Νόσος COVID-19

Καθηγητής Γιώργος Δημόπουλος MD, PhD, FCCP, FECMM
gdimop@med.uoa.gr

ΕΘΝΙΚΟ ΚΑΙ ΚΑΠΟΔΙΣΤΡΙΑΚΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΑΘΗΝΩΝ
ΙΑΤΡΙΚΗ ΣΧΟΛΗ

Β΄ΚΛΙΝΙΚΗ ΕΝΤΑΤΙΚΗΣ ΘΕΡΑΠΕΙΑΣ
Πανεπιστημιακό Νοσοκομείο ΑΤΤΙΚΟΝ
Χαιδάρι - Αθήνα


CONFLICT OF
INTEREST
No!

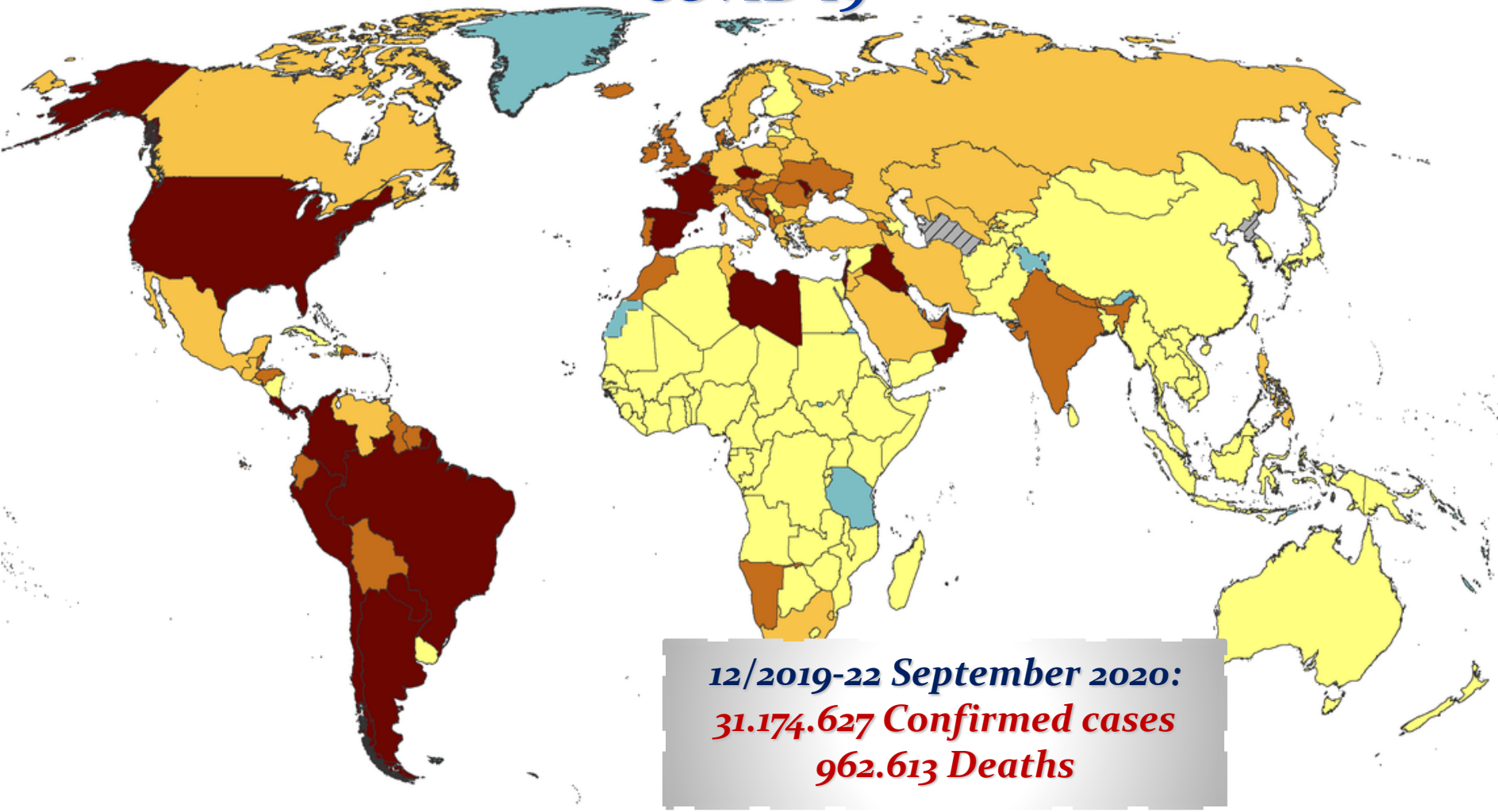
Νόσος COVID-19
Ιστορική αναδρομή

- 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

Νόσος COVID-19
Δομή του ιού

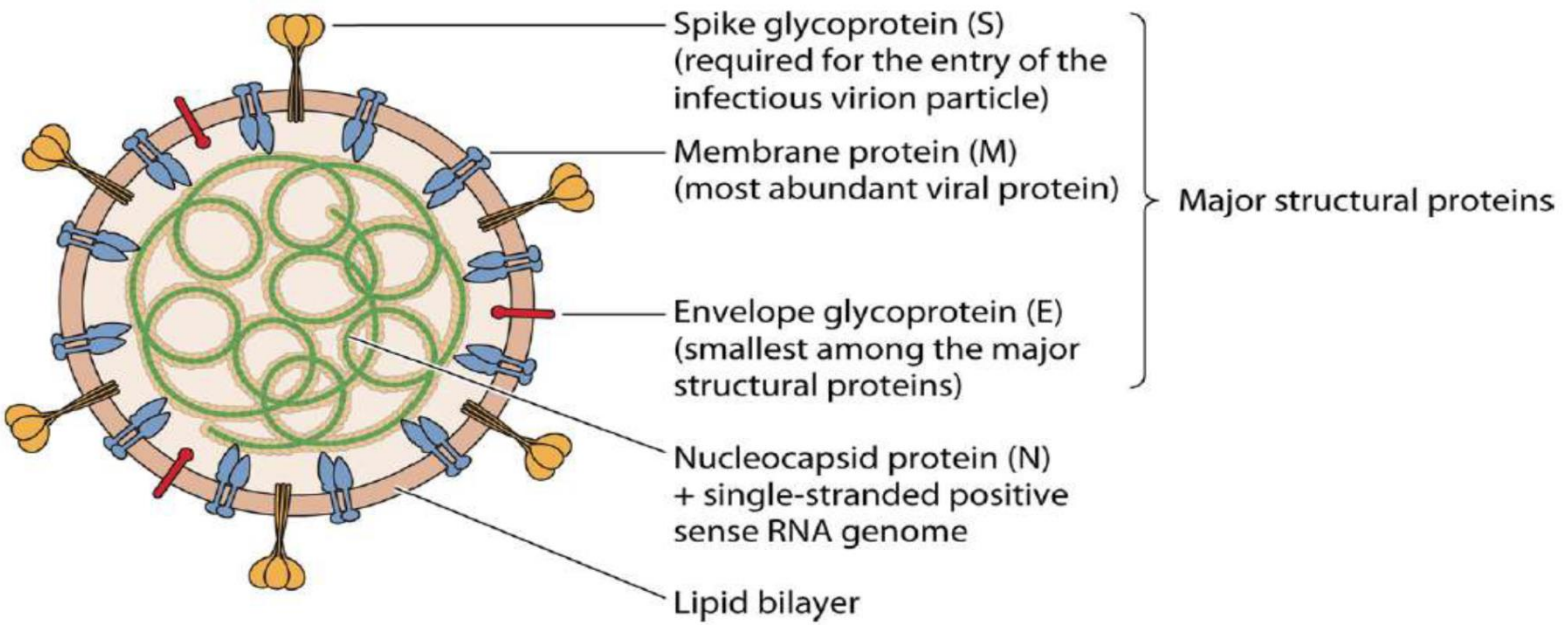
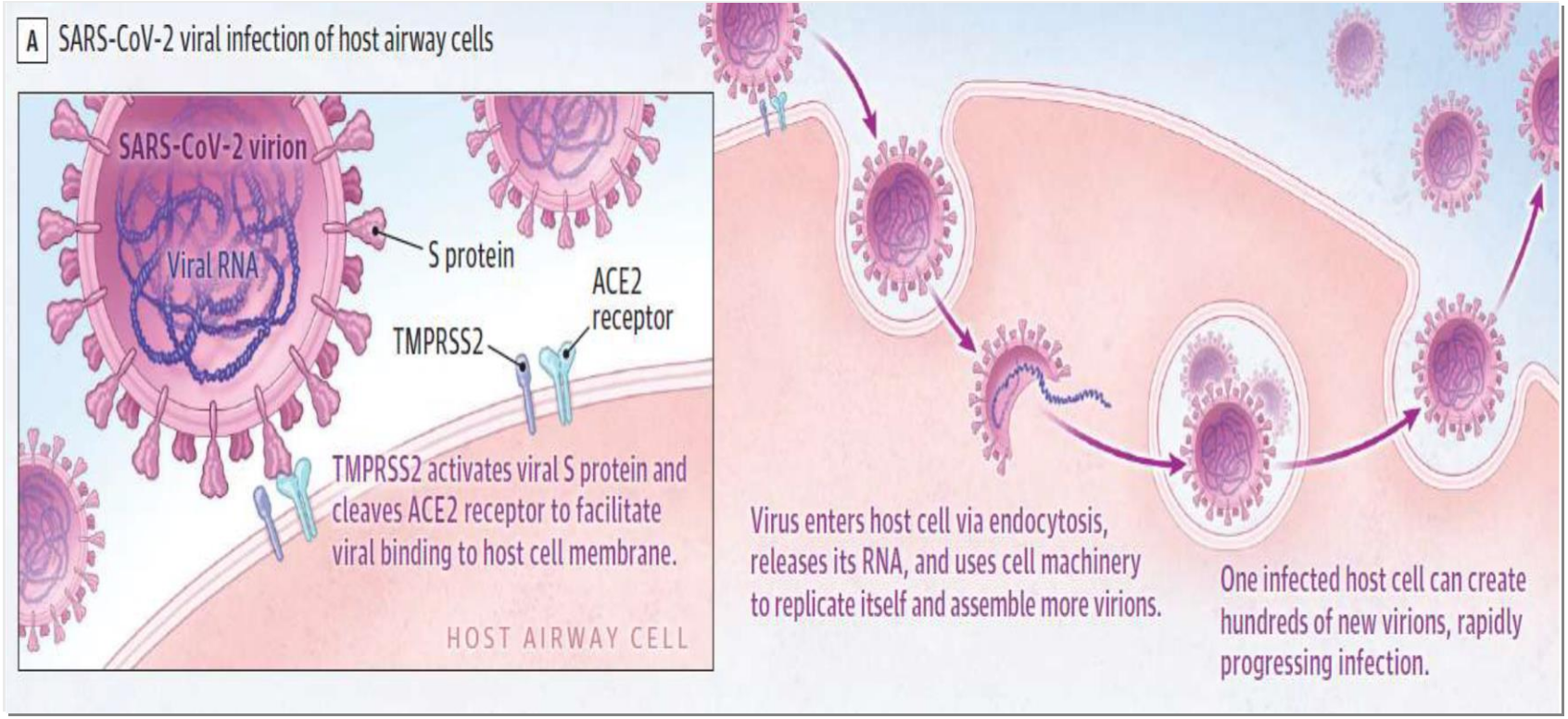


FIG 2 SARS-CoV-2 virus structure.

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

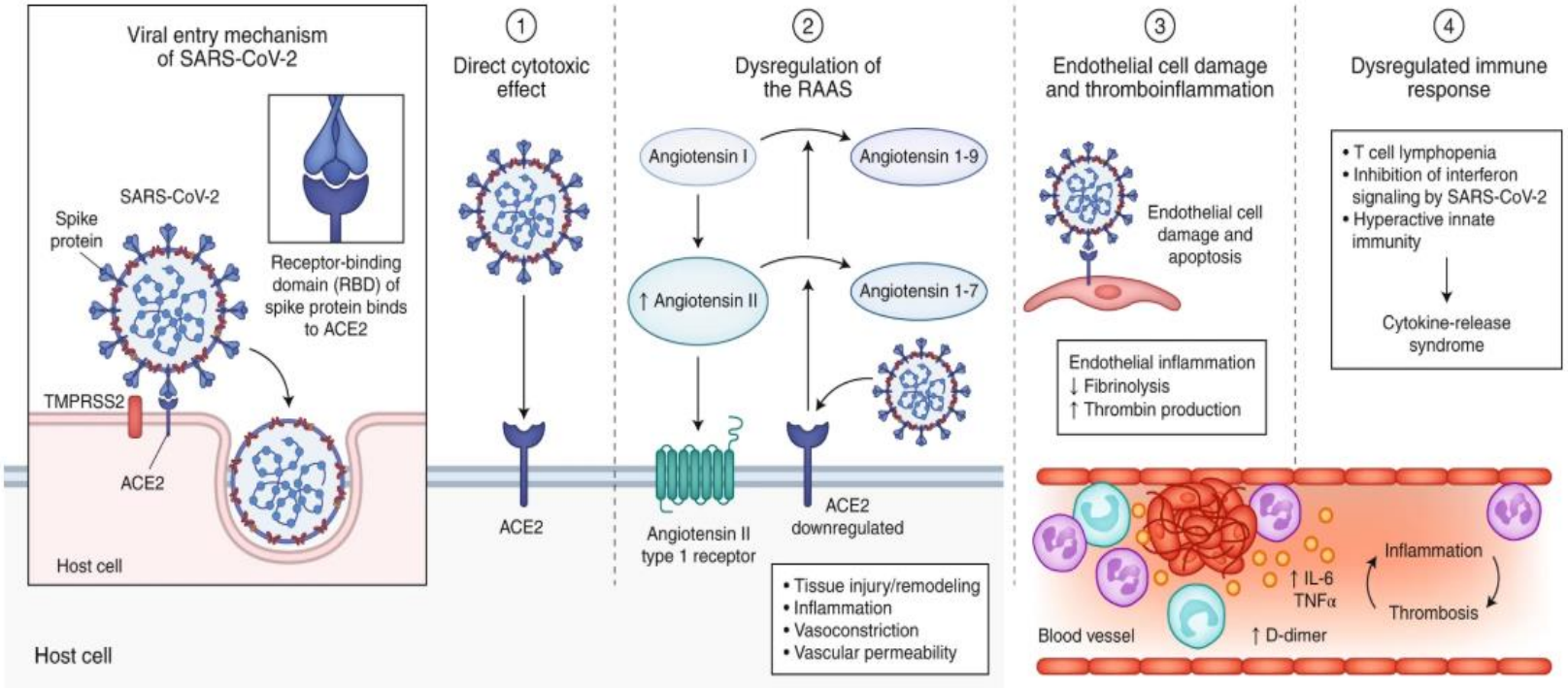
Νόσος COVID-19
Είσοδος του ιού στον ανθρώπινο οργανισμό



Νόσος COVID-19
Παθοφυσιολογία

Fig. 1: Pathophysiology of COVID-19.

From: Extrapulmonary manifestations of COVID-19



Νόσος COVID-19
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

Νόσος COVID-19
ACE2 Υποδοχέας

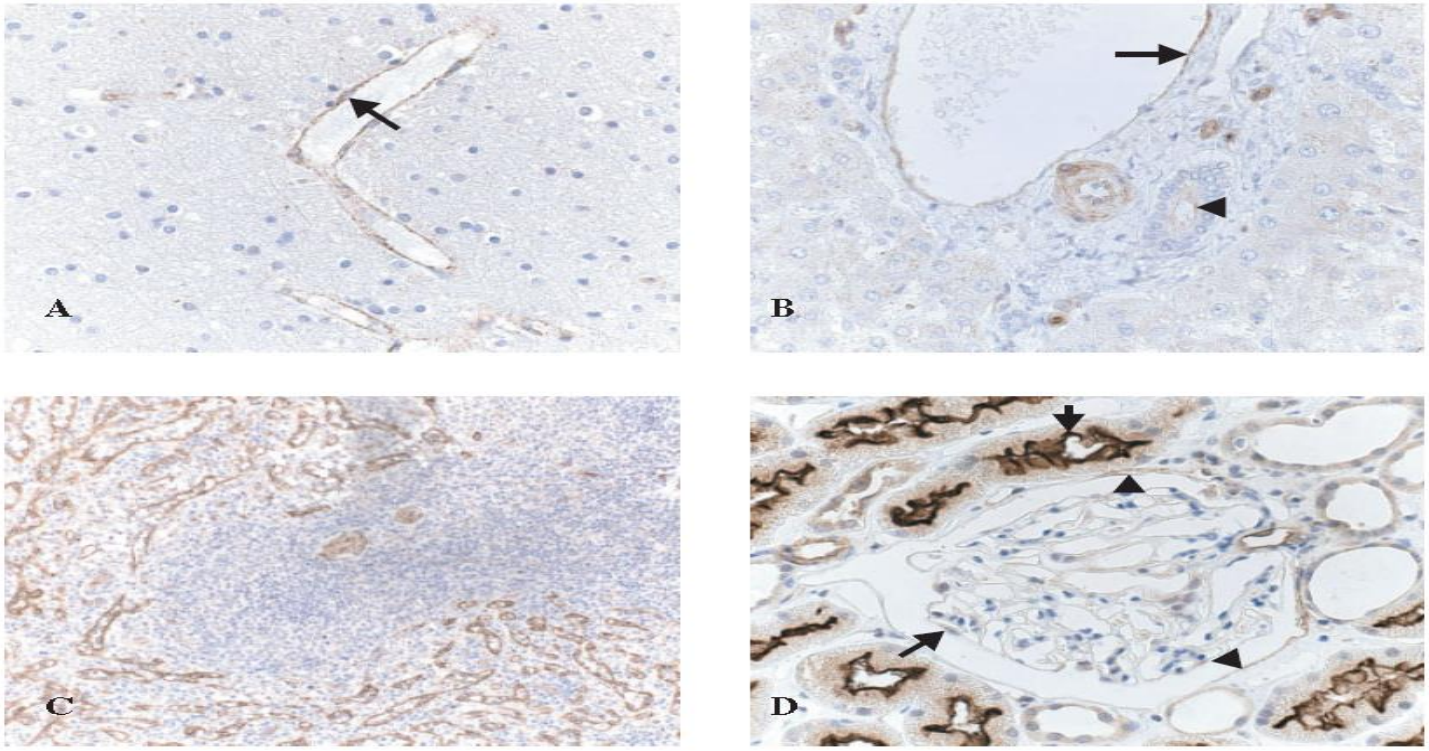


Figure 4. In the brain (A), ACE2 is expressed only in endothelium (arrow) and vascular smooth muscle cells. In the liver (B), Kupffer cells, hepatocytes, and the endothelium of sinusoids are negative. Luminal staining in bile ducts is occasionally observed (arrow-head). Vascular endothelium (arrow) and 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

Νόσος COVID-19
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

Νόσος COVID-19
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)	

Νόσος COVID-19
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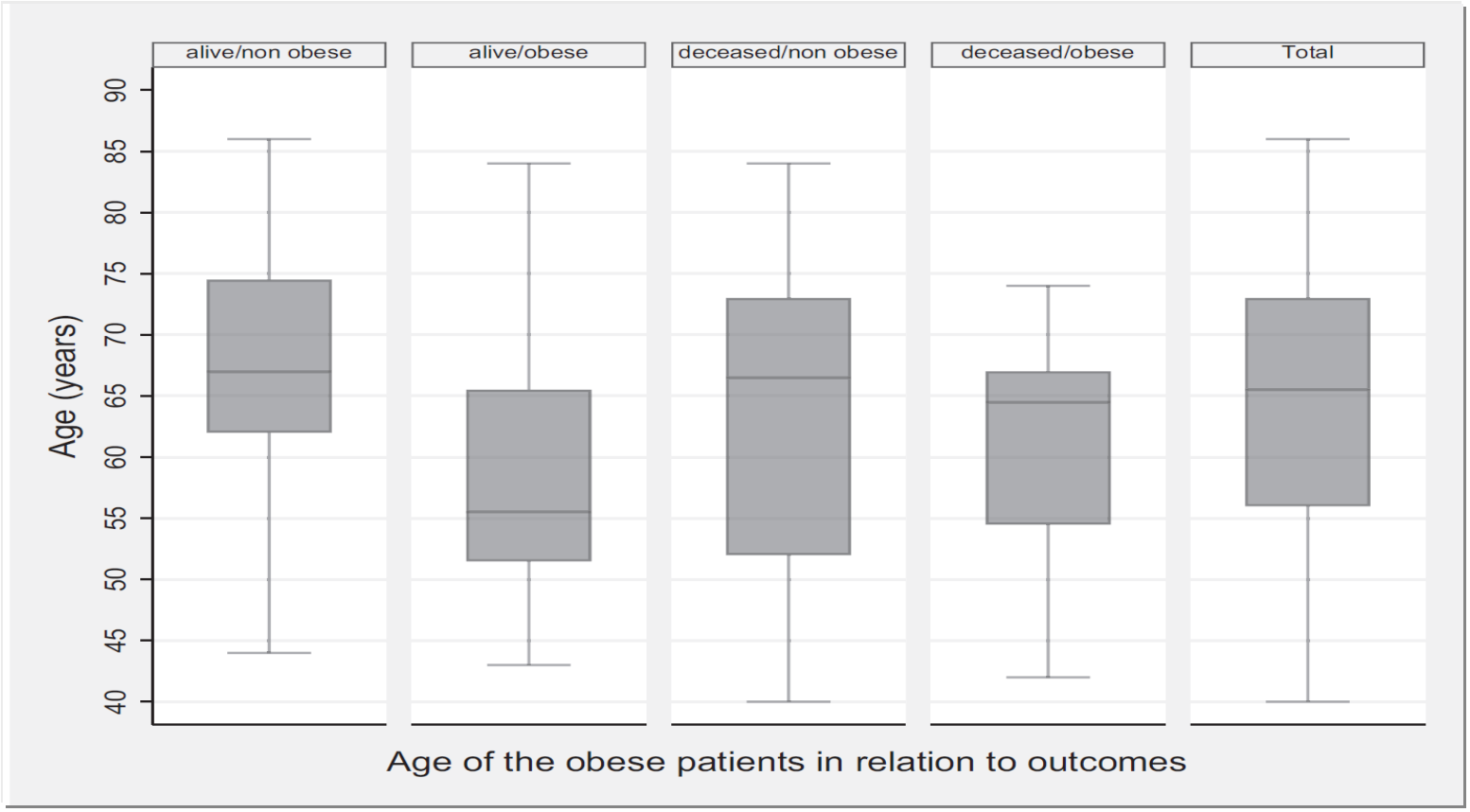
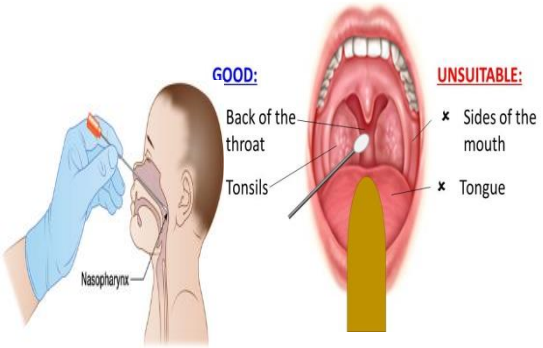


Diabetes Research and Clinical Practice 2020

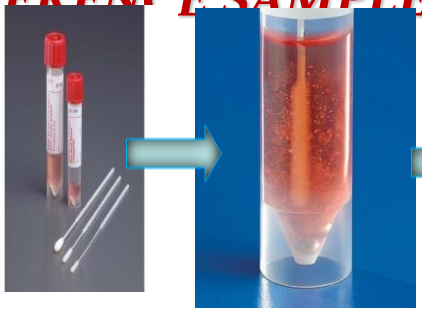
CLINICAL SAMPLE

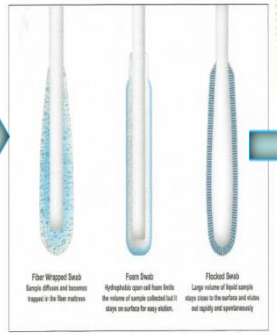
DIRECT MOLECULAR DETECTION



NASOPHARYNGEAL SWAB:

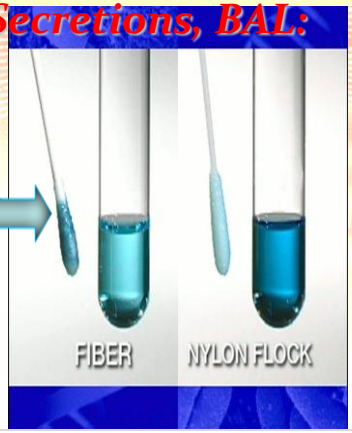
REFERENCE SAMPLE





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

Νόσος COVID-19
Συστηματική νόσος

Νόσος COVID-19
Συστηματική νόσος

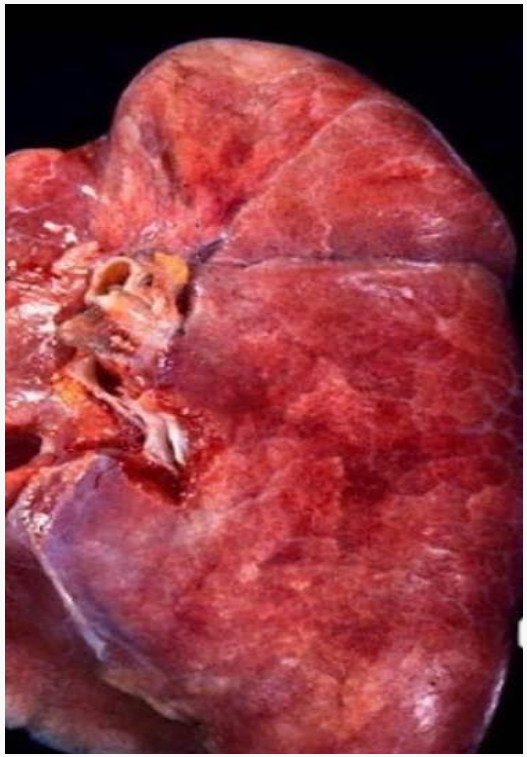
Η νόσος COVID-19 πρέπει να θεωρείται σαν

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

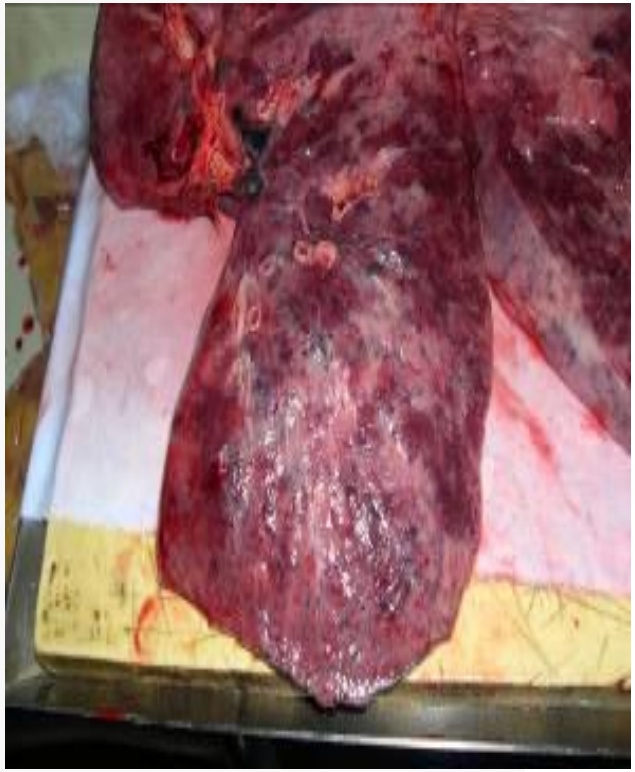
Νόσος COVID-19

Post-mortem findings in CoVID-19 pneumonia

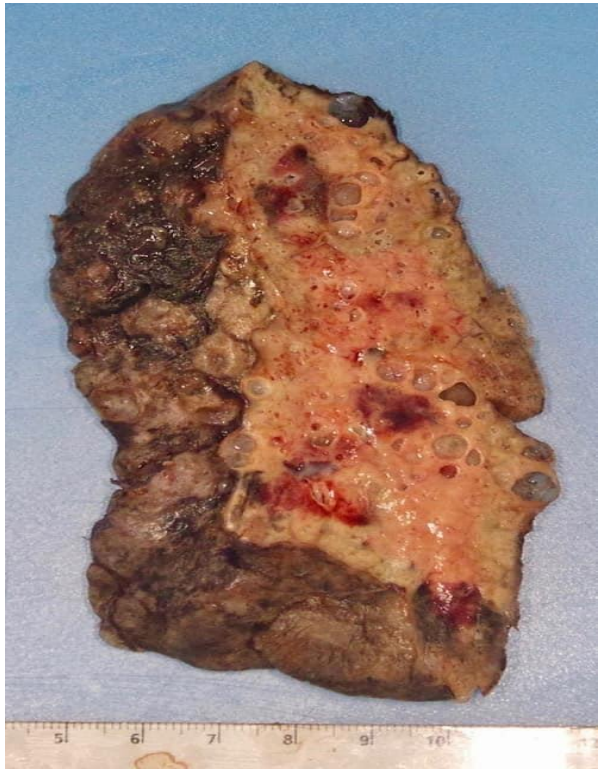
Normal



ARDS



COVID-19



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

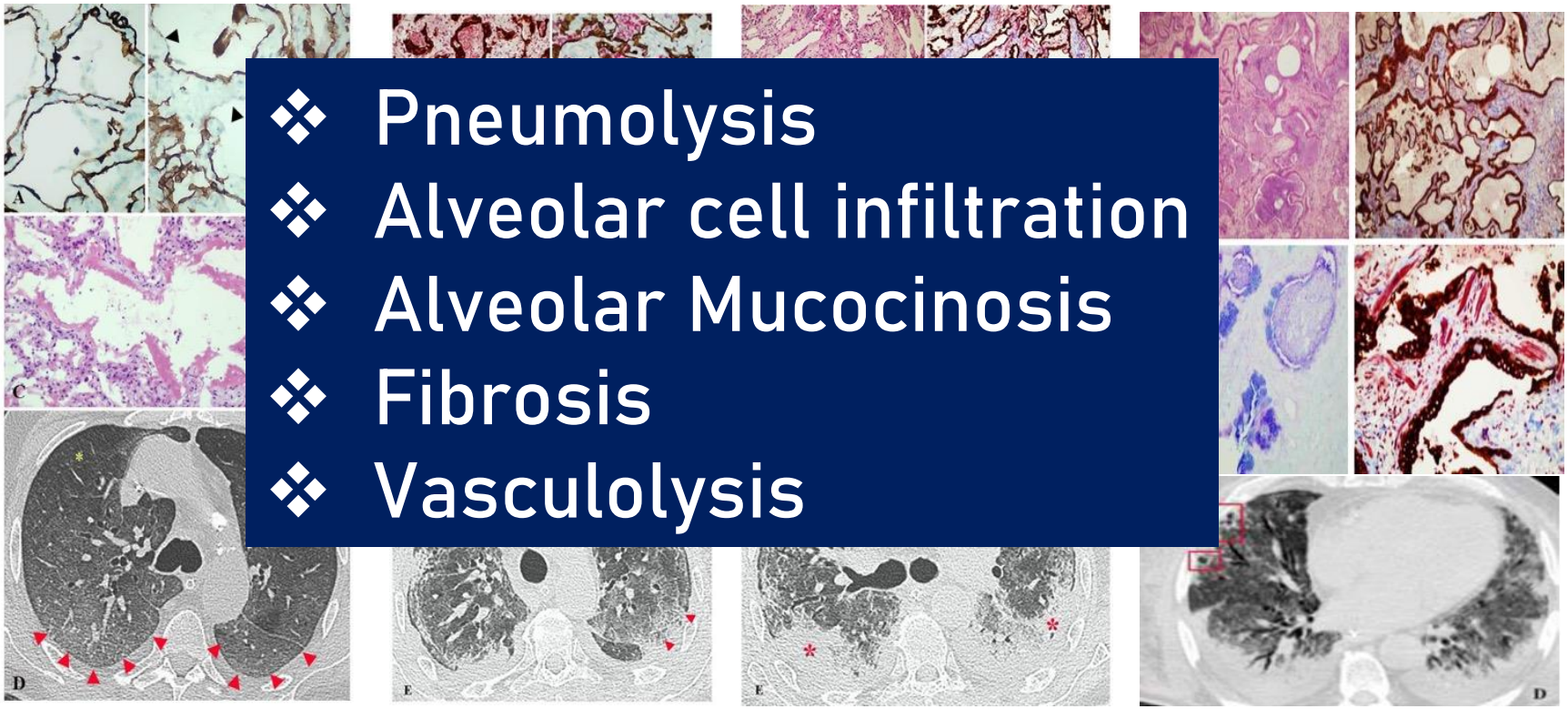
Νόσος COVID-19
Fibrosis & evolution of CoVID-19

Early DAD pattern

Mid DAD pattern

Late DAD pattern

Late DAD ("Honeycombing")

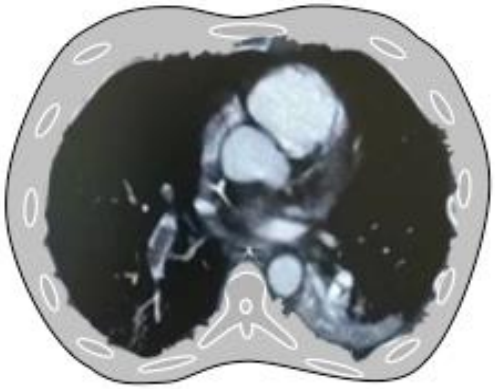


- Pneumolysis
- Alveolar cell infiltration
- Alveolar Mucocinosis
- Fibrosis
- Vasculolysis

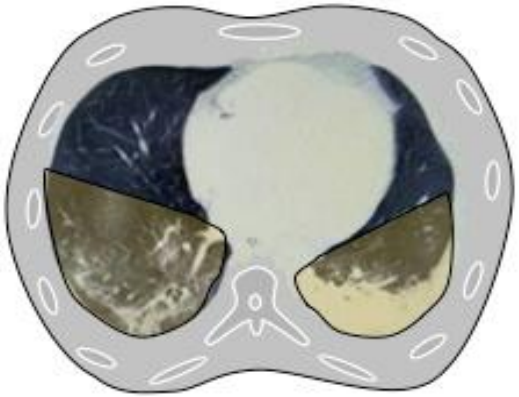
Barisione M, Grillo F, Ball L et al, Virchows Archiv 2020

Νόσος COVID-19
Distinct phenotypes in CoVID-19 patients

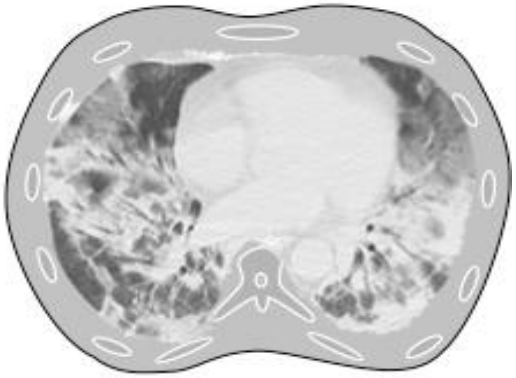
Phenotype 1
multiple, focal, over-perfused ground glass opacities and normally aerated areas



Phenotype 2
atelectasis and peribronchial opacities inhomogeneously distributed and hypoperfused

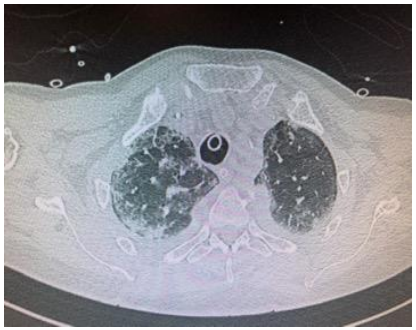


Phenotype 3:
patchy ARDS-like pattern inhomogeneously distributed and hyper and hypoperfused

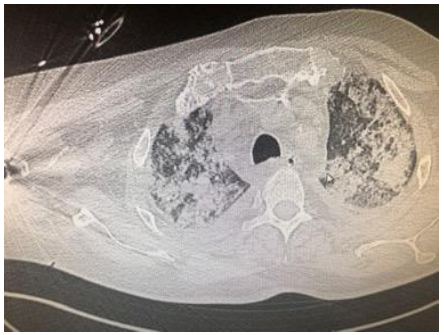


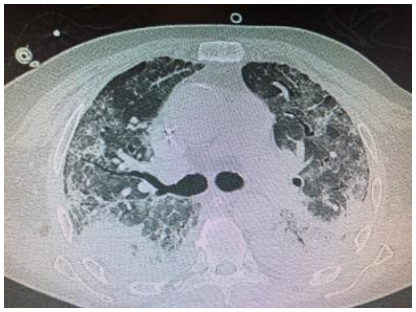
Robba C et al. Respir Physiol Neurobiol. 2020 May 10:103455

Νόσος COVID-19
CT lung evolution in CoVID-19

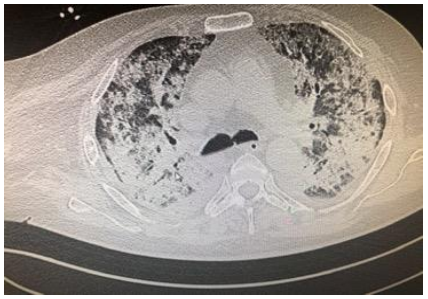


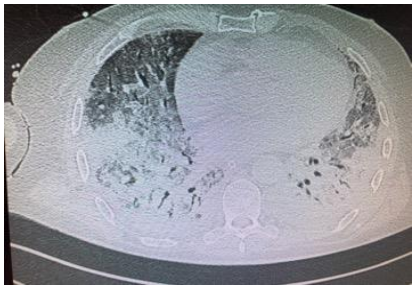
In critically ill patients



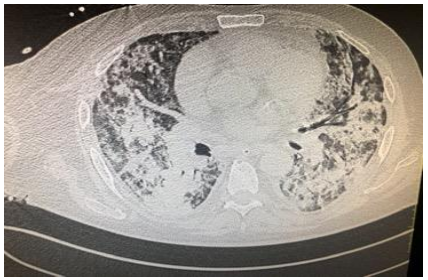


Phenotype 1 is rare
Phenotype 3 is frequent





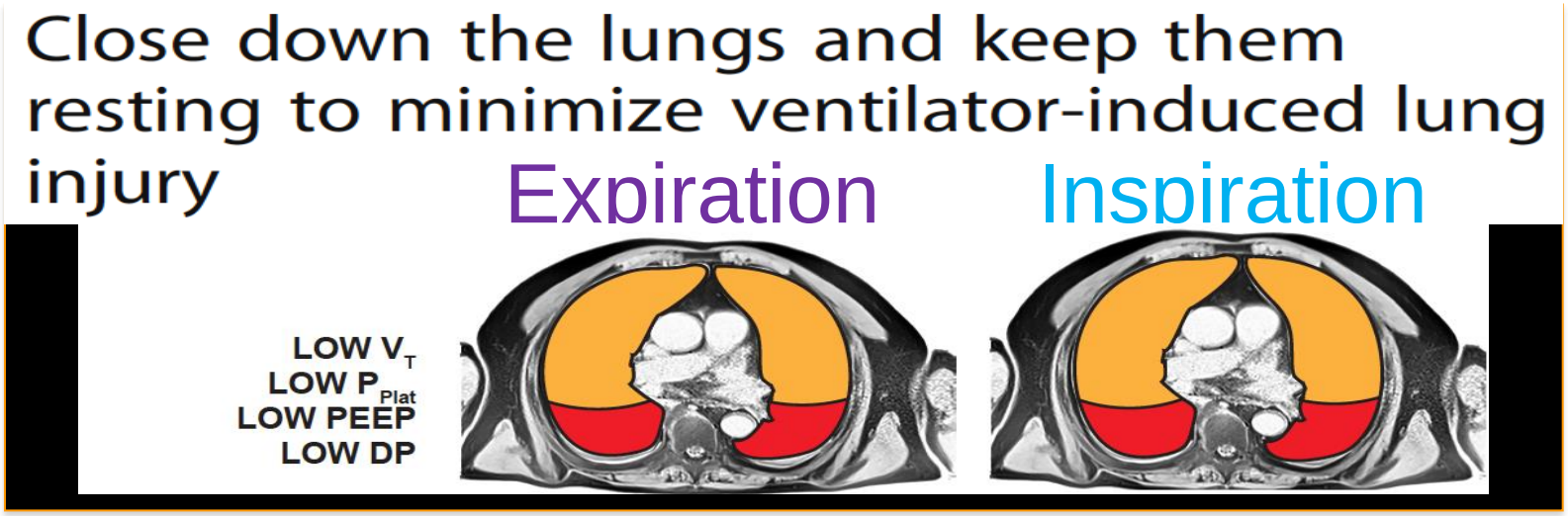
Phenotype 3
evolves in pneumolysis, fibrosis,
& complicated with VAP



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

Νόσος COVID-19

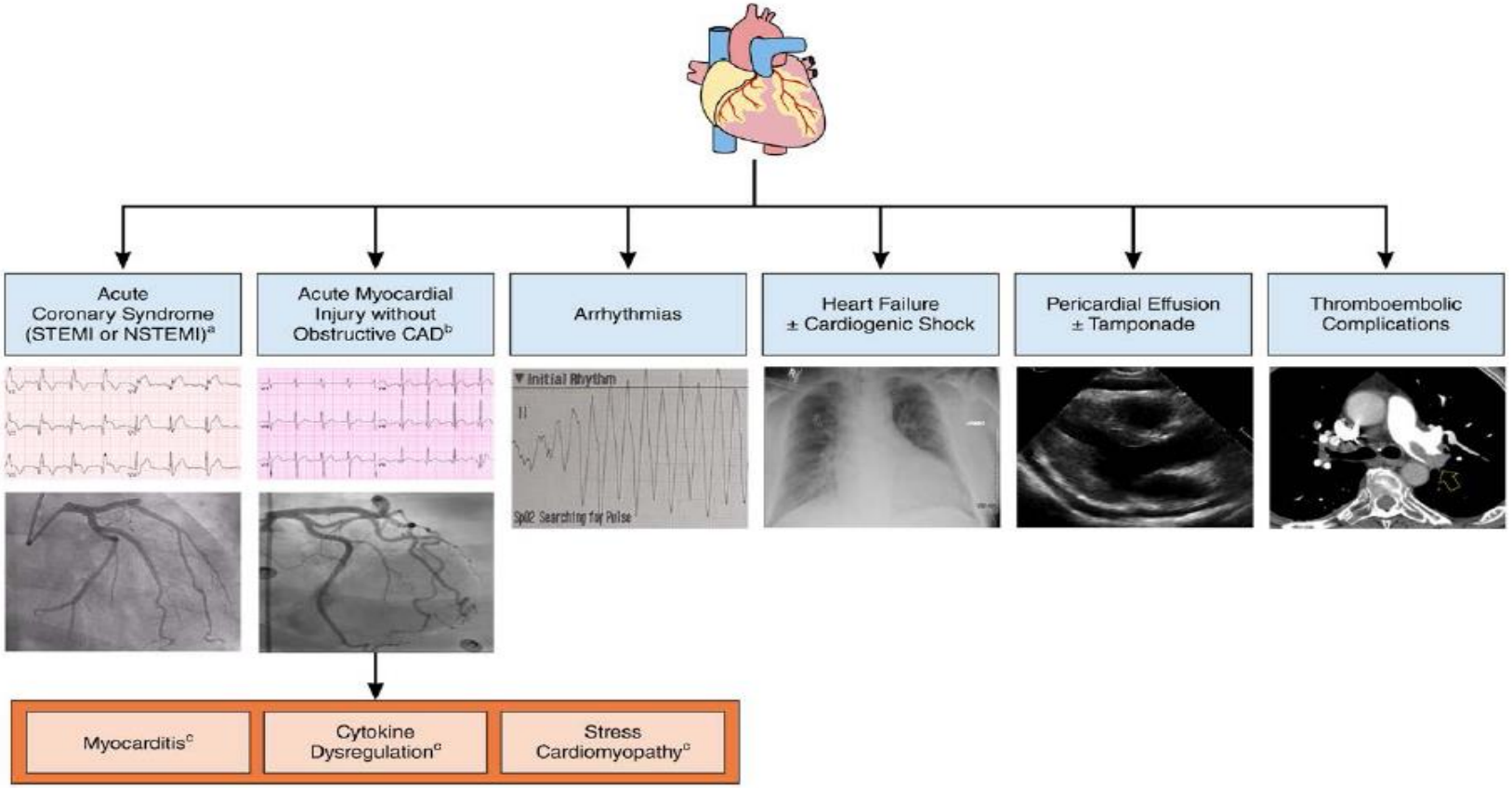
Less is more = Primum non nocere !



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 !

Νόσος COVID-19
Καρδιακή νόσος



Hendren et al Circulation 2020

Νόσος COVID-19
Καρδιακή νόσος

Wuhan/China

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

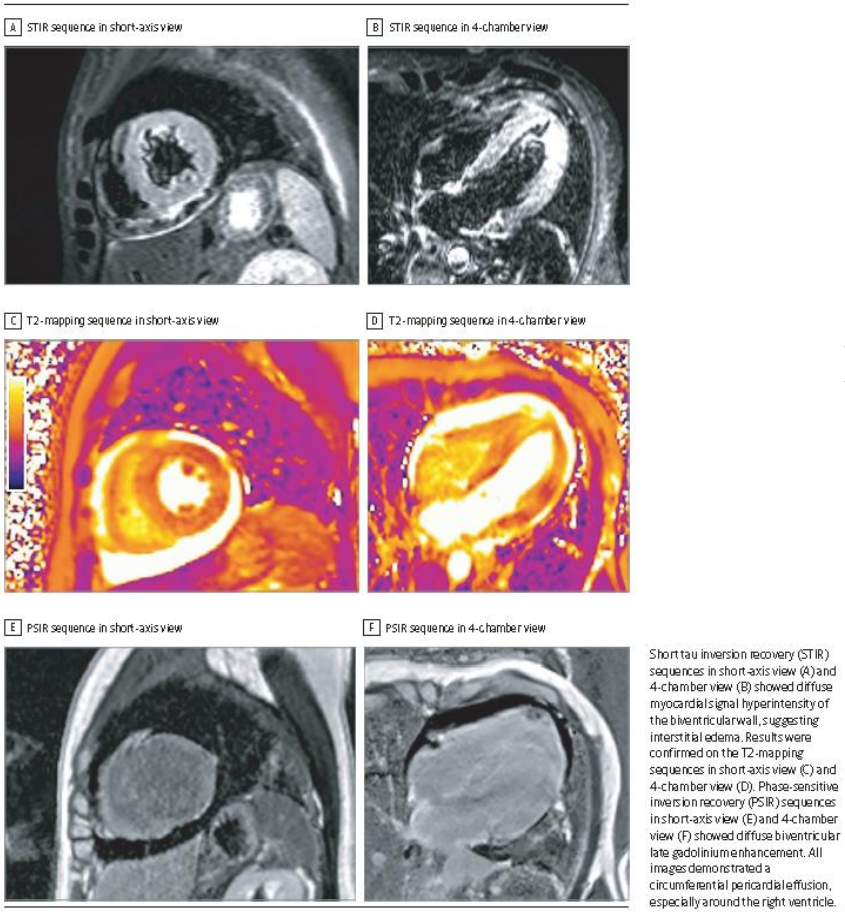
Πρόσφατα δεδομένα

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

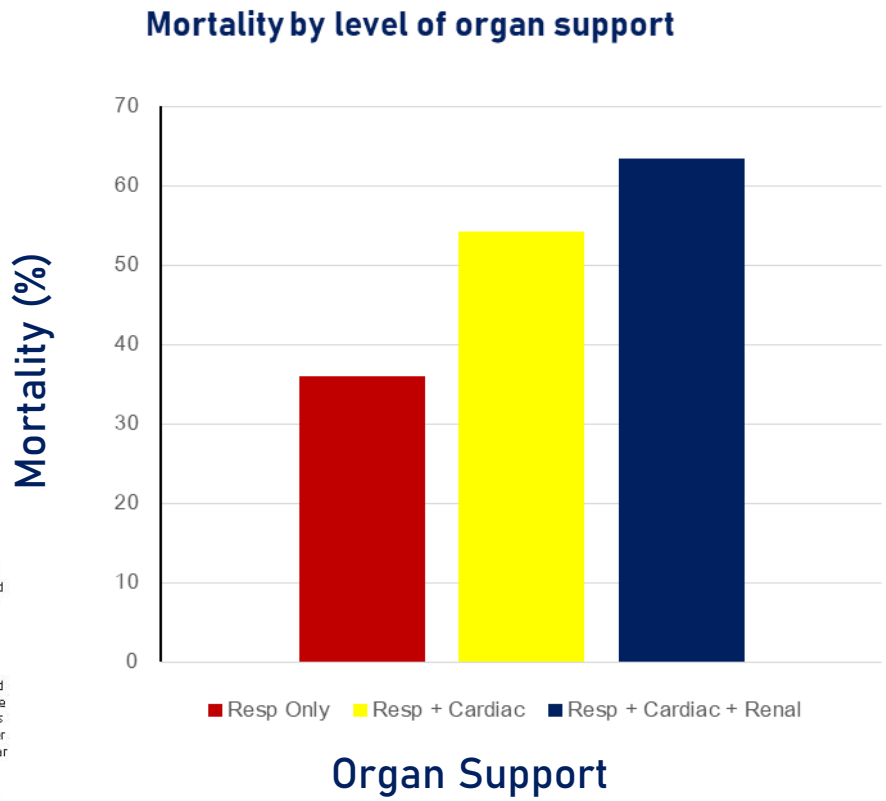
Mt Sinai, NY

- 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

Νόσος COVID-19
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

Νόσος COVID-19
Καρδιακή νόσος – Μακροπρόθεσμες βλάβες

Cardiac events in pneumonia
= poorer long term prognosis

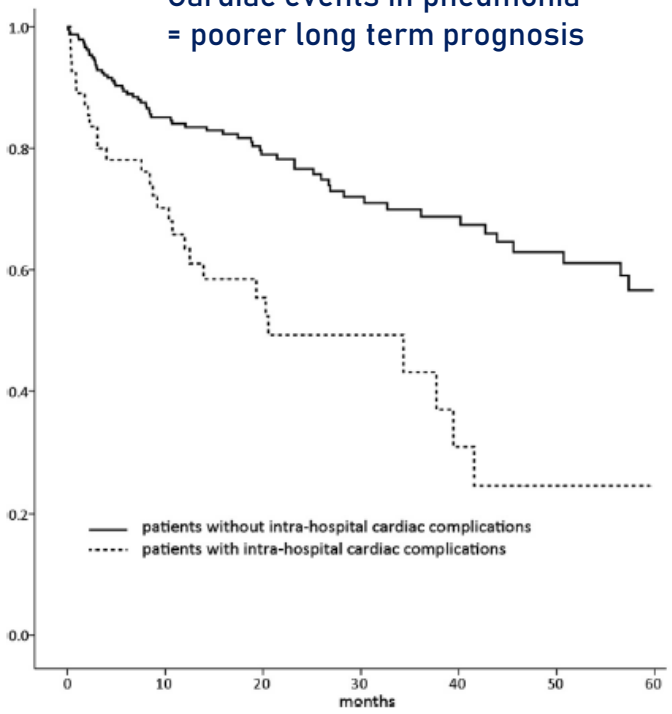
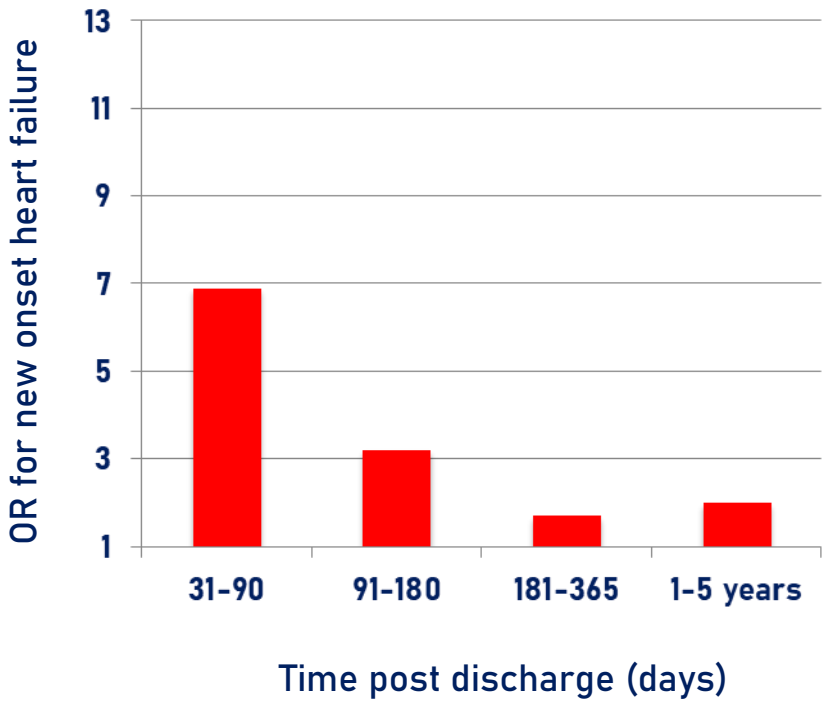


Figure 1. Kaplan-Meier estimates of time to primary outcome events (death for any cause) in patients with or without intrahospital cardiac complications.

Cangemi et al Am J Cardiol 2015

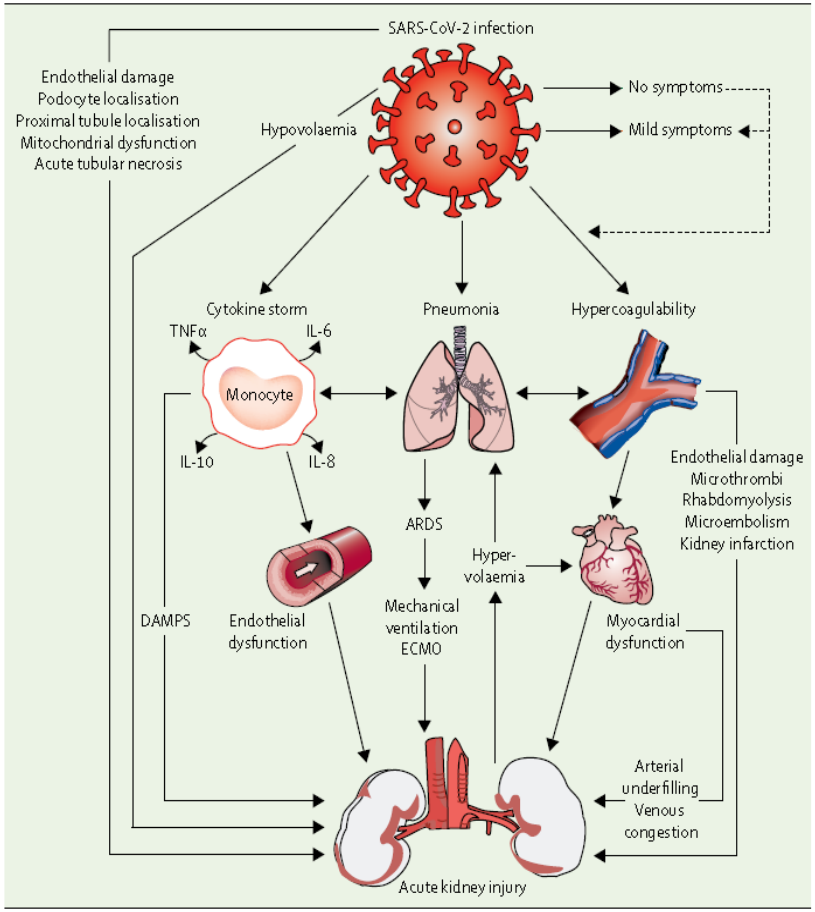
New onset heart failure post pneumonia



Corrales-Medina et al Am Heart J 2015

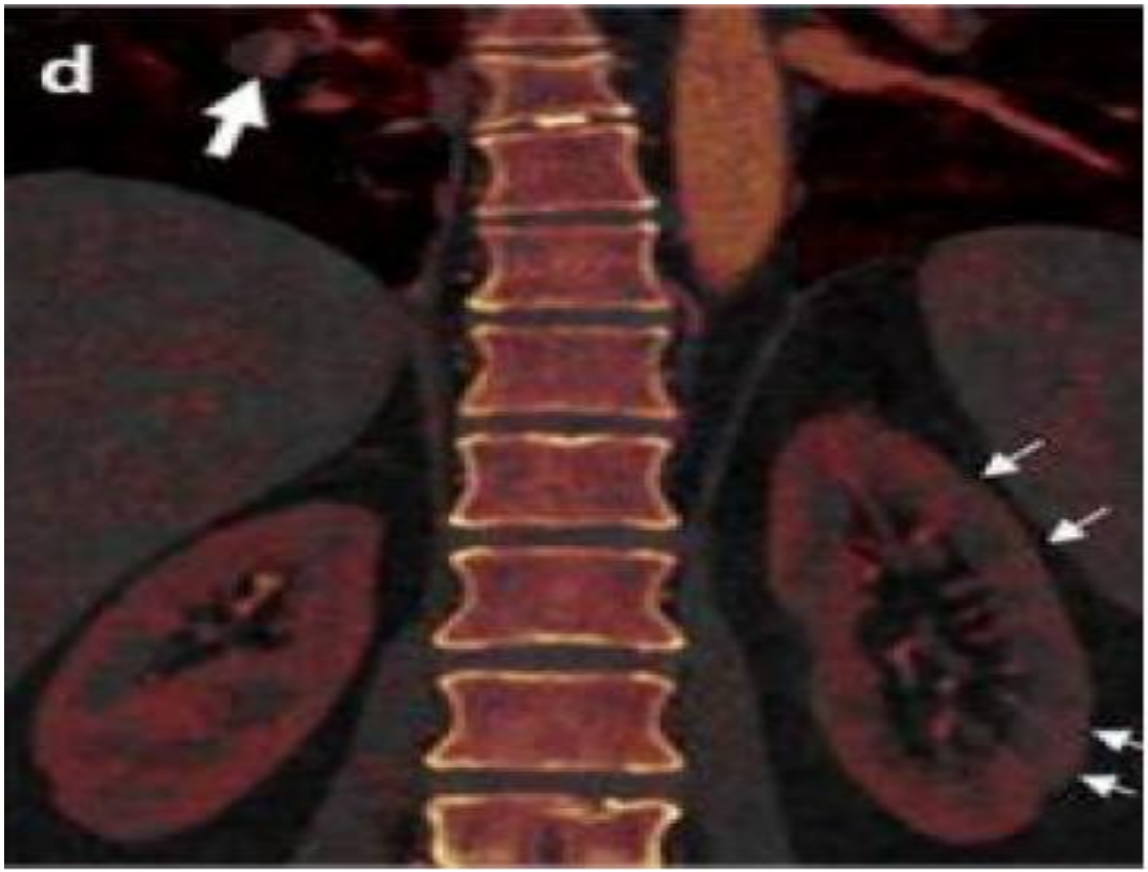
Νόσος COVID-19
Νεφρική νόσος

- 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

Νόσος COVID-19
Νεφρική νόσος



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

Νόσος COVID-19
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

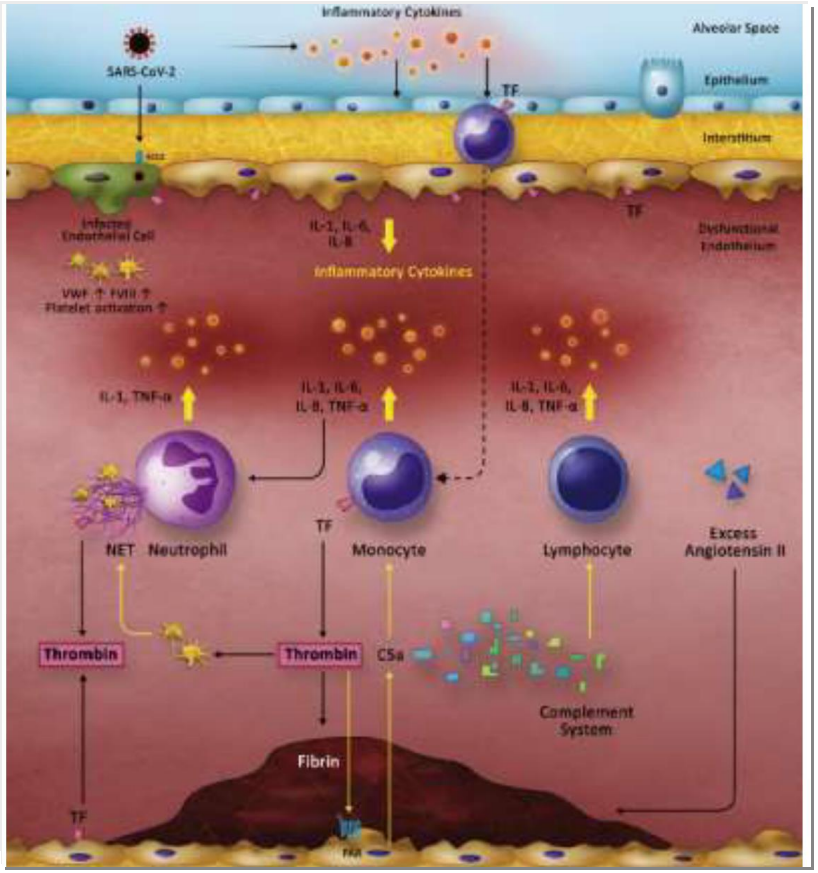
Νόσος COVID-19
Προσβολή ΚΝΣ

- 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

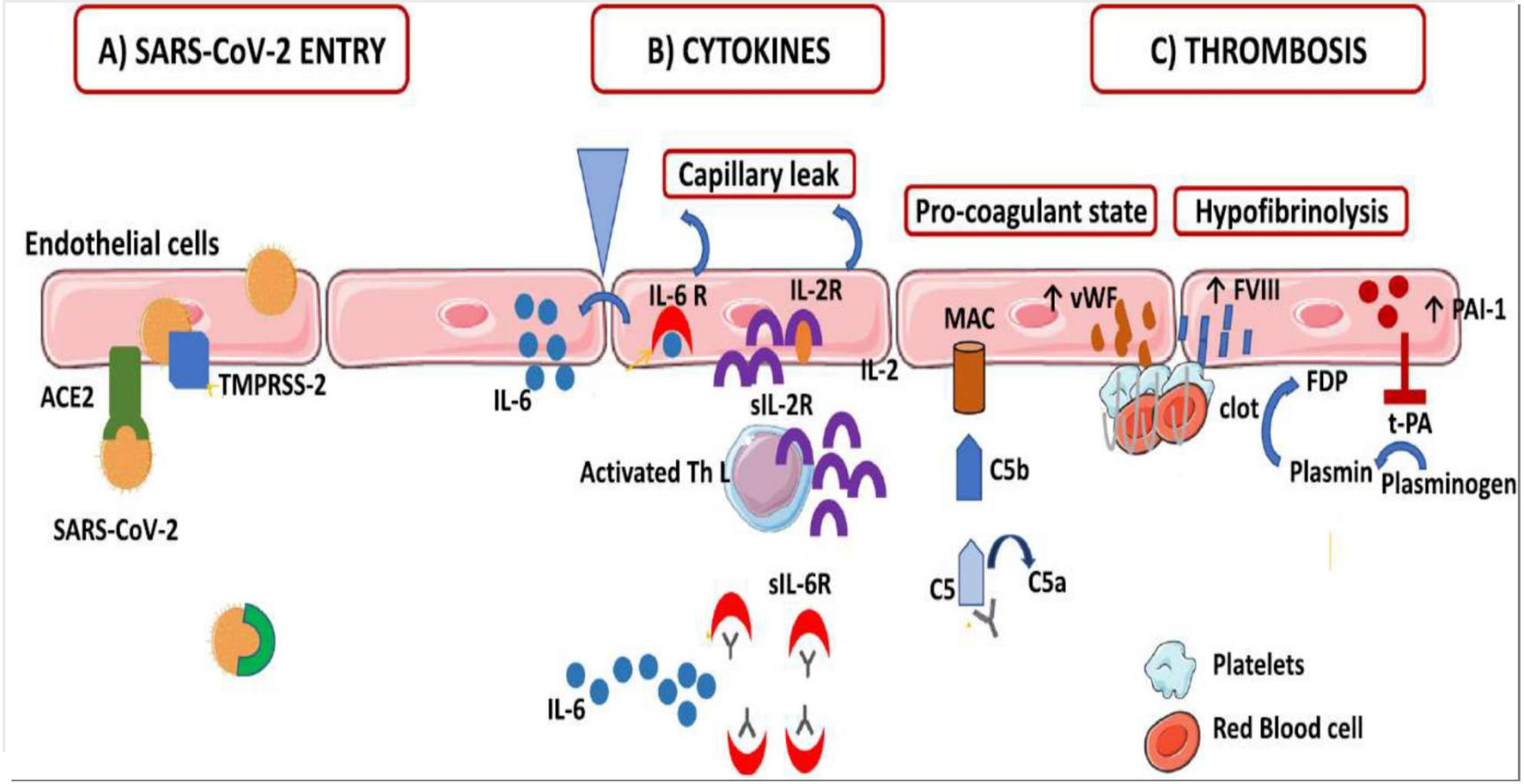
↓

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

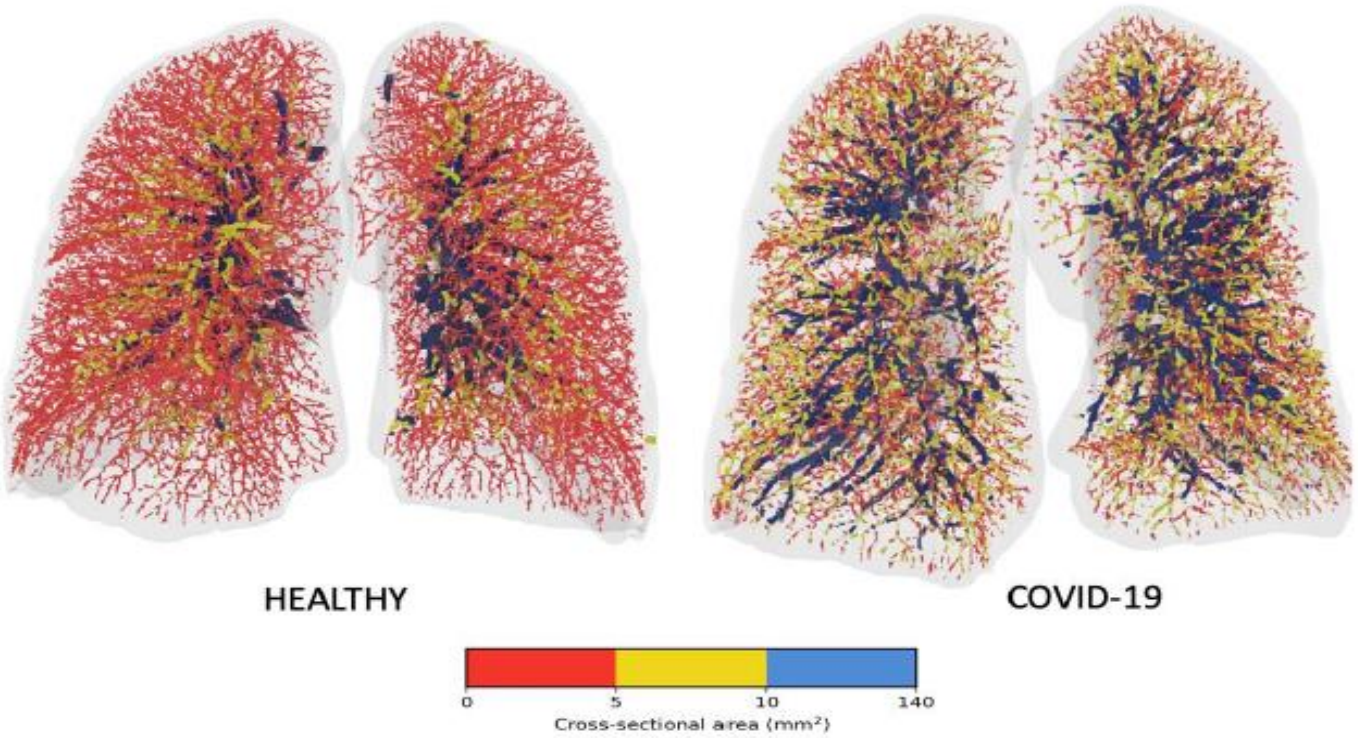
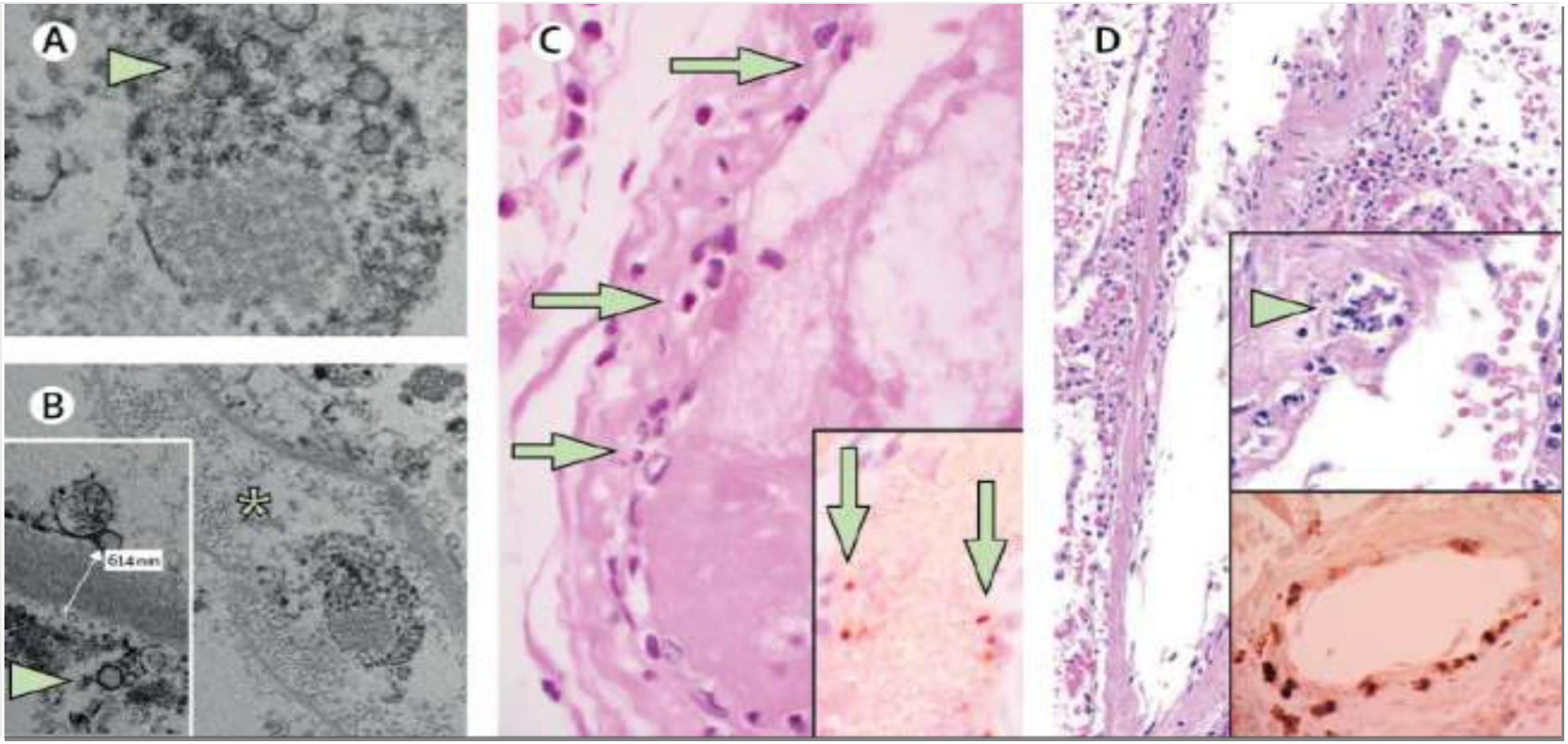


Figure 4: Visual representation of the blood vessels colored according to their size. Red denotes the small vessels, yellow the mid-size vessels and blue the larger vessels.

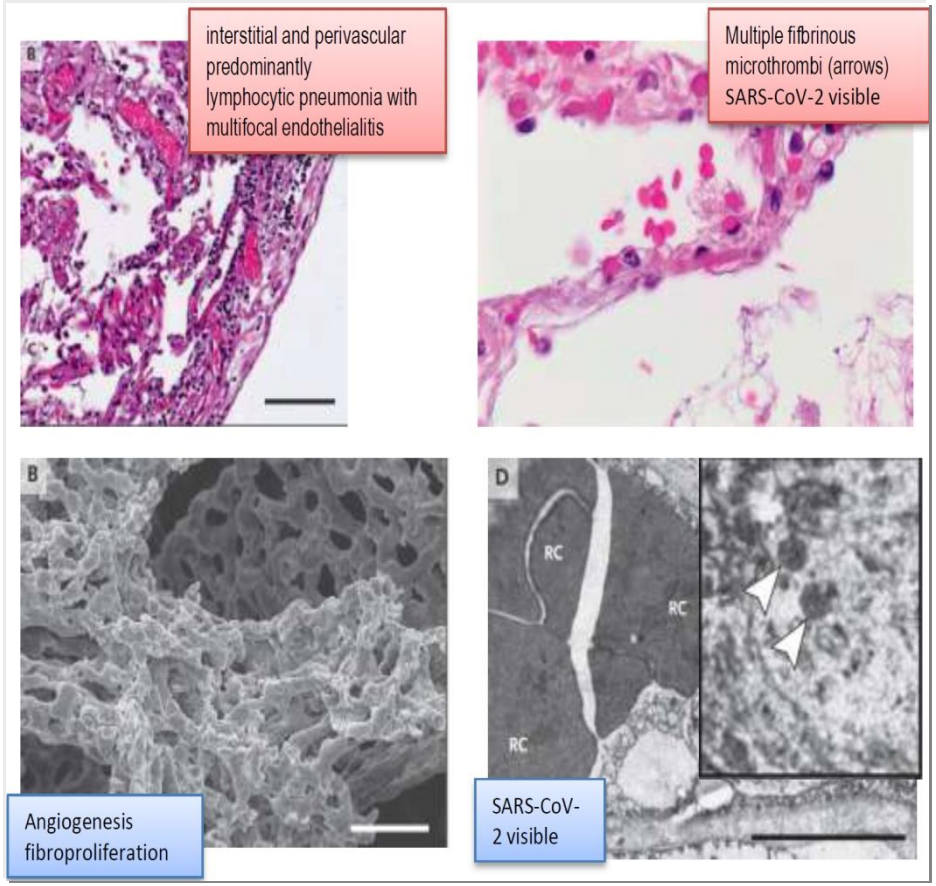
Lins M et al Acta Radiol 2020

Νόσος COVID-19
Ενδοθηλίτις



Varga Z et al- Lancet 2020

Νόσος COVID-19
COVID-19 vs Influenza : ενδοθηλιακές βλάβες



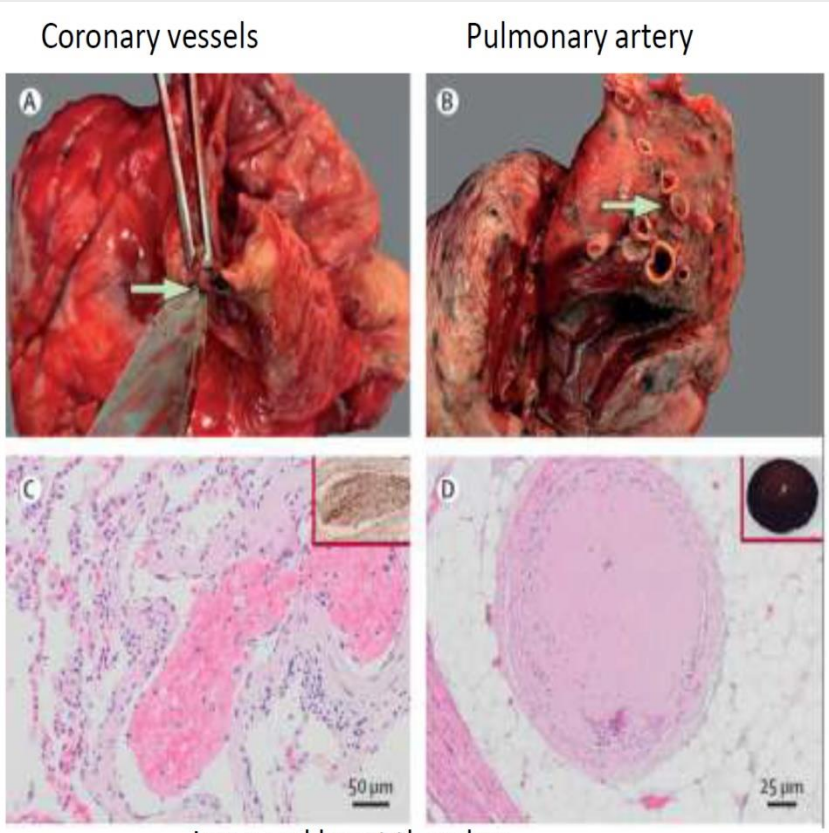
COVID-19 : Πνεύμων
- Σοβαρή ενδοθηλιακή βλάβη
- Παρουσία ιών ενδοκυττάρια
- Κατεστραμμένες μεμβράνες

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

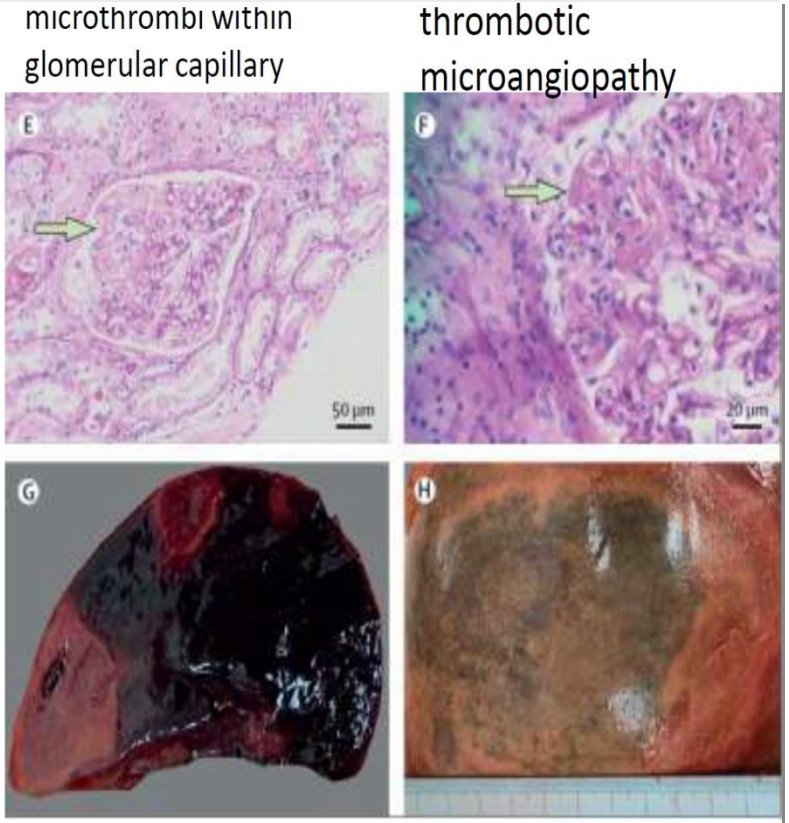
Αγγειογένεσις
- 2.7 φορές περισσότερη απότι στην γρίπη

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

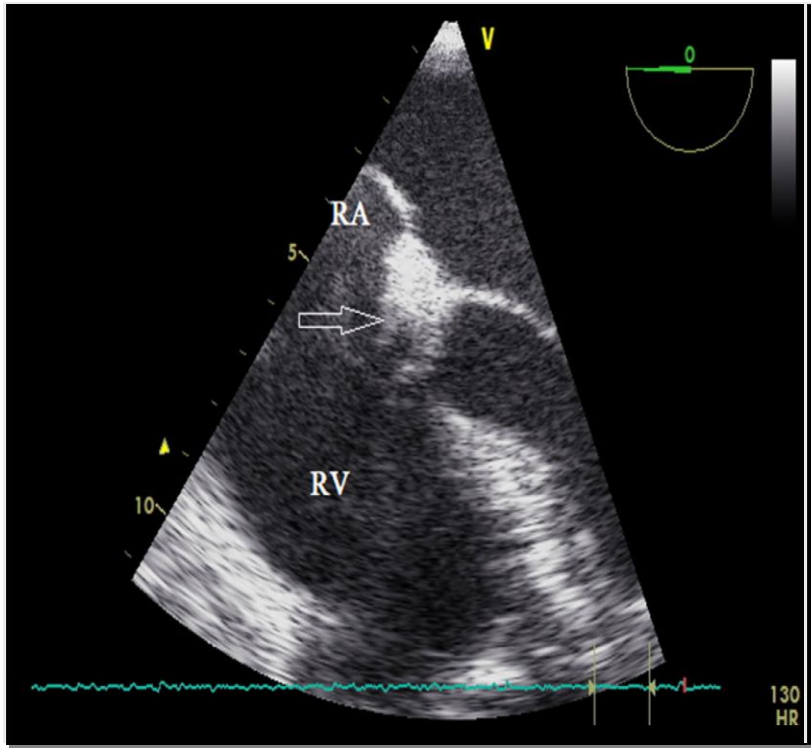
Hanley et al - ***Lancet Microbe 2020*** Published **Online** August 20, 2020 https://doi.org/10.1016/S2666-5247(20)30115-4

Νόσος COVID-19
Θρομβωτικά συμβάματα

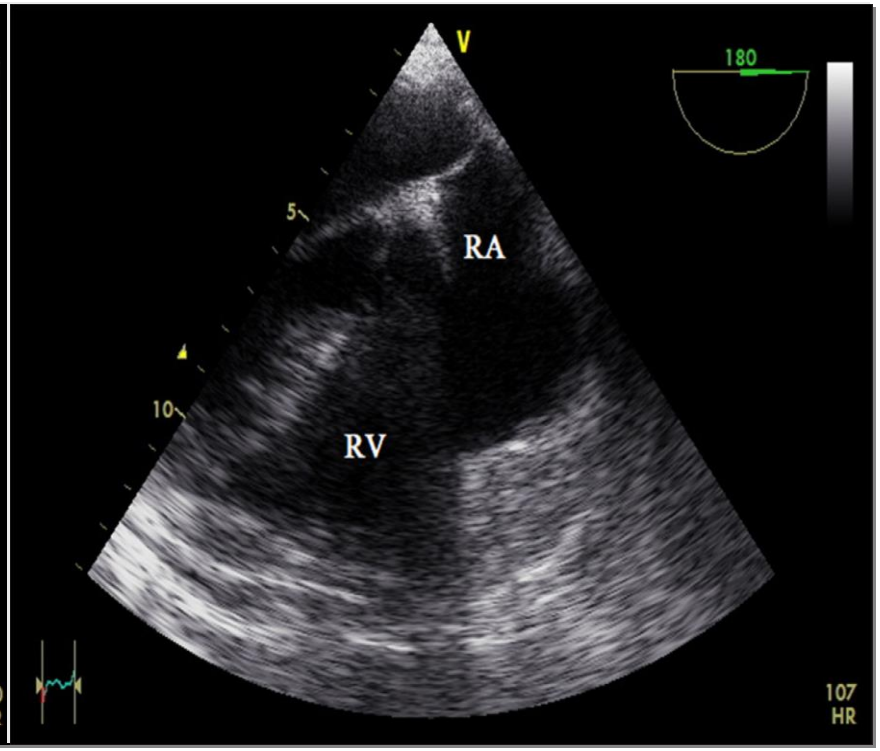
A Severe COVID-19 Case Complicated by Right Atrium Thrombus

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

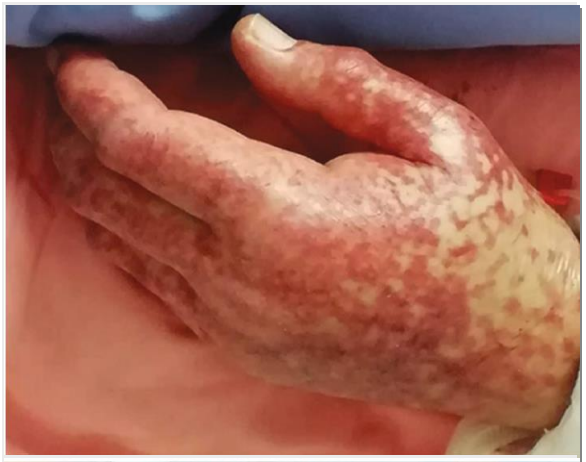
Νόσος COVID-19
Προσβολή άλλων οργάνων

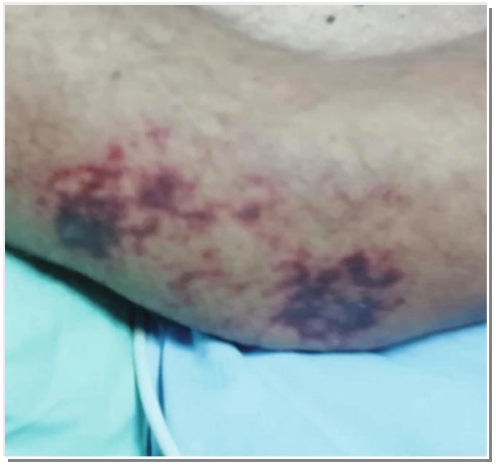
- GIT
  - Diarrhoea
  - Abdominal pain
- Liver
  - Mild elevations LFT's common
  - Severe hepatitis is extremely uncommon
- Skin
  - Vasculitis (covid-toes), erythema, urticaria, chicken-pox like lesions
- Kawasaki-like syndrome in children
- ??????????????????

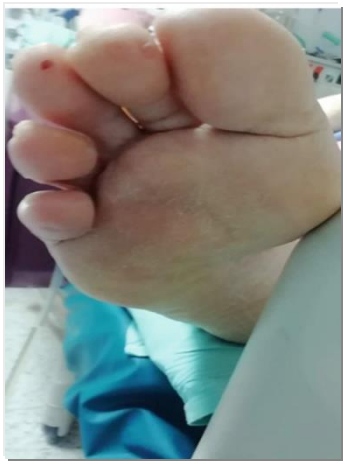
Patel et al J Clin Virol 2020
Gupta et al Nature Med 2020

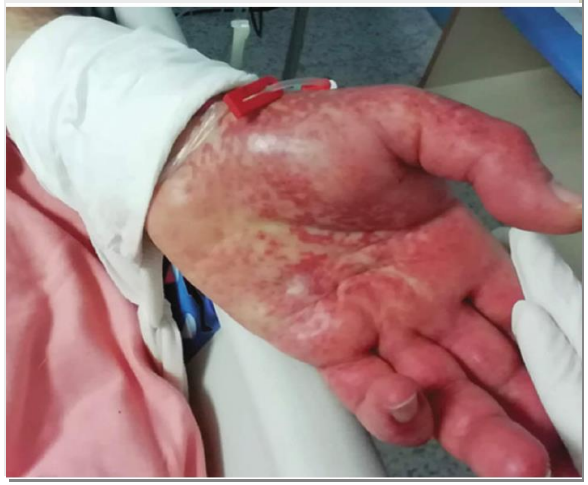
Νόσος COVID-19

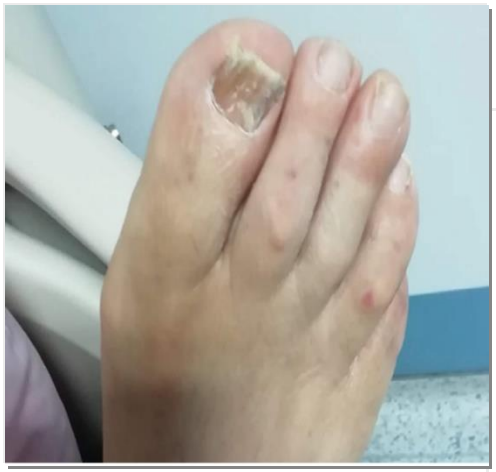
Δερματικές βλάβες



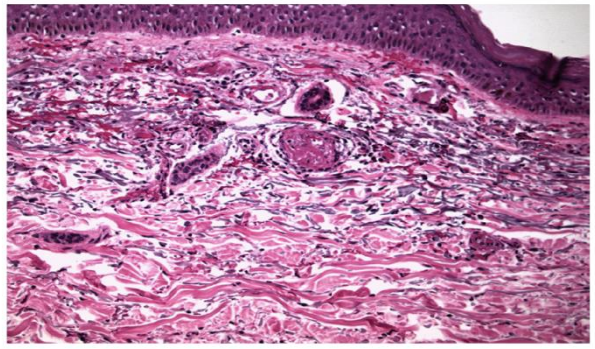








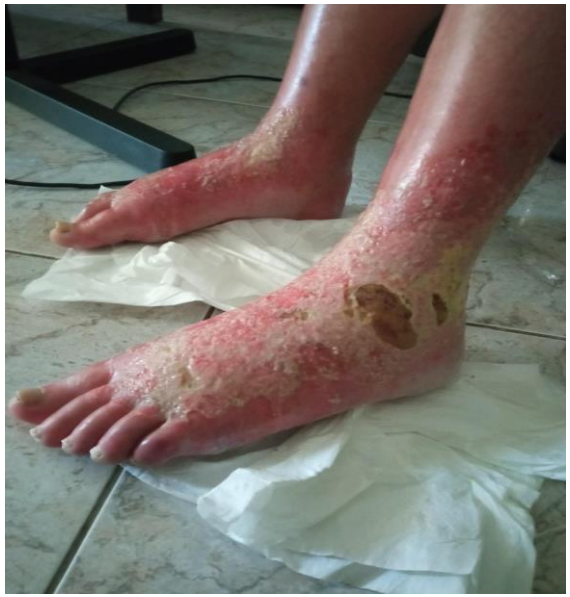
Endovascular fibrin clots. Generalized inflammation with a mainly perivascular pattern.

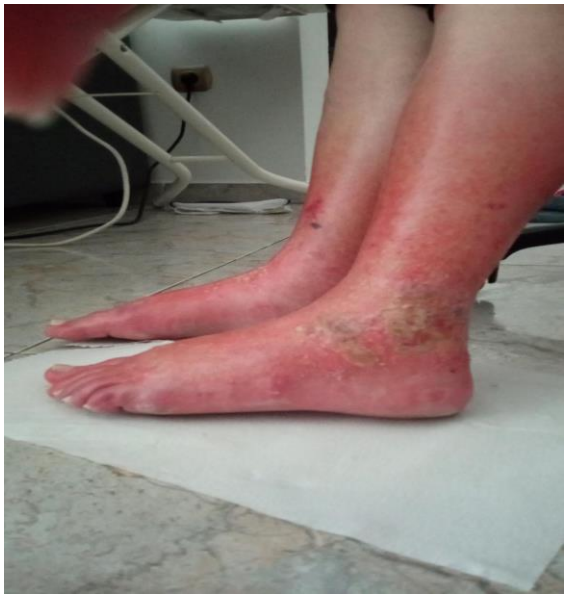


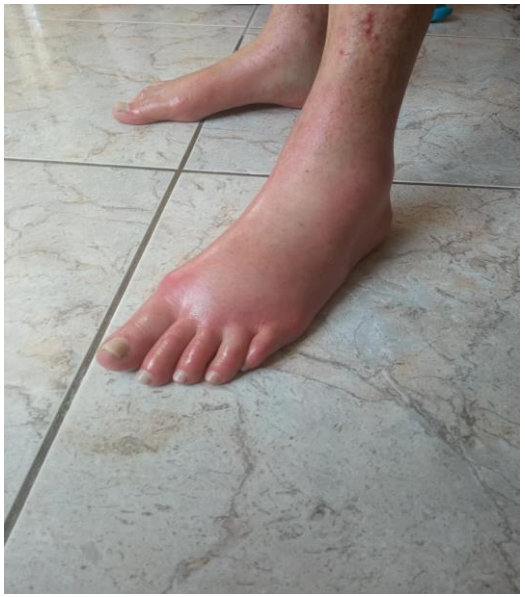
Anna Kyriakoudi al, Case Reports in Critical Care Volume 2021, Article ID 6644853,

Νόσος COVID-19

Δερματικές βλάβες - Ερυθρομελαλγία







COVID-19 and co-infections

- Since the start of the COVID-19 pandemic, superinfections have been observed frequently in hospitalised patients
  - **Frequency increases with severity of disease**
- Invasive fungal infections are an important cause of morbidity and mortality in this population
  - ***Candida* spp and *Aspergillus* spp most common but also other less common opportunistic pathogens**
  - **Fungal pathogens with decreased susceptibility to antifungal therapies are emerging**
- Complex interplay of:
  - **Pre-existing conditions**
  - **High prevalence of risk factors (ICU stay, invasive lines and devices, broad-spectrum antibiotics)**
  - **COVID-19 specific mechanisms including dysregulated inflammatory and immune response**
- Essential to maintain a high index of suspicion to facilitate early diagnosis and prompt and appropriate treatment

Chiurlo M, et al. New Microbiol. 2021;44(2):71–83.

Fungal co-infections associated with COVID-19

Retrospective study from China

- Fungal co-infections associated with COVID-19 might be missed or misdiagnosed
- COVID-19 patients show:
  - Overexpression of inflammatory cytokines
  - Impaired cell-mediated immune response with decreased $CD4^+$ T and $CD8^+$ T-cell counts, indicating susceptibility to fungal co-infection

Song, et al. Mycopathologia. 2020;185(4):599–606.

Yeast infections in COVID-19 patients

- **A recent review of published reports of invasive yeast infections among critically ill COVID-19 patients showed the following:[1]**
  - *C. albicans* (19/43; 44.1%)
  - *C. auris* (10/43; 23.2%)
  - *C. glabrata, C. parapsilosis, C. tropicalis, and S. cerevisiae* (2/43; 4.6% each)
  - *C. krusei* and *Rhodotorula* sp. (1/43; 2.3% each)
- ***C. auris* was the most prevalent species in a study from India, *C. albicans* the most common in other reports**
- **Multidrug-resistant MDR *C. auris* is a particular concern and a report from Italy suggested its spread could have been facilitated by the COVID-19 pandemic[2]**
- **Diagnosis of candidemia/invasive candidiasis continues to be challenging[1]**
  - Use of multiple techniques can improve sensitivity
- **In one study, the mortality rate in COVID-19 pts with invasive yeast infection was 47.1% (95% CI, 26.2–69.0)[3]**
  - 27.3% (95% CI, 9.8–56.6) in patients on appropriate antifungal therapy
  - 83.3% (95% CI, 43.7–97.0) in those not receiving appropriate antifungal therapy (P=0.0498)

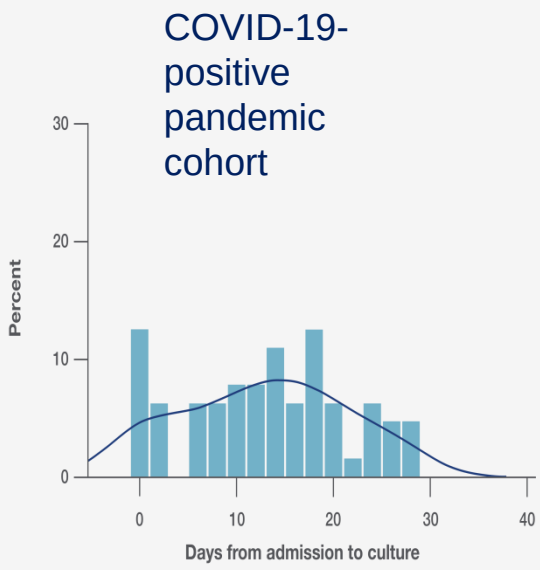
1. Arastehfar A, et al J Fungi (Basel). 2020;6(4):211; 2. Di Pilato V, et al. J Fungi (Basel). 2021;7(2):140; 3. White PL, et al. Clin Infect Dis. 2020. Epub ahead of print.

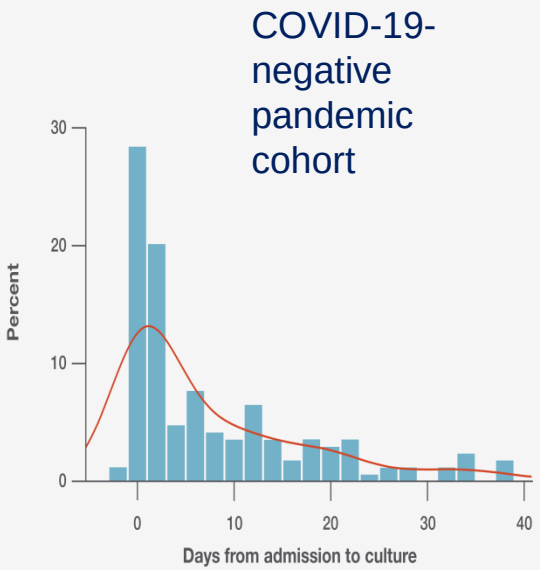
Risk factors for invasive candidiasis

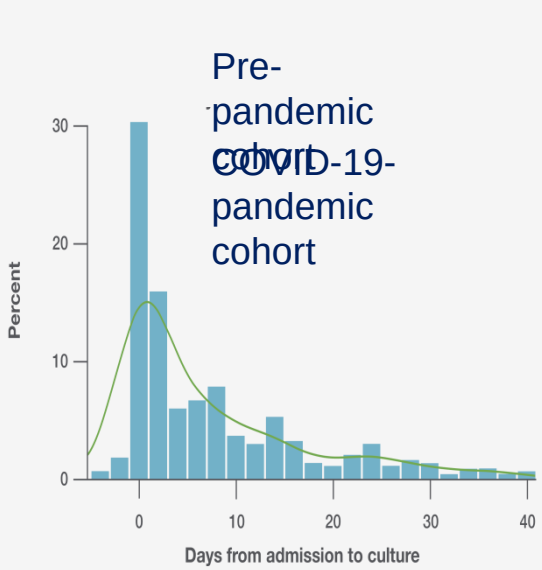
- Risk factors predisposing ICU patients to invasive candidiasis are present in many COVID-19 patients[1]
  - Diabetes mellitus, broad-spectrum antibiotic use, long ICU stay, central venous catheters
- Some risk factors are more specifically linked to severe COVID-19[1]
  - Corticosteroid use, ECMO, increased clotting tendency
- One study showed no difference in the rates of invasive candidiasis between COVID-19 and non-COVID-19 patients in the ICU[2]

1. Arastehfar A, et al J Fungi (Basel). 2020;6(4):211; 2. White PL, et al. Clin Infect Dis. 2020. Epub ahead of print.

Case-level analysis to compare characteristics of candidemia in patients with and without COVID-19







Time in days between hospital admission and initial *Candida* culture

- Median for patients with COVID-19: 14 days (IQR: 7–18)
- Median for patients without COVID-19: 4 days (IQR: 0–14)

IQR, interquartile range.

Seagle, et al. Clin Infect Dis. 2021; doi: 10.1093/cid/ciab562.

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)

Prospective screening of patients with PCR-confirmed COVID-19 for IFIs

- 135 adults (median age: 57 years, male/female: 2.2/1)
- IFI incidence: 26.7%
  - **14.1% aspergillosis**
  - **12.6% yeast infections**
- Overall mortality rate: 38%
  - 53% in patients with fungal disease versus 31% in patients without fungal disease (p=0.0387)
- The mortality rate was reduced by the use of antifungal therapy
  - 38.5% in patients receiving therapy versus 90% in patients not receiving therapy (p=0.008)
- Increased risk of aspergillosis in patients treated with corticosteroids (p=0.007) or with a history of chronic respiratory disease (p=0.05)

BAL, bronchoalveolar lavage; BDG, (1-3)-β-D-Glucan; COVID-19, coronavirus disease 2019; CI, confidence interval; GM-EIA, galactomannan enzyme immunoassay; IFD, invasive fungal disease;
IFI, invasive fungal infection; NBL, nondirected bronchial lavage; PCR, polymerase chain reaction.
White, et al. Clin Infect Dis. 2020;ciaa1298.

Incidence and mortality of CAPA

One-group meta-analysis

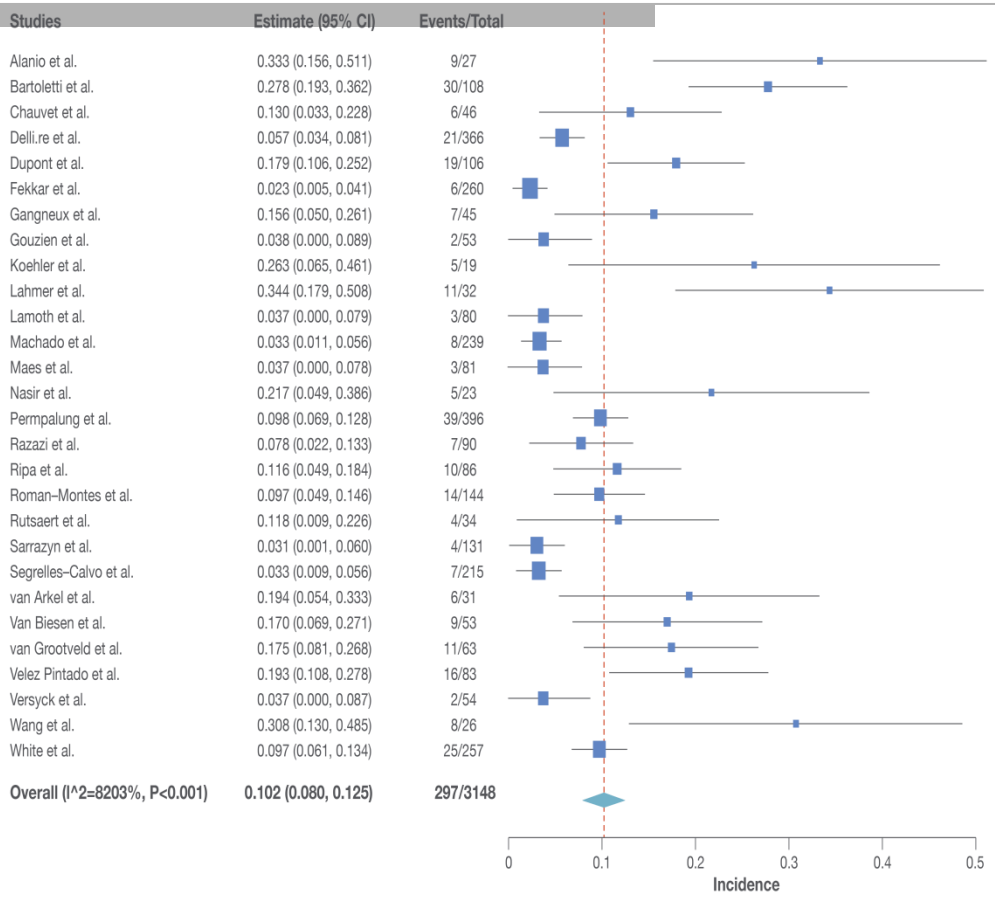
- 28 observational studies (3148 patients), 23 conducted in Europe,
  2 in Mexico and 1 each in China, Pakistan and the USA
- Routine screening for secondary IFIs in 13 studies
- The modified AspICU algorithm was the most commonly used case definition and diagnostic algorithm for pulmonary aspergillosis (used in 15 studies)

CAPA, COVID-19 associated aspergillosis; IFI, invasive fungal infection.

Mitaka, et al. Mycoses. 2021

Incidence and mortality of CAPA

Pooled estimate of the **incidence** of **CAPA** in the ICU

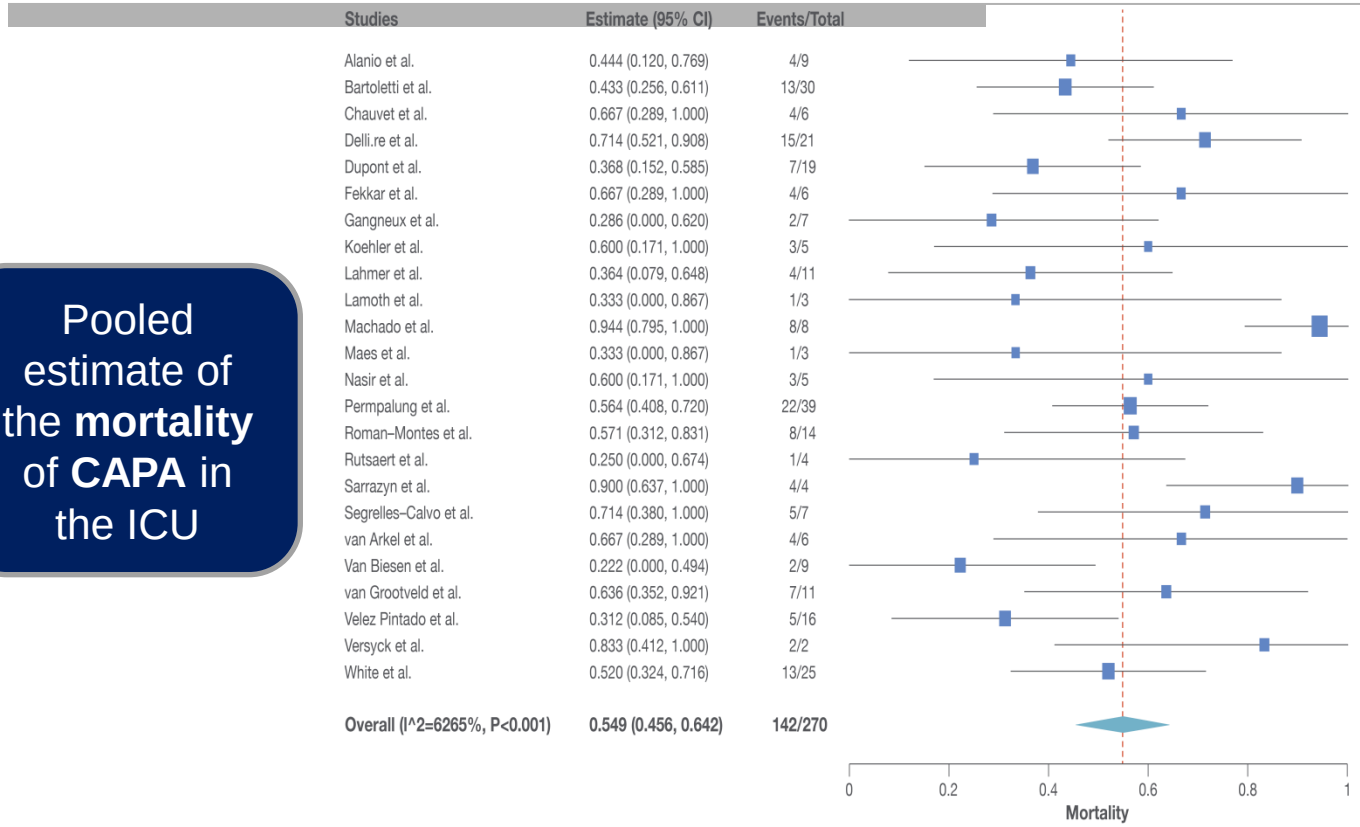


Incidence of CAPA: 10.2%
95% CI, 8–12.5
I^2 = 82.0%

CAPA, COVID-19 associated aspergillosis; IFI, invasive fungal infection; I^2, measure of heterogeneity; ICU, intensive care unit.
Mitaka, et al. Mycoses. 2021 Apr 25;10.1111/myc.13292.

Incidence and mortality of CAPA

Pooled estimate of the **mortality** of **CAPA** in the ICU



Mortality of CAPA: 54.9%
95% CI, 45.6–64.2
I^2 = 62.7%

CAPA, COVID-19 associated aspergillosis; IFI, invasive fungal infection; I^2, measure of heterogeneity; ICU, intensive care unit.
Mitaka, et al. Mycoses. 2021 Apr 25;10.1111/myc.13292. (

Epidemiology and incidence of CAPA in a Greek tertiary care academic reference hospital

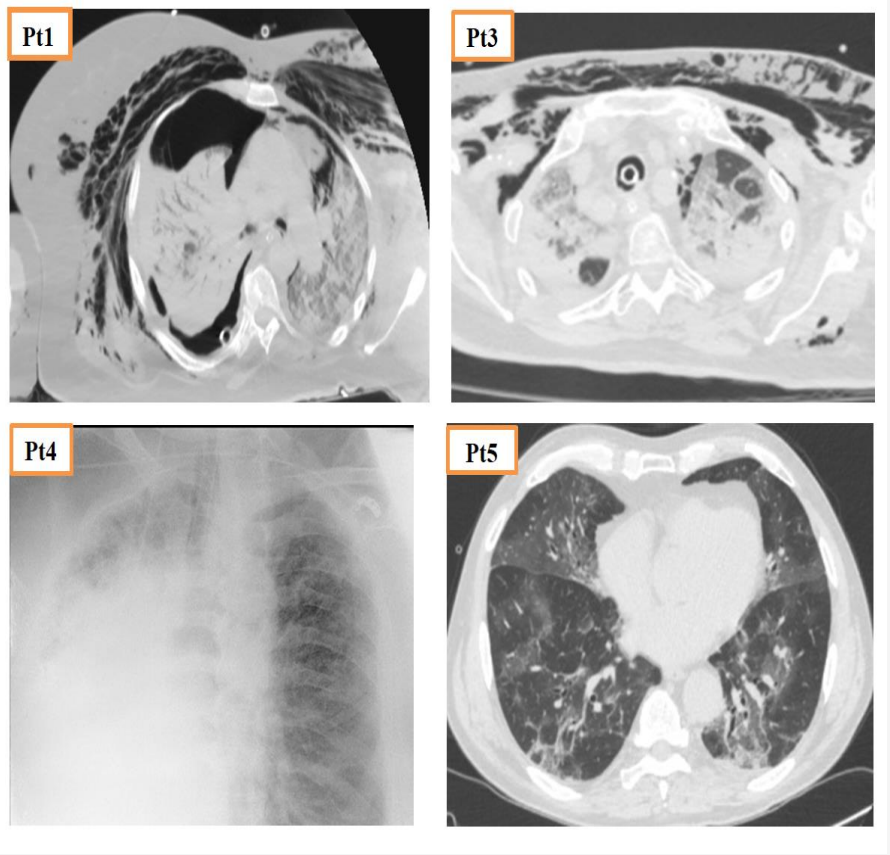
- 179 ICU patients with COVID-19/ARDS, no history of immunosuppression
- 6 patients **(3.3%)** with CAPA (November 2020–April 2021)
  - 4 probable and 2 possible, 5/6 with co-infection with multidrug-resistant gram-negative pathogens
- Median time from intubation to diagnosis: 6 days (range 1–14 days)
  - Mortality: **67%** (4/6)
    - 1/4 attributed to CAPA (2 died due to bacterial septic shock and 1 due to multi-organ failure)

Bronchial secretions/BAL	
A. fumigatus	1
A. flavus	1
A. fumigatus + *A. flavus*	1
A. fumigatus + *A. terreus*	1
A. terreus	1
Culture negative	1

- All isolates were susceptible to antifungal drugs
- Serum GM+ 4/6 patients (67%)
- PCR+ 5/6 patients (83%; + in 2 consecutive samples in 3/5)
- BDG+ in sera in 4/6 patients (67%; in consecutive samples)
- Positive bronchial secretions had GM indices >9.95 and PCR Ct <34 (viral load)

ARDS, acute respiratory distress syndrome; BDG, beta-D-glucan; Ct, cycle threshold; GM, galactomannan.
Paramythiotou, Dimopoulos et al. Infect Dis Ther. 2021

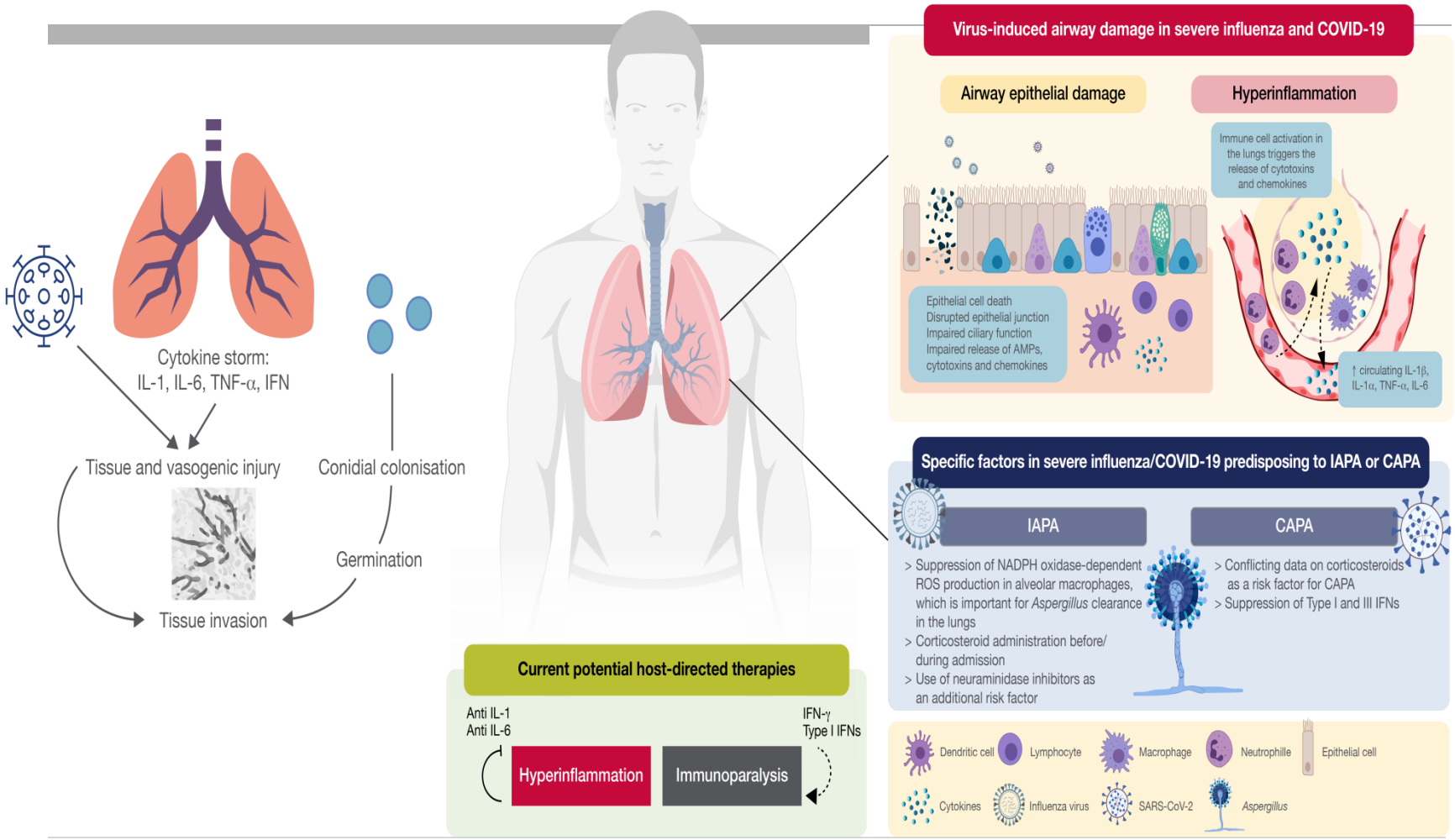
Epidemiology and incidence of CAPA in a Greek tertiary care academic reference hospital



Lung images of patients with CAPA

CAPA, COVID-19-associated pulmonary aspergillosis.
Speakers own images. Paramythiotou, Dimopoulos G et al. Infect Dis Ther. 2021

Proposed pathogenesis of CAPA



AMP, anti-microbial peptide; CAPA, COVID-19-associated pulmonary aspergillosis; IFN, interferon; IL, interleukin; IAPA, influenza-associated pulmonary aspergillosis;
TNF, tumour necrosis factor.
Apostolopoulou, et al. Diagnostics (Basel). 2020;10(10):807, Dewi, et al. Cur Opin Microb. 2021;62:21–37.

Algorithms for the diagnosis of CAPA

Study	Study design	Diagnostic criteria	Proven	Probable	Putative	IAPA criteria	Colonization	Mortality
[36]	Prospective	EORTC/MSG modified AspICU		8			9	8/8
[16]	Retrospective	Modified AspICU algorithm			5			3/5
[26]	Retrospective	Modified AspICU algorithm			5		4	3/5
[9]	Prospective	EORTC/MSG modified AspICU		1	8			4/9
[61]	Prospective	Modified AspICU algorithm			19			7/19
[19]	Case report	AspICU algorithm			1			1/1
[21]	Retrospective	EORTC/MSG		8				NA
[64]	Case report	Modified AspICU algorithm			1			0/1
[22]	Case report	Modified AspICU algorithm			1			1/1
[25]	Case report	Post mortem histopathology	1					1/1
[35]	Retrospective	Modified AspICU algorithm			15			NA
[51]	Prospective	EORTC/MSG		7				5/7
[54]	Case report	IAPA criteria				1		0/1
[32]	Prospective	AspICU algorithm, modified AspICU algorithm, CAPA criteria			25			13/25
[31]	Case series	AspICU algorithm			2			2/2
[65]	Case report	EORTC/MSG		1				0/1
[66]	Case report	EORTC/MSG		1				0/1
[28]	Cohort study	AspICU algorithm			9			2/9
[27]	Cohort study	Modified AspICU algorithm, IAPA criteria			2	1		1/3
[67]	Retrospective	AspICU algorithm			4		3	4/4
[68]	Case report	EORTC/MSG		1				1/1
[33]	Prospective	AspICU algorithm, Modified AspICU algorithm			7		8	2/7
[58]	Prospective	Modified AspICU algorithm			14			8/14
[18]	Case report	AspICU algorithm			1			1/1
[55]	Case report	EORTC/MSG		1				1/1
[69]	Case report	EORTC/MSG		1				1/1
[24]	Case report	AspICU algorithm			1			1/1
[30]	Retrospective	EORTC/MSG, AspICU algorithm		1	7			6/8
[23]	Case report	AspICU algorithm			1			1/1
[20]	Case report	EORTC/MSG post mortem	1					1/1
[34]	Case report	AspICU algorithm			2			2/2
[41]	Retrospective	EORTC/MSG, AspICU algorithm, Modified AspICU algorithm		1	5			4/6
[8]	Prospective	IAPA criteria				30		13/30
[17]	Cohort study	IAPA criteria				6		4/6
[10]	Case series	AspICU algorithm	4		3			4/7
Total			**6**	**31**	**138**	**38**	**24**	**105/190 (55%)**

- EORTC/MSG[1]
- AspICU[2]*
- Modified AspCU[3]
- IAPA criteria[4]
- CAPA criteria[5]

***The most commonly used**

[1] Donnelly, et al Clin Infect Dis. 2020;71(6):1367–1376

[2] Blot, et al Am J Respir Crit Care Med. 2012;186(1):56–64

[3] Schauwvlieghe, et al. Lancet Respir Med. 2018;6(10):782–792

[4] Verweij, et al. Intensive Care Med. 2020;46(8):1524–1535

[5] Koehler, et al. Lancet Infect Dis. 2021;21(6):e149–e162

CAPA, COVID-19-associated pulmonary aspergillosis; IAPA, influenza-associated pulmonary aspergillosis; Dimopoulos, et al. J Intensive Med.

Similarities and differences between CAPA and IAPA

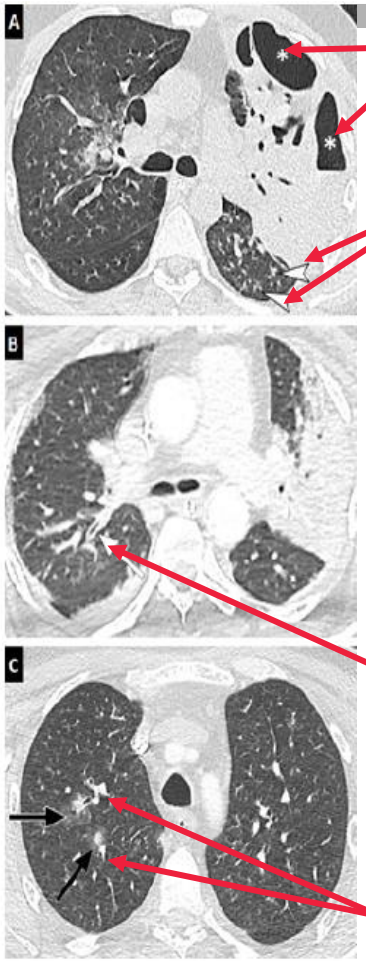
- **22.5%** of patients admitted to ICU with severe viral infection (influenza or COVID-19) developed IPA:
  - 10 patients with CAPA and 17 with IAPA

Similarities between CAPA and IAPA	Differences between CAPA and IAPA
➢ Similar prevalence of IPA between COVID-19 and influenza-associated ARDS	➢ Higher proportion of older patients in CAPA group
➢ Background of patients	➢ Lower Day 1 SOFA score in CAPA patients
➢ Similar clinical courses in ICU, with a trend for a longer median interval between ICU admission and IPA diagnosis in CAPA	➢ Higher ratio of PaO2 to FiO2 in CAPA patients
➢ Higher mortality in patients with IPA than without IPA in both CAPA and IAPA patients	➢ Lower proportion of ECMO among CAPA patients
	➢ Therapeutic drug monitoring of voriconazole is more challenging for CAPA patients
	➢ Lower proportion of patients presenting radiological features suggestive of IPA among CAPA patients

ARDS, acute respiratory distress syndrome; CAPA, COVID-19-associated pulmonary aspergillosis; ECMO, extracorporeal membrane oxygenation; IFN, interferon; IL, interleukin; IPA, invasive pulmonary aspergillosis; SOFA, Sequential Organ Failure Assessment; TNF, tumour necrosis factor. Reizine, et al. J Fungi. 2021;7:388.

Chest CT scan of IAPA and CAPA patients

IAPA



Cavity formation

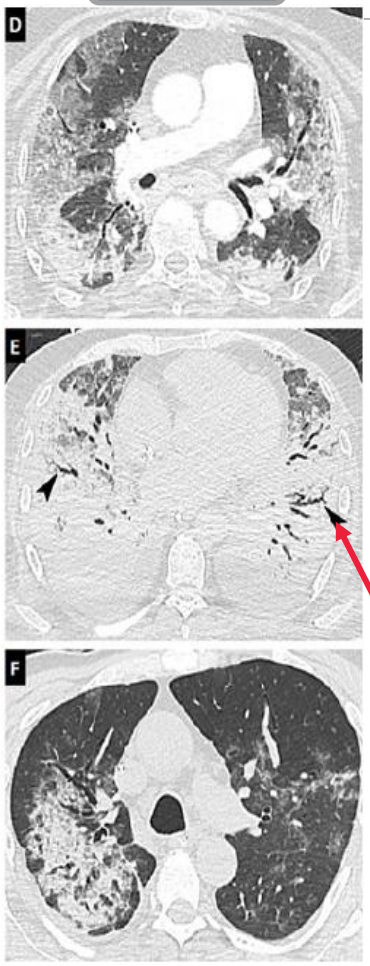
‘Tree-in-bud’

Unilateral or bilateral areas of consolidation with air bronchogram (A,B)

Bronchial wall thickening

Occasionally, nodules with halo signs

CAPA



Bilateral areas of ground-glass opacity and/or crazy paving (D)

Findings observed in (D,E) can be seen frequently in severe COVID-19 patients

Extensive areas of consolidation associated with peripheral traction bronchiectasis

More rarely, unilateral areas of consolidation (F)

CAPA, COVID-19-associated pulmonary aspergillosis; CT, computer tomography; IAPA, influenza-associated pulmonary aspergillosis.

Reizine, et al. J. Fungi. 2021;7:388.

Fungal co-infections associated with COVID-19

No time to confirm IFIs in critically ill COVID-19 patients

Think ‘empirical treatment’!

- CAPA diagnosis is challenging[1]
  a) Independent association between CAPA and 30-day mortality was demonstrated among intubated patients although a causal link remains to date unproven[1]
  b) Use of corticosteroids or anti-IL6 antibody in critically ill patients with COVID-19
     i. Corticosteroids ➔ well known risk factors for IFI[2]
     ii. IFIs ➔ in patients treated with anti-IL6 antibody[3]

Empirical use of antifungals?

- Without waiting for the final evidence of fungal microbiology, in case of a clinical suspicion of IFI (patients receiving immunomodulating therapies)

CAPA, COVID-19-associated pulmonary aspergillosis; ICU, intensive care unit; IFI, invasive fungal infection; IL, interleukin.

1. Bartoletti, et al. Clin Infect Dis. 2020;ciaa1065; 2. Brüggemann, et al. Clin Infect Dis. 2020;ciaa1211; 3. Falcone, et al. J Antimicrob Chemother. 2021;76(4):1078–1084.

Management of CAPA

When to consider CAPA?

1. **CAPA occurs predominantly in patients on mechanical ventilation >5 days**
2. Risk factors: High-dose or long administration of corticosteroids; EORTC/ MSGERC host/risk factor; structural lung disease
3. Diagnostic work-up recommended in clinically deteriorating patients with no other explanation or with cavitary and/or nodular lesions on CT scan. Halo sign and hypodense consolidation lesions may be absent in CAPA. Bronchoscope inspection of airways warranted

How to diagnose CAPA?

1. Bronchoscopy with BAL
2. Microbiological investigations of BAL: microscopy, culture, GM, and/or Aspergillus PCR
3. **Mucosal biopsy when plaques are visible in trachea and/or bronchi**
4. Serum GM or BDG are not recommended for patient monitoring, but when positive indicative of advanced CAPA. Serum BDG not specific for *Aspergillus*
5. **Patients with cavitary lung lesions, exclude necrotising pneumonia due to bacterial pathogen (e.g. *S. pneumoniae, S. aureus*)**

How to treat CAPA?

1. **Antifungal prophylaxis is not recommended in mechanically ventilated COVID-19 patients**
2. Empirical antifungal treatment for visible plaques in trachea and/or bronchi or in patients rapidly deteriorating
3. Antifungal therapy in IATB confirmed and Aspergillus+ BAL, GM or PCR tests
4. 1L voriconazole, as per (inter)national guidelines
5. TDM for patients receiving voriconazole
6. **Stop empirical antifungal if BAL GM and culture are negative**

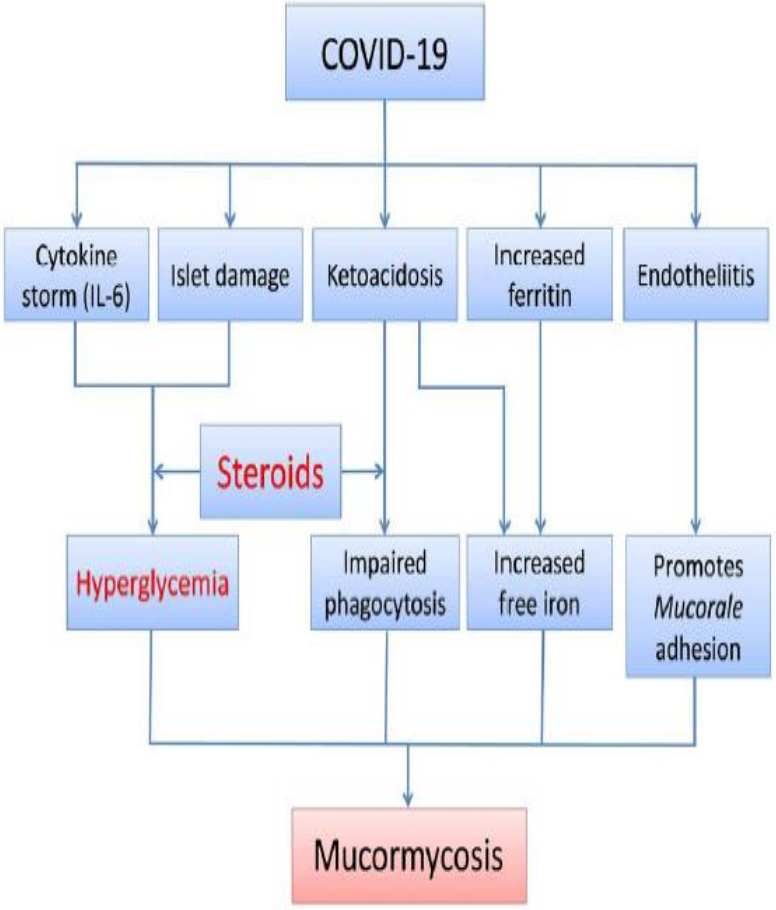
BAL, bronchoalveolar lavage; CAPA, COVID-19-associated pulmonary aspergillosis; GM, galactomannan; IATB, invasive *Aspergillus* tracheobronchitis; MSGERC, The Mycoses Study Group Education and Research Consortium TDM, therapeutic drug monitoring.

Verweij, et al. Intensive Care Med. 2021;June 23:1-16.

COVID-19-Associated Mucormycosis (CAM)

Systematic review

- 30 case reports/case series, 99 patients with CAM
- **Most cases from India (72%)**
- Male (78%), **diabetes mellitus (85%)**
- Prior history of COVID-19 in 37% of patients with mucormycosis developing after initial recovery
- Median time interval between COVID-19 diagnosis and CAM diagnosis: **15 days**
- **Steroids in 85% of cases**
  - Rhino-orbital mucormycosis (42%)
  - Rhino-orbito-cerebral mucormycosis (24%)
  - Pulmonary mucormycosis (10%)
- Mortality rate: **34%**
- Adjunctive surgery (in 81% of patients) was associated with better clinical outcomes (p<0.001)



Pal, et al. Mycoses. 2021;June 16.

COVID-19 and *Pneumocystis jirovecii* co-infection

- *Pneumocystis jirovecii* pneumonia (PJP) shares similar symptoms with COVID-19 and hence coinfection may not be appreciated in patients with severe SARS-CoV-2 infection[1,2]
- Unexpectedly high incidence of BAL samples positive for *P. jirovecii* by PCR in an observational study of HIV-negative COVID-19 patients in an ICU[3]
  - 10 of 108 patients (9.3%)
  - Not clear if this was colonisation or infection
  - 5 of these also met the criteria for CAPA
- Awareness may be lower because PJP is usually associated with T-cell deficiency[2,3]
  - In one reported case, an 83-year-old female with PJP and COVID-19 was found to have CD4+ lymphopenia (291 cells/µl) despite being HIV negative[2]
  - In another report, co-infection led to the diagnosis of AIDS[4]
    - Immunosuppression caused by HIV might have resulted in COVID-19 being milder

AIDS, acquired immunodeficiency syndrome; BAL, bronchoalveolar lavage; CAPA, COVID-19-associated pulmonary aspergillosis; HIV, human immunodeficiency virus; PJP, *Pneumocystis jirovecii* pneumonia

1. Bhatt et al. Discoveries(Craiova). 2021;9(1):e126: 2. Menon, et al. Am J Respir Crit Care Med. 2020;202(1):136–138; 3. Alanio et al. J Infect. 2021;82(4):84-123;.
4. Mang, et al. Clin Infect Dis. 2021;72(8):1487-1489.

COVID-19 and *Cryptococcus* co-infection

- Several reports of co-infection with SARS-CoV-2 and *Cryptococcus* spp.
  - Meningoencephalitis in a 73-year-old immunocompetent woman[1]
  - A 75-year-old kidney transplant patient with decompensated cirrhosis and COVID-19 who developed fungemia due to *Cryptococcus neoformans*[2]
  - Cryptococcaemia in a 60-year-old man with confirmed COVID-19 and multiple comorbidities who died[3]
- Immune dysregulation, including T-cell depletion, and cumulative risk factors in COVID-19 patients increase the risk of cryptococcal infection along with other secondary opportunistic infections[1]
- The high mortality of cryptococcal infection highlights the importance of early suspicion, prompt diagnosis and appropriate management[3,4]

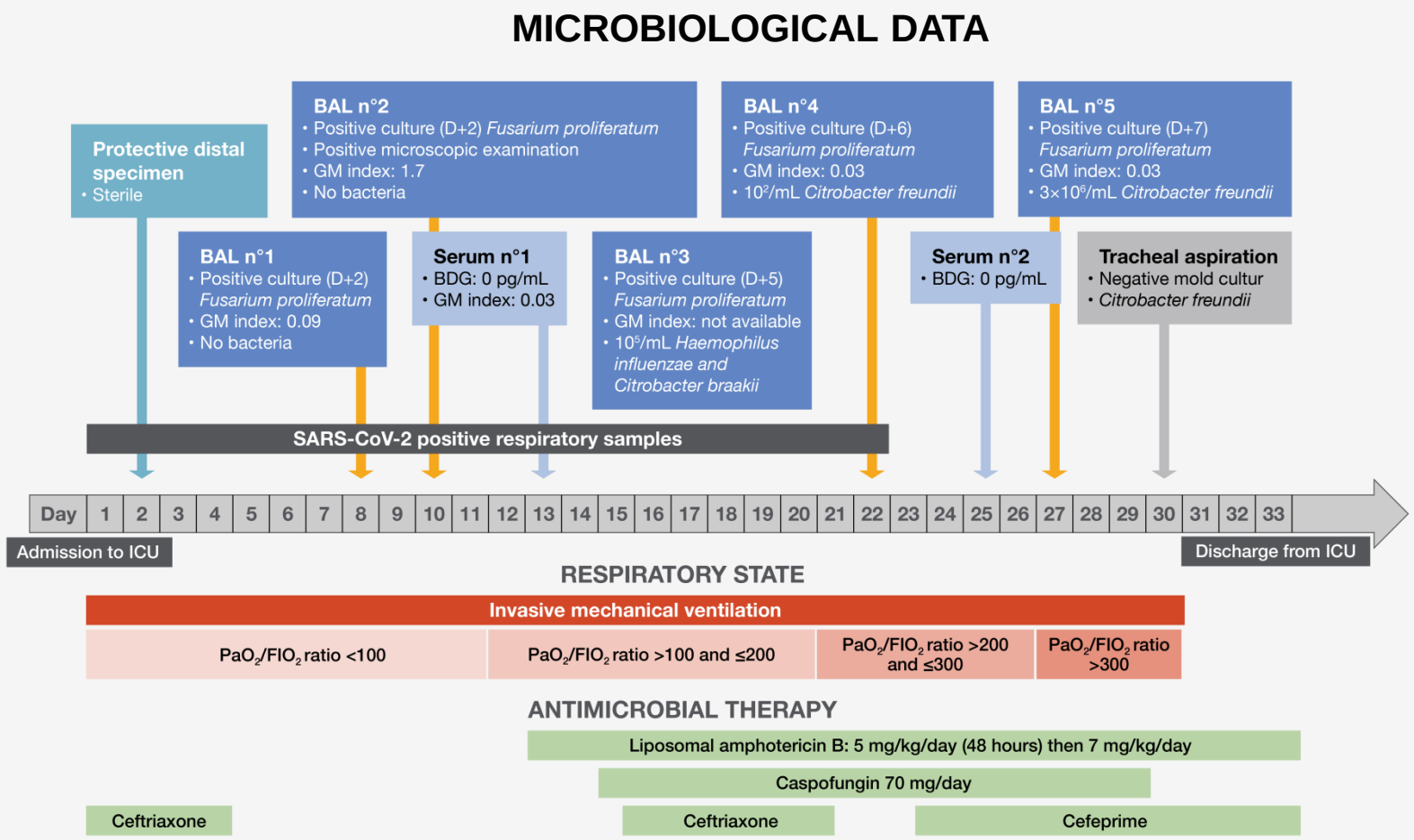
1. Ghanem et al. Case Rep Infect Dis. 2021;2021:5597473; 2. Passarelli et al. SN Compr Clin Med. 2020:1-5; 3. Khatib et al. Clin Case Rep. 2020;9(2):853-855; 4. Bhatt et al. Discoveries (Craiova). 2021;9(1):e126.

COVID-19 and histoplasmosis

- COVID-19 may facilitate the development of acute pulmonary histoplasmosis[1]
- Clinicians need to be alert to this in endemic areas
  - Lung damage due to COVID-19 or corticosteroids may reactivate latent *H. capsulatum*
- Diagnosis is challenging as symptoms are non-specific
- Multiple case reports
  - In two patients in Brazil, culture and urinary GM were negative; diagnosis by Western blot and fungal DNA detection[1]
  - In another Brazilian case, COVID-19 was an incidental finding as a result of a PET-CT scan in a woman being treated for histoplasmosis[2]
  - COVID-19 co-infection reported in patients with HIV-associated histoplasmosis[3-5]

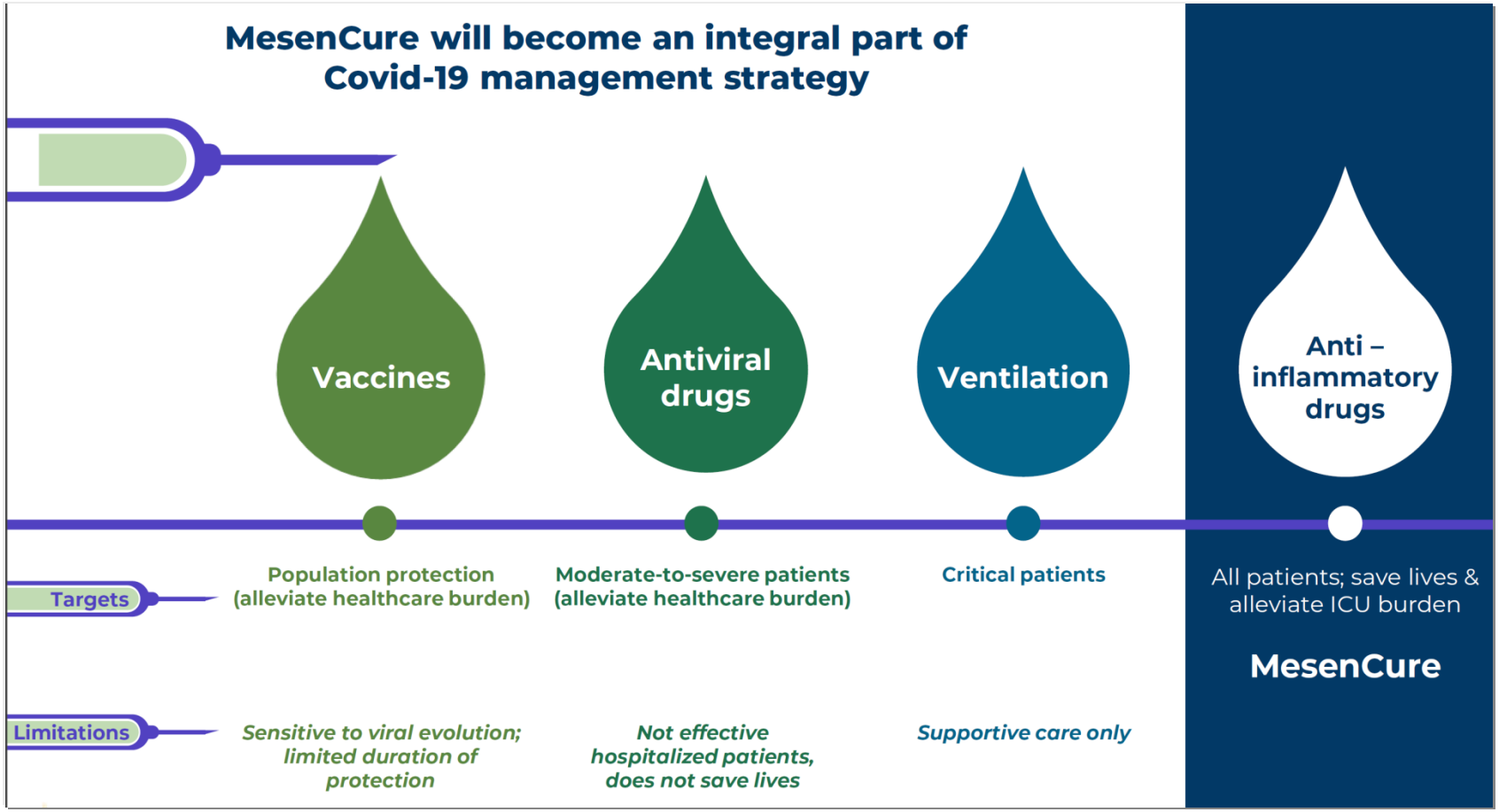
1. de Macedo et al. J Fungi (Basel). 2021;7(5):346; 2. Stasiak et al. Am J Trop Med Hyg. 2021;104(5):1651–4; 3. Messina et al. J Fungi (Basel). 2020;6(4):275; 4. Basso et al. Mycopathologia. 2021;186(1):109-112; 5. Bertolini et al. Int J STD AIDS. 2020;31(12):1222-1224.

COVID-19 and fusariosis



BAL, bronchoalveolar lavage; BDG, β-D-glucan; D, days; FIO_2, fraction of inspired oxygen; GM, galactomannan; PaO_2, partial pressure of oxygen.
Poignon, et al. Clin Microbiol Infect. 2020;26(11):1582-1584

Νόσος COVID-19
Αρχές θεραπείας



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.

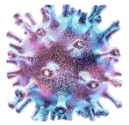
Νόσος COVID-19
Προφύλαξη με Υδροξυχλωροκίνη

- 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

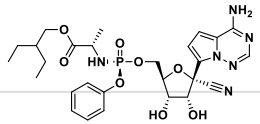
Νόσος COVID-19
Θεραπεία με Remdesivir (RDV)

- 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%)



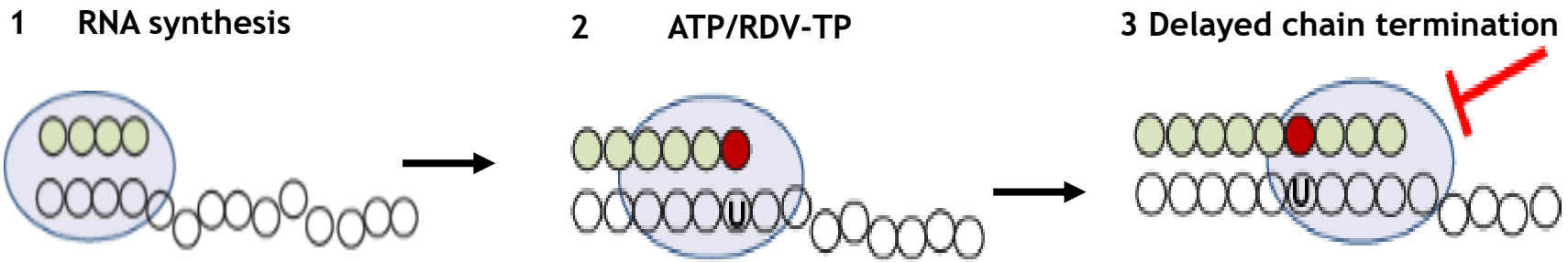
Sheahan TP, et al. Sci Transl Med 2017;9:eaal3653, Warren et al, 2016 Nature
https://www.gilead.com/purpose/advancing-global-health/covid-19/working-to-supply-remdesivir-for-covid-19

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

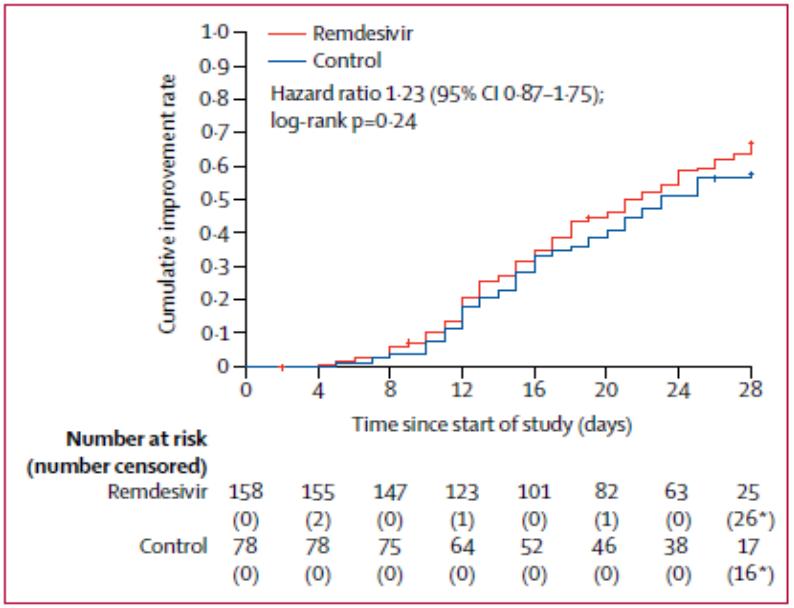


Figure 2: **Time to clinical improvement in the intention-to-treat population**
Adjusted hazard ratio for randomisation stratification was 1·25 (95% CI 0·88–1·78). *Including deaths before day 28 as right censored at day 28, the number of patients without clinical improvement was still included in the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

Νόσος COVID-19
Θεραπεία με Remdesivir (RDV)- Κλινικές μελέτες

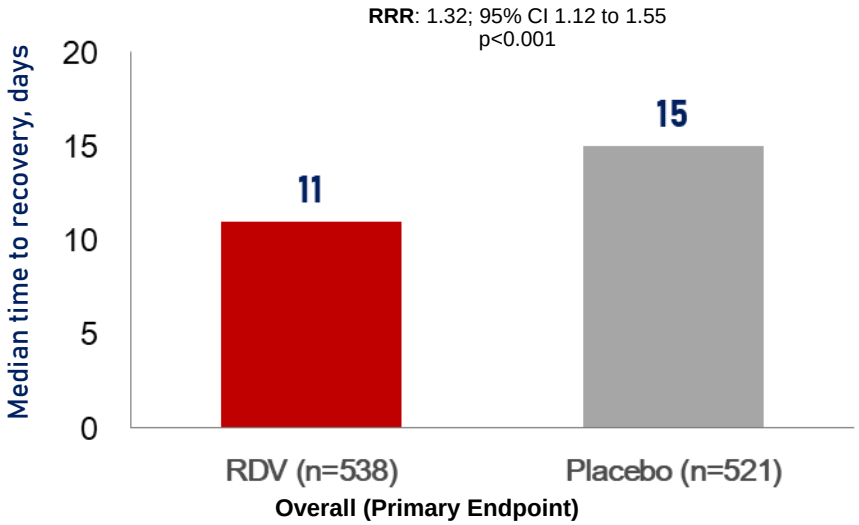
Data Source		Target N	Hospitalized patients			Placebo or Standard of Care	Key Question	Data Available- Key Publication
			Moderate	Severe	Critical			
NIH NIAID ACTT1 NCT04280705	Randomized Double blind	1063	M	S	C	P	Is RDV safe and effective treatment for COVID-19 patients?	**Beigel NEJM May 2020:** RDV 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

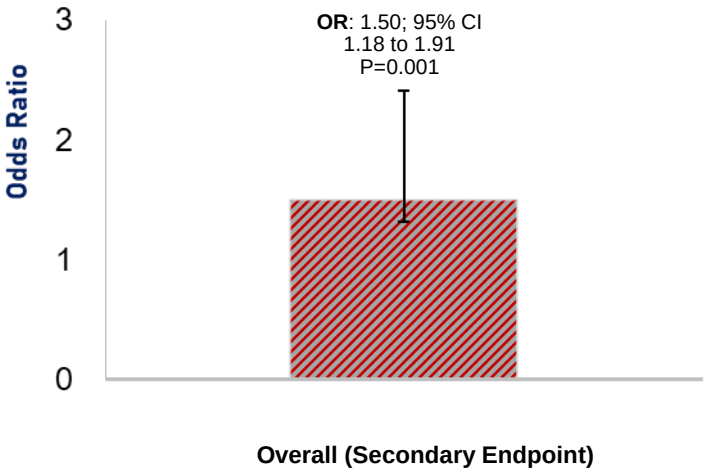
Νόσος COVID-19
NIAID Study (ACTT-1)

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*



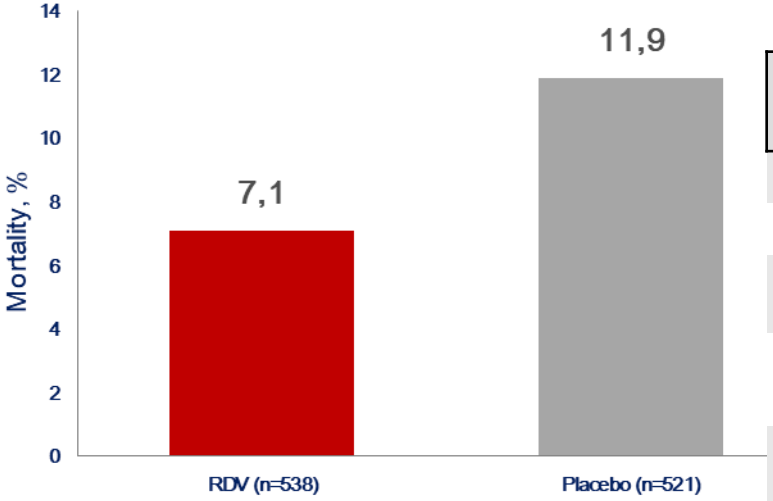
RDV produced 50% higher rate of clinical improvement on the ordinal scale compared to placebo

*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)

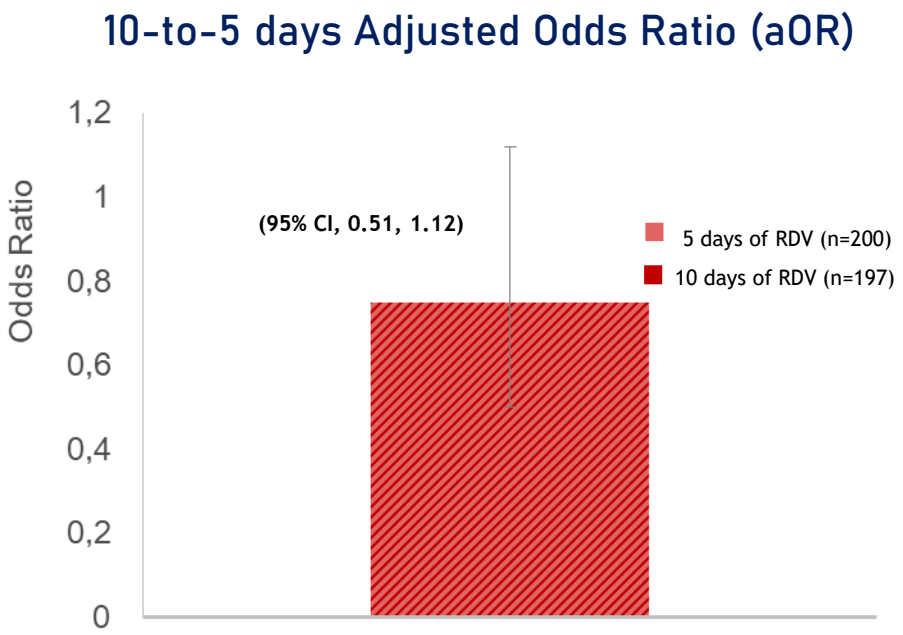
SAEs were numerically lower in RDV (21%) compared to placebo (27%)

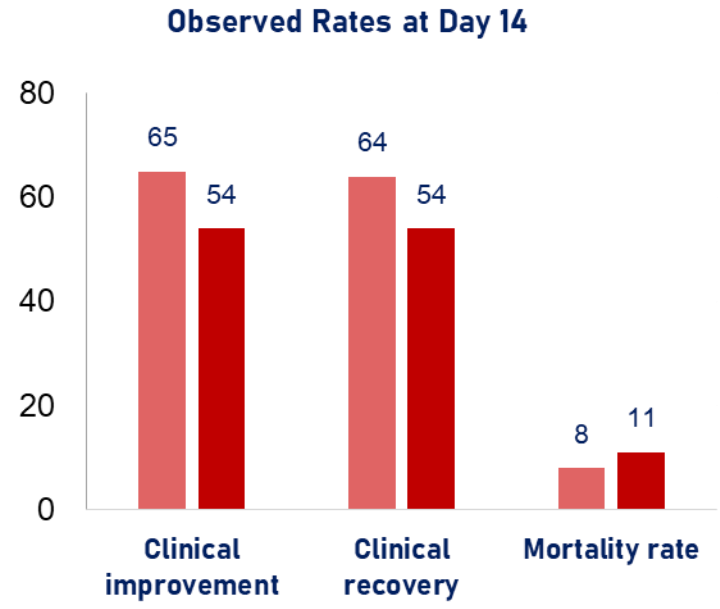
4 SAE events (2 in each arm) were judged by site investigators to be related to the study product

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





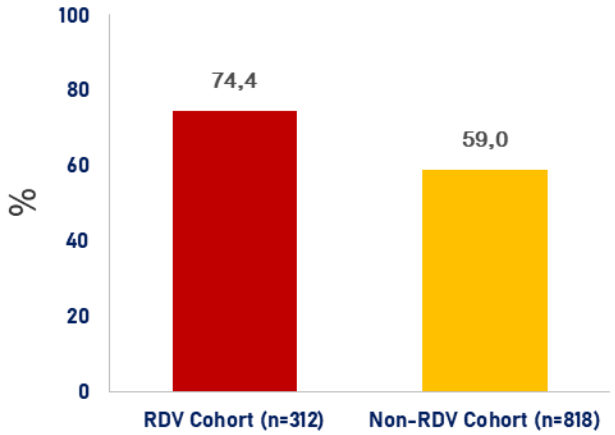
- Clinical improvement- defined as an improvement of two or more points from baseline on a predefined 7-point scale, ranging from hospital discharge to increasing levels of oxygen support to death
- Clinical recovery- defined as no longer requiring oxygen support or discharged from the hospital

Goldman et al. NEJM 27 May 2020

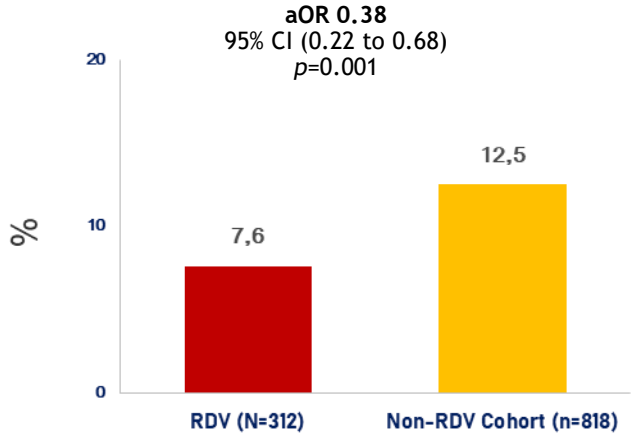
Νόσος COVID-19
Analysis of RDV vs Standard of Care

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

Recovered by Day 14



Mortality at Day 14



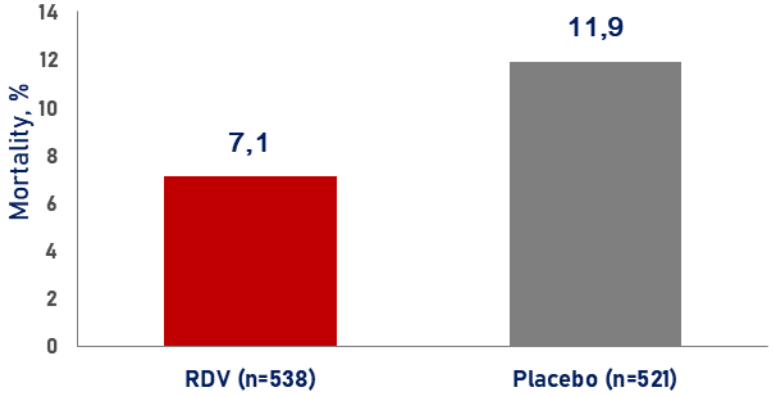
By Day 14, RDV was associated with significantly improved recovery
and 62% reduced odds of death compared to a retrospective RW standard of care cohort

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)

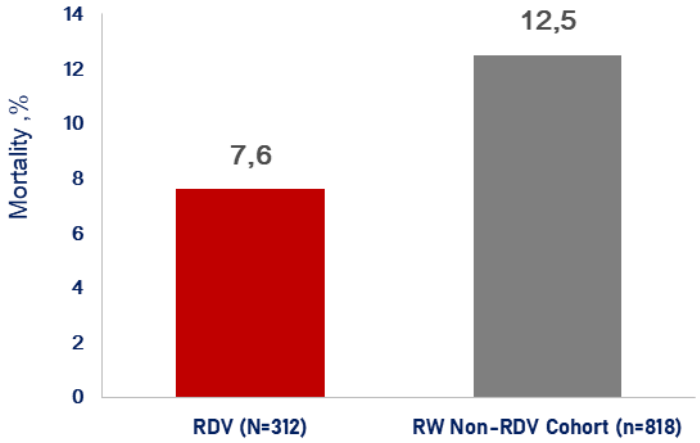


Ordinal scale[3]	4	5	6	7
Deaths	0.46	**0.22**	1.12	1.06
HR (95% CI)	(0.04, 5.08)	**(0.08, 0.58)**	(0.53, 2.38)	(0.59, 1.92)

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]

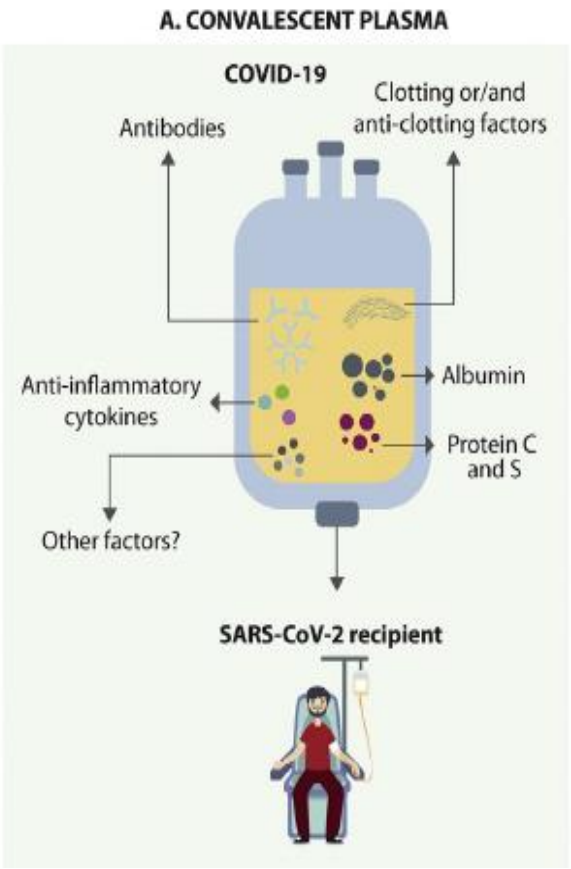
aOR 0.38
95% CI (0.22 to 0.68), *p*=0.001

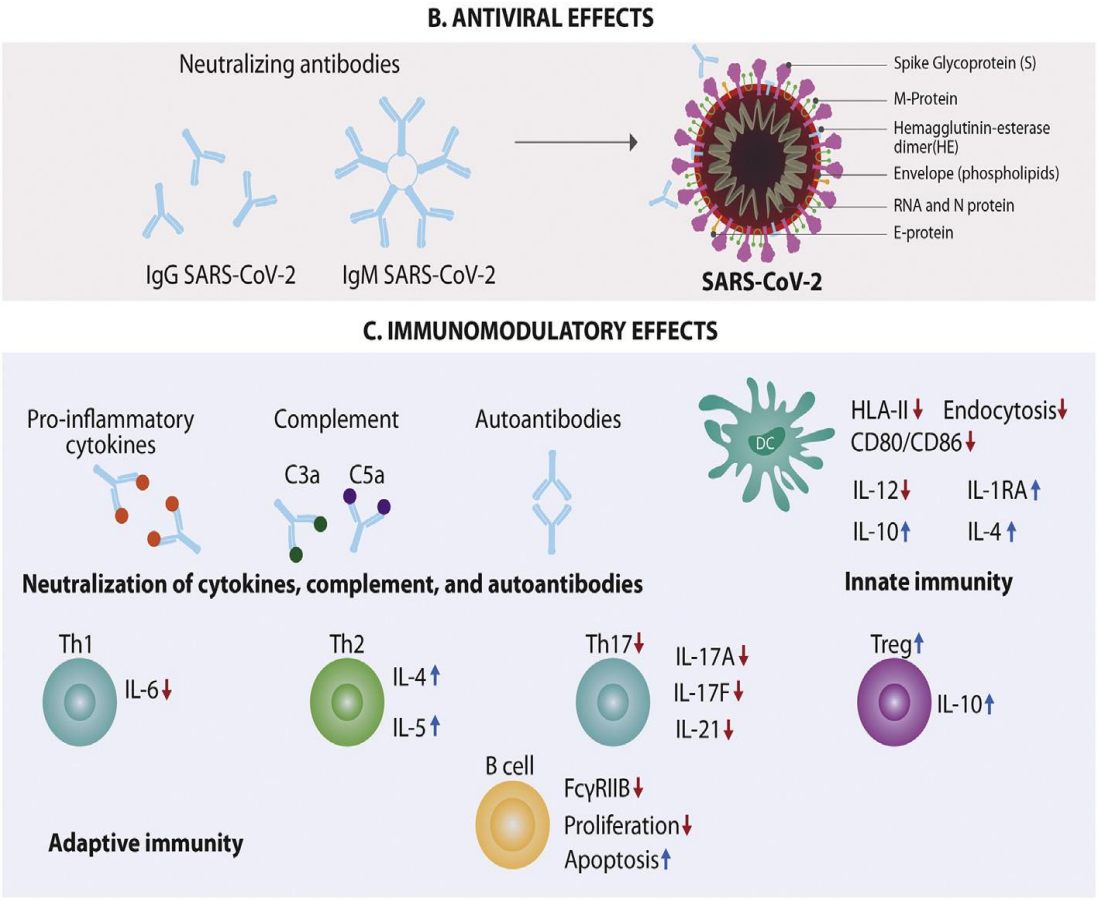


RDV used in clinical trial was associated with 62% reduced odds of death compared to a RW- SoC cohort [2]

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





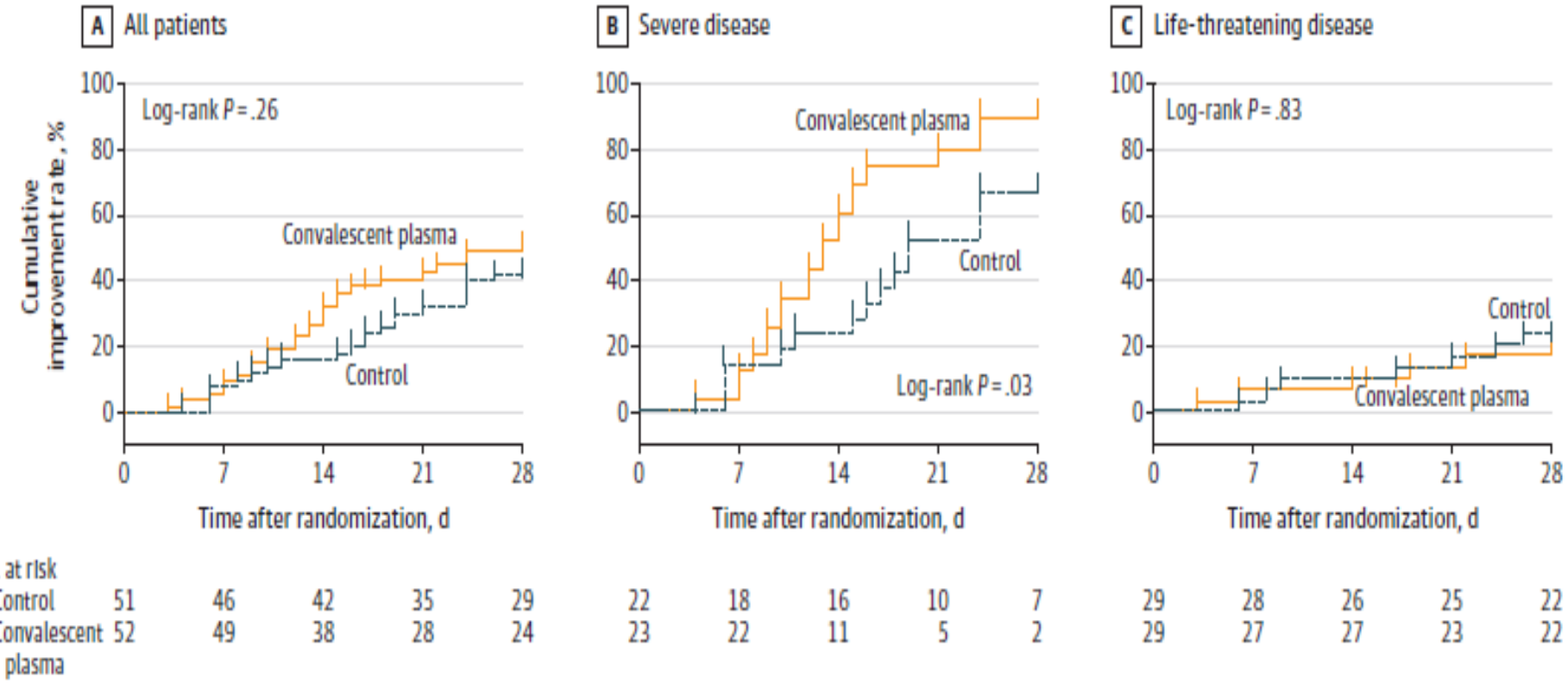
JAMA | Original Investigation

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

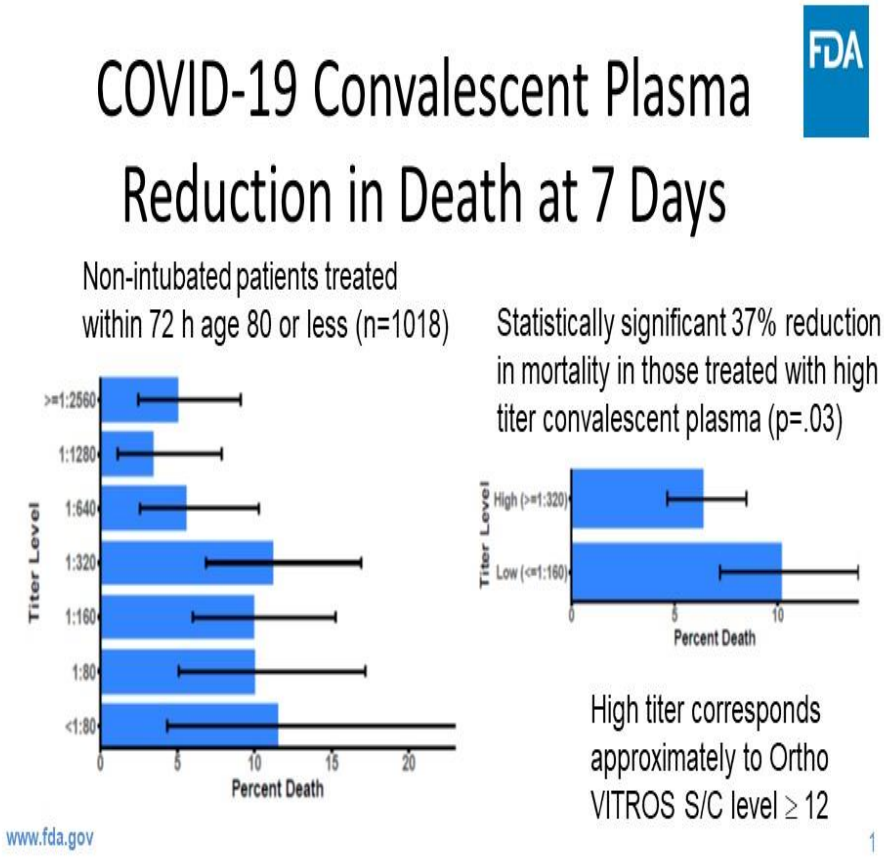
A Randomized Clinical Trial

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

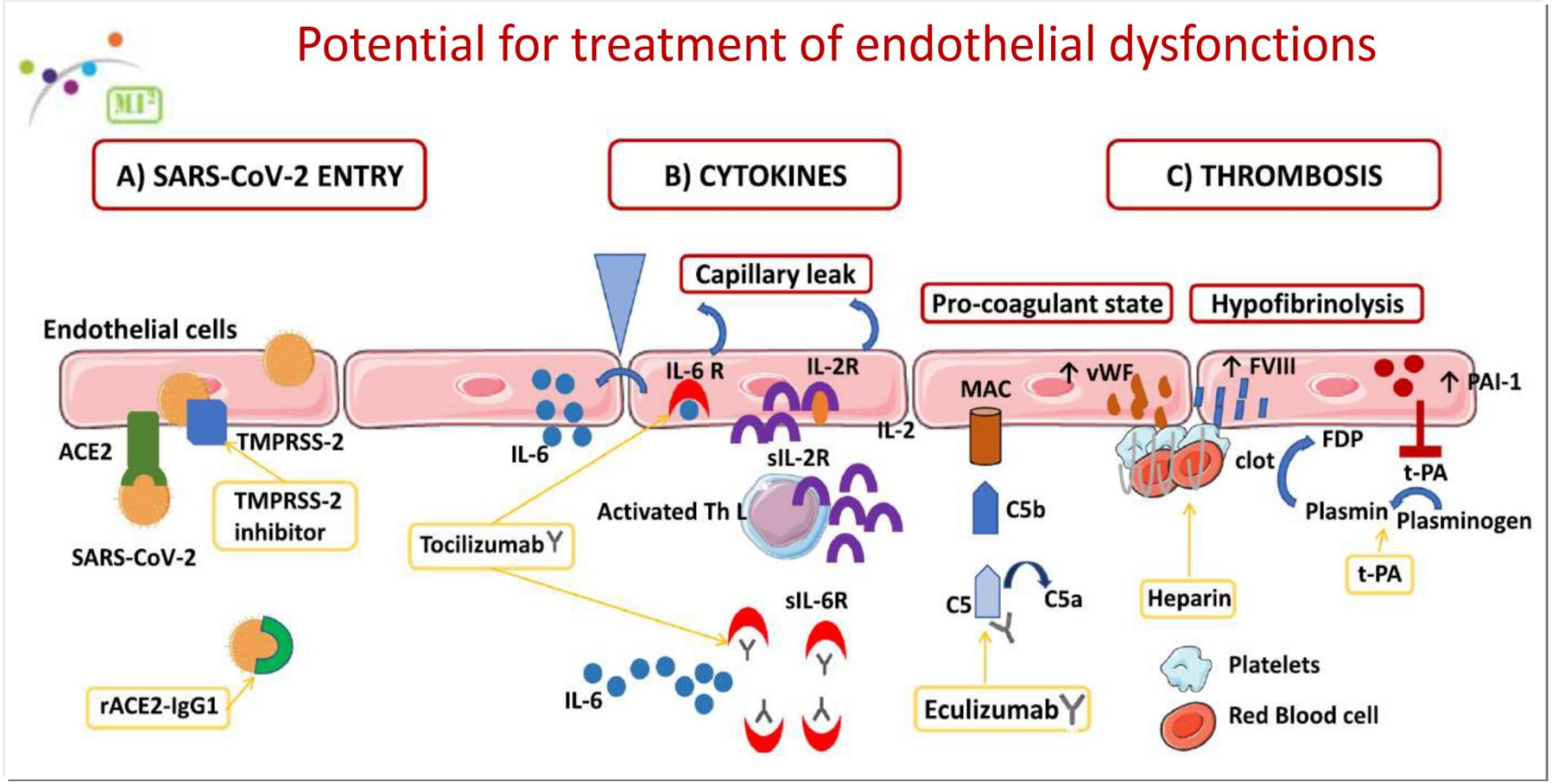
FDA, revised information for investigational COVID-19 convalescent plasma; https:://www.fda.gpv/vaccines blood-biologics/investigational-new-drug-ind-or-device-exemptio nide-process-cber/revised- information –investigational-covid-19-convalescent-plasma.Asssesed April 08,2020

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

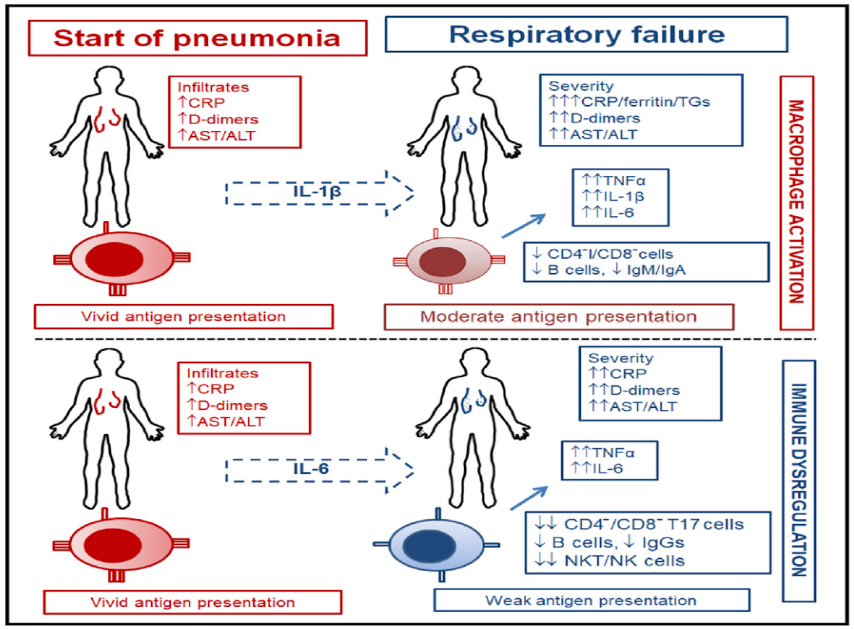
Νόσος COVID-19
Ανοσοθεραπεία

Clinical and Translational Report

Cell Host & Microbe

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

Graphical Abstract



Authors

Evangelos J. Giamarellos-Bourboulis, Mihai G. Netea, Nikoletta Rovina, ..., Nikolaos Koulouris, Charalambos Gogos, Antonia Koutsoukou

Correspondence

egiamarel@med.uoa.gr

In Brief

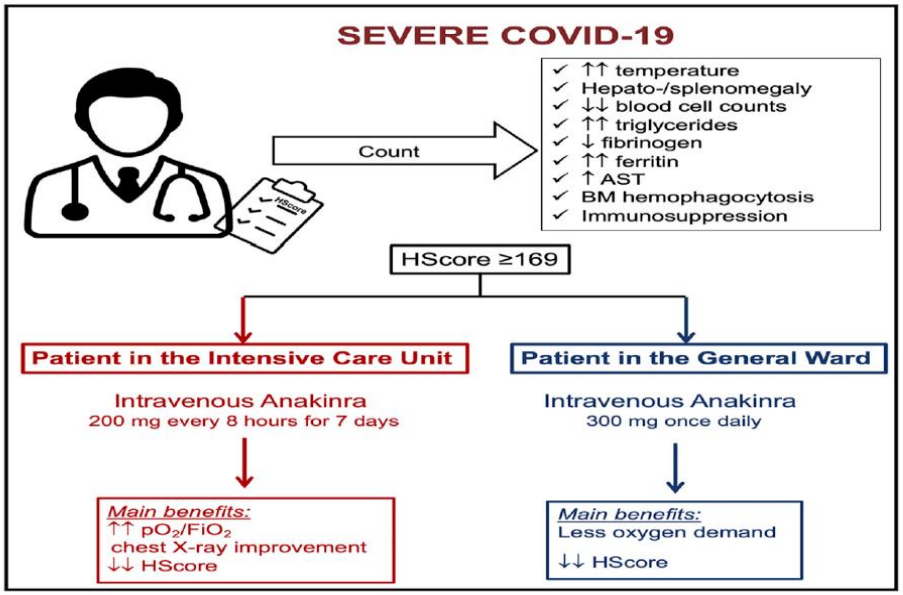
Proper management of COVID-19 mandates better understanding of disease pathogenesis. Giamarellos-Bourboulis et al. describe two main features preceding severe respiratory failure associated with COVID-19: the first is macrophage activation syndrome; the second is defective antigen-presentation driven 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
George Dimopoulos, Quirijn de Mast, Nikolaos Markou, ..., Alexandra Lachana, Frank L. van de Veerdonk, Evangelos J. Giamarellos-Bourboulis

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.

Νόσος COVID-19
Ανοσοθεραπεία

nature medicine

ARTICLES

https://doi.org/10.1038/s41591-021-01499-z

Check for updates

OPEN

Early treatment of COVID-19 with anakinra guided by soluble urokinase plasminogen receptor plasma levels: a double-blind, randomized controlled phase 3 trial

Evdoxia Kyriazopoulou[1], Garyfallia Poulakou[2], Haralampos Milionis[3], Simeon Metallidis[4], Georgios Adamis[5], Konstantinos Tsiakos[6], Archontoula Fragkou[7], Aggeliki Rapti[6], Christina Damoulari[1], Massimo Fantoni[8], Ioannis Kalomenidis[9], Georgios Chrysos[10], Andrea Angheben[11], Ilias Kainis[12], Zoi Alexiou[13], Francesco Castelli[14], Francesco Saverio Serino[15], Maria Tsilika[1], Petros Bakakos[16], Emanuele Nicastri[17], Vassiliki Tzavara[18], Evangelos Kostis[19], Lorenzo Dagna[20], Panagiotis Koufargyris[1], Katerina Dimakou[21], Spyridon Savvanis[7], Glykeria Tzatzagou[22], Maria Chini[23], Giulio Cavalli[20], Matteo Bassetti[24], Konstantina Katrini[1], Vasileios Kotsis[25], George Tsoukalas[26], Carlo Selmi[27], Ioannis Bliziotis[28], Michael Samarkos[29], Michael Doumas[30], Sofia Ktena[1], Aikaterini Masgala[31], Ilias Papanikolaou[32], Maria Kosmidou[3], Dimitra-Melia Myrodia[2], Aikaterini Argyraki[33], Chiara Simona Cardellino[11], Katerina Koliakou[34], Eleni-Ioanna Katsigianni[34], Vassiliki Rapti[2], Efthymia Giannitsioti[10], Antonella Cingolani[8], Styliani Micha[34], Karolina Akinosoglou[35], Orestis Liatsis-Douvitsas[34], Styliani Symbardi[36], Nikolaos Gatselis[37], Maria Mouktaroudi[1,34], Giuseppe Ippolito[17], Eleni Florou[34], Antigone Kotsaki[1], Mihai G. Netea[38,39], Jesper Eugen-Olsen[40], Miltiades Kyprianou[34], Periklis Panagopoulos[41], George N. Dalekos[37] and Evangelos J. Giamarellos-Bourboulis[1,34] ✉

454 were excluded

- suPAR < 6 ng ml^{-1} (n = 405)
- pO_2/FiO_2 < 150 mmHg (n = 23)
- Withdrew consent before randomization (n = 12)
- Unwillingness not to remain pregnant during the study period (n = 3)
- Age < 18 years (n = 2)
- Anti-cytokine biologicals the last month (n = 2)
- Stage IV solid tumor malignancy (n = 2)
- Absence of radiological findings of pneumonia (n = 1)
- Primary immunodeficiency (n = 1)
- Neutrophils < 1,500 per mm^3 (n = 1)
- Transfer to another hospital before randomization (n = 1)
- Oral or IV ≥ 0.4 mg kg^{-1} prednisone for >15 last days (n = 1)

- 189 patients were allocated to the placebo arm
- 405 patients were allocated to the anakinra arm

Main Results of SAVE-MORE