CLINICAL CARE OPTIONS®
INFECTIOUS DISEASE

Comprehensive COVID-19 Slideset: Symptoms and Clinical Manifestations

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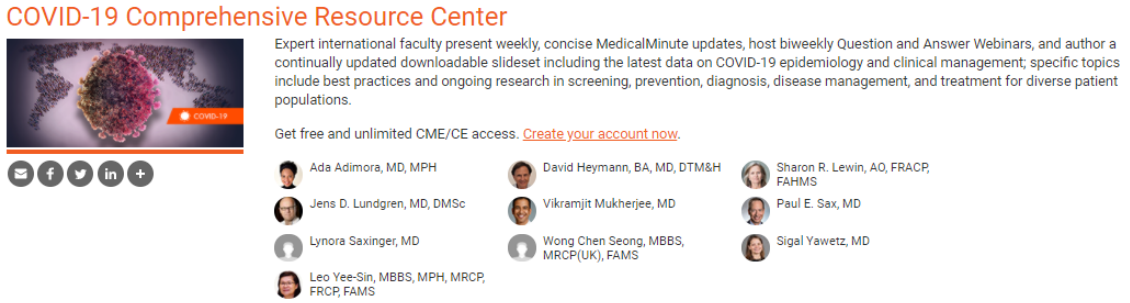

MedicalMinute	Topic/Studies Covered
1 Remdesivir EUA	ACTT-1 trial
2 SARS-CoV-2 serology	Ab: detection, neutralizing; POC testing
3 COVID-19 diagnosis	Ab, RNA, chest CT, diagnosis timeframe
4 Clinical presentation	Incubation, symptoms, disease severity
5 Mild/mod COVID-19	ACTT-1, SIMPLE-moderate, SIMPLE-severe
6 Racial disparities	Incidences, hospitalizations, deaths
7 Sev/crit COVID-19	Def, management, NIH and IDSA guidelines
8 Dexamethasone data	RECOVERY trial, recommendations, caveats
9 Immunocompromise	HIV, malig, organ tx, immunomodulators
10 COVID-19 in children	Incidence, severity, MIS-C, remdesivir EUA

MedicalMinute	Topic/Studies Covered
11 Vaccines in phase III	Moderna, Oxford, CanSino trials
12 Viral transmission	Droplets, aerosols, phys dist, air circ, masks
13 Pregnancy	Labor/delivery, transmission, remdesivir
14 Diagnostics, epi	Tests: antibody, antigen, RT-PCR for RNA
15 Coagulopathy	Anticoagulation, thromboprophylaxis
16 Adaptive immunity	IgG durability, memory T-cells, reinfection
17 Convalescent plasma	Li study in JAMA, conCOVID, FDA EUA
18 Herd Immunity	R_0, pop heterogeneity, immune duration
19 Long-term sequelae	Pulmonary and extra-pulmonary sequelae
20 Corticosteroids	RECOVERY, CoDex, REMAPCAP, CapeCOVID

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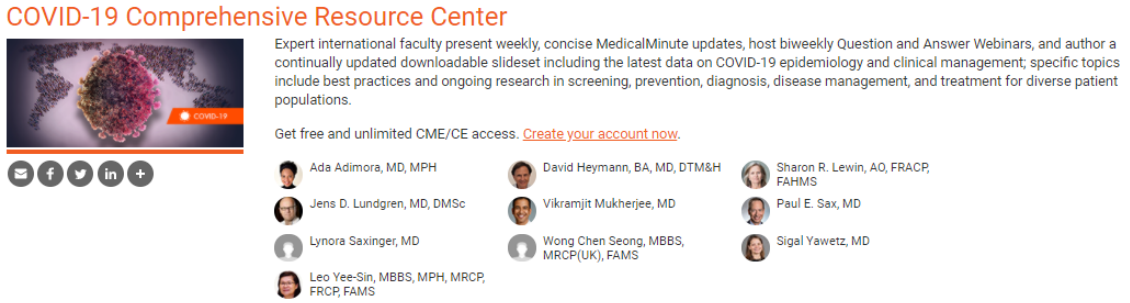

MedicalMinute	Topic/Studies Covered
21 Comorbidities	Cancer, CVD (BRACE-corona), DM, CKD
22 Immunomodulation	TESEO, COVACTA, EMPACTA, ongoing trials
23 Coinfections	Secondary infection incidence in COVID-19
24 Treatment updates	ACTT-1, SOLIDARITY, remdesivir approval
25 Reinfection	Reinfection with SARS-CoV-2, Ab kinetics
26 Epi in HCWs	Infection rates in HCWs vs gen pop
27 SARS-CoV-2 mutation	Mutations/rates, global distribution, impact
28 HIV and COVID-19	Mortality/comorbidity in larger studies, Ad5
29 Vaccine hesitancy	Factors that impact hesitancy, survey data
30 Vaccine updates	Safety and efficacy, EUAs, global concerns

MedicalMinute	Topic/Studies Covered
31 Treatment update	Baricitinib, anti-spike antibodies, ivermectin
32 Antigen testing	Antigen test algorithms, EUAs, at-home test
33 Anticoagulation	Update on thromboprophylaxis trials, data
34 Investigational agents	TMPRSS2 inhibitors, CRISPR-Cas13, IFN Λ

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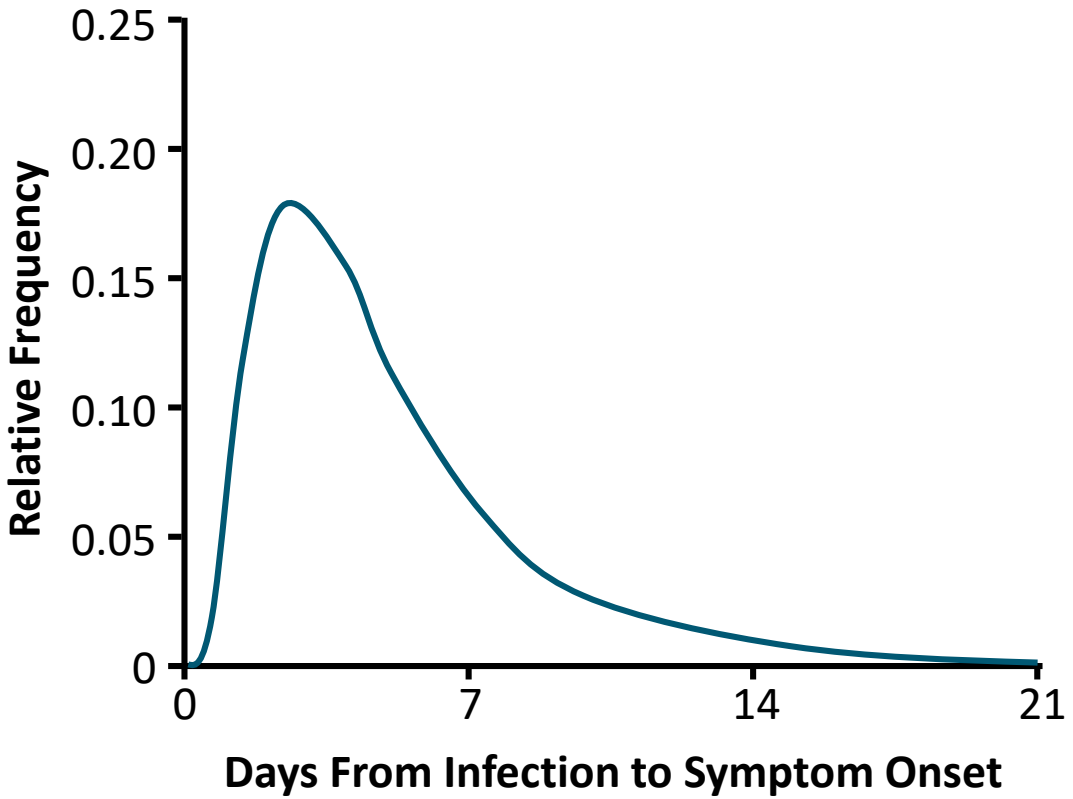
Natural History, Clinical Presentation, and Symptom Spectrum

COVID-19 Incubation: Infection to Illness Onset

- Among 10 confirmed NCIP cases in Wuhan, Hubei province, China[1]
  - Mean incubation: 5.2 days (95% CI: 4.1-7.0)
- Among 181 confirmed SARS-CoV-2 infections occurring outside of Hubei province[2]
  - Median incubation: 5.1 days (95% CI: 4.5-5.8)
  - Symptom onset by Day 11.5 of infection in 97.5% of persons

Estimated Incubation Period Distribution[1]

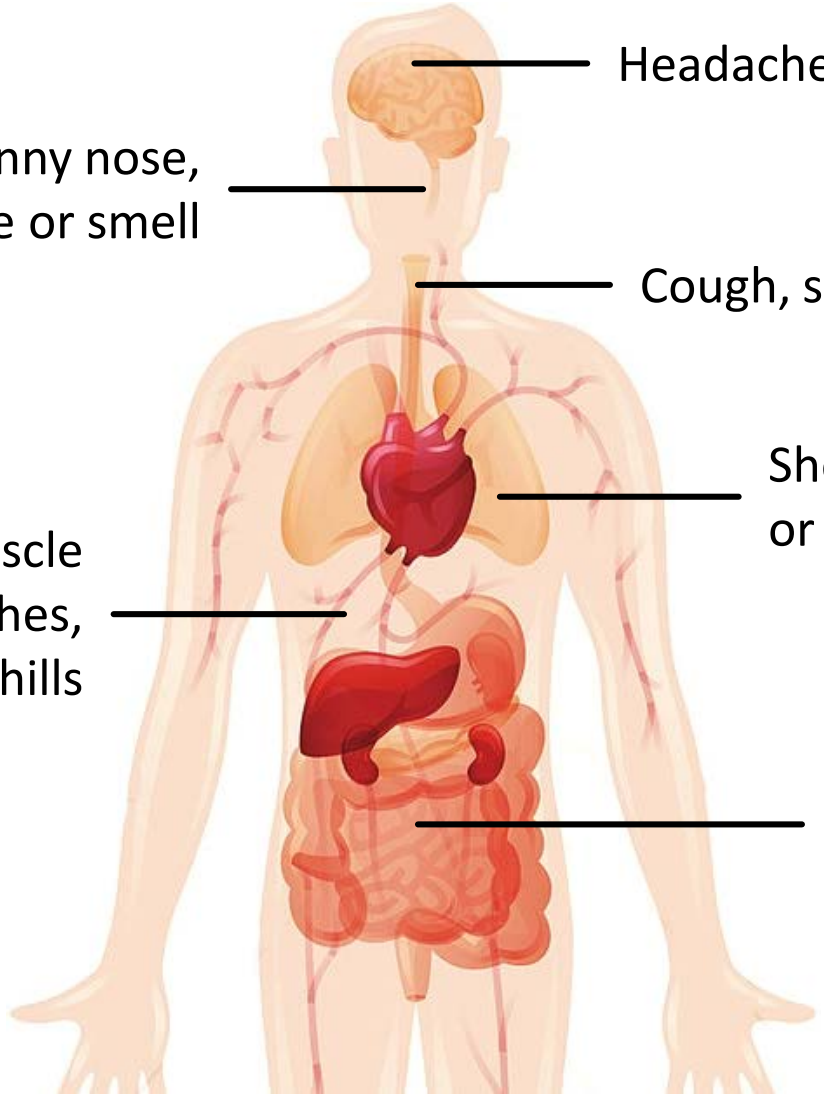


1. Li. NEJM. 2020;382:1199. 2. Lauer. Ann Intern Med. 2020;172:577.

Slide credit: clinicaloptions.com

Primary Symptoms of COVID-19

"Symptoms may appear **2-14 days after exposure** to the virus"



Li. J Med Virol. 2020;92:577.
https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html

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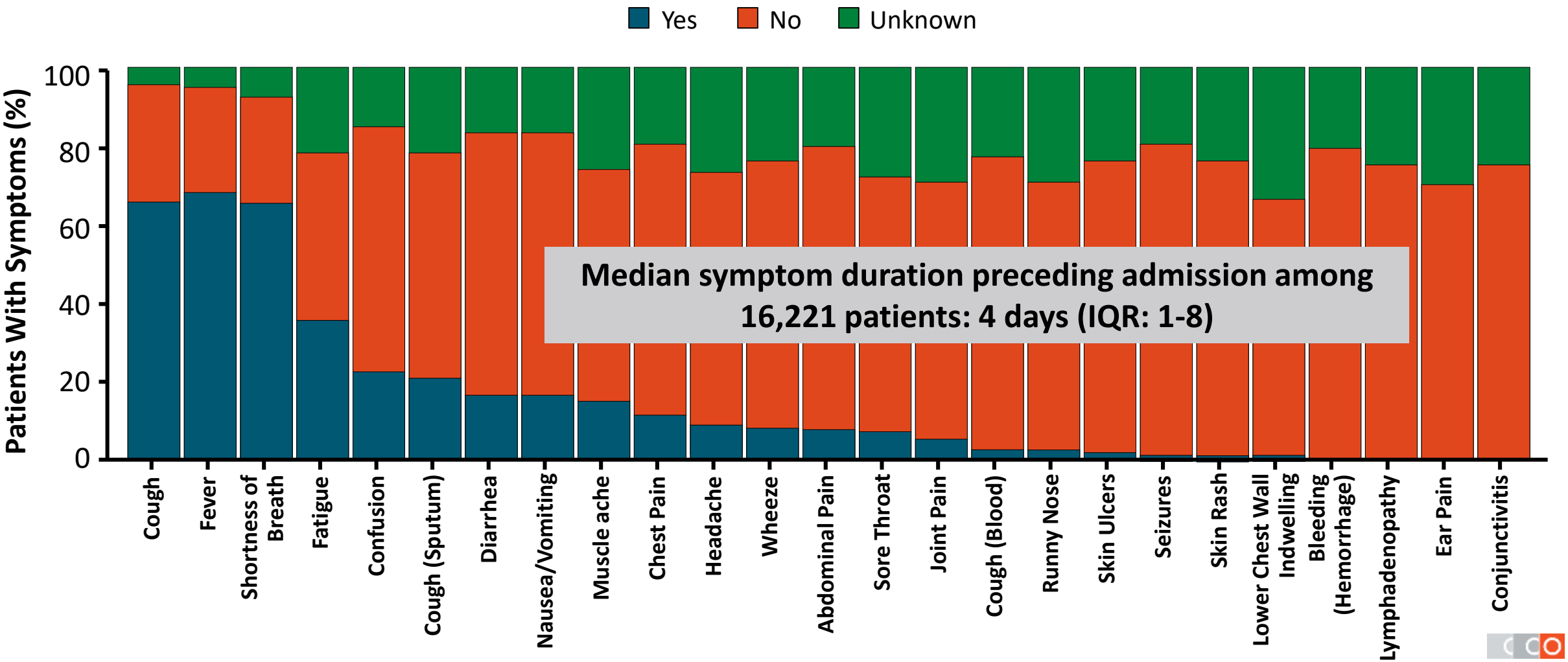
Frequency of Presenting Symptoms Among COVID-19–Positive Hospitalized Patients in the UK



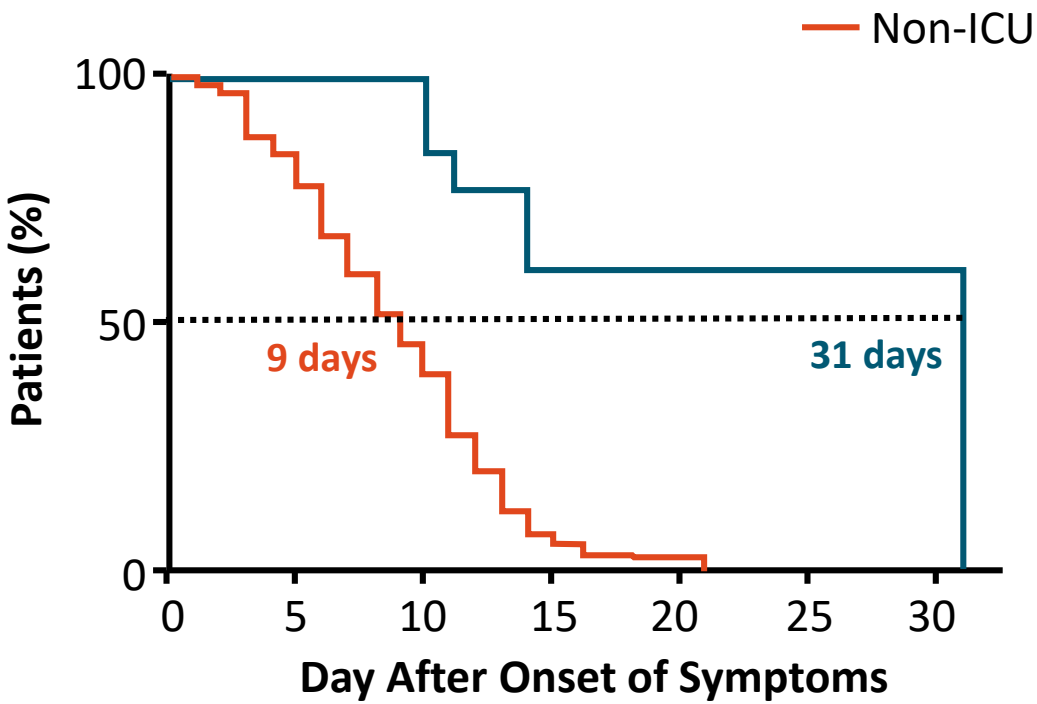
Docherty. BMJ. 2020;369:m1985.

Slide credit: clinicaloptions.com

Clinical Course of Fever by Requirement for ICU Care Among COVID-19 Patients in Shanghai, China

Fever

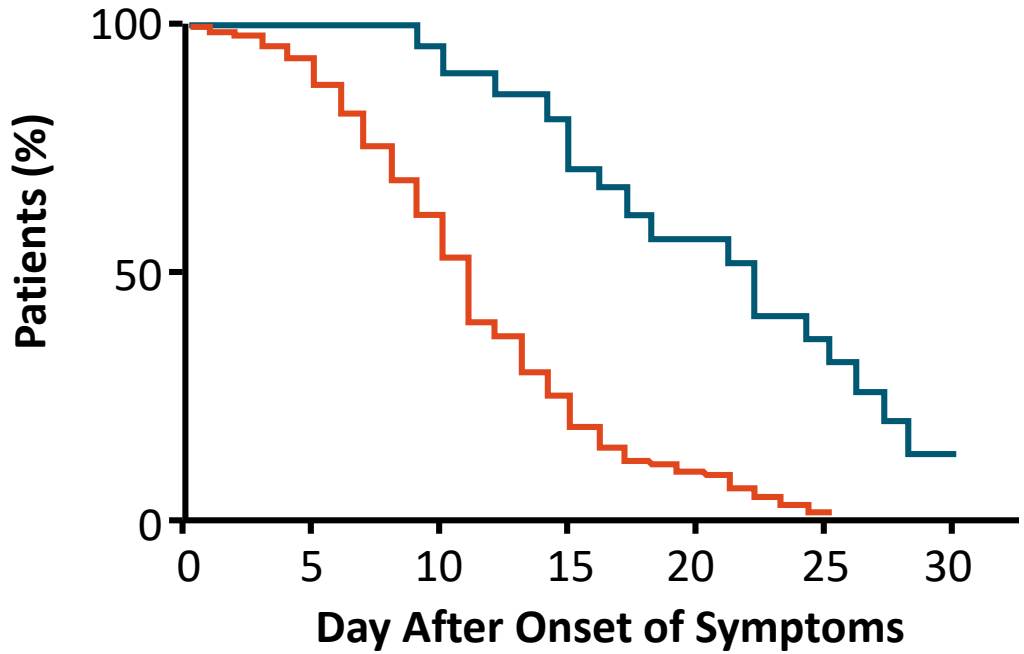
HR: 5.83 (95% CI: 3.86-8.80; *P* < .0001)



Patients at Risk, n			
ICU	22	13	3
Non-ICU	213	93	3

PCR Positivity

HR: 3.17 (95% CI: 2.29-4.37; *P* < .0001)



Patients at Risk, n						
ICU	21	21	20	17	12	7
Non-ICU	227	207	149	49	19	1

Chen. J Infect. 2020;80:e1.

COVID-19 Clinical Presentation May Vary by Age, Sex

- Observational study of Europeans with mild-to-moderate COVID-19 (ie, no ICU admission) via standardized questionnaire during March 22-April 10, 2020 (N = 1420)[1]
  - **Mean duration of symptoms** (n = 264): 11.5 ± 5.7 days
  - Ear, nose, throat complaints more common in **young patients**; fever, fatigue, loss of appetite, diarrhea in **elderly patients** (*P* < .01)
  - Loss of smell, headache, nasal obstruction, throat pain, fatigue more common in **women**; cough, fever in **men** (*P* < .001)
- Among 17 fatal COVID-19 cases detailed by the China National Health Commission, **median time from first symptom to death**: 14 days (range: 6-41)[2]
  - Numerically faster in **older patients**: 11.5 days if ≥ 70 yrs vs 20 days if < 70 yrs (*P* = .033)

Symptom,[1] %	N = 1420
Headache	70.3
Loss of smell	70.2
Nasal obstruction	67.8
Asthenia	63.3
Cough	63.2
Myalgia	62.5
Rhinorrhea	60.1
Taste dysfunction	54.2
Sore throat	52.9
Fever (> 38°C)	45.4

1. Lechien. J Intern Med. 2020;288:335. 2. Wang. J Med Virol. 2020;92:441.

Slide credit: clinicaloptions.com

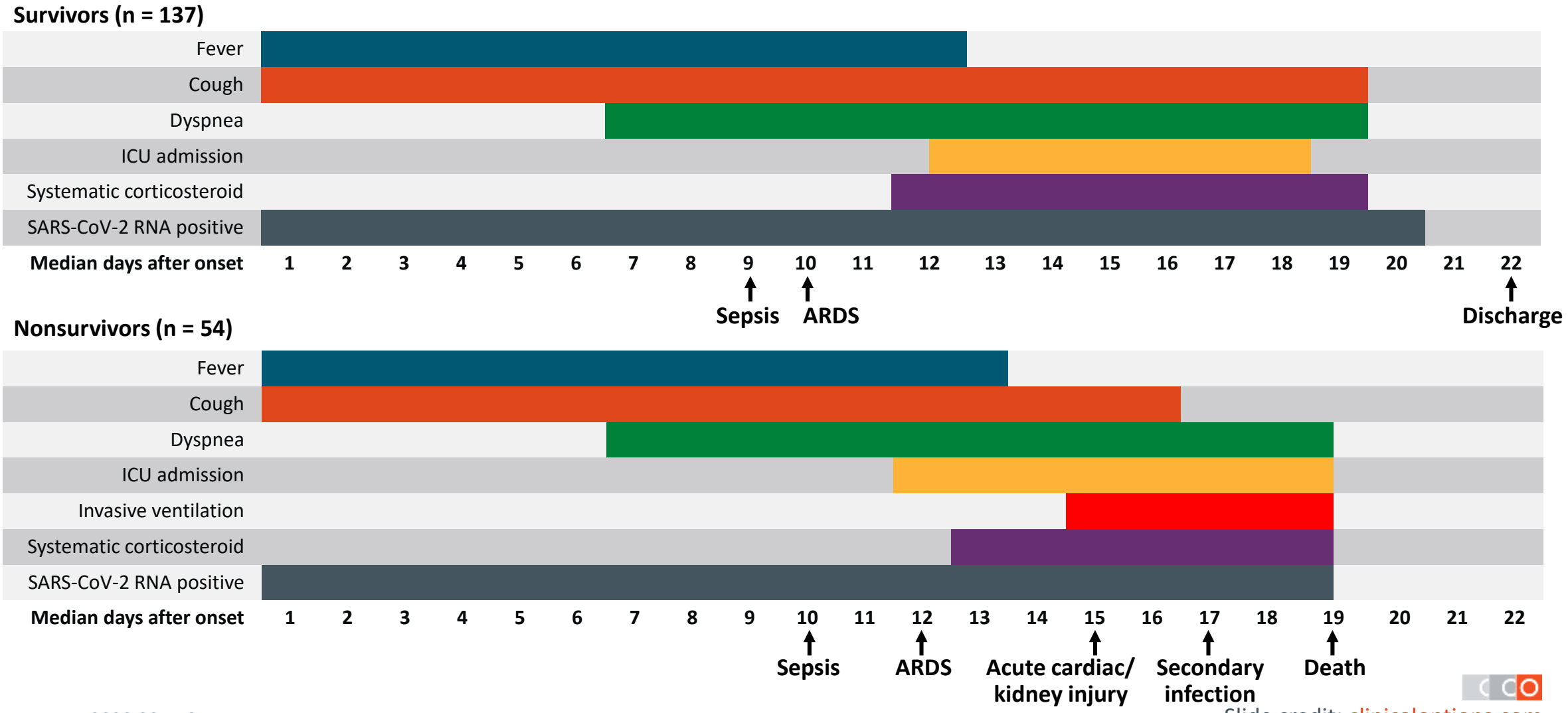
Radiographic and Lab Abnormalities by Disease Severity Among COVID-19 Patients in Mainland China

Radiographic or Lab Finding	All Patients (N = 1099)	Nonsevere Disease (n = 926)	Severe Disease (n = 173)
Abnormalities on chest radiograph,* n/N (%)	162/274 (59.1)	116/214 (54.2)	46/60 (76.7)
Abnormalities on chest CT,* n/N (%)	840/975 (86.2)	682/808 (84.4)	158/167 (94.6)
Median white cell count per mm^3 (IQR)	4700 (3500-6000)	4900 (3800-6000)	3700 (3000-6200)
Median lymphocyte count per mm^3 (IQR)	1000 (700-1300)	1000 (800-1400)	800 (600-1000)
Median platelet count x 1000 per mm^3 (IQR)	168 (132-207)	172 (139-212)	137.5 (99-179.5)
C-reactive protein ≥ 10 mg/L, n/N (%)	481/793 (60.7)	371/658 (56.4)	110/135 (81.5)
D-dimer ≥ 0.5 mg/L, n/N (%)	260/560 (46.4)	195/451 (43.2)	65/109 (59.6)
Lactate dehydrogenase ≥ 250 U/L, n/N (%)	277/675 (41.0)	205/551 (37.2)	72/124 (58.1)
AST > 40 U/L, n/N (%)	168/757 (22.2)	112/615 (18.2)	56/142 (39.4)
ALT > 40 U/L, n/N (%)	158/741 (21.3)	120/606 (19.8)	38/135 (28.1)

*Ground-glass opacity, local patchy shadowing, bilateral patchy shadowing, or interstitial abnormalities.

Guan. NEJM. 2020;382:1708.

Variation in Clinical Course and Outcome Among Patients Hospitalized With COVID-19 in Wuhan, China



Zhou. Lancet. 2020;395:1054.

Slide credit: clinicaloptions.com

Probing Long-term Sequelae of COVID-19

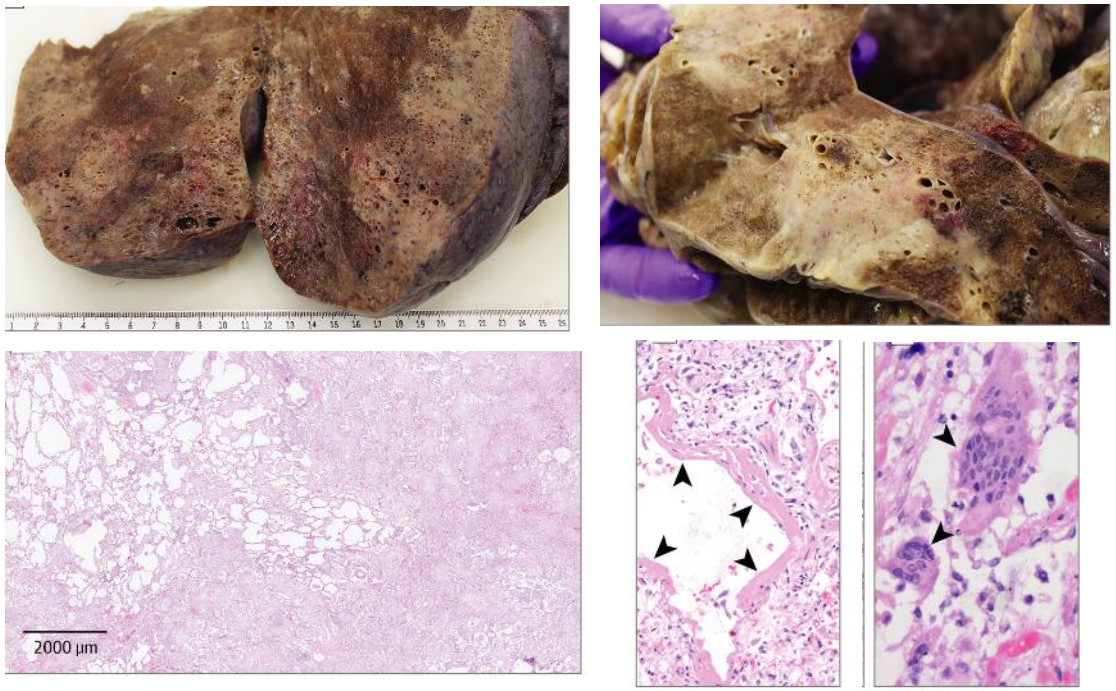
- Limited peer-reviewed data focused on the occurrence or prevalence of COVID-19–related long-term sequelae
- Reasonable to anticipate manifestations based on established knowledge of SARS-CoV-2 pathophysiology, other coronavirus infection outcomes
  - Pulmonary, cardiovascular, and neurologic perturbations proposed
  - SARS-CoV-2 entry receptor ACE2 expressed across extrapulmonary tissues[1-3]
  - Among patients recovering from severe SARS-CoV or MERS-CoV infection, impaired diffusing capacity for carbon monoxide and exercise capacity common during first 6 mos following discharge; after 6 mos, posttraumatic stress disorder (39%), depression (33%), and anxiety (30%) still considerable[4]

1. Zhou. Nature. 2020;579:270. 2. Hoffmann. Cell. 2020;181:271.
3. Gupta. Nat Med. 2020;26:1017. 4. Ahmed. J Rehabil Med. 2020;52:jrm00063.

Pulmonary Sequelae

- Diffuse alveolar damage noted in multiple, small postmortem studies of COVID-19
  - N = 38 from northern Italy[1]
  - N = 10 from Germany[2]
- Platelet–fibrin thrombi indicative of coagulopathy observed in small arterial vessels of some patients[1]

Macroscopic and Histologic Lung Findings[2]



1. Carsana. Lancet Infect Dis. 2020;20:1135. 2. Schaller. JAMA. 2020;323:2518.

Slide credit: clinicaloptions.com

Long-term Lung and Bone Ramifications of Hospital-Acquired SARS Infection

- Prospective, observational cohort study of medical staff infected with SARS in 2003; 15-yr follow-up of lung and bone outcomes via pulmonary CT scans and function tests, hip joint MRIs and function questionnaires (N = 71)
  - Percentage of lung area with pulmonary lesions diminished from 9.4% to 3.2% in first yr ($P < .001$), then stabilized until last assessment in 2018
  - Percentage of osteonecrotic volume by MRI of femoral head declined substantially from 38.8% to 30.4% in first 2 yrs ($P = .0002$), then slowly to 2013 and plateaued until last assessment in 2018

"Pulmonary interstitial damage and functional decline caused by SARS mostly recovered, with a greater extent of recovery within 2 yrs after rehabilitation. Femoral head necrosis induced by large doses of steroid pulse therapy in SARS patients was not progressive and was partially reversible."

Zhang. Bone Res. 2020;8:8.

Slide credit: clinicaloptions.com

Characterization of COVID-19 Patients Returning for Care After Hospitalization

- Retrospective cohort study of patients with confirmed SARS-CoV-2 infection discharged from 5 NYC hospitals (N = 2864)
  - 3.6% (n = 103) sought emergency care after median 4.5 days
  - 2.0% (n = 56) required inpatient readmission
- One half of patients returning for care experienced **respiratory distress**
- Compared with patients not returning for care, those seen again had:
  - More COPD (6.8% vs 2.9%) and hypertension (36.0% vs 22.1%)
  - Shorter median length of initial stay (4.5 vs 6.7 days)

Somani. J Gen Intern Med. 2020;25:2638.

Slide credit: clinicaloptions.com

Extrapulmonary Manifestations of COVID-19: Which of These Return or Last?

Dermatologic
- Petechaie
- Livedo reticularis
- Erythematous rash
- Urticaria
- Vesicles
- Pernio-like lesions

Neurologic
- Headaches
- Dizziness
- Encephalopathy
- Guillain-Barré
- Ageusia
- Myalgia
- Anosmia
- Stroke

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

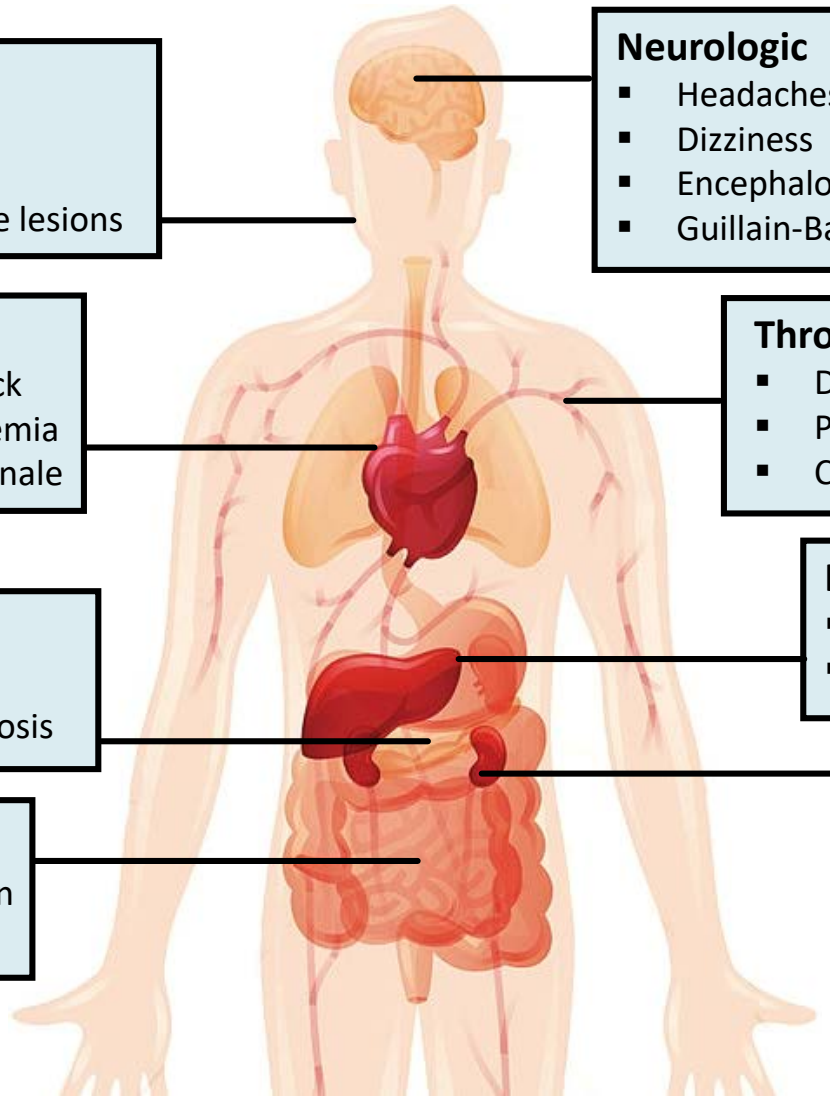
Thromboembolism
- Deep vein thrombosis
- Pulmonary embolism
- Catheter-related thrombosis

Endocrine
- Hyperglycemia
- Diabetic ketoacidosis

Hepatic
- Elevated ALT/AST
- Elevated bilirubin

Gastrointestinal
- Diarrhea
- Nausea/vomiting
- Abdominal pain
- Anorexia

Renal
- Acute kidney injury
- Proteinuria
- Hematuria

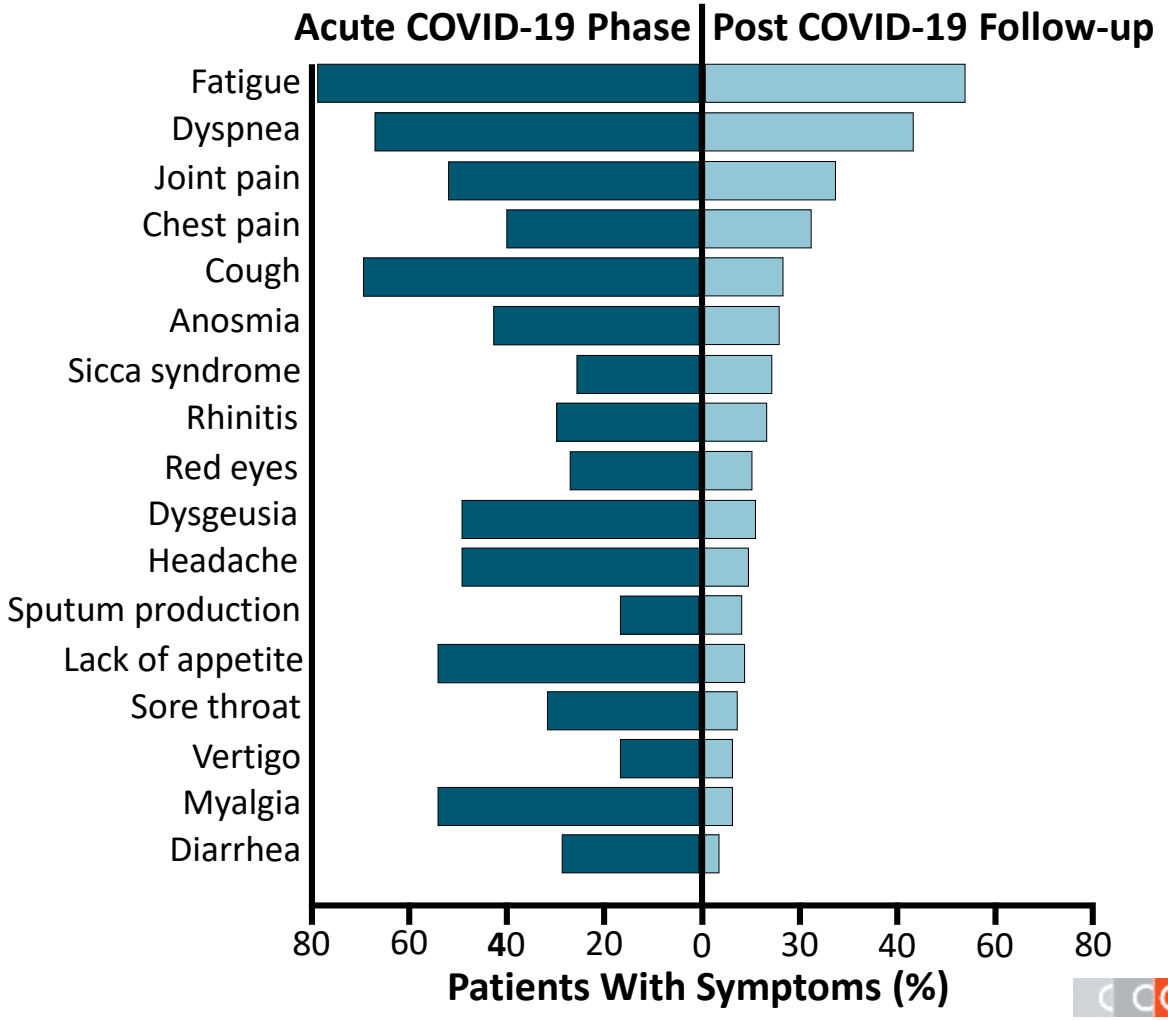


Gupta. Nat Med. 2020;26:1017.

Slide credit: clinicaloptions.com

COVID-19 Symptom Persistence: Experience From Italy

- Postacute outpatient service for patients who recovered from COVID-19 (N = 143)
  - Mean hospital stay: 13.5 days
- Assessed by standardized questionnaire at mean of 60.3 days after onset of first COVID-19–related symptom
  - 32% had 1-2 persistent symptoms
  - 55% had ≥ 3 persistent symptoms
  - None with fever, signs of acute illness
- 44% of patients reported lower QoL



Carfì. JAMA. 2020;324:603.

Slide credit: clinicaloptions.com

Predicting Delayed Return to Usual Health Among COVID-19 Outpatients in the United States

Characteristic, n (% of Subgroup)			Returned to Usual Health Within 14-21 Days of Positive SARS-CoV-2 RT-PCR		*P* Value
			Yes (n = 175)	No (n = 95)	
Age	▪ 18-34 yrs	(n = 85)	63 (74)	22 (26)	.010
	▪ 35-49 yrs	(n = 96)	65 (68)	31 (32)	
	▪ ≥ 50 yrs	(n = 89)	47 (53)	42 (47)	
Number of medical conditions	▪ 0	(n = 123)	87 (71)	36 (29)	.003
	▪ 1	(n = 57)	41 (72)	16 (28)	
	▪ 2	(n = 39)	21 (54)	18 (46)	
	▪ ≥ 3	(n = 44)	19 (43)	25 (57)	
Individual medical conditions	▪ Hypertension	(n = 64)	33 (52)	31 (48)	.018
	▪ Obesity (ie, BMI > 30)	(n = 51)	23 (45)	28 (55)	.002
	▪ Psychiatric condition	(n = 49)	23 (47)	26 (53)	.007
	▪ Immunosuppressive condition	(n = 15)	6 (40)	9 (60)	.047

Tenforde. MMWR Morb Mortal Wkly Rep. 2020;69:993.

Slide credit: clinicaloptions.com

Cardiovasular Sequelae

- Prospective, observational cohort study sourcing recovered patients from the University Hospital Frankfurt COVID-19 Registry (N = 100)[1]
  - CV magnetic resonance performed at median 71 days from diagnosis
  - Abnormal findings in 78% of patients, myocardial inflammation in 60%; independent of preexisting comorbidities, severity of acute SARS-CoV-2 infection, and time from diagnosis
  - Reduced left ventricular ejection fraction, increased left ventricle volumes and native T1/T2 vs risk-matched controls

"There are no data on how acute treatment of COVID-19 may affect . . . long-term cardiac recovery and function. Patients with ostensibly recovered cardiac function may still be at risk of cardiomyopathy and cardiac arrhythmias."[2]

1. Puntmann. JAMA Cardiol. 2020;5:1265. 2. Mitrani. Heart Rhythm. 2020;17:1984.

Slide credit: clinicaloptions.com

Neurologic Sequelae

Sensory Deficits: Olfactory and Gustatory Dysfunction

- Systematic review and meta-analysis including 24 studies of confirmed COVID-19 (N = 8438)[1]
  - Pooled prevalence
    - Anosmia: 41.0%, ageusia: 38.2%
    - Decreased among older patients
- *"Not yet clear whether COVID-19–related OGDs are transient or permanent"*[1]
  - In one prospective cohort (N = 3191), resolution typical within 3 wks[2]

"Respiratory virus infections are associated with neurological and psychiatric sequelae, including Parkinsonism, dementia, depression, posttraumatic stress disorder, and anxiety . . . Significant long-term neurological and psychiatric sequelae have to be anticipated in COVID-19, especially in survivors of severe disease."[3]

- Cognitive monitoring of recovered patients may be necessary

1. Agyeman. Mayo Clin Proc. 2020;95:1621. 2. Lee. J Korean Med Sci. 2020;35:e174. 3. Iadecola. Cell. 2020;183:16.

Slide credit: clinicaloptions.com

Coagulopathy in COVID-19

Burden of Thrombosis in Patients With COVID-19

Study Country	Design	Population	N	Thromboprophylaxis	Screening	VTE Rate, %
China[1]	Retrospective	ICU	81	No	No	25.0
France[2]	Prospective	ICU	150	Yes	No	11.7*
France[3]	Retrospective	ICU	26	Yes	Yes	69.0
France[4]	Retrospective	ICU	107	Yes	No	20.6†
The Netherlands[5]	Retrospective	ICU	184	Yes	No	27.0
Italy[6]	Retrospective	Inpatient	388	Yes	No	21.0
United Kingdom[7]	Retrospective	ICU	63	Yes	No	27.0

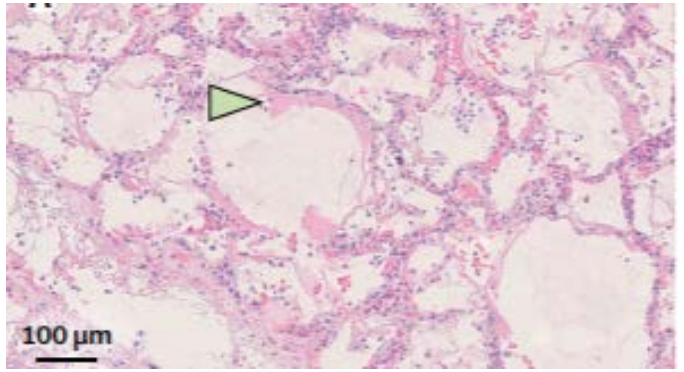
*Pulmonary embolisms in COVID-19 ARDS vs 2.1% in matched non-COVID-19 ARDS. †Pulmonary embolism vs 6.1% in non–COVID-19 ICU patients.

1. Cui. J Thromb Haemost. 2020;18:1421. 2. Helms. Intensive Care Med. 2020;46:1089. 3. Llitjos. J Thromb Haemost. 2020;18:1743. 4. Poissy. Circulation. 2020;142:184. 5. Klok. Throm Res. 2020;191:145. 6. Lodigiani. Thromb Res. 2020;191:9. 7. Thomas. Thromb Res. 2020;191:76.

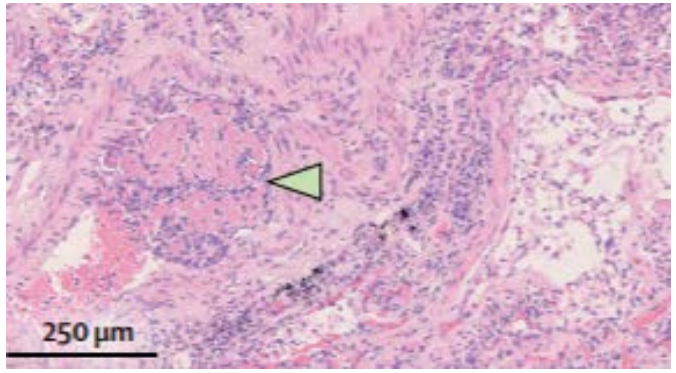
Autopsy Evidence of Lung Damage in COVID-19

- Prospective study to compare clinical findings with data from autopsy (N = 12)[1]
  - 7/12 patients had unsuspected bilateral DVT
  - 4/7 died from PE

Alveolar Damage[2]



Organizing Microthrombus[2]



1. Wichmann. Ann Intern Med. 2020;173:268. 2. Carsana. Lancet Infect Dis. 2020;20:1135.

Slide credit: clinicaloptions.com

Laboratory Predictors of Thrombosis in COVID-19

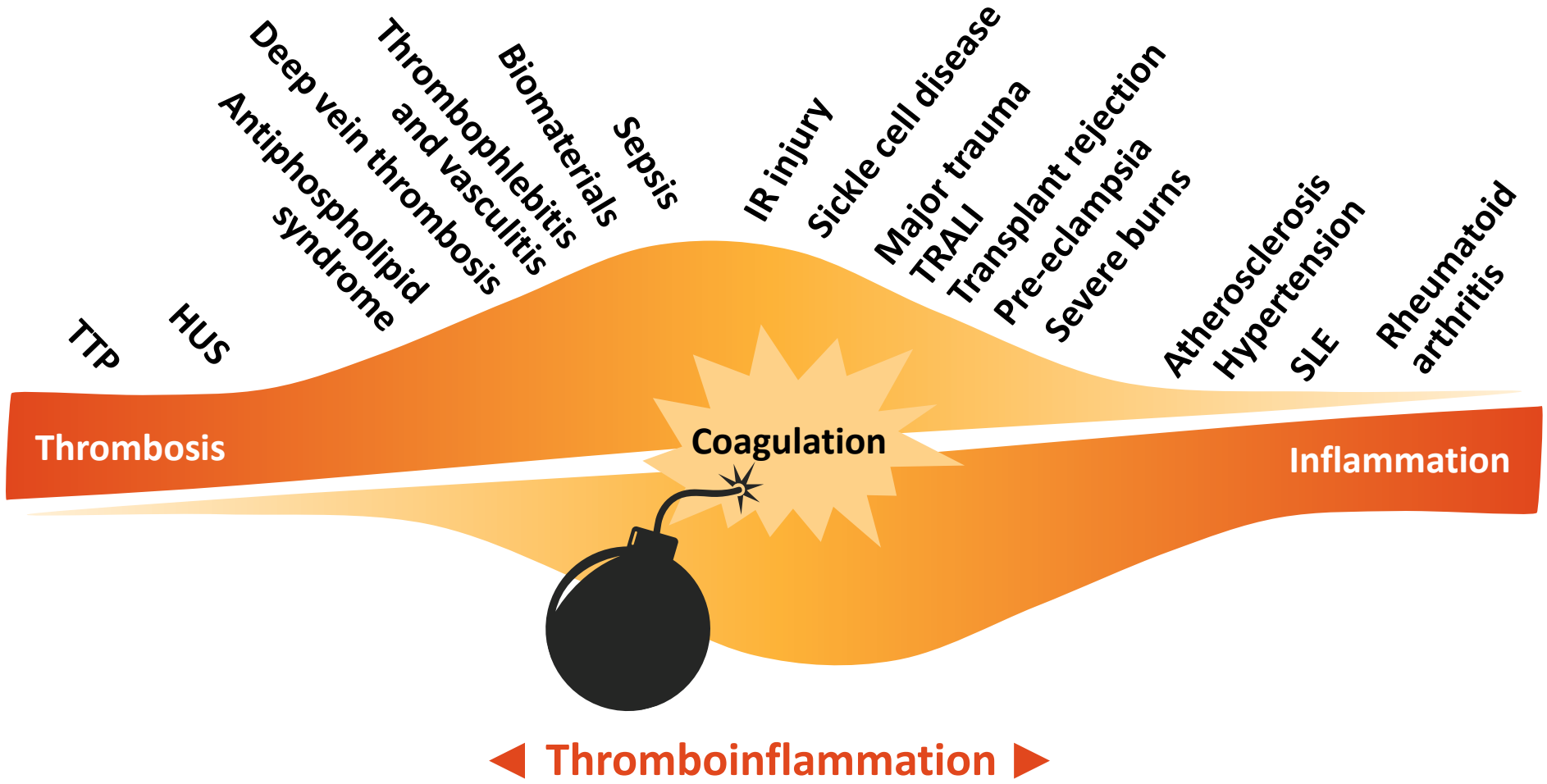
Median Value	No Thrombotic or Bleeding Complication (n = 347)	Thrombotic Complication (n = 38)	*P* Value
D-dimer, ng/mL			
▪ Initial	891	1538	.0002
▪ Minimum	760	1336	.0006
▪ Peak	1377	4001	< .0001
Fibrinogen, mg/dL			
▪ Initial	579	696	.0045
▪ Minimum	549	669	.0028
▪ Peak	662	828	.0001
CRP, mg/L			
▪ Initial	63.3	124.7	.0011
▪ Minimum	35.4	94.2	< .0001
▪ Peak	130.3	277.7	< .0001

Median Value	No Thrombotic or Bleeding Complication (n = 347)	Thrombotic Complication (n = 38)	*P* Value
ESR, mm/hr			
▪ Initial	38	47	.020
▪ Minimum	36	43	.079
▪ Peak	56	91	.0077
Ferritin, μg/L			
▪ Initial	504	825	.015
▪ Minimum	453	750	.0056
▪ Peak	707	1182	.0020

Al-Samkari. Blood. 2020;136:489.

Slide credit: clinicaloptions.com

COVID-19 Coagulopathy: Thromboinflammation



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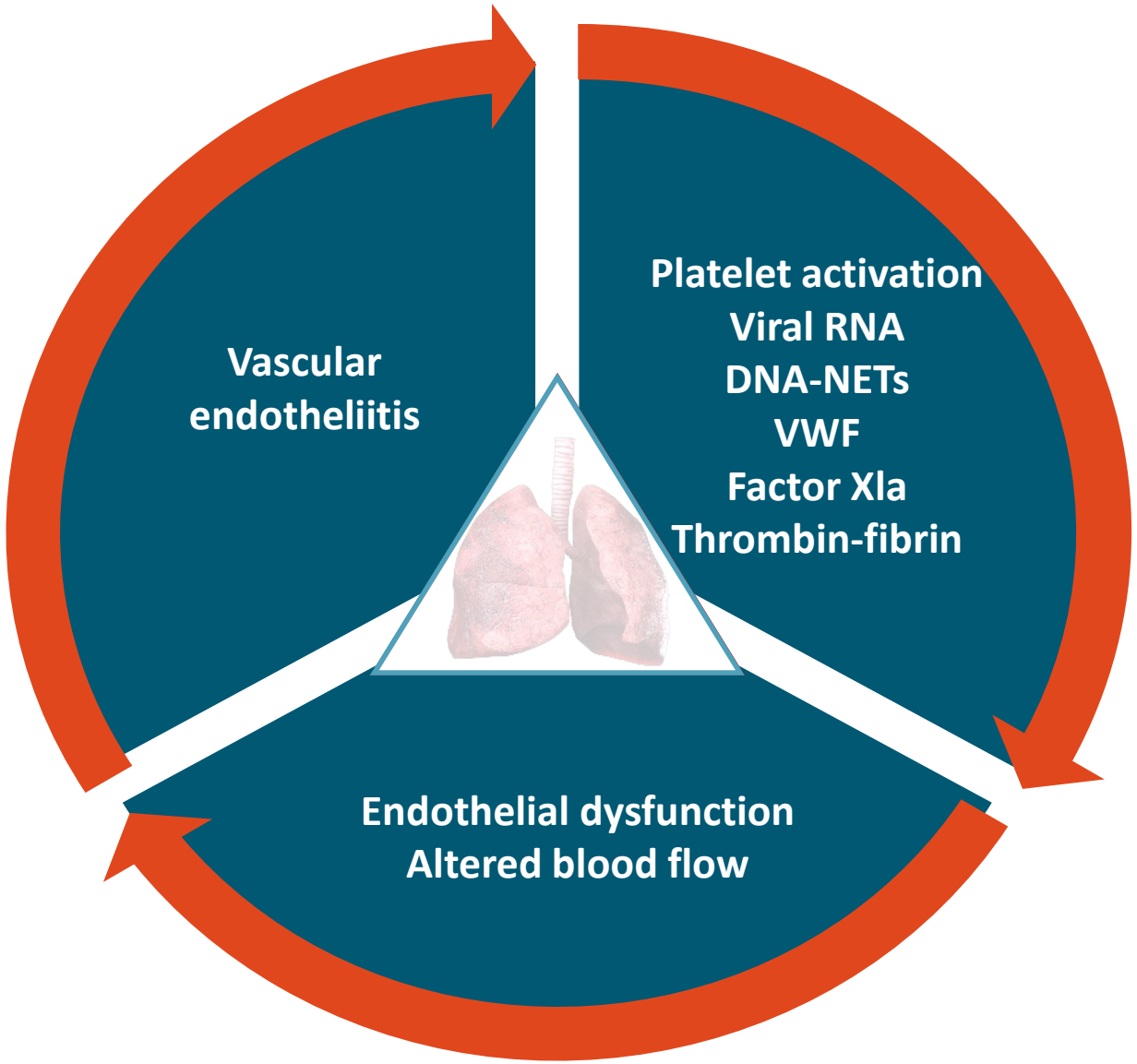
Endotheliitis

- Postulated to be a central feature of pathophysiology[1]
- SARS-CoV-2 binds to host cells via the ACE2 receptor[1,2]
- High density of ACE2 receptors on endothelial cells[1,2]
- Endotheliitis and viral inclusions in endothelial cells have been reported in COVID-19 autopsy series[2]

1. Ackermann. NEJM. 2020;383:120. 2. Varga. Lancet. 2020;395:1417.

Virchow's Triad in COVID-19



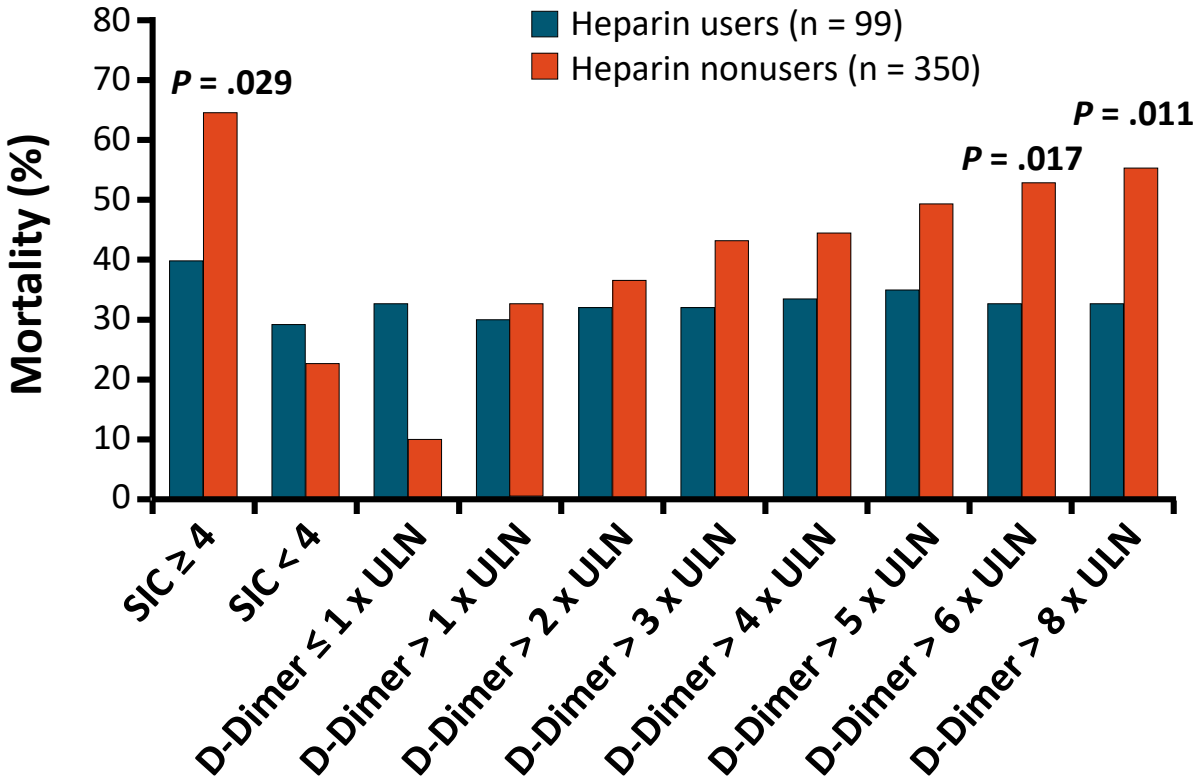
Becker. J Thromb Thrombolysis. 2020;15:1.

Slide credit: clinicaloptions.com

Anticoagulant Therapy in Patients With Severe COVID-19 and Coagulopathy

- Single-center, retrospective study in Wuhan, China, compared 28-day mortality with **prophylactic heparin or low-molecular-weight heparin for ≥ 7 days** vs **no heparin or heparin for < 7 days** in patients with severe COVID-19 (N = 449)
  - Severe COVID-19: RR ≥ 30 breaths/min, SaO_2 ≤ 93% at rest, or PaO_2/FiO_2 ratio ≤ 300 mm Hg
  - No difference in 28-day mortality between heparin users and nonheparin users in overall population (30.3% vs 29.7%; *P* = .910)

28-Day Mortality Stratified by SIC Score* and D-Dimer Levels†



*SIC score includes PT, platelet count, and SOFA. †ULN = 0.5 µg/mL

Tang. J Thromb Haemost. 2020;18:1094.

Slide credit: clinicaloptions.com

Treatment Dose Anticoagulation and In-Hospital Survival Among Patients With COVID-19

- Single-center, retrospective study at Mount Sinai Health System, New York, compared survival with treatment dose anticoagulation vs prophylactic dose or no anticoagulation in hospitalized patients with COVID-19, March 14 - April 11, 2020 (N = 2773)
  - Median hospitalization duration: 5 days
  - Median anticoagulation duration: 3 days
- Longer duration of TDAC associated with reduced mortality risk (aHR*: 0.86/day; 95% CI: 0.82-0.89; *P* < .001)

Outcome	TDAC (n = 786)	No TDAC (n = 1987)
In-hospital mortality, %	22.5	22.8
Median survival, days	21	14
Mechanical ventilation, %	29.8	8.1†
▪ In-hospital mortality, %	29.1	62.7
▪ Median survival, days	21	9
Major bleeding, %	3	1.9

*Adjusted for age, sex, ethnicity, BMI, history of hypertension, heart failure, atrial fibrillation, type 2 diabetes, anticoagulation use prior to hospitalization, and admission date. †*P* < .001.

Paranjpe. JACC. 2020;76:122.

Slide credit: clinicaloptions.com

Prophylactic Dose vs Therapeutic Dose Anticoagulation in COVID-19

- Retrospective, 2-center, cohort study comparing in-hospital mortality with prophylactic vs therapeutic AC dosing of enoxaparin or heparin begun preemptively at admission, April 1-25, 2020 (N = 374)
  - Excluded therapeutic AC for thrombotic indication; prophylactic AC group received only prophylactic dosing for whole inpatient duration

Outcome	Prophylactic Dose AC (n = 299)	Therapeutic Dose AC (n = 75)
In-hospital mortality, %	14.4	38.7
Crude risk ratio (95% CI) ▪ *P* value	2.7 (1.8-4.0) < .001	
Adjusted risk ratio* (95% CI) ▪ *P* value	2.3 (1.0-4.9) .04	

*Full logistic model included AC dosage, age, ethnicity, diabetes, history of heart disease or cancer, hyperlipidemia, intensive care, peak CRP, mechanical ventilation, and antibiotic use.

Motta. Crit Care Explor. 2020;2:e0309.

Slide credit: clinicaloptions.com

High-Dose Anticoagulation in Severe COVID-19: Retrospective Observational Study Design

New

- 538 consecutive adult patients admitted to 8 ICUs in France, for PCR-confirmed, severe COVID-19
- Received thromboprophylaxis during ≥ 1 of 6 predefined time periods from ICU admission through ICU Day 14
- Primary outcome: incidence of thrombotic complications
- Data collected from March 21 to April 10, 2021
- French national guidelines published on April 3, 2021, expanded recommendations for high-dose thromboprophylaxis to additional risk groups, including severe COVID-19 pneumonia requiring oxygen by HFNC or invasive ventilation
  - Permitted pre/post comparison of standard vs high-dose thromboprophylaxis with LMWH or UFH in patients with COVID-19 in ICU
    - High-dose arm included intermediate- or therapeutic-dose anticoagulation

Tacquard. Chest. 2021;[Epub].

Slide credit: clinicaloptions.com

High-Dose Anticoagulation in Severe COVID-19: Baseline Characteristics and Thrombotic Events

New

- 538 participants at baseline:
  - 389 (73%) males
  - Median age: 63 yrs (IQR: 55-71)
  - Median BMI: 29 (IQR: 26.0-33.0)
- At ICU admission, median D-dimer levels significantly higher in patients who developed TC (2.59 mg/L; IQR: 1.30-7.72) vs those without TC (1.5 mg/L; IQR: 0.99-2.97)
  - Remained significantly higher during 14 days in ICU

Thrombosis Type	Incidents n (%)	Cumulative Incidence, % (95% CI)
All thromboses*	122 (100)	22.7 (19.2-26.3)
▪ PE	64 (52)	12.0 (9.2-14.7)
▪ DVT	18 (15)	5.0 (2.7-7.3)
▪ Catheter	14 (11)	3.9 (1.9-5.9)
▪ Stroke	4 (3)	1.1 (0.1-2.2)
▪ Other	2 (2)	0.5 (0-1.3)
▪ Infarctions		
▪ Mesenteric	1 (2)	0.2 (0-0.8)
▪ Myocardial	1 (1)	0.2 (0-0.8)
▪ Medical device		
▪ CRRT filter	13 (11)	22.8 (11.8-33.7)
▪ ECMO	5 (4)	11.6 (1.9-21.3)

*Data from 538 patients; for PE, DVT, catheter, stroke, and other thromboses, n = 360 (one center did not submit data).

Tacquard. Chest. 2021;[Epub].

High-Dose Anticoagulation in Severe COVID-19: Results

New

- High-dose thromboprophylaxis associated with reduced risk of TC (HR: 0.81; 95% CI: 0.66-0.99)
  - No increased risk of bleeding vs standard dose
- Cumulative exposure to high-dose thromboprophylaxis was associated with reduction in PE incidence (HR: 0.72; 95% CI: 0.53-0.98)
- Cumulative exposure to high-dose thromboprophylaxis *not* associated with reduced mortality at Day 14 (HR: 1.12; 95% CI: 0.78-1.62)

Risk Factors Associated With TC	Multivariate Analysis Odds Ratio (95% CI)	*P* Value
Higher D-dimer level at ICU admission	1.45 (1.10-1.91)	.01
Requiring ECMO*	2.35 (0.99-5.57)	< .05

*25 patients received ECMO in those with TC vs 19 in those without TC.

- No increased risk of TC in obese patients, suggesting high-dose thromboprophylaxis effective in this high-risk group

Tacquard. Chest. 2021;[Epub].

Slide credit: clinicaloptions.com

Guidance on Thromboprophylaxis

Recommending Organization*

NIH[1]	ASH[2]
▪ Hospitalized adults with COVID-19 should receive prophylactic dose anticoagulation ▪ Anticoagulant or antiplatelet therapy should not be used to prevent arterial thrombosis outside of the usual SoC for patients without COVID-19 ▪ Currently insufficient data to recommend for or against the use of thrombolytics or increasing anticoagulant doses for VTE prophylaxis in hospitalized COVID-19 patients outside of clinical trial ▪ Hospitalized patients should not be routinely discharged on VTE prophylaxis (extended VTE prophylaxis can be considered in patients with low bleeding risk and high VTE risk)	▪ All hospitalized adults with COVID-19 should receive thromboprophylaxis with low-molecular-weight heparin over unfractionated heparin, unless bleeding risk outweighs thrombosis risk ▪ Fondaparinux is recommended in the setting of heparin-induced thrombocytopenia ▪ In patients in whom anticoagulants are contraindicated or unavailable, use mechanical thromboprophylaxis (eg, pneumatic compression devices) ▪ Outside of clinical trials, discourage empiric use of full-dose heparin or low-molecular-weight heparin in COVID-19 patients with no other indication for therapeutic anticoagulation

*Additional recommendations available from the International Society on Thrombosis and Haemostasis,[3] and CHEST.[4]

1. NIH. COVID-19 Treatment Guidelines. Antithrombotic therapy in patients with COVID-19. Last updated February 11, 2021.
2. American Society of Hematology. COVID-19 and VTE/anticoagulation: FAQs. Last updated February 25, 2021.
3. Spyropoulos. J Thromb Haemost. 2020;18:1859. 4. Moores. Chest. 2020;158:1143.

Key Ongoing Anticoagulation Trials for COVID-19

- Multi-trial international platform assessing **therapeutic anticoagulation with IV unfractionated heparin or SC LMWH** vs **standard pharmacologic thromboprophylaxis** in COVID-19 patients without a medical indication for blood thinners
- As of December 2020, based on deliberations across oversight boards, enrollment of **critically ill COVID-19 patients** requiring ICU support paused[1]
  - Therapeutic AC drugs did not reduce need for organ support; potential for harm could not be excluded; recruitment of moderately ill hospitalized COVID-19 patients still ongoing
- Interim results from > 1000 **moderately ill hospitalized patients** support use of full-dose blood thinners; safe and superior to standard preventative dosing in primary endpoint of need for ventilation or other organ-supportive interventions[7]

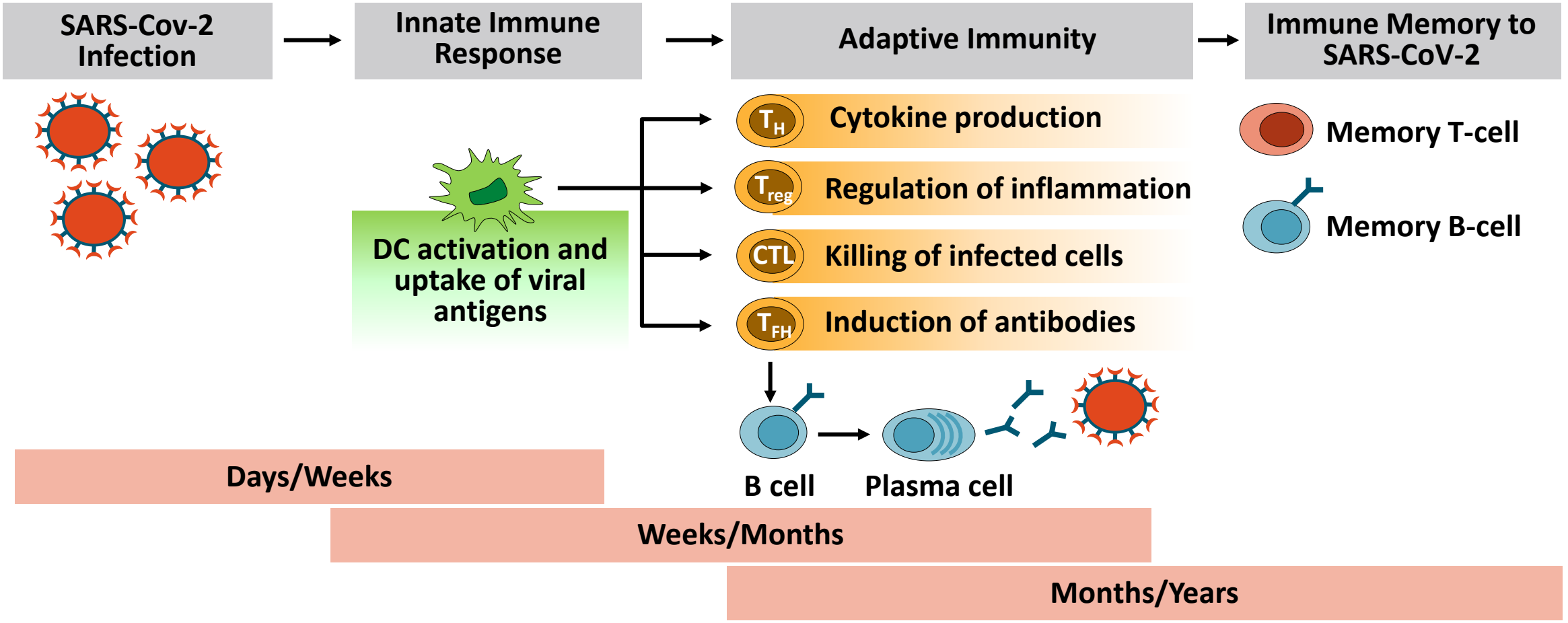
Trials Involved
REMAP-CAP[2,3]
ACTIV-4 ACUTE[4,5]
ATTACC[6]

1. https://www.nhlbi.nih.gov/news/2020/nih-activ-trial-blood-thinners-pauses-enrollment-critically-ill-covid-19-patients. 2. NCT02735707.
3. https://www.remapcap.org/. 4. NCT04505774. 5. https://fnih.org/sites/default/files/final/activ-4a.pdf. 6. NCT04372589.
7. https://www.nhlbi.nih.gov/news/2021/full-dose-blood-thinners-decreased-need-life-support-and-improved-outcome-hospitalized.

Slide credit: clinicaloptions.com

Duration of Immunity

Potential Immune Correlates of Protection to SARS-CoV-2 Infection



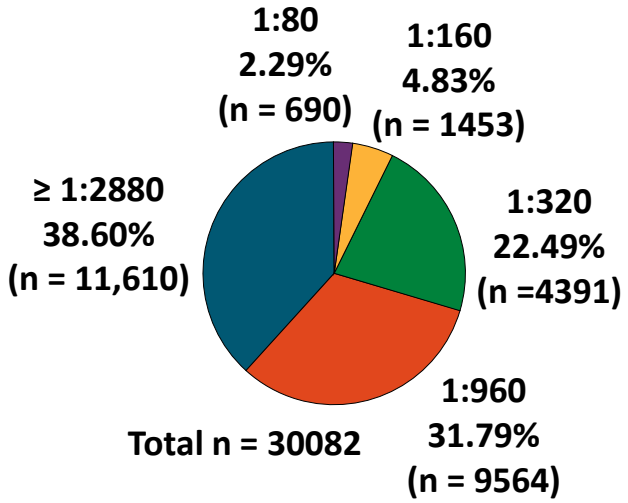
Cox. Nat Rev Immunol. 2020;20:581.

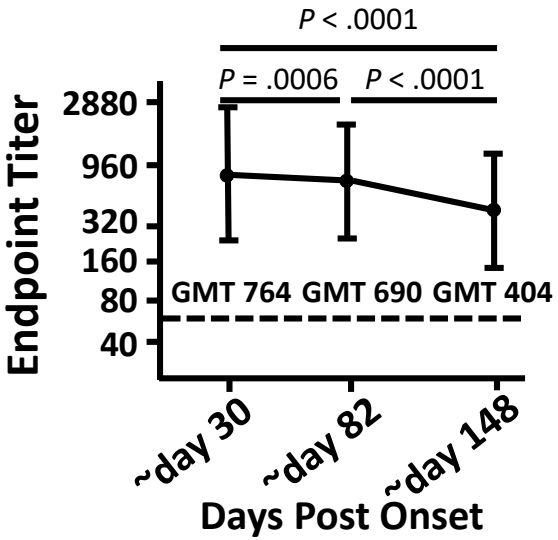
Slide credit: clinicaloptions.com

Stability of Antibody Response Following COVID-19 Recovery

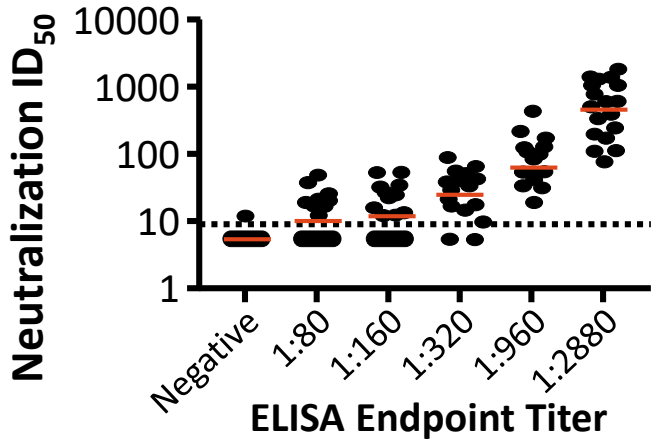
- Antibody responses were assessed in individuals screened at Mount Sinai Health System in NYC (N = 30,082)
  - Screened patients either had PCR-confirmed SARS-CoV-2 infection or suspected disease
  - Additional samples collected through voluntary employee screening
  - < 5% of symptomatic cases required emergency department evaluation or hospitalization
  - 121 individuals donated serial blood samples at ~ 30, 82, and 148 days after symptom onset

Binding IgG Antibodies to Spike Protein





Neutralization* by ELISA Titer



Spearman r = 0.87
P < .0001

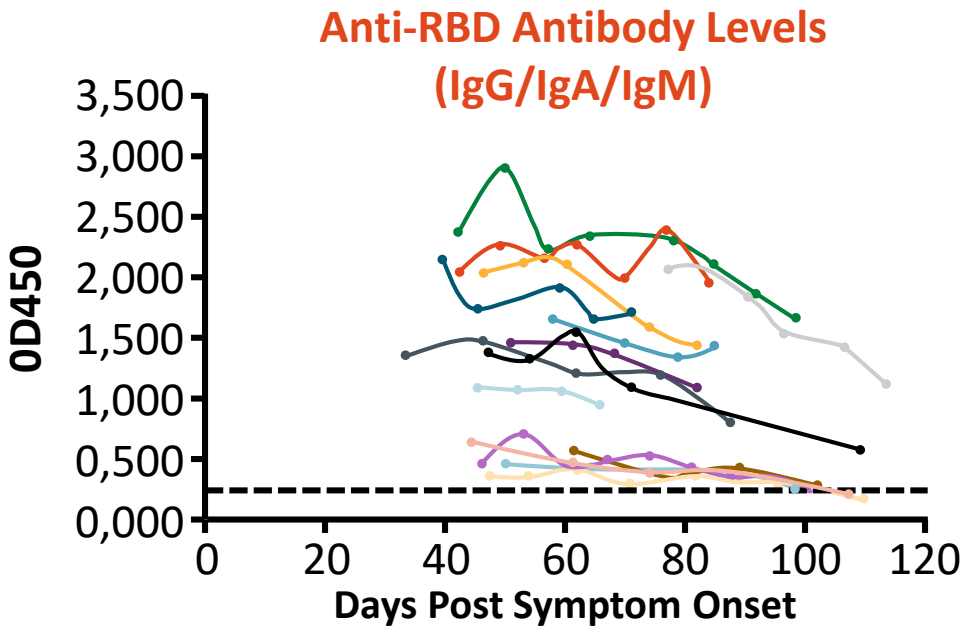
*Microneutralization assay.

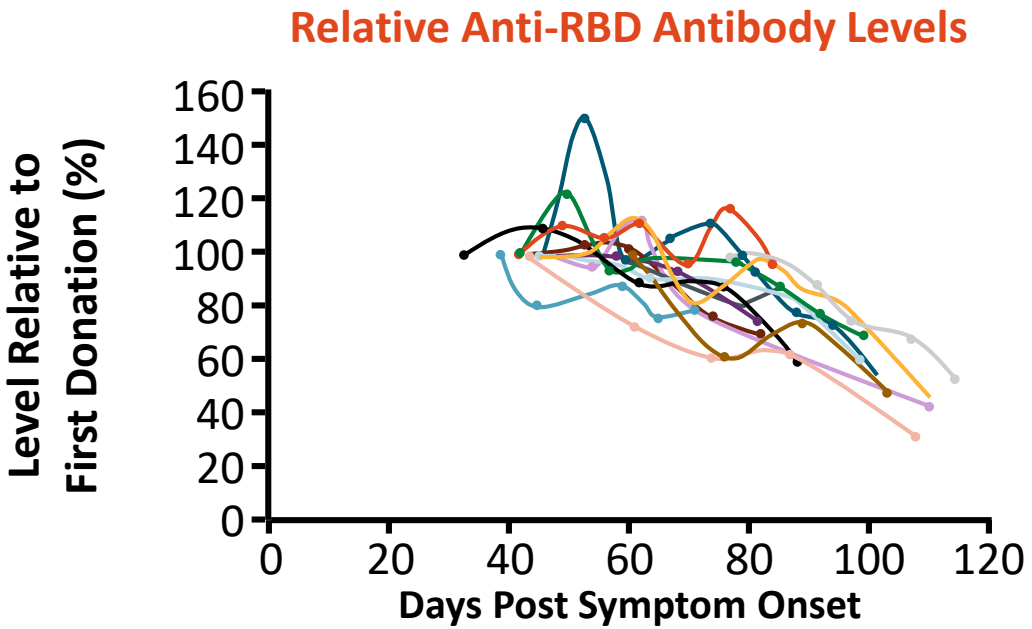
Wajnberg. Science. 2020;370:1227.

Slide credit: clinicaloptions.com

Antibody Decline Following COVID-19 Infection

- Longitudinal assessment of antibody responses in convalescent plasma from individuals who donated 4-9 times following recovery from COVID-19; first donation was 33-77 days post symptoms and last donation was 66-114 days post symptoms (N = 15)
  - Symptoms ranged from mild to severe, but no donors were hospitalized for COVID-19
- Level of antibodies remained stable through Day 76 then decreased more rapidly



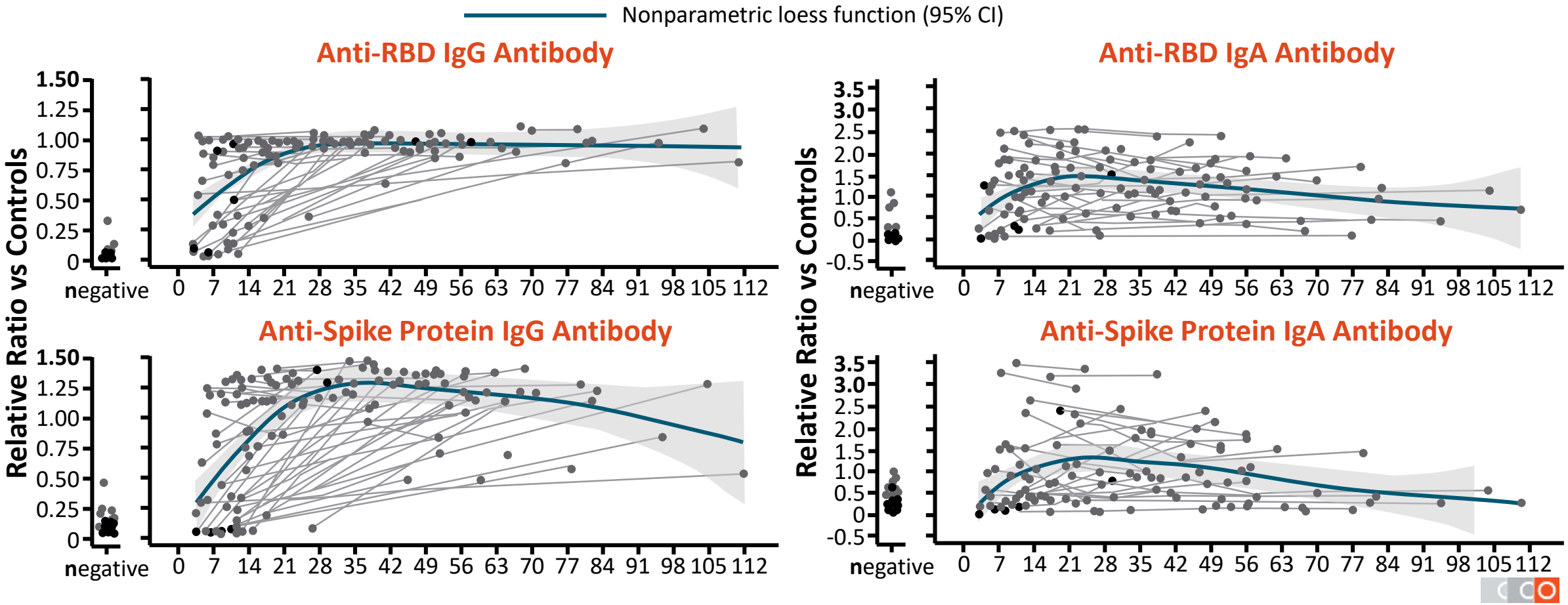


Perreault. Blood. 2020;136:2588.

Slide credit: clinicaloptions.com

Differences in IgG and IgA Following COVID-19 Infection

- Changes in antibody levels assessed in patients with COVID-19 (N = 57)

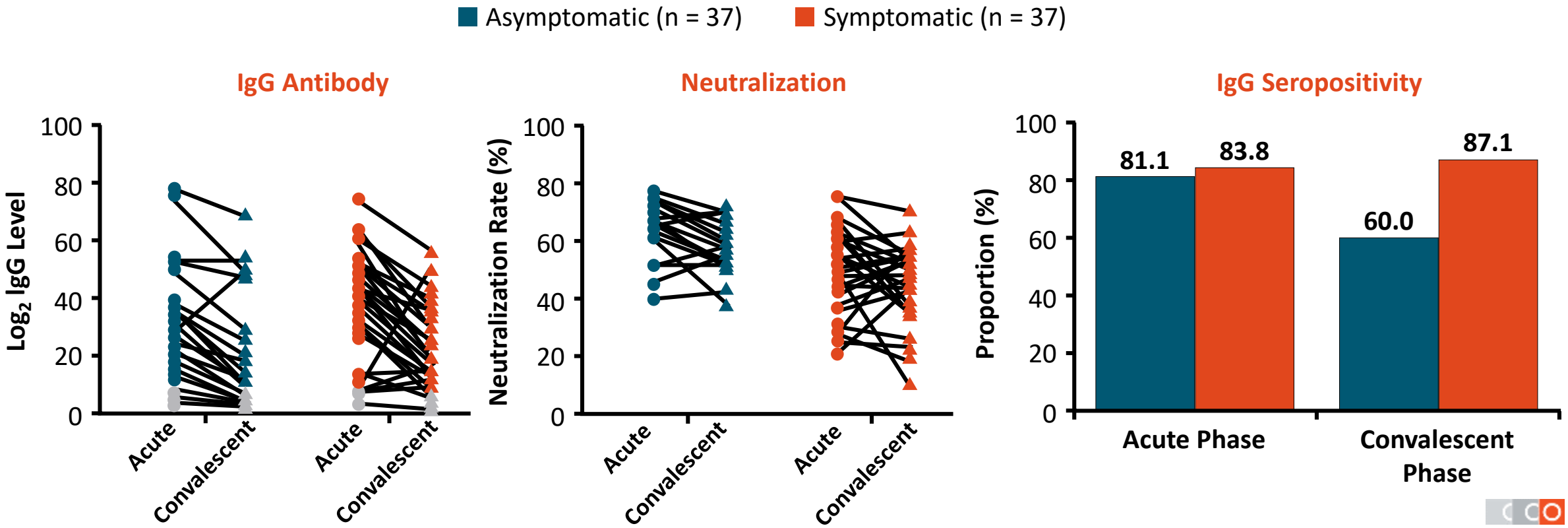


Isho. Sci Immunol. 2020;5:eabe5511.

Slide credit: clinicaloptions.com

Antibody Dynamics Among COVID-19 Patients by Symptomology

- Antibody assessments in patients in Wuhan with mild or asymptomatic COVID-19 during acute infection and the early convalescent phase (8 wks post isolation)

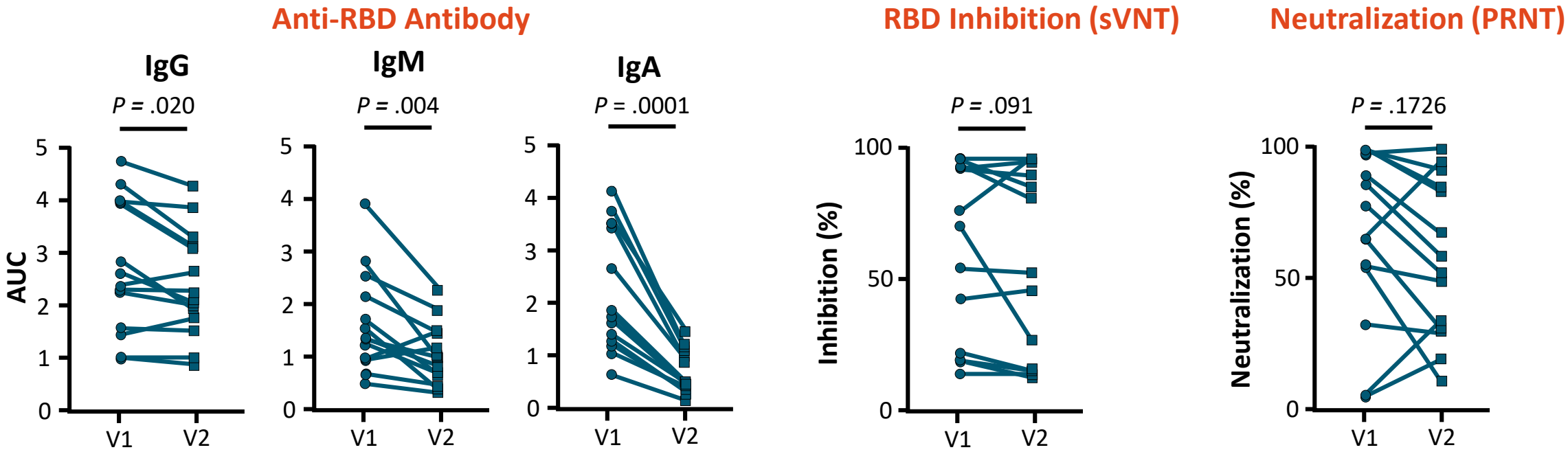


Long. Nat Med. 2020;26:1200.

Slide credit: clinicaloptions.com

Decline in IgM and IgA but Persistent Neutralization Activity in Mild COVID-19 Infection

- Longitudinal assessment of antibody response at ~ 1 mo and ~ 3 mos post symptom onset* in patients who recovered from mild COVID-19 (N = 15)



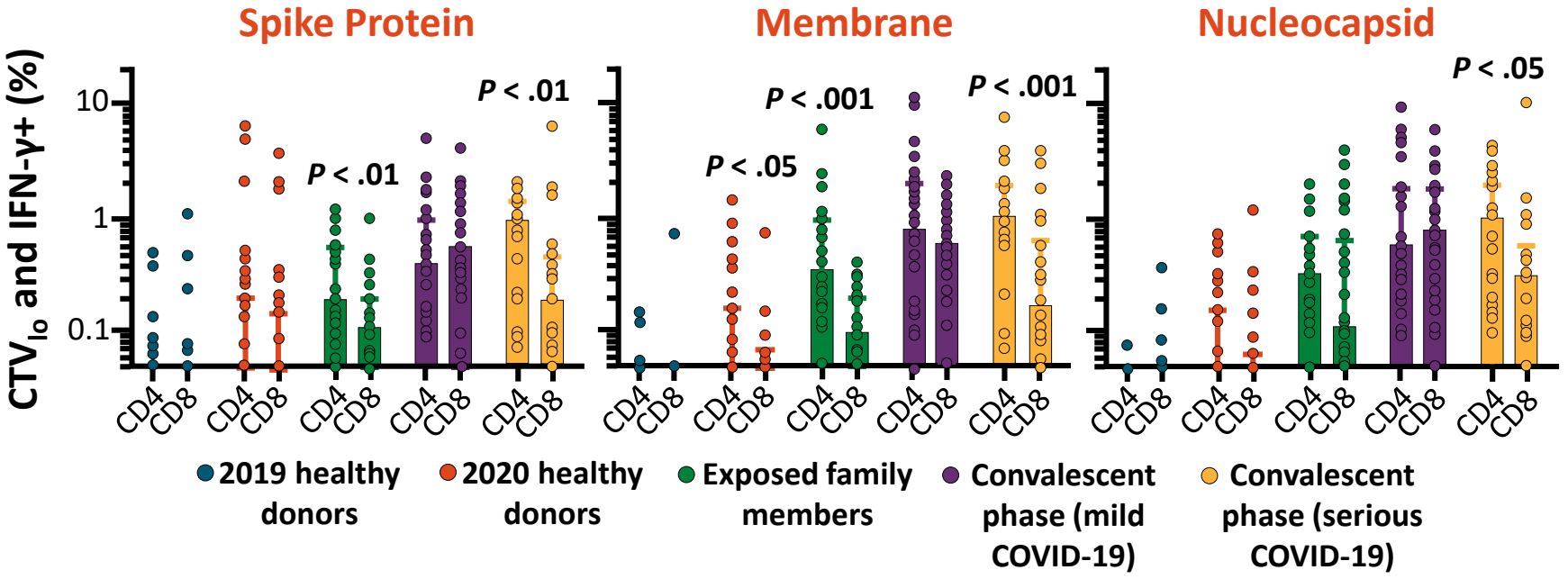
*Visit 1: ≥ 20 days after positive PCR test (median 35.5 days post symptom onset). Visit 2: Median 86 days post symptom onset.

Rodda. Cell. 2021;184:169.

Slide credit: clinicaloptions.com

T-Cell Response Duration Following SARS-CoV-2 Infection or Exposure

- Assessment of proliferation (CTV_{lo}) and functionality (IFN-γ secretion) of SARS-CoV-2–specific T-cells in convalescent patients (n = 54), exposed family members (n = 28), or healthy donors (n = 61)
  - T-cell stimulation with peptides spanning the immunogenic domains of spike, membrane, and nucleocapsid proteins



Sekine. Cell. 2020;183:158.

Slide credit: clinicaloptions.com

Summary: Duration of T-Cell Reponses to SARS-CoV-2

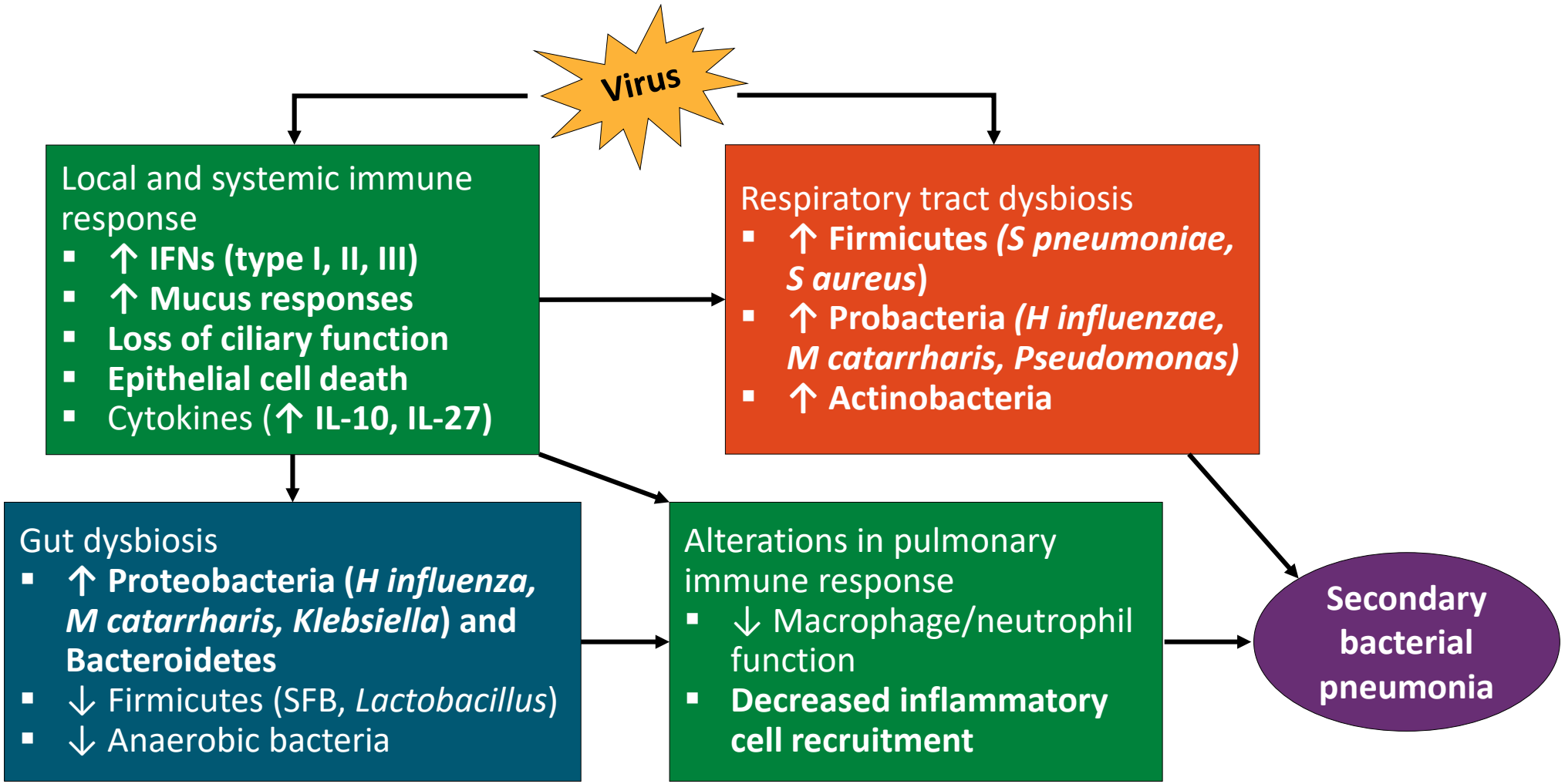
- 100% of individuals with prior severe COVID-19 and 87% with prior mild COVID-19 demonstrated SARS-CoV-2–specific memory T-cell responses in convalescent phase (25-58 days after disease onset)[1]
- SARS-CoV-2–specific CD4+ and CD8+ T-cell recall responses were present in 41% of seronegative individuals, including individuals in the convalescent phase with a history of mild COVID-19 (3/31), exposed family members (9/28), and healthy individuals (5/31)[1]
- In another study, spike-specific memory CD4+ and CD8+ T-cells were maintained ~ 3 mos following symptom onset in patients with mild SARS-CoV-2 (N = 15)[2]

1. Sekine. Cell. 2020;183:158. 2. Rodda. Cell. 2021;184:169.

Slide credit: clinicaloptions.com

Coinfections and COVID-19

A Proposed Model for Viral-Induced Susceptibility to Secondary Bacterial Pneumonia



Hanada. Front Immunol. 2018;9:2640.

Slide credit: clinicaloptions.com

2009 Influenza A Pandemic: A Historical Perspective on Influenza and Bacterial Secondary Infection

- Prospective, observational, multicenter study of 645 adults with confirmed H1N1 influenza, in 148 Spanish ICUs
- **113/645 (17.5%) were diagnosed with community-acquired respiratory coinfection within 2 days of admission**
- Coinfected patients older and more ill; no differences in comorbidities between study groups
- Coinfection associated with ↑ ICU mortality (26.2% vs 15.5%; OR: 19.43; 95% CI: 1.21-3.09), but this trend did not achieve statistical significance when adjusted for disease severity and comorbidities

Patient Parameter	Coinfected (n = 113)	Not Coinfected (n = 532)	*P* Value
Mean age, yrs (SD)	47.5 (15.7)	43.8 (14.2)	< .05
Mean APACHE II on admission (SD)	16.1 (7.3)	13.3 (7.1)	< .05
Mean SOFA on admission (SD)	7.0 (3.8)	5.2 (3.5)	< .05
Mechanical ventilation, %	69	58.5	< .05
Mean no. days in the ICU (IQR)	11 (5-23)	8 (4-17)	= .01

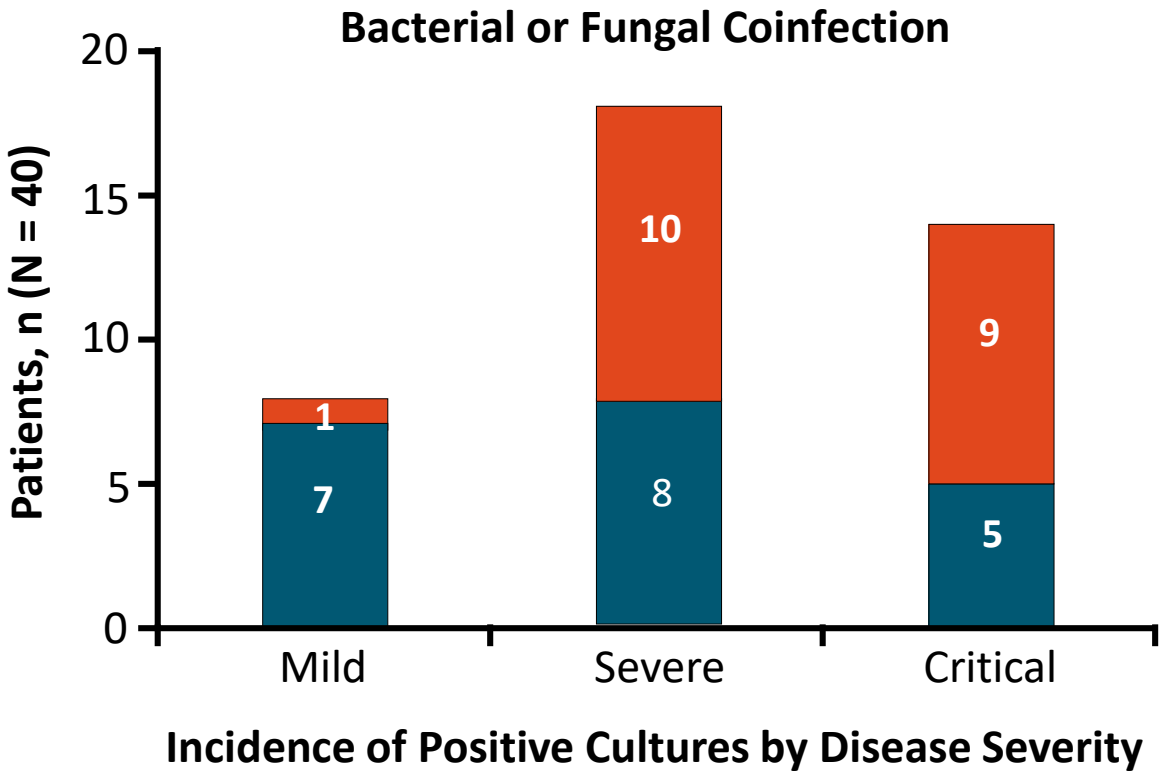
Conclusion: Bacterial coinfection contributed to increased length of ICU stay

Martin-Loeches. Chest. 2011;139:555.

Slide credit: clinicaloptions.com

Incidence of Bacterial Coinfection in Patients With COVID-19: February 4-28, 2020, in Wuhan, China

- Retrospective, cohort study of 354 hospitalized patients with confirmed COVID-19; mean age: 62 yrs (range: 23-90)
- 116 patients tested for coinfection based on clinical suspicion:
  - 3 positive results for viral coinfection from 76 patients tested by sputum PCR
  - 20 positive results for bacterial or fungal coinfections from 40 patients tested by culture of BAL fluids or blood
- No distinction made between community-acquired and hospital-acquired coinfections



- **3 most prevalent pathogens: *A baumanii*, *E coli*, and *Candida albicans***

Lv. Microbes Infect. 2020;22:195.

Association of Coinfection With COVID-19 Severity: February 4-28, 2020 in Wuhan, China

Multivariable Regression Analysis of Factors Associated With COVID-19 Severity*			
Factors†	**F Value**	**R Value**	***P* Value**
Coinfection	10.507	0.257	.014
Coinfection + lymphocyte count	9.722	0.341	< .001
Coinfection + lymphocyte count + D-dimer level	8.022	0.375	< .001

*Categorized as mild, severe, or critical.
†Defined ahead of data collection.

- **Patients with coinfection had significantly higher white blood cell, neutrophil, and lymphocyte counts, as well as significantly increased levels of D-dimer, IL-6, IL-10, CRP, and PCT vs patients without coinfection**
- **Coinfection associated with worse COVID-19 severity in Cox regression, especially in patients with elevated lymphocyte counts and D-dimer levels**

Lv. Microbes Infect. 2020;22:195.

Bacterial Coinfection in SARS-CoV-2 vs Influenza A/B Cohorts: Retrospective Study in the UK, 2019-2020

- Blood culture positivity and bacteremia rates statistically similar between groups
  - **SARS-CoV-2 group:** 643/836 patients had blood cultures
    - **Blood culture positive: 9.3%** (60/643)
    - **True bacteremia: 3.3%** (21/643)
      - 2 respiratory, 3 central line, 16 unrelated nonrespiratory
  - **Influenza group:** 133/216 patients had blood cultures
    - **Blood culture positive: 6%** (8/133)
    - **True bacteremia: 1.5%** (2/133)

Blood Culture Results, n	SARS-CoV-2 (n = 643)		Influenza A/B (n = 133)	
	CA	HCAI	CA	HCAI
Respiratory bacteremias	1	1	2	0
Nonrespiratory bacteremias	11	8	0	0
No growth	583		133	
Contaminants*	36		6	

*Coagulase negative *Staphylococci.*

- **Among patients with SARS-CoV-2, relative risk of death with true pathogens in blood vs baseline admitted patients: 1.51 (*P* = .3543)**

Hughes. Clin Microbiol Infect. 2020;26:1395.

Slide credit: clinicaloptions.com

Bacterial Coinfection in SARS-CoV-2 vs Influenza A/B Cohorts: Outcomes

- Respiratory culture positivity rates statistically similar between groups
  - **SARS-CoV-2 group: 34.8%** (39/112 tested)
  - **Influenza group: 21.1%** (8/38 tested)
- No patients in **SARS-CoV-2** group were coinfected with influenza or RSV (0/250 tested)
- Among patients with **SARS-CoV-2**, relative risk of death with positive sputum culture vs baseline admitted patients: RR: 0.90 (*P* = .8462)

Respiratory Culture Results, n	SARS-CoV-2 (n = 112)		Influenza A/B (n = 38)	
	CA	HCAI	CA	HCAI
Bacterial	13	24	4	4
Fungal				
▪ *Candida* spp*	10	14	0	7
▪ *Aspergillus* spp	1	2	0	1
No growth	64		22	

*Deemed contaminants from the oropharynx; not treated.

Hughes. Clin Microbiol Infect. 2020;26:1395.

Community-Acquired vs Hospital-Acquired Coinfections in Spanish COVID-19 Cohort

- Retrospective analysis of hospitalized patients with COVID-19: N = 989

Baseline Characteristic	No Coinfection (n = 917)	CA Coinfection (n = 31)	P_a Value vs No Coinfection	HA Superinfection* (n = 43)	P_b Value vs No Coinfection
Median age, yrs (IQR)	61 (48-74)	63 (54.5-74)	.671	67 (55.8-74.3)	.006
Male sex, n (%)	51.0 (55.6)	18 (58.1)	.956	26 (60.5)	.822
Comorbidities,† n (%)					
▪ CKD	47 (5.1)	8 (25.8)	< .001	6 (14)	.013
▪ Cancer	77 (8.4)	1 (3.2)	.259	8 (18.6)	.021
Inflammatory markers, median (IQR)					
▪ CRP	7.06 (3.3-13.3)	6.8 (3.2-9.8)	.714	11.8 (5.6-17.9)	.012
▪ Ferritin	544 (150-1100)	208 (154-432)	.042	797 (296-1743)	.575
▪ Lymphocytes	0.9 (0.6-1.2)	0.8 (0.6-1.1)	.892	0.783 (0.5-1.1)	.088
▪ Lactate dehydrogenase	287 (233-372)	264 (221-378)	.477	311.5 (248-472)	.193

***2 patients with CA infection developed HA superinfection.** †Other comorbidities (HTN, DM, CVD, COPD) not significantly different between those with and without coinfection.

Garcia-Vidal. Clin Microbiol Infect. 2021;27:83.

Slide credit: clinicaloptions.com

Community-Acquired vs Hospital-Acquired Coinfections in Spanish COVID-19 Cohort: Outcomes

- 3.1% (31/989) CA coinfection rate lower than expected from past influenza pandemics[1,2] and not associated with higher mortality
- 4.3% (43/989) HA superinfection rate associated with longer hospital stays, more ICU admissions, and higher mortality rate

Outcome	No Coinfection (n = 917)	CA Coinfection (n = 31)	P_a Value vs No Coinfection	HA Superinfection* (n = 43)	P_b Value vs No Coinfection
Median hospital stay, days (IQR)	9 (5-15)	8 (4.5-11.5)	.565	20 (11-27.8)	< .001
ICU admission, n (%)	109 (11.9)	8 (25.8)	.02	29 (67.4)	< .001
Median time in ICU, days (IQR)	3 (1-10)	3 (0-9)	.888	5 (0.5-20)	.095
Death, n (%)	86 (9.4%)	5 (16.1)	.21	8 (18.6)	.047

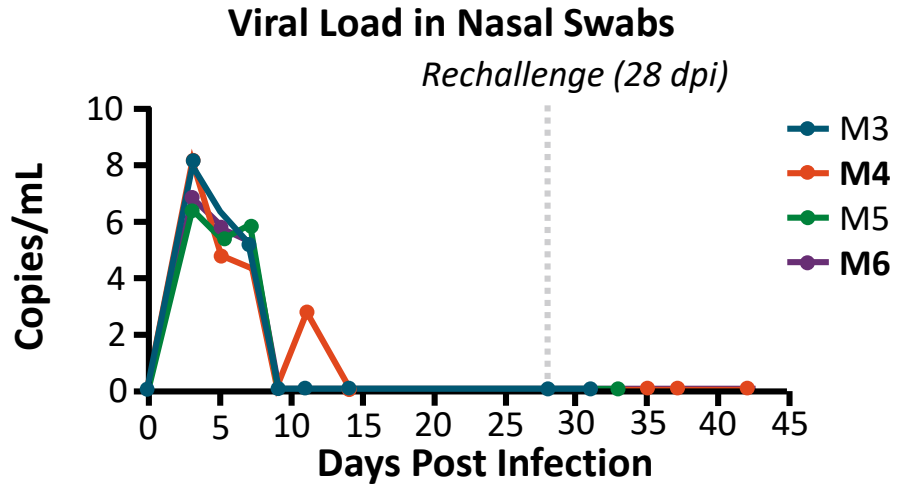
***2 patients with CA infection developed HA superinfection.**

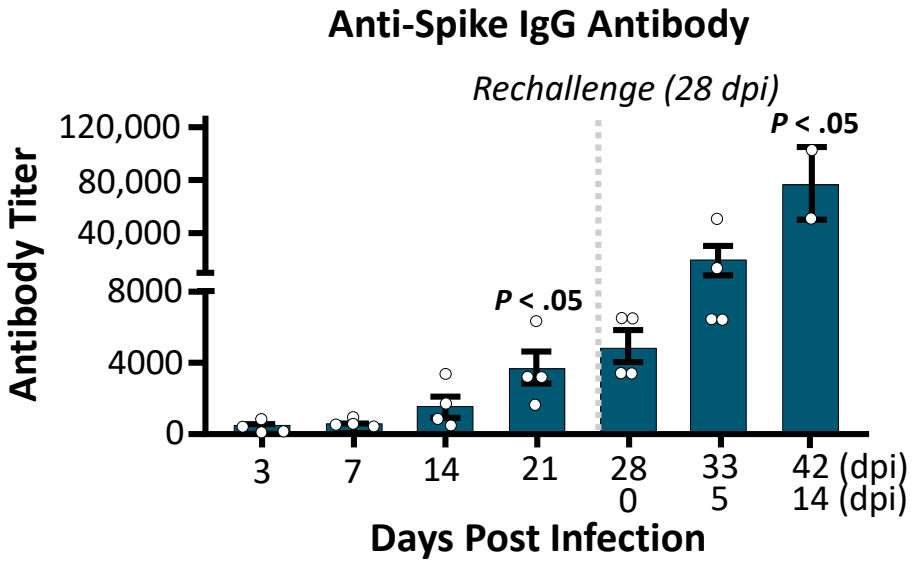
1. Garcia-Vidal. Clin Microbiol Infect. 2021;27:83. 2. Martin-Loeches. Chest. 2011;139:555.

Reinfection With SARS-CoV-2

Protection From Reinfection With SARS-CoV-2 in Rhesus Macaque Model

- 6 adult rhesus macaques were intrarectally infected with SARS-CoV-2 at 1 x 10^6 $TCID_{50}$, 4 of which were rechallenged 28 days post infection
  - 1 additional macaque challenged initially at Day 28 as control for rechallenge
- No changes in body temperature following initial infection, but transient increase following rechallenge
- 4/7 had weight loss following initial infection but no weight loss after rechallenge
- No evidence of reinfection



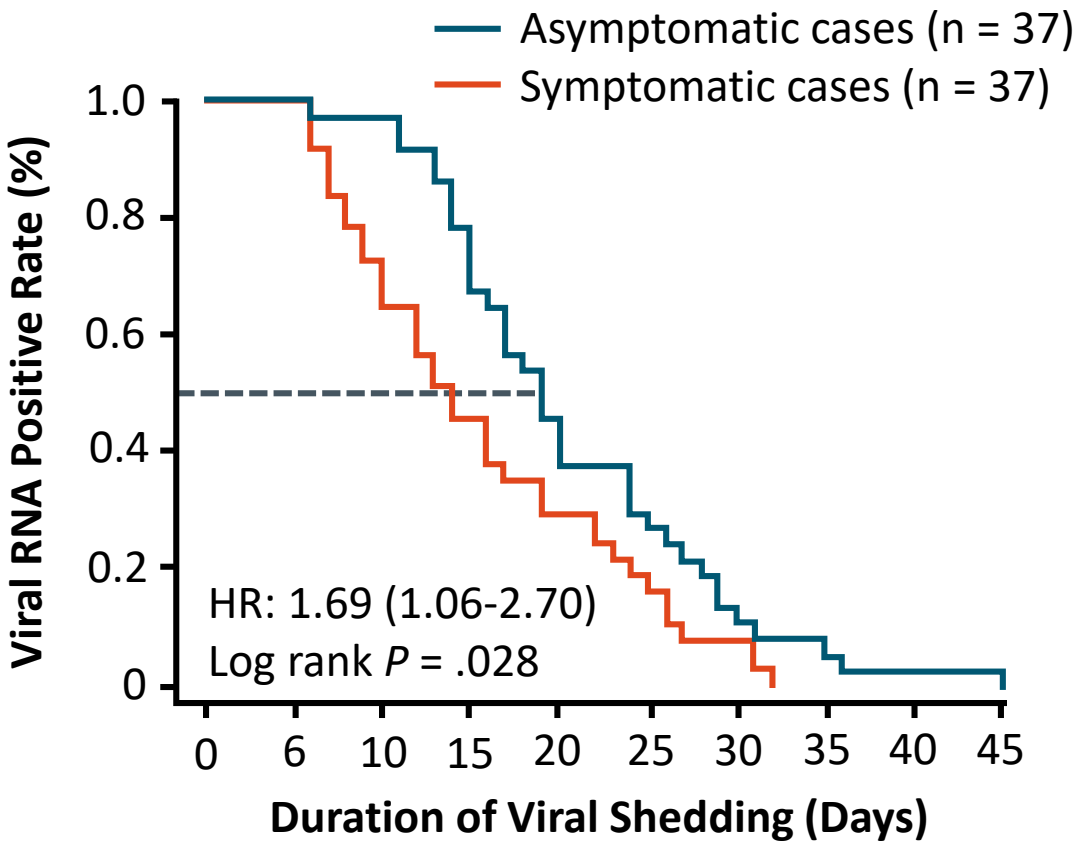


Deng. Science. 2020;eabc5343.

Slide credit: clinicaloptions.com

Duration of Viral Shedding in Patients With COVID-19

- 178 patients with confirmed SARS-CoV-2 infections identified by contact screening in Wanzhou District, China, by April 10, 2020
- 37/178 (20%) were asymptomatic in the preceding 14 days and during the in-hospital isolation period
- 37 sex-, age-, and comorbidity-matched controls identified among symptomatic infections, also hospitalized for isolation
- Asymptomatic cases shed virus significantly longer than symptomatic cohorts
  - Not known how long shed virus remains infective

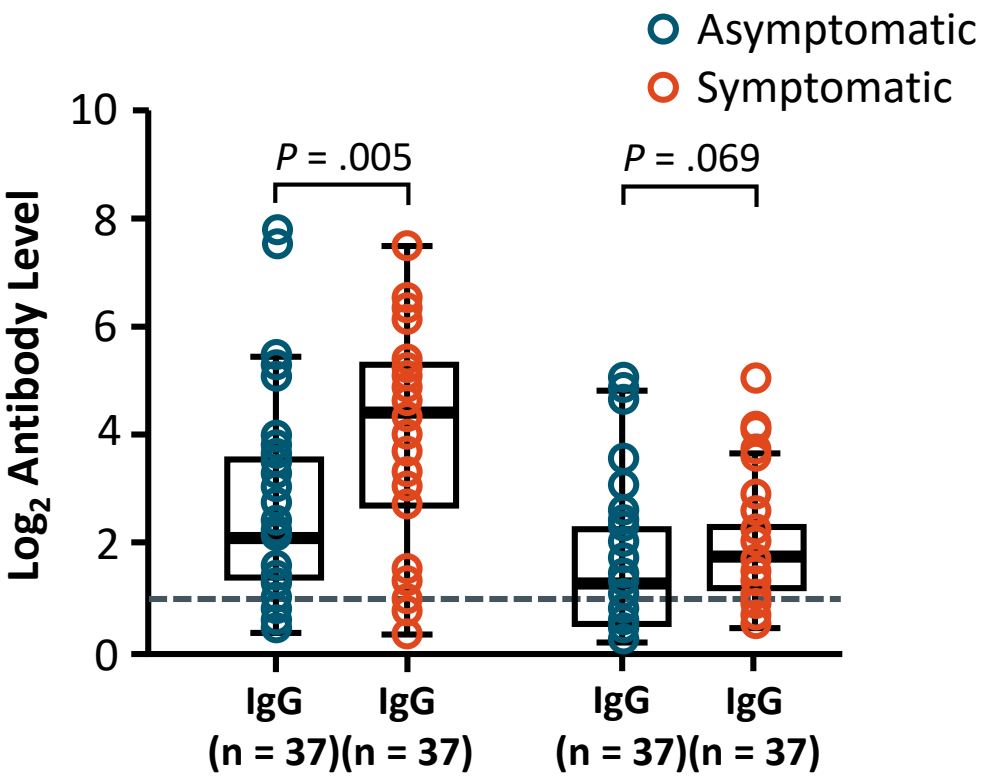


Long. Nat Med. 2020;26:1200.

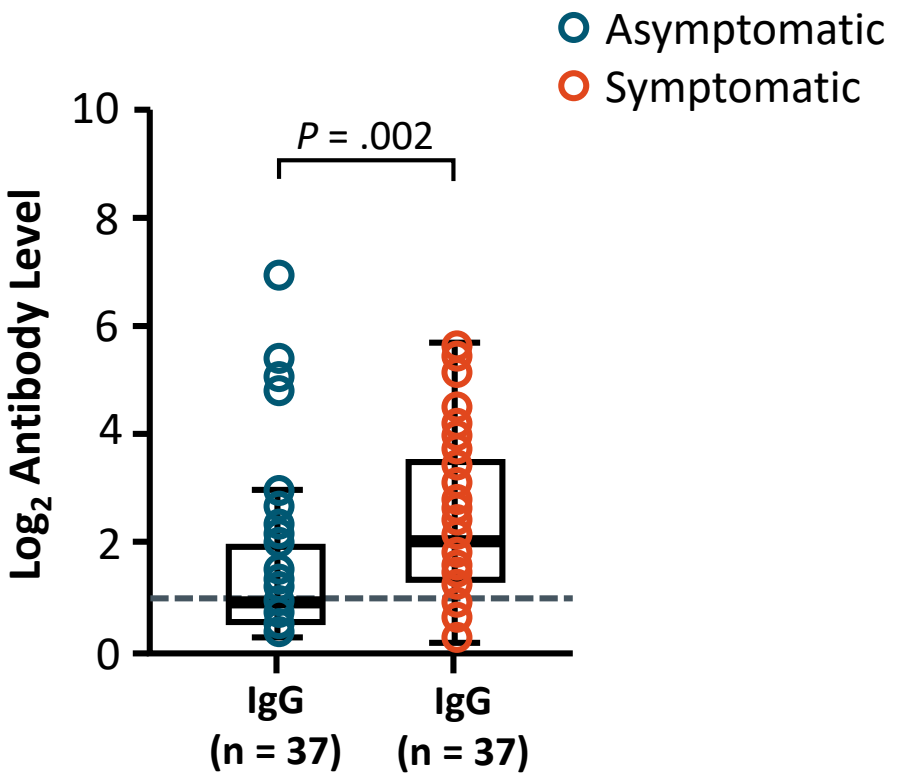
Slide credit: clinicaloptions.com

Antibody Response in COVID-19: Acute Phase vs Early-Convalescent Phase

Antibodies in Acute Phase COVID-19



IgG Levels 8 Wks After Discharge From Hospital

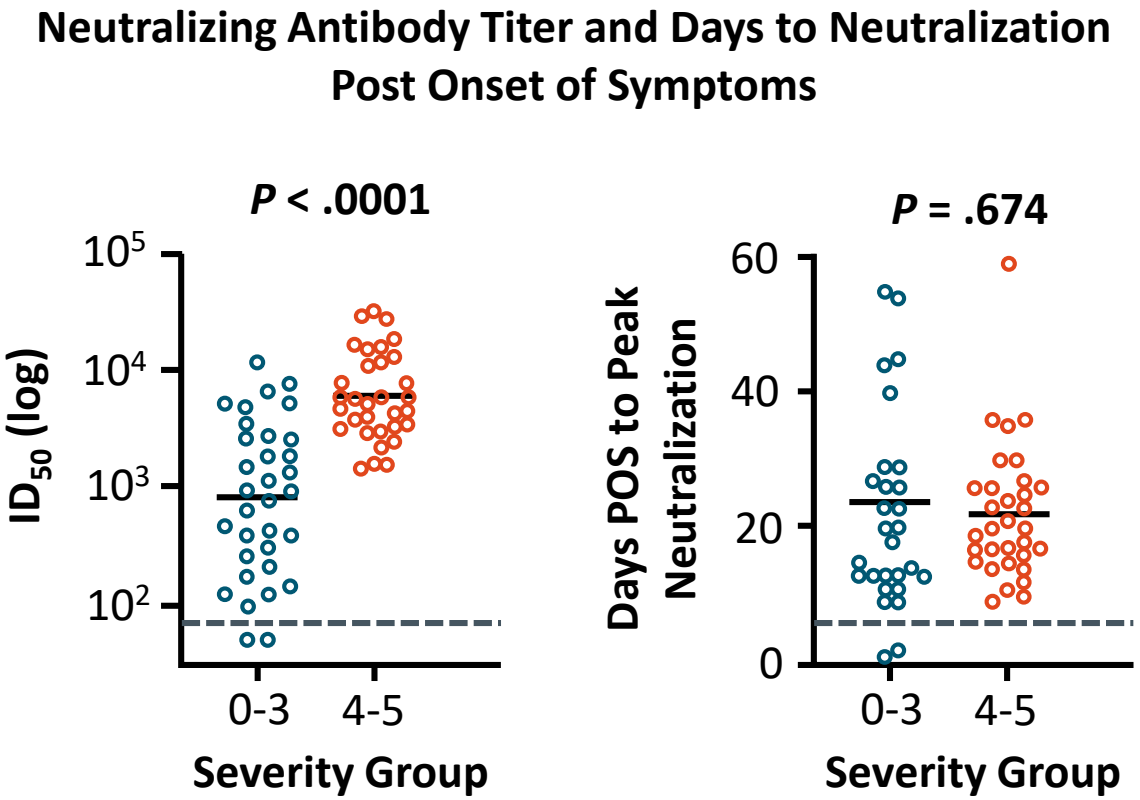


Long. Nat Med. 2020;26:1200.

Slide credit: clinicaloptions.com

Neutralizing Antibody Response in SARS-CoV-2 Infection

- 269 sequential serum samples collected at 2 London Hospitals from 65 patients diagnosed with SARS-CoV-2 by RT-PCR
- Persons with more severe disease had a greater magnitude of neutralizing antibody response
  - Days to peak neutralization did not differ by disease severity

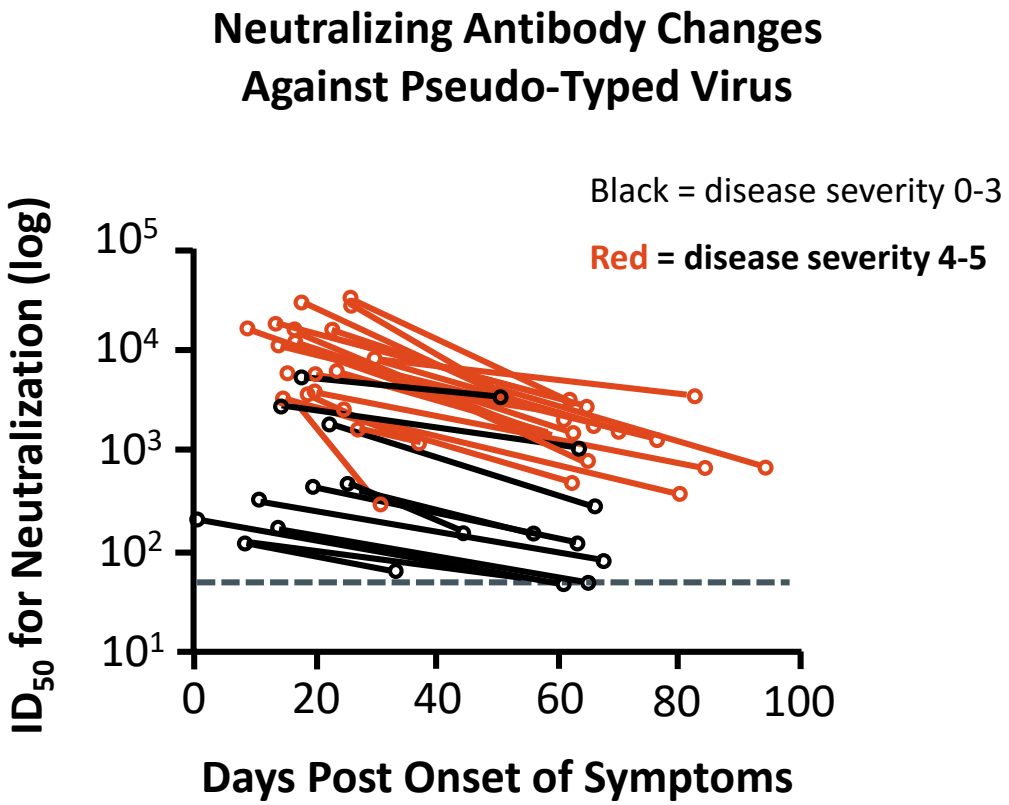


Seow. Nat Microbiol. 2020;5:1598.

Slide credit: clinicaloptions.com

Kinetics of Neutralizing Antibody Reponses in SARS-CoV-2 Infection

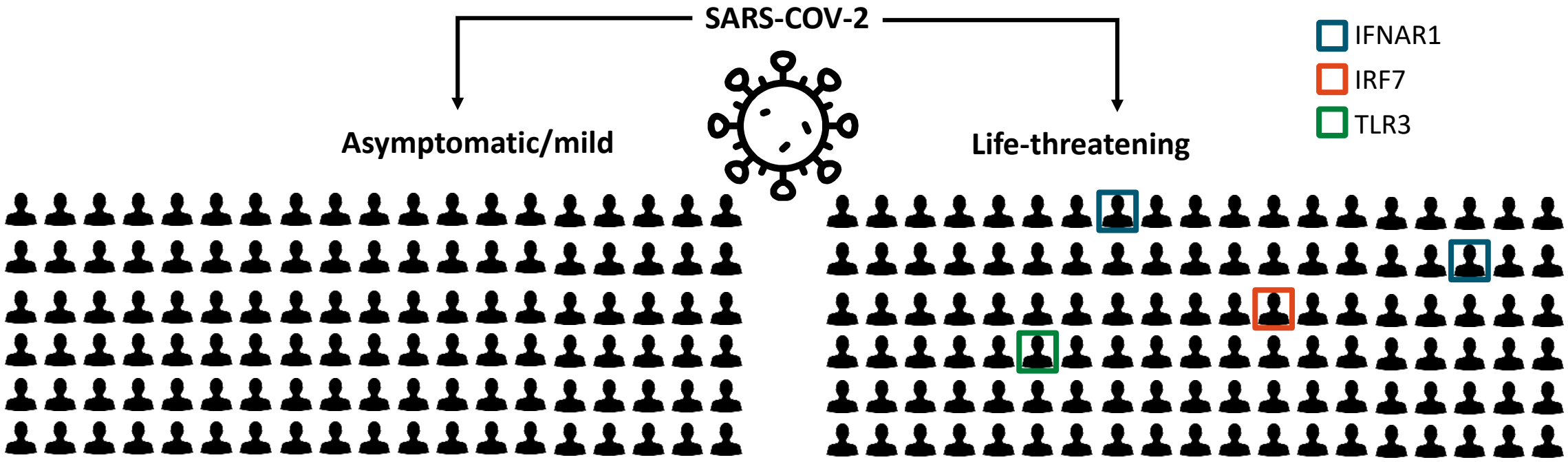
- Average time to *detectable* neutralization = 14.3 days POS (range: 3-59)
- Average time to *peak* neutralization = 23.1 days POS (range: 1-66)
- Patients with low neutralizing Ab response (ID_{50} 100-300) return to baseline or undetectable at approximately 50 days
- Patients with robust neutralizing Ab responses maintain titers > 1000 even after initial decline



Seow. Nat Microbiol. 2020;5:1598.

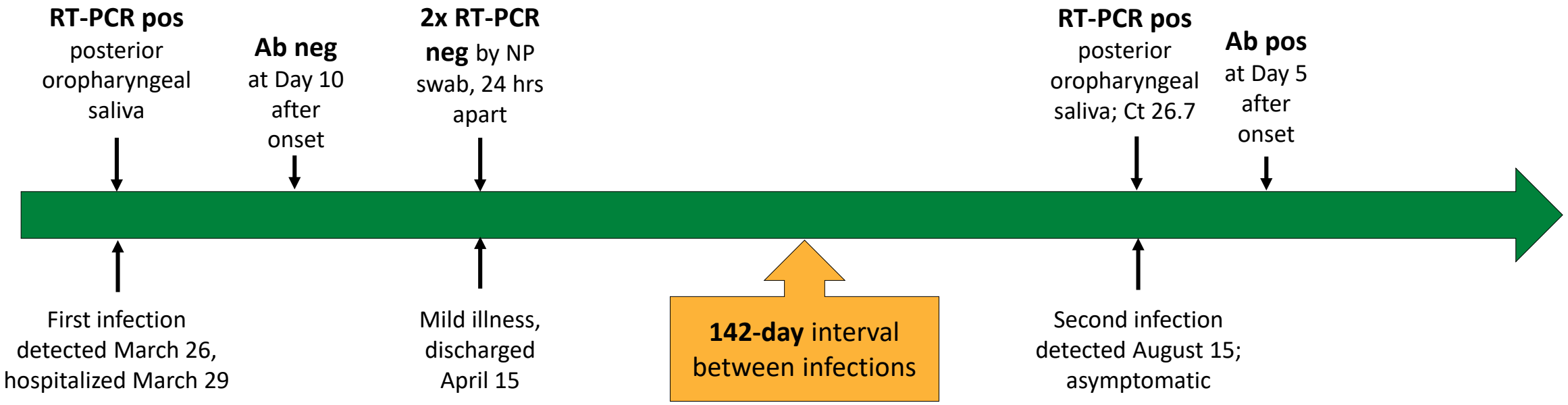
Genetic Differences in Immune Response May Predict COVID-19 Disease Severity: Type I IFN

- Genome or exome of 659 patients with life-threatening COVID-19 sequenced for comparison with 534 patients with asymptomatic or mild disease
- 23/659 (3.5%) of patients with life-threatening COVID-19 pneumonia had genetic defects at 8 of 13 candidate loci associated with TLR3 and IRF7 induction and amplification of type I IFNs



Zhang. Science. 2020;370,422.

Hong Kong Case: First Report, 33-Yr-Old Male



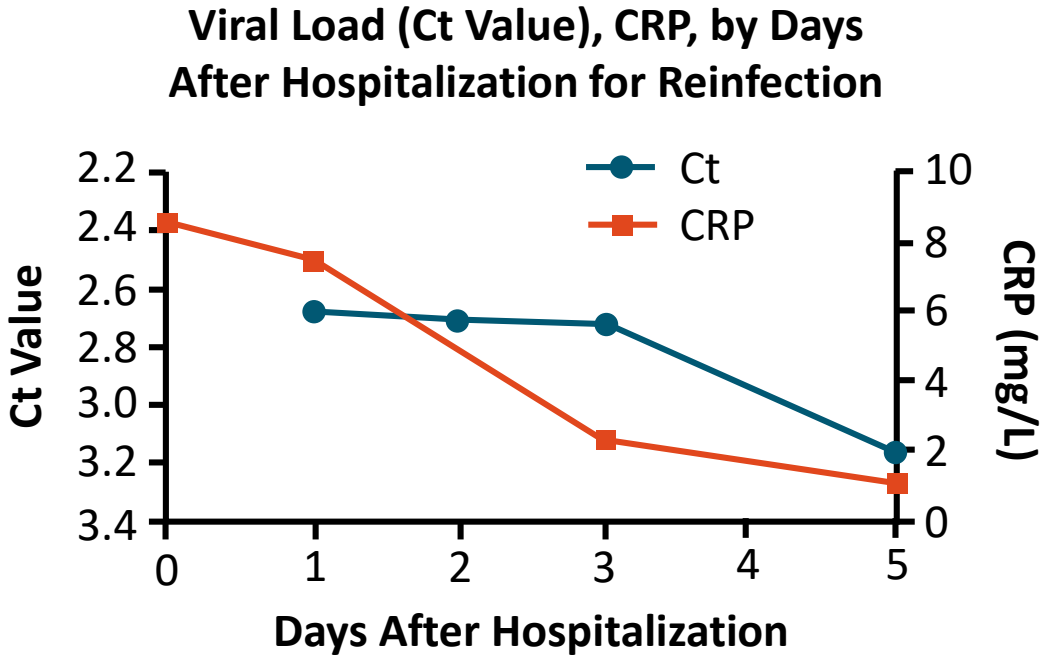
- Patient otherwise healthy and immunocompetent; recovered from first infection and traveled to Spain
- Reinfection detected by SARS-CoV-2 screening at Hong Kong airport when patient returned, via UK

To. Clin Infect Dis. 2020;[Epub].

Slide credit: clinicaloptions.com

Hong Kong Case: Viral Load and Immune Response

- Although patient remained asymptomatic during reinfection, he had elevated CRP (8.6 mg/L) that declined during hospital course
- Serial real-time PCR values showed increasing Ct (decreasing viral load) during hospital course
- No antibodies detected by Day 10 of first infection, but seroconversion appeared on Day 5 of reinfection
- Taken together, elevated CRP, relatively high viral load with gradual decline, and seroconversion during second infection are highly suggestive of acute reinfection



SARS-CoV-2 Ab	Days After Hospitalization for Reinfection			
	1	2	3	5
IgG (S/CO)	Negative (0.07)	Negative (0.09)	Negative (0.33)	Positive (4.84)

To. Clin Infect Dis. 2020;[Epub].

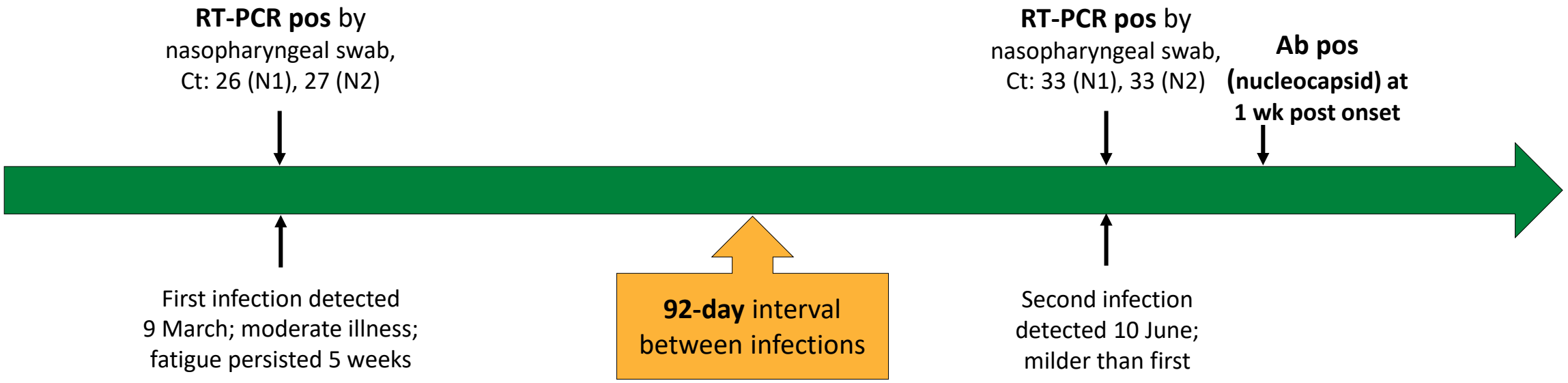
Slide credit: clinicaloptions.com

Hong Kong Case: Genomic Analysis

- Samples analyzed by whole genome sequencing
- **First viral genome**
  - GISAID clade V, Nextstrain Clade 19A, Pangolin lineage B.2, probability 0.99
  - Related to strains found in the United States and United Kingdom in March/April
- **Second viral genome**
  - GISAID clade G, Nextstrain Clade 20A, Pangolin lineage B.1.79, probability 0.70
  - Related to strains found in United Kingdom and Switzerland in July/August
  - 24 nucleotide difference between strains, consistent with reinfection by a distinct strain

To. Clin Infect Dis. 2020;[Epub].

Belgium Case: Reinfection in a 51-Yr-Old Female



- Patient immunocompetent, but used inhaled corticosteroids daily
- No travel history; second infection detected when similar but milder symptoms appeared

Van Elslande. Clin Infect Dis. 2020;[Epub].

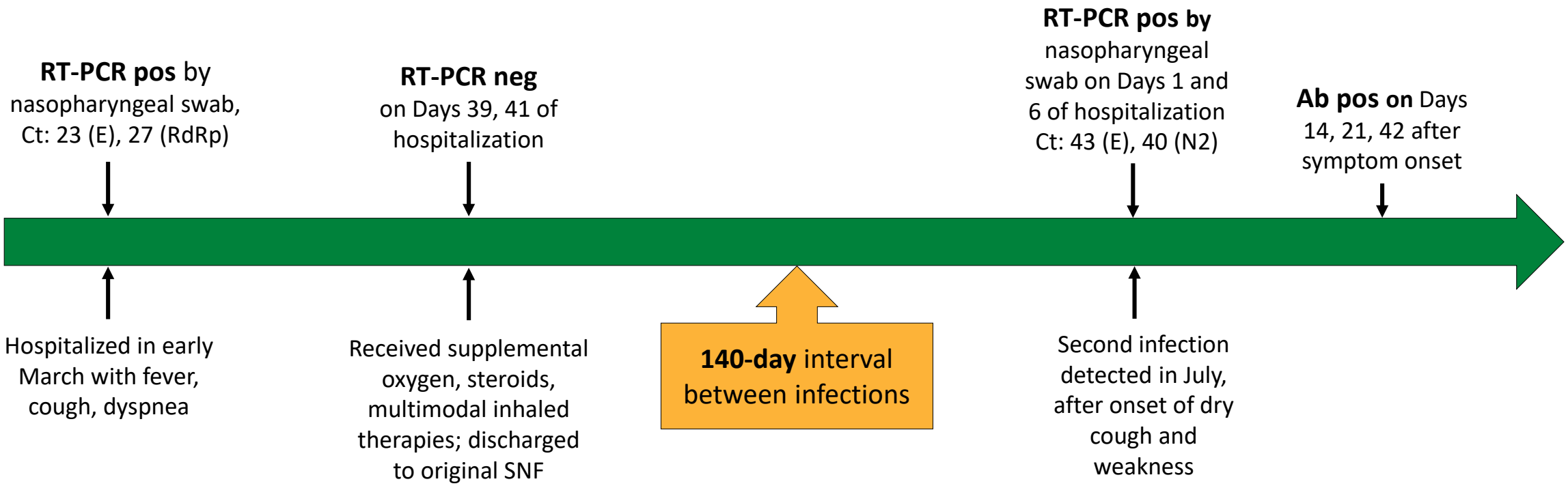
Slide credit: clinicaloptions.com

Belgium Case: Genomic Analysis

- Full-length genome sequencing or viral culture needed, as PCR can remain positive up to 104 days post-infection
  - Typically asymptomatic and mild cases exhibit longer RNA shedding when compared with severe cases
- First virus lineage was B.1.1 while second lineage was A
- 11/29,903 mutations across the 2 strains
  - 5 amino acid differences in spike (3), nucleocapsid (1), and ORF1a (1) proteins
- This difference consistent with other contemporaneous circulating strains in Belgium, suggesting reinfection

Van Elslande. Clin Infect Dis. 2020;[Epub].

Washington, USA, Case: Patient 60-69 Yrs of Age



- Patient resides in a SNF; has hypertension and severe emphysema, on home oxygen
- Reinfection occurred after patient moved to a new SNF; reinfection less severe than first infection

Goldman. medRxiv. 2020;[Preprint]. Note: This study has not been peer reviewed.

Slide credit: clinicaloptions.com

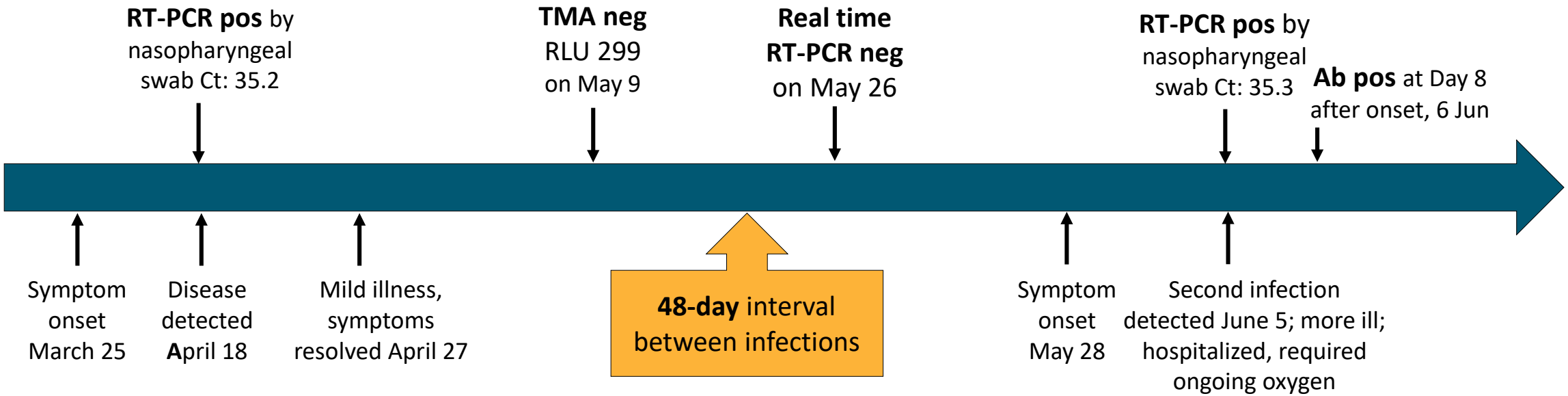
Washington, USA, Case: Genomic Analysis

- Total of 10 intrahost SNV, of which 5 type the March sequence to clade 19B, and 5 type the July sequence to clade 20A
- March sequence shares C18060T with the first US case, WA1
  - Introduced by traveler from Wuhan, China, returning to Puget Sound, Washington, in January 2020
- July sequence (but not March sequence) has A23403G mutation, which confers D614G amino acid change in spike protein
  - Defines SARS-CoV-2 strain with greater replicative fitness
  - Introduced separately to US East Coast via Europe

Goldman. medRxiv. 2020;[Preprint]. Note: This study has not been peer reviewed.

Slide credit: clinicaloptions.com

Nevada, USA:
First North American Report, 25-Yr-Old Male



- **First infection**: this otherwise healthy, immunocompetent patient presented to a community testing event with symptoms
- **Reinfection**: patient presented to urgent care with symptoms, was hospitalized 5 days later

Tillett. Lancet Infect Dis. 2021;21:52.

Slide credit: clinicaloptions.com

Nevada, USA, Case: Genomic Analysis

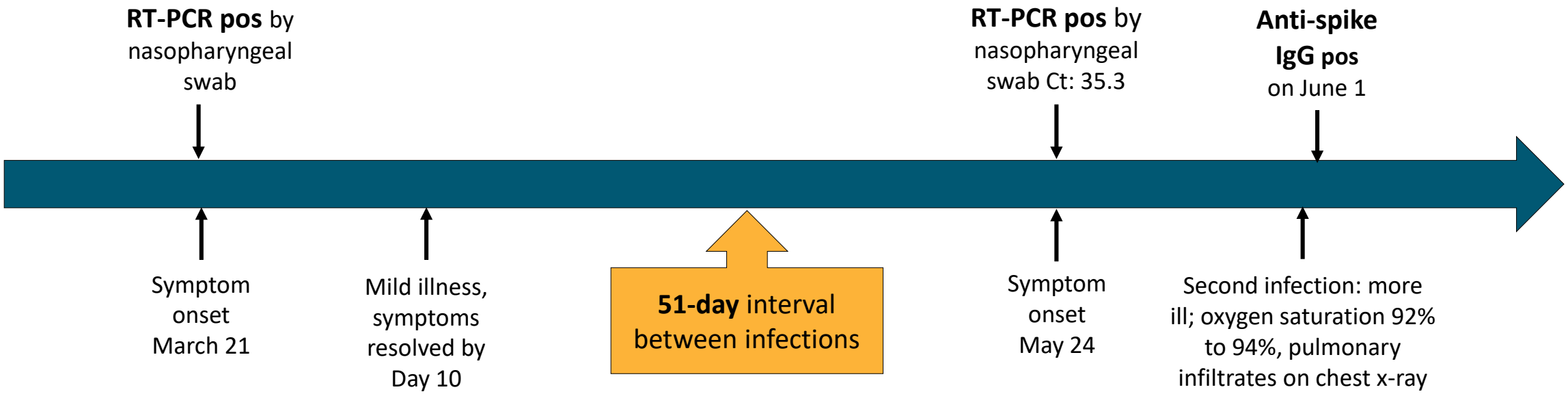
- Both viral sequences had 5 SNVs that are hallmarks of clade 20C, the predominant clade in Nevada at time of collection
- Specimen A (first infection) showed 4 SNVs not seen in specimen B
- Specimen B had 7 SNVs not seen in specimen A

- *Was this continuous infection and in vivo evolution?*
  - Extrapolated rate of SNV and MNV accumulation in specimens A and B of 83.64 substitutions per yr would be 2-3 times higher than currently observed rates
  - 4 SNVs in specimen A would first have to revert to ancestral type (Wuhan Hu 1)—highly unlikely
- *No—specimen B very likely a different strain of SARS-CoV-2*

Tillett. Lancet Infect Dis. 2021;21:52.

Slide credit: clinicaloptions.com

Virginia, USA: 42-Yr-Old Male



- Patient is a healthy, immunocompetent military healthcare worker; first exposure was in the workplace
- Second exposure was a household cohabitant; possibly a higher inoculum

Larson. Clin Infect Dis. 2020;[Epub].

Slide credit: clinicaloptions.com

Virginia, USA, Case: Genomic Analysis

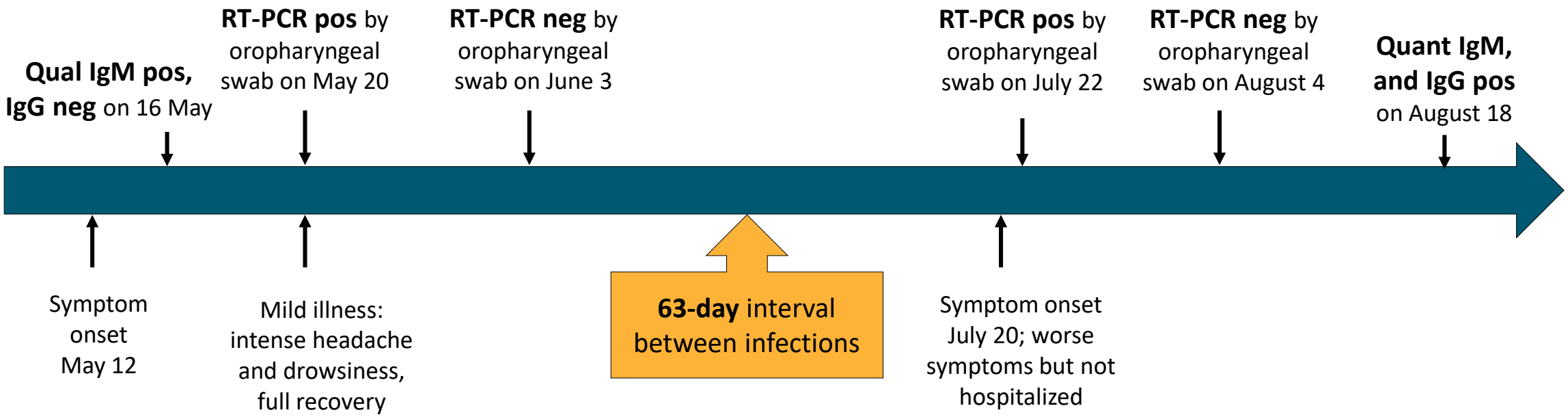
- Only a partial genome sequence available for first viral specimen
  - Sequence fragments totaled 4126 base pairs
- Nearly complete genome sequence for second specimen: 27,268 base pairs
  - Lineage B.1.26
  - Encoded D614G variation in spike protein
- Comparison of partial and nearly complete sequences identified 1 high-confidence variation
- **Increased severity of second infection due to . . .**
  - *immune enhancement?*
  - *a more pathogenic strain?*
  - *a larger inoculum?*

Larson. Clin Infect Dis. 2020;[Epub].

Slide credit: clinicaloptions.com

Ecuador Case:
First South American Report, 46-Yr-Old Male

Updated



- Immunocompetent patient; presented with symptoms of headache, drowsiness; made a full recovery
- Second exposure after close contact with an infected relative; fever, odynophagia, back pain, cough, dyspnea

Prado-Vivar. Lancet Infect Dis. 2020;[Epub]. Prado-Vivar. SSRN. 2020;[Preprint]. Note: This study has not been peer reviewed.

Slide credit: clinicaloptions.com

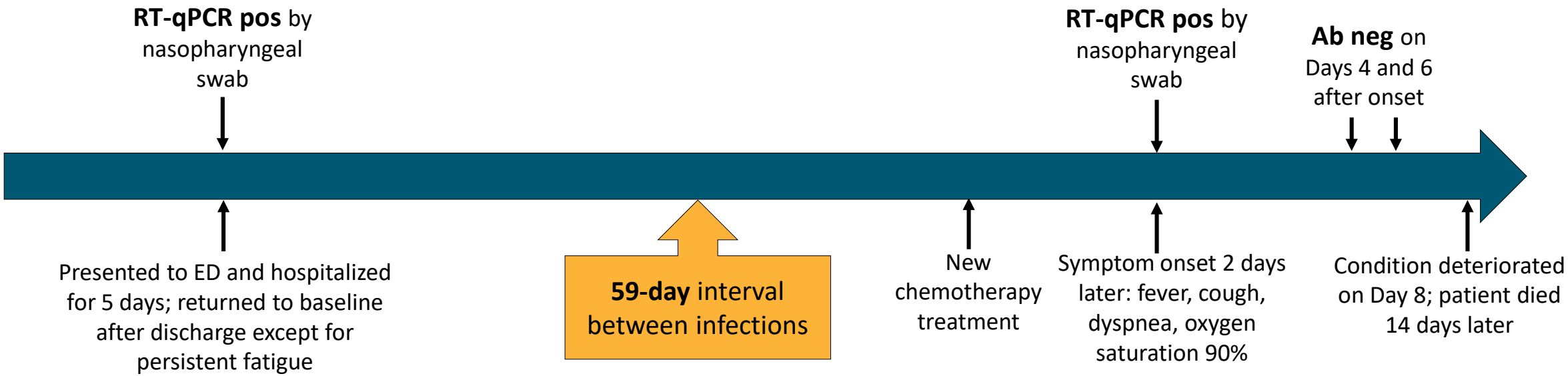
Ecuador Case: Genomic Analysis

- First viral sequence
  - Nextclade 20A, GISAID lineage B1.p9
  - 8 SNPs, 4 AA changes compared to Wuhan Hu 1 reference strain
- Second viral sequence
  - Nextclade 19B, GISAID lineage A.1.1
  - 10 SNPs, 5 AA changes compared to Wuhan Hu 1 reference
- **No shared mutations between the 2 viral sequences**

Prado-Vivar. SSRN. 2020;[Preprint]. Note: This study has not been peer reviewed.

Slide credit: clinicaloptions.com

Netherlands Case: 89-Yr-Old Female



- Patient immunocompromised by Waldenström macroglobulinemia, treated with B-cell–depleting therapy
- **Genomic analysis (inconclusive):** viral sequences varied at 10 nucleotide positions; this exceeds predicted mutation rate of 5-6 per 2 mos and may indicate distinct viral variants

Mulder. Clin Infect Dis. 2020;[Epub].

Slide credit: clinicaloptions.com

Summary of 7 Case Reports

Location	Age, Yrs	Sex	First Infection (Ct)	Second Infection (Ct)	Intervening Period (Days)	Antibodies First Infection	Antibodies After Reinfection
Hong Kong	33	Male	Mild (N/A)	Asymptomatic (27)	142	Negative	IgG+
Belgium	51	Female	Mild (26, 27)	Milder (33, 33)	93	N/A	IgG+
Washington, USA	60s	N/A	Severe (23, 27)	Milder (43, 40)	140	N/A	IgM+, IgG+
Nevada, USA	25	Male	Mild (35)	Worse (35)	48	N/A	IgM+, IgG+
Virginia, USA	42	Male	Mild (N/A)	Worse (N/A)	51	N/A	N/A
Ecuador	46	Male	Mild (37)	Worse (N/A)	63	IgM-, IgG-	IgM+, IgG+
Netherlands	89	Female	Hospitalized (N/A)	Died (N/A)	59	N/A	N/A

Iwasaki. Lancet Infect Dis. 2021;21:3. Goldman. medRxiv. 2020;[Epub]. Note: This study has not been peer reviewed.
Larson. Clin Infect Dis. 2020;[Epub]. Mulder. Clin Infect Dis. 2020;[Epub].

CDC Remarks on Reinfection

Updated

"Cases of reinfection with COVID-19 have been reported but remain rare."

"The duration and robustness of immunity to SARS-CoV-2 remains under investigation . . . For SARS-CoV-2, reinfection appears to be uncommon during the initial 90 days after symptom onset of the preceding infection."

- If a person is *asymptomatic* during the 90-day period following recovery from COVID-19, re-testing is unlikely to yield new information given the potential for persistent viral RNA shedding
- If a person becomes *symptomatic* during the 90-day period following recovery from COVID-19 and no other diagnosis is identified, then evaluation for reinfection and isolation may be warranted in consultation with an infectious disease or infection control expert

CDC. Reinfection with COVID-19. Last updated October 27, 2020.
CDC. Interim guidance on duration of Isolation and precautions for adults with COVID-19. Last updated February 13, 2021.

Slide credit: clinicaloptions.com

Assessing Disease Severity and Risk Factors for Severe Disease

NIH Guidelines: Defining a COVID-19 Severity Spectrum

Stage	Characteristics
Asymptomatic or presymptomatic infection	▪ Positive virologic test for SARS-CoV-2 (ie, NAAT or antigen test) but no symptoms consistent with COVID-19
Mild illness	▪ Varied symptoms (eg, fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste or smell) but no shortness of breath, dyspnea, or abnormal chest imaging
Moderate illness	▪ $SpO_2 \geq 94\%$ and lower respiratory disease evidenced by clinical assessment or imaging
Severe illness	▪ $SpO_2 < 94\%$, $PaO_2/FiO_2 < 300$ mm Hg, respiratory rate > 30 breaths/min, or lung infiltrates > 50%
Critical illness	▪ Respiratory failure, septic shock, and/or multiorgan dysfunction

NIH COVID-19 Treatment Guidelines. Clinical spectrum of SARS-CoV-2 infection. Last updated December 17, 2020.

Slide credit: clinicaloptions.com

COVID-19 Severity in Mainland China

- Observational study of COVID-19 cases diagnosed in China's Infectious Disease Information System as of February 11, 2020 (N = 72,314)
  - No deaths among confirmed case patients with noncritical disease or who were ≤ 9 yrs of age

Disease Classification, %	Confirmed Cases* (n = 44,672)
Mild	**80.9**
Severe	13.8
Critical	4.7
Missing	0.6

Characteristic	Case-Fatality Rate, % (n/N)
All confirmed cases*	2.3 (1023/44,672)
▪ **Critical**	**49.0 (1023/2087)**
▪ ≥ 80 yrs of age	14.8 (208/1408)
▪ Cardiovascular disease	10.5 (92/873)
▪ 70-79 yrs of age	8.0 (312/3918)
▪ Diabetes	7.3 (80/1102)
▪ Chronic respiratory disease	6.3 (32/511)
▪ Hypertension	6.0 (161/2683)
▪ Cancer	5.6 (6/107)

*Positive for viral nucleic acid by throat swab.

Wu. JAMA. 2020;323:1239. http://weekly.chinacdc.cn/en/article/id/e53946e2-c6c4-41e9-9a9b-fea8db1a8f51

Slide credit: clinicaloptions.com

Host Factors Predicting COVID-19 Disease Severity

- Cohort study of SARS-CoV-2 RNA–positive patients in Shanghai during January 20 - February 25, 2020 (N = 326)
- In multivariate analysis of critical (n = 16) vs asymptomatic, mild, or severe (n = 310) confirmed COVID-19 cases, predictors of increased disease severity included:
  - **Older age** (*P* = .002)
  - **Lymphocytopenia** (*P* = .002)
- Lymphocyte declines correlated with high levels of IL-6 and IL-8 in patients exhibiting severe/critical disease

Zhang. Nature. 2020;583:437.

Slide credit: clinicaloptions.com

Comorbidity Status at Hospital Admission Among COVID-19–Positive Patients in New York City Area

- Case series of sequentially hospitalized patients admitted to 12 Northwell Health system hospitals in NYC, Long Island, and Westchester County, NY during March 1 - April 4, 2020 (N = 5700)
  - Median number of total comorbidities at admission: 4 (IQR: 2-8)

Comorbidity Number, %	Admissions (N = 5700)
> 1	87.6
1	6.3
None	6.1

Specific Comorbidity, %	Admissions (N = 5700)
Hypertension	56.6
Obesity	41.7
Diabetes	33.8

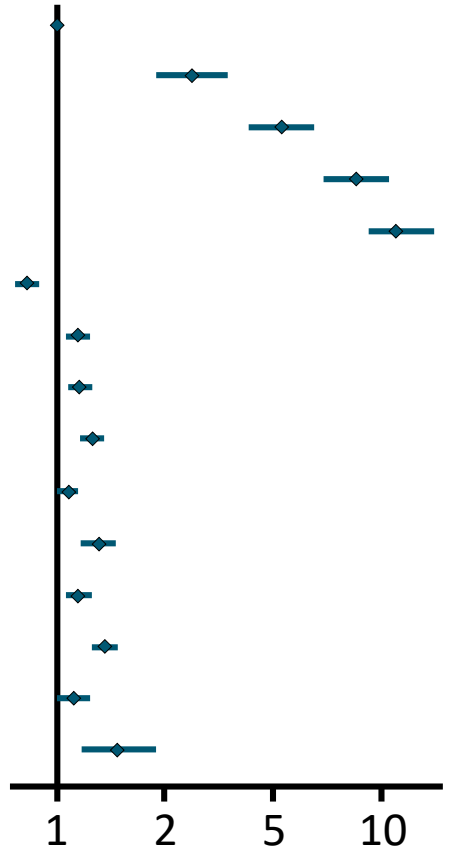
Richardson. JAMA. 2020;323:2052.

Slide credit: clinicaloptions.com

Predictors of Mortality Among COVID-19–Positive Hospitalized Patients in the UK

- Prospective observational cohort study of hospital admissions in England, Wales, and Scotland during February 6 - April 19, 2020 (N = 20,133)
  - Significantly increased risk of mortality among **older patients, men, and those with chronic comorbidities**

Multivariate Survival Analysis



Characteristic	HR (95% CI)	*P* Value
< 50 yrs		
50-59 yrs	2.63 (2.06-3.35)	< .001
60-69 yrs	4.99 (3.99-6.25)	< .001
70-79 yrs	8.51 (6.85-10.57)	< .001
≥ 80 yrs	11.09 (8.93-13.77)	< .001
Female sex	0.81 (0.75-0.86)	< .001
Chronic cardiac disease	1.16 (1.08-1.24)	< .001
Chronic pulmonary disease	1.17 (1.09-1.27)	< .001
Chronic kidney disease	1.28 (1.18-1.39)	< .001
Diabetes	1.06 (0.99-1.14)	.087
Obesity	1.33 (1.19-1.49)	< .001
Chronic neurological disorder	1.17 (1.06-1.29)	.001
Dementia	1.40 (1.28-1.52)	< .001
Malignancy	1.13 (1.02-1.24)	.017
Moderate/severe liver disease	1.51 (1.21-1.88)	< .001

Docherty. BMJ. 2020;369:m1985.

Slide credit: clinicaloptions.com

4C Mortality Score: Development, Performance, and Implications for Practice

- Prospective observational study of **mortality risk among adults hospitalized with COVID-19** in England, Scotland, and Wales
  - Derivation cohort recruited February 6 to May 20, 2020; validation cohort recruited May 21 to June 29, 2020
- **Aim**: Define and test a pragmatic tool to predict mortality based on 8 variables assessable at hospital admission
- **Outcome**: Better discriminatory ability vs 15 existing risk stratification scores (AUROC of 0.774 vs 0.614-0.764)

Deaths by 4C Mortality Score Risk Groups, n (%)	Derivation Cohort (n = 35,463)	Validation Cohort (n = 22,361)
Low (0-3)	45 (1.7)	20 (1.2)
Intermediate (4-8)	751 (9.1)	486 (9.9)
High (9-14)	6310 (34.9)	3666 (31.4)
Very high (≥ 15)	4320 (66.2)	2557 (61.5)
Overall	11,426 (32.2)	6729 (30.1)

"Patients with a [low risk score] might be suitable for management in the community, while those within the intermediate risk group…might be suitable for ward level monitoring. Meanwhile patients with a score of ≥ 9 [may require] aggressive treatment, including the initiation of steroids and early escalation to critical care if appropriate."

Knight. BMJ. 2020;370:m3339.

Slide credit: clinicaloptions.com

4C Mortality Score: Calculation

Characteristic		4C Mortality Score
Age, yrs	▪ < 50	-
	▪ 50-59	+2
	▪ 60-69	+4
	▪ 70-79	+6
	▪ ≥ 80	+7
Sex at birth	▪ Female	-
	▪ Male	+1
Comorbidities,* n	▪ 0	-
	▪ 1	+1
	▪ ≥ 2	+2
Respiratory rate, breaths/min	▪ < 20	-
	▪ 20-29	+1
	▪ ≥ 30	+2

Characteristic		4C Mortality Score
SpO_2 on room air, %	▪ ≥ 92	-
	▪ < 92	+2
Glasgow coma scale score	▪ 15	-
	▪ < 15	+2
Urea, mmol/L	▪ < 7	-
	▪ 7-14	+1
	▪ > 14	+3
CRP, mg/L	▪ < 50	-
	▪ 50-99	+1
	▪ ≥ 100	+2

Potential score range: 0-21. *By Charlson comorbidity index with addition of clinician-defined obesity.

Knight. BMJ. 2020;370:m3339.

Population Mortality and Fatality Trends

Terminology

Measure	Numerator	Denominator	Reported As
Mortality (general definition)	Number of deaths due to specific cause	Total population	Usually per 100,000 persons
CDC-reported COVID mortality	Number of deaths due to COVID	Total number of deaths	% (multiplied by 100)
Case-fatality rate	Number of deaths due to COVID	Total COVID cases	% (multiplied by 100)

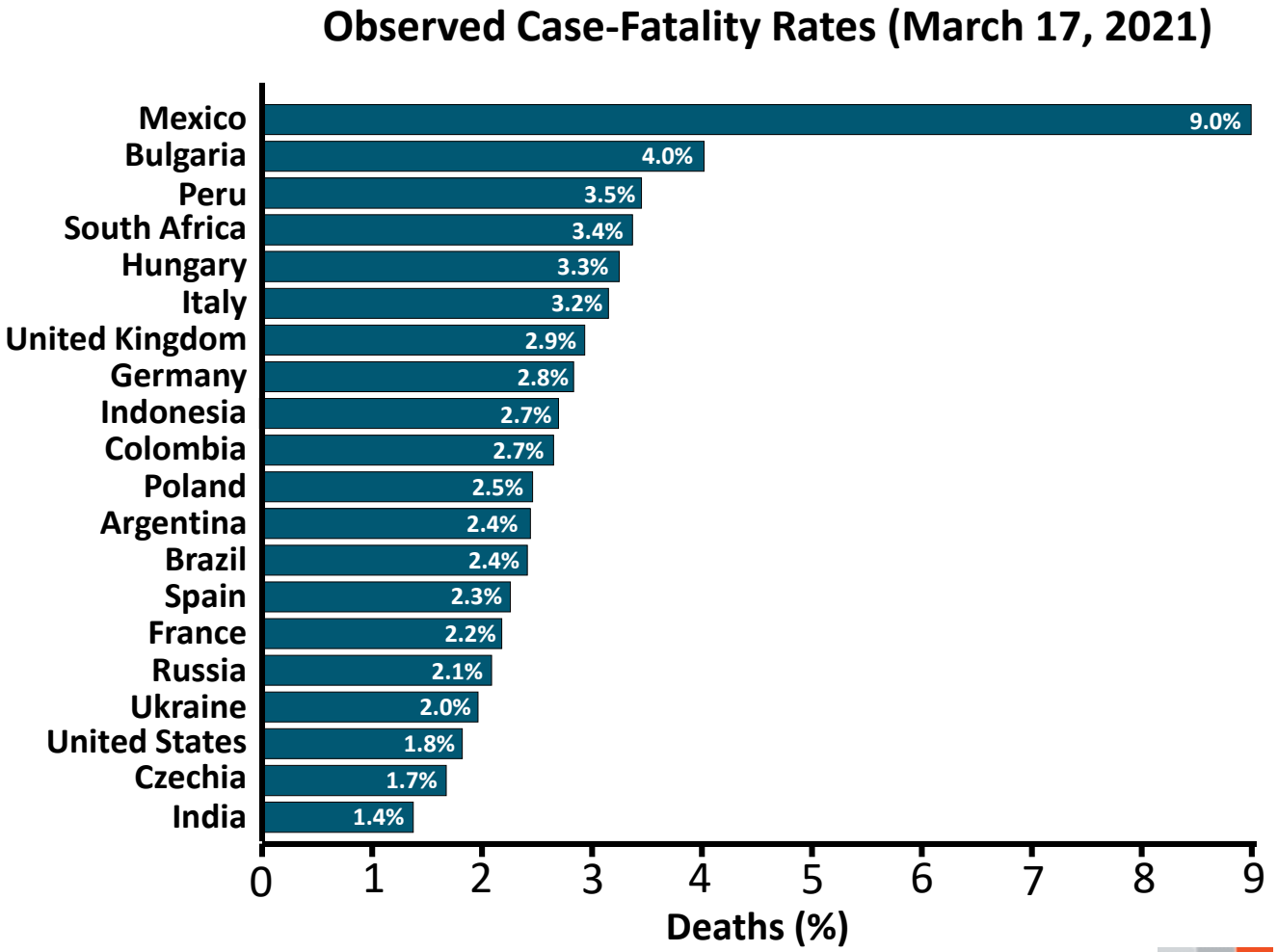
CDC. Principles of Epidemiology in Public Health Practice, Third Edition. An Introduction to Applied Epidemiology and Biostatistics. https://www.cdc.gov/csels/dsepd/ss1978/lesson3/section3.html

Slide credit: clinicaloptions.com

Case-Fatality Rates by Country

Updated

- Mortality differences between countries and time periods could be caused by differences in:
  - Testing → countries only test people with severe symptoms; the case fatality rate will be higher than one with widespread testing for asymptomatic cases
  - Demographics → mortality high for older persons or persons with high-risk comorbidities
  - Healthcare system characteristics → hospital overwhelm, etc
  - Unknown factors

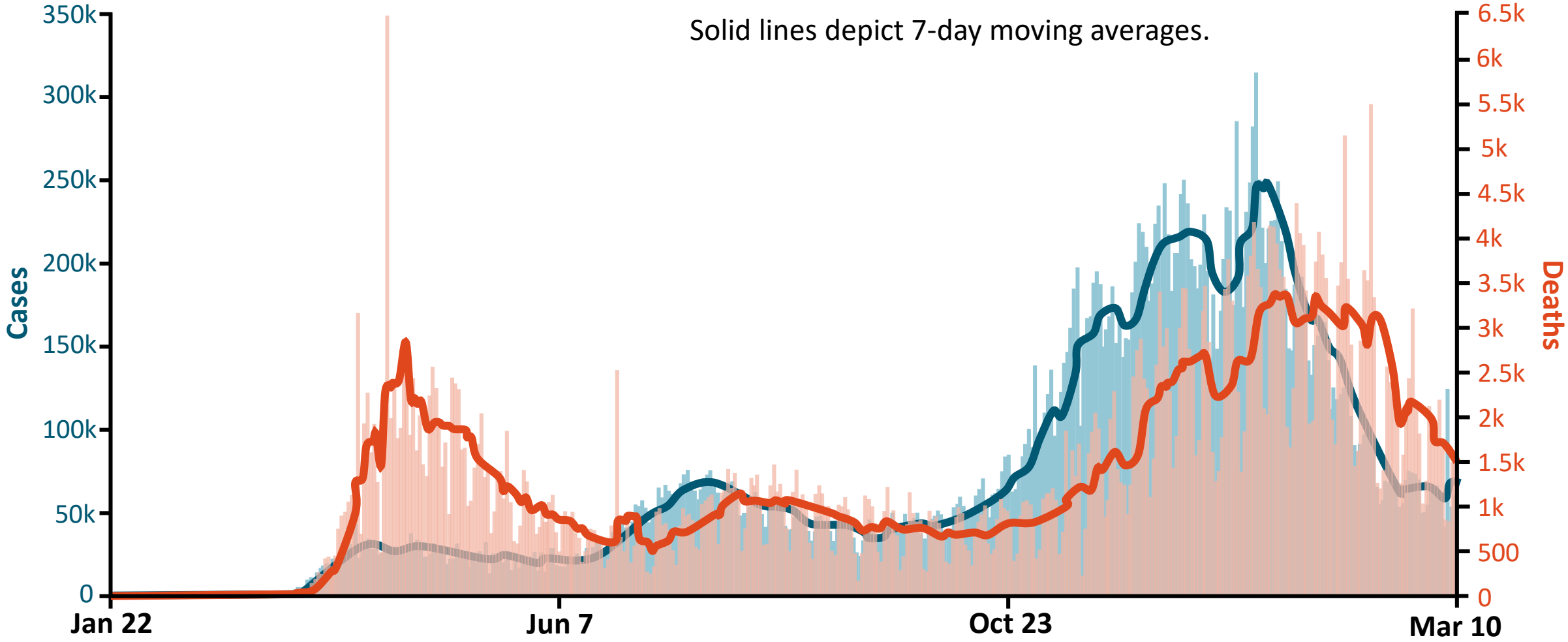


https://coronavirus.jhu.edu/data/mortality

Slide credit: clinicaloptions.com

CDC: COVID-19 Reported Cases and Mortality

Updated

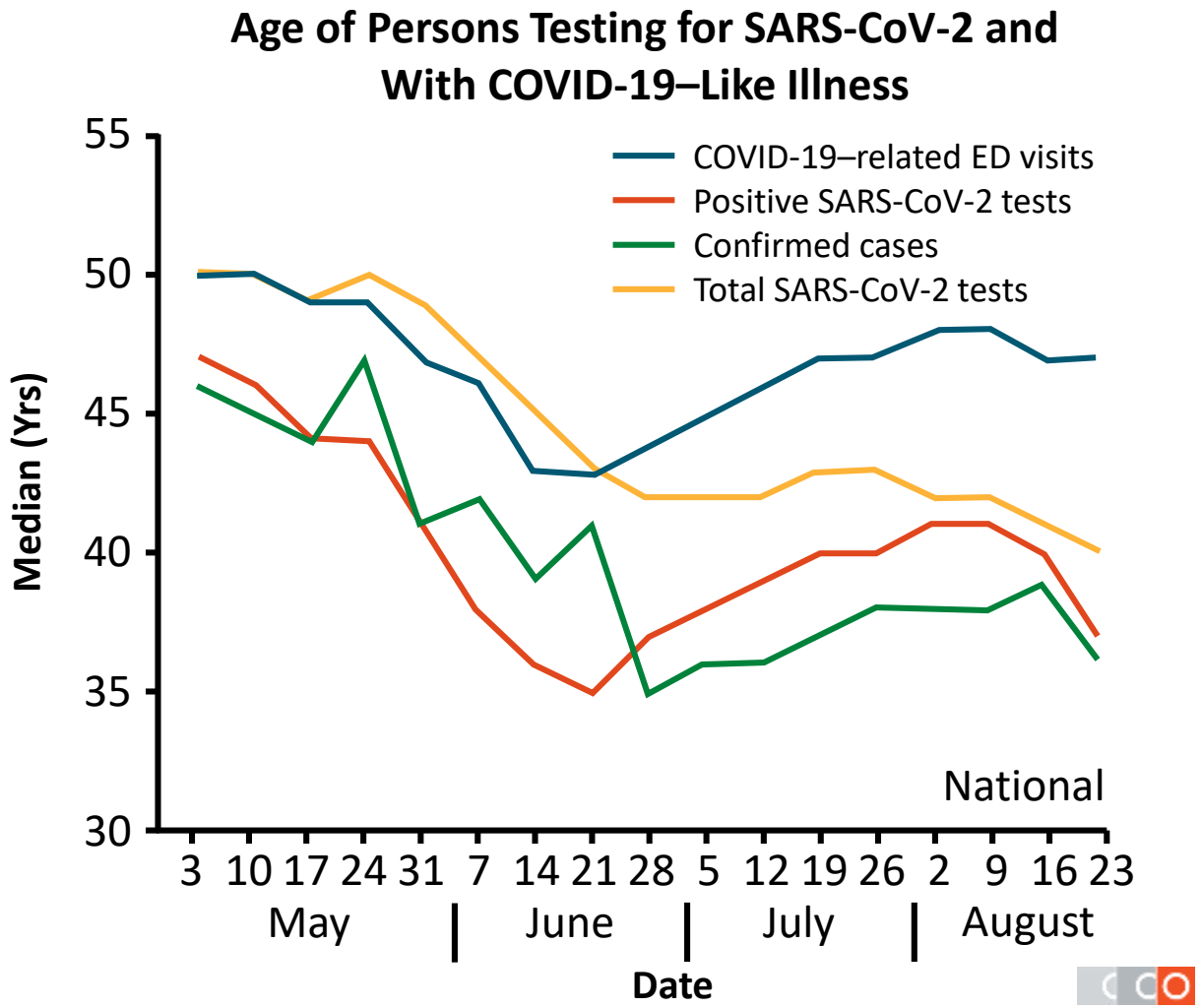


https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covidview/index.html

Slide credit: clinicaloptions.com

CDC: Changing Demographics of COVID-19 Infections in the US

- During June-August 2020, COVID-19 affected more younger persons in the US than during January-May → could affect mortality estimates
- Median age of persons being tested also declined, but lagged behind the declines in median age of positive results or confirmed cases
  - Suggests infection patterns drove testing patterns



Boehmer. MMWR Morb Mortal Wkly Rep. 2020;69:1404.

Slide credit: clinicaloptions.com

Age-Specific Case-Fatality Rate in Italy Over Time

Updated

- Based on national-level surveillance system data from Italy, average age of COVID-19 cases in Italy in first 2 mos of outbreak was 50 yrs vs 31 yrs in August/September[1]
- Age-specific CFR rates did not vary over time → less severe COVID-19 clinical outcomes might be due to increasing proportion of infections in younger persons[1]
- CFR in Italy has continued to decline; last reported CFR was 3.2% vs 14.1% in August[1,2]

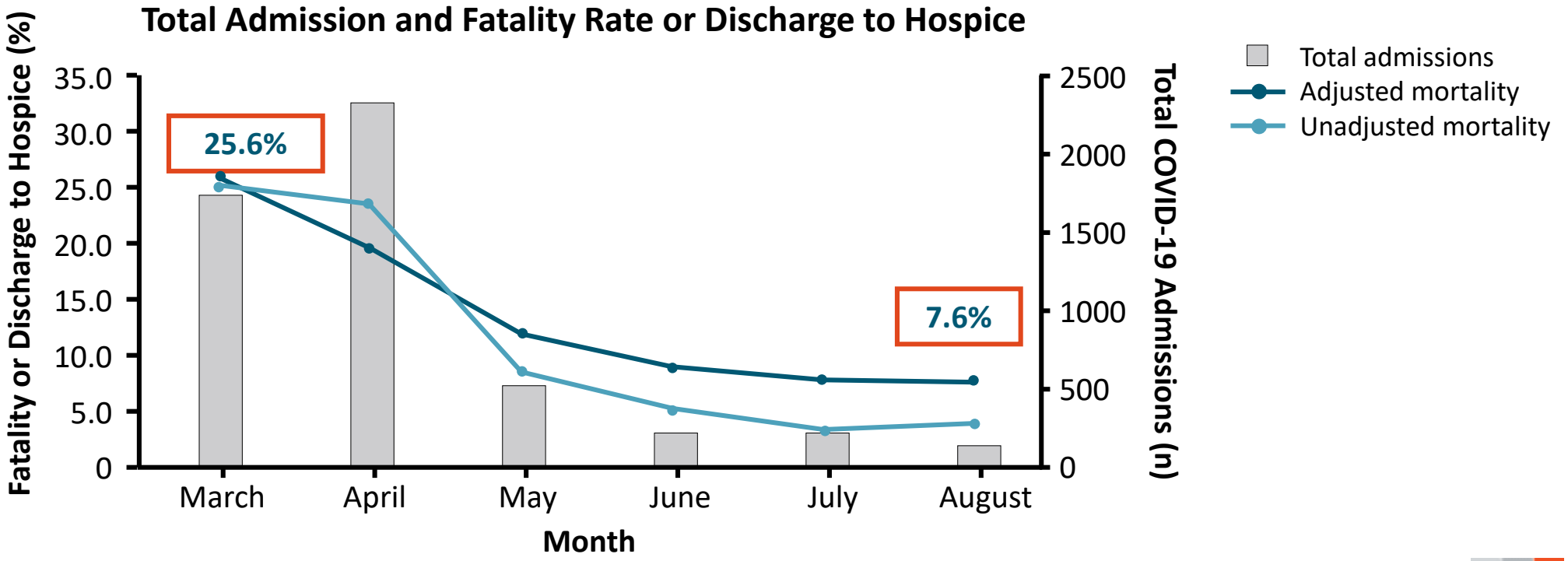
CFR by Age, %[1]	April 16	June 16	August 18
0-19 yrs	0	0.1	0.1
20-29 yrs	0.1	0.1	0.1
30-39 yrs	0.3	0.3	0.3
40-49 yrs	0.9	0.9	0.9
50-59 yrs	2.5	2.7	2.8
60-69 yrs	9.5	10.6	10.9
70-79 yrs	24.1	26.0	26.7
≥ 80 yrs	28.8	32.3	34.6
Total	**12.6**	**13.9**	**14.1**

1. Signorelli. Int J Public Health. 2020;65:1435. 2. https://coronavirus.jhu.edu/data/mortality.

Slide credit: clinicaloptions.com

Risk-Adjusted Fatality Rates for Patients Hospitalized With COVID-19 in NYC

- Assessment of in-hospital case fatality rates or discharge to hospice in persons hospitalized with laboratory confirmed COVID-19 from March through August 2020 at 3 academic hospitals in NYC (N = 5,121)
  - Decrease in case fatality observed across age groups



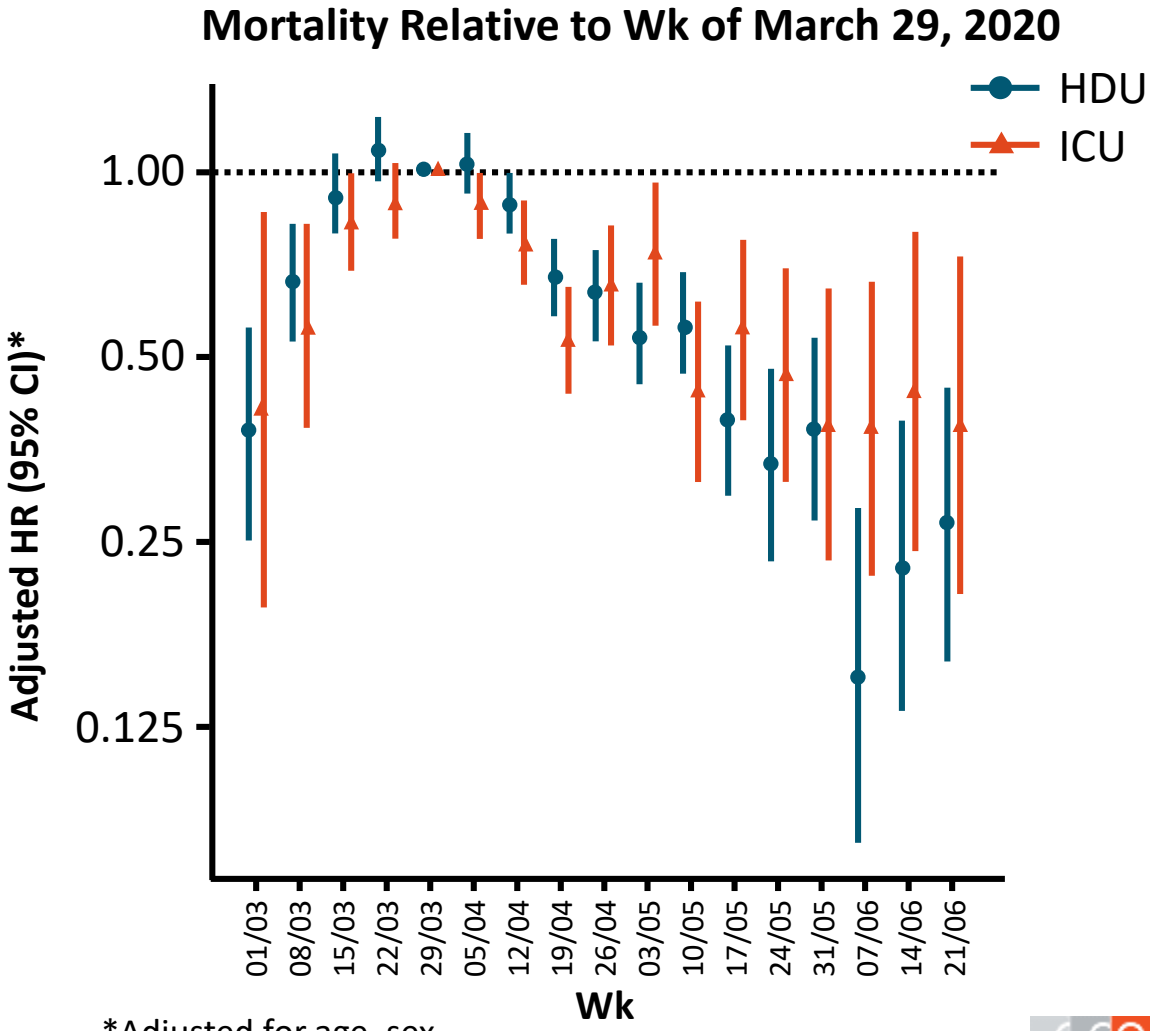
*Adjusted for age, sex, race/ethnicity, BMI, smoking history, admission oxygen saturation, D-dimer, ferritin, C-reactive protein, and high-risk comorbidities.

Horwitz. J Hosp Med. 2021;16:90.

Slide credit: clinicaloptions.com

Mortality in Patients With COVID-19 in Critical Care in England

- Assessment of in-hospital all-cause mortality in persons with COVID-19 (N = 21,082) reported to the COVID-19 Hospitalisation in England Surveillance System
- Unadjusted survival at 30 days increased from 58.0% in March to 80.4% in June in the ICU
  - 71.6% to 92.7% in the high dependency unit
- Survival improvements consistent across subgroups (age, sex, ethnicity, and comorbidities)



*Adjusted for age, sex, ethnicity, and comorbidities.

Dennis. Crit Care Med. 2021;49:209.

Slide credit: clinicaloptions.com

Complexities of Calculating Mortality and Case-Fatality Rates in Hospitals and ICUs

- Rates should be adjusted for the changing demographics of people admitted over time, but these detailed data can be difficult to obtain
- Thresholds for hospital admission may have changed over time, with less severely ill patients being admitted as space became less limited
  - Potentially adjusted for in NYC dataset by adjusting for clinical and laboratory values that reflect disease severity (eg, oxygen saturation, C-reactive protein)

Horwitz. J Hosp Med. 2021;16:90.

Slide credit: clinicaloptions.com

COVID-19 Mortality: Potential Improvements and Lessons Learned

- Increasing clinical experience
  - Appropriate timing of ventilation
  - Best way to supply supplemental oxygen
- Decreasing hospital volume
- Pharmacologic treatments: systemic corticosteroids and remdesivir
- Nonpharmacologic management, such as proning
- Lower viral load exposure from mask wearing and social distancing?

Horwitz. J Hosp Med. 2021;16:90.

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