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COVID-19

COVID-19 Lessons Learned: A Global Perspective

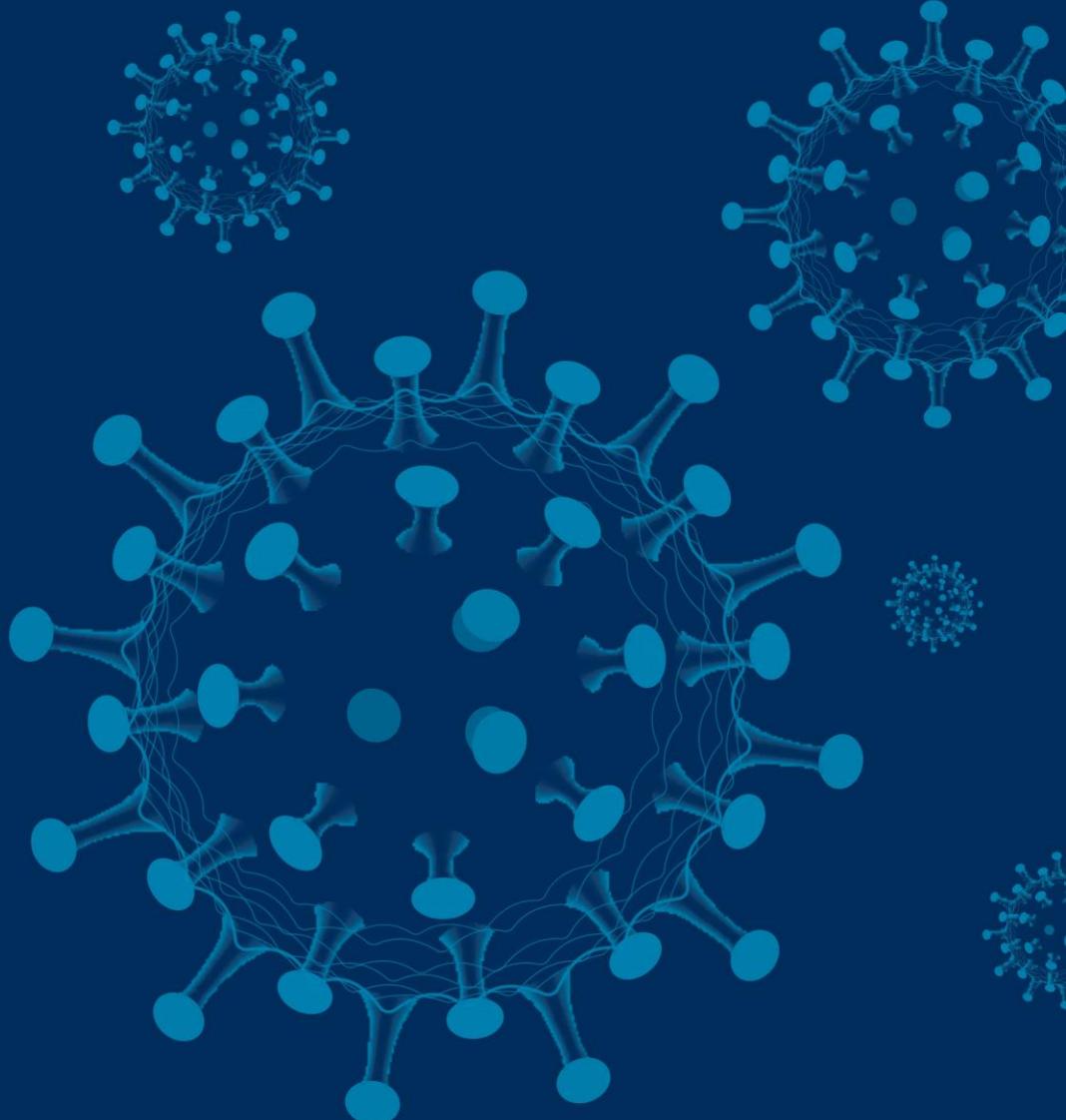
Jagat Narula, MD, FACC moderator

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Otavio Berwanger, MD

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July 14, 2020





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COVID-19

What I Had Wish I Had Known?

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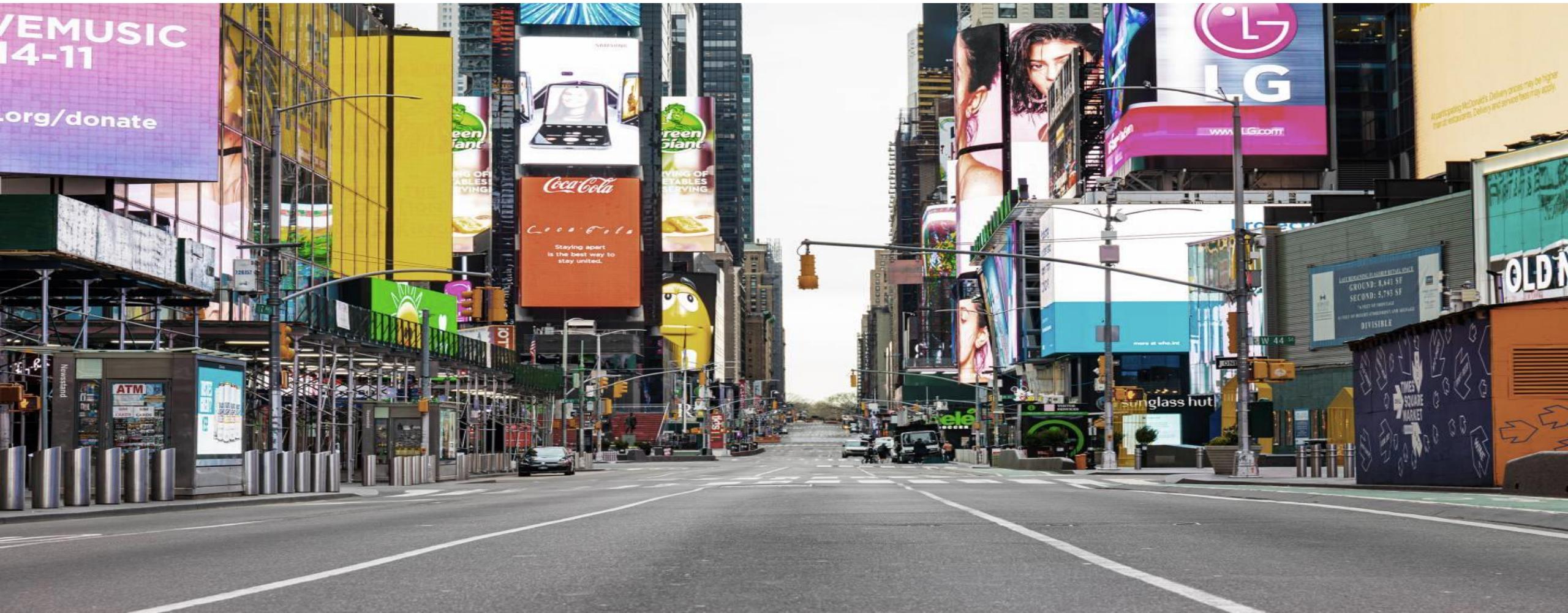
Agenda

- Characterization of Data from CUIMC
- COVID-19 is a multisystem disease
- My Columbia Clinical Experience and Some Takeaways



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COVID-19 Hub



	Women (n, %) 1063 (42.2%)	Men (n, %) 1454 (57.8%)
Demographics		
Age, years, median, IQR	69 (58, 67)	65 (53, 75)
BMI*	28.7 (24.8, 34.1)	27.5 (24.4, 31.5)
Race/ethnicity		
Hispanic	528 (49.7%)	716 (49.2%)
Non-Hispanic white	93 (8.7%)	134 (9.2%)
Non-Hispanic black	134 (12.6%)	179 (12.3%)
Others/Missing	308 (29.0%)	425 (29.2%)
Comorbidities		
Hypertension	618 (58.1%)	762 (52.4%)
Diabetes	393 (37.0%)	541 (37.2%)
CAD	118 (11.1%)	208 (14.3%)
Heart Failure	120 (11.3%)	153 (10.5%)
Chronic lung disease	236 (22.2%)	204 (14.0%)
CKD	136 (12.8%)	215 (14.8%)
Stroke/TIA	90 (8.5%)	130 (8.9%)
Cancer	97 (9.1%)	143 (9.8%)
Atrial arrhythmias	87 (8.2%)	130 (8.9%)

Unpublished data. Columbia University Medical Center

Biochemical Values in Critically Ill Patients

Study population (n=257)	
Lactate (mmol/L)	1.5 (1.1-2.2), 223
Creatinine (mg/dL)	1.5 (0.9-2.4)
Proteinuria	189/218 (87%)
Urine protein concentration (mg/dL)	100 (30-300)
White blood cell count ($\times 10^3$ cells per μ L)	9.8 (6.6-12.7)
Lymphocyte count ($\times 10^3$ cells per μ L)	0.8 (0.6-1.2), 228
Platelet count ($\times 10^3$ cells per μ L)	199 (148-270)
Bilirubin (mg/dL)	0.6 (0.4-0.8), 242
Aspartate aminotransferase (U/L)	61 (42-104), 242
Alanine aminotransferase (U/L)	39 (27-67), 242
Creatine kinase (U/L)	236 (103-646), 223
Prothrombin time (s)	14.7 (14.0-15.8), 241
Interleukin-6 (pg/mL)	26 (11-69), 237
High-sensitivity C-reactive protein (mg/L)	158 (92-254), 253
Ferritin (ng/mL)	924 (472-1789), 253
D-dimer (μ g/mL)	1.6 (0.9-3.5), 244
High-sensitivity cardiac troponin T (ng/L)	19 (9-52), 254
Procalcitonin (ng/mL)	0.35 (0.17-1.1), 255

Data are median (IQR) or n (%). Data are median (IQR), n if fewer patients were assessed for those laboratory studies than the total number of patients in the study.

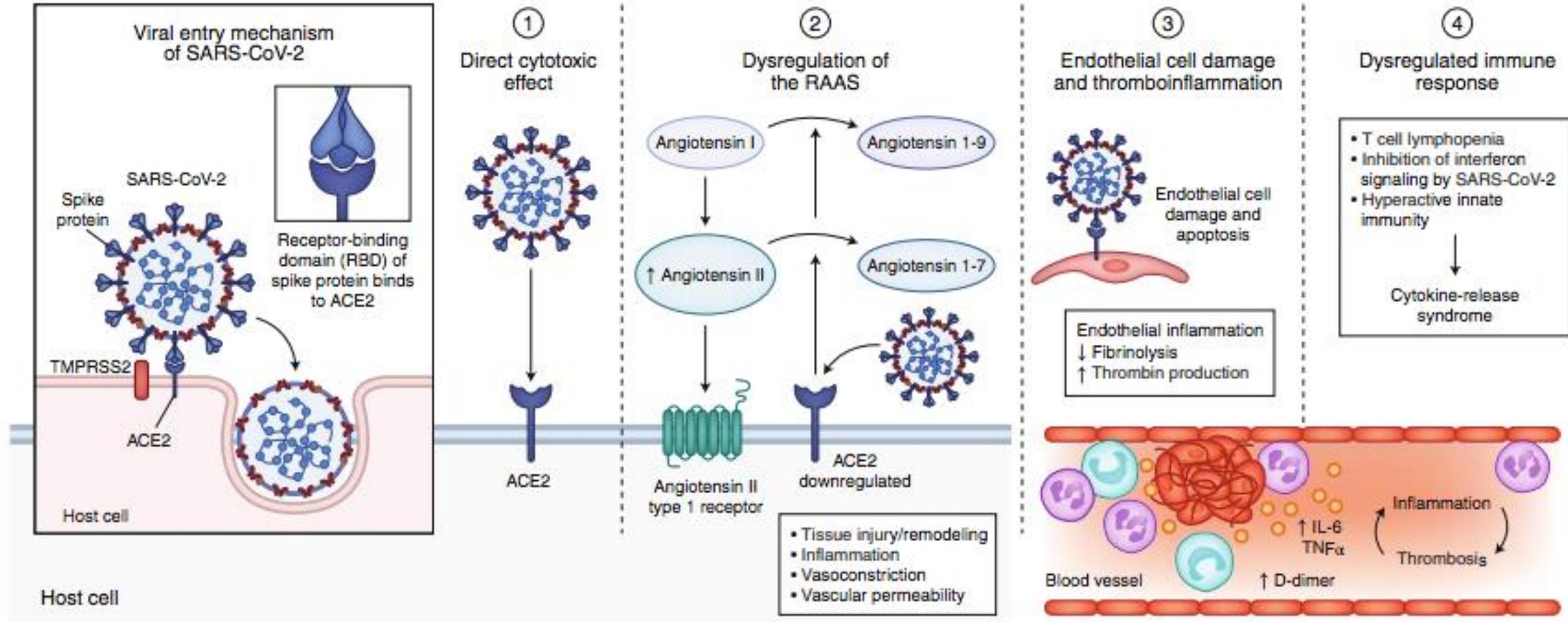
Table 2: Biochemical and biomarker values

Cummings M et al. *Lancet*. 2020. 395: 1763-70

Extrapulmonary manifestations of COVID-19

Aakriti Gupta  ^{1,2,3,20}, Mahesh V. Madhavan  ^{1,2,20}, Kartik Sehgal  ^{4,5,6,20}, Nandini Nair⁷,
Shiwani Mahajan  ^{3,8}, Tejasav S. Sehrawat  ⁹, Behnood Bikdeli ^{1,2,3}, Neha Ahluwalia ¹⁰, John C. Ausiello⁷,
Elaine Y. Wan¹, Daniel E. Freedberg¹¹, Ajay J. Kirtane², Sahil A. Parikh^{1,2}, Mathew S. Maurer¹,
Anna S. Nordvig¹², Domenico Accili⁷, Joan M. Bathon¹³, Sumit Mohan  ^{14,15}, Kenneth A. Bauer^{4,6},
Martin B. Leon^{1,2}, Harlan M. Krumholz  ^{3,8,16}, Nir Uriel¹, Mandeep R. Mehra¹⁷, Mitchell S. V. Elkind  ^{12,15},
Gregg W. Stone^{2,18}, Allan Schwartz¹, David D. Ho¹⁹, John P. Bilezikian⁷ and Donald W. Landry¹⁴ 

Pathophysiology



Gupta A, Madhavan MV, Sehgal K et al. *Nature Medicine*. 2020

Neurologic

Headaches
Dizziness
Encephalopathy
Guillain-Barré
Ageusia
Myalgia
Anosmia
Stroke

**Renal**

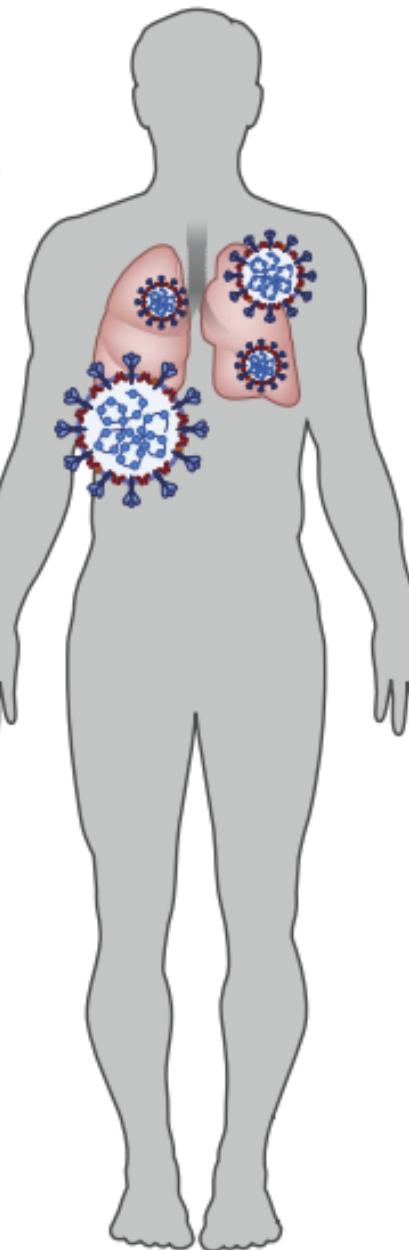
Acute kidney injury
Proteinuria
Hematuria

**Hepatic**

Elevated
aminotransferases
Elevated bilirubin

**Gastrointestinal**

Diarrhea
Nausea/vomiting
Abdominal pain
Anorexia

**Thromboembolism**

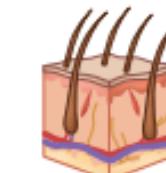
Deep vein thrombosis
Pulmonary embolism
Catheter-related thrombosis

**Cardiac**

Takotsubo cardiomyopathy
Myocardial injury/myocarditis
Cardiac arrhythmias
Cardiogenic shock
Myocardial ischemia
Acute cor pulmonale

**Endocrine**

Hyperglycemia
Diabetic ketoacidosis

**Dermatological**

Petechiae
Livedo reticularis
Erythematous rash
Urticaria
Vesicles
Pernio-like lesions

Gupta A, Madhavan MV, Sehgal K
et al. *Nature Medicine*. 2020

Hematologic Manifestations

- Laboratory markers:
 - Cell counts: lymphopenia, leukocytosis, neutrophilia, thrombocytopenia
 - Inflammatory markers: elevations in ESR, CRP, ferritin, interleukin-6, lactate dehydrogenase
 - Coagulation indices: elevated D-dimer and fibrinogen, prolonged prothrombin time and partial thromboplastin time

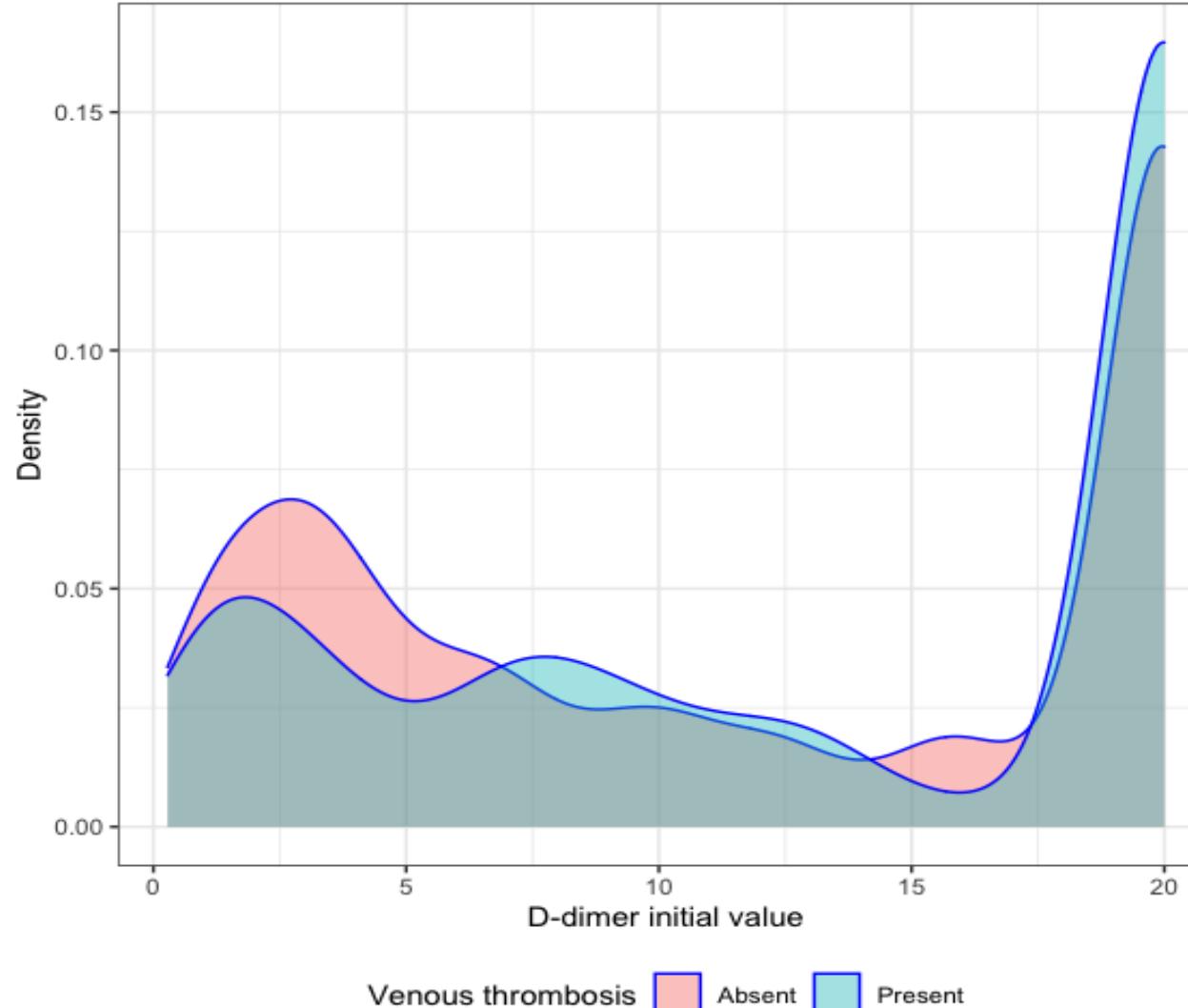
Hematologic Manifestations

- Arterial thrombotic complications: myocardial infarction, ischemic stroke, acute limb, and mesenteric ischemia
- Venous thrombotic complications: deep vein thrombosis and pulmonary embolism
- Catheter-related thrombosis: thrombosis in arterial and venous catheters and extracorporeal circuits

Clinical Considerations

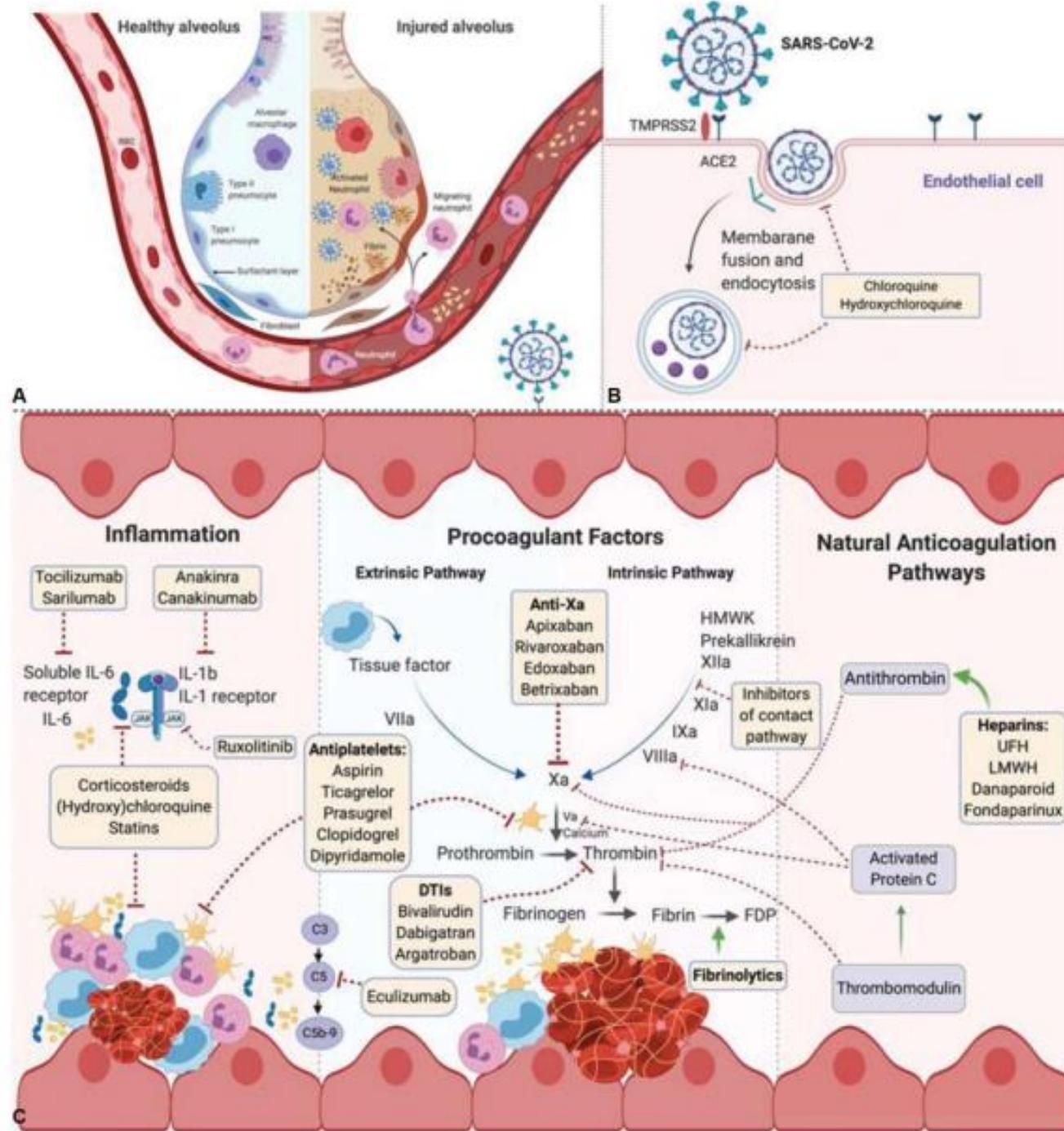
- Strongly consider pharmacological prophylaxis for venous thromboembolism in the absence of absolute contraindications
- There is no evidence for empiric therapeutic anticoagulation currently, but clinical trials are ongoing
- Consider post-hospitalization extended thromboprophylaxis on an individual patient basis, particularly for those with history of critical illness
- Do not base decisions about anticoagulation on D-dimer values alone. They should be used in the context of the clinical presentation.

Distribution of D-dimer in relation with thromboembolism



Median peak D-Dimer values exceeded 10 mg/dL even in patients with negative venous imaging studies. D-Dimer values alone should not prompt routine initiation of therapeutic anticoagulation in COVID-19 patients

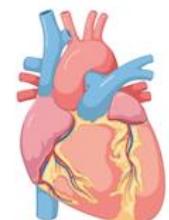
Unpublished data. Columbia University Medical Center



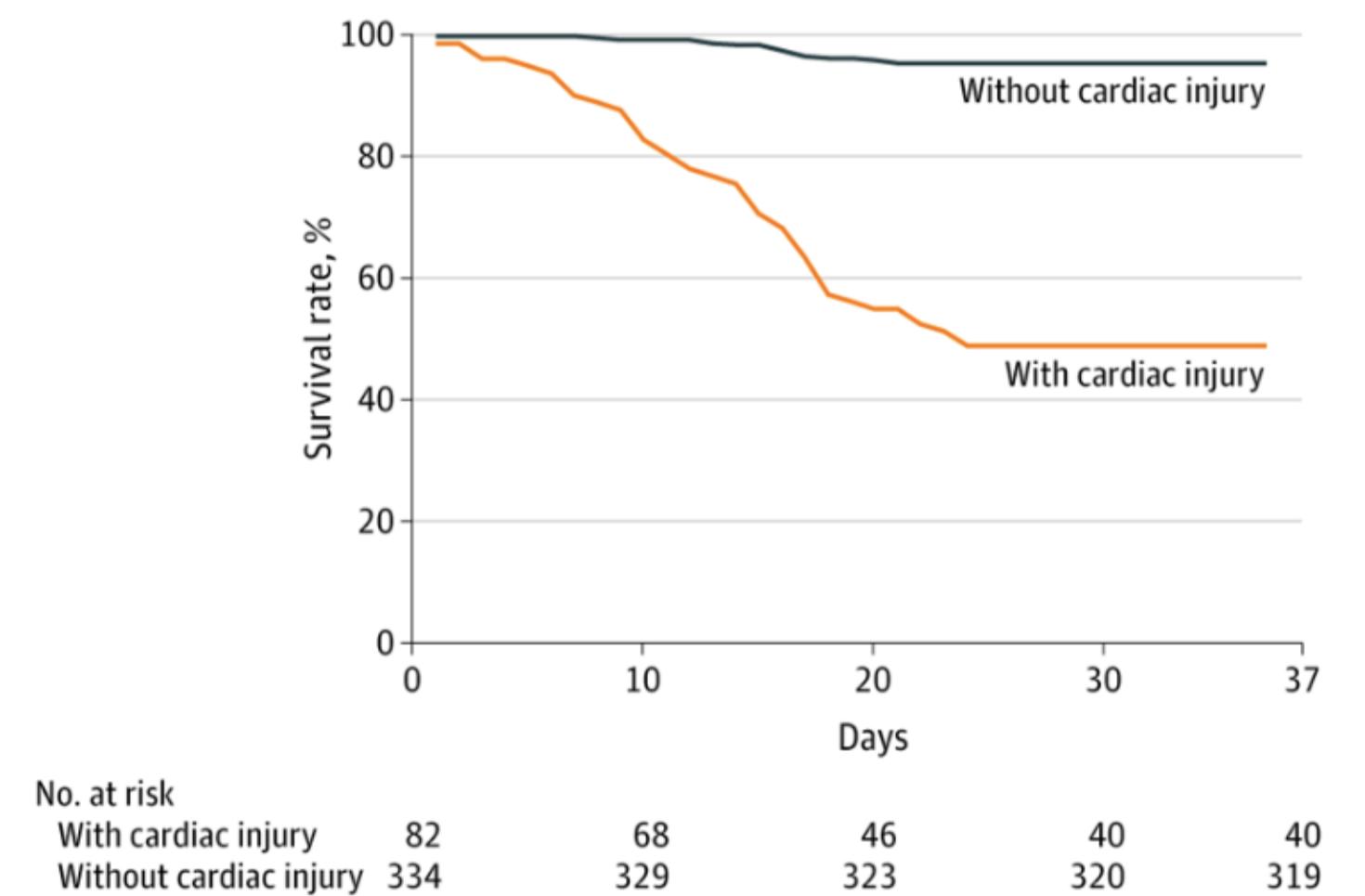
Bikdeli B, Madhavan MV, Gupta A.
Thromb Haemost 2020; 120(07):
1004-1024

Cardiovascular Manifestations

- Myocardial ischemia and myocardial infarction (type 1 and 2)
- Myocarditis
- Arrhythmia: new-onset atrial fibrillation and flutter, sinus tachycardia, sinus bradycardia, QT_c prolongation (often drug-induced), torsades de pointes, sudden cardiac death, pulseless electrical activity
- Cardiomyopathy: biventricular, isolated right or left ventricular dysfunction
- Cardiogenic shock



Acute cardiac injury: poor prognosis



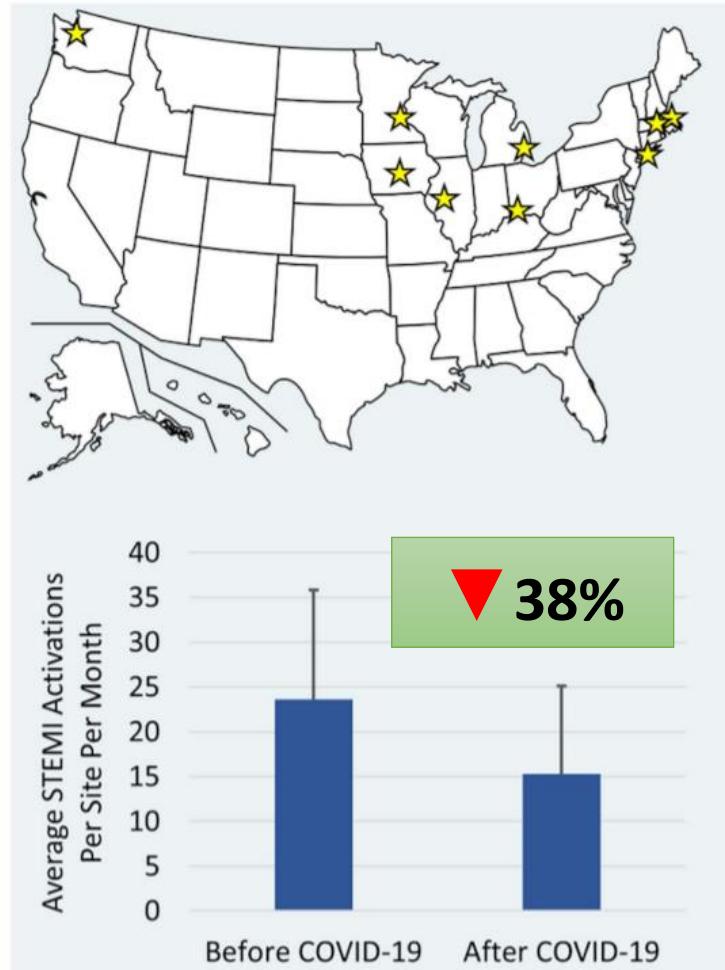
COVID-19 and cardiac arrhythmia

- Prevalent in cohort studies new onset atrial fibrillation, heart block, and ventricular arrhythmias
 - 17% of hospitalized patients, 44% ICU
- Metabolic disarray associated with critical illness as a risk factor
 - Hypoxemia
 - Acidemia
 - Electrolyte derangement
- Prolonged QTc common
 - 6% of 4250 patients with COVID-19 had prolonged QTc (>500 milliseconds) at the time of admission

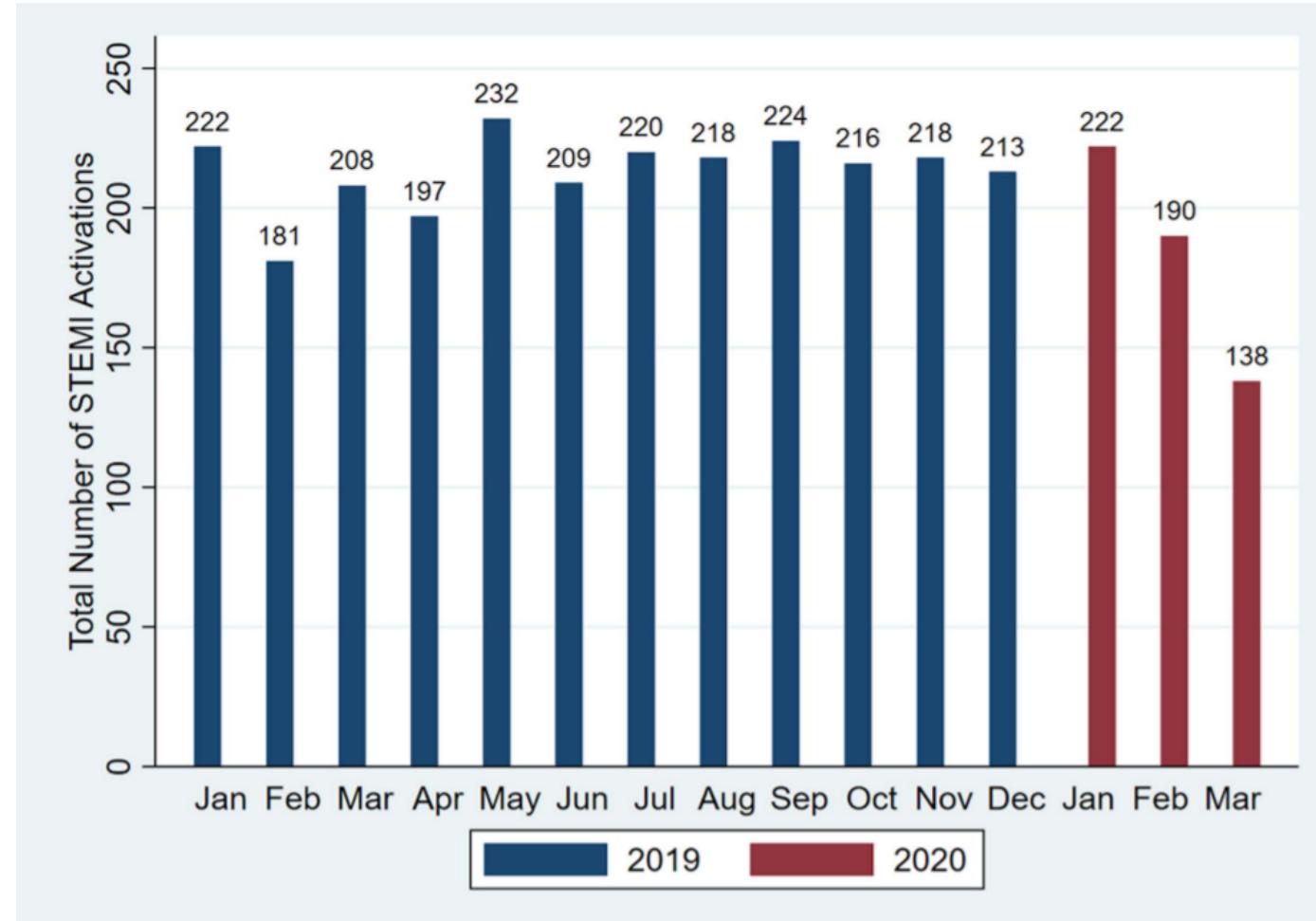
Clinical Considerations

- Continue ACE inhibitors/ARBs if patients already on them
- Perform ECG/telemetry monitoring for patients at medium-to-high risk for torsades de pointes who are being treated with QTc prolonging drugs
- Carefully consider utility of diagnostic modalities including cardiac imaging, invasive hemodynamic assessments, and endomyocardial biopsies
- Primary PCI remains preferred approach for most patients with STEMI
- Consider point-of-care ultrasound to assess for regional wall motion abnormalities to help distinguish type 1 myocardial infarction from myocarditis

STEMI Activations: United States

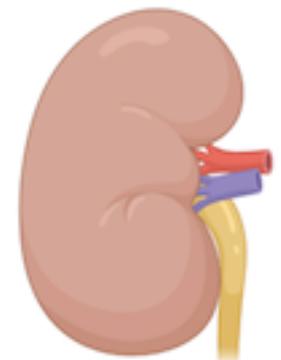


Garcia S. 2020. J Am Coll Cardiol. doi:10.1016



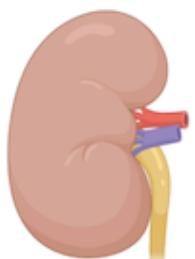
Renal manifestations

- Acute kidney injury - more than 50%, and 29% RRT at CUIMC ICU
- Electrolyte abnormalities (hyperkalemia, hyponatremia and hypernatremia among others)
- Proteinuria - 87% of critically ill at CUMC
- Hematuria
- Clotting of extracorporeal circuits used for RRT



Clinical Considerations

- Evaluate urine analysis and **protein-to-creatinine ratio at admission**
- Consider **shared RRT protocols**, utilize peritoneal dialysis
- Consider **empiric low-dose systemic anticoagulation** during initiation and day-to-day management of extracorporeal circuits



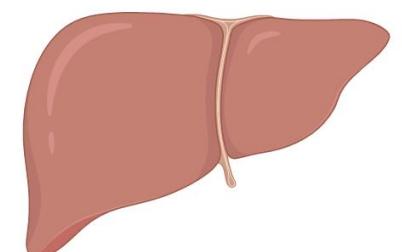
GI manifestations

Clinical Presentations

- Nausea/vomiting, diarrhea, abdominal pain
- Rare cases of mesenteric ischemia and gastrointestinal bleeding
- Laboratory markers: elevated hepatic transaminases and low serum albumin

Clinical Recommendations

- Prioritize testing for SARS-CoV-2 among patients who present with gastrointestinal symptoms, when testing resources are scarce
- Utilize diagnostic endoscopy only for therapeutic reasons (large volume gastrointestinal bleeding or biliary obstruction)
- Avoid additional diagnostic tests for aminotransferase elevations <5 times upper limit of normal unless additional features raise the pre-test probability of actionable findings (e.g., hyperbilirubinemia, right upper quadrant pain, hepatomegaly)

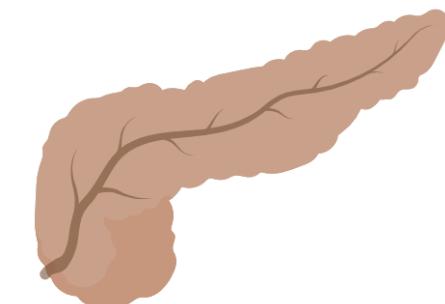


Endocrine manifestations

- Hyperglycemia
- Diabetic ketoacidosis even in patients with previously undiagnosed diabetes
- Euglycemic ketosis
- Severe illness in patients with pre-existing diabetes and obesity

Clinical Recommendations

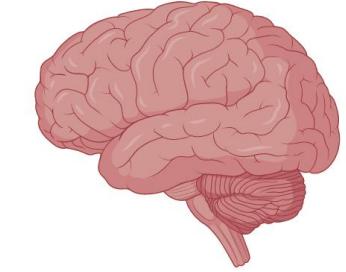
- Measure **hemoglobin A1C** in patients without known history of diabetes mellitus who present with hyperglycemia and/or ketoacidosis
- Consider checking **serum ketones** in patients with hyperglycemia who are on SGLT2i



Neurologic manifestations

Clinical Presentations

- Headache, dizziness
- Ageusia, anorexia, myalgias, fatigue,
- Stroke
- Encephalopathy, encephalitis, GBS, AHNE
- Conjunctivitis



Clinical Recommendations

- Utilize remote video evaluation, whenever possible, for hospitalized COVID-19 patients with stroke
- Continue adherence to established guidelines for acute ischemic stroke, including thrombolysis and thrombectomy, while recognizing the need to minimize use of personal protective equipment

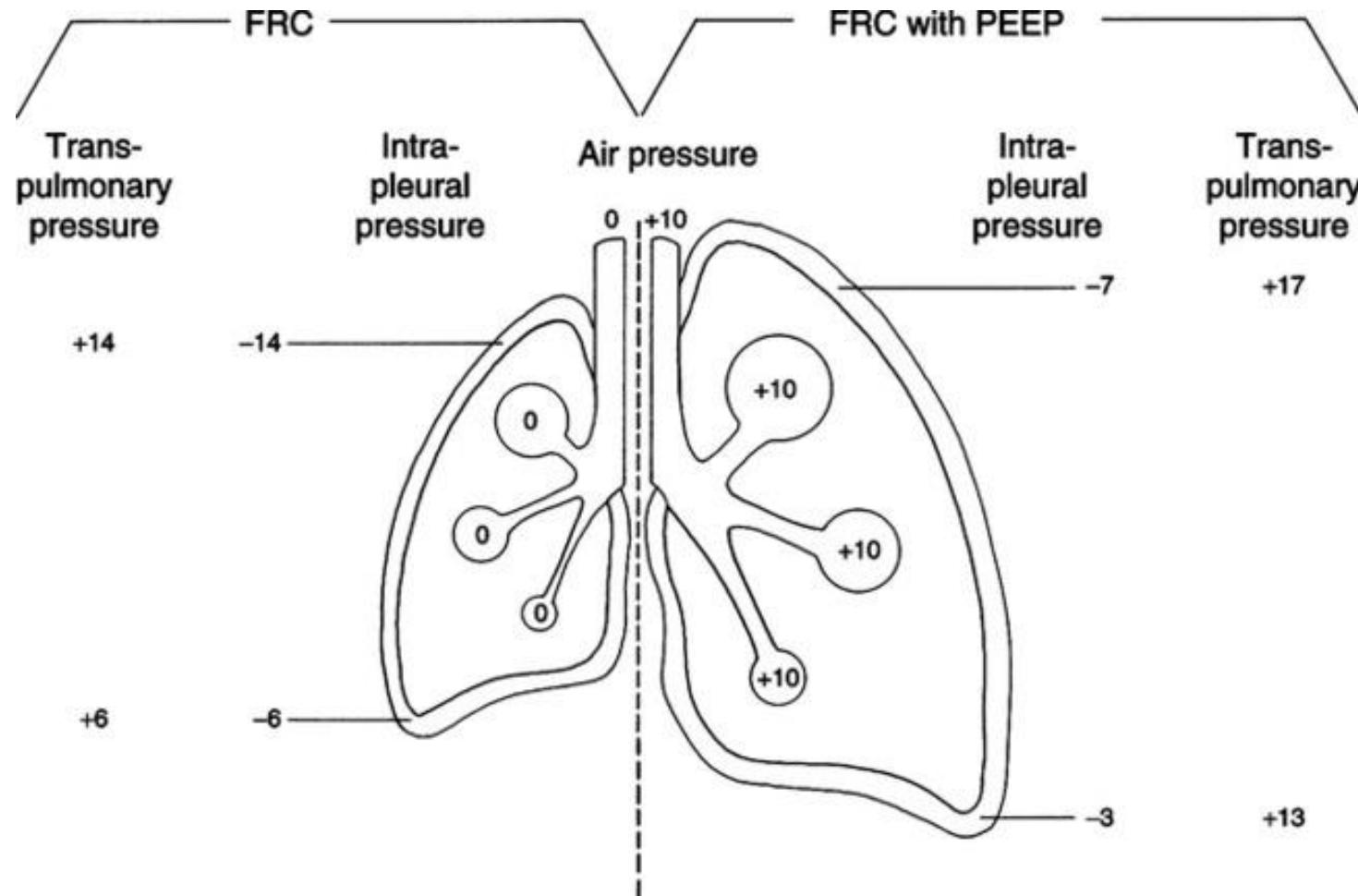
My Columbia Experience

- Deployed in the Intensive Care Unit for majority of the time between March through June
- Small and big changes in our hospital system
- A lot of love to go around!

Takeaways From My COVID-19 Experience



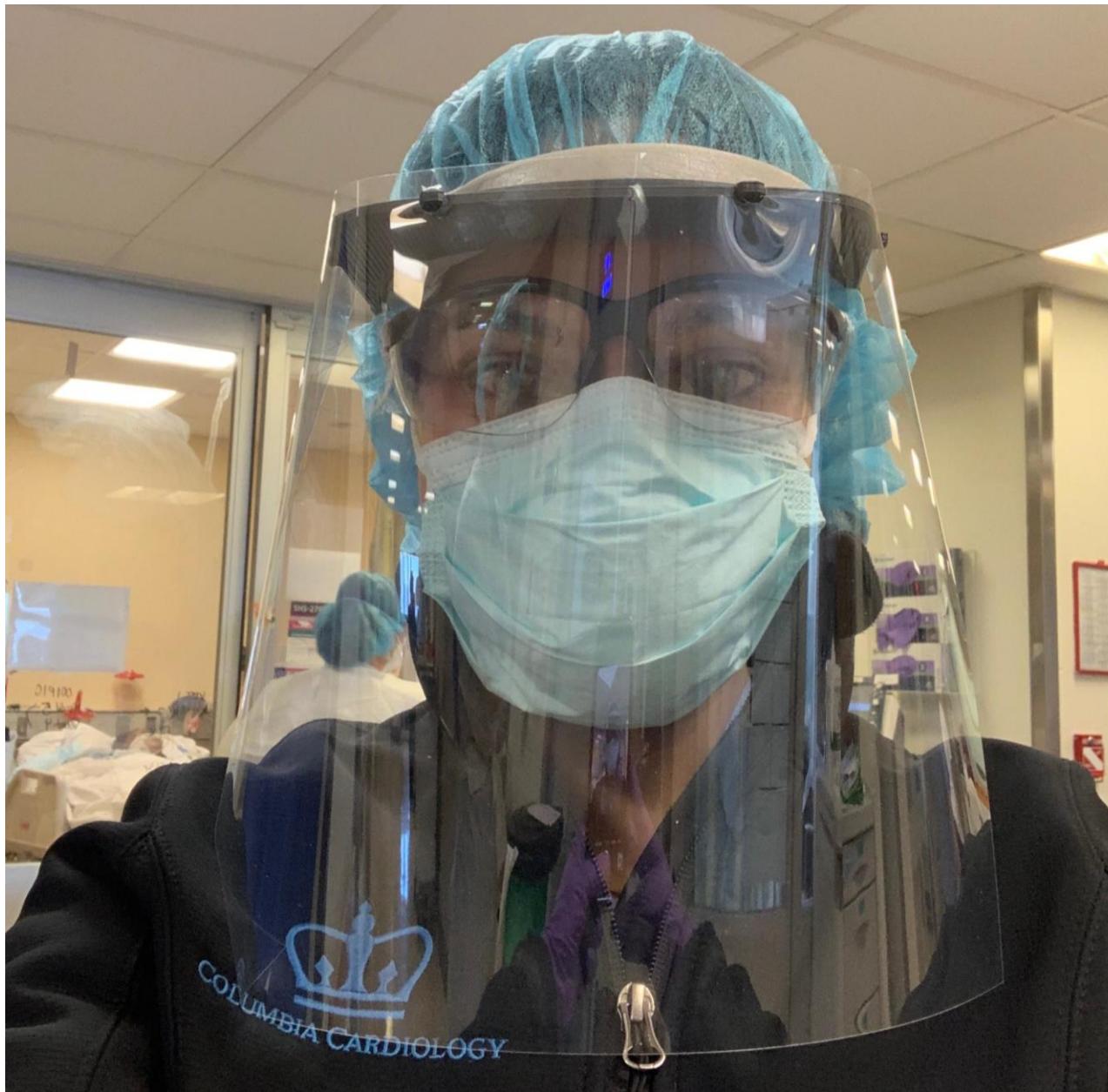
Position infusion pumps outside the patients' rooms using extended tubing



Be cautious of high PEEP strategy – high risk of pneumothorax!



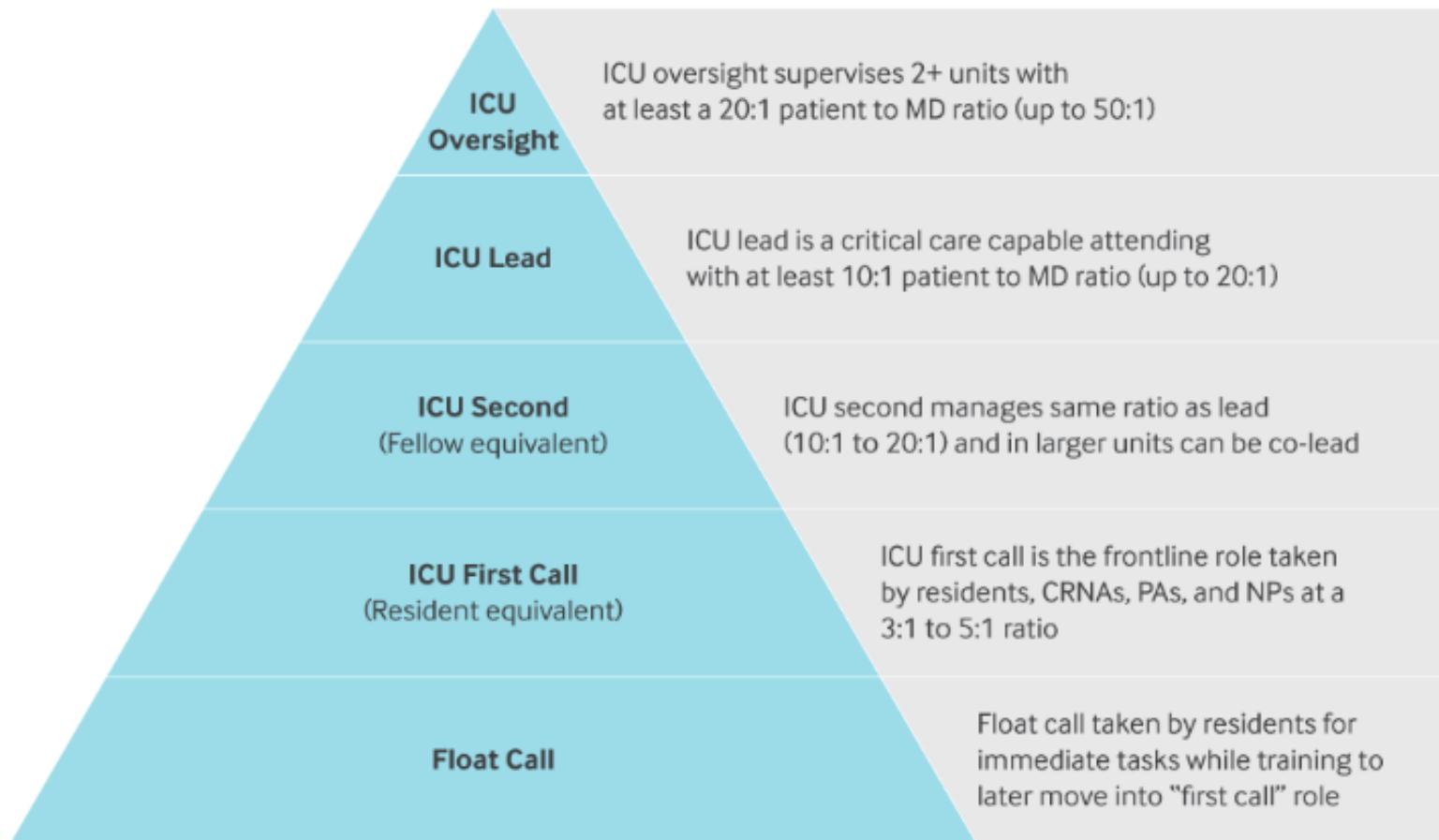
- Utilize **awake proning** as much as possible in patients with low $\text{PaO}_2/\text{FiO}_2$ ratio
- Associated with improved oxygenation and lower rates of mechanical intubation



PPE:

- 3D printed face shields that were produced at scale
- Covered N95 mask with a surgical mask for preservation
- Make a list of tasks needed to be done in the patient room, and one person should take care of them

Supervised ICU Physician Pyramid-Staffing Model



Source: NYP/CUIMC/WC COVID-19 critical care medicine planning committee*

NEJM Catalyst (catalyst.nejm.org) © Massachusetts Medical Society

Be creative with physician roles

From dermatologists to cardiothoracic surgeons – we were all COVIDologists!



- Utilize point-of-care ultrasound as much as possible – Can be utilized for cardiac assessment for myocardial ischemia or pulmonary embolism
- High threshold for CT with contrast given that patients have high susceptibility for renal injury



Utilize telehealth as
much as possible

But....

Have systems in place
that can facilitate safe
patient care when
patients need to be seen



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Takeaways

- COVID-19 is a multisystem disease. This has implications for both, diagnosis and treatment, and for long-term follow up after discharge.
- Severely ill patients with COVID-19 frequently manifest with cardiac and thromboembolic complications.
- Pathways to facilitate care of patients without COVID-19, but with life-threatening conditions like ACS or HF need to be in place.
- Healthcare workers, physicians, and hospital systems need to be creative about how to best care for patients with COVID-19 while minimizing exposure to healthcare personnel.



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COVID-19

The Search For Effective Therapy

Prof. Otavio Berwanger (MD; PhD)
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Flávia Machado - **BRICNet**

Renato Delascio Lopes - **Brazilian Clinical Research Institute (BCRI)/Duke University**



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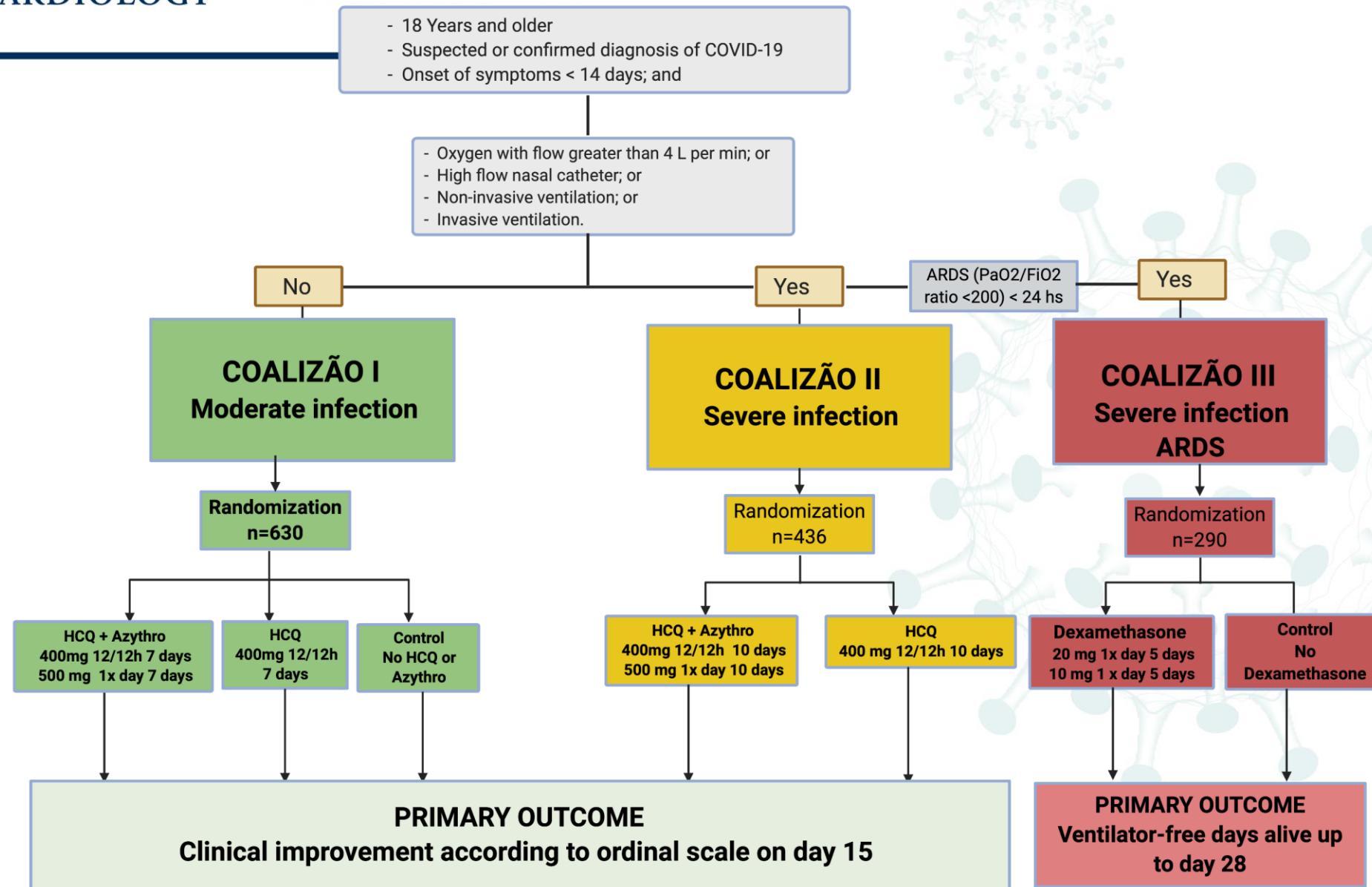
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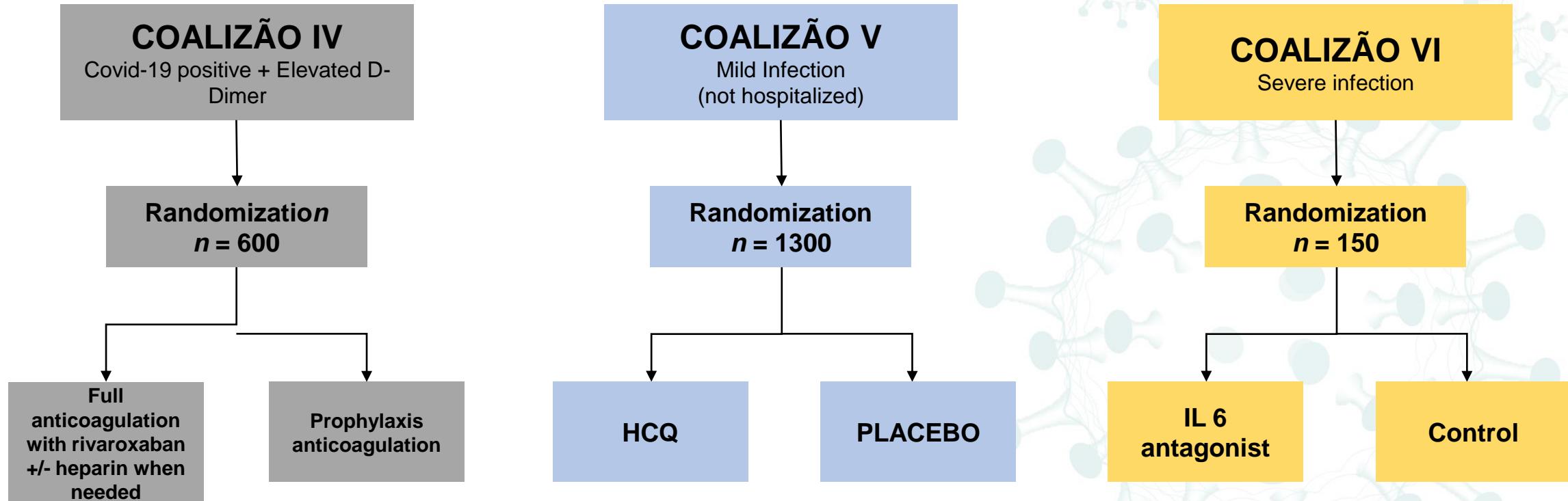
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COVID-19

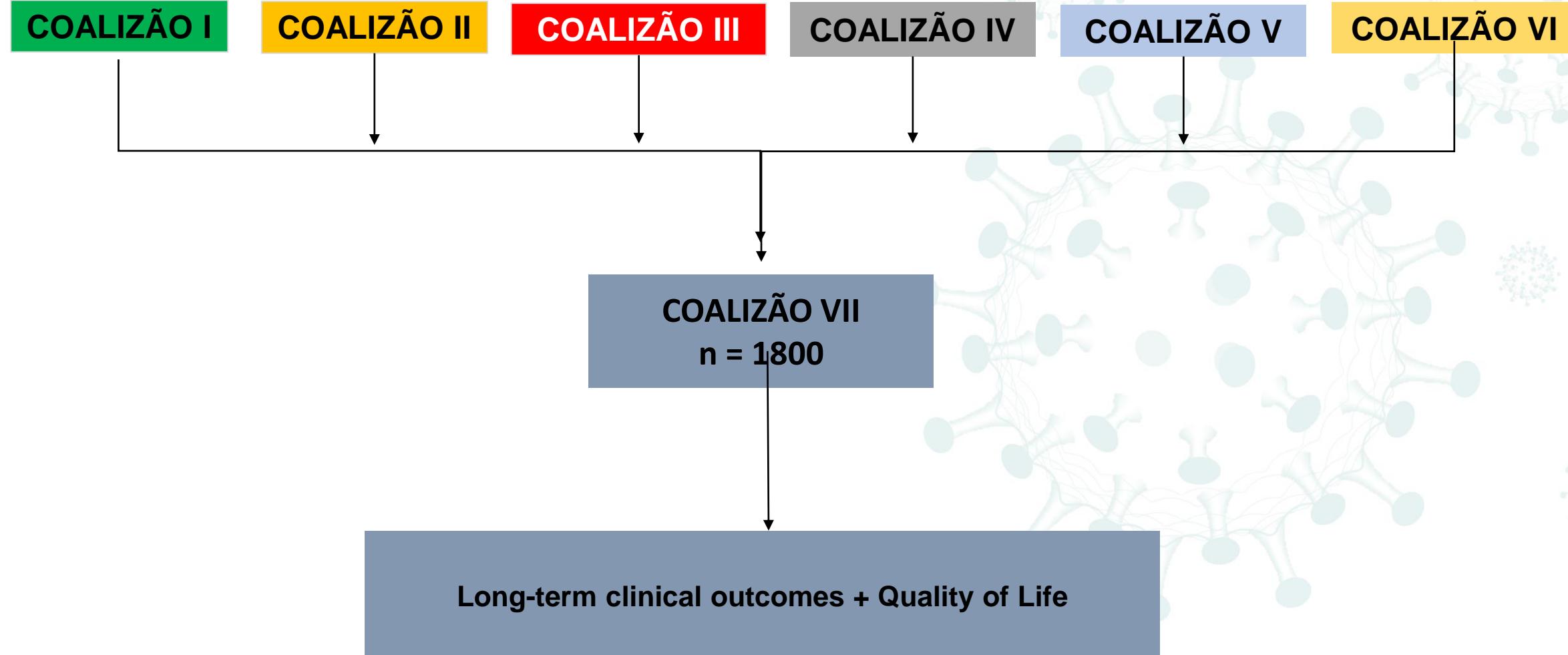






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COVID-19





Hospitalized adults with pneumonia caused by SARS CoV2

Randomized,
Double-Blind

**Tofacitinib BID for 14 days
(or until hospital discharge)
+ standard of care**

**Matching Placebo BID for 14 days
(or until hospital discharge)
+ standard of care**

**Daily Visits while hospitalized,
Follow-up at 14 and 28 days**

**Daily Visits while hospitalized,
Follow-up at 14 and 28 days**

Death or respiratory failure (1, 2 or 3 on the 8-point NIAID ordinal scale of disease severity) at Day 28

Takeaways

- RCTs represent the gold standard for assessing the efficacy and safety of COVID-19 therapies
- Collaboration is key for conducting large-scale and high quality RCTs in a timely manner
- “Knowledge is the Enemy of Disease” – we need to follow the scientific pathway

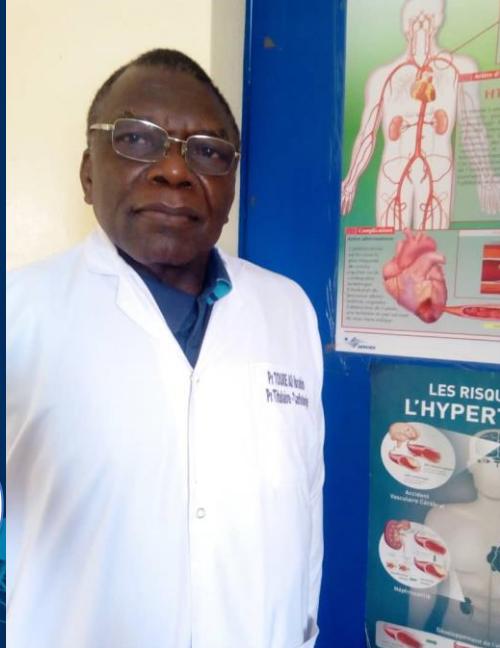


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COVID-19 Hub



An overview of the COVID-19 pandemic as it looks like in AFRICA



PROF TOURE ALI IBRAHIM MD PhD

VICE PRESIDENT WEST PANAFRICAN SOCIETY OF CARDIOLOGY(PASCAR)

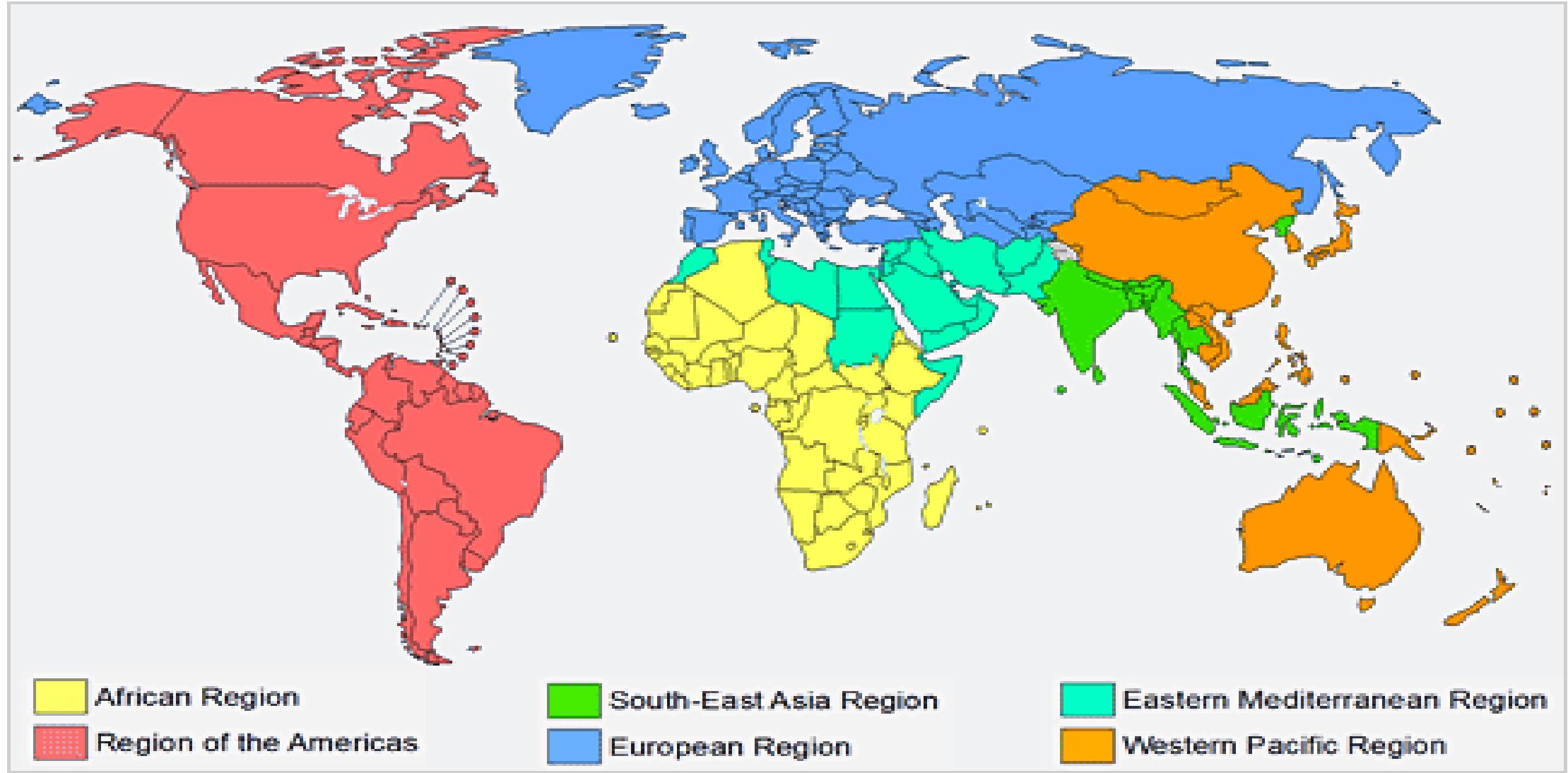
Past Dean of the faculty of medical sciences of NIGER(west Africa)

Chairman of internal medicine department LAMORDE Teaching Hospital NIAMEY NIGER

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Within the WHO system, Africa is divided between two regional offices :

- ✓ The WHO Regional Office for Africa comprises 47 countries which include Algeria and most of sub-Saharan Africa.
- ✓ While the WHO Regional Office for the Eastern Mediterranean includes an additional seven African countries (Djibouti, Egypt, Libya, Morocco, Somalia, Sudan and Tunisia).



- **Brazzaville/Cairo** – COVID-19 infections in Africa on July 9th 2020 surpassed 523706, and there is concern as a growing number of countries are experiencing a sharp rise in cases according to WHO AFRO last report.
- So far, in less than five months, the virus has claimed 12244 lives, overtaking the 11 308 lives lost in the world's worst Ebola outbreak in West Africa between 2014 and 2016.

- Cases have more than doubled in 22 countries in the region over the past month.
- Nearly two-thirds of countries are experiencing community transmission. Algeria, Egypt, Ghana, Nigeria and South Africa account for about 71% of COVID-19 cases.
- South Africa alone accounts for 43% of the continent's total cases(224665 cases and 3602deaths).
- However, the accelerating growth trend is not uniform across the continent, with some countries recording a steady rise in cases, indicating a protracted pandemic.

- Eritrea, Gambia, Mali, Niger ,Seychelles and Togo are witnessing long doubling times and low growth rates. Seychelles had not experienced a case in nearly two months, but in the past week had dozens of new imported cases, linked to crew members of an international fishing vessel.
- Although Egypt accounts for 15 % of cumulative cases(78304 cases with 3564deaths ,Nigeria 30249 cases with 684 deaths)....Niger has 963 cases with 68 deaths(6.9%) has seen a decline in the past weeks with.

- *“With more than a third of countries in Africa doubling their cases over the past month, the threat of COVID-19 overwhelming fragile health systems on the continent is escalating,”* said Dr Matshidiso Moeti, World Health Organization (WHO) Director for Africa.
- “So far the continent has avoided disaster and if countries continue to strengthen key public health measures such as testing, tracing contacts and isolating cases, we can slow down the spread of the virus to a manageable level.” He conclude

- 88% of COVID-19 infections are among people aged 60 and below, likely due to Africa's relatively young population.
- However, the likelihood of dying from COVID-19 rises with increasing age and the existence of co-morbidities, with the risk of death among patients aged 60 years and above being 10 times higher compared with those below 60.
- *"Communities across the continent have a crucial role to play in controlling the pandemic, especially as countries begin easing lockdowns and opening up their borders,"* said Dr Ahmed Al-Mandhari, WHO Director for the Eastern Mediterranean.

- "As governments continue to implement public health measures, individuals must remain as cautious and vigilant as ever to protect themselves, their families, and their communities.
- Hand washing, mask use, physical distancing and other preventative measures are key to controlling transmission, saving lives, and ensuring that already overwhelmed health systems are not stretched to breaking point."
- As COVID-19 continues to spread, thousands of health workers have also fallen ill. Equipping and protecting health workers is one of the central pillars of the COVID-19 response.

- WHO is working to support countries respond to COVID-19 by providing technical guidance, crucial medical equipment and has remotely trained more than 25 000 health workers.
- WHO has also organized more than 420 shipments of key equipment, including more than 3000 oxygen concentrators, 23 000 GeneXpert diagnostic testing machines and almost 4 million pieces of personal protective equipment for health care workers.

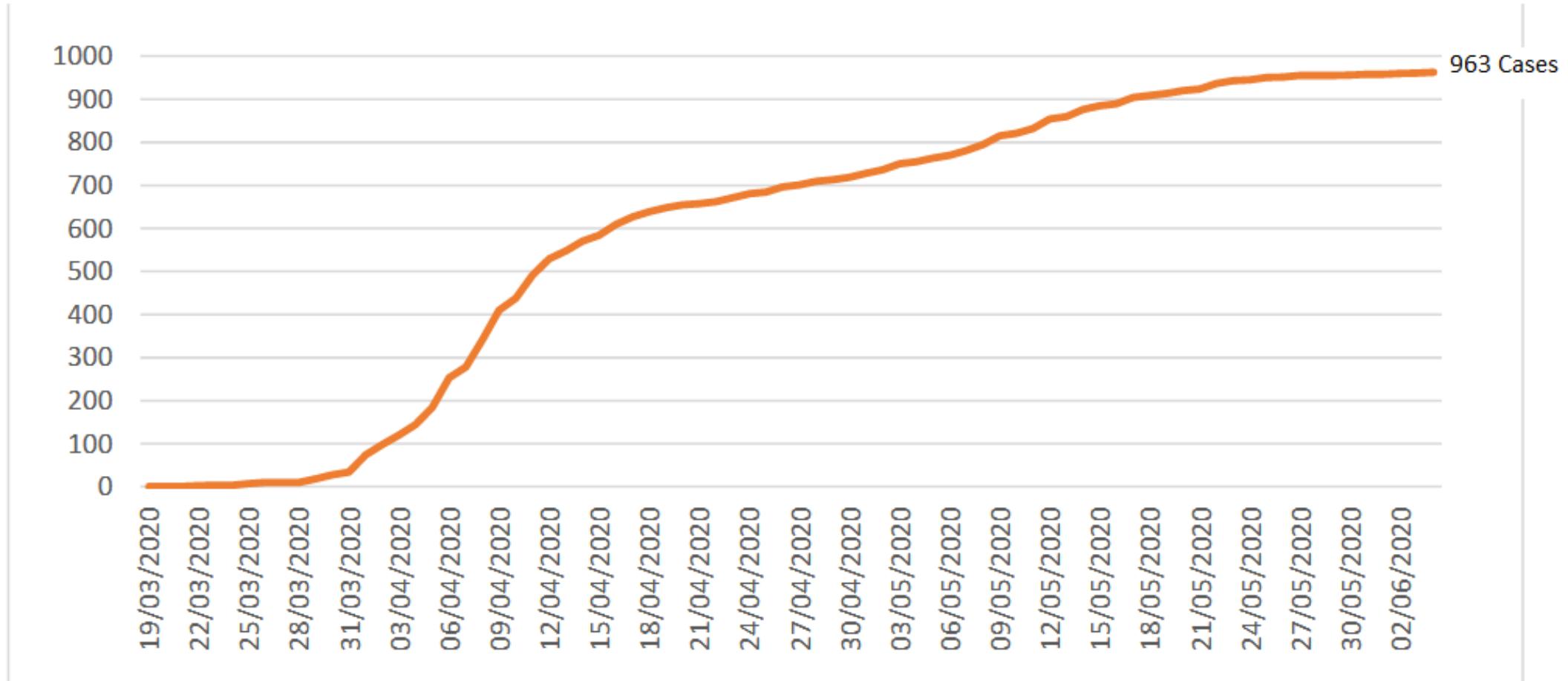
According to the 170th WHO report on the Covid-19, on July 8,2020 :

- 11,669,259 confirmed cases with 539,906 deaths worldwide
- 397,942 confirmed cases with 7,415 deaths in Africa.

Which means Africa represents

- 3,41 % of the worldwide total cases
- 1,37 % of the worldwide total deaths from COVID-19

TABLE 1 : Evolution, in Niger, of the number of positive cases for COVID-19, from March 19 to June 4th, 2020



Source : NHI, from data published by the PHM

TABLE 2 : Evolution of the trend of new positive cases for COVID-19, from March 19 to June 4, 2020

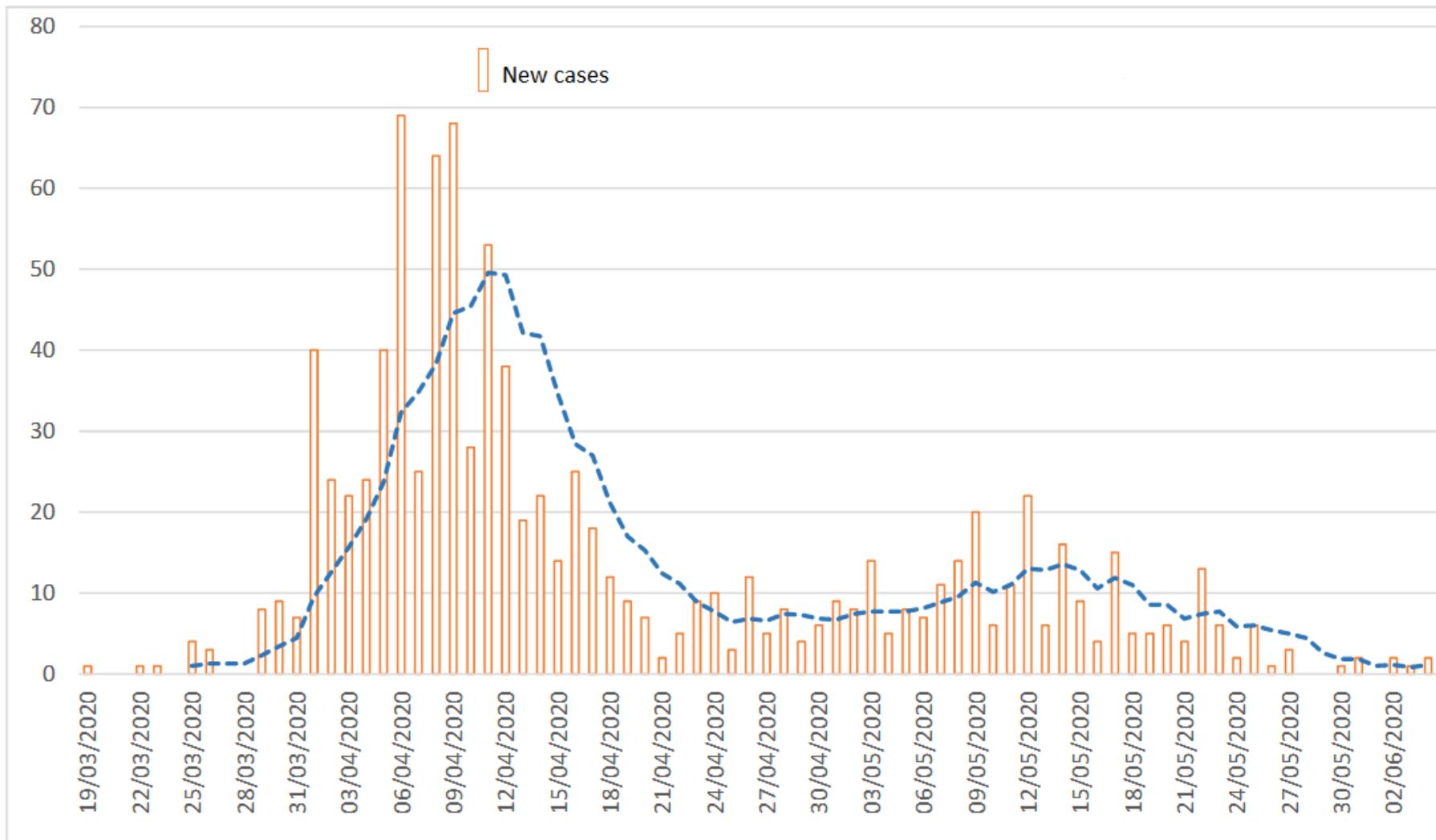
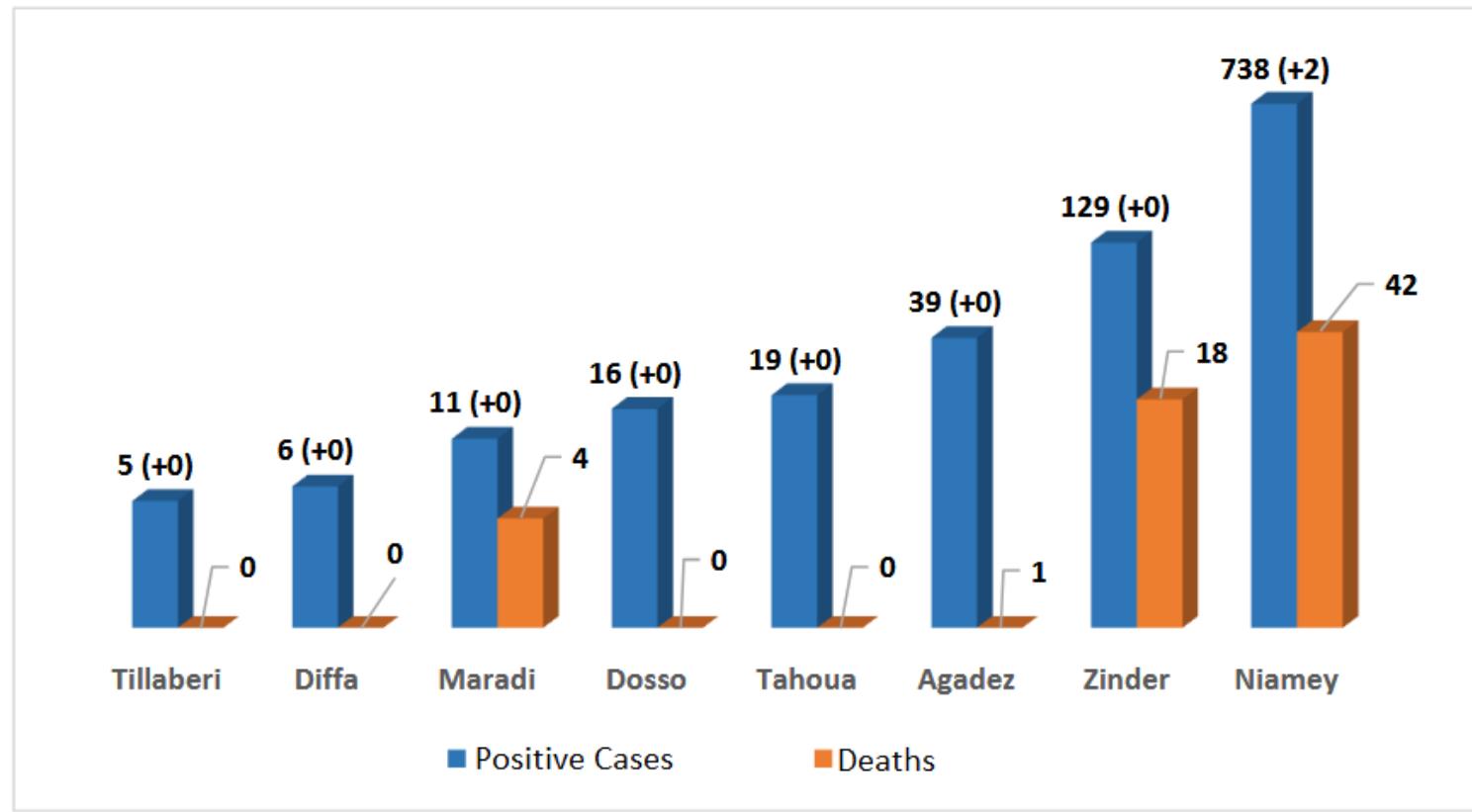


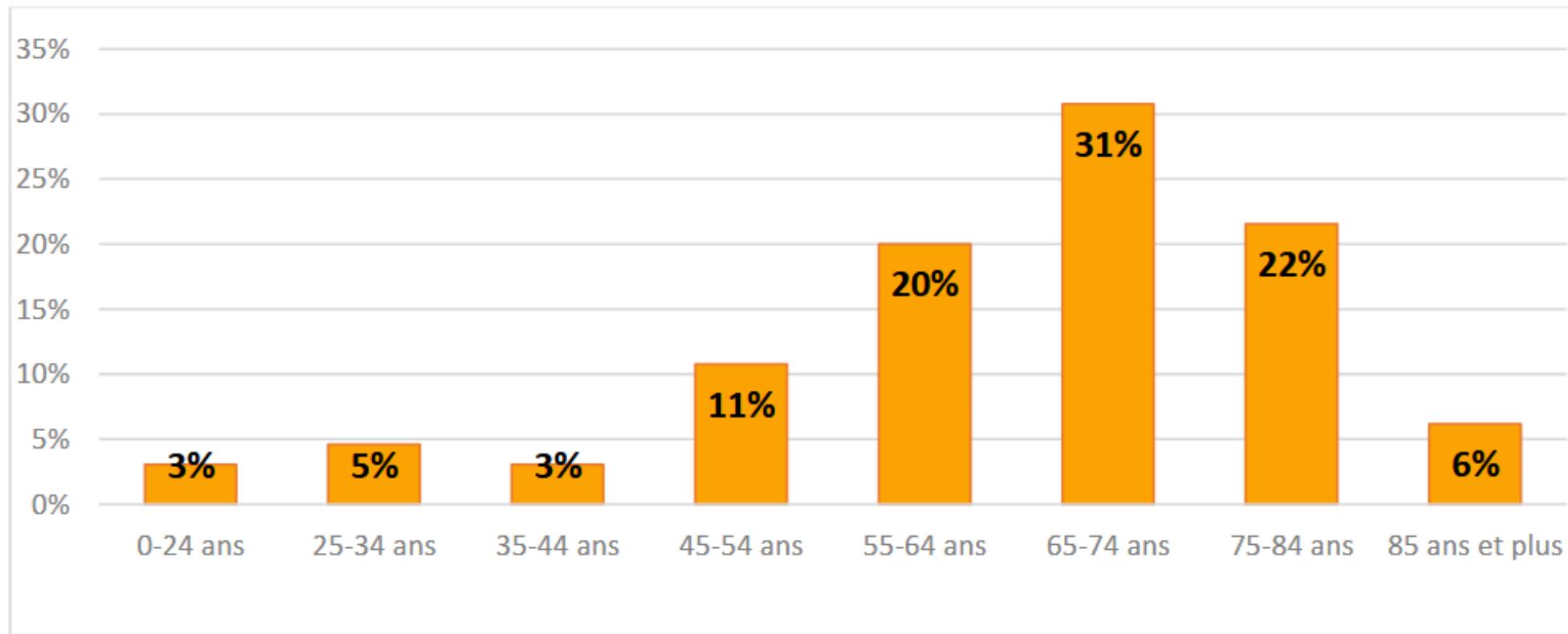
TABLE 3 : Situation in Niger of the number of people infected and deceased with COVID-19, by region, as of June 4, 2020



Source : NHI, from data published by the PHM

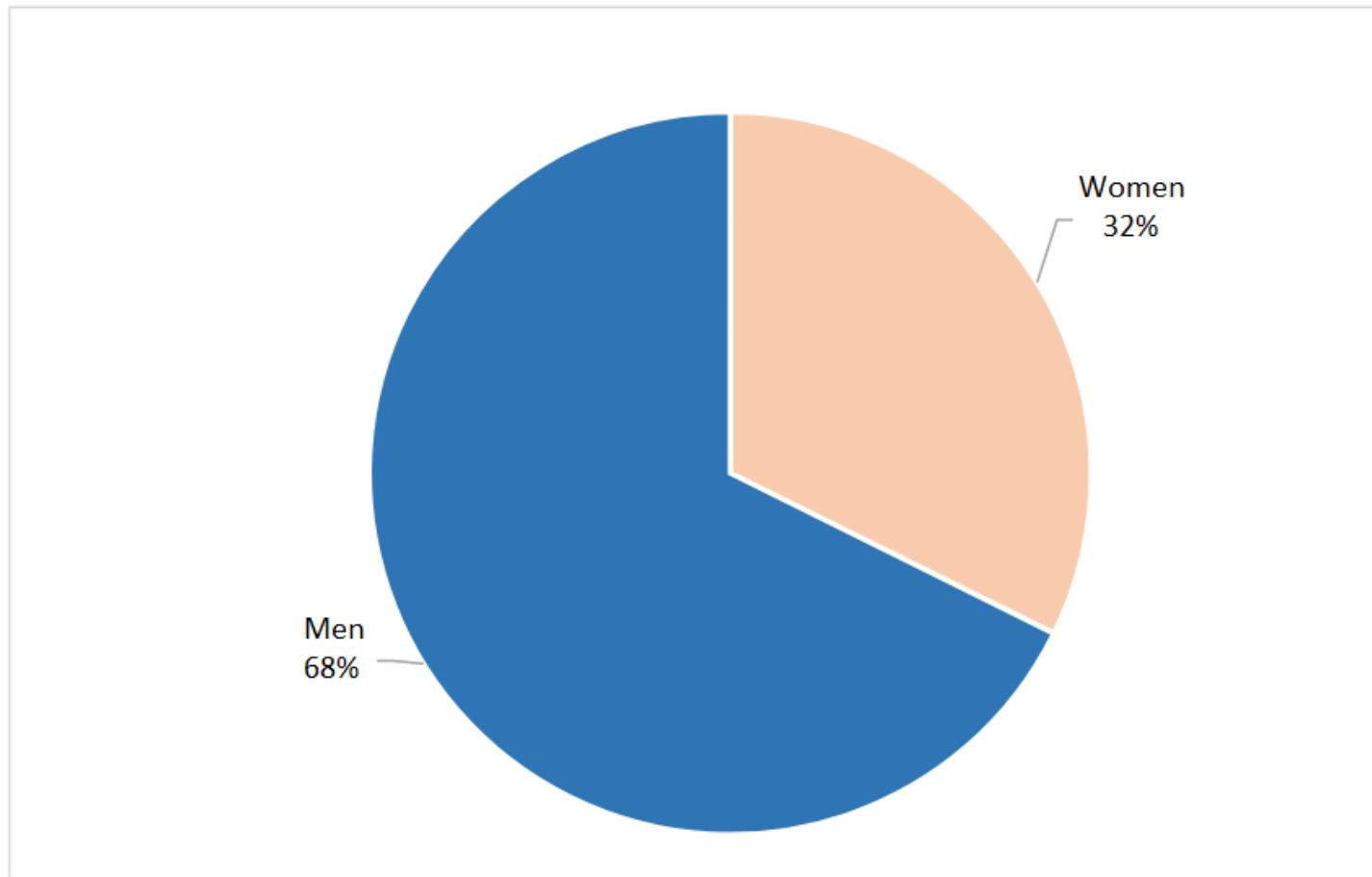
The numbers in brackets represent the new positive cases recorded between June 3rd and June 4th 2020

TABLE 4 : Repartition (in %) of deaths linked to COVID-19 by age group, as of June 4th 2020



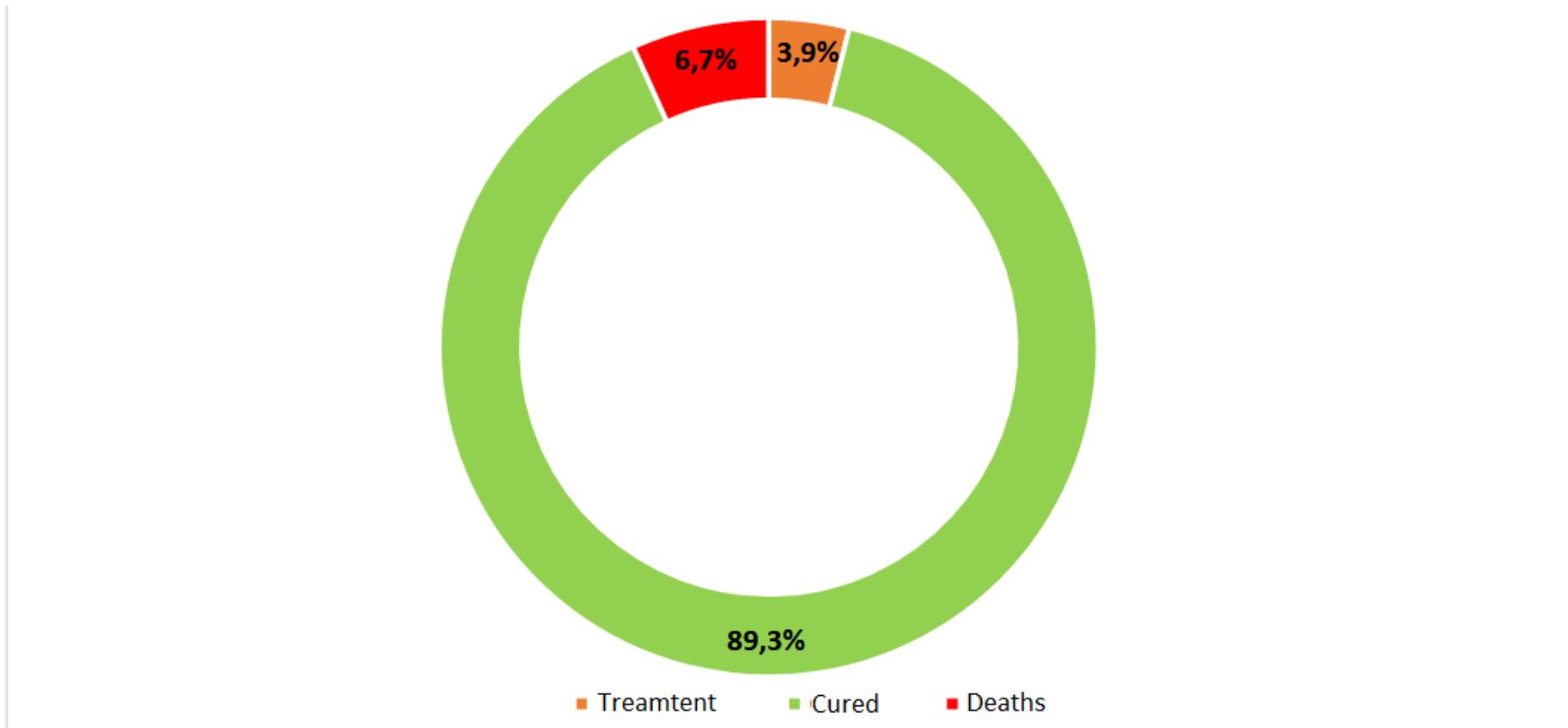
Source : NHI, from data published by the PHM

TABLE 5 : Distribution (in %) of deaths linked to COVID-19 by sex, as of June 4th 2020



Source : NHI, from data published by the PHM

TABLE 6 : Proportion of active cases, deaths and cured patients from COVID-19, in Niger, as of June 4th 2020



Source : NHI, from data published by the PHM

According to the 170th WHO report on the Covid-19, on July 8,2020 :

- 11,669,259 confirmed cases with 539,906 deaths worldwide
- 397,942 confirmed cases with 7,415 deaths in Africa.

Which means Africa represents

- 3,41 % of the worldwide total cases
- 1,37 % of the worldwide total deaths from COVID-19

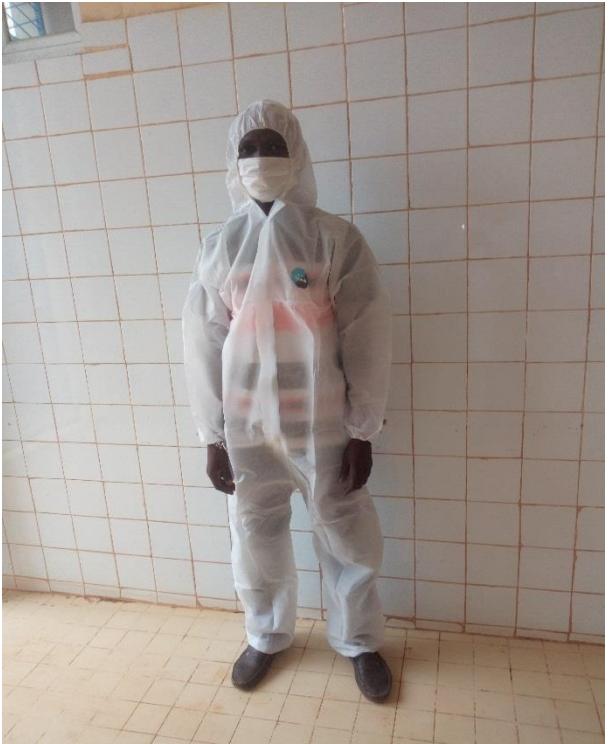
CLINICAL FINDINGS OF COVID-19 IN AFRICA

- The same as in other parts of the world seemingly less severe cases are founded.
- Mortality less severe
- Less means to fight against COVID-19
- Very less human resources
- Sociocultural barriers to understand distancing and preventive measures

COVID-19 personal protective equipment (PPE)

Updated 18 June 2020

Recommendations from UK



Types of PPE masks

- A fluid-resistant (Type-IIR) surgical face masks is used to protect against droplets.
- If worn by the patient, it will minimise dispersal of large respiratory droplets which will protect staff against both droplet and contact transmission.
- If worn by staff, it will protect against droplet transmission, when within 1-2 m of the patient. Risk reduction by at least 80% is estimated .

- The terms filtering facepiece FFP2, FFP3 and N95 are used in reference to high performance filtering masks. Filtration is achieved by a combination of a web of polypropylene microfibres and electrostatic charge.
- There are three classes of protection, adhering to the European standard EN 149 + A1:2009 , each with an assigned protection factor which indicates the degree to which the mask will reduce concentration of the hazardous substance. For FFP1, FFP2 and FFP3 these are 4-, 10- and 20-fold, respectively .

- In the detail of the standard it states that the total inward leak of particles must not exceed in 92% of exercise tests: 25% for FFP1; 11% for FFP2; and 5% for FFP3.
- It also states that the mean inward leak in 8 of 10 wearers should not exceed: 22% for FFP2; 8% for FFP2; and 2% for FFP3 masks. Finally, the penetration of test aerosols, both saline and paraffin oils, should not exceed: 20% for FFP1; 6% for FFP2; and 1% for FFP3 masks.

- These tests to be performed on masks as delivered and during simulated use. Perhaps this last provides the best measure of filtration, meaning that the overall filter efficiency of FFP1, FFP2 and FFP3 masks is 80%, 94% and 99% .
- The N95 designation means that under test conditions (certified under 42 CFR 84 of National Institute for Occupational Safety and Health and the United States CDC), the respirator blocks at least 95% of solid and liquid aerosol test particles.

- The N, R and P masks describe their increasing resistance to oils but the number (95, 99 or 100) refers to the minimum percentage of particles filtered under test conditions .
- Filtration performance during use is likely to be higher than indicated, as testing is undertaken in the ‘worse case setting’ of high air flow and using high penetrating aerosols.

- As such, the FFP3 is likely to be twice as effective as the FFP2 mask, and broadly both are equivalent or superior to an N95 mask. These masks should be fluid resistant when used for medical purposes. FFP2/3 and N95 masks do not work unless they fit well to the face and create a seal.
- Individual mask fit-testing should be undertaken by all relevant members of staff before they are worn on clinical duty. All the above tests assume the face seal exists. This requires a large stock of equipment simply in order to test the equipment.

- Done properly, mask fit-testing should have a failure rate < 5% and if it is much higher this should bring into question whether the correct testing procedure is being undertaken. FFP2/3 and N95 masks should be fit-checked before each use, i.e. the user should confirm a seal before entering the area of risk.
- The WHO recommends that FFP2/3 and N95 masks can be, if undamaged, for up to four hours, which is approximately the median healthcare worker tolerance time, though this is highly variable [28,29].

Appropriate levels of PPE

- Standard infection control procedures should already be in place. Those described here are specific to reducing the risk of viral transmission to the healthcare worker. The PPE used in each setting should be appropriate to the mode of infection. Currently multiple terms are used to describe PPE, which seem undefined, inconsistently used and do not match PPE to the modes of infection transmission.

- Contact precaution PPE is appropriate for staff in the same room as patients with COVID-19, and where aerosol generating procedures are not undertaken, but who remain more than two metres from the patient (some sources state one metre but that allows no margin for error).
- Droplet precaution PPE is appropriate when caring for a patient or being within two metres. Eyewear is added based on a risk assessment.

Difficulties and challenges in Africa

- Denial of illness
- Stigmatization of patients with COVID
- Insufficient compliance with barrier measures (wearing a mask, closing borders, distancing)
- Containment of contacts and suspects in rural areas
- Reopening of borders (carrying out tests, confinement, resources to be mobilized, barrier measures, etc.).
- Management of seasonal returns.
- Sociocultural and educational barriers





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