PainWeek

Apocalypse Now…or Later?
Chronic Pain After COVID-19

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Title & Affiliation

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Disclosure

- None

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Learning Objectives

- Describe the reported pathophysiology associated with COVID-19
- List the potential risk factors for the development of long COVID-19
- Describe the potential treatment options for long COVID-19

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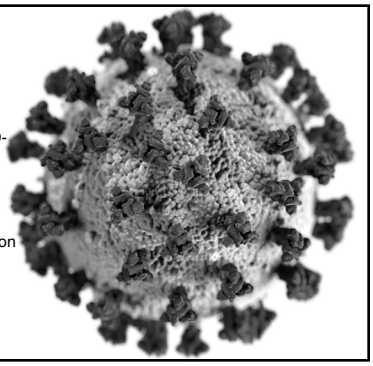
Outline

- Introduction & 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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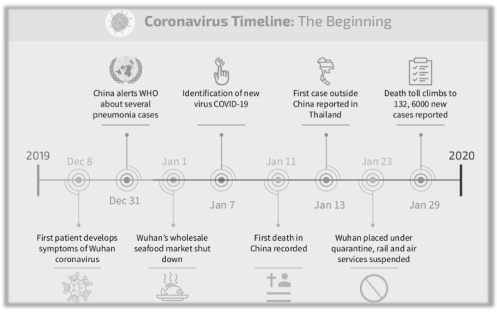

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https://www.weforum.org/agenda/2020/04/coronavirus-spread-covid19-pandemic-timeline-milestones

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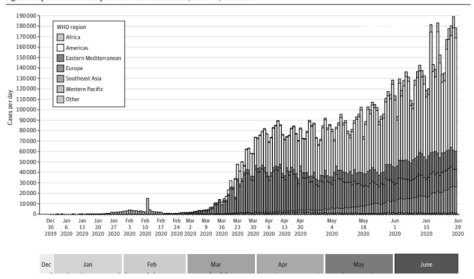
Figure 1. Key Events in the Early Coronavirus Disease 2019 (COVID-19) Pandemic



Wiersinga WJ, et al. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19) A Review. JAMA. 2020;324(8):782-793.

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Pathophysiology

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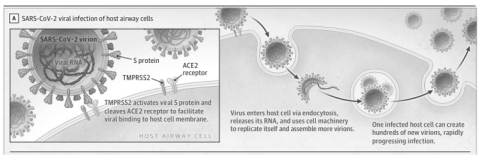
Pathophysiology



- 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.

Wiersinga WJ, et al. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19) A Review. JAMA. 2020;324(8):782-793.

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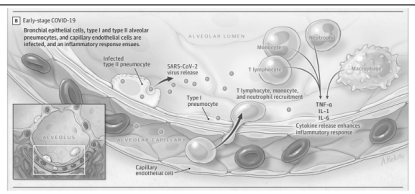
Pathophysiology



- 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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Wiersinga WJ, et al. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19) A Review. JAMA. 2020;324(8):782-793.

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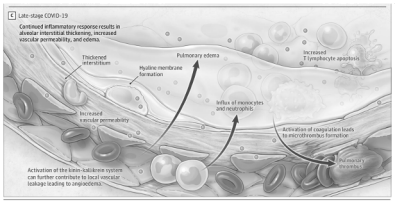
Pathophysiology



- 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 WJ, et al. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19) A Review. JAMA. 2020;324(8):782-793.

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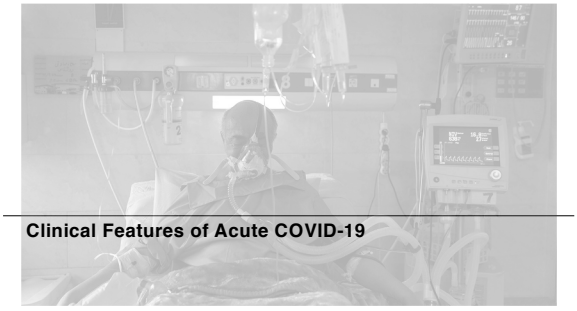

Clinical Features of Acute COVID-19

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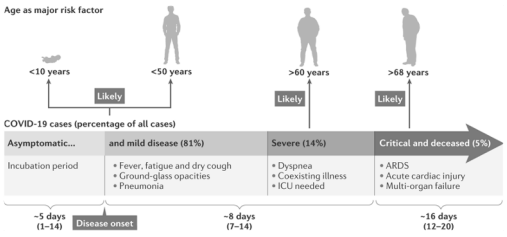
Clinical Features of Acute COVID-19



Hu, B., Guo, H., Zhou, P. et al. Characteristics of SARS-CoV-2 and COVID-19. Nat Rev Microbiol 19, 141–154 (2021).

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Multisystem Inflammatory Syndrome in Children (MIS-C)

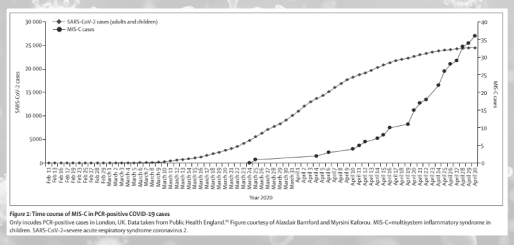

Figure 2: Time course of MIS-C in PCR-positive COVID-19 cases
Only incudes PCR-positive cases in London, UK. Data taken from Public Health England.[4] Figure courtesy of Alasdair Bamford and Myrsini Kaforou. MIS-C=multisystem inflammatory syndrome in children. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

Jiang L, et al. COVID-19 and multisystem inflammatory syndrome in children and adolescents. Lancet Infect Dis. 2020 Nov;20(11):e276-e288.

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Multisystem Inflammatory Syndrome in Children (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	214 (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)

Ahmed M, et al. Multisystem inflammatory syndrome in children: A systematic review. / EClinicalMedicine 26 (2020) 100527.

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Acute COVID-19 Risk Factors

- Older age
- Male sex
- Non-white ethnicity
- Pre-existing disability
- Pre-existing comorbidities
  - Obesity
  - Cardiovascular disease
  - Respiratory disease
  - Hypertension

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Crook H., et al. Long covid—mechanisms, risk factors, and management. BMJ 2021;374:n1648.

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Acute COVID-19 Treatment

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Acute COVID-19 Treatment

- Supportive 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 WJ, et al. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19) A Review. JAMA. 2020;324(8):782-793.

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Acute COVID-19 Treatment

- Supportive 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 pts 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 WJ, et al. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19) A Review. 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[1], Anastasia Kotanidou[1] and Ilias I. Siempos[2,3*]

- 12 studies, involving 8944 critically ill patients with COVID-19, were included.
- No statistically detectable difference on all-cause mortality between pts undergoing early versus late intubation (3981 deaths; 45.4% versus 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 E, et al. 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. 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 WJ, et al. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19) A Review. JAMA. 2020;324(8):782-793.

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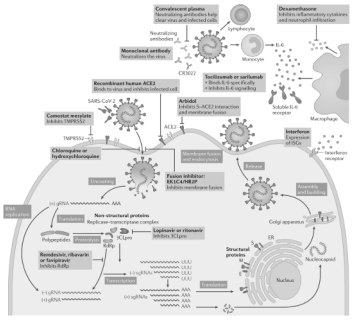
SARS-CoV-2 Targets



Hu, B., Guo, H., Zhou, P. et al. Characteristics of SARS-CoV-2 and COVID-19. Nat Rev Microbiol 19, 141–154 (2021).

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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.

Wiersinga WJ, et al. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19) A Review. JAMA. 2020;324(8):782-793.

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Long COVID-19 Terminology & Risk Factors

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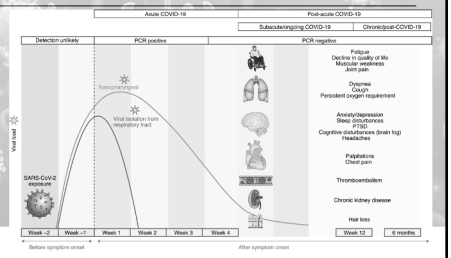
Long COVID-19 Timeline Delineation

- 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 A., et al. Post-acute COVID-19 syndrome. Nature Medicine 2021; (27): 601–615.

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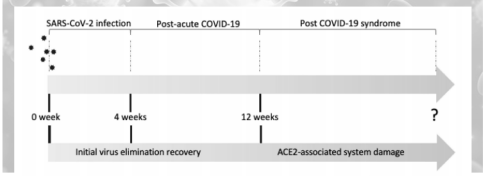
Long COVID-19 Timeline Delineation

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



Yan, Z.; Yang, M.; Lai, C.-L. Long COVID-19 Syndrome: A Comprehensive Review of Its Effect on Various Organ Systems and Recommendation on Rehabilitation Plans. Biomedicines 2021, 9, 966

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Long COVID-19 Risk Factors

- Age (P=0.01)
  - with the ≥50 years age group having the 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)

Crook H., et al. Long covid—mechanisms, risk factors, and management. 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.
  - –more than five 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% versus 20.7%).
  - –Age group most affected by long COVID-19 symptoms is:
    - 35-49 years (26.8%)
    - followed by 50-69 years (26.1%)
    - followed by ≥70 years group (18%).

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Crook H., et al. Long covid—mechanisms, risk factors, and management. BMJ 2021;374:n1648.

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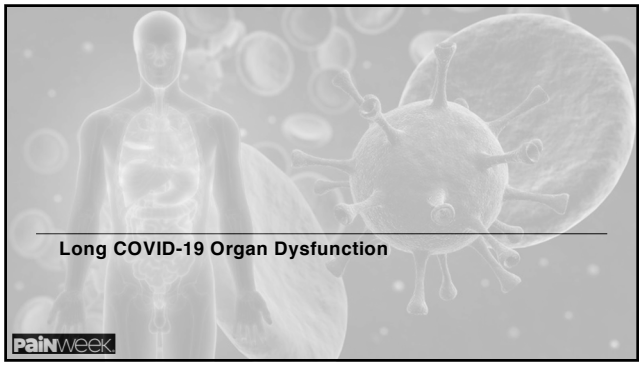

Long COVID-19 Organ Dysfunction

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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, Z.; Yang, M.; Lai, C.-L. Long COVID-19 Syndrome: A Comprehensive Review of Its Effect on Various Organ Systems and Recommendation on Rehabilitation Plans. 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.

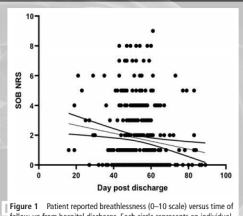

Figure 1 Patient reported breathlessness (0–10 scale) versus time of follow-up from hospital discharge. Each circle represents an individual patient at follow-up, with interpolation line and 90% CI. A higher score represents more severe breathlessness.

Mandal S, Barnett J, Brill SE, 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) LUS findings correlate with chest CT and accurately assess the resolution of residual lung tissue abnormalities; and (2) LUS findings correlate with the duration of COVID-19 symptoms in COVID-19 survivors and can be used in home settings
MRI	(1) This is used to assess cardiac involvement in patients recovered from COVID-19; (2) 58% of recovered patients had abnormal MRI findings, including myocardial oedema (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

Alqahtani JS, Alghamdi SM, Aldhahir AM, Althobiani M, Raya RP, Oyelade T. Thoracic imaging outcomes in COVID-19 survivors. 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; micro-thrombosis, 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 the COVID-19 myocarditis patients survived the acute episode; ongoing subclinical myocarditis may evolve into myocardial dysfunction and sudden cardiac death.

Yan, Z.; Yang, M.; Lai, C.-L. Long COVID-19 Syndrome: A Comprehensive Review of Its Effect on Various Organ Systems and Recommendation on Rehabilitation Plans. 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

Yan, Z.; Yang, M.; Lai, C.-L. Long COVID-19 Syndrome: A Comprehensive Review of Its Effect on Various Organ Systems and Recommendation on Rehabilitation Plans. 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

Yan, Z.; Yang, M.; Lai, C.-L. Long COVID-19 Syndrome: A Comprehensive Review of Its Effect on Various Organ Systems and Recommendation on Rehabilitation Plans. 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.

Yan, Z.; Yang, M.; Lai, C.-L. Long COVID-19 Syndrome: A Comprehensive Review of Its Effect on Various Organ Systems and Recommendation on Rehabilitation Plans. 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, Z.; Yang, M.; Lai, C.-L. Long COVID-19 Syndrome: A Comprehensive Review of Its Effect on Various Organ Systems and Recommendation on Rehabilitation Plans. 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 and 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, Z.; Yang, M.; Lai, C.-L. Long COVID-19 Syndrome: A Comprehensive Review of Its Effect on Various Organ Systems and Recommendation on Rehabilitation Plans. Biomedicines 2021, 9, 966

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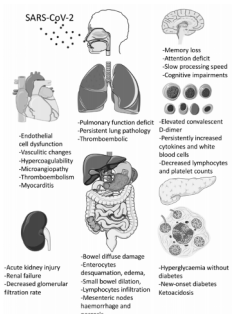

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1-year outcomes in hospital survivors with COVID-19: a longitudinal cohort study

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

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.

Lancet 2021; 398: 747–58

See Editorial page 771

*These authors contributed

- Ambidirectional cohort study of COVID-19 survivors.
- At 6-month and 12-month follow-up visit, survivors were interviewed with questionnaires on symptoms and health-related quality of life (HRQoL), and received a physical examination, a 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).

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Huang L., et al. 1-year outcomes in hospital survivors with COVID-19: a longitudinal cohort study. Lancet 2021; 398: 747–58.

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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%)	619/1272 (49%)	<0·0001	211/307 (69%)	151 (47%)	<0·0001	543/828 (66%)	420/860 (49%)	<0·0001	77/92 (84%)	49 (52%)	<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%)	117/1272 (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%)	152/1272 (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%)	22/860 (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

PainWeek

Huang L., et al. 1-year outcomes in hospital survivors with COVID-19: a longitudinal cohort study. Lancet 2021; 398: 747–58.

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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%)	0·15
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

PainWeek

Huang L., et al. 1-year outcomes in hospital survivors with COVID-19: a longitudinal cohort study. Lancet 2021; 398: 747–58.

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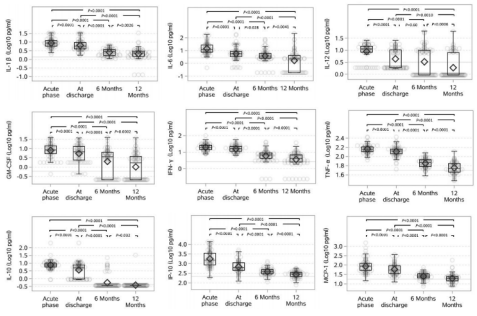

Huang L., et al. 1-year outcomes in hospital survivors with COVID-19: a longitudinal cohort study. Lancet 2021; 398: 747–58.

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Long COVID-19 Treatment

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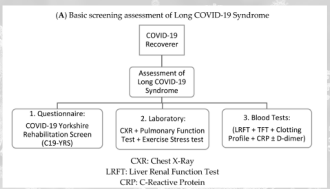
Recommended Rehabilitation Model for Long COVID-19

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



Yan, Z.; Yang, M.; Lai, C.-L. Long COVID-19 Syndrome: A Comprehensive Review of Its Effect on Various Organ Systems and Recommendation on Rehabilitation Plans. Biomedicines 2021, 9, 966

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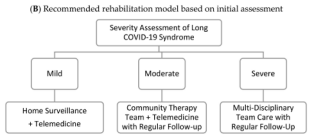
Recommended Rehabilitation Model for Long COVID-19



Yan, Z.; Yang, M.; Lai, C.-L. Long COVID-19 Syndrome: A Comprehensive Review of Its Effect on Various Organ Systems and Recommendation on Rehabilitation Plans. Biomedicines 2021, 9, 966

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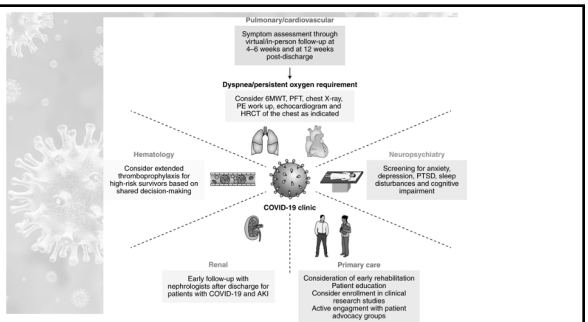

Nalbandian A., et al. Post-acute COVID-19 syndrome. Nature Medicine 2021; (27): 601–615.

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Long COVID-19 Pulmonary Symptom Treatment

- Recognized non-pharmacological 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.

Crook H., et al. Long covid—mechanisms, risk factors, and management. 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.

PAINWEEK

Crook H., et al. Long covid—mechanisms, risk factors, and management. 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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Crook H., et al. Long covid—mechanisms, risk factors, and management. BMJ 2021;374:n1648.

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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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Crook H., et al. Long covid—mechanisms, risk factors, and management. BMJ 2021;374:n1648.

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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 H., et al. Long covid—mechanisms, risk factors, and management. BMJ 2021;374:n1648.

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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 H., et al. Long covid—mechanisms, risk factors, and management. 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 under way 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 H., et al. Long covid—mechanisms, risk factors, and management. 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 pts, with a systematic review concluding that 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.
- Two 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 pro-inflammatory 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 H., et al. Long covid—mechanisms, risk factors, and management. BMJ 2021;374:n1648.

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Conclusions

- For many patients, full recovery from COVID-19 will take more than 1 year and raises 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.

painweek

The Lancet. Understanding long COVID: a modern medical challenge. 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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The Lancet. Understanding long COVID: a modern medical challenge. Lancet. 2021 Aug 28;398(10302):725.

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