PAINWEEK

Apocalypse Now. . . Or Later?

Michael Bottros, MD

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Disclosures

- None

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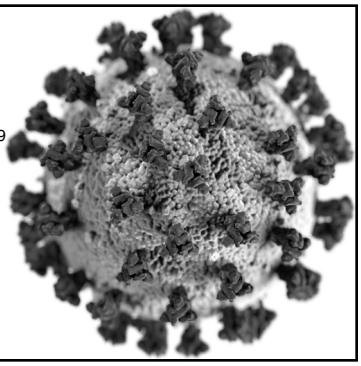
Outline

- Introduction and Timeline
- Pathophysiology
- Clinical Features of Acute COVID-19
- Acute COVID-19 Treatment
- Long COVID-19 Terminology
- Risk Factors
- Long COVID-19 Organ Dysfunction
- Long COVID-19 Treatment
- Conclusions



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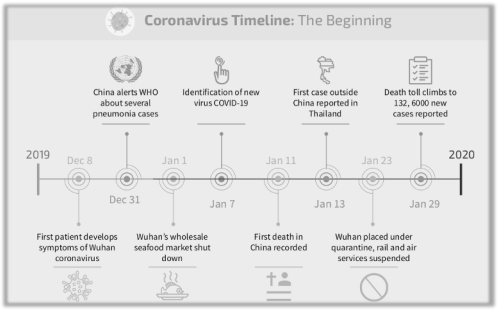

painweek www.weforum.org/agenda/2020/04/coronavirus-spread-covid19-pandemic-timeline-milestones.

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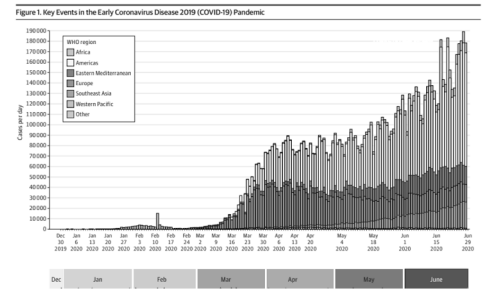

painweek Wiersinga et al. *JAMA*. 2020;324(8):782-793.

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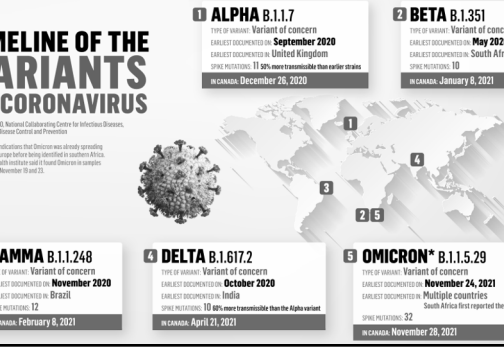

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Pathophysiology

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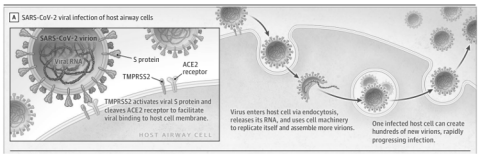
Pathophysiology



SARS-CoV-2 targets cells through the viral structural spike (S) protein that binds to the angiotensin converting enzyme 2 (ACE2) receptor. The serine protease type 2 transmembrane serine protease (TMPRSS2) in the host cell further promotes viral uptake by cleaving ACE2 and activating the SARS-CoV-2 S protein

painweek Wiersinga et al. *JAMA*. 2020;324(8):782-793.

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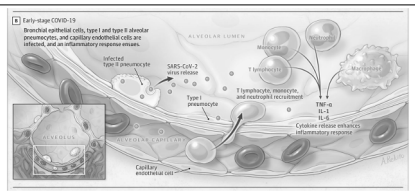
Pathophysiology



In the **early** stage, viral copy numbers can be high in the lower respiratory tract. Inflammatory signaling molecules are released by infected cells and alveolar macrophages in addition to recruited T lymphocytes, monocytes, and neutrophils

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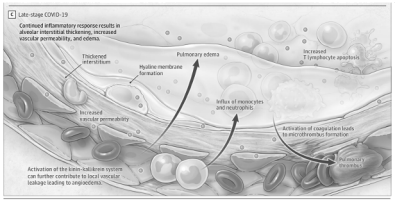
Pathophysiology



In the **late** stage, pulmonary edema can fill the alveolar spaces with hyaline membrane formation, compatible with early-phase acute respiratory distress syndrome

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Wiersinga et al. *JAMA*. 2020;324(8):782-793.

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bioRxiv
THE PREPRINT SERVER FOR BIOLOGY

bioRxiv posts many COVID19-related papers. A reminder: they have not been formally peer-reviewed and should not guide health-related behavior or be reported in the press as conclusive.

New Results — Follow this preprint

SARS-CoV-2 infects human adipose tissue and elicits an inflammatory response consistent with severe COVID-19

Giovanny J. Martinez-Colon, Kalani Ratnasiri, Heping Chen, Sizun Jiang, Elizabeth Zanley, Arjun Rustagi, Rosa Verma, Han Chen, Jason R. Andrews, Kirsten D. Mertz, Alexander Tsankov, Dan-Arsiguey Jack Boyd, Garry P. Nolan, Christian M. Schürch, Matthias S. Matter, Catherine A. Blish, Tracey L. McLaughlin

doi: https://doi.org/10.1101/2021.10.24.465626

- Identification of 2 cellular targets of SARS-CoV-2 infection in adipose tissue: mature adipocytes and adipose tissue macrophages
  - Adipose tissue macrophage infection is largely restricted to a highly inflammatory subpopulation of macrophages, present at baseline, that is further activated in response to SARS-CoV-2 infection
  - Preadipocytes, while not infected, adopt a proinflammatory phenotype
- SARS-CoV-2 RNA was detectable in adipocytes in COVID-19 autopsy cases and is associated with an inflammatory infiltrate
- Findings may indicate that adipose tissue supports SARS-CoV-2 infection and pathogenic inflammation and may explain the link between obesity and severe COVID-19

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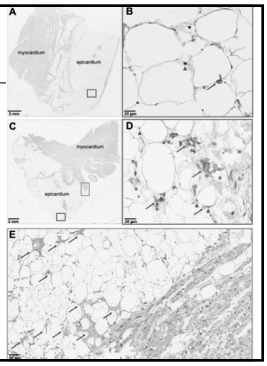
SARS-CoV-2 RNA, Immune Infiltration: Present in Adipose Tissue of Autopsy Samples from COVID-19 Patients

RNA *in situ* hybridization (ISH) on epicardial fat from heart autopsies from patients who succumbed to COVID-19. Assays were performed using probes against SARS-CoV-2 Spike mRNA

(A and C) Overview of the heart tissue section (2mm) and **(B and D)** magnified view (20um) of the represented region

Red arrowheads = ISH positive signals
Blue arrows = inflammatory cells

(E) Interface of epicardial fat and myocardium (50um). Note the inflammatory infiltration (blue arrows) only in the epicardial fat.
Image has been rotated 90°



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Martínez-Colón et al. 2021.10.24.465626; doi: https://doi.org/10.1101/2021.10.24.465626.

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Clinical Features of Acute COVID-19

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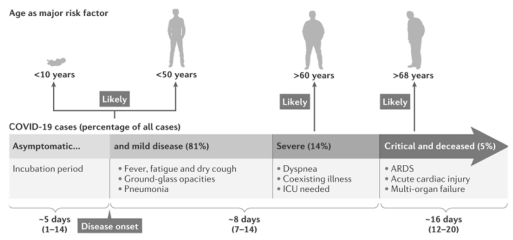
Clinical Features of Acute COVID-19



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Hu et al. Nat Rev Microbiol. 2021;19:141-154.

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Multisystem Inflammatory Syndrome in Children (MIS-C)

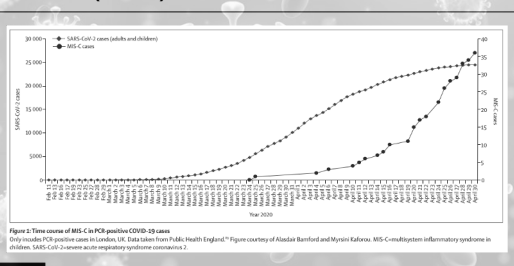

Figure 2: Time course of MIS-C in PCR-positive COVID-19 cases
Only incudes PCR-positive cases in London, UK. Data taken from Public Health England.[16] Figure courtesy of Alasdair Bamford and Myrsini Kaforou. MIS-C=multisystem inflammatory syndrome in children. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

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Jiang et al. *Lancet Infect Dis*. 2020 Nov;20(11):e276-e288.

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MIS-C

	# Patients with available data	N (%)
CONSTITUTIONAL		
Fever	662	662 (100.0)
Myalgia, fatigue	662	89 (13.4)
Lymphadenopathy	662	92 (13.9)
GASTROINTESTINAL		
Abdominal pain, diarrhea	662	488 (73.7)
Vomiting	662	452 (68.3)
Loss of appetite	662	73 (11.0)
HEAD, EYES, EARS, NOSE, THROAT		
Conjunctivitis	662	343 (51.8)
Cheilitis	662	216 (32.6)
Tongue swelling	662	31 (4.7)
Sore throat	662	59 (8.9)
RESPIRATORY		
Dyspnea, shortness of breath	662	121 (18.3)
Cough	662	86 (13.0)
Rhinorrhea, nasal congestion	662	47 (7.1)
NEUROLOGIC		
Headache, dizziness	662	129 (19.5)
Somnolence, altered mental status, lethargy, fussy	662	66 (10.0)
DERMATOLOGIC		
Rash	662	372 (56.2)
Edema to extremities	662	128 (19.3)

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Ahmed et al. *EClinicalMedicine.* 2020;26:100527.

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Acute COVID-19 Risk Factors

- Older age
- Male sex
- Nonwhite ethnicity
- Pre-existing disability
- Pre-existing comorbidities
  - –Obesity
  - –Cardiovascular disease
  - –Respiratory disease
  - –Hypertension

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Crook et al. *BMJ.* 2021;374:n1648.

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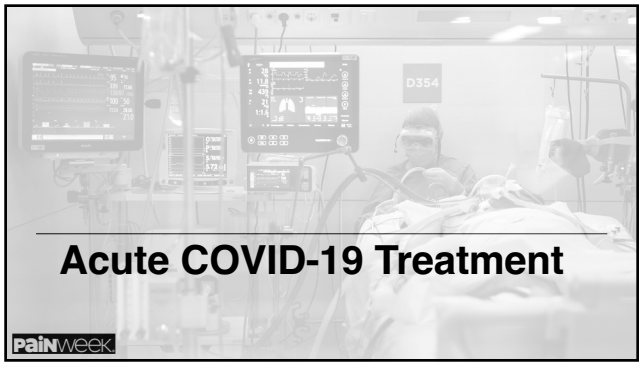

Acute COVID-19 Treatment

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Acute COVID-19 Treatment

Care and respiratory support

- Currently, best practices for supportive management of acute hypoxic respiratory failure and ARDS should be followed
- More than 75% of patients hospitalized with COVID-19 require supplemental oxygen therapy
- For patients who are unresponsive to conventional oxygen therapy, heated high-flow nasal canula oxygen may be administered
- For patients requiring invasive mechanical ventilation, lung protective ventilation with low tidal volumes (4-8 mL/kg, predicted body weight) and plateau pressure less than 30 mg Hg is recommended

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Wiersinga et al. *JAMA*. 2020;324(8):782-793.

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Acute COVID-19 Treatment

Care and respiratory support

- The threshold for intubation is controversial (many patients have normal work of breathing but severe hypoxemia)
- "Earlier" intubation allows time for a more controlled intubation process (important due to logistical challenges of moving patients to an airborne isolation room and donning PPE)
- However, hypoxemia in the absence of respiratory distress is well tolerated, and patients may do well without mechanical ventilation
- Earlier intubation thresholds may result in treating some patients with mechanical ventilation unnecessarily and exposing them to additional complications

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Wiersinga et al. *JAMA*. 2020;324(8):782-793.

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Papoutsi et al. Crit Care (2021) 25:121
https://doi.org/10.1186/s13054-021-03540-6

Critical Care

RESEARCH Open Access

Effect of timing of intubation on clinical outcomes of critically ill patients with COVID-19: a systematic review and meta-analysis of non-randomized cohort studies

Eleni Papoutsi[1*], Vassilis G. Giannakoulis[1*], Eleni Xourgia[1], Christina Routsi[2], Anastasia Kotanidou[3] and Ilias I. Siempos[2,4]@

- 12 studies, involving 8944 critically ill patients with COVID-19, were included
- No statistically detectable difference on all-cause mortality between patients undergoing early vs late intubation (3981 deaths; 45.4% vs 39.1%; RR 1.07, 95% CI 0.99-1.15, P=0.08)
- Timing of intubation may have no effect on mortality and morbidity of critically ill patients
- These results might justify a wait-and-see approach, which may lead to fewer intubations.
- Relevant guidelines may therefore need to be updated

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Papoutsi et al. *Crit Care*. 2021;25:121.

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Acute COVID-19 Pharmacological Treatment

The following classes of drugs are being evaluated or developed for the management of COVID-19:

- Antivirals (eg, remdesivir, favipiravir)
- Antibodies (eg, convalescent plasma, hyperimmune immunoglobulins)
- Anti-inflammatory agents (dexamethasone, statins)
- Targeted immunomodulatory therapies (eg, tocilizumab, sarilumab, anakinra, ruxolitinib)
- Anticoagulants (eg, heparin)
- Antifibrotics (eg, tyrosine kinase inhibitors)

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Wiersinga et al. *JAMA*. 2020;324(8):782-793.

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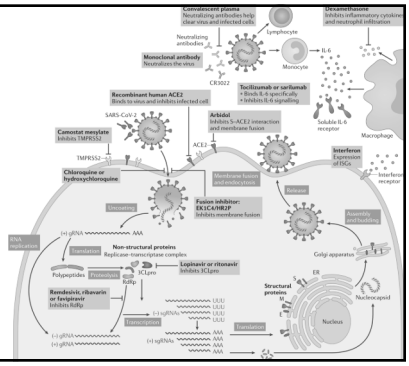
SARS-CoV-2 Targets



Hu et al. *Nat Rev Microbiol*. 2021;19:141-154.

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Acute COVID-19 Pharmacological Treatment

- It is likely that different treatment modalities might have different efficacies at different stages of illness and in different manifestations of disease
- Viral inhibition would be expected to be most effective early in infection
- In hospitalized patients, immunomodulatory agents may be useful to prevent disease progression and anticoagulants may be useful to prevent thromboembolic complications

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Wiersinga et al. *JAMA*. 2020;324(8):782-793.

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Long COVID-19 Terminology and Risk Factors

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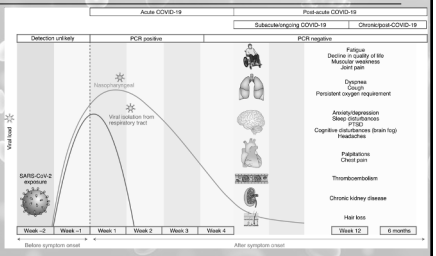
Long COVID-19 Timeline Delineation

- Acute COVID-19 usually lasts until 4 weeks from the onset of symptoms, beyond which replication-competent SARS-CoV-2 has not been isolated
- Post-acute COVID-19 is defined as persistent symptoms and/or delayed or long-term complications beyond 4 weeks from the onset of symptoms



Nalbandian. *Nature Med*. 2021;(27):601-615.

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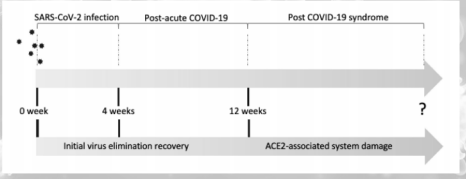
Long COVID-19 Timeline Delineation

UK National Institute for Health and Care Excellence (NICE) Guidelines



Yan et al. *Biomedicines*. 2021;9:966.

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Long COVID-19 Risk Factors

- Age (P=0.01): with ≥50 age group having greatest odds ratio
- Number of pre-existing medical conditions (P=0.003), with a greater number of conditions associated with a greater odds ratio of not returning to "usual health"
  - Hypertension (OR=1.3, P=0.018)
  - Obesity (OR=2.31, P=0.002)
  - A psychiatric condition (OR=2.32, P=0.007)
  - An immunosuppressive condition (OR=2.33, P=0.047)

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Crook et al. *BMJ*. 2021;374:n1648.

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Long COVID-19 Risk Factors

- Patients with a more severe acute phase may transform into the development of more severe symptoms of long COVID
  - >5 symptoms during the initial COVID-19 infection
- Some factors associated with acute COVID-19 do not also increase risk for long COVID-19
  - Long COVID-19 symptoms higher in women compared with men (23.6% vs 20.7%)
  - Age group most affected by long COVID-19 symptoms:
    - 35-49 years (26.8%)
    - Followed by 50-69 years (26.1%)
    - Followed by ≥70 years group (18%)

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Crook et al. *BMJ*. 2021;374:n1648.

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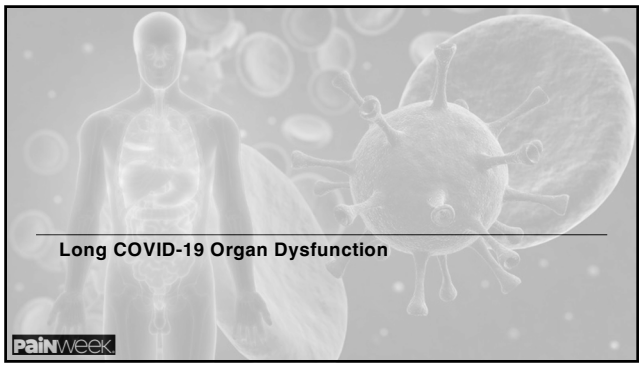

Long COVID-19 Organ Dysfunction

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Long COVID-19 Syndrome Based on Organ System

System	Main Diagnosis	Features	Possible Mechanisms	Prognosis
Respiratory system	Acute respiratory distress syndrome (ARDS)	Extensive bilateral diffuse alveolar damage with cellular fibromyxoid exudates; desquamation of pneumocytes and hyaline membrane formations; diffusion impairment and pulmonary fibrosis	SARS-CoV-2 spike S1 domain protein binding to ACE2 receptor; post-ARDS fibrosis with diffuse alveolar damage	Pulmonary function deficit 6 months after infection; extensive diffuse impairment; long-term in-situ thrombosis

ARDS

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Yan et al. *Biomedicines*. 2021;9:966.

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Long COVID-19 Syndrome: Respiratory

Symptom persistence* (n=276)	
Breathlessness Oxygen alone/CPAP/IV (%)	54.8/63.3/57.7
Cough Oxygen alone/CPAP/IV (%)	32.2/36.7/46.2
Fatigue Oxygen alone/CPAP/IV (%)	67.3/73.3/76.9
Poor sleep quality Oxygen alone/CPAP/IV (%)	61.1/93.3/76.9

Data reported as mean (±SD), median (IQR) or % as appropriate.
*Persistence defined as symptom score ≥1.
IV, invasive ventilation.

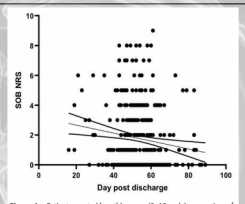

Figure 1 Patient reported breathlessness (0–10 scale) versus time of follow-up from hospital discharge. Each circle represents an individual patient at follow-up, with interpolation line and 90% CI. A higher score represents more severe breathlessness.

ARDS

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Mandal et al. *Thorax*. Epub ahead of print. doi:10.1136/ thoraxjnl-2020-215818.

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Long COVID-19 Syndrome: Respiratory

Thoracic Imaging Tools	Image Findings in COVID-19 Survivors
Chest X-Ray (CXR)	(1) CRX does not correlate with abnormal CT findings or prolonged functional disability in infected patients; (2) Changes in CXR findings are associated with recovery duration and severity of COVID-19; and (3) The overall effectiveness of CRX is uncertain
CT Scan	(1) Abnormal CT findings were detected in 71% of COVID-19 survivors; unresolved lung tissue pathology presents mainly in the form of residual GGO; and (2) CT findings show a significant correlation with disease severity
Lung Ultrasound (LUS)	(1) Findings correlate with chest CT, accurately assess resolution of residual lung tissue abnormalities; and (2) Findings correlate with duration of COVID-19 symptoms in COVID-19 survivors, can be used in home settings
MRI	(1) Used to assess cardiac involvement in patients recovered from COVID-19; (2) 58% of recovered patients had abnormal MRI findings, including myocardial edema (54%) and late gadolinium enhancement (31%); and (3) Fibrosis and compromised right ventricle function have also been found in patients who have recovered from COVID-19

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Alqahtani et al. *World J Radiol*. 2021 Jun 28;13(6):149-156.

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Long COVID-19 Syndrome Based on Organ System

System	Main Diagnosis	Features	Possible Mechanisms	Prognosis
Cardiovascular system	Endothelitis; microthrombosis, capillary damage; hypercoagulability; microangiopathy; thromboembolism; myocarditis; atrial fibrillation; supraventricular tachycardia	Increased target-to-blood pool ratio; capillary disturbance; impaired oxygen diffusion	Cytokine storm and macrophage activating syndrome-caused endothelial dysfunction	Majority (81%) of COVID-19 myocarditis patients survived acute episode; ongoing subclinical myocarditis may evolve into myocardial dysfunction and sudden cardiac death

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Yan et al. *Biomedicines*. 2021;9:966.

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Long COVID-19 Syndrome Based on Organ System

System	Main Diagnosis	Features	Possible Mechanisms	Prognosis
Hematological system	Thromboembolism	Elevated convalescent D dimer and C-reactive protein levels; persistently increased biomarkers of inflammation	N/A	Prognostic biomarkers for monitoring clinical progression of long COVID-19 patients need to be investigated

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Yan et al. *Biomedicines*. 2021;9:966.

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Long COVID-19 Syndrome Based on Organ System

System	Main Diagnosis	Features	Possible Mechanisms	Prognosis
Urinary system	Acute kidney injury; renal failure	Declined glomerular filtration rate (eGFR); kidney infarction	High abundance of ACE2 expression in kidneys	Significant risks of mortality and morbidity

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Yan et al. *Biomedicines*. 2021;9:966.

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Long COVID-19 Syndrome Based on Organ System

System	Main Diagnosis	Features	Possible Mechanisms	Prognosis
Digestive system	Gastrointestinal impairment and dysfunction; hepatic and cholestatic liver injury; pancreatic injury	Bowel diffuse damage; Enterocyte desquamation, edema, small bowel dilation, lymphocytes infiltration and mesenteric node hemorrhage and necrosis	Rich in ACE2 and furin expression; fecal-oral transmission; plasma cell and lymphocytic infiltration into lamina propria of intestinal tissues	Liver enzymes remain persistently elevated 14 days after discharge, while liver function in majority of survivors normalized 2 months after hospital discharge

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Yan et al. *Biomedicines*. 2021;9:966.

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Long COVID-19 Syndrome Based on Organ System

System	Main Diagnosis	Features	Possible Mechanisms	Prognosis
Endocrine system	Hyperglycemia without diabetes mellitus; new-onset diabetic mellitus; starvation ketoacidosis	High blood glucose level; impaired glucose metabolism	Intruding pancreatic β-islet cells, triggering autoimmune responses because of the exposure of the antigen from damaged islet cells	Possible long-term treatment of diabetes mellitus needed

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Yan et al. *Biomedicines*. 2021;9:966.

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Long COVID-19 Syndrome Based on Organ System

System	Main Diagnosis	Features	Possible Mechanisms	Prognosis
Neurological system	Mood changes; cognitive difficulties; headache; fatigue; dizziness; memory loss; confusion; and attention deficit	Hypoxic injury; microbleeds; neuronal inflammation	Blood vessel damage, impaired oxygen supply, viral infiltration into the central nervous system and inflammatory cytokine-mediated cellular damage; indirect T-cell and microglia damage in the brain (similar to strokes, neuroinflammatory diseases)	Over 40% survivors without prior psychiatric conditions lived with depression within 90 days of recovery from severe COVID-19 associated respiratory failure, while 70% of them did not receive treatment for depression

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Yan et al. *Biomedicines*. 2021;9:966.

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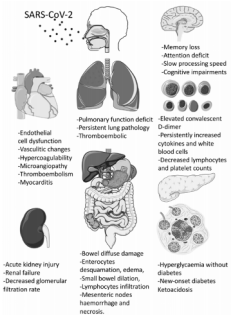

Yan et al. *Biomedicines*. 2021;9:966.

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Articles

1-year outcomes in hospital survivors with COVID-19: a longitudinal cohort study

Lixue Huang*, Qun Yao*, Xiaoying Gu*, Qiongya Wang*, Lili Ren*, Yeming Wang*, Ping Hu*, Li Guo*, Min Liu, Jiuyong Xu, Xueyang Zhang, Yali Qiu, Yongxing Fan, Xia Li, Caihong Li, Ting Yu, Jason Xia, Ming Wei, Li Chen, Yanqing Li, Fan Xiao, Dan Liu, Jianwei Wang†, Xiangyang Wang†, Bin Cao†

Lancet 2021; 398: 747–58
See Editorial page 725
*These authors contributed

Summary

Background The full range of long-term health consequences of COVID-19 in patients who are discharged from hospital is largely unclear. The aim of our study was to comprehensively compare consequences between 6 months and 12 months after symptom onset among hospital survivors with COVID-19.

- Ambidirectional cohort study of COVID-19 survivors
- At 6-month and 12-month follow-up visits, survivors were interviewed with questionnaires on symptoms and health-related quality of life (HRQoL); received physical examination, 6-min walking test, and laboratory tests
- Non-COVID-19 controls matched for age, sex, and comorbidities were interviewed and completed questionnaires to assess prevalent symptoms and HRQoL
- Primary outcomes were symptoms, modified British Medical Research Council (mMRC) score, HRQoL, and distance walked in 6 min (6MWD)

Huang et al. *Lancet*. 2021;398:747-758.

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	Total (n=1276)			Scale 3: not requiring supplemental oxygen (n=318)			Scale 4: requiring supplemental oxygen (n=864)			Scale 5-6: requiring HFNC, NIV, or IMV (n=94)		
	6 month	12 month	p value	6 month	12 month	p value	6 month	12 month	p value	6 month	12 month	p value
Sequelae symptom												
Any one of the following symptoms	831/1227 (68%)	620/1272 (49%)	<0·0001	211/307 (69%)	151 (47%)	<0·0001	543/828 (66%)	420/860 (49%)	<0·0001	77/92 (84%)	49 (57%)	<0·0001
1. Fatigue or muscle weakness	636/1230 (52%)	255/1272 (20%)	<0·0001	158/307 (51%)	65 (20%)	<0·0001	410/831 (49%)	169/860 (20%)	<0·0001	68/92 (74%)	21 (22%)	<0·0001
2. Sleep difficulties	335/1230 (27%)	215/1272 (17%)	<0·0001	84/307 (27%)	49 (15%)	<0·0001	217/831 (26%)	152/860 (18%)	<0·0001	34/92 (37%)	14 (15%)	0·0002
3. Hair loss	268/1230 (22%)	135/1272 (11%)	<0·0001	68/307 (22%)	29 (9%)	<0·0001	177/831 (21%)	98/860 (11%)	<0·0001	23/92 (25%)	8 (9%)	0·0003
Smell disorder	135/1230 (11%)	57/1272 (4%)	<0·0001	35/307 (11%)	17 (5%)	0·0030	86/831 (10%)	34/860 (4%)	<0·0001	14/92 (15%)	6 (6%)	0·033
Palpitations	118/1230 (10%)	112/1272 (9%)	0·88	32/307 (10%)	23 (7%)	0·12	72/831 (9%)	87/860 (10%)	0·17	14/92 (15%)	7 (7%)	0·09
4. Joint pain	132/1225 (11%)	157/1272 (12%)	0·13	42/308 (14%)	37 (12%)	0·49	74/826 (9%)	103/860 (12%)	0·018	16/91 (18%)	17 (18%)	1·00
Decreased appetite	97/1230 (8%)	37/1272 (3%)	<0·0001	28/307 (9%)	6 (2%)	<0·0001	58/831 (7%)	27/860 (3%)	0·0003	11/92 (12%)	4 (4%)	0·05
Taste disorder	89/1230 (7%)	37/1272 (3%)	<0·0001	22/307 (7%)	6 (2%)	0·0007	59/831 (7%)	31/860 (4%)	0·0007	8/92 (9%)	0	0·0047
Dizziness	69/1230 (6%)	65/1272 (5%)	0·56	22/307 (7%)	16 (5%)	0·24	41/831 (5%)	40/860 (5%)	0·71	6/92 (7%)	9 (10%)	0·41
Diarrhoea or vomiting	17/1229 (1%)	11/1272 (1%)	0·26	8/307 (3%)	5 (2%)	0·41	9/830 (1%)	4/860 (0%)	0·17	0/92 (0%)	2 (2%)	0·16
Chest pain	57/1225 (5%)	92/1272 (7%)	0·0023	17/308 (6%)	25 (8%)	0·14	36/826 (4%)	63/860 (7%)	0·0055	4/91 (4%)	4 (4%)	1·00
Sore throat or difficult to swallow	47/1230 (4%)	44/1272 (3%)	0·57	19/307 (6%)	11 (3%)	0·08	24/831 (3%)	29/860 (3%)	0·55	4/92 (4%)	4 (4%)	1·00
Skin rash	39/1230 (3%)	55/1272 (4%)	0·10	12/307 (4%)	15 (5%)	0·53	23/831 (3%)	38/860 (4%)	0·05	4/92 (4%)	2 (2%)	0·41
Myalgia	33/1225 (3%)	54/1272 (4%)	0·013	10/308 (3%)	12 (4%)	0·64	20/826 (2%)	36/860 (4%)	0·018	3/91 (3%)	6 (6%)	0·26
Headache	25/1225 (2%)	61/1272 (5%)	0·0001	7/308 (2%)	16 (5%)	0·050	15/826 (2%)	40/860 (5%)	0·0010	3/91 (3%)	5 (5%)	0·48

Huang et al. *Lancet*. 2021;398:747-758.

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	Total (n=1276)			Scale 3: not requiring supplemental oxygen (n=318)			Scale 4: requiring supplemental oxygen (n=864)			Scale 5–6: requiring HFNC, NIV, or IMV (n=94)		
	6 month	12 month	p value	6 month	12 month	p value	6 month	12 month	p value	6 month	12 month	p value
EQ-5D-5L questionnaire*												
Mobility: problems with walking around	76/1191 (6%)	115/1271 (9%)	0·0058	17/310 (5%)	24/317 (8%)	0·37	45/796 (6%)	83/860 (10%)	0·0004	14/85 (16%)	8 (9%)	0·05
Personal care: problems with washing or dishing	9/1191 (1%)	20/1271 (2%)	0·033	0/310 (0%)	3/317 (1%)	0·08	8/796 (1%)	13/860 (2%)	0·20	1/85 (1%)	4 (4%)	0·32
Usual activity: problems with usual activity	18/1182 (2%)	18/1271 (1%)	0·86	3/309 (1%)	2/317 (1%)	0·56	11/789 (1%)	13/860 (2%)	0·68	4/84 (5%)	3 (3%)	0·32
Pain or discomfort	321/1186 (27%)	371/1271 (29%)	0·13	84/307 (27%)	84/317 (26%)	0·76	201/794 (25%)	255/860 (30%)	0·020	36/85 (42%)	32 (34%)	0·37
Anxiety or depression	274/1187 (23%)	331/1271 (26%)	0·015	74/309 (24%)	78/317 (25%)	0·83	170/794 (21%)	226/860 (26%)	0·0013	30/84 (36%)	27 (29%)	0·32
Quality of life†	80·0 (75·0–90·0)	80·0 (70·0–90·0)	0·044	80·0 (70·0–90·0)	80·0 (70·0–90·0)	0·91	80·0 (75·0–90·0)	80·0 (75·0–90·0)	0·0058	80·0 (70·0–85·0)	80·0 (70·0–85·0)	0·38

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Huang et al. *Lancet*. 2021;398:747-758.

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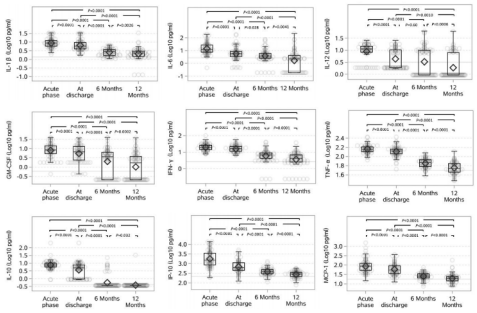

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Huang et al. *Lancet*. 2021;398:747-758.

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Long COVID-19 Treatment

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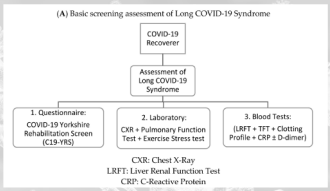
Recommended Rehabilitation Model for Long COVID-19

UK National Institute for Health and Care Excellence (NICE) Guidelines



Yan et al. *Biomedicines*. 2021;9:966.

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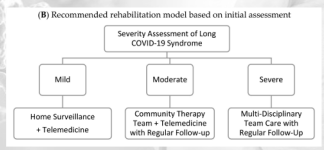
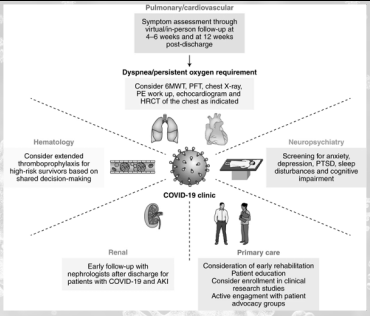
Recommended Rehabilitation Model for Long COVID-19



Yan et al. *Biomedicines*. 2021;9:966.

47



Nalbandian et al. *Nat Med*. 2021;27:601-615.

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Long COVID-19: Pulmonary Symptom Treatment

- Recognized nonpharmacological strategies for managing dyspnea include breathing exercises, pulmonary rehabilitation, and maintaining optimal body positioning for postural relief
- Patients with pulmonary fibrosis resulting from COVID-19 should be managed in accordance with NICE guidelines on idiopathic pulmonary fibrosis
  - –Antifibrotic therapies may be advantageous

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Crook et al. *BMJ*. 2021;374:n1648.

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Long COVID-19: Cardiovascular Symptom Treatment

- NICE guidelines recommend β blockers for several cardiac complaints, including angina, cardiac arrhythmias, and acute coronary syndromes, therefore, β blockers may be useful in the treatment of cardiovascular manifestations of long COVID-19
- Myocarditis may resolve naturally over time; however, supportive and/or immunomodulating therapy may improve recovery, as a systematic review describes
- A review has also suggested that anticoagulants may be used to reduce the risks associated with hypercoagulability

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Crook et al. *BMJ*. 2021;374:n1648.

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Long COVID-19: Cognitive Impairment Treatment

- Cognitive impairment in long covid, sometimes called “brain fog,” has been compared to “chemobrain”
- Mayo Clinic recommendations suggest strategies to manage chemobrain including repeating exercises, tracking what influences deficits, and using stress relief and coping strategies
- Medications including methylphenidate, donepezil, modafinil, and memantine may be considered
- Luteolin, a natural flavonoid, may alleviate cognitive impairment by inhibiting mast cell and microglia activation, but clinical trials are required

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Repurposing Drugs for COVID-19 Treatment

- Antihistamines have been implicated as a possible treatment
  - –A study that employed cellular experiments suggesting that histamine-1 antagonists may be able to reduce the COVID-19 infection rate by inhibiting SARS-CoV-2 from entering ACE2 expressing cells
  - –Systematic reviews and molecular studies have suggested that histamine-1 and histamine-2 antagonists are viable candidates for further clinical trials in COVID-19
  - –It remains to be seen whether antihistamines have potential for treating long COVID-19

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Repurposing Drugs for COVID-19 Treatment

- Antidepressants have been proposed to reduce the effects of long COVID-19
  - –Antidepressant use has been associated with reduced risk of intubation or death in acute COVID-19
  - – A meta-analysis of antidepressant drug treatment for MDD has shown that use of antidepressants, including SNRIs and SSRIs, results in a reduction in peripheral inflammatory markers

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Crook et al. *BMJ*. 2021;374:n1648.

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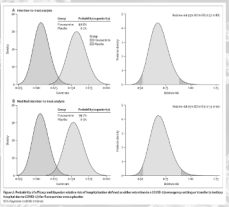
Repurposing Drugs for COVID-19 Treatment

Specifically, fluvoxamine (100 mg twice daily for 10 days) in high-risk outpatients with early diagnosed COVID-19 reduced the need for hospitalization



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ob Health. 2022; 10: e42-51 published online October 27, 2021: doi.org/10.1016/ S2214-

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Repurposing Drugs for COVID-19 Treatment

- Low dose naltrexone (4.5 mg) has been used in centralized pain states to reduce microglial cell activation and inflammation in conditions such as fibromyalgia and complex regional pain syndrome
- Studies have yet to be performed specifically to treat long COVID-19

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Crook et al. *BMJ*. 2021;374:n1648.

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Emerging Long COVID-19 Treatments

- Clinical trials exploring the efficacy of hyperbaric oxygen (NCT04842448), montelukast (NCT04695704), and deupirfenidone (NCT04652518) to treat respiratory conditions in long COVID-19 are ongoing
- A trial of breathing exercises and singing is also underway to assess their utility in improving breathing abnormalities in patients with long COVID-19 (NCT04810065)
- A trial to assess the effectiveness of an 8 week exercise program in patients with long COVID-19 and fatigue is ongoing (NCT04841759).

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Crook et al. *BMJ*. 2021;374:n1648.

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Emerging Long COVID-19 Treatments

- Vitamin C supplementation may prove useful in treating fatigue in long COVID-19 patients, with a systematic review concluding high dose intravenous vitamin C could be a beneficial treatment option
  - LOVIT-COVID (NCT04401150) is an ongoing clinical trial aimed at assessing the effects of high dose IV vitamin C on hospitalized patients with COVID-19
- 2 trials examining the effects of nicotinamide riboside, a dietary supplement, are ongoing (NCT04809974, NCT04604704) with the expectation that the molecule reduces cognitive symptoms and fatigue by modulating the proinflammatory response
- A clinical trial is currently ongoing assessing the effectiveness of a probiotic supplement to normalize the composition of the gut microbiome and reduce inflammation in long COVID-19 (NCT04813718)

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Crook et al. *BMJ*. 2021;374:n1648.

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Conclusions

- For many patients, full recovery from COVID-19 will take >1 year, raising important issues for health services and research
- Only 0.4% of patients with COVID-19 said that they had participated in a professional rehabilitation program
  - –The reason for such low use of rehabilitation services is unclear, but poor recognition of long COVID and lack of clear referral pathways have been common problems worldwide

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Lancet. *Lancet.* 2021 Aug 28;398(10302):725.

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Conclusions

- The effect of long COVID on mental health warrants further and longer-term investigation
  - –Proportion of COVID-19 survivors who had anxiety or depression slightly increased between 6 months and 12 months
- Persistent long COVID-19 symptoms loom over any post COVID-19 public health plan
- Uncertainty if insurers will cover rehabilitation for these patients
- Concerns for disparities and inequities associated with service access

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Lancet. *Lancet.* 2021 Aug 28;398(10302):725.

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Apocalypse Now. . . Or Later?

Michael Bottros, MD

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