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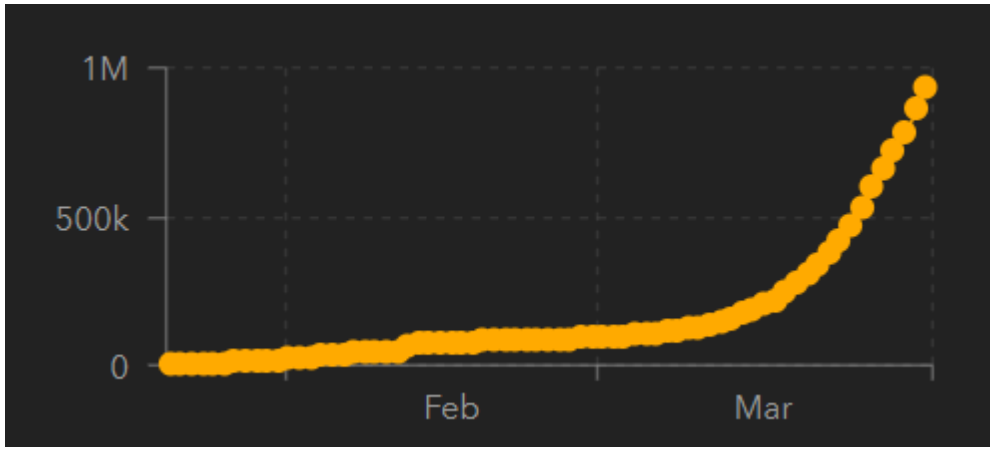
Testing in the time of COVID-19

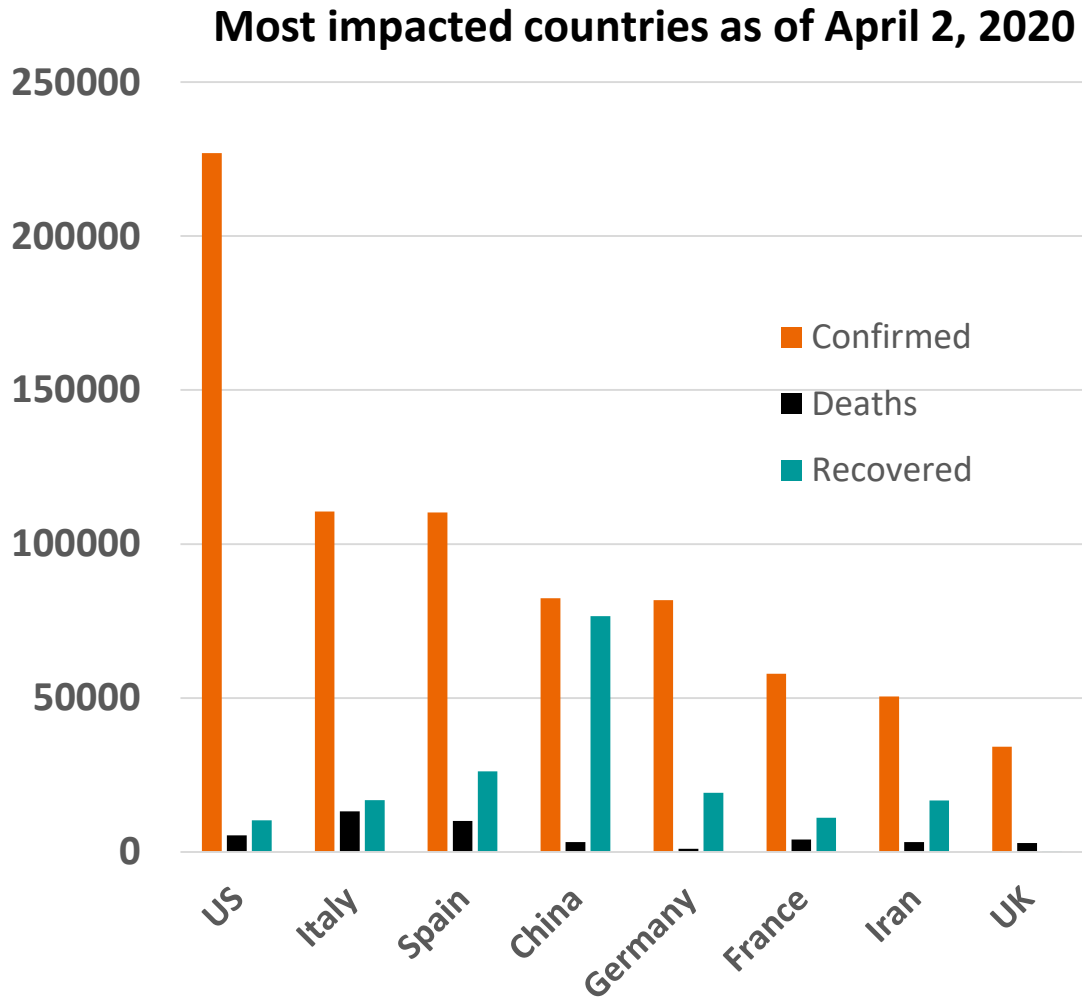
Information for Laboratories

April, 2020

COVID-19 a growing pandemic

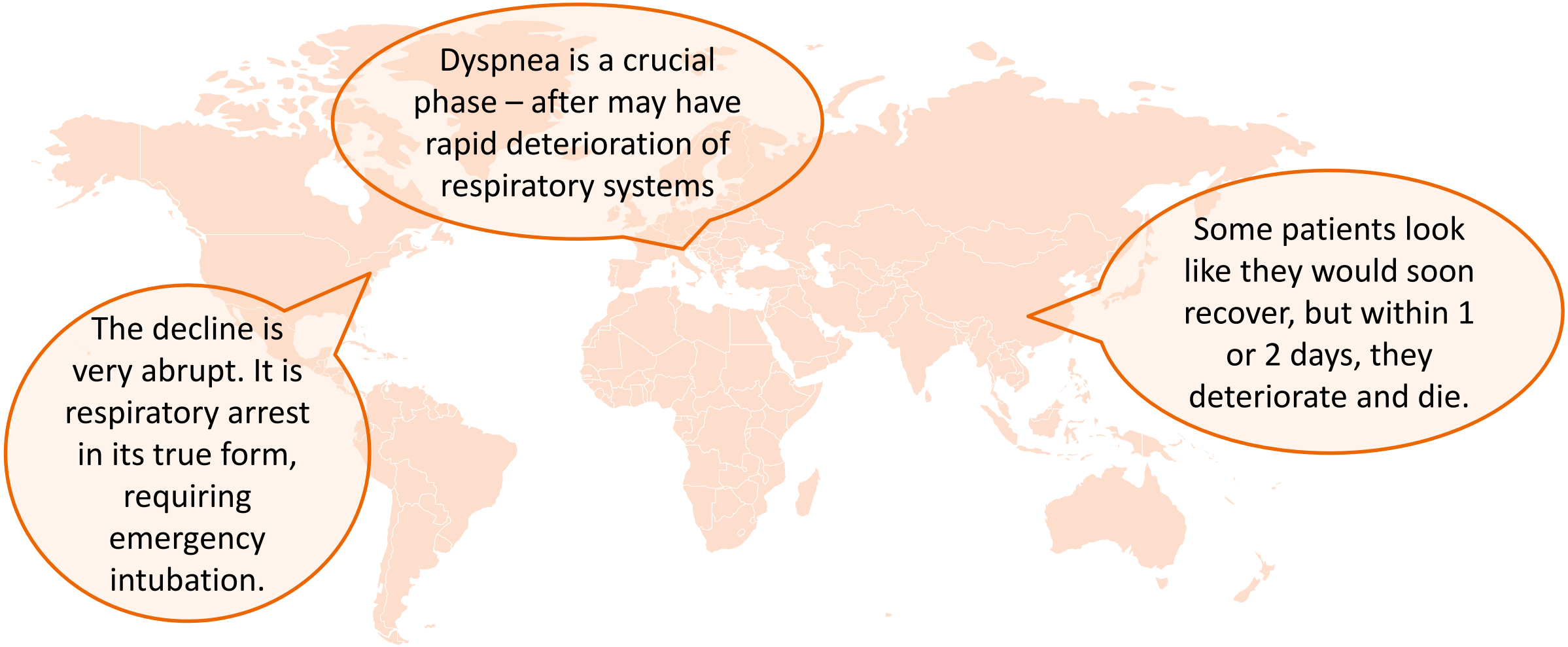


Almost one million confirmed positives cases worldwide at the end of March 2020



https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6. Accessed April 2, 2020

Observations from the front lines: rapid, often unpredictable, respiratory failure and cardiac arrest in some patients



Cascella et al. Features, Evaluation and Treatment COVID-19. https://www.ncbi.nlm.nih.gov/books/NBK554776/ [Updated March 20, 2020]
Coronavirus in New York – Report from the Front Lines. https://edhub.ama-assn.org/jn-learning/video-player/18331693
COVID-19 update from China. https://edhub.ama-assn.org/jn-learning/video-player/18234510

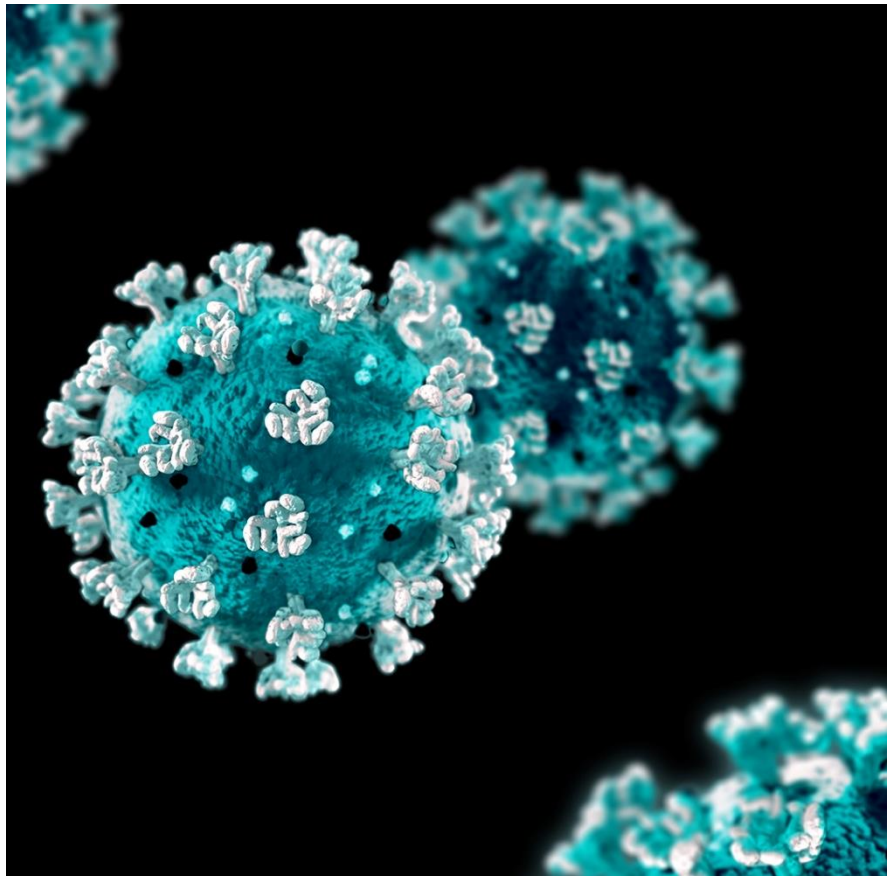
Observations from the front lines: rapid, often unpredictable, respiratory failure and cardiac arrest in some patients

Observation	Questions
Patients with initially mild symptoms can develop hypoxemia (oxygen saturation < 93%)	For hospitals where mild patients are discharged home, who might require hospital admission/ closer monitoring?
Patients apparently well managed in hospital can develop sudden, abrupt respiratory failure requiring emergency intubation.	Which patients are at higher risk and may benefit from early intubation or more aggressive management?
Patients apparently well managed in hospital can develop sudden cardiac arrest	Which patients are at higher risk and may need close monitoring?
Patients on mechanical ventilation who improve, pass all weaning parameters and are extubated, can rapidly relapse and require re-intubation.	Who can be safely extubated?

Current clinical symptoms alone may be insufficient in the assessment of patients with COVID-19. How can we better triage and monitor these patients?

Cascella et al. Features, Evaluation and Treatment COVID-19. https://www.ncbi.nlm.nih.gov/books/NBK554776/ [Updated March 20, 2020]
Coronavirus in New York – Report from the Front Lines. https://edhub.ama-assn.org/jn-learning/video-player/18331693

The novel coronavirus: Defining terms



SARS-CoV-2 (“Severe **A**cute **R**espiratory **S**yndrome **C**oronavirus **2”)**

SARS-CoV-2 is the **virus** that causes COVID-19

COVID-19 (“Corona**Vi**rus **D**isease 20**19”)**

COVID-19 is the **disease** resulting from infection with the novel coronavirus

https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it

The novel coronavirus: Defining terms

SARS-CoV-2:

- Family: Coronavirus (CoV); large family of single-stranded RNA viruses that have been isolated in different animal species
- Closely related to SARS and MERS
- High rate of human-to-human transmission. 1 person may infect >2 others on average.
- Viral receptor appears to be angiotensin converting enzyme 2 (ACE2)
- May be multiple routes of transmission, as virus found in blood and fecal swabs. Respiratory most common

COVID-19:

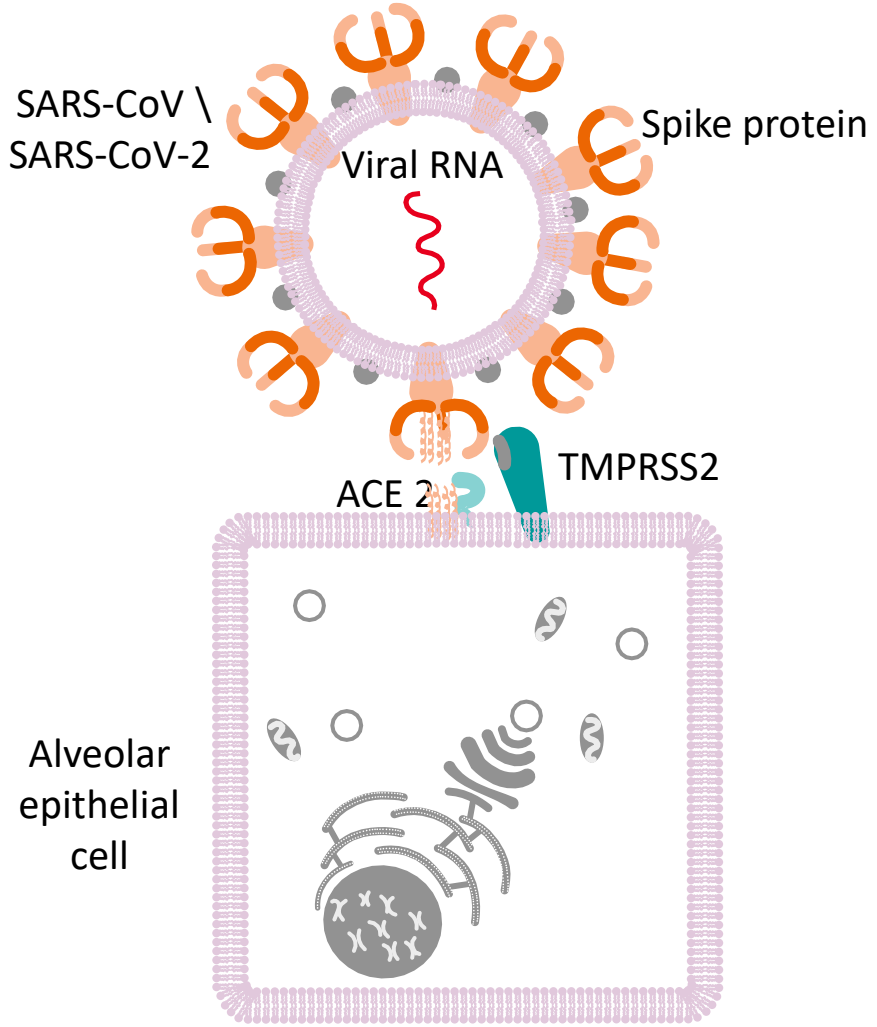
Existing data suggests:

- COVID-19 virus spreads primarily through droplets of saliva or discharge from the nose with coughing (or sneezing) but may also be airborne
- Significant environmental stability (remains infectious) on surfaces/aerosols
- Incubation period: 2-14 days (assumed based on what is known for MERS-CoV)
- Treatment is supportive – no drug or vaccine with proven efficacy

https://www.who.int/health-topics/coronavirus#tab=tab_1. Accessed March 26, 2020
N van Doremalen, et al. Aerosol and surface stability of HCoV-19 (SARS-CoV-2) compared to SARS-CoV-1. The New England Journal of Medicine. DOI: 10.1056/NEJMc2004973 (2020).
Guo et al. Military Medical Research (2020) 7:11
https://www.ncbi.nlm.nih.gov/books/NBK554776 Accessed March 26, 2020

What is known about Coronaviruses?

- SARS-CoV-2: ssRNA, betacoronavirus, 60-140 nm diameter
- Studies from SARS and MERS: Inactivated by UV-C, 75°C heat, >70% ethanol, 0.2% sodium hypochlorite, 0.5% H2O2, 0.25% povidone iodine, etc
- Chlorhexidine did not significantly inactivate CoV
- Viral entry via ACE2. TMPRSS2 protease primed the viral S protein for ACE2 binding
- Microarray analysis: high ACE2+TMPRSS2 expression in lung alveolar type 2, esophageal upper epithelium, ileum absorptive enterocytes, colonic enterocytes
- AT2 cells responsible for surfactant production, immune regulation, regeneration/repair



Zhu et al. N Engl J Med 2020; 382:727-733
Zhou et al. Cell Discov. 2020 Mar 16;6:14
Song W, et al. PLoS Pathog 2018;14:e1007236.
Darnell et al. J Virol Methods. 2004 Oct;121(1):85-91.
Kampf et al. J Hosp Infect. 2020 Mar;104(3):246-251.
Hoffmann et al. Cell. 2020. doi: 10.1016/j.cell.2020.02.052
Meng et al. https://doi.org/10.1101/2020.02.08.926006

Clinical classification and transmission of COVID-19

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Clinical classification

Incubation period median 5 days, range 1–27 days → Patients with mild symptoms in week 1... → ...may progress in week 2 → **Progression may be rapid and sudden.**

Human-to-human transmission

Possible transmission during asymptomatic phase 4–6 days before the onset of symptoms.

Possible transmission after remission of the symptoms

Possible transmission	Highest risk of transmission during symptomatic phase	Possible transmission

Disease spectrum

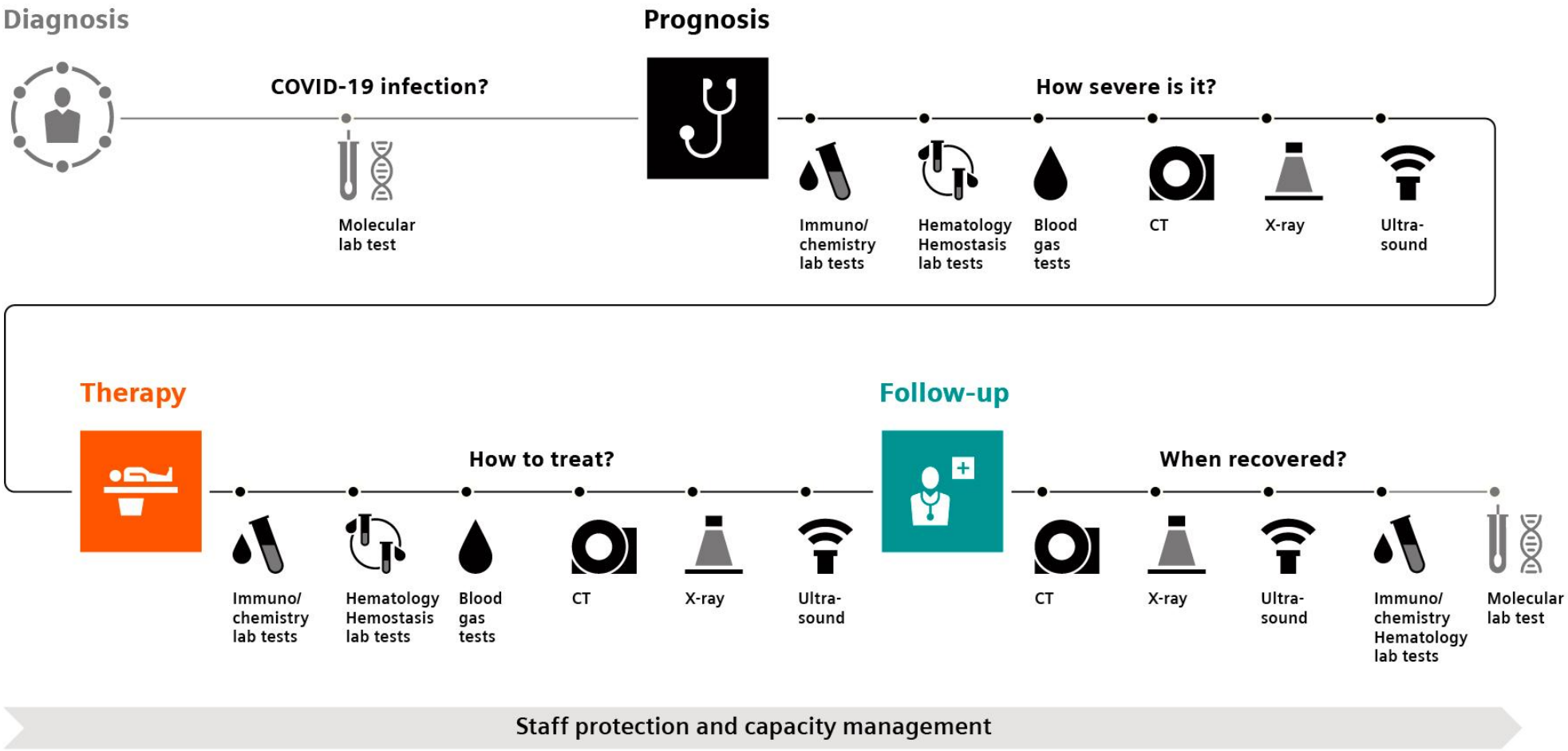
Asymptomatic	Symptomatic			Remission
No symptoms	Mild to Moderate	Severe	Critical	
1.2–17.6%	80%	10–15%	2–5%	
Infectious virus can be shed, viral loads may be comparable to symptomatic patients	No signs (mild) or some signs (moderate) of pneumonia on imaging	• Respiratory distress of ≥30 breath per minute • Oxygen saturation ≤93% at rest • PaO2/FiO2 ≤300 mmHg • Lung lesion progression >50% in 24–48h	• Respiratory failure requiring mechanical ventilation • Shock • Any organ failure requiring ICU care • Case/fatality rate current estimation 0.3 to 4%	

World Health Organization. Coronavirus disease 2019 (COVID-19) Situation Report – 44. https://www.who.int/emergencies/diseases/novel-coronavirus2019/situation-reports/, https://www.ifcc.org/ifcc-news/2020-03-26-ifcc-information-guide-on-covid-19/, Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19), March 22, 2020 ,Content source: National Cent Immunization and Respiratory Diseases (NCIRD) Division of Viral Diseases JAMA.2020 Feb7. doi:10,1001/jama,20201585, Ann Transl Med 2020;8(3):48, http://dx.doi.org/10.21037/atm.2020.02.06, Lippi G, Plebani M. Laboratory abnormalities in patients with COVID-2019 infection. Clin Chem Lab Med. 2020 Mar 3. doi: 10.1515/cclm-2020-0198., Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19) https://www.massgeneral.org/news/coronavirus/coronavirus-latest-updates, Jingyuan Liu, https://doi.org/10.1101/2020.02.10.20021584 doi: Hematologic parameters in patients with COVID-19 infection 10.1002/ajh.25774

COVID-19 presents challenges for healthcare works

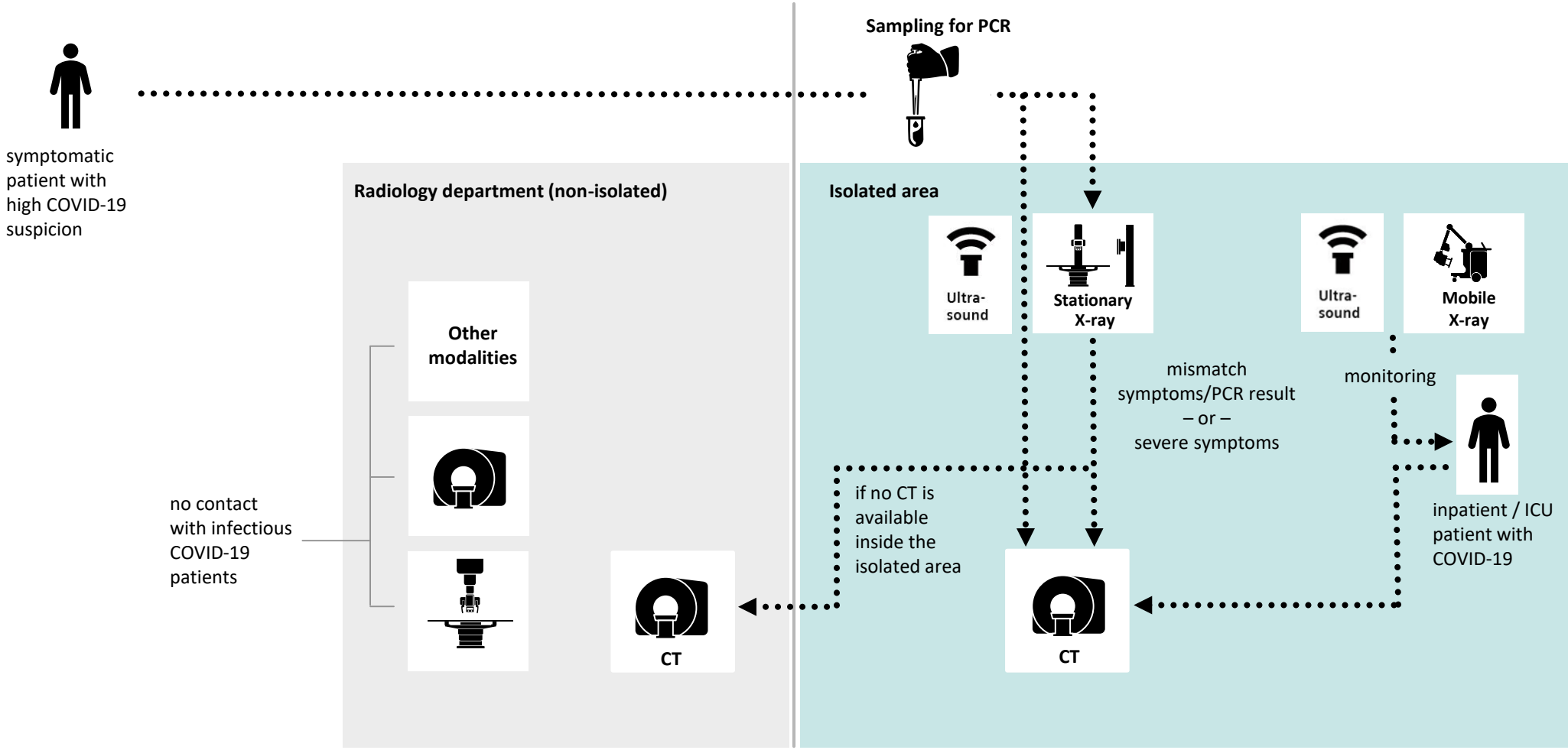
- Shortage/lack of PPE (personal protective equipment) such as masks, gloves, gowns, face-shields
  - Especially shortage of N95 masks
- Shortage of hospital beds and other critical equipment, in particular ICU monitored beds and ventilators
- Lack/limited numbers of COVID-19 test kits
- Loss of clinical staff to illness/burnout or insufficient staffing to meet demand

COVID-19 patient pathway



Status: 27.03.2020

Example of Clinical Setup with an Isolated Area for COVID-19 Cases



https://healthcare-in-europe.com/en/news/imaging-the-coronavirus-disease-covid-19.html, https://doi.org/10.1148/radiol.2020200988, [1] Jokerst et al. J Am Coll Radiol 2018;15:S240-S251, Broder. Imaging the Chest: The Chest Radiograph. https://doi.org/10.1016/B978-1-4160-6113-7.10005-5, ACR Recommendations for the use of Chest Radiography and Computed Tomography (CT) for Suspected COVID-19 Infection, [4] German Radiological Society: https://www.drg.de/de-DE/5995/covid-19/, [5] Arentz et al. JAMA. Published online March 19, 2020. , oi:10.1001/jama.2020.4326, [6] Hosseiny et al. AJR 2020; 214:1-5

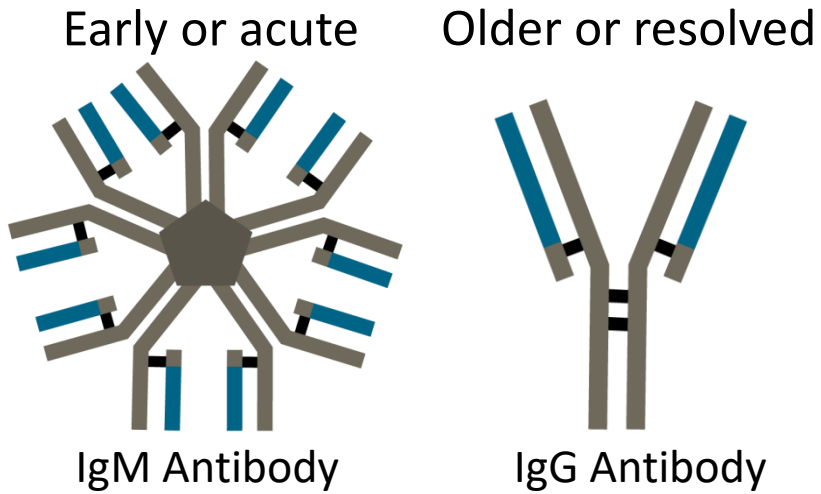
Testing for COVID-19

Molecular: Detection of viral RNA

- Confirms infection
- Lab-based (rt-PCR) and Point-of-care (POC)

Serology: Detection of antibodies

- Lab-based and POC



- IgG indicates prior/resolving infection
- IgG can aid in prevalence assessment in the community
- It is yet to be proven that IgG seroconverted individuals may be immune to subsequent infection

Diagnosis: RT-PCR is more sensitive during early disease, serology is more sensitive 2-3 weeks after symptom onset

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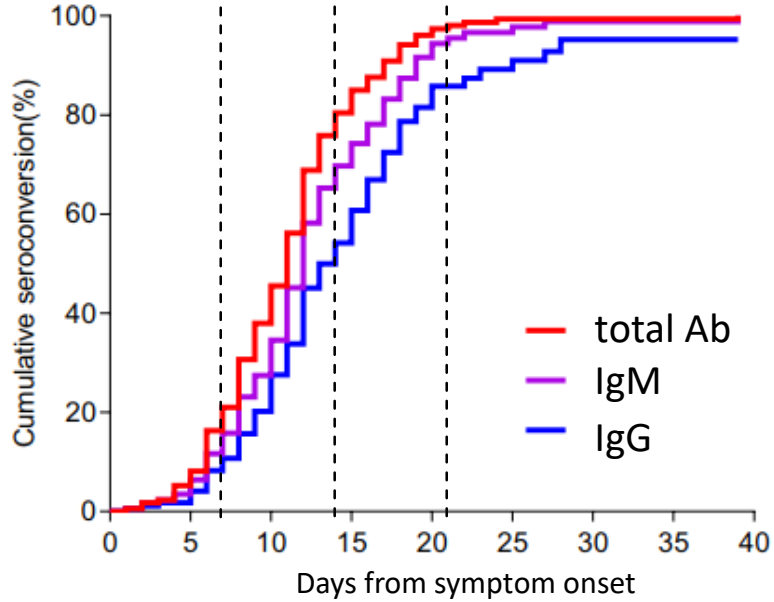
Table: Sensitivity of different methods by time from symptom onset

Time from symptom onset	RT-PCR sensitivity	Total Ab sensitivity	IgM sensitivity	IgG sensitivity	PCR+Ab sensitivity
day 1-7 (n=94)	66.7%	38.3%	28.7%	19.1%	78.7%
day 8-14 (n=135)	54.0%	89.6%	73.3%	54.1%	97.0%
day 15-39 (n=90)	45.5%	100%	94.3%	79.8%	100%

Cumulative seroconversion by day from onset



Preprint: Zhao et al. https://doi.org/10.1101/2020.03.02.20030189

CDC recommends collecting and testing an upper respiratory specimen for COVID-19

Nasopharyngeal specimen is the preferred choice for swab-based SARS-CoV-2 testing.

When collection of a nasopharyngeal swab is not possible, the following are acceptable alternatives:

- An oropharyngeal (OP) specimen collected by a healthcare professional
- A nasal mid-turbinate (NMT) swab collected by a healthcare professional or by onsite self-collection (using a flocked tapered swab)
- An anterior nares specimen collected by a healthcare professional or by onsite self-collection (using a round foam swab)

Samples should be stored at 2-8 degrees Celsius. If over 72 hours freeze at -70 degrees Celsius prior to testing.

https://www.cdc.gov/coronavirus/2019-nCoV/lab/guidelines-clinical-specimens.html Accessed March 26, 2020

Course of patients at risk and/or infected by COVID-19

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Identification of high risk patients

- Age >55 years
- Any age with severe obesity BMI >40
- Pre-existing pulmonary disease (chronic lung disease or moderate to severe asthma, COPD, lung cancer, pulmonary hypertension, emphysema (smoking, A1AT deficiency))
- Chronic kidney disease
- Diabetes
- History of:
  - hypertension (treated and untreated)
  - cardiovascular disease
  - liver disease
  - transplants or other immunosuppression (ex. cancer treatment)
- All patients with HIV
- Patients with endocrine pathologies
- Use of biologic drugs

Patient triage

Epidemiologic surveillance

Laboratory testing:

- RT-PCR
- Anti-SARS-CoV-2 antibodies

Diagnosis

Virus detection:

- Molecular testing (RT-PCR)
- Imaging Chest CT

Recovery

Epidemiologic surveillance

Laboratory testing:

- Anti-SARS-CoV-2 antibodies (IgG, IgM)

Confirm immunization

Therapeutic monitoring

Laboratory testing:

- Arterial blood gas
- Complete blood count
- Acute phase proteins, inflammation & coagulation
- Liver, kidney, cardiac function biomarkers
- Additional testing related to comorbidities

Imaging:

- Chest CT (ground glass opacification)

World Health Organization. Coronavirus disease 2019 (COVID-19) Situation Report – 44. https://www.who.int/emergencies/diseases/novel-coronavirus2019/situation-reports/, https://www.ifcc.org/ifcc-news/2020-03-26-ifcc-information-guide-on-covid-19/, Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19), March 22, 2020 ,Content source: National Cent Immunization and Respiratory Diseases (NCIRD) Division of Viral Diseases JAMA.2020 Feb7. doi:10,1001/jama,20201585, Ann Transl Med 2020;8(3):48, http://dx.doi.org/10.21037/atm.2020.02.06, Lippi G, Plebani M. Laboratory abnormalities in patients with COVID-2019 infection. Clin Chem Lab Med. 2020 Mar 3. doi: 10.1515/cclm-2020-0198., Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19) https://www.massgeneral.org/news/coronavirus/coronavirus-latest-updates, Jingyuan Liu, https://doi.org/10.1101/2020.02.10.20021584 doi: Hematologic parameters in patients with COVID-19 infection 10.1002/ajh.25774

The essential role of laboratory diagnostics in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection

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Current recommended lab testing (WHO, ESICM)

Recommended daily labs	CBC with differential (trend total lymphocyte count) Comprehensive metabolic panel: • Electrolytes: Na, K, Total CO_2, Chloride • Total protein and Albumin • Creatinine • Bilirubin, ALT, AST CPK (total creatine kinase) Lactate
Risk stratification	D-dimer, Ferritin, CRP, ESR, LDH, Cardiac troponin
Viral serologies	HBV, HCV, HIV 1/2/O

Frequent laboratory abnormalities in patients with COVID-19*

Decreased

- Blood lymphocyte count (35–75%)
- Albumin (50–98%)
- Hemoglobin (41–50%)

Increased

- Neutrophil count
- Erythrocyte sedimentation rate (ESR; up to 85%)
- C-reactive protein (CRP; 75–93%)
- Lactate dehydrogenase (LDH; 27–92%)
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Total bilirubin
- Cardiac troponin
- Procalcitonin (6–25%)
- Prothrombin time (PT)
- D-dimer (36–43%)

Approximate percentage of patients

Additional essential lab testing	Test	Potential clinical significance
Arterial blood gas	pH, PaCO2, PaO2, and aHCO3	For ventilator adjustments
Hematology	Lymphopenia with atypical lymphocytes Leukocytosis, Neutrophilia, low eosinophils Thrombocytopenia: Platelet count	Decreased immunological response to the virus Bacterial (super) infection Consumption (disseminated) coagulopathy
Hemostasis	Prothrombin time, D-Dimer	Activation of blood coagulation and/or disseminated coagulopathy PT and D-dimer are significant predictors of disease severity
Inflammation/Infection	CRP, Ferritin, IL6, TNFα, SAA Procalcitonin	Severe viral infection/viremia Bacterial (super) infection
Cardiac	High-sensitivity troponin, CK-MB, BNP/NT-proBNP	Increased levels may be associated with higher mortality†
Liver	Albumin, ALT, AST, Bilirubin	Impairment of liver function, Liver injury
Renal	Creatinine, Cystatin C	Kidney injury

†This information represents a potential novel clinical utility. Data have not been reviewed by FDA or any other regulatory agency

World Health Organization. Coronavirus disease 2019 (COVID-19) Situation Report – 44. https://www.who.int/emergencies/diseases/novel-coronavirus2019/situation-reports/, https://www.ifcc.org/ifcc-news/2020-03-26-ifcc-information-guide-on-covid-19/, Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19), March 22, 2020 ,Content source: National Cent Immunization and Respiratory Diseases (NCIRD) Division of Viral Diseases JAMA.2020 Feb7. doi:10,1001/jama,20201585, Ann Transl Med 2020;8(3):48, http://dx.doi.org/10.21037/atm.2020.02.06, Lippi G, Plebani M. Laboratory abnormalities in patients with COVID-2019 infection. Clin Chem Lab Med. 2020 Mar 3. doi: 10.1515/cclm-2020-0198., Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19) https://www.massgeneral.org/news/coronavirus/coronavirus-latest-updates, Jingyuan Liu, https://doi.org/10.1101/2020.02.10.20021584 doi: Hematologic parameters in patients with COVID-19 infection 10.1002/ajh.25774

Patients with comorbidities that are infected by COVID-19 have a worse prognosis, expanding the role of the laboratory

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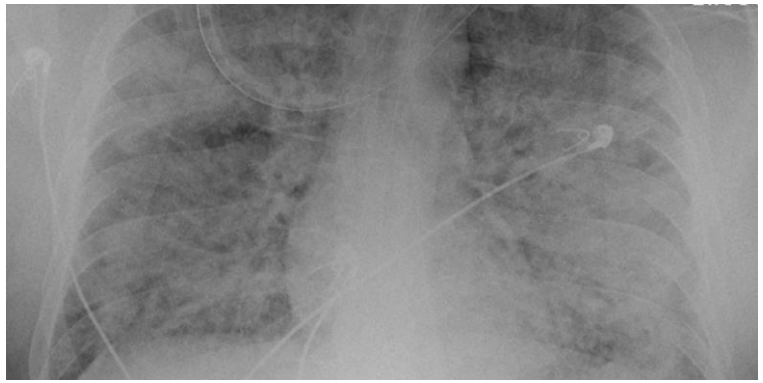
Patients with comorbidities (like diabetes mellitus, hypertension, cardiovascular, chronic lung and chronic kidney disease) are particularly susceptible to COVID-19 infection and are likely to have more severe illness

	Comorbidities	Additional testing	Impact of COVID-19
	Cardiovascular disease	Troponin, Natriuretic peptides, CKMB	Precipitates cardiac complications like: acute heart failure, myocardial infarction, myocardial injury, cardiac arrest.
	Chronic kidney disease	Blood: Creatinine, Cystatin C, eGFR Urine: Albumin	Challenges for patients on dialysis, in particular, in-center hemodialysis; uremic patients are particularly vulnerable to infection and may exhibit greater variations in clinical symptoms and infectivity.
	Heart/liver/kidney transplant	Immunosuppressant Drugs: Mycophenolate, Cyclosporine, Tacrolimus, Sirolimus, Everolimus	Patients may be more vulnerable due to immunocompromised status.
	Viral co-infection	Hepatitis B serologies (anti-HBs, anti-HBc, and HBsAg) Hepatitis C serology (anti-HCV), unless positive in past HIV 1/2/O, CD4 count	Viral serologies assist in interpretation of ALT elevations, present in ~25% of COVID-19 patients. HIV patients may get severe side effects when taking Tocilizumab (drug being used for COVID-19 pneumonia).‡ Hepatitis patients are at higher risk for liver complications.
	Diabetes	Blood glucose	Patients with diabetes who are infected with COVID-19 may see their glycemic control deteriorate during the illness.
	Chronic lung disease	LDH	Patients may be more vulnerable due to lung function insufficiency.
	Chronic liver disease	Albumin, AST, ALT, Total Protein, Bilirubin, PT INR	Patients may be more vulnerable due to liver function insufficiency.

‡PDR Tocilizumab https://www.pdr.net/drug-summary/Actemra-tocilizumab-2359#1

World Health Organization. Coronavirus disease 2019 (COVID-19) Situation Report – 44. https://www.who.int/emergencies/diseases/novel-coronavirus2019/situation-reports/, https://www.ifcc.org/ifcc-news/2020-03-26-ifcc-information-guide-on-covid-19/, Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19), March 22, 2020 ,Content source: National Cent Immunization and Respiratory Diseases (NCIRD) Division of Viral Diseases JAMA.2020 Feb7. doi:10,1001/jama,20201585, Ann Transl Med 2020;8(3):48, http://dx.doi.org/10.21037/atm.2020.02.06, Lippi G, Plebani M. Laboratory abnormalities in patients with COVID-2019 infection. Clin Chem Lab Med. 2020 Mar 3. doi: 10.1515/cclm-2020-0198., Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19) https://www.massgeneral.org/news/coronavirus/coronavirus-latest-updates, Jingyuan Liu, https://doi.org/10.1101/2020.02.10.20021584 doi: Hematologic parameters in patients with COVID-19 infection 10.1002/ajh.25774

Acute Respiratory Distress Syndrome (ARDS) and COVID-19
Role of Arterial Blood Gas (ABG)



ARDS:

- Defined by the amount of oxygen in arterial blood to the fraction of oxygen in inspired air

ABG:

- Measures pH (acidity and alkalinity) and the levels of oxygen (pO_2) and carbon dioxide (pCO_2)

Healthy Lungs:
Oxygen is passed from alveolus (air sacs) to the capillaries to the red blood cells.

COVID-19 Patients:
Coronavirus damages walls of air sacs that help pass oxygen, causing them to thicken and limit the amount of oxygen that gets passed

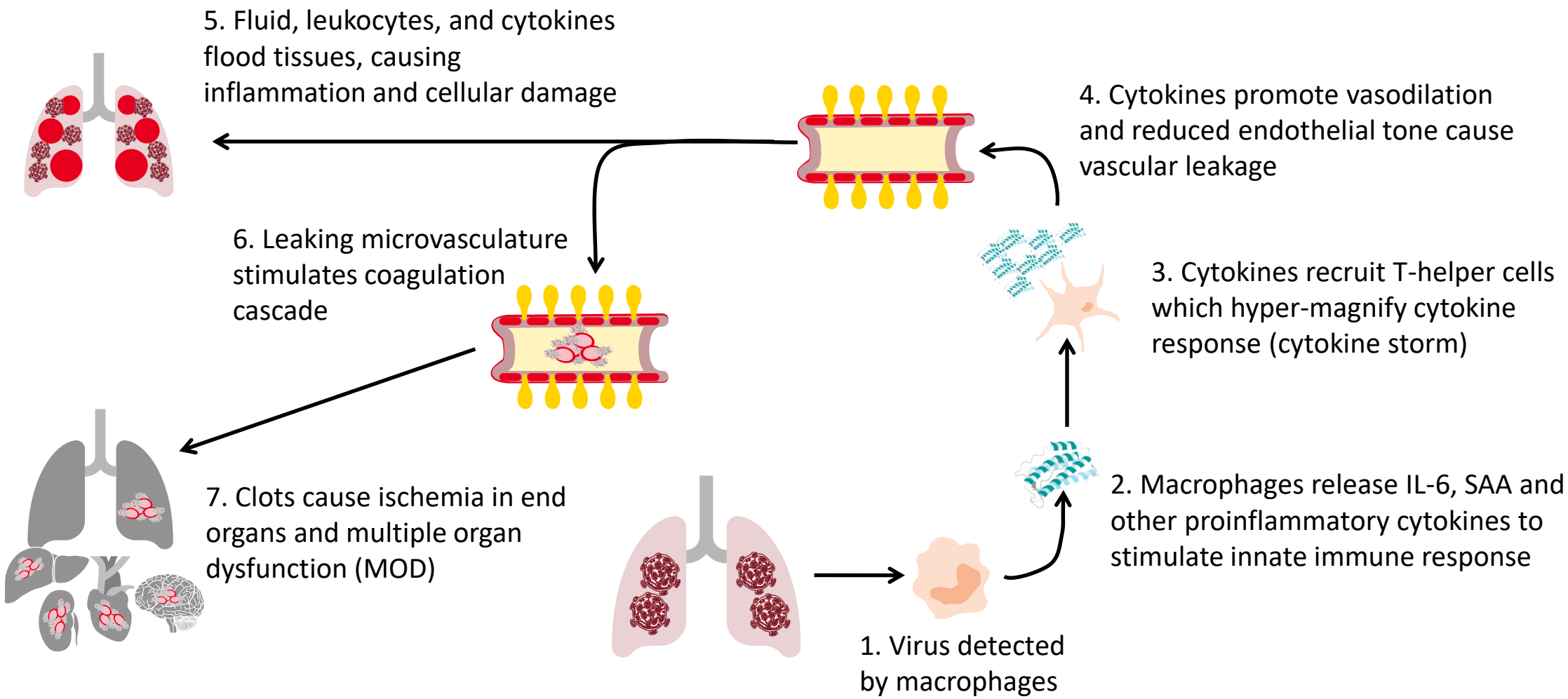
ABG test provides a status of the patient's oxygenation levels, enabling caregivers to determine if adjustments to ventilator settings or other treatments are required

Observations from China Study:
Review of 191 patients examined for risk factors found:

- 50 out of 54 died of ARDS
- 9 out of 137 survived ARDS

Zhou F et al . Lancet 2020;395:1054-1062
https://health.clevelandclinic.org/heres-the-damage-coronavirus-covid-19-can-do-to-your-lungs/ Accessed April 2, 2020

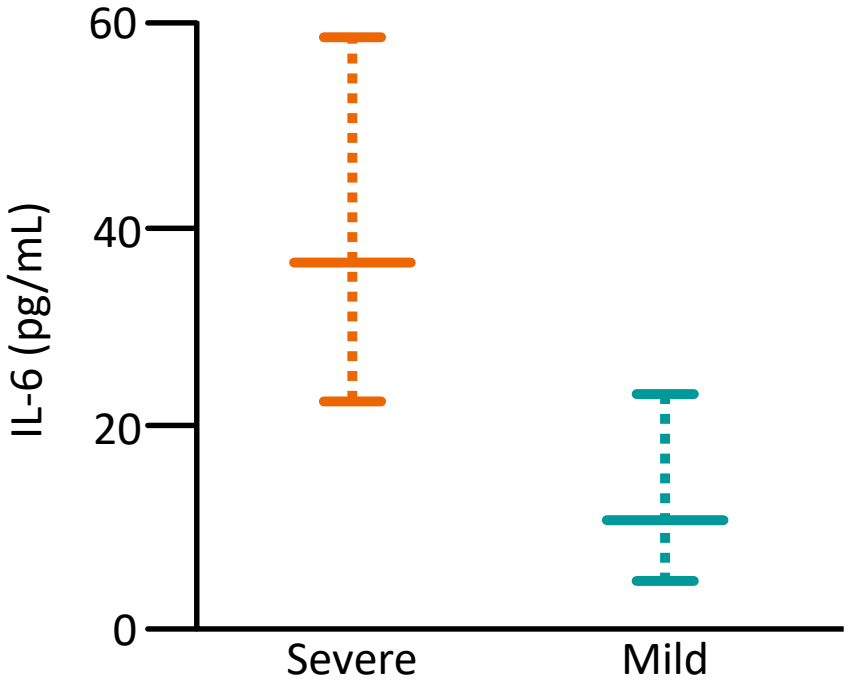
Cytokine response to COVID-19 infection (cytokine storm)



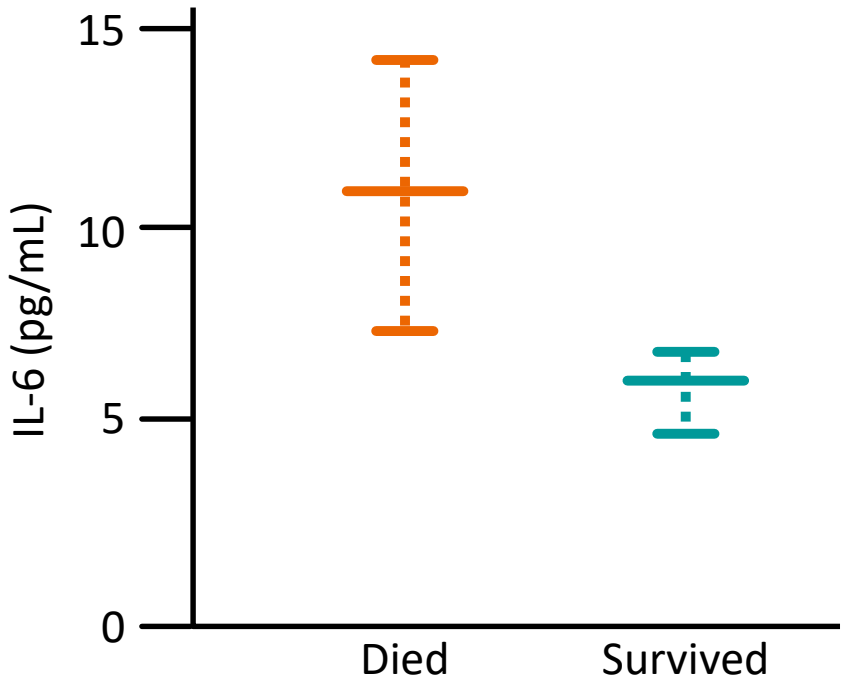
Wiersinga WJ, et al. Virulence 2014;5:36-44.
Chen C, et al. Zhonghua Shao Shang Za Zhi 2020;36:E005.

Elevated IL-6 levels observed in patients with COVID-19 infection

IL-6 is elevated in COVID-19 patients with severe disease

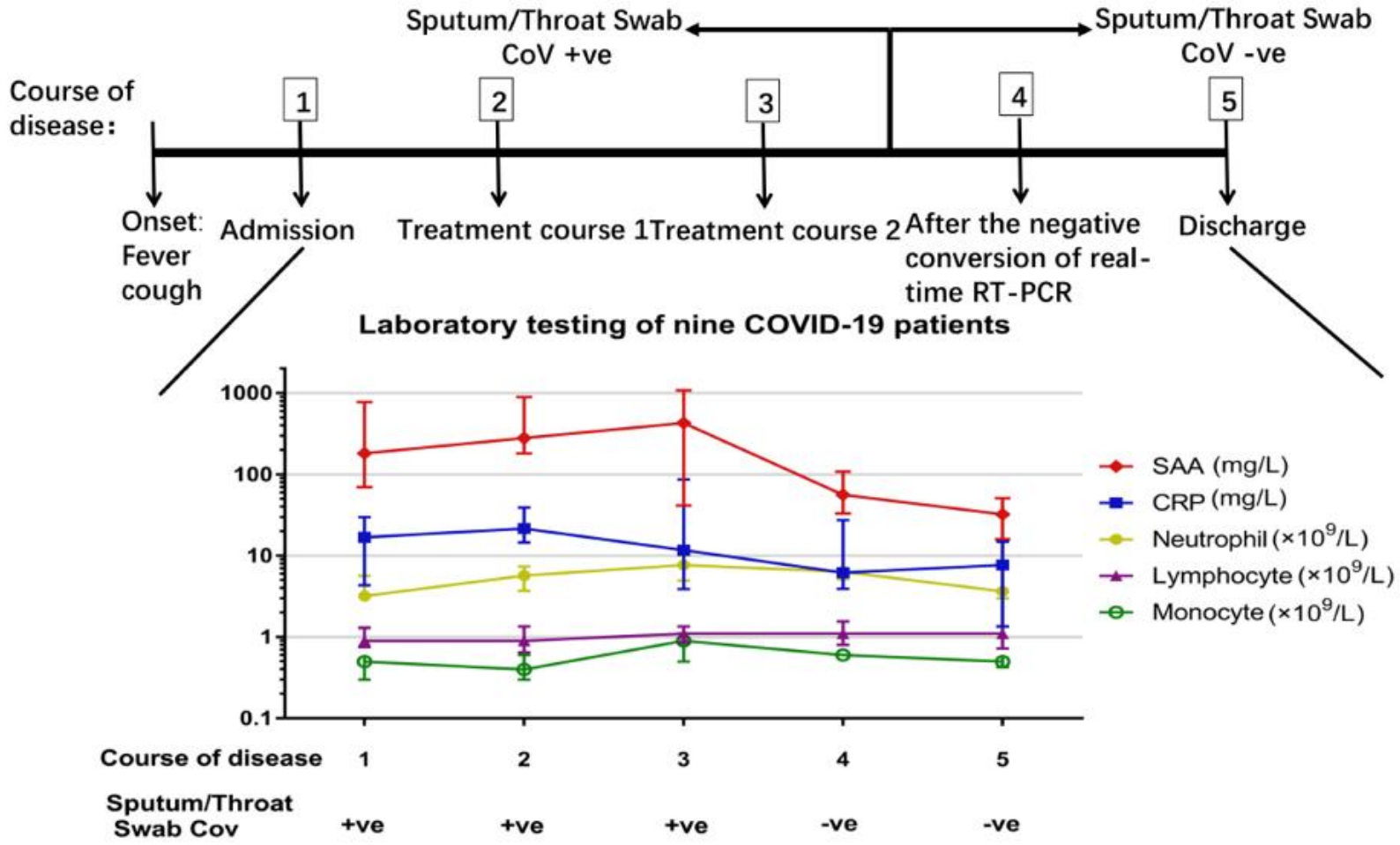


IL-6 is higher in non-survivors



Gao Y, et al. J Med Virol 2020. https://doi.org/10.1002/jmv.25770 (Accessed 3/31/2020)
Zhou F, et al. The Lancet 2020. https://doi.org/10.1016/S0140-6736(20)30566-3 (Accessed 3/31/2020)
This information represents a potential novel clinical utility. Data have not been reviewed by FDA or any other regulatory agency

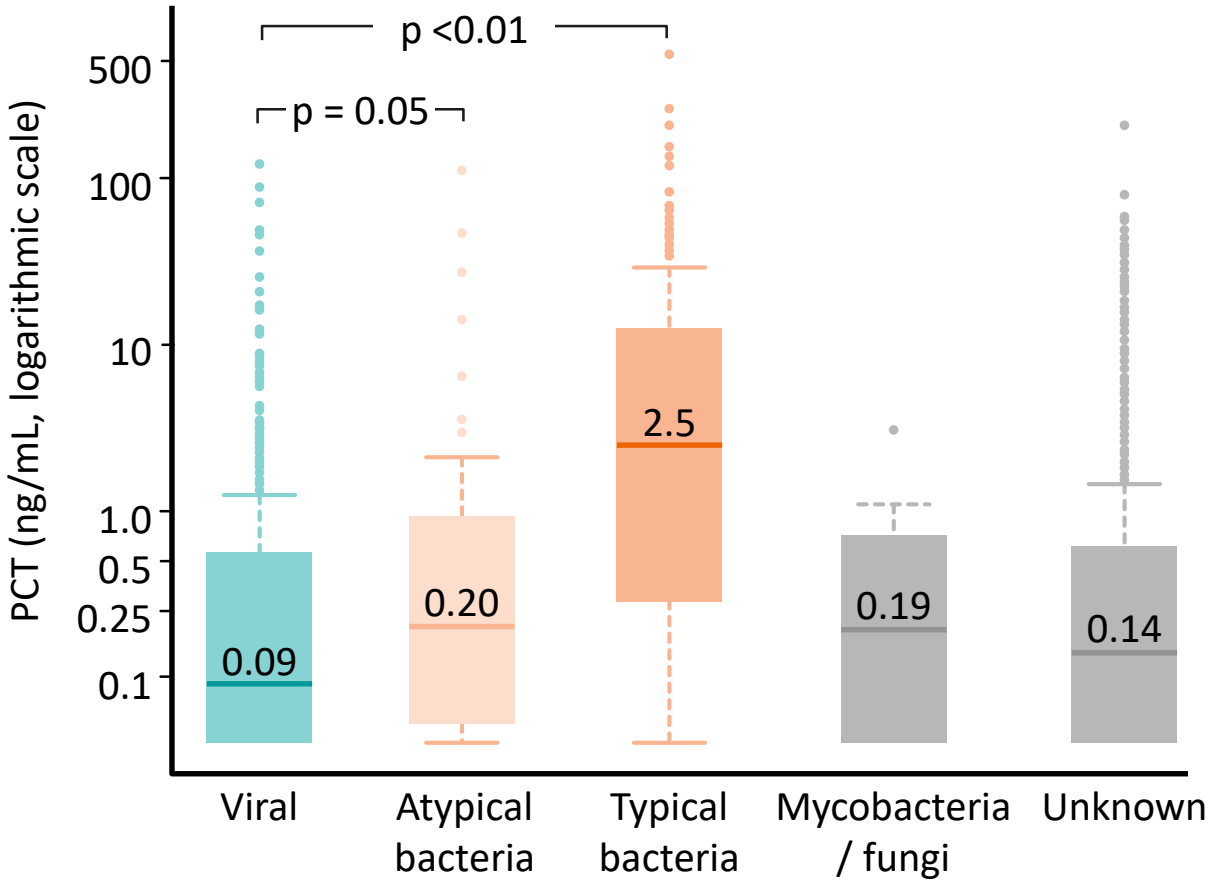
Elevated SAA levels observed in patients with COVID-19 infection



Zhang Y, et al. J Translational Medicine BMC 2020 DOI: 10.21203/rs.3.rs-19724/v1C .

This information represents a potential novel clinical utility. Data have not been reviewed by FDA or any other regulatory agency

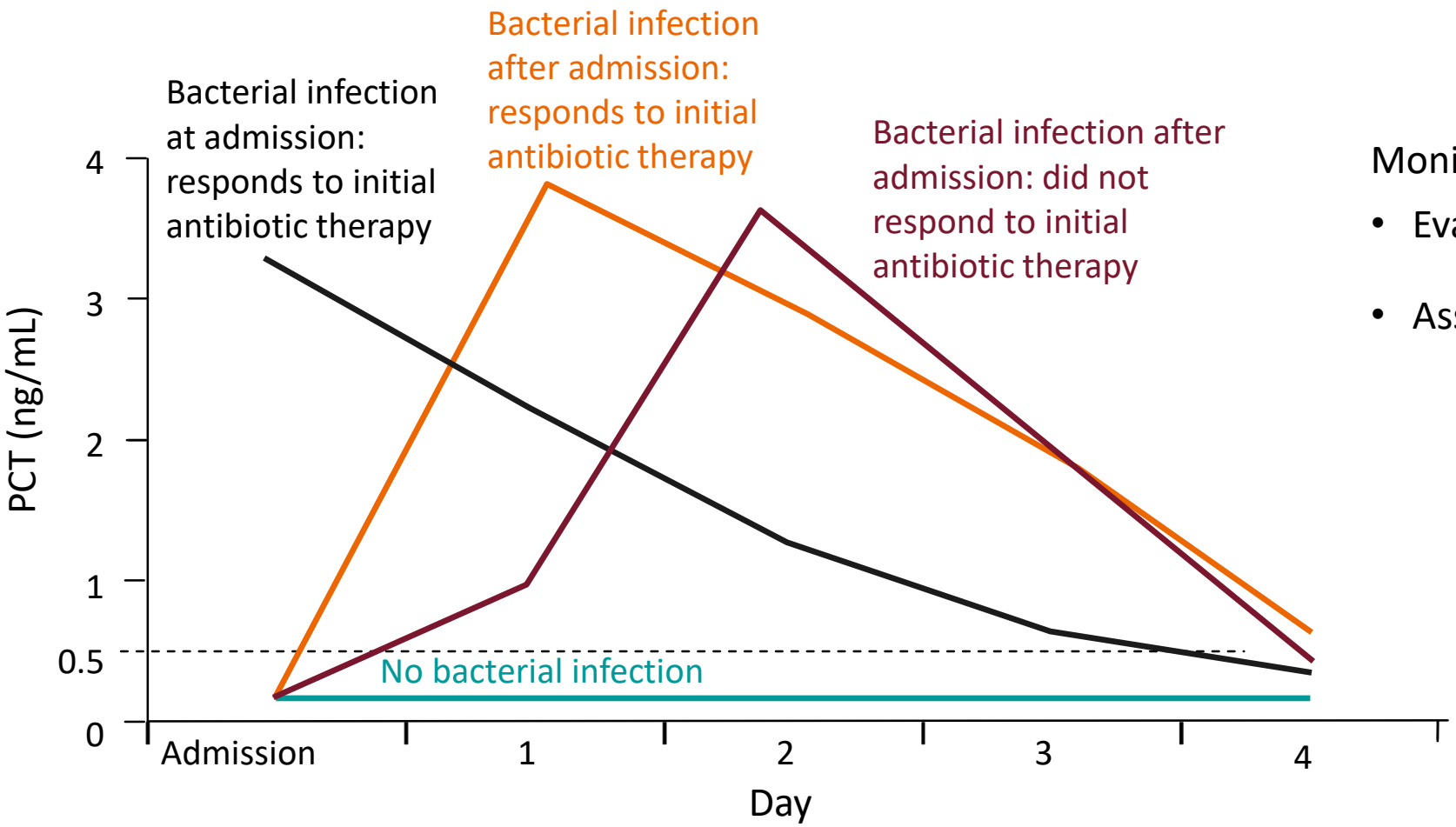
PCT may help determine if bacteria are present and pathogenic in patients suspected to have COVID-19



- PCT on admission can aid in early risk assessment
- Bacterial sepsis can occur secondary to viral sepsis or severe viral infection
- In a study of community acquired pneumonia patients, median PCT in patients infected with typical bacteria was substantially higher than PCT in patients with infections of viral origins. The difference between the medians is statistically significant.

Self WH, et al. Clin Infect Dis 2017;65:183-90.

PCT remains valuable during hospitalization

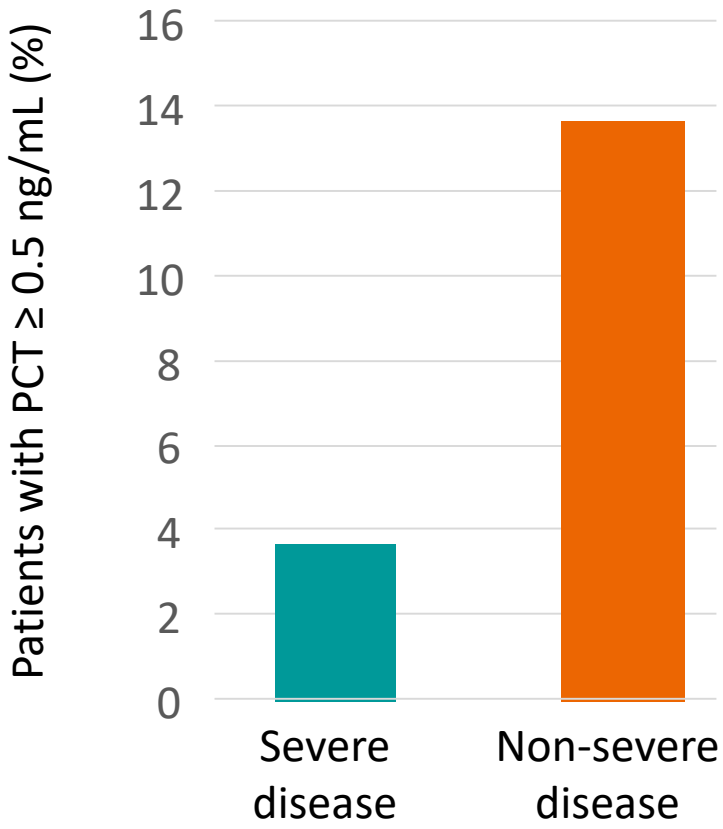


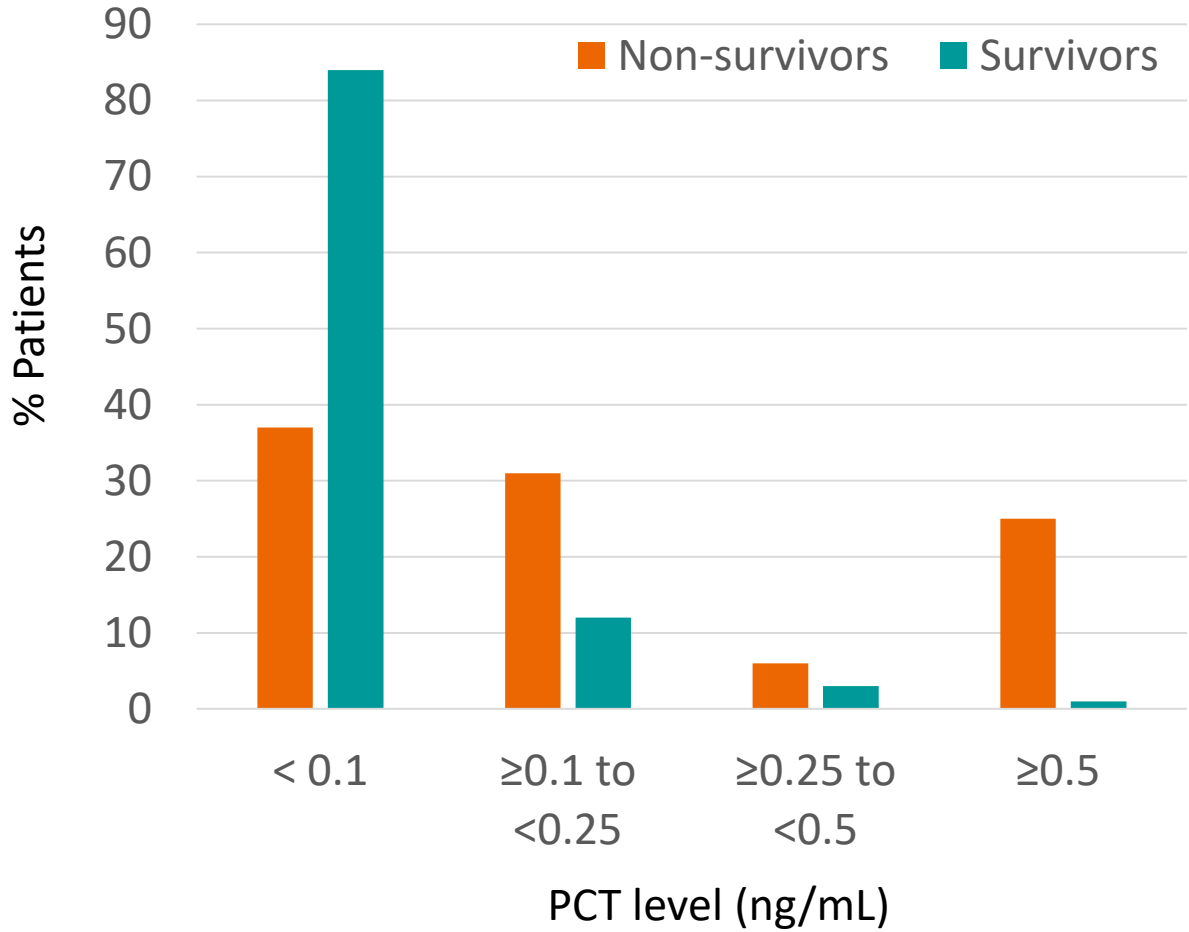
Monitor to:

- Evaluate risk of bacterial co-infection
- Assess efficacy of antibiotics

Schuetz P, et al. Arch Intern Med. 2011;171(15):1322-31.
Siemens Healthineers Atellica® IM B·R·A·H·M·S Procalcitonin Assay package insert, 11200767_EN Rev. 01, 2018-07.
Case report PCT examples courtesy of M. Broyles, Pharm D. Five Rivers Medical Center, Pocahontas, AR.

Prevalence of bacterial co-infection in COVID-19 patients





Guan WJ, et al. N Engl J Med 2020. https://www.nejm.org/doi/full/10.1056/NEJMoa2002032 (Accessed 3/31/2020).
Zhou F, et al. The Lancet 2020. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30566-3/fulltext (Accessed 3/31/2020).

D-dimer elevations in COVID-19 non-survivors

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Study 1:

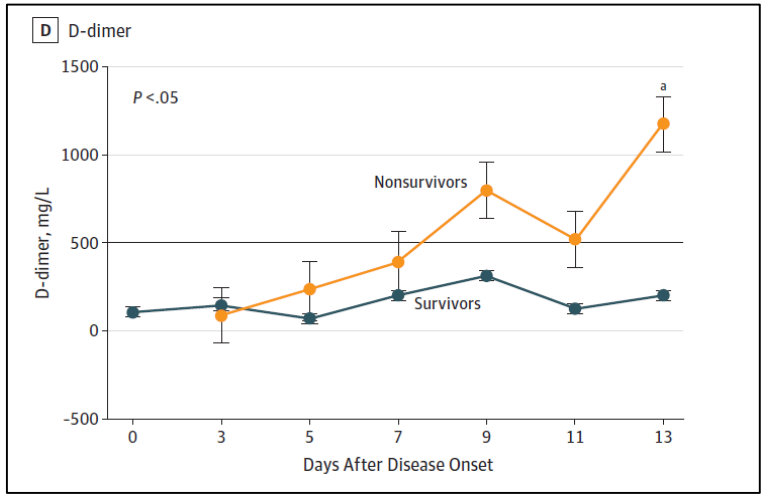
- 183 consecutive patients with confirmed severe COVID-19 induced pneumonia
- Significantly elevated D-dimer levels in non-survivors (0.61 µg/L (0.35-1.29) vs. 2.12 µg/L (0.77-5.27); p < 0.001)
- 71.4% of non-survivors but only 0.6% survivors met the criteria of disseminated intravascular coagulation (DIC)

Laboratory evaluation of DIC:

- PT/PTT (prolonged)
- D-dimer (elevated)
- Platelets (decrease)
- Fibrinogen (decrease)

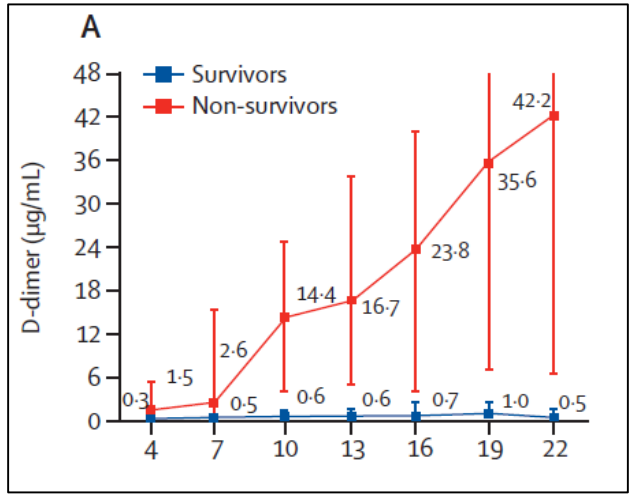
Study 2:

D-dimer profile of 33 patients with COVID-19



Study 3:

D-Dimer level >1 µg/L was a strong predictor of non-survival in 191 COVID-19 patients with an odds ratio of 18.4



Adapted from Tang N et al. J Thromb Haemost 2020. doi: 10.1111/jth.14768. [Epub ahead of print}. Wang H et al. JAMA 2020;323:1061-1069
Zhou F et al . Lancet 2020;395:1054-1062
This information represents a potential novel clinical utility. Data have not been reviewed by FDA or any other regulatory agency

Cardiovascular complications: patients with elevated cardiac troponin are at very high risk

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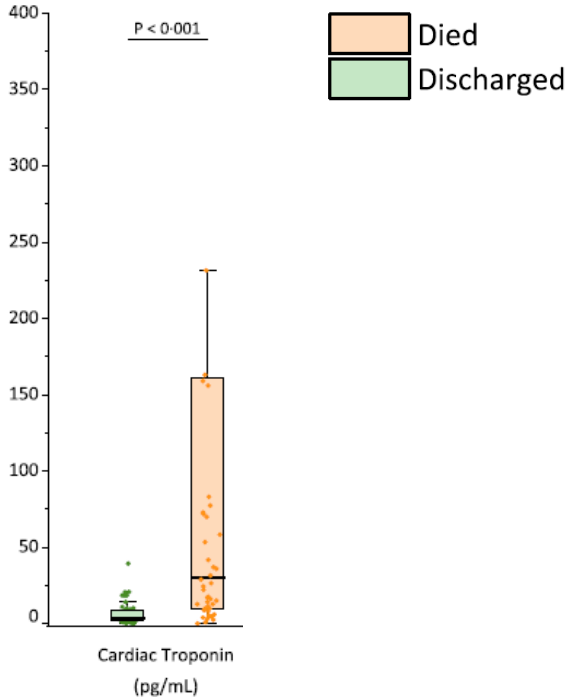
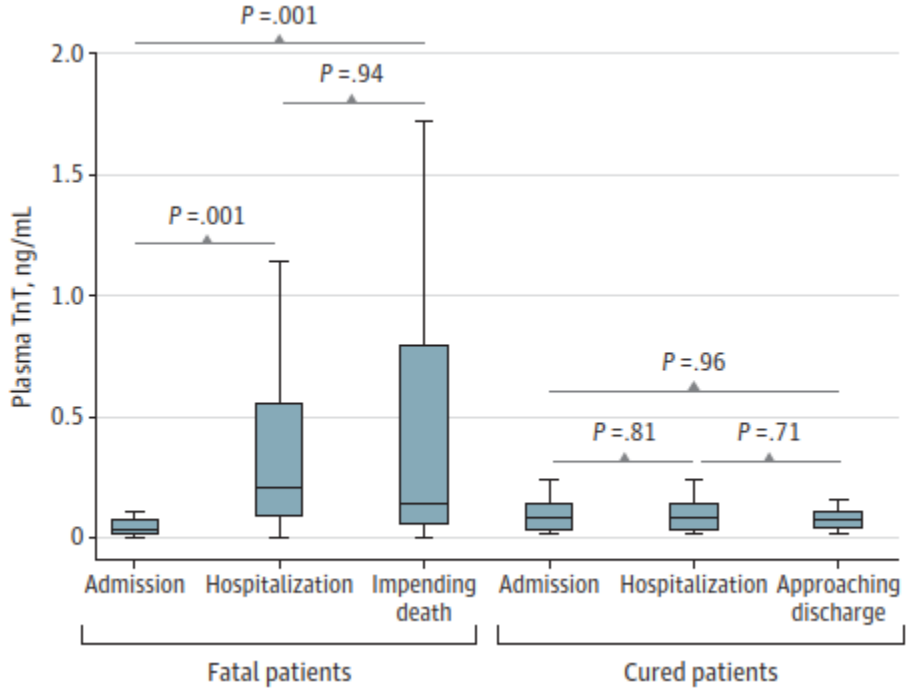
Patients with elevated cTn have higher mortality



Non-survivors had increasing cTn over the course of hospitalization



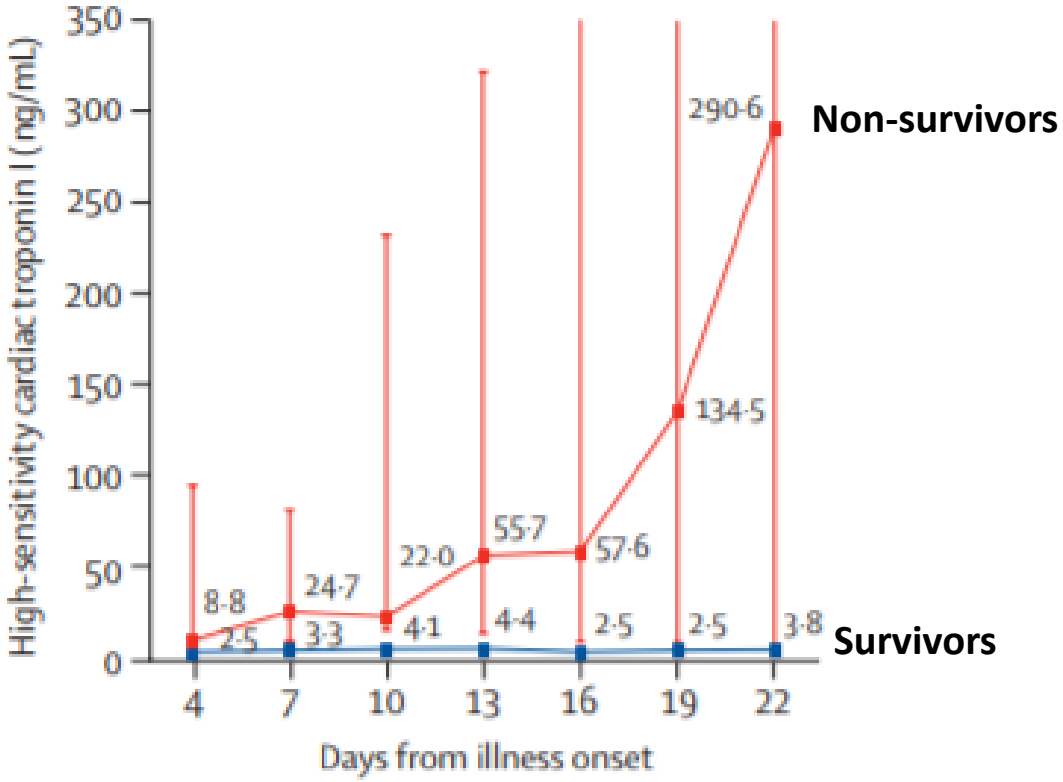
Ruan, Q. Intensive Care Medhttps://doi.org/10.1007/s00134-020-05991-x
N=187 hospitalized patients in Wuhan, China, CVD history included hypertension, coronary heart disease and cardiomyopathy, Guo et al. JAMA Cardiol. 2020. doi: 10.1001/jamacardio.2020.1017

This information represents a potential novel clinical utility. Data have not been reviewed by FDA or any other regulatory agency

Cardiac Troponin elevations in severely ill COVID-19 patients: Potential prognostic factor

SIEMENS Healthineers

cTnI in hospitalized COVID-19 patients in Wuhan, China



	Survivors (n=137)	Non-survivors (n=54)
Hs-cTnI Median (IQR)	3.0 (1.1 - 5.5)	22.2 (5.6 - 83.1)
cTnI > 99th p (28ng/L)	1/95 (1%)	23/50 (46%)

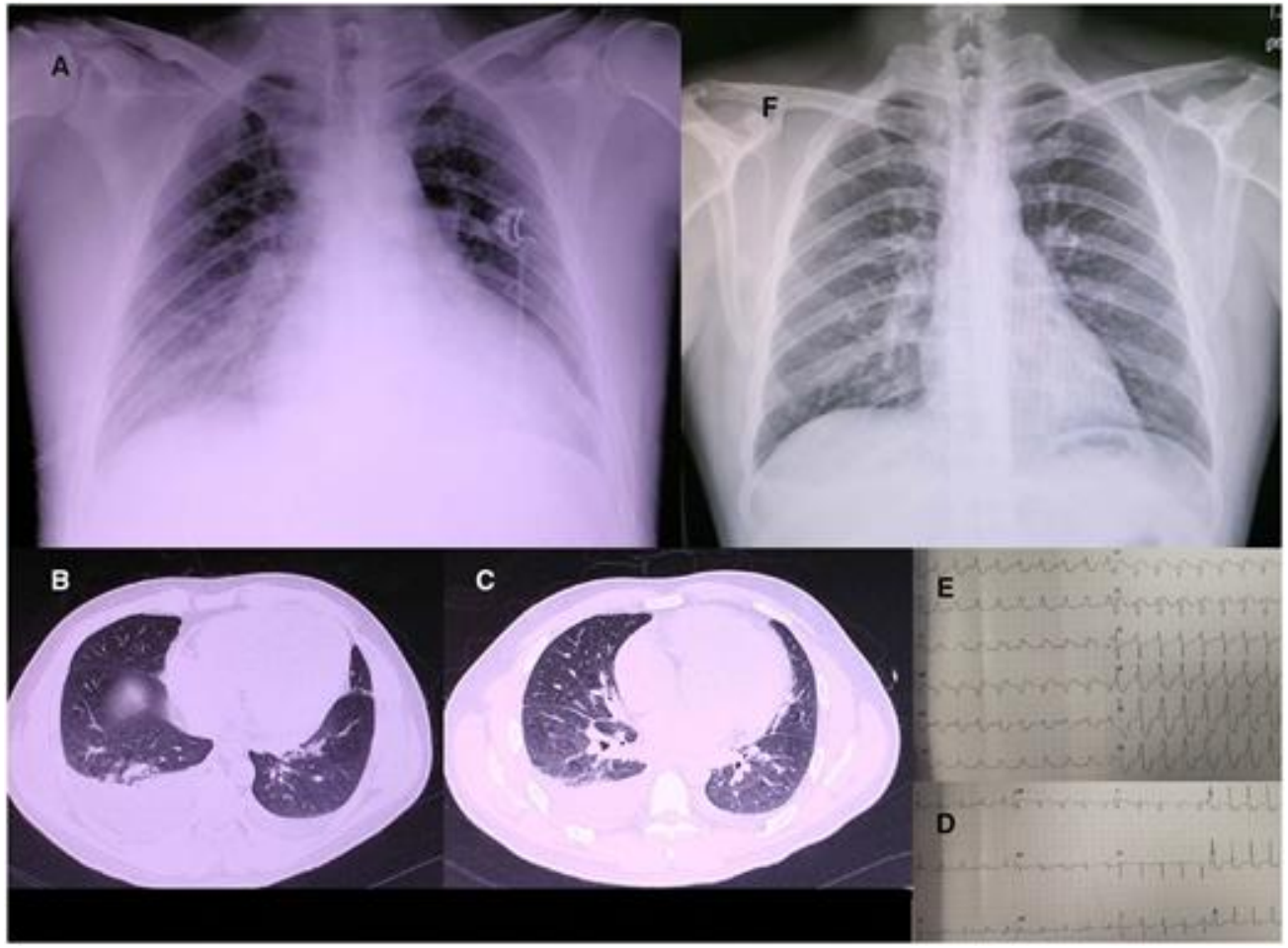
Note that increasing cTnI may not be Type I MI:

- Myocardial ischaemia in COVID-19 may be secondary to hypoxemia/ tachycardia
- Myocardial damage in COVID-19 may be due to 'cytokine storm'/ catecholamines

Zhou et al. Lancet. 2020. doi: 10.1016/S0140-6736(20)30566-3
Xiong et al. Eur Heart J. 2020. doi: 10.1093/eurheartj/ehaa231

This information represents a potential novel clinical utility. Data have not been reviewed by FDA or any other regulatory agency

Case Report: Fulminant myocarditis secondary to COVID-19, “disguised” as myocardial infarction



- M 37y, chest pain, dyspnea, diarrhea for 3 days
- ECG showed III and AVF ST segment elevation
- cTnT > 10,000ng/L; CK-MB 112.9 ng/L
- **Coronary angiography revealed no stenosis**

- Echocardiography: Left ventricular EF 27%
- X-ray showed enlargement of the heart
- Chest CT indicated pulmonary infection
- Sputum: SARS-CoV-2 positive

- Diagnosis: COVID-19 infection, fulminant myocarditis, cardiogenic shock
- Treatment: glucocorticoid + immunoglobulin

- 1week later: normal X-ray, LVEF 66%, cTnT 220.5ng/L

Hu et al. Eur Heart J. 2020 https://doi.org/10.1093/eurheartj/ehaa190

We are in this together –
Our response to the COVID-19 pandemic

SIEMENS Healthineers

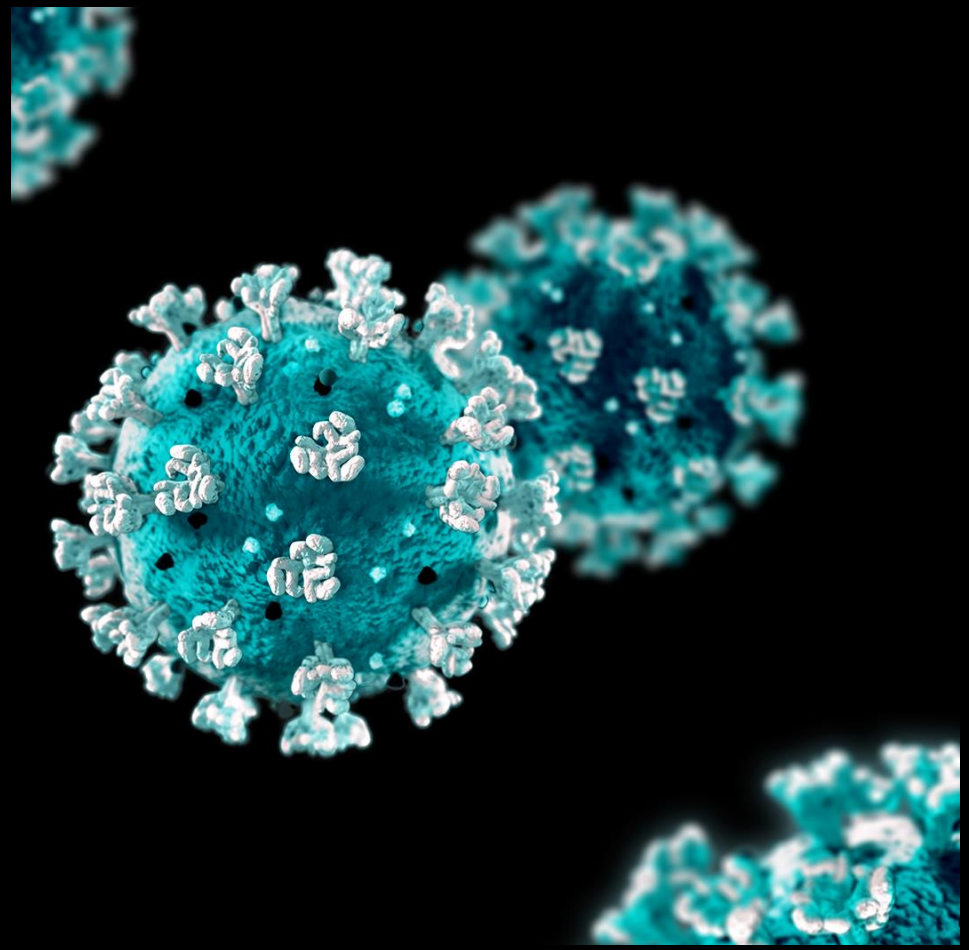
We are fully committed to supporting our partners throughout the healthcare system to provide the best possible care for patients.

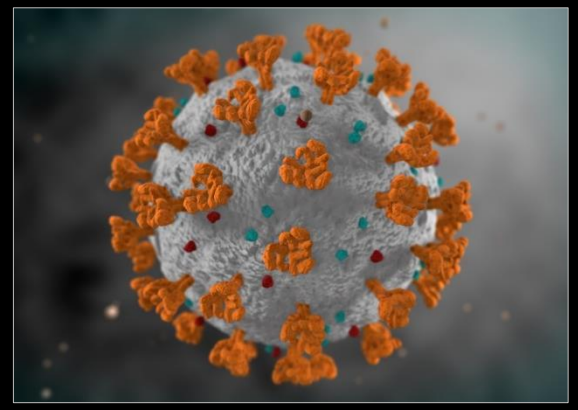
The coronavirus (SARS-CoV-2) pandemic continues to spread, confronting healthcare professionals around the world with unprecedented clinical and operational challenges. As they struggle to deal with this extraordinary situation, at the same time they must also continue to care for other patients.

At Siemens Healthineers, we are aware of the urgency and complexity of the current situation, and we are working hard to provide the best possible support to healthcare providers at each stage of COVID-19 patient care: diagnosis, prognosis, therapy and follow-up.

Our aspiration to drive innovations forward so people live healthier and longer lives is more valid today than ever before. We are stepping up as a partner to support healthcare systems helping them to deliver high-value care to patients and families. Please do not hesitate to contact us in case of questions or suggestions.

Siemens Healthineers Response: Laboratory Diagnostics





FTD SARS-CoV-2 Assay

Chemistry/Immunoassay

Hemostasis/Hematology

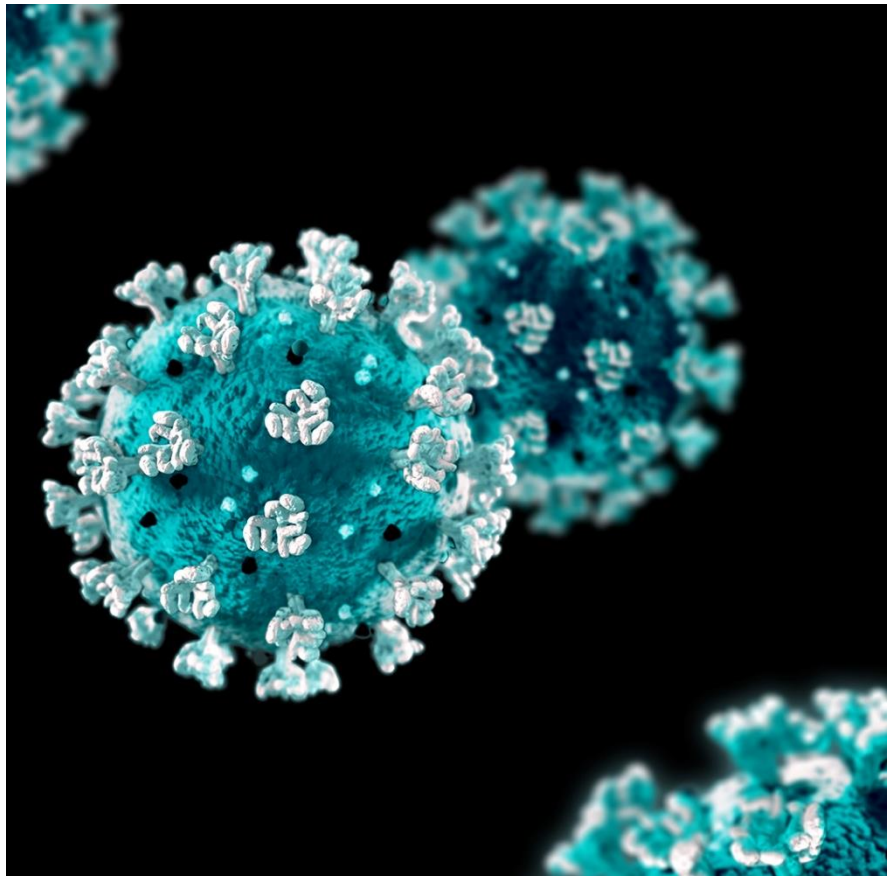
Blood Gas Testing

*SARS-CoV-2 serology assay in development†

†In development; not available for sale. Future availability cannot be guaranteed

Computed Tomography, Radiology, Ultrasound and Molecular Imaging Hybrid Devices

COVID-19 Summary



- The SARS-CoV-2 virus is novel, highly infectious and populations lack immunity. Asymptomatic transmission likely.
- Disease severity and clinical presentation varies enormously, from asymptomatic to severe. Risk factors for severity include age and comorbidities such as diabetes, hypertension, and pulmonary disease. Viral sepsis can drive pathology.
- Molecular testing confirms the presence of virus. Serology testing identifies antibodies to the virus indicating current or prior infection.
- Multiple testing modalities are utilized to inform diagnosis and treatment.
- We are fully committed to supporting our partners in the healthcare system to provide the best possible care for patients.

https://www.who.int/health-topics/coronavirus#tab=tab_1. Accessed March 26, 2020
N van Doremalen, et al. Aerosol and surface stability of HCoV-19 (SARS-CoV-2) compared to SARS-CoV-1. The New England Journal of Medicine. DOI:10.1056/NEJMc2004973 (2020).

Thank you for your enthusiasm!

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