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1 **Prevalence of Post-acute COVID-19 Syndrome Symptoms at Different Follow-up Periods: A**
2 **Systematic Review and Meta-Analysis**

3
4 **Running title:** PACS Symptoms at Different Follow-up Periods

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51 **Abstract**

52 **Background:** Post-acute COVID-19 Syndrome is now recognized as a complex systemic disease that is
53 associated with substantial morbidity.

54 **Objectives:** To estimate the prevalence of persistent symptoms and signs at least 12 weeks after
55 acute COVID-19 at different follow-up periods.

56 **Data sources:** Searches were conducted up to October 2021 in Ovid Embase, Ovid Medline, and
57 PubMed.

58 **Study eligibility criteria:** Articles in English that reported the prevalence of persistent symptoms
59 among individuals with confirmed SARS-CoV-2 infection and included at least 50 patients with a
60 follow-up of at least 12 weeks after acute illness.

61 **Methods:** Random-effect meta-analysis was performed to produce pooled prevalence for each
62 symptom at 4 different follow-up time intervals. Between-studies heterogeneity was evaluated using
63 the I^2 statistic and was explored via meta-regression, considering several a priori study level
64 variables. Risk of bias was assessed using the Joanna Briggs Institute (JBI) tool and the Newcastle-
65 Ottawa Scale for prevalence studies and comparative studies, respectively.

66 **Results:** After screening 3209 studies, a total of 63 studies were eligible, with a total COVID-19
67 population of 257,348. The most commonly reported symptoms were fatigue, dyspnea, sleep
68 disorder and concentration difficulty (32%, 25%, 24%, and 22% respectively at 3-<6 months follow-
69 up), effort intolerance, fatigue, sleep disorder and dyspnea (45%, 36%, 29% and 25% respectively at
70 6-<9 months follow-up), fatigue (37%) and dyspnea (21%) at 9-<12 months and fatigue, dyspnea,
71 sleep disorder, myalgia (41%, 31%, 30%, and 22% respectively at >12 months follow-up). There was
72 substantial between-studies heterogeneity for all reported symptoms prevalence.

73 Meta-regressions identified statistically significant effect modifiers: world region, male gender,
74 diabetes mellitus, disease severity and overall study quality score. Five of six studies including a
75 comparator group consisting of COVID-19 negative cases observed significant adjusted associations
76 between COVID-19 and several long-term symptoms.

77 **Conclusions:** This systematic review found that a large proportion of patients experience PACS 3 to
78 12 months after recovery from the acute phase of COVID-19. However, available studies of PACS are
79 highly heterogeneous. Future studies need to have appropriate comparator groups, standardized
80 symptoms definitions and measurements and longer follow-up.

81 INTRODUCTION

82 A significant number of patients who have recovered from acute COVID-19 infection are reporting
83 lasting symptoms resulting in impairment of everyday activities beyond the initial acute period. These
84 post COVID-19 patients suffer from a phenomenon known as "long" or "chronic" COVID-19 or more
85 recently, Post-Acute Sequelae of COVID-19 or Post-Acute COVID-19 syndrome (PACS) (1,2).

86

87 The terms "long COVID-19" and "post-acute COVID-19 syndrome (PACS)" lack a unified definition. The
88 definition endorsed by the National Institute for Health and Care Excellence (NICE) and the World Health
89 Organization (WHO) as a set of "signs and symptoms that emerge during or after an infection consistent
90 with COVID-19, persist for more than 12 weeks, and are not explained by an alternative diagnosis" (3,4).

91 Many experts including the NICE panel also agree to subdivide into two categories: 1- post-COVID-19
92 subacute phase of ongoing symptoms that last 4-12 weeks after the onset of illness, and 2- chronic
93 phase or long COVID-19, defined as symptoms and abnormalities that last more than 12 weeks after the
94 onset of illness and are not explained by an alternative diagnosis (2,4).

95

96 This timeframe distinction is important because it differentiates between the acute illness and the
97 sequelae of possibly an irreversible tissue damage with varying degrees of dysfunction and symptoms
98 potentially involving several possible conditions as suggested by some experts: post-intensive care
99 syndrome, post-thrombotic or hemorrhagic complications, acute-phase immune-mediated
100 complications, and/or multi-systemic inflammatory syndrome in children or adults (5). Globally, the
101 number of patients recovering from COVID-19 infection continues to grow at an unprecedented rate.
102 Therefore, we sought to perform a systematic review and meta-analysis of available literature to

103 estimate the prevalence of persistent symptoms and signs after at least 12 weeks of acute COVID-19 at
104 different follow-up (FU) periods.

105

106 **METHODS**

107 This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)
108 guideline for study design, search protocol, screening, and reporting (6,7).

109 **Literature Search and Studies Selection**

110 The literature was searched by a medical librarian for the concepts of long-term symptoms in patients
111 infected by Covid-19. Search strategies were created using a combination of keywords and standardized
112 index terms. Searches were originally run in November 2020 and updated in January and September
113 2021 in Ovid Embase, Ovid Medline (including publication ahead of print, in-process & other non-
114 indexed citations) and PubMed.gov which includes preprints. Results were limited to English language
115 and primarily adult studies. All citations were exported to EndNote where 4,539 duplicates were
116 removed leaving 3,921 citations. Search strategies are provided in the supplementary material
117 (Supplement 1).

118 Articles were considered eligible for inclusion if they (1) were written in the English language; (2) were
119 peer-reviewed cohort, case-control or cross-sectional studies that reported the prevalence of persistent
120 symptoms among individuals with SARS-CoV-2 infection; (3) included at least 50 patients (4) had follow-
121 up of at least 3 months after symptoms onset (as per the NICE definition), (5) all patients with laboratory
122 confirmed COVID-19 and (6) follow-up reported as mean, median or set-interval following symptoms
123 onset, diagnosis, acute illness or initial CT chest imaging. Where studies had overlapping investigated
124 populations, studies with larger sample sizes were prioritized with the remainder excluded (8).

125 We subsequently identified a subgroup of these eligible studies that included studies with a comparator
126 group consisting of non-COVID cases.

127 **Identification of Studies**

128 Six reviewers (O.O., M.S.A., M.O., N.A.F., R.A., B.A.S.) examined the titles and abstracts of articles in
129 pairs, using the above pre-defined selection criteria. This was followed by a full text review of each
130 article to confirm meeting the eligibility criteria. Disagreements regarding inclusion of a full-text article
131 were discussed and agreed with the senior reviewer (IT).

132 **Data Collection**

133 Data were extracted simultaneously by six reviewers in duplicates (OO, NAF, BAS, RA, MSA, MO) into a
134 pre-specified data collection form, with any discrepancies resolved in consultation with the senior
135 reviewer (IMT). Data were collected across the following domains: study characteristics, follow-up
136 method, baseline demographics and symptom prevalence. Full details of the data collation variables can
137 be found in the supplementary material (Supplement 2).

138 **Quality Assessment**

139 The reviewers independently assessed the risk of bias for each study using the Joanna Briggs Institute
140 (JBI) critical appraisal tool for prevalence studies. JBI critical appraisal checklist for studies reporting
141 prevalence consists of nine questions: (1) Sample frame suitability,(2) Sampling method appropriateness
142 (3) Sample size adequacy,(4) Proper description of study subjects and setting, (5) Sufficient coverage of
143 the identified sample (6) Usage of valid methods for identification of the condition, (7) Standard and
144 reliable way of measurement of the condition for all participants, (8) Appropriate statistical analysis and
145 (9) Adequate response rate (9). Each study was assessed across each of these questions and determined
146 as either 'Yes', 'No' or 'Unclear'. Studies were assigned an overall score, reflecting the number of
147 questions with a 'Yes' response.

148 Studies with a comparator group consisting of non-COVID cases were assessed using the Newcastle-
149 Ottawa Scale (NOS) (10).The NOS rates observational studies based on 3 parameters: selection,
150 comparability between exposed and unexposed groups, and exposure and outcome assessment. These
151 3 domains can have a maximum score of 4, 2, and 3 stars, respectively. Studies with <5 stars are
152 considered low quality, 5–7 stars moderate quality, and >7 stars high quality.

153 **Data Synthesis**

154 Our outcome of interest was prevalence of symptoms at follow-up across four different follow up
155 intervals: 3-<6 months, 6-<9 months, 9-<12 months and ≥ 12 months. Due to varying definitions of “day
156 0” to follow up across the literature, we accepted definitions of “day 0” that include COVID-19 symptom
157 onset, COVID-19 diagnosis or hospital discharge after acute illness. We further categorized studies
158 according to the severity of COVID-19, which was defined in this context as patients’ setting during
159 acute illness: ranging from outpatient (OP), general inpatient wards (IP) or intensive care unit (ICU)
160 settings. Where symptoms prevalence at follow-up was not reported separately based on COVID-19
161 severity, studies were described as “mixed”, for example “mixed IP/ICU”.

162 The range of persistent COVID-19 symptoms reported to date was then identified and categorized.
163 Given the exchangeable terminology to refer to symptoms across studies, the following terms were
164 grouped: “sleep disturbance” to refer to insomnia, daytime sleepiness, sleep difficulties, and/or sleep
165 disorders, “concentration difficulties” to refer to confusion, change in level of consciousness and/or
166 concentration, “cognitive impairment” to refer to cognitive dysfunction, brain fog, and/or cognition
167 difficulties, “loss of taste” to refer to taste dysfunction, alteration of taste, dysgeusia, and parageusia,
168 “loss of smell” to refer to smell dysfunction, alteration of smell, anosmia, hyposmia, smell blindness, and
169 olfactory disorders. Signs and symptoms were divided into 7 main systems: mental health, respiratory

170 system, cardiovascular system, musculoskeletal system, nervous system, gastrointestinal system and
171 other.

172 **Statistical Analyses**

173 The total cohort number and the number of patients with different symptoms or complaints were
174 extracted from each study at different follow up times into 4 intervals: 3-<6 months, 6-<9 months, 9-<12
175 months and ≥ 12 months. We performed separate meta-analyses for the aforementioned follow up
176 intervals where ≥ 3 studies reported symptom prevalence at that follow up interval. The arcsine
177 transformation was used to obtain a pooled estimate of the prevalence of each symptom. As
178 conventional meta-analysis models assume normally distributed data, the arcsine-based
179 transformations are applied to the proportion data to yield better approximations to the normal
180 distribution and they have the important advantage of stabilizing variances (11,12). We used
181 DerSimonian and Laird random effect model with inverse variance method to pool prevalence (13). We
182 performed subgroup meta-analyses by severity of acute COVID-19 in the included studies, thereby
183 allowing a visual display of heterogeneity due the differences in the severity of illness in reporting
184 studies. We evaluated between-studies heterogeneity using the I^2 statistic, which estimates the
185 variability percentage in effect estimates that is due to heterogeneity rather than to chance (14). Two-
186 tailed $p < 0.05$ were considered statistically significant.

187 We performed meta-regression to explore between studies heterogeneity. We considered several a
188 priori chosen study level variables based on clinical plausibility (Supplement 3). Meta-regression was
189 performed for each symptom where ≥ 10 studies reported prevalence at any given follow-up interval as
190 per the Cochrane Handbook for Systematic Reviews (15). The regression coefficients obtained from the
191 meta-regression analyses describe how the outcome variable (the pooled prevalence) changes with a
192 unit increase in the continuous explanatory variable and changes for the category of interest compared

193 to a reference category for a categorical variable. The statistical significance was considered as
194 $p < 0.01$ for the results of the meta-regression and we reported if a variable was found to be a significant
195 contributor to heterogeneity. All statistical analyses were performed using Stata 12 statistical software
196 StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC. (16).

197

198 **RESULTS**

199 Of the 3209 abstracts screened, 152 full-text articles were reviewed with 63 included in the final analysis
200 (Figure 1) (17–79). After full article review, the most common reason for exclusion was the absence of
201 reported data on symptom prevalence at stated follow-up ($n=36$), followed by the inclusion of COVID-19
202 patients without laboratory confirmed COVID-19 ($n=23$). Of the 63 included studies (total COVID-19
203 population = 257348), six were from North America (COVID-19 sample size = 237261), twelve from East
204 Asia (COVID-19 sample size = 10162), thirty-seven from Europe (COVID-19 sample size = 8998) and eight
205 from North Africa, the Middle East, or South Asia (COVID-19 sample size = 927) (Table 1). The majority of
206 included studies were single center ($n = 43$), followed by multicenter ($n = 18$) with two nationwide
207 studies. Only four studies included follow up equal to or greater than 365 days (sample size = 1246),
208 with five studies with follow up of 270 to 364 days (sample size = 3758), twenty-five studies with follow
209 up of 180 to 269 days (sample size = 243576) and the majority of studies with follow up of 90 to 179
210 days ($n = 33$, sample size = 9323).

211 **Meta-analyses of prevalence of symptoms at different follow up periods**

212 Meta-analysis highlighted the substantial heterogeneity between symptom prevalence's reported across
213 studies, with I^2 statistics ranging from 75.4% (difficulty concentrating at 3-<6 months follow up) to 99.4%
214 (fatigue at 9-<12 months follow up), with the vast majority of symptoms across all follow up intervals
215 producing an $I^2 \geq 90\%$. The most commonly reported symptoms between 3-<6 months are fatigue (32%,

216 95% CI = 22-44%, number of studies = 25, sample size = 7268) followed by dyspnea (25%, 95% CI = 17-
217 34%, number of studies = 28, sample size = 8132), sleep disorder (24%, 95% CI = 8-44%, number of
218 studies = 8, sample size = 4369) and concentration difficulty (22%, 95% CI = 15-31%, number of studies =
219 5, sample size, = 466). Between 6-<9 months, the most common symptoms reported were effort
220 intolerance (45%, 95% CI – 25-67%, number of studies = 5, sample size = 850), fatigue (36%, 95% CI = 27-
221 46%, number of studies = 19, sample size 8191), sleep disorder (29%, 95% CI 15-45%, number of studies
222 = 12, sample size = 242000), and dyspnea (25%, 95% CI = 20-30%, number of studies = 13, 4384). In the
223 9-<12 months period, the meta-analysis included 9 symptoms with the highest prevalence reported for
224 fatigue (37%, 95% CI = 16-62%, number of studies = 5, sample size = 3758) and dyspnea (21%, 95% CI =
225 14-28%, number of studies = 5, sample size = 3758), with loss of taste being the least reported (6%, 95%
226 CI 1-13%, number of studies = 3, sample size = 1742). Similarly, fatigue was the most reported symptom
227 (41%, 95% CI 30-53%, number of studies = 4, sample size = 1246) in the >12 months period. It is
228 noteworthy that fatigue, dyspnea, myalgia, and sleep disorder were most reported in the >12 months
229 interval; while cough, headache, loss of taste and loss of smell were most common at 6-<9 months
230 (Figure 2, Panels A-B, Supplement 6, Panels C-D).

231 **Exploring Heterogeneity**

232 Due to a limited number of studies reporting symptom prevalence at 9-<12 months or ≥12 months,
233 meta-regression was performed for symptom prevalence at 3-<6 months and 6-<9 months (Supplement
234 6). Observed statistically significant effect modifiers included: world region where the study was
235 conducted, percentage of study participants who were men, and those who had DM, disease severity
236 category as defined earlier and the overall study quality score.

237 Studies reporting results from Asian populations reported a lower prevalence of fatigue, dyspnea, loss of
238 smell and loss of taste at 3-6 month follow up and a lower prevalence of fatigue at 6-9 month follow up.

239 A higher proportion of men was found to be associated with a lower prevalence of cough and loss of
240 smell at 6-9 months follow up, whilst a higher proportion of diabetes mellitus as a comorbidity was
241 associated with a lower prevalence of loss of smell and taste at 3-6 and 6-9 month follow up. Studies
242 investigating patients in ICU were associated with a higher prevalence of dyspnea compared to studies
243 investigating an OP population at 3-6 month and 6-9 month follow up intervals. Higher study quality was
244 found to be associated with lower prevalence of dyspnea at 3-6 months and cough at 6-9 months follow
245 up.

246 **Studies with a COVID-19 negative comparator group**

247 A total of 6 studies reporting symptoms prevalence included a comparator group consisting of COVID-19
248 negative cases, with a summary of their findings presented in Table 2 (17,24,26,37,59,62). Of these, 2
249 studies compared long term symptom prevalence of COVID-19 cases to either influenza, pneumonia or
250 other respiratory tract infection cases (17,26). Overall, all but one study reported higher prevalence of
251 symptoms or adverse event in cases following COVID-19 compared to respective comparator groups,
252 with one negative study specifically assessing olfactory and gustatory dysfunction at 6 months (37). Two
253 out of 6 studies were rigorously designed. One study observed that COVID-19 cases had significantly
254 higher hazard of mood disorder, anxiety and insomnia when compared to matched cohorts with
255 influenza or respiratory tract infection (26). Another study observed that COVID-19 cases have
256 significantly higher prevalence of symptoms at 6 and 9 months follow-up when compared to community
257 controls, including fatigue, sleep difficulties, hair loss, smell disorder, taste disorder, palpitations, chest
258 pain and headaches (45).

259 **Quality Assessment**

260 Studies without comparator groups

261 The studies were generally assessed to have good quality with a mean average critical appraisal score
262 across all studies of 7.97/9. The question that affected the scores the most was “Was the sample size
263 adequate?”, with few studies demonstrating appropriate sample size calculations nor representing a
264 significantly large enough sample to provide high external validity (Table S1).

265 Studies with comparator groups

266 Study quality was assessed via the NOS as moderate to high, ranging from 5 to 9 (maximum 9), with a
267 number of studies using an non-representative sample of healthcare workers (37,59), or having
268 comparability concerns by not adequately matching cases with the comparator group (17,37,59,62)
269 (Table S2).

270

271 **DISCUSSION**

272 **Summary of the findings**

273 In this systematic review and meta-analysis of 63 studies with a total of 257,348 COVID-19 patients from
274 different world regions, we observed that patients report several clinically significant symptoms across
275 many organs systems 3 months post-acute COVID-19. In addition, we observed that the high between-
276 studies heterogeneity of reported symptoms prevalence could at least be partially explained by clinically
277 plausible effect modifiers such as acute COVID-19 severity, and certain patients’ demographics and
278 comorbidities (26,45,80,81).

279 Our findings lend more support to the initiatives of several countries and organizations that have started
280 to fund more research and disseminate guidelines to better understand, diagnose and treat PACS
281 (8,82,83).

282

283 **Mechanisms**

284 It remains unknown what proportion of these lingering symptoms are true sequelae of COVID-19 vs. the
285 effects of underlying chronic diseases or pandemic effects on individuals and societies (84,85). Although
286 most studies did not have a control group, the association of certain symptoms with COVID-19 infection
287 among the 6 studies that had appropriate comparator groups supports our findings of a significant
288 burden of PACS. Recent rigorously conducted comparative studies that examined the risk of new clinical
289 sequelae rather than persistent symptoms at 6-month follow-up have shown a higher risk of long-term
290 complications and incident diagnoses after acute COVID-19 infection, among non-hospitalized cases
291 when compared to a matched non-COVID cohort, and hospitalized COVID-19 cases when compared to
292 matched hospitalized influenza cases or when compared to other non-COVID viral lower respiratory
293 tract illnesses. An increasing risk gradient of new sequelae was observed with increasing COVID-19
294 severity (86,87).

295 Nevertheless, the mechanisms that explain these chronic symptoms after COVID-19 are not yet fully
296 understood. In addition to the direct effects of SARS-CoV-2, the immune response to the virus is
297 believed to be partly responsible for the appearance of these lasting symptoms, possibly through
298 facilitating an ongoing hyperinflammatory process (88). Several hypotheses have been proposed to
299 explain the long-term outcomes of COVID-19 infection: a) Sequelae of COVID-19 organ involvement
300 during acute infection, b) COVID-19 patients with chronic symptoms may harbor the virus in several
301 potential tissue reservoirs across the body, which may not be identified by nasopharyngeal swabs, c)
302 cross reactivity of SARS-CoV-2-specific antibodies with host proteins resulting in autoimmunity, d)
303 delayed viral clearance due to immune exhaustion resulting in chronic inflammation and impaired tissue
304 repair, e) mitochondrial dysfunction and impaired immunometabolism, and f) alterations in microbiome
305 leading to long-term health consequences of COVID-19 (88–91).

306

307 **Comparison to other studies**

308 Our systematic review provides a rigorous and unique update of previous attempts by other
309 investigators. First, a number of previous reviews either did not assess the included studies for risk of
310 bias or utilized an inappropriate assessment tool, such as the Newcastle-Ottawa Scale for non-
311 comparative studies. We observed that the quality of included studies to be a significant contributor to
312 heterogeneity of reported symptoms prevalence, with lower quality studies reporting higher prevalence
313 of certain symptoms (92,93). Second, other systematic reviews have included studies with short follow-
314 up periods between one and three months after acute illness and hence do not provide an indication of
315 persistent and chronic symptoms that are defined beyond 12 weeks as per NICE (92–95). Third, although
316 previous studies have performed meta-analysis, with Michelen et al. performing meta-regression for
317 variables of ICU admission and proportion female and Iqbal et al. performing thorough sub-group
318 analysis, no previous systematic review has separated symptoms prevalence across different follow-up
319 intervals or considered other important effect-modifiers for meta-regression (96,97). Finally, and
320 importantly, we present the first attempt to identify and assess studies including an appropriate non-
321 COVID group to provide additional evidence of the association between COVID-19 and the high
322 prevalence of symptoms at follow-up.

323 Although our review included the most recent eligible studies with the largest sample size, there is a
324 degree of consistency between the findings of symptoms prevalence between our meta-analyses and
325 others. We report a prevalence of fatigue of 32%, 36%, 47% and 41% across follow up periods from 3 to
326 6 months, 6 to 9 months, 9 to 12 months and greater than 12 months respectively, which is comparable
327 to the findings of Michelen et al. (30.1%) and Iqbal et al. (37%). This similarity is also the case for
328 dyspnea, with previous meta-analysis reporting estimates of prevalence between 25 and 35%, as well as
329 myalgia and hair loss.

330

331 **Strengths and Limitations**

332 Our study is the largest and most comprehensive systematic review of persistent symptoms after acute
333 COVID-19 to date. However, it has a number of limitations inherent to the included studies and studies
334 design. As noted by previous systematic reviews on this topic, studies included in our review lacked
335 uniform symptom terminology, standardized recording methods, and grouping of multiple symptoms
336 under umbrella terms. This limited our ability to compare prevalence and frequency of these symptoms
337 across the studies. Severity of illness was not described in numerous studies, with results presented for
338 whole cohorts and not presented as sub-groups. Thus, grouping all symptoms of various disease severity
339 yield inaccurate estimates of symptoms frequencies. The high observed statistical heterogeneity as
340 measured by I^2 limit the interpretation of the pooled frequencies, although our extensive meta-
341 regression illuminates significant contributors to this heterogeneity; namely severity as defined by
342 highest level of medical care, geographic location, prevalence of diabetes and method of assessing
343 symptom at follow-up (98).

344 We agree with Nasserie et al. in their recommendations about areas of improvement in future research
345 of PACS whether in the conduct of studies or reporting of the various characteristics of symptoms for
346 such conditions including the use of a standardized definition for symptoms and time-zero and including
347 an objective measure of symptom severity and duration. There is a need for further rigorously
348 conducted cohort studies in order to quantify the relative risk of developing long term symptoms
349 following acute COVID-19 infections in comparison to non-COVID-19 comparator group, including
350 healthy controls and those with other acute respiratory infections (94,97,99).

351

352 **CONCLUSION**

353 In this large systematic review, we observed, with high degree between-study heterogeneity, that a
354 large proportion of COVID-19 patients have persisting and varying symptoms for several months after
355 the acute infection. While there remain many unanswered questions about PACS, our study brings more
356 evidence from a large number of patients and across different worldwide populations about the
357 prevalence of the long-term effects of COVID-19. Our data support the recent global efforts to conduct
358 additional research to address its underlying mechanisms, epidemiology, diagnosis, and treatment of
359 PACS.

360

361 **Conflict of interest statement**

362 The authors declare no conflicts of interest.

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370 Authors are listed in alphabetical order. Conceptualization: I.M.T. and T.K.; Supervision: I.M.T. and

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Table 1. Summary of all included studies in descending order by sample size.

Study	Study Design	Location	Sample size	Day zero	Follow-up in days	Assessment Method	Severity
Taquet et al.	Nationwide	USA	236379	Diagnosis date	180	EMR	Mixed IP/OP/ICU
Mei et al.	Multicenter	China	3677	Hospital discharge	144	In person	IP
César Fernández-de-las-Peñas et al.	Multicenter	Spain	1950	Hospital discharge	340	Telephone	Mixed IP/ICU
Chaolin Huang et al.	Single center	China	1733	Hospital discharge	186	In-person	Mixed IP/ICU
Huang et al.	Single center	China	1276	Symptom onset	185, 349	In-person	Mixed IP/ICU
Fernández-de-las-Peñas et al.	Multicenter	Spain	1142	Hospital discharge	213	Telephone, EMR	Mixed IP/ICU
Kim et al.	Single center	South Korea	822	Symptom onset or diagnosis date	195	Online	Mixed IP/OP/ICU
Shang et al.	Multicenter	China	796	Hospital discharge	180	Telephone	Mixed IP/ICU
Søraas et al.	Multicenter	Norway	676	Diagnosis date	132	Online	OP
Qin et al.	Single center	China	647	Hospital discharge	90	In person	IP
Maestre-Muñiz et al.	Single center	Spain	543	Hospital discharge	365	In person	Mixed OP/IP
Qu et al.	Multicenter	China	540	Hospital discharge	90	Telephone, Online	IP
Knut Stavem et al.	Multicenter	Norway	458	Symptom onset	117.5	Online, Postal/Mail	OP
Menges et al.	Nationwide	Switzerland	431	Diagnosis date	220	Online	Mixed IP/OP/ICU
Shoucri et al.	Single center	USA	364	Diagnosis date	158	In-person, telephone	Mixed IP/OP/ICU

Zayet et al.	Single center	France	354	Diagnosis date	289.1	Telephone, online	Mixed IP/OP/ICU
Augustin et al.	Single center	Germany	353	Symptom onset	207	In person	Mixed IP/ICU
Yin et al.	Single center	China	337	Symptom onset	203.4	In person	Mixed IP/ICU
Sigfrid et al.	Multicenter	United Kingdom	327	Hospital discharge	222	Telephone, In person, Postal	Mixed IP/ICU
Boscolo-Rizzo et al.	Multicenter	Italy	304	Symptom onset	365	Telephone	OP
DM Lombrado et al.	Single center	Italy	303	Diagnosis date	371	Telephone, EMR	Mixed IP/OP/ICU
Sathyamurthy P et al.	Single center	India	279	Hospital discharge	90	Telephone	Mixed IP/ICU
Blomberg et al.	Single center	Norway	247	Diagnosis date	180	In person	OP
Clavario et al.	Single center	Italy	200	Hospital discharge	180	In-person	IP
Darcis et al.	Single center	Belgium	199	Hospital discharge	94, 180	In person	Mixed IP/ICU
Riestra-Ayora et al.	Single center	Spain	195	Diagnosis date	180	Telephone	Mixed OP/IP
Jennifer A. Frontera t al.	Multicenter	USA	192	Symptom onset	201	Telephone	Mixed IP/ICU
Pablo Parente-Arias et al	Multicenter	Spain	151	Symptom onset	100.5	Telephone, EMR	Mixed OP/IP
Han et al.	Multicenter	China	144	Symptom onset	180	In-person	Mixed IP/ICU
Sonnweber et al.	Multicenter	Austria	135	Symptom onset	103	In-person	Mixed IP/OP/ICU
Froidure et al.	Single center	Belgium	134	Hospital discharge	95	In person	Mixed IP/ICU
Suárez-Robles et al.	Single center	Spain	134	Hospital discharge	90	Telephone	Mixed IP/ICU

González-Hermosillo et al.	Single center	Mexico	130	Hospital discharge	90, 180	Telephone	Mixed IP/ICU
Nguyen et al.	Single center	France	125	Symptom onset	221.7	Telephone	IP
Garrigues et al.	Single center	France	120	Hospital admission	110.9	Telephone	IP/ICU*
Mattioli et al.	Single center	Italy	120	Diagnosis date	126	In person	Mixed OP/IP
Tawfik et al.	Multicenter	Egypt	120	Diagnosis date	120	In person	Mixed OP/IP
Leila Simani et al.	Single center	Iran	120	Hospital discharge	180	In-person	Mixed IP/ICU
Jacobson et al.	Single center	USA	118	Diagnosis date	119.3	In person	Mixed IP/OP/ICU
Caruso et al.	Single center	Italy	118	Initial CT chest	180	In person	Mixed IP/ICU
Motiejunaite et al.	Single center	France	114	Diagnosis date	90	In-person	Mixed IP/OP/ICU
Schandl et al.	Single center	Sweden	113	ICU discharge	152	In person	ICU
Aranda et al.	Single center	Spain	113	Diagnosis date	240	In person	Mixed IP/ICU
Mechi et al.	Single center	Iraq	112	Diagnosis date	274	In person	OP
Skala et al.	Multicenter	Czech Republic	102	Diagnosis date	90	In-person	Mixed OP/IP
T. J. M. Wallis et al.	Single center	United Kingdom	101	Hospital admission	96	Telephone, in-person	Mixed IP/ICU
Lindahl et al.	Single center	Finland	101	Hospital discharge	180	Online	Mixed IP/ICU
Biadsee et al.	Single center	Israel	97	Diagnosis date	231	Telephone	OP
Seeßle et al.	Single center	Germany	96	Symptom onset	152, 365	In person	Mixed OP/IP

Boari et al.	Single center	Italy	91	Hospital discharge	120	In-person	Mixed IP/ICU
Taboada et al.	Multicenter	Spain	91	ICU discharge	180	In-person	ICU
Mumoli et al.	Single center	Italy	88	Hospital admission	91	In person	IP
Parry et al.	Single center	India	81	Initial CT chest	100.6	EMR	Mixed IP/OP/ICU
Wong et al.	Multicenter	Canada	78	Symptom onset	91	In-person	Mixed IP/ICU
Dieter Munker et al.	Multicenter	Germany	76	Diagnosis date	120	In-person	Mixed IP/OP/ICU
Liang et al.	Single center	China	76	Hospital discharge	90	In-person	Mixed IP/ICU
Noel-Savina et al.	Single center	France	72	Diagnosis date	129	In-person	Mixed IP/ICU
Elkan et al.	Single center	Israel	66	Hospital discharge	270	Online, telephone	IP
Jessica González et al.	Single center	Spain	62	Hospital discharge	90	In-person, EMR	ICU
Yiping Lu et al.	Single center	China	60	Symptom onset	90	In-person	Mixed IP/ICU
Fortini et al.	Single center	Italy	59	Hospital discharge	123	In-person, telephone	IP
Wu et al.	Single center	China	54	Hospital discharge	180	In person	IP
Seyed Mohammad Hossein Tabatabaei et al.	Single center	Iran	52	Initial CT chest	91	EMR	Mixed IP/OP/ICU

IP = inpatient, OP = outpatient, ICU = intensive care unit, EMR = electronic medical records.

*ICU and IP results presented separately

Table 2. Summary of studies reporting Long COVID-19 symptom prevalence with a comparator group. mMRC = modified Medical Research Council.

Authors	Study Design (average follow up in days)	COVID-19 group definition	Comparator group definition	Symptom/outcome assessment method	Newcastle-Ottawa Scale (NOS)	Summary of findings
Huang et al.	Ambidirectional cohort (185 days and 349 days).	Patients with laboratory confirmed COVID-19 discharged from Jin Yin-tan Hospital (Wuhan, China). (n = 1164)	Community adults without COVID-19 from two districts of Wuhan city, matched with cases 1:1 by age, sex and comorbidities.* (n=1164)	Interview, physical examination, questionnaires.	7/9	COVID-19 patients had significantly higher prevalence of any of the following symptoms, as well as prevalence for each individual symptom: fatigue or muscle weakness, sleep difficulties, hair loss, smell disorder, palpitations, joint pain, decreased appetite, taste disorder, dizziness, diarrhea or vomiting, chest pain, sore throat or difficulty swallowing, skin rash, myalgia, headache, cough. COVID-19 patients had significantly higher mMRC dyspnea scores and reported significantly more difficulty with mobility, personal care, pain or discomfort, anxiety or depression and overall Quality of Life.
Taquet et al.	Retrospective cohort (180 days).	Patients with confirmed COVID-19 diagnosis, aged ≥ 10 years and alive at time of analysis. Data collected using the TriNetX Analytics Network, consisting of anonymized data from 81 million patients, primarily in the USA.	Propensity matched patients from the same database, with COVID-19 cases matched separately with influenza or respiratory tract infection (RTI, including influenza). Matched for age, sex, race, ethnicity and co-morbidities. ** (influenza n =	ICD-10 codes, EMR.	9/9	COVID-19 had significantly higher hazard compared to both the matched influenza cohort and RTI cohort for mood disorder, anxiety disorder, psychotic disorder, substance use disorder and insomnia.

		(matched with influenza cases n = 105579, matched with other respiratory tract infections (RTI) n = 236038)	105579, RTI n = 236038)			
Riestra-Ayora et al.	Prospective cohort [†] (180 days).	Health workers from a tertiary care hospital with suspected and symptomatic COVID-19, confirmed by PCR.(n = 195)	Health workers from a tertiary care hospital with suspected COVID-19 with negative PCR, matched for sex and age.. (n = 125)	Interview.	5/9	There was no statistically significant difference in the recovery rate from olfactory dysfunction recovery between those with positive PCR for COVID-19 and those with suspected COVID-19 with negative PCR.
Mattioli et al.	Prospective cohort (126 days).	Healthcare workers at University Hospital of Brescia (Italy) with previous confirmed diagnosis of mild-moderate COVID-19. (n = 120)	Healthcare workers from the same hospital not previously affected by COVID-19. (n = 30)	Interview, physical examination, questionnaires.	5/9	COVID-19 cases did not differ significantly from non-COVID controls in terms of neurological or cognitive deficits, but had significantly higher scores for anxiety and depression.
Elkan et al.	Retrospective cohort [†] (270 days).	Adult patients discharged from Shamir Medical Center (Israel) with confirmed COVID-19. (n = 42)	Age and sex matched patients hospitalized during the same period as COVID-19 patients due to pneumonia or respiratory infection with	Questionnaire.	6/9	Although there are baseline differences in between groups in terms of co-morbidities, COVID-19 cases had significantly lower self-reported "health change" compared to controls.

			negative COVID-19 PCR. (n = 42)			
Søraas et al.	Prospective cohort (132 days).	Adults testing positive for COVID-19 across four laboratories in South-Eastern Norway, excluding participants later hospitalized. (n = 676)	Adults testing negative for COVID-19 across the same sites, excluding participants later hospitalized. (n = 6006)	Questionnaire.	9/9	COVID-19 positive participants were significantly more likely to report a worsening of health compared to one year prior to follow-up when compared to COVID-19 negative participants.***

*Cardiovascular disease, chronic respiratory disease, chronic kidney disease, hypertension, and diabetes.

**obesity, hypertension, diabetes, chronic kidney disease, asthma, chronic lower respiratory diseases, nicotine dependence, substance use disorder, ischaemic heart disease and other forms of heart disease, socioeconomic deprivation, cancer, haematological cancer, chronic liver disease, stroke, dementia, organ transplant, rheumatoid arthritis, lupus, psoriasis, and disorders involving an immune mechanism.

***Multivariate regression model including age, sex, chronic diseases, smoking, health professional occupation, income level, fitness and time from COVID-19 testing to follow-up.

†Study design was derived from manuscript method section and not author description.