

Review

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Presence of SARS-CoV-2 RNA in COVID-19 survivors with post-COVID symptoms: a systematic review of the literature

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Abstract

Introduction: Viral persistence is one of the main hypotheses explaining the presence of post-COVID symptoms. This systematic review investigated the presence of SARS-CoV-2 RNA in plasma, stool, urine, and nasal/oral swab samples in individuals with post-COVID symptomatology.

Content: MEDLINE, CINAHL, PubMed, EMBASE, Web of Science databases, as well as medRxiv/bioRxiv preprint servers were searched up to November 25th, 2023. Articles investigating the persistence of SARS-CoV-2 RNA in plasma, stool, urine or nasal/oral swab samples in patients with post-COVID symptoms were included. Methodological quality was

assessed using the Newcastle–Ottawa Scale or Cochrane’s Risk of Bias (Rob) tool.

Summary: From 322 studies identified, six studies met all inclusion criteria. The sample included 678 COVID-19 survivors (52 % female, aged from 29 to 66 years). The methodological quality was moderate in 88 % of the studies (n=5/6). Three papers investigated the presence of SARS-CoV-2 RNA in plasma, three studies in nasal/oral swabs, two studies in stool samples, one in urine and one in saliva. The follow-up was shorter than two months (<60 days after) in 66 % of the studies (n=4/6). The prevalence of SARS-CoV-2 RNA ranged from 5 to 59 % in patients with post-COVID symptoms the first two months after infection, depending on the sample tested, however, SARS-CoV-2 RNA was also identified in COVID-19 survivors without post-COVID symptoms (one study).

Outlook: Available evidence can suggest the presence of persistent SARS-CoV-2 RNA in post-COVID patients in the short term, although the biases within the studies do not permit us to make firm assumptions. The association between post-COVID symptoms and SARS-CoV-2 RNA in the samples tested is also conflicting. The lack of comparative group without post-COVID symptoms limits the generalizability of viral persistence in post-COVID-19 condition.

Keywords: long-COVID; viral persistence; RNA; post-COVID-19; review

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Introduction

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the agent responsible for the rapid spread of coronavirus disease 2019 (COVID-19), has caused one of the most important worldwide health crises of the present century. Over the course of the last years, the rapid emergence of several SARS-CoV-2 variants has perpetuated its transmission, resulting in a staggering 774 million confirmed

cases and more than 7 million reported deaths globally (data at February 8, 2024) [1]. Substantial efforts had been focused on management of COVID-19 symptoms at the acute phase [2, 3], the introduction of vaccines for decreasing mortality rates [4], and the prevention in the spread of SARS-CoV-2 variants [5].

The presence of long-lasting symptoms once the acute phase of a SARS-CoV-2 infection has elapsed pose a growing concern. Although there are different definitions for the presence of symptoms after a SARS-CoV-2 infection, the terms long-COVID [6] and post-COVID-19 condition [7] are the most accepted. More than 100 post-COVID symptoms affecting cardiovascular, respiratory, neurological, or musculoskeletal systems had been described [8]. The presence of post-COVID symptoms is associated with worse health-related quality of life [9], an increase in healthcare resource utility, and an increase in direct and indirect medical costs [10].

Several meta-analyses reported that up to 50 % of individuals who had survived a SARS-CoV-2 infection develop a plethora of long-lasting post-COVID symptoms from several months [11, 12] up to one year after [13, 14] the infection. A recent meta-analysis found that almost 30 % of COVID-19 survivors still experience post-COVID symptoms two-years after the infection [15].

Long-COVID denotes symptoms and signs affecting multiple tissues and organs, and these symptoms vary depending on the predominant pathophysiological mechanism operating [16]. Thus, underlying mechanisms behind long-COVID are not fully understood and different mechanisms are proposed [17, 18]. Among the mechanisms, viral persistence is postulated as one hypothesis explaining the development of post-COVID symptoms [19]. It is possible that the SARS-CoV-2 pathogen may establish a persistent long-lasting infection. Such a persistent reservoir or remnants would be able to generate pathogen-associated molecular patterns (PAMPs), e.g., viral RNA or bacterial cells wall, and could engage host pattern recognition receptors (PRRs) triggering innate host immune activation [20].

Several studies have attempted to identify the presence of viral persistence in patients with post-COVID symptoms; however, most studies have investigated laboratory signs, i.e., the adaptative immune response, associated with the presence of SARS-CoV-2 rather than the presence of viral RNA [21]. The narrative review by Proal et al. [21] suggests that viral persistence could be time-dependent (i.e., there is a tendency for the infection to disappear with time) and tissue-dependent (i.e., the virus may be present in tissues potentially associated with specific post-COVID symptoms). In fact, SARS-CoV-2 RNA has been found in specific human tissues

including the lungs [22] or gastrointestinal tract [23] which could explain the development of post-COVID symptoms in the respiratory (e.g., dyspnea) or gastrointestinal (e.g., diarrhea) systems, respectively. However, the presence of more systemic symptoms such as fatigue, muscle weakness, or pain could be associated with viral persistence in generalized samples such as plasma.

No previous review has systematically investigated the presence of persistent SARS-CoV-2 RNA in people with post-COVID symptomatology. Thus, this review investigated the presence of SARS-CoV-2 RNA (viral persistence) in plasma, stool, urine or nasal/oral swab samples in individuals with post-COVID symptoms. We aimed to identify potential biases in the current literature and provide future research directions.

Methods

A systematic review of studies investigating the presence of SARS-CoV-2 RNA in plasma, stool, urine and nasal/oral swab samples in patients with post-COVID symptoms according to the 2020 Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement was performed [24]. The review design was prospectively registered in Open Science Framework (OSF) database (<https://osf.io/wvfhfu>).

Literature search

Electronic literature searches were conducted between 1st and 10th of December 2023 by two authors for published studies up to November 25, 2023 on the following databases: PubMed/MEDLINE, CINAHL, EMBASE, and Web of Science databases, as well as on medRxiv and bioRxiv preprint servers. Searches were conducted with the assistance of an experienced health science librarian. We screened the reference list of the papers for identifying other studies. The combinations of search terms using Boolean operators on each database are outlined in Table 1.

Selection criteria

The inclusion and exclusion criteria were described according to the Population, Intervention, Comparison and Outcome (PICO) principle:

Population: Adults (>18 years) who previously infected by SARS-CoV-2 and diagnosed with real-time reverse transcription-polymerase chain reaction (RT-PCR) assay or SARS-CoV-2 serological test.

Intervention: Not applicable

Comparison: Not applicable

Outcome: Articles published up to 25th November 2023 investigating the persistence of SARS-CoV-2 RNA in plasma, stool, urine or nasal/oral swab samples in patients with post-COVID symptoms. Articles should collect any post-COVID symptom such as fatigue, dyspnea, pain, brain fog, memory loss, skin rashes, palpitations, and cough, in addition to the SARS-CoV-2 RNA persistence.

Table 1: Database formulas during literature search.

PubMed search formula
#1 “post-acute COVID-19 syndrome” [MeSH terms] OR “long-COVID” [all fields] OR “long-COVID symptoms” [all fields] OR “long hauler” [all fields] OR “post-COVID-19” [all fields] OR “post-acute COVID-19 symptoms” [all fields] OR “post-COVID sequelae” [all fields]
#2 “virus persistence” [all fields] OR “virus shedding” [MeSH terms] OR “viral shedding”[all fields] OR “viral presence”[all fields]
#3 “SARS-CoV-2 RNA” [all fields]
#4 #1 AND #2 AND #3
Medline/ CINAHL (via EBSCO) search formula
#1 (post-acute COVID-19 syndrome) OR (long-COVID) OR (long-COVID symptoms) OR (long hauler) OR (post-COVID-19) OR (post-acute COVID-19 symptoms) OR (COVID-19 sequelae)
#2 (viral persistence) OR (viral shedding) OR (presence)
#3 (SARS-CoV-2 RNA)
#4 #1 AND #2 AND #3
EMBASE search formula
(Post-acute COVID-19 syndrome) OR (long-COVID) OR (long-COVID symptoms) OR (long hauler) OR (post-COVID-19) OR (post-acute COVID-19 symptoms) OR (COVID-19 sequelae) AND (persistence) OR (viral shedding) OR (presence) AND (SARS-CoV-2 RNA)

Screening process, study selection and data extraction

Observational cohorts and case-control studies where the presence of SARS-CoV-2 RNA in in plasma, stool, urine or nasal/oral swab samples in a cohort of patients who had developed post-COVID symptomatology after an acute SARS-CoV-2 infection were included in this review. Research letters or correspondence were included if they showed new data. Case studies/case series, editorials and opinion articles without new data were excluded. Only human studies of living individuals and full-text English language papers were considered. Post-mortem studies were also excluded.

The title/abstract of each article identified during the database search was screened by two authors. First, duplicates were removed. Full text of eligible articles was analyzed by the same two authors. Data including authors, country, design, sample size, setting, age, post-COVID symptoms, sample of SARS-CoV-2 RNA analysis, and follow-up were extracted from each study. Both authors needed to have a consensus on both study selection and data-extraction. Discrepancies at any stage of the screening process were resolved by asking a third author, if needed.

Methodological quality/risk of bias

The Newcastle–Ottawa Scale (NOS), a nine-star rating system evaluating the risk of bias and methodological quality of observational (case-control and cohort) studies was applied by two authors [25]. In cohort studies, the NOS evaluates the following items: case selection (i.e., cohort representativeness, selection of non-exposed cohort, case definition, outcome), comparability (i.e., proper control for age, sex, or other factors, between-group comparisons) and exposure (i.e., outcome

assessment, enough and adequate follow-up). In case-control studies, NOS items are adapted. For instance, case selection item includes adequate case definition and control selection. Thus, the quality of longitudinal cohort studies or case-control studies was classified as: high quality (7–9 stars), moderate quality (5–6 stars), or low quality (≤4 stars). Methodological quality was also evaluated by two authors. If disagreement between both authors was identified, a third researcher arbitrated the final decision.

Data synthesis

Meta-analysis was not deemed appropriate due to the high heterogeneity between studies. Thus, we conducted a qualitative synthesis of the data by addressing population, methodological quality of the studies, and limitations.

Patient and public involvement

Patients were not involved in the study since this was a review of the literature.

Results

Study selection

The electronic search identified 322 potential titles for screening. After removing duplicates (n=52) and papers not investigating the presence of SARS-CoV-2 RNA in plasma, stool, urine, or nasal/oral swab samples (n=243), 25 papers remained for title and abstract examination. Twelve (n=12) were excluded after title and abstract examination, leading to fifteen articles for full-review. Five (n=5) were excluded because they analyzed SARS-CoV-2 RNA during the acute phase of the infection and the remaining four (n=4) were excluded because two analyzed SARS-CoV-2 RNA post-mortem [22, 26], one analyzed SARS-CoV-2 protein spike but not RNA [27], and one investigated SARS-CoV-2 RNA but at the cerebrospinal fluid [28]. Thus, a total of six peer-reviewed articles [29–34] were finally included (Figure 1).

Sample characteristics

The sample consisted of 678 individuals (52 % female, ages ranged from 29 to 66 years) who had survived a SARS-CoV-2 infection [29–34]. Three studies [29, 30, 34] included only hospitalized patients (n=188), one [31] included just non-hospitalized subjects (n=111), and the remaining two [32, 33] mixed hospitalized and non-hospitalized individuals (n=379). Three papers [29, 33, 34] investigated the presence of SARS-CoV-2 RNA in plasma samples, three studies [30, 31, 33] analyzed nasal/oral swab samples, two [29, 31] used stool

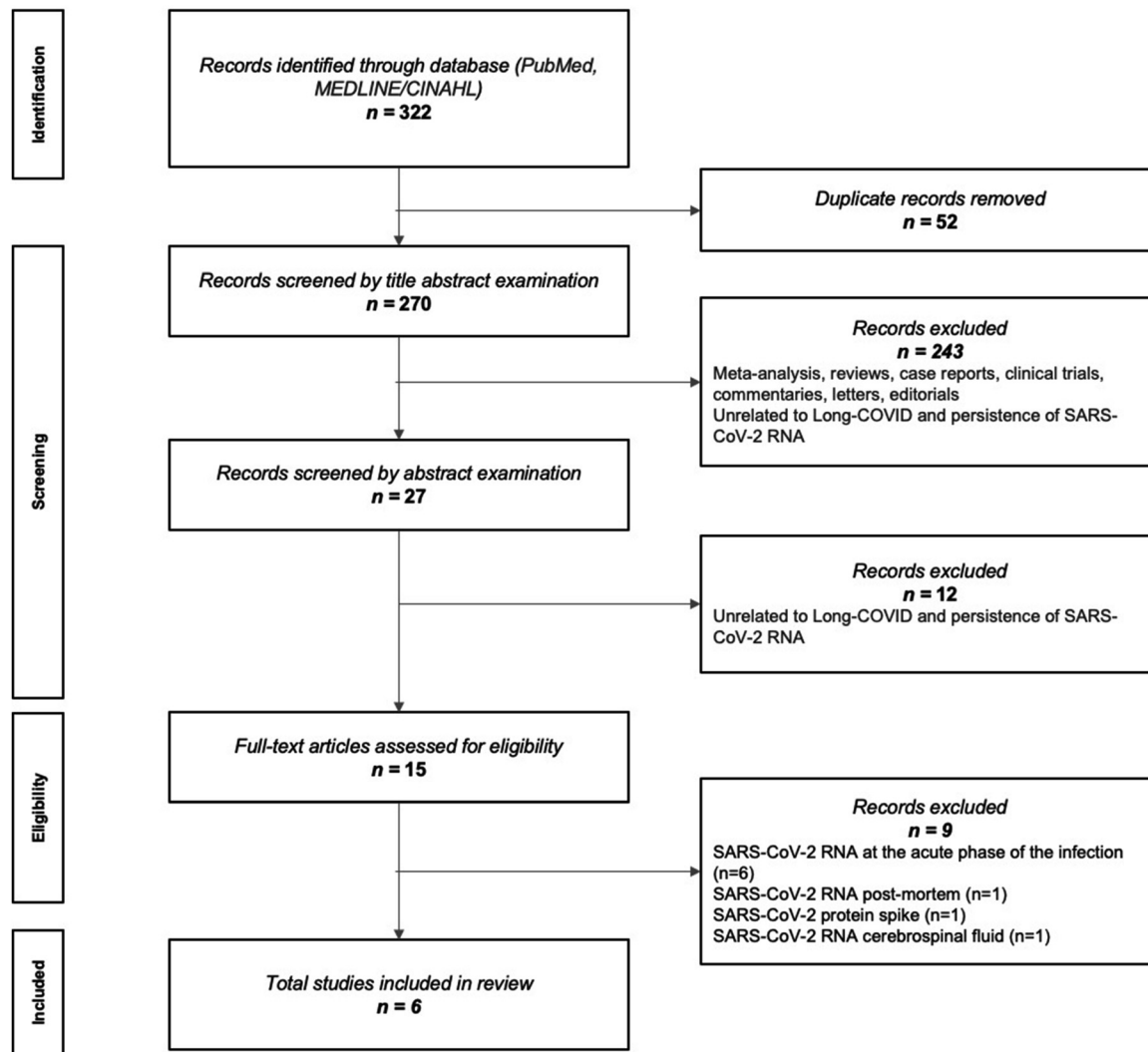


Figure 1: Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram.

samples, one [29] collected urine samples, and one [32] collected saliva samples. Four studies [29, 30, 32, 33] included follow-up periods shorter than two months (<60 days after), one study [31] included follow-ups of three (n=120 days) and six (n=210 days) months after the infection, and the last one [34] included a follow-up of six (n=201 days) months after. None of the studies used a specific definition of long-COVID or post-COVID -19 condition [29–34]. Table 2 summarizes the main findings of those studies included in the current systematic review.

Methodological quality

Five observational cohorts [29–33] and one case-control study [34] were included (Table 3). No disagreement between

authors in methodological quality was identified. All cohort studies [29–33] were of moderate methodological quality (mean: 5.6, SD: 0.5 stars). The case-control study [34] was of high quality (8 stars). The main methodological flaw was proper comparability in both main factor, that is, the lack of a control or comparative group, or additional factors, e.g., age and sex matching (Figure 2).

Viral persistence of SARS-CoV-2 RNA in plasma sample

Two moderate-quality cohort studies [29, 33] and one high-quality case-control study [34] including 385 COVID-19 survivors investigated the presence of SARS-CoV-2 RNA in plasma. The cohort studies found that 25 % [29] and 44 % [33]

Table 2: Main findings of the studies included in the review about the presence of persistent SARS-CoV-2 RNA.

Author Country	Sample (F/M)	Age, years	Post-COVID symptoms	Samples analyzed for viral RNA	Days from infection	Main findings
Tejerina et al. [29] Spain	29 H (18/11)	Median (IQR) 45 (36–56)	Fatigue, muscle pain, dyspnea, tachycardia, and low-grade fever	Plasma, urine, and stool	55 days after infection	<u>Plasma:</u> Thirteen (44.8 %) patients tested positive in viral RNA 55 days after infection <u>Stool:</u> Five (17.2 %) patients tested positive in viral RNA 55 days after infection <u>Urine:</u> Four (13.7 %) patients tested positive in viral RNA 55 days after infection Fifteen (51.7 %) patients tested positive in one determination. Five (17 %) patients were positive in two determinations. Two (6.8 %) patients were positive in three determinations
Zhang et al. [30] China	112 H (60/62)	Median (IQR) 54 (40–66)	Fever, cough, fatigue, shortness of breath, chill, palpitations	Throat swabs	57 days after infection	Six (5.3 %) patients showed persistent viral RNA shedding 45 days after infection The peak viral load was higher in the severe disease group than in the mild group ($p=0.002$)
Natarajan et al. [31] USA	111 NH (46/65)	Median (IQR) 36 (29–51)	Gastrointestinal symptoms (abdominal pain, nausea, vomiting)	Stool (n=60) and oropharyngeal swabs (n=111)	120 days (range 75–165) 210 days (range 166–255) 300 days	<u>Throat swabs:</u> No presence of viral RNA at four months after infection <u>Stool:</u> Seven (12.7 %) patients tested positive in viral RNA 120 days after infection Two (3.8 %) patients tested positive in viral RNA 210 days after infection No viral RNA was present in stool sample 300 days after infection
Peluso et al. [32] USA	70 H/NH (34/36)	Median (IQR) 43 (36–53)	Fever/chills, cough, dyspnea, sore throat, runny nose, chest pain, palpitations, fatigue, smell/taste changes, gastrointestinal and musculoskeletal symptoms	Saliva (n=61)	Median (IQR) 53 days (38–64)	Seven (11.5 %) patients tested positive in viral RNA 53 days after infection No relationship between post-COVID symptoms and SARS-CoV-2 RNA detection in saliva was observed
Su et al. [33] USA	309 H/NH (170/139)	Mean (SD) 56 (18)	Fatigue, cough, anosmia	Plasma and nasal swab	Median (IQR) 53 days (38–64.5)	Seventy-seven (25 %) patients tested positive in viral RNA 53 days after infection
Craddock et al. [34] USA	47 H (26/21) 33 cases (20/13) 14 controls (6/8)	Median (IQR) 49 (42–63)	Fatigue, dyspnea, brain fog, sleep disturbances, mood changes, loss of taste/ smell, fever, myalgias, headache, chest pain, and cough	Plasma	Median (IQR) 201 days (183–266) 235 days (144–263)	Twenty (59 %) patients with post-COVID symptoms tested positive in viral RNA 201 days after infection Four (28 %) patients without post-COVID symptoms tested positive in viral RNA 235 days after infection

of COVID-19 survivors with post-COVID symptoms tested positive for SARS-CoV-2 RNA in plasma 55 days after the acute infection. It should be considered that the sample size of Tejerina et al. [29] was small ($n=29$). Craddock et al. [34] reported that 59 % of patients with post-COVID symptoms tested positive for SARS-CoV-2 RNA in plasma against 28 % of patients without post-COVID symptoms up to 6–7 months after the acute infection. Again, this study also included a small sample size ($n=47$, 33 cases – 14 controls) [34].

Viral persistence of SARS-CoV-2 RNA in nasal/oral swab or saliva sample

Tree moderate-quality cohort studies [30, 31, 33] including 532 COVID-19 survivors investigated the presence of SARS-CoV-2 RNA in nasal/oral swab samples and reported conflicting results. Natarajan et al. [31] did not find persistent SARS-CoV-2 RNA in nasal or oral swab samples four months after the infection. On the contrary, Zhang et al. [30]

Table 3: Methodological quality (Newcastle–Ottawa Scale – NOS) of the studies included in the review.

Study	Selection				Comparability		Outcome		Total score
	Representative of the exposed cohort	Selection of nonexposed cohort	Ascertainment of exposure	Outcome of interest	Main factor	Additional factors	Assessment of outcomes	Sufficient follow-up	
Tejerina et al. 2023 [29]	★	★	★	★			★	★	6/9
Zhang et al. 2020 [30]	★	★	★	★			★	★	6/9
Natarajan et al. 2022 [31]	★		★				★	★	5/9
Peluso et al. 2021 [32]	★	★	★				★	★	5/9
Su et al. 2022 [33]	★	★	★	★			★	★	6/9
Craddock et al. 2022 [34]	★	★	★	★	★		★	★	8/9

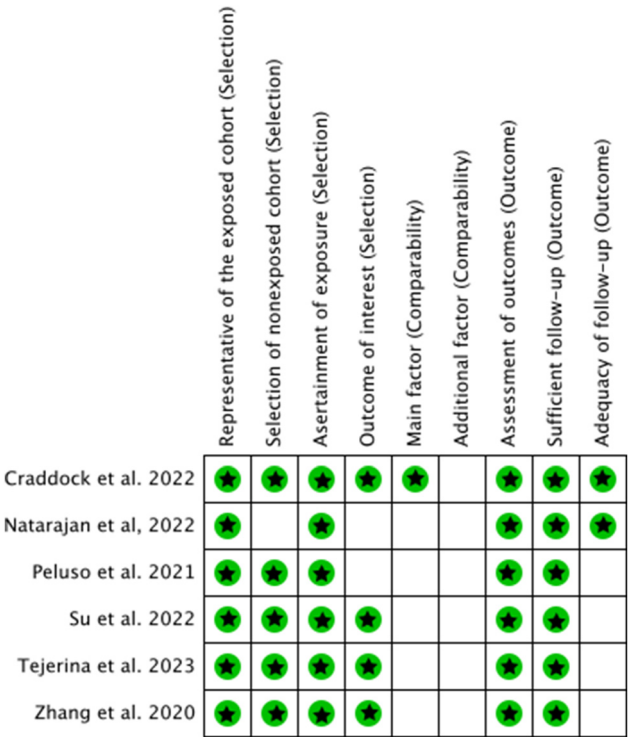


Figure 2: Plot of methodological quality of studies investigating the presence of SARS-CoV-2 RNA in plasma, stool, urine, or nasal/oral swabs.

identified that 5.3 % of patients had persistent SARS-CoV-2 RNA shedding in nasal/oral swab samples 45 days after infection, and Su et al. [33] reported the presence of persistent SARS-CoV-2 RNA in nasal/oral swab samples in up to 25 % of their sample at 53 days after infection. Similarly, Peluso et al. [32] found the presence of persistent SARS-CoV-2 RNA in saliva sample in 11.5 % of patients 53 days after infection, although no association between post-COVID symptoms and SARS-CoV-2 RNA detection in saliva was observed.

Viral persistence of SARS-CoV-2 RNA in urine and stool samples

Two moderate-quality cohort studies [29, 31] including 140 COVID-19 survivors analyzed the presence of SARS-CoV-2 RNA in stool [29, 31] and urine [29] samples. The results were consistent showing that almost 15 % of COVID-19 survivors with post-COVID symptoms tested positive in persistent SARS-CoV-2 RNA in stool and urine [29, 31] samples during the first 4 months after the infection. The presence of SARS-CoV-2 RNA in stool dropped down to 3.8 % of patients at a follow-up of seven months after [31]. However, these results are based on two studies with small sample size (<50 patients on each study).

Discussion

Although several studies, have investigated the topic of viral persistence [21], this review presents the first comprehensive analysis of available evidence on the presence of persistent SARS-CoV-2 RNA in generalized samples including plasma, urine, stool, and nasal/oral swab samples. We were able to identify six peer-reviewed studies, most ($n=5/6$, 88 %) of moderate methodological quality. The results revealed that the prevalence of SARS-CoV-2 RNA ranged from 5 to 59 % in patients with post-COVID symptoms the first months after the infection, depending on the sample tested. The presence of SARS-CoV-2 RNA at long-term follow-ups is lacking. Thus, the association of persistent SARS-CoV-2 RNA in generalized samples, e.g., plasma or nasal/oral swab sample, with specific post-COVID symptoms is heterogeneous, although this assumption should be considered with caution at this stage.

Several points of available evidence should be discussed. First, the most important source of bias in most studies (88 %) was the absence of a group of COVID-19 survivors without post-COVID symptoms as a comparative group. Just one study included a small ($n=14$) comparative group [34]. In fact, this study found that up to 28 % of subjects who had survived SARS-CoV-2 infection but have not developed post-COVID symptoms also tested positive for SARS-CoV-2 RNA. Without the inclusion of a comparison group in most of the published studies, we cannot confirm if the persistence of SARS-CoV-2 RNA is also present in COVID-19 survivors without post-COVID symptoms.

Second, it is important to consider the plethora of post-COVID symptoms that a patient can experience. In fact, none of the studies included in the current review used the definition of post-COVID-19 condition, as 66 % ($n=4/6$) of the studies included a follow-up period shorter than 60 days [7]. It has been hypothesized that viral persistence could be post-COVID symptom-specific since different symptoms may be mediated by different mechanisms. This hypothesis agrees with the proposal that reservoirs of SARS-CoV-2 RNA can also be tissue-specific. In fact, single studies have identified SARS-CoV-2 RNA in human tissues such as the lungs [22] or brain [26]. In the current review, the association between persistent SARS-CoV-2 RNA and specific post-COVID symptoms was diverse. Su et al. [33] identified an association between persistent SARS-CoV-2 RNA in nasal/oral swab samples and post-COVID ageusia/anosmia, whereas Natarajan et al. [31] reported an association between the presence of fecal SARS-CoV-2 RNA and gastrointestinal post-COVID symptoms. Interestingly, a recent meta-analysis identified three clusters of post-COVID symptoms: cardiorespiratory (including fatigue, dyspnea, chest pain, muscle pain, headache, palpitations), systemic inflammatory (including dizziness, muscle pain, gastrointestinal symptoms,

hair loss, muscle weakness, sleep disorders), and neurological (including headache, anosmia, paresthesia, neuropathy, dizziness, vision and balance problems, memory problems, poor concentration) clusters [35]. Future studies could group post-COVID symptomatology by clusters and identify the presence of SARS-CoV-2 RNA in those biological samples/tissues associated to symptoms exhibited by each cluster.

Third, according to the World Health Organization, “post-COVID-19 condition occurs in people with a history of probable or confirmed SARS-CoV-2 infection, usually three months from the onset of infection, with symptoms that last for at least two months and cannot be explained by an alternative diagnosis” [7]. In the current review, follow-ups were shorter than two months (<60 days after) in 66 % of the studies [29, 30, 32, 33]. Thus, these patients would not satisfy the definition of post-COVID-19 condition. Interestingly, the results from studies including long-term follow-ups were contradictory. Natarajan et al. [31] did not find SARS-CoV-2 RNA in nasal/oral swabs samples four months after the infection, whereas Craddock et al. [34] reported that 59 % of patients with post-COVID symptoms tested positive for SARS-CoV-2 RNA in plasma six months after infection. We do not know if this discrepancy is related to the fact that viral persistence is related to the sample tested or to the fact that it disappears with long-term follow-ups.

Fourth, another topic to discuss is if viral persistence is associated with COVID-19 severity. Although differences in long-COVID symptomatology between hospitalized and non-hospitalized COVID-19 survivors is not clear [36], subjects needing hospitalization commonly report moderate to severe COVID-19 disease and exhibit a higher viral load, whereas non-hospitalized patients present mild to moderate COVID-19 disease and a lower viral load. In such a scenario, exhibiting a higher viral load has been hypothesized to be an important factor for the development of long-COVID; however, the conclusions of recent meta-analyses on this assumption are not conclusive [37, 38]. The population cohorts of the studies included in this review were heterogeneous, as three studies [29, 30, 34] included only hospitalized patients, one [31] only non-hospitalized, and the remaining two [32, 33] mixed both cohorts. Accordingly, it is not possible to conclude if the presence of SARS-CoV-2 RNA is associated to hospitalization and, hence, to a more severe disease or higher viral load.

Although this is the first review systematically summarizing evidence on the presence of SARS-CoV-2 RNA in patients with post-COVID symptomatology, the result should be considered according to several different limitations. First, the small number of studies and the heterogeneity in their design limit the extrapolation of any conclusion. Thus, different follow-ups, study designs

(prospective or retrospective), cohorts (hospitalized or non-hospitalized), and biological samples were identified. In addition, most studies (66 %) did not consider the definition of post-COVID-19 condition. Second, we included studies just investigating the presence of SARS-CoV-2 RNA in adults who had survived COVID-19. In addition, our results should not be extrapolated to children. A recent narrative review on viral persistence in children who had survived COVID-19 confirmed a similar situation as that on adults, that is, most studies have investigated the presence of SARS-CoV-2 reservoir in cadavers or the presence of spike proteins, but they did not directly measure SARS-CoV-2 RNA [39]. Third, we did not include studies investigating the presence of SARS-CoV-2 spike protein since the presence of these proteins represents the immune response of the host derived from a “potential” viral reservoir, but it does not address directly the presence of SARS-CoV-2 RNA [21]. Interestingly, Swank et al. [27] found that persistent SARS-CoV-2 spike proteins in plasma can lead to systemic post-COVID symptoms such as chronic fatigue, but they also identified a fluctuating nature of spike proteins, suggesting that viral persistence could exhibit periods of inactivity associated with the host immune response. Accordingly, the lack of SARS-CoV-2 RNA persistence does not exclude the presence of SARS-CoV-2 proteins due to the innate host's immune response against infection. Future studies investigating SARS-CoV-2 RNA persistence in COVID-19 survivors should consider those gaps identified in this review, particularly the inclusion of comparative groups of COVID-19 patients without experiencing post-COVID symptoms, a clear definition of post-COVID-19 and longer follow-up periods.

Conclusions

The results of this review would suggest the presence of persistent SARS-CoV-2 RNA in patients with post-COVID symptoms in the short-term, although the low number of patients in the studies, the differing samples tested, the heterogeneous results, and the lack of a comparative group of patients without long COVID symptoms do not permit us to make firm conclusions. No long-term data are currently available. The association between the presence of post-COVID symptoms and SARS-CoV-2 RNA in the generalized samples tested is conflicting. The lack of a comparative group limits the generalizability of viral persistence in patients with post-COVID symptomatology. These findings could explain the inconsistent results of clinical trials investigating the effect of antivirals at the acute phase of infection for reducing the risk of post-COVID symptoms [40].

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Informed consent: Not applicable.

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