Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Original article

Prevalence of post-COVID-19 symptoms in hospitalized and non-hospitalized COVID-19 survivors: A systematic review and meta-analysis

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ABSTRACT

Background: Single studies support the presence of several post-COVID-19 symptoms; however, no meta-analysis differentiating hospitalized and non-hospitalized patients has been published to date. This meta-analysis analyses the prevalence of post-COVID-19 symptoms in hospitalized and non-hospitalized patients recovered from COVID-19
. *Methods:* MEDLINE, CINAHL, PubMed, EMBASE, and Web of Science databases, as well as medRxiv and bioRxiv preprint servers were searched up to March 15, 2021. Peer-reviewed studies or preprints reporting data on post-COVID-19 symptoms collected by personal, telephonic or electronic interview were included. Methodological quality of the studies was assessed using the Newcastle-Ottawa Scale. We used a random-effects models for meta-analytical pooled prevalence of each post-COVID-19 symptom, and I^2 statistics for heterogeneity. Data synthesis was categorized at 30, 60, and ≥90 days after
. *Results:* From 15,577 studies identified, 29 peer-reviewed studies and 4 preprints met inclusion criteria. The sample included 15,244 hospitalized and 9011 non-hospitalized patients. The methodological quality of most studies was fair. The results showed that 63.2, 71.9 and 45.9% of the sample exhibited ≥one post-COVID-19 symptom at 30, 60, or ≥90days after onset/hospitalization. Fatigue and dyspnea were the most prevalent symptoms with a pooled prevalence ranging from 35 to 60% depending on the follow-up. Other post-COVID-19 symptoms included cough (20–25%), anosmia (10–20%), ageusia (15–20%) or joint pain (15–20%). Time trend analysis revealed a decreased prevalence 30days after with an increase after 60days
. *Conclusion:* This meta-analysis shows that post-COVID-19 symptoms are present in more than 60% of patients infected by SARS-CoV-2. Fatigue and dyspnea were the most prevalent post-COVID-19 symptoms, particularly 60 and ≥90 days after.

1. Introduction

The world is suffering a dramatic situation of catastrophic proportions due to the rapid worldwide spread of the coronavirus disease 2019 (COVID-19) caused by the pathogen acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. Symptoms associated with SARS-CoV-2 infection are heterogeneous and affect different systems such as respiratory (cough, sore throat, rhinorrhea, dyspnea), musculoskeletal (myalgias), gastrointestinal (diarrhoea, vomiting), and neurological (headaches, myopathy, ageusia, anosmia) [2].

Understandably, most literature has concentrated on the potential pathophysiology of the disease and on the management of acute cases at hospitalization periods. However, a second pandemic has emerged: post-COVID-19 sequalae and "long-haulers" [3]. Since millions of people will

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survive to SARS-CoV-2 infection; the number of individuals suffering COVID-19 sequelae, i.e., long hauler, will dramatically increase with time [4]. Therefore, identification of the COVID-19 aftermaths will be crucial for healthcare professionals.

Current evidence suggests the presence of a plethora of symptoms in subjects recovered from COVID-19. However, literature investigating the symptoms after SARS-CoV-2 infection is on its infancy in comparison with the literature available on the acute COVID-19 phase. Different terms are currently used for describing the presence of post-COVID-19 symptoms (e.g., post-COVID-19 syndrome, persistent post-COVID), being "long COVID" probably the most expanded term [5]. "Long COVID" is used to describe illness in people who have recovered from COVID-19 but still exhibit symptoms for far longer than would be expected [5]. In the last months, an increasing number of studies assessing the presence of post-COVID-19 symptoms have been published. In fact, a meta-analysis has been recently published as a preprint [6]. This meta-analysis found that 80% of COVID-19 survivors exhibited at least one post-COVID-19 symptom, being fatigue (58%), headache (44%), attention disorders (27%), hair loss (25%), and dyspnea (24%) the most frequent [6]. However, this review pooled prevalence rates without considering follow-up periods after symptoms and did not differentiate between hospitalized and non-hospitalized patients [6]. These two considerations are highly important to properly determine the presence of post-COVID-19 symptoms [7].

This study presents a systematic review and meta-analysis pooling prevalence data of post-COVID-19 symptoms differentiating between hospitalized and non-hospitalized COVID-19 survivors and analysing the prevalence of post-COVID-19 symptoms at different timepoints. The research questions of this systematic review and meta-analysis were: what is the prevalence of post-COVID-19 symptoms in individuals recovered from SARS-CoV-2 infection?, is there any difference in post-COVID-19 between hospitalized and non-hospitalized patients? and, what is the time-course of post-COVID-19 symptoms in the next months following SARS-CoV-2 infection?

2. Methods

This systematic review and meta-analysis adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement as appropriate [8]. It was also prospectively registered in the Open Science Framework Registry database with the following link https://doi.org/10.17605/OSF.IO/ESWQZ.

2.1. Systematic literature search

Electronic literature searches were conducted on MEDLINE, CINAHL, PubMed, EMBASE, and Web of Science databases, as well as on preprint servers medRxiv and bioRxiv, for studies published to March 20, 2021. We also screened the reference list of the identified papers. Database search strategies were conducted with the assistance of an experienced health science librarian. Searches were limited to human studies by using the following terms: "long COVID syndrome", "long COVID symptoms", "long haul COVID", "long hauler COVID", "chronic COVID syndrome", "chronic COVID symptoms", "post-acute COVID syndrome", "post-acute COVID symptoms", "persistent COVID syndrome", "post-COVID", "COVID sequalae" OR "persistent COVID symptoms". The inclusion/exclusion criteria were formulated by using the Population, Intervention, Comparison, Outcome (PICO) questions:

Population: Adults (>18 years), positively diagnosed of SARS-CoV-2 infection with real-time reverse transcription-polymerase chain reaction (PCR) assay of nasopharyngeal/oral swab samples, during the first wave of the pandemic (from January 1 to June 30, 2020). We included both hospitalized and non-hospitalized patients.

Intervention: Not applicable

Comparison: Not applicable

Outcomes: Monitorization or collection of the presence of multiple symptoms in COVID-19 survivors after SARS-CoV-2 infection, i.e., hospital discharge or symptoms onset, by either personal, telephonic, or electronical interview. Studies monitoring just changes in immunological, serological or radiological outcomes without assessment of post-COVID −19 symptoms were excluded.

2.2. Screening process, study selection and data extraction

This review/meta-analysis considered original research including observational cohort or case-control studies where samples of COVID-19 survivors, either hospitalized or non-hospitalized, were followed for the presence of symptoms for more than two weeks after infection. Based on pre-existing data and timeframes [7], we selected 30, 60, and ≥90 days after symptoms onset as pre-endpoints selected for the analysis. Editorials, opinion, and correspondence articles were excluded.

Two authors reviewed the title and abstract of publications identified in the databases. First, the duplicates were removed. Second, title and abstract of the articles were screened for potential eligibility and posterior full-read text. Data including authors, country, sample size, clinical data, settings (hospitalization/no hospitalization), symptoms at onset, and post-COVID-19 symptoms at different follow-up periods were extracted from each study. Both authors had to achieve a consensus on data-extraction. Discrepancies between the reviewers at any stage of the screening process were resolved by asking a third author, if necessary.

2.3. Methodological quality

The methodological quality of the studies was independently assessed by two authors using the Newcastle-Ottawa Scale, a star rating system that evaluates the risk of bias of case-control and cohort studies [9]. This scale, when applied to cohort studies, includes the following sections: case selection, comparability, and exposure. Case selection includes representativeness of cohort, selection of non-exposed cohort, ascertainment of exposure (case definition), and outcome of interest no present at start. Comparability evaluates the analysis of comparison (e.g., controlled for age, gender, or other factors) between groups (exposed and non-exposed). Exposure includes outcome assessment, long enough follow-up period, and adequate follow-up. In longitudinal cohort studies or case-control studies, a maximum of 9 stars can be awarded. In cross-sectional cohort studies, a maximum of 3 stars can be awarded. Studies scoring 3 are considered of good quality, those scoring 2 are of fair quality and studies scoring 1 are of poor quality [9]. Methodological quality of the included studies was determined by two authors and the differences, if existed, were discussed. In the case of disagreement, a third researcher arbitrated a consensus decision.

2.4. Data synthesis and analysis

The meta-analysis was conducted with the *R* software 4.0.0 using *meta* and *dmetar* packages. Percentages and frequencies of each symptom at onset/hospitalization and each symptom were extracted from studies and an overall proportion was calculated reporting a single proportion using the *metaprop* function. We used a random-effects model because potential heterogeneity was expected. An I^2 value ≥75% was considered to indicate serious heterogeneity. We were not able to assess funnel plot asymmetry due to an insufficient number of studies investigating the same post-COVID-19 symptom at a particular follow-up. We calculated sample size-weighted mean scores for each study reporting data alongside 95% confidence intervals (95%CI) in addition to any potential meta-analytical summary effect on the pooled prevalence data for each post-COVID-19 symptom. Data synthesis was categorized by time after onset/hospitalization into three follow-up periods (symptoms at 30 days, 60 days, and ≥90 days). To determine the time-course of post-COVID-19 symptoms over time (from onset to ≥90 days after), Freeman-Tukey double arcsine transformation was conducted using the *escalc* function in the *metafor package*. The *rma.mv* (meta-analytic

multilevel random effect model with moderators via linear mixed-effect models) was used to carry out a multilevel metanalysis with three levels to identify time and time *subgroup effect. For meta-analyses of studies reporting outcomes at multiple time points, it may be reasonable to assume that the true effects are correlated over time according to an autoregressive structure; therefore, a heteroscedastic autoregressive (HAR) model was adopted. Grouping by gender was not possible due to lack of data (see discussion section).

For quantitative data (age, days at hospital), overall means and standard deviations (SD) were calculated using the *pool.groups* function from the *dmetar* package. Median and interquartile range (IQR) were converted to mean and SD as described by Luo et al. [10]. When necessary, data were estimated from graphs with the GetData Graph Digitizer v.2.26.0.20 software.

2.5. Role of the funding source

There was no funding source for this study.

2.6. Patient and public involvement

Patients were not involved in the study since this was a meta-analysis of the literature.

3. Results

3.1. Study selection

The selection process is shown in **Fig. 1**. The electronic search identified 15,577 potential titles. After removing duplicates and papers not directly related to post-COVID-19 symptoms, 64 studies remained. Twenty-six ($n = 26$) were excluded after title/abstract examination. One preprint was excluded because it analysed risk factors and clusters but not detailed specific post-COVID-19 symptoms [11]; one study was excluded because it was a case series [12]; another one because mortality rate, not post-COVID-19 symptoms, was analyzed [13]; and the last one because it included children, not adults, with COVID-19 [14].

A total of 29 published studies [15–43] and five medRxiv preprints [44–48] were initially included in the review/meta-analysis (**Fig. 1**). One preprint [44] was excluded because the same study has been posteriorly published in a peer-reviewed journal [30]. Therefore, a total of 29 peer-reviewed studies [15–43] and four medRxiv preprints [45–48] were included in the systematic review and meta-analysis.

3.2. Sample characteristics

The characteristics of the COVID-19 populations of the included

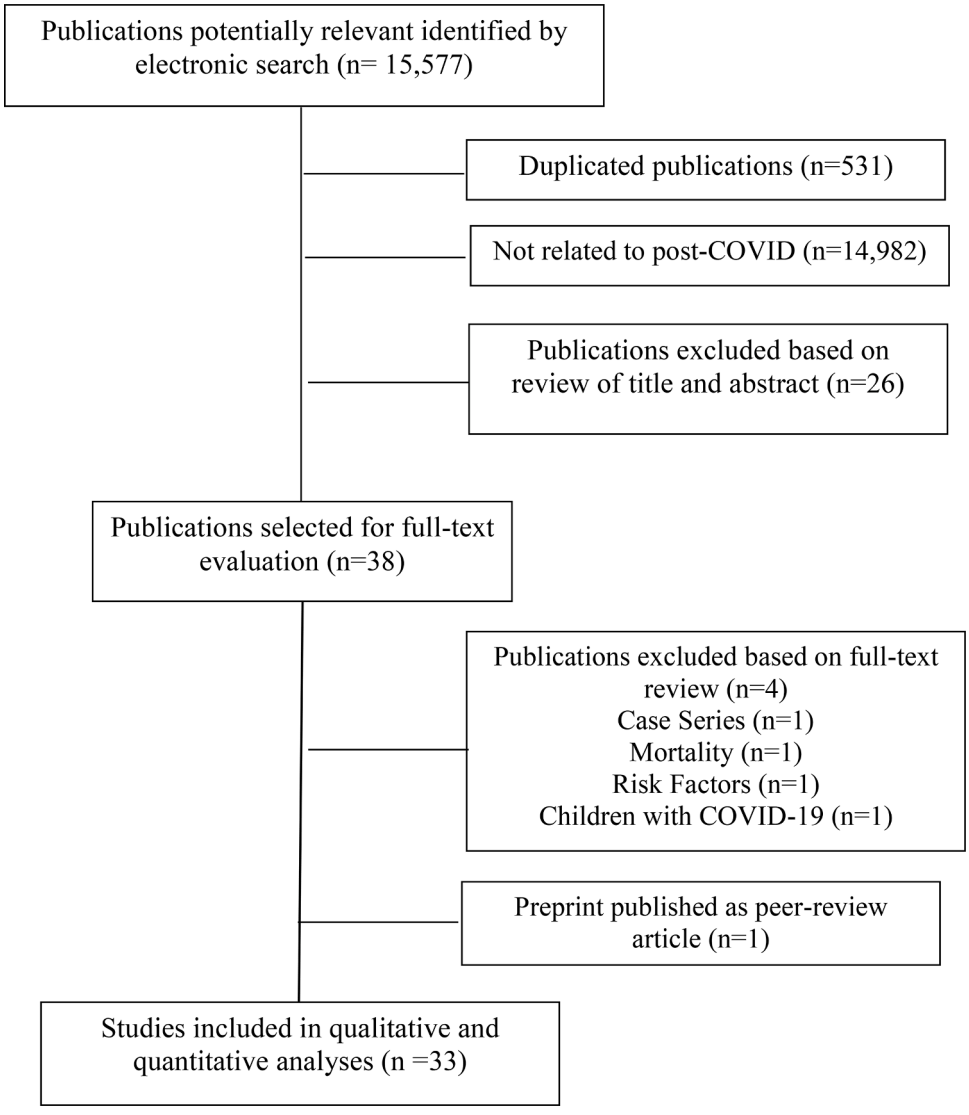

Fig. 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram.

studies are shown in Table 1. The total sample comprised 24,255 COVID-19 survivors (52.26% female; mean ± SD age: 47.8 ± 16.6 years); 15,244 were hospitalized (42.7% female; age: 48.6 ± 17.4) whereas 9011 (70.2% female; age: 44.3 ± 14.8) were non-hospitalized patients. The mean length of hospital stay due to SARS-CoV-2 infection was 12.5 days (SD 6.8). From those hospitalized, 402 patients (8%) required ICU admission (mean stay: 15 ± 14.6 days).

Almost 50% of the total sample exhibited at least one pre-existing comorbidity (one: 26.3%, 95%CI 25.3–28.0%; two: 17.6%, 95%CI 15.1–20.5%; ≥ three: 25.6%, 95%CI 11.4 −47.8%) with hypertension (22.9%, 95%CI 16.2–31.5%) and obesity (22.2%, 95%CI 13.9 −33.5%) being the most prevalent. Pre-existing comorbidities were, in general, more prevalent in hospitalized patients than in non-hospitalized patients. Table 2 summarizes the pooled prevalence of demographic and clinical data of COVID-19 survivors separated by hospitalization. Hospitalization data were collected from medical records in all studies.

3.3. Methodological quality

Thirty studies (88%) were cross-sectional, just one was of good quality (3/3 stars), 28 were considered of fair quality (2/3 stars), and two of poor quality (1/3 stars). One was a longitudinal cohort study with high methodological quality (8/9 stars), and two were case-control studies of poor quality (5/9 stars, with 0 stars in the comparability domain). No disagreement between authors was observed. Table 3 presents the Newcastle-Ottawa Scale scores for each study and a summary of every item.

3.4. Symptoms at onset or hospital admission experienced by COVID-19 patients

Supplementary Table summarizes which study assessed each COVID-19 onset symptom and each post-COVID-19 symptom. Sixteen studies (48.5%) collected the post-COVID-19 data by telephonic interviews, whereas ten studies (30%) collected data face-to-face interviews.

Pooled data of symptoms at onset and post-COVID-19 symptoms experienced by the total sample, including both hospitalized and non-hospitalized COVID-19 patients, are shown in Table 4. In the total sample, the most common symptoms experienced at SARS-CoV-2 infection were fatigue (63.4%), cough (60.2%), fever (55.3%), ageusia (46.0%), anosmia (45.7%) and dyspnea (44.1%). Among hospitalized patients, the most common onset symptoms at hospital admission included cough (65.2%), fever (59.45%), fatigue (48.0%), dyspnea (50.9%), anosmia (34.3%) and ageusia (34.0%). In non-hospitalized patients, the most common onset symptoms were fatigue (71.89%), myalgia (59%), cough (56%), fever (52.5%), anosmia (51.9%), and ageusia (51.8%). Most pooled data showed high level of heterogeneity ($I^2 \geq 75\%$).

Interestingly, non-hospitalized patients experienced chest pain (28.0% vs. 10.1%, $P = 0.008$), myalgias (59.0% vs. 15.6%, $P = 0.004$), sore throat (45.8% vs. 5.6%, $P = 0.009$), anosmia (51.9% vs. 34.36%, $P = 0.006$), ageusia (51.8% vs. 34.0%, $P = 0.022$), diarrhoea (36.0% vs. 14.1%, $P = 0.014$), vomiting (12.2% vs. 2.7%, $P = 0.011$), nausea (24.16% vs. 4.3%, $P = 0.007$), palpitations (28.37% vs. 7.2%, $P = 0.022$) and vertigo (31.9% vs. 5.74%, $P = 0.045$) significantly more frequently

Table 1
Characteristics of the included studies investigating post-COVID-19 symptoms.

Study	Country	Participants (Male/ Female)	Hospitalization	Age Mean (SD)	Data assessment	Days onset to follow-up (median)
Carvalho et al. 2020 [15]	France	150 (66 / 84)	YES	49 (15)	Telephone	30-60
Garrigues et al. 2020 [16]	France	120 (73 / 47)	YES	63.2 (15.7)	Telephone	100
Carfì et al 2020 [27]	Italy	143 (90 / 53)	YES	56.5 (14.6)	Face-to-face	60
Mandal et al. 2020 [37]	UK	384 (239 / 145)	YES	59.9 (16.1)	Telephone	54
Arnold et al. 2020 [40]	UK	110 (68 / 42)	YES	60 IQR 46-73	Face-to-face	90
Jacobs et al. 2020 [41]	Italy	183 (112 / 71)	YES	57 IQR 48-68	Telephone	35
Townsend et al. 2020 [42]	Ireland	128 (59 / 69)	YES	49.5 (15)	Face-to-face	63
Wang et al. 2020 [43]	China	131 (59 / 72)	YES	49 (36, 62)	Face-to-face	28
Halpin et al. 2021 [18]	UK	100 (54 / 46)	YES	66.66	Telephone	50
Xiong et al. 2021 [22]	China	538 (245 / 293)	YES	52 IQR 41-62	Telephone	97
Huang et al. 2021 [23]	China	1,733 (897 / 836)	YES	57 IQR 47-65	Face-to-face	186
Kamal et al. 2020 [29]	Egypt	287 (103 /184)	YES	32.3 (8.5)	Postal	60
Moreno-Pérez et al. 2021 [24]	Spain	277 (146 /131)	YES	56 (42-67.5)	Face-to-face	77
Perlis et al. 2021 [47]	USA	5,437 (3,189/2,248)	YES	37.87 (11.92)	Website	60
Jacobson et al. 2021 [26]	USA	22 (14 /8)	YES	50.6 (15.1)	Face-to-face	138
Sykes et al. 2021 [25]	UK	134 (88 / 46)	YES	59.6 (14)	Virtual	113
Zhou et al. 2021 [32]	China	89 (46 / 43)	YES	43 (31-52)	Face-to-face	21
Venturelli et al. 2021 [33]	Italy	767 (515/ 252)	YES	63 (13.6)	Telephone	81
Suarez-Robles et al. 2021 [34]	France	134 (515 / 252)	YES	58.5 (18.5)	Telephone	90
COMEBAC Study Group et al. 2021 [35]	France	478 (277 / 201)	YES	60.9 (16.1)	Telephone	113
Mumblit et al. 2021 [46]	Russia	2,649 (1,296/1,353)	YES	56 (46-66)	Telephone	217.5
Chopra et al. 2021 [36]	USA	1250 (648 / 602)	YES	62 (50-72)	Telephone	60
Nehme et al. 2020 [38]	Switzerland	669 (268 / 401)	NO	42.8 (13.7)	Telephone	40
Tenforde et al. 2020 [39]	USA	270 (130 / 140)	NO	42.5 IQR 31-54	Telephone	21
Goertz et al. 2020 [17]	Netherland	2113 (310 / 1,803)	NO	47 IQR 39-54.0	Website	80
Galván-Tejada et al. 2020 [19]	Mexico	219 (111 / 108)	NO	NR	Face-to-face	30
Stavem et al. 2020 [20]	Norway	451 (198 / 253)	NO	49.8 (15.2)	Postal/Web	95
Petersen et al. 2020 [21]	Faroe Islands	180 (82 / 98)	NO	39.9 (19.4)	Telephone	120
Cirulli et al. 2020 [45]	USA	357 (NR)	NO	56 IQR 18-89	Electronic	30-60-90
Sudre et al. 2020 [30]	Multi-country	4,182 (1,192 / 2,990)	NO	42 (32-53)	Website	30-60
Logue et al. 2021 [28]	USA	177 (76 /101)	NO	48 (15.2)	Electronic	169
Jacobson et al. 2021 [26] *	USA	96 (49 / 47)	NO	41.6 (12.5)	Face-to-face	115
Iqbal et al 2021 [31]	Pakistan	158 (71 / 87)	NO	32.1 (12.4)	Telephone	38
Peluso et al. 2021 [48]	USA	135 (100 / 79)	NO	48 (37-57)	Telephone	3 to 36 weeks

SD: standard deviation; IQR: Interquartile range; NR: Not Reported
* Jacobson et al included both hospitalized and non-hospitalized patients

Table 2
Pooled means of demographic and clinical data differentiated by hospitalized (n=15,244) and non-hospitalized (n=9,011) COVID-19 patients.

	Hospitalized (n=15,244)	Non-Hospitalized (n=9,011)
Age, mean (SD), years *	48.7 (17.4)N=12,595 - 22 studies	44.3 (14.8)N=8,792 - 11 studies
Gender, male/femalen (%) *	9,189 (57.5%) /6,791 (42.5%)	2,584 (29.7%) /6,107 (70.3%)
Medical co-morbidities		
Without comorbidities *	38.7% [30.9; 47.0]N= 2,799 / 977I^2 = 88% - 2 studies	55.2% [48.0; 62.2]N = 2,062 / 3,507I^2 = 93% - 4 studies
1 comorbidity	27.7% [26.1; 29.4]N = 755 / 2,799I^2 = 74% - 2 studies	25.6% [24.0; 27.2]N = 726 / 2,838I^2 = 61% - 3 studies
2 comorbidities	19.6% [18.3; 20.9]N = 698 / 3,566I^2 = 0% - 3 studies	15.8% [12.3; 20.0]N = 413 / 2,838I^2 = 89% - 3 studies
3 or more comorbidities	29.6% [10.9; 59.0]N = 591 / 2,883I^2 = 98% - 3 studies	16.1% [12.2; 20.9]N = 44 / 274I^2 = N/A -1 study
Obesity	29.0% [21.2; 38.2]N = 841 / 3,687I^2 = 96% - 5 studies	12.7 [4.3; 32.0]N = 1,155 / 4,491I^2 = 93% - 3 studies
Hypertension *	30.9% [21.6; 42.1]N = 3,548 / 9,127I^2 = 98% - 15 studies	13.0% [7.9; 20.7]N = 224 / 1,375I^2 = 81% - 6 studies
Diabetes *	14.2% [9.8; 20.1]N = 1,557 / 9,128I^2 = 97% - 15 studies	4.1% [2.1; 8.1]N = 180 / 5,106I^2 = 90% - 6 studies
Heart Disease *	11.6% [7.8; 17.0]N = 487 / 8,864I^2 = 96% - 14 studies	2.3% [1.3; 4.0]N = 100 / 4,929I^2 = 78% - 5 studies
Asthma	9.3% [5.5; 15.4]N = 219 / 5,619I^2 = 96% - 8 studies	12.0% [8.8; 16.1]N = 562 / 5,245I^2 = 89% - 5 studies
COPD *	6.0% [4.1; 8.7]N = 195 / 8,252I^2 = 94% - 11 studies	2.2% [1.2; 4.0]N = 10 / 454I^2 = 0% - 2 studies
Cancer	4.4% [2.5; 7.7]N = 140 / 7,975I^2 = 95% - 10 studies	1.9% [0.8; 4.2]N = 6 / 315I^2 = 0% - 2 studies
Kidney disease *	5.3% [2.7; 9.8]N = 567 / 7,504I^2 = 98% - 10 studies	0.6% [0.4; 0.9]N = 27 / 4,475I^2 = 0% - 3 studies
Immune Disorders	3.3% [1.3; 7.3]N = 92 / 4,707I^2 = 93% - 8 studies	4.6% [3.0; 7.2]N = 19 / 409I^2 = 0% - 2 studies
Stay at the hospital, mean (SD), days	12.6 (6.8)N=7,299 - 15 studies	
ICU) admission Yes/No, n (%)Stay at ICU, mean (SD), days	492 (8%)N=4,507 - 12 studies14.97 (14.6)N= 391 - 7 studies	

COPD: Chronic Obstructive Pulmonary Disease; ICU: Intensive Care Unit; SD: Standard Deviation
* Significant differences between non-hospitalized and hospitalized COVID-19 patients

than hospitalized COVID-19 patients.

3.5. Post-COVID-19 symptoms experienced by COVID-19 survivors (Total sample)

A total of 63.2% of the sample (95%CI 43.9–78.9, 7 studies, I^2: 97%) exhibited one or more post-COVID-19 symptoms 30 days after onset/ hospitalization, 71.9% (95%CI 53.3–85.2, 3 studies, I^2: 94%) 60 days after, and 45.9% (95%CI 28.2–64.7, 7 studies, I^2: 96%) ≥90 days after. Most comparisons showed serious/large heterogeneity (I^2 ≥75%). A greater proportion of hospitalized patients (P = 0.003) showed one or more post-COVID −19 symptoms 60 days after (78.5% 95%CI 60.1–88.9) as compared to non-hospitalized patients (56.2% 95%CI 48.5–63.72), without differences at 30 days (P = 0.186) or ≥90 days (P = 0.305) after.

Overall, thirty days after onset/hospital admission (mean: 30.3 ± 6.3 days), the most frequent post-COVID-19 symptoms were cough (18.6%), anosmia (16.5%), ageusia (15.7%), dyspnea (13.2%), fatigue (11.7%) and confusion (8%), without significant differences between the hospitalized and non-hospitalized patients (Table 4).

Overall, sixty days after onset or hospitalization (mean: 60.4 ± 6.6 days), the most frequent post-COVID-19 symptoms were fatigue (56.2%), dyspnea (27.2%), chest pain (23.6%), headache (19.8%), joint pain (19%), and cough (18.9%). Non-hospitalized individuals showed higher prevalence of sore throat (67%), headache (48%) and anosmia (37%) than hospitalized patients (4%, 11%, and 11.5%, respectively), but the differences did not reach statistical significance due to the heterogeneity in the comparison (Table 4).

More than ninety days after onset/hospitalization (mean: 118.4 ± 40.0 days), the most frequent post-COVID-19 symptoms included fatigue (35.3%), dyspnea (26.3%), anosmia (11%), myalgia (10.9%), joint pain (10.3%), and ageusia (10%). At this follow-up period, non-hospitalized patients reported significantly higher prevalence of anosmia (15.5% vs. 8.1%, P = 0.012), chest pain (14.9% vs. 7.7%; P = 0.02), sputum (10.7 vs. 3.4, P = 0.002), and vertigo (12.7% vs. 4.2%, P = 0.02) than hospitalized patients (Table 4).

3.6. Post-COVID-19 symptoms classified by groups: hospitalized/non-hospitalized

Of the twenty-one studies [15,16,18,22–25,27,29,32–37,40–43,46,47] investigating the presence of post-COVID-19 symptoms in hospitalized patients, four analyzed symptoms 30 days after hospital discharge [15,33,41,43], nine showed a follow-up period of 60 days [15,18,24,27,29,36,37,42,47], whereas ten reported symptoms ≥90 days after discharge [16,22,23,25,26,33–35,40,46]. Overall, hospitalized COVID-19 patients were assessed a mean of 83.6 ± 48.4 after hospital discharge. Among twelve studies [17,19–21,26,28,30,31,38,39,45,48] with non-hospitalized patients, four studies evaluated post-COVID-19 symptoms 30 days after onset [19,31,38,45] two had a follow-up of 60 days [30,45], whereas seven analysed symptoms after ≥90 days [17,20,21,26,28,45,48]. The sample of non-hospitalized patients was assessed a mean of 73.9 ± 46.4 days after onset of symptoms.

Within hospitalized patients, the most common post-COVID-19 symptoms included: cough (26.6%), skin rashes (14%), ageusia (11.4%), anosmia (11.1%), confusion (9.3%) and dyspnea (9.2%) 30 days after hospitalization; fatigue (53.9%), dyspnea (24.4%), joint pain (22.8%), chest pain (21.0%), cough (13.8%), and anosmia (11.5%) 60 days after hospitalization; and fatigue (38.5%), dyspnea (33.3%), cough (10.4%), myalgia (9.7%), joint pain (9.4%) and palpitations (9.1%) ≥90 days after hospitalization (Fig. 2).

Within non-hospitalized patients, the most common post-COVID-19 symptoms were anosmia (19.9%), ageusia (18.3%), dyspnea (15.7%), cough (13.9%), fatigue (11.8%), and headache (10.9%) 30 days after the onset of symptoms; sore throat (67.0%), fatigue (63.2%), headache (48.2%), cough (40.7%), dyspnea (39.9%), and anosmia (37.7%) 60 days after symptom onset; and fatigue (29.8%), dyspnea (19.1%), anosmia (15.5%), chest pain (14.9%), and ageusia (13.2%) ≥90 days after (Fig. 2).

Fig. 2 graphs the time-course of the eight most prevalent symptoms from onset/ hospitalization to 30, 60 and ≥90 days after in hospitalized and non-hospitalized patients. The random effect model showed significant effect for time (all, P<0.001) for fatigue, dyspnea, headache, myalgias, cough, anosmia and ageusia symptoms, but not for chest pain: symptoms dropped at 30 days relative to baseline and raised up again at 60 and ≥90 days after. Significant group *time effects were also found showing that this tendency was more pronounced in hospitalized than non-hospitalized patients.

Table 3
Newcastle - ottawa quality assessment scale - quality appraisal cohort/cross-sectional studies.

Cohort Study	Selection Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome of interest nor present at start	Comparability Study controls for age/gender	Study controls for additional factor	Exposure Assessment of outcome	Long enough follow-up	Adequate follow-up	Score
Carvalho et al. 2020 [15]	★		★							2/3
Garrigues et al. 2020 [16]	★		★							2/3
Carfi et al 2020 [27]	★		★							2/3
Mandal et al. 2020 [37]	★		★							2/3
Arnold et al. 2020 [40]	★		★							2/3
Jacobs et al. 2020 [41]	★		★							2/3
Townsend et al. 2020 [42]	★		★							2/3
Wang et al. 2020 [43]	★		★							3/3
Halpin et al. 2021 [18]	★		★							2/3
Xiong et al. 2021 [22]	★		★							2/3
Huang et al. 2021 [23]	★		★							2/3
Nehme et al. 2020 [38]	★		★							2/3
Tenforde et al. 2020 [39]	★		★							2/3
Goertz et al. 2020 [17]	★									1/3
Stavem et al. 2020 [20]	★		★							2/3
Petersen et al. 2020 [21]	★		★							2/3
Cirulli et al. 2020 [45]	★	★	★	★	★	★		★	★	8/9
Sudre et al. 2020 [30]	★		★							2/3
Kamal et al. 2020 [29]			★							1/3
Chopra et al. 2021 [36]	★		★							2/3
Jacobson et al. 2021 [26]	★		★							2/3
Sykes et al. 2021 [25]	★		★							2/3
Moreno-Pérez et al. 2021 [24]	★		★							2/3
Iqbal et al 2021 [31]	★		★							2/3
Zhou et al. 2021 [32]	★		★							2/3
Venturelli et al. 2021 [33]	★		★							2/3

(*continued on next page*)

Table 3 (*continued*)

	Adequate case definitions	Representativeness of cases	Selection of controls	Definitions of controls	Controlled for age	Controlled for additional factors	Ascertainment of exposure	Same method for cases and controls	Non-response rate	Score
Suárez-Robles et al. 2020 [34]	★		★							2/3
Mumblit et al. 2021 [46]	★		★							2/3
Perlis et al. 2021 [47]	★		★							2/3
Peluso et al. 2021 [48]	★		★							2/3
COMEBAC Study Group et al. 2021 [35]	★		★							2/3
Case-Control Study										
Galván-Tejada et al. 2020 [19]	★	★	★	★				★		5/9
Logue et al. 2021 [28]	★	★	★	★				★		5/9

4. Discussion

4.1. Findings

This systematic review/meta-analysis revealed that more than 60% of COVID-19 survivors exhibit at least one post-COVID-19 symptom for more than 30 days after onset or hospitalization. The prevalence of each symptom in isolation was 10–15% at 30 days and 40–60% at 60 days or longer after onset/hospitalization (Fig. 2). Fatigue and dyspnea were the most prevalent post-COVID-19 symptoms in hospitalized and non-hospitalized patients, particularly at 60 and ≥90 days of follow-up, whereas the prevalence of other symptoms, e.g., headache, anosmia, ageusia, chest pain, or palpitations, was lower and highly variable.

The preprint meta-analysis by Lopez-Leon et al. observed that fatigue, headache, attention disorder, hair loss or dyspnea were the most frequent post-COVID-19 symptoms [6]. They reported overall prevalence of post-COVID-19 symptoms without distinction between hospitalized/non-hospitalized patients or considering the follow-up period [6]; therefore, the comparison between prevalence rates is not feasible. Another systematic review have reported that main post-COVID-19 sequelae were post-infectious fatigue, persistent reduced lung function and carditis; however, this review did not pooled data on post-COVID symptoms since it focused on functional impairments [49]. Another meta-analysis reported that the most common respiratory post-COVID-19 symptoms reported by hospitalized COVID-19 survivors included fatigue, dyspnoea, chest pain, and cough showing prevalence rates of 52%, 37%, 16% and 14%, respectively between 3 weeks and 3 months after hospital discharge [50]. These prevalence data are similar to our pooled data observed at 60days follow-up; however, Cares-Marambio et al. [50] pooled studies without distinction on follow-up periods. Our systematic review/meta-analysis examined the prevalence of post-COVID-19 symptoms considering if patients were hospitalized or not and also separated by follow-up periods. We were able to identify 29 peer-reviewed studies as well as four medRxiv preprints providing prevalence data on post-COVID-19 symptoms from both hospitalized and non-hospitalized COVID-19 survivors at different follow-up periods; the highest number of studies pooled to date; however, most studies were of fair methodological quality and also showed high heterogeneity in their results. Nevertheless, it should be remarked that more and more studies assessing post-COVID-19 symptoms will be published and future updated meta-analyses will be needed.

The most common symptoms experienced by patients at onset/hospitalization in the overall sample were fatigue, cough, fever, ageusia, anosmia and dyspnoea in agreement with a previous meta-analysis showing similar symptoms at SARS-CoV-2 infection [51]. Nevertheless, some differences in prevalence rates can be found. Compared to the current meta-analysis, Alimohamadi et al. found similar prevalence of cough (58.5%), but higher prevalence of fever (81.2%) and lower rate of fatigue (38.5%) [51]. There is clear evidence supporting that clinical manifestations of COVID-19 are highly heterogeneous.

A relevant finding was that post-COVID-19 symptoms experienced 30days after onset/hospitalization decreased dramatically in prevalence as compared to the acute phase but increased 60days after (Fig. 2). The reasons of these findings are still unknown and need to be confirmed in well-designed longitudinal studies; however, it should be noted that most prevalence data were based on a small number of studies and comparisons had large heterogeneity. In fact, studies conducted in Europe reported higher prevalence rates of fatigue (50–70%) or dyspnea (30–40%) as post-COVID-19 symptoms [15–18,20,27,37, 40–42] whereas Chinese studies reported, in general, lower prevalence rates of these symptoms (12–20%) [22,23,32,43]. Factors such as younger age and lower pre-existing medical comorbidities in Chinese studies could explain these discrepancies; however, the magnitude of these different prevalence rates would suggest other relevant factors e.g., racial disparities [52] or blood type [53]. Future studies investigating the epidemiology of post-COVID-19 symptoms attending to these factors are

Table 4
Pooled prevalence of symptoms at onset, and Post-COVID-19 Symptoms 30, 60, and ≥90 days after Onset/Hospitalization.

	Onset			30 days after			60 days after			≥90 days dafter		
	T	H	NH	T	H	NH	T	H	NH	T	H	NH
Fever	**55.3%**	**59.4%**	**52.5%**	-	-	-	-	-	-	-	-	-
95%CI	42.9; 67.1	33.7; 80.9	41.4; 63.4	-	-	-	-	-	-	-	-	-
I^2	98%	99%	98%	-	-	-	-	-	-	-	-	-
Event/Total	5,217/ 10,967	3,172/ 6,549	2,045 / 4,418	-	-	-	-	-	-	-	-	-
Studies	15	6	7	-	-	-	-	-	-	-	-	-
Dyspnea	**44.1%**	**50.9%**	**38.9%**	**13.2%**	**9.2%**	**15.7%**	**27.2%**	**24.5%**	**39.9%**	**26.3%**	**33.3%**	**19.1%**
95%CI	29.3; 60.1	25.8; 75.5	23.0; 57.5	6.6; 29.3	2.0; 33.0	7.7; 29.3	14.9; 44.4	12.7; 41.9	9.7; 80.3	9.4; 34.9	23.4; 45.0	9.4; 34.9
I^2	99%	98.0%	99%	96%	95%	97%	99%	99%	99%	99%	97%	99%
Event/Total	3,123 /5,815	483 / 1,397	2,640 /4,418	279 /1,741	76 / 464	203 / 1,277	1,211/ 7,962	792 / 7,246	419 / 716	2,617 /4,385	483 / 4,385	1,677 /3,314
Studies	17	8	9	8	3	5	10	8	2	15	8	7
Fatigue	**63.4%**	**48.0%**	**71.9%**	**11.7%**	**7.7%#**	**11.8%**	**56.2%**	**53.9%**	**63.2%**	**35.3%**	**38.4%**	**29.8%**
95%CI	48.3; 76.2	28.8; 67.8	48.3; 76.2	3.1; 35.3	7.1; 8.0	6.5; 20.5	28.3; 80.7	40.5; 66.8	1.9; 99.3	25.3; 46.8	30.4; 47.4	12.3; 56.3
I^2	99%	98%	99%	95%	0%	88%	98.0%	96%	99%	99%	99%	99%
Event/Total	3,531 /5,134	458 / 1,105	3,073 /4,029	230 / 1,297	114 / 403	116/ 894	1,295 /2,029	740 / 1,319	555 / 710	4,409 /9,876	1,753 /6,567	2,000 /3,309
Studies	13	5	8	6	3	3	8	6	2	17	10	7
Chest Pain	**16.5%**	**10.1%**	**28.0%** *	**6.6%**	**1.1%**	**10.9%**	**23.6%**	**21.0%**	**28.5%**	**9.4%**	**7.7%**	**14.9%** *
95%CI	8.0; 30.9	3.5; 25.6	14.4; 47.3	1.5; 25.2	0.0; 77.1	3.3; 30.6	11.9; 41.5	14.4; 29.7	5.8; 72.2	6.7; 13.1	5.2; 11.2	9.9; 21.7
I^2	99	97	99	94%	100%	97%	98%	84%	99%	94.6%	93%	89%
Event/Total	1,561 /3,990	115 / 1,072	1,446 /2,918	106 / 832	27 / 281	79 / 551	481 / 1,27	131 / 560	350 / 718	920 / 8,945	252 / 6,437	553 / 2,508
Studies	9	5	4	5	2	3	5	3	2	13	9	4
Myalgia	**37.0%**	**15.6%**	**59.0%** *	**4.9%**	**2.0%**	**9.6%#**	**14.7%**	**8.1%**	**32.1%**	**10.9%**	**9.7%**	**12.6%**
95%CI	21.2; 56.1	4.3; 42.9	53.2; 64.6	1.3; 17.2	0.0; 27.8	7.0; 12.9	5.1; 35.5	3.5; 17.3	6.8; 75.3	6.6; 17.7	3.9; 22.0	7.8; 19.9
I^2	98%	95%	90%	81%	82%	0%	99%	98%	99%	99%	98%	97%
Event/Total	2,556 /4,956	258 / 1,225	2,298 /3,731	78 / 789	41 / 403	37 / 386	660 / 6,570	286 / 5,857	374 / 713	1,198 /5,286	191 / 5,826	878 / 3,312
Studies	13	6	7	5	3	2	5	3	2	14	7	7
Headache	**36.7%**	**11.8%**	**51.6%**	**7.4%**	**1.1%**	**11.0%**	**19.8%**	**11.3%**	**48.2%**	**6.3%**	**3.6%**	**10.9%**
95%CI	18.5; 59.8	1.2; 60.3	32.9; 69.8	2.3; 21.5	0.0; 72.9	4.2; 25.7	5.3; 52.4	4.7; 24.8	3.1; 96.5	3.2; 12.0	1.3; 9.9	5.7; 19.7
I^2	98%	99%	99%	95%	99%	97%	99%	99%	99%	99%	97%	97%
Event/Total	2,866 /4,889	143 / 567	2,723 /4,322	142 / 1,370	29 / 314	113 / 1,056	833 / 6,858	312 / 6,144	521 / 714	1,157 /8,637	95 / 5,775	867 / 2,862
Studies	1	4	8	4	2	4	6	4	2	12	6	6
Eye irritation	**15.3%**	**17.7%**	**13.9%**	**7.0%**	**5.3%#**	**9.7%**	**9.8%**	**9.8%**	**-**	**5.1%**	**-**	**5.1%**
95%CI	8.6; 25.6	9.0; 32.0	6.0; 28.8	3.4;24.6	2.2; 12.5	3.4; 24.6	5.9; 15.8	5.9; 15.8	-	1.4; 17.2	-	1.4; 17.2
I^2	96%	93%	97%	88%	68%	94%	N/A	N/A		97%	-	97%
Event/Total	688 / 3,242	59 / 326	629 / 2,916	57 / 649	17 / 272	40 / 377	14 / 143	14 / 143	-	262 / 2,564	-	262 / 2,564
Studies	5	2	3	4	2	2	1	1	-	2	-	2
Sputum	**18.9%**	**14.8%**	**25.5%**	**4.7%**	**4.7%**	**-**	**7.7%**	**7.7%**	**-**	**6.5%**	**3.4%#**	**10.7%** *
95%CI	13.0; 26.7	9.2; 22.9	17.1; 36.1	0.0; 49.5	0.0; 49.5	-	3.9; 13.3	3.9; 13.3	-	3.1; 13.1	2.2; 5.1	4.5; 23.3
I^2	96%	86%	96%	99%	99%		N/A	N/A		96%	38%	94%
Event/Total	1,025 /3,645	156 / 995	869 / 2,650	49 / 403	49 / 403	-	11 / 143	11 / 143	-	413 / 2,965	23 / 672	390 / 2,293
Studies	7	4	3	3	3	-	1	1	-	4	2	2
Rhinitis	**27.3%#**	**1.2%**	**38.9%#**	**0.1%**	**0.0%**	**0.006%**	**7.3%**	**7.3%**	**-**	**4.0%**	**4.5%**	**4.0%**
95%CI	12.6; 49.6	0.0; 9.0	36.5; 41.3	0.002; 34.6	0.0; 1.0	0.003; 10.7	3.7; 14.0	3.7; 14.0	-	1.7; 9.3	0.1; 26.1	1.6; 9.8
I^2	31%	99%	15%	99%	N/A	N/A	94%	94%	-	94%	N/A	95%
Event/Total	672 / 1,892	43 / 274	629 / 1,618	11 / 310	0 / 131	11 / 179	280 / 5,580	280 / 5,580	-	65 / 2,767	1 / 22	64 / 2,745
Studies	8	2	6	2	1	1	2	2	-	6	1	5
Sore Throat	**26.7%**	**5.6%**	**45.8%** *	**1.0%#**	**1.5%**	**0.6%**	**15.2%**	**4.2%#**	**67.0%**	**4.9%**	**4.5%**	**7.3%**
95%CI	12.1; 49.1	0.1; 29.6	38.1; 53.7	0.3; 3.0	0.4; 5.9	0.01; 3.9	2.4; 56.4	3.7; 4.7	63.0; 70.8	2.7; 8.7	1.9; 10.2	2.0; 23.0
I^2	98%	98%	96%	0%	N/A	N/A	99%	36%	N/A	98%	97	97%
Event/Total	1,975 /4,269	71 / 812	1,904/ 3,457	3 / 310	2 / 131	1 / 179	609 / 6,138	235 / 5,580	374 / 558	692 / 5,523	103/ 3,196	589 / 3,196
Studies	9	3	6	2	1	1	3	2	1	9	3	6
Cough	**60.2%**	**65.2%**	**56.0%**	**18.6%**	**26.5%**	**13.9%**	**18.9%**	**13.8%**	**40.7%**	**8.6%**	**10.4%**	**6.7%**
95%CI	53.3; 66.8	54.2; 74.3	48.2; 63.5	10.6; 30.7	14.4; 43.8	6.2; 28.3	10.1; 32.6	8.3; 22.0	11.9; 77.8	5.3; 13.7	5.7; 18.3	3.0; 14.3
I^2	95%	92%	97%	96%	92%	97%	99%	98%	99%	98.6%	97%	97%
Event/Total												

(*continued on next page*)

Table 4 (*continued*)

	3,438 /5,697	838 / 1,375	2,600 /4,322	334/ 1,829	153 / 553	181/ 1,276	812 / 7,293	401 / 6,575	411 / 718	1,061 /8,219	374 / 4,904	687 / 3,315
Studies	15	7	8	9	4	5	4	5	2	8	15	7
Anosmia	**45.7%**	**34.4%**	**51.9%** *	**16.5%**	**11.1%**#	**19.9%**	**17.3%**	**11.8%**	**37.6%**	**11.0%**	**8.1%**	**15.5%** *
595%CI	38.3; 53.2	24.9; 45.3	45.7; 58.1	9.9; 26.3	8.2; 15.0	10.3; 34.8	8.3; 32.1	7.4; 18.1	8.3; 80.2	8.0; 15.0	5.0; 12.9	12.5; 19.0
I^2	95.6%	89%	95%	95%	26%	96%	99%	97%	99%	95%	96%	77%
Event/Total	1,927 /4,317	197 / 586	1,730 /3,731	198 / 1,099	37 / 333	161 / 766	840 / 7,191	428 / 6,475	412 / 716	841 / 9.357	302 / 6,042	460 / 3,315
Studies	11	4	7	6	2	4	7	5	2	16	9	7
Ageusia	**46.0%**	**34.0%**	**51.8%** *	**15.7%**	**11.4%**#	**18.3%**	**9.0%**	**8.93**	**9.6%**	**10.0%**	**7.6%**	**13.2%**
95%CI	37.3; 54.9	23.1; 46.9	43.7; 59.0	9.2; 25.6	8.4; 15.3	8.8; 34.1	6.3; 12.7	5.8; 13.4	5.9; 15.3	6.6; 15.1	3.8; 14.6	10.0; 17.1
I^2	95%	91%	96%	96%	32%	97%	94%	95%	N/A	95%	96%	77%
Event/Total	2,031 /4,442	161 / 476	1,870 /3,966	230 / 1,428	38 / 333	192 / 1,095	377 / 6,354	362 / 6,198	15 / 156	561 / 7,655	176 / 4,697	342 / 2,958
Studies	9	3	6	6	2	4	5	4	1	11	6	5
Joint Pain	**30.0%**	**32.0%**	**28.7%**	**6.9%**	**6.8%**	**7.3%**	**19.0%**	**22.9%**	**10.4%**	**10.3%**	**9.4%**	**11.2%**
95%CI	20.1; 42.1	19.0; 48.7	17.0; 45.8	2.0; 21.1	2.7; 16.2	0.7; 46.8	10.7; 31.5	12.8; 37.4	6.5; 16.3	7.1; 14.7	5.0; 16.7	7.2; 17.1
I^2	95%	94%	95%	96%	85%	97%	81.9%	91%	N/A	97%	94%	94%
Event/Total	1,348 /3,716	145 / 436	1,203 /3,280	132 / 996	40 / 422	92 / 544	168 / 714	152 / 560	16 / 154	803 / 6,420	80 / 3,382	549 / 3,038
Studies	8	3	5	6	3	3	4	3	1	9	4	5
Diarrhoea	**23.9%**	**14.1%**	**36.0%** *	**4.1%**	**4.2%**	**3.3%**#	**8.5%**	**5.3%**	**18.2%**	**3.1%**	**2.2%**	**3.9%**
95%CI	16.2; 33.8	6.1; 29.3	32.2; 40.0	1.7; 9.7	0.9; 17.5	1.9; 5.6	2.7; 23.7	2.5; 10.8	2.4; 67.0	1.9; 4.9	1.1; 4.3	2.3; 6.7
I^2	94%	87%	77%	81%	78%	0%	98%	80%	98%	94%	90%	87%
Event/Total	1,669 /5,106	223 / 1,375	1,446 /3,731	49 / 945	36 / 553	13 / 392	331 / 1,267	38 / 550	293 / 717	404 / 8,459	1551 / 5,143	249 / 3,316
Studies	14	7	7	6	4	2	5	3	2	11	4	47
Vomiting	**7.5%**	**2.7%**#	**12.2%** *	**0.9%**	**0.0%**	**2.8%**	**-**	**-**	**-**	**0.8%**	**0.3%**	**1.3%**#
95%CI	3.7; 14.5	0.1; 8.5	8.2; 17.8	0.05; 14.0	0.0; 1.0	0.3; 21.4	-	-	-	0.3; 2.2	0.01; 0.6	0.7; 2.3
I^2	958%	64%	95%	77%	N/A	89%	-	-	-	83%	N/A	61%
Event/Total	361 / 3,686	23 / 669	338 / 3,017	24 / 529	0 / 131	24 / 398	-	-	-	40 / 5,448	7 / 2,609	33 / 2,839
Studies	6	2	4	3	1	2	-	-	-	5	1	4
Nausea	**15.5%**	**4.3%**	**24.2%** *	**3.8%**	**0.8%**	**5.4%** *	**3.1%**	**-**	**3.1%**	**4.9%**	**-**	**4.9%**
95%CI	8.6; 26.2	1.1; 15.3	18.4; 31.0	1.5; 9.0	0.1; 5.2	2.8; 10.7	1.3; 7.3	-	1.3; 7.3	2.4; 9.5	-	2.4; 9.5
I^2	96%	91%	94%	81%	N/A	82%	N/A	-	N/A	86%	-	86%
Event/Total	1,199 /4,510	40 / 779	1,159 /3,731	39 / 743	1 / 131	38 / 612	5 / 160	-	5 / 160	280 / 2,769	-	280 / 2,769
Studies	10	3	7	4	1	3	1	-	1	5	-	5
Skin Rashes	**5.7%**	**-**	**5.7%**	**4.6%**	**14.0%**	**2.5%**#	**6.7%**	**9.4%** *	**2.5%**	**2.7%**	**3.0%**	**2.4%**
95%CI	4.1; 7.9	-	4.1; 7.9	1.6; 12.6	9.3; 20.5	0.1; 4.6	3.4; 12.7	6.9; 12.6	0.9; 6.7	1.8; 4.0	1.8; 5.1	1.3; 4.3
I^2	78%	-	78%	91%	N/A	0%	75%	8%	N/A	76%	83%	76%
Event/Total	205 / 3,376	-	205 / 3,376	31 / 545	21 / 150	10 / 395	42 / 569	38 / 407	4 / 162	179 / 7,303	117 / 4,532	62 / 2,771
Studies	6	-	6	3	1	2	2	2	1	9	4	5
Palpitations	**15.2%**	**7.2%**	**28.4%** *	**3.5%**	**0.9%**	**4.6%**	**3.0%**	**2.1%**	**4.9%**	**10.0%**	**9.1%**	**11.1%**
95%CI	3.7; 45.8	0.1; 42.9	7.5; 65.9	1.7; 7.2	0.02; 33.3	2.9; 7.1	0.6; 13.8	0.1; 22.9	2.5; 9.6	6.4; 15.3	5.6; 14.5	5.1; 22.6
I^2	99%	95%	N/A	90%	99%	0%	85%	91%	N/A	99%	93%	96%
Event/Total	1,320 /2,961	141 / 669	1,179 /2,292	27 / 675	9 / 281	18 / 394	23 / 579	15 / 417	8 / 162	1,164 8,221	459 / 5,711	705 / 2,510
Studies	4	2	2	4	2	2	2	2	1	9	5	4
Confusion	**13.2%**#	**9.6%**	**14.3%**	**8.0%**#	**9.3%**	**7.0%**	**6.8%**	**-**	**6.8%**	**8.7%**	**9.1%**	**8.0%**
95%CI	11.3; 15.4	5.3; 17.0	12.0; 17.1	5.7; 11.1	5.8; 14.4	4.2; 11.2	3.8; 11.9	-	3.8; 11.9	5.3; 13.8	5.6; 14.5	3.4; 17.8
I^2	52.0%	77%	0%	0%	N/A	N/A	0%	-	0%	99%	93%	98%
Event/Total	136 / 1,028	32 / 303	104 / 725	32 / 3981	17 / 183	15 / 215	11 / 161	-	11 / 161	1,174/ 8,672	459 / 5,711	715 / 2,961
Studies	4	2	2	1	1	1	1	-	1	10	5	5
Vertigo	**17.7%**	**5.7%**	**31.9%** *	**2.3%**	**0.0%**	**4.3%**	**6.2%**#	**6.3%**	**6.2%**	**7.9%**	**4.2%**	**12.6%** *
95%CI	6.3; 40.7	0.0; 29.0	18.7; 48.9	0.6; 8.2	0.0; 1.0	2.7; 6.8	4.0; 9.6	3.3; 11.6	3.4; 11.2	3.8; 15.8	2.3; 7.5	5.9; 25.1
I^2	98%	92%	98%	0%	N/A	0%	0%	N/A	N/A	99%	89%	95%
Event/Total	1,250 /2,918	27 / 274	1,223 /2,644	17 / 524	0 / 131	17 / 393	19 / 304	9 / 143	10 / 161	709 / 4,616	115 / 2,203	594 / 2,413
Studies	5	2	3	3	1	2	2	1	1	5	2	3

T: Total sample, H: Hospitalized COVID-19 patients; NH: Non-hospitalized COVID-19 patients; CI: Confidence interval

* Statistically significant differences between hospitalized and non-hospitalized patients; # No heterogeneity between studies (I^2<75%)

Supplementary Table S1
: Studies investigating each post-COVID-19 symptom at onset and at different follow-up periods.

Symptom	Onset	Follow-up Period		
		30	**60**	**>90**
Fever	Carvalho et al. 2020 [15] Arnold et al. 2020 [40] Jacobs et al. 2020 [41]Wang et al. 2020 [43] Tenforde et al. 2020 [39] Goertz et al. 2020 [17] Stavem et al. 2020 [20] Petersen et al. 2020 [21]Cirulli et al. 2020 [45]Logue et al. 2021 [28] Jacobson et al. 2021 [26]Peluso et al. 2021 [48]	-	-	-
Dyspnea	Carvalho et al. 2020 [15] Arnold et al. 2020 [40] Garrigues et al. 2020 [16]Carfi et al 2020 [27] Mandal et al. 2020 [37] Jacobs et al. 2020 [41]Wang et al. 2020 [43] Halpin et al. 2021 [18]Xiong et al. 2021 [22] Tenforde et al. 2020 [39] Goertz et al. 2020 [17] Stavem et al. 2020 [20] Petersen et al. 2020 [21]Cirulli et al. 2020 [45]Logue et al. 2021 [28]	Carvalho et al. 2020 [15] Jacobs et al. 2020 [41] Wang et al. 2020 [43] Nehme et al. 2020 [38] Galván-Tejada et al. 2020 [19]Cirulli et al. 2020 [45]Iqbal et al 2021 [31] Peluso et al. 2021 [48]	Carvalho et al. 2020 [15] Carfi et al 2020 [27] Mandal et al. 2020 [37] Halpin et al. 2021 [18] Cirulli et al. 2020 [45] Sudre et al. 2021 [30] Kamal et al. 2020 [29] Chopra et al. 2021 [36] Moreno-Pérez et al. 2021 [24]	Carvalho et al. 2020 [15] Arnold et al. 2020 [40] Goertz et al. 2020 [17] Stavem et al. 2020 [20] Petersen et al. 2020 [21] Cirulli et al. 2020 [45] Logue et al. 2021 [28] Jacobson et al. 2021 [26] Peluso et al. 2021 [48] Sykes et al. 2021 [25] Venturelli et al. 2021 [33] Suárez-Robles et al. 2020 [34] COMEBAC Study Group et al. 2021 [35]

Supplementary Table S1 (*continued*)

	Jacobson et al. 2021 [26]Peluso et al. 2021 [48]Peluso et al. 2021 [48]			
Fatigue	Carfi et al 2020 [27] Arnold et al. 2020 [40] Jacobs et al. 2020 [41]Wang et al. 2020 [43]Xiong et al. 2021 [22] Nehme et al. 2020 [38] Tenforde et al. 2020 [39] Goertz et al. 2020 [17] Petersen et al. 2020 [21]Cirulli et al. 2020 [45]Logue et al. 2021 [28]Iqbal et al 2021 [31]Peluso et al. 2021 [48]	Jacobs et al. 2020 [41] Wang et al. 2020 [43] Nehme et al. 2020 [38] Cirulli et al. 2020 [45] Peluso et al. 2021 [48]	Carfi et al 2020 [27] Mandal et al. 2020 [37] Townsend et al. 2020 [42]Halpin et al. 2021 [18]Cirulli et al. 2020 [45]Sudre et al. 2021 [30]Kamal et al. 2020 [29] Moreno-Pérez et al. 2021 [24]Zhou et al. 2021 [32]	Arnold et al. 2020 [40] Garrigues et al. 2020 [16]Xiong et al. 2021 [22]Huang et al. 2021 [23]Goertz et al. 2020 [17]Petersen et al. 2020 [21]Cirulli et al. 2020 [45]Logue et al. 2021 [28]Jacobson et al. 2021 [26]Peluso et al. 2021 [48]Sykes et al. 2021 [25]Venturelli et al. 2021 [33] Suárez-Robles et al. 2020 [34] COMEBAC Study Group et al. 2021 [35]
Chest Pain	Carvalho et al. 2020 [15] Arnold et al. 2020 [40] Garrigues et al. 2020 [16]Carfi et al 2020 [27]Wang et al. 2020 [43]Xiong et al. 2021 [22] Tenforde et al. 2020 [39] Goertz et al. 2020 [17]Cirulli et al. 2020 [45]Peluso et al. 2021 [48]	Carvalho et al. 2020 [15] Wang et al. 2020 [43] Cirulli et al. 2020 [45] Iqbal et al 2021 [31]Peluso et al. 2021 [48]	Carvalho et al. 2020 [15] Carfi et al 2020 [27] Cirulli et al. 2020 [45] Sudre et al. 2021 [30]	Arnold et al. 2020 [40] Garrigues et al. 2020 [16]Xiong et al. 2021 [22]Huang et al. 2021 [23]Goertz et al. 2020 [17]Cirulli et al. 2020 [45]Jacobson et al. 2021 [26]Peluso et al. 2021 [48]Sykes et al. 2021 [25] COMEBAC Study Group et al. 2021 [35]
Myalgia	Arnold et al. 2020 [40] Garrigues et al. 2020 [16]Carfi et al 2020 [27] Jacobs et al. 2020 [41]Wang et al. 2020 [43]Xiong	Jacobs et al. 2020 [41] Wang et al. 2020 [43] Cirulli et al. 2020 [45] Peluso et al. 2021 [48]	Carfi et al 2020 [27] Cirulli et al. 2020 [45] Sudre et al. 2021 [30] Moreno-Pérez et al. 2021 [24]Zhou et al. 2021 [32]	Arnold et al. 2020 [40] Xiong et al. 2021 [22] Huang et al. 2021 [23] Goertz et al. 2020 [17] Stavem et al. 2020 [20] Petersen et al. 2020 [21] Cirulli et al.

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Supplementary Table S1 (*continued*)

	et al. 2021 [22] Tenforde et al. 2020 [39] Goertz et al. 2020 [17] Stavem et al. 2020 [20] Petersen et al. 2020 [21]Cirulli et al. 2020 [45]Logue et al. 2021 [28]Peluso et al. 2021 [48]			2020 [45] Logue et al. 2021 [28] Jacobson et al. 2021 [26] Peluso et al. 2021 [48] Sykes et al. 2021 [25]
Headache	Arnold et al. 2020 [40]Carfi et al 2020 [27] Mandal et al. 2020 [37] Townsend et al. 2020 [42]Wang et al. 2020 [43] Nehme et al. 2020 [38] Tenforde et al. 2020 [39] Goertz et al. 2020 [17] Stavem et al. 2020 [20] Petersen et al. 2020 [21]Cirulli et al. 2020 [45]Logue et al. 2021 [28]Peluso et al. 2021 [48]	Jacobs et al. 2020 [41] Wang et al. 2020 [43] Nehme et al. 2020 [38] Cirulli et al. 2020 [45] Iqbal et al 2021 [31]Peluso et al. 2021 [48]	Carfi et al 2020 [27] Cirulli et al. 2020 [45] Sudre et al. 2021 [30] Kamal et al. 2020 [29] Moreno-Pérez et al. 2021 [24]	Arnold et al. 2020 [40] Huang et al. 2021 [23] Goertz et al. 2020 [17] Stavem et al. 2020 [20] Petersen et al. 2020 [21] Cirulli et al. 2020 [45] Logue et al. 2021 [28] Jacobson et al. 2021 [26] Peluso et al. 2021 [48] Venturelli et al. 2021 [33] Suárez-Robles et al. 2020 [34] COMEBAC Study Group et al. 2021 [35]
Eyes irritation	Carfi et al 2020 [27] Jacobs et al. 2020 [41] Goertz et al. 2020 [17] Stavem et al. 2020 [20]Cirulli et al. 2020 [45]	Jacobs et al. 2020 [41] Galván-Tejada et al. 2020 [19]Iqbal et al 2021 [31]	Carfi et al 2020 [27] Zhou et al. 2021 [32]	Goertz et al. 2020 [17] Stavem et al. 2020 [20]
Sputum	Carfi et al 2020 [27] Wang et al. 2020 [43] Xiong et al. 2021 [22] Goertz et al. 2020 [17]	Jacobs et al. 2020 [41] Wang et al. 2020 [43]	Carfi et al 2020 [27] Zhou et al. 2021 [32]	Xiong et al. 2021 [22] Goertz et al. 2020 [17] Petersen et al. 2020 [21] Suárez-Robles et al. 2020 [34]

Supplementary Table S1 (*continued*)

	Petersen et al. 2020 [21]Cirulli et al. 2020 [45]			
Rhinitis	Carfi et al 2020 [27] Wang et al. 2020 [43] Halpin et al. 2021 [18] Tenforde et al. 2020 [39] Stavem et al. 2020 [20] Petersen et al. 2020 [21]Cirulli et al. 2020 [45]Logue et al. 2021 [28]Peluso et al. 2021 [48]	Wang et al. 2020 [43] Peluso et al. 2021 [48]	Carfi et al 2020 [27]	Stavem et al. 2020 [20] Petersen et al. 2020 [21] Logue et al. 2021 [28] Jacobson et al. 2021 [26] Peluso et al. 2021 [48]
Sore Throat	Carfi et al 2020 [27] Wang et al. 2020 [43] Xiong et al. 2021 [22] Goertz et al. 2020 [17] Stavem et al. 2020 [20] Petersen et al. 2020 [21]Cirulli et al. 2020 [45]Logue et al. 2021 [28]Peluso et al. 2021 [48]	Wang et al. 2020 [43] Peluso et al. 2021 [48]	Carfi et al 2020 [27] Sudre et al. 2021 [30]	Xiong et al. 2021 [22] Huang et al. 2021 [23] Goertz et al. 2020 [17] Stavem et al. 2020 [20] Petersen et al. 2020 [21] Logue et al. 2021 [28] Jacobson et al. 2021 [26] Peluso et al. 2021 [48] Sykes et al. 2021 [25]
Cough	Carvalho et al. 2020 [15] Arnold et al. 2020 [40] Garrigues et al. 2020 [16]Carfi et al 2020 [27] Jacobs et al. 2020 [41]Wang et al. 2020 [43] Halpin et al. 2021 [18]Xiong et al. 2021 [22] Nehme et al. 2020 [38] Tenforde et al. 2020 [39] Goertz	Carvalho et al. 2020 [15] Jacobs et al. 2020 [41] Wang et al. 2020 [43] Halpin et al. 2021 [18] Nehme et al. 2020 [38] Galván-Tejada et al. 2020 [19]Cirulli et al. 2020 [45]Iqbal et al 2021 [31] Peluso et al. 2021 [48]	Carvalho et al. 2020 [15] Carfi et al 2020 [27] Halpin et al. 2021 [18] Cirulli et al. 2020 [45] Chopra et al. 2021 [36] Moreno-Pérez et al. 2021 [24]Zhou et al. 2021 [32]	Arnold et al. 2020 [40] Garrigues et al. 2020 [16]Xiong et al. 2021 [22]Goertz et al. 2020 [17]Stavem et al. 2020 [20]Petersen et al. 2020 [21]Cirulli et al. 2020 [45]Sudre et al. 2021 [30]Logue et al. 2021 [28]Jacobson et al. 2021 [26]Peluso et al. 2021 [48]Sykes et al. 2021 [25]Venturelli et al. 2021 [33] Suárez-Robles

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	et al. 2020 [17] Stavem et al. 2020 [20] Petersen et al. 2020 [21]Cirulli et al. 2020 [45]Logue et al. 2021 [28]Peluso et al. 2021 [48]			et al. 2020 [34] COMEBAC Study Group et al. 2021 [35]
Anosmia	Carvalho et al. 2020 [15] Arnold et al. 2020 [40]Carfi et al 2020 [27] Jacobs et al. 2020 [41] Tenforde et al. 2020 [39] Goertz et al. 2020 [17] Stavem et al. 2020 [20] Petersen et al. 2020 [21]Cirulli et al. 2020 [45]Logue et al. 2021 [28]Peluso et al. 2021 [48]	Carvalho et al. 2020 [15] Jacobs et al. 2020 [41] Galván-Tejada et al. 2020 [19]Cirulli et al. 2020 [45]Iqbal et al 2021 [31] Peluso et al. 2021 [48]	Carvalho et al. 2020 [15] Carfi et al 2020 [27] Cirulli et al. 2020 [45] Sudre et al. 2021 [30] Chopra et al. 2021 [36] Moreno-Pérez et al. 2021 [24]	Arnold et al. 2020 [40] Garrigues et al. 2020 [16]Huang et al. 2021 [23]Goertz et al. 2020 [17]Stavem et al. 2020 [20]Petersen et al. 2020 [21]Cirulli et al. 2020 [45]Logue et al. 2021 [28]Jacobson et al. 2021 [26]Peluso et al. 2021 [48]Sykes et al. 2021 [25]Venturelli et al. 2021 [33] Suárez-Robles et al. 2020 [34]Mumblit et al. 2021 [46] COMEBAC Study Group et al. 2021 [35]
Ageusia	Carvalho et al. 2020 [15]Carfi et al 2020 [27] Mandal et al. 2020 [37] Jacobs et al. 2020 [41] Nehme et al. 2020 [38] Goertz et al. 2020 [17] Stavem et al. 2020 [20] Petersen et al. 2020 [21]Cirulli et al. 2020 [45]	Carvalho et al. 2020 [15] Jacobs et al. 2020 [41] Nehme et al. 2020 [38] Galván-Tejada et al. 2020 [19]Cirulli et al. 2020 [45]Iqbal et al 2021 [31]	Carvalho et al. 2020 [15] Carfi et al 2020 [27] Cirulli et al. 2020 [45] Chopra et al. 2021 [36]	Garrigues et al. 2020 [16]Huang et al. 2021 [23]Goertz et al. 2020 [17]Stavem et al. 2020 [20]Petersen et al. 2020 [21]Cirulli et al. 2020 [45]Jacobson et al. 2021 [26]Sykes et al. 2021 [25] Suárez-Robles et al. 2020 [34]Mumblit et al. 2021 [46]
Joint Pain	Arnold et al. 2020 [40]Carfi et al 2020	Carvalho et al. 2020 [15] Jacobs et al. 2020 [41]	Carvalho et al. 2020 [15] Carfi et al 2020 [27]	Arnold et al. 2020 [40] Goertz et al. 2020 [17]

Supplementary Table S1 (*continued*)

	[27] Jacobs et al. 2020 [41] Goertz et al. 2020 [17] Stavem et al. 2020 [20] Petersen et al. 2020 [21]Cirulli et al. 2020 [45]Peluso et al. 2021 [48]	Cirulli et al. 2020 [45] Iqbal et al 2021 [31]Peluso et al. 2021 [48]	Cirulli et al. 2020 [45] Kamal et al. 2020 [29]	Stavem et al. 2020 [20] Petersen et al. 2020 [21] Cirulli et al. 2020 [45] Peluso et al. 2021 [48] Suárez-Robles et al. 2020 [34]Mumblit et al. 2021 [46]
Diarrhoea	Carvalho et al. 2020 [15] Arnold et al. 2020 [40] Garrigues et al. 2020 [16]Carfi et al 2020 [27] Mandal et al. 2020 [37] Jacobs et al. 2020 [41]Wang et al. 2020 [43]Xiong et al. 2021 [22] Tenforde et al. 2020 [39] Goertz et al. 2020 [17] Stavem et al. 2020 [20] Petersen et al. 2020 [21]Cirulli et al. 2020 [45]Logue et al. 2021 [28]Peluso et al. 2021 [48]	Carvalho et al. 2020 [15] Wang et al. 2020 [43] Cirulli et al. 2020 [45] Peluso et al. 2021 [48]	Carvalho et al. 2020 [15] Carfi et al 2020 [27] Cirulli et al. 2020 [45] Sudre et al. 2021 [30] Moreno-Pérez et al. 2021 [24]	Arnold et al. 2020 [40] Huang et al. 2021 [23] Goertz et al. 2020 [17] Stavem et al. 2020 [20] Petersen et al. 2020 [21] Cirulli et al. 2020 [45] Logue et al. 2021 [28] Jacobson et al. 2021 [26] Peluso et al. 2021 [48]
Vomiting	Wang et al. 2020 [43] Xiong et al. 2021 [22] Tenforde et al. 2020 [39] Goertz et al. 2020 [17] Stavem et al. 2020 [20]Peluso et al. 2021 [48]	Wang et al. 2020 [43] Galván-Tejada et al. 2020 [19]Peluso et al. 2021 [48]	-	Goertz et al. 2020 [17] Stavem et al. 2020 [20] Jacobson et al. 2021 [26] Peluso et al. 2021 [48]
Nausea	Arnold et al. 2020 [40]Wang et al. 2020 [43]Xiong	Wang et al. 2020 [43] Galván-Tejada et al. 2020 [19]Cirulli	Cirulli et al. 2020 [45]	Goertz et al. 2020 [17] Stavem et al. 2020 [20] Petersen et al.

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	et al. 2021 [22] Tenforde et al. 2020 [39] Goertz et al. 2020 [17] Stavem et al. 2020 [20] Petersen et al. 2020 [21]Cirulli et al. 2020 [45]Logue et al. 2021 [28]Peluso et al. 2021 [48]	et al. 2020 [45]Peluso et al. 2021 [48]		2020 [21] Cirulli et al. 2020 [45] Logue et al. 2021 [28] Peluso et al. 2021 [48]
Cutaneous sign	Goertz et al. 2020 [17] Stavem et al. 2020 [20] Petersen et al. 2020 [21]Cirulli et al. 2020 [45]Logue et al. 2021 [28]Peluso et al. 2021 [48]	Carvalho et al. 2020 [15] Cirulli et al. 2020 [45] Peluso et al. 2021 [48]	Carvalho et al. 2020 [15] Cirulli et al. 2020 [45] Moreno-Pérez et al. 2021 [24]	Cirulli et al. 2020Huang et al. 2021 [23]Goertz et al. 2020 [17]Stavem et al. 2020 [20]Petersen et al. 2020 [21]Cirulli et al. 2020 [45]Logue et al. 2021 [28]Peluso et al. 2021 [48]Sykes et al. 2021 [25]Venturelli et al. 2021 [33] Suárez-Robles et al. 2020 [34]Mumblit et al. 2021 [46]
Palpitations	Wang et al. 2020 [43] Xiong et al. 2021 [22] Goertz et al. 2020 [17]Peluso et al. 2021 [48]	Carvalho et al. 2020 [15] Wang et al. 2020 [43] Cirulli et al. 2020 [45] Peluso et al. 2021 [48]	Carvalho et al. 2020 [15] Cirulli et al. 2020 [45] Kamal et al. 2020 [29]	Xiong et al. 2021 [22] Huang et al. 2021 [23] Goertz et al. 2020 [17] Cirulli et al. 2020 [45] Jacobson et al. 2021 [26] Peluso et al. 2021 [48] Venturelli et al. 2021 [33] Suárez-Robles et al. 2020 [34]Mumblit et al. 2021 [46]
Confusion	Garrigues et al. 2020 [16] Jacobs et al. 2020 [41] Tenforde et al. 2020 [39] Stavem et al. 2020 [20]	Jacobs et al. 2020 [41] Cirulli et al. 2020 [45]	Cirulli et al. 2020 [45]	Stavem et al. 2020 [20] Cirulli et al. 2020 [45] Logue et al. 2021 [28] Mumblit et al. 2021 [46]
Vertigo	Carfi et al 2020 [27] Wang et al. 2020 [43] Goertz et al. 2020 [17]Cirulli et al. 2020 [45]Peluso et al. 2021 [48]	Wang et al. 2020 [43] Cirulli et al. 2020 [45]	Carfi et al 2020 [27] Cirulli et al. 2020 [45]	Xiong et al. 2021 [22] Huang et al. 2021 [23] Goertz et al. 2020 [17] Cirulli et al. 2020 [45] Peluso et al. 2021 [48]

needed.

The occurrence of respiratory symptoms following SARS-CoV-2 infection is similar to that present in severe acute respiratory syndrome (SARS) survivors, who also exhibit symptoms 6–12 months after the infection [54], but contrasts with that observed after community-acquired bacterial pneumonia where almost all patients are asymptomatic 10 days after the infection [55]. In addition, a main difference between SARS-CoV-2 and other respiratory infectious diseases is the presence of a plethora of post-infectious symptoms, e.g., joint pain, ageusia, anosmia, chest pain, nausea, headaches or palpitation, affecting systems other than the respiratory system. This meta-analysis confirms the presence of several post-COVID-19 symptoms supporting a multisystemic involvement; it also shows that time-course of symptoms fluctuates depending on the follow-up period and whether the COVID-19 patient was hospitalized or not. These considerations are highly important to properly define the timeframe of post-COVID-19 symptoms [7].

To determine the underlying mechanisms behind these symptoms is beyond the scope of the current review, but two main hypotheses are currently discussed, although not alone. First, a prolonged pro-inflammatory response (hyper-inflammatory cytokine storm) related to SARS-CoV-2 infection can provoke an atypical response of the immune system and mast cells, promoting a cascade of events affecting the respiratory, immune, and central nervous systems [56]. Second, social and emotional factors around COVID-19 pandemic, e.g., posttraumatic stress, hospitalization, treatments received, catastrophic social alarm, lockdown, laboral and familiar situations, and psychological disorders, such as anxiety or depression, may contribute to these post-COVID-19 symptoms.

Although the underlying mechanisms explaining this plethora of symptoms are unknown, their complexity and heterogeneity supports that post-COVID-19 sequalae will need from a multidisciplinary approach [57].

4.2. *Strengths and weaknesses of the review*

The results of this review and meta-analysis summarizing prevalence rates of post-COVID-19 symptoms should be considered according to its strengths and weaknesses. The main strength was the rigorous methodology applied for literature search, study selection, screening for eligibility, assessment of methodological quality, and pooling analysis of prevalence data from more than 30 studies. Nevertheless, some weaknesses should be also recognized. First, a meta-regression could not be conducted because of the presence of serious/large heterogeneity between the studies. In fact, most of comparisons showed large heterogeneity. Second, the small number of studies in some comparisons limit the generality of the current results. Similarly, the number of patients requiring ICU admission was small, so no conclusions regarding this population can be achieved. Third, just two studies reported prevalence data separately by gender [22,25]; however, they reported different follow-ups and different post-COVID-19 symptoms; therefore, gender differences were not possible to be analyzed. Fourth, most studies included Caucasian subjects, with just four including Chinese people and none including African people; therefore, racial influence on the

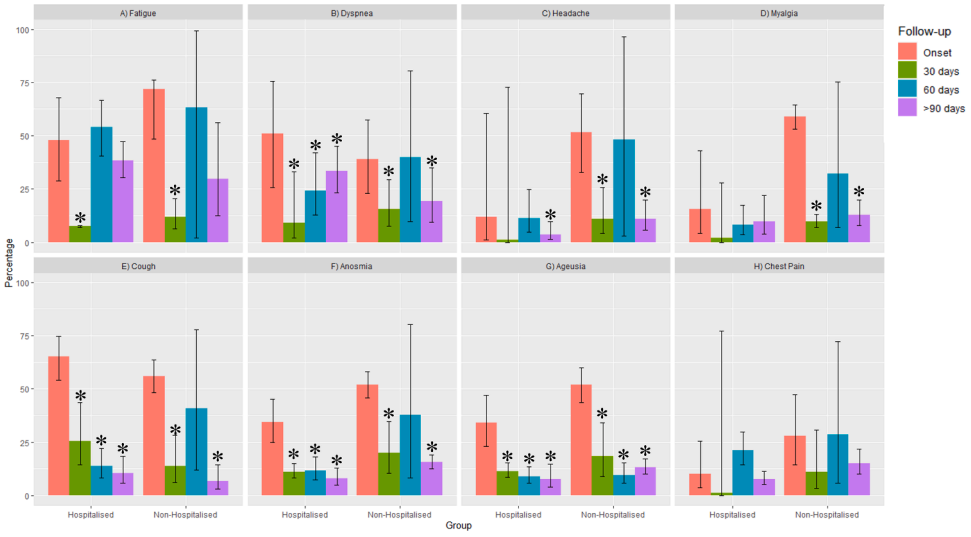

Fig. 2. Time course of the eight most prevalent COVID-related symptoms at onset/hospital admission and 30days, 60days and ≥90 days after.
* Statistically significant effect ($P<0.001$) showing a time trend during the different follow-up periods.

presence of post-COVID-19 symptoms remains unknown. Finally, post-COVID-19 symptoms were mostly self-reported by the patients themselves and collected by telephonic interview, electronical websites, postal or face-to-face interviews (table 1). Development of specific patient-reported outcome measures (PROM) for COVID-19 will be helpful to obtain homogeneous data. Interestingly, Tran et al. have recently developed the long COVID Symptom and Impact Tools, which could help for more standardized collection of post-COVID-19 symptoms [58].

4.3. Future research direction

This systematic review and meta-analysis investigating prevalence rates of post-COVID-19 symptoms provides updated data on the presence of persistent post-COVID-19 symptoms in COVID-19 survivors; however, it opens several questions for future studies. First, due to the relapsing and remitting nature of post-COVID-19 symptoms, it is important to identify those time frames where these symptoms should be considered as residual (post-acute COVID) or as real (long-term) post-COVID-19 symptom. In fact, time frames are important for proper description of post-COVID-19 symptomatology [7]. For instance, symptoms appearing soon (i.e., the first 30 days after symptoms onset) after recovery from acute infection have been considered as post-acute sequelae of COVID-19 (PASC), whereas symptoms appearing later, i.e., 3 months or longer, after infection could be considered as the real post-COVID-19 syndrome [7]. Second, identification of risk factors associated with post-COVID-19 symptoms is crucial. Some studies included in this review identified, by using multivariate analyses, potential risk factors, such as older age [15,17,38], female gender [22,23,25,41,46], longer hospital stance [15], pre-existing comorbidities [17], or number of symptoms at the acute stage [15,17] associated with a higher number of post-COVID-19 symptoms. However, contradictory findings were also observed. For instance, whereas some studies reported that females were more prone to exhibit post-COVID-19 symptoms when compared with males [22,23,25,41,46], others did not find such association with female gender [21,24,26,30,45,47]. The heterogeneity in the methodology between the studies could explain these discrepancies in the results and does not permit to determine firm conclusions. Studies investigating risk factors associated with post-COVID-19 symptoms are urgently needed to promote focus on this issue in healthcare systems and, thereby, facilitate counselling and management strategies for these patients. A relevant topic for considering in future studies would be a potential participation of the patients into the designs since COVID-19 patients are highly active and their point of view may be crucial for designing studies according to their needs [59]. Studies investigating underlying mechanisms explaining post-COVID-19 symptoms are needed for better management of this group of individuals, the long-haulers [4].

5. Conclusions

This review/meta-analysis has revealed that more than 60% of individuals infected by SARS-CoV-2 exhibited at least one post-COVID-19 symptom after onset or hospital admission. Fatigue and dyspnea were the most prevalent post-COVID-19 symptoms experienced by both hospitalized and non-hospitalized patients, particularly 60 and ≥90 days after onset/ hospitalization. The prevalence rate of other post-COVID-19 symptoms including headache, anosmia, ageusia, chest pain, joint pain or palpitations was lower and more variable. Early identification of post-COVID-19 symptoms will ensure immediate action and counselling of these “long haulers”, who may otherwise struggle with unrecognized and unmanaged symptoms.

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Data sharing statement

This study will not share any individual data or document from any participant.

Transparency declaration

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned have been explained

CRediT authorship contribution statement

César Fernández-de-las-Peñas: Conceptualization, Visualization, Writing – review & editing, Data curation, Writing – original draft. **Domingo Palacios-Ceña:** Conceptualization, Visualization, Data curation. **Víctor Gómez-Mayordomo:** Conceptualization, Visualization, Data curation, Writing – original draft. **Lidiane L Florencio:**

Conceptualization, Visualization, Formal analysis, Data curation, Writing – original draft. **María L. Cuadrado:** Conceptualization, Visualization, Formal analysis, Data curation, Writing – original draft. **Gustavo Plaza-Manzano:** Conceptualization, Visualization, Writing – review & editing, Data curation. **Marcos Navarro-Santana:** Conceptualization, Visualization, Writing – review & editing, Formal analysis, Data curation.

Declaration of Competing Interest

No conflict of interest is declared by any of the authors

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