Η Πνευμονολογία συναντά τις άλλες ειδικότητες στην εποχή του COVID-19

Αιματολογικές διαταραχές και υπερπηκτικότητα

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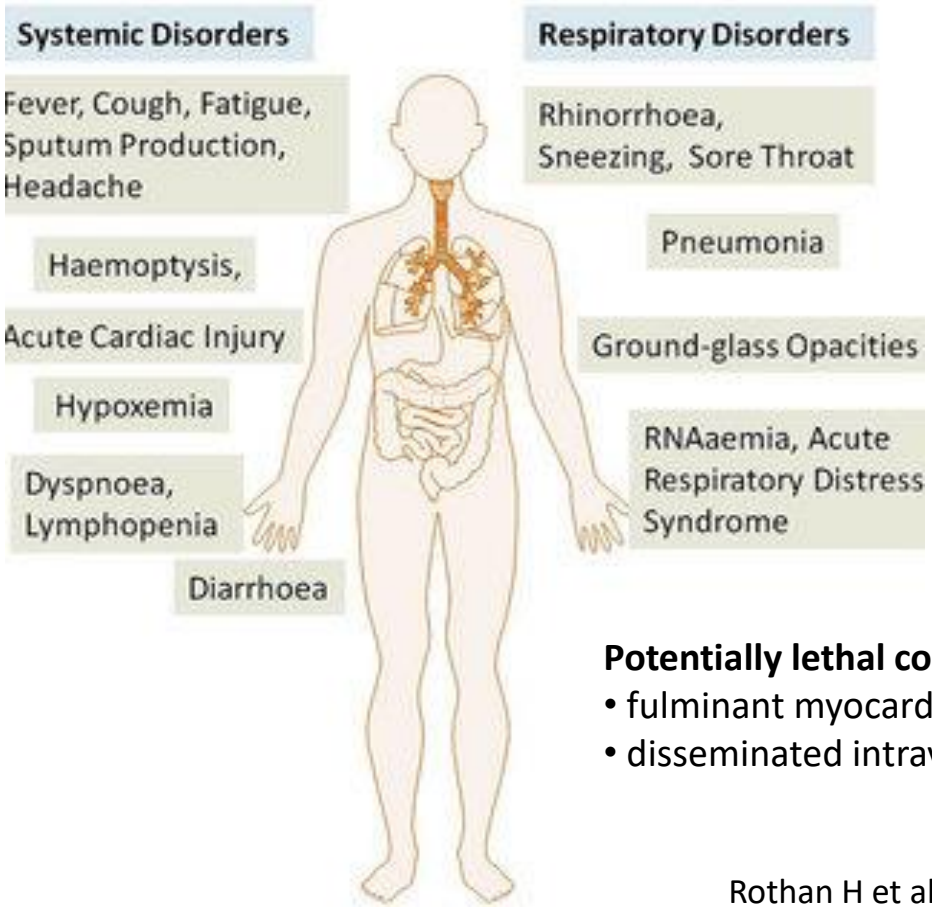
COVID-19 – Συστηματικές εκδηλώσεις



Potentially lethal complications

- fulminant myocarditis
- disseminated intravascular coagulopathy (DIC)

Rothan H et al. DOI: 10.1016/j.jaut.2020.102433

Full Blood Count and Biochemistry Findings
Correlation with Prognosis

Lymphopenia

First author (year)	Sample size	Main findings
Guan (2020)	1099	Lymphocytopenia was present in **83.2%** of patients on admission. 92.6% (50/54) of patients with the composite primary endpoint (**admission to an intensive care unit, use of mechanical ventilation, or death**) presented with lymphocytopenia vs. 82.5% (681/825) of patients without the primary endpoint (p=0.056). **Severe cases** presented lymphocytopenia more frequently (96.1%, 147/153) vs. non-severe cases (80.4%, 584/726); p<0.001
Huang (2020)	41	85% (11/13) of patients **needing ICU care** presented low lymphocyte count vs. 54% (15/28) of patients that did not need ICU care (p=0.045).
Wang (2020)	138	**ICU cases** presented with lower lymphocyte count (median:0.8, IQR: 0.5-0.9) vs. non-ICU cases (median: 0.9, IQR: 0.6-1.2); p=0.03. Longitudinal decrease was noted in **non-survivors**.
Wu (2020)	201	Lower lymphocyte count was associated **with ARDS development** (HR=0.37, 95%CI: 0.21-0.63, p<0.001 in the incremental model)
Bhatraju (2020)	24 ICU patients	Lymphocytopenia was common (**75%** of patients), with a median lymphocyte count of 720 per mm^3 (IQR: 520 to 1375).

Terpos E et al. Am J Hematol. 2020.

Lymphopenia

First author (year)	Sample size	Main findings
Young (2020)	18	Lymphopenia was present in 7 of 16 patients (39%). Median lymphocyte count was 1.1 (IQR: 0.8-1.7) in patients that required supplemental O_2 and 1.2 (IQR:0.8-1.6) in those that did not.
Fan (2020)	69	Lymphopenia at admission (4/9 of ICU patients vs. 1/58 non-ICU patients, p<0.001) and nadir lymphopenia during hospital stay (7/9 of ICU patients vs. 1/58 non-ICU patients, p<0.001) were associated with **need for ICU**.
Yang (2020)	52 critically ill patients	Lymphocytopenia occurred in 44 **(85%) of critically ill patients**, with no significant difference between survivors and non-survivors. A numeric difference in lymphocyte count was noted in non-survivors vs. survivors (0.62 vs.0.74).
Zhou (2020)	191	Lower lymphocyte count was associated with **higher odds of death** at the univariate analysis (OR=0.02, 95%CI: 0.01-0.08; p<0.0001); at the multivariate analysis, the finding lost significance (OR=0.19, 95%CI: 0.02-1.62; p=0.13)
Arentz (2020)	21 ICU patients	Low lymphocyte count was noted in **14/21 (67%) of critically ill patients**.
Deng (2020)	January 1, 2020 to February 21, 2020	On admission, **patients in the death group** exhibited significantly lower lymphocyte count (median: 0.63, IQR: 0.40-0.79) $\times 10^9$/L vs. 1.00, IQR: 0.72- 1.27 $\times 10^9$/L, p < 0.001). Patients in the death group also exhibited **lower lymphocyte/WBC ratio** (median: 7.10, IQR: 4.45, 12.73% vs. 23.5, IQR: 15.27-31.25%, p<0.001).
Tan (2020)	90 patients at the validation cohort	Lymphocytes <20% on day 10-12 signal a pre-severe disease and lymphocytes <5% on day 17-19 denote a critical illness.

Terpos E et al. Am J Hematol. 2020.

COVID-19 associated lymphopenia

- **Lymphocytes express the ACE2 receptor** [1] thus SARS-CoV-2 may directly infect those cells and ultimately lead to their lysis.
- The **cytokine storm** is characterized by markedly increased levels of interleukins (mostly IL-6, IL-2, IL-7, granulocyte colony stimulating factor, interferon-γ inducible protein 10, MCP-1, MIP1-a) and tumor necrosis factor (TNF)-alpha, which may promote **lymphocyte apoptosis**. [2,3]
- Substantial cytokine activation may be also associated with **atrophy of lymphoid organs**, including the spleen, and further impairs lymphocyte turnover.[4]
- Coexisting **lactic acid acidosis**, which may be more prominent among cancer patients who are at increased risk for complications from COVID-19,[5] may also **inhibit lymphocyte proliferation.**[6]

1. Xu H *et al. Int J Oral Sci* 2020 24; **12**(1)**:** 8.
2. Singh S *et al. PLoS One* 2014; **9**(5)**:** e98020.
3. Liao YC *et al. J Immunol* 2002 ; **169**(8)**:** 4288-4297.
4. Chan JF *et al. Clin Infect Dis* 2020 Mar 26.
5. You B *et al. Lancet Oncol* 2020 Mar 25.
6. Fischer K *et al. Blood* **109**(9)**:** 3812-3819.

Thrombocytopenia

First author (year)	Sample size	Main findings
Guan (2020)	1099	Thrombocytopenia was present in **36.2%** of patients on admission. **Severe cases** presented thrombocytopenia more frequently (57.7%, 90/156) vs. non-severe cases (31.6%, 225/713); p<0.001
Huang (2020)	41	8% (1/13) of patients needing ICU care presented low platelet count vs. 4% (1/27) of patients that did not need ICU care (p=0.45).
Wang (2020)	138	**No significant difference** (p=0.78) was noted in platelet count between ICU cases (median:142, IQR: 119-202) vs. non-ICU cases (median: 165, IQR: 125-188); p=0.78.
Wu (2020)	201	Platelet counts **did not differ between patients with ARDS** vs. those without ARDS (difference: -4.00, 95%CI: −27.00 to +20.00, p=0.73). Accordingly, no significant difference was noted in dead vs. alive ARDS patients (p=0.10).
Young (2020)	18	Median platelet count was 156 (IQR: 116-217) in patients that required supplemental O_2 and 159 (IQR: 128-213) in those that did not; no statistical comparison was undertaken.
Fan (2020)	69	Low platelets **were not associated with ICU care** either at admission (p=0.67) or as a nadir during hospital stay (p=0.69)
Yang (2020)	52 critically ill patients	Platelet count noted in non-survivors was 191 (63) and 164 (74) in survivors; no statistical tests were presented.
Arentz (2020)	21 ICU patients	Mean baseline platelet count was 235 (ranging between 52 and 395), whereas the reference range was 182-369 × 10^9/L
Zhou (2020)	191	Median platelet count was **lower in non-survivors** (165.5, IQR: 107.0–229.0) vs. survivors (220.0, IQR: 168.0–271.0), p<0.0001
Lippi (2020)	9 published studies	Platelet count was significantly **lower in patients with more severe COVID-19** (WMD -31×10^9/L, 95% CI, -35 to -29×10^9/L), with very high heterogeneity

Terpos E et al. Am J Hematol. 2020.

Procalcitonin, ferritin and C-reactive protein

- **More severe cases** showed a more marked increase compared with the non-severe ones (81.5% versus 56.4% for **CRP**, 13.7% versus 3.7% for **procalcitonin** and 58.1% versus 37.2% for **LDH**).
- In a retrospective cohort study including 191 patients with COVID-19 from Wuhan, China, **non-survivors**, as compared with survivors, presented more often with high **LDH** ($p<0.0001$), high **procalcitonin** ($p<0.0001$), increased serum **ferritin** levels ($p=0.0008$) and elevated **IL-6** ($p<0.0001$).
- Higher **CRP** has been linked to unfavorable aspects of COVID-19 disease, such as **ARDS development, higher troponin-T levels and myocardial injury, and death**.
- A meta-analysis of four published studies showed that increased **procalcitonin** values were associated with a nearly 5-fold higher risk of severe infection (OR=4.76; 95% CI: 2.74-8.29, $I^2=34\%$) .
- Wu et al. showed that higher serum **ferritin** was associated with **ARDS** development (HR=3.53, 95%CI: 1.52-8.16, p=0.003)

Terpos E et al. Am J Hematol. 2020.

Coagulation parameters
Elevated D-dimers

First author (year)	Sample size	Main findings
Guan (2020)	1099	Patients with the composite primary endpoint (**admission to an intensive care unit, use of mechanical ventilation, or death**) presented with elevated D-dimer more frequently: 69.4% (34/49) vs. 44.2% (226/511; p=0.001). Accordingly, **severe cases** presented elevated D-dimer more frequently (59.6%, 65/109) vs. non-severe cases (43.2%, 195/451); p=0.002
Huang (2020)	41	Patients necessitating **ICU care** presented with higher D-dimer levels (median: 2.4; IQR: 0.6-14.4) vs. non-ICU patients (median: 0.5, IQR: 0.3-0.8), p=0.0042.
Wang (2020)	138	**ICU cases** presented with higher D-dimer level (median:414, IQR: 191-1324) vs. non-ICU cases (median: 166, IQR: 101-285); p<0.001. Longitudinal increase was noted in non-survivors.
Wu (2020)	201	Higher D-dimer level was associated with **ARDS development** (HR=1.03, 95%CI: 1.01-1.04, p<0.001) and **poor survival** (HR=1.02, 95%CI: 1.01-1.04, p=0.002) in the incremental models.
Zhou (2020)	191	Higher D-dimer was associated with **higher odds of death** (OR=18.42, 95%CI: 2.64–128.55; p=0.0033)
Lippi (2020)	553 (4 published studies)	D-dimer values were considerably higher in COVID-19 patients with **severe disease** than in those without (WMD= 2.97mg/L; 95% CI: 2.47–3.46 mg/L).

Terpos E et al. Am J Hematol. 2020.

Hematological Findings in French Patients

	Normal range	Non-ICU patients (n=223)	ICU patients (n=77)	P
Age (years)	NA	66 (53-76)	62 (53-70)	<0.040
PT (sec)	<13.6 sec	14.0 (13.3-15.0)	14.6 (13.8-15.7)	0.002
Fibrinogen (g/L)	1.8 – 4.0	5.9 (4.7-7.0)	6.9 (6.0-7.7)	<0.0001
D-dimer (ng/mL)	<500 for age under 60 years	1228 (650-2031)	2168 (1074-4219)	<0.0001
Antithrombin (%)	80 - 120	96 (84-107)	87 (75-99)	0.0001
Protein C (%)	70 - 130	97 (79-112)	89 (72-100)	0.005
Red blood cells ($x10^9$/L)	4.0 - 5.2	4.3 (4.0-4.8)	4.2 (3.5-4.6)	0.028
Hemoglobin (g/dL)	12.0 - 16.0	12.6 (11.3-13.7)	11.9 (10.1-13.2)	0.005
Hematocrit (%)	35.0 - 47.0	37.2 (34.2-40.3)	34.8 (30-38.7)	0.002
Platelets ($x10^9$/L)	150 - 400	240 (176-307)	211 (154-261)	0.004
White blood cells ($x10^9$/L)	4.0 - 10.0	6.7 (5.1-8.8)	7.9 (6.1-10.8)	0.007
Neutrophils ($x10^9$/L)	1.5 - 7.0	5.0 (3.4-6.7)	6.6 (4.9-9.6)	0.0001
Lymphocytes ($x10^9$/L)	1.5 - 4.0	1.04 (0.70-1.49)	0.74 (0.52-1.10)	0.0001
Monocytes ($x10^9$/L)	0.1 - 1.0	0.49 (0.30-0.69)	0.31 (0.20-0.48)	<0.0001
Eosinophils ($x10^9$/L)	0.03 - 0.7	0.02 (0-0.07)	0.01 (0-0.05)	0.126
Basophils ($x10^9$/L)	<0.1	0.01 (0.01-0.02)	0.01 (0.01-0.02)	0.290

Gerotziafas et al. Lancet 2020 (submitted)

COMPASS-COVID-19 risk assessment model (RAM) for prediction to ICU admission

Predictors	OR (95%CI)	p
Obesity (BMI≥30 versus BMI<30 kg/m^2	6.56 (2.98-14.46)	<0.001
Gender Male versus female	2.59 (1.29-5.21)	0.007
DIC ISTH score ≥5 versus <5	2.58 (1.07-6.21)	0.034
Lymphocytes (x10^9/L) <1 versus ≥1	2.21 (1.17-4.19)	0.015
Hemoglobin (g/dL) <11 versus ≥11	2.25 (1.13-4.48)	0.021

COMPASS-COVID-19 RAM	
Predictors for risk of worsening disease	Score
Obesity (BMI>30)	19
Male gender	10
DIC-ISTH score ≥5	9
Lymphocytes <10^9/L	8
Hemoglobin <11 g/dL	8
Total ≥ 18 : high risk for worsening disease	– –

Validation of the COMPASS-COVID-19 risk assessment model

The validation cohort included 120 patients stratified at the C-group (n=89) and the W-group (n=31).

The score at 18 points cut-off value identified as high risk for disease worsening 90% of patients at the W-group and 38% of the patients at the C-group.

The sensitivity and the specificity of the score were 94% and 58% respectively and the negative and positive predictive values were 96% and 45% respectively.

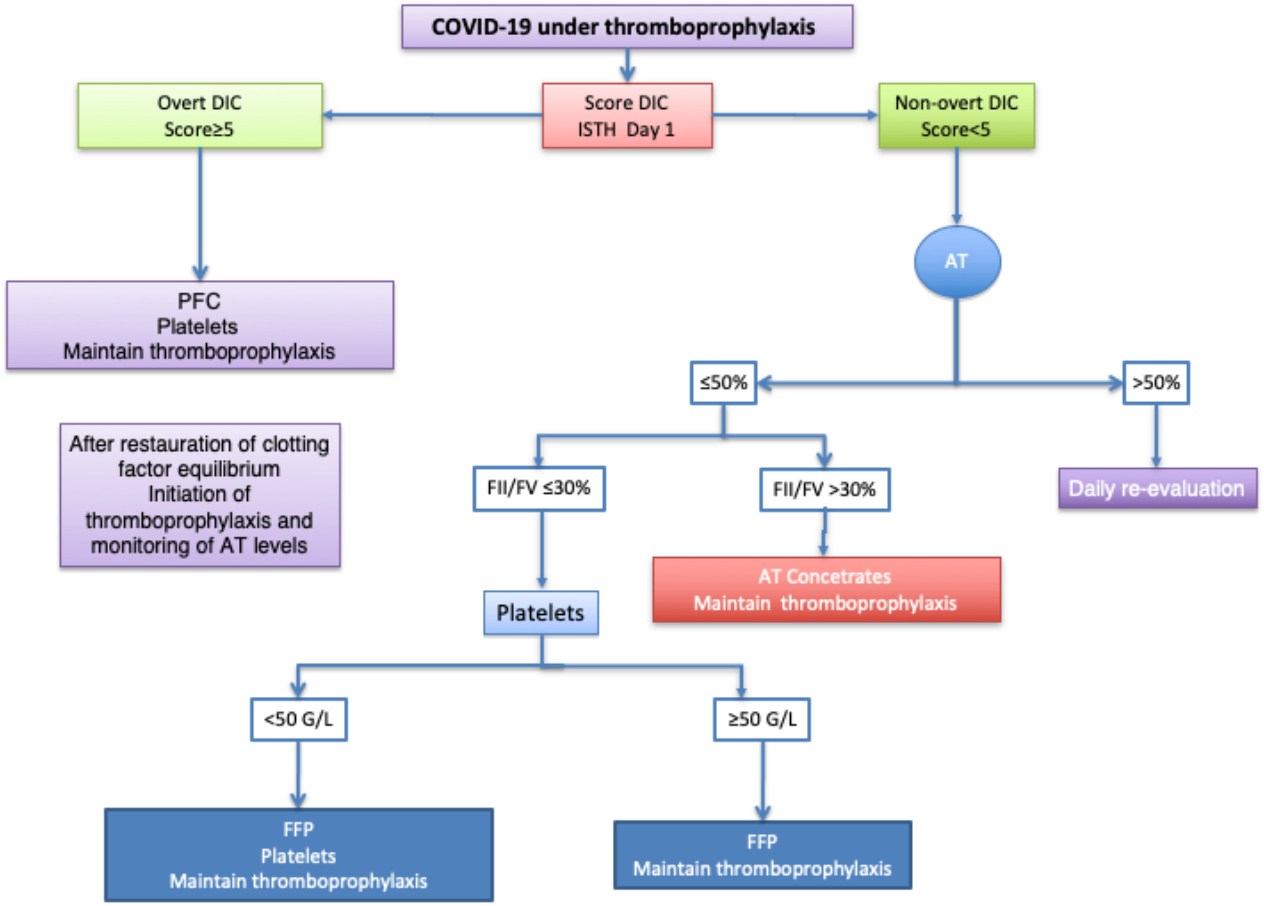
Gerotziafas et al. Lancet 2020 (submitted)

ISTH score for overt DIC

Factors	Points	ISTH Overt DIC
Platelet counts	3	–
	2	$<50 \times 10^9$/L
	1	$\geq 50, <100 \times 10^9$/L
FDP	3	Strong increase
	2	Moderate increase
	1	–
Prothrombin time[a]	2	≥ 6 seconds
	1	$\geq 3, <6$ seconds
Fibrinogen	1	<100 g/mL
SIRS score	1	–
Points required to be criteria positive		5 points

Wada H et al. doi: 10.1111/jth.12155.

Disseminated intravascular coagulopathy (DIC)



FFP: Fresh frozen plasma; AT: antithrombin

Terpos E et al. Am J Hematol 2020 doi: 10.1002/ajh.25829.

VTE risk – Padua Prediction Score

	Padua Prediction Score <4 (n=619)	Padua Prediction Score ≥4 (n=407)	OR (95% CI)*	p value*
High bleeding risk†	7 (1%)	44 (11%)	8·51 (3·74–19·35)	<0·0001
Intensive care unit admission	5 (1%)	47 (12%)	12·82 (5·00–32·91)	<0·0001
Mechanical ventilation	6 (1%)	57 (14%)	13·17 (5·56–31·19)	<0·0001
Mortality	0 (0%)	14 (3%)	–	–
Age, years	42 (33–55)	52 (40–64)	–	<0·0001
≥70‡	19 (3%) of 559	56 (15%) of 384	4·85 (2·83–8·31)	<0·0001

Data are n (%) or median (IQR). *Adjusted by age. †Bleeding risk was evaluated according to a previous study.[7] ‡A threshold of 70 years was selected on the basis of the Padua Prediction Score and age data were not available for all patients.

Table: Bleeding score, outcomes, and age of patients with COVID-19 with high and low risk of venous thromboembolism according to the Padua Prediction Score

Wang T et al. Lancet Haematol. 2020 May;7(5):e362-e363.

VTE Prophylaxis for Patients with COVID-19

- All in-patients should have VTE risk assessment : on admission and if condition changes
- All in-patients should have LMWH prophylaxis with enoxaparin, irrespective of mobility, unless contraindicated.
- Choose the dose of prophylactic LMWH according to body weight and renal function.
- Mild prolongation of PT and/or APTT only, if due to COVID coagulopathy, is NOT a contraindication to LMWH prophylaxis.
- Do not administer prophylactic LMWH if platelets < 25 or Clauss fibrinogen < 0.8g/l or active bleeding occurring.
- If there is an unexplained 50% fall in platelet count in the absence of worsening coagulopathy, consider HIT (Heparin Induced Thrombocytopenia). Carry out a 4Ts score and seek haematology advice.
- Do not give additional prophylactic LMWH to patients continuing oral anticoagulation prescribed prior to admission.

NHS Guidance on Covid Coagulopathy. Version 2.4 01/05/2020

Covid-19 coagulation disorders Management

- 1) Early diagnosis and follow-up of DIC, by applying the (ISTH score prognosis, appropriate critical care support).
- 2) Identification of patients at high risk.
- 3) Optimization of thromboprophylaxis regimen; **LMWH are the first line choice drug.**
- 4) The anti-inflammatory properties of LMWH may be an added benefit in COVID-19 patients in order to regulate the complex 'immunothrombosis' process.

Terpos E et al. Am J Hematol. 2020 Apr 13. doi: 10.1002/ajh.25829.

Ευχαριστώ για την προσοχή σας

COVID-19 pandemia: dilemmas and challenges for cardiologist in the ER

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Professor of Cardiology
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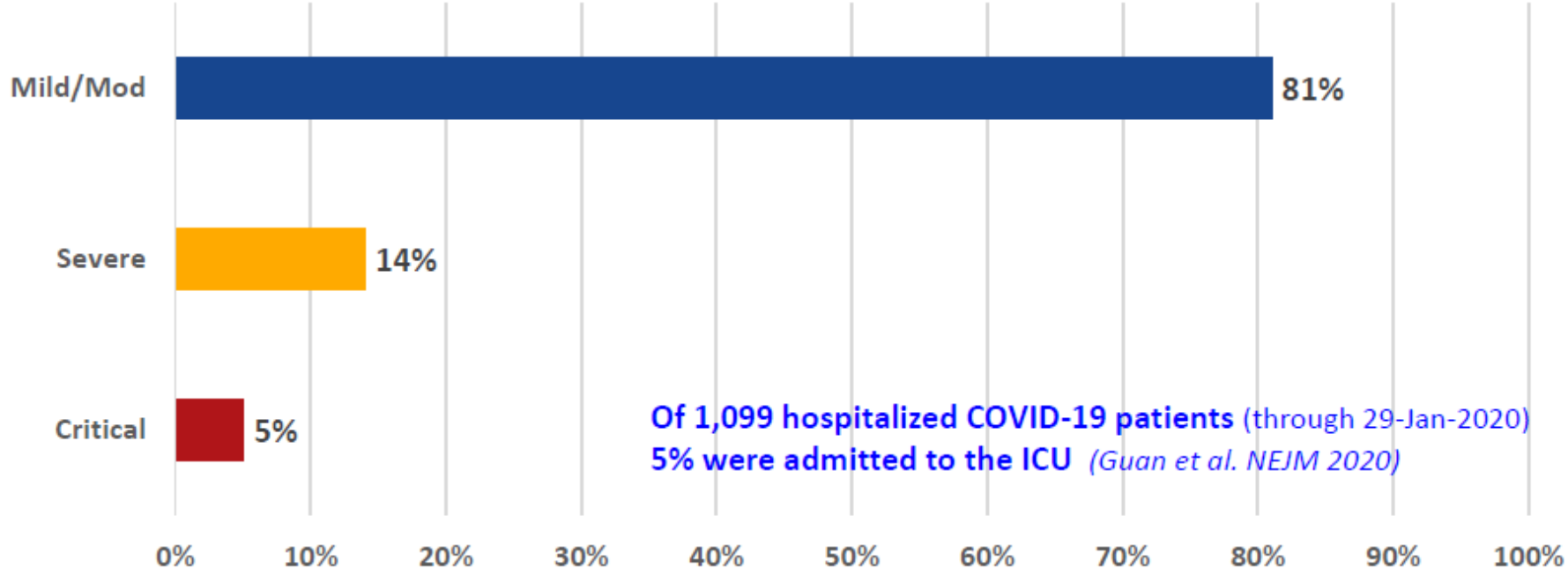
Most patients had mild to moderate disease, but nearly 20% had severe or critical illness

COVID-19 - China through 11-Feb-2020 (N=44,415)



Of 1,099 hospitalized COVID-19 patients (through 29-Jan-2020)
5% were admitted to the ICU *(Guan et al. NEJM 2020)*

Links: *Wu JAMA 2020*

Early Cardiac Implications From Case Reports on COVID-19

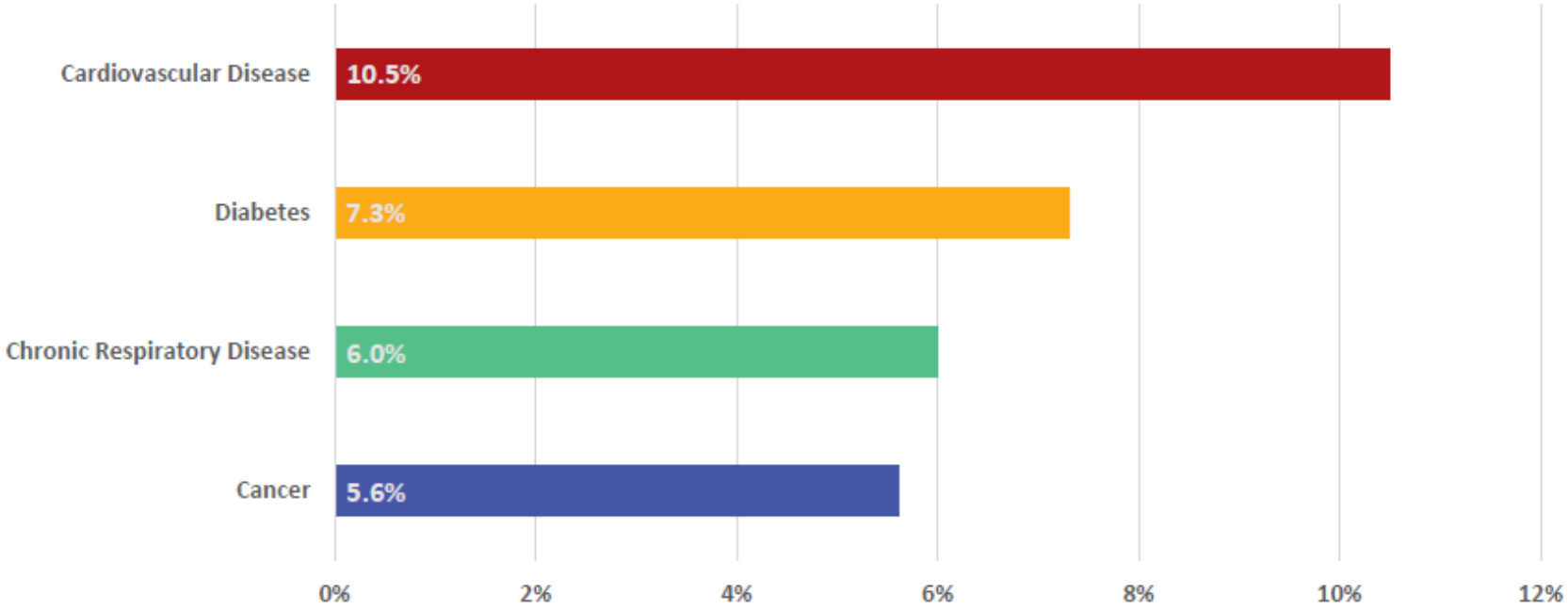
- In the most recent large-scale reporting from China CDC, 25% of patients with complete medical histories have comorbidities, the majority of which are cardiovascular- or diabetes-related; while lower than initial reports, 53% of all COVID-19 confirmed patients in the study were missing documentation of underlying conditions[xii]
- Overall the case mortality rate remains low at 2.3%; however, the mortality rate jumps to 6% in hypertensives, 7.3% in diabetics, 10.5% in patients with cardiovascular disease, and 14.8% for patients ≥ 80 years of age[xii]
- Notably, the case mortality rate for underlying cardiovascular disease (10.5%) is greater than in patients with underlying chronic respiratory disease (6.3%)

AMERICAN COLLEGE of CARDIOLOGY

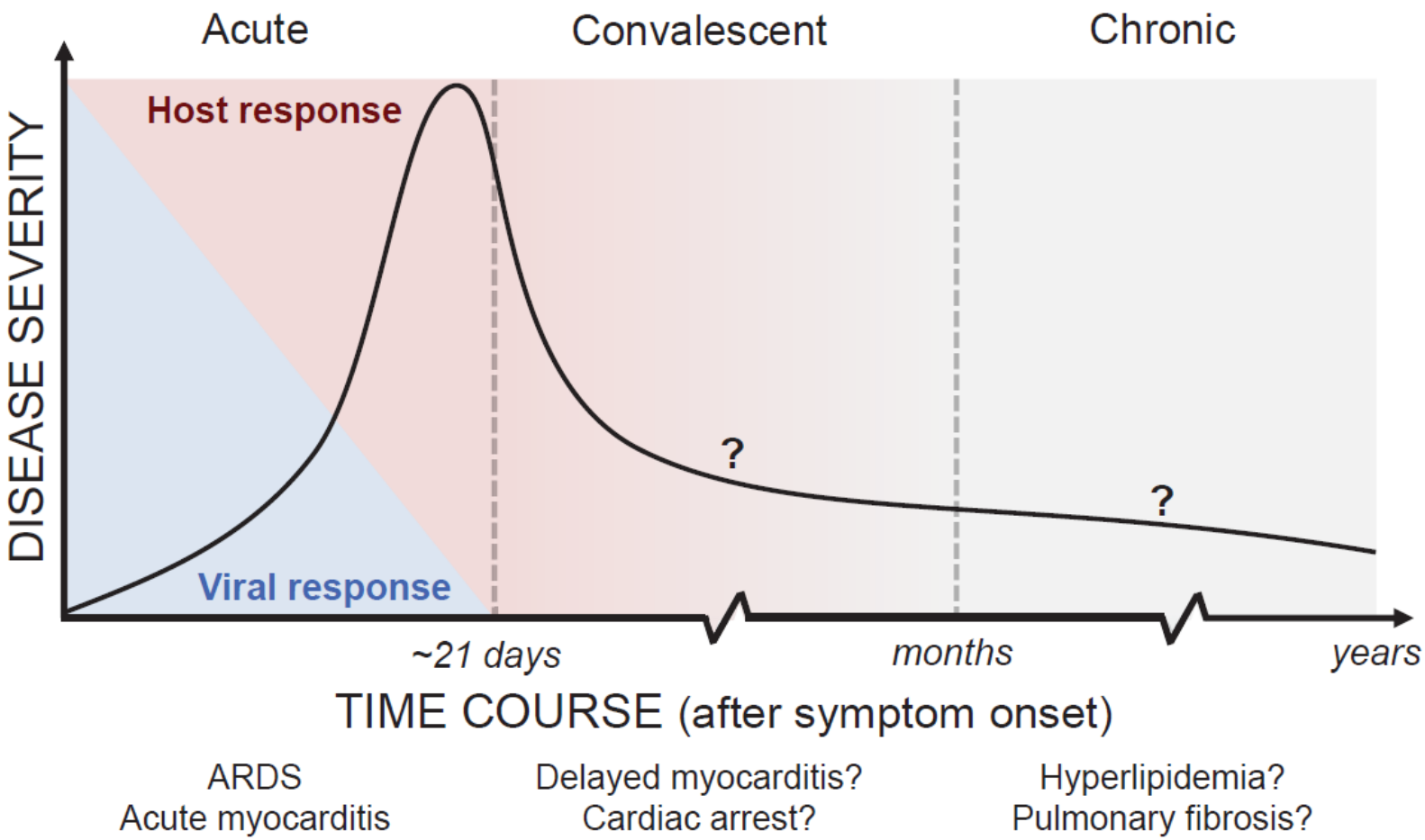
ACC Clinical Bulletin
Cardiac Implications of Novel Coronavirus (COVID-19)

Mortality from COVID-19 is highest among persons with underlying medical conditions

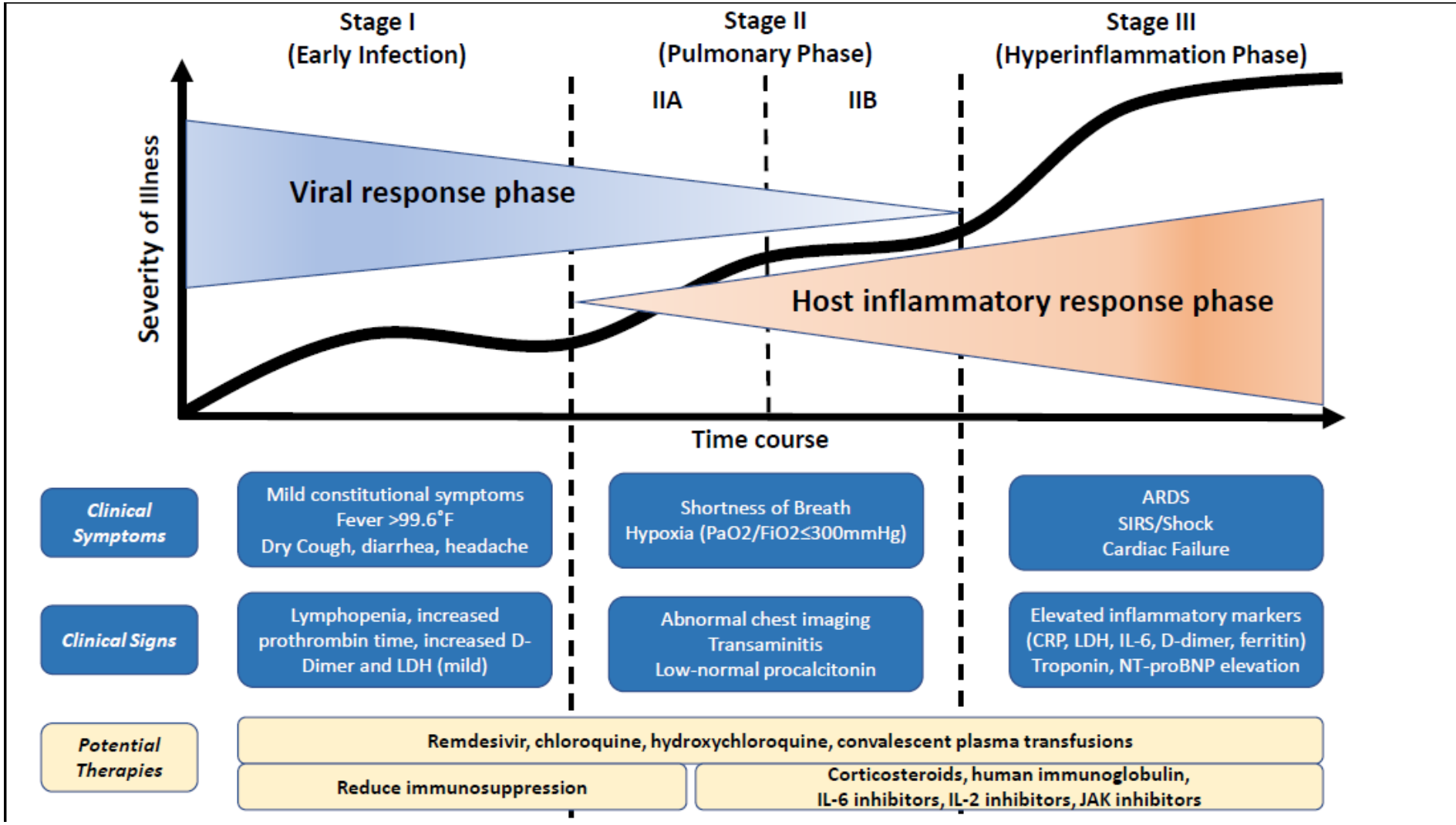
COVID-19 - China through 11-Feb-2020



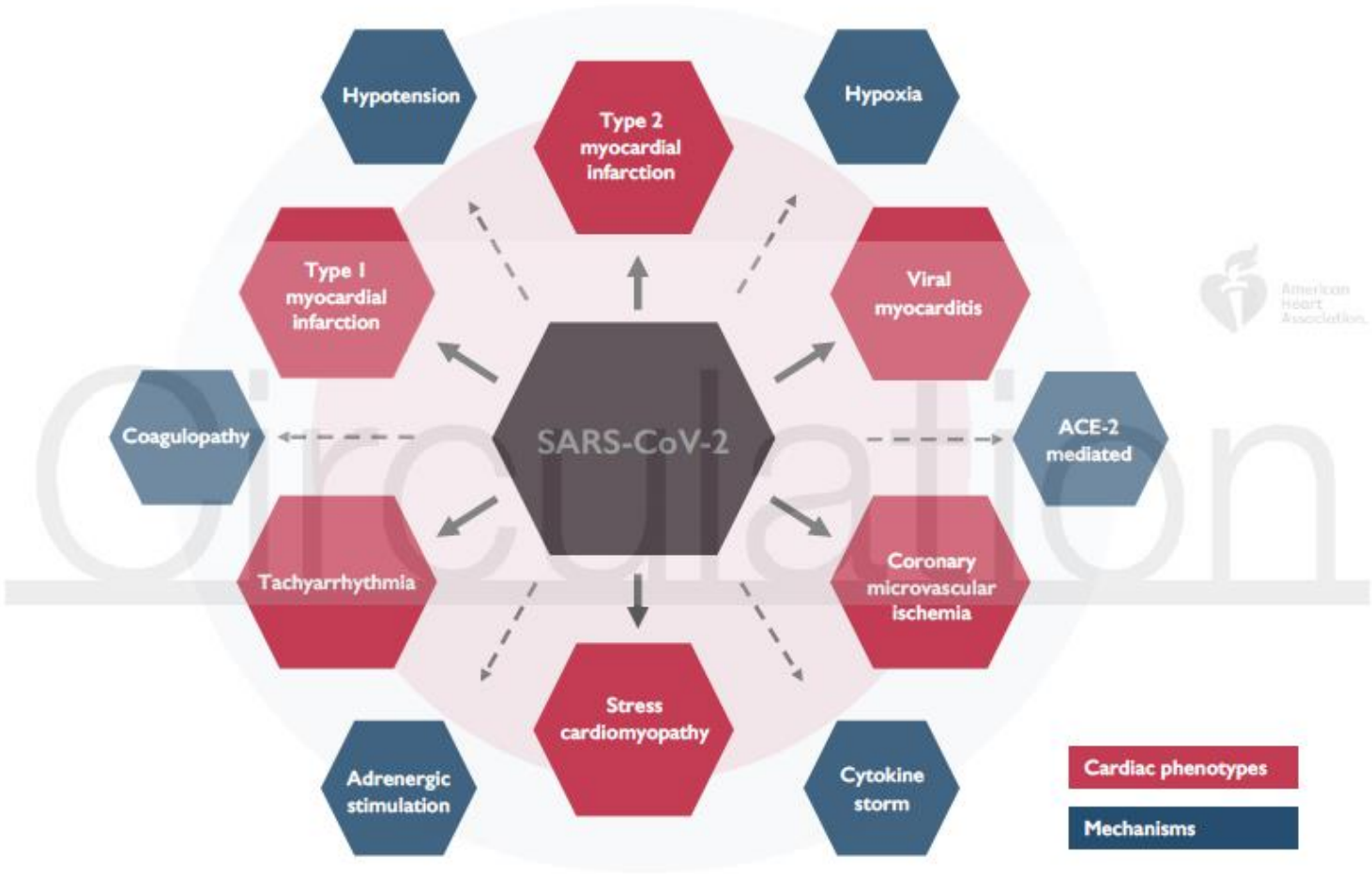
Link: China COVID-19 Epi Team 2020


Acute
Convalescent
Chronic
Host response
Viral response
DISEASE SEVERITY
?
?
~21 days
months
years
TIME COURSE (after symptom onset)
ARDS
Acute myocarditis
Delayed myocarditis?
Cardiac arrest?
Hyperlipidemia?
Pulmonary fibrosis?

COVID-19 Illness in Native and Immunosuppressed States:



Potential mechanisms of acute myocardial injury in COVID-19 and related cardiac phenotypes



10.1161/CIRCULATIONAHA.120.047008

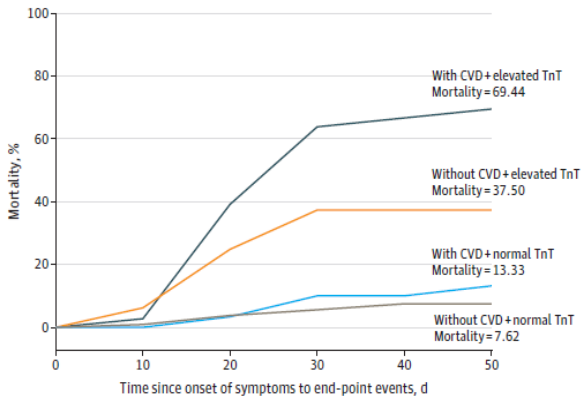
Cardiovascular complications in coronavirus disease

Manifestation	Incidence	Remarks
Acute cardiac injury* (most commonly defined as elevation of cardiac troponin I above 99th percentile upper reference limit)	8–12% on average [10]	• Most commonly reported cardiovascular abnormality • Can result from any of the following mechanisms- •Direct myocardial injury •Systemic inflammation •Myocardial oxygen demand supply mismatch •Acute coronary event •Iatrogenic • Strong adverse prognostic value
Acute coronary event	Not reported, but appears to be low	Potential mechanisms- • Plaque rupture due to inflammation/increased shear stress • Aggravation of pre-existing coronary artery disease
Left ventricular systolic dysfunction	Not reported	Any of the causes of myocardial dysfunction mentioned above can lead to acute left ventricular systolic dysfunction
Heart failure	Reported in one study- 52% in those who died, 12% in those who recovered and were discharged [5]	• Any of the causes of myocardial dysfunction mentioned above can lead to acute heart failure • Increased metabolic demand of a systemic disease can cause acute decompensation of pre-existing stable heart failure
Arrhythmia	16.7% overall; 44.4 in severe illness, 8.9% in mild cases [8]	Both tachyarrhythmia and bradyarrhythmia can occur but exact nature not described
Potential long-term consequences	Too early to assess	Too early to ascertain for coronavirus disease 2019. However, patients recovering from a similar earlier illness- Severe Acute Respiratory Syndrome- continued to have long-term abnormalities of lipid and glucose metabolism and of cardiovascular homeostasis [12]

Diabetes & Metabolic Syndrome: Clinical Research & Reviews 14 (2020) 247–250

Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19)

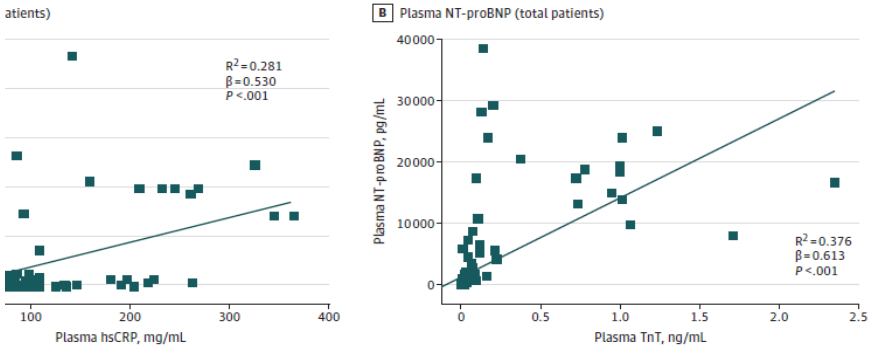
Figure 2. Mortality of Patients With Coronavirus Disease 2019 (COVID-19) With/Without Cardiovascular Disease (CVD) and With/Without Elevated Troponin T (TnT) Levels



No. at risk

Without CVD + normal TnT (n = 105)	102	86	41	10	0
Without CVD + elevated TnT (n = 16)	15	12	7	1	0
With CVD + normal TnT (n = 30)	29	25	10	4	0
With CVD + elevated TnT (n = 36)	34	20	8	2	0

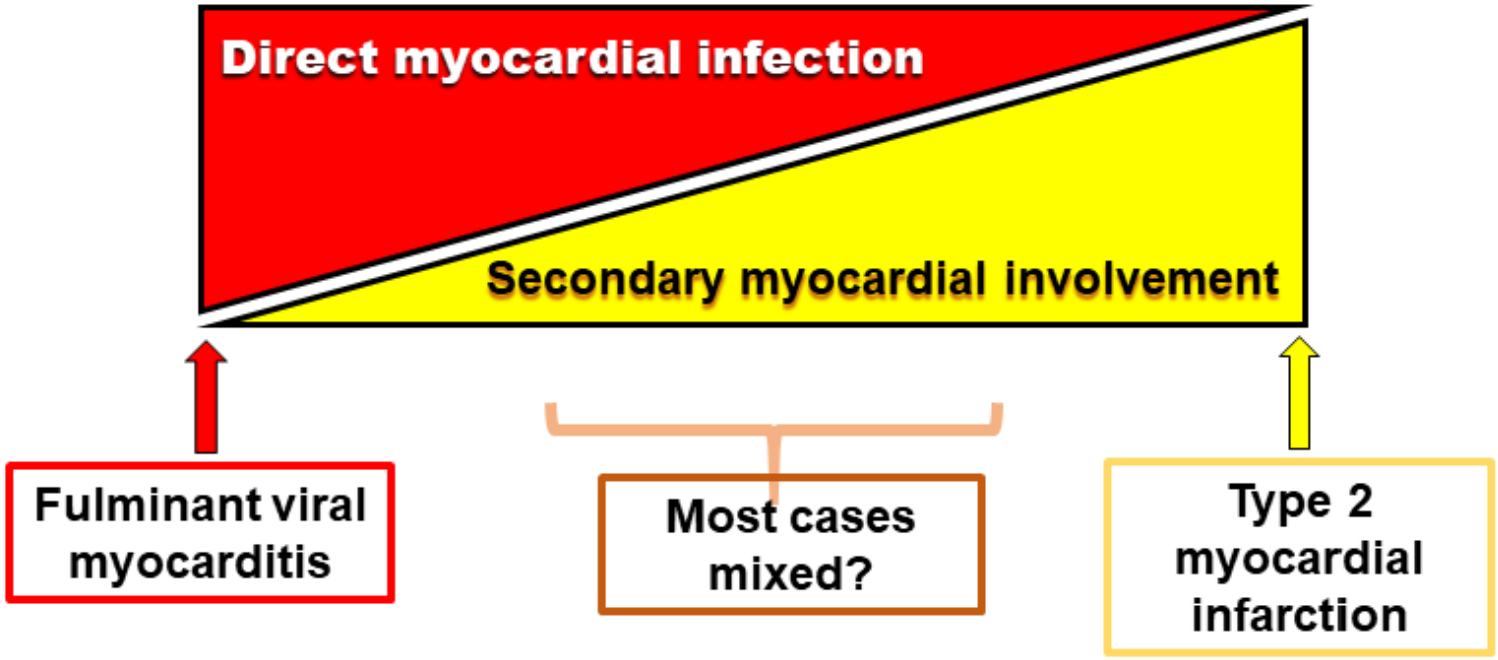
tween Plasma TnT and NT-proBNP With hsCRP



high-sensitivity C-reactive protein levels (hsCRP), and N-terminal pro–brain natriuretic peptide (NT-pro BNP) collected on admission.

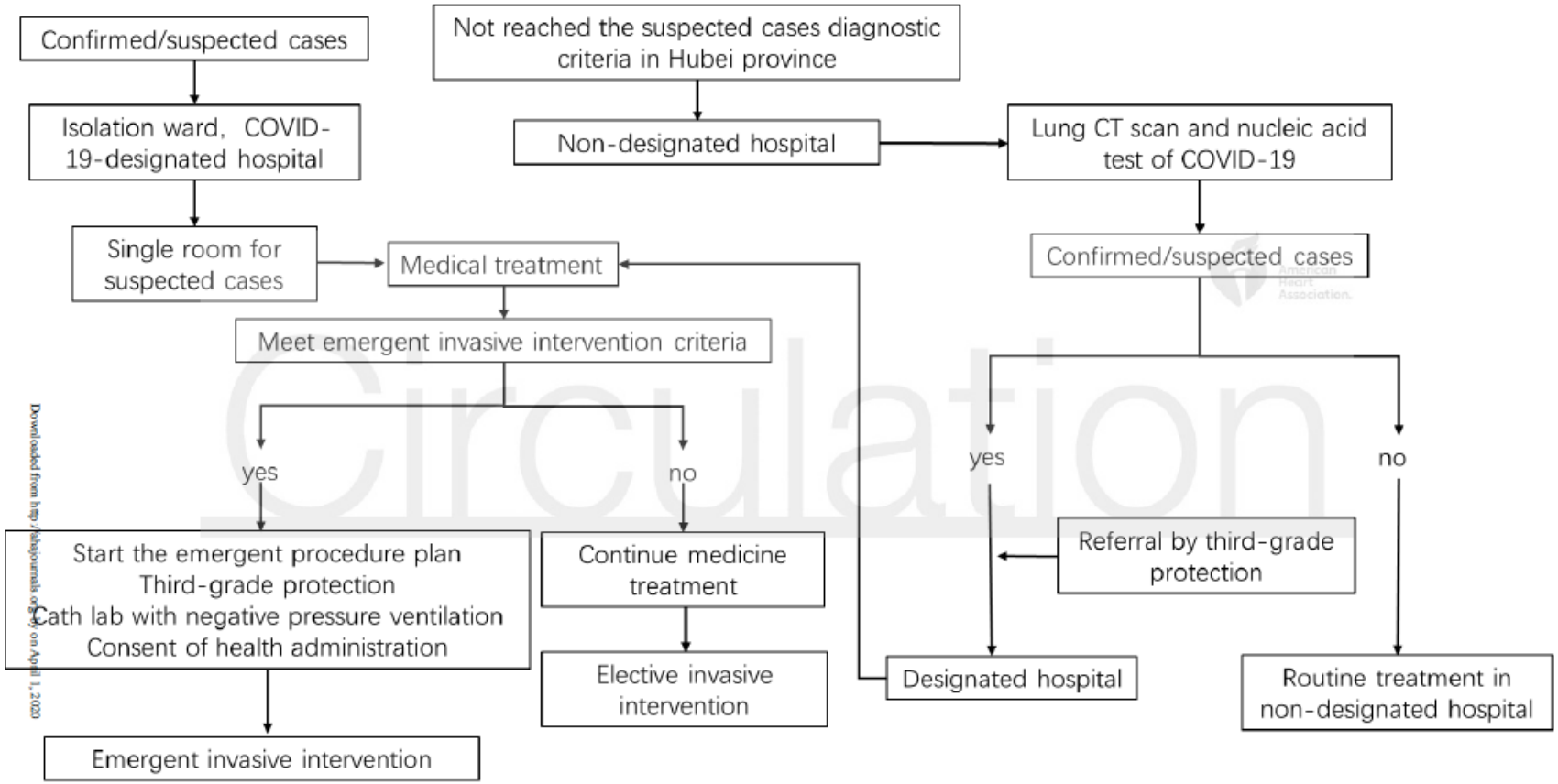
JAMA Cardiology Published online March 27, 2020

The Heart in COVID19: Primary Target or Secondary Bystander?



JACC: Basic to Translational Science 2020

CSC Expert Consensus on Principles of Clinical Management of Patients with Severe Emergent Cardiovascular Diseases during the COVID-19 Epidemic



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CSC Expert Consensus on Principles of Clinical Management of Patients with Severe Emergent Cardiovascular Diseases during the COVID-19 Epidemic

Table 1. Patients with severe emergent cardiovascular diseases for whom hospitalization and conservative medical treatment is recommended during COVID-19 epidemic.

Patients with severe emergent cardiovascular diseases
1. Patients with STEMI for whom thrombolytic therapy is indicated[*].
2. STEMI patients presenting after exceeding the optimal window of time for revascularization but yet with worsen symptoms, such as severe chest pain, continuous ST-segment elevation, or myocardial infarction-related mechanical complications.
3. High risk NSTE-ACS patients (GRACE score ≥ 140).
4. Patients with uncomplicated Stanford type B aortic dissection[#].
5. Patients with acute pulmonary embolism.
6. Patients with acute exacerbation of heart failure.
7. Patients with hypertensive emergency.

STEMI, ST-segment elevation myocardial infarction; NSTE-ACS, non-ST elevation acute coronary syndromes; GRACE, Global Registry of Acute Coronary Events.

[*]The third- generation thrombolytic agents are preferred.

[#]For Stanford type A aortic dissection, surgical treatment is recommended.

10.1161/CIRCULATIONAHA.120.047011

CSC Expert Consensus on Principles of Clinical Management of Patients with Severe Emergent Cardiovascular Diseases during the COVID-19 Epidemic

Table 2. Severe cardiovascular diseases requiring urgent or emergent intervention or surgery.

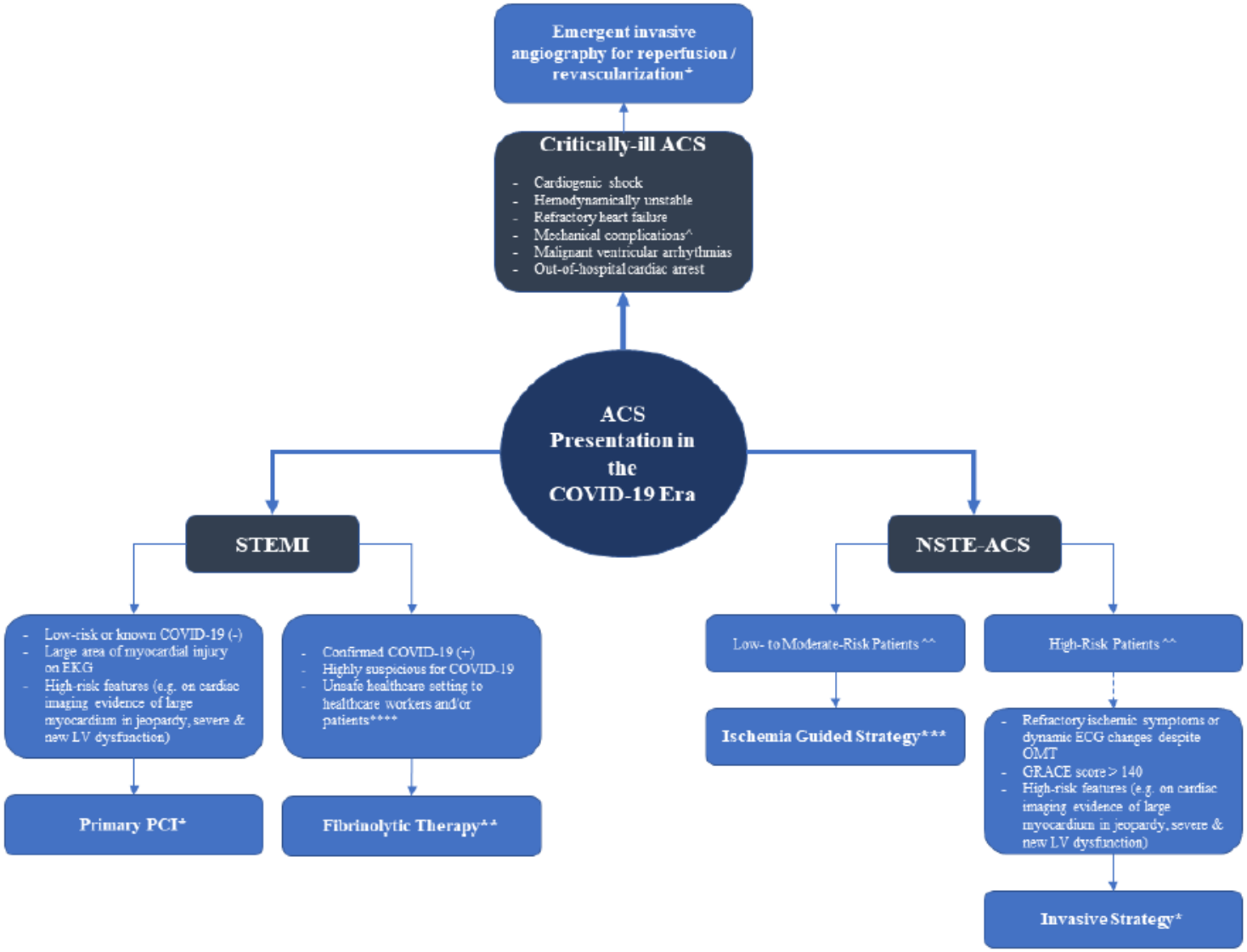
Patients with severe cardiovascular diseases
1. Acute STEMI with hemodynamic instability.
2. Life-threatening NSTEMI indicated for urgent revascularization.
3. Stanford type A or complex Type B acute aortic dissection.
4. Bradyarrhythmia complicated with syncope or unstable hemodynamics mandating implantation of a temporary (bedside implantation as far as possible), or, if indicated, permanent pacemaker.
5. Pulmonary embolism presenting with hemodynamic instability for whom regular intravenous thrombolytic therapy might lead to excessively risk of intracranial bleeding, and trans-catheter low-dose thrombolysis in the pulmonary artery may be required.

STEMI, ST-segment elevation myocardial infarction; NSTEMI, Non-ST segment elevation myocardial infarction.

10.1161/CIRCULATIONAHA.120.047011

Current perspectives on Coronavirus 2019 (COVID-19) and cardiovascular disease: A white paper by the *JAHA* editors

Figure 3. Invasive Therapies for ACS Patients in the COVID-19 Era.



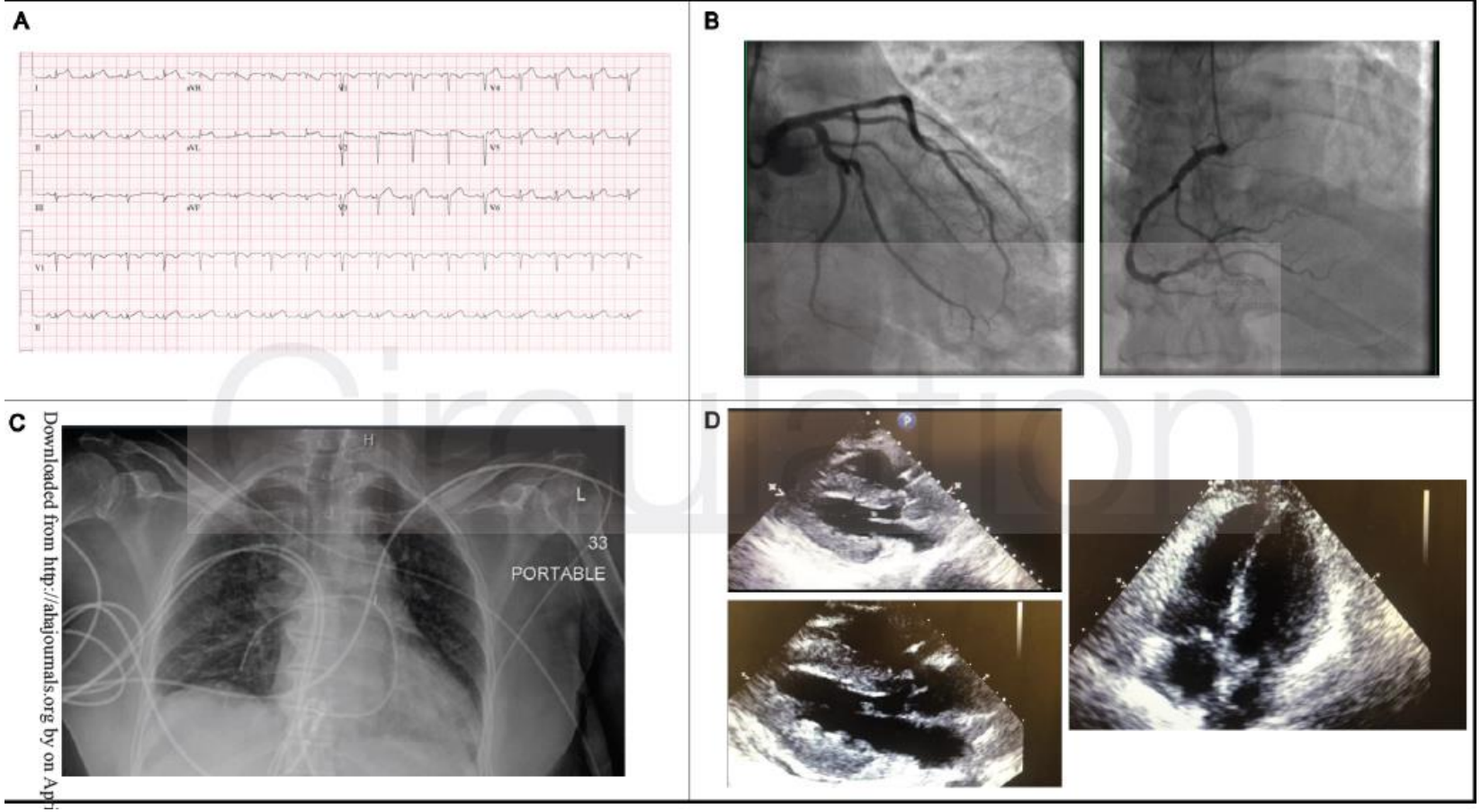


Figure 1. Chest Pain and ST-elevation. Initial electrocardiogram showed sinus tachycardia, low voltage QRS complexes in the limb leads and diffuse ST elevation in leads I, II, aVL and leads V2-V6 (**Panel A**); Coronary angiogram demonstrated mild disease in the left anterior descending artery and left circumflex artery and 40% stenosis in the mid right coronary artery (**Panel B**); Chest radiography demonstrated clear lungs (**Panel C**); Transthoracic echocardiogram with severe increased left ventricular wall thickness and left ventricular ejection fraction approximately 30% with trace circumferential pericardial effusion (**Panel D**).

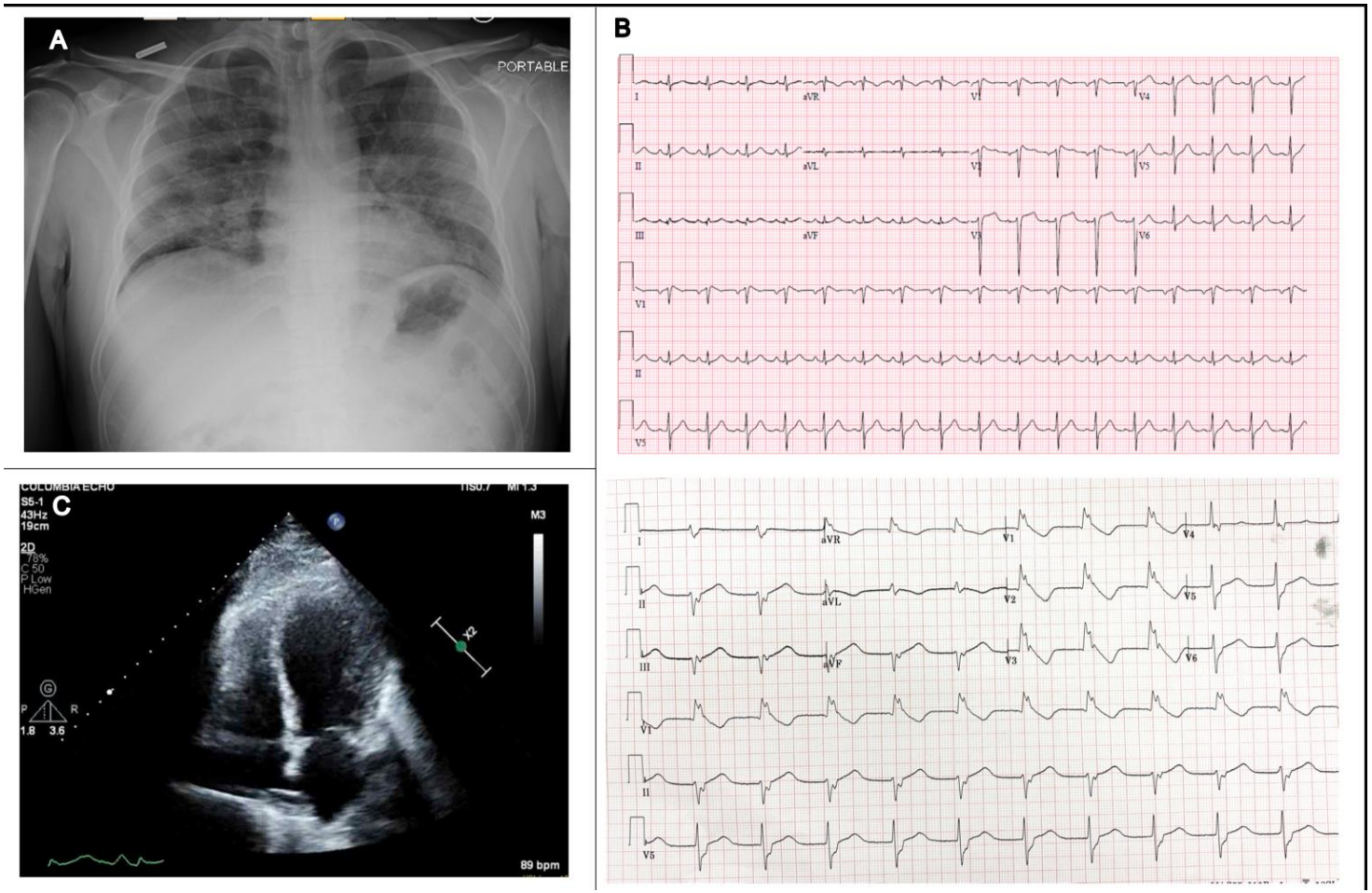


Figure 2. Cardiogenic shock rescued by VAV ECMO. Chest radiograph showed diffuse ill-defined airspace opacities bilaterally (**Panel A**); Initial electrocardiogram (Top) demonstrated sinus tachycardia with incomplete right bundle branch block; Repeat electrocardiogram (Bottom) demonstrated accelerated idioventricular rhythm (**Panel B**); Transthoracic echocardiogram demonstrated left ventricular end-diastolic diameter of 4.5 cm, left ventricular ejection fraction 20-25%, with akinesis of mid left ventricular segments (**Panel C**).

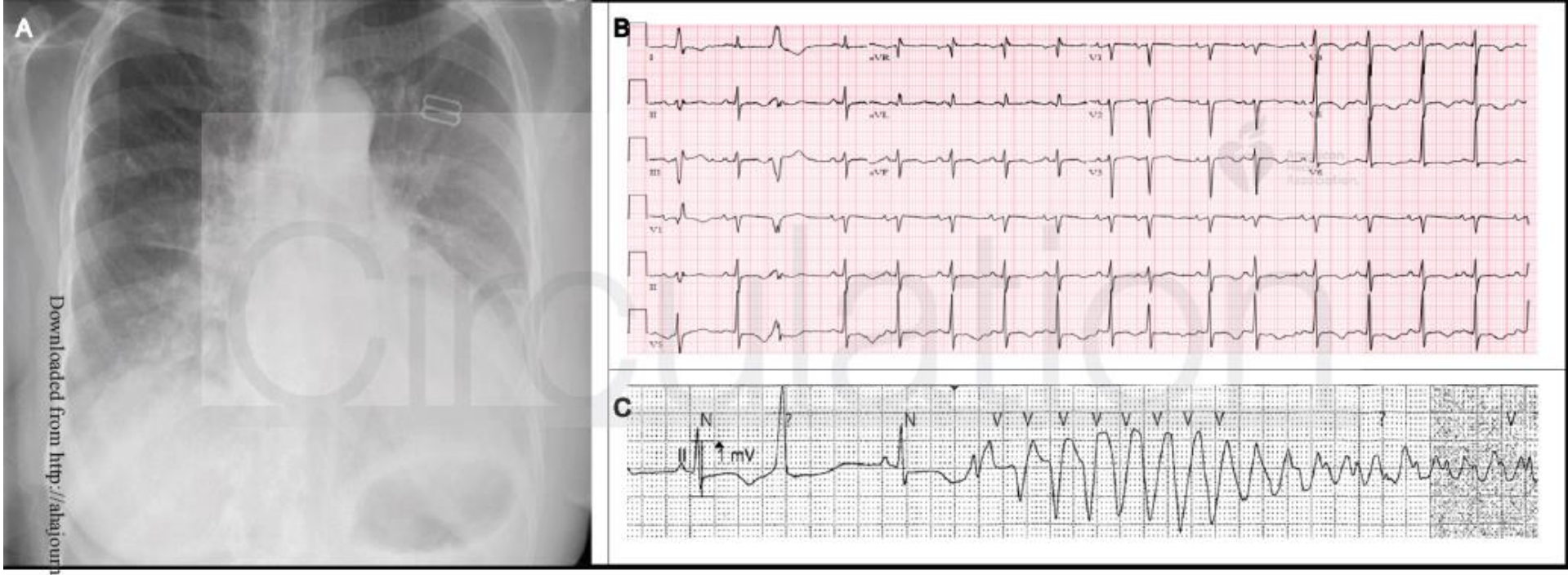


Figure 3. Decompensated Heart Failure. Chest radiography shows pulmonary vascular congestion, patchy airspace opacities at bases and bilateral pleural effusions (**Panel A**); Electrocardiogram shows sinus rhythm with premature atrial and ventricular complexes, lateral T-wave inversions and a prolonged QT interval (**Panel B**). Telemetry strip shows prolonged QT interval and Torsades de Pointes following R-on-T phenomenon (**Panel C**).

The Variety of Cardiovascular Presentations of COVID-19

COVID-19 Associated Cardiovascular Disease

ST Segment Elevation

- Myopericarditis should be strongly considered in patient with chest pain, ECG changes, and biomarker elevation. Maintain a low threshold to assess for cardiogenic shock in this setting
- Use bedside TTE and possibly CCTA to triage cases prior to cardiac catheterization, Consider a conservative strategy in appropriately selected cases
- Consider bedside pulmonary artery catheterization and bedside IABP placement. IABP may be preferred device for cardiogenic shock due to lower management requirements
- Even if clinical presentation is dominated by cardiac manifestations and there is no no fever, COVID-19 should be in differential

Cardiogenic Shock

- Myocardial dysfunction may be caused by direct injury by virus or secondary to cytokine storm
- ECMO provides circulatory (VA) and respiratory support (VV). Low flows on VA ECMO may be sufficient
- Stabilization and recovery of profound cardiac dysfunction related to COVID-19 is possible with temporary mechanical circulatory support
- ECMO requires high resource utilization and should be used judiciously during the COVID-19 pandemic

Decompensated Heart Failure

- Preexisting cardiac conditions (congestive heart failure, atrial fibrillation, hypertension) may be exacerbated by COVID-19
- Invasive hemodynamic monitoring may be beneficial in select cases to manage both cardiac and respiratory failure
- The use of QT-prolonging agents (azithromycin, hydroxychloroquine) should be closely monitored in patients with underlying cardiomyopathies

Heart Transplant Recipient

- Heart transplant recipients exhibit similar symptoms of COVID-19 infection as non-transplant population
- Consider holding anti-metabolite (mycophenolate mofetil or azathioprine) in patients requiring hospitalization for COVID-19 infection
- COVID-19 pandemic imposes challenging decisions for heart transplant programs, including maintaining safety of heart failure patients on waitlist and safety of post-transplant patients

10.1161/CIRCULATIONAHA.120.047164

Cardiac Ultrasound Evaluation of COVID-19 Patients

COVID-19
Suspected or Confirmed

YES

Cardiac Symptoms And/Or Hypotension

NO → **Consider NO Cardiac Ultrasound**

YES

CARDIAC Ultrasound
with Troponin, BNP and EKG

Tamponade

- **Pericardial Effusion**
- **RV Diastolic Collapse**
- **RA Systolic Collapse**
- **IVC Dilated and Noncollapsible**
- EKG: electrical alternans

STEMI:

- **Regional Wall Motion Abnl**
- EKG (STEMI especially Inf/Lat Leads)
- Trop Elevation

Myocarditis

- **Decreased Global LV EF**
- **IVC Dilated and Noncollapsible**
- Trop Elevation
- BNP Elevation

Pericarditis

- **Pericardial Effusion**
- **Thickened Pericardium**
- EKG: diffuse STE or PR depression

Massive Pulmonary Embolism

- **McConnell's Sign**
- **RV/LV ratio >1.0**
- **Flattened Intraventricular Septum (D-Sign)**
- **IVC Dilated and Noncollapsible**
- EKG: sinus tach, S1Q3T3
- Trop elevation
- BNP elevation

Myopericarditis

- **Findings of Myocarditis and Pericarditis**

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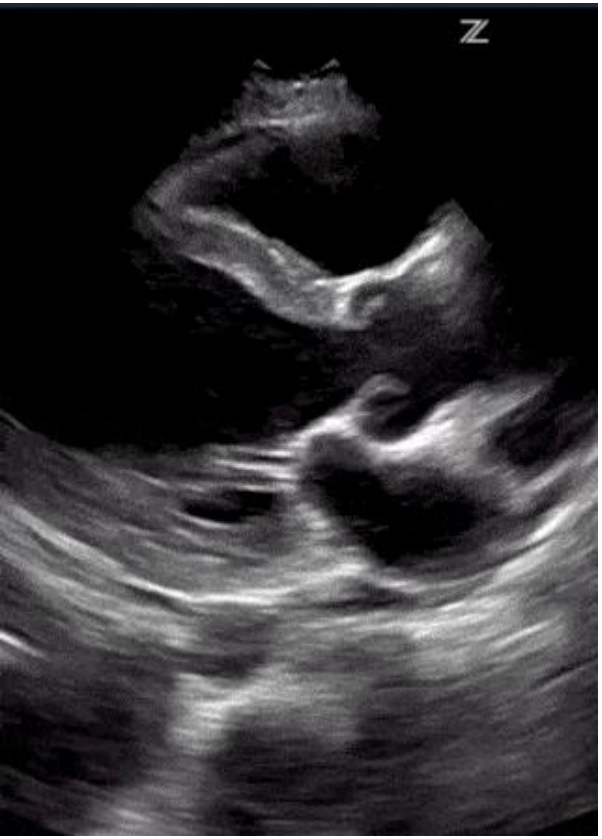
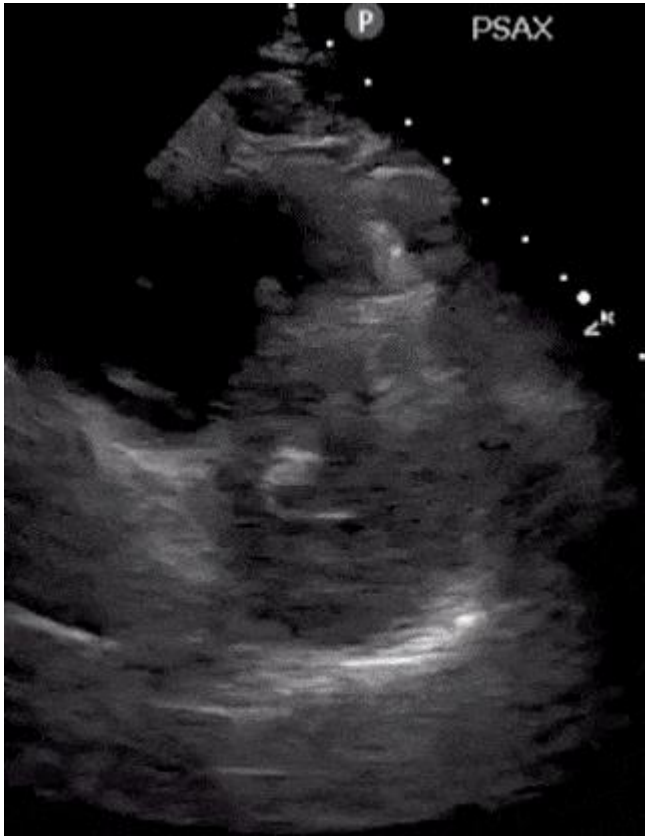
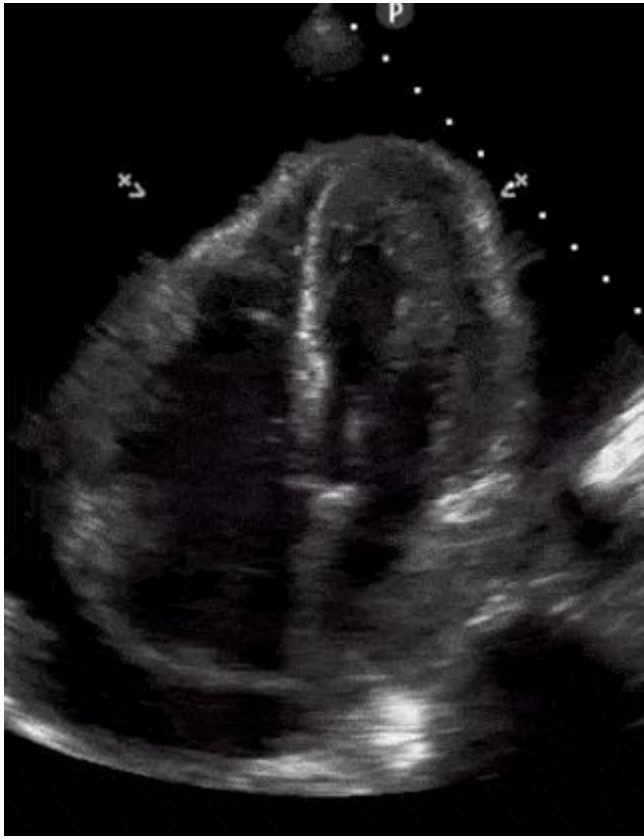
ECHO Images







Findings of lung ultrasonography of novel corona virus pneumonia during the 2019–2020 epidemic

Qian-Yi Peng[1], Xiao-Ting Wang[2*], Li-Na Zhang[1*] and Chinese Critical Care Ultrasound Study Group (CCUSG)

Table 1 CT and ultrasonographic features of COVID-19 pneumonia

Lung CT	Lung ultrasound
Thickened pleura	Thickened pleural line
Ground glass shadow and effusion	B lines (multifocal, discrete, or confluent)
Pulmonary infiltrating shadow	Confluent B lines
Subpleural consolidation	Small (centomeric) consolidations)
Translobar consolidation	Both non-translobar and translobar consolidation
Pleural effusion is rare.	Pleural effusion is rare
More than two lobes affected	Multilobar distribution of abnormalities
Negative or atypical in lung CT images in the super-early stage, then diffuse scattered or ground glass shadow with the progress of the disease, further lung consolidation	Focal B lines is the main feature in the early stage and in mild infection; alveolar interstitial syndrome is the main feature in the progressive stage and in critically ill patients; A lines can be found in the convalescence; pleural line thickening with uneven B lines can be seen in patients with pulmonary fibrosis

Intensive Care Med
https://doi.org/10.1007/s00134-020-05996-6

Initial Ultrasound Evaluation of COVID-19 Patients

COVID-19
Suspected or Confirmed

YES

Vital Signs Normal?

YES → **STOP!**
NO Ultrasound
(Consider *Discharge*)

NO

LUNG + CARDIAC Ultrasound

*Appropriate PPE and Disinfection of US Machines

DDX:

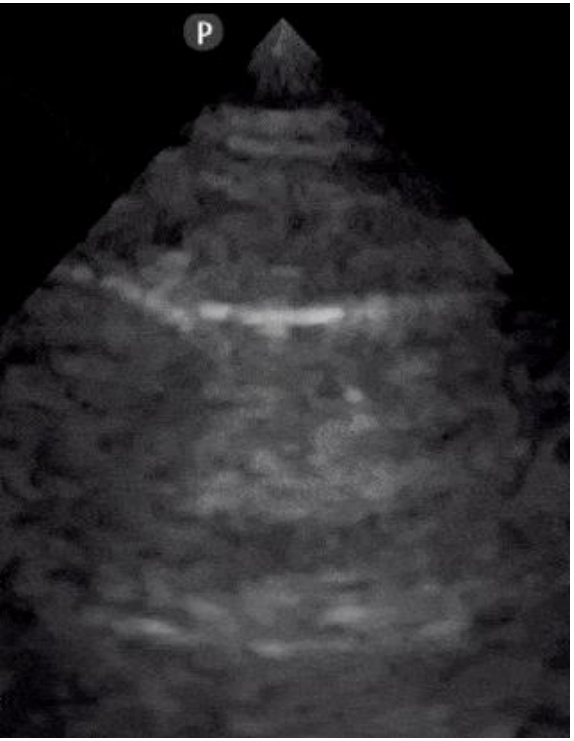
- COVID-19
- Other Viral PNA
- Bac PNA
- Tamponade
- PE
- CHF
- PTX
- COPD
- Hypovolemia

Start Appropriate Treatment

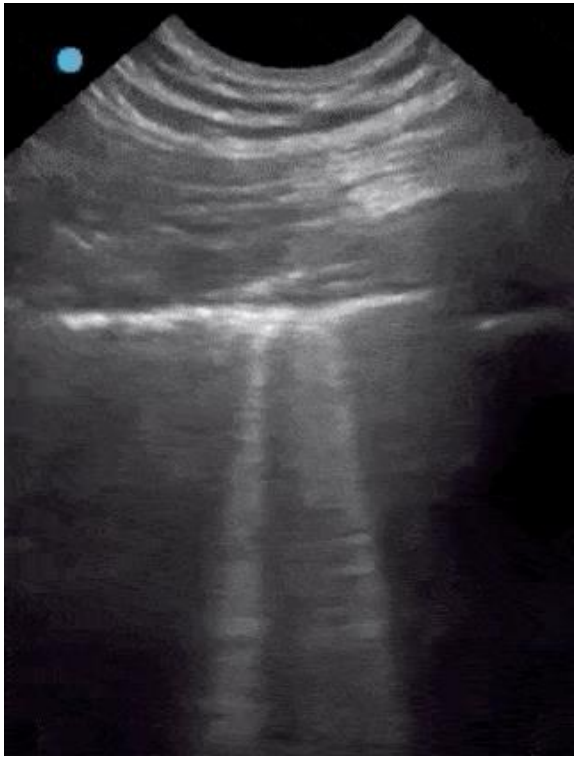
Admit to *ICU* vs *Step Down* vs *Med Surg*
Based on Vital Signs and Pathology

Pocus101.com

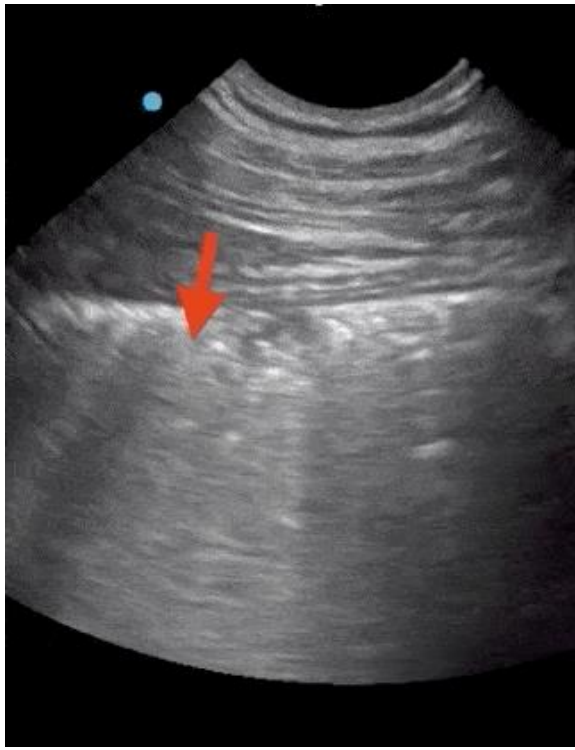
Lung ultrasound images



Normal lung

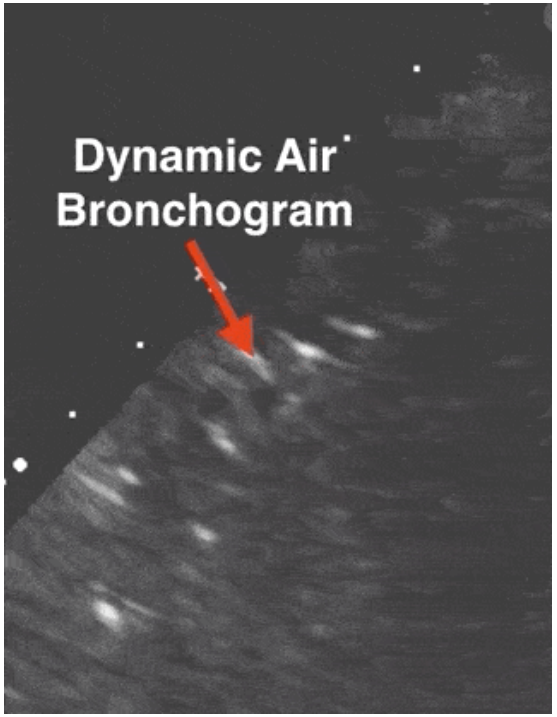


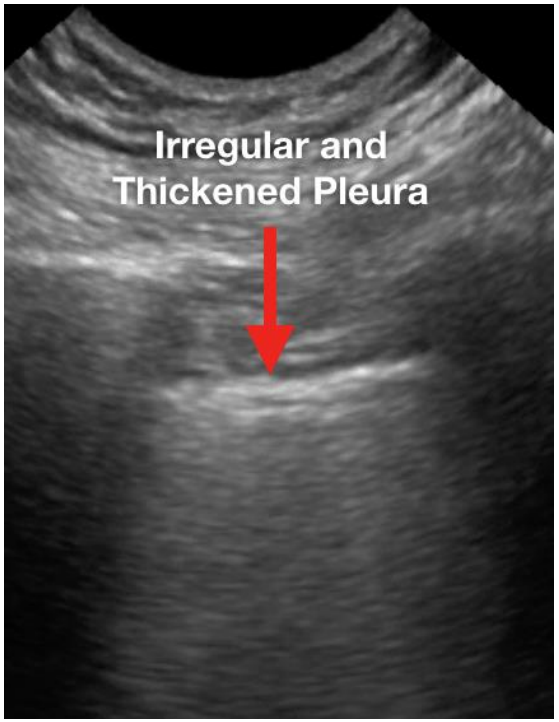
Few B-lines

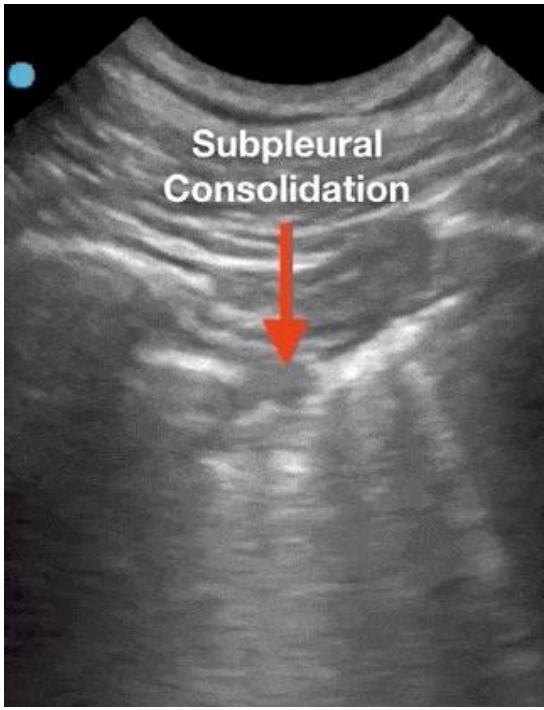


COVID ARDS

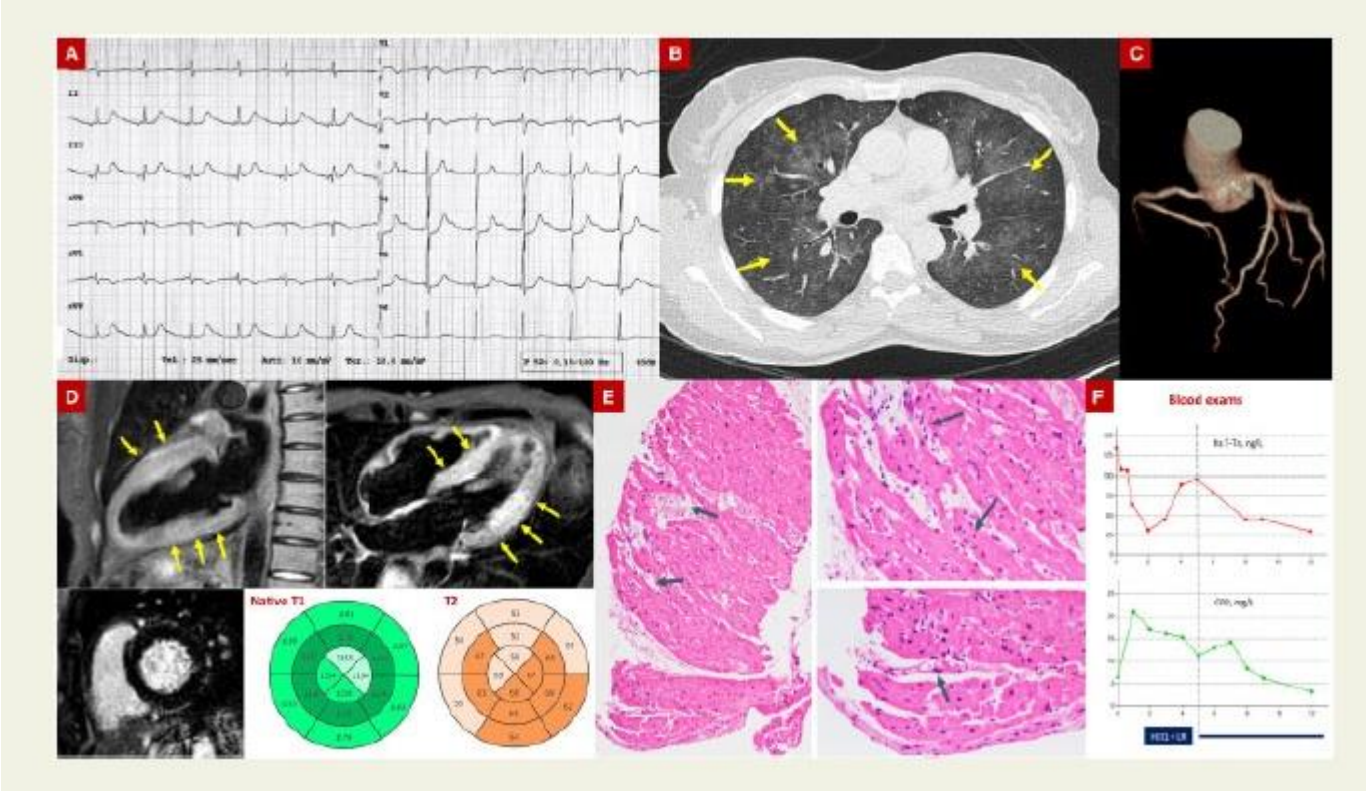
Lung ultrasound images







Acute myocarditis presenting as a reverse Tako-Tsubo syndrome in a patient with SARS-CoV-2 respiratory infection



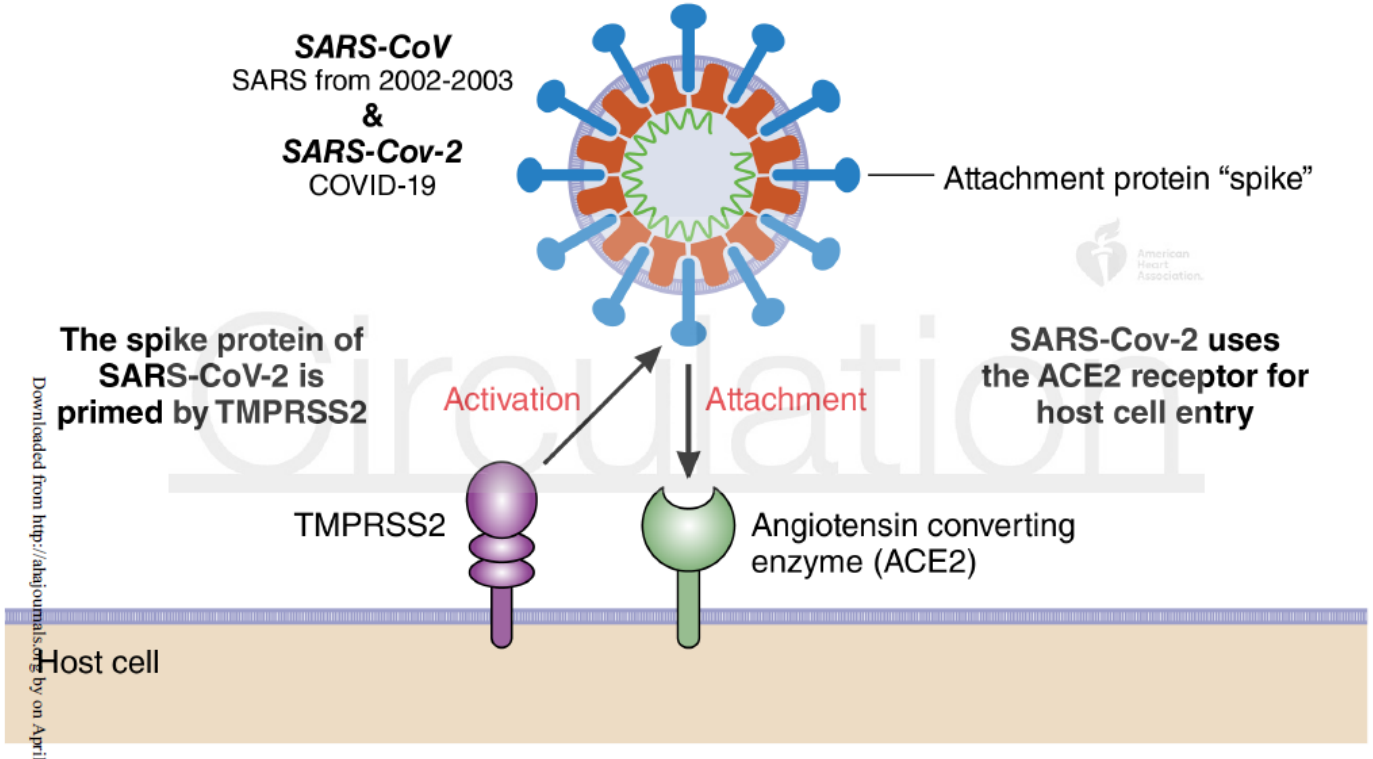
European Heart Journal, ehaa286,
https://doi.org/10.1093/eurheartj/ehaa286

Table 3. Summary of clinical reports describing arrhythmias in COVID-19 patients. Search strategy: ("SARS-CoV-2" OR "COVID-19" OR "novel coronavirus") AND ("arrhythmia" OR "tachycardia" OR "bradycardia" OR "cardiac arrest"), date of search 4 April 2020.

Reference	Location	Type of study	Setting	N	N with arrhythmia	Remarks
Guo et al[6]	Wuhan, China	Single-center retrospective case series	Hospitalized patients	187	11 (6%) VT/VF	Only VT/VF reported. Almost all (9/11 patients with VT/VF) had increased troponin-T levels.
Du et al[22]	Wuhan, China	Multi-center retrospective case series	Fatal cases	85	51 (60%) type of arrhythmia unknown	Report on 85 fatal cases. No information on type of arrhythmia.
Wang et al[5]	Wuhan, China	Single-center retrospective case series	Hospitalized patients	138	23 (17%) type of arrhythmia unknown	No information on type of arrhythmia. Arrhythmic occurrence relates to severity of disease: 44% of 36 ICU patients had arrhythmias.

ICU: intensive care unit, VF: ventricular fibrillation, VT: ventricular tachycardia

Figure 4. SARS-CoV-2 binds to the ACE2 receptor following activation of the spike protein by TMPRSS2



10.1161/CIRCULATIONAHA.120.046941

Renin–Angiotensin–Aldosterone System Inhibitors in Patients with Covid-19

Muthiah Vaduganathan, M.D., M.P.H., Orly Vardeny, Pharm.D., Thomas Michel, M.D., Ph.D., John J.V. McMurray, M.D., Marc A. Pfeffer, M.D., Ph.D., and Scott D. Solomon, M.D.

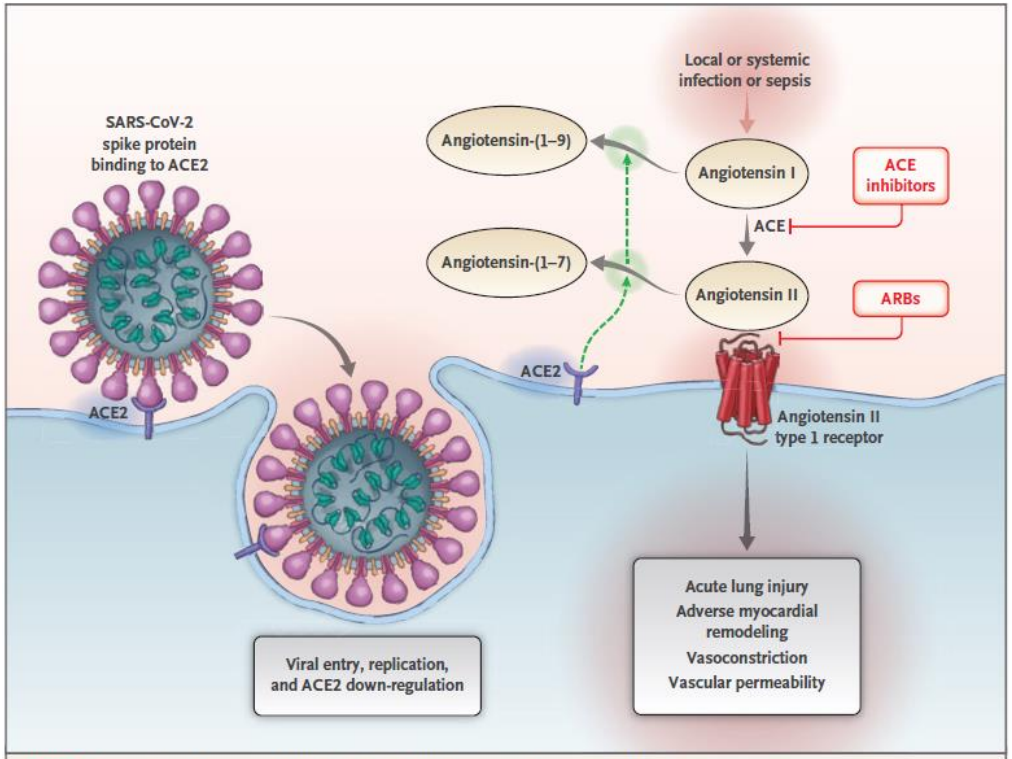


Figure 1. Interaction between SARS-CoV-2 and the Renin–Angiotensin–Aldosterone System.
Shown is the initial entry of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) into cells, primarily type II pneumocytes, after binding to its functional receptor, angiotensin-converting enzyme 2 (ACE2). After endocytosis of the viral complex, surface ACE2 is further down-regulated, resulting in unopposed angiotensin II accumulation. Local activation of the renin–angiotensin–aldosterone system may mediate lung injury responses to viral insults. ACE denotes angiotensin-converting enzyme, and ARB angiotensin-receptor blocker.

The NEW ENGLAND JOURNAL of MEDICINE

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Key Points Related to the Interplay between Covid-19 and the Renin–Angiotensin–Aldosterone System

- ACE2, an enzyme that physiologically counters RAAS activation, is the functional receptor to SARS-CoV-2, the virus responsible for the Covid-19 pandemic
- Select preclinical studies have suggested that RAAS inhibitors may increase ACE2 expression, raising concerns regarding their safety in patients with Covid-19
- Insufficient data are available to determine whether these observations readily translate to humans, and no studies have evaluated the effects of RAAS inhibitors in Covid-19
- Clinical trials are under way to test the safety and efficacy of RAAS modulators, including recombinant human ACE2 and the ARB losartan in Covid-19
- Abrupt withdrawal of RAAS inhibitors in high-risk patients, including those who have heart failure or have had myocardial infarction, may result in clinical instability and adverse health outcomes
- Until further data are available, we think that RAAS inhibitors should be continued in patients in otherwise stable condition who are at risk for, being evaluated for, or with Covid-19

The NEW ENGLAND JOURNAL of MEDICINE

COVID-19 Illness and Heart Failure: A Missing Link?

Mandeep R. Mehra, MD, MSc, Frank Ruschitzka, MD

Table: Clinical Cardiovascular Concerns in COVID-19 Illness

COVID-19 Infection	Concern	Interpretation
Asymptomatic or early mild disease with constitutional symptoms (fever, dry cough, diarrhea and headache)	Should background cardiovascular medications be modified?	• There is no clear evidence that ACEi or ARB should be discontinued • NSAIDs should be avoided
Moderate disease with pulmonary complications and shortness of breath (including hypoxia)	Is there a cardiovascular contribution to the lung complications?	• Check troponin (evidence of myocardial injury and prognosis) • Check natriuretic peptides • Consider cardiac echocardiography to evaluate for evidence of underlying structural heart disease, high filling pressures • Avoid overuse of intravenous fluids which may worsen underlying pulmonary edema
Advanced stage disease with hypoxia, vasoplegia and shock	Is there evidence of cardiogenic contribution to shock and what therapy may be potentially curative?	• Check for evidence of hyperinflammation or a cytokine release storm (elevated troponin, natriuretic peptides, CRP and serum ferritin>1000 ng/ml (measure IL-6 levels if available) • If cardiac function is reduced (LVEF <0.50%), consider supportive care with inotropic therapy but move to consider anti-cytokine therapy with drugs such as tocilizumab and corticosteroids

ACEi = Angiotensin Converting Enzyme Inhibitors; ARB= Angiotensin Receptor Blockers; CRP= C Reactive Protein; IL = Interleukin [Note that therapy in COVID-19 remains experimental]

Secondary Impact of the COVID-19 Pandemic on Patients With Heart Failure

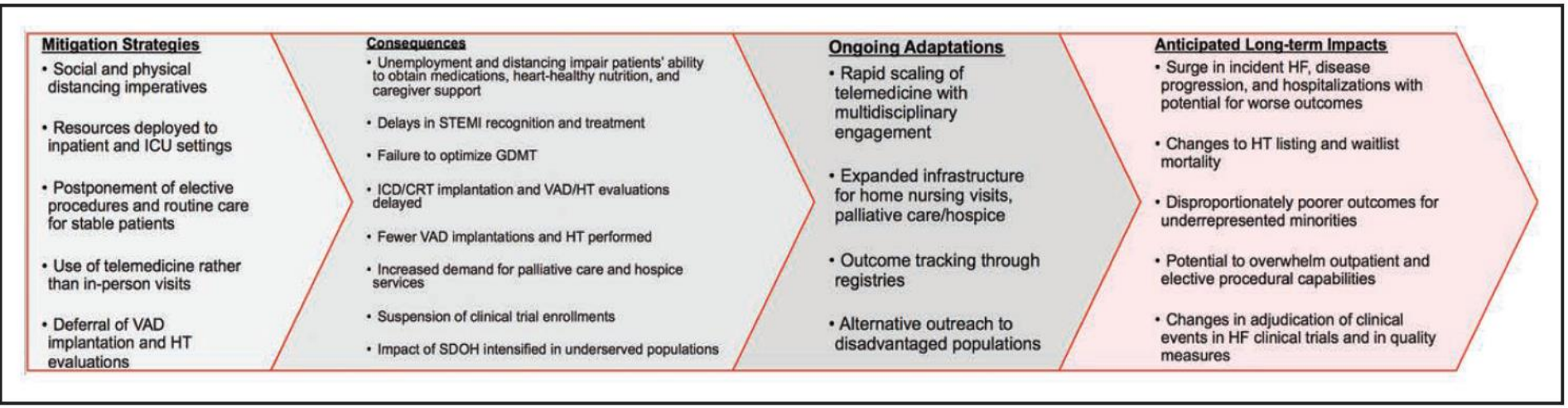
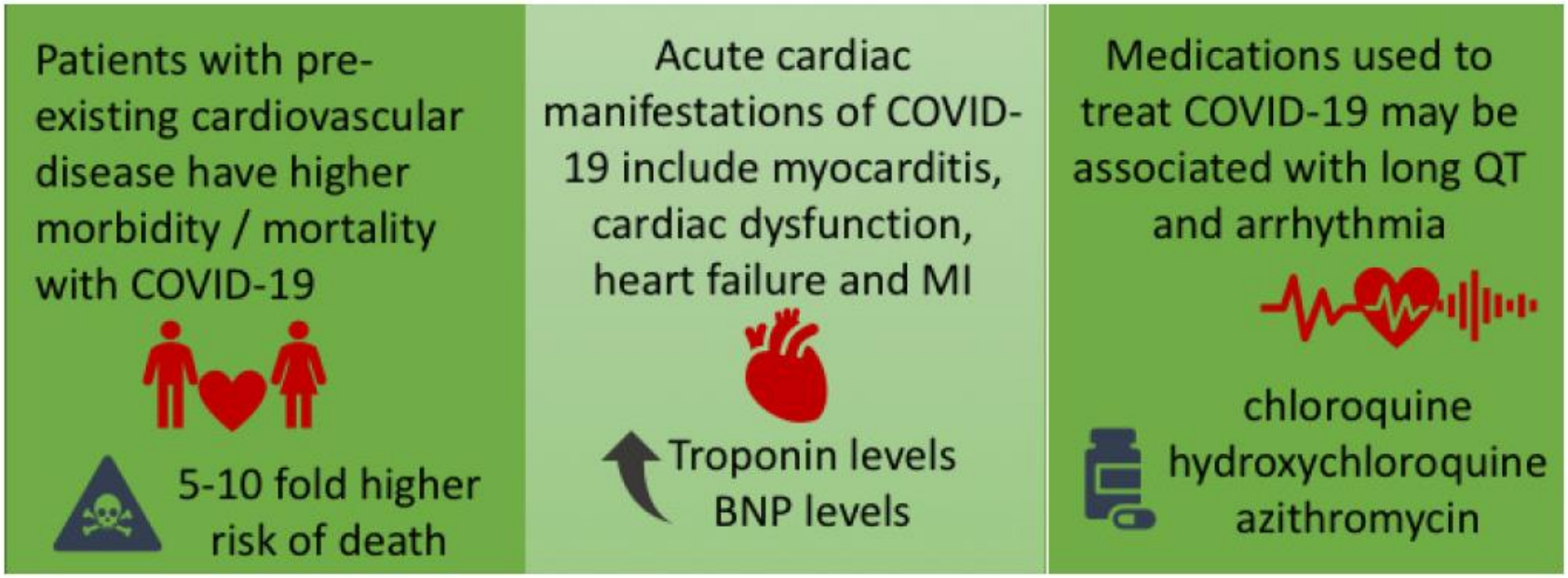
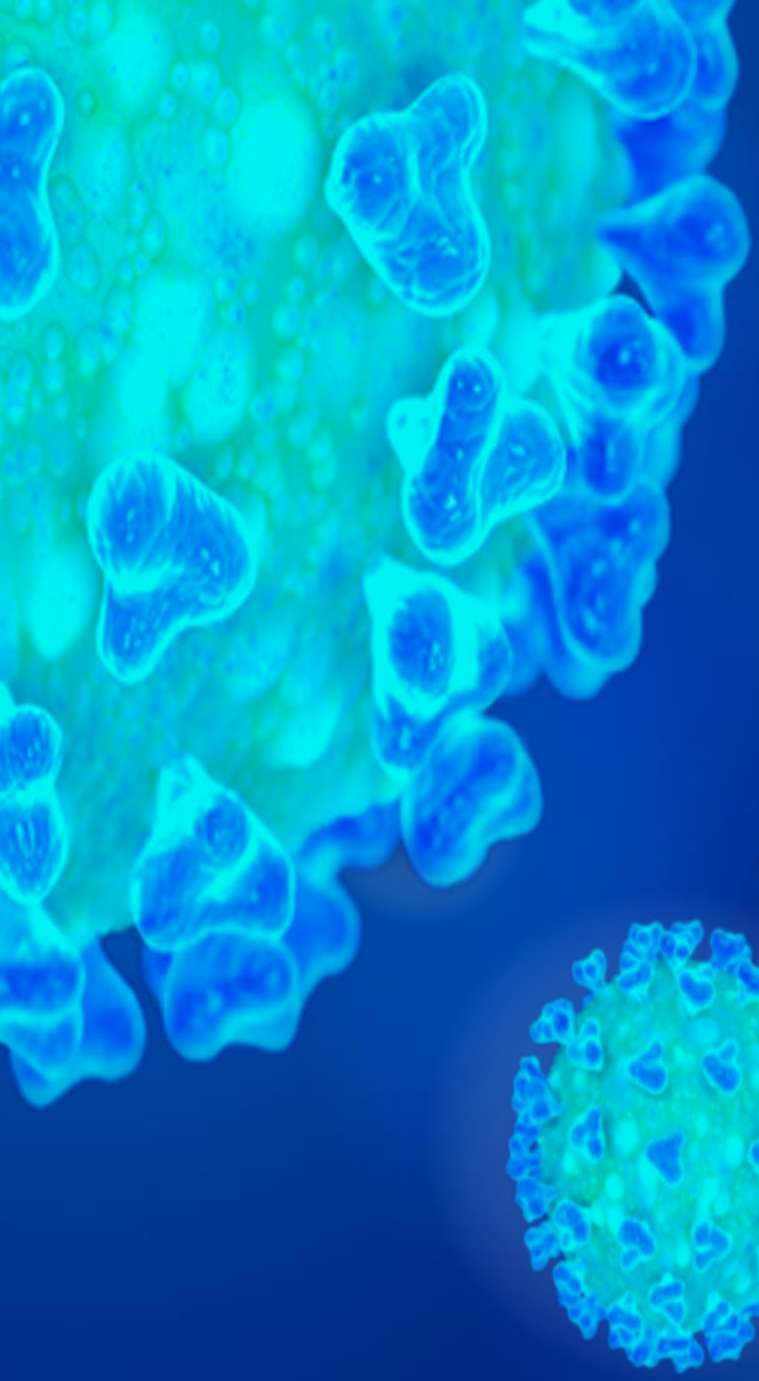


Figure. Mitigation strategies, consequences, ongoing adaptations to, and anticipated impacts of disruptions in heart failure care delivery imposed by the coronavirus disease 2019 (COVID-19) pandemic.

Figure 1. Acute cardiovascular manifestations of COVID-19





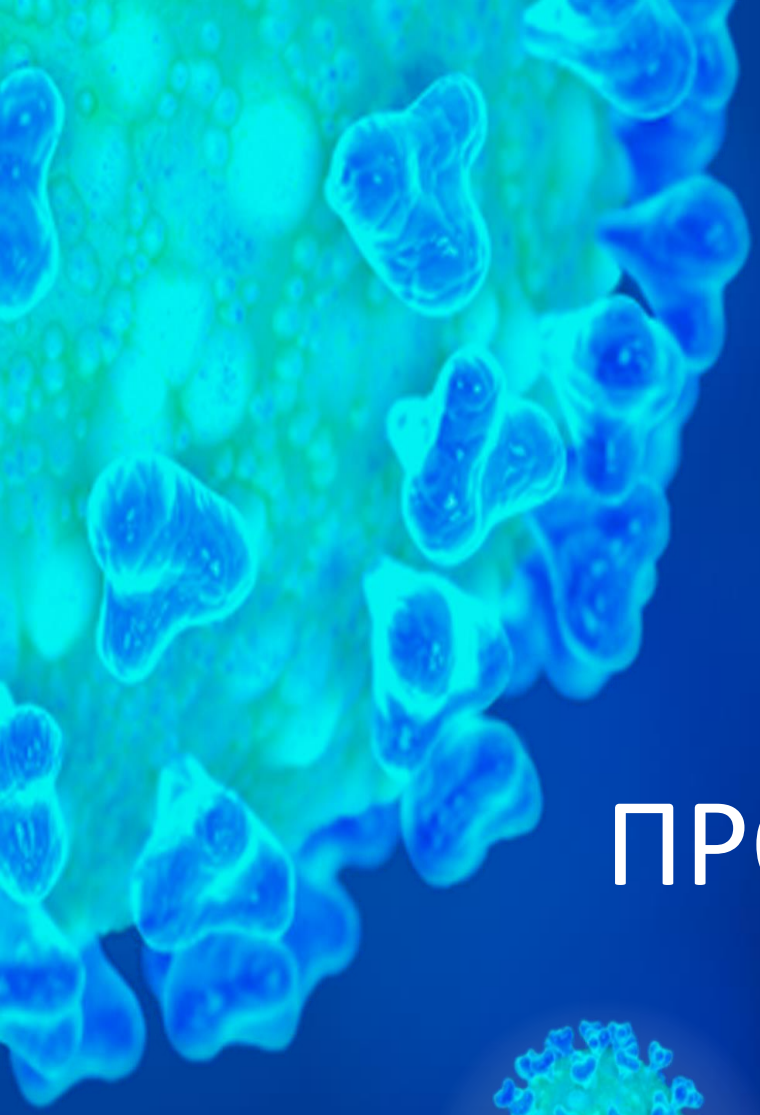
COVID-19

ΝΕΥΡΙΚΟ ΣΥΣΤΗΜΑ

Γεώργιος Τσιβγούλης – Καθηγητής Νευρολογίας ΕΚΠΑ
Β΄ Νευρολογική Κλινική, Νοσοκομείο «Αττικόν»

ΠΕΡΙΓΡΑΜΜΑ ΟΜΙΛΙΑΣ

1. Προσβολή Νευρικού Συστήματος.
2. Φάσμα νευρολογικών εκδηλώσεων σε λοίμωξη από SARS-CoV-2.
3. Ανεπιθύμητες ενέργειες φαρμάκων έναντι COVID-19 με νευρολογικές εκδηλώσεις.
4. Διάγνωση και Διαχείριση ασθενών με νευρολογικές εκδηλώσεις και νόσο COVID-19.
5. Το αντίκτυπο της πανδημίας στους νευρολογικούς ασθενείς.



01.

ΠΡΟΣΒΟΛΗ ΝΕΥΡΙΚΟΥ ΣΥΣΤΗΜΑΤΟΣ

Άμεση προσβολή ή παράπλευρη απώλεια;

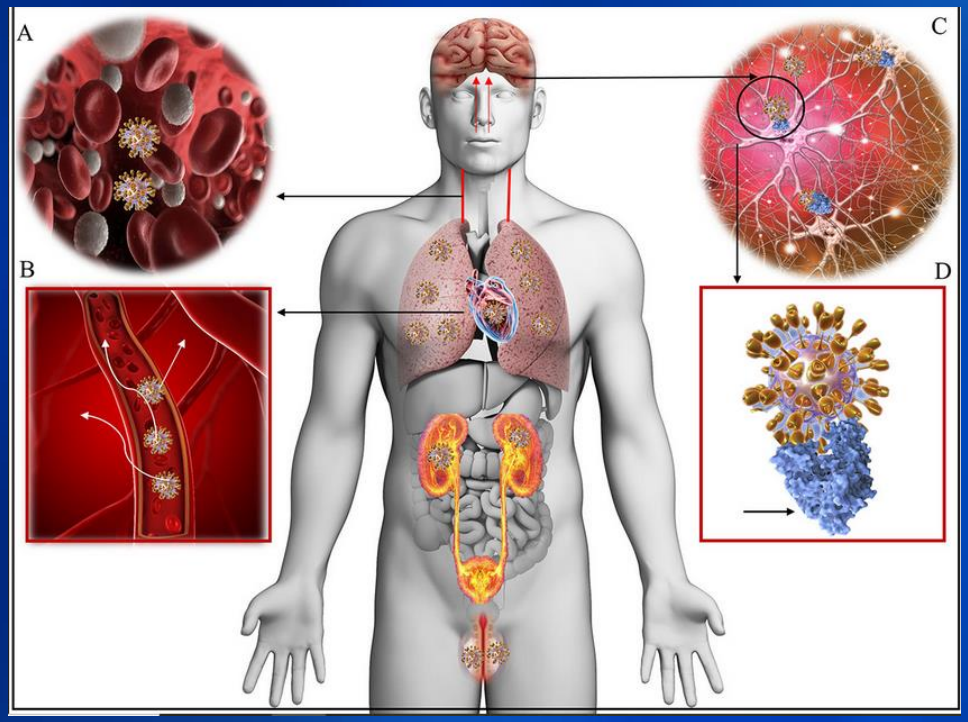
ΚΡΙΣΙΜΗ ΝΟΣΟΣ

- **COVID-19:** χαρακτηριστικά προκαλεί εκδηλώσεις από το **αναπνευστικό** σύστημα.
- 5% των ασθενών εμφανίζουν **βαριά μορφή της νόσου** και θα χρειαστούν μηχανικό αερισμό και νοσηλεία σε Μονάδες Εντατικής Θεραπείας (**ΜΕΘ**).
- Οι **νοσηλευόμενοι σε ΜΕΘ συχνά εμφανίζουν επιπλοκές από το νευρικό σύστημα**, λόγω:
    - Παρατεταμένης κατάκλισης & ακινητοποίησης
    - Χορήγησης αναισθητικών & μυοχαλαρωτικών φαρμάκων
    - Υποξίας - υπερκαπνίας
    - Ηλεκτρολυτικών διαταραχών
    - Υπερπηκτικότητας ή Διάχυτης Ενδοαγγειακής Πήξης
    - Μη ελεγχόμενης ανοσιακής απάντησης και «καταιγίδας» κυτταροκινών
    - Σηπτικού σοκ & πολύ-οργανικής ανεπάρκειας

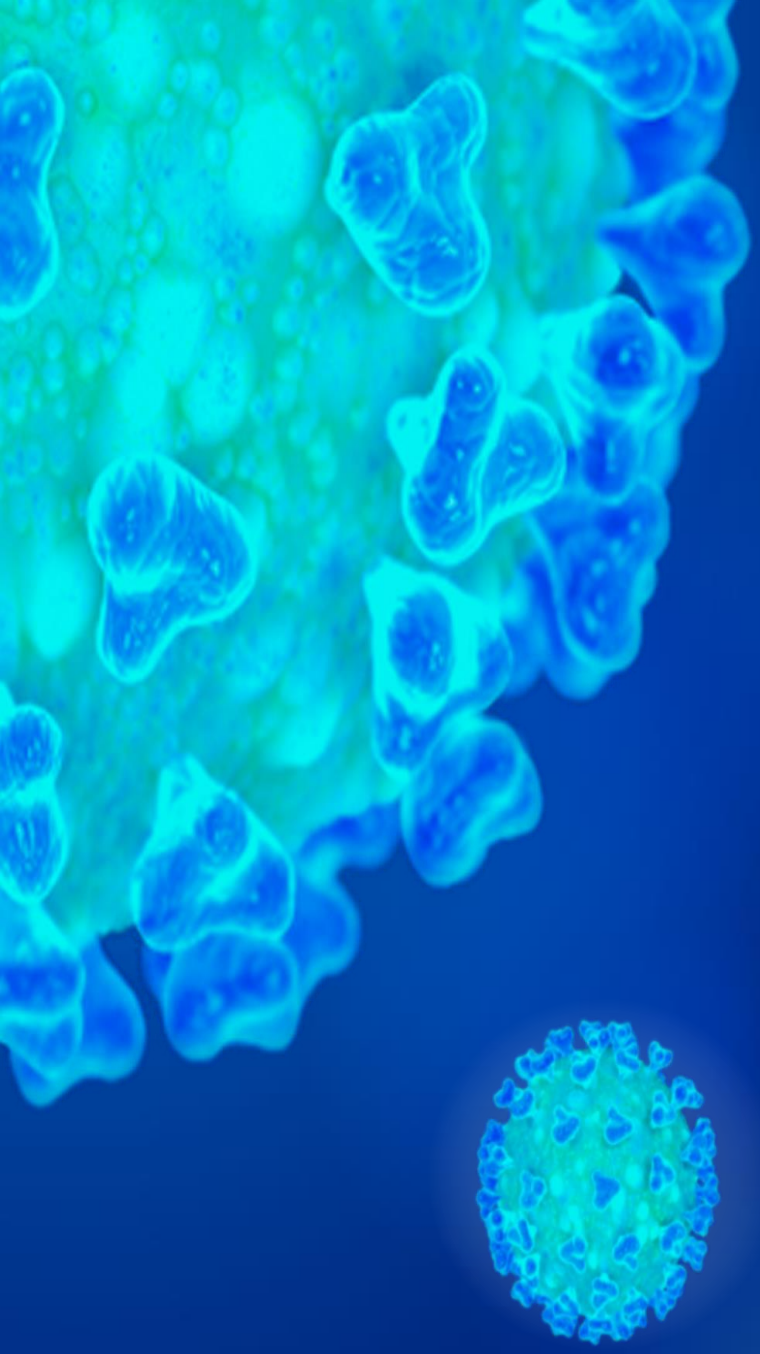
- Το ερώτημα παραμένει:
- **Μπορεί ο ιός SARS-CoV-2 να προσβάλει άμεσα το νευρικό σύστημα?**

ΥΠΟΔΟΧΕΑΣ ACE2

- Ο ιός SARS-CoV-2 (όπως και ο ιός SARS-CoV) προσδένεται στον υποδοχέα ACE2.
- Τα εγκεφαλικά κύτταρα και οι γραμμωτές μυϊκές ίνες εκφράζουν τον ACE2.



1. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol. 2004;203(2):631-637.
2. Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 Virus Targeting the CNS: Tissue Distribution, Host-Virus Interaction, and Proposed Neurotropic Mechanisms. ACS Chem Neurosci. 2020;11(7):995-998.



02.

ΝΕΥΡΟΛΟΓΙΚΕΣ ΕΚΔΗΛΩΣΕΙΣ

Σε λοίμωξη από SARS-CoV-2

ΦΑΣΜΑ ΝΕΥΡΟΛΟΓΙΚΩΝ ΕΚΔΗΛΩΣΕΩΝ

ΚΕΝΤΡΙΚΟ ΝΕΥΡΙΚΟ ΣΥΣΤΗΜΑ

- Κεφαλαλγία (13.6%)
- Ζάλη (16.8%)
- Αγγειακά Εγκεφαλικά Επεισόδια (5% ισχαιμικά, 0.5% αιμορραγικά, 0.5% θρόμβωση φλεβωδών)
- Επιληπτικές κρίσεις (0.5%)
- Σύγχυση (65%)
- Διέγερση (69%)
- Διαταραχή Επιπέδου Συνείδησης (7.5%)
- Εγκεφαλίτιδα/Μηνιγγίτιδα (περιγραφές περιστατικών)
- Νεκρωτική Εγκεφαλίτιδα (περιγραφές περιστατικών)

ΠΕΡΙΦΕΡΙΚΟ ΝΕΥΡΙΚΟ ΣΥΣΤΗΜΑ

- Οξεία Φλεγμονώδης Πολυνευροπάθεια (GBS, 0.5%)
- Πολυνευροπάθεια Κρίσιμης Νόσου (critical illness polyneuropathy
- Ανοσμία/Υποσμία (5-70%)

ΜΥΪΚΟ ΣΥΣΤΗΜΑ

- Μυαλγία (14.9%)
- Μυοπάθεια Κρίσιμης Νόσου

ΑΕΕ & COVID-19

- Ισχαιμικό ΑΕΕ: 5%
  - υπερπηκτικότητα λόγω φλεγμονής (αυξημένα επίπεδα D-Dimer)
  - Εν τω βάθει φλεβοθρόμβωση και παράδοξη εμβολή μέσω ΑΩΤ
  - ενδοθηλιακή καταστροφή και ενεργοποίηση αιμοπεταλίων,
  - αφυδάτωση,
  - διαταραχές καρδιακού ρυθμού και κινητικότητας μυοκαρδίου.

- Αιμορραγικό ΑΕΕ: 0.5%
  - σύνδεση του ιού στον υποδοχέα ACE2 και απενεργοποίηση αυτού → διαταραχές στη ρύθμιση της αρτηριακής πίεσης,
  - διαταραχές του μηχανισμού της πήξης (θρομβοπενία) και διάχυτη ενδοαγγειακή πήξη.

- Θρόμβωση φλεβωδών κόλπων: 0.5%
  - αφυδάτωση και
  - υπερπηκτικότητα.

Li Y, Wang M, Zhou Y, Chang J, Xian Y, Mao L, et al. Acute Cerebrovascular Disease Following COVID-19: A Single Center, Retrospective, Observational Study. https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3550025. Published 2020. Accessed April 4, 2020.

ΑΕΕ & COVID-19

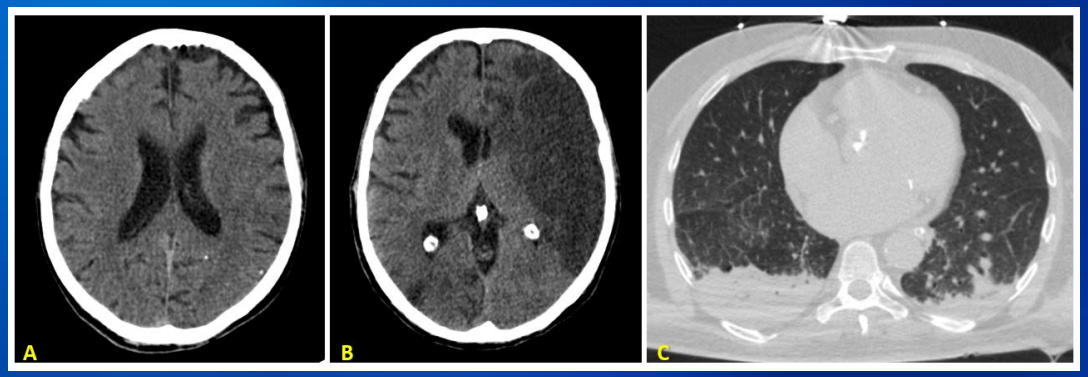
Συννοσηρότητα ή αιτιολογική συσχέτιση;

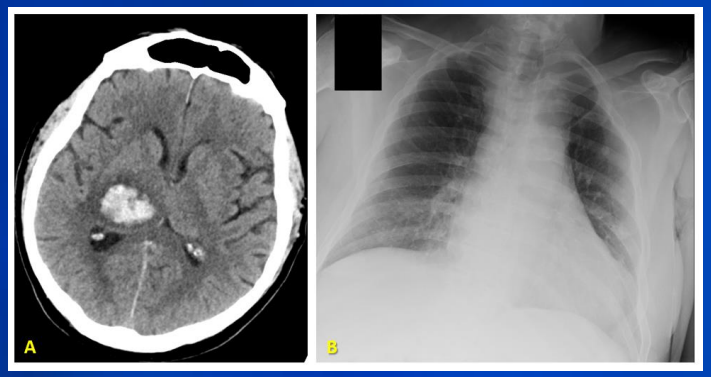
- Κοινοί παράγοντες κινδύνου για ΑΕΕ & σοβαρή COVID-19 νόσο

Risk Factor	COVID-19 Disease	Cerebrovascular Diseases
Advanced Age	+	+
Heart Failure	+	+
Coronary Artery Disease	+	+
Hypertension	+	+
Dyslipidemia	-	+
Diabetes Mellitus	+	+
Obesity	+	+
Chronic Obstructive Pulmonary Disease	+	-
Asthma	+	-
Chronic Kidney Failure	+	+
Liver disease	+	+
Malignancy	+	+
Smoking	+	+
Immunosuppression	+	-

Tsivgoulis et al. TAND (under review).

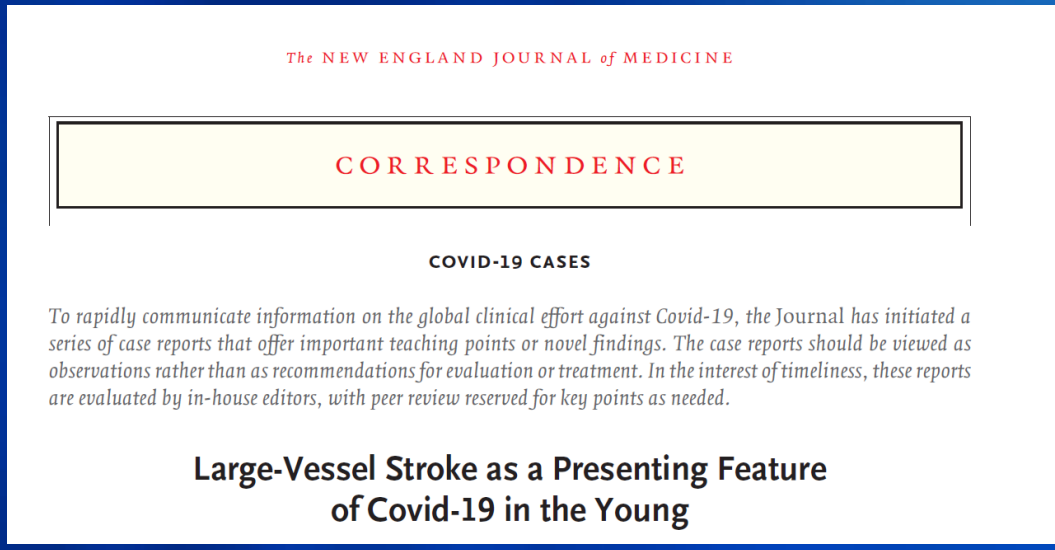
Συννοσηρότητα ή αιτιολογική συσχέτιση;
ΑΕΕ & COVID-19





Tsivgoulis et al. Ther Adv Neurol Disord (under review).

ΑΕΕ & COVID-19


The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

COVID-19 CASES

To rapidly communicate information on the global clinical effort against Covid-19, the Journal *has initiated a series of case reports that offer important teaching points or novel findings. The case reports should be viewed as observations rather than as recommendations for evaluation or treatment. In the interest of timeliness, these reports are evaluated by in-house editors, with peer review reserved for key points as needed.*

Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young

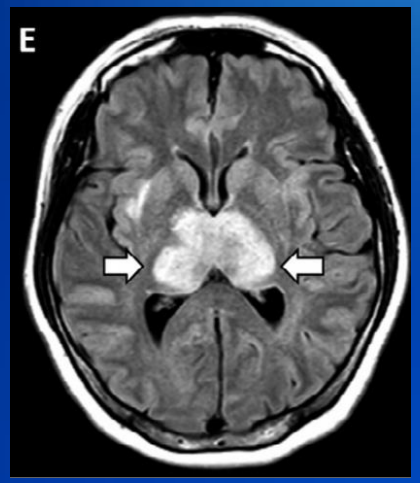
- Νέοι ασθενείς (<50 έτη)
- Χωρίς γνωστούς παράγοντες κινδύνου
- 80% συμπτώματα νόσου COVID-19 πριν την εκδήλωση του ΑΕΕ
- Απόφραξη μεγάλου αγγείου
- Σοβαρή αναπηρία και θάνατος
- 60% D-Dimer>1.500ng/ml

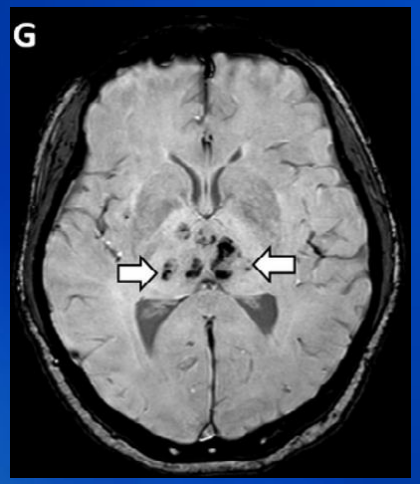
Oxley et al. N Engl J Med (e-pub ahead of print)

COVID-19 &
Acute Hemorrhagic Necrotizing Encephalopathy

- Πυρετός, βήχας, διαταραχή νοητικού επιπέδου
- RT-PCR ρινοφάρυγγα (+) – ΕΝΥ δεν εξετάστηκε
- Χαρακτηριστική απεικόνιση σε MRI εγκεφάλου
- Θεραπεία με IVIg (η χορήγηση ώσεων κορτικοειδών αποφεύχθηκε λόγω COVID-19)

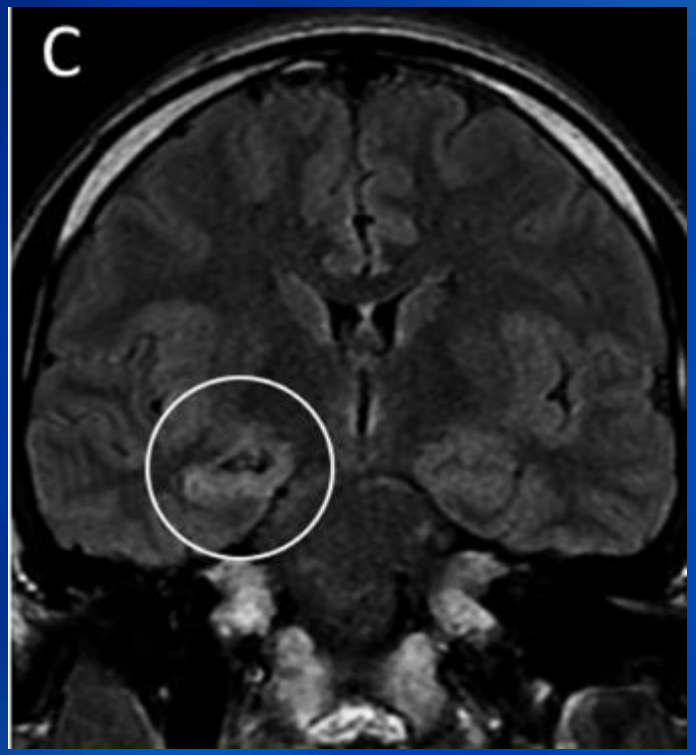
- Πιθανός μηχανισμός: **cytokine storm & διαταραχή αιματοεγκεφαλικού φραγμού**





Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B. COVID-19–associated Acute Hemorrhagic Necrotizing Encephalopathy: CT and MRI Features. [Epub ahead of print 2020, Mar 31]. Radiology.2020; https://doi.org/10.1148/radiol.2020201187.

COVID-19 & meningitis / encephalitis



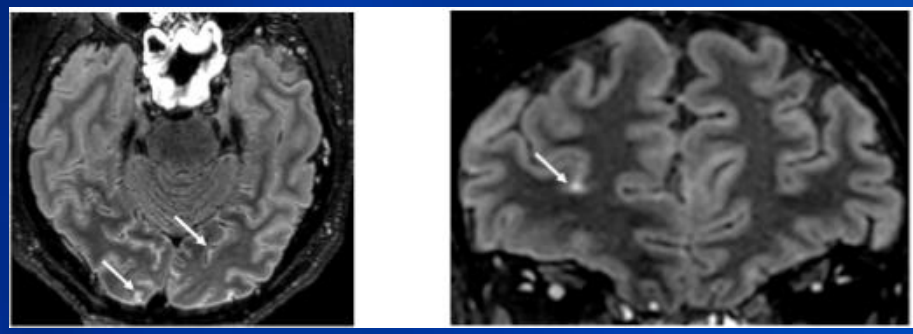
- Πυρετός, κακουχία
- Διαταραχή επιπέδου συνείδησης & status epilepticus
- Αυχενική δυσκαμψία (+)
- RT-PCR SARS-CoV-2 **ρινοφάρυγγα (-) & ΕΝΥ (+)**
- MRI εγκεφάλου: προσβολή κροταφικού λοβού δεξιά και σύστοιχου κροταφικού κέρατος πλάγιας κοιλίας

- **Εργαστηριακό λάθος** από επιμόλυνση ΕΝΥ;
- Ή ένδειξη **άμεσης προσβολής**;

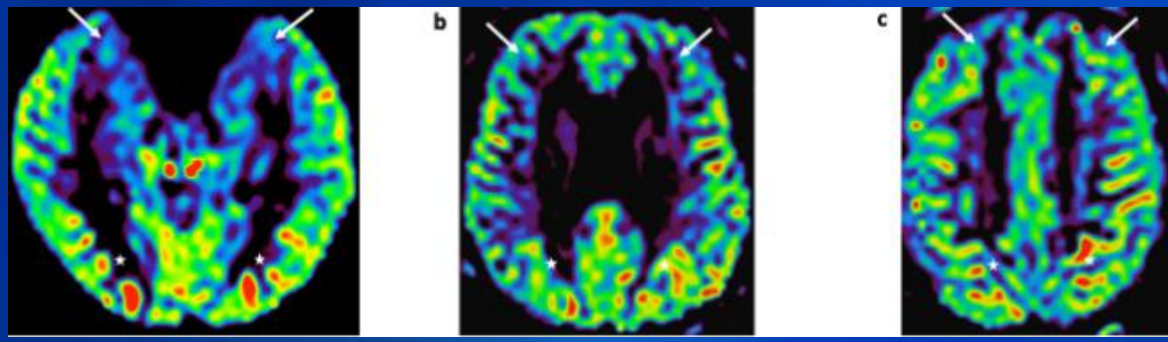
Moriguchi T, Harii N, Goto J, Harada D, Sugawara H, Takamino J, et al. A first Case of Meningitis/Encephalitis associated with SARS-Coronavirus-2. [published online ahead of print, 2020 Apr 3]. International Journal of Infectious Diseases. 2020; doi: 10.1016/j.ijid.2020.03.062.

COVID-19 & meningitis / encephalitis

- Σύγχυση 65%
- Διέγερση 69%
- Διαταραχές εκτελεστικών λετουργιών 36%
- Παθολογικά σημεία πυραμιδικής οδού 67%
- Ισχαιμικό ΑΕΕ: 3 ασθενείς
- RT-PCR SARS-CoV-2 **ΕΝΥ (-)**
- **Όμως ΕΝΥ παθολογικό σε 7 ασθενείς: ολιγοκλωνικές ζώνες, αυξημένη πρωτεΐνη και IgG**



- **MRI εγκεφάλου:**
  - Λεπτομηνιγγική ενίσχυση
  - Μετωπο-κροταφική υποαιμάτωση
  - Ισχαιμικό ΑΕΕ



Helms J, Kremer S, Merdji H, Clere-Jehl R, Schenck M, Kummerlen C, et al. Neurologic Features in Severe SARS-CoV-2 Infection. [published online ahead of print, 2020 Apr 15].New England Journal of Medicine. 2020. doi: 10.1056/NEJMc2008597

COVID-19 &
Προσβολή Περιφερικού Νευρικού Συστήματος

Table 1. Characteristics of Five Patients with Guillain–Barré Syndrome after the Onset of Covid-19.*

Patient No.	Onset of Neurologic Syndrome	Neurologic Signs and Symptoms	CSF Findings†	Antiganglioside Antibodies‡	MRI Results	Treatment and Outcomes at Week 4
1	7 Days after fever, cough, and ageusia	Flaccid areflexic tetraplegia evolving to facial weakness, upper-limb paresthesia (36 hr), and respiratory failure (day 6)	Day 2 (first lumbar puncture): normal protein level; no cells; negative PCR assay for SARS-CoV-2 Day 10 (second lumbar puncture): protein level, 101 mg/dl; white-cell count, 4 per mm^3; negative PCR assay for SARS-CoV-2	Negative	Head: normal Spine: enhancement of caudal nerve roots	Received 2 cycles of IVIG; had poor outcomes, including persistence of severe upper-limb weakness, dysphagia, and lower-limb paraplegia
2	10 Days after fever and pharyngitis	Facial diplegia and generalized areflexia evolving to lower-limb paresthesia with ataxia (day 2)	Day 3: protein level, 123 mg/dl; no cells; negative PCR assay for SARS-CoV-2	Not tested	Head: enhancement of facial nerve bilaterally Spine: normal	Received IVIG; had improvements, including decrease in ataxia and mild decrease in facial weakness
3	10 Days after fever and cough	Flaccid tetraparesis and facial weakness evolving to areflexia (day 2) and respiratory failure (day 5)	Day 3: protein level, 193 mg/dl; no cells; negative PCR assay for SARS-CoV-2	Negative	Head: normal Spine: enhancement of caudal nerve roots	Received 2 cycles of IVIG; had poor outcomes, including ICU admission owing to neuromuscular respiratory failure and flaccid tetraplegia
4	5 Days after cough and hyposmia	Flaccid areflexic tetraparesis and ataxia (day 4)	Day 5: normal protein level; no cells; negative PCR assay for SARS-CoV-2	Not tested	Head: normal Spine: normal	Received IVIG; had mild improvement but unable to stand 1 mo after onset
5	7 Days after cough, ageusia, and anosmia	Facial weakness, flaccid areflexic paraplegia (days 2–3), and respiratory failure (day 4)	Day 3: protein level, 40 mg/dl; white-cell count, 3 per mm^3; CSF:serum albumin ratio, 1.2%; negative PCR assay for SARS-CoV-2	Negative	Head: not performed Spine: normal	Received IVIG and plasma exchange; had bacterial pneumonia during IVIG treatment, which delayed plasma exchange

* Covid-19 denotes coronavirus disease 2019, CSF cerebrospinal fluid, ICU intensive care unit, IVIG intravenous immune globulin, MRI magnetic resonance imaging, PCR polymerase chain reaction, and SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.

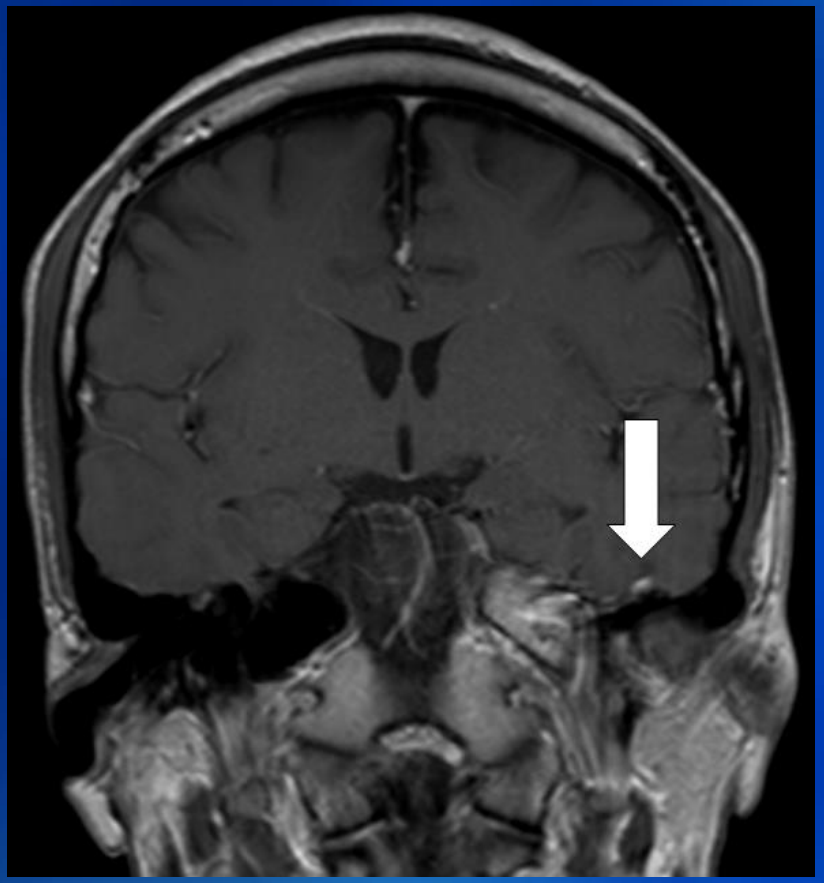
† On CSF analysis, all the patients had a normal glucose level and IgG index and a polyclonal pattern on electrophoresis. The normal range for the protein level is 15 to 45 mg per deciliter.

‡ An enzyme-linked immunosorbent assay was used to test for antibodies to GM1, GQ1b, and GD1b.

Toscano G, Palmerini F, Ravaglia S, Ruiz L, Invernizzi P, Cuzzoni MG, et al. Guillain–Barré Syndrome Associated with SARS-CoV-2. [published online ahead of print, 2020 Apr 17]. New England Journal of Medicine. 2020. doi: 10.1056/NEJMc2009191.

COVID-19 & ΚΡΑΝΙΑΚΗ ΝΕΥΡΙΤΙΔΑ

- Ασθενής με RT-PCR (+) στο ρινοφάρυγγα
- Πάρεση **προσωπικού νεύρου** αριστερά την 3η μέρα νοσηλείας.



Tsivgoulis et al. Ther Adv Neurol Disord (under review).

ΑΝΟΣΜΙΑ & ΥΠΟΣΜΙΑ

- **Υπογευσία**: 5.6% & **Υποσμία**: 5-70%
- Συχνή εκδήλωση, **χωρίς οι ασθενείς να εμφανίζουν ρινική συμφόρηση.**
- AAO-HNS πρότεινε να συμπεριληφθεί στα κύρια συμπτώματα ελέγχου COVID-19

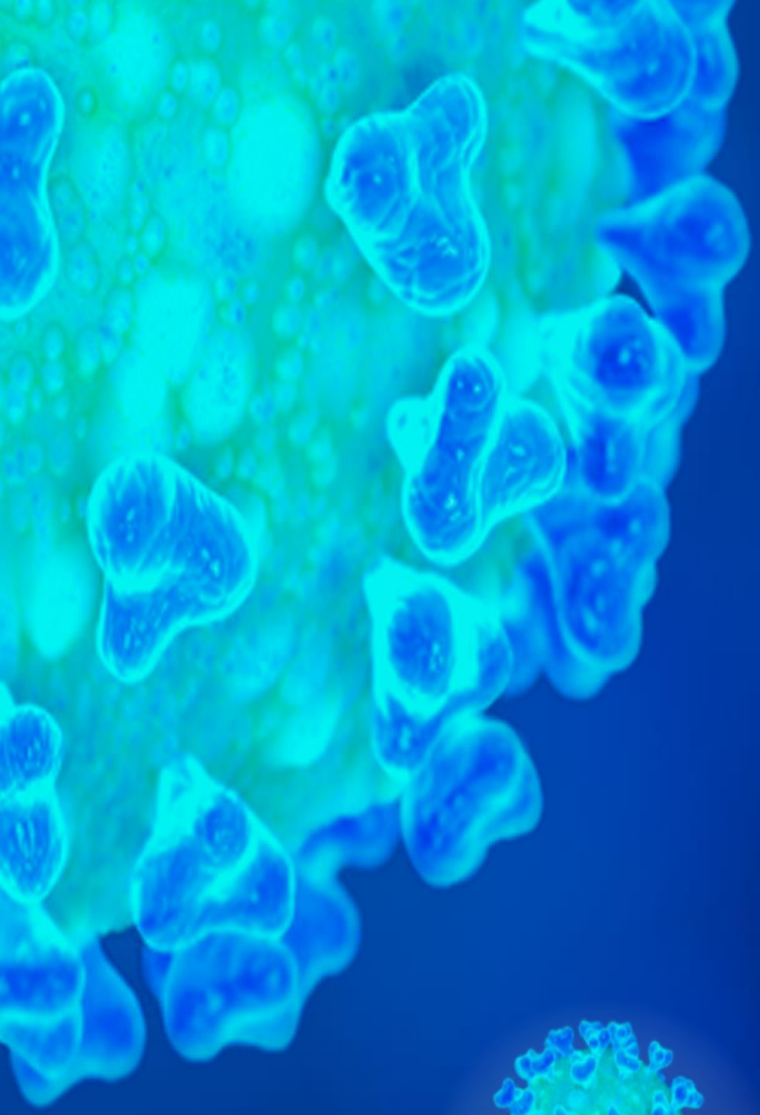
Table 2. Characteristics of Altered Sense of Smell or Taste in 202 Patients Positive for SARS-CoV-2

	No. of patients	Prevalence, % (95% CI)[a]
Severity of alteration of sense of smell or taste		
None	72	35.6 (29.1-42.7)
Very mild	5	2.5 (2.5-5.7)
Mild or light	23	11.4 (7.4-16.6)
Moderate	27	13.4 (9.0-18.9)
Severe	27	13.4 (9.0-18.9)
As bad as it can be	48	23.8 (18.1-30.2)
Time of onset of alteration of sense of smell or taste		
None	72	35.6 (29.1-42.7)
Only symptom	6	3.0 (1.1-6.4)
Prior to other symptoms	24	11.9 (7.8-17.2)
Concomitant with other symptoms	46	22.8 (17.2-29.2)
After other symptoms	54	26.7 (20.8-33.4)

Abbreviation: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a] 95% CIs were calculated using Clopper-Pearson method.

- Spinato G, Fabbris C, Polesel J, et al. Alterations in Smell or Taste in Mildly Symptomatic Outpatients With SARS-CoV-2 Infection. JAMA. 2020 Apr 22. [Epub ahead of print]. doi: 10.1001/jama.2020.6771.
- Mao L, Jin H, Wang M, He Q, Chang J, Hong C, et al. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. [Published online ahead of print, 2020 Apr 20]. JAMA Neurology. 2020. doi:10.1001/jamaneurol.2020.1127.
- American Academy of Otolaryngology - Head and Neck Surgery. AAO-HNS: Anosmia, Hyposmia, and Dysgeusia Symptoms of Coronavirus Disease. https://www.entnet.org/content/aao-hns-anosmia-hyposmia-and-dysgeusia-symptoms-coronavirus-disease. Accessed April 4, 2020.
- Lechien J, Chiesa-Estomba C, De Siati D, Horoi M, Le Bon S, Rodriquez A, et al. Olfactory and Gustatory Dysfunctions as a Clinical Presentation of Mild to Moderate forms of the Coronavirus Disease (COVID-19): A Multicenter European Study. https://www.entnet.org/sites/default/files/uploads/lechien_et_al._-_covid19_-_eur_arch_otorhinolaryngol_.pdf. Published 2020. Accessed April 4, 2020.



03.

ΑΝΕΠΙΘΥΜΗΤΕΣ ΕΝΕΡΓΕΙΕΣ ΦΑΡΜΑΚΩΝ

Έναντι COVID-19 με νευρολογικές εκδηλώσεις

ΧΛΩΡΟΚΙΝΗ

- Κεφαλαλγία
- Ζάλη
- Εξωπυραμιδικά συμπτώματα: δυστονία, δυσκινησία, τρόμος
- Αλληλεπίδραση με αντιεπιληπτικά φάρμακα → ο επιληπτικός ουδός μπορεί να μειωθεί.
- Σε συγχορήγηση με αμινογλυκοσίδες επηρεάζει τη νευρομυϊκή σύναψη → προσοχή σε ασθενείς με MG και άλλες νευρομυικές διαταραχές.
- Αλληλεπίδραση με NOACs → προκαλεί μείωση της απέκκρισης και αύξηση αιμορραγικού κίνδυνου

Medicines.org.uk. Plaquenil-Hydroxychloroquine sulfate 200mg Film-coated Tablets-Summary Of Product Characteristics (SPC)-Emc). https://www.medicines.org.uk/emc/product/1764/smpc. Published 2015. Accessed April 4, 2020.

ΑΝΤΙ-ΙΙΚΟΙ ΠΑΡΑΓΟΝΤΕΣ

- **RITONAVIR**
- Αλληλεπίδραση με NOACs → προκαλεί μείωση της απέκκρισης και αύξηση αιμορραγικού κίνδυνου

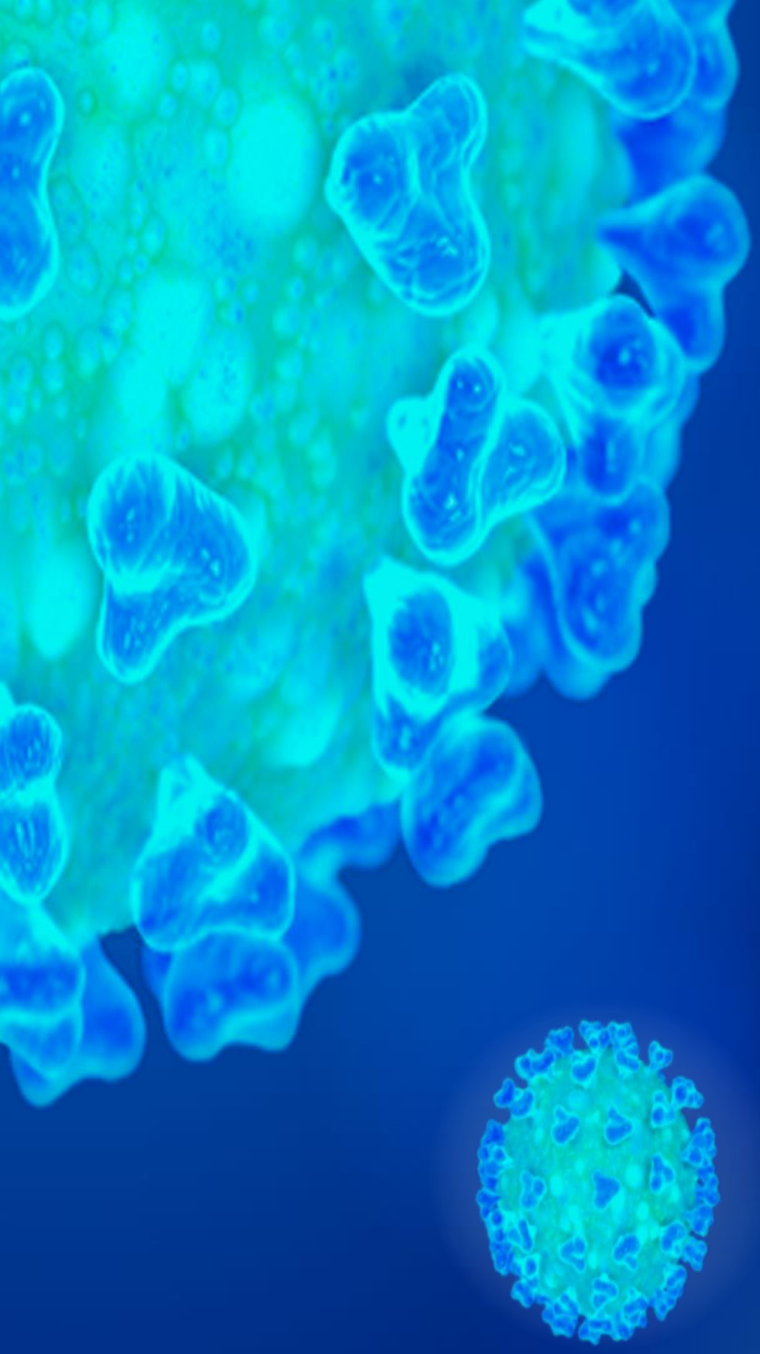
- **REMDESIVIR**
- Οργανικό ψυχοσύνδρομο

- Medicines.org.uk. Eliquis 5 mg film-coated tablets-Summary Of Product Characteristics (SPC)-Emc). https://www.medicines.org.uk/emc/product/2878/smpc. Published 2015. Accessed April 4, 2020.
- Medicines.org.uk. Pradaxa 150 mg hard capsules-Summary Of Product Characteristics (SPC)-Emc). https://www.medicines.org.uk/emc/product/4703/smpc. Published 2015. Accessed April 4, 2020.
- Medicines.org.uk. Xarelto 15 mg film-coated tablets-Summary Of Product Characteristics (SPC)-Emc). https://www.medicines.org.uk/emc/product/6402/smpc. Published 2015. Accessed April 4, 2020.
- Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, et al. Compassionate Use of Remdesivir for Patients with Severe Covid-19. [published online ahead of print, 2020 Apr 10]. New England Journal of Medicine. 2020. doi: 10.1056/NEJMoa2007016.

ΚΟΛΧΙΚΙΝΗ

- Αδυναμία
- Μυαλγία/μυοτοξικότητα
- Αύξηση CK
- Επιδείνωση νευρομυϊκών συμπτωμάτων από COVID-19.

Cocco G, Chu DC, Pandolfi S. Colchicine in clinical medicine. A guide for internists. Eur J Intern Med. 2010;21(6):503-508



04.

ΔΙΑΓΝΩΣΗ & ΔΙΑΧΕΙΡΙΣΗ

Ασθενών με νευρολογικές εκδηλώσεις και νόσο COVID-19

ΔΙΑΓΝΩΣΗ

- Οι νευρολογικές εκδηλώσεις δεν είναι σπάνιες και αναμένονται στη νόσο COVID-19.
- Ο θεράπων ιατρός πρέπει να βρίσκεται σε εγρήγορση για την ύπαρξη νευρολογικών συμπτωμάτων.
- Εργαστηριακές εξετάσεις: **CK και d-dimers**.
- Συνεκτίμηση από Ειδικό Νευρολόγο.
- Σε σημειολογία από το ΚΝΣ συστήνεται **απεικονιστικός** έλεγχος.

Localization in the Nervous System	Neurological symptoms
Central Nervous System	Headache
	Dizziness
	Stroke symptoms
	Seizures
	Confusion
	Agitation
	Delirium
	Stupor
	Coma
Peripheral Nervous System	Hypogeusia
	Hyposmia
	Generalized Weakness
Muscles	Myalgias
	Weakness

Tsivgoulis et al. Ther Adv Neurol Disord (under review).

ΔΙΑΧΕΙΡΙΣΗ ΕΞΩΤΕΡΙΚΟΥ ΑΣΘΕΝΗ ΜΕ ΝΕΥΡΟΛΟΓΙΚΑ ΣΥΜΠΤΩΜΑΤΑ ΣΤΟ ΤΕΠ

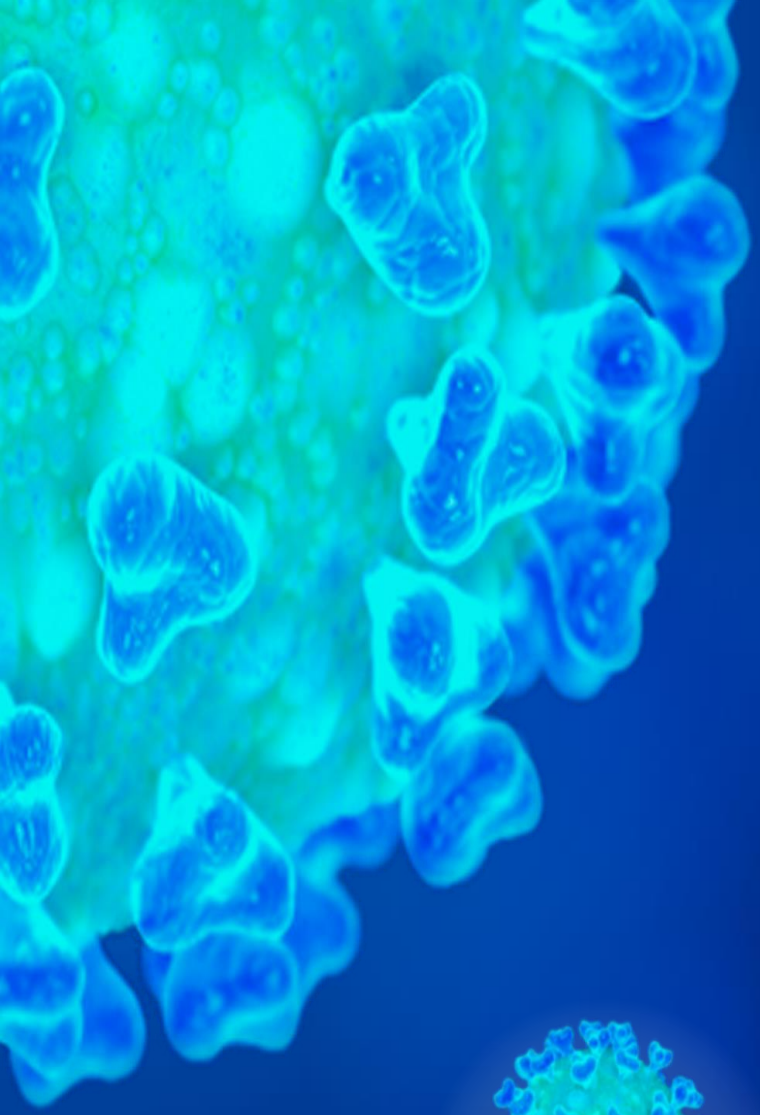
- Λήψη ιστορικού με έμφαση στην αναζήτηση συμπτωμάτων συμβατών με COVID-19 τόσο από τον ασθενή όσο και τους οικείους του.
- Θερμομέτρηση του ασθενή.
- Σε θετικό ιστορικό ή πυρετό → λήψη δείγματος από το ρινοφάρυγγα και απομόνωση του ασθενή μέχρι το αποτέλεσμα του τεστ. Προσοχή σε λοιπά εργαστηριακά ευρήματα (λεμφοπενία, LDH, φερριτίνη).
- Σε εμφάνιση οξέος ΑΕΕ δεν επιτρέπεται η αναμονή του τεστ.
- **Protected Code stroke** → οι ασθενείς αντιμετωπίζονται ως COVID-19 θετικοί με τα απαραίτητα μέσα ατομικής προστασίας (PPE) από το λιγότερο δυνατό προσωπικό.
- Πραγματοποίηση CT θώρακος στον ίδιο χρόνο με τη CT εγκεφάλου για αποφυγή μετέπειτα άσκοπης μετακίνησης.

Khosravani H, Rajendram P, Notario L, Chapman MG, Menon BK. Protected Code Stroke. Stroke. 2020;STROKEAHA120029838. doi:10.1161/STROKEAHA.120.029838.

ΔΙΑΧΕΙΡΙΣΗ ΝΟΣΗΛΕΥΟΜΕΝΟΥ COVID-19 ΑΣΘΕΝΗ ΜΕ ΝΕΥΡΟΛΟΓΙΚΑ ΣΥΜΠΤΩΜΑΤΑ

- Αντιμετώπιση υποκείμενων μηχανισμών (αντιμετώπιση υποξίας – υπερκαπνίας, διαταραχών πήξης, ηλεκτρολυτικών διαταραχών).
- Ρύθμιση αναισθητικών & μυοχαλαρωτικών παραγόντων.
- Υποστήριξη καρδιακής λειτουργίας.
- Απεικονιστικός έλεγχος σε νευρολογική σημειολογία που δεν παρέρχεται παρά τα παραπάνω μέτρα.
- **Νευρολογική εκτίμηση με όλα τα απαραίτητα μέτρα PPE. Στόχος η επαφή με τον ασθενή (εάν είναι αναγκαία) να γίνει μόνο μία φορά.**
- Χρήση **τηλε-ιατρικής** όπου αυτό είναι δυνατόν.

Hurley D. COVID-19 Neurology Heroes: A Neurology Resident in Memphis— ‘They Didn’t Have Anything to Tell Me’. (published online, 2020 Apr 7). NeurologyToday. 2020. Available at: https://journals.lww.com/neurotodayonline/blog/breakingnews/pages/post.aspx?PostID=930. Accessed April 12, 2020.



05.

ΤΟ ΑΝΤΙΚΤΥΠΟ

Στους νευρολογικούς ασθενείς

ΤΟ ΑΝΤΙΚΤΥΠΟ ΤΗΣ ΠΑΝΔΗΜΙΑΣ

- **Σε όλους τους νευρολογικούς τομείς.**
- **ΑΕΕ**: Μείωση του αριθμού εισαγωγών ασθενών με ΑΕΕ λόγω φόβου → δε χορηγείται εγκαίρως η θεραπεία → αυξημένος κίνδυνος για μόνιμη αναπηρία.
- **MS** και άλλα νευροανοσολογικά νοσήματα: Δυσχέρεια προγραμματισμού των ραντεβού για έγχυση ενδοφλέβιων νοσοτροποποιητικών αγωγών. Σε περίπτωση λοίμωξης είναι υπαρκτή η ανάγκη αναβολής της θεραπείας. Αντενδείκνυται η χορήγηση alemtuzumab, cladribine, ocrelizumab λόγω της βαρειάς λεμφοπενίας που προκαλούν.
- **Άνοια** και άλλα νευροεκφυλιστικά νοσήματα: Ιδιαίτερα ευαίσθητος πληθυσμός. Σημαντικό ποσοστό διαμένει σε κλειστές μονάδες φροντίδας. Οι ασθενείς δεν ακολουθούν εύκολα τα μέτρα υγιεινής.
- **Νευρο-μεταβολικά νοσήματα**: Δυσχέρεια στον προγραμματισμό των τακτικών εγχύσεων ενζυμικής υποκατάστασης ή άλλης αγωγής σε ασθενείς που είναι ήδη επιβαρυμένοι.
- **Προγραμματισμένες εξετάσεις** σε νευρολογικούς ασθενείς αναβάλλονται.

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The importance of being a Neurologist (during a dramatic pandemic)

Stefano Gelibter*

Before being Neurologists, we are Physicians and before being Physicians, we are Human. How can we cc

The neurologist, as a physician, has two options. The first one is to keep on taking care of neurological

The role of the Neurologist is precisely this. It has always been this: facing uncertainties and adversities, ') whatever they are. Both choices require qualities that neurology training gave to us. Neurologists are used to s, challenge complexity and they do it with a favored viewpoint over human behavior and lives. We admit ignorance daily, in the Socratic meaning of "*I know that I know nothing*". We often live with doubts and questions rather than with certainties and answers. The continuous exchange of ideas and opinions is our nourishment.