COVID-19 Clinical management: Living guidance, 25 January 2021

Web annex

GRADE recommendations – additional information

Chapter 10. Management of moderate COVID-19: pneumonia treatment

Review

Shah S, Majmudar K, Stein A, et al. Novel Use of Home Pulse Oximetry Monitoring in COVID-19 Patients Discharged From the Emergency Department Identifies Need for Hospitalization [published online ahead of print, 2020 Jun 17]. Acad Emerg Med. 2020;10.1111/acem.14053.
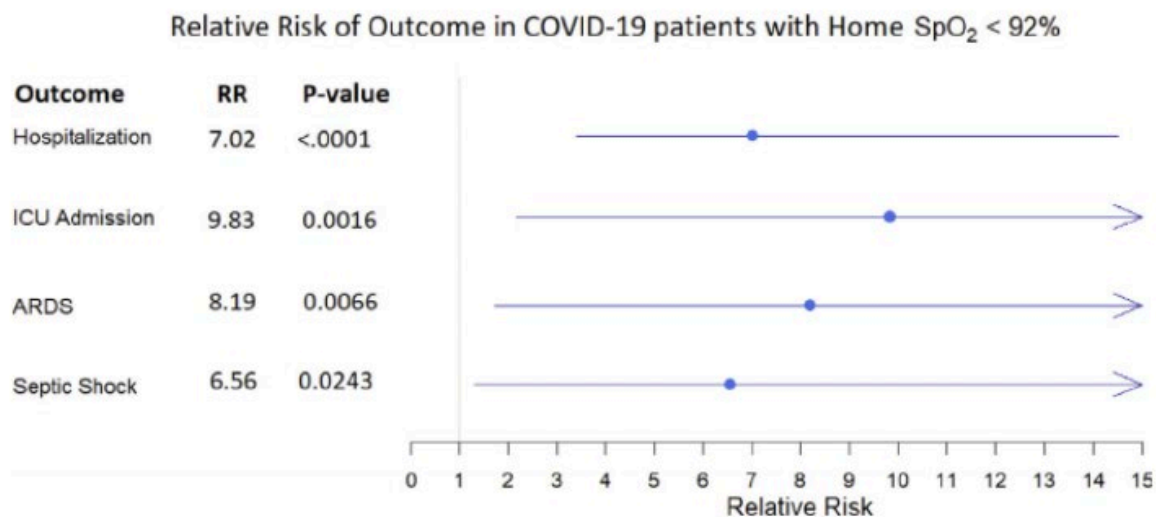

Figure 1. Relative risk (RR) of hospitalization, ICU admission, development of ARDS, and development of septic shock in COVID-19 patients with home SpO_2 < 92%.

Search strategy

We conducted systematic searching of the WHO Global COVID-19 literature database (https://search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/) on 2 December 2020. The database includes both peer-reviewed publications and preprints. The search strategy (see **below**) was developed and conducted by Tomas Allen, WHO Information Specialist. One reviewer (HH) independently screened records to identify eligible studies.

Summary of studies table

Concept	Search string				Results (2 December 2020)
#1- Pulse Oximetry	Oximeter* OR pulse OR "saturation oxygen blood"~5				312

Author	Title Journal Date	Study design	Population Setting	Intervention	Outcomes
Shah, 2020	Home pulse oximetry in COVID-19 patients discharged from the emergency department *Academic Emergency Medicine* 17 June 2020	Single arm prospective cohort study	Enrolled 209 patients with suspected COVID-19 at a single hospital in Chicago, USA; 79 patients tested positive for COVID-19 and 77 were included (2 withdrew)	Patients were given home pulse oximeter and instructed to record their SpO_2 every 8 hours and instructed to return to ED if sustained home $SpO_2 < 92\%$	-Subsequent hospitalization occurred in 22/77 (29%) -19/77 (25%) of patients had home $SpO_2 < 92\%$ -58/77 (75%) of patients had home $SpO_2 \geq 92\%$ Patients with home $SpO_2 < 92\%$: -17/19 came back to ED, and 16/17 were hospitalized -8/16 (50%) did not have worsening symptoms and only returned to ED for incidental finding of low home SpO_2 Patients with home $SpO_2 \geq 92\%$ -11/58 (19%) of patients returned to the ED where 5/11 were discharged and 6/11 were hospitalized

Author	Title Journal Date	Study design	Population Setting	Intervention	Outcomes
					-Resting home SpO$_2$ < 92% was associated with an increased likelihood of hospitalization compared to SpO$_2$ ≥ 92%: RR 7.0; 95% CI 3.4–14.5 -Resting home SpO$_2$ < 92% was associated with increased risk of ICU admission (RR = 9.8; 95% CI = 2.2–44.6, p < 0.002), ARDS (RR = 8.2; 95% CI = 1.7–38.7, p < 0.007), and septic shock (RR = 6.6; 95% CI = 1.3–32.9, p = 0.02). Resting home SpO$_2$ < 92% was not associated with increased mortality (p = 0.5). -16/49 (33%) of non-hospitalized patients stated they would have returned to the ED if they did not have a pulse oximeter to reassure them at home.
Kyriakides, 2020	Analysis of an ambulatory care pathway for patients with COVID-19 utilising remote pulse oximetry ABSTRACT ONLY *BMJ Emergency Medicine Journal* 23 November 2020	Single arm prospective cohort study	20 patients with confirmed or suspected COVID-19 discharged from London ED	Home pulse oximetry (3x/day for 7 days) with telephone follow up	-17/20 (85%) patients discharged with home pulse oximetry + telephone follow-up avoided hospitalization -3/20 (15%) were reassessed and admitted to hospital
Vinton, 2020	Interactive home monitoring of ED patients with suspected or confirmed COVID-19 ABSTRACT ONLY *Annals of Emergency Medicine* 1 October 2020	Single arm prospective cohort study	52 patients with confirmed or suspected COVID-19 who had risk factors for severe disease Patients would have required admission without remote monitoring	Interactive Home Monitoring (IHM) program, which included a pulse oximeter (also blood pressure cuff, thermometer, iPad, and 24-hr assistance) Patients were remotely managed by advanced practitioner providers who addressed changes in vital signs and escalated care when appropriate	-6/52 (12%) of patients returned to hospital and required admission -3/6 admitted for hypoxia 0/6 required intubation, non-invasive positive pressure ventilation, or respiratory support beyond 2–4 L of supplemental oxygen

References
1. Shah S, Majmudar K, Stein A, et al. Novel Use of Home Pulse Oximetry Monitoring in COVID-19 Patients Discharged From the Emergency Department Identifies Need for Hospitalization [published online ahead of print, 2020 Jun 17]. Acad Emerg Med. 2020;10.1111/acem.14053.
2. Kyriakides J, et al. Analysis of an ambulatory care pathway for patients with COVID-19 utilising remote pulse oximetry. Emergency Medicine Journal. 2020;37(12):843.
3. Vinton D, N Thomson. Interactive Home Monitoring of ED Patients with Suspected or Confirmed COVID-19. Annals of Emergency Medicine. 2020; 76(4, Supplement):S21.

Chapter 11. Management of severe COVID-19: severe pneumonia treatment

Reviews

Weatherald J, Solverson K, Zuege DJ, Loroff N, Fiest KM, Parhar KK. Awake prone positioning for COVID-19 hypoxemic respiratory failure: A rapid review. Journal of Critical Care. 2020 Aug 27.

Jagan N, Morrow LE, Walters RW, Klein LP, Wallen TJ, Chung J, Plambeck RW. The POSITIONED Study: Prone Positioning in Nonventilated Coronavirus Disease 2019 Patients—A Retrospective Analysis. Critical Care Explorations. 2020;2(10).

Ferrando C, Mellado-Artigas R, Gea A, Arruti E, Aldecoa C, Adalia R, et al. Awake prone positioning does not reduce the risk of intubation in COVID-19 treated with high-flow nasal oxygen therapy: a multicenter, adjusted cohort study. Critical Care. 2020;24(1):1-1.

Characteristics of additional studies identified subsequent to the Weatherald [2] rapid review

Study	Study design, sample size	Patient characteristics	Key findings
Jagan 2020 [6]	Retrospective, observational, uncontrolled, n=105	Proned: Age: 56 ± 14.4 Not proned: Age: 65.8 ±16.3 , p=0.002 No other remarkable characteristics	Intubation rate 10% in prone, 27.7% in supine, p=0.031 Time to intubation longer in proned patients, log rank p = 0.023 Risk of intubation 69% lower in proned patients, HR = 0.31, CI 0.10-0.90, p = 0.032, aHR = 0.30, CI 0.09-0.96, p =0.034 Time to discharge lower in prone: 9 days Vs. 14 days in non proned Discharged alive: HR: 1.57 CI 1.02-2.42, p = 0.039 , aHR:0.85, CI-0.47-1.53, p = 0.587 s/f ratios were used as a surrogate of P/F ratios, and were noted to decrease in the first 24 hours of admission (p<0.001)
Ferrando 2020 [7]	Prospective, multicenter adjusted observational cohort, n=199	No significant differences in persons grouped under 2 categories of those who received HFNO and HFNO with prone positioning	HFNO Vs. HFNO + PP Intubation: Crude analysis- HR: 0.879 (0.538 – 1.435), p = 0.60, 28-day (crude) mortality: 1.046 (0.402 – 2.722) p = 0.92 Other clinical outcomes noted a decrease in respiratory rate (p=0.004) in patients receiving HFNO + PP. Other differences were not statistically different, such as improvement in SpO2, P/F ratio.

Data extraction tables for key outcomes: Weatherald [2] rapid review, Jagan [6], Ferrando [7]

Study				Study				Study		
Coppo	18	56		Coppo	5	56		Coppo	5	56
Golestrani-Eraghi	2	10		Golestrani-Eraghi	2	10		Elharrar	10	24
Moghadam	0	10		Ng	1	10		Retucci	1	26
Elharrar	5	24		Retucci	2	26		Dong	4	25
Ng	1	10		Sartini	1	15		Froelich	1	3
Retucci	7	26		Thompson	3	29		Solverson	8	17
Sartini	1	15		Tu	0	9		**Pain**	**29**	**151**
Thompson	16	29		Zhang	10	23				
Tu	2	9		Bastoni	4	10				
Caputo	13	50		Burton-Papp	0	20				
Zhang	8	23		Damarla	0	10				
Bastoni	6	10		Dong	0	25				
Burton-Papp	7	30		Ripoll-Gallardo	7	13				
Cohen	0	2		Solverson	2	17				
Damarla	2	10		Xu	0	10				
Despres	3	6		Jagan	0	40				
Dong	0	25		Halifax	0	11				
Froelich	0	3		**Mortality**	**37**	**334**				
Huang	1	3								
Paul	0	2								
Ripoll-Gallardo	9	13								
Solverson	7	17								
Sztajnbok	0	2								
Xu	0	10								
Ferrando	22	55								
Intubation	**130**	**450**								

Search strategy

A targeted search of two electronic databases (WHO COVID-19 database and Cochrane COVID-19 register) for relevant systematic reviews, and any additional randomized controlled trials or large observational studies conducted since, and thus not included in, the identified systematic reviews, was undertaken. The following trials registries: www.clinicaltrials.gov and WHO ICTRP (https://www.who.int/ictrp/en/) were also searched to 2 December 2020 to identified relevant ongoing, planned or as yet unreported clinical trials.

All records were uploaded into Endnote X9. One reviewer (AR) independently screened all records to identify eligible studies, a second reviewer (LA) checked the data extraction. Only studies that directly addressed the issue of prone positioning were included in the review, thus excluding studies that reported clinical course generically, as it was not possible to link outcomes and isolate the effect of prone positioning. Included studies were limited to systematic reviews (including "rapid reviews"), randomized trials and cohort studies. Case-series were excluded.

The following search strategy was used to search the WHO COVID-19 literature databases:

[entry date:([20200812 TO 20201202]) AND (proning OR pronation OR "Positional asphyxia" OR " postural asphyxia" OR "face* down"~4 OR (prone AND (position OR ventil*)) OR mh:"prone position" OR mh:("Patient Positioning"))]

References

1. Guérin C, Reignier J, Richard JC, Beuret P, Gacouin A, Boulain T, et al. Prone positioning in severe acute respiratory distress syndrome. New England Journal of Medicine. 2013;368(23):2159-68.
2. Weatherald J, Solverson K, Zuege DJ, Loroff N, Fiest KM, Parhar KK. Awake prone positioning for COVID-19 hypoxemic respiratory failure: A rapid review. Journal of Critical Care. 2020 Aug 27.
3. Reddy MP, Subramaniam A, Lim ZJ, Zubarev A, Afroz A, Billah B, et al. Prone positioning of non-intubated patients with COVID-19. A Systematic Review and Meta-analysis. MedRxiv. 2020 Oct.
4. Anand S, Baishya M, Singh A, Khanna P. Effect of awake prone positioning in COVID-19 patients-A systematic review. Trends in Anaesthesia and Critical Care. 2020 Sep 28.
5. Qadri SK, Ng P, Toh TSW, Loh SW, Tan HL, Lin CB, et al. Critically Ill Patients with COVID-19: A Narrative Review on Prone Position. Pulm Ther. 2020;6(2):233-246. doi: 10.1007/s41030-020-00135-4. Epub 2020 Oct 21. PMID: 33085052.

6. Jagan N, Morrow LE, Walters RW, Klein LP, Wallen TJ, Chung J, Plambeck RW. The POSITIONED Study: Prone Positioning in Nonventilated Coronavirus Disease 2019 Patients—A Retrospective Analysis. Critical Care Explorations. 2020;2(10).

7. Ferrando C, Mellado-Artigas R, Gea A, Arruti E, Aldecoa C, Adalia R, et al. Awake prone positioning does not reduce the risk of intubation in COVID-19 treated with high-flow nasal oxygen therapy: a multicenter, adjusted cohort study. Critical Care. 2020;24(1):1-1.

Chapter 14. Prevention of complications in hospitalized and critically ill patients with COVID-19

Care bundles

Appendix: Additional data on care bundles

No.	Study	Author	URL & Journal	Type of Study	Elements of Bundle
1.	Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial	Peek_GJ, Mugford_M, Tiryvoipati_R, et al.	https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(09)61069-2/fulltext Lancet	RCT	Trial group Protocol Pressure-restricted mechanical ventilation at 30 cm H_2O Positive end expiratory pressure titrated to optimum SaO_2 FiO_2 titrated to maintain SaO_2 at more than 90% Diuresis to dry weight Target packed cell volume of 40% Prone positioning Full nutrition ECMO (acc. to published institutional protocols)
2.	Implementation of Protocolized Care in ARDS Improves Outcomes	Duggal_A, Panitchote_A, Siuba_M, et al.	In press (Oct 13), DOI: 10.4187/respcare.07999 Respiratory Care 2020	Single-centre, interventional, comparative study before and after protocol implementation	Protocol (1) Implementation of lung-protective ventilation strategies for all patients with ARDS; (2) PEEP and FIO_2 titration based on the third ARDSnet PEEP/FIO_2 table; (3) fluid conservation strategies based on the FACCT lite17 protocol; (4) strategies to minimize asynchrony with the ventilator in the first 48 hrs of ARDS; (5) early (i.e. within 48 hrs) use of adjunctive therapies (prone ventilation and neuromuscular blocking agents) in patients with moderate-to severe ARDS (PaO_2=FIO_2 < 150). *Adjunctive therapies with no mortality benefit* (e.g. inhaled vasodilators, recruitment manoeuvres, extracorporeal membrane oxygenation) or the use of prone ventilation and neuromuscular blocking agents beyond 48 hrs were considered to be rescue therapies

3.	Improvement in process of care and outcome in patients requiring intensive care unit admission for community acquired pneumonia	Georges_H, Journaux_C, Devos_P, et al.	https://bmcinfectdis.biomedcentral.com/articles/10.1186/1471-2334-13-196
			
			BMC Infectious Diseases
				Before and after study	Bundle derived from SSC Guidelines:
					
					Non-invasive mechanical ventilation(NIMV) within 48 hrs of admission
					Mechanical ventilation within 48 hrs of admission
					Fluid administration within 24 hrs of admission
					Vasoactive drugs within 48 hrs of admission
					    Dobutamine
					    Dopamine
					    Norepinephrine
					    Epinephrine
					Dual therapy
					Adequate antimicrobial therapy/ documented pneumonia
					Antimicrobial therapy within 8 hrs of admission
					Combination of a 3rd GC and levofloxacin
					Insulin therapy
					Intensive insulin therapy
					Mean tidal volume, mL/kg
					Low-dose steroid administration
					Transfusion
					Number of red blood cell units transfused per patient
					Systematic postextubation NIMV

No.	Study	Author	URL & Journal	Type of Study	Elements of Bundle

					ANTIBIOTICS
					Monotherapy
					   Amoxicillin
					   Amoxicillin clavulanate
					   Cetotaxime or Ceftriaxone
					   Other
					Combination therapy
					   Amoxicillin and Ofloxacin
					   Amoxicillin and Ciprofloxacin
					   Amoxicillin clavulanate and Ofloxacin
					   Amoxicillin clavulanate and Ciprofloxacin
					   Cetotaxime or Ceftriaxone and Ofloxacin
					   Cetotaxime or Ceftriaxone and Ciprofloxacin
					   Amoxicillin and Levofloxacin
					   Amoxicillin clavulanate and Levofloxacin
					   Cetotaxime or Ceftriaxone and Levofloxacin
					   Other combination

4.	Compliance with severe sepsis bundles and its effect on patient outcomes of severe community acquired pneumonia in a limited resources country	Guo_G, Li_HY, Li_YM, et al.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4223141/
			
			Arch Med Sci 2014;10(5):970-978.
				Prospective cohort study of 212 severe CAP patients	Severe sepsis bundles
					
					(i) 6-hour severe sepsis bundle:
					  1. Serum lactate measured.
					  2. Blood cultures obtained prior to antibiotic administration.
					  3. Initial empirical antibiotics administered within 1 h.
					  4. In the event of hypotension and/or serum lactate > 4 mmol/l:
					    a. Deliver an initial minimum of 20 ml/kg of crystalloid (or colloid equivalent: 1.1 ml/kg of 20% albumin or 4.8 ml/kg of 6% hydroxyethyl starch).
					    b. Apply vasopressors (noradrenaline or dopamine) for hypotension not responding to initial fluid resuscitation to maintain mean arterial pressure (MAP) ≥ 65 mm Hg.
					  5. In the event of persistent septic shock and/or serum lactate > 4 mmol/l, administration of inotropic dobutamine and/or transfusion of packed red blood cells (when haemoglobin (Hb) < 70 g/l) to achieve a central venous pressure (CVP) of ≥ 8 mm Hg and central venous oxygen saturation ($ScvO_2$) of ≥ 70%.
					
					(ii) 24-hour severe sepsis bundle:
					
					  1. Low dosage corticosteroid (40–60 mg/day of methylprednisolone) administered for septic shock requiring continued infusion of vasopressors.
					
					  2. Glucose control maintained < 8.3 mmol/l.
					
					  3. For mechanically ventilated patients maintain inspiratory plateau pressures < 30 cm H_2O.

5.	Critically Ill Adults With Coronavirus Disease 2019 in New Orleans and Care With an Evidence-Based Protocol	David R. Janz, Scott Mackey, Nirav Patel, et al	https://pubmed.ncbi.nlm.nih.gov/32941862/
			Chest. 2020 Sep 14 doi: 10.1016/j.chest.2020.08.2114 [Epub ahead of print]
			PMCID: PMC7487861
			PMID: 32941862
				Multi-center, retrospective, observational cohort study	Pilot Evidence Based Protocol
					
					1. Non-invasive Positive Pressure Ventilation Prior to Tracheal Intubation
					2. Care of the Tracheally Intubated Patient
					  i. Tidal volume selection
					  ii. Positive end-expiratory pressure selection
					  iii. Prone positioning
					  iv. Fluid Management
					  v. Sedation Management
					3. Care of the Patient at the Time of Extubation
					
					(More guidance on these aspects of protocol available)

6.	A multicenter clinical study of bundle treatment for moderate or severe acute respiratory distress syndrome	Yue M, Liu F, Zhao L, Zhang F, Wang C	https://europepmc.org/article/med/25124901 http://www.chinadoi.cn/portal/mr.action?doi=10.3760/cma.j.issn.2095-4352.2014.08.004	Multicenter Observational Study	No information on ventilation group in abstract. Full text inaccessible/needs Chinese translation

No.	Study	Author	URL & Journal	Type of Study	Elements of Bundle
7.	A multicenter clinical study of bundle treatment for moderate or severe acute respiratory distress syndrome	Yue M, Liu F, Zhao L, Zhang F, Wang C	https://europepmc.org/article/med/26138424	Multicenter prospective observational study	Bundle treatment restrictive fluid management respiratory support high-dose ambroxol combined with Xuebijing injection, prevention of ventilation associated pneumonia (VAP), individualized sedation plan, installation of continuous blood purification treatment for critical patients. A special team was organized to ensure the successful implementation of all bundle measures.
8.	Design and application of bundle treatment plan in the early stage for severe human infection by avian influenza H7N9 [Article in Chinese]	Ling Wang, Xiaobin Fang, Yongling Yang	https://pubmed.ncbi.nlm.nih.gov/29308753/	Prospective observational study	Bundle treatment group was given bundle treatment on the basis of conventional treatment, including isolation, anti-virus, respiratory support, restrictive fluid management, immunotherapy, inhibition of inflammation, antibiotic therapy, nutritional support, prevention of hospital acquired infection (HAP), individual sedation, continuous blood purification (CBP) for acute kidney injury (AKI) and severe acute respiratory distress syndrome (ARDS) patients, and intensive care. Conventional treatment group was given conventional treatment such as isolation, anti-virus, symptomatic treatment, and traditional Chinese medicine and so on.

Search strategy

Databases: MEDLINE; CENTRAL; EMBASE; covid-19.cochrane.org; Clinical Trial Registry – ICTRP platform

Database: Ovid MEDLINE(R) ALL <1946 to October 26, 2020>
1 exp coronavirus/ (38803)
2 exp Coronavirus Infections/ (41916)
3 (coronavirus* or corona virus* or Covid or Covid19 or Covid2019 or SARS-CoV* or SARSCov* or ncov* or 2019nCoV or new CoV* or novel
CoV*).ti,ab,kf. (79267)
4 covid-19.rs. (31740)
5 severe acute respiratory syndrome coronavirus 2.os. (26892)
6 1 or 2 or 3 or 4 or 5 (87402)
7 6 and (201912* or 2020*).dt,ez,dp. (69076)
8 Respiratory Distress Syndrome, Adult/ (19932)
9 exp Severe Acute Respiratory Syndrome/ (5232)
10 (ards or ardss or sars or mers or respiratory distress syndrome*).ti,ab,kf. (64916)
11 ((acute or adult) adj3 respiratory adj3 (distress or syndrome*)).ti,ab,kf. (33292)
12 (((pulmonary* or lung* or alveol*) adj3 (dysfunction* or edema* or oedema* or collapse* or injur* or failure*)) or ((stiG or shock) adj3
lung*)).ti,ab,kf. (69951)
13 Acute Lung Injury/ (6360)
14 Acute Chest Syndrome/ (279)
15 (acute adj chest adj syndrome*).ti,ab,kf. (1072)
16 Pneumonia, Viral/ (37193)
17 (pneumonitis or (pneumon* adj3 (viral or virus))).ti,ab,kf. (17860)
18 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 (200498)
19 Patient Care Bundles/ (886)
20 Critical Pathways/ (6930)
21 Clinical Protocols/ (28350)
22 Critical Care/mt (13720)
23 Critical Care Nursing/mt (393)
24 Intensive Care Units/mt (17)
25 ((ICU or PICO or care or evidence or treatment or clinical or critical) adj3 (package* or checklist* or check list* or algorithm* or bundl*
or map* or path or paths or pathway* or protocol*)).ti,ab,kf. (96902)
26 19 or 20 or 21 or 22 or 23 or 24 or 25 (138697)
27 18 and 26 (2601)
28 (2000* or 2001* or 2002* or 2003* or 2004* or 2005* or 2006* or 2007* or 2008* or 2009* or 2010* or 2011* or 2012* or 2013* or 2014* or
2015* or 2016* or 2017* or 2018* or 2019* or 2020*).dt,ez,dp,ed. (20314566)
29 27 and 28 (2297)
30 exp animals/ not humans.sh. (4749020)
31 29 not 30 (2217)

Database: Embase <1974 to 2020 October 26>
1 exp coronaviridae infection/ (22148)
2 exp coronavirinae/ (20631)
3 (coronavirus* or corona virus* or Covid or Covid19 or Covid2019 or SARS-CoV* or SARSCov* or ncov* or 2019nCoV or new CoV* or novel
CoV*).ti,ab,kw. (78056)
4 1 or 2 or 3 (88837)
5 4 and (201912* or 2020*).dc,dp. (66661)
6 adult respiratory distress syndrome/ (39674)
7 severe acute respiratory syndrome/ (9521)
8 (ards or ardss or sars or mers or respiratory distress syndrome*).ti,ab,kw. (81001)
9 ((acute or adult) adj3 respiratory adj3 (distress or syndrome*)).ti,ab,kw. (42467)
10 (((pulmonary* or lung* or alveol*) adj3 (dysfunction* or edema* or oedema* or collapse* or injur* or failure*)) or ((stiG or shock) adj3
lung*)).ti,ab,kw. (101692)
11 exp acute lung injury/ (15627)
12 acute chest syndrome/ (2364)
13 (acute adj chest adj syndrome*).ti,ab,kw. (2188)
14 exp virus pneumonia/ (25392)
15 (pneumonitis or (pneumon* adj3 (viral or virus))).ti,ab,kw. (27823)
16 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 (261931)
17 care bundle/ (1373)
18 clinical pathway/ (8603)
19 clinical protocol/ (100892)
20 critical illness/dm (248)
21 ((ICU or PICO or care or evidence or treatment or clinical or critical) adj3 (package* or checklist* or check list* or algorithm* or bundl*
or map* or path or paths or pathway* or protocol*)).ti,ab,kw. (149647)
22 17 or 18 or 19 or 20 or 21 (239946)
23 16 and 22 (2996)
24 (2000* or 2001* or 2002* or 2003* or 2004* or 2005* or 2006* or 2007* or 2008* or 2009* or 2010* or 2011* or 2012* or 2013* or 2014* or
2015* or 2016* or 2017* or 2018* or 2019* or 2020*).dc,dp. (23808570)
25 23 and 24 (2737)
26 (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti,ab.) (6058022)
27 25 not 26 (2567)

Cochrane Database of Systematic Reviews
Issue 10 of 12, October 2020
https://www.cochranelibrary.com/advanced-search/search-manager?search=4086252
#1 MeSH descriptor: [Coronavirus] explode all trees 72
#2 MeSH descriptor: [Coronavirus Infections] explode all trees 395
#3 (coronavirus* or (corona near virus*) or Covid or Covid19 or Covid2019 or SARS-CoV* or (SARS next CoV*) or SARSCov* or ncov* or
2019nCoV or (new next CoV*) or (novel next CoV*)):ti,ab,kw 1761
#4 #1 or #2 or #3 with Cochrane Library publication date in The last year 1671
#5 MeSH descriptor: [Respiratory Distress Syndrome, Adult] explode all trees 1359
#6 MeSH descriptor: [Severe Acute Respiratory Syndrome] explode all trees 235
#7 MeSH descriptor: [Acute Lung Injury] explode all trees 477
#8 MeSH descriptor: [Acute Chest Syndrome] explode all trees 37
#9 MeSH descriptor: [Pneumonia, Viral] explode all trees 147
#10 (ards or ardss or sars or mers or (respiratory near distress near syndrome*)):ti,ab,kw 6135
#11 ((acute or adult) near respiratory near (distress or syndrome*)):ti,ab,kw 3373
#12 (((pulmonary* or lung* or alveol*) near (dysfunction* or edema* or oedema* or collapse* or injur* or failure*)) or ((stiG or shock) near
lung*)):ti,ab,kw 7758
#13 (acute near chest near syndrome*):ti,ab,kw 259
#14 (pneumonitis or (pneumon* near (viral or virus))):ti,ab,kw 1651
#15 #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 15052
#16 MeSH descriptor: [Patient Care Bundles] explode all trees 27
#17 MeSH descriptor: [Critical Pathways] explode all trees 193
#18 MeSH descriptor: [Clinical Protocols] explode all trees 18389
#19 MeSH descriptor: [Critical Care] explode all trees and with qualifier(s): [methods - MT] 825
#20 MeSH descriptor: [Critical Care Nursing] explode all trees and with qualifier(s): [methods - MT] 19
#21 ((ICU or PICO or care or evidence or treatment or clinical or critical) near (package* or checklist* or (check next list*) or algorithm* or
bundl* or map* or path or paths or pathway* or protocol*)):ti,ab,kw 34927
#22 #16 or #17 or #18 or #19 or #20 or #21 49005
#23 #15 and #22 843

#24 #23 with Cochrane Library publication date Between Jan 2000 and Dec 2020 777
Trials 768 / reviews 9

covid-19.cochrane.org
bundl* or pathway* or "care protocol" or "care package" or "care algorithm" or "care protocols" or "care packages" or "care algorithms" or
"treatment protocol" or "treatment package" or "treatment algorithm" or "treatment protocols" or "treatment packages" or "treatment
algorithms" or "clinical protocol" or "clinical package" or "clinical algorithm" or "clinical protocols" or "clinical packages" or "clinical
algorithms" or "critical protocol" or "critical package" or "critical algorithm" or "critical protocols" or "critical packages" or "critical
algorithms"
594 matching studies

WHO Clinical Trial Registry – ICTRP platform
Standard search
bundl* AND respiratory 15
bundl* AND pneumon* 19
pathway* AND respiratory 30
pathway* AND pneumon* 11
care protocol* AND respiratory 13
care protocol* AND pneumon* 5
treatment protocol* AND respiratory 13
treatment protocol* AND pneumon* 14

References
1. Devlin JW, Skrobik Y, Gelinas C, Needham DM, Slooter AJC, Pandharipande PP, et al. Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. Crit Care Med. 2018;46:e825-e873.
2. Klompas M, Branson R, Eichenwald EC, Greene LR, Howell MD, Lee G, et al. Strategies to prevent ventilator-associated pneumonia in acute care hospitals: 2014 update. Infect Control Hosp Epidemiol. 2014;35(Suppl 2):S133-154.
3. O'Grady NP, Alexander M, Burns LA, Dellinger EP, Garland J, Heard SO, et al. Healthcare Infection Control Practices Advisory Committee. Guidelines for the prevention of intravascular catheter-related infections. Clin Infect Dis. 2011;52:e162-193.
4. Klompas M, Li L, Kleinman K, Szumita PM, Massaro AF. Associations Between Ventilator Bundle Components and Outcomes. JAMA Intern Med. 2016;176:1277-1283

Chapter 24. Care of COVID-19 patients after acute illness (new chapter)

National Institute for Health and Care Excellence (NICE, United Kingdom)
COVID-19 rapid evidence review: management of the long-term effects of COVID-19, made available in confidence to WHO GDG, November 2020

9 PICOs

Literature search strategy

Database	Platform	Date searched	Segment searched
CDSR	Wiley	28/10/2020	Cochrane Database of Systematic Reviews Issue 10 of 12, October 2020
CENTRAL	Wiley	28/10/2020	Cochrane Central Register of Controlled Trials Issue 10 of 12, October 2020
CINAHL main search	EBSCOhost	27/10/2020	1981-current
Embase main search	Ovid	27/10/2020	Embase 1974 to 2020 October 26
MEDLINE ALL main search	Ovid	27/10/2020	Ovid MEDLINE(R) ALL 1946 to October 26, 2020
PsycINFO main search	Ovid	27/10/2020	APA PsycInfo 1806 to October Week 3 2020

Literature searched up to 27–28 Oct 2020: 4104 identified, 505 full text screen, 100 references included in full final guidance doc, each PICO had between 14–20 relevant studies per question.

Evidence summaries as below credited to NICE, United Kingdom.

References

1. COVID-19 rapid guideline: managing the long-term effects of COVID-19. NICE guideline. Published: 18 December 2020 www.nice.org.uk/guidance/ng188.
2. Andrenelli E, Negrini F, de Sire A, et al. Rehabilitation and COVID-19: a rapid living systematic review 2020 by Cochrane Rehabilitation Field. Update as of 30 September 2020. Eur J Phys Rehabil Med-6672.
3. Greenhalgh T, Knight M, A'Court C, et al. Management of post-acute covid-19 in primary care. BMJ. 2020;370:m3026.

Summary of studies: National Institute for Health and Care Excellence
COVID-19 rapid evidence review: management of the long-term effects of COVID-19 November 2020

PICO	QUESTION
#1	What risk factors are associated with developing post-COVID-19 syndrome? **Evidence**: 8 cohort studies, 4 cross-sectional studies, 1 international longitudinal survey Key results NICE undertook a comprehensive systematic review of the available evidence (multiple appropriate databases), up to 28 Oct 2020, to assess whether there are any identifiable risk factor(s) that are associated with any long-term effects of acute COVID-19 illness. They identified 13 potentially relevant studies: 8 cohort studies, 4 cross-sectional studies, 1 international longitudinal survey. The cross-sectional studies and survey (n=5 studies), did not provide the appropriate level of evidence to definitively address the question of risk factors, particularly as the participants included in these studies were self-selected, and were disproportionally white, female, aged 30-60 years, and mostly from high-income countries. Similarly, the sampling techniques used in the included cohort studies may have introduced selection bias (e.g. the participants recruited were those subscribing to a COVID-19 symptom app) and thus the findings of these studies are not likely to be representative of the overall population of people who have experienced an acute COIVD-19 illness. Most studies excluded patients with severe COVID-19. Despite these methodological shortcomings, the findings of two of the included cohort studies were that being initially hospitalized, experiencing initial dyspnoea, have an existing respiratory co-morbidity, and the number of symptoms present in first week after diagnosis were predictors of increased risk of persistent symptoms at longer-term (e.g. day 60) timepoint. One other cohort study (using logistic regression) found no association between age, gender, need for hospitalization, cardiovascular and pulmonary comorbidities, diabetes and obesity and the persistence of symptoms at 60 days. Hence none of the identified studies could be used to draw firm conclusions on specific, well-validated risk factors for the longer-term effects of COVID-19.

PICO	QUESTION
#2	What is the prevalence of symptoms or clusters of symptoms (physical and mental health) and problems carrying out usual activities, including work, education and leisure, among people who have symptoms of COVID-19 for a duration of 4 to 12 weeks? **Evidence**: 12 cohort studies, 9 cross-sectional studies

Outcomes: Symptoms and conditions

Low quality evidence from 8 studies recorded various symptoms reported by participants between 4-12 weeks from onset of acute COVID-19 illness or hospital discharge. Prevalence of these symptoms were wide ranging. The most common symptoms reported across the studies are reported in Table 3.

Table 3: Common symptoms reported across studies in hospitalised people

Symptom	Number of studies	Number of people (n)	Prevalence (range, %)
Shortness of breath	6	619	32.2% to 74.3%
Fatigue	6	950	28.3% to 67.8%
Cough	4	795	7.1% to 42.6%
Sleep disturbance	3	659	17.7% to 56.5%
Cognitive impairment	3	248	18% to 21.6%
Sore throat	3	680	3.2% to 9%
Loss of smell	2	142	12% to 14.6%
Loss of taste	2	142	9% to 10%

Compared to COVID-free volunteers (n=184), Xiong 2020 reported that for COVID-19 survivors (n=583), there was a significant difference for all groups of symptoms recorded at 3 months after hospital discharge (all p values <0.01).

Landi 2020 tested participants at follow-up (approx. 8 weeks from COVID-19 onset) for SARS-CoV-2 infection. 22/131 (16.7%) tested positive. Comparison of symptoms at follow-up between positive and negative tests showed that only sore throat (p=0.04) and rhinitis (p=0.05) were significant for the positive test group.

Outcomes: Carrying out usual activities (including work, education and leisure)

Weerahandi 2020 reported that people experienced worse physical and mental health after COVID-19 illness compared to before (all p values <0.001) and also experienced worsened ability to carry out social activities (p <0.001) at 1 month from discharge.

Halpin 2020 reported that 44/100 (44%) people reported worsened usual activities and that 15/100 (15%) were off sick from work at 4 to 6 weeks from discharge).

Mazza 2020 (n=402) performed a psychiatric assessment around a month after hospital discharge. They found that a significant proportion of people self-rated symptoms in the pathological range: overall, 55.7% scored in the clinical range in at least one psychopathological dimension, 36.8% in two, 20.6% in three, and 10% in four. People with previous psychiatric history a more significant impact on mental health (all p values <0.001).

Outcomes: Symptoms and conditions

Low quality evidence from 13 studies recorded various symptoms reported by participants between 4-12 weeks from onset of acute COVID-19 illness. Prevalence of these symptoms were wide ranging. The most common symptoms reported across the studies are reported in Table 4.

Table 4: Common symptoms reported across studies in non-hospitalised people

Symptom	Number of studies	Number of people (n)	Prevalence (range, %)
Loss of smell	8	3110	7.2% to 51.3%
Loss of taste	7	2960	5% to 51.3%
Shortness of breath	6	2999	7.7% to 71%
Chest pain	6	2999	6.9% to 44%
Joint pain	6	2999	2% to 31.4%
Headache	5	2849	5% to 38%
Fatigue	4	2823	27% to 87%
Palpitations	4	2510	10% to 32%
Fever	4	2710	2% to 11%
Cognitive impairment	2	679	1.9% to 28.6%

Eiros 2020 carried out CMR investigations in health-care workers with previous COVID-19 illness. They found that CMR abnormalities were found in 104/139 (74.8%) 10 weeks after initial illness.

Taquet 2020 retrospectively analysed data for 44,779 people with a diagnosis of COVID-19 without prior psychiatric illness. They found that at 3 months a diagnosis of COVID-19 led to significantly more first diagnoses of psychiatric illness (HR 1.58 to 2.24, all P values <0.0001). The most frequent diagnosis was anxiety disorder, and the other most common disorders were adjustment disorder, generalised anxiety disorder and PTSD to a lesser extent. Those not requiring hospital admission for COVID-19 were still more at risk of psychiatric sequelae compared to other illnesses (influenza, other respiratory infections, skin infections, cholelithiasis, urolithiasis and fracture of a large bone; all p values <0.001).

Poyraz 2020 assessed psychological wellbeing of people with probable or confirmed COVID-19. They reported that 72 (25.4%) had moderate to severe PTSD symptoms 48.7 days since diagnosis of COVID-19 illness.

Cirulli 2020 conducted longitudinal surveys on the general population in the USA regardless of history of COVID-19 infection or test. They found that the specific long-term symptoms of anosmia, ageusia, difficulty concentrating, dyspnoea, memory loss, confusion, headache, heart palpitations, chest pain, pain with deep breaths, tachycardia, and dry cough were significant after 30 days in 233 people who had previously tested positive for SARS-CoV-2 compared to 3652 COVID-19 negative controls (p<0.001). However, adjusting for initial numbers of symptoms only long-term anosmia, ageusia, memory loss, and headache remained significantly associated with COVID-19 status. These symptoms remained significant in people who had been COVID-19 positive after 60 days. Tachycardia became significant at 60 days. After 90 days, all of these 5 symptoms, except for memory loss, remained significant in COVID-19 positive cases.

Goertz 2020 conducted a survey with participants from 2 Facebook groups and those registered on the Lung Foundation Netherlands website. They found that there was a median change of −7 (IQR = −10 to −4) symptoms per person (p<0.001) at around 3 months from initial illness. The difference in median change of symptoms was highest in non-hospitalised patients with confirmed COVID-19 compared to hospitalised, non-hospitalised symptom-based COVID-19 and non-hospitalised suspected-based COVID-19 diagnosis (p<0.001).

Patient-led research (Assaf 2020, n=640) found that the majority of participants with symptoms experienced fluctuations both in the type (70%) and intensity (89%) of symptoms over the course of being symptomatic.

Outcomes: Carrying out usual activities (including work, education and leisure)

	Poyraz 2020 assessed psychological wellbeing of patients with probable or confirmed COVID-19. They reported that 19 (9.4%) of people were still on temporary disability leave 8.7 days since diagnosis of COVID-19 illness. Goertz found that self-reported health status at follow-up was significantly worse compared to before the infection (p<0.001).

PICO	QUESTION
#3	What is the prevalence of symptoms or clusters of symptoms (physical and mental health) and problems carrying out usual activities, including work and leisure, among people who have symptoms of COVID-19 beyond 12 weeks? **Evidence**: 1 cohort study, 2 cross-sectional studies Key results Hospitalised people **Outcomes: Symptoms and conditions** Very low-quality evidence from 2 studies recorded various symptoms reported at 12+ weeks from onset of acute COVID-19 illness by participants who were previously hospitalised. Prevalence of these symptoms were wide ranging. The symptoms most commonly reported across both studies were breathlessness (6.7% and 94.6%) and pain (10.5% and 45.9%). Dennis 2020 reported that 164 (100%) of hospitalised people were experiencing fatigue at 3 to 5 months from initial illness. The majority of this cohort also reported cough, fever, myalgia headache joint pain, chest pain, wheezing and worsened mobility. Tomasoni 2020 assessed their cohort with a HADS questionnaire (n=100). They found that 29% had abnormal results for anxiety and 11% were abnormal or depression. 33% had abnormal results for both anxiety and depression. Patients with abnormal HADS showed a higher proportion (77% vs 43%; P = 0.002) of physical symptoms persistence, compared to subjects displaying normal HADS. **Outcomes: Carrying out usual activities (including work, education and leisure)** No evidence was identified. Non-hospitalised people **Outcomes: Symptoms and conditions** Very low-quality evidence from 2 studies recorded various symptoms at 12+ weeks from onset of acute COVID-19 illness reported by participants who had not previously been hospitalised. Prevalence of these symptoms were wide ranging. The symptoms most commonly reported across both studies were breathlessness (8.9% and 87.1%), fatigue (20.5% and 97.6%), myalgia (7.1% and 87.6%) and headache (3.6% and 87.1%). Klein 2020 noted that fatigue, breath difficulty, memory disorders and hair loss, were not typically reported during the 6-weeks follow-ups and were therefore new symptoms. Other symptoms such as muscle aches, headache and chemosensory changes usually reported at earlier timepoints. **Outcomes: Carrying out usual activities (including work, education and leisure)** No evidence was identified.

PICO	QUESTION
#4	What investigations should be carried out to determine appropriate management or treatment of symptoms?

Evidence: 12 cohort studies, 1 cross-sectional study, 1 case study

Key results

Almost all of the studies identified did not strictly meet all the PICO criteria as people were not specifically enrolled for persistent and ongoing symptoms. These studies followed up people approximately 4-6 weeks following acute COVID-19 illness. During this follow up, several investigations and assessments were carried out. These fell into the following categories: screening or assessment with questionnaires, physical tests, imaging or laboratory investigations.

Questionnaires and screening tools

There were four studies that used tools for mental health screening. These tools included GAD7, PHQ9, PTSD-5 and trauma screening and cognitive impairment assessments. All four studies reported adverse mental health outcomes for based on these assessments. Raman 2020 reported a significant difference in PHQ-9 scores 2 to 3 months after COVID-19 illness compared to controls who had not had COVID-19 illness (p=0.009).

There were also four studies that performed a level of functional assessment during follow up. These assessments included assessments such as the SF-36 questionnaire, Epworth Sleepiness Scale, Fatigue Severity Scale, the Modified Rankin score and the pain, enjoyment of life and general activity scale. Two studies used a new Post-COVID-19 functional status assessment (PCFS). Raman 2020 found that functional status (including physical functioning, role limitations due to physical or emotional health, energy and social functioning) was significantly worse in people 2-3 months after acute COVID-19 illness compared to those who did not have COVID-19 (all p values <0.05). Aliae 2020 found that most people approximately 35 days since acute COVID-19 illness had a range of functional restrictions ranging from negligible to severe on PCFS.

D'Cruz 2020 concluded that assessment should ideally be a face to face, holistic approach with a focus on rehabilitation and general wellbeing.

Physical tests, imaging or laboratory investigations

Respiratory tests were commonly used in the studies. These included spirometry, pulmonary function tests and assessment using the Medical Research Council (MRC) Breathlessness Scale. Most studies found that people were still experiencing significant breathlessness at follow-up after acute COVID-19 illness. Raman 2020 found that people who had COVID-19 reported breathlessness (MRC dyspnoea score ≥2) 2-3 months after acute illness 36/53 (64%) compared to 3/29 (10.3%) who had not had COVID-19(p<0.0001).

Exercise tests were performed in many of the studies. The most common investigation was the 6-minute walk test. Other tests included

the sit to stand test and the 4-metre gait speed test. Studies reported limitations in exercise such as limited distance walked and desaturation in people followed up after acute COVID-19 illness.

Many studies used imaging when following up people after acute COVID-19 illness. These were mostly chest X-ray, CT and MRI. D'Cruz 2020 reported that only 15/119 (13%) of people had evidence of COVID-related lung disease at 4-6 weeks after hospital discharge. However they concluded that a chest X-ray is a poor marker of recovery as people were showing abnormalities in other investigations, regardless of chest x-ray results. Dennis 2020 found that multi-organ MRI showed 70% of a low-risk population with ongoing symptoms had impairment of 1 or more organs at 4 months after initial symptoms. Huang 2020a found that cardiac MRI in 15/26 (58%) people experiencing cardiac symptoms around 47 days after onset of symptoms had abnormal findings. These manifestations included myocardial oedema, fibrosis and impaired right ventricle function.

Blood investigations carried out in the studies included routine tests, inflammatory markers and those for iron deficiency and anaemia. Dennis 2020 found that triglycerides (p=0.002), cholesterol (p=0.021), LDL-cholesterol (p=0.005) and transferrin saturation (p=0.005) were more likely to be abnormal in hospitalised (n=164) versus non-hospitalised individuals (n=37). Sonnweber 2020 reported that COVID19 is associated with prolonged alterations of iron homeostasis which may be linked to severe initial disease.

PICO	QUESTION
#5	What pharmacological and non-pharmacological interventions improve the ongoing physical or mental health symptoms and problems carrying out usual activities, including work, education and leisure, following acute COVID-19?

Evidence: 1 rapid living systematic review, 1 rapid narrative review with practice recommendations for primary care

Key results

No primary research studies were identified. A rapid living systematic review also found no evidence on rehabilitation interventions in the post-acute or chronic phases of COVID-19. Low quality evidence from a rapid narrative review of indirect evidence proposed self-management and medical management interventions for primary care with additional community mental health support, safety netting and referral. The proposed medical management included listening and empathy, and the need for this was reinforced by the

	patient lived experience evidence, where acceptance and understanding emerged as a prominent theme. The proposed self-management was also reinforced by the patient lived experience evidence, particularly in terms of pacing and goal setting.
	Subgroups No subgroup data were identified.

PICO	QUESTION
#6	What monitoring is helpful to assess deterioration or recovery in people with ongoing physical and mental health symptoms and problems carrying out usual activities, including work, education and leisure, following acute COVID-19? **Evidence**: 1 cohort study, 1 rapid narrative review with practice recommendations, and 1 case study with practice recommendations in the form of a proposed pathway **Key results** A cohort study, D'Cruz et al (2020), found that persistent symptoms, adverse mental health outcomes and physiological impairment are common 2 months after severe COVID-19, and that follow-up chest radiograph is a poor marker of recovery. Consequently, the authors recommended holistic face-to-face assessment to facilitate early recognition and management of post-COVID sequelae. Salawu et al (2020) provided expert consensus recommendations based on local practice in a case series study. At 4- to 6-weeks, assessment identified suitable patients who may benefit from a tele-rehabilitation program; and provided them with the opportunity to enrol. At 12-weeks, nurse-led assessment included review of repeat chest x-ray (CXR). Patients were referred to multidisciplinary team (MDT) rehabilitation if a need for specialist rehabilitation was identified; or alternatively discharged to primary care. Greenhalgh et al (2020) provided practice recommendations based on a rapid narrative evidence review, combined with expert opinion. These were relevant for both monitoring and referral. See results table 1 for further details. **Subgroups** No subgroup data were identified, although it should be noted that D'Cruz et al (2020) and Salawu et al (2020) both used direct data from patients hospitalised with severe COVID-19 only.

PICO	QUESTION
#7	What symptoms or signs indicate that referral to specialist care is needed for assessment or management of post-COVID-19 syndrome? [N.B. Referral in this context indicates referral specifically for post-COVID-19 syndrome, rather than referral for specialist assessment and treatment for other conditions.] **Evidence**: 1 rapid narrative review with practice recommendations **Direct/Indirect**: Indirect **Key results** SAME as #6

PICO	QUESTION
#8	What components should be included in a service model for the delivery of services to people with post-COVID-19 syndrome? **Evidence**: 3 institutional case studies, 2 narrative reviews, 1 case series, 1 parliamentary report

Key components
Very low quality evidence from narrative descriptions of service models indicated the following emergent themes for components:

Disease severity
Most models were focused on people discharged from hospital following more severe illness, including those needing intensive care. Only 2 models also covered non-hospitalised patients.

Follow up and monitoring
Most models included an initial follow up monitoring component between 4 and 8 weeks since hospital discharge, or at the point of presentation in general practice for non-hospitalised patients, and a further follow up at 12 weeks. Some models also included longer term follow up components at 6 and 12 months, particularly for serious functional impairment.

Multidisciplinary teams
All of the service models included multidisciplinary components, highlighting the need to integrate specialist expertise to allow comprehensive investigation and individualised management strategies, including rehabilitation. The composition of the multidisciplinary teams (MDTs) varied but the most common disciplines represented were respiratory medicine, rehabilitation, neurology, psychology, physiotherapy, occupational therapy. One model also included a separate post COVID-19 mental health MDT comprising psychology, psychiatry and liaison and community services. Some models stipulated the need for clearly defined roles, including pathway co-ordinators and a clinician contact responsible for overall care and navigating the system.

Individualised interventions
The majority of models stressed the importance of individualised management strategies, beginning with self-management interventions.

Mode of delivery
The service models demonstrated differing approaches to the use of remote and face to face components in clinical practice. Some models focused on virtual assessment and rehabilitation, some primarily involved face-to-face components and others were hybrid approaches combining both modes of delivery. The approaches were based on indirect evidence or expert opinion. Two of the models used the same telephone screening tool (C19-YRS) developed specifically for screening people who are recovering from COVID-19 in the community for new or ongoing symptoms. No validation data was reported for the screening tool.

Subgroups
All the service models included components for people who had been discharged from hospital. Two models included components for people who had not been admitted to hospital. The only components specific to people in primary care were to conduct follow up assessment on presentation and not at a prescribed timepoint.

One model was configured specifically for older people without defining the age group. The model included an in-person clinic component with multiple healthcare visits to carry out investigations and individualise management strategies. An exercise component was included in this model for physical rehabilitation.

One model was specific to cardiopulmonary follow-up of people discharged from hospital following severe or critical COVID-19 illness and people with chronic conditions discharged from hospital following moderate, severe or critical COVID-19 illness. This model provided guidance for specialist referral and testing dependent upon the patient's signs and symptoms, as well as radiological and laboratory findings.

PICO	QUESTION

#9	What are the views and experiences of patients, their families and carers?
	
	Evidence: 4 surveys to support groups and through social media, 1 online survey, 1 semi-structured interviews by telephone or video call, 1 thematic analysis, 1 individual narrative, 1 focus group
	
	Key results
	
	Analytical theme 1: symptoms
	Evidence from multiple studies showed that patients with long-term symptoms of COVID-19 experienced a far wider range of symptoms than the three symptoms recognized for acute COVID-19 illness (high temperature, new continuous cough and change or loss to sense of smell or taste). These symptoms varied in severity and duration, with symptoms fluctuating over time ('coming and going'), and new symptoms appearing at different stages of the illness. Symptoms also arose in different parts of the body over time.
	    "From week four I started to get chest pains and then breathlessness, gradually other symptoms developed including dry mouth, sore tongue, joint pains, fatigue, rash and tachycardia." (Maxwell, p8)
	    "The symptoms were like a game of whack-a-mole. Different ones would surge at different times and in different places in my body." (Assaf *et al*, p21)
	
	Analytical theme 2: discordance between patient experiences and official advice or public perceptions
	Many study participants reported that their lived experience of long-term symptoms of COVID-19 contrasted with the picture created by official advice. The public perception of the illness is that it is a binary illness – either mild and treated easily at home or serious, requiring hospitalisation – with no variation or allowances made for ongoing symptoms.
	    "So, COVID-19, it's either a mild infection or you die? No. But no one is prepared to think about us." (Kingstone *et al*, p8)
	    "I think the term "mild" should be removed… I know that people who were admitted to the hospital were worse, but we who stayed home did not have MILD cases in all cases" (Maxwell, p11)
	People felt they were led to believe that they would require a short recovery period and would be back at work in two weeks. This was considered to be the norm and expected by employers and the public. The lived experience, for some, was different.
	    "After nearly 6 months I have started to feel some improvement, although doing anything remotely physical results in a flare up of symptoms..." (Maxwell, p7)
	This discordance between patient experience and official advice/public perception was considered to have a direct effect on the mental and emotional state of those experiencing prolonged illness, often leading to uncertainty about what to do about their symptoms.
	    "None of us knew this [the symptoms] because we're all on our own, in a little bubble, thinking I'm the only one. Why am I the one who has still got it?" (Maxwell, p14)
	
	Analytical theme 3: self-management of symptoms
	Patients with long-term effects of COVID-19 reported the need to make adjustments to their lifestyle, including pacing themselves and setting realistic goals, in order to self-manage their symptoms.
	    "…I really have to pace myself… I couldn't do two or three household chores back-to-back, I have to do a chore, sit down for 15, 20 minutes and then do the next, which frustrates me…." (Kingstone *et al*, p6)
	A number of patients described self care in the form of supplements, vitamins, medications, therapeutic massage, etc.
	    "I started taking vitamin D. Had a joint vitamin C and zinc thing, which I didn't take every day but I took some multivitamins, but then I was a bit unsure really…So anyway, then I took nothing for a while, and then I more recently started the vitamin D again, and I'm on B12 just because of all the burning in my feet … and a probiotic and some omega-3." (Kingstone *et al*, p5)
	
	Analytical theme 4: emotional responses from patients and society
	Patients described experiencing a range of emotions as part of their illness journey. Anxiety was reported in more than one study and related to multiple aspects of the illness including uncertainty about the cause of symptoms, concern that they may never recover completely, and anxiety due to not being believed by healthcare professionals, family and friends.
	    ".... I was really frightened, terrified and just thought I might die on a couple of occasions ... maybe not "I'm going to die right now", but definitely "I'm never going to get better from this" kind of feeling." (Kingstone *et al*, p8)
	    "I finally found a GP who took me seriously last Saturday when I was at the point of crying talking to her, just understanding that people's symptoms are real and diverse." (Maxwell, p16)
	Other emotional responses included a feeling of helplessness and a sense of relief on finding a healthcare professional who believed them. There was also a sense of stigma associated with long-term effects of COVID-19, with patients both experiencing a sense of shame and blame (internally generated stigma), but also expressing a fear that employers and others in the community may stigmatise them for having long-term effects of COVID-19 (externally generated stigma).
	
	Analytical theme 5: effects on self-identity, relationships and lifestyle
	From the studies that conducted interviews or focus groups it was apparent that for many patients there was a feeling that their self identity had been changed by ongoing COVID-19 symptoms. People reported an impact on how they viewed themselves, before and after COVID-19 illness. There was a feeling they had to reconsider who they were and what they could do within the context of family and work. The phrase "compared with how

I used to be" was used by multiple participants (Kingstone et al, 2020). Ladds et al (p16) commented on the concept of a "spoiled identity" where an identity as "healthy, independent and successful" was threatened.

Interviews with doctors and other clinicians in one study showed that many were worried about their professional abilities and the impact of cognitive deficits due to long-term COVID-19 on their ability to perform their jobs.

> "[T]he medicolegal aspect is huge and I think possibly certainly feels that way as a GP and it's scary to not be able to recognise potentially where you have deficits because if you can't recognise them then that's an unknown unknown in what can you do with that." (Ladds et al, p10)

Family members were also considered to have been impacted and were seen as requiring support. One interview participant described the impact her symptoms had on her family and how she felt they didn't believe her:

> "I think, at first, they just thought, 'Oh, for god's sake, she's napping again'. I feel like I constantly have to explain. I'm just exhausted and I just want to know why I'm so exhausted … I used to enjoy running, and exercising, and stuff like that. I rarely even go on walks now because I know if I walk to the end of the street, they're (lungs) going to start hurting." (Kingstone et al, p5)

Analytical theme 6: healthcare access – barriers and facilitators

Studies reported a general perception among participants that the NHS and doctors were too busy dealing with acute cases of COVID-19 to have capacity to deal with anything else, including patients with long-term symptoms. This was perceived to be a barrier to accessing healthcare. This perception appeared to be strengthened by difficulties people experienced when trying to access primary care, especially if they were seeking a face-to-face consultation.

> "I think the message to avoid hospital and the GP unless you had specific symptoms was very unhelpful, particularly as I didn't have, and never have had, a cough or fever" (Maxwell, p12)

> "I was initially contacting a certain GP, and that GP literally just went "you need to stay at home and rest, there's nothing we can do", and that frustrated me because it didn't seem like they were being caring, it felt like I was nagging them and being a hypochondriac and that's how I was being treated…" (Kingstone et al, p7)

In general, it appears that study participants found accessing care to be "complex, difficult and exhausting" (Ladds et al, p10). This difficulty in accessing care and perceived lack of access, led to patients describing how they felt they had to manipulate the inflexible algorithm-driven systems in order to receive care, which led to feelings of guilt and anger.

> "…did the e-consult – I had to do it a couple of times – I kind of learned to answer the questions to get it to send a message to my GP surgery… If you say you've got heart palpitations or breathlessness it's telling you to call 111 which I didn't want to do. And so I had to downplay symptoms [laughs] to get through. I cancelled it and did it again." (Ladds et al, p12)

Others reported resorting to private healthcare to access tests with the aim of provoking NHS follow-up. Some patients felt they needed to conduct their own research and construct their own care pathways, taking the lead in arranging consultations with specialists and circumventing bottlenecks in the system. This was reported as a route often employed by medical professionals who themselves were suffering from ongoing symptoms of COVID-19 and were having difficulty in accessing the care they believed they required (Ladds et al, p12).

> "I've had to do a lot of this myself, to be honest. It was in the early on stages, I actually rang around the hospitals to see if there was anything, so, but there wasn't anything. I just rang the switch board and said, 'What's the deal with people who've had Covid?' But they said nothing. Gosh, yeah, I was desperate. I'm sorry, I'm one of these people who want answers and I wasn't getting any answers" (Ladds et al, p12)

Those who reported experiencing long-term symptoms described a perceived lack of support within the system. Some patients described how NHS111 (the national telehealth helpline) had directed them to their GP who then directed them back to NHS111 (Ladds et al, p11). There was what appeared to be a lack of guidance for those who don't need to be admitted to hospital but are no longer in the acute phase of the illness. It was suggested by study authors that there was a need for support for patients with long-term symptoms of COVID-19 to help them to self-manage their symptoms.

Patients who felt they had received satisfactory care and access to healthcare were generally those who had been offered follow-up appointments and who felt their healthcare providers gave them ongoing support, even if that was only in the form of a video or telephone call.

> "... actually just the experience of being heard and feeling like somebody got it and was being kind about it, but you know it was okay that they couldn't do anything, I just kind of needed to know that I wasn't losing it really and it was real what I was experiencing, I think so that was really helpful." (Kingstone et al, p8)

Analytical theme 7: telemedicine - limitations and benefits

The use of telemedicine to facilitate interactions with healthcare services was generally perceived by patients to have limitations affecting access to effective healthcare. Remote consulting with primary care was viewed by some patients as potentially limiting direct access to GPs, disrupting continuity of care (people often couldn't see the same GP every time), and making the communication of symptoms more challenging.

> "The focus when you do get a new GP speaking to you seems to be that they go back to the beginning …. And I think if there was the same GP who we are able to consult regularly they would build a picture of your baseline and I think that's what's lost with digital ways of working." (Ladds et al, p11)

Some patients also felt that strict adherence to protocols for telemedicine-delivered care affected patient safety or led to mismanagement of their care.

"... I remembered ringing my GP from the floor on my lounge laying on my front and kind of saying I'm really short of breath, you know, do you think I should try an inhaler do I need to go back to A&E and I was kind of told well you don't really sound too out of breath over the phone .... I really felt at that point right if you could see me you would see that I am really like broken" (Ladds *et al*, p14)

One positive view expressed in relation to telemedicine was that it did increase accessibility of primary care during periods of societal restrictions aimed at controlling the spread of COVID-19.

"My doctor was available via messaging, telephone, and telemedicine. She also contracted COVID-19 so she shared her experience with recovery and it helped me stay calm that I was on the right track." (Assaf *et al*, p23)

Analytical theme 8: lack of knowledge, information and understanding among healthcare professionals and patients

A common observation among patients with long-term symptoms was the lack of knowledge about long-term symptoms of COVID-19 among the healthcare professionals they encountered. While the reason behind this lack of knowledge was understood there was a general feeling that there needed to be acknowledgement of this within the healthcare community.

"Well yeah, I feel like there's a lack of knowledge. And I really wasn't able to get any answers, I know, you know this is obviously a novel illness. But just even for one doctor to look into it a bit and come back to me, didn't happen." (Kingstone *et al*, p7)

"Not really, just I think all the way through I found doctors that I've come into contact with are just really at a bit of a loss for it. I think at the beginning, particularly when things were going on, and not clearing up it was kind of put on me as just being a strange case ... and my GP was going, "Well, you're just weird, you know"." (Kingstone *et al*, p7)

Many of the research participants were referred to online support groups by healthcare professionals who recognised the limitations of their own knowledge (Ladds *et al*, p15). However, there were also reports of anxiety and depression triggered by knowledge garnered from these online groups.

" …Internet support groups, yeah on the Facebook groups that I'm on, I mean to be honest, I try not to read that group too much because it depresses me, makes me a bit anxious." (Kingstone *et al*, p6)

There were also reports of conflicting or inconsistent advice from health professionals (Maxwell, p12). Focus group participants suggested they would rather be told that the professional didn't have the knowledge required to address their illness. There specifically appears to be a lack of understanding around long-term symptoms in the context of COVID-19.

The absence of knowledge and information about long-term symptoms of COVID-19 symptoms was reported to create anxiety and confusion for patients. Ladds *et al* (p7) reported that confusion felt by people was intensified by the lack of medical knowledge, understanding and guidance from healthcare professionals.

The importance of finding a GP who was understanding, empathetic and who provided support to those experiencing ongoing symptoms was highlighted by Kingstone *et al* (2020). All participants emphasised the key role of the GP in supporting them at every stage.

"I have to say it was a really powerful experience speaking to the GPs ... the two more recent ones, actually just the experience of being heard and feeling like somebody got it and was being kind about it, but you know it was okay that they couldn't do anything, I just kind of needed to know that I wasn't losing it really and it was real what I was experiencing, I think so that was really helpful." (Kingstone *et al*, p8)

Analytical theme 9: desirable features of healthcare services/service delivery

When asked what features of healthcare delivery or services they would like to see, patients with long-term symptoms spoke about wanting to be listened to, to be believed and understood, and to be offered practical advice on coping.

"... actually just the experience of being heard and feeling like somebody got it and was being kind about it, but you know it was okay that they couldn't do anything, I just kind of needed to know that I wasn't losing it really and it was real what I was experiencing, I think so that was really helpful." (Kingstone *et al*, p8)

Patients asked for face-to-face assessments; they talked about the need for one-stop clinics with multidisciplinary teams who could look at their wide-ranging symptoms and treat them holistically. A case manager to oversee individual patients and ensure that all aspects of their care had been considered was suggested, along with meaningful referral pathways and criteria.

"What would be most helpful is if all main hospitals could have a Covid clinic that had experts from respiratory, cardiology, rheumatology, neurology, physiotherapy etc, so you could go along for half a day and see people from these different departments, they can refer you for tests and you can get a plan in place, we are having such a range of symptoms that GPs are struggling to know what to do with you" (Maxwell, p17)

"... there was a view that it would be helpful if people living with Covid19 could have a 'quarter back' or case manager to oversee and coordinate investigations and support services across different medical specialities." (Maxwell, p17)

Analytical theme 10: social media and support groups

Social media and support groups (online or face-to-face) were valued by patients with long-term symptoms of COVID-19 as opportunities to share experiences, knowledge and resource links with others in a similar situation. Communication through social media and support groups validated patient experiences and provided reassurance they were not alone in their struggle with long-term symptoms.

"At least I know I'm not alone. And I think people who actually have had the disease tend to know a little bit more about it... I actually think that the support group has given more knowledge than the doctors have." (Ladds *et al*, p15)

Analytical theme 11: seeking acceptance and understanding

Patients expressed a strong desire to find acceptance and understanding about their experiences of long-term symptoms of COVID-19, both among healthcare professionals and among family and friends. There was a widespread perception that healthcare professionals doubted patients' descriptions of long-term symptoms of COVID-19, ignored patient concerns, misdiagnosed symptoms, or were dismissive of patient experiences.

"There was one GP who just thought it was all anxiety ... she said, "There's nothing wrong with your lungs. This is all anxiety. You must treat your anxiety. There's nothing wrong with you. How are you going to manage the pandemic if you don't treat your anxiety?" That was really upsetting because I knew I was short of breath..." (Kingstone *et al*, p7)

These perceptions led to difficulties in patients identifying an empathetic healthcare professional who could provide the necessary support. When a patient succeeded in finding an empathetic healthcare professional, they described developing a strong therapeutic bond, and feeling both validated and listened to.

"... actually just the experience of being heard and feeling like somebody got it and was being kind about it, but you know it was okay that they couldn't do anything, I just kind of needed to know that I wasn't losing it really and it was real what I was experiencing, I think so that was really helpful." (Kingstone *et al*, p8)

Subgroups

No relevant subgroups were identified in the analysis (duration of symptoms was not reported in the studies in order to define sub-groups by this measure).

WHO reference number: WHO/2019-nCoV/clinical/web_annex/2021.1