

Long-COVID-19 Symptoms after Infection in COVID Long-Haulers

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Abstract

The negative molecular swab does not mean that the body and mind are healed: even months after Sars-CoV-2 infection, patients may continue to have symptoms. The symptoms mainly present at 6 - 12 months in patients recovered from COVID-19 are: asthenia, breathlessness, difficulty in breathing deeply, myalgia, psychological disorders and difficulty in concentrating such as “brain fog”. The study was conducted from June 2021 to July 2021 at Health Prevention Department in Benevento (Campania Region, South Italy). 133 patients accepted the questionnaire in the form of a telephone interview. The purpose of this study is precisely to highlight how, although a year after infection, a number of patients still show post-COVID symptoms. In particular, 77 out of 133 positive patients became Long-Haulers (58%).

Keywords

COVID-19, Long-COVID, Long-Haulers

1. Introduction

On December 31, 2019, Chinese health authorities reported that an outbreak of atypical pneumonia of unknown aetiology had developed in the city of Wuhan (Hubei province, central-eastern China). Many of the initial cases reported attendance at the Wuhan wholesale fish market, where wild animals of disparate species are also for sale, used for food purposes. On January 9, 2020, the Chinese Center for Disease Control announced that it had identified the causative agent: a new coronavirus, first provisionally named 2019-nCoV and officially named SARS-CoV-2 by the International Committee on Taxonomy of Viruses on 11 February 2020,

which was quickly sequenced and made available to the scientific community and subsequently confirmed the possibility of human-to-human transmission of the virus. Coronaviruses are a group of related RNA viruses common in many animal species (such as camels and bats) but in some cases, rarely, they can change and infect humans and then spread to the population, mainly causing the infections of upper respiratory tract and the gastrointestinal tract. The severity of these conditions is highly variable, since coronaviruses are responsible for both a large number of common cold syndromes and severe respiratory syndromes such as SARS (Severe Acute Respiratory Syndrome) and MERS (Middle East Respiratory Syndrome). They owe their name to the appearance of the virions at the electron microscope, linked to the presence of the S proteins of the viral peplomer that create an image that resembles a royal crown or the solar corona [1]. The host receptor for SARS-CoV-2 cell entry is the Angiotensin-Converting Enzyme 2 (ACE2). SARS-CoV-2 binds to ACE2 through the receptor binding-domain of its spike protein and enters the cells. SARS-CoV-2 coronavirus was sequenced in mid-January by Chinese researchers and subsequently in other laboratories around the world, including Italy, one of the Lazzaro Spallanzani National Institute for Infectious Diseases. The results show that SARS-CoV-2 shares 79.5% of the gene sequence of the SARS coronavirus and 96.2% that of a bat coronavirus [2]. The animal species of origin (reservoir) has not yet been identified with certainty, although it is supposed to be bats of the *Rhinolophus affinis* species, with direct transmission to humans or with any other intermediate hosts (currently not identified). It is possible that the permanence of bats in close contact with other animals and with humans has favored mutations and the passage of species, again in analogy to what happened with other respiratory syndromes due to other Betacoronaviruses, but zoonotic transmission from the Wuhan fish market has not been established in all cases [3]. Like other viruses, SARS-CoV-2 mutates over time. Some variants have attracted particular attention due to their rapid spread within populations and evidence of increased transmissibility and possible “immune leak” [4]. The World Health Organization (WHO) has designated each variant with a nomenclature based on the Greek alphabet. Most mutations in the SARS-CoV-2 genome consist of changes in the amino acid sequence in the Spike protein that are associated with greater transmissibility and contagiousness of the virus.

The incubation period for the infection is estimated to be between 2 and 14 days, with an average of 5 days. The transmission potential of SARS-CoV-2 begins before the development of symptoms and is greatest at the onset of the disease [5]. Infected individuals are more likely to be contagious in the early stages of disease when levels of viral RNA detected by upper respiratory tract samples are highest (approximately two days before and one day after the onset of symptoms and decreased within seven days) [6]. Prolonged detection of viral RNA in respiratory specimens does not indicate prolonged infectivity and there appears to be a viral RNA level threshold below which infectivity is unlikely [7].

The risk of transmission from a SARS-CoV-2 infected individual varies with the type and duration of exposure, the use of preventive measures, and the likely individual factors (for example, the amount of virus present in respiratory secretions) [8]. In fact, the risk of transmission after contact with an individual with COVID-19 increases with proximity and duration of contact and appears higher with prolonged contact indoors [9]. Therefore, most secondary infections have been described among family contacts, in health care settings where personal protective equipment was not used (including hospitals, long-term care facilities) and in other congregational contexts where people reside or work in confined spaces [10].

The risk of transmission with more indirect contact (eg, passing someone on the street with an infection, handling objects that had previously been handled by someone with an infection) is not well established and is likely to be very low.

The most common symptoms of an upper respiratory tract infection by coronaviruses in humans include fever, cough, headache, pharyngodynia, difficult breathing, and general malaise for a short period of time [11]. In severe cases, the infection can cause pneumonia or Bronchopneumonia, severe acute respiratory syndrome, renal failure, up to death [12]. The involvement of the lower respiratory tract and complications are more frequent in people with pre-existing chronic diseases of the cardiovascular and/or respiratory system and in people with the impaired immune system, in infants and the elderly [13].

The picture of SARS-CoV-2 infection is that of acute viral pneumonia [14]. The onset symptoms of SARS-CoV-2 infection are rather non-specific and occur in a syndromic form in 90% of cases:

- hyperpyrexia even high, above 39°C;
- generally dry cough, more rarely productive;
- malaise and asthenia;
- dyspnoea;
- pharyngodynia;
- headache;
- myalgia;
- anosmia and/or dysgeusia.

Unlike other human coronaviruses, gastrointestinal symptoms such as diarrhea, nausea and vomiting are rare.

COVID-19 pandemic has led to a growing population of individuals recovering from acute SARS-CoV-2 infection [15]. However, a number of these patients may experience a wide range of symptoms after recovery from acute illness, which is referred to by several terms including “Long-COVID”, “post-COVID conditions” and Post-Acute Sequelae of SARS-CoV-2 Infection (PASC) [16].

Although there are no widely accepted definitions of the stages of recovery from COVID-19, the Centers for Disease Control and Prevention (CDC) has proposed the following categories:

- Acute COVID-19: symptoms of COVID-19, up to four weeks after the onset of the disease;

- Post-COVID-19 conditions: a wide range of symptoms (physical and mental) that develop during or after COVID-19, continue for ≥ 4 weeks and are not explained by an alternative diagnosis.

These phases reflect symptomatic recovery and are not related to active viral infection and infectivity [17].

2. Materials and Methods

This study was conducted on 133 patients, 60 females (45.1%) and 73 males (54.9%) with Sars-CoV-2 infection during the first wave of COVID-19 pandemic in Benevento, a city of Campania Region (South Italy). We proposed a questionnaire in the form of telephone interview to a group of 192 COVID-19 positive patients treated by Health Prevention Department. Only 133 patients accepted the interview. Interview was conducted from June 2021 to July 2021 after 11 - 12 months of their recovery from the infection. The age of 133 patients ranged from 3 years to 91 years (**Table 1**); under-18 patients answered with parentals authorization. The patients, non-hospitalized, were classified into three groups: asymptomatic; pauci-symptomatic (patients with anosmia and/or dysgeusia and/or asthenia and/or low-grade fever and/or headache and/or myalgia); mild-moderate symptomatic (TB $> 37.5^{\circ}\text{C}$ and/or cough and/or dyspnea).

133 patients' positives from March 2020 to June 2020, were classified: 97 (73%) were asymptomatic, 23 (17%) pauci-symptomatic, 13 (10%) with symptoms mild-moderate.

Patients answered questions about their symptoms, physical and mental, after their COVID-19 infection. They reported their clinical conditions after their recovery.

3. Results

Patients with Long COVID-19 symptoms are appointed as Long-Haulers. They

Table 1. Characteristic of COVID-19 positive patients.

Age	Male	Female	Total
0 - 9	1	0	1
10 - 19	6	6	12
20 - 29	12	9	21
30 - 39	10	4	14
40 - 49	10	15	25
50 - 59	17	17	34
60 - 69	11	5	16
70 - 79	1	1	2
80 - 89	4	3	7
90+	1	0	1
Total	73	60	133

have exhibited symptoms even after their recovery (**Table 2**). In particular 77 of 133 positive patients are resulted Long-Haulers (58%). In these patients the symptoms reported were: dyspnea (12%), shortness of breath (21%), chest pain or tightness (17%), breathlessness (22%) tachycardia (19%), hypertension (1%), anosmia and/or dysgeusia (23%), skin rash (2%), asthenia (57%), headache (6%), dizziness (5%), osteoarticular pains (46%), anxiety (27%), depression (10%), poor memory and concentration (25%), brain fog (28%), insomnia (7%).

Pulmonary and cardiovascular manifestations were more frequently in patients with diabetes, bpco, and hypertension. Psychological symptoms, such as anxiety and depression, were more frequently in adolescent patients and the same in female gender. Cognitive symptoms were more frequently in asymptomatic patient.

4. Discussion

The negative molecular swab does not mean that the body and mind are healed: even months after Sars-CoV-2 infection, patients may continue to have symptoms [18]. The symptoms mainly present at 6 - 12 months in patients recovered from

Table 2. Long-COVID-19 symptoms of positive patients.

Physical Symptoms	%
Dyspnea	12%
Shortness of Breath	21%
Chest Pain or Tightness	17%
Breathlessness	22%
Tachycardia	19%
Hypertension	1%
Anosmia and/or Dysgeusia	23%
Skin Rash	2%
Asthenia	57%
Headache	6%
Dizziness	5%
Osteoarticular Pains	46%
Psychological Symptoms	
Anxiety	27%
Depression	10%
Cognitive Symptoms	
Poor Memory and Concentration	25%
Brain Fog	28%
Insomnia	7%

COVID-19 are: asthenia, breathlessness, difficulty in breathing deeply, myalgia but also psychological disorders and difficulty in concentrating such as “brain fog” [19].

Pulmonary manifestation

Patients who have been affected by SARS-CoV-2 interstitial pneumonia may develop fibrosis irreversible and fibrotic interstitial disease [20]. This is due to the persistence of chronic inflammation [21]. However, the abnormal lung function may be reversible with time or with treatments [22]. Even in patients asymptomatic to COVID infection, the presence of pulmonary opacities on CT is observed in some cases [23]. It is still to be assessed whether the persistence of these lesions will remain over time [24].

Cardiovascular and hematologic manifestations

Various cardiovascular complications have been associated in COVID-19 patients such as hypotension, cardiomegaly, bradycardia and tachycardia [25]. However, most of the complications have returned to normal after 3 - 4 weeks of healing, with the exception of tachycardia which is present after 6 - 12 months even in patients who have been affected by COVID-19 in a paucysymptomatic status [26]. Furthermore, the release of pro-inflammatory cytokines, which occurs in COVID-19 infection, increases the risk of hypertension and cardiovascular problems [27]. Chronic inflammatory state, the release of pro-thrombotic factors and the endothelitis that develop during SAR-CoV-2, increases the possibility of venous and arterial thrombotic complications [28]. In addition, the increase in the expression of the ACE2 enzyme at the level of the endothelial cells that occurs during infection and continues healing thereafter, increases the thrombotic and inflammatory state [29].

Renal manifestations

Acute renal failure has been reported in many patients with severe conditions of SARS-CoV-2 infection, this underlines how COVID-19 can be a systemic disease and not just lung disease [30]. Other kidney impairments observed are hematuria and proteinuria [31]. However, in patients at home and therefore in mild-moderate conditions [32], we did not observe kidney impairments as a consequence of the infection [33].

Gastrointestinal manifestations

Gastrointestinal disorders, after respiratory ones, are the most present in patients with COVID-19, even in cases where no other symptoms occur [34]. In particular, patients experience anorexia, nausea, abdominal pain, diarrhea [35]. The presence of SARS-CoV-2 viral particles was observed in the faeces and damage to the gastrointestinal and hepatic mucosa was observed in subjects affected [36]. The long-term gastrointestinal symptoms that have been most observed are difficulty in digestion and a sense of heaviness after meals [37].

Neurological and psychosocial manifestations

In cases of severe infections, stroke is associated with the increase in thrombotic risk [38]. In mild-moderate infections, we observe more frequently the pres-

ence of polyneuropathies, hyposmia, headache, weakness and altered consciousness [39]. Another common symptom is difficulty thinking clearly and memory deficits [40]. It is not yet established whether this may be due to a direct action of the virus on neurons [41]. The most frequent consequences in patients with mild, moderate or severe COVID-19 are psychological disturbances [42]. Depressive syndromes and anxiety syndromes occur mainly in women. And the presence of these syndromes should not be underestimated even in young patients, especially in the adolescent phase [43]. The lockdown, isolation in the event of positivity, the zeroing of social and often working life, has created psychological and social problems with enormous difficulty also in reintegrating into the world of work [44].

5. Conclusion

SARS-CoV-2, the virus that causes COVID-19, was identified in December 2019. There is still a lot to learn about it, but our understanding of the virus and COVID-19 is evolving by the day. Researchers will learn more about how and why the coronavirus affects different people in such a variety of ways, and why some people experience no symptoms at all while others have life-threatening organ damage or lasting disability. New insights will provide avenues for therapies and hope for people living with long-term COVID-19 effects.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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