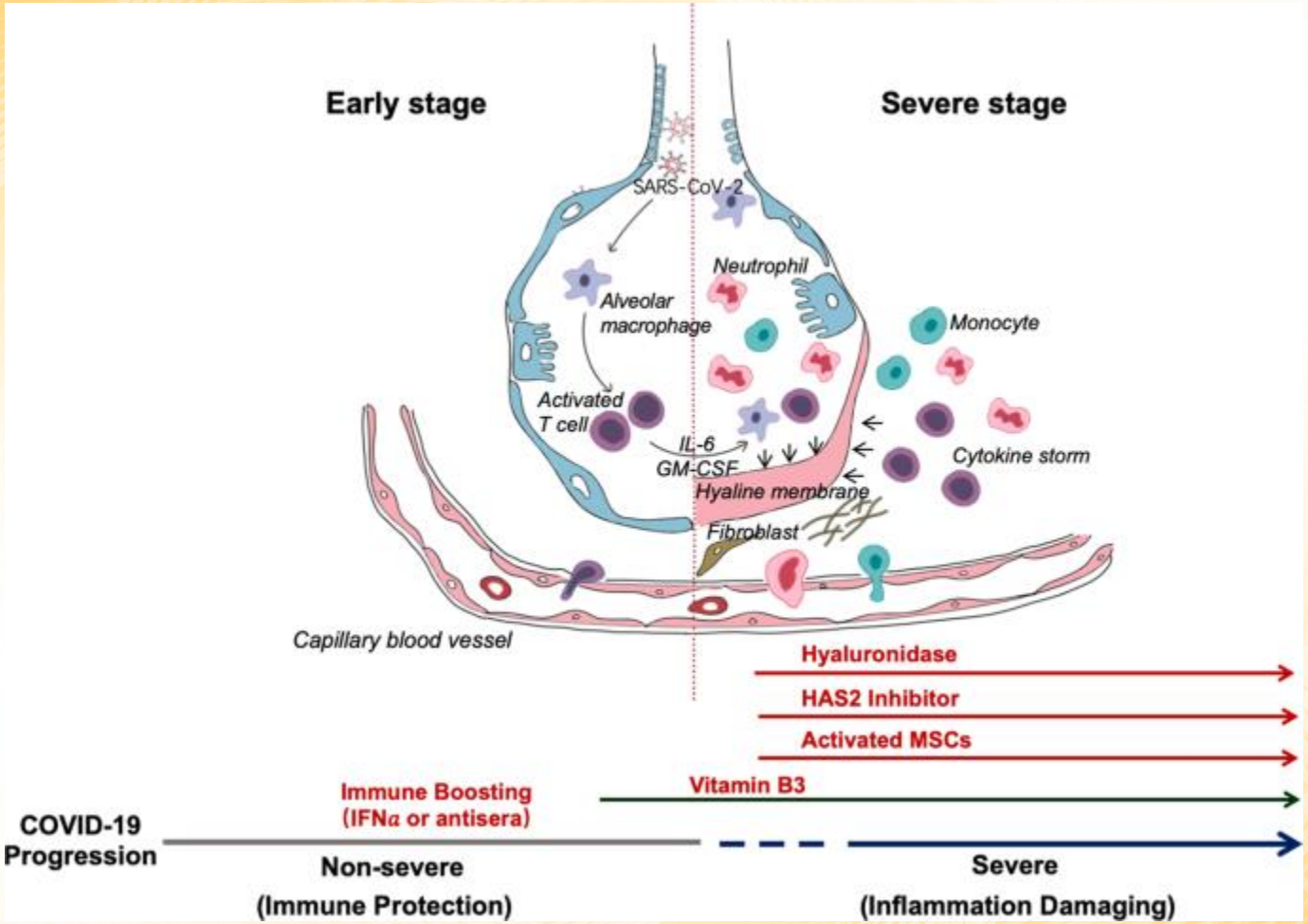

Cardiovascular diseases
Underlying comorbidities
• Hypertension
• Coronary heart disease
• Diabetes mellitus
Cardiovascular complications
Acute cardiac injury
↑ Troponin level
Myocarditis
Direct infection?
Acute coronary syndrome
Heart failure
Arrhythmia
• QT prolongation
• VF or VT
• AF
Thromboembolism
Long-term effect
Common cardiovascular drugs
• ACE inhibitors
• ARBs
• Thiazolidinediones
COVID-19
Susceptibility
Severity
No association?
Viral infection
Pneumonia
Acute respiratory distress syndrome
Systemic inflammation
Potential COVID-19 drugs with possible cardiovascular side effects
• Hydroxychloroquine
• Azithromycin
• Lopinavir–ritonavir
• Remdesivir?


SARS-CoV 2
COVID-19 infection
Epithelial cells
ROS
Cell death
NLRP3
NF-κB
Immune invasion
Macrophages trigger
Activated T cells
Macrophages
Neutrophils
Cytokines
↑IL-1, ↑IL-2, ↑IL-6, ↑TNF-α, ↑IFN-γ
Cytokine storm
PRR activation
PAMPs + DAMPs
Tissue damage
Inflammatory cascade
Bacterial infection
Acute respiratory distress syndrome
Sepsis
Multi-organ dysfunction syndrome
Death
Lungs
Dry/productive cough, rhinorrhoea, sneezing, sore throat, dyspnoea, haempotysis, increasing fever
Gastrointestinal tract
Nausea, vomiting, diarrhoea, infection of lower GI
Brain
Headache, impaired consciousness, confusion, acute cerebrovascular diseases (stroke), skeletal muscle injury, anosmia, hypogeusia, brain inflammation
Cardiovascular system
Heart palpitations, chest tightness, blood clots, heart attacks, cardiac inflammation
Liver
Raised AST
Kidneys
Oliguria, haematuria, proteinuria, rapid fall in blood pressure
Microcirculation
Hypoxemia
Eyes
Conjunctivitis

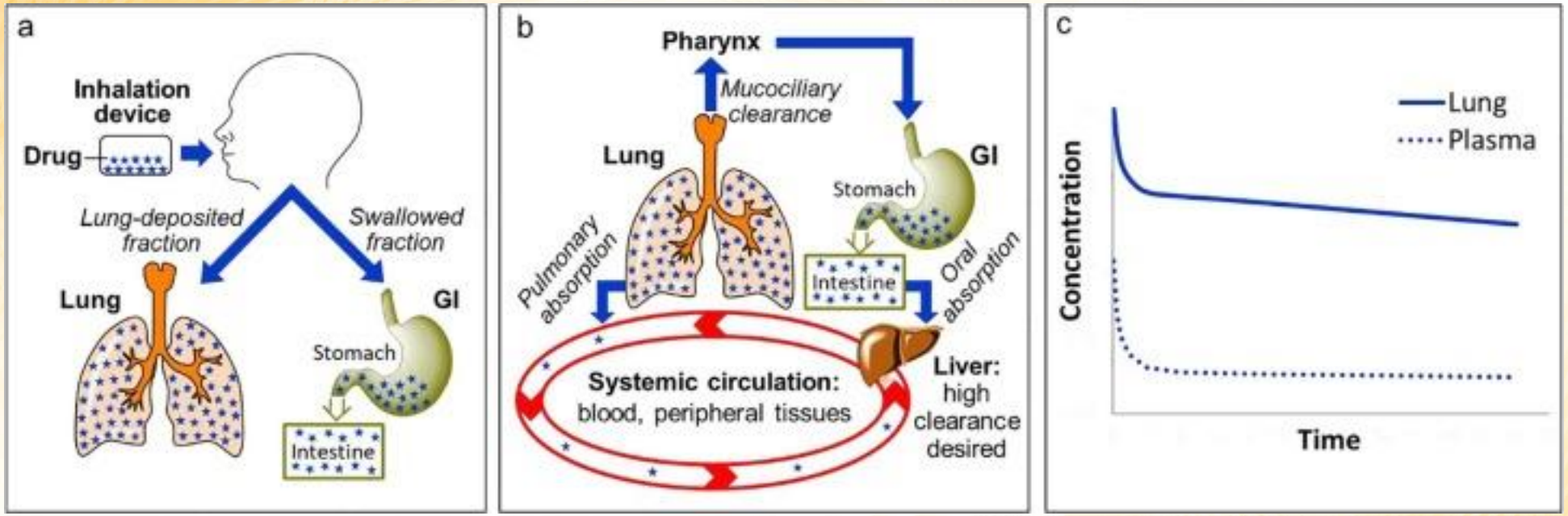
Immune Response: Cytokine Storm



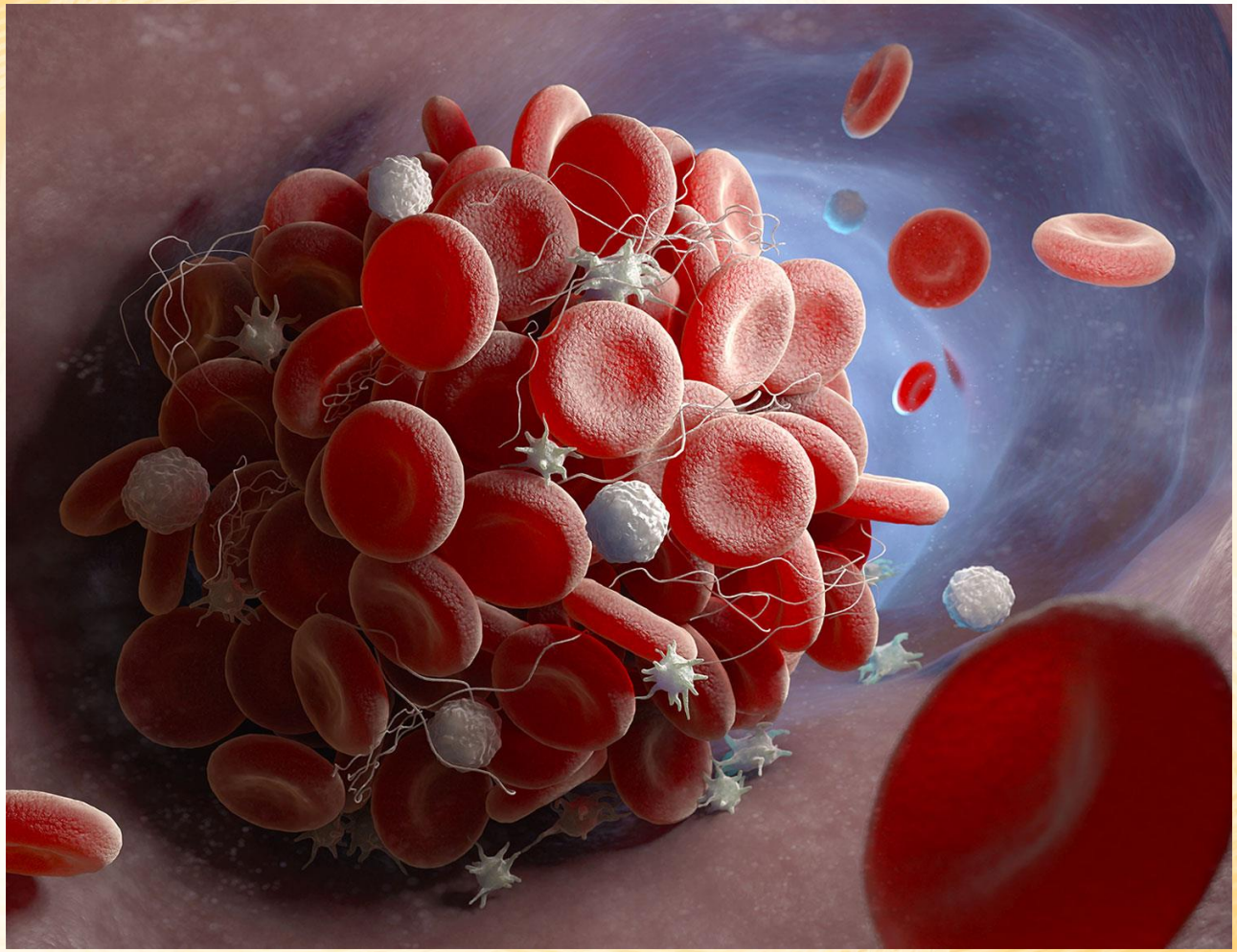
Effects at the Alveolar Level



Treatment JAK Inhibitor



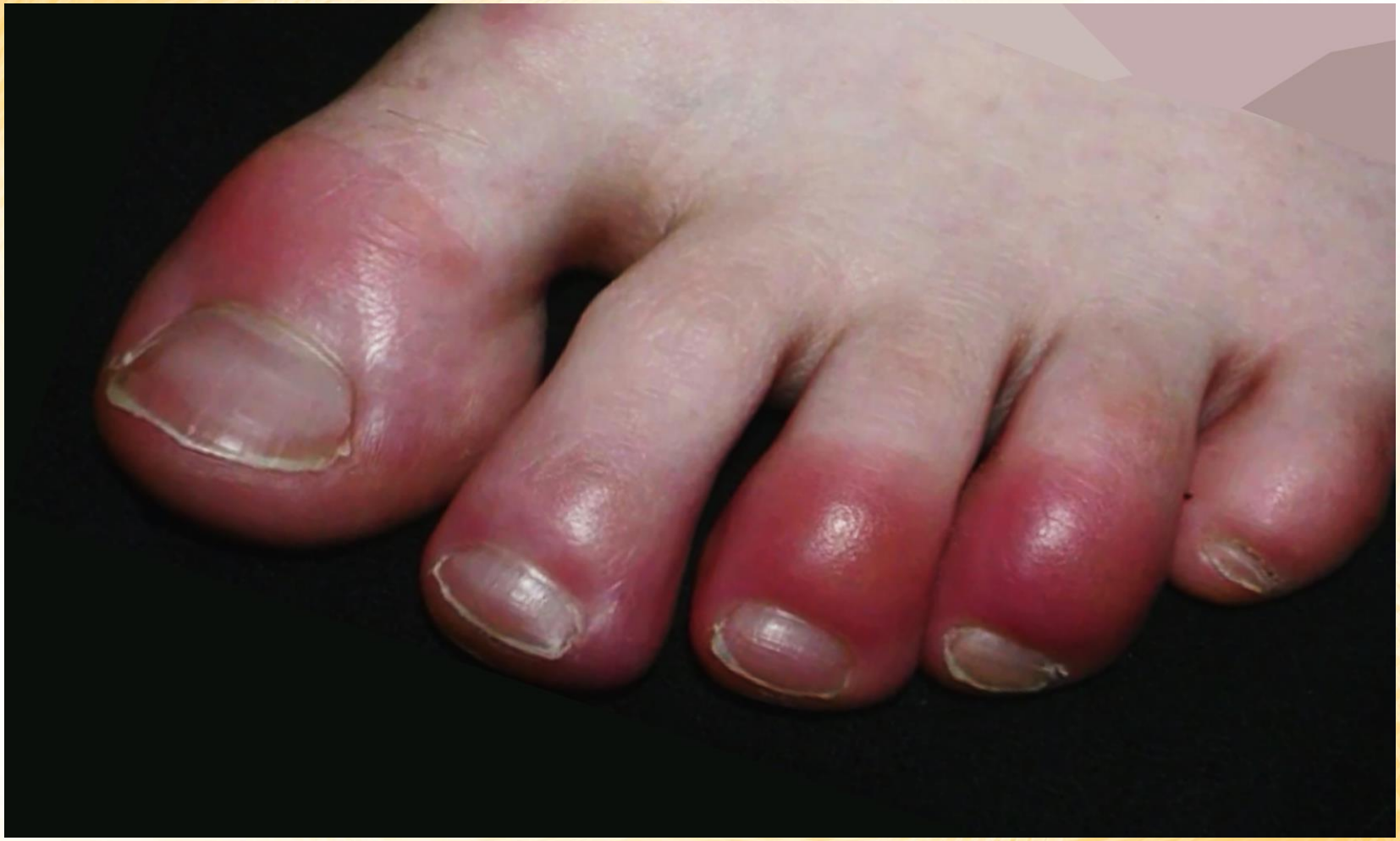
Clotting During COVID



Blood Clotting

- Changes in blood platelets triggered by COVID-19 could contribute to the onset of heart attacks, strokes, and other serious complications
- Inflammatory proteins produced during infection significantly alter the function of platelets, making them "hyperactive" and more prone to form dangerous and potentially deadly blood clots.
- Using differential gene analysis, the researchers found that SARS-CoV-2, the virus that causes COVID-19, appears to trigger genetic changes in platelets.
- In laboratory studies, they studied platelet aggregation, an important component of blood clot formation, and observed COVID-19 platelets aggregated more readily. They also noted that these changes significantly altered how platelets interacted with the immune system, likely contributing to inflammation of the respiratory tract that may, in turn, result in more severe lung injury.
- Emerging evidence suggests COVID-19 is associated with an increased risk of blood clotting, which can lead to cardiovascular problems and organ failure in some patients, particularly among those with underlying medical problems such as diabetes, obesity, or high blood pressure.

COVID Toes



COVID-19 Is Linked To Rare Recurrent Blood Clots

- Researchers at Rutgers Robert Wood Johnson Medical School are reporting the first instance of COVID-19 triggering a rare recurrence of potentially serious blood clots in people's arms.
- The discovery, published in the journal *Viruses*, improves the understanding of how inflammation caused by COVID-19 can lead to upper extremity blood clots and how best to treat them. The case study is part of a larger Rutgers study of 1,000 hospitalized patients diagnosed with COVID-19 who were admitted and discharged between March and May 2020.

Often, blood clots are preceded by chronic inflammatory conditions exacerbated by immobility, and rarely do they occur in patients who are otherwise healthy and active at baseline."

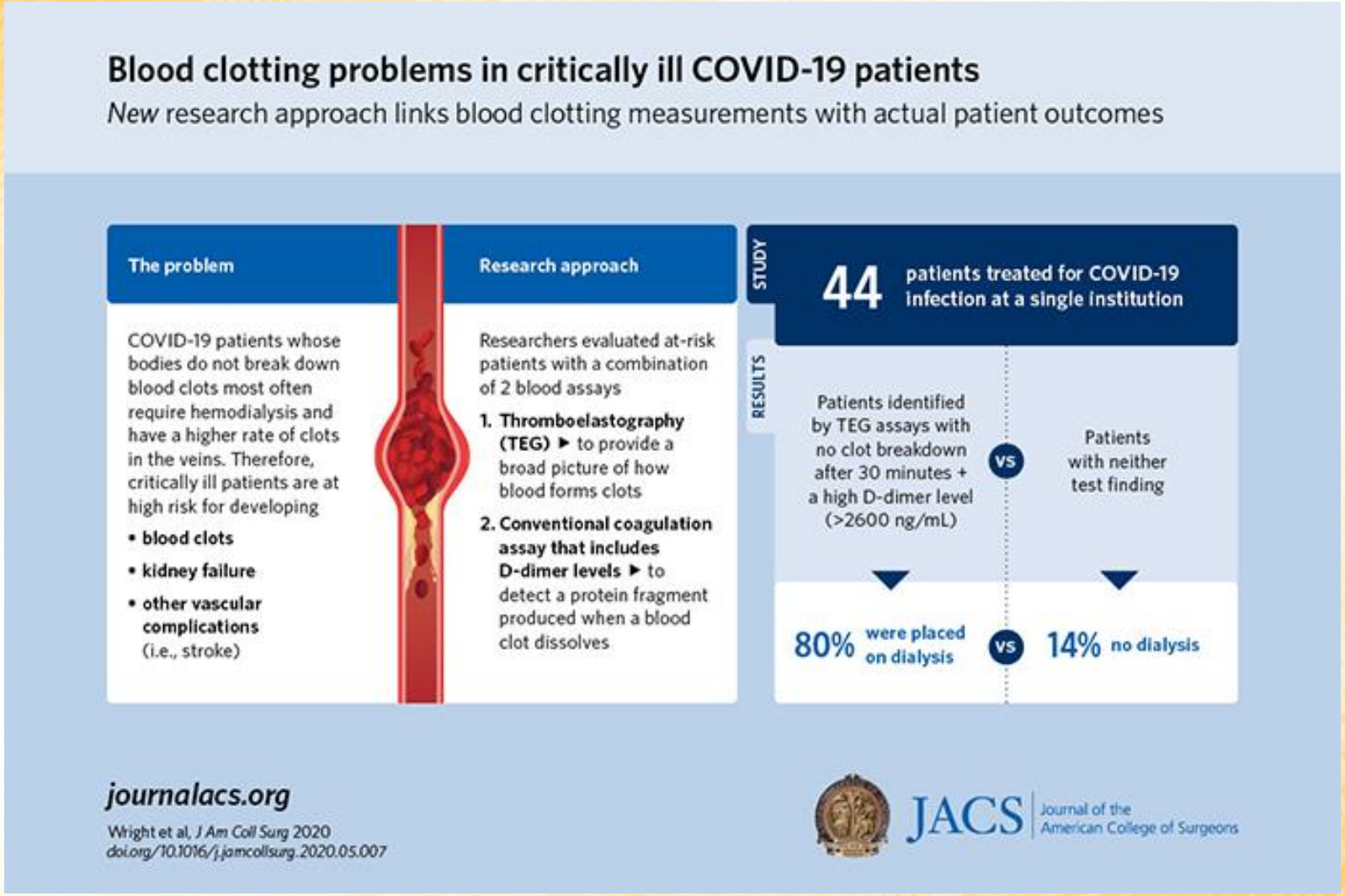
Risk of Deep Vein Thrombosis and Pulmonary Embolism in COVID Patients

- The research, conducted at the Medical University of Vienna in Austria, found that the risk of VTE is considerably higher in COVID-19 than in other comparable serious medical illnesses. Deep vein thrombosis was detected in almost half of the hospitalized COVID-19 patients who had been systematically screened for thrombosis using ultrasound.
- The overall VTE risk in hospitalized patients with COVID-19 is 14%, despite rigorous thromboprophylaxis regimens in most studies. Further, high heterogeneity in VTE rates was found between different patient subgroups. The rate was highest in patients admitted to intensive care units, with 23% of patients suffering VTE. Patients admitted to general wards suffered VTE in 8% of the cases. These findings underline the high risk of VTE in COVID-19 patients.

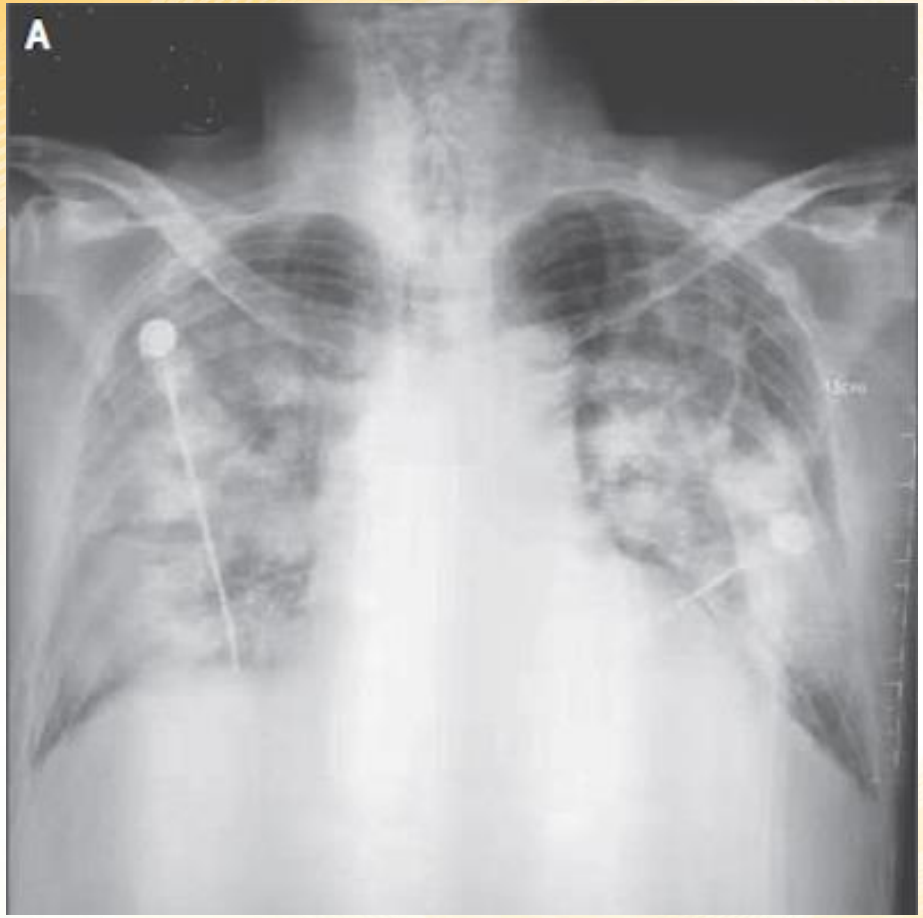
COVID-19 Frequently Causes Neurological Injuries

- Without directly invading the brain or nerves, the virus responsible for COVID-19 causes potentially damaging neurological injuries in about one in seven infected. These injuries range from temporary confusion due to low body-oxygen levels, to stroke and seizures in the most serious cases.
- Led by researchers at NYU Grossman School of Medicine, the study showed no cases of brain or nerve inflammation (meningitis or encephalitis), indicating no immediate invasion of these organs by the pandemic virus, SARS-CoV-2.
- While this should reassure patients, the neurological complications of COVID-19 should be taken seriously because they dramatically raise a patient's risk of dying while still in hospital (by 38 percent), researchers say.
- Such adverse effects also raise a coronavirus patient's likelihood (by 28 percent) of needing long-term or rehabilitation therapy immediately after their stay in hospital
- Half of those neurologically affected were over the age of 71, which researchers say is significantly older than the other 3,885 patients with COVID-19 (at a media age of 63) who did not experience brain dysfunction. Most were men (66 percent) and white (63 percent). Frontera notes that the study results do suggest that Blacks are not at greater risk of neurological complications than other COVID-19 patients, which is "welcome news," given that Blacks are widely known to be at greater risk of death from coronavirus infection.

Increase Hemodialysis

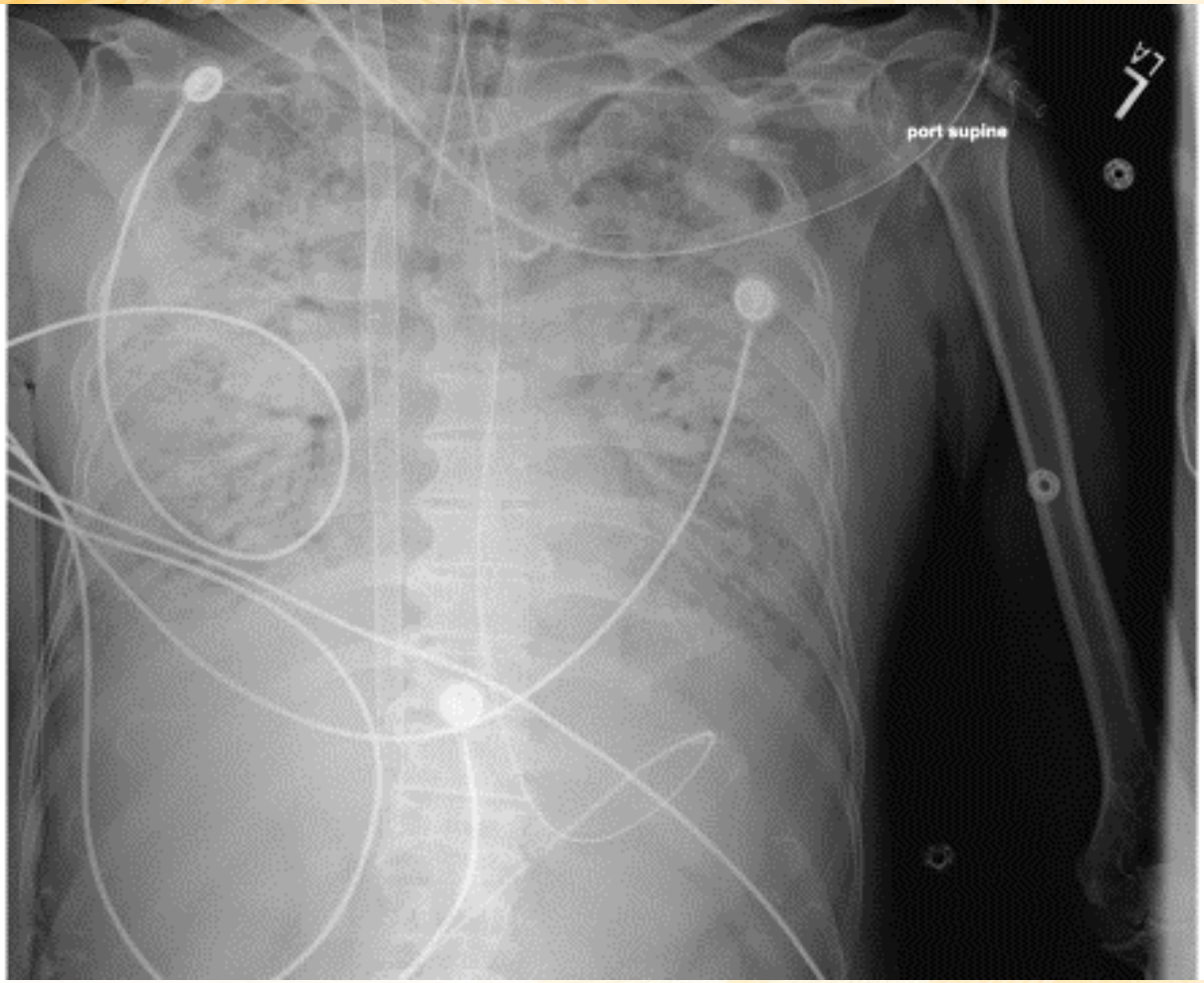


X-ray Findings

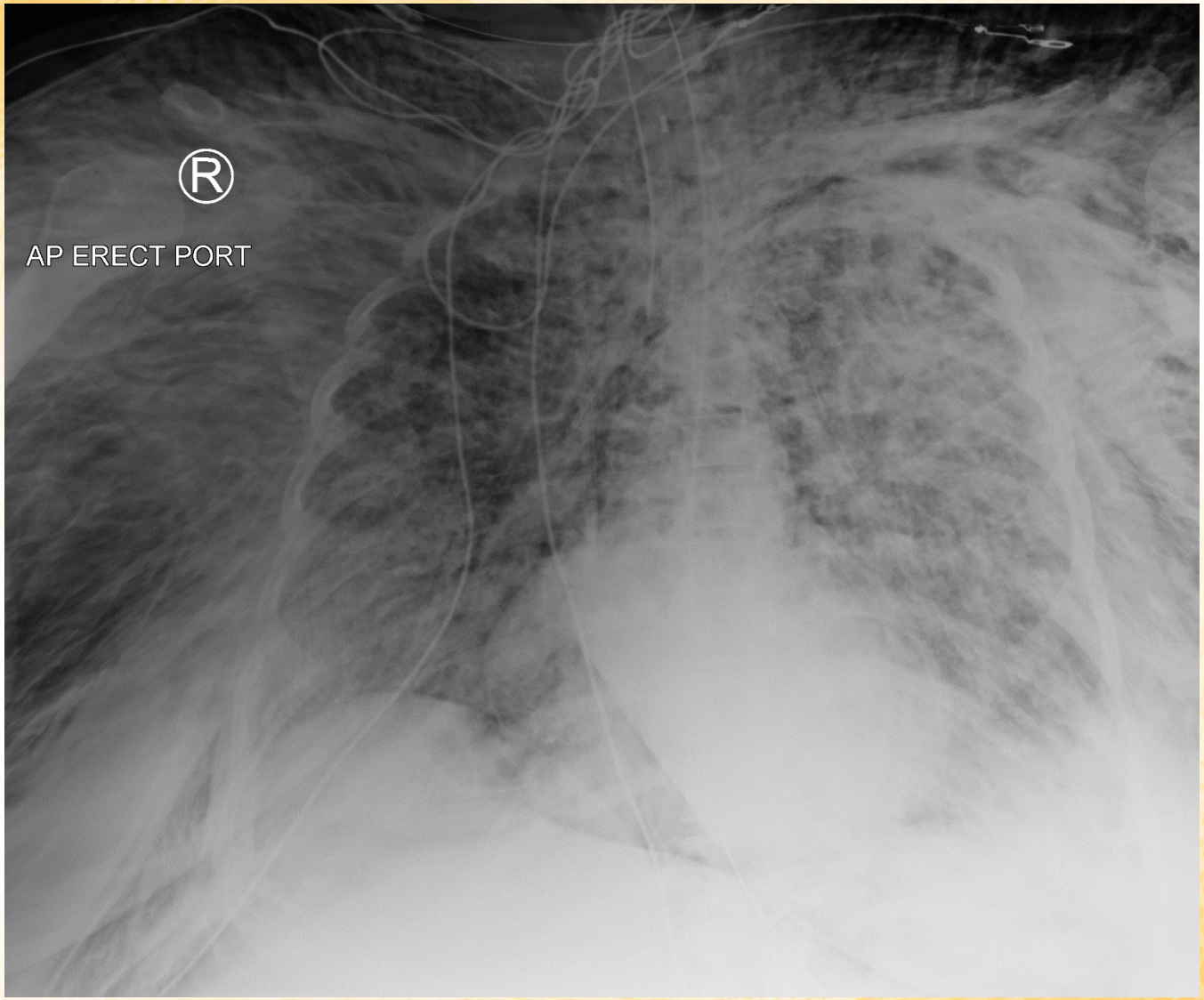


COVD-19
Patient
3-5 days after developing respiratory symptoms

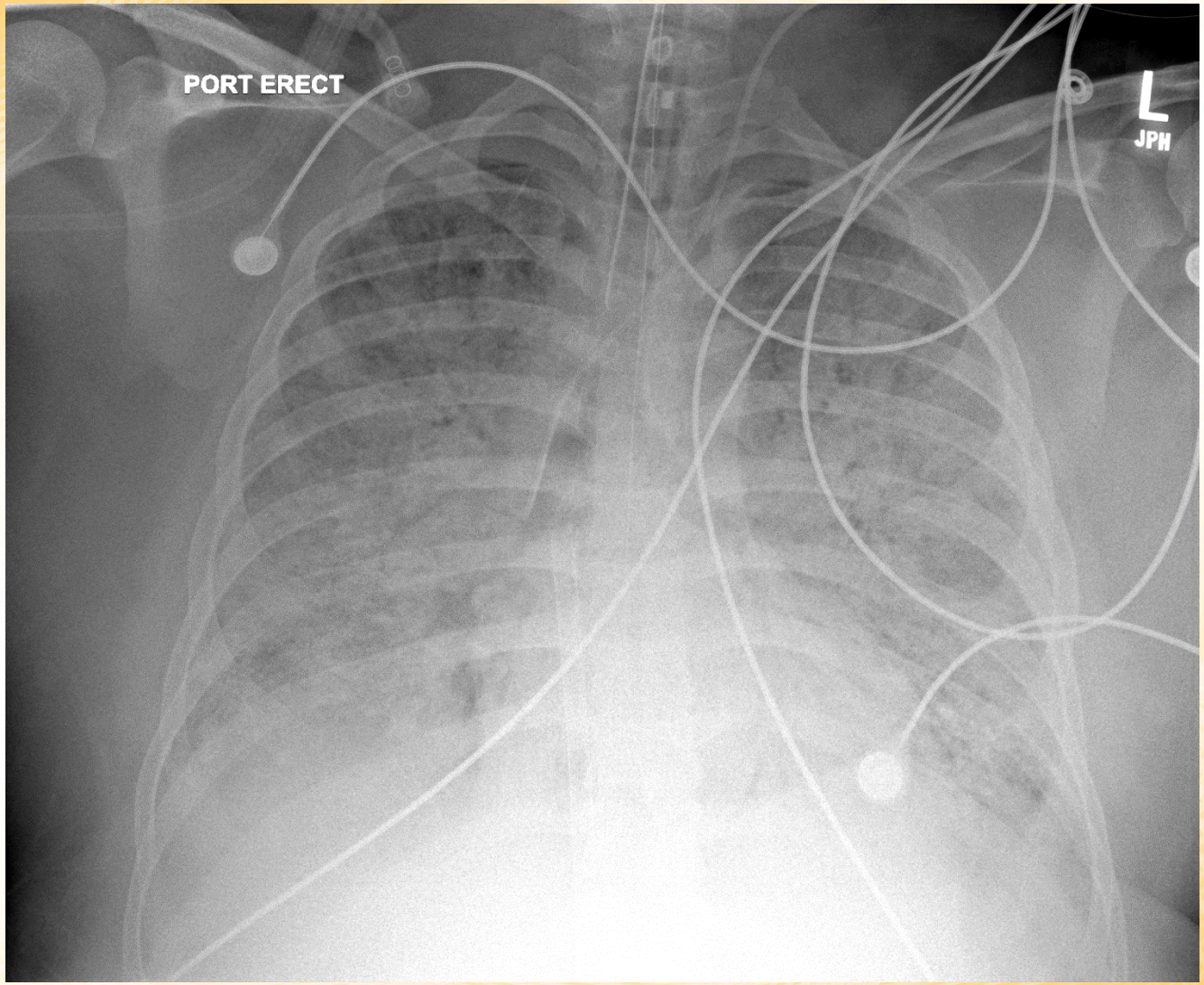
Profound ARDS

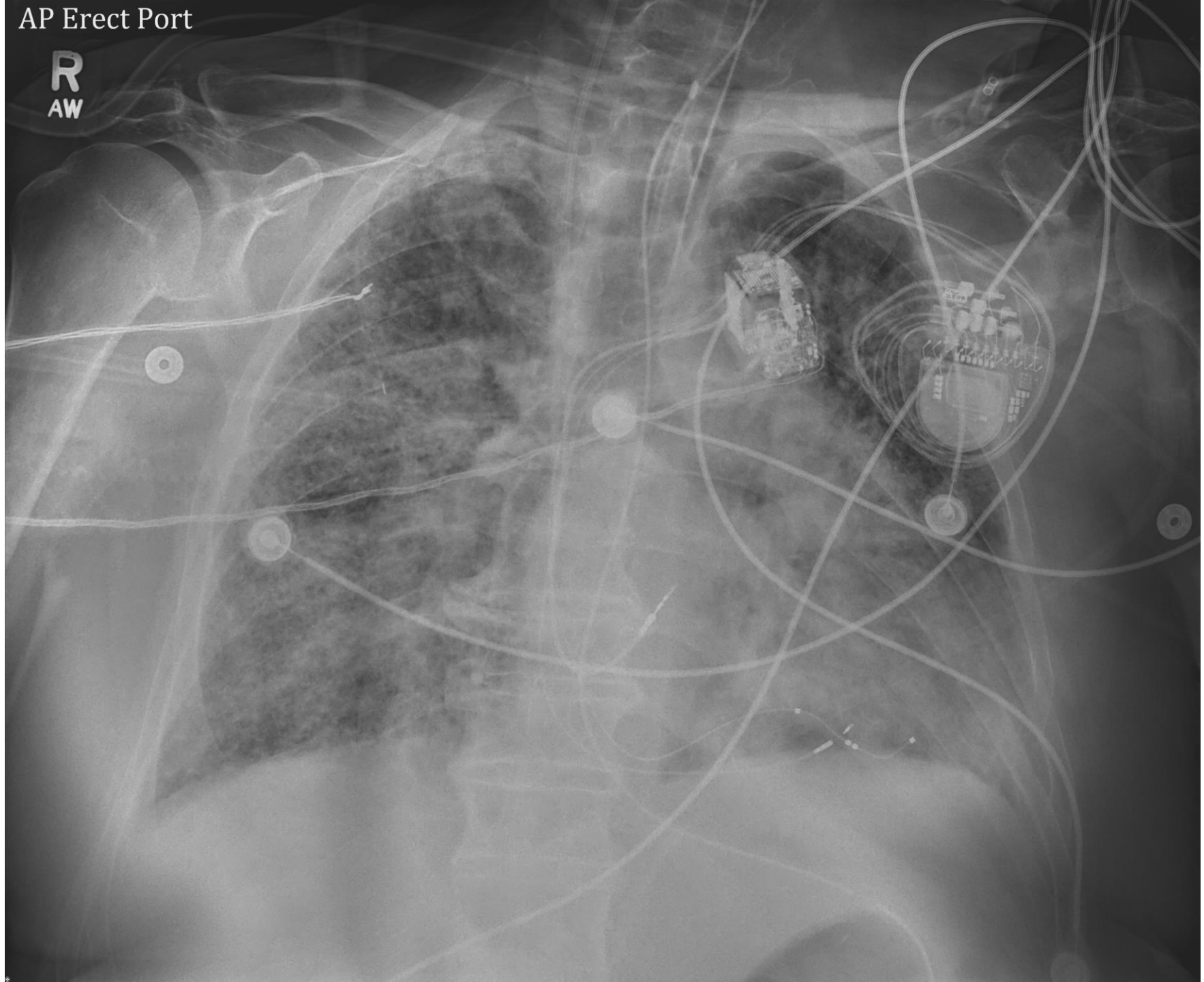


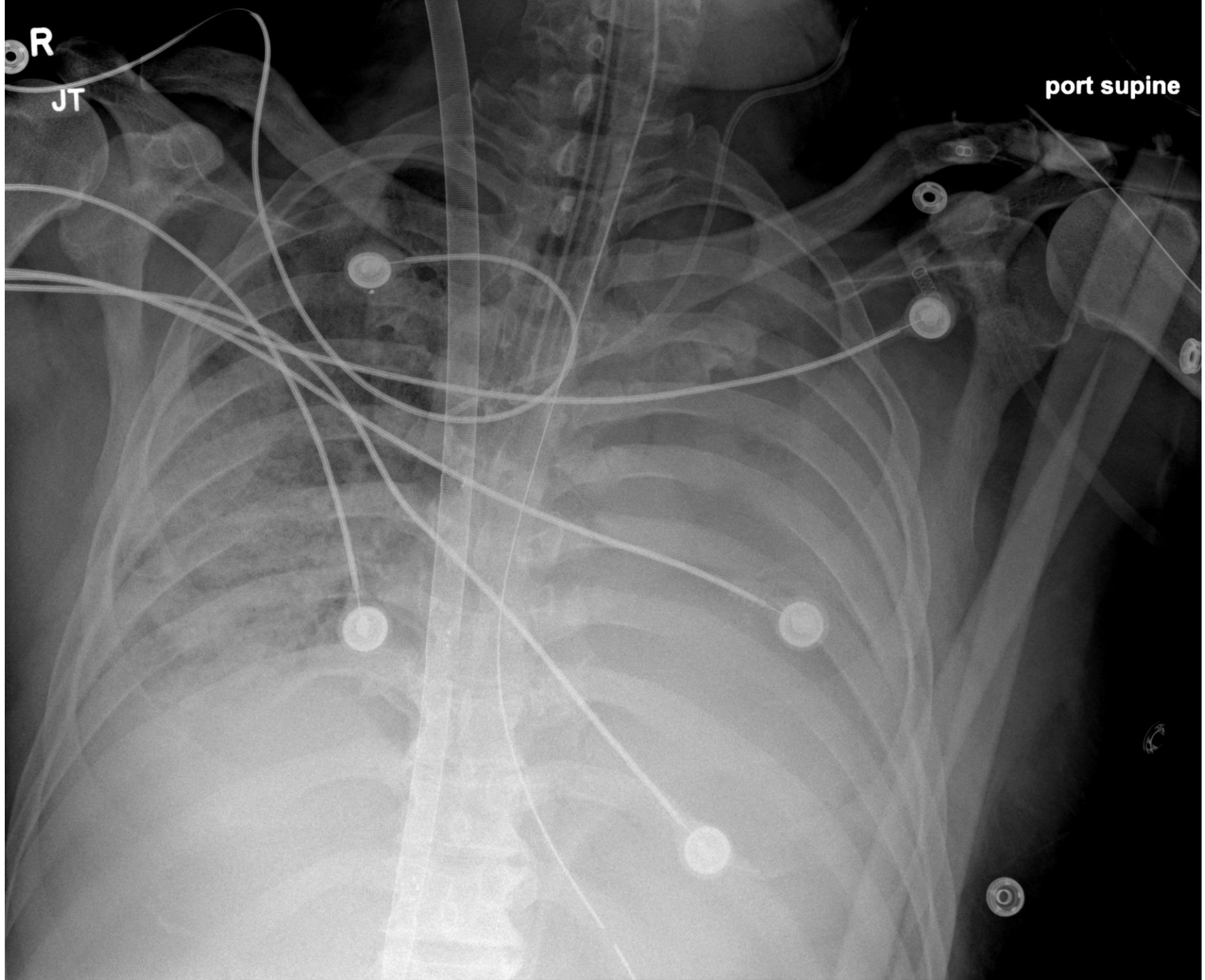
Barotrauma Via HFPV

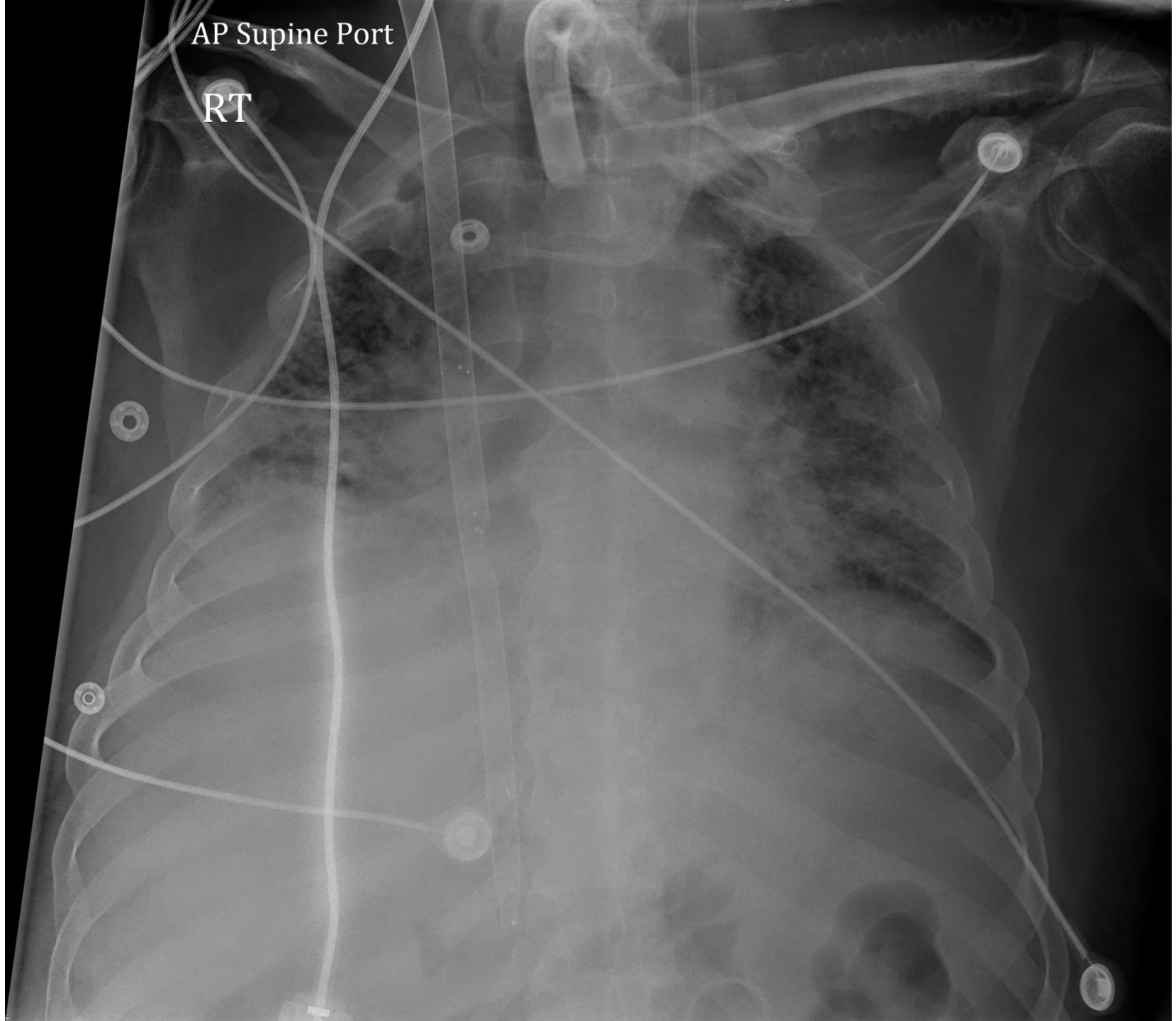


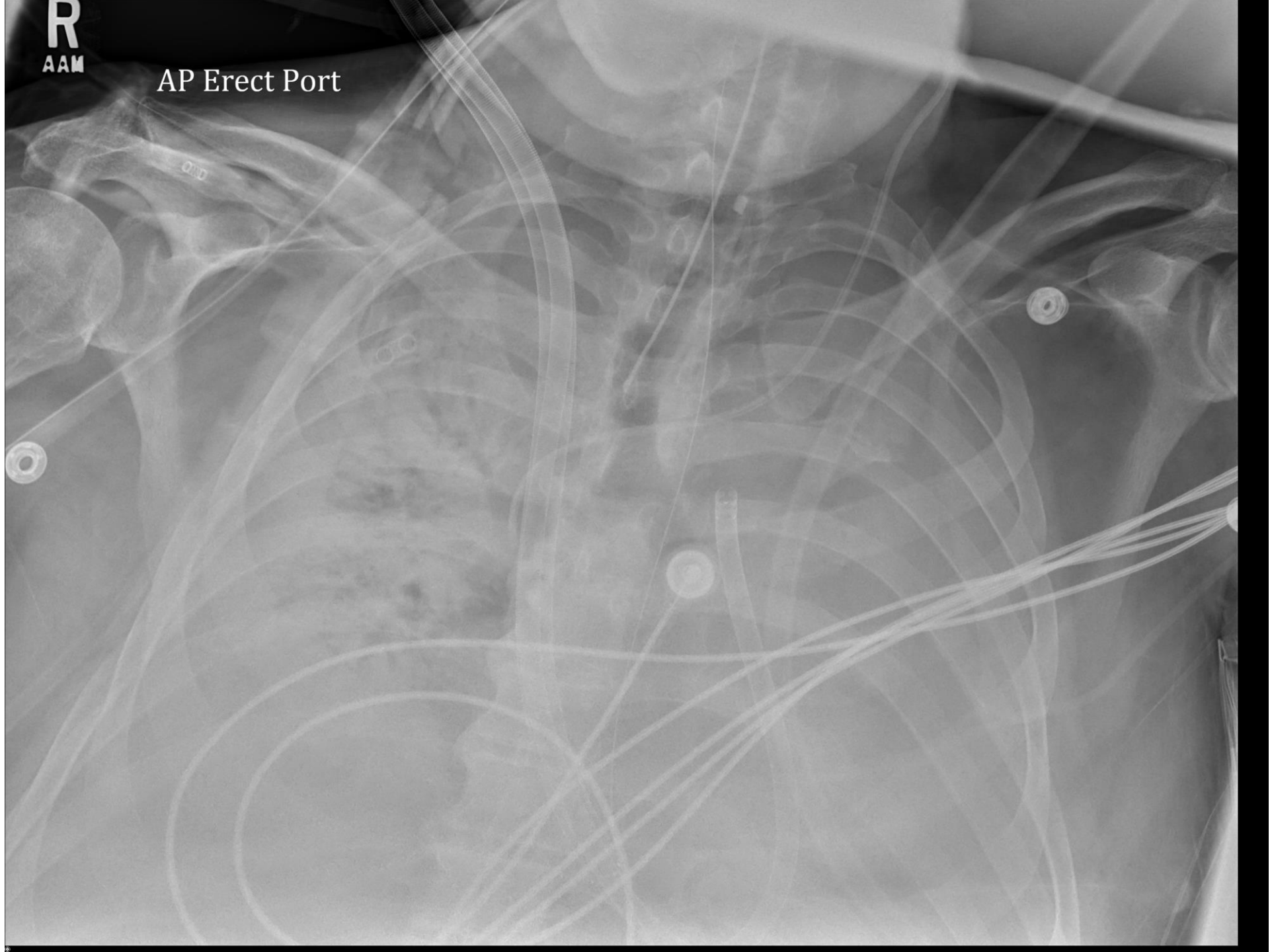
End-stage COVID

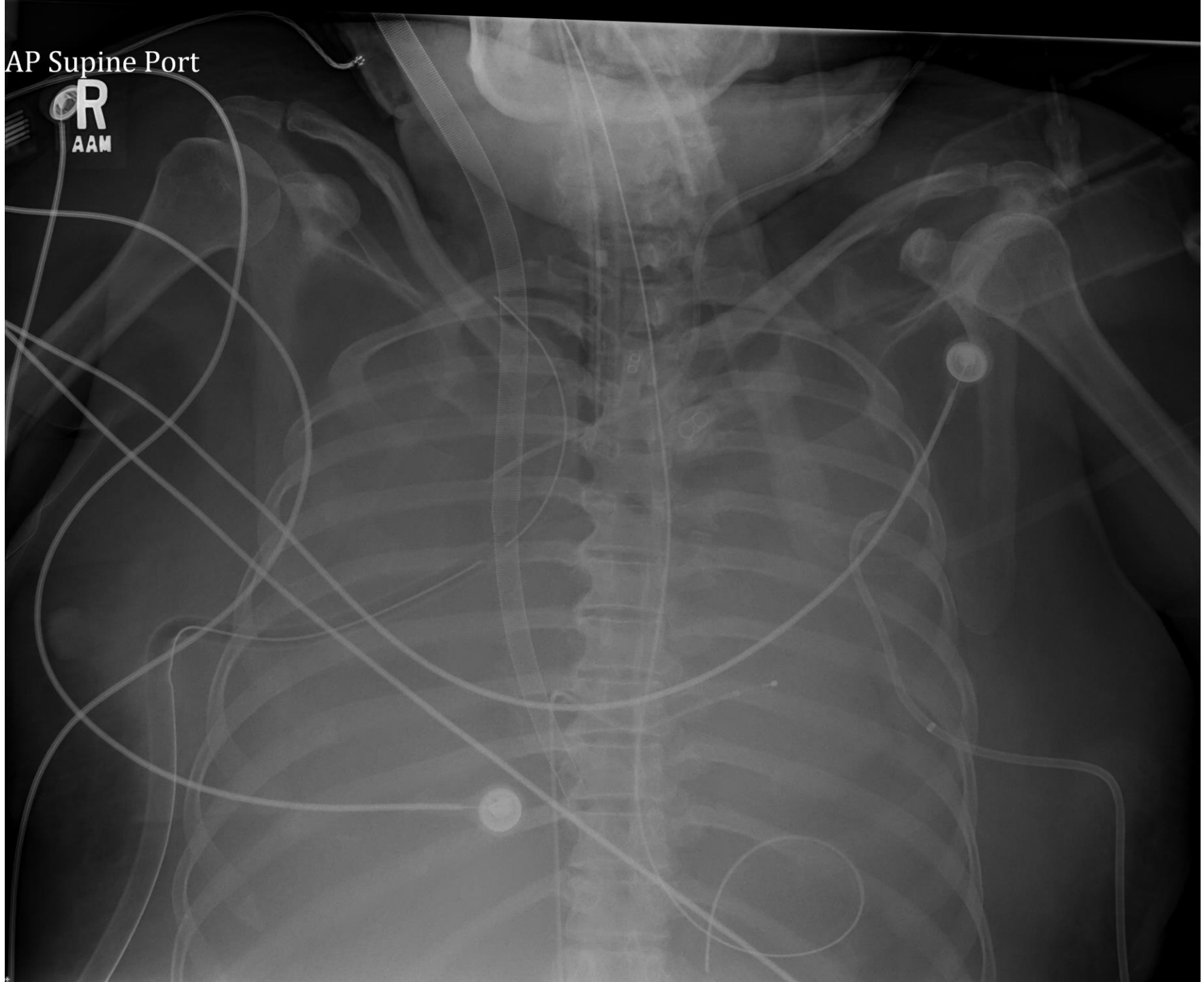



AP Erect Port
R
AW

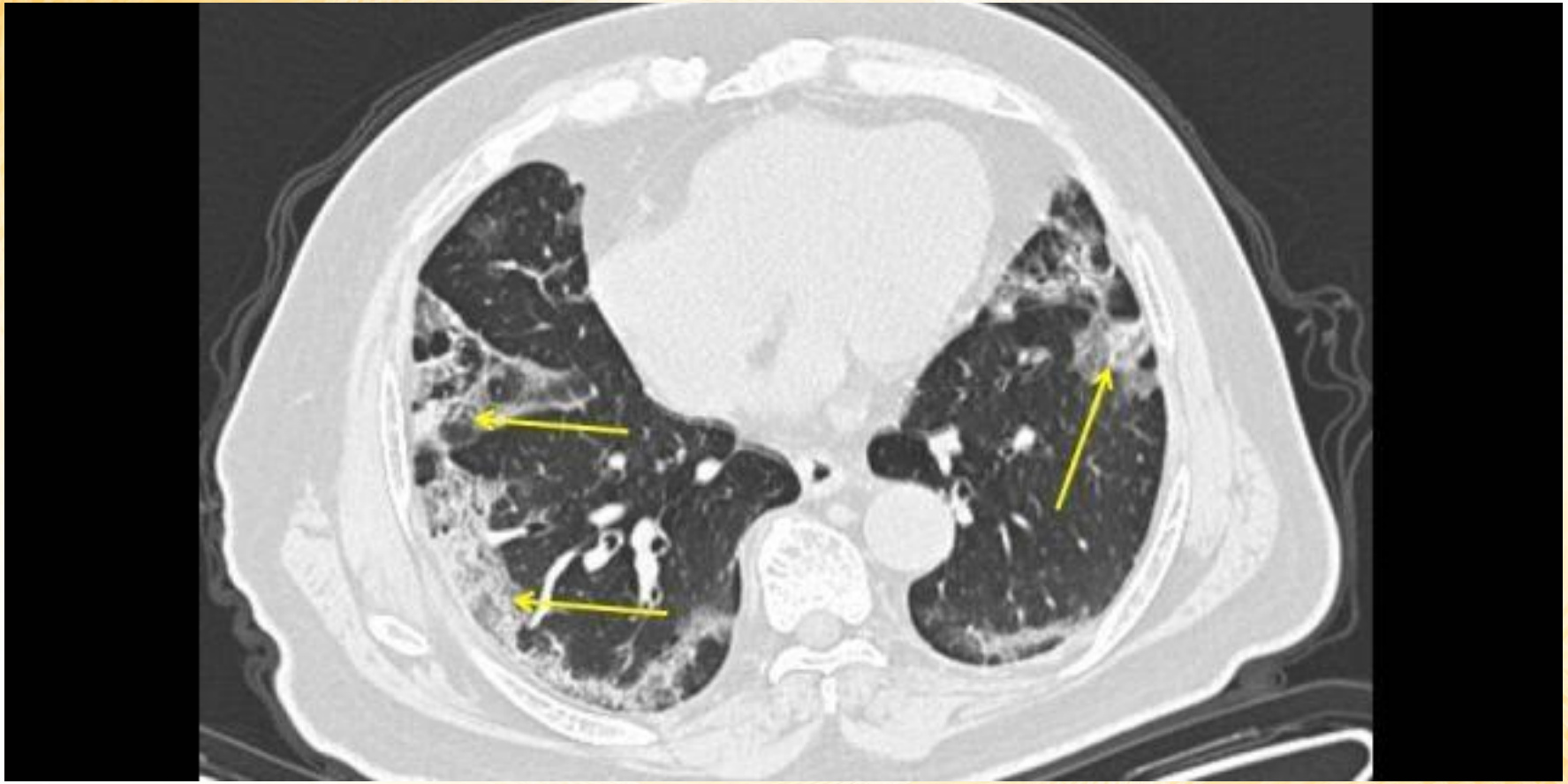

R
JT
port supine


AP Supine Port
RT

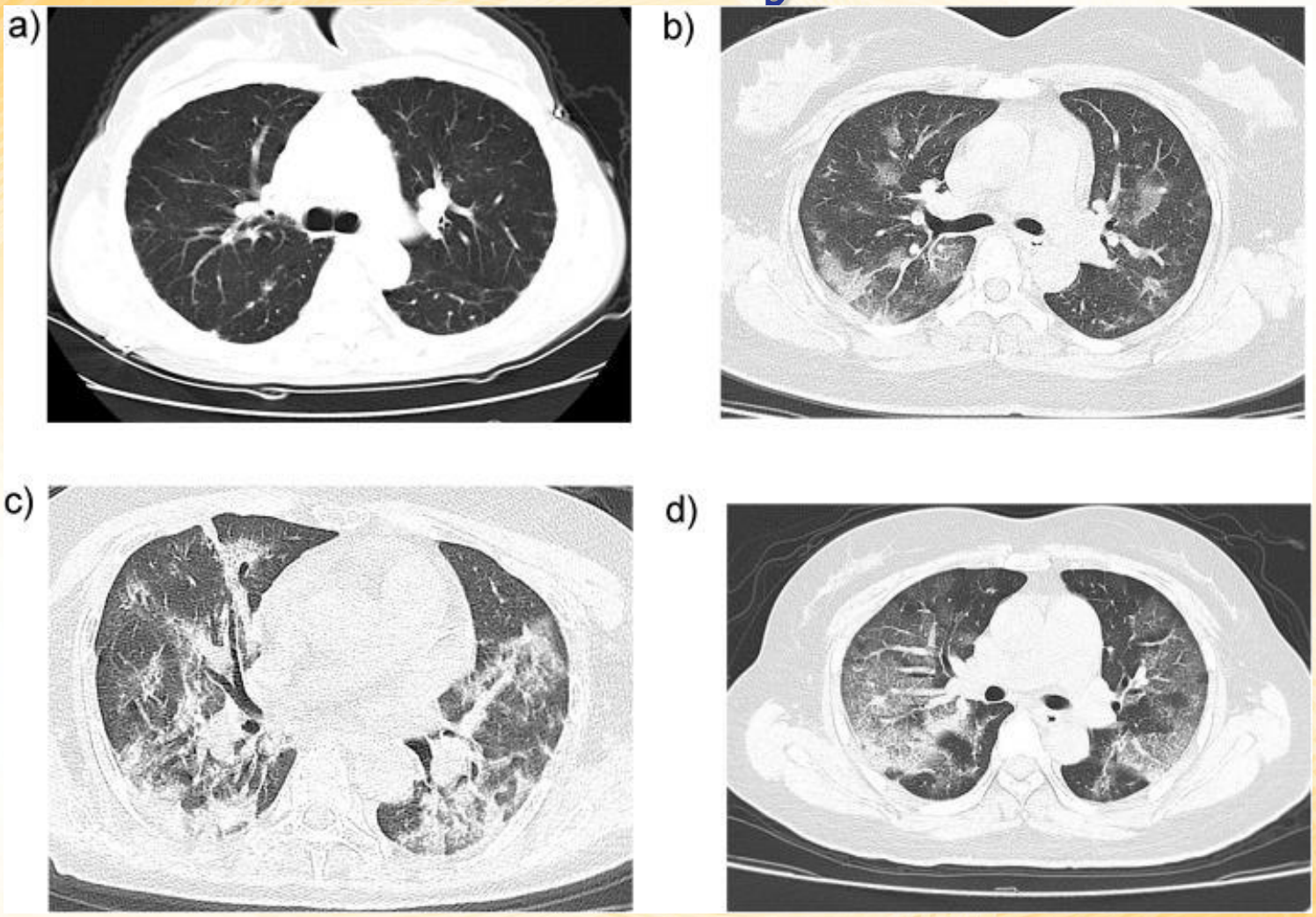

R
AAM
AP Erect Port

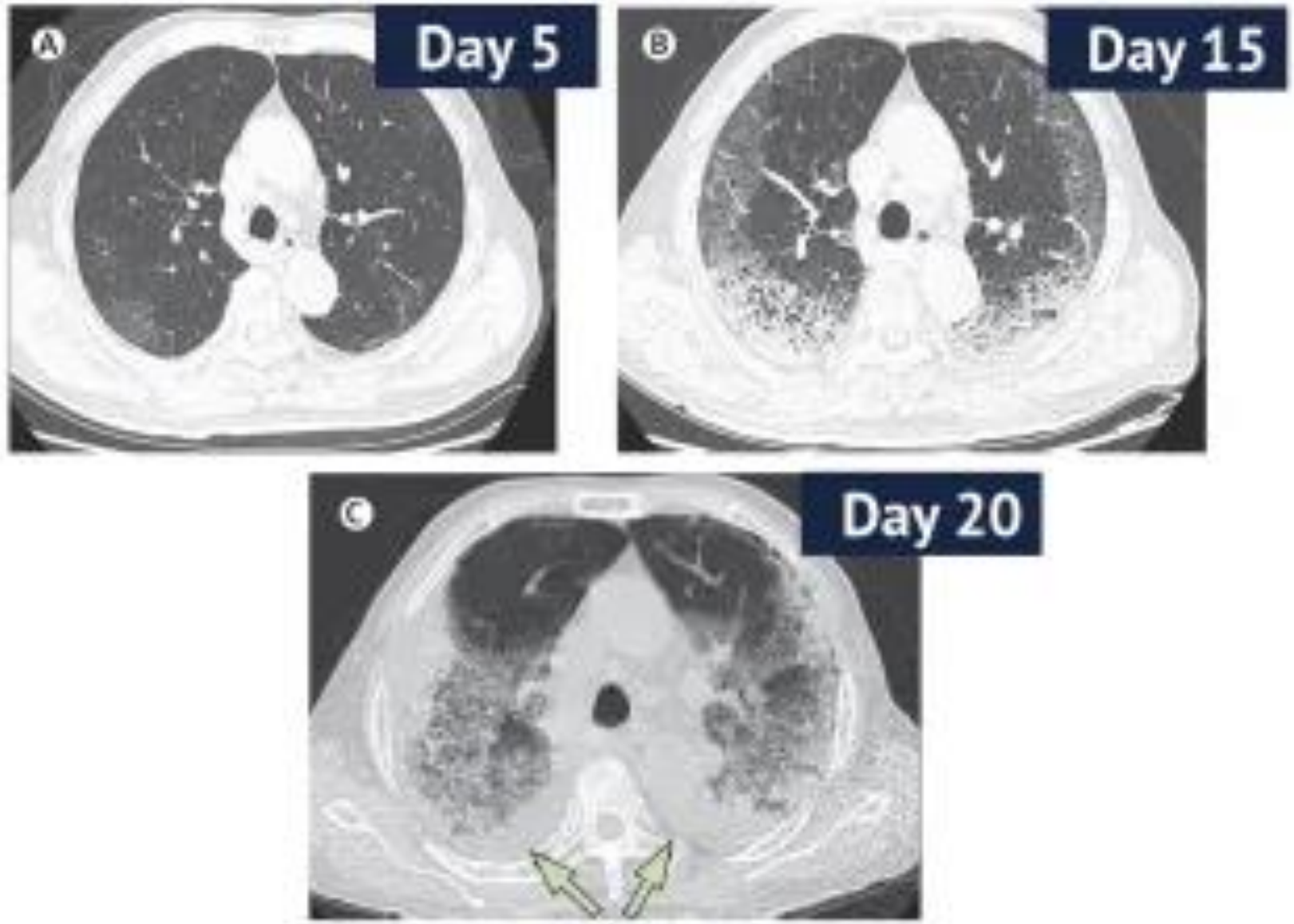

AP Supine Port
R
AAM

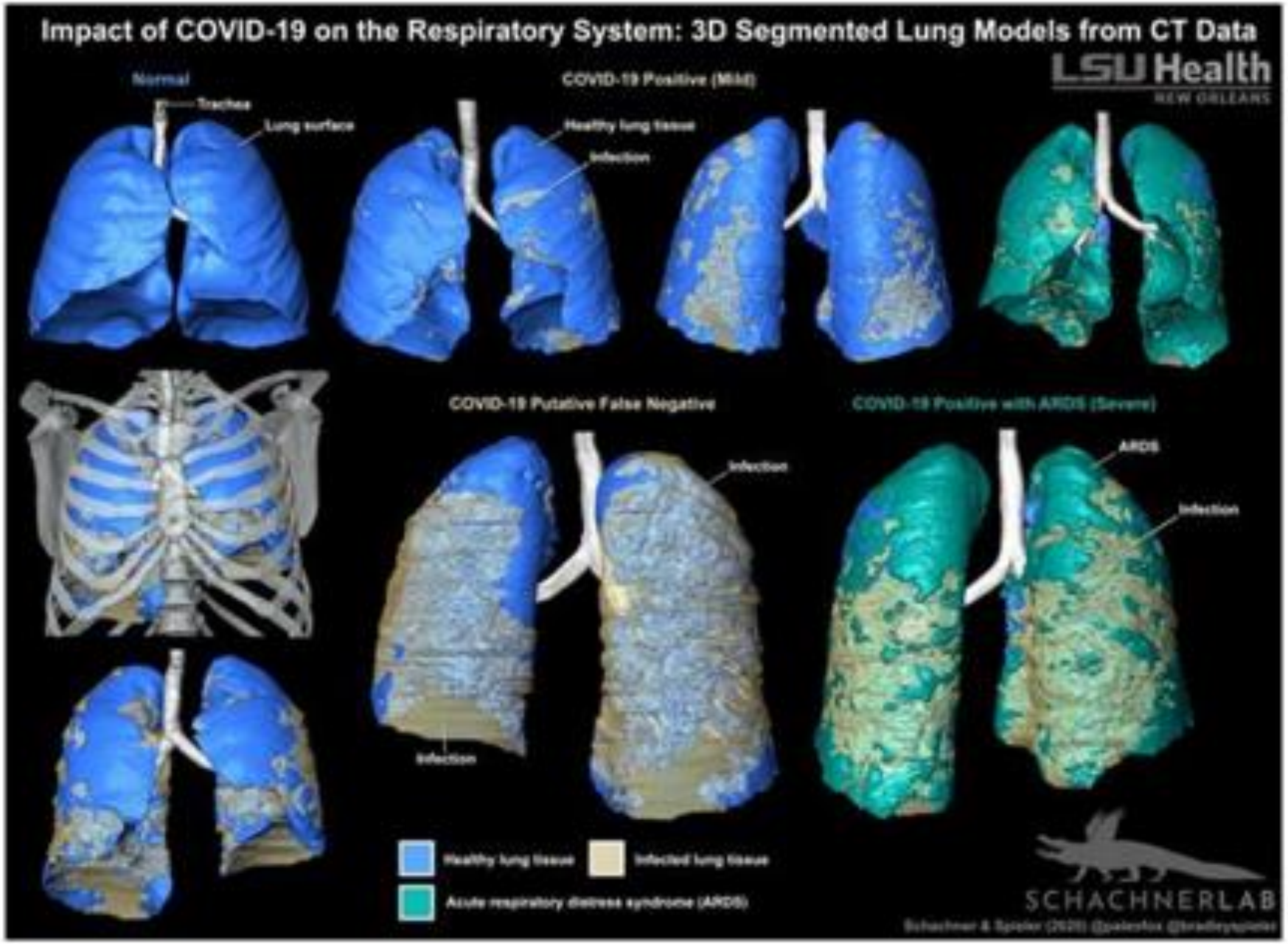
COVID-19 Patient
Cat-scan



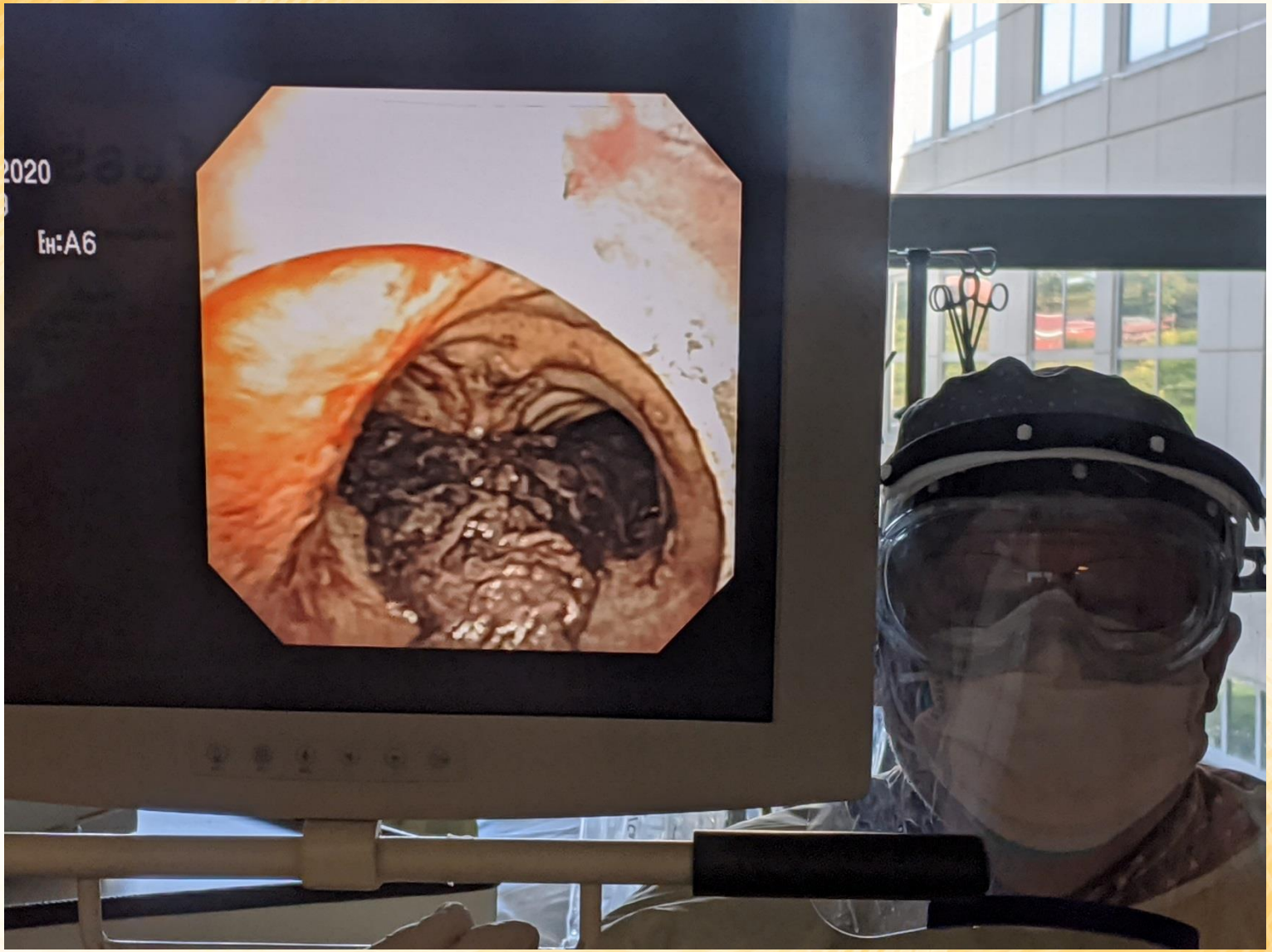
Progression of COVID
3-14 days




A
Day 5
B
Day 15
C
Day 20


Impact of COVID-19 on the Respiratory System: 3D Segmented Lung Models from CT Data
LSU Health
NEW ORLEANS
Normal
Trachea
Lung surface
COVID-19 Positive (Mild)
Healthy lung tissue
Infection
COVID-19 Putative False Negative
Infection
Infection
COVID-19 Positive with ARDS (Severe)
ARDS
Infection
Healthy lung tissue
Infected lung tissue
Acute respiratory distress syndrome (ARDS)
SCHACHNERLAB

Bronchoscopy



Hyperspace - CC RESPIRATORY CARE - Production - KENNETH M.

Patient Lookup | In Basket | References | My Reports | Transport Command Center (View Only)

Print | Web Links | OnBase | Log Out

KENNETH M. EpicCare

hart Review | Results Review | Orders | Respiratory

es by ... | My Last Note | Mark All as Not New | Refresh | Legend | Note Editor Settings

scharge | Emergency | Plan of Care | Periop | Events | Med Student | AICU Notes | Utilization Review

here are new updates. Sort by new notes

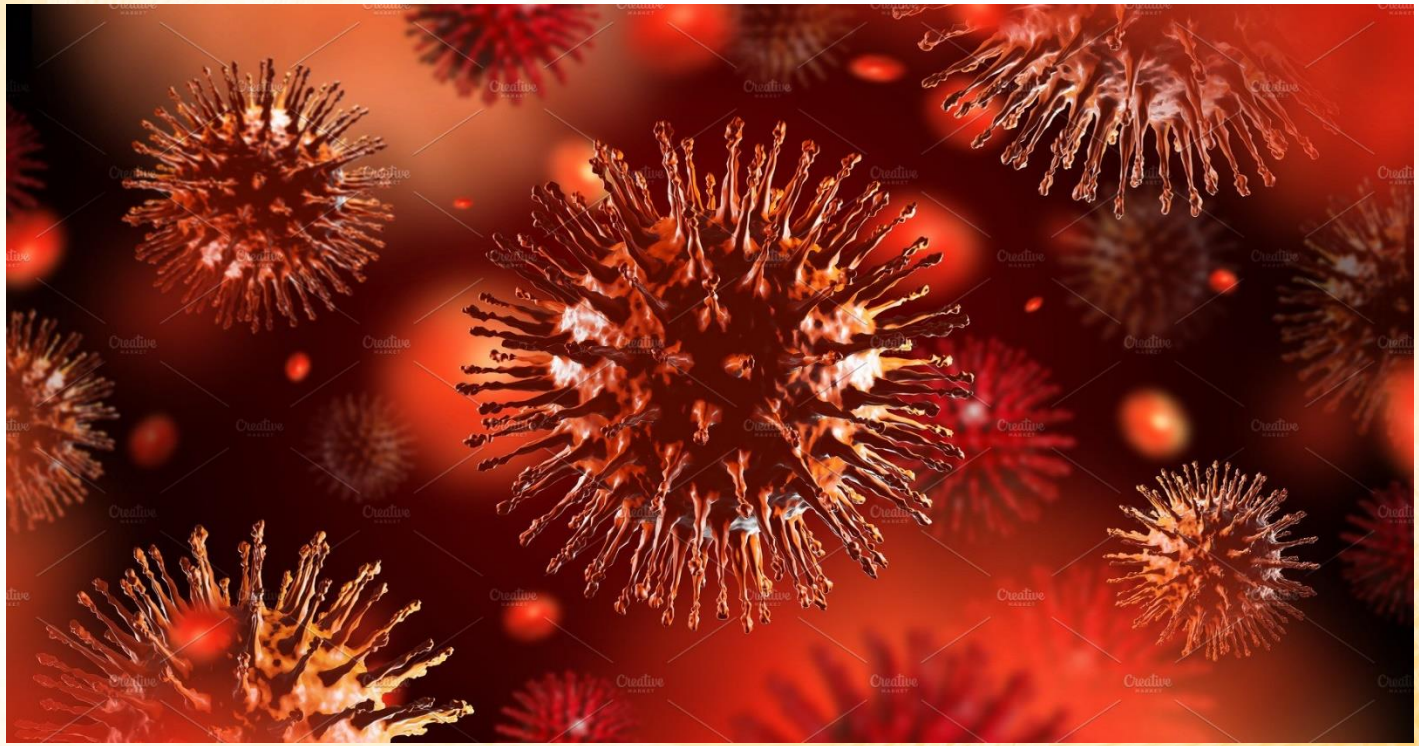
Addendum | Copy | Delete | Sign | Route | Remove Cosign | Tag

Hide copied text

Hover for details

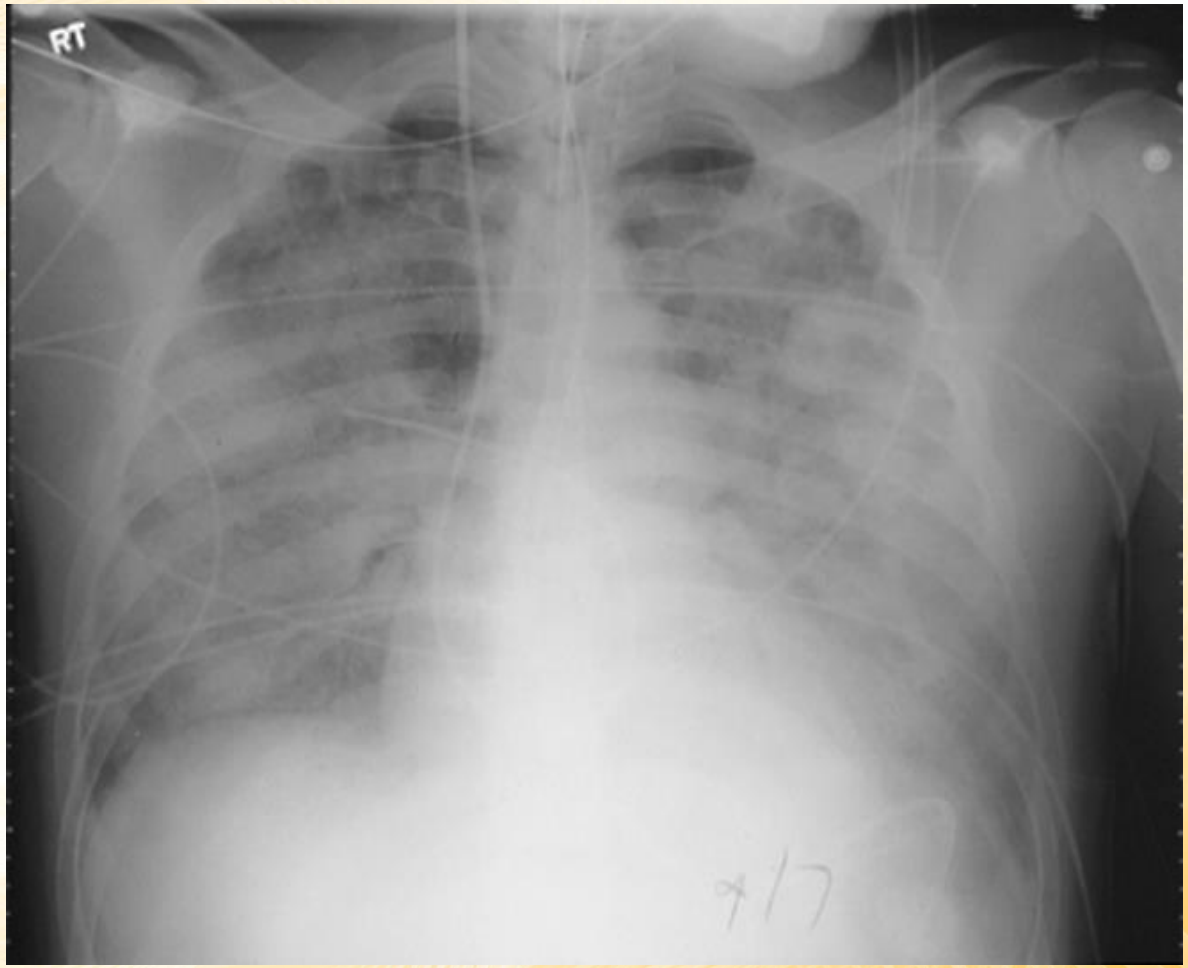
Flu Mask 1918

COVID Induced ARDS



ARDS is a Syndrome – NOT a Specific Disease

- The “Berlin Definition”:
  - 1. Acute
  - 2. Bilateral
  - 3. Hypoxemia
  - 4. NOT CHF
- ARDS is heterogeneous:
  - Etiologies
  - Severity
  - Pathology
  - Trajectory
  - Biomarker profiles



ARDS is Heterogeneous - Etiologies

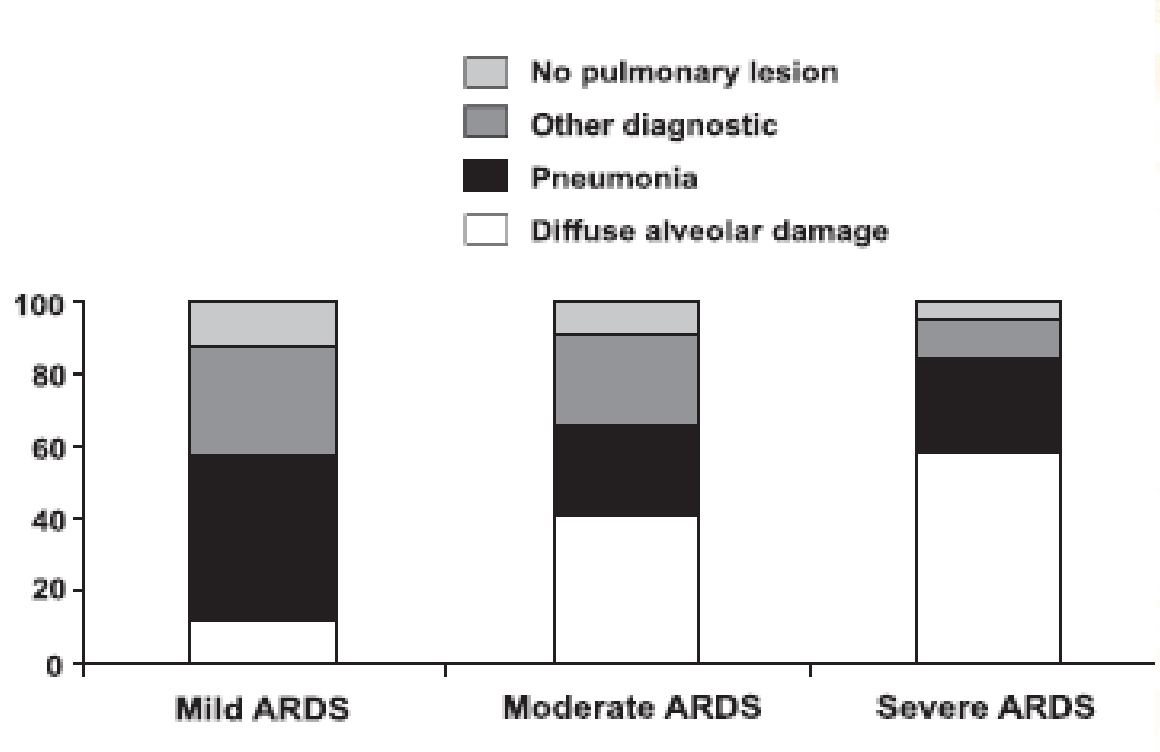
- Primary lung injury
  - Aspiration
  - Infectious pneumonia (COVID -19 starts as a viral pneumonia)*
  - Contusion
  - Inhalation injury
- Secondary lung injury (lung is one of many organs hit by MSOF)
  - Sepsis
  - Pancreatitis
  - TRALI

*Can evolve into a sepsis/MSOF syndrome

Berlin P/F Ratio Criteria

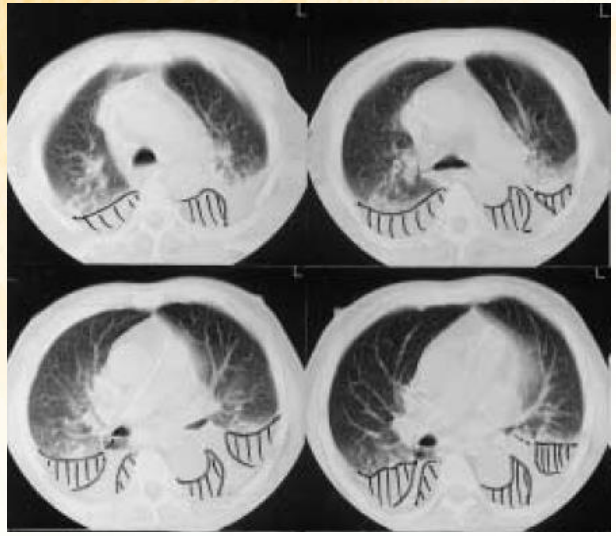
- **Mild**
  - P/F <300>200
  - Mortality 24%
- **Moderate**
  - P/F <200>100
  - Mortality 34%
- **Severe**
  - P/F <100
  - Mortality 44%
  - COVID-19 >50% China/Italy

ARDS is Heterogeneous - Pathology

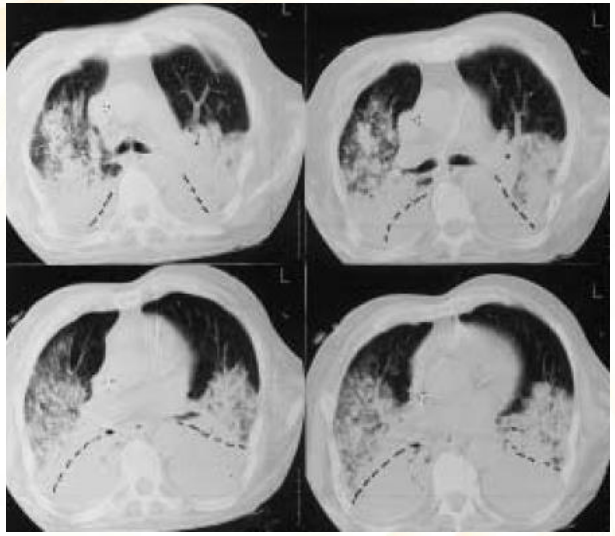


ARDS is Heterogeneous - Distribution

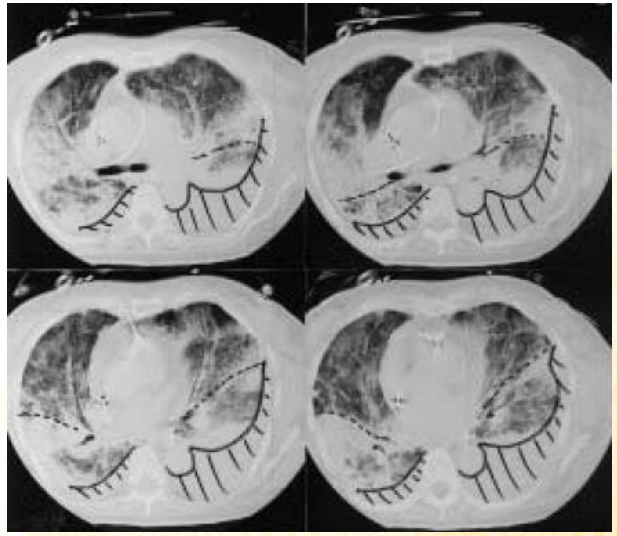
Important implications for positive pressure ventilation –
majority of patients do NOT have diffuse disease



Lobar
37%



Patchy
41%



Diffuse
22%

Puybasset L, et al. Intensive Care Med 2000; 26:857

We have seen all of these patterns in COVID-19

Pathophysiology

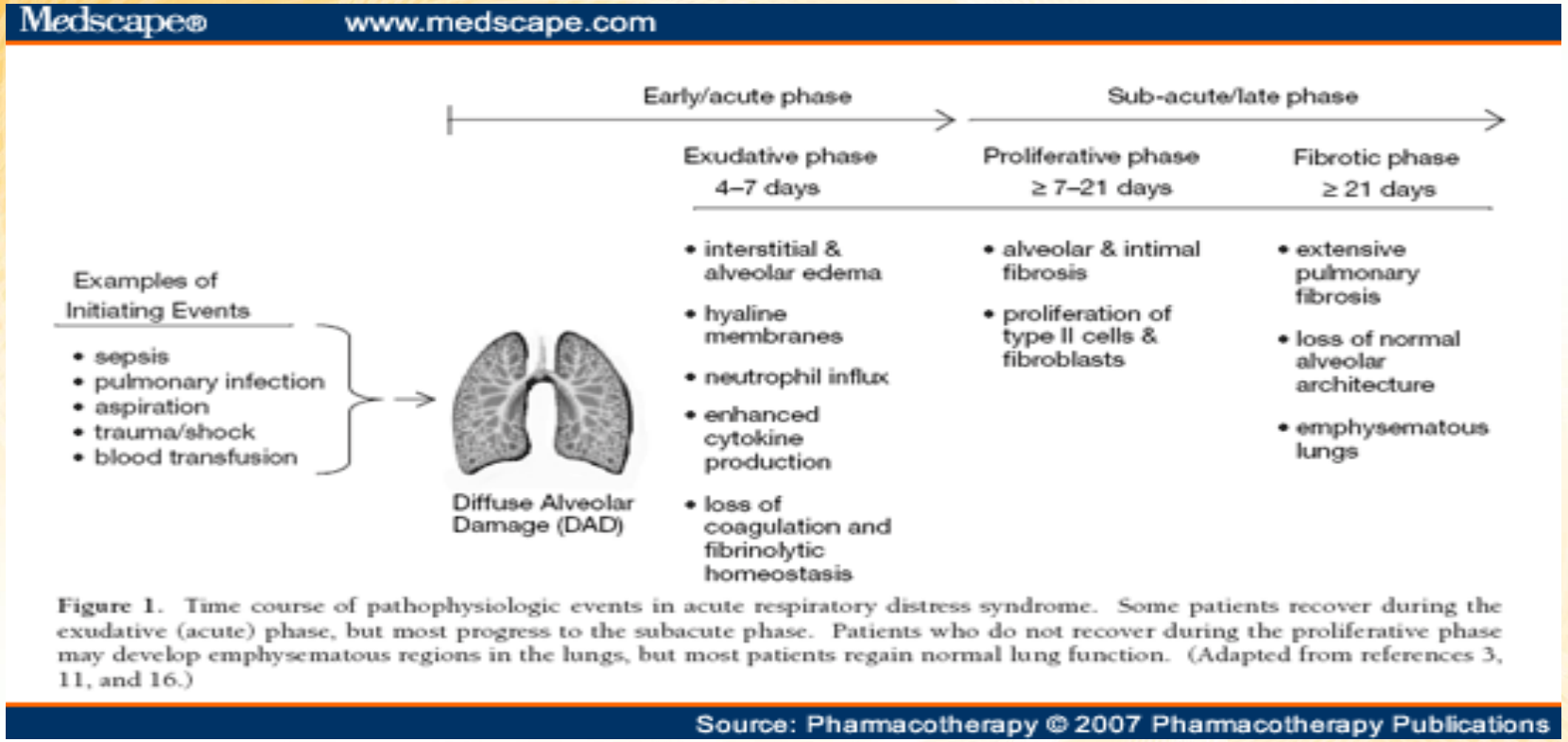


Figure 1. Time course of pathophysiologic events in acute respiratory distress syndrome. Some patients recover during the exudative (acute) phase, but most progress to the subacute phase. Patients who do not recover during the proliferative phase may develop emphysematous regions in the lungs, but most patients regain normal lung function. (Adapted from references 3, 11, and 16.)

http://www.medscape.com/viewarticle/558310_3

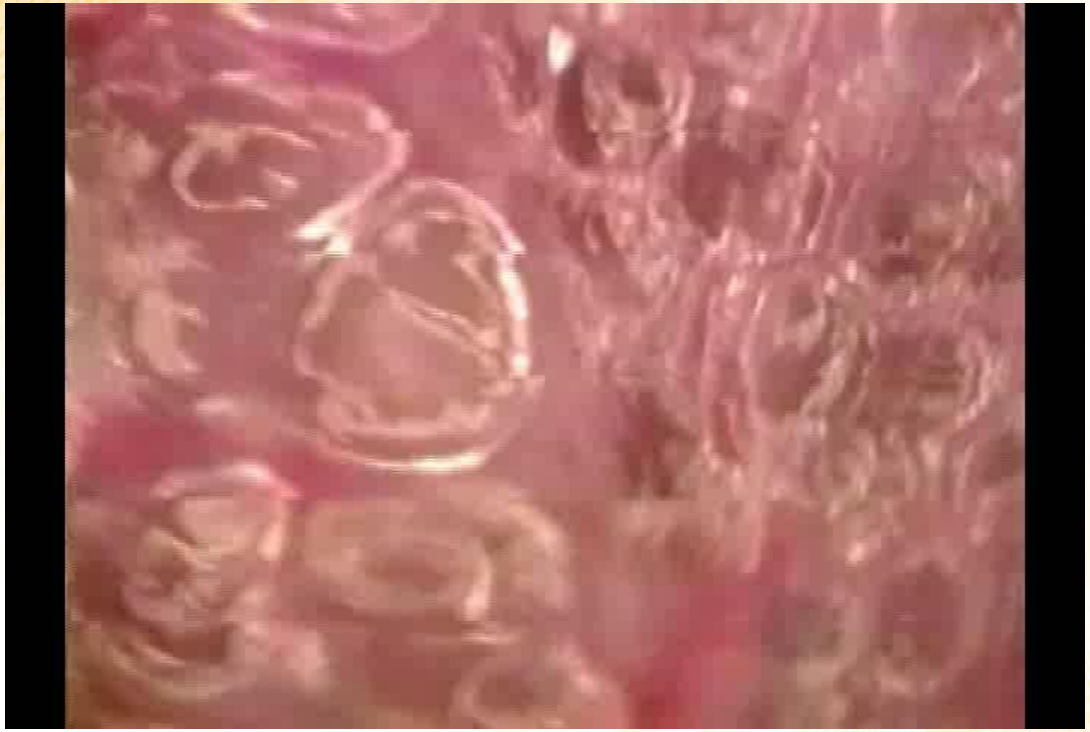
Pathophysiology

- The injured lung goes through 3 phases:
  - Exudative
  - Proliferation
  - Fibrotic

Exudative Phase

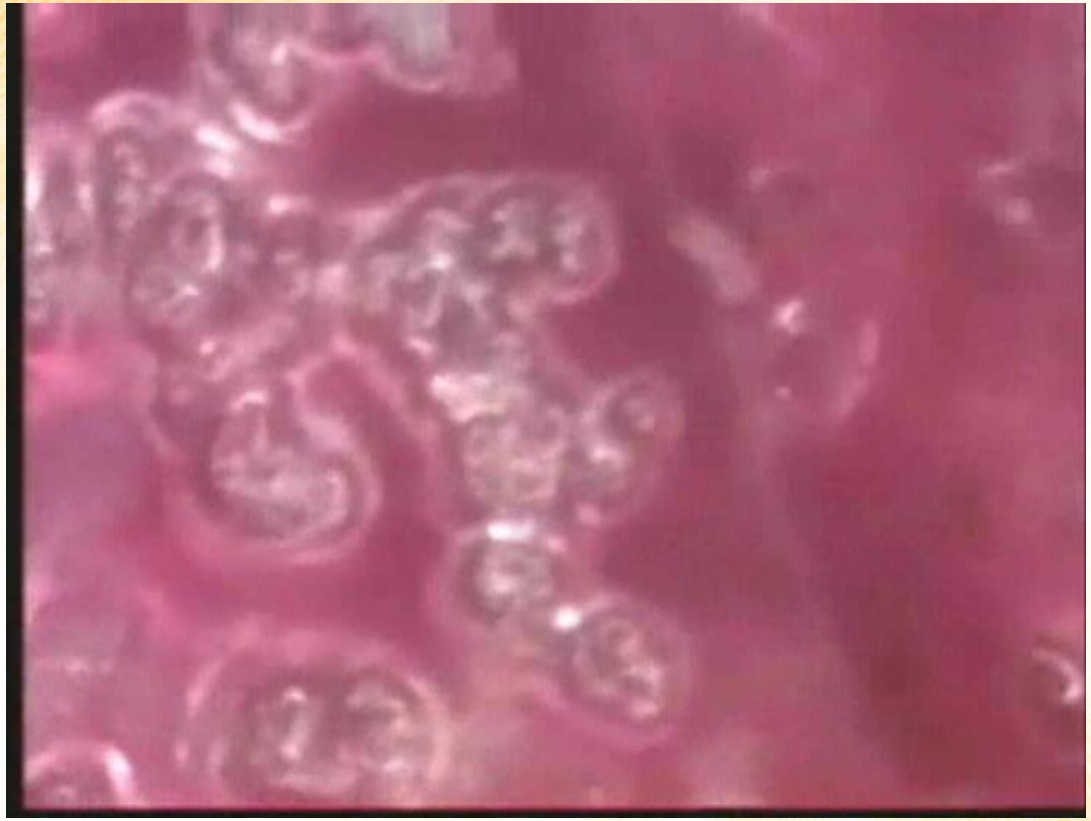
- Occurs in the first week after onset of respiratory failure
- Inflammatory cells migrate into the lungs and release substances to cause **capillary leakage**
- Type I pneumocytes swell and detach from basement membrane
- Increased pulmonary vascular permeability
- Alveolar collapse

Uninjured Alveoli



Permission granted from Gary Neiman

Injured Alveoli



Permission granted from Gary Neiman

Proliferative Phase

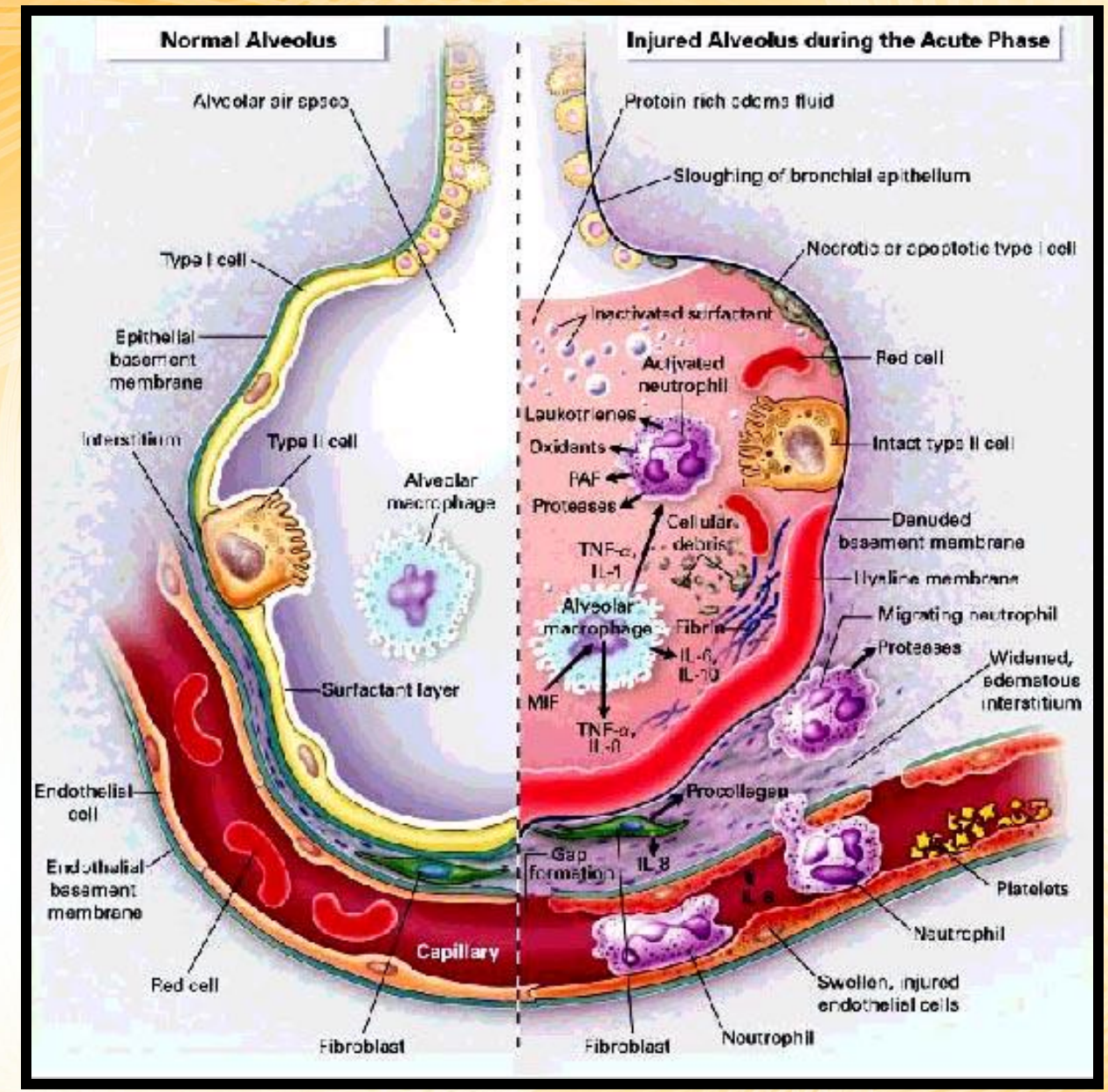
- Usually prominent in 2nd and 3rd week after onset
- Type II cells proliferate and reline membrane
- Fibroblast infiltration – migration through breaks in membrane forming granulation tissue
- Surfactant abnormalities occur – damage to Type II and alveolar flooding destabilize the surfactant layer- **Marked by poor gas diffusion**

Fibrotic Phase

- May begin as early as two weeks after injury
- Extensive remodeling by collagenous tissue
- Alveolar duct fibrosis
- Elastic collagen replaced by rigid collagen – resulting in stiff lung
- Extent of fibrosis correlates with mortality
- **VD/VT>60% Large amount of wasted ventilation good predictor of mortality (Kallet)**

Structural Changes

- Damage to type I alveolar epithelial cells
- Increase edema influx
- Loss of surfactant
- Poor fluid clearance mechanism
- Development of a hyaline membrane
- Reduction in gas exchange
- Pulmonary Fibrosis development
- “Liver” lung appearance

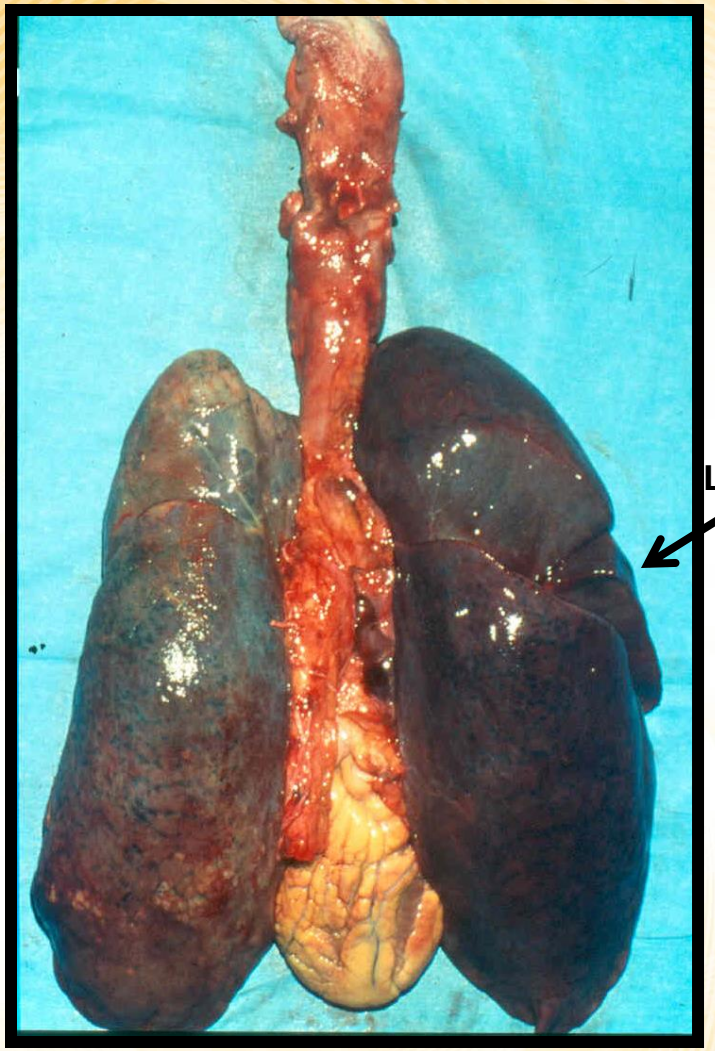

Normal Alveolus
Alveolar air space
Type I cell
Epithelial basement membrane
Interstitium
Type II cell
Alveolar macrophage
Surfactant layer
Endothelial cell
Endothelial basement membrane
Capillary
Red cell
Fibroblast
Injured Alveolus during the Acute Phase
Protein rich edema fluid
Sloughing of bronchial epithelium
Necrotic or apoptotic type I cell
Inactivated surfactant
Activated neutrophil
Red cell
Leukotrienes
Oxidants
PAF
Proteases
Intact type II cell
Cellular debris
TNF-α, IL-1
Denuded basement membrane
Hyaline membrane
Alveolar macrophage
Fibrin
Migrating neutrophil
Proteases
IL-6, IL-10
MIF
TNF-α, IL-8
Widened, edematous interstitium
Procollagen
Gap formation
IL-8
Platelets
Neutrophil
Swollen, injured endothelial cells
Fibroblast
Neutrophil

ARDS Post-mortem Findings

Dense infiltration with leukocytes and proteinaceous material

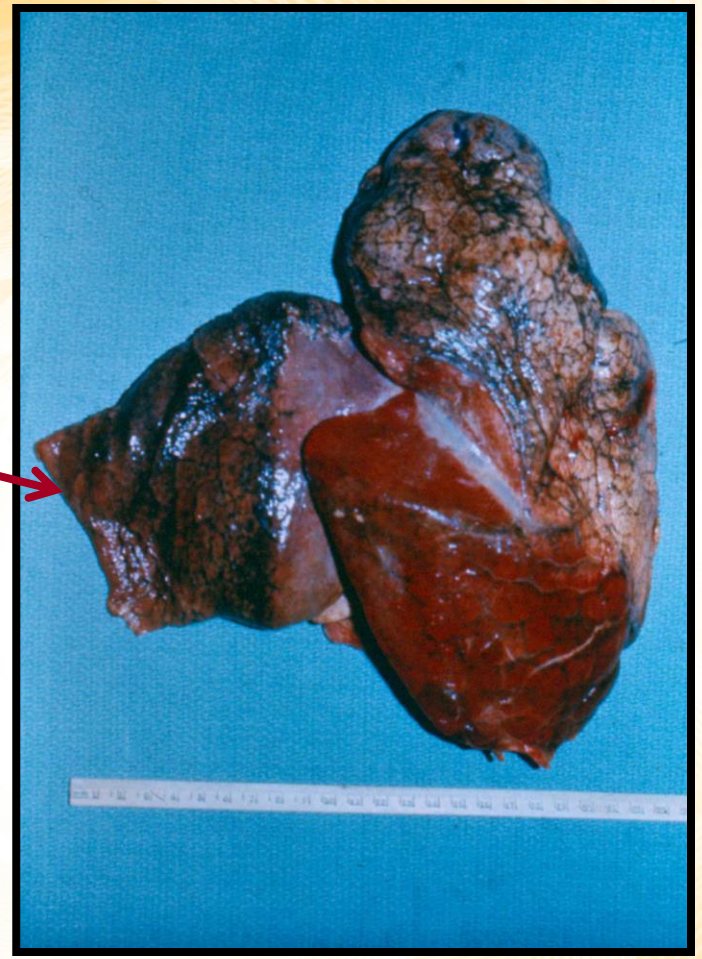
Wet, heavy, congested lungs with collapsed alveoli

Pneumonia revealed in up to 75 % of cases

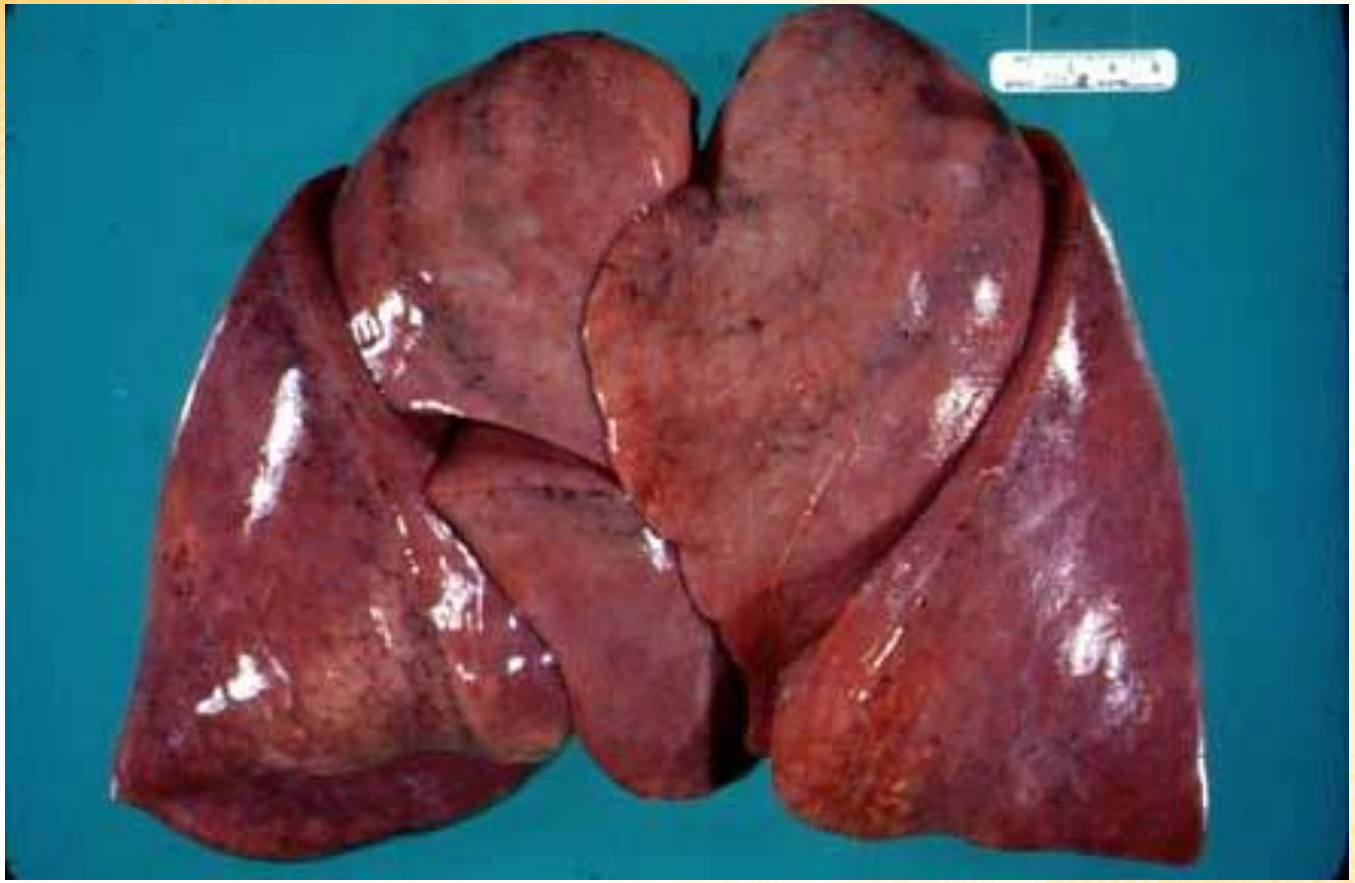


Liver like appearance

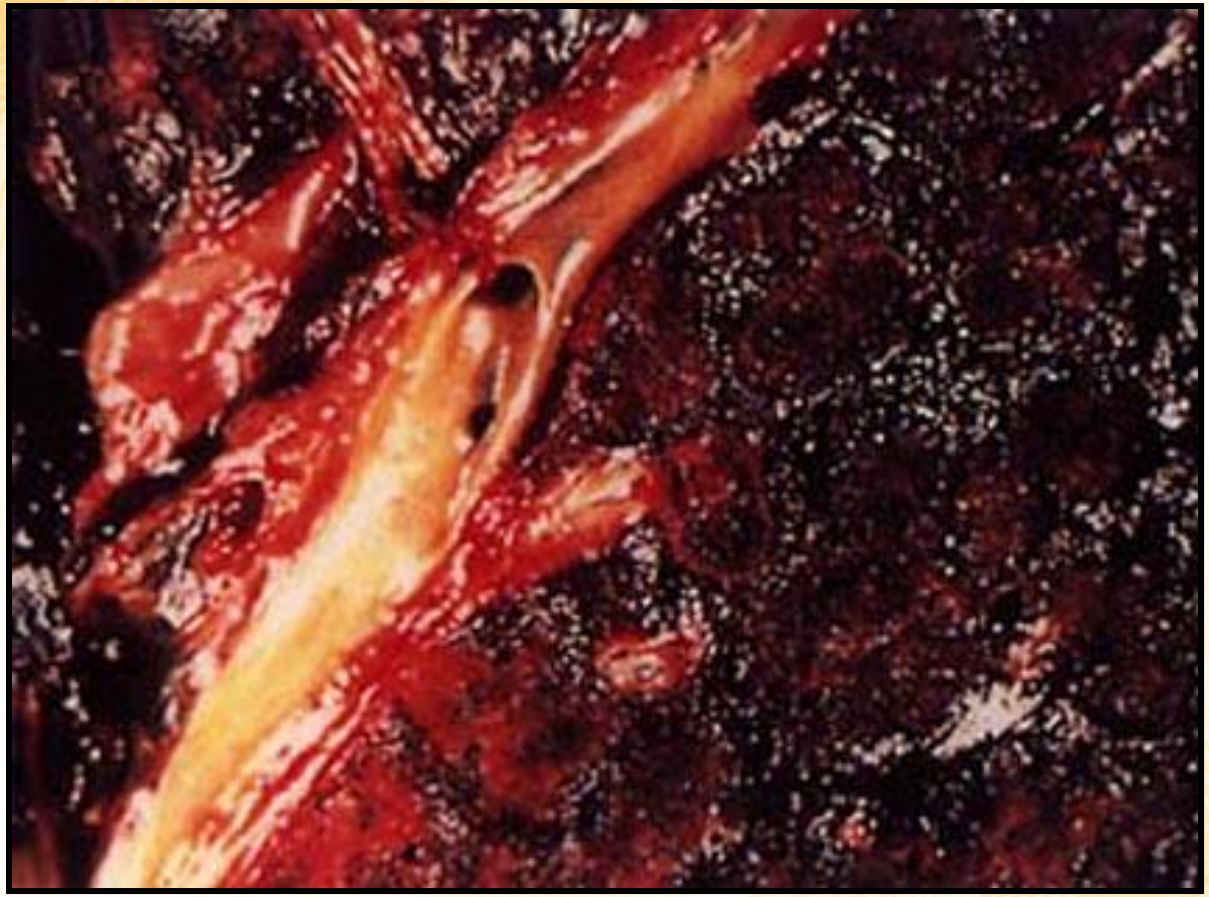
Dependent hemorrhagic injury

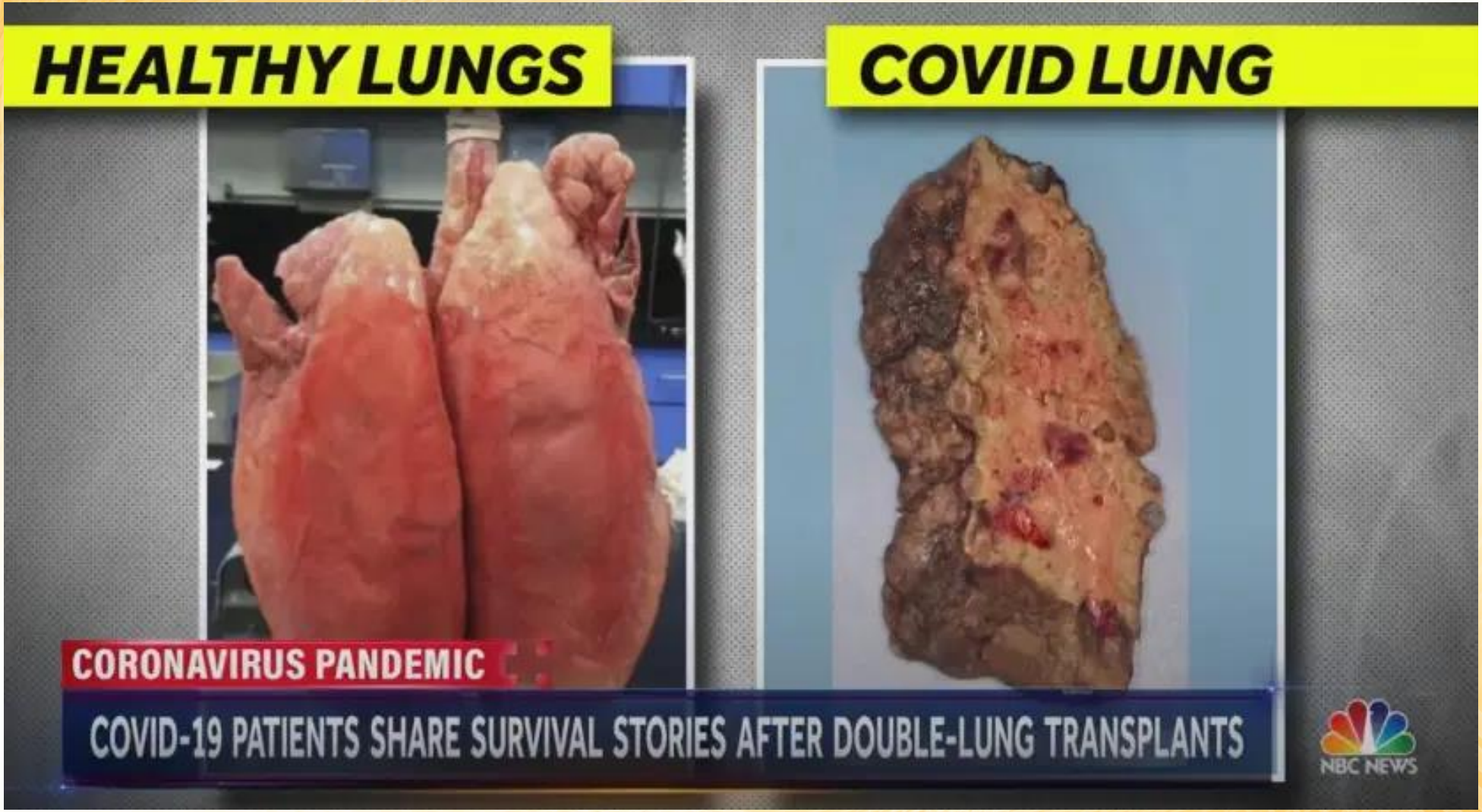


Wet Heavy lung



Pneumonia Induced ARDS

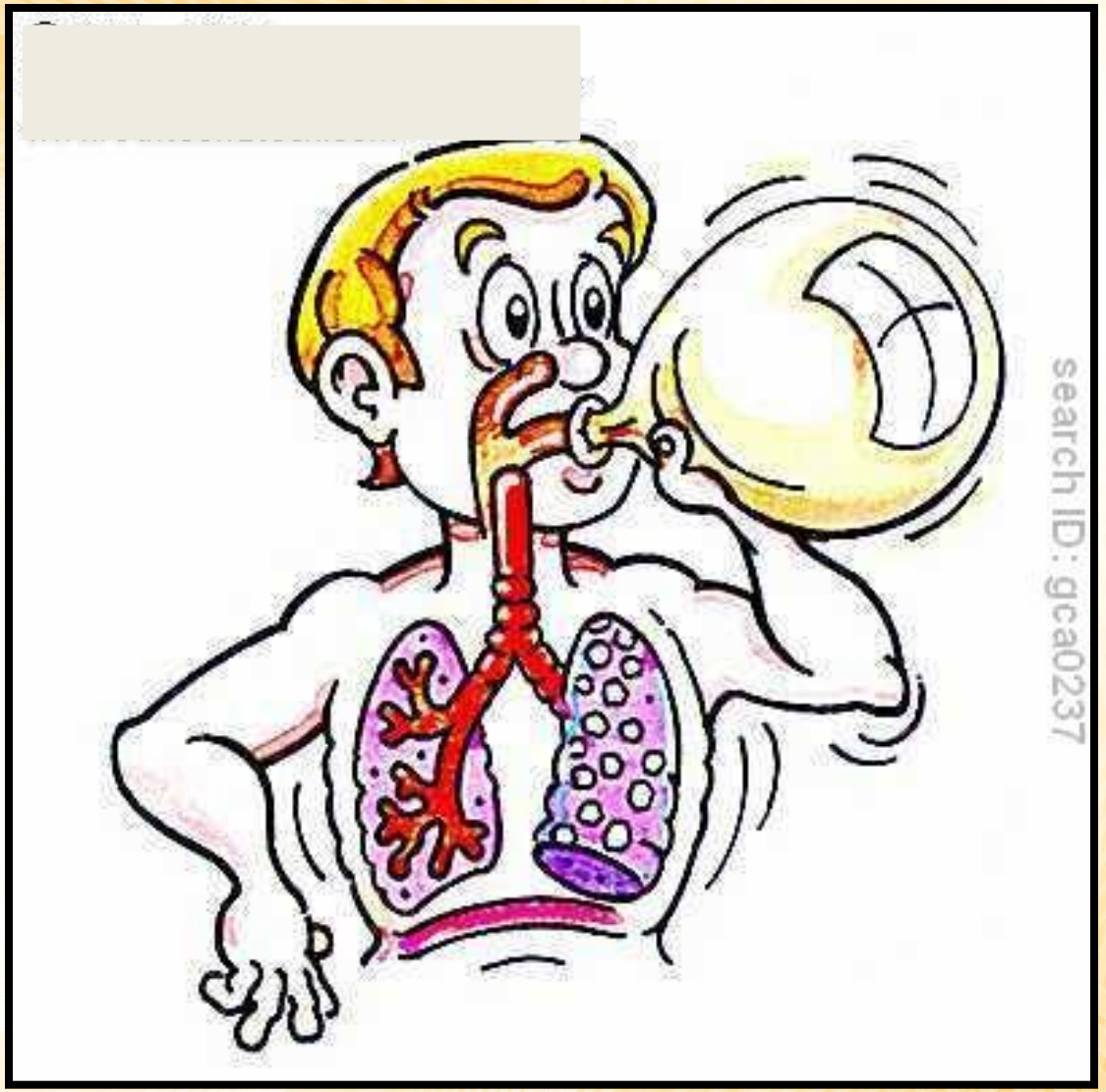


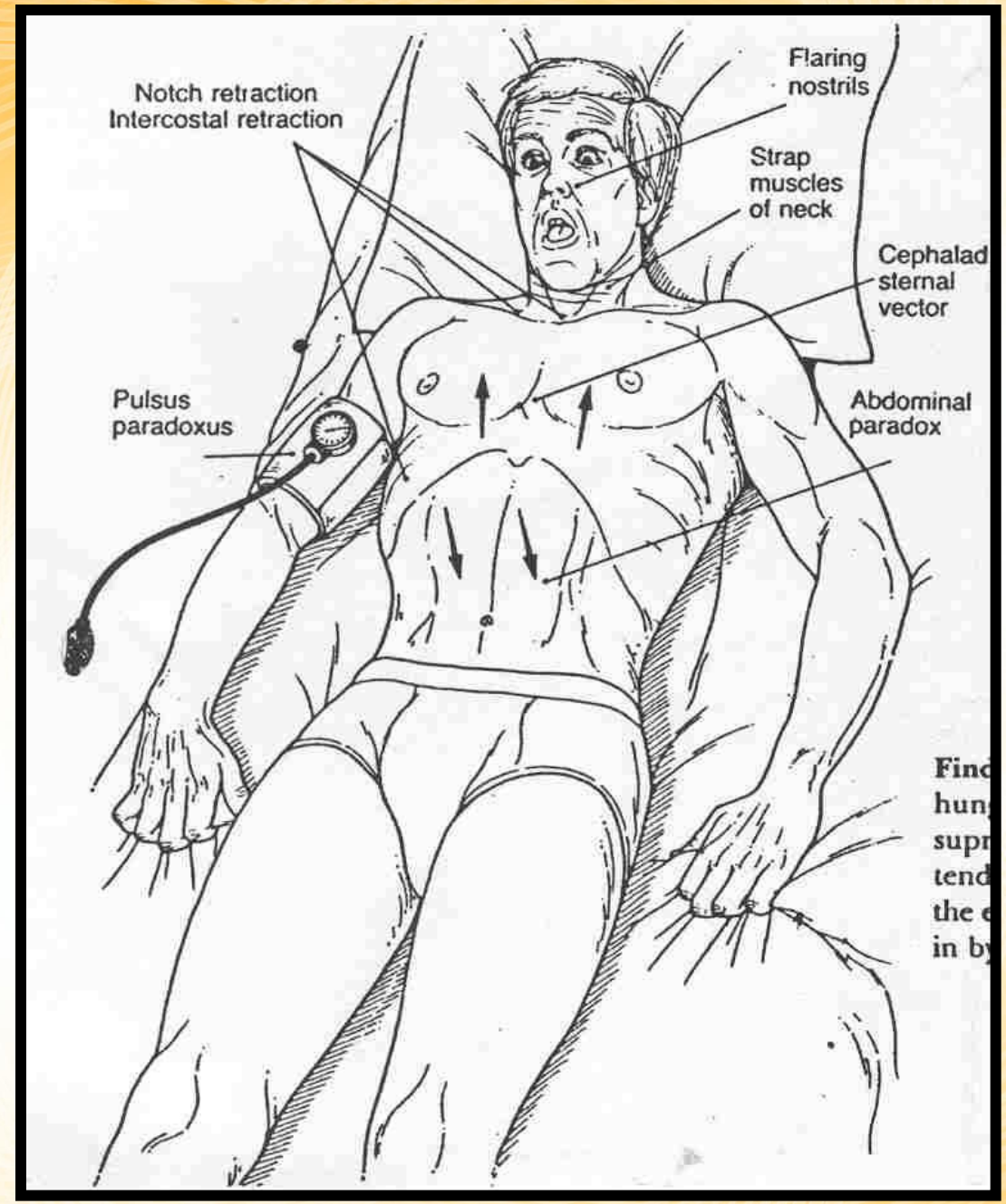

HEALTHY LUNGS
COVID LUNG
CORONAVIRUS PANDEMIC
COVID-19 PATIENTS SHARE SURVIVAL STORIES AFTER DOUBLE-LUNG TRANSPLANTS
NBC NEWS

Clinical Manifestations Of ARDS

- Dyspnea
- Tachypnea (rapid, shallow breathing)
- Severe Hypoxemia – refractory to O2 therapy
- Intercostal and suprasternal retraction on inspiration
- CXR reveals diffuse bilateral infiltrates (not always a reliable study) **CAT SCAN Better!!**

WOB Associated with ARDS




Notch retraction
Intercostal retraction
Flaring nostrils
Strap muscles of neck
Cephalad sternal vector
Pulsus paradoxus
Abdominal paradox

COVID Two Different ARDS?

Luciano Gattinoni
Department of Anesthesiology and Intensive Care, Medical University of Göttingen

COVID-19 pneumonia, Type L ("Happy hypoxemia")

At the beginning, COVID-19 pneumonia presents with the following characteristics:

- **Low elastance: the nearly normal compliance indicates that the amount of gas in the lung is nearly normal CLT>30cm**
- **Low ventilation to perfusion (VA/Q) ratio: since the gas volume is nearly normal, hypoxemia may be best explained by the loss of regulation of perfusion and by loss of hypoxic vasoconstriction. Accordingly, at this stage, the pulmonary artery pressure, should be near normal.**
- **Low lung weight: Only ground-glass densities are present on CT scan, primarily located subpleurally and along the lung fissures. Consequently, lung weight is only moderately increased.**
- **Low lung recruitability: the amount of non-aerated tissue is very low, consequently the recruitability is low.**

Acts like a diffusion deficient-poor DLCO

Treatment of Phenotype L

- Higher threshold for intubation
- Early prone
- High FIO2 administered >70%
- Lower PEEP

COVID-19 pneumonia, Type H

The Type H patient

- High elastance: The decrease of gas volume due to increased edema accounts for the increased lung elastance. CLT<30cm
- High right-to-left shunt: This is due to the fraction of cardiac output perfusing the non-aerated tissue which develops in the dependent lung regions due to the increased edema and superimposed pressure.
- High lung weight: Quantitative analysis of the CT scan shows a remarkable increase in lung weight (> 1.5 kg), on the order of magnitude of severe ARDS • High lung recruitability: The increased amount of non-aerated tissue is associated, as in severe ARDS, with increased recruitability .

The Type H pattern, 20 – 30% of patients in our series, fully fits the severe ARDS criteria: hypoxemia P/F<100 torr

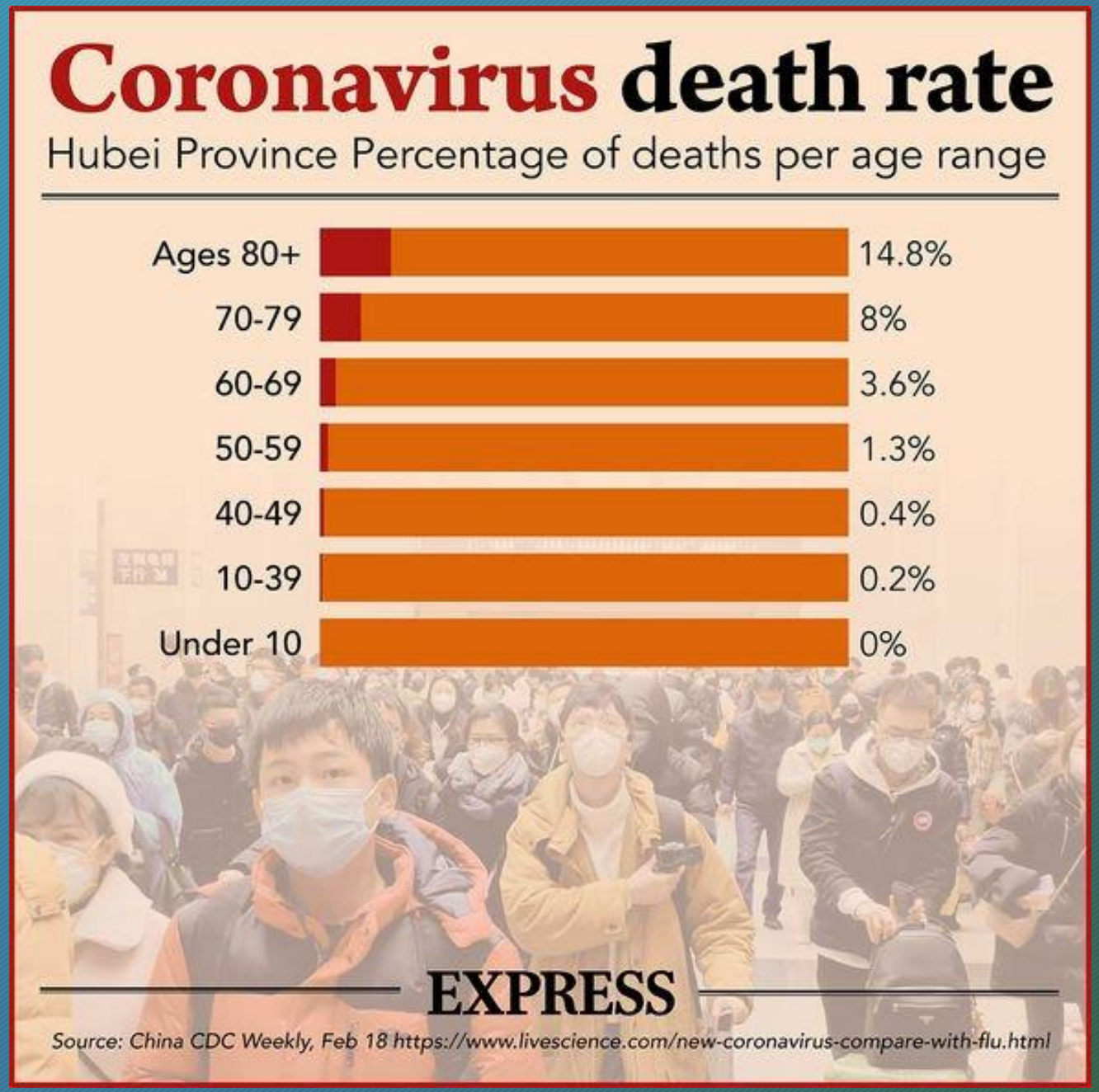
Treatment of Phenotype H

- Early intubation
- High PEEP
- Paralytic
- Prone inhaled pulmonary Vasodilators
- ?ECMO

Mechanical Ventilation During the First year of the COVID-19 Pandemic

- RC Jour Aug 2021Vol 66 1341-1359
- Richard Kallet UC Trauma Division
- Argues that COVID is not a true ARDS but really a mutifocal pneumonia associated with pulmonary vasoconstriction and lung tissue inflammation
- ARDS may occur later in the disease but not intially

Outcomes

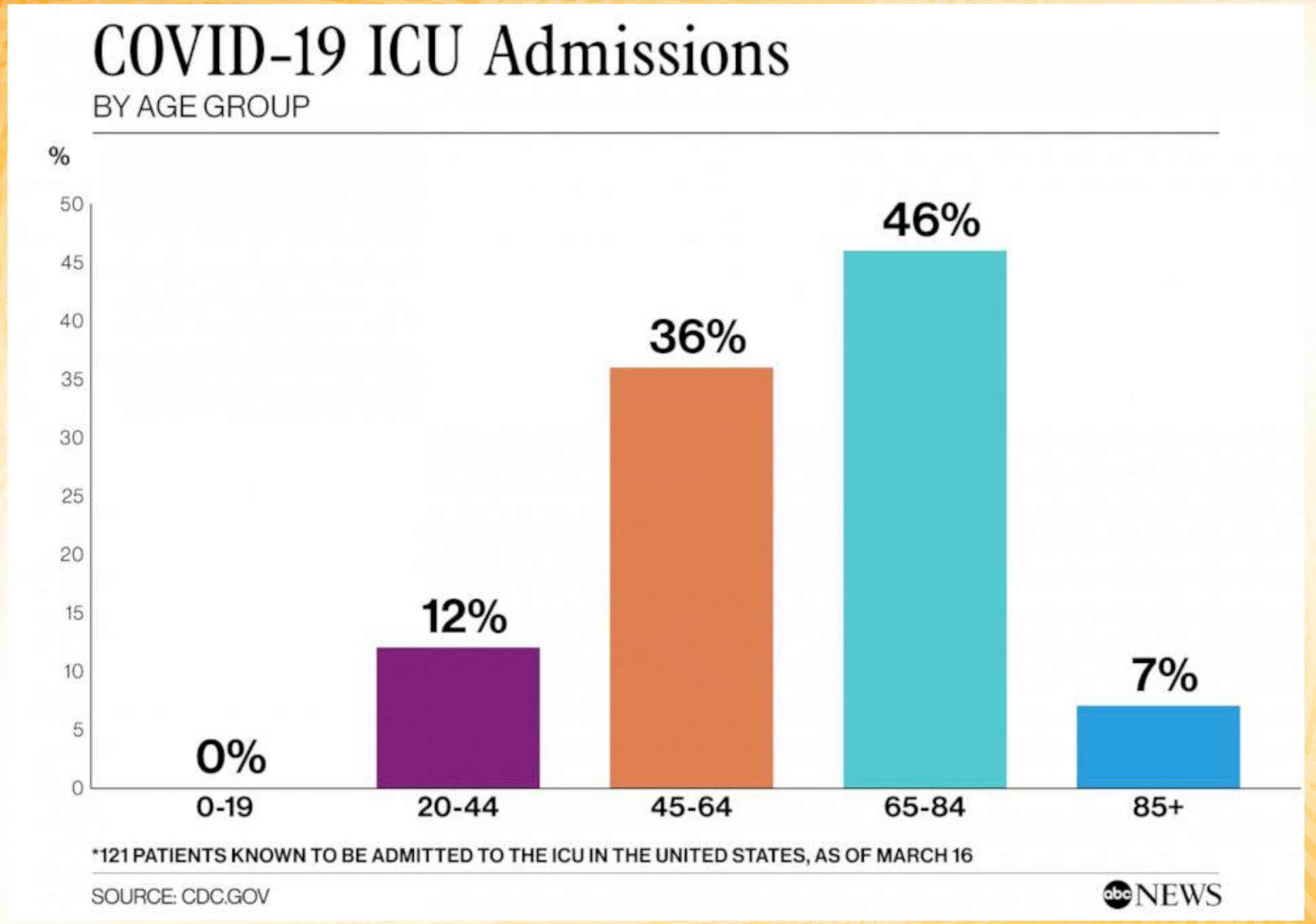

Coronavirus death rate
Hubei Province Percentage of deaths per age range
Ages 80+
14.8%
70-79
8%
60-69
3.6%
50-59
1.3%
40-49
0.4%
10-39
0.2%
Under 10
0%
EXPRESS
Source: China CDC Weekly, Feb 18 https://www.livescience.com/new-coronavirus-compare-with-flu.html

The research, which was published online in the *American Journal of Respiratory and Critical Care Medicine*, studies the electronic health records of 85 COVID-19 patients who died between Jan 9 and Feb 15, 2020 after treatment at two Wuhan hospitals.

Some of the clinical characteristics of the patient fatalities included:

- 65.8 median age
- 72.9 % were men
- Most common symptoms: fever, dyspnea, and fatigue
- Most common comorbidities: hypertension, diabetes, and coronary heart disease
- 80%+ of patients had very low counts of eosinophils on admission
- Complications included: respiratory failure, shock, ARDS and cardiac arrhythmia
- Most patients received antibiotics, antivirals and glucocorticoids
- Some were given intravenous immunoglobulin or interferon alpha-2b
- **The majority of patients studied died from multiple organ failure**

COVID-19 Fatalities Shared These Characteristics


COVID-19 ICU Admissions
BY AGE GROUP
%
50
45
40
35
30
25
20
15
10
5
0
0%
12%
36%
46%
7%
0-19
20-44
45-64
65-84
85+
*121 PATIENTS KNOWN TO BE ADMITTED TO THE ICU IN THE UNITED STATES, AS OF MARCH 16
SOURCE: CDC.GOV
abc NEWS

COVID-19'S EFFECT BY AGE

Cases, deaths and death rate in California show the coronavirus' greater impact on older residents.

Age	Cases	Deaths	Death rate
0-4 yrs	1,353	0	0%
5-17 yrs	4,901	0	0%
18-34 yrs	29,987	42	0.1%
35-49 yrs	27,751	188	0.7%
50-59 yrs	18,410	355	1.9%
60-64 yrs	7,554	272	3.6%
65-69 yrs	5,545	374	6.7%
70-74 yrs	4,147	430	10.4%
75-79 yrs	3,229	500	15.5%
80+ yrs	7,534	1,882	25.0%

Source: George Lemp, DrPH, MPH, data from COVID19.ca.gov through May 30

BAY AREA NEWS GROUP

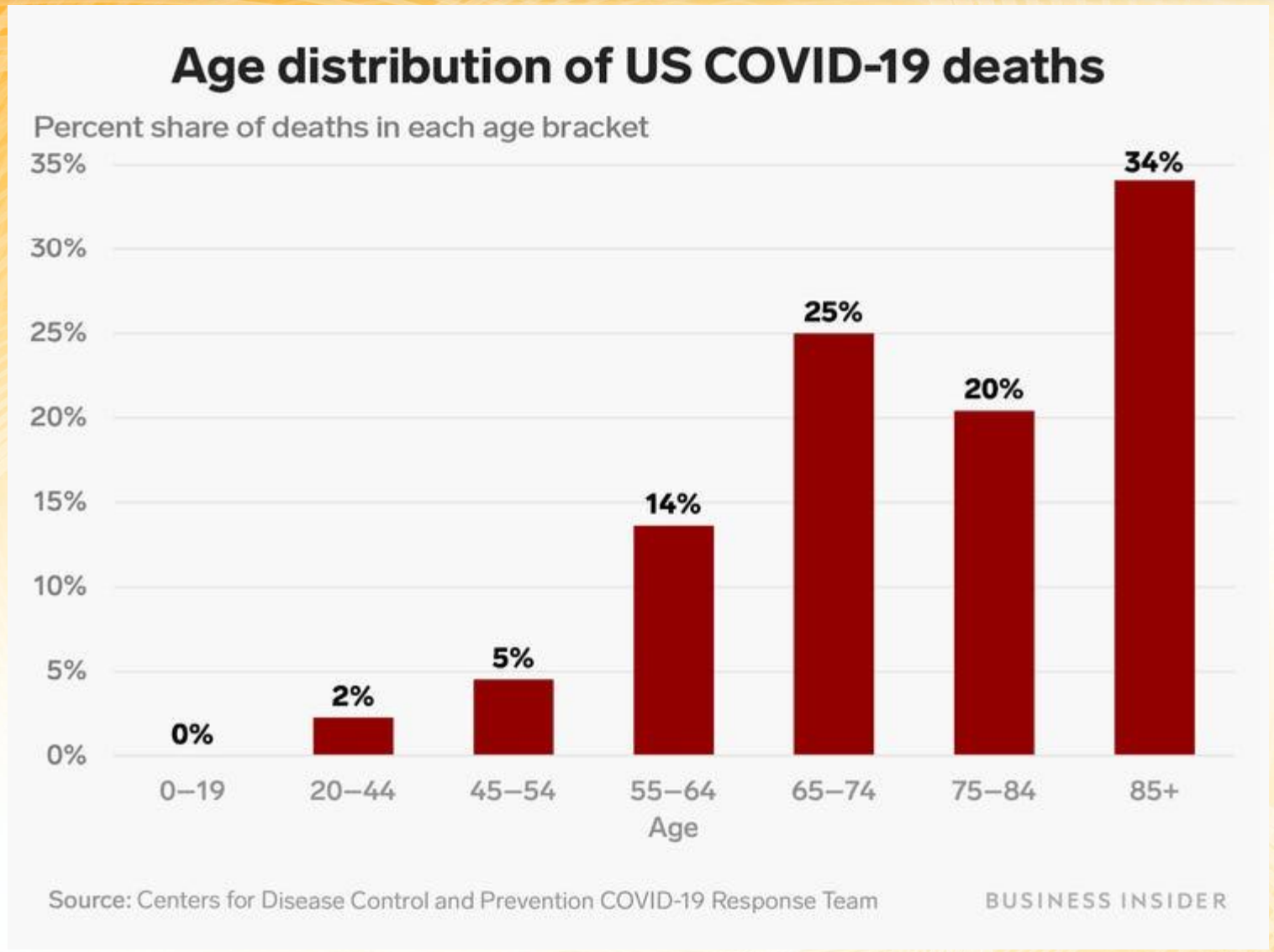

Age distribution of US COVID-19 deaths
Percent share of deaths in each age bracket
35%
30%
25%
20%
15%
10%
5%
0%
0%
2%
5%
14%
25%
20%
34%
0–19
20–44
45–54
55–64
65–74
75–84
85+
Age
Source: Centers for Disease Control and Prevention COVID-19 Response Team
BUSINESS INSIDER

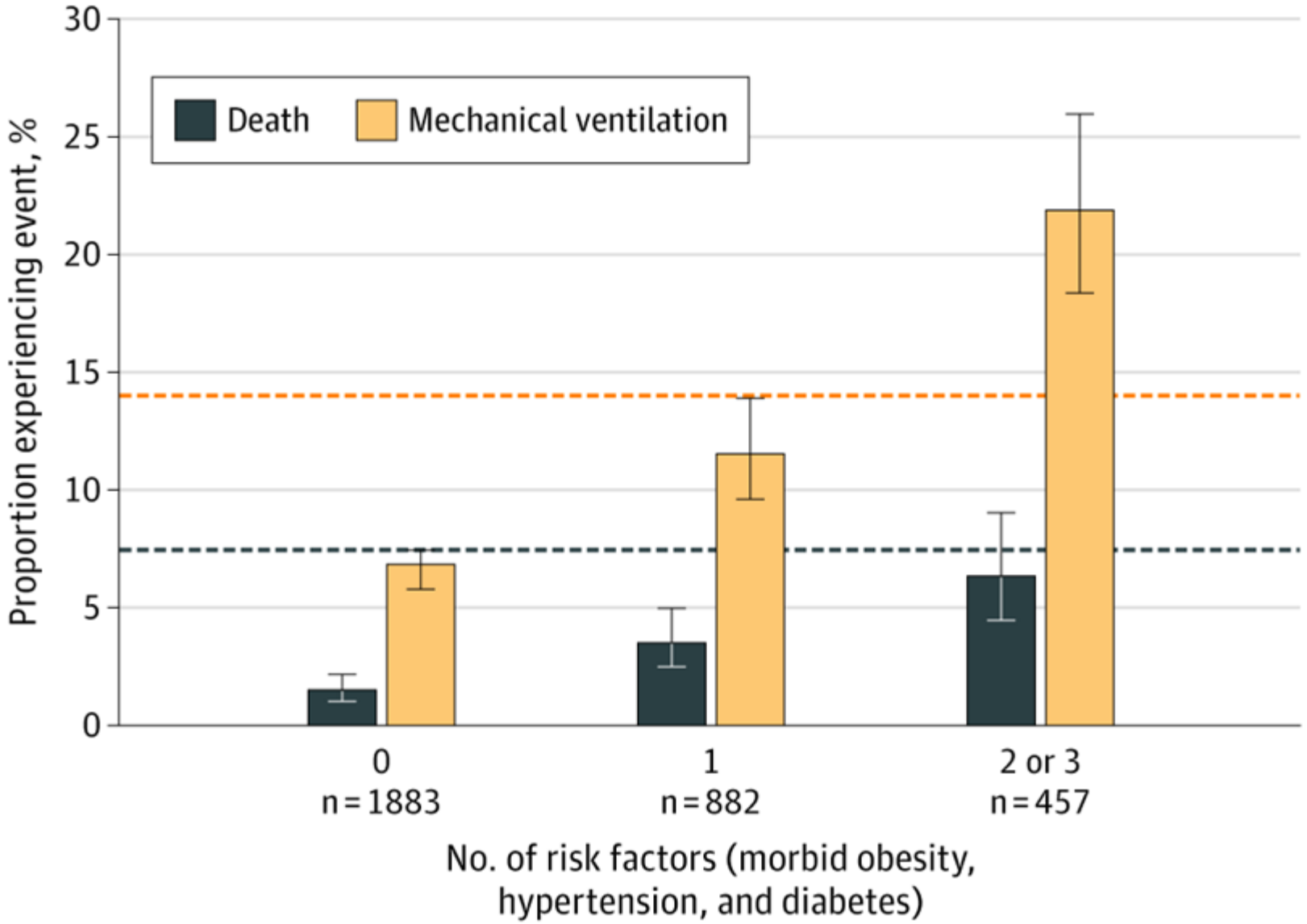
Table. Baseline Characteristics of Young Adults Age 18 to 34 Years With COVID-19[a]

Characteristic	No. (%)			*P* value
	Full case series (N = 3222)	No death or ventilation (n = 2879)	Death or ventilation (n = 343)	
Age, mean (SD), y	28.3 (4.4)	28.3 (4.4)	28.3 (4.5)	.90
Men	1849 (57.6)	1626 (56.7)	223 (65.0)	.003
Race/ethnicity				
White non-Hispanic	536 (16.6)	479 (16.6)	57 (16.6)	
White Hispanic	350 (10.9)	324 (11.3)	26 (7.6)	
Black non-Hispanic	748 (23.2)	675 (23.4)	73 (21.3)	.14
Black Hispanic	14 (0.4)	13 (0.5)	1 (0.3)	
Other/unknown	1574 (48.9)	1388 (48.2)	186 (54.2)	
Black and/or Hispanic	1838 (57.0)	1669 (58.0)	169 (49.3)	.002
Discharge month				
April 2020	1680 (52.1)	1495 (51.9)	185 (53.9)	
May 2020	1063 (33.0)	936 (32.5)	127 (37.0)	.004
June 2020	479 (14.9)	448 (15.6)	31 (9.0)	
Region				
Northeast	1298 (40.3)	1161 (40.4)	137 (39.9)	
South	1130 (35.1)	1032 (35.9)	98 (28.6)	.002
Midwest	558 (17.3)	488 (17.0)	70 (20.4)	
West	233 (7.2)	195 (6.8)	38 (11.1)	
Any obesity, BMI ≥ 30	1187 (36.8)	1007 (35.0)	180 (52.5)	<.001
Morbid obesity, BMI ≥ 40	789 (24.5)	649 (22.5)	140 (40.8)	<.001
Asthma	545 (16.9)	495 (17.2)	50 (14.6)	.22
Hypertension	519 (16.1)	412 (14.3)	107 (31.2)	<.001
Smoking	513 (15.9)	472 (16.4)	41 (12.0)	.03
Diabetes	588 (18.2)	494 (17.2)	94 (27.4)	<.001

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); COVID-19, coronavirus disease 2019.

[a] Race/ethnicity groups include only patients whose race and ethnicity were reported. Patients with missing data for 1 or both were considered other/unknown.

COVID outcomes
Patients
18-34 age group



COVID-19
Phenotypes and Clinical Implications

- Is COVID-19 ARDS? Yes If yes, is there a specific phenotype (or phenotypes)? Like ARDS in general, multiple phenotypes
- Are there special ventilator management strategies needed for COVID-19? No
- What are respiratory adjuncts that can be helpful in COVID-19 Several
- Is the mortality for COVID-19 higher than other mechanically ventilated patients? No

Mortality in COVID-19 Mechanically Ventilated Patients

New York City (JAMA April 29 2020 – n=1148):

- 35 discharged, 282 dead, 831 still on vent (89% mortality)

Boston (AJRCCM April 22 2020 – n=66):

- 41 discharged, 11 dead, 14 still on vent (22% mortality)

Emory (medRx Apr 26 2020 – n= 165)

- 86 discharged, 47 dead, 32 still in ICU (14 still on vent) (26% mortality)

Duke data (July 1 2020 – n=47)

- 26 discharged, 10 dead, 11 still in ICU (28% mortality)

- LVHN Outcome Data
- Nov 20 2020

Site	Total Ventilated Pt.	Liberation	Expired	Still ventilated
Muhl	51	29	20	2
CC	115	56	48	11
LVH-H	26	14	11	1
LVH-P	40	20	15	5
LVH-S	12	3	7	2
Total	234	110 (51%)	95 (41%)	21 (8%)

Outcomes

May 1 2021

Site	Total Ventilated Pt.	Liberation	Expired	Still ventilated
Muhl	109	47	61	1
CC	320	141	170	8
LVH-H	41	22	18	2
LVH-P	74	29	45	0
LVH-S	19	5	14	0
Total	556	239 (43.2%)	304 (54.5%)	11 (2%)

Outcomes

June 21 2021

Site	Total Ventilated Pt.	Liberation	Expired	Still ventilated
Muhl	118	49	67	2
CC	343	155	187	1
LVH-H	43	24	19	0
LVH-P	77	30	47	0
LVH-S	19	5	14	0
Total	600	263	334	3

COVID-19 Reduced Americans' Life Expectancy by 1.13 Years

The COVID-19 pandemic, which claimed more than 336,000 lives in the United States in 2020, has significantly affected life expectancy, USC and Princeton researchers have found

The researchers project that, due to the pandemic deaths last year, life expectancy at birth for Americans will shorten by 1.13 years to 77.48 years, according to their study published Thursday in the *Proceedings of the National Academy of Sciences*. That is the largest single-year decline in life expectancy in at least 40 years and is the lowest life expectancy estimated since 2003.

The declines in life expectancy are likely even starker among Black and Latino communities. For Black Americans, the researchers project their life expectancy would shorten by 2.10 years to 72.78 years, and for Latino Americans, by 3.05 years to 78.77 years.

Whites are also impacted, but their projected decline is much smaller — 0.68 years — to a life expectancy of 77.84 years.

Overall, the gap in life expectancy between Blacks and whites is projected to widen by 40%, from 3.6 to more than 5 years — further evidence of the disease's disparate impact on minority populations.

Why Males May Have a Worse Response to COVID-19

- **Sex differences in COVID-19**
  - Reports of SARS-CoV-2 infection rates are similar between males and females, but male sex is a significant risk factor for more serious COVID-19 disease and death. In fact, one study revealed that men are 2.4 times more likely to die from COVID-19. I find it interesting that higher death rates in men also occurred in other coronavirus diseases like severe acute respiratory syndrome, caused by SARS-CoV, and Middle East respiratory syndrome.
  - Based on data from the Centers for Disease Control and Prevention as of Oct. 5, 2020, the risk of death from COVID-19 in men 30-49 years old was also found to be more than twice that of females.
- **Males with SARS-CoV-2 show greater inflammation**
  - Men showed higher levels of cytokines that trigger inflammation, like IL-8 and IL-18, than women. Higher quantities of these cytokines are linked to more severe disease. In severe cases of COVID-19, fluid builds up in the lungs, reducing the oxygen available in the body for normal functions. This can lead to tissue damage, shock and potentially the failure of multiple organs.
- **Females with SARS-CoV-2 are better prepared to eliminate the virus**
  - Compared to men, women had a higher number of T cells – essential for eliminating the virus – that were activated, primed and ready to respond to the SARS-CoV-2 infection. Men with lower levels of these activated T-cells were more likely to have severe disease.

The Rise of ‘COVID Parties’

- Parties in which young people try to catch Covid-19 to gain immunity could become the norm if the virus is not eradicated, a Cambridge professor has suggested, prompting others to caution that the long-term effects of infection are not yet known.
- In the cases of the latter, he suggested: “You’ll get it when you’re young and not get sick. People will be invited to parties – like chickenpox parties – so you don’t get it when you’re older, but we’ll have to wait and see.”
- While some have raised concerns about waning immunity, Lehner again was optimistic, saying that a reinfection was likely to be less severe than the first, while reinfection, so far, seems rare.

Does COVID Symptoms Regress?

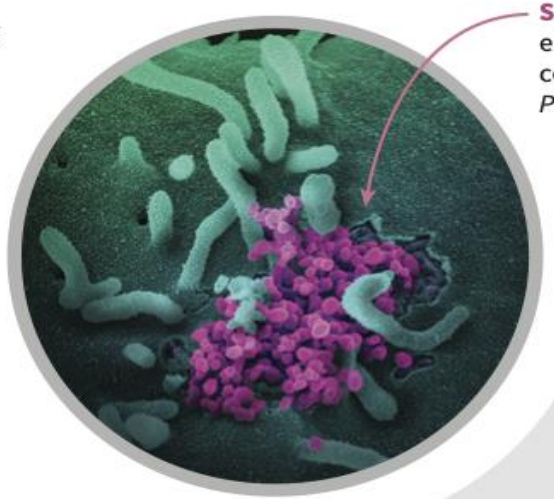
COVID-19: reports of unusual lingering effects

While much attention has been paid to severe and fatal cases of the disease, reports are emerging about long-lasting symptoms experienced by some who were initially hit by mild forms of the illness

Listed complaints

As of late June some people had reported 14 weeks of ongoing symptoms

- Fatigue, headaches, mood swings
- Chest pain, breathing difficulties, palpitaions
- Loss of taste and smell, tinnitus, pins and needles
- Gastric problems, loss of appetite, weight loss
- Confusion, dizziness, numb limbs, hallucinations
- Skin problems, rashes, lesions
- Blood clots on lungs, stroke, DVT



SARS-CoV-2 virions emerging from cells in a lab
*Picture by *NIH*

Possible causes

Most COVID-19 cases appear to clear up after about 10 days. It is unclear exactly why some people continue to experience symptoms for longer

Cytokine knock-on
The immune system can overreact to the virus and trigger a cytokine storm. This causes inflammation and could have ongoing effects

Blood clots
Microclots in the lung could reduce oxygen supply and cause exhaustion

Gut inflammation
The virus may affect beneficial gut bacteria; this could leave effects that persist

Residual virus
Some patients continue to test positive for the virus for a long time after the first diagnosis

*Source: New Scientist/blogs.bmj.com - Paul Garner/US media -- NYT, The Atlantic/*National Institues of Health*

Recovery from COVID-19 can take a long time, even in young adults with no chronic conditions

1 in 5 previously healthy young adults* weren't back to usual health 14-21 days after testing positive

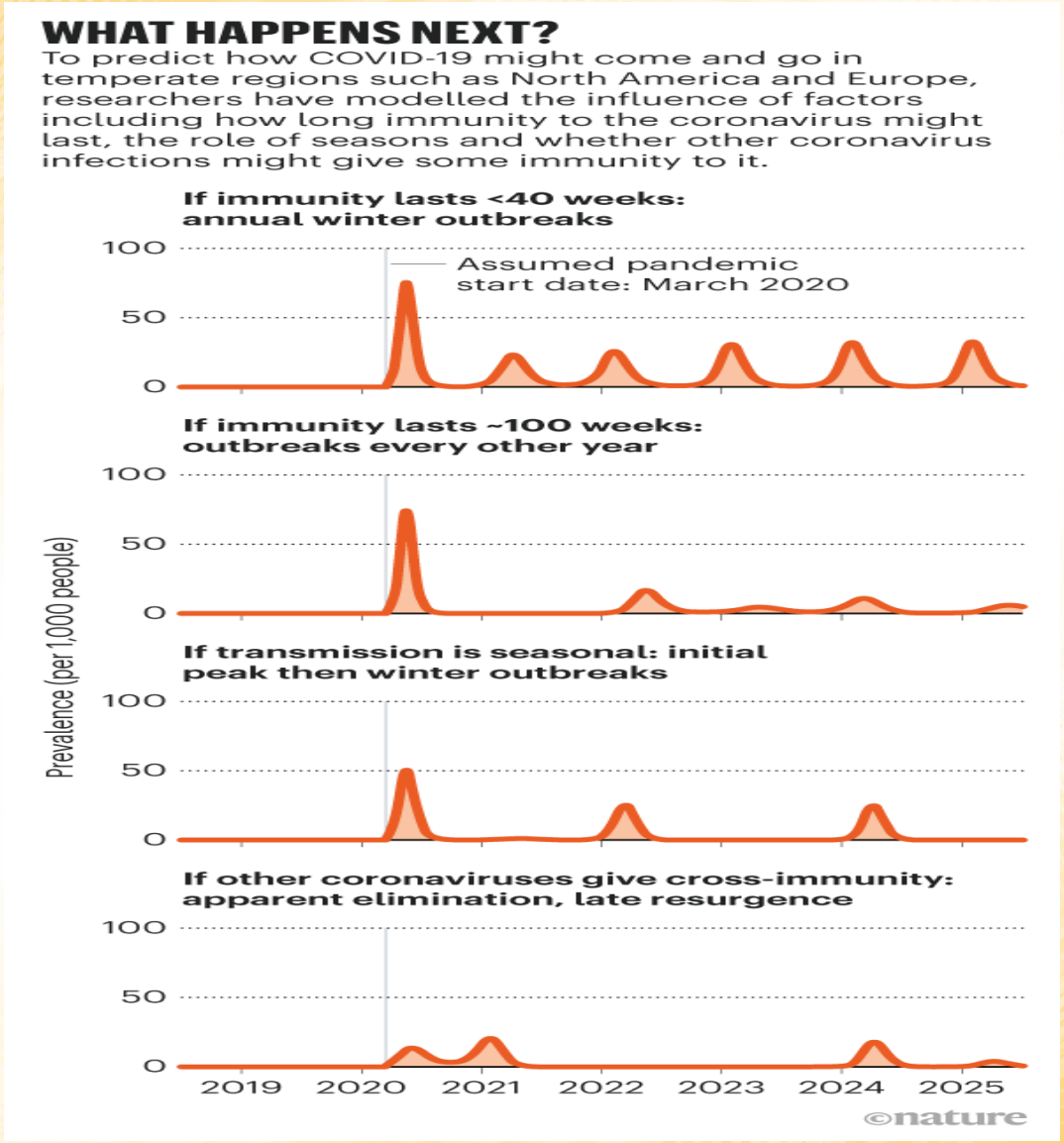
*ages 18-34
Random sample of adult outpatients with COVID-19 from 14 U.S. academic health care systems

To stay well and protect others…

- Stay 6 feet away from others not living in your household
- Wash hands often
- Wear face coverings consistently and correctly in public

CDC.GOV bit.ly/MMWR72420 MMWR

Future of COVID



First Documented COVID-19 Reinfection, Immunity May Not Last

- That is almost unassailable evidence that the man was infected a second time, and another indication, albeit far from definitive, that immunity to SARS-CoV-2 may not last very long.
- Interestingly, the patient was asymptomatic during his second infection, the authors said.
- Reinfection was suspected in a few previous cases of COVID-19, but never documented. Many experts believed what appeared to be reinfection was simply prolonged infection.
- Epidemiological, clinical, serological and genomic analyses confirmed that the patient had reinfection instead of persistent viral shedding from first infection.

Most Frequent Post-COVID Symptoms

Number of respondents in a survey of people with long-term symptoms who said they suffered from:

Fatigue	1,567
Muscle or body aches	1,046
Shortness of breath or difficulty breathing	1,020
Difficulty concentrating or focusing	924
Inability to exercise or be active	916
Headache	902
Difficulty sleeping	782
Anxiety	746
Memory problems	714
Dizziness	656

Source: "COVID-19 'Long Hauler' Symptoms Survey Report," Indiana University School of Medicine and Survivors Corps, July 2020

A Third of COVID Survivors Have Long-Haul Symptoms

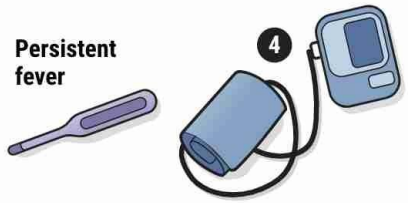
- About 33% of COVID-19 patients who were never sick enough to require hospitalization continue to complain months later of symptoms like fatigue, loss of smell or taste and "brain fog," University of Washington (UW) researchers found.
- The brain fog's particularly debilitating to folks who do a lot of intellectual work and often work from home via computer," Ganesh said. "They just can't focus on the computer that long, and the bright lights bother them and give them headaches. They're just not as productive as they used to be, and it's very frustrating for them.
- Nearly 31% of patients said they had a worse health-related quality of life now, compared to before getting COVID-19, the researchers reported.

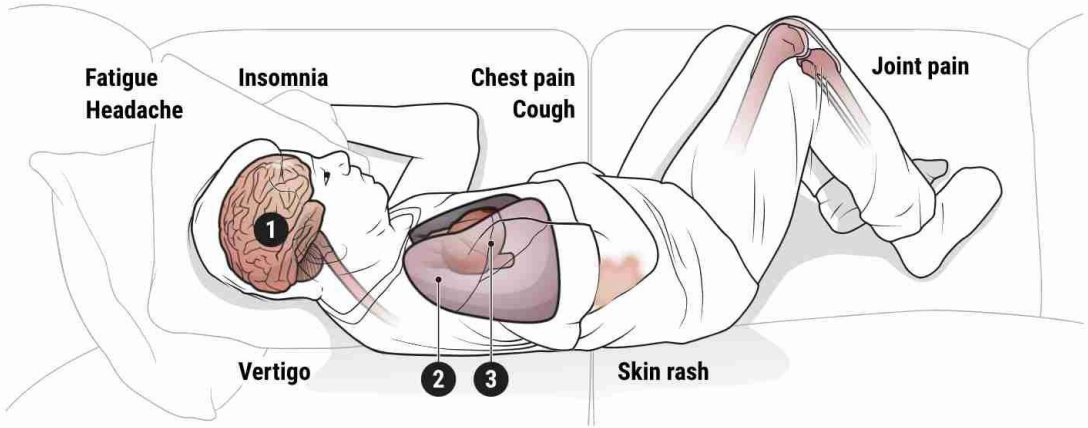
More Than a Quarter of Long COVID Patients Still Not Recovered After 6 Months

- How long can some COVID symptoms linger? New research suggests that more than a quarter of adults who had COVID-19 in 2020 weren't fully recovered six to eight months later.
- There's growing evidence that COVID-19 can cause long-term physical and mental health problems. These cases -- called long-haul COVID -- are a growing issue for health care systems.
- This study included 431 people in Zurich, Switzerland, who tested positive for SARS-CoV-2 (the virus that causes COVID-19) between February and August 2020. They all completed an online health questionnaire about seven months after their initial diagnosis. Their average age was 47.
- Nearly 9 in 10 of the participants had symptoms when they were diagnosed, and 19% were hospitalized at the time of their diagnosis.
- Overall, 26% of the patients reported in the questionnaire they had not fully recovered after their initial COVID-19 diagnosis. Of those, 55% reported fatigue; 25% had shortness of breath, and 26% had symptoms of depression.

Pain that lingers

A subset of COVID-19 patients experiences ongoing symptoms and complications such as organ damage, and researchers are proposing reasons for some of them (bottom). Scientists are trying to identify such symptoms, how common they are, how long they last, who's at risk, and how to treat and prevent them.





1 Brain fog
Difficulty thinking can occur after acute COVID-19 infection. The virus may damage brain cells, and inflammation in the brain or body may also cause neurologic complications. Other viral infections can also lead to brain fog.

2 Shortness of breath
Doctors are eyeing lung and heart complications including scarring. Patients who become critically ill with COVID-19 seem more likely to have lingering shortness of breath, but those with mild cases are also at risk.

3 Heart arrhythmia
The virus can harm the heart, and doctors are concerned about long-term damage. How the heart heals after COVID-19 could help determine whether a patient develops an irregular heartbeat.

4 Hypertension
Some patients have high blood pressure after an acute infection, even when cases were relatively mild and people were previously healthy, possibly because the virus targets blood vessels and heart cells.

Prolonged Brain Dysfunction in COVID-19 Survivors: A Pandemic in its Own Right?

- One in three survivors of COVID-19, those more commonly referred to as COVID-19 long-haulers, suffered from neurologic or psychiatric disability six months after infection, a recent landmark study of more than 200,000 post-COVID-19 patients showed.
- Researchers looked at 236,379 British patients diagnosed with COVID-19 over six months, analyzing neurologic and psychiatric complications during that time period. They compared those individuals to others who had experienced similar respiratory illnesses that were not COVID-19.
- They found a significant increase in several medical conditions among the COVID-19 group, including memory loss, nerve disorders, anxiety, depression, substance abuse and insomnia. Additionally, the symptoms were present among all age groups and in patients who were asymptomatic, isolating in home quarantine, and those admitted to hospitals.
- The results of this study speak to the seriousness of long-term consequences of COVID-19 infection. Numerous reports of brain fog, post-traumatic stress disorder, heart disease, lung disease and gastrointestinal disease have peppered the media and puzzled scientists over the past 12 months, begging the question: What effect does COVID-19 have on the body long after the acute symptoms have resolved?

- Several other viruses, including a large majority of those that cause common upper and lower respiratory infections, have been shown to produce such chronic symptoms as anxiety, depression, memory problems and fatigue. Experts believe that these symptoms are likely due to long-term effects on the immune system. Viruses trick the body into producing a persistent inflammatory response resistant to treatment.
- Myalgic encephalomyelitis, also known as chronic fatigue syndrome, is one such illness. Researchers believe this condition results from continuous activation of the immune system long after the initial infection has resolved.
- In contrast to other viral infections, the COVID-19 survivors in the study reported persistent symptoms lasting more than six months, with no significant improvement over time. The abundance of psychiatric symptoms was also notable and likely attributable to both infection and pandemic-related experience.

Man Needed Double Lung Transplant, Wishes He'd Been Vaccinated

- A 24-year-old Georgia man who contracted COVID-19 and required a double lung transplant, and who remains hospitalized, has expressed his regret he did not get vaccinated for the virus, which has so far killed more than 607,000 Americans.
- Blake Bargatze had told his parents he was putting off receiving a COVID-19 vaccine because he felt uncertain about its possible side effects.
- Bargatze, who had no preexisting medical conditions and has endured prolonged intensive care stays at hospitals in three different states over the last three months, believes he contracted COVID-19 during an April visit to Florida.
- Many complications occurred during his hospital stay that caused extensive damage to his lungs, requiring the need for a double lung transplant to survive. Blake was transferred to the University of Maryland Medical Center on June 12th. He remains on the ventilator and ECMO as he waits for the lung transplant."

Many ICU staff have experienced mental health disorders in COVID-19 pandemic

- In a study of 515 healthcare staff working in intensive care units (ICUs) in seven countries, the researchers found that 48 percent of participants had mental health problems - depression, insomnia and post-traumatic stress disorder (PTSD).
- The team also found a 40 per cent increase in these conditions for those who spent more than six hours in personal protective equipment (PPE), compared to those who didn’t.

In Conclusion

- COVID-19 pathophysiology is more than just respiratory dysfunction
- The body's response to the disease may be more deadly than the disease itself
- There is a subset of COVID patients that symptoms continue to manifest long beyond "recovery".

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