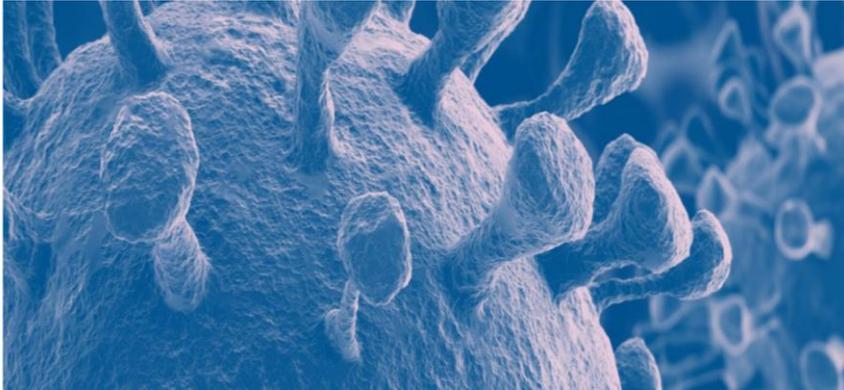


# Insuficiencia Respiratoria y COVID



Dr. Agustín Acuña Izcaray

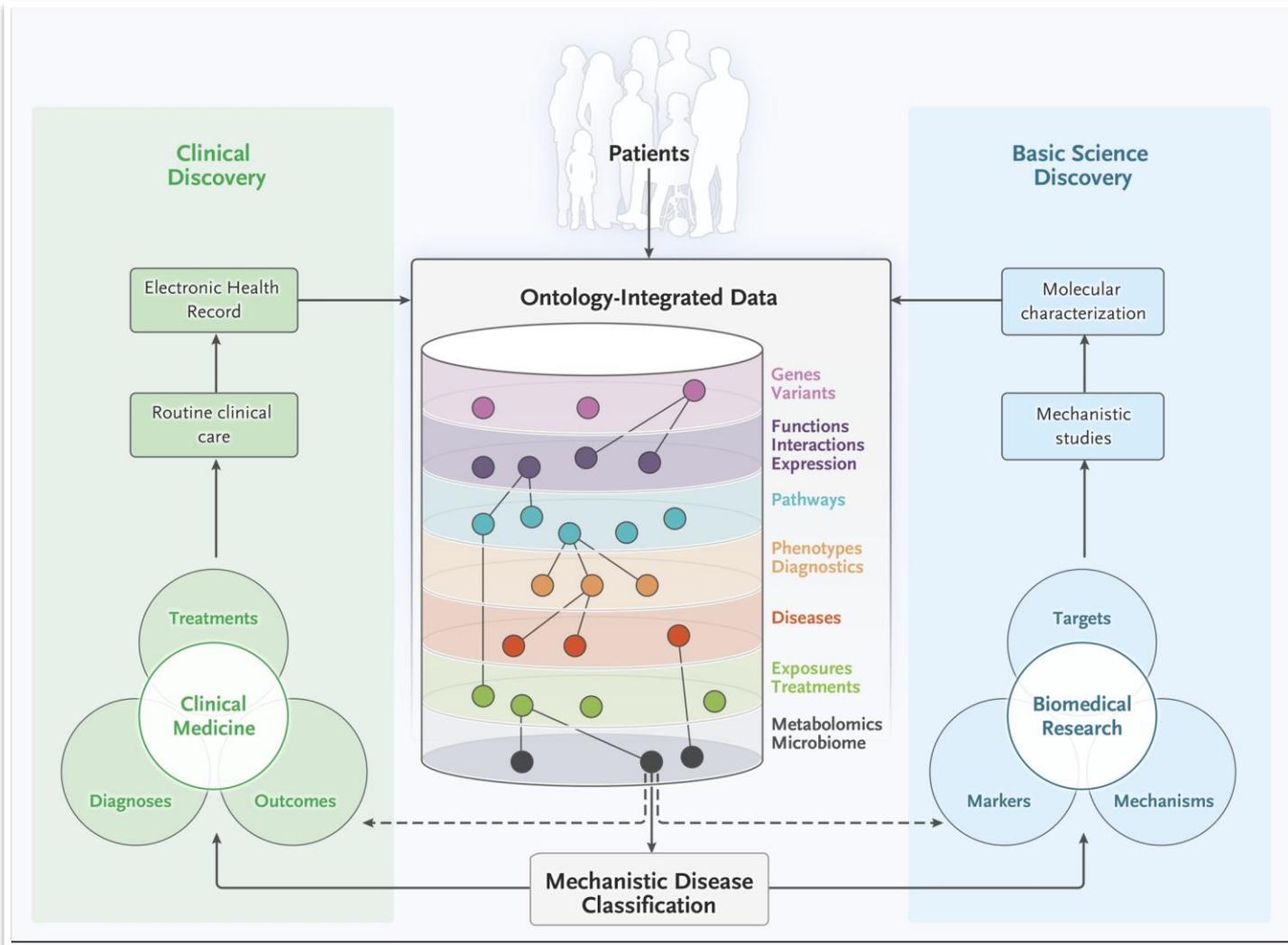


# Agenda

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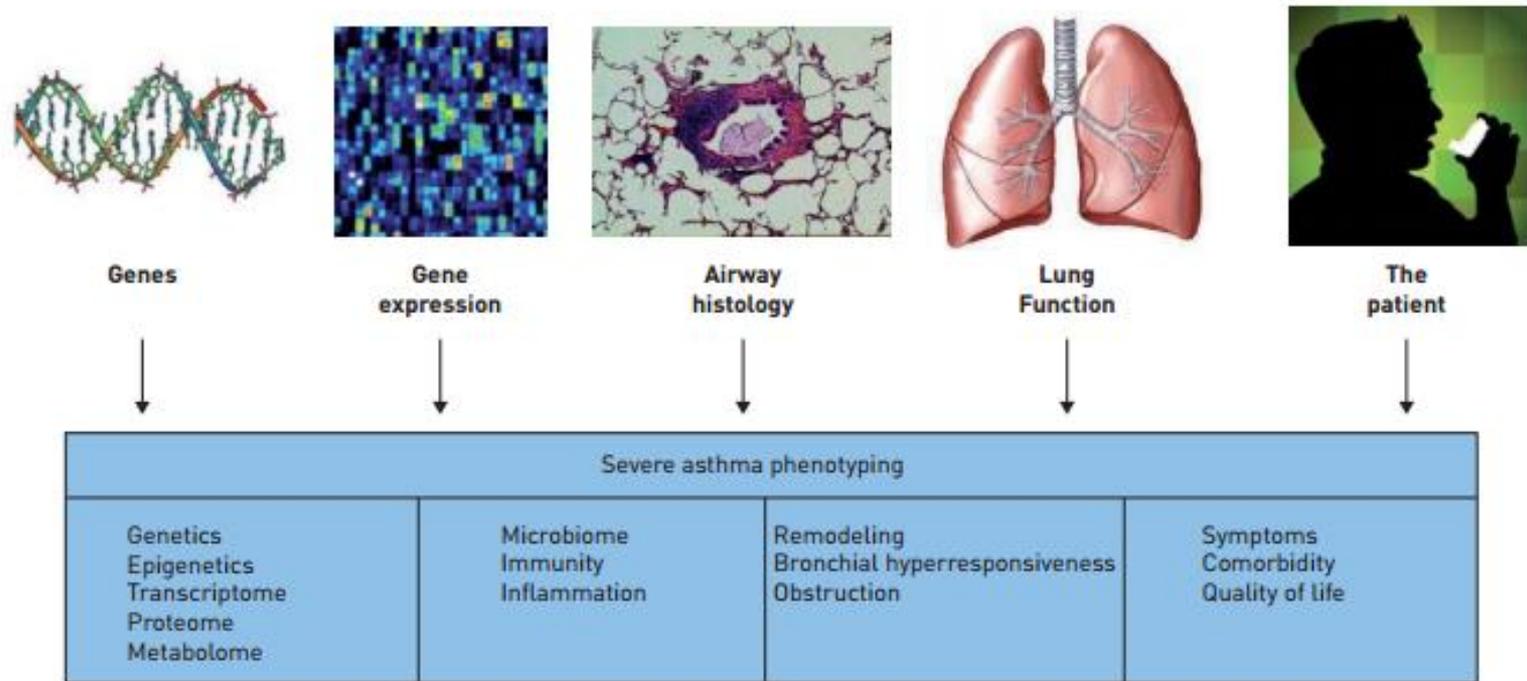
- **Epidemiología y características clínicas.**
- **Patogenia de la IRA en la infección por SARS CoV2**
- **Mecanismos fisiopatológicos de la IRA**

# SARS COV-2 / COVID-19. Desafío para describir una nueva enfermedad



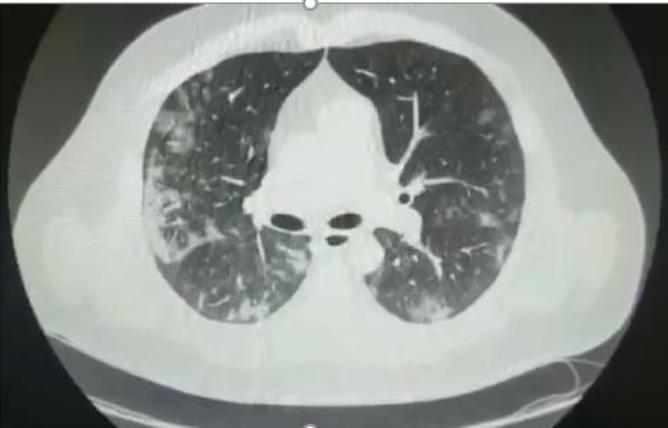
Haendel MA et al. N Engl J Med 2018;379:1452-1462

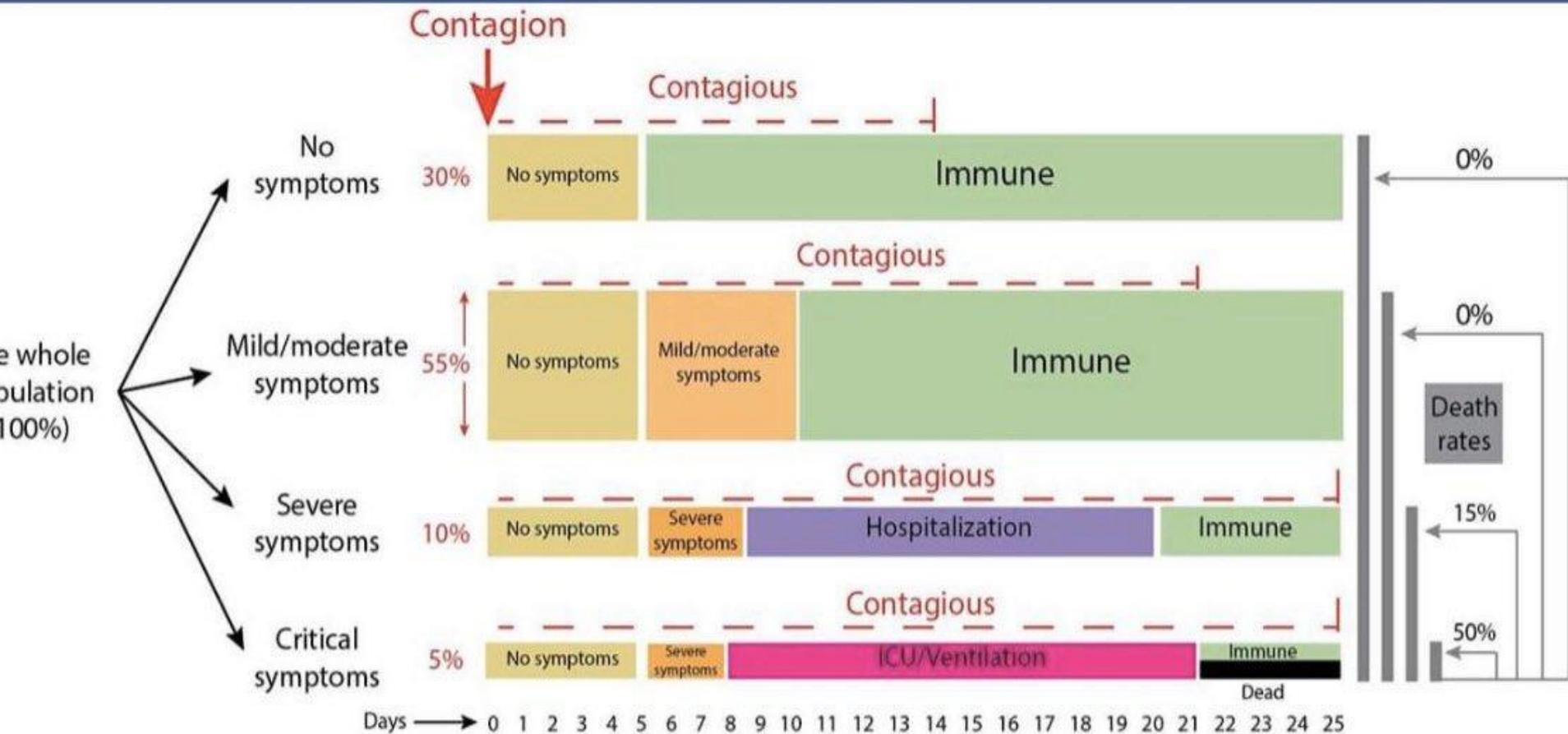
# De los Endotipos a los Fenotipos



# Espectro clínico del COVID-19

N=1



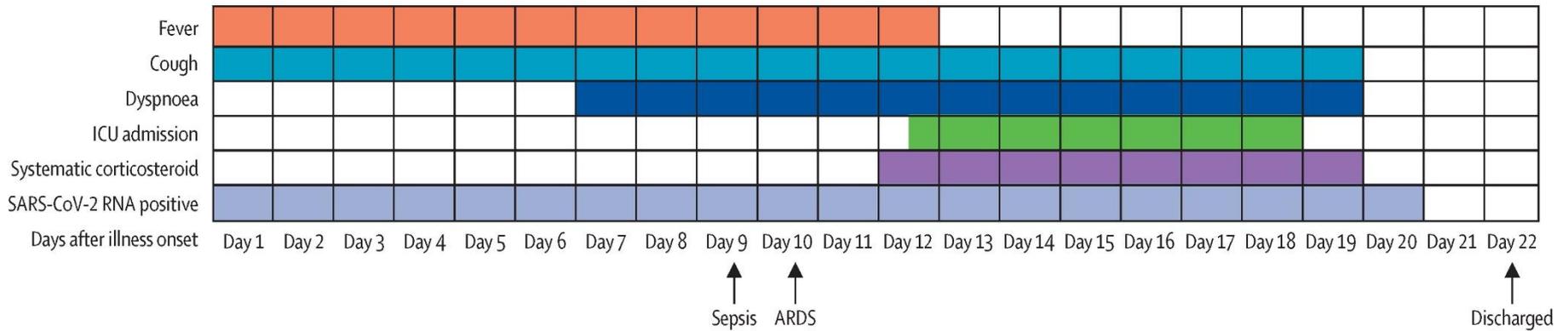


References:

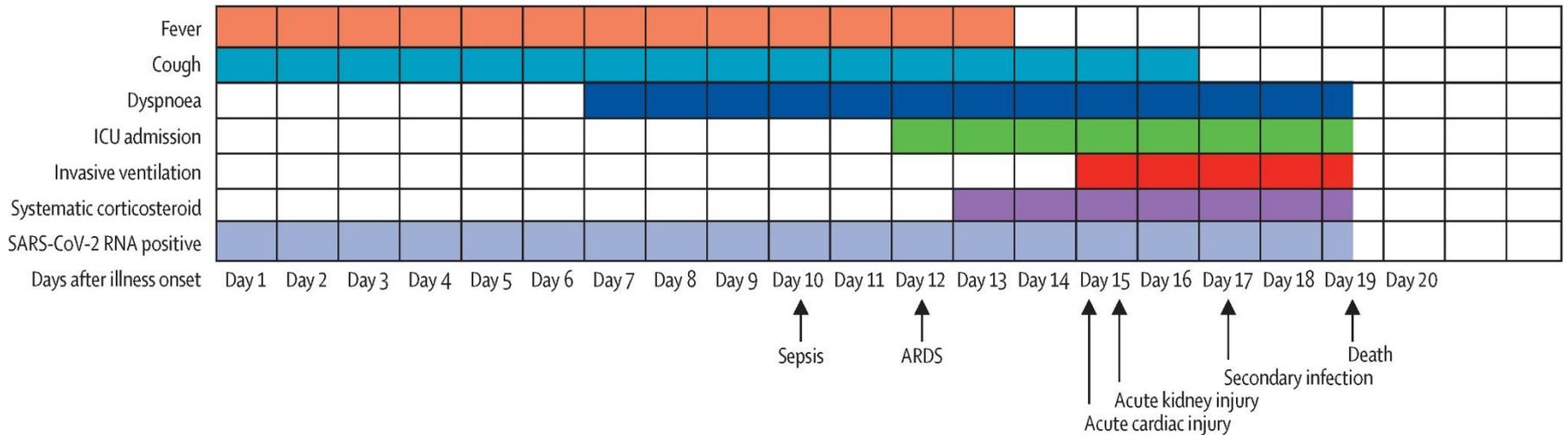
1. The Incubation Period of Coronavirus Disease 2019 (COVID-19) From Publicly Reported Confirmed Cases: Estimation and Application. Lauer SA et al. Ann Intern Med. 2020 Mar 10.
2. Impact of non-pharmaceutical interventions (NPIs) to reduce COVID19 mortality and healthcare demand. Neil M Ferguson et al. Imperial College COVID-19 Response Team. 16 March 2020.
3. Viral dynamics in mild and severe cases of Covid-19. Yang Liu et al. The Lancet, March 19, 2020.

# Curso clínico y factores de riesgo

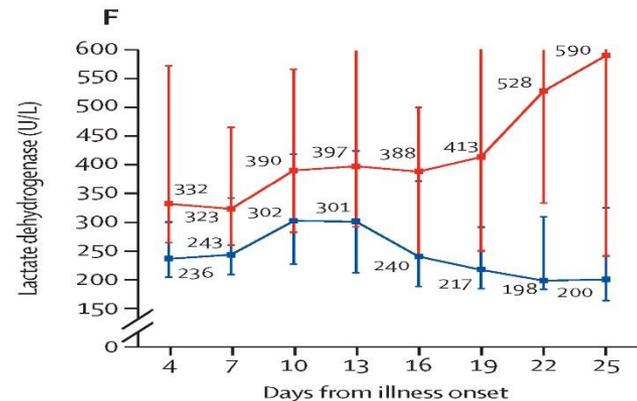
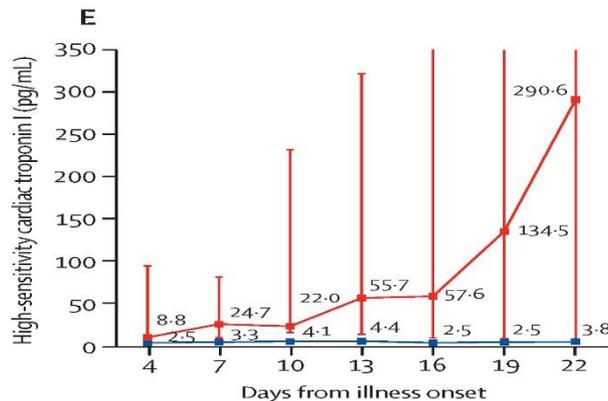
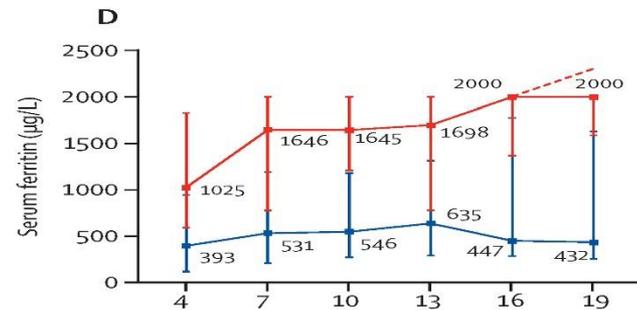
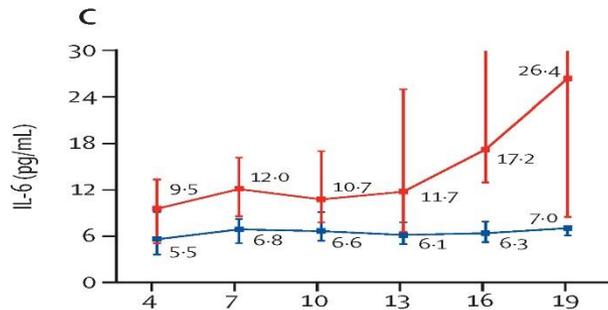
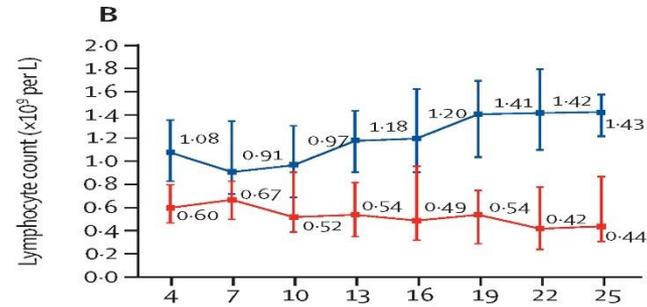
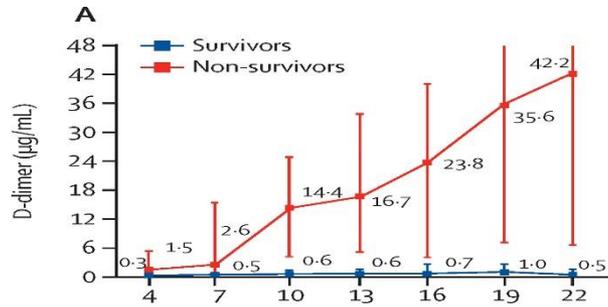
## Survivors



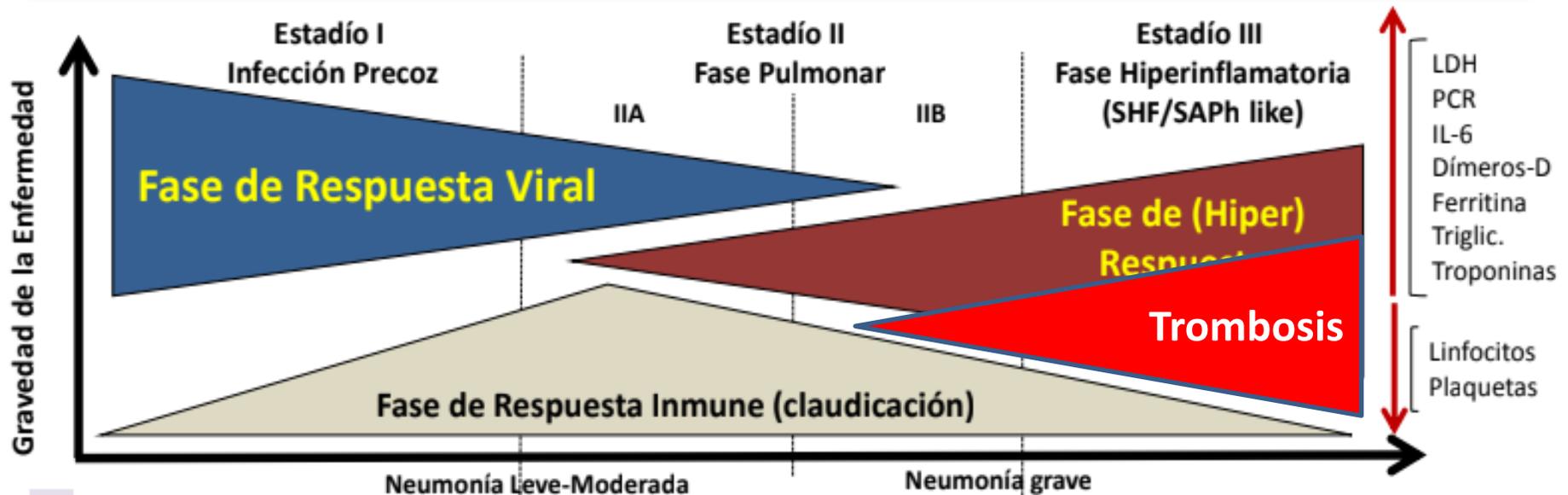
## Non-survivors



# Curso clínico y factores de riesgo



## Esquema fisiopatogénico de SARS-CoV-2 y estrategia terapéutica múltiple



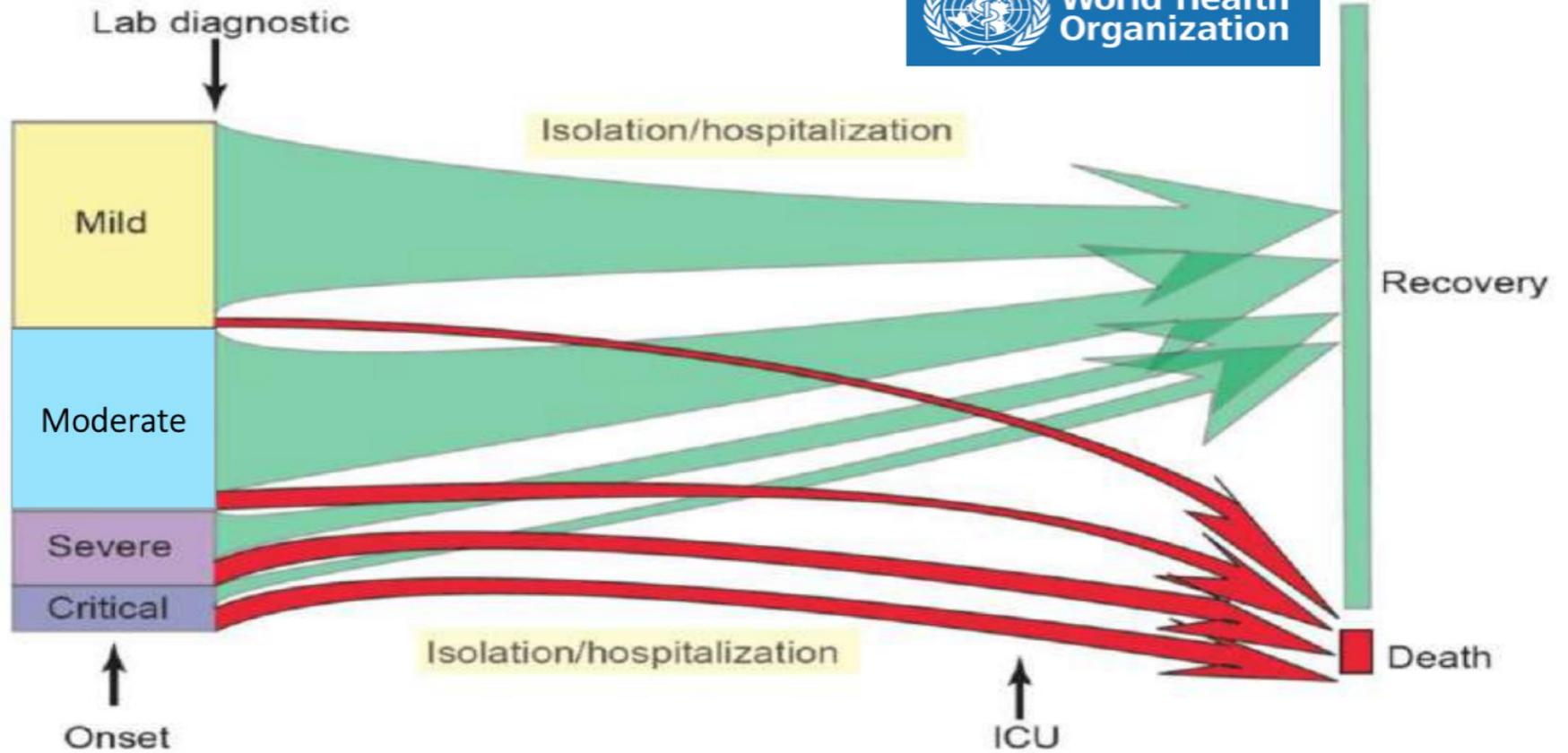
	Curso evolutivo		
	Neumonía Leve-Moderada		Neumonía grave
<b>Semiología</b>	Sintomatología constitucional, Fiebre, tos seca, diarrea, cefalea, alteraciones gusto y olfato	Disnea, Hipoxemia (PaO <sub>2</sub> /FiO <sub>2</sub> ≤ 300 mmHg)	SHF reactivo, SAPH-like, SDRA, Sepsis/Shock, Fallo cardiaco
<b>Laboratorio</b>	Linfocitosis o inicio linfopenia, aumento de PCR, tiempo de protrombina, Dímeros-D y LDH	Infiltrados pulmonares (bilaterales) Elevación de transaminasas, PCT normal o baja, Linfopenia creciente	Elevación de marcadores inflamatorios y de disfunción endotelial o coagulación (LDH, Ferritina, PCR, IL-6, Dímeros-D), Aumento de troponina y pro-BNP

Modificado de Siddiqqi et al JHLT 2020.

Protocolo de Hospital Universitario y politecnico.La Fe , Valencia- España.



World Health Organization



Immediate Goals	Intermediate Goals	Long-term goals
<b>Diagnostics:</b> RNA assays, antibody & antigen assays, point of care detection	Diagnostics: Multiplex diagnostic platforms	Diagnostics: Prognostic markers
<b>Therapeutics:</b> Remdesivir, favipiravir, chloroquine, plasma, TCM	Therapeutics: intravenous immunoglobulin (IVIg)	Therapeutics: Innovative approaches (CRISPR-CAS; RNAi; Cell-based; positive hits from library screening)
<b>Vaccines:</b> Development of animal models	Vaccines: mRNA candidates and candidate viral vectors	Vaccines: inactivated candidates and subunit candidates

# Agenda

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- Epidemiología y características clínicas.
- **Patogenia de la IRA en la infección por SARS CoV2**
- Mecanismos fisiopatológicos de la IRA

# ACE 2. La Protagonista

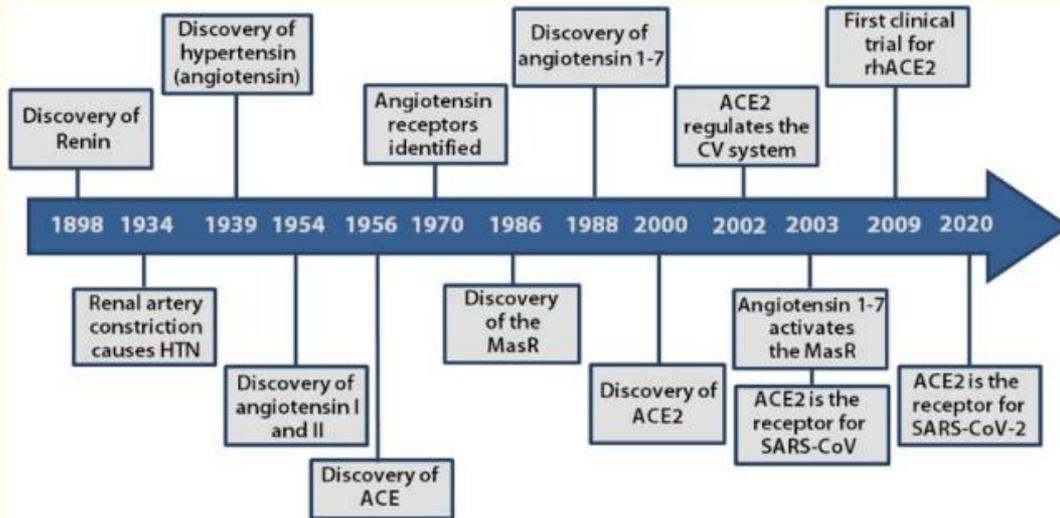
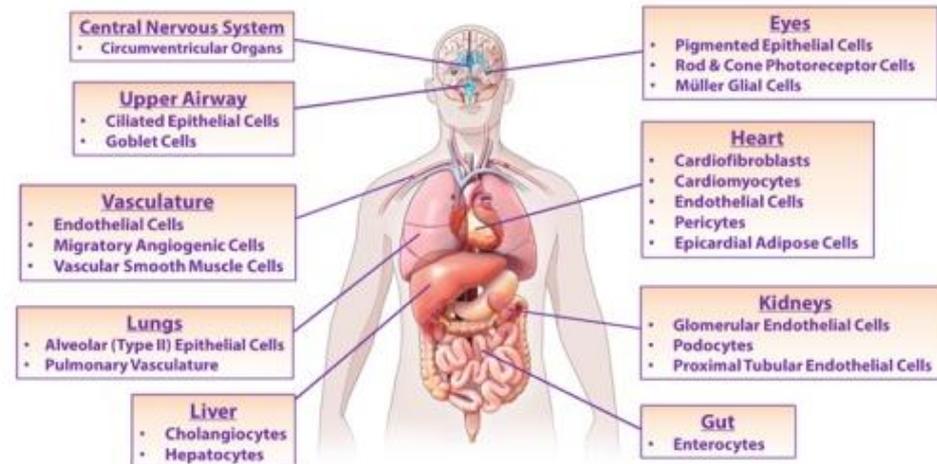


Figure 1

## ACE2 Expression



[Circ Res. 2020 May 8; 126\(10\): 10.1161/CIRCRESAHA.120.317015.](https://doi.org/10.1161/CIRCRESAHA.120.317015)

nature  
medicine

BRIEF COMMUNICATION

<https://doi.org/10.1038/s41591-020-0868-6>

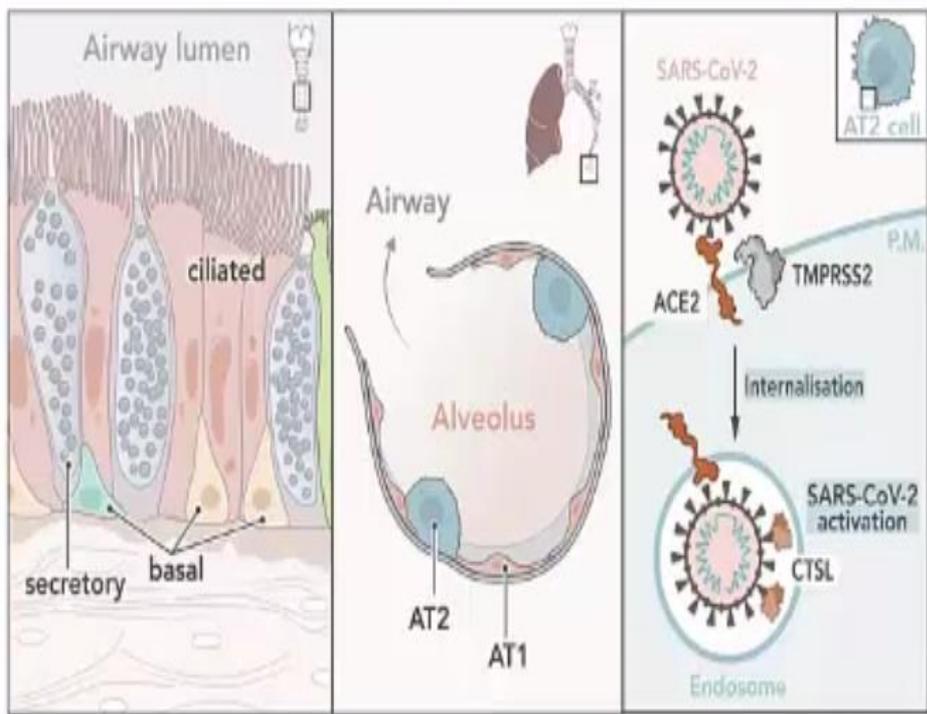
Check for updates

SARS-CoV-2 entry factors are highly expressed  
in nasal epithelial  
immune genes

Cell

Article

**SARS-CoV-2 Receptor ACE2 Is an Interferon-Stimulated Gene in Human Airway Epithelial Cells and Is Detected in Specific Cell Subsets across Tissues**

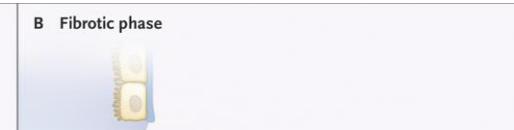
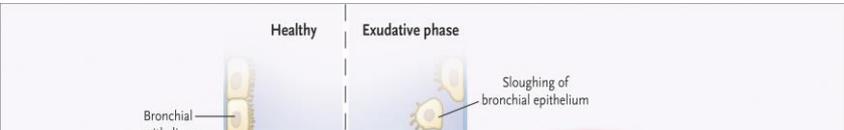


Yu Zhao *et al.*, BioRxiv, Jan 2020  
doi: <https://doi.org/10.1101/2020.01.26.919985>

Sungnak *et al.*, Nat Med (2020)

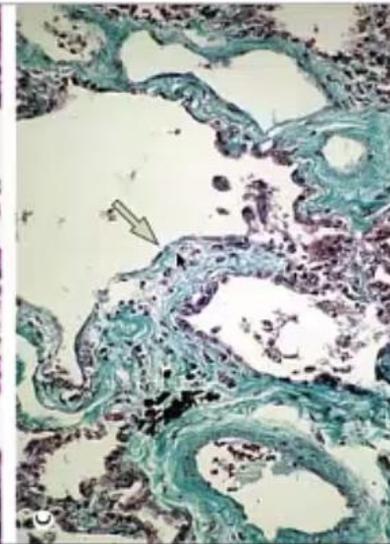
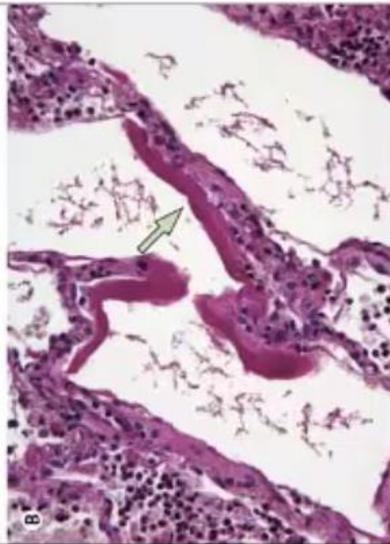
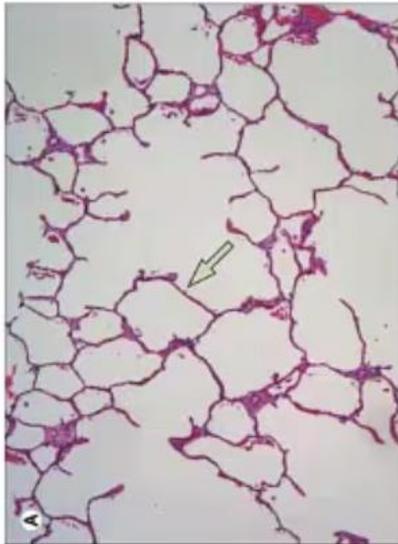
Ziegler *et al.*, Cell (2020)

# Inmunopatología del SDRA



## ARDS.....

- Thille *et al Lancet RM* 2013

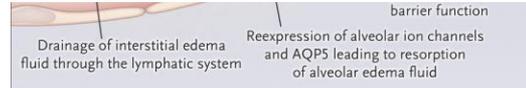


Damage to basement membrane leading to failure in epithelialization

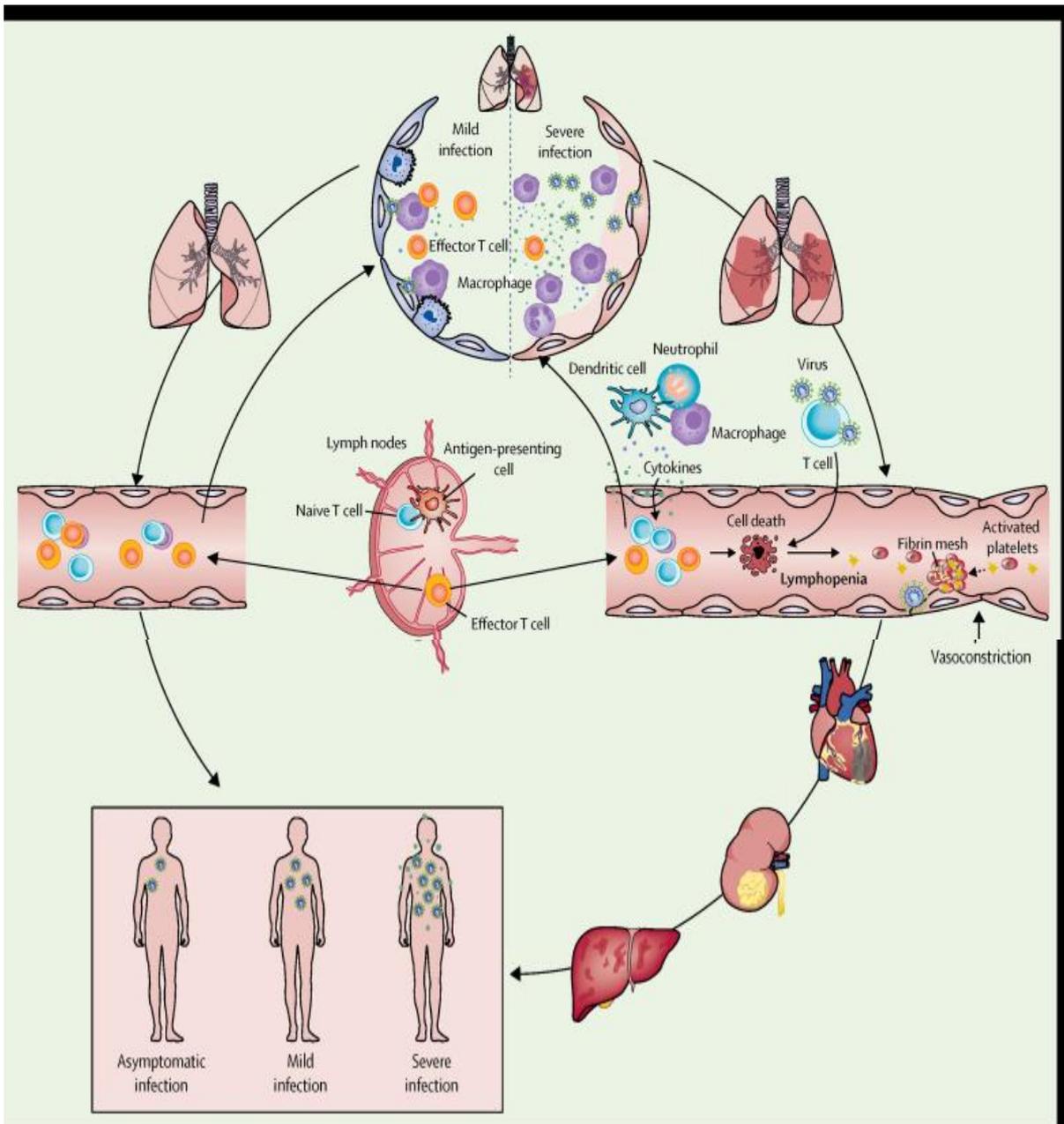
Denuded basement membrane and lack of surfactant production

Spread and extensive deposition of extracellular matrix leading to interstitial and alveolar fibrosis

Proliferative and prolonged activation of fibroblasts and differentiation into highly synthetic myofibroblasts



# SARS COV 2 y Sepsis viral





# PROGRESS

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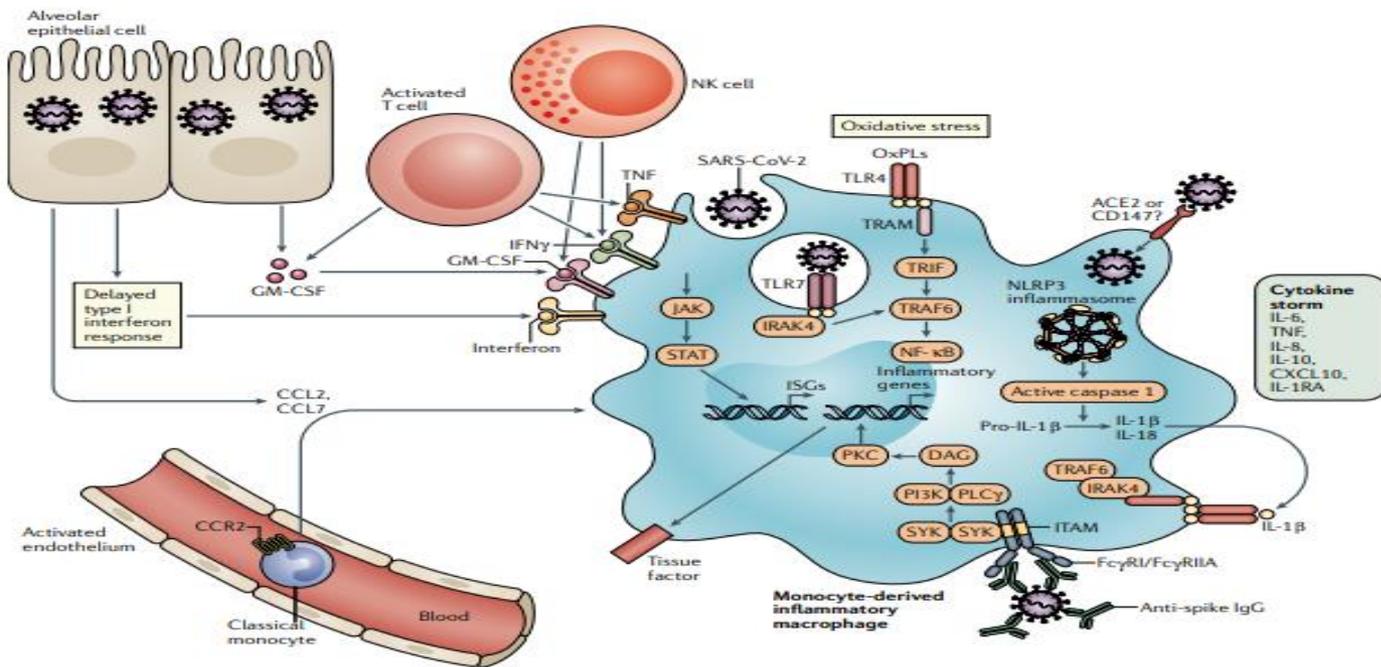
## Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages

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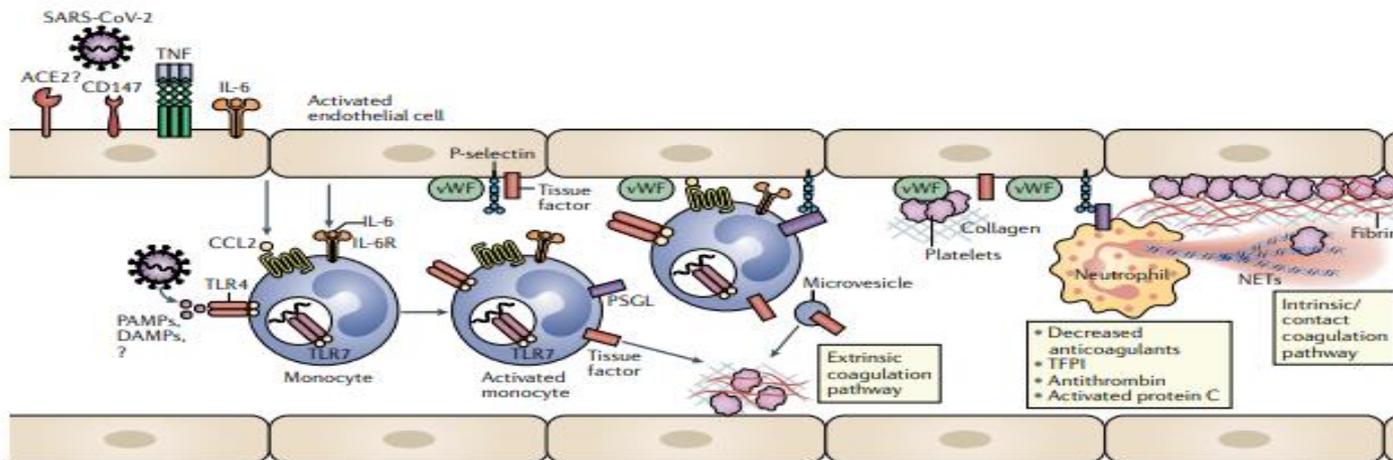
Miriam Merad and Jerome C. Martin 

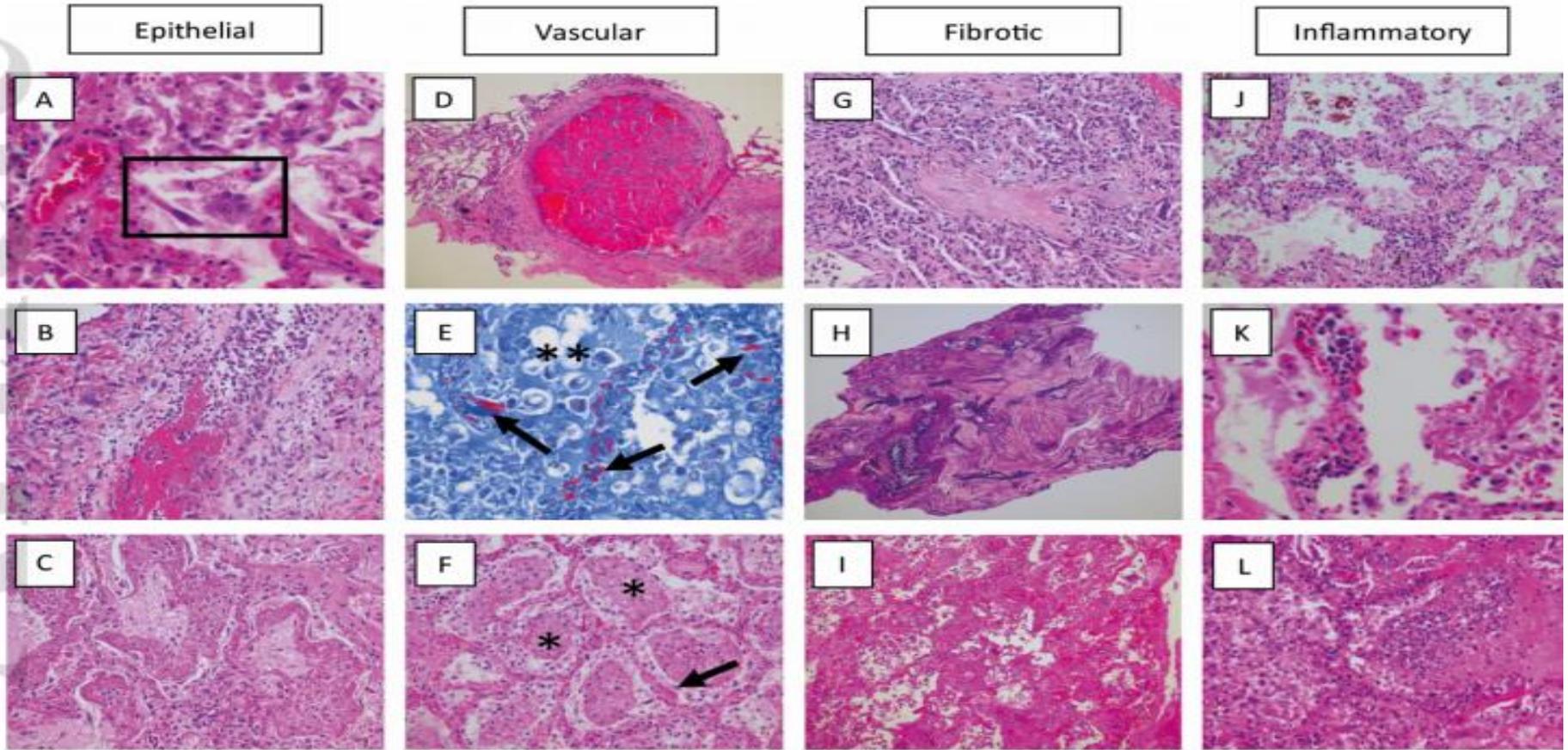
lymph nodes and kidney<sup>10,11</sup>, as observed in post-mortem analysis.

Given that the morbidity and mortality seen in COVID-19 is associated with excessive inflammation, a better understanding of the immunological underpinnings of the differential responses seen in patients infected with SARS-CoV-2 is necessary to better identify therapeutic targets. Dozens of immunomodulatory agents are rapidly going



## PROGRESS





Jan von der Thüsen, Menno van der Eerden. Histopathology and Genetic Susceptibility in COVID-19 Pneumonia.

Eur J Clin Invest. 2020 Apr 30. doi: 10.1111/eci.13259

# Agenda

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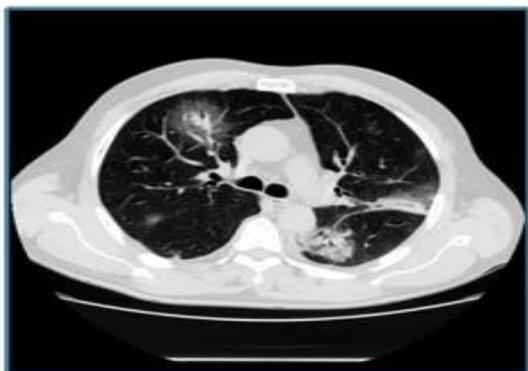
- Epidemiología y características clínicas.
- Patogenia de la IRA en la infección SARS CoV2
- **Mecanismos fisiopatológicos de la IRA**



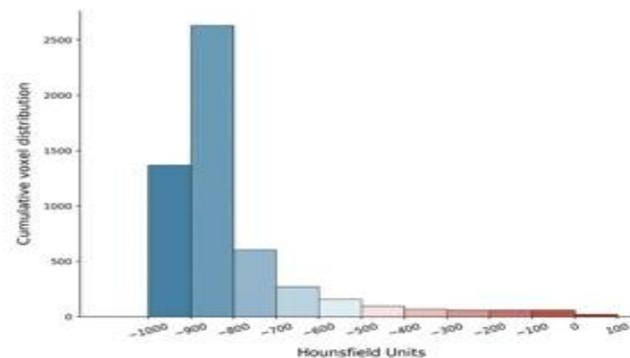
# COVID-19 pneumonia: different respiratory treatments for different phenotypes?

Luciano Gattinoni<sup>1\*</sup>, Davide Chiumello<sup>2</sup>, Pietro Caironi<sup>3,4</sup>, Mattia Busana<sup>1</sup>, Federica Romitti<sup>1</sup>, Luca Brazzi<sup>5</sup> and Luigi Camporota<sup>6</sup>

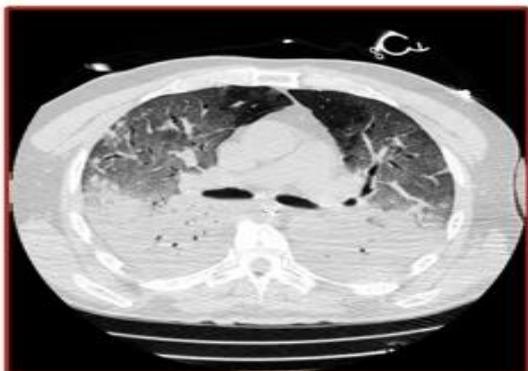
A



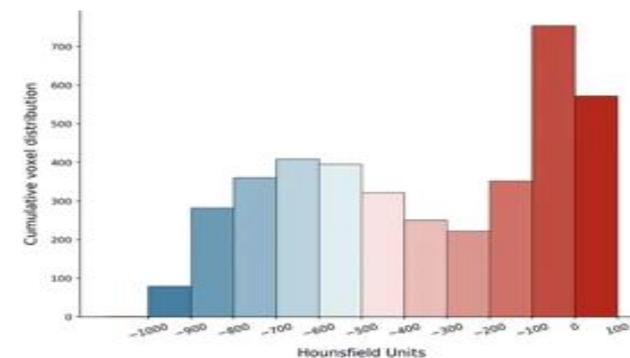
$\text{PaO}_2/\text{FiO}_2$   
95 mmHg



B



$\text{PaO}_2/\text{FiO}_2$   
84 mmHg

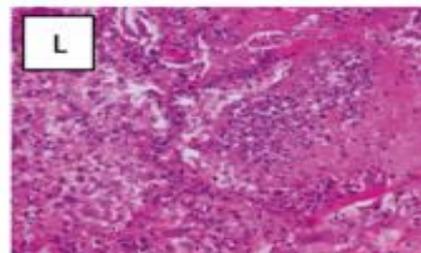
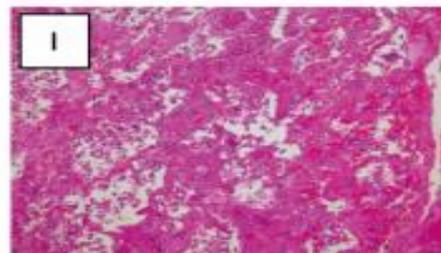
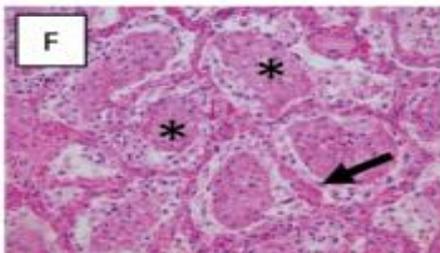
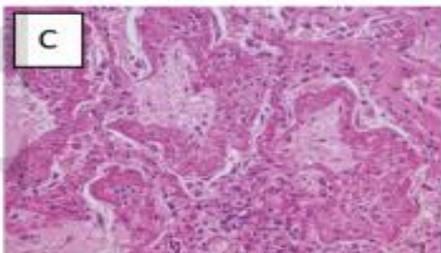
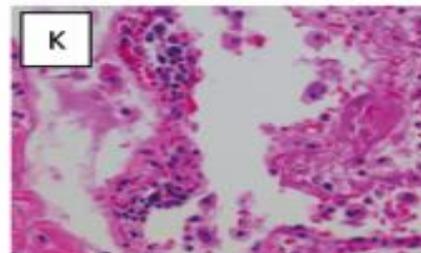
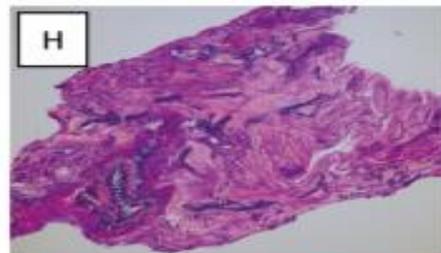
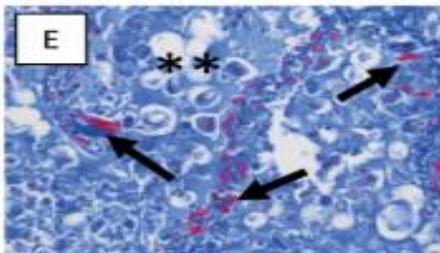
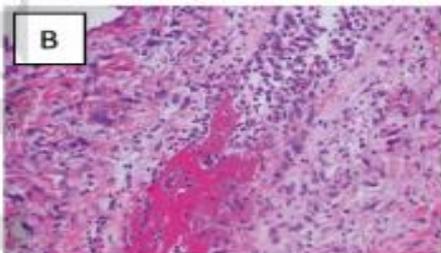
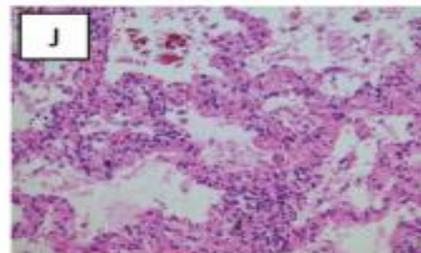
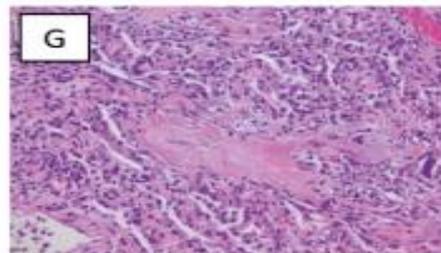
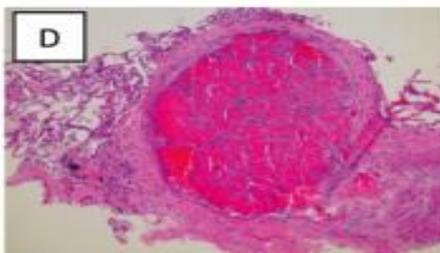
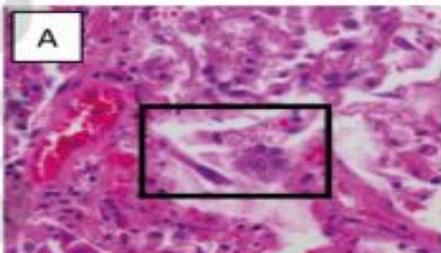


Epithelial

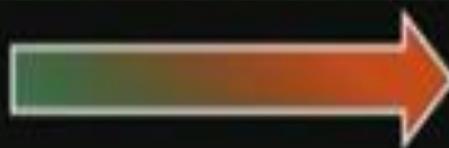
Vascular

Fibrotic

Inflammatory

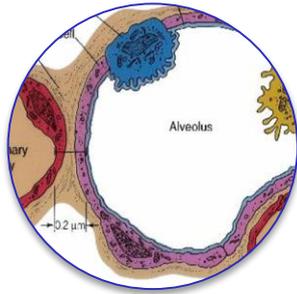


Phenotype L



Phenotype H

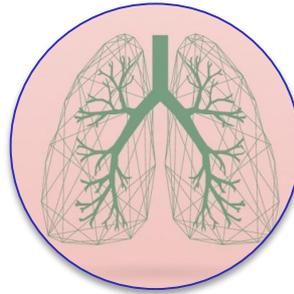
# Compromiso Respiratorio. Epectros o Dominios



Intersticio

**Trastorno de difusión**

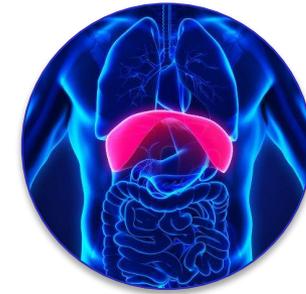
Sind de llenado alveolar  
SDRA/neumonitis/alveolitis



Vías Aéreas

**V/Q bajo**

Hipoventilación



Circulación  
pulmonar o  
neuromuscular

**V/Q alto**

Respuesta inmuntrombótica



# COCLUSIONES

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- **La COVID 19 tiene un espectro clínico amplio.**
- **La patogenia de la IRA por infección por SARS Cov -2 no es igual a un a la del SDRA**
- **Los mecanismos de hipoxemia pueden ser múltiples y su evaluación temprana permitirá mejorar nuestra aproximación terapéutica.**