Νόσος COVID-19

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ΕΘΝΙΚΟ ΚΑΙ ΚΑΠΟΔΙΣΤΡΙΑΚΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΑΘΗΝΩΝ
ΙΑΤΡΙΚΗ ΣΧΟΛΗ

Β΄ΚΛΙΝΙΚΗ ΕΝΤΑΤΙΚΗΣ ΘΕΡΑΠΕΙΑΣ
Πανεπιστημιακό Νοσοκομείο ΑΤΤΙΚΟΝ
Χαιδάρι - Αθήνα


CONFLICT OF
INTEREST
No!

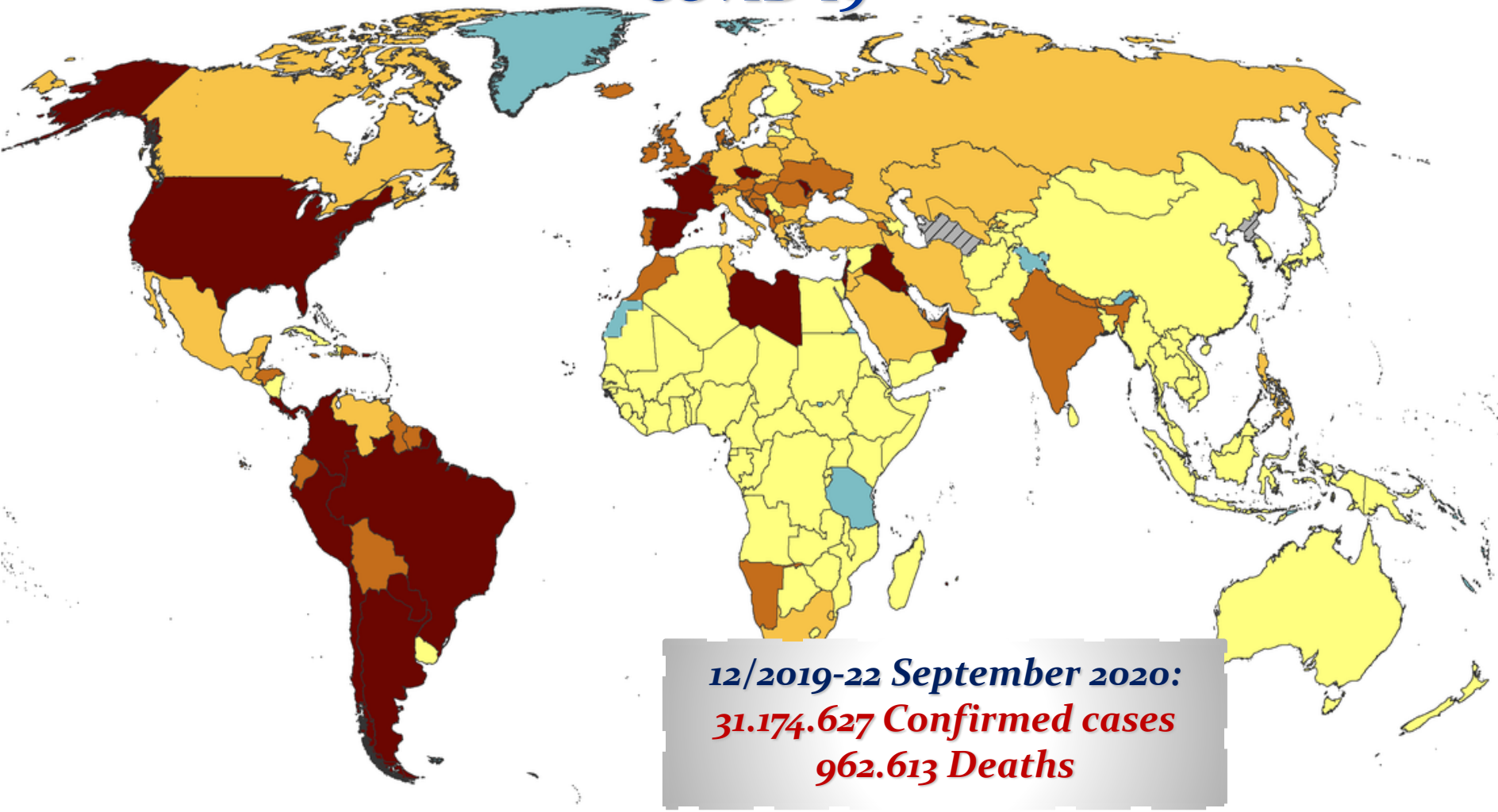
Νόσος COVID-19
Ιστορική αναδρομή

- **Δεκέμβριος 2019 :** Wuhan China
  - ✓ ασθενείς με πνευμονία που τάχιστα εξελίσσετο σε ΑΑ και ARDS
- **17 Ιανουαρίου 2020 :** ταυτοποίηση αιτίου

Στη πρόσφατη ιστορία της Ιατρικής ίσως είναι η μόνη λοίμωξη που μέσα σε 2 μήνες από ενδημία χαρακτηρίσθηκε πανδημία

- **20 Μαρτίου 2020** : lockdown
- **Ιούνιος 2020** : μεγάλη μείωση κρουσμάτων στην Ελλάδα
- **Σεπτέμβριος 2020** : 2ο κύμα

COVID-19



12/2019-22 September 2020:
31.174.627 Confirmed cases
962.613 Deaths

14-day COVID-19 case notification rate per 100 000, as of 22 of September, 2020

< 20.0 | 20.0 - 59.9 | 60.0 - 119.9 | ≥ 120.0 | No new cases reported

No cases reported by WHO and no cases identified in the public domain

Date of production: 22/09/2020

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Δομή του ιού

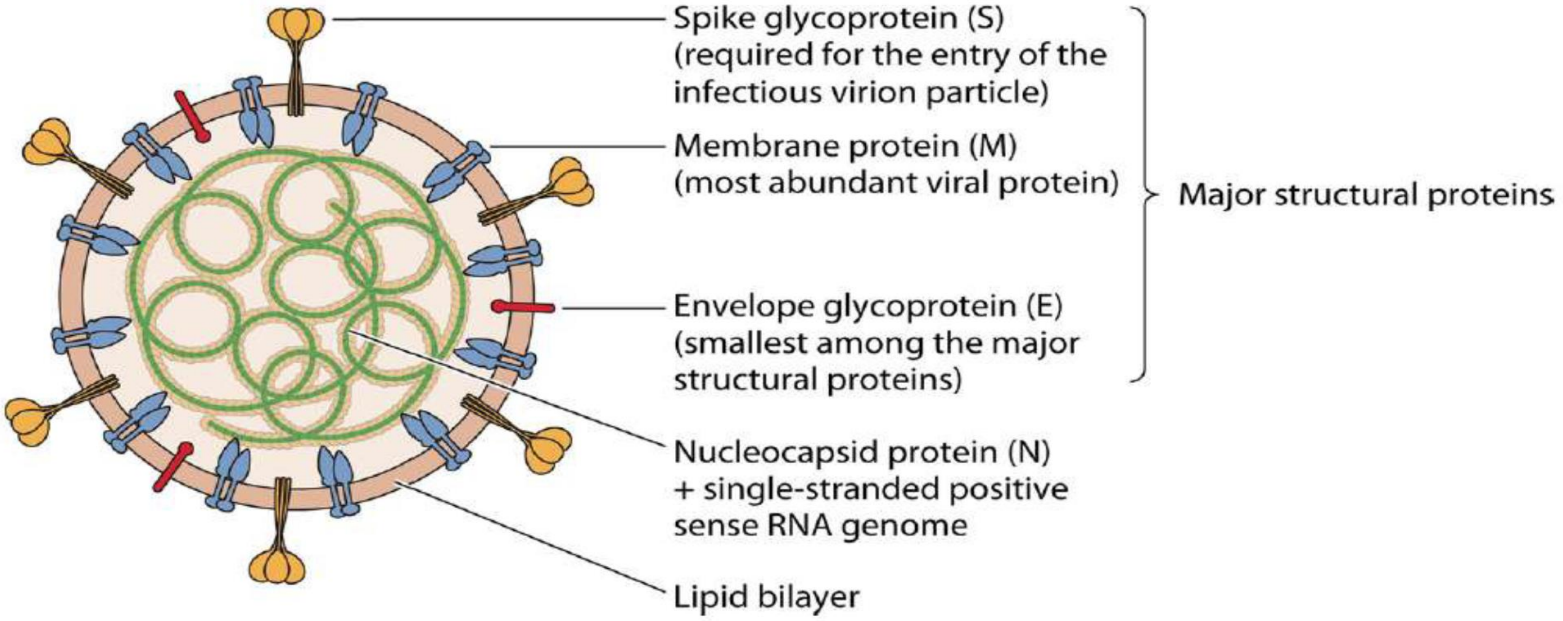

FIG 2 SARS-CoV-2 virus structure.

Dhama K et al - 2020.- Coronavirus disease 2019–COVID-19. Clin Microbiol Rev 33:e00028-20. https://doi.org/10 .1128/CMR.00028-20.

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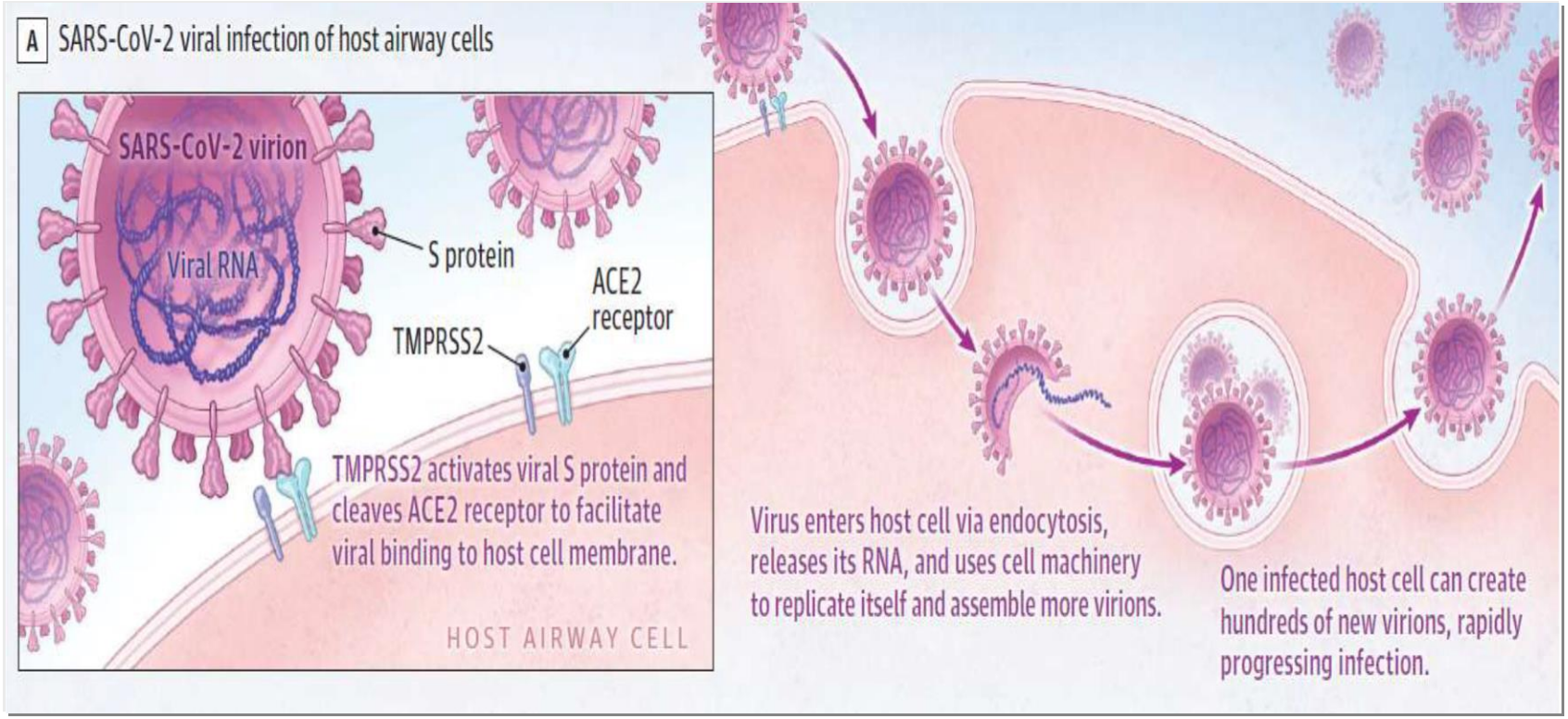
Είσοδος του ιού στον ανθρώπινο οργανισμό



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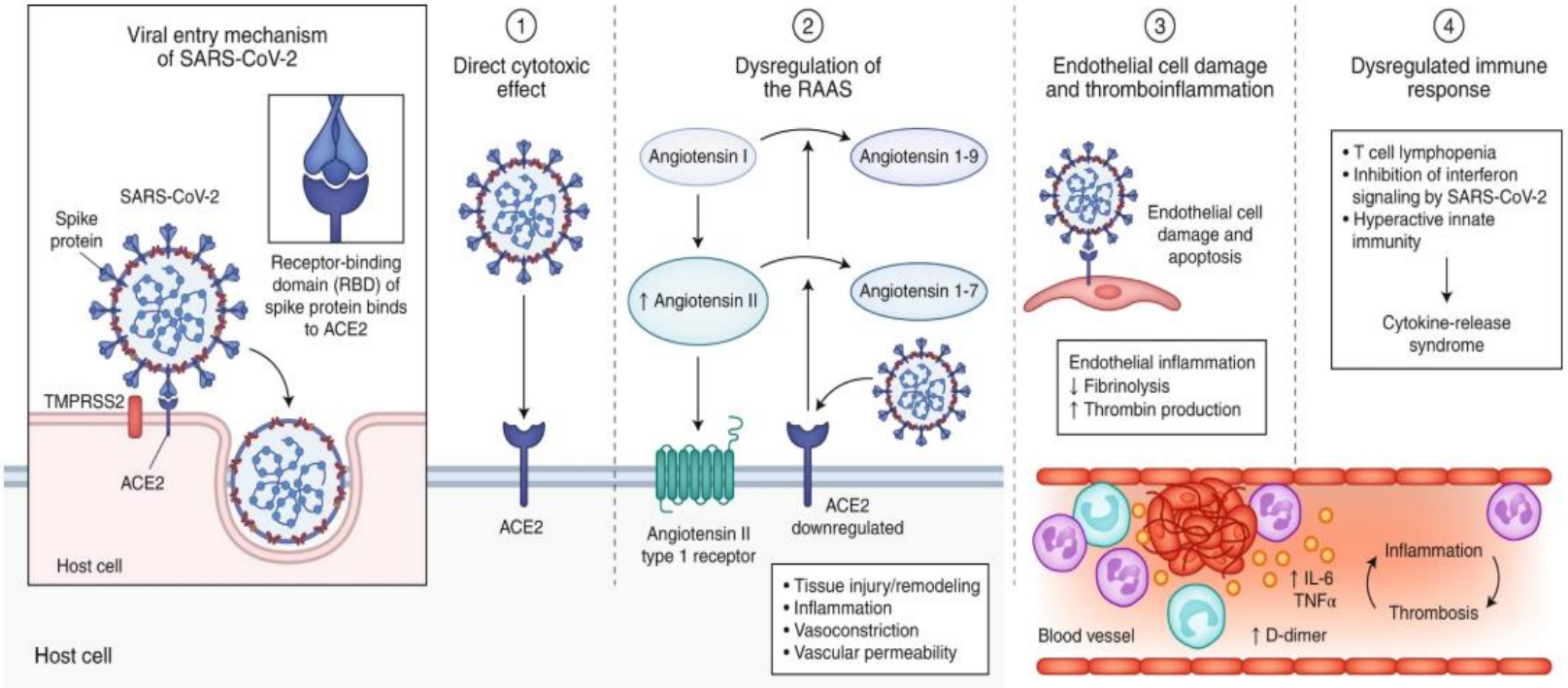
Παθοφυσιολογία

Fig. 1: Pathophysiology of COVID-19.

From: Extrapulmonary manifestations of COVID-19



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ACE2 Υποδοχέας

- Lung alveolar epithelial cells
- Enterocytes of the small intestine
- Arterial and venous endothelial cells
- Arterial smooth muscle cells

Hamming et al J Pathol 2004

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ACE2 Υποδοχέας

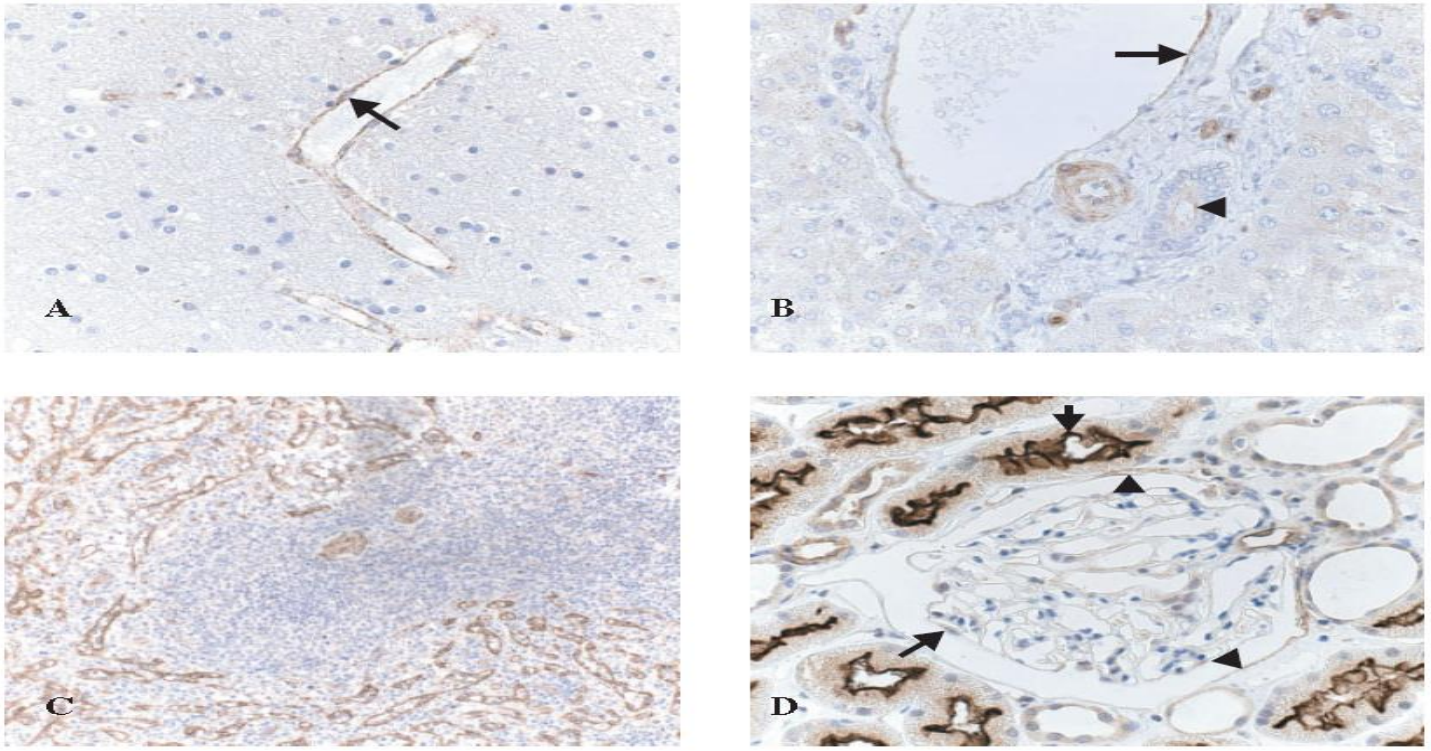

Figure 4. In the brain (A), ACE2 is expressed only in endothelium (arrow) and vascular smooth muscle cells. In the liver (B), Kupffer cells, hepatocytes, and the endothelium of sinusoids are negative. Luminal staining in bile ducts is occasionally observed (arrow-head). Vascular endothelium (arrow) and smooth muscle cells are positive. In the spleen (C), ACE2 is not expressed in cells of the immune system. Vascular and red pulp sinus endothelium is positive. In the kidney (D), ACE2 is present in glomerular visceral (arrow) and parietal (arrow-head) epithelium, in the brush border (short arrow) and cytoplasm of proximal tubular cells, and in the cytoplasm of distal tubules and collecting ducts

Hamming et al J Pathol 2004

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Παράγοντες κινδύνου

- **Μεγάλη ηλικία**

  Κατά την πορεία φάνηκε ότι στόχο της λοίμωξης αποτελούν και
  - οι νεότερες ηλικίες
  - άτομα χωρίς συνυπάρχοντα νοσήματα

- **Συνυπάρχοντα νοσήματα**
  - Σακχαρώδης Διαβήτης ΙΙ
  - Αρτηριακή Υπέρταση
  - Χρόνιες νόσοι του αναπνευστικού
  - Ανοσοκαταστολή
  - Ενεργή κακοήθεια
  - Παχυσαρκία

Huang C et al Lancet 2020;395:497-550

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Παχυσαρκία

Demographic and clinical features of critically ill patients with COVID-19 in Greece: The burden of diabetes and obesity

P. Halvatsiotis [a,*], A. Kotanidou [b], K. Tzannis [a], E. Jahaj [b], E. Magira [b], M. Theodorakopoulou [c], G. Konstandopoulou [c], E. Gkeka [d], C. Pourzitaki [d], N. Kapravelos [e], S. Papoti [e], M. Sileli [e], C. Gogos [f], D. Velissaris [f], N. Markou [g], E. Stefanatou [g], G. Vlachogianni [h], E. Aimoniotou [h], A. Komnos [i], T. Zafeiridis [i], P. Koulouvaris [j], A. Armaganidis [c], A. Bamias [a], G. Dimopoulos [c]

- 90 ασθενείς από όλες τις ΜΕΘ της Ελληνικής Επικράτειας

Parameters	Group A N = 21 (23.3%)	Group B N = 24 (26.7%)	Group C N = 45 (50%)	p-value
Age (years)	≤55	56–65	≥66	
	Median (25–75th percentile)			
BMI (kg/m^2)	30.8 (28–35.1)	29.4 (26.5–32.9)	27.7 (26–29.3)	0.003*

Parameters	Group A N = 21 (23.3%)	Group B N = 24 (26.7%)	Group C N = 45 (50%)	p-value
Mechanical ventilation				0.636
No	2 (9.5)	3 (12.5)	3 (6.7)	
Yes	19 (90.5)	21 (87.5)	42 (93.3)	
Outcome				0.902
Death in ICU	7 (35)	8 (34.8)	11 (25.6)	
Discharged	3 (15)	3 (13)	6 (14)	
Still in ICU	10 (50)	12 (52.2)	26 (60.4)	

Diabetes Research and Clinical Practice 2020

Νόσος COVID-19

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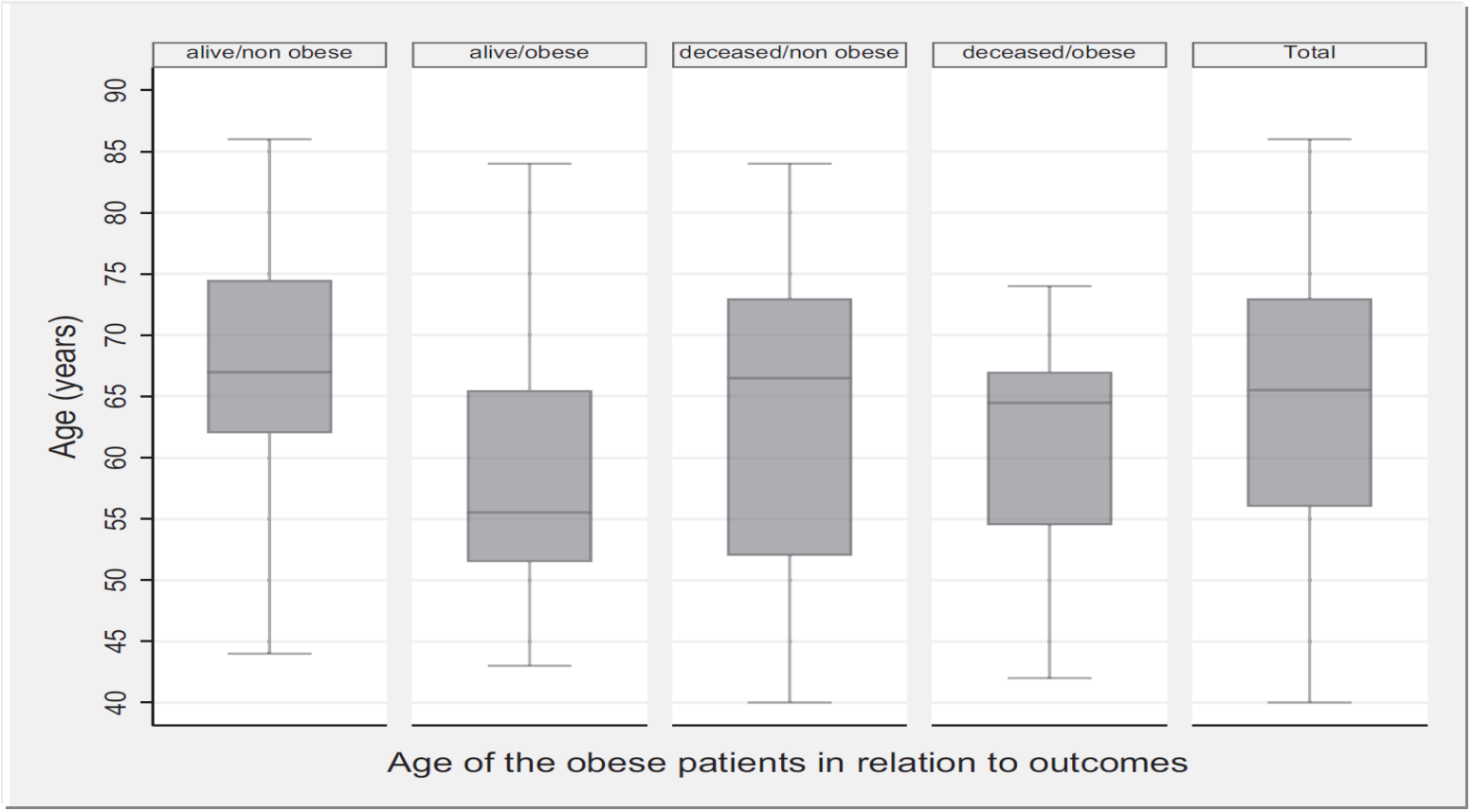
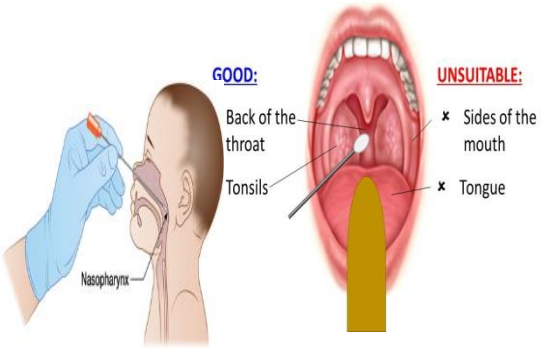
P. Halvatsiotis [a,*], A. Kotanidou [b], K. Tzannis [a], E. Jahaj [b], E. Magira [b], M. Theodorakopoulou [c], G. Konstandopoulou [c], E. Gkeka [d], C. Pourzitaki [d], N. Kapravelos [e], S. Papoti [e], M. Sileli [e], C. Gogos [f], D. Velissaris [f], N. Markou [g], E. Stefanatou [g], G. Vlachogianni [h], E. Aimoniotou [h], A. Komnos [i], T. Zafeiridis [i], P. Koulouvaris [j], A. Armaganidis [c], A. Bamias [a], G. Dimopoulos [c]



Diabetes Research and Clinical Practice 2020

CLINICAL SAMPLE

DIRECT MOLECULAR DETECTION

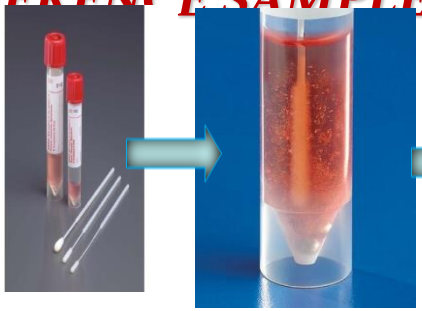


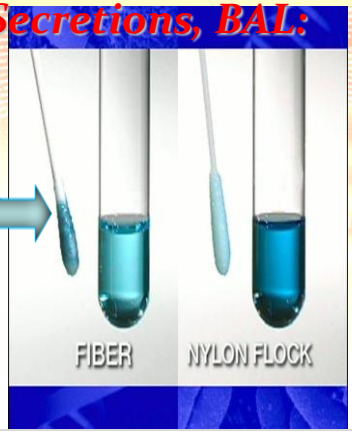
NASOPHARYNGEAL SWAB:

REFERENCE SAMPLE

For Intubated Patients:

Sputum, Bronchial Secretions, BAL:





ATTENTION! USE OF “Synthetic Flocked Swab”
(Low material’s adsorption for efficient Vortex elution)

WHICH MOLECULAR METHODS?

Diagnostic strategies for SARS-CoV-2 infection and interpretation of microbiological results

Caruana G et al.
CMI 2020; Accepted Article
https://doi.org/10.1016/j.cmi.2020.06.019

Table 1. Advantages and disadvantages of molecular diagnostic methods for detection of SARS-CoV-2.

NAAT extraction method	Advantages	Disadvantages
rRT-PCR	Reference method, high sensitivity and specificity, compatibility with automation and multi-panels	Long TAT without automation
Nested PCR	Increased sensitivity due to the added pre-amplification step	Longer TAT and lower specificity due to the higher risk of contamination
RT-LAMP	Shorter TAT	Possible slightly lower sensitivity
RT-iiPCR		Possible slightly lower sensitivity
Gene expert	Automation, high sensitivity and specificity, molecular rapid test	High costs, limited number of samples per time

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Συστηματική νόσος

Νόσος COVID-19

Συστηματική νόσος

Η νόσος COVID-19 πρέπει να θεωρείται σαν

- Πνευμονίτις
- Οξεία ενδοθηλίτις και διάχυτη θρόμβωσις
- Πιθανή μυοκαρδίτις
- Κατάσταση που προκαλεί βλάβες σε «δευτεροπαθή» όργανα

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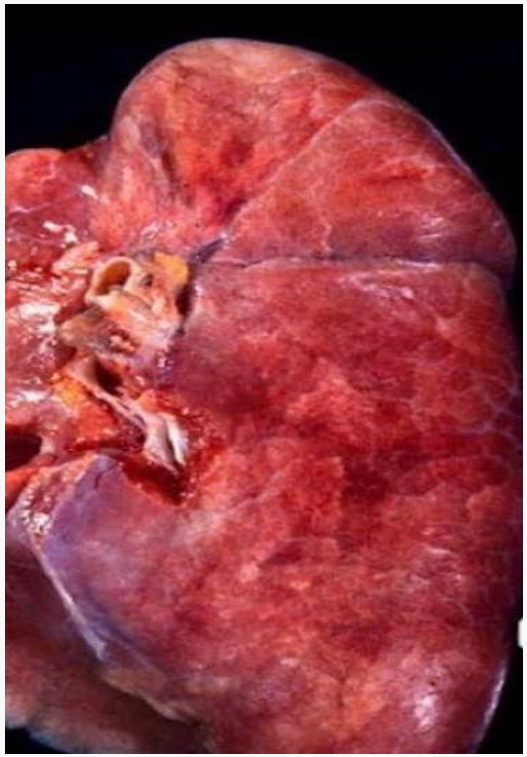
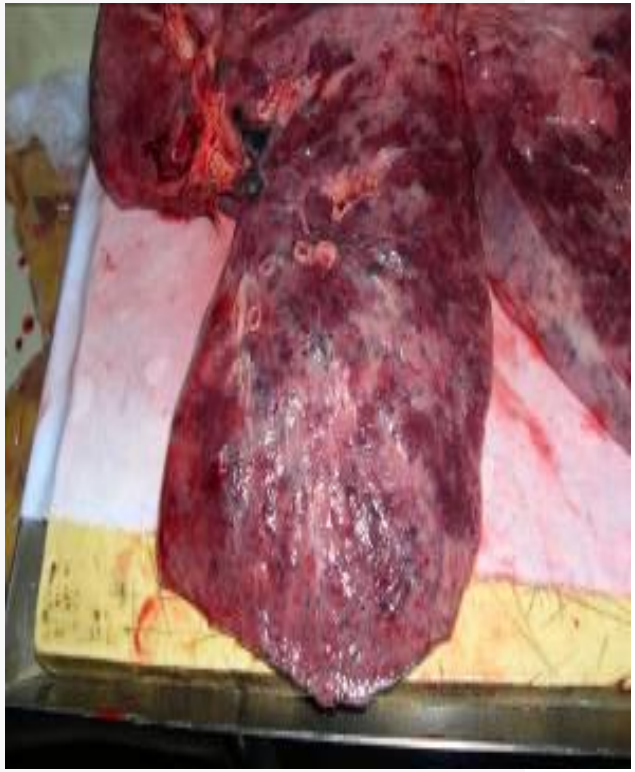
Post-mortem findings in CoVID-19 pneumonia

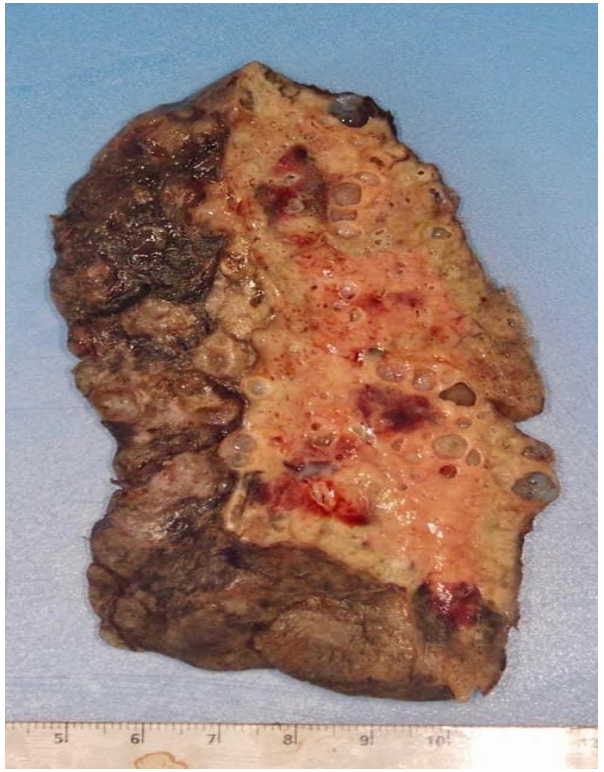
Normal



ARDS



COVID-19



Barisione M, Grillo F, Ball L et al, Virchows Archiv 2020

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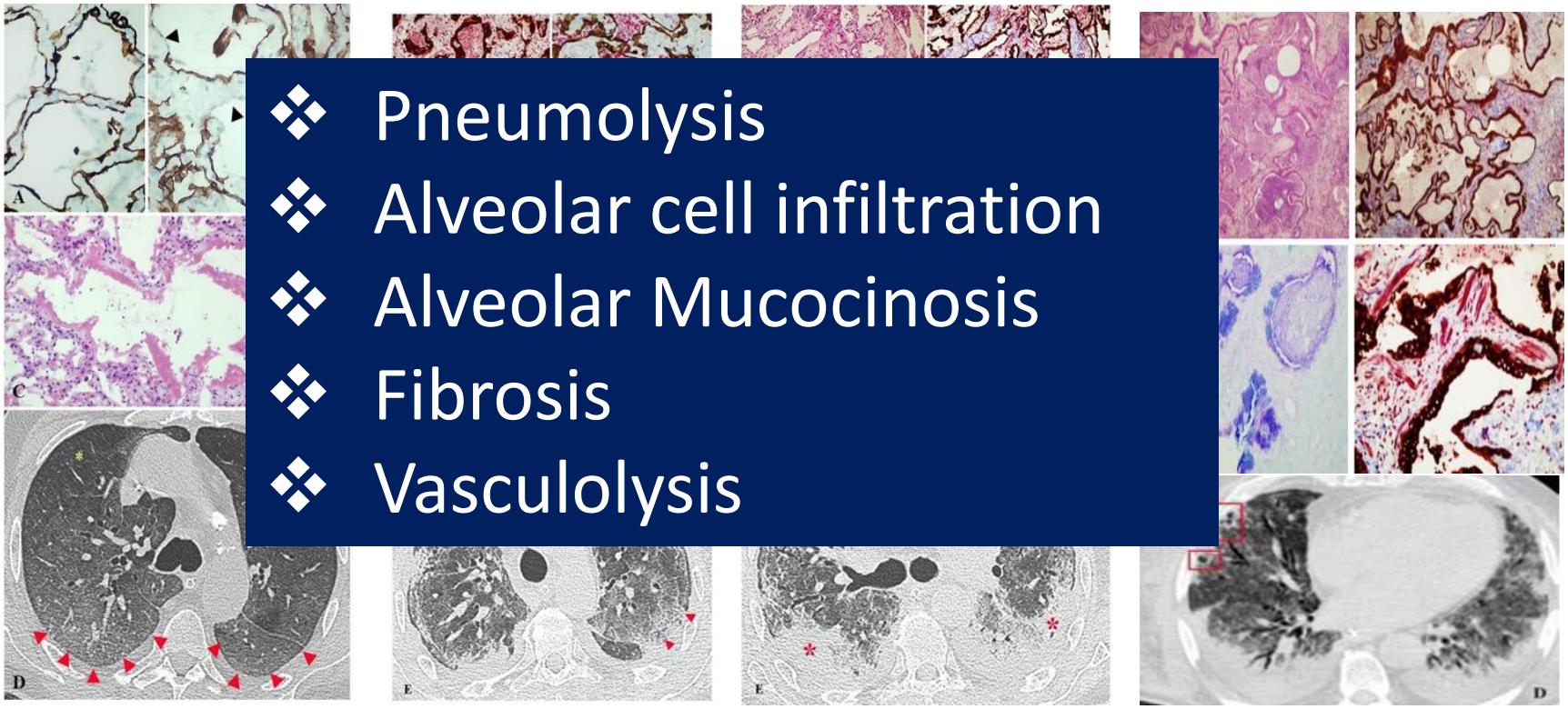
Fibrosis & evolution of CoVID-19

Early DAD pattern

Mid DAD pattern

Late DAD pattern

Late DAD ("Honeycombing")



- Pneumolysis
- Alveolar cell infiltration
- Alveolar Mucocinosis
- Fibrosis
- Vasculolysis

Barisione M, Grillo F, Ball L et al, Virchows Archiv 2020

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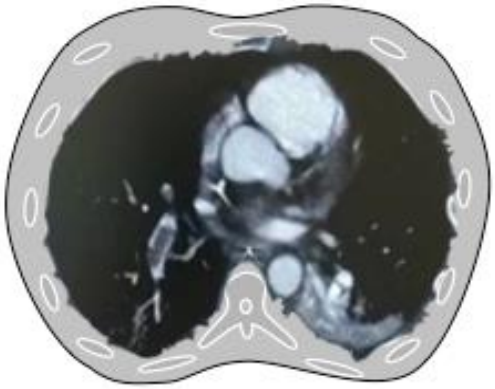
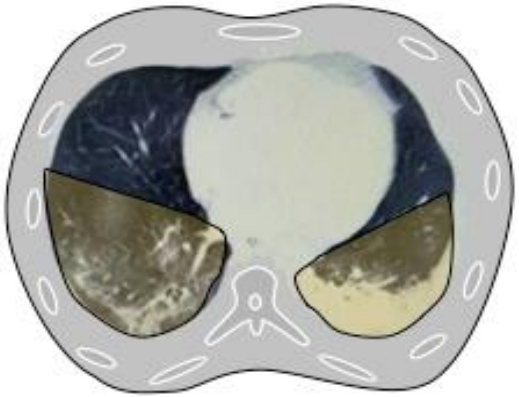
Distinct phenotypes in CoVID-19 patients

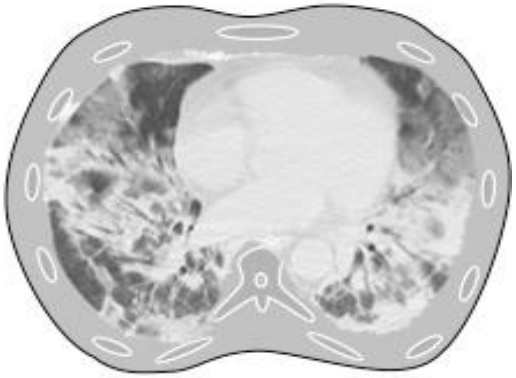
Phenotype 1
multiple, focal, over-perfused ground glass opacities and normally aerated areas



Phenotype 2
atelectasis and peribronchial opacities inhomogeneously distributed and hypoperfused



Phenotype 3:
patchy ARDS-like pattern inhomogeneously distributed and hyper and hypoperfused



Robba C et al. Respir Physiol Neurobiol. 2020 May 10:103455

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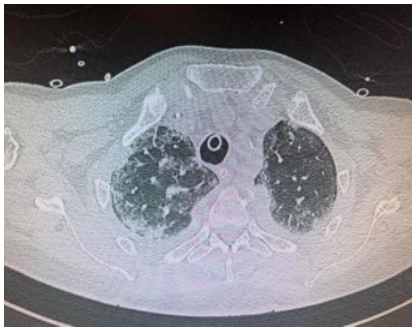
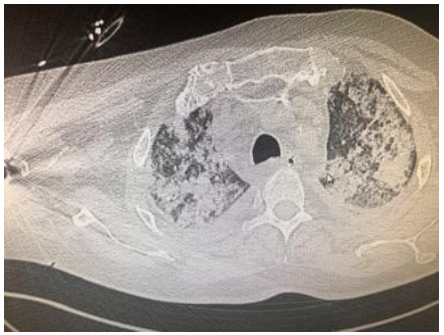
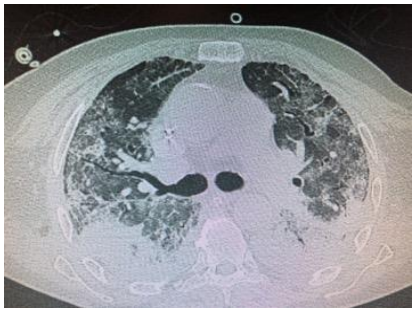
CT lung evolution in CoVID-19

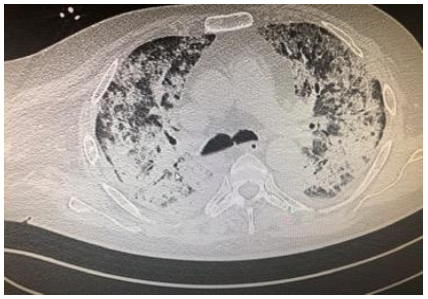


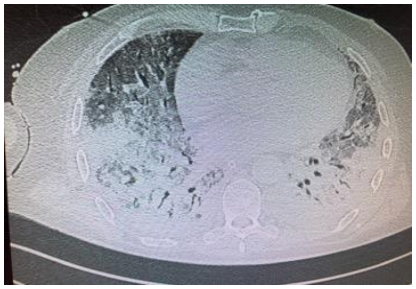
In critically ill patients



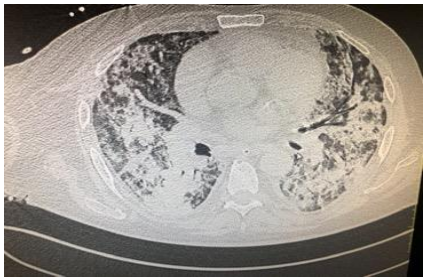


Phenotype 1 is rare
Phenotype 3 is frequent





Phenotype 3
evolves in pneumolysis,
fibrosis,
& complicated with VAP



Robba C et al. Respir Physiol Neurobiol. 2020 May 10:103455

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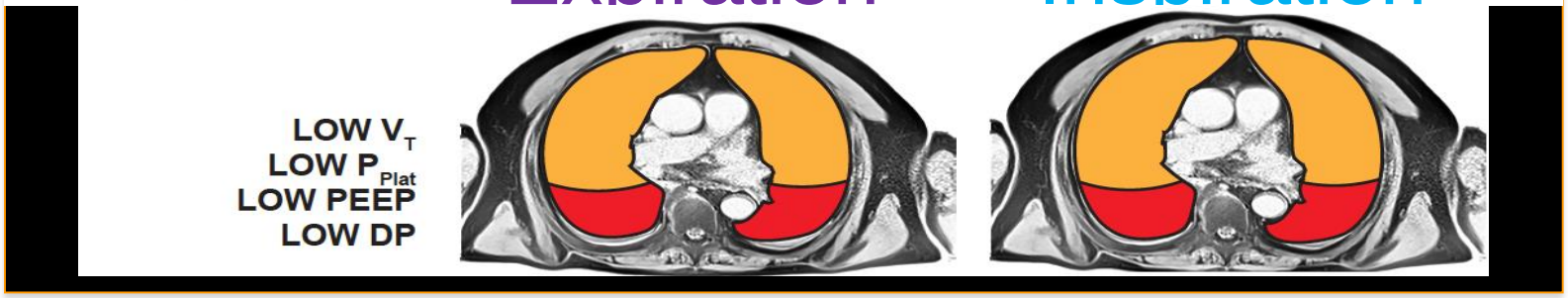
Less is more = Primum non nocere !

Close down the lungs and keep them resting to minimize ventilator-induced lung injury



Just "gently" ventilate the aerated lung
keeping ~~atelectasis~~ the consolidated lungs at rest !

Minimal PEEP for minimal $SatO_2$(88-95%)/PaO_2(55-80 mmHg)
Minimal Right Ventricle impairment !

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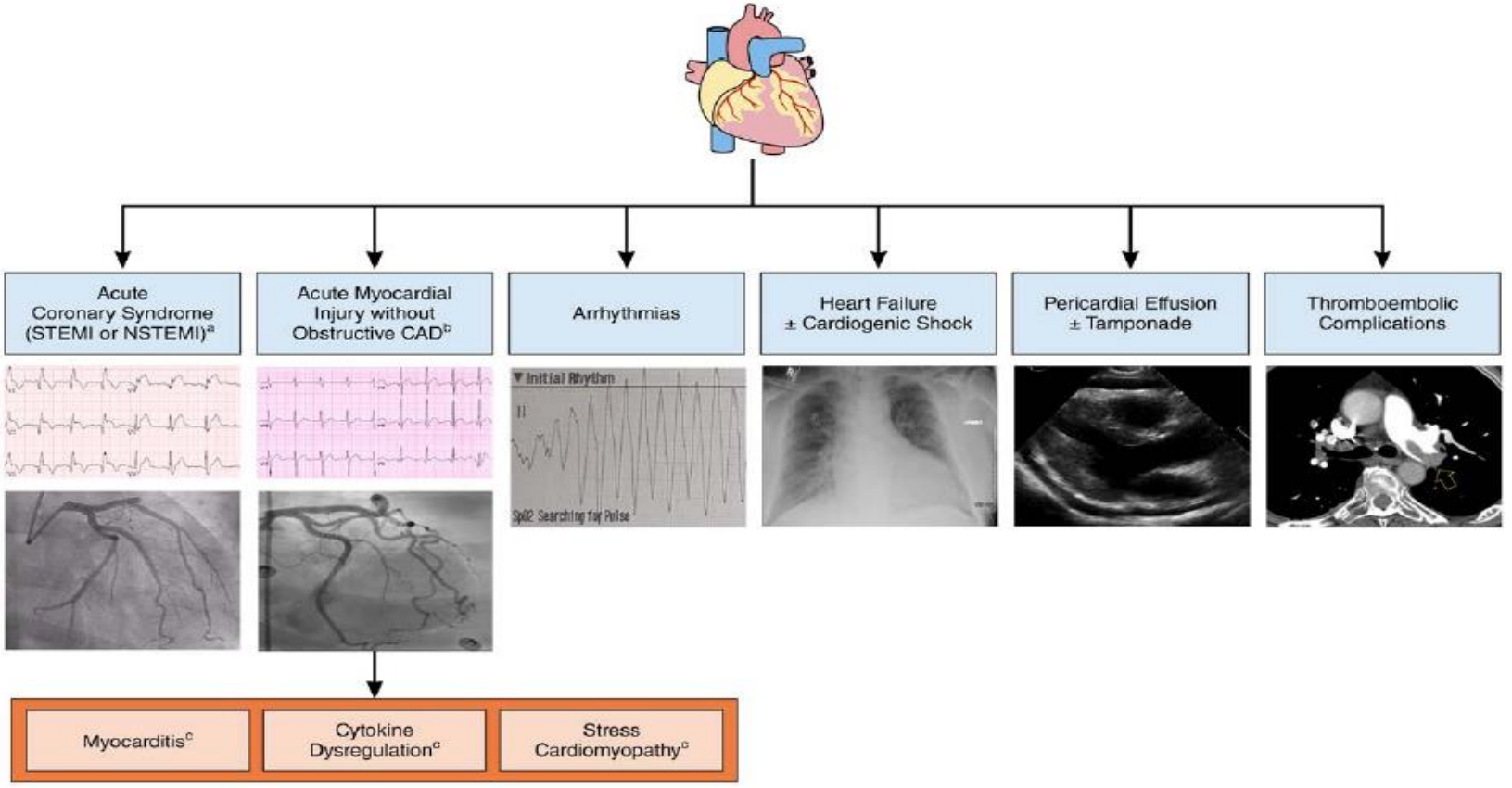
Καρδιακή νόσος



Hendren et al Circulation 2020

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Καρδιακή νόσος

Wuhan/China

- 3-12% μυοκαρδίτις
- 40-60% κοιλιακές αρρυθμίες

Πρόσφατα δεδομένα

- Μυοκαρδιακή βλάβη 7-23% των νοσηλευομένων
- Επιβεβαιωμένη μυοκαρδίτις <10%

Mt Sinai, NY

- 2736 patients admitted to Feb 27 – April 12
- 36% had an elevated troponin-I (>0.03 ng/ml)
- 3.1% had a troponin-I > 0.1ng/ml on admission
- 6.3% had a troponin-I > 0.1ng/ml at any point

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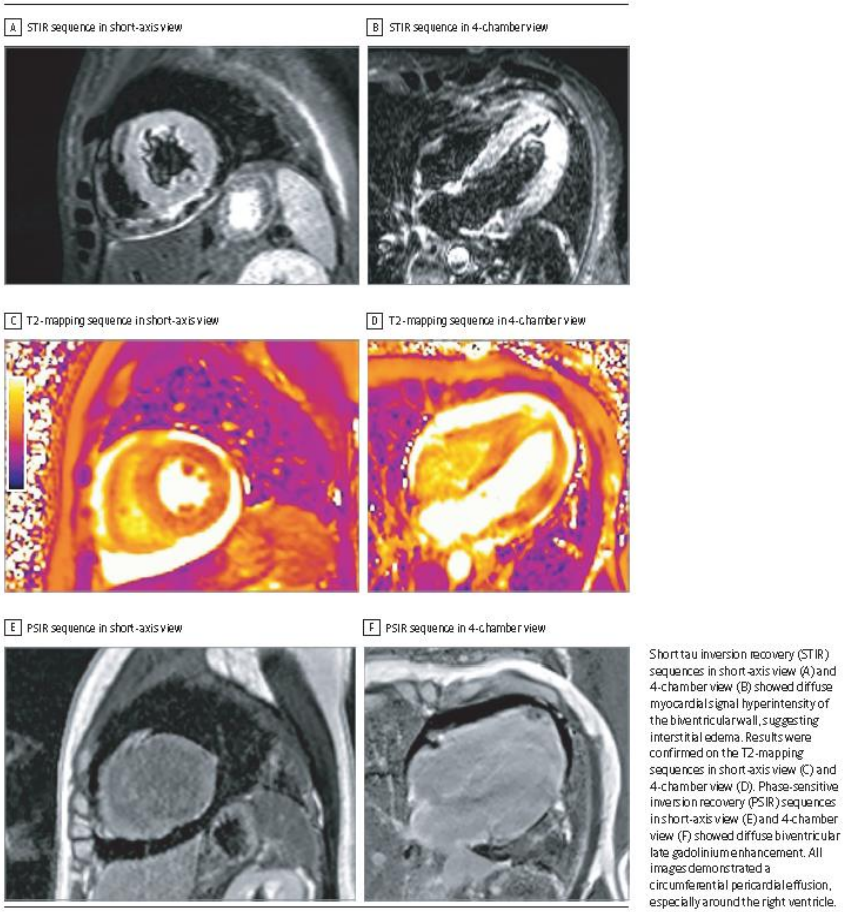
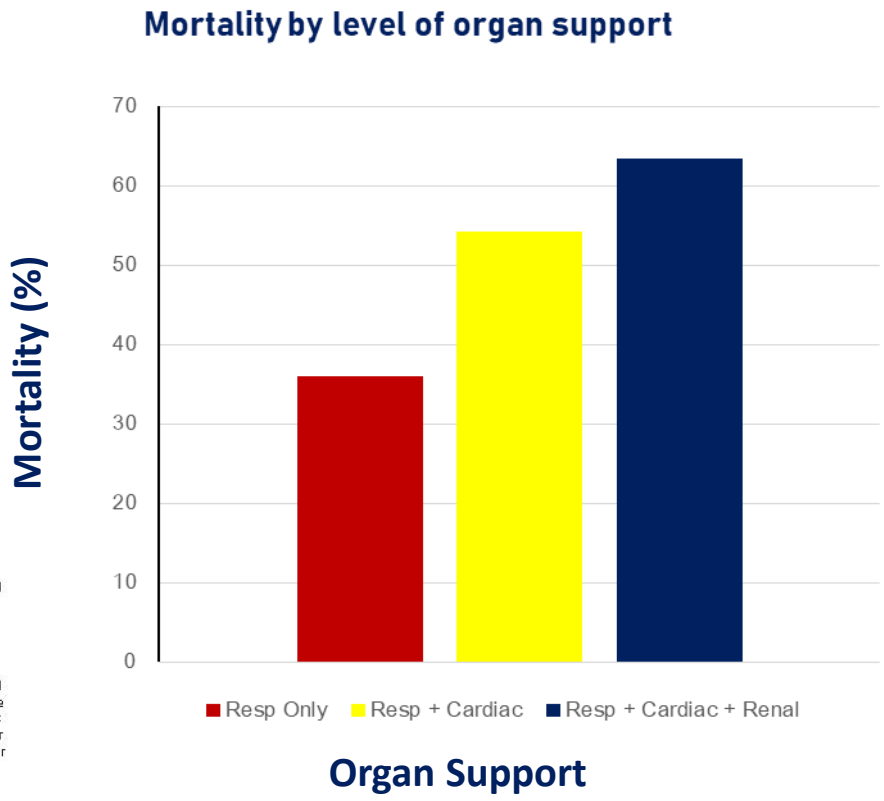
Καρδιακή νόσος



Short tau inversion recovery (STIR) sequences in short-axis view (A) and 4-chamber view (B) showed diffuse myocardial signal hyperintensity of the biventricular wall, suggesting interstitial edema. Results were confirmed on the T2-mapping sequences in short-axis view (C) and 4-chamber view (D). Phase-sensitive inversion recovery (PSIR) sequences in short-axis view (E) and 4-chamber view (F) showed diffuse biventricular late gadolinium enhancement. All images demonstrated a circumferential pericardial effusion, especially around the right ventricle.



Riccardo et al JAMA Cardiol 2020
Derived from www.icnarc.org sept 7 report

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Καρδιακή νόσος – Μακροπρόθεσμες βλάβες

Cardiac events in pneumonia
= poorer long term prognosis

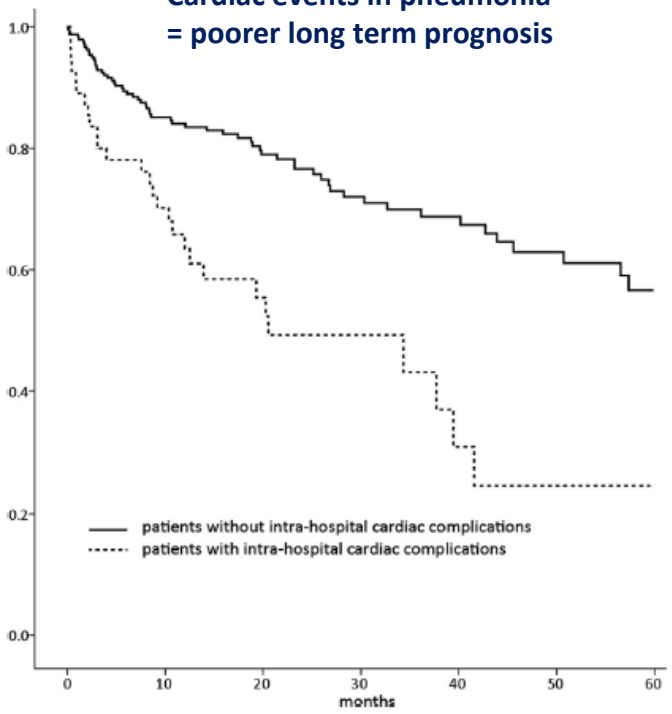
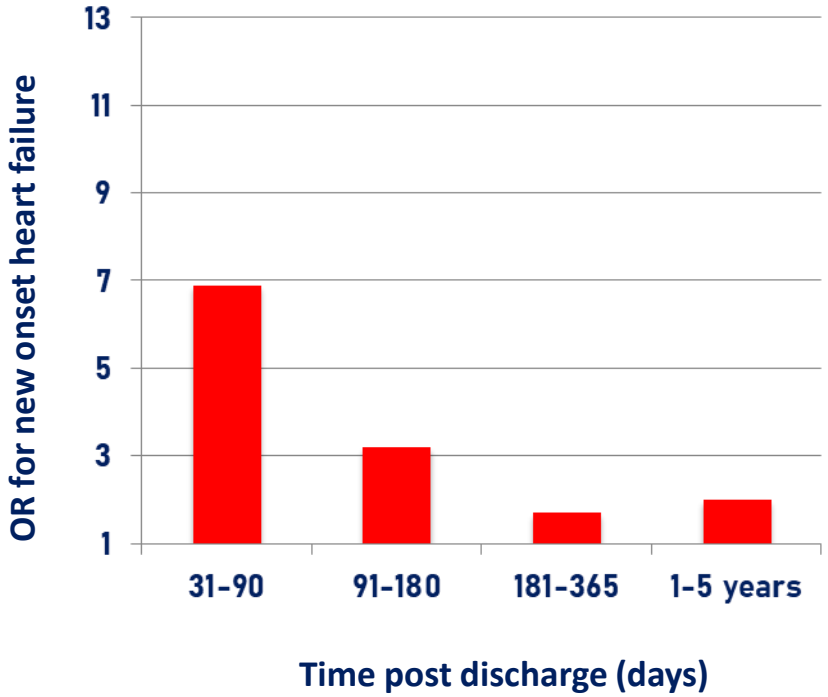


Figure 1. Kaplan-Meier estimates of time to primary outcome events (death for any cause) in patients with or without intrahospital cardiac complications.

Cangemi et al Am J Cardiol 2015

New onset heart failure post pneumonia



Corrales-Medina et al Am Heart J 2015

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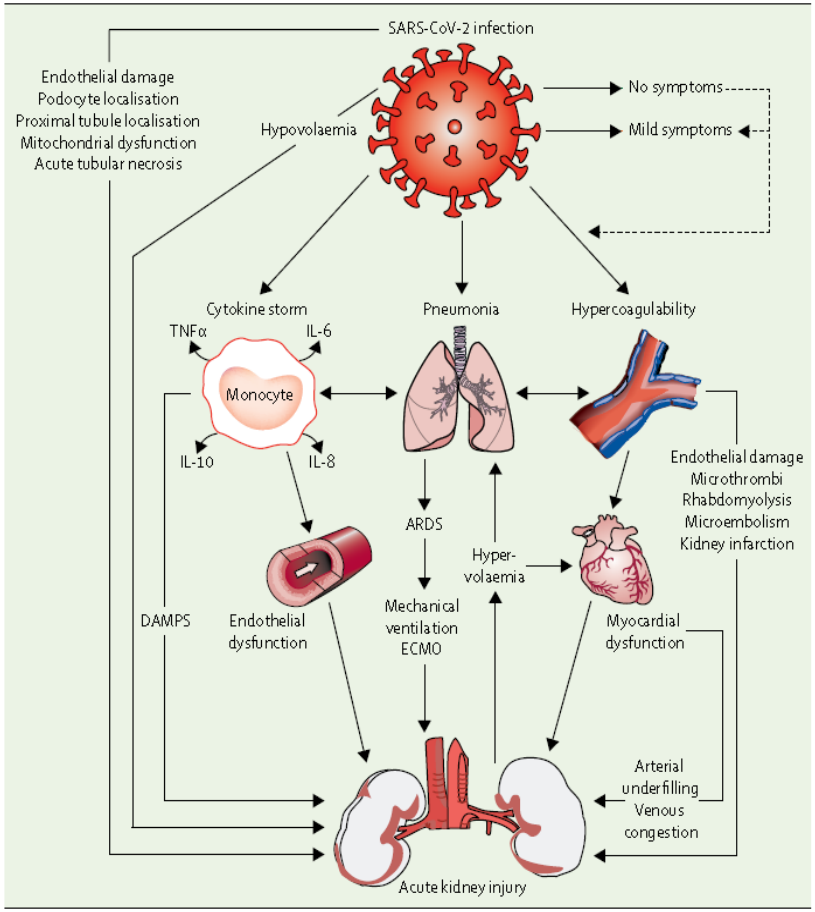
Νεφρική νόσος

- Primary vs secondary
  - Probably secondary
- Pei et al J Am Soc Nephrol 2020
  - 333 patients : China
  - 251 (75.4%) abnormal urine dipstick
  - 35 (10.5%) developed AKI
- ICNARC 26% dialysis need
- New York ICU 31% (Cummings et al Lancet 2020)
- Autopsy series mostly acute tubular necrosis (Vasquez-Bonilla et al Hum Pathol 2020)



Ronco et al Lancet Resp Med 2020

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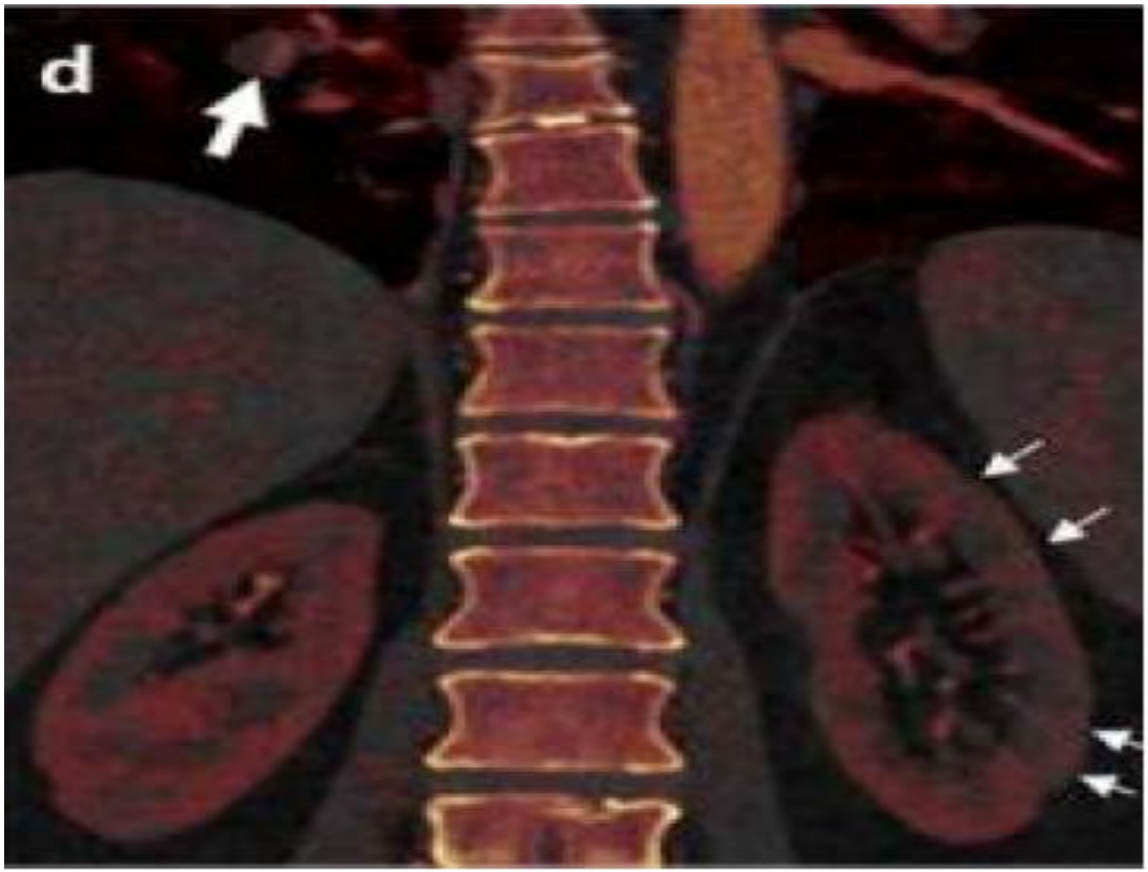
Νεφρική νόσος



Idilman et al Eur Radiol 2020;Aug 29:1-10

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Προσβολή ΚΝΣ

- Anosmia / ageusia : up to 2/3rds
- Ischaemic stroke
  - 2-6% in hospitalised patients, higher in severe disease
  - 6 % Wuhan (Li et al), 2% Milan (Lodigiana et al),
  - 23% France (Helms et al) – ICU population
- Encephalopathy
- Encephalitis
  - 8 cases reported to date
- Guillain-Barre
  - 19 cases reported to date
- Acute disseminated encephalomyelitis and myelitis
  - 2 cases reported to date

Ahmad et al J Clin Neurosci 2020
Ellul et al Lancet Neurol 2020

Νόσος COVID-19

Προσβολή ΚΝΣ

- Kironomos et al Radiology 2020
  - 185 consecutive Hospitalised patients with COVID-19
  - 222 brain CT, 47 brain MRI, 7 spinal MRI
  - 74% of the MRI's showed microvascular pathology
  - 44% had leukoencephalopathy
- Bryce et al, 2020
  - Autopsy 6/20 microthrombi and acute infarction

Νόσος COVID-19

Προσβολή ΚΝΣ

- Possible accelerated dementia

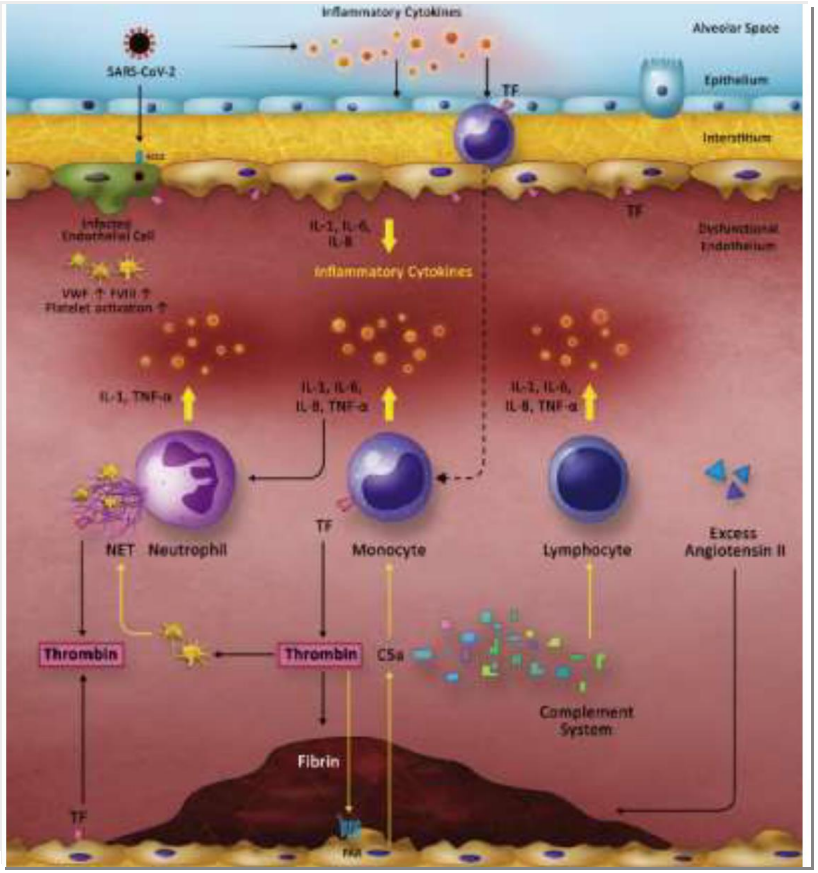
  Heneka et al Alzheimer Res Ther 2020

- Depression and chronic fatigue
- Concerns over possible increased Parkinsons
  - 3-5x increase post 1918 H1N1

  Beauchamp et al J Parkinsons Dis 2020

Νόσος COVID-19

Υπερπηκτική φάση



Απευθείας προσβολή ενδοθηλιακών κυττάρων μέσω του υποδοχέα ACE2

↓

Ενεργοποίηση / δυσλειτουργία ενδοθηλίου

↓

Έκφραση ιστικού παράγοντα (TF), ενεργοποίηση αιμοπεταλίων και αυξημένα επίπεδα VWF/FVIII

↓

Παραγωγή θρομβίνης και σχηματισμός θρόμβων

↓

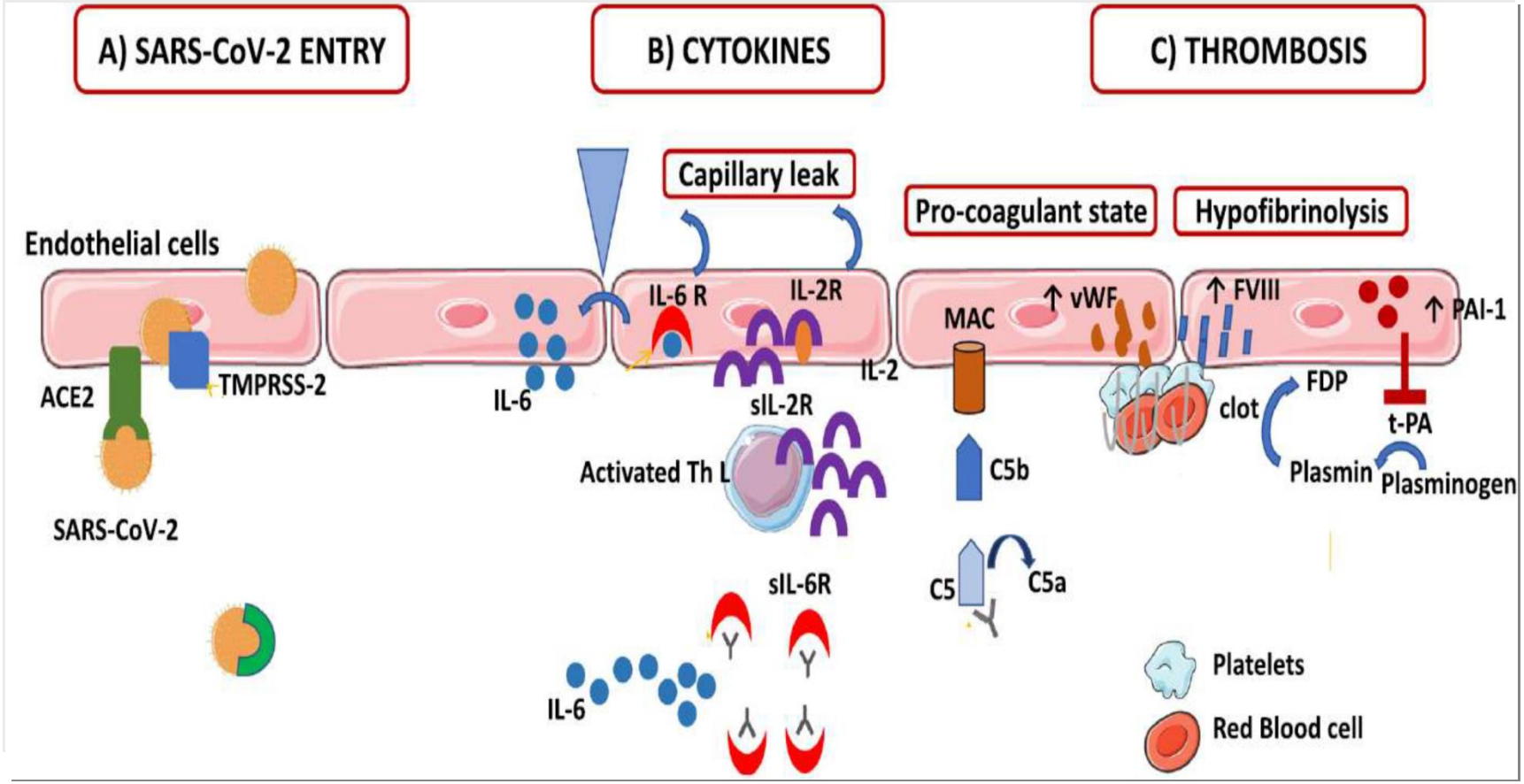
Η θρομβίνη προάγει την φλεγμονή

1. με την δράση της στα αιμοπετάλια, προάγοντας τον σχηματισμό NET (neutrophil extracellular trap) στα ουδετερόφιλα
2. ενεργοποιώντας το ενδοθήλιο μέσω του υποδοχέα PAR που απελευθερώνει C5A και οδηγεί στην περαιτέρω ενεργοποίηση των μονοκυττάρων

Varga Z et al- Lancet 2020

Νόσος COVID-19

Υπερπηκτική φάση



Pons S- Crit Care 2020

Νόσος COVID-19

Συστηματική Ενδοθηλίτις

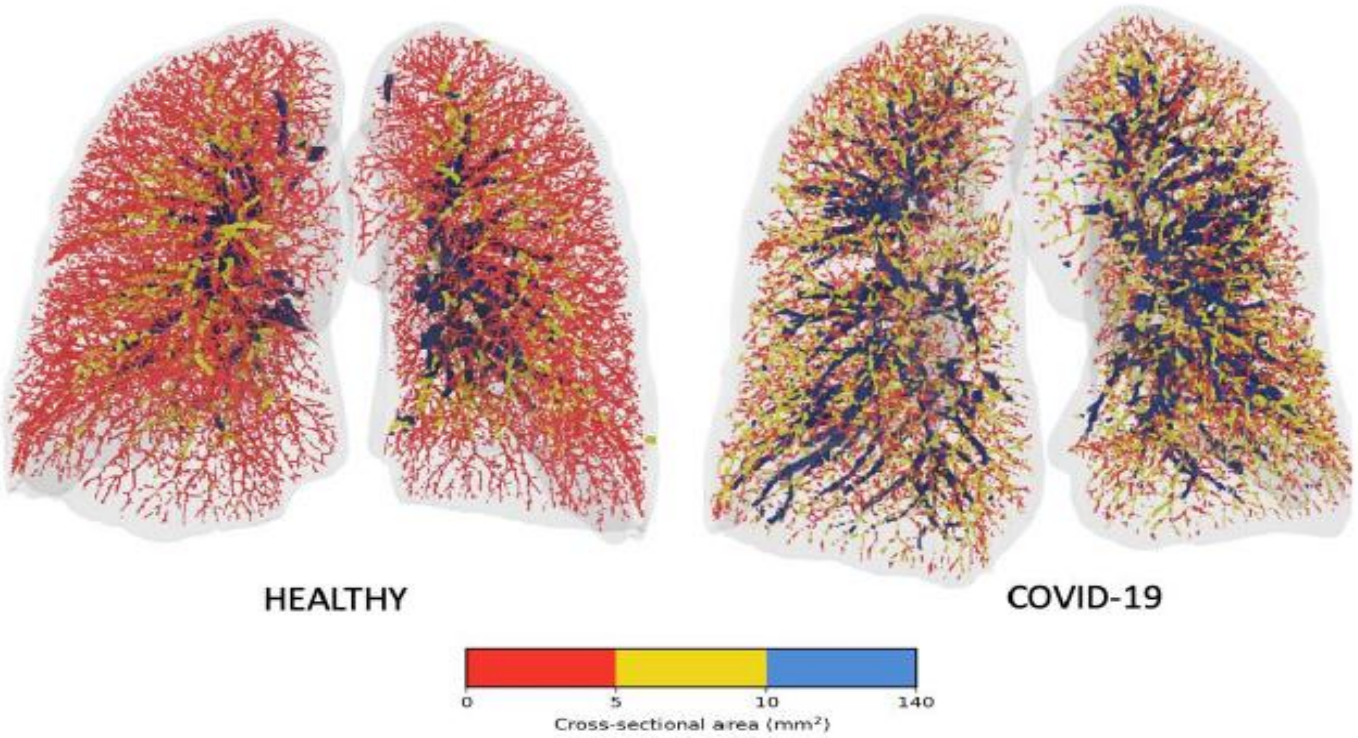
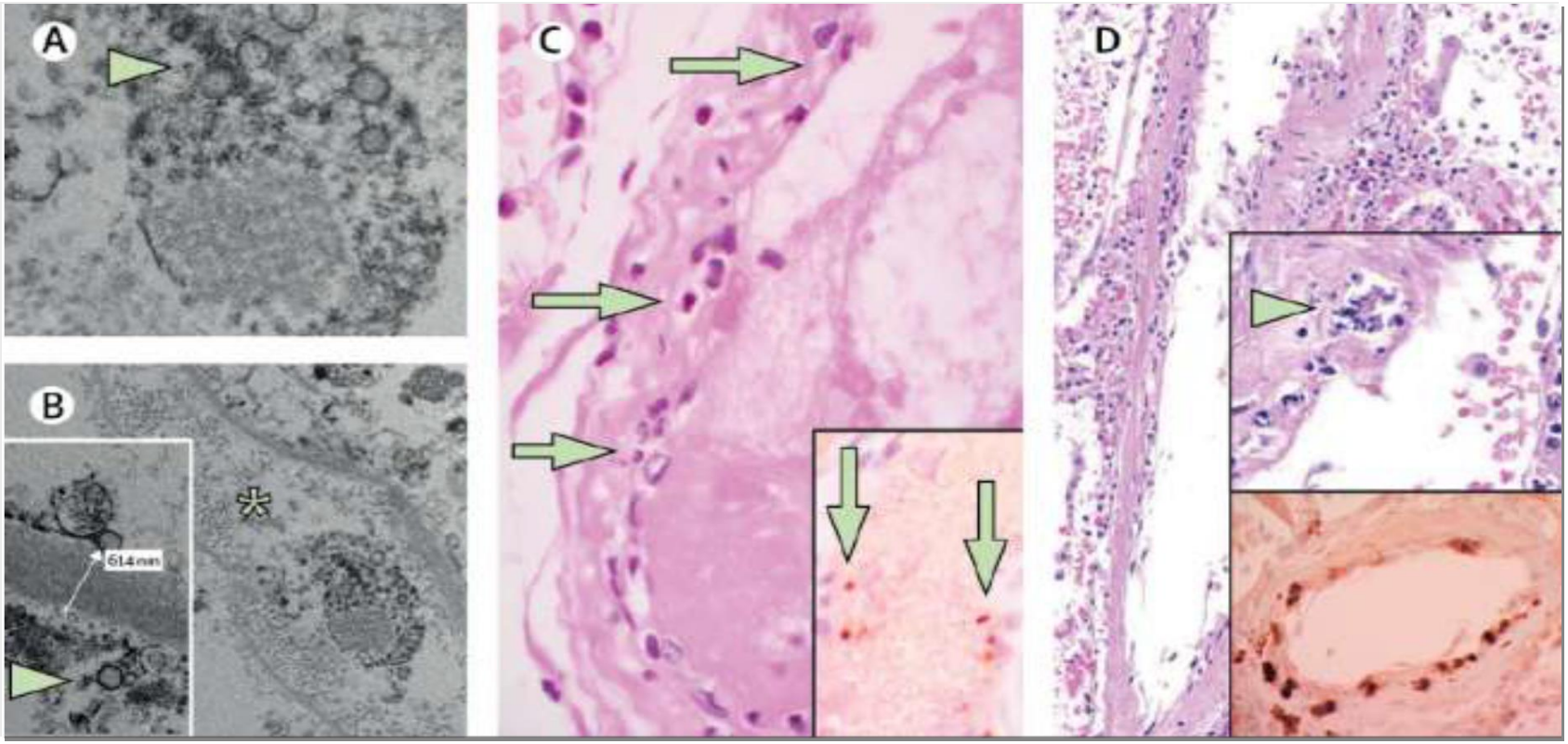


Figure 4: Visual representation of the blood vessels colored according to their size. Red denotes the small vessels, yellow the mid-size vessels and blue the larger vessels.

Lins M et al Acta Radiol 2020

Νόσος COVID-19

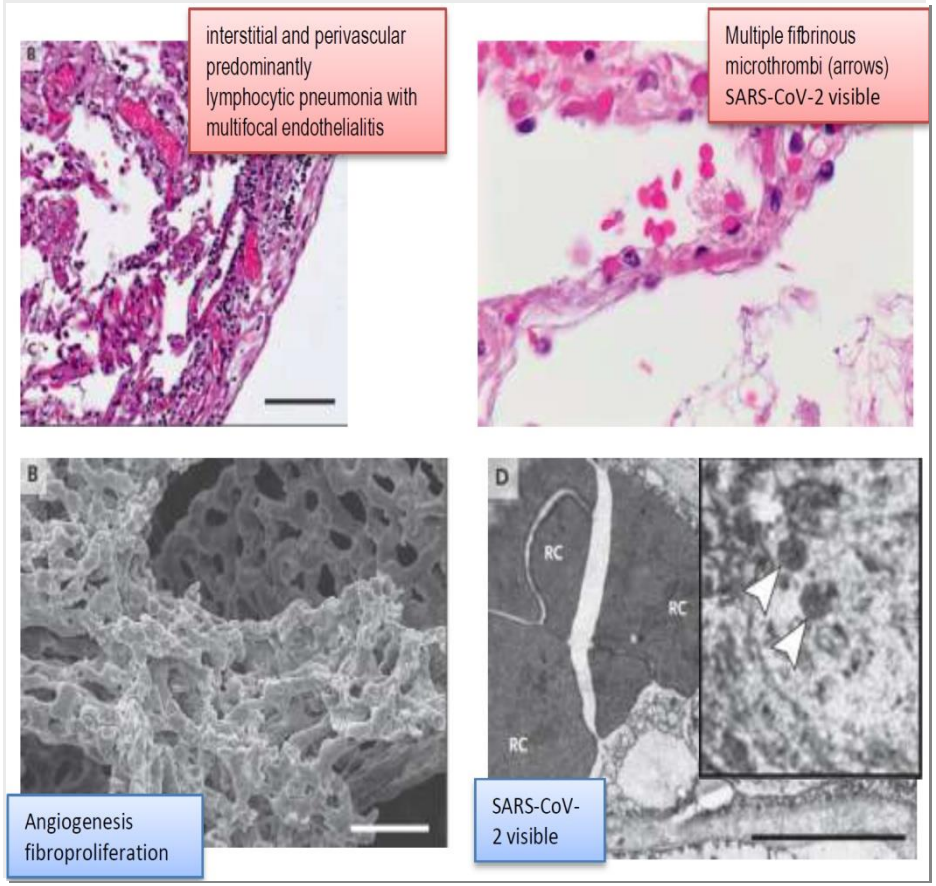
Ενδοθηλίτις



Varga Z et al- Lancet 2020

Νόσος COVID-19

COVID-19 vs Influenza : ενδοθηλιακές βλάβες



COVID-19 : Πνεύμων

- Σοβαρή ενδοθηλιακή βλάβη
- Παρουσία ιών ενδοκυττάρια
- Κατεστραμμένες μεμβράνες

Μικροαγγειοπάθεια

- Οι μικροθρόμβοι στα κυψελιδικά τριχοειδή είναι 9 φορές περισσότεροι απότι στην γρίπη.

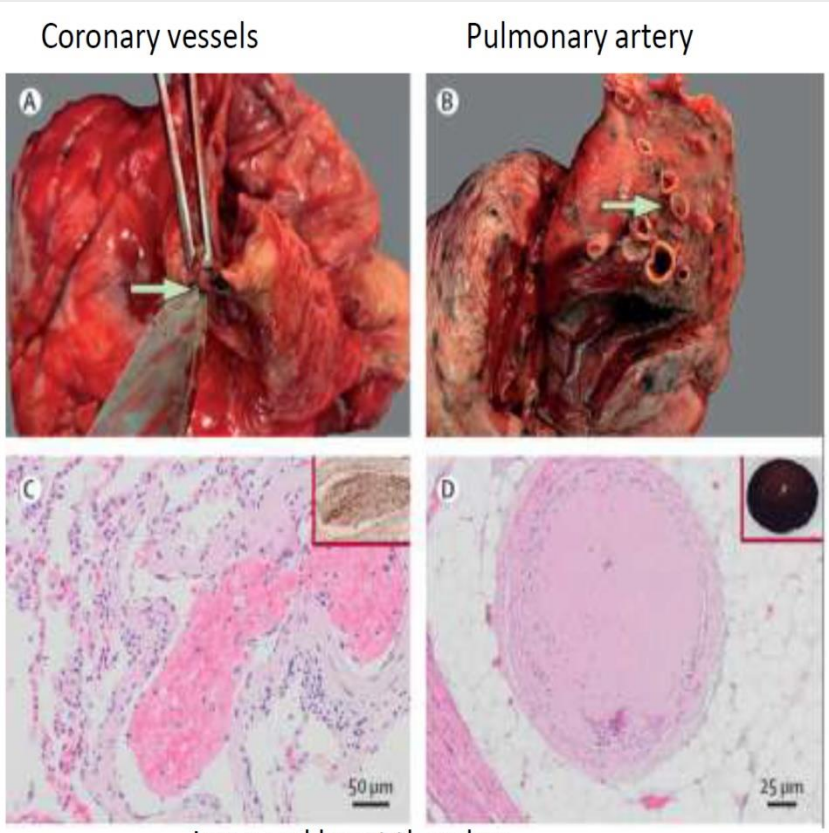
Αγγειογένεσις

- 2.7 φορές περισσότερη απότι στην γρίπη

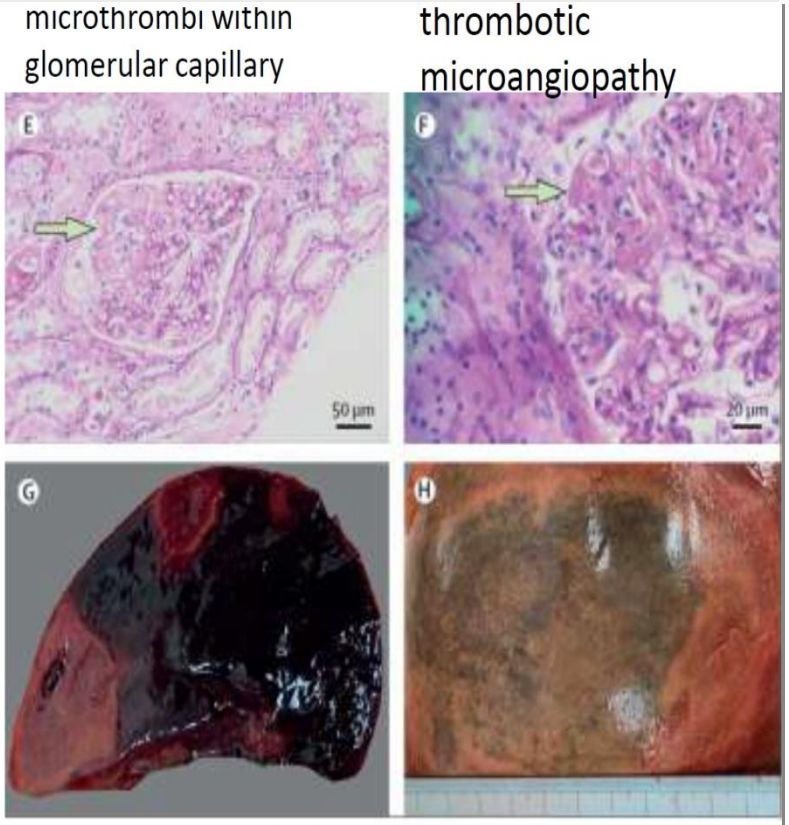
Ackermann M et al - N Engl J Med 2020;383:120-8.

Νόσος COVID-19

Θρομβωτικά συμβάματα



Lung and heart thombus



Macroscopic splenic and hepatic infarction

Hanley et al - ***Lancet Microbe 2020*** Published **Online** August 20, 2020 https://doi.org/10.1016/S2666-5247(20)30115-4

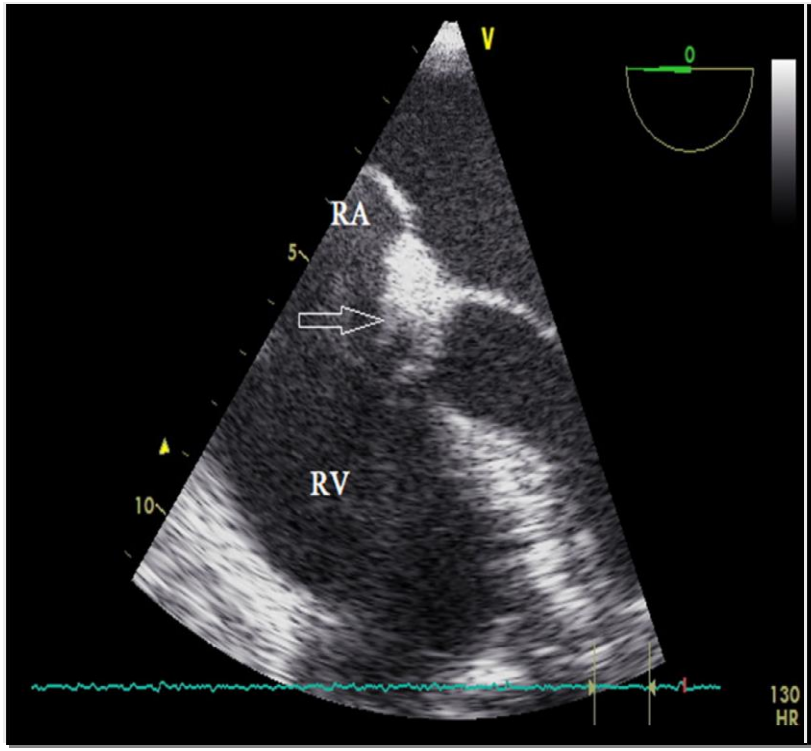
Νόσος COVID-19

Θρομβωτικά συμβάματα

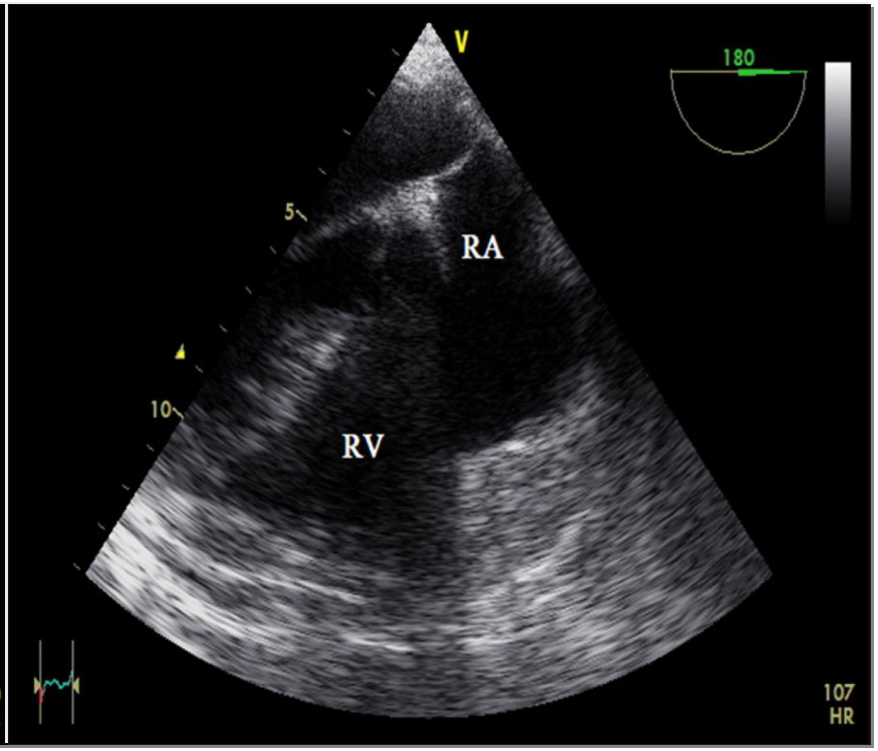
A Severe COVID-19 Case Complicated by Right Atrium Thrombus

Anastasia Anthi
Dimitrios Konstantonis
Maria Theodorakopoulou
Olympia Apostolopoulou
Irene Karampela
Georgia Konstantopoulou
Stavroula Patsilinakou
Apostolos Armaganidis
George Dimopoulos

2nd Department of Critical Care, Attikon University Hospital, National and Kapodistrian University of Athens, Athens, Greece



TEE, mid-esophageal 4-chamber view (ICU day15)
Thrombus in the right atrium



TEE, mid-esophageal 4-chamber view (ICU day36)
No evidence of residual thrombus

Am J Case Report 2020 ;21:e926915

Νόσος COVID-19

Προσβολή άλλων οργάνων

- **GIT**
  - Diarrhoea
  - Abdominal pain
- **Liver**
  - Mild elevations LFT's common
  - Severe hepatitis is extremely uncommon
- **Skin**
  - Vasculitis (covid-toes), erythema, urticaria, chicken-pox like lesions
- **Kawasaki-like syndrome in children**
- **??????????????????**

Patel et al J Clin Virol 2020

Gupta et al Nature Med 2020

Νόσος COVID-19

Influenza Associated Pulmonary Aspergillosis (IAPA)

Influenza patients

- requiring hospitalization: ~0.1% (mortality 4%)
- requiring intensive care: ~5 – 10% (mortality: 20 - 25%)

IPA in ICU patients with Influenza : 19%

- 14% in non-immunosuppressed patients
- 32% in immunosuppressed patients
- 5% in control group (CAP with neg. airway influenza PCR)

Influenza = Independent risk factor for IPA (aOR 5.2 (95% CI, 2.6-10.3)

- Other risk factors: high APACHE II, male sex, **corticosteroids**

➜ use of corticosteroids contra-indicated in influenza

Verwey PE, et al. ICM 2020
Schauwvlieghe A, et al. Lancet Respir Med 2018

Νόσος COVID-19

Influenza Associated Pulmonary Aspergillosis (IAPA)

1η hypothesis
Severe damage of epithelial membrane because or the viral infection leading to fungal invasion.

Pathogenesis
Local and systemic effects

2nd hypothesis
Increased use of corticosteroids

Local damage
↓
Tracheobronchial mucosa
↓
Disruption of normal ciliary clearance
↓
Colonization
↓
Infection

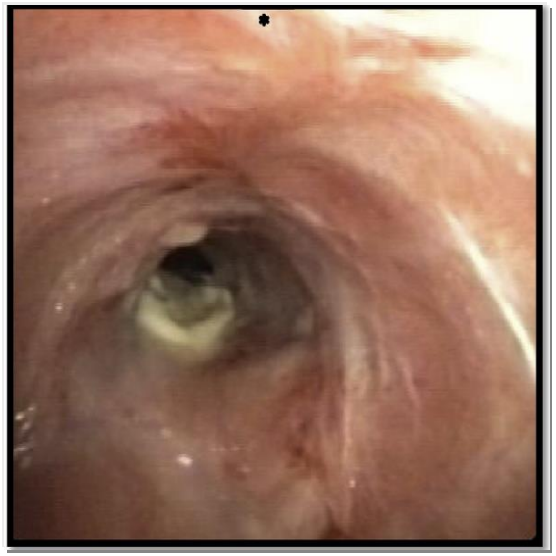
Affect Th1/Th2 response/cytokines
↓
Lymphopenia

The reasons that some, but not all, patients with severe influenza infection develop aspergillosis remains unknown !!!!!!!!!!!!!!!!

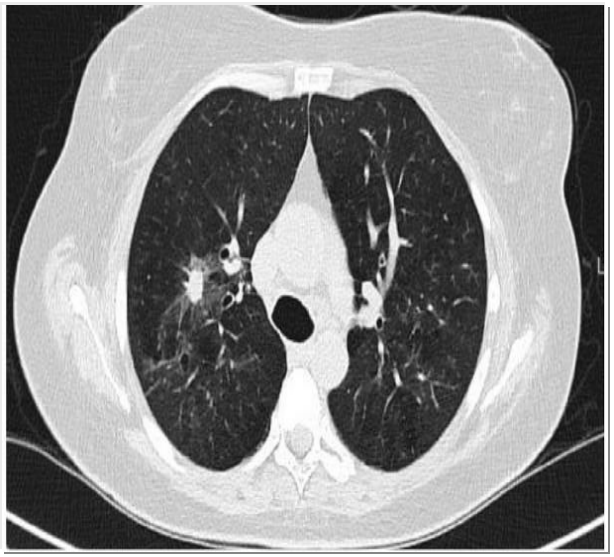
Lee N et al PLoS One 2011; 6: e26050, Fox A et al PLoS One 2012;7:e31535

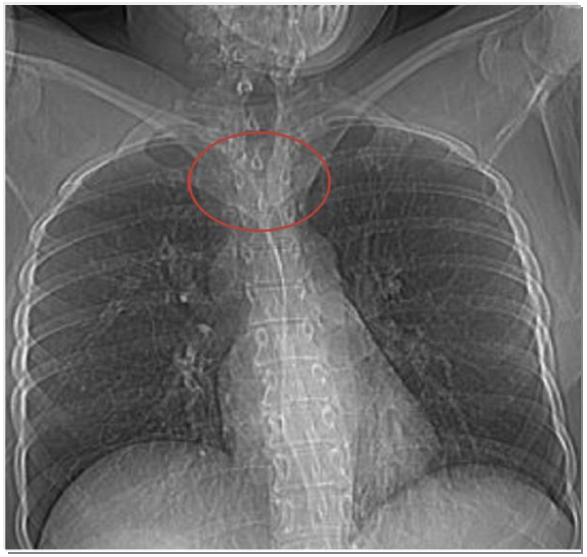
Νόσος COVID-19

Influenza Associated Pulmonary Aspergillosis (IAPA)



Tracheobronchitis with obstruction





Tracheal stenosis

Koehler et al. / Clinical Microbiology and Infection 25 (2019) 1501e1509

Νόσος COVID-19

COVID-19-Associated Pulmonary Aspergillosis

Multiple case report and limited case series

- Largest cohort so far**: Whyte et al. (CID 2020)**
- Multicenter, prospective cohort
- Study focus: ICU patients with deteriorating respiratory function one week post COVID diagnosis ➜ mycological examination with blood and deep respiratory samples, Total n=135
- IFD: 26.7% - IPA: 14.1%, yeast infection: 12.6%
- Risk factors for IPA: corticosteroid use and chronic respiratory disease
- Overall mortality: 38% (53% in patients with IFD)

Νόσος COVID-19

Αλγόριθμοι και κριτήρια για διάγνωση

Factor	IAPA	CAPA
Host/Risk	57% EORTC/MSGERC host factor negative [9]	85% EORTC/MSGERC host factor negative [59, 60]
	IAPA associated with corticosteroid use [7]	IPA developed in SARS-2003-infected patients receiving corticosteroids [61]
		Lymphopenia and chemokine-producing monocyte-derived FCN1 + macrophages causing hyperinflammation [62]
Virus	Cell entry through sialic acids-2,6Gal: epithelial layer in lung including larger airways [63]	Cell entry through ACE2: type 2 pneumocytes and ciliated cells [64]
	Immune modulation by suppression of the NADPH oxidase complex [65]	No evidence for immunomodulatory effect on known antifungal host defense mechanisms, although this has not been extensively studied yet
Fungal infection	Invasive *Aspergillus* tracheobronchitis in up to 55% of patients [7–9]	Invasive *Aspergillus* tracheobronchitis not yet reported [59, 60]
	Median time between ICU admission and IAPA diagnosis 2–3 days [7–9]	Median time between ICU admission and CAPA diagnosis 6 days [59]
Aspergillus diagnostics	BAL GM positive in > 88% [7–9]	BAL GM commonly positive, diagnostic performance currently unknown [59, 60]
	Serum GM positive in 65% [7–9]	Serum GM positive in 3 of 14 (21%) COVID-19 patients [59, 60]
Secondary infections	In 80 of 342 (23.4%) ICU patients, most frequent pathogens *S. pneumoniae*, *Pseudomonas aeruginosa* and *S. aureus* [66]	In four of 13 (31%) ICU patients, pathogens not specified [67]
ICU mortality	45% in IAPA compared with 20% in influenza without IAPA ($p < 0.0001$) [9]	33% in CAPA cases compared with 17% in COVID-19 without CAPA ($p = 0.4$) [59] (although mortality rates due to COVID-19 without CAPA vary enormous between countries and we have no clear data yet on the true mortality in ICU of COVID-19)

Verwey PE, et al. ICM 2020

Νόσος COVID-19

Άλλες μυκητιακές λοιμώξεις

Invasive pulmonary fusariosis in an immunocompetent critically ill patient with severe COVID-19

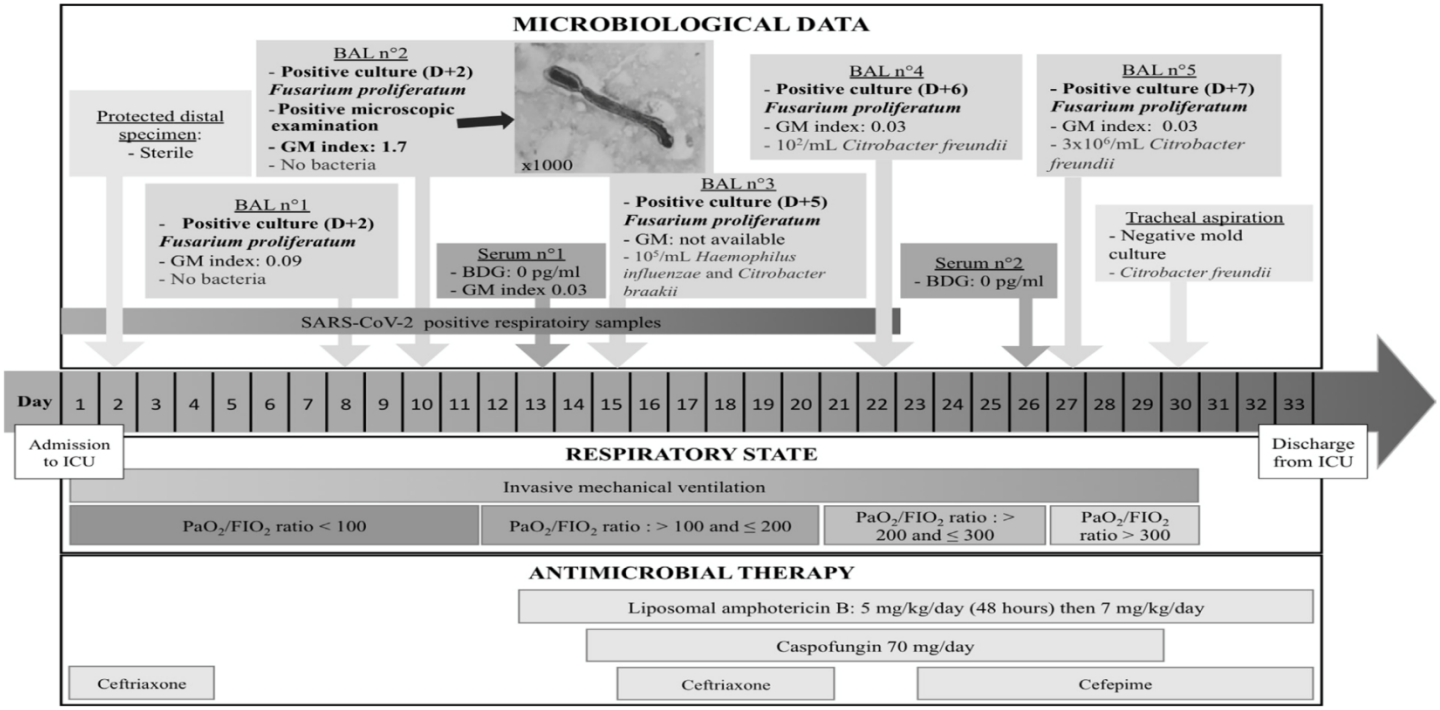


Fig. 1. Timeline for an immunocompetent patient who developed invasive pulmonary fusariosis during severe COVID-19. Day 1 is the day the patient was admitted to the intensive care unit. D, days; BAL, bronchoalveolar lavage; GM, galactomannan index determination; BDG, β-D-glucan dosage.

Poignon C, et al. CMI 2020

Νόσος COVID-19

Θεραπεία- Υδροξυχλωροκίνη

Chloroquine and hydroxychloroquine

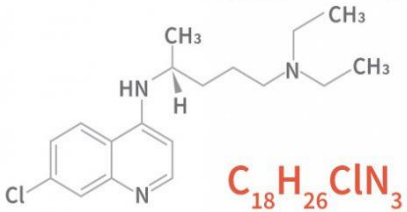
CHLOROQUINE

Sold under different brand names (Example: Nivaquine Aralen, Resochin)

HYDROXYCHLOROQUINE

Variant of chloroquine, generally well tolerated

Sold as Plaquenil



$C_{18}H_{26}ClN_3$

◆ MAIN USE

To treat and prevent malaria

◆ METHOD OF ADMINISTRATION

Oral (available as injectable solution)

◆ RISK

Very dangerous, can lead to cardiac damage, damage of the retina; overdose lead to death. Do not use without medical advice

◆ ALSO USED IN

Autoimmune diseases like lupus and rheumatoid arthritis

Some types of sun allergies

Clinical trials are ongoing in Europe and United States to study the effectiveness of the medicines against COVID-19

In France, **hydroxychloroquine** can be administered to corona-virus patients in hospitals under medical supervision

© AFP

Νόσος COVID-19

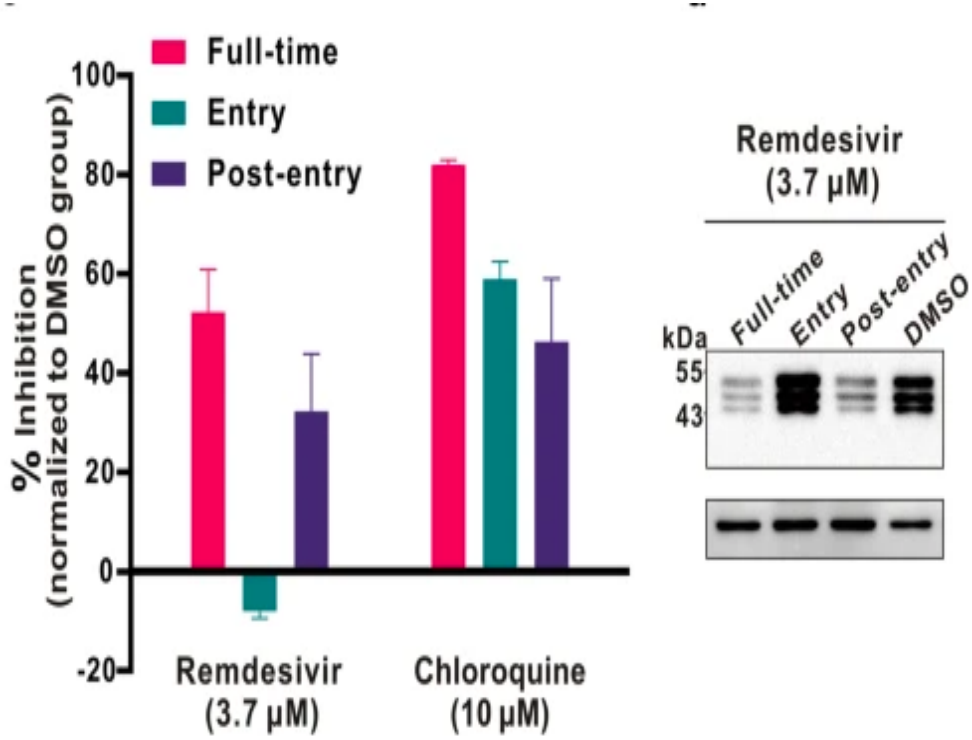
Θεραπεία- Χλωροκίνη/Υδροξυχλωροκίνη

- **Hydroxychloroquine and chloroquine**
  - **antimalarial drugs** that elicit immunomodulatory effects and are therefore also used to treat **autoimmune conditions**
    - ✓ *systemic lupus erythematosus, rheumatoid arthritis*
- Potential **broad-spectrum antiviral drug**
  - via alkalinization of the phagolysosome, which inhibits the pH-dependent steps of viral replication.
  - By interfering with the glycosylation of cellular receptors of SARS-CoV
  - Chloroquine has an immune-modulating activity, which may synergistically enhance its antiviral effect in vivo
- Chloroquine : active *in vitro* against multiple other viruses but
  - has not proven fruitful in clinical trials
  - Worse clinical outcomes in human studies of Chikungunya virus infection

Yan, Y. et al. *Cell Res.* **23**, 300–302 (2013), Wang M, et al. *Cell Res* **30,** 269–271 (2020), Liu, J., Cao, R., Xu, M. *et al. Cell Discov* **6,** 16 (2020).

Νόσος COVID-19

Υδροξυχλωροκίνη- *In vitro* activity



- Vero E6 cells were infected with nCoV-2019 BetaCoV/ Wuhan in the presence of varying concentrations of chloroquine.
- Efficacies were evaluated
  - by quantification of viral copy numbers in the cell supernatant via quantitative real-time RT-PCR (qRT-PCR)
  - confirmed with visualization of virus nucleoprotein (NP) expression through immunofluorescence microscopy at 48 h post infection

Wang M, et al. *Cell Res* **30,** 269–271 (2020)

Νόσος COVID-19

Θεραπεία- Υδροξυχλωροκίνη

- Hydroxychloroquine, more potent than chloroquine *in vitro*.
- Less toxic
- Based on PK models
  - a loading dose of 400 mg PO BID, followed by 200 mg BID for 4 days.
- In February, 2020, 7 clinical trial registries were found in Chinese Clinical Trial Registry (http://www.chictr.org.cn) for using HCQ
- The US FDA granted emergency use authorization for chloroquine
- A consensus statement from a multicenter collaboration group in China,
  - chloroquine phosphate 500 mg (300 mg base) twice daily PO for 10 days may be considered in patients with COVID-19 pneumonia.
  - 100 patients have demonstrated significant improvement with this regimen without documented toxicity

Liu, J., Cao, R., Xu, M. *et al. Cell Discov* **6,** 16 (2020), **Gao J**, Tian Z, Yang X. Biosci Trends. 2020 Mar 16;14(1):72-73

Νόσος COVID-19

Θεραπεία- Υδροξυχλωροκίνη

- **FRANCE :** hydroxychloroquine ➔ more potent therapy
  - improved safety profile to treat and prevent the spread of COVID-19.
  - One study in France evaluated patients treated with hydroxychloroquine against a control group who received standard of care.
  - After dropping 6 patients from the analysis for having incomplete data, the 20 remaining patients receiving hydroxychloroquine had improved nasopharyngeal clearance of the virus on day 6 (70% [14/20] vs 12.5% [2/16])
- **FRANCE :** between 12 March and 31 March 2020
  - 181 patients (18-80 years) with SARS-CoV-2 pneumonia who required oxygen but not ICU
  - Hydroxychloroquine (treatment group) versus standard care
  - survival without transfer to the ICU at day 21 was 76 vs 75%
  - Overall survival at day 21 was 89% vs 91% in the control group
  - Survival without ARDS at day 21 was 69% vs 74%
  - No benefit

Colson P, Rolain JM, Lagier JC, Brouqui P, Raoult D. Int J Antimicrob Agents. 2020 Apr;55(4):105932, Mahevas M, et al. BMJ . 2020 May 14;369:m1844.

Νόσος COVID-19

Θεραπεία- Υδροξυχλωροκίνη

- 1400 COVID-19 patients : New York
- Hydroxychloroquine : in 811 patients
  - it was associated with a higher risk of intubation or death
  - HR 2.37
  - Patients who received hydroxychloroquine were older, were more likely to have comorbidities, and had more severe illness
- April 2020 :FDA / EMA bans its use outside of clinical trials

- WHO. “Solidarity” clinical trial for COVID-19 treatments
- RECOVERY trial investigators. https://www.recoverytrial.net

Geleris J, Sun Y, Platt J, et al. Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19. N Engl J Med 2020; 382:2411.

Νόσος COVID-19

Θεραπεία- Υδροξυχλωροκίνη

- **Data from controlled trials suggest that they do not provide a clinical benefit for patients with COVID-19**
  - RECOVERY trial investigators. No clinical benefit from use of hydroxychloroquine in hospitalised patients with COVID-19. https://www.recoverytrial.net/news/statement-from-the-chief-investigators-of-the-randomised-evaluation-of-covid-19-therapy-recovery-trial-on-hydroxychloroquine-5-june-2020-no-clinical-benefit-from-use-of-hydroxychloroquine-in-hospitalised-patients-with-covid-19.
  - WHO. “Solidarity” clinical trial for COVID-19 treatments: Update on hydroxychloroquine. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments .
  - Tang W, Cao Z, Han M, et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. BMJ 2020; 369:m1849
  - Cavalcanti AB, Zampieri FG, Rosa RG, et al. Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19. N Engl J Med 2020.

Νόσος COVID-19

Θεραπεία- Αζιθρομυκίνη

- Pros
  - Macrolide
  - Anti-inflammatory effect
  - Possible bacterial co-infection in patients with pneumonia
  - Rate of bacterial co-infection 11%
- **Cons**
  - No direct action on coronaviruses
  - Side effects (cardiotoxicity) when combined with chloroquine
  - Azithromycin and hydroxychloroquine ➔QTc prolongation

Νόσος COVID-19

Θεραπεία- Υδροξυχλωροκίνη + Αζιθρομυκίνη

- Multicenter, randomized, open-label, three-group, controlled trial
- no supplemental oxygen or a maximum of 4 liters /min
- 667 patients radomised to 3 arms 1:1:1
  - standard care
  - standard care plus hydroxychloroquine (400 mg twice daily)
  - standard care plus hydroxychloroquine (400 mg twice daily) plus azithromycin at a dose of 500 mg once daily for 7 days
  - the proportional odds of having a higher score on the seven-point ordinal scale at 15 days was not affected by either hydroxychloroquine alone (odds ratio, 1.21; 95% confidence interval [CI], 0.69 to 2.11; P = 1.00) or hydroxychloroquine plus azithromycin
  - Prolongation of the corrected QT interval and elevation of liver-enzyme levels were more frequent in patients receiving hydroxychloroquine, alone or with azithromycin, than in those who were not receiving either agent.

N Engl J Med . 2020 Jul 23;NEJMoa2019014.

Νόσος COVID-19

Προφύλαξη με Υδροξυχλωροκίνη

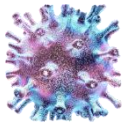
- Randomized, double-blind, placebo-controlled trial
  - Within 4 days after exposure
  - placebo or hydroxychloroquine (800 mg once, followed by 600 mg in 6 to 8 hours, then 600 mg daily for 4 additional days)
- 821 asymptomatic participants
  - 87.6% (high-risk exposure to a confirmed Covid-19 contact)
  - Incidence of new illness compatible with Covid-19
  - Hydroxychloroquine (49 of 414 [11.8%])
  - Placebo (58 of 407 [14.3%]), p=0.35
  - Side effects : more common with hydroxychloroquine (40.1% vs. 16.8%)

Boulware DR, et al. NEJM 2020; August

Νόσος COVID-19

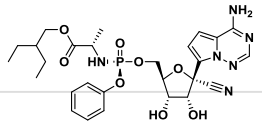
Θεραπεία με Remdesivir (RDV)

- **In vitro activity against an array of RNA virus families including:**
  - *Filoviridae, Paramyxoviridae, Pneumoviridae,* and *Coronaviridae*



- **Intravenous administration once daily via 30-120 min infusion**
  - Loading dose: RDV 200mg
  - Maintenance dose: RDV 100mg
  - Available in injection solution and lyophilized powder for reconstitution

- **Inhaled RDV formulation is under investigation**
- RDV is not suitable PO due to almost complete first pass metabolism
- Metabolism is thought to be predominantly mediated by hydrolase activity
- Major routes of elimination include renal (74%) and biliary (18%)



Sheahan TP, et al. Sci Transl Med 2017;9:eaal3653, Warren et al, 2016 Nature
https://www.gilead.com/purpose/advancing-global-health/covid-19/working-to-supply-remdesivir-for-covid-19

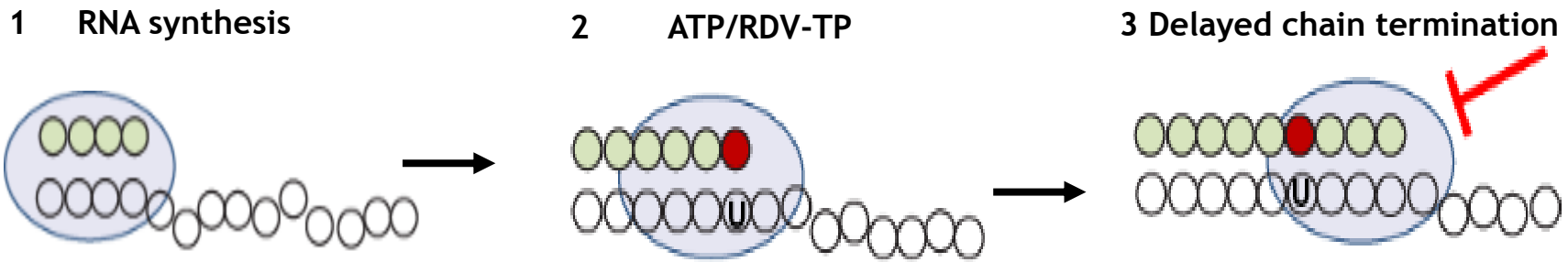
Νόσος COVID-19

Θεραπεία με Remdesivir (RDV)

- **Remdesivir (RDV)** is a prodrug of a nucleoside analog that inhibits viral RNA-dependent RNA polymerase with broad spectrum antiviral activity observed in vitro against member of several viral families including filoviruses (e.g. Ebola) and coronaviruses (e.g. SARS-CoV and MERS-CoV)[4]

RDV Mode of Action

- RDV intracellularly undergoes rapid conversion to active nucleoside triphosphate (**RDV-TP**), GS-443902[4]
- **RDV-TP** is efficiently incorporated into the nascent RNA chain by viral RNA-dependent RNA polymerase (RdRp) resulting in delayed RNA chain termination during viral replication[4,5]



Zhu, Na; et al. *New England Journal of Medicine*. United States. 382 (8): 727–733. doi:10.1056/NEJMoa2001017, Zhou et al *Nature* Feb 3, 2020, Lu et al. Lancet 2020, Warren TK, et al. Nature 2016;531:381-5, Gordon, et al. 2020 https://www.jbc.org/cgi/doi/10.1074/jbc.AC120.013056Lo MK, et al. Sci Reports 2017;7:43395.

Νόσος COVID-19

Θεραπεία με Remdesivir (RDV)

Grein G. NEJM 2020

53 patients treated with Remdesivir

- 30 patients (57%) were receiving MV
- 4 (8%) were ECMO.

Follow-up of 18 days

- **36 patients (68%)** improvement in oxygen-support
- 25 patients (47%) were discharged
- 7 patients (13%) died

- Insufficient statistical power
- Treatment started late
- Absence on data regarding virus recovery
- No data on Rem R.

Wang. Lancet 2020

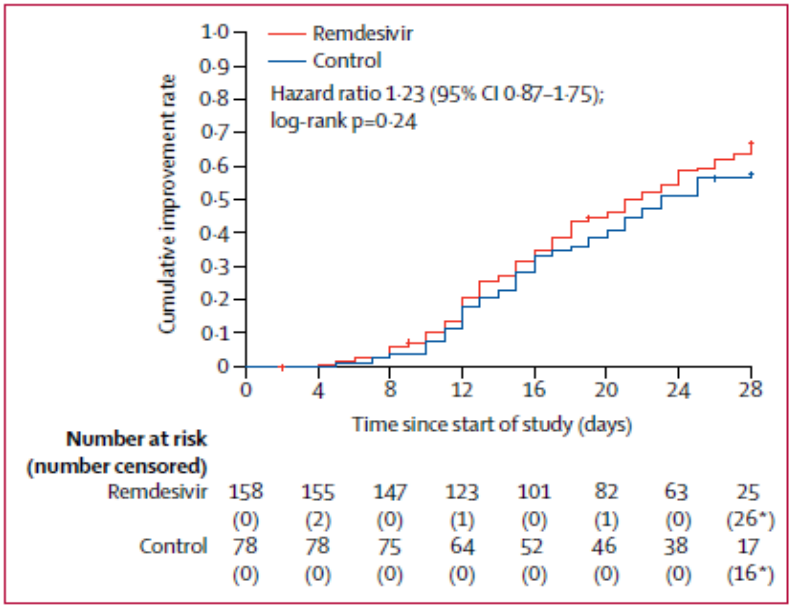


Figure 2: **Time to clinical improvement in the intention-to-treat population**
Adjusted hazard ratio for randomisation stratification was 1·25 (95% CI 0·88–1·78). *Including deaths before day 28 as right censored at day 28, the number of patients without clinical improvement was still included in the number at risk.

Νόσος COVID-19

Θεραπεία με Remdesivir (RDV)- Κλινικές μελέτες

Data Source		Target N	Hospitalized patients			Placebo or Standard of Care	Key Question	Data Available- Key Publication
			Moderate	Severe	Critical			
NIH NIAID ACTT1 NCT04280705	Randomized Double blind	1063	M	S	C	P	Is RDV safe and effective treatment for COVID-19 patients?	**Beigel NEJM May 2020:** RDV superior to PBO in time to recovery[1]
GILEAD GS-US-540-5773 NCT04292899	Randomized Open label	400		S			Is a 5 day treatment course as effective and safe as a 10 day course of RDV?	**Goldman NEJM May 2020:** Similar 5 day/10 day efficacy in severe COVID-19 (non-mechanically ventilated)[2]
GILEAD Non-RDV GS-US-540-5807	Real-world, Retrospective	818*		S		SoC	Is RDV effective when compared to RW non-RDV cohort?	**Olender Clinical Infectious Diseases July 2020:** RDV was associated with significantly improved recovery compared with standard of care ($p<0.001$)[3]

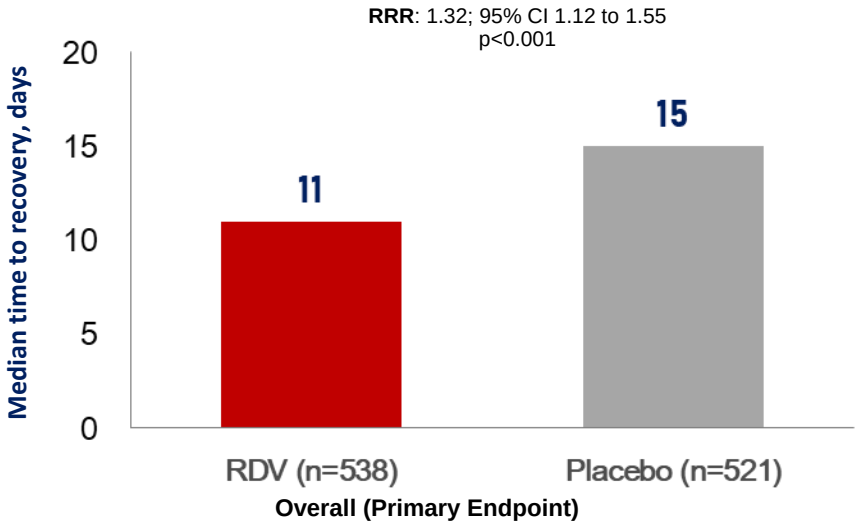
*N = non-RDV cohort. 312 patients were inc. in RDV cohort within this study

Beigel JH et al. NEJM 22 May 2020, Goldman et al. NEJM 27 May 2020, Olender SA, et al. Clinical Infectious Diseases, 24 July 2020

Νόσος COVID-19

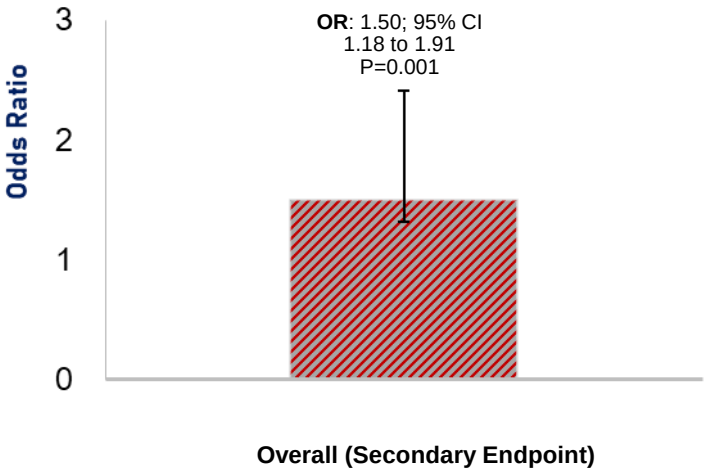
NIAID Study (ACTT-1)

Preliminary efficacy results of RDV compared to placebo



RDV produced 32% faster time to recovery and reduced time to recovery from 15 to 11 days compared to placebo

Improvement at Day 15*



RDV produced 50% higher rate of clinical improvement on the ordinal scale compared to placebo

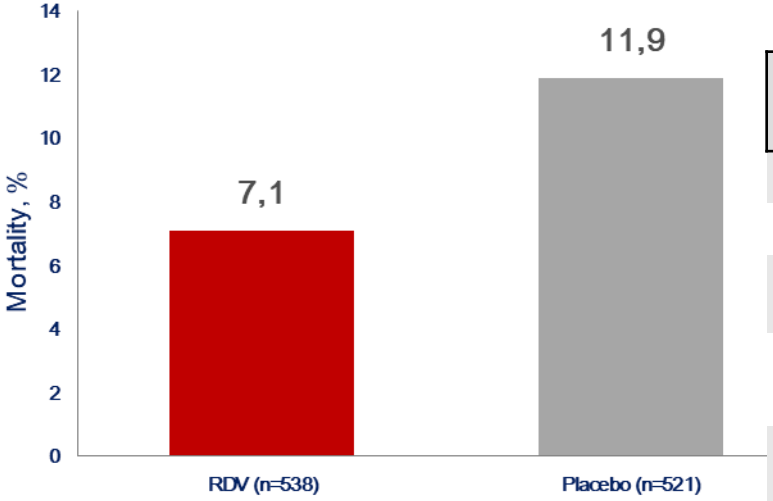
*Improvement/recovery was defined as the first day during the 28 days after enrollment on which a patient satisfied categories 1,2, or 3 on the eight category ordinal scale

Beigel JH et al. NEJM 22 May 2020

Νόσος COVID-19

NIAID Study (ACTT-1)

Mortality by 14 Day in Overall Population



Recovery and Death by Day 14 according to Ordinal Score at Baseline

Baseline ordinal scale	4		5		6		7	
	RDV (n=67)	Placebo (n=60)	RDV (n=222)	Placebo (n=199)	RDV (n=98)	Placebo (n=99)	RDV (n=125)	Placebo (n=147)
Number of Recoveries	61	47	**177**	**128**	47	43	45	51
Median days (95% CI)	5 (4-6)	6 (4-8)	**7 (6-8)**	**9 (7-11)**	16 (NE-10)	22 (NE-12)	(NE-NE)	28 (NE-22)
RRR (95% CI)*	1.38 (0.94, 2.03)		**1.47 (1.17, 1.84)**		1.20 (0.79, 1.81)		0.95 (0.64, 1.42)	
Deaths HR (95% CI)	0.46 (0.04-5.08)		**0.22 (0.08, 0.58)**		1.12 (0.53, 2.38)		1.06 (0.59, 1.92)	

There was a non- statistically significant trend toward lower mortality in the RDV group vs the placebo group by Day 14

RDV was associated with shorter time to recovery and survival benefit among patients with a baseline ordinal score of 5

Beigel JH et al. NEJM 22 May 2020; SmPc Veklury July 3, 2020. COVID-19 Treatment Guidelines, NIH
https://www.covid19treatmentguidelines.nih.gov/antiviral-therapy/remdesivir/

Νόσος COVID-19

NIAID Study (ACTT-1)

Preliminary Results of NIAID Study (ACTT-1): Safety Summary

Organ Class	Serious AEs	Remdesivir (N= 541) No. (%)	Placebo (N=522) No. (%)
Any System Organ Class	Any	114 (21.1)	141 (27.0)
Renal and urinary	Acute kidney injury [a]	4 (0.7)	7 (1.3)
	Glomerular filtration rate decreased [a]	3 (0.6)	2 (0.4)
Infections and infestations	Pneumonia viral	3 (0.6)	7 (1.3)
Respiratory, Thoracic and mediastinal disorders	Respiratory failure	28 (5.2)	42 (8.0)
	Acute respiratory failure	9 (1.7)	12 (2.3)
Vascular disorder	Hypotension	2 (0.4)	12 (2.3)

SAEs were numerically lower in RDV (21%) compared to placebo (27%)

4 SAE events (2 in each arm) were judged by site investigators to be related to the study product

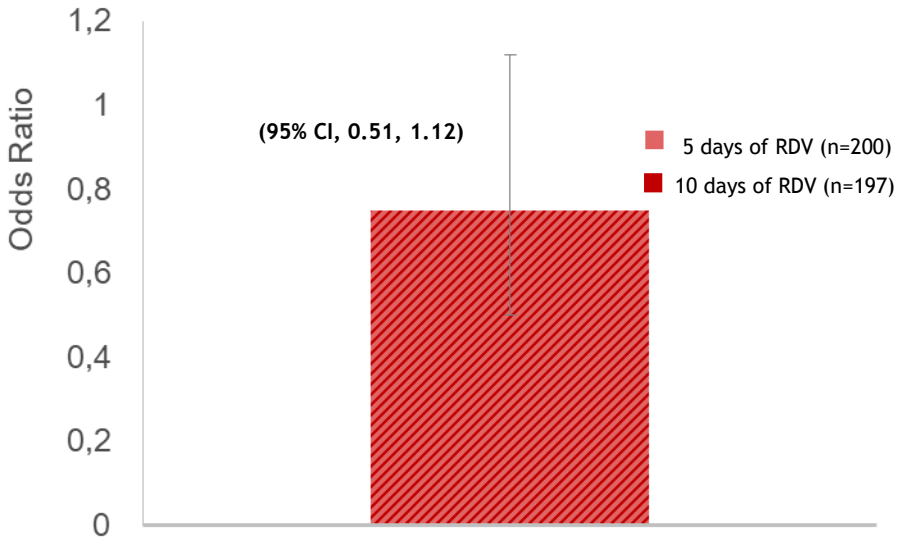
a. The combined number of subjects with either glomerular filtration rate decreased and/or acute kidney injury are 7 for Remdesivir and 9 for Placebo.

Beigel JH et al. NEJM 22 May 2020

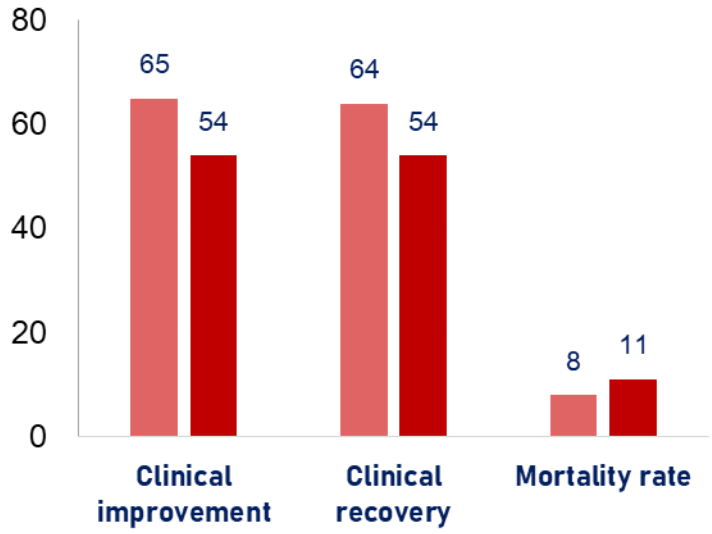
Νόσος COVID-19

SIMPLE Study

10-to-5 days Adjusted Odds Ratio (aOR)



Observed Rates at Day 14



- **Clinical improvement-** defined as an improvement of two or more points from baseline on a predefined 7-point scale, ranging from hospital discharge to increasing levels of oxygen support to death
- **Clinical recovery-** defined as no longer requiring oxygen support or discharged from the hospital

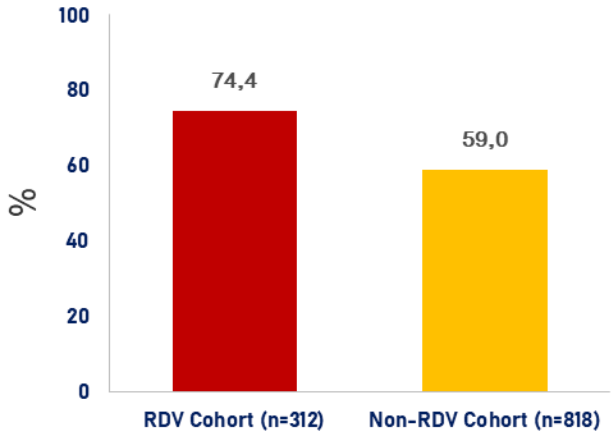
Goldman et al. NEJM 27 May 2020

Νόσος COVID-19

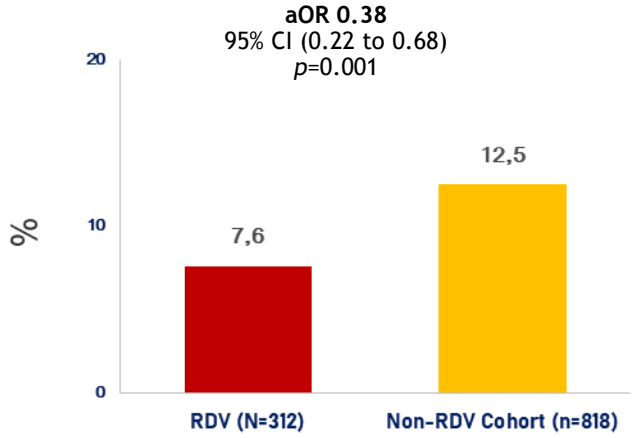
Analysis of RDV vs Standard of Care

Phase 3 trial and a retrospective cohort of patients with severe COVID-19 treated with SoC

Recovered by Day 14



Mortality at Day 14



By Day 14, RDV was associated with significantly improved recovery and 62% reduced odds of death compared to a retrospective RW standard of care cohort

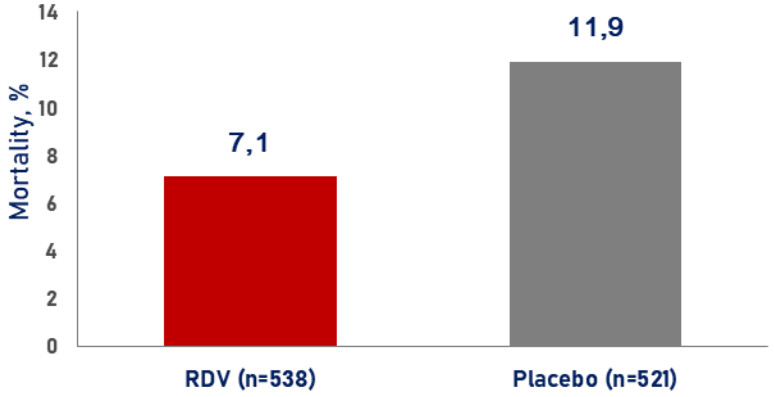
Olender SA, et al. Clinical Infectious Diseases, 24 July 2020

Νόσος COVID-19

Mortality at Day 14: RDV vs Placebo or SoC

ACTT- 1 : Mortality by Day 14[1]*

HR: 0.70
95% CI (0.47 to 1.04)

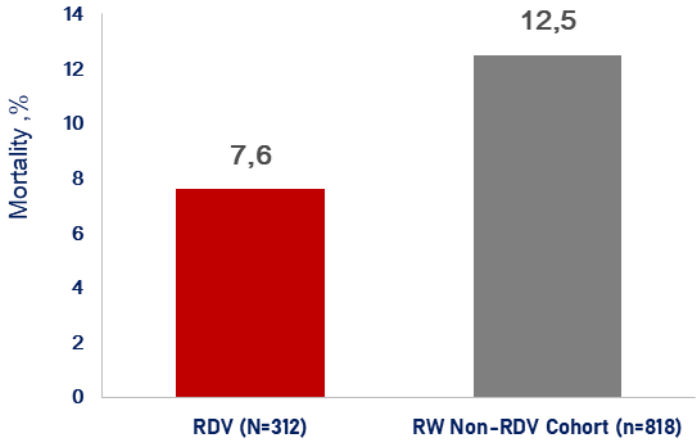


Ordinal scale[3]	4	5	6	7
Deaths HR (95% CI)	0.46 (0.04, 5.08)	**0.22** **(0.08, 0.58)**	1.12 (0.53, 2.38)	1.06 (0.59, 1.92)

Hospitalized patients on RDV numerically trended towards lower mortality vs placebo with a survival benefit in those requiring supplemental O_2 [1]

Study 5773/ RW Study 5807 Analysis
Mortality at Day 14[2]

aOR 0.38
95% CI (0.22 to 0.68), *p*=0.001

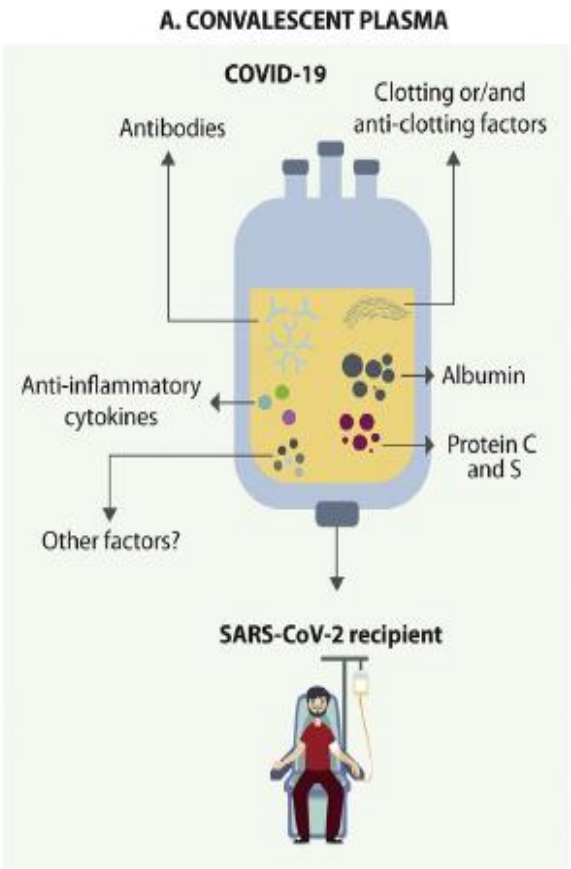


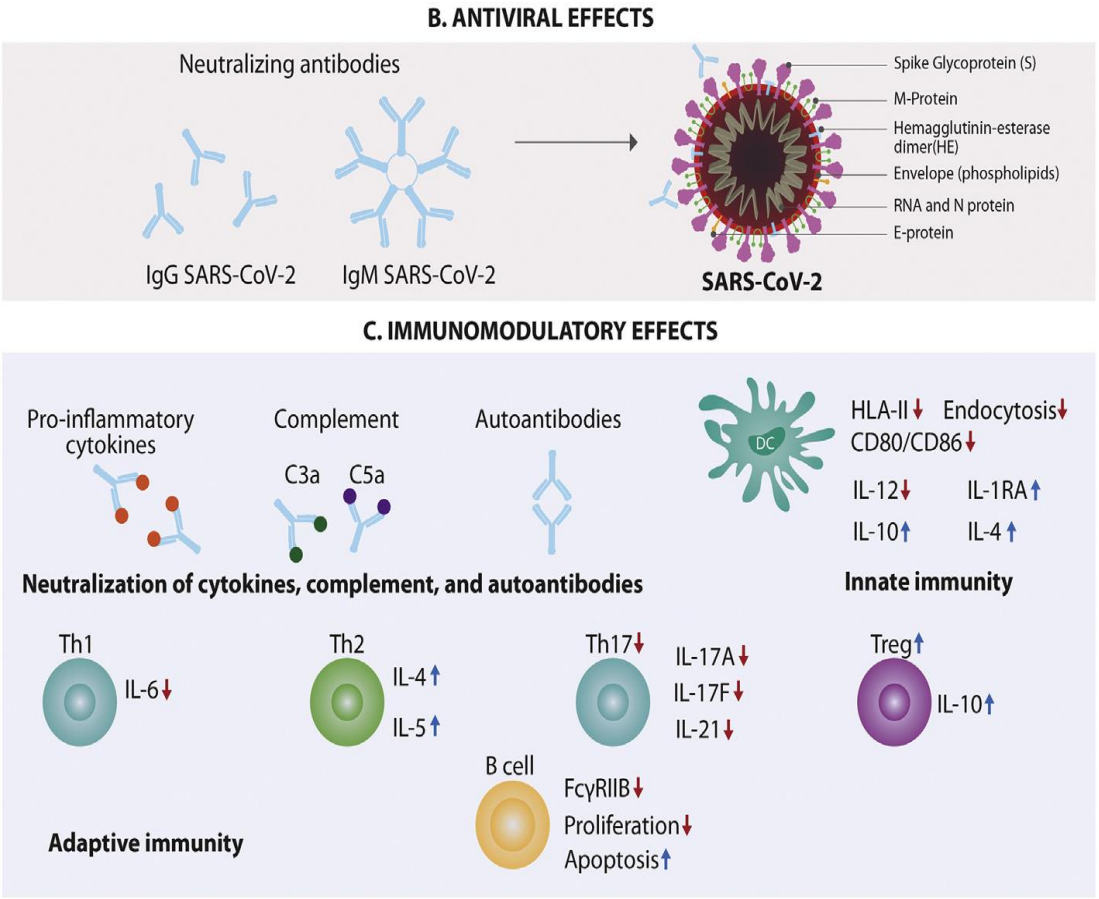
RDV used in clinical trial was associated with 62% reduced odds of death compared to a RW- SoC cohort [2]

Beigel JH et al. NEJM 22 May 2020, Olender SA, et al. IDSA. 2020, COVID-19 Treatment Guidelines, NIH
https://www.covid19treatmentguidelines.nih.gov/antiviral-therapy/remdesivir/

Νόσος COVID-19

Θεραπεία με πλάσμα





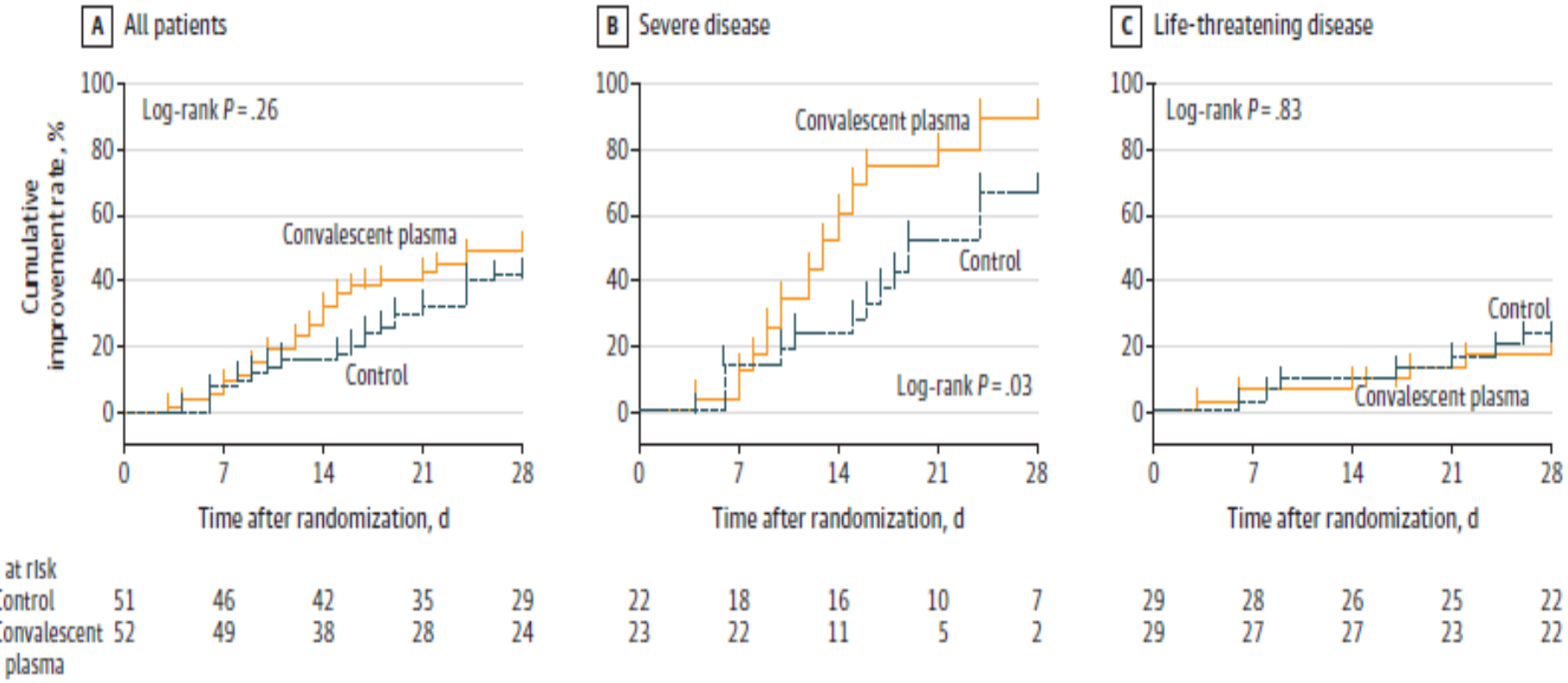
JAMA | Original Investigation

Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19

A Randomized Clinical Trial

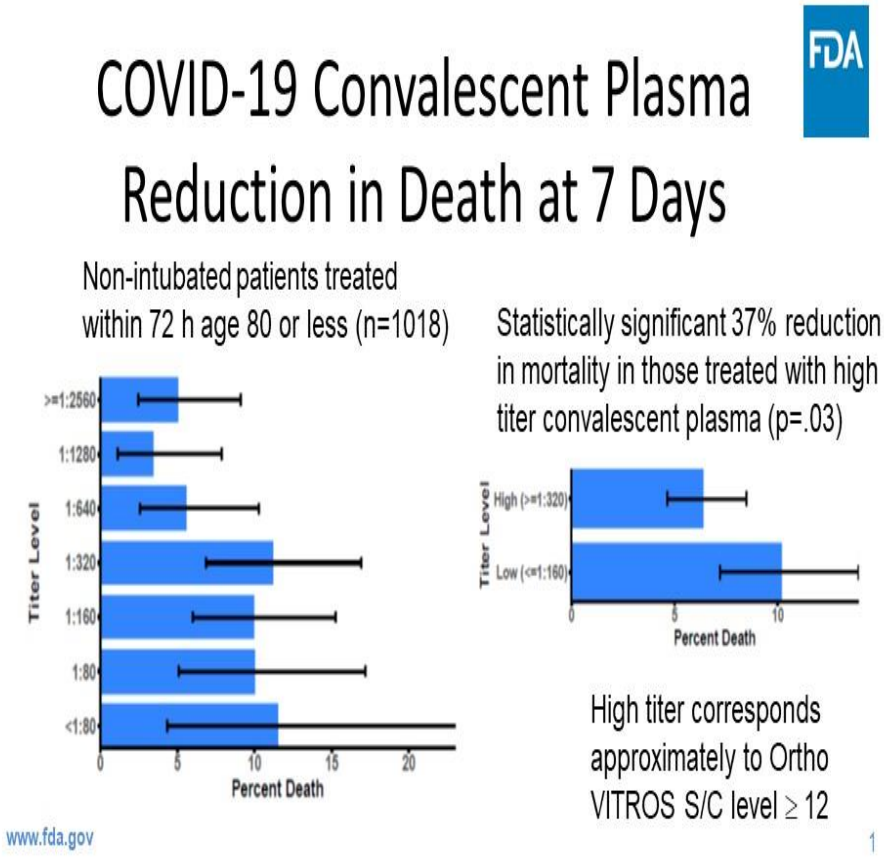
Ling Li, MD, PhD; Wei Zhang, MD; Yu Hu, MD, PhD; Xunliang Tong, MD, PhD; Shangen Zheng, MD; Juntao Yang, PhD; Yujie Kong, MD; Lili Ren, PhD; Qing Wei, MD; Heng Mei, MD, PhD; Caiying Hu, MD; Cuihua Tao, MD; Ru Yang, MD; Jue Wang, MD; Yongpei Yu, PhD; Yong Guo, PhD; Xiaoxiong Wu, MD; Zhihua Xu, MD; Li Zeng, MD; Nian Xiong, MD; Lifeng Chen, MD; Juan Wang, MD; Ning Man, MD; Yu Liu, PhD; Haixia Xu, MD; E. Deng, MS; Xuejun Zhang, MS; Chenyue Li, MD; Conghui Wang, PhD; Shisheng Su, PhD; Linqi Zhang, PhD; Jianwei Wang, PhD; Yanyun Wu, MD, PhD; Zhong Liu, MD, PhD

Figure 2. Time to Clinical Improvement in Patients With COVID-19



Νόσος COVID-19

Θεραπεία με πλάσμα



- **According to the FDA, eligible recipients of convalescent plasma should be**
  - COVID-19 positive patients with severe disease (dyspnea, respiratory frequency ≥ 30/min, blood oxygen saturation 93% or less, partial pressure of arterial oxygen to fraction of inspired oxygen ratio less than 300, and/or lung infiltrates > 50% within 24 to 48hours)

OR

  - a life-threatening disease (respiratory failure, septic shock, multiple organ dysfunction)
  - Patients must give informed consent

Food and Drug Administration. Revised Information for Investigational COVID-19 Convalescent Plasma. 2020; https://www.fda.gov/vaccines blood-biologics/investigational-new-drug-ind-or-device-exemptio nide-process-cber/revised-information-investigational-covid-19-convalescent-plasma. Accessed April 08, 2020.

Νόσος COVID-19

Θεραπεία με πλάσμα – Δότες

- Eligible donors could be recovered COVID-10 patients who had been proven positive either by a diagnostic test (nasopharyngeal swab at the time of illness, or antibody-posiitve patients on whom a diagnostic test had not been perforemd during their illness.
- The level of neutralizing a antibody titers should be greater than 1:160 whereas a titer of 1:80 could be deemd acceptable
- Symptoms must have resolved completely at least 28 days prior to donation
- Alternatively a symptom-free interval of at least 14 days prior to donation and negative resutls in oner or more nasopharyngeal swabs or in blood based molecula diagnostic tests are necessitated
- Male donors are eligible
- Special attention to female donors who should be negative for HLA antibodies in case of previous pregnance.
- General donor eligibility requirements along with the additional criteria for plasmapheresis should be also met including infection status control

FDA, revised information for investigational COVID-19 convalescent plasma; https:://www.fda.gpv/vaccines blood-biologics/investigational-new-drug-ind-or-device-exemptio nide-process-cber/revised- information –investigational-covid-19-convalescent-plasma.Asssesed April 08,2020

Νόσος COVID-19

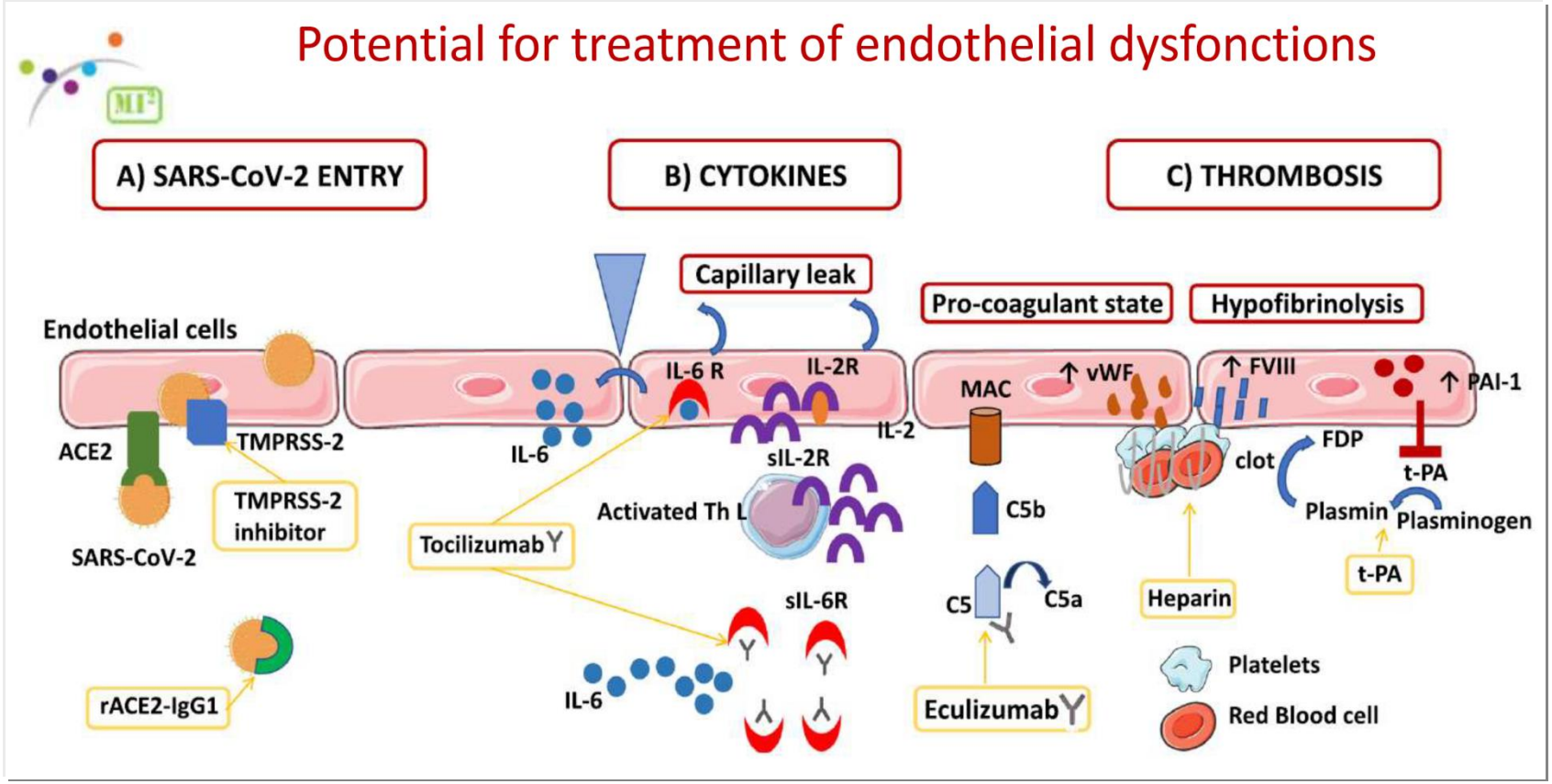
Θεραπεία με πλάσμα – Ασφάλεια

Known SE and hazards associated with plasma transfusion include

- Transfusion-transmitted infections (e.g. HIV, hepatitis B, hepatitis C)
- Allergic reactions
- Anaphylactic reactions
- Febrile non-hemolytic reactions
- Transfusion-related acute lung injury (TRALI)
- Transfusion-associated cardiac overload (TACO)
- Hemolytic reactions
- Hypothermia
- Metabolic complications
- Post-transfusion purpura have also been described

Νόσος COVID-19

Ανοσοθεραπεία



Pons S- Crit Care 2020

Νόσος COVID-19

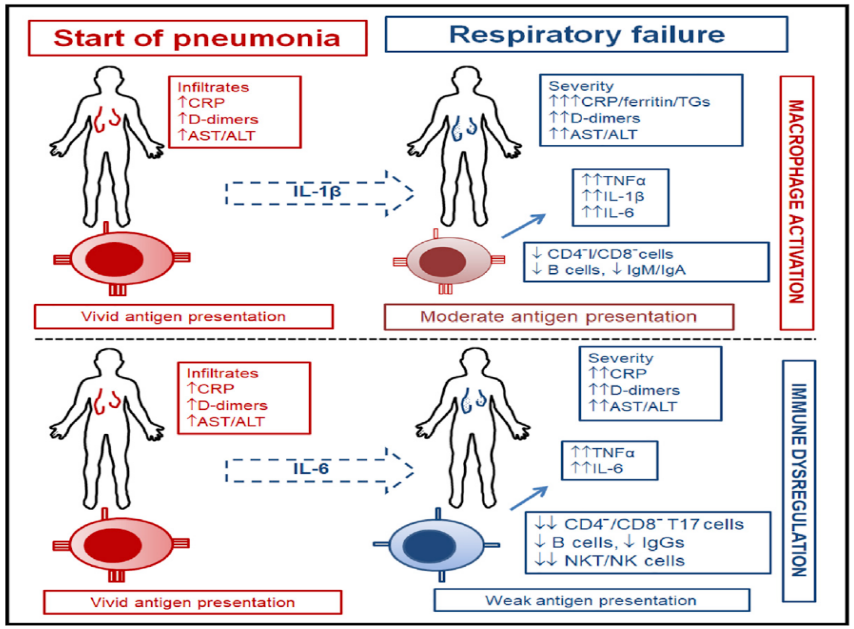
Ανοσοθεραπεία

Clinical and Translational Report

Cell Host & Microbe

Complex Immune Dysregulation in COVID-19 Patients with Severe Respiratory Failure

Graphical Abstract



Authors

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In Brief

Proper management of COVID-19 mandates better understanding of disease pathogenesis. Giamarellos-Bourboulis et al. describe two main features preceding severe respiratory failure associated with COVID-19: the first is macrophage activation syndrome; the second is defective antigen-presentation driven by interleukin-6. An IL-6 blocker partially rescues immune dysregulation *in vitro* and in patients.

Νόσος COVID-19

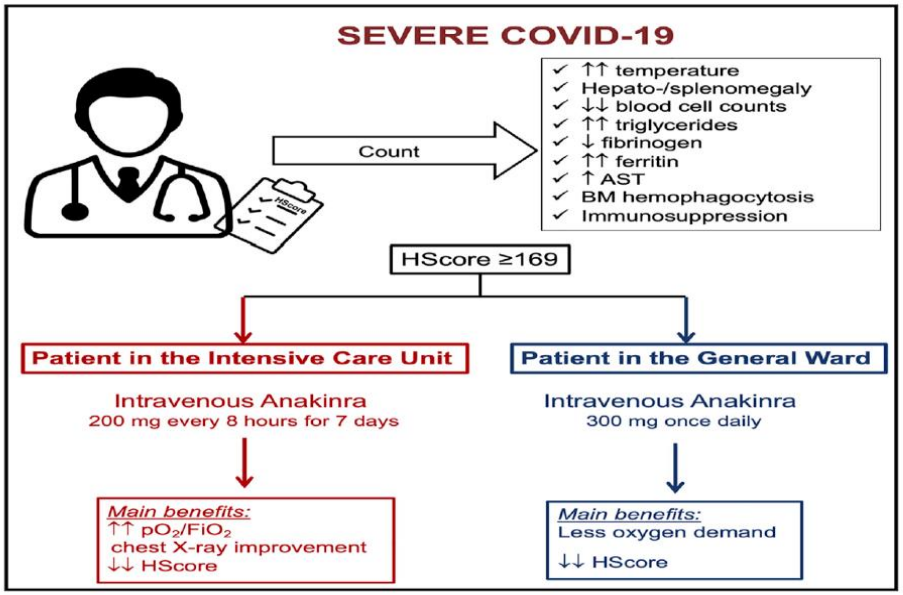
Ανοσοθεραπεία

Clinical and Translational Report

Cell Host & Microbe

Favorable Anakinra Responses in Severe Covid-19 Patients with Secondary Hemophagocytic Lymphohistiocytosis

Graphical Abstract



Authors

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Correspondence

egiamarel@med.uoa.gr

In Brief

Complex immune dysregulation in severe COVID-19 suggests the use of immunomodulation therapies. Dimopoulos et al. describe eight cases of COVID-19 patients who all had secondary hemophagocytic lymphohistiocytosis and showed favorable responses in respiratory function upon treatment with the interleukin-1 receptor antagonist Anakinra.

ΘΕΡΑΠΕΥΤΙΚΟΣ ΑΛΓΟΡΙΘΜΟΣ ΑΣΘΕΝΟΥΣ ΜΕ COVID-19 ΛΟΙΜΩΞΗ ΣΤΟ ΝΟΣΟΚΟΜΕΙΟ 27/8/20

Οι οδηγίες θα αναπροσαρμόζονται σύμφωνα με νεότερα επιστημονικά δεδομένα για την νόσο COVID-19

ΑΡΧΙΚΕΣ ΕΞΕΤΑΣΕΙΣ ΓΙΑ ΤΗΝ ΕΚΤΙΜΗΣΗ ΑΥΤΩΝ ΠΟΥ ΘΑ ΕΙΣΑΧΘΟΥΝ ΣΤΟ ΝΟΣΟΚΟΜΕΙΟ

•ΣΕ ΟΛΟΥΣ: Γενική αίματος, σάκχαρο, ουρία, κρεατινίνη, ηπατική βιοχημεία, LDH, CK, CRP, τροπονίνη, φερριτίνη, έλεγχος πήξης, D-dimers, παλμική οξυμετρία ή αέρια αίματος. Περαιτέρω εξετάσεις κατά περίπτωση.

•ΣΕ ΟΛΟΥΣ: Απλή CXR ή CTX, ΗΚΓ 12 ΑΠΑΓΩΓΩΝ και ΠΡΟΣΔΙΟΡΙΣΜΟΣ QT

Παλμική οξυμετρία >94% (FiO_2 21%)
ΚΑΙ
CRP <1,5mg/dL (όριο < 0,5mg/dL)
ΚΑΙ
Φερριτίνη <500μg/L
ΚΑΙ
Άνευ παραγόντων κινδύνου
ΚΑΙ
Α/α θώρακος ή CTX ΧΩΡΊΣ ΔΙΗΘΗΜΑΤΑ

Νοσηλεία οίκοι
Βλέπε οδηγίες αντιμετώπισης COVID-19 εκτός νοσοκομείου

Παλμική οξυμετρία ≤ 94% (FiO_2 21%)
Ή
CRP >1,5mg/dL (όριο < 0,5mg/dL)
Ή
Φερριτίνη >500μg/L Ή παράγοντες κινδύνου
Ή
ΔΙΗΘΗΜΑΤΑ στην Α/α θώρακος ή CTX

Dexamethasone[1] (max 10 ημ) ή ισοδύναμο της Dexamethazone + Remdesivir[2] (5 ημ)

Επί αδυναμίας χορήγησης Remdesivir εξετάστε το ενδεχόμενο χορήγησης χλωροκίνης ή υδροξυχλωροκίνης[3*] με τη διαδικασία χορήγησης φαρμάκου εκτός ενδείξεων ή με ένταξη σε κλινική μελέτη +/- αζιθρομυκίνη[4] + αντιμικροβιακή αγωγή για πνευμονία εκ της κοινότητας

Κλινική σταθερότητα για 7-10 ημέρες
ΚΑΙ
Βελτίωση δεικτών φλεγμονής
ΚΑΙ
Άνευ συμπτωμάτων ≥ 3 ημέρες

Εξιτήριο και σε δεύτερο χρόνο PCR

- **Επιδείνωση αναπνευστικής λειτουργίας**
  - $SatO_2$ ≤ 93%
  - PaO_2/FiO_2 < 300 mm Hg
  - Αναπνοές > 24/min

  ή/και
- **ARDS/ανάγκη μηχανικού αερισμού**
  ή/και
- **Shock**
  ή/και
- **Κλινικοεργαστηριακά δεδομένα συνδρόμου απελευθέρωσης κυτταροκινών**
  - ↑ CRP >5mg/dL)
  - ↑ Φερριτίνης (> 1000 μg/L)
  - ↑ LDH (> 250 U/L)
  - ↑ D-dimers (>1000 ng/mL)
  - ↓ λεμφοκυττάρων (< 800/μL)

- Αποκλεισμός βακτηριακής επιλοίμωξης (μέτρηση προκαλσιτονίνης, διεύρυνση του φάσματος της αντιμικροβιακής αγωγής)
- Αναζήτηση άλλων αιτίων επιδείνωσης, π.χ. επιδείνωση καρδιακής ανεπάρκειας, μυοκαρδίτιδας οξύ στεφανιαίο σύνδρομο, πνευμονική εμβολή, φαρμακευτική τοξικότητα

- Εάν ο ασθενής δεν έχει λάβει Remdesivir ή dexamethasone χορηγήστε
  Remdesivir + dexamethasone (10 ημ)

- Εάν η επιδείνωση συνέβη υπό Remdesevir + dexamethasone, εξετάστε τη δυνατότητα χορήγησης πλάσματος(https://www.clinicaltrials.gov/ct2/show/NCT04408209),Tocilizumab, Anakinra ή άλλου ερευνητικού φαρμάκου στο πλαίσιο κλινικής μελέτης ή χορήγησης φαρμάκου εκτός ενδείξεων όπως ΄Tocilizumab, Anakinra

Οι νοσηλευόμενοι ασθενείς με COVID-19 πρέπει να λαμβάνουν θρομβοπροφύλαξη.

Για την **προφύλαξη φλεβοθρόμβωσης ιδέ ΣΥΣΤΑΣΕΙΣ ΘΡΟΜΒΟΠΡΟΦΥΛΑΞΗΣ ΣΕ ΑΣΘΕΝΕΙΣ ΜΕ COVID-19 / ΤΜΗΜΑ ΑΙΜΟΣΤΑΣΗΣ Ε.Α.Ε (updated 20/07/2020)** https://www.eae.gr

*στο πλαίσιο ερευνητικού πρωτοκόλλου (κατ' άρθρ. 38, ΠΝΠ 30.3.20) εγκεκριμένου από τον ΕΟΦ ή στο πλαίσιο διαδικασίας χορήγησης σε ασθενείς ως φάρμακο εκτός εγκεκριμένης ένδειξης (αρθρ. 36, ΠΝΠ 30.3.20)
**σε ασθενείς με γνωστή καρδιοπάθεια ή ισχυρές ενδείξεις καρδιοπάθειας, στο πλαίσιο ερευνητικού πρωτοκόλλου εγκεκριμένου από τον ΕΟΦ ή στο πλαίσιο των προϋποθέσεων του αρθρ. 36, περ.α-β, παρ.1
[1] **Dexamethasone** 6 mg/day ή Methylprednisolone 32 mg/day ή Prednisone 40 mg/day. [2]**Remdesevir:** 200mg την πρώτη ημέρα και στη συνέχεια 100mg/ημέρα για 5-10 ημέρες. Προσοχή διακοπή της χορήγησης εάν ALT>5X ΦΤ ή GFR <30ml/min. [3]**Υδρόξυχλωροκίνη**: 400mg x 2 την πρώτη ημέρα και 200mg X 2 /ημέρα x 7 ημέρες (λήψη με φαγητό ή γάλα) ή **Φωσφορική χλωροκίνη**: 500mg x 2 για 5-7 ημέρες. ΠΡΟΣΟΧΗ για πιθανή καρδιοτοξικότητα: παράταση QT> 500msec, Myasthenia gravis, porphyria, επιληψία και αλληλεπιδράσεις με άλλα φάρμακα – βλέπε http://www.covid19-druginteractions.org. [4]**Αζιθρομυκίνη:** 500mg x 1 επί 3 ημέρες.

Νόσος COVID-19

ΔΕΝ ΥΠΑΡΧΕΙ ΚΟΡΩΝΟΙΟΣ !!!!!!!!!!!!!!!!!!!!!!!!!