Philippine COVID-19 Living Clinical Practice Guidelines
Institute of Clinical Epidemiology, National Institutes of Health, UP Manila
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EVIDENCE SUMMARY

Should certain risk factors be used to predict the development of long COVID?

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RECOMMENDATION

There is insufficient evidence in using symptoms*, biologic factors or severity of acute COVID-19 in predicting the development of long covid symptoms. *(Very low certainty of evidence)*

**The most common symptoms of long COVID identified were fatigue, dyspnea, sleep disturbance, anxiety or depression, and memory impairment.*

Consensus Issues
Predicting the development of long COVID-19 using risk factors can help identify which patients should be followed up more closely. However, there is insufficient evidence on the predictive risk factors, precluding any recommendation to be made.

Key Findings

- Evidence for this review was obtained from 37 observational studies included in two systematic reviews as well as three additional observational studies describing possible risk factors for the development of long COVID.
- Majority of hospitalized patients diagnosed as having long COVID presented with the following symptoms: weakness, fatigue, dyspnea, cognitive/memory impairment, sleep disorder, and anxiety/psychosocial symptoms.
- For patients in the community setting, dyspnea, reduced quality of life, weakness, chest pain, palpitations, arthralgia, and myalgia were highly common. Older age, female sex, presence of comorbidities, and more severe status during the initial infection were likely to be associated with the development of long COVID during follow-up, although studies showed inconsistent results.
- Very low certainty evidence showed that some of these risk factors were associated with individual symptoms characteristic of long COVID. Our analysis was limited by the significant heterogeneity among the studies included, the different time frames of follow-up, and the studies' inclusion criteria.

Introduction

The current understanding of COVID-19 has gone past the acute phase of infection as recent literature recognizes the chronic effects of illness. Long COVID, post-COVID syndrome or post-acute sequelae of COVID-19 (PASC) refers to the persistence or new-onset COVID-19-related symptoms among patients with probable or confirmed COVID-19 after the acute phase of illness and could not be explained by other conditions.[1] This condition however has different temporal cut-off, prompting the World Health Organization (WHO) to come up with clinical definition citing three months after the acute phase as the time to consider symptoms as part of long COVID and

these symptoms usually may extend for 2 months.[1] Uncertain information about this condition remains as affected people present differently and with varied durations of symptoms. A better understanding of this condition especially with the identification of the people who could possibly develop it can lead to better appropriation of resources for long-term patient support and services both at an individual and societal level.[2,3]

Review Methods

Systematic literature search was performed for studies that investigated the presentation, biologic factors, and laboratory or imaging tests of patients with suspected or confirmed COVID-19 who developed long COVID symptoms (population). A comprehensive literature search was done in PubMed, MedRxiv, Google scholar, and Cochrane Library on October 23, 2021 using a combination of free text and MeSH terms related to “long COVID,” “post-COVID-19 syndrome,” “post-acute COVID,” “long haul COVID,” “risk factors,” and “predictors”. Systematic reviews were considered for inclusion in this review due to the expected wide range of results and volume of observational studies on the topic. The methodological quality of each included systematic review was assessed using the AMSTAR-2 tool. To supplement the yield, further search for observational or clinical studies was done following the date of last search of the systematic review with the highest quality. Studies describing only symptoms of long COVID or follow-up studies with no or insufficient data regarding initial presentation were excluded.

Results

Characteristics of Included Studies

Three relevant systematic reviews that described the potential risk factors associated with long COVID symptoms were identified.[4-6] Two of these were rated as high quality reviews, while one was rated low (see Appendix). The latter only included five studies describing possible risk factors for long COVID descriptively (no statistical analysis), were also included in the two hence only results from the studies included in the two high quality reviews (64 studies encompassing 16,391 patients) were added in the analysis.[5,6] Three additional studies [7-9] were found after the last search date of Michelen review on March 17, 2021. Two of these additional studies included pulmonary imaging reports [7,8] and one on neurologic sequelae of COVID-19 [9]. One study reported chest CT imaging findings after one, three, and six months of hospital discharge and described what factors led to persistent pulmonary findings. Another study used chest radiograph [8] as imaging modality to determine the resolution or persistence of abnormal findings after 12 weeks follow-up.

Due to the wide scope of long COVID, all the reviews employed a wide search strategy. Preprints or non-peer reviewed articles were excluded in both systematic reviews. In the two systematic reviews, 41 studies investigated potential risk factors, of which four were duplicates thereby yielding a total of 37 unique studies. The remaining studies reported the symptoms of patients on follow-up and were used to identify the common symptoms of long COVID.

The definition of long COVID varied between the systematic reviews. Martimbianco et al. [5] defined it as symptoms for more than three weeks after the initial infection, hence excluding studies with symptoms presenting less than this period. Michelen et al. [6] included studies with a follow-up period more than 12 weeks, following the definition of the National Institutes of Health. The latter review also excluded studies with less than 100 participants to avoid a small study effect.

Methodological quality of included studies

Overall, the studies included in this review ranged from low quality/high risk of bias to high quality cohort studies. Concerns for bias arise from incomplete or unclear recruitment process, unclear assessment of response for the outcomes, several studies employing different data collection methods, and questionable generalizability of results to the wider population with COVID-19. The systematic review by Martimbianco et al. [5] used the National Institute of Health Quality Assessment Tool for case series studies for all included studies. Of the 25 included studies, five were deemed as moderate quality studies while the rest were of high quality. The systematic review by Michelen et al. [6] used a validated tool by Hoy et al. made for prevalence studies. Of the included studies, risk of bias was rated as high in 12 (31%) studies, moderate in 22 (56%) studies, and low in 5 (13%) studies. For the three additional observational studies, risk of bias was rated low based on the Cochrane risk of bias tool for cohorts. The last study set a six month follow-up period and described the psychiatric and neurological symptoms at follow-up and their associated factors. This study was assessed to have a low risk of bias.[9] Appendix 3 shows the methodological assessment employed by the included systematic reviews.

Most commonly reported / most prevalent[1] symptoms of long COVID

Due to the significant heterogeneity of the studies, pooling of the risk factors was not done. The most common symptoms of long COVID are shown in Table 1. Michelen et al. [6] provided point prevalence and corresponding interval estimates while Martimbianco et al. [5] only presented ranges.

Table 1. Most commonly reported symptoms of patients with long COVID

Michelen et al. [6]			Martimbianco et al. [5]			
Symptoms	**Studies**	**Prevalence (95% CI)**	**Symptoms**	**Studies**	**Maximum %**	**Minimum %**
HOSPITALIZED						
Weakness	1	54.48 (46-62.7)	**Fatigue/ asthenia**	18	64	6.6
Reduced quality of life	1	47.96 (43.77-52.18)	**Dyspnea**	16	61	5.5
Weight loss	1	37.31 (29.55-45.79)	**Cough/ sputum production**	13	59	1.8
Fatigue	11	37.10 (26.45-49.06)	**Cognitive/ memory/ concentration impairment**	9	57.1	18
Memory impairment	3	34.78 (23.64-47.88)	**Post-traumatic stress/ psychological symptoms/ mood changes**	5	57.1	5.8
Other respiratory symptoms	2	32.43 (2.22-91.02)	**Sleep disorder/ insomnia**	5	53	21.7

[1] Occurring in at least 25% of the population in the studies

Michelen et al. [6]			Martimbianco et al. [5]			
Symptoms	**Studies**	**Prevalence (95% CI)**	**Symptoms**	**Studies**	**Maximum %**	**Minimum %**
Dyspnea	14	28.68 (18.48-41.64)	**Physical dysfunction**	4	28.3	4
Anxiety	4	25.58 (6.36-63.49)				
COMMUNITY SETTING (MIXED POPULATIONS)						
Dyspnea	3	32.57 (14.26-58.38)	**Chest pain**	7	89	0.4
Reduced quality of life	2	30.34 (7.43-70.27)	**Pain and discomfort**	3	66	19
Weakness	1	29.82 (25.42-34.61)	**Palpitations**	4	62	9
			Arthralgia	9	54.7	5.9
			Myalgia	10	50.6	2

Majority of hospitalized patients deemed to have long COVID had the following most commonly reported symptoms: weakness, fatigue, dyspnea, cognitive/memory impairment, sleep disorder, and anxiety/psychosocial symptoms. For patients in the community setting, dyspnea, reduced quality of life and weakness, chest pain, palpitations, arthralgia, and myalgia were highly common. Anosmia was reported to persist among non-hospitalized COVID-19 patients.

Data from two additional observational studies also reflected the same findings from the reviews. The study by Wallis noted that 65% of previously hospitalized COVID patients presented with persistent symptoms, the most common of which were fatigue (41%) and dyspnea/breathlessness (38%). On the other hand, the study by Pilloto found the following symptoms to persistent at 6-month follow up: fatigue (34%), memory complaints (32%), sleep disorder (32%), myalgia (30%), depression (27%).

Risk factors associated with the development of individual symptoms in long COVID

The reported risk factors varied across studies, with inconsistent or contradicting results as summarized in Table 2. However, more studies have reported that advanced age, females, and more severe status during the initial infection were likely to be associated with the development of long COVID during follow-up.

Evidence was limited regarding certain risk factors and their association with individual symptoms that are typically seen for patients with long COVID. Fatigue was associated with older age, but studies show inconsistent results regarding its relationship with females and initial COVID severity. Sleep disturbance and psychosocial symptoms were both associated with severe COVID and female sex. Functional impairment was associated with severe COVID, presence of comorbidities, and older age.

Appendix 4 provides the risk factors with reported significant associations to date based on the living systematic review by Michelen et al. Of the included studies, only 13 was able to perform multivariate analysis (Appendix 5).

Table 2. Risk factors associated with the most common individual symptoms of long COVID from studies that have multivariate analysis (no pooling of studies done)

Symptom	Risk factor	Description
Fatigue	Severity	• More severe presentation OR 2.69 (95% CI 1.46-4.96)
	Sex	• Females at risk p=0.02 from one study • Females show more symptoms of fatigue or muscle weakness OR 2.69 (1.46-4.96)
Dyspnea	Severity	• More severe disease as evidence by DLCO < 80% OR 592 (95% CI 2.28-15.37)
	Sex	• Females showed higher risk of lung diffusion impairment OR 4.6 (95% CI, 1.85-11.48)
Functional impairment	Severity	• ICU admission OR 3.1 (95% CI, 1.3-7.9) • ICU admission or use of mechanical ventilation OR 1.049 (1.009-1.090)
	Old age	• OR 2.6 (95% CI, 1.192-5.671) based on one study • Based on walking ability, P< 0.02 according to one study
	Comorbid	• Increasing number of comorbidities increases risk for limitation in walk test p<0.01
Anxiety/depression or any psychiatric symptoms	Severity	• History of prior psychiatric condition and presence of psychopathology after one month p =.006 and p = <0.0001
	Sex	• Females at risk for persistence of depressive symptoms according to one study p =0.003 • Increase risk for anxiety or depression, OR 1.77 (95% CI 1.05-2.97)

Evidence to Decision

Due to varying and incomplete data on long covid, no studies were found about the cost-effectiveness on the approach of predicting its development. An individualized approach and follow-up plan would still be beneficial in addressing symptoms after the acute phase of the disease.

Recommendations from Other Groups

The National Institute for Health and Care Excellence (NICE) defines post COVID as persistence of COVID-19 symptoms for more than 12 weeks with no other proven diagnosis. They recommend that patients diagnosed or suspected of having COVID-19 should be advised about the unique course of recovery of individuals (i.e., patients may have persistent symptoms or may develop new symptoms differently which can occur at different times) and that these are not dependent on the severity of their acute COVID-19 illness. Initial consultation is advised if symptoms persist for more than four weeks and a screening questionnaire should be used to capture all possible symptoms. Due to the wide symptomatology of COVID-19 and its post-acute phase, shared decision making between the patients and healthcare workers should guide the course of monitoring and management.[10] The CDC likewise emphasized this shared decision-making framework in managing patients after their acute COVID-19 infection due to the incomplete understanding of post-COVID-19 symptoms.[11]

Research Gaps

Current knowledge on the natural course of COVID-19 including the duration of symptoms after the acute phase of the disease is still growing. Evidence is inconsistent because of the significant

heterogeneity of the population base and multiple factors that have to be considered. There are currently 51 listed observational studies in Clinicaltrials.gov that aim to investigate the symptoms and laboratory findings of the post-acute phase of COVID-19. No study aimed to specifically investigate the risk factors or predictors of its development.

References

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Appendix 1. Evidence to Decision

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (7)					There is still a lot of uncertain information about long COVID as affected people present differently and with varied durations of symptoms.
Benefits	Large (2)	Moderate (1)	Small (2)	Uncertain (2)			A better understanding of long covid especially with the identification of the people who could possibly develop it can lead to better appropriation of resources for long-term patient support and services both at an individual and societal level
Harms	Large (1)	Moderate (1)	Small (4)	Uncertain (1)			
Balance of Benefits and Harms	Favors the use of using risk factors (1)	Probably favors the use of using risk factors (4)	Does not favor the use of risk factors (2)				
Certainty of Evidence	High (1)	Moderate	Low (3)	Very low (3)			Very low (from observational studies with varying results and significant heterogeneity)
Accuracy	Very Accurate (1)	Accurate (1)	Inaccurate (2)	Very Inaccurate (1)	Uncertain (3)		
Values	Important uncertainty or variability (2)	Possibly important uncertainty or variability (3)	Possibly NO important uncertainty or variability (2)	No important uncertainty or variability			
Resources Required	Uncertain (2)	Large cost	Moderate Cost (1)	Negligible cost or savings (4)	Moderate savings	Large savings	

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Certainty of evidence of required resources	No included studies (2)	Very low (3)	Low (2)	Moderate	High (1)		
Cost effectiveness	No included studies (4)	Favors using risk factors (2)	Does not favor either using the risk factors or the comparator	Favors comparison (1)			
Equity	Uncertain (2)	Reduced (2)	Probably no impact	Increased (3)			
Acceptability	Uncertain (2)	No	Yes (5)				
Feasibility	Uncertain (3)	No	Yes (4)				

Appendix 2. Characteristics of Included Studies

Table 1. Characteristics of the included systematic reviews

Review Year Journal	Review aim	Search strategy	PICO	Data Analysis
Martimbianco et al 2021 Sao Paolo, Brazil *Int J Clin Pract.* [5]	To identify, systematically evaluate and summarise the best available evidence on the frequency of long COVID-19, the characteristics of its clinical manifestations, and the adopted criteria for its diagnosis, and potential risk factors	**Databases:** CINAHL, CENTRAL, EMBASE, Health Systems Evidence, LILACS, Caribbean Health Sciences Literature, MEDLINE, McMaster Daily News COVDI-19, Oxfird COVID-19 evidence service, WHO, opengrey database **Language restrictions:** none **Strategy:** (Pubmed) MeSH terms for COVID-19 OR SARS-CoV 2 AND long-COVID OR post-acute viral syndrome Extensive search strategy for each database available **Last date of search:** February 1, 2021 **Exclusion criteria:** single case reports, pre-print or no peer-review process	**Population:** patients with symptoms after COVID-19 disease or those considered to have long covid symptoms **Intervention:** follow-up assessment **Outcome:** primary outcomes: frequency of long COVID-19 or persistence of clinical manifestations after the acute phase as defined by the authors of the primary studies, frequency of signs and symptoms after the acute phase of COVID-19 Secondary outcomes: frequency of the criteria used to define long COVID-19, mean duration of long COVID-19, risk factors associated with the occurrence of long COVID-19 **Study design:** experimental, observational longitudinal comparative, cross-sectional, controlled or uncontrolled before-and-after studies, **Preprints:** not included **Definitions:** temporal criteria to define long-COVID varies from 3 to 24 weeks after acute phase or hospital discharge	**Risk of bias:** Cochrane Risk of bias tool for RCTs, ROBINS-1 for cohorts, case-control, before-after study, and non-randomised trials. Joanna Briggs Institute checklist for analytical cross-sectional studies, NIH quality assessment tool for case series and single arm cohorts. **Publication bias:** not assessed **Subgroup analysis:** none **Sensitivity analysis:** no meta-analysis **Statistical analysis** Random-effects meta-analyses using RevMan 5.4 Qualitative synthesis
Michelen *et al* 2021 *BMJ Globl Health* [6]	To synthesize and continually update the evidence on the character and prevalence of long COVID	**Databases:** Medline, CINAHL, Global health (Ovid), WHO Global research Database on COVID-19, Litcovid, google scholar **Language restrictions:** none **Strategy:** wide search strategy employed. Main strings of keywords and phrases associated with “long covid” “hospitalization” and “quarantine”, “symptoms” and “complications”. Full search strategy available **Last date of search:** March 17, 2021 **Exclusion criteria** <100 subjects, reviews and opinion pieces, unclear follow-up period or follow-up less than 12 weeks post onset	**Population:** laboratory confirmed and/or clinically diagnosed COVID-19 with symptoms or outcomes assessed at 12 or more weeks post COVID-19 onset **Intervention:** Follow-up assessment at 12 or more weeks after onset of COVID-19 **Outcome:** Signs and symptoms Imaging and diagnostics Risk factors **Study design:** All study design except for reviews and opinion pieces **Preprints:** excluded	**Risk of bias:** using validated tool for prevalence studies by Hoy et al. **Publication bias:** Funnel plot **Subgroup analysis:** Hospitalised, Non-hospitalised or mixed Physiologic clustering of symptoms Settings Continents Follow-up timing **Sensitivity analysis** Meta-regression analysis on percentage of females and ICU patients Freeman-Tukey double arcsine transformation using inverse variance to examine impact of high risk of bias **Statistical analysis:**

Review Year Journal	Review aim	Search strategy	PICO	Data Analysis
				Proportion of symptoms estimated using exact method. Random intercept logistic regression model with Hartung-Knapp modification I2 to assess heterogeneity Metaprop and ggplot2 in R (v.4.0.5) via RStudio (V.1.3.1093)

Table 2. Characteristics of the additional studies identified

Review Year Journal	PICO	Data Analysis	Key Findings
Liu, et al, 2021 Quant Imaging Med Surg [7]	**Population**: COVID-19 survivors discharged from Chonqing University Three Gorges Hospital from Feb 10,2020 to March 15, 2020 China **Intervention**: Chest CT imaging (non contrast enhanced) using one of two standard machines. Imaging taken at the supine position Cardiopulmonary exercise texting on a treadmill **Control**: CT at admission, at discharge, at 1, 3 and 6 months after discharge **Outcome**: Total opacity score, lung volume, volume of opacity, percentage of opacity *Pulmonary function* **Method**: prospective cohort study (single center) **Exclusions**: -did not undergo CT scan at admission or discharge -had mild type COVID-19 -had history of lung cancer, tuberculosis or interstitial lung disease	**Risk of bias:** Cochrane RoB tool for cohorts (low) **Statistical analysis** Kolmogorov-Smirnov analysis to test variance in homogeneity Continuous variables compared using 2 independent samples t-test (homogeneity of variance) or Mann-Whitney U test (heterogeneity of variance) Categorical variables compared by the X^2 test or Fisher's exact test between groups	N=52 (26 male, 26 female) 32 moderate20 severe Median age 50.5 (IQR 41.3-57) 39/52 with complete resolution (28 in moderate group, 11 in severe group, p< 0.001) **Risk factors of incomplete resolution at 6 months (using chi square test):** Age > 50 years old (p<0.004) Severe COVID-19 (p<0.008) Hospital stay > 18 days (p<0.006) Mechanical ventilation (p<0.002) Steroid therapy (p<0.002) immunoglobulin therapy (p<0.004) Opacity score >4 at discharge (p<0.001) Volume of opacity at discharge > 235 ml (p<0.001) Males and females no difference (p<0.749)
Wallis et al, 2021 Respir Res [8]	**Population**: Hospitalized COVID-19 patients in University Hospital Southampton NHS Foundation Trust seen for virtual check-up after 12weeks, UK **Intervention**: On follow-up 12 weeks after discharge, chest radiograph and blood tests obtained **Control**: Baseline and 12-week follow-up chest radiograph severity score **Outcome**: chest radiograph severity score resolution vs persistence **M**: prospective cohort study (single center) **Exclusions**:	**Risk of bias:** Cochrane RoB tool for cohorts (low) **Statistical analysis** Between group comparisons for continuous variables using Mann-Whitney U test Correlation between continuous variables using Spearman's correlation coefficients Difference in distribution of categorical variables between independent groups using chi square test or Fisher's exact test	N=101 (53.5% male) Median age 53.0 (IQR, 45-63) Clinical outcomes: 65% had one or more persistent symptoms Fatigue (41%) Breathlessness (38%) 32/101 (31.6%) had persistent chest radiograph changes **Risk factors** Longer length of stay (20.5 vs 8 days, p< 0.01) HR 1.060 (1.032-1.090)

Review Year Journal	PICO	Data Analysis	Key Findings
	Discharged to a nursing home, had severe dementia, had metastatic malignancy with less than 1 yr predicted survival rate	Time to event analysis using cox regression analysis	Current or previous smokers (56% vs 23%, p <0.02) HR 3.286 (1.352-7.982) Obesity HR 2.717 (1.114406.454) Not significant Admission to level 2 or 3 facility (45% vs 19%, p 0.01)□ not statistically significant after Age Oxygen support Ethnicity Asthma diabetes Hypertension Sex
Pilotto et al, 2021 Neurological Sciences [9]	**Population**: COVID-19 survivors discharged between February and April 2020 from a COVID-19 unit of the ASST Spedali Civili Brescia Hospital, Italy **Intervention**: Follow-up study at 6 months (standard evaluation od med history, self-reported neurological symptoms and complete neurologic exam) **Outcome:** Presence of neurological signs and symptoms, Risk factors **Method**: longitudinal study **Exclusions**: premorbid neurologic conditions	**Risk of bias:** Cochrane RoB tool for cohorts (low) **Statistical analysis** Dichotomous variables Fisher's exact test Continuous variables using ANOVA with Bonferroni correction Univariable and multivariable logistic regression models to assess risk factors	N=165 Symptoms at follow-up Fatigue (34%) Memory complaints (31.5%) Sleep disorders (31.5%) Myalgia (30.3%) Depressive symptom/anxiety (26.7%) **Risk factors** Moderate/severe group increased risk for: Memory complaints OR 2.6, 95% 1.18-5.8) Decrease in independency in ADL OR 2.6 (95% CI, 1.12-6.2) Confusion OR 2.9 (95%CI, 1.12-7.8) Fatigue OR2.1 (95% CI, 0.95-4.6) Visual disturbance OR 3.5, 95% CI (1.5-8.4) Predictors for symptoms development: Premorbid comorbidities (p=0.006, beta 0.26) Age at admission (p=0.04, beta 0.17) Severity (p=0.04, beta 0.22) Predictors for neurologic abnormalities: Duration of hospitalization (p=0.02) Premorbid comorbidities (p=0.03)

Appendix 3. Detailed Study Appraisal

Table 1. Assessment of included studies using AMSTAR

AMSTAR Items	Iqbal[4] (2021)	Martimbianco[5] (2021)	Michelen[6] (2021)
Date of last search	March 2021	February 1,2021	March 17,2021
Rating of overall confidence in the results of the review[§]	**LOW**	**HIGH**	**HIGH**
1. Research questions, inclusion criteria include PICO components	YES	YES	YES
2.* Protocol registered before commencement of the review	YES	YES	YES
3. Selection of study designs to be included were explained	YES	YES	YES
4.* Adequacy of literature search	YES	YES	YES
5. Study selection done by at least 2 reviewers	YES	YES	YES
6. Data extraction done by at least 2 reviewers	YES	YES	YES
7.* Justification for excluding individual studies	YES	YES	YES
8. Described included studies in adequate detail	YES	YES	YES
9.* ROB from individual studies being included in the review	YES	YES	YES
10. Reported sources of funding for studies included	NO	YES	YES
11.* Appropriateness of meta-analytical methods	YES	YES	YES
12. Potential impact of ROB in individual studies	YES	YES	YES
13.* Consideration of ROB when interpreting review results	YES	YES	YES
14. Sufficient explanation of heterogeneity	YES	YES	YES
15.* Assessment of presence and likely impact of publication bias	NO	NO	YES
16. Reported potential COI sources, funding they received	YES	YES	YES

NOTES:

[§] AMSTAR-2 rating for overall confidence.

*Multiple non-critical weaknesses may diminish confidence in the review and it may be appropriate to move the overall appraisal down from moderate to low confidence.

- **High** - No or 1 non-critical weakness: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest
- **Moderate** - More than 1 non-critical weakness*: the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review
- **Low** - 1 critical flaw with or without non-critical weaknesses: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest
- **Critically low** - More than 1 critical flaw with or without non-critical weaknesses: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies

Table 2. Risk of bias assessment using Cochrane risk of bias tool for observational studies

Study	Selection	Exposure	Outcome at start	Adjustment	Prognostic factors	Assessment of outcome	Follow-up	Co-interventions	Risk of Bias
Liu	Y	Y	N/A	Y	Y	Y	Y	Y	Low
Wallis	Y	Y	N/A	Y	Y	Y	Y	Y	Low
Pilloto	Y	Y	Y	Y	Y	Y	Y	Y	low

Table 3. Methodological quality of included studies in Martimbianco et al., using the NIH Quality Assessment Tool for Case Series Studies

Criteria/Judgment		1	2	3	4	5	6	7	8	9	Score	%	Quality*
1	Bellan 2021	Yes	Yes	Yes	Yes	NA	Yes	NA	Yes	Yes	7/7	100	High
2	Carfi 2020	No	Yes	Yes	Yes	NA	Yes	NA	No	Yes	5/7	71.4	Moderate
3	Carvalho-Schneider 2020	Yes	Yes	Yes	Yes	NA	Yes	NA	Yes	Yes	7/7	100	High
4	El Sayed 2020	Yes	Yes	Yes	Yes	NA	Yes	NA	Yes	Yes	7/7	100	High
5	Garrigues 2020	No	Yes	Yes	Yes	NA	Yes	NA	Yes	Yes	7/7	100	High
6	Guedj 2020	No	Yes	Yes	Yes	NA	No	NA	Yes	Yes	6/7	85.7	High
7	Halpin 2020	No	Yes	Yes	Yes	NA	Yes	NA	Yes	Yes	7/7	100	High
8	Huang 2021	Yes	Yes	Yes	Yes	NA	Yes	NA	Yes	Yes	7/7	100	High
9	Jacobs 2020	No	Yes	Yes	Yes	NA	Yes	NA	Yes	Yes	6/7	85.7	High
10	Liang 2020	Yes	Yes	Yes	Yes	NA	Yes	NA	Yes	Yes	7/7	100	High
11	Lu 2020	Yes	Yes	Yes	Yes	NA	No	NA	Yes	Yes	6/7	85.7	High
12	Moreno-Perez 2021	Yes	Yes	Yes	Yes	NA	Yes	NA	Yes	Yes	7/7	100	High
13	Nehme 2020	Yes	Yes	Yes	Yes	NA	Yes	NA	No	No	5/7	71.4	Moderate
14	Otte 2020a /Otte 2020b	Yes	Yes	Yes	Yes	NA	Yes	NA	Yes	No	6/7	85.7	High
15	Petersen 2020	Yes	Yes	Yes	Yes	NA	Yes	NA	Yes	Yes	7/7	100	High
16	Puchner 2021	Yes	Yes	Yes	Yes	NA	Yes	NA	Yes	Yes	7/7	100	High
17	Ramani 2021	No	Yes	Yes	Yes	NA	Yes	NA	No	No	4/7	57.1	Moderate
18	Rosales-Castillo 2021	No	Yes	Yes	Yes	NA	Yes	NA	NA	Yes	5/6	83.3	High
19	Roth 2021	No	Yes	Yes	Yes	NA	Yes	NA	NA	Yes	5/6	83.3	High

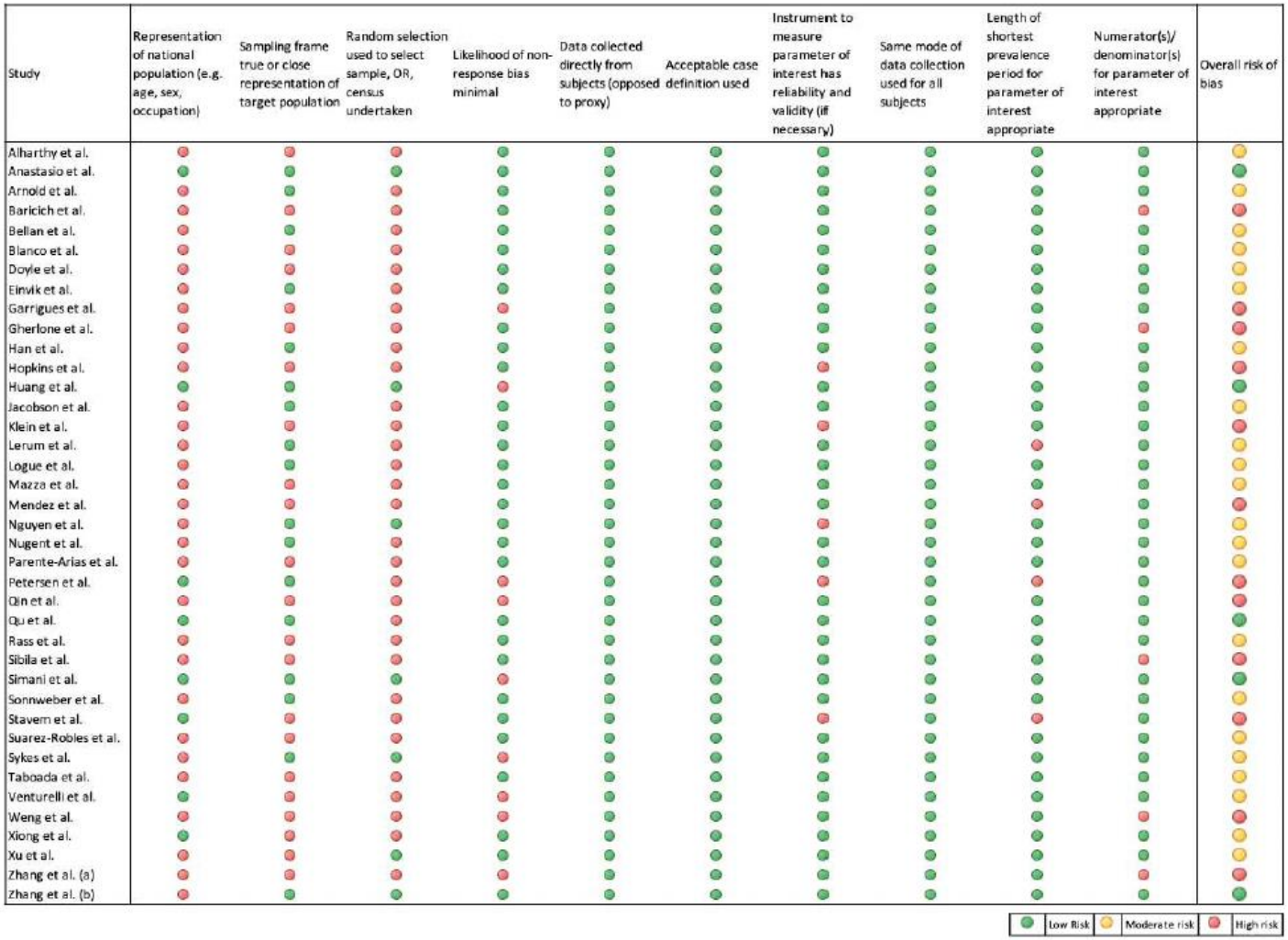
Criteria/Judgment		1	2	3	4	5	6	7	8	9	Score	%	Quality*
20	Simani 2021	Yes	Yes	Yes	Yes	NA	Yes	NA	Yes	Yes	7/7	100	High
21	Suarez-Robles 2020	Yes	Yes	Yes	Yes	NA	Yes	NA	NA	Yes	6/6	100	High
22	Tarazona-Fernandez 2020	No	Yes	Yes	Yes	NA	Yes	NA	NA	No	4/6	66.7	Moderate
23	Van den Borst 2020	Yes	Yes	Yes	Yes	NA	Yes	NA	Yes	Yes	7/7	100	High
24	Xiong 2021	Yes	Yes	Yes	Yes	NA	Yes	NA	Yes	Yes	7/7	100	High
25	Zhao 2020	No	Yes	Yes	Yes	NA	No	NA	Yes	No	4/7	57.1	Moderate

NA: not applied; NR: nor reported.

NIH Quality Assessment Tool for Case Series Studies

*(1) Was the study question or objective clearly stated? (2) Was the study population clearly and fully described, including a case definition? (3) Were the cases consecutive? (4) Were the subjects comparable? (5) Was the intervention clearly described? (6) Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants? (7) Was the length of follow-up adequate? (8) Were the statistical methods well-described? (9) Were the results well-described? * Considering the frequency of compliance with the relevant items, at the discretion of the review authors, the studies were categorized as presenting: high quality (80% or more of accomplished items), moderate quality (=>50% to <80%) or low quality (< 50%).*

Table 4. Risk of Bias assessment for studies included in the SR by Michelen et al.



Appendix 4. Results of Included Studies

Table 1. Long COVID symptoms reported in the included studies

Study	Symptoms by system								
	Cardio-Pulmonary	Gastro-intestinal	Musculo-skeletal	Neuro-cognitive	Neurologic and neuro-muscular	Psychological and social	Systemic	Upper respiratory	Others
IQBAL ACUTE POST COVID Symptom proportion (# of studies) (95% CI) Total (T) Subgroup analysis based on Community (C) Previously hospitalized (H) Mixed (M)	Cough T (5): 0.07 (0.03-0.11) C (1) 0.14 (0.07-0.24) H (3): 0.07 (0.05-0.10) M (1): 0.03 (0.01- 0.05) Dyspnea T (6): 0.35 (0.16-0.56) H (5): 0.41 (0.32-0.51) M (1): 0.05 (0.04-0.08)				Ageusia T (7): 0.20 (0.07-0.36) C (3): 0.41 (0.21-0.62) H (3): 0.06 (0.01-0.14) M (1): 0.14 (0.08-0.21) Anosmia T (9) 0.21 (0.11-0.33) C (5) 0.51 (0.42-0.61) H (3): 0.06 (0.02-0.13) M (1): 0.07 (0.04-0.13)	Depression T (3): 0.20 (0.09-0.33) H (2): 0.14 (0.08-0.21) M (1) 0.31 (0.27-0.36)	Fatigue: T (9): 0.37 (0.20-0.56) C (3): 0.15 (0.11-0.19) H (4): 0.62 (0.54-0.71) M (2): 0.26 (0-0.69)		
CHRONIC POST COVID	Cough T (5): 0.11 (0.07-0.17) H (3): 0.16 (0.12-0.20) M (2):0.07 (0.05-0.09) Chest pain/tightness T (6): 0.17 (0.05-0.35) H (2): 0.10 (0.06-0.14) M (4): 0.21 (0.05-0.44)				Ageusia T (6): 0.18 (0.10-0.28) C (2): 0.21 (0.11-0.33) H (1): 0.11 (0.06-0.17) M (3): 0.18 (0.05-0.37) Anosmia T (8): 0.17 (0.10-0.25) C (2): 0.34 (0.15-0.55) H (3): 0.16 (0.12-0.20_		Fatigue: T (9): 0.48 (0.23-0.73) C (3): 0.61 (0.09-0.99) H (2): 0.47 (0.32-0.63) M (4): 0.38 (0.04-0.82)		Sleep disturbance T (4): 0.44 (0.08-0.85) C (1): 0.88 (0.86-0.89) H: 0.28 (0.23-0.33)

Study	Symptoms by system								
	Cardio-Pulmonary	Gastro-intestinal	Musculo-skeletal	Neuro-cognitive	Neurologic and neuro-muscular	Psychological and social	Systemic	Upper respiratory	Others
	Dyspnea T (7): 0.39 (0.16-0.64) H (4): 0.43 (0.35-0.52) M (3): 0.32 (0.01-0.80)				M (3):0.09 (0.03-0.19) Headache T/M (3): 0.12 (0-0.44)				
Martimbianco	Any CV symptom N=1 13% Chest pain N= 7 studies 0.4-89% Cough/sputum production N= 13 studies 1.8-59% Dyspnea N= 16 studies 5.5-61% Palpitations N= 4 studies 9-62%	Diarrhea and GI symptoms N= 9 studies 1.3-33% Fecal incontinence N= 1 study 3% Lack of appetite N= 2 studies 6.2-8%	Arthralgia N= 9 studies 5.9-54.7% Limb numbness N= 1 study 6.6% Limb edema N=1 study 2.6% Myalgia N= 10 studies 2-50.6% Mobility dysfunction N= 2 studies 6.6-7%	Cognitive/memory/ concentration impairment N= 9 studies 18-57.1%	Ageusia/dysgeusia (N=15 studies) 1-21.6% Anosmia (N=19 studies) 0-26.2% Headache N= 10 studies 2-39% Hearing loss N=1 study 1.6% Sensitivity d/o 1 study 7.5% Tremor 1 study 1.6% Vision changes 1 study 1.6%	Communication difficulty N=1 6% Depression and anxiety N= 5 studies 3-25% PTS/mood changes/ psychological symptoms N= 5 studies 5.8-57.1% Functional impairment N= 2 studies 5.7-50% Physical dysfunction N= 4 studies 4-28.3% Sleep disturbance N= 5 studies 21.7-53%	Chills N= 1 study 4.6% Fatigue/asthenia N= 17 studies 6.6-64% Fever N= 6 studies 0-20% Pain and discomfort N= 3 studies 19-66% Vertigo/dizziness N= 3 studies 2.6-6%	Rhinitis 1 study 16.7% Red eyes 1 study 13.9% Sore throat/throat pain N= 5 studies 3.2-11%	Cutaneous signs N=4 studies 1.5-20% Hair loss N= 3 studies 20-28.6% Laryngeal sensitivity N= 1 study 17% Swallow problem 1 study 8% Sweating 1 study 23.6% Urinary incontinence 1 study 10% Voice change

Study	Symptoms by system								
	Cardio-Pulmonary	Gastro-intestinal	Musculo-skeletal	Neuro-cognitive	Neurologic and neuro-muscular	Psychological and social	Systemic	Upper respiratory	Others
									1study 20%
Michelen Subgroup analysis Hospitalised (H) Non-hospitalised (c) Mixed (M) (N studies), proportion (95% CI)	Breathlessness/ dyspnea H (14): 28.68 (18.48-41.64) M (3): 32.57 (14.26-58.38) C (4) 13.72 (8.51-21.37) Chest pain H (11): 5.92 (2.45-13.63) M (2): 6.18 (0.01- 97.66) C (1) 14.58 (8.83-23.13) Cough H (11): 10.52 (5.93-17.98) M (3): 4.91 (0.25-51.82) C (3) 5.95 (1.53-20.5) Excessive sputum/ expectoration H (5): 6.02 (3.2-11.03) C (1): 3.55 (2.18-5.71) Other CVS symptoms H (2): 4.2 (0-99.97)	Diarrhea H (7): 2.93 (0.9-9.12) M (1): 8.89 (5.12-15) C (3) 4.16 (0.72-20.65) Nausea or vomiting H (2) 5.84 (0-100) M (1): 8.89 (5.12-15) C (2): 3.66 (0-98.24) Stomach/abd pain H (2): 4.63 (0.03-89.2) M (1): 0.65 (0.27-1.56) C (1): 3.33 (2.01-5.44) Weight loss H (1): 37.31 (29.55-45.79) C (1): 10.83 (8.23-14.12)	Impaired mobility H (5): 17.33 (4.75- 46.83) M (1): 5.19 (2.49-10.48) Joint pain/ arthralgia H (8): 9.36 (5.25-16.14) C (1): 9.31 (6.95-12.36) Muscle pain/myalgia H (7): 12.46 (4.3-31.09) M (4): 10.86 (3.45-29.36) C (2): 10.76 (0.24-85.64)	Confusion M (4): 10.86 (3.45-29.36) C (1): 9.31 (6.95-12.36) Memory impairment H (3): 34.78 (23.64-47.88 M (2): 8.06 (0-99.97) C (1): 15.62 (9.64-24.32) Other cognitive impairment H (1): 9.7 (5.72-15.99) M (2): 23.55 (0-100)	Decreased sensation or sensibility H (1) 7.46 (4.06-13.31) M (1): 14.81 (9.76-21.85) Headache H (5): 2.98 (0.47-16.53) M (3): 3.30 (0.12-50.2) C (4): 8.82 (4.41-16.85) Smell disturbance H (9): 12.16 (7.98-18.1) M (6): 14.63 (5.46-33.72) C (5): 22.19 (11.69-38.04) Taste disturbance H (8): 11.07 (6.9-17.28) M (5): 14.5 (3.4-44.98) C (5): 16.83 (7.91-32.26) Tingling/paresthesia	Anxiety H(4): 25.58 (6.36-63.49) M (3): 11.60 (6.03-21.15) Care dependency H (1) 1.55 (1.05-2.29) M (2): 12 (0.39-82.45) Depression H (2) 10.38 (0-9.83) M (4) 6.8 (3.99 11.37) Low mood/ dysphoria H (2): 9.49 (0-100) M (1): 0 (0-100) PTSD H (3) 10.52 (3.06-30.44) M (3) 8.73 (0.46-66.23) C (1) 7.03 (5.02-9.78) Reduced QoL H (1) 47.96 (43.77-52.18)	Dizziness H (2) 4.21 (0.08-83.74 M (2): 3.78 (0.03-83.74) C (1): 6.68 (4.68-9.45) Fatigue H (11): 37.10 (26.45-49.06) M (3) 21.04 (10.48-37.75) C (4): 24.6 (20.11-29.72) Fever H (4) 0.85 (0.02-24.2) M (1) 21.04 (10.48-37.75) C (3): 1.41 (0.06-24.82) Sweat or night sweats H (1) 23.61 (20.21-27.38) M (1) 24.14 (17.87-31.76) Weakness H (1): 54.48 (46-62.7) M (1) 29.82 (25.42-34.61)	Nasal congestion H (1): 4.55 (0.64-26.15) C (3): 4.99 (2.72-8.99) Other respi symptoms H (2): 32.43 (2.22-91.02) C (1): 2.88 (1.68-4.9) Sore throat H (4) 4.81 (1.6-13.6) M (2) 4.39 (0.32-39.44)	Hair loss H(4): 23.54 (17.68-30.61) M (1): 3.17 (1.81-5.49) C (1): 10.42 (5.70-18.29) Skin rash H (3): 3.53 (0.75-15.11) C (1): 1.55 (0.74-3.22)

Study	Symptoms by system								
	Cardio-Pulmonary	Gastro-intestinal	Musculo-skeletal	Neuro-cognitive	Neurologic and neuro-muscular	Psychological and social	Systemic	Upper respiratory	Others
	M (1): 0.13 (0.02-0.92) Palpitations H (6): 12.43 (7.78-19.29_ M (2): 4.67 (0.60-28.47) C (1): 7.29 (3.52-14.51)				H (1): 3.28 (1.24-8.41) M (1): 21.48 (15.36- 29.21) Tremors H (1): 4.65 (3.16-6.79) M (1): 9.63 (5.67-15.88) C (1) 0.89 (0.33-2.34) Visual disturbance M (1): 6.67 (3.5-12.32) C (1) 4.21 (2.7-6.51) Walking/gait abnormality H (2) 4.01 (0.34-33.61) M (1) 5.19 (2.49-10.48)	M (2) 30.34 (7.43-70/27) Sleep disorder H (5): 25.81 (18.85-34.26) M (4): 10.66 (1.76-44.22)			

Table 2. Symptoms associated with the development of long COVID as reported by the included studies

Studies	Factors (Studies)	Long COVID symptoms associated with (if specified)
Martim-bianco [5] (14 studies)	**Severity** (9 studies)	● 1 study: **hospital admission** during the acute phase **led to persistent symptoms** ● 2 studies: **hospital admission had no effect** to development of persistent symptoms ● 1 study: **ICU admission led to functional impairment** on follow-up ● 3 studies: **ICU admission has no association** with any long covid symptoms ● 1 study: mild to moderate symptoms had higher risk for dyspnea compared to those with severe disease during the acute phase ● 1 study: those with severe disease requiring HFNC, NIV or MV were at risk to develop dyspnea, fatigue or muscle weakness, mobility problems, pain or discomfort, anxiety or depression and a DLCO of < 80%
	Specific symptoms (2 studies)	● 2 studies: **no specific symptoms** were found to be predictive of long covid based
	Age (10 studies)	● 4 studies: **no association for age** and prolonged symptoms of COVID-19 ● 6 studies: **older age led to symptoms of long covid**, including functional impairment, dyspnea, fatigue or muscle weakness, and persistence of symptoms during the acute phase
	Sex (8 studies)	● 3 studies: **female sex** was associated with fatigue or muscle weakness, anxiety or depression and persistent symptoms ● 1 study: **male sex** was associated with fatigue or muscle weakness ● 4 studies: **no association** with any long covid symptoms
	Comorbid condition (5 studies)	● 1 study: **COPD was linked** to functional impairment ● 4 studies: **comorbid conditions are not predictive** of long covid symptoms
	Others	● Other investigated factors that were **not seen to be associated** with long covid were smoking status (1 study), educational level (1 study), treatment received during the acute phase (2 studies) and inflammatory markers (1 study)
Michelen [6] (39 studies)	**Severity** (22 studies)	**Dyspnea/shortness of breath during acute phase** ● 3 studies: RF for persistent symptoms in general, physical decline, fatigue, polypnea and increased resting heart rate ● 1 study: not associated **Prolonged hospital stay** ● 2 studies: RF for lung pathology and limitation of functional status **Admission to ICU/requiring mechanical ventilation** ● 7 studies: RF for limitation of functional status/physical impairment, persistence of symptoms, DLCO < 80%, persistent CT abnormalities, new neurologic symptoms, anxiety, dyspnea and fatigue

Studies	Factors (Studies)	Long COVID symptoms associated with (if specified)
		● 2 studies: not RF **Pneumonia/lung pathology during acute phase** ● 2 studies: RF for dyspnea and increase pulmonary CT imaging findings ● 5 studies: severity not associated with any symptoms
	Age (6 studies)	● 6 studies: older age is a risk factor for the development of functional impairment, persistence of initial symptoms, mobility problems, sleep or neurologic disturbance, and poor quality of life scores
	Sex (10 studies)	● 8 studies: female gender is reported to be associated with a risk for functional impairment, persistence of initial symptoms, fatigue or muscle weakness, pain or discomfort, anxiety or depression, DLCO < 80%, sleep disturbance and poor quality of life scores ● 2 studies: male gender thought to be a risk for mobility problem and spirometric abnormality on follow-up
	Comorbid condition (7 studies)	● 7 studies: presence of comorbid conditions is associated with increased risk for functional impairment, persistence of initial symptoms, mobility problems, anxiety or depression and spirometric abnormality
Additional studies identified		
Liu	● Age more than 50 years old, severe COVID-19 status during the acute phase, hospital stay >18 days, mechanical ventilation, steroid or immunoglobulin therapy were associated with incomplete resolution of pulmonary pathologies imaged via a chest CT scan. ● Having an imaging opacity score of >4 and volume of opacity >235 mL at discharge were predictive of persistence of pulmonary findings after 6 months of the initial infection. ● Sex was not associated with persistence of pulmonary pathology.	
Wallis	● Among admitted patients with COVID-19, those who had a longer hospital stay (20 days or more), were current or previous smoker and who are obese were more prone to have persistence of pulmonary abnormalities on chest radiographs after 12 weeks of discharge. ● Severity of condition, age, oxygen support, sex, ethnicity, and comorbid conditions such as asthma, diabetes or hypertension were not associated with persistence of chest x-ray findings	
Pilloto	● Those with moderate to severe conditions during the acute phase of infection had an increased risk for memory problems, functional impairment, confusion, fatigue and visual disturbance ● An older age, presence of comorbidities, and more severe condition had more symptoms at follow-up ● Longer duration of hospitalization and presence of comorbidities were associated with neurologic abnormalities on follow-up	

Table 3. Risk factors associated with individual symptoms of long COVID

Symptom	Risk factor	Description
Fatigue	Severity	● One study stated that those who required HFNC, NIV or MV during the acute phase were at increased risk to develop fatigue (OR 2.69, 95%CI 1.46-4.96) ● One study reported that patients that had fatigue had more severe disease during the acute phase (p <0.02) ● One study reported that those with moderate to severe condition had increased risk to develop fatigue on follow-up (OR 2.1, 95% CI 0.95-4.6)
	Older age	● Older population was at risk for fatigue in one study (OR 1.17, 95%CI 1.07-1.27) ● Another study stated that the age group of 41-60 years old (47%) and 61-80yrs old (42%) had less incidence of fatigue compared to 20-40yrs old (11%)
	Sex	● Female sex was associated with fatigue in one study (OR 1.33, 95%CI, 1.05-1.67). ● Another study reported that 66% of those with fatigue were females. ● One study found that male sex was more predisposed to fatigue (OR 2.65, 95%CI 1.07-6.9)
Dyspnea	Severity	● One study said that dyspnea on follow-up was worse in mild cases compared to moderate to critical patients (p<0.001) ● This was countered by one study that said those requiring HFNC, NIV or MV were prone to develop dyspnea (OR 2.15, 95%CI 1.28-3.59) ● Two studies also said that severity of initial symptoms were predictive of dyspnea (p=0.001, p <0.05)
Sleep disturbance	Severity	● Severity of initial symptoms are predictive according to one study (p=0.001)
	Sex	● Female were at risk according to one study (p=0.009)
Functional impairment	Severity	● ICU admission is a risk factor for functional impairment according to one study (OR 2.59, 95% CI 1.06-6.36) ● The severity ofa initial symptoms are also predictive of functional impairment (OR 3.1, 95%CI 1.3-7.9)
	Old age	● Old age was predictive according to three studies ○ OR 0.96 (95% CI 0.93-0.99) ○ p=0.028 ○ OR 2.6 (95%CI 1.19-5.67)
	Comorbids	● Presence of comorbidity is RF according to one study (p=0.031) while another study specified COPD as a predictive factor COPD (OR 12.7, 95% CI 1.41-1114.85)

	Sex	● Females are at risk for functional impairment according to one study (p= 0.003).
Anxiety/depression or any psychiatric symptoms	Severity	● Those requiring HFNC, NIV, MV during the acute phase were prone to develop these symptoms (OR 1.77, 95% CI 1.05-2.97) ● Severity of initial symptoms specifically neuropsychiatric symptoms (p=<0.001) and GI symptoms (p=0.016)
	Sex	● Female sex was more associated with anxiety/depression or any psychiatric symptoms with an OR of 1.8 (95%CI 1.39-2.34) in one study. This is supported by two other studies with p=0.003 and p=0.001. ● One study found no difference between males and females

Appendix 5. Significant risk factors for long COVID

Source: Michelen, et al. BMJ Global Health 2021; 6:e005427. doi: 10.1136/bmjgh-2021-005427

Supplement 14: Risk factors

Study	Category	Risk factor	Associated with	Method	P Value/ CI
Nguyen et al.	Sex	Female sex	Persistent symptoms	Chi-squared or the Fisher exact test	p = 0.02
Mazza et al.	Sex	Female sex	Persistence of depressive symptomatology	Multivariate GLM analysis	(Wilks' λ = 0.92; F = 5.76; p = 0.003)
	Comorbidities	Previous psychiatric diagnosis			(Wilks' λ = 0.93; F = 5.29; p = 0.006)
	Severity	Presence of psychopathology at one-month			(Wilks' λ = 0.82; F = 15.16; p < 0.001)
Parentes-Arias et al.	Age	<60 years	Olfactory dysfunction	Multivariable-adjusted ORs	p = 0.028
	Sex	Female sex			p = 0.003
	Comorbidities	1 comorbidity			p = 0.031
Xiong et al.	Sex	Female sex	Covid-19 sequelae	Multivariable logistic regression model	Physical decline/fatigue (p < 0.01) Postactivity polypnoea (p= 0.04) Alopecia (p < 0.01)
	Severity	Dyspnea during hospitalisation	Physical decline/fatigue, postactivity polypnoea and resting heart rate increases	Univariate analysis	Physical decline/fatigue (p=.02) Postactivity polypnoea (p=.01) Resting heart rate increases (p=.01)
Sykes et al.	Sex	Female sex	Persistent symptoms	Chi-Square and Mann–Whitney U testing	Anxiety (p=0.001),low mood (p=0.031), myalgia (p=0.022), fatigue (p=0.004), sleep disturbance (p=0.009), and memory impairment (p=0.001)
Taboada et al.	Age	Age	Limitations in the functional status (grade II-IV of PCSF)	Multivariate logistic regression model	(OR = 2.600, 95% CI: 1.192–5.671)
	Severity	Length of hospital stay			(OR = 1.049, 95% CI: 1.009–1.090)
	Severity	Admission to ICU / mechanical ventilation			P < 0.001
Qu et al.	Sex	Female sex	Poor QoL scores	Logistic regression	(OR: 1.79, 95% CI: 1.04–3.06)
	Age	Older age (≥60 years)			(OR: 2.44, 95% CI: 1.33–4.47)
	Severity	Physical symptom after discharge			(OR: 40.15, 95% CI: 9.68–166.49)
Einvik et al.	Sex	Female sex	Symptoms of post-traumatic stress	Multivariable linear regression	NR
	Ethnicity	Born outside Norway			

	Severity	Dyspnoea during COVID-19			
Gherlone et al.	Comorbidities	COPD	Dry mouth	Multivariable analysis	(OR= 9.10, 95% CI: 1.8 -68.49)
Stavem et al.	Severity	Number of symptoms (10–23)	Symptoms at follow-up	Multivariable negative binomial regression analysis	(OR= 4.16, 95% CI:2.57 to 6.72, p<0.001)
	Comorbidities	≥2			(OR=2.52, 95%CI: 1.58 to 4.02, p<0.001)
Baricich et al.	Severity	ICU admission	Physical impairment	Multivariable logistic regression model	(OR: 3.1, 95%CI: 1.3-7.9, p=0.01)
	Age	Age	walking ability (SPPB)		p <0.02
	Comorbidities	Number or comorbidities	walking ability (SPPB) 2MWT		p <0.01 p <0.04
	Sex	Male gender	SPPB total score		p <0.01
Jacobson et al.	Ethnicity	Latin ethnicity	lower expected 6-MWT	Multivariate analysis	(-7.40 [-11.55-{-3.25}], p=0.001
	Comorbidities	BMI			(-0.52 [-0.81-{-0.22}], p=0.001)
	Severity	Persistence of symptoms at follow up	Shortness of breath		P=0.004
Petersen et al.	Age	Individuals in age group 50-66 compared with the youngest groups: 0-17 years 18-34 years	Persistent symptoms	Age-stratified analysis	p=0.003 p=0.001
Alharthy et al.	Severity	Increased incidence of dyspnoea and fever prior to hospital admission, decreased ICU admission PaO2/FiO2 ratio < 100, longer duration of mechanical ventilation, increased inflammatory biomarkers such as lactate dehydrogenase, ferritin, and D-dimers on ICU admission, and significant lung abnormalities detected by LUS	Persistent symptoms	Continuous variables using the Wilcoxon rank sum or the student's t-test. Categorical variables were examined using the Fisher's exact test or the Chi square test	p < 0.05

Michelen M, et al. BMJ Global Health 2021; 6:e005427. doi: 10.1136/bmjgh-2021-005427

Anastasio et al.	Severity	Pneumonia and ARDS	Shortness of breath	Pearson's correlation coefficient and Cox regression were used	Patients who developed ARDS showed higher SBP (p=0.05) and DBP (p=0.02) and lower SpO2 during 6 MWT (p=0.004), FVC (p=0.004) and TLC (p<0.001). Patients without ARDS showed higher SR (p<0.001), RV (p<0.001), TLC (p<0.001) and RV/TLC (p=0.05).
Han et al.	Severity	Higher baseline CT lung involvement score (>=18 out of a possible score of 25)	Fibrotic-like changes in the lung at 6 months	Multivariate analysis	(OR: 4.2, 95%CI: 1.2-14)
Blanco et al.	Severity	Severity of the disease	DLCO <80% and a lower serum lactate dehydrogenase level	Multivariate analysis	DLCO<80% (OR 5.92; 95%CI 2.28–15.37; p < 0.0001) Serum lactate dehydrogenase (OR 0.98; 95%CI 0.97–0.99)
Lerum et al.	Severity	ICU admission	Persistent CT abnormalities and problems in usual activities	Mann–Whitney U-tests or Chi-squared tests	p=.031
Bellan et al.	Severity	Higher DLCO	Decreased risk of physical impairment	Univariate analysis and logistic regression models	(OR, 0.96 [95% CI, 0.94-0.98]; P < .001)
	Comorbidities	COPD	Increase risk of physical impairment		(OR, 12.70 [95% CI, 1.41-114.85]; P = .02)
Sonnweber et al.	Severity	Age, gender, and pre-existing diseases such as cardiovascular diseases, pulmonary diseases, diabetes mellitus type 2, and malignancy	Persistence of symptoms, patient performance status, and CT findings at follow-up	Friedman's or Wilcoxon signed-rank test	p=0.042 to p<0.001
Mendez et al.	Sex	Female sex	Impaired DLCO	Linear regression analysis	0.002
	Severity	ICU patients	Pulmonary embolism		p<0.001
		D-dimer levels	Impaired DLCO		p= 0.011
Blanco et al.	Severity	Lower serum LDH levels	Impaired DLCO	Multivariate analysis	OR 0.98; 95% CI 0.97-0.99; p 0.002
Qin et al.	Severity	Higher TSS of the chest and ARDS lymphocyte count, MPA diameter on admission and ARDS	Impaired DLCO	Univariable analysis	TSS>10.5 (OR: 10.5; 95%CI: 2.5-44.1; P=0.001) ARDS (OR: 4.6; 95%CI: 1.4-15.5; P=0.014)
		Long hospital stay	Lung sequelae		

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Rass et al.	Severity	ICU patients	New neurological diseases	Chi-square or Kruskal-Wallis test	P=0.001
	Age	Elderly	Neurological signs	NR	NR
Weng et al.	Severity	Less severe (Lower frequency of supplemental oxygen therapy (79% vs 94%; p=0·016), and lower frequency of ICU admission	Gastrointestinal sequelae	Univariable and multivariable logistic regressions	p=0·016
		Treated more often with proton pump inhibitors (PPIs) and corticosteroids and were less frequently treated with enteral nutrition			PPI (p=0.000) Corticosteroids (p=0.024) Enteral nutrition (p=0.007)
Arnold et al.	Severity	Severe cases	Lower physical score	Mann Whitney-U and Kruskal Wallis tests for continuous data and Fisher's exact test or Chi-squared testing for categorical data.	NR
Sibila et al.	Sex	Male gender	Spirometric abnormalities 3 months after discharge,=	NR	Reduced FEV1: (76.9% vs 51.2%, p = 0.005) Reduced FVC: (76.3% vs 51.6%, p = 0.008)
	Comorbidities	Cardiovascular disease and diabetes			Reduced FEV1: Cardiovascular disease (34.2% vs 9.4%, p = 0.001) Diabetes (28.9% vs 12%, p = 0.02) Reduced FVC: Cardiovascular disease (29.7% vs 11.0%, p = 0.009)
Huang et al.	Severity	Participants with severity scale 5–6	Higher risk of lung diffusion impairment, anxiety or depression, and fatigue or muscle weakness	Multivariable analysis	OR 4·60 (95% CI 1·85–11·48) for diffusion impairment, OR 1·77 (1·05–2·97) for anxiety or depression, and OR 2·69 (1·46–4·96) for fatigue or muscle weakness
	Sex	Female sex			

ARDS: Acute respiratory distress syndrome; BMI: Body mass index; CT: Computerised Topography; DCLO: diffusing capacity for carbon monoxide; ICU: Intensive care unit; LDH: Lactate dehydrogenase; LUS: lung ultrasound; MWT: minute walking test; NR: Not reported; OR: Odds Ratio; PCSF: post covid functional status; QoL: Quality of life; SPPB: Short Physical Performance Battery test; TSS: Toxic shock syndrome

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