

Post-Acute Sequelae of COVID-19 Checklist (PASC-C): a screening tool for Long COVID physical, psychological, and cognitive symptoms

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Abstract

Background. The management of Long COVID symptoms is necessary. This study proposes a screening tool for psycho-physical COVID-19 sequelae. Patients' experiences after COVID-19 are also described.

Method. 84 COVID-19 patients (66.2±11.0 years old; 71.4% male) underwent a phone interview 1-2 years after the disease using the *ad-hoc* "Post-Acute Sequelae of COVID-19 Checklist (PASC-C)". It explores 30 physical, psychological, and cognitive symptoms clustered into 10 areas, with possible clinical recommendations in case of high severity scores (>50) of a symptom or the presence of two or more ones within the same area.

Results. Overall, fatigue (69%), dyspnea (52.4%), memory disturbances (44%), joint-muscle pain (41.7%), vision/hearing loss (40.5%), anxiety (40.5%) persist one-two years after COVID-19 disease. Being a survivor was primarily defined in terms of being "lucky".

Conclusions. PASC-C seems promising in monitoring psycho-physical sequelae of Long COVID and providing tailored suggestions to care for the patient over time.

Key words

- Long COVID
- physical symptoms
- psychological disorders
- cognitive impairments
- screening
- rehabilitation

INTRODUCTION

It is evident that COVID-19 [1] may cause enduring effects, as shown by the increasing rate of patients reporting various sequelae of symptoms after infection [2-4], even if the molecular tests no longer show SARS-CoV-2 on swabs. Current evidence suggests that 10-20% of subjects report struggling with a heterogeneous complex of subacute and chronic clinical manifestations [5], which may affect multiple organ systems, precluding a full return to the previous health status [6]. These

patients and these multifaceted clinical conditions are known by the terms "Long COVID-haulers" and "Long COVID", respectively [7].

The National Institute for Health and Care Excellence (NICE), the Scottish Intercollegiate Guidelines Network (SIGN), and the Royal College of General Practitioners (RCGP) have identified two different conditions as a result of COVID-19 disease, which are not yet explained by an alternative diagnosis [8]. In detail, after the acute phase of COVID-19, patients

may cope with both the “persistent symptomatic COVID-19 disease”, struggling with signs and symptoms lasting from 4 to 12 weeks, and the “post-COVID-19 syndrome”, in case signs and symptoms – developed during or after the acute disease – last for more than 12 weeks [8]. These two terms are included in the “Long COVID” condition, which has been defined as “signs and symptoms that continue or develop after 4 weeks from COVID-19 acute infection” [8, 9].

Overall, the prevalence of Long COVID symptoms varies greatly among different studies, affecting subjects regardless of sex, age, and the severity of the acute infection [8]. Specifically, it has been identified more than one hundred possible symptoms [10], proving the multi-systemic nature of this condition impacting physical, psychological, and cognitive levels. More in detail, it has emerged that the possible and predictable clinical manifestations in COVID-19 survivors may have pulmonary, cardiovascular, renal, hematological, and gastrointestinal nature, as well as they may concern the central nervous system too [11, 12]. At a cognitive level, 36% of Long COVID patients may experiment cognitive impairment [12], leading to a new condition named “brain fog”, characterized by mild impairment in memory, language, and executive functions [6, 12, 13]. These cognitive deficits are debilitating, worsening daily functioning and decreasing health-related quality of life (HRQoL) [14], and may evolve into multiple neuro-cognitive impairments [15]. In fact, mental health consequences may persist after COVID-19 disease even leading to psychopathological outcomes [16], both in hospitalized [17] and non-hospitalized [18] patients. The clinical manifestation includes depression, anxiety, panic disorders, post-traumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), sleep disturbances, chronic pain, and fatigue. Moreover, the variety of symptoms and the focus of professionals on specific symptoms according to their specialization, may leave patients with the impression that they are not fully understood and globally taken in care [19].

To date, in the literature, some clinical tools to assess various COVID-19 sequelae have been proposed. For instance, we can read about an online screening tool comprehensive of 14 questions assessing post-acute COVID-19 syndrome [20]. Specifically, the authors investigated if general PASC symptoms (e.g., fatigue, impairment of sense of smell/taste) were experienced as problematic by the subjects through the use of a 4-point Likert scale. Similarly, a single-center study proposed a questionnaire investigating also comorbidity, characteristics of the acute phase of COVID-19, and the presence of persistent symptoms [21]. Again, a remote COVID-19 rehabilitation assessment tool investigates pain, fatigue, sleep, mood, and functional limitations [22]. Other authors proposed an impact tool that analyses symptoms experienced in the last 30 days, concerning digestion, eyes, skin and hair and others [23]. However, the majority of previous studies focus on specific symptoms [24, 25] and, to the best of our knowledge, a proper clinical and multidisciplinary assessment of this syndrome has not yet been reached, even if it is considered a global health challenge to be addressed [26].

Indeed, current Long COVID tools assess only a small part of the possible sequelae after the acute phase of COVID-19, or only for a limited time, without a focus on the period before, during, and after the acute phase. It is crucial to propose a full-comprehensive clinical screening tool to ameliorate the interface between general practitioners and specialists in order to effectively follow the patients over time [27], as well as to provide the patient with holistic care [19]. To bridge this gap, the main aim of this study is to preliminary present the multidimensional Post-Acute Sequelae of COVID-19 Checklist (PASC-C), a clinical checklist that has been developed to assess possible physical, psychological, and cognitive sequelae over time, focusing on time before and after the disease. Data concerning its feasibility are therefore presented.

A secondary aim is to correlate PASC-C perceived severity symptoms with HRQoL. Specifically, the HRQoL is assessed in relation to functional, pneumological, allergic, gastroenteric, cardiological, dermatological, neurocognitive, and psychological symptoms, as well as to sleep disorders and other complaints (i.e. weight loss/gain, hyper-sweating, discontinuous fever).

CHECKLIST PASC-C

PASC-C has been developed by the Units of Psychology, Neurophysiopathology, Respiratory Function and Sleep Medicine and by the Department of Cardiac Rehabilitation of the Montescano Institute of “Istituti Clinici Scientifici Maugeri IRCCS” (*Servizio di Psicologia, Servizio di Neurofisiopatologia, Servizio di Medicina del Sonno e Dipartimento di Cardiologia Riabilitativa dell'Istituto di Montescano*), to assess the presence of possible physical, psychological, and cognitive Long COVID symptoms. This checklist has been constructed through the discussion of the daily clinical experience and the review of existing literature. In particular, Lopez-Leon and colleagues' systematic review was considered a milestone as unveiled more than 50 symptoms related to sequelae of COVID-19 and fostered further studies for procedures and tools useful to take care of these patients [28]. From a practical point of view, after the study of the literature, weekly 1-hour sessions of in-person and online discussions were scheduled among the healthcare professionals from the above-mentioned units in order to select which symptoms deserve consideration and to revise the tool until reaching a full consensus for each item. In this regard, PASC-C included only symptoms that were reported as very frequent according to both Lopez-Leon and colleagues' systematic review and clinical experience [28]. The scope was to address every family symptom that a patient might have after contracting COVID-19, including sleep difficulties, general complaints, dermatological, gastroenteric, cardiological, neurological, and psychological symptoms. Subsequently, the schedule was presented to some colleagues from the same hospitals in order to collect their oral feedback. Thus, PASC-C presented below and used in this pilot study obtained the unanimous agreement of all authors.

This instrument is composed by the two sections described below.

The first one is called “Subjective physical, psychological, and cognitive symptoms” and it is structured into 10 different areas, covering a total of 30 symptoms. The presence of each symptom is investigated at three different times: a) during the COVID-19 disease, with information concerning its duration; b) at the moment of the interview, with a subjective estimation of the perceived severity, rated on a Likert scale from 0 (lowest severity) to 100 (highest severity); c) before the COVID-19 disease. In the case of reported premorbid symptoms, it is investigated whether COVID-19 disease has worsened them. To note, the premorbid condition has been investigated to exclude symptoms not ascribable to COVID-19, thus, unveiling patients who already had symptomatology before the disease and who have not experimented with a worsening health condition.

The presence of high severity score (>50), or in the presence of two or more symptoms for an area would suggest a referral to a healthcare professional with a specific expertise. The areas and symptoms of PASC-C is present in the *Supplementary material* available online in English language. The Italian version of the questionnaire is available upon request to the Authors.

Moreover, PASC-C investigates the occurrence of stressful events or illnesses in the period following COVID-19 disease, if patients have already sought healthcare assistance, and ongoing or past pharmacological or nonpharmacological therapies.

The second PASC-C section, called “subjective experiences of being a COVID-survivor”, regards a series of questions to investigate the subjective experiences of patients after COVID-19 disease, in order to get a deep and comprehensive evaluation from a qualitative point of view. Patients have been asked about their subjective experience of surviving COVID-19 disease, for example, based on the attribution of positive or negative personal meaning to this disease experience. Furthermore, it has been investigated if subjective perceptions of their general functionality levels (e.g., physical, cognitive) have worsened, unvaried, or improved due to COVID-19 disease. Possible significant changes made in any area of their lives (e.g., work, family, interpersonal) after the disease have also been explored. Finally, patients have been invited to reveal if they wanted to add anything else: they could say something more, express their emotions, or ask any other questions.

The administration time of PASC-C is around 15 minutes, but the timing might vary depending on the number of symptoms and clinical details reported by patients.

MATERIALS AND METHODS

Participants

The target clinical population was constituted of 104 adult patients (>18 years old) taken in care for SARS-CoV-2 infection in the IRCCS Istituti Clinici Scientifici Maugeri who were entered into a short-term follow-up after the acute event, according to a research protocol aimed to evaluate the possible presence of cardiological COVID-19 sequela. Specifically, the patients of this study were recruited from four different hospitals

(Milan, Montescano, Pavia, Tradate) which are affiliated with the same Institution (IRCCS ICS Maugeri). The location of these hospitals is strategic and informative as Lombardy was the Italian region most impacted during the COVID-19 pandemic and healthcare physicians are currently managing the pandemic sequelae over time [29-31].

This study was part of a broader research project and approved by the Institutional Review Board and Central Ethics Committee of the ICS Maugeri SpA SB (Approval Number 2450 CE. Participants signed a written informed consent to take part in this research.

After 1-2 years after the acute infection, these patients were proposed with a phone interview through the PASC-C Checklist (Approval Number 2653 CE).

Participants provided oral consent at the beginning of the phone interview as this research is a prosecution of the above-mentioned study. The interviews were conducted in a silent room by a psychologist through a proper phone line in order to safeguard personal data. No kind of remuneration was provided.

Out of the 104 participants of the former study, 84 completed the full phone interview. Indeed, 20 of them have not carried out the telephone interview for various reasons, such as lack of motivation due to a current good health condition (n=9), unavailability to reach them by phone (n=8), deaths (n=2), and severe clinical conditions (n=1).

Instruments

During the interview, the above-described Post-Acute Sequelae of COVID-19 Checklist (PASC-C) and the EuroQol-Visual Analogue Scale (EQ-VAS) [32] were administered.

EQ-VAS is an instrument developed by the EuroQol Group in 2009 [32] to evaluate patients' subjective actual global health status. It consists of a hybrid Visual Analogue Scale (VAS), which is a vertical line ranging from the worst imaginable health (0) to the best imaginable health (100) [32]. Previous research stated the equivalence of EQ-VAS results between telephone and paper-pencil administration [33].

Data analysis

Descriptive statistics are reported as mean and standard deviation (SD) for continuous variables, and frequency percentages for discrete variables.

Possible differences in the severity of symptoms between gender and age were analysed by t-test and the association between variables was assessed by Pearson correlation coefficient *r*. Moreover, frequencies have been considered to analyze the patients' subjective perceptions and evaluations of their overall functioning level as a result of the COVID-19 disease.

All statistical analyses were carried out using IBM SPSS Statistics Software (version 27.0).

The qualitative descriptive analysis of patients' narrations of their personal meaning regarding the acute and post-acute disease phase and the experience of being a COVID-19 survivor has been displayed into frequency tables. Patient's personal and significant changes in their lives after COVID-19 disease have been explored

individually, in order to group them into common categories with their frequencies through a bottom-up approach.

RESULTS

Subjective physical, psychological, and cognitive symptoms

The sample was composed of patients with a mean age of 66.2 ± 11.0 years old, mainly male (71.4%), married (64.3%), and in retirement (53.6%), no-smoker people (64.3%).

Moreover, the majority are in pre-obesity status according to BMI (46.4%), and were previously hospitalized due to COVID-19 (89.3%). Overall, 36% stated no comorbidities, while 39% reported at least one comorbidity and the remaining 25% complained of two to four comorbidities.

Moreover, we have analysed possible differences in the severity of symptoms, present at the time of assessment) between gender and age (<65 years old vs >66 years old). No similar analysis has been conducted concerning hospitalization as the sample was too unbalanced concerning this variable. Overall, gender was the only factor that varied: women reported higher musculoskeletal pain (56.00 ± 30.89 vs 38.26 ± 22.09 ; $t = -2.07$; $p = .05$), higher levels of anxiety (84.00 ± 18.38 vs 57.92 ± 29.78 ; $t = -2.56$; $p = .02$) and more traumatic experiences (87.14 ± 11.13 vs 58.39 ± 34.24 ; $t = -2.15$; $p = .04$) than men.

Table 1 displays the frequencies of Long COVID symptoms still present and divided in the different areas. In addition, symptoms severity and the percentage of the clinical recommendations are also provided. Briefly, the most frequent symptoms were fatigue (69.0%), dyspnea (52.4%), joint-muscle pain (41.7%), memory problems (44.0%), and anxiety (40.5%). Table 1 shows also the associations between the global health status (EQ-VAS mean score 68.7 ± 21.2) and symptom severity of each PASC-area.

Overall, self-rated results of the EQ-VAS ranged from the minimum 0 (worst health status) to the maximum 100 (best health status), with 64.3% who have rated themselves under 75.

DISCUSSION

This study presents preliminary data collected through a new tool called "Post-Acute Sequelae of COVID-19 Checklist" (PASC-C) focusing on physical, psychological, and cognitive COVID-19 sequelae over time.

Our patient population with a mean age of around 66 years old is coherent with literature that highlights the relationship between having more than 60 years old and higher severity of COVID-19 symptoms and risk of developing Long COVID syndrome [34-36]. Similarly, the higher prevalence of male gender and the high percentage of comorbidities and overweight are in line with the existing literature suggesting these characteristics as risk factors for highlighting a more complex clinical condition [37, 38]. Concerning gender difference, in our sample, females suffer more from musculoskeletal pain and complain of higher anxiety symptoms and more traumatic experiences. Regarding this, previ-

Table 1. Post-Acute Sequelae of COVID-19 Checklist (PASC-C) results

Areas and symptoms	n (%)	Severity 0-100 M (DS)	Correlation with EQ VAS r (p)
Functional			0.528 (0.0001)
Fatigue	58 (69.0)	49.9 (25.6)	
Hearing/sight loss or tinnitus	34 (40.5)	39.3 (24.7)	
Motor difficulties	27 (32.1)	45.2 (25.6)	
Ageusia	15 (17.9)	45.0 (24.2)	
Anosmia	13 (15.5)	55.0 (25.6)	
Pneumological			0.407 (0.0001)
Dyspnea	44 (52.4)	50.2 (27.6)	
Other respiratory difficulties	33 (39.3)	57.3 (27.0)	
Cough	16 (19.0)	42.4 (28.2)	
Sleep disorders			0.352 (0.001)
Insomnia	33 (39.3)	58.4 (25.4)	
Sleepiness	7 (8.3)	60.0 (25.6)	
Hypersomnia	0	-	
Algic			0.347 (0.001)
Joint/muscle pain	35 (41.7)	45.3 (27.0)	
Headache	10 (11.9)	56.7 (23.1)	
Gastroenteric			0.156 (0.156)
Gastrointestinal complaints	19 (22.6)	54.2 (26.1)	
Nausea/Vomit	7 (8.3)	51.4 (29.7)	
Cardiological			0.145 (0.188)
Palpitation/increase heart rate	24 (28.6)	43.9 (25.6)	
Chest pain/discomfort	18 (21.4)	50.0 (24.9)	
Neurocognitive			0.368 (0.001)
Memory problems	37 (44.0)	55.8 (26.0)	
Paraesthesia	31 (36.9)	42.6 (26.6)	
Attention difficulties	25 (29.8)	50.8 (31.1)	
Balance disturbances	18 (21.4)	42.1 (26.6)	
Confusion/disorientation	11 (13.1)	58.9 (32.5)	
Psychological			0.248 (0.023)
Anxiety	34 (40.5)	65.6 (29.2)	
Mood disorders	26 (31.0)	65.0 (30.7)	
Traumatic experiences	24 (28.6)	66.4 (32.2)	
Dermatological			0.202 (0.065)
Hair loss	23 (27.4)	61.3 (28.5)	
Skin erythema	15 (17.9)	48.7 (26.4)	
Other			0.258 (0.018)
Weight loss/gain	22 (26.2)	42.3 (18.5)	
Hyper-sweating	21 (25.0)	39.1 (22.6)	
Discontinuous fever	1 (1.2)	80.0	

ous literature has shown that COVID-19 affects gender in a different way over time [39]. Specifically, it has been demonstrated that women complain of less severe short-term health problems, but experience worse long-term COVID-19 sequelae, such as depression and poor quality of life, and perform less physical activity [39]. In this sense, our results are aligned with previous data, as depict a female gender more characterized by adverse physical and psychological experiences.

As expected, PASC-C revealed percentages of Long COVID symptoms still persistent one-two years after the disease, consistently with the evidence in literature regarding current and previous coronaviruses (SARS-CoV-1 and MERS-CoV). Symptoms may cover all clinical areas [11]. The most frequent self-reported symptoms in this study were fatigue (69%), dyspnea (52.4%), memory problems (44%), joint/muscle pain (41.7%), vision/hearing loss or tinnitus (40.5%), and anxiety (40.5%). These frequencies confirm the results of the review of López-León, *et al.* [28], who found fatigue (58%) and dyspnea (24%) as the most common Long COVID symptoms in their study. Despite Long COVID symptoms vary enormously across studies and there is still no common agreement, more recent studies tried to categorize persistent symptoms in wider categories or clusters [18, 23, 40]. Moreover, various studies proposed questionnaires and investigations on specific symptoms or aspects or disease phases [20-25], but a general clinical tool to collect the multifaceted plethora of Long COVID symptoms is still lacking. Accordingly, PASC-C was divided into ten symptom areas to cover miscellaneous manifestations and to provide clinical recommendations. In addition, a recent systematic review and meta-regression presented modeled estimates regarding individuals with at least 1 of 3 self-reported Long COVID symptom clusters, such as persistent fatigue with bodily pain or mood swings, cognitive problems, or ongoing respiratory problems, in accordance with psychological (22.1%), pneumological (19.1%), functional (16.6%), neurocognitive (14.8%) areas in our study [40]. As far as we know, this is the first clinical tool trying to both collect all kinds of Long COVID symptoms and to provide tailored further clinical suggestions.

Regarding the general health status of Long COVID patients, in a study of previously hospitalized patients with COVID-19, Taboada, *et al.* [41] found a decrease in their quality of life (EQ-VAS) at six months follow-up (87.58 ± 11.68 vs 66.36 ± 18.26 , $p < 0.001$). Their health status score was equivalent to our EQ-VAS data, which confirmed a poor HRQoL in these patients still struggling with persistent disease. Our study highlighted several significant negative correlations between EQ-VAS total score and PASC-C symptoms' severity in functional, pneumological, sleep disorders, algic, neurocognitive, and psychological areas. These significant associations with a valid instrument as EQ-VAS was already found in another Long COVID study [23]. The added value of PASC-C Checklist is its ability to identify what areas may worsen the quality of life and, in turn, request specific clinical attention. This early detection may allow the optimization of human and economic resources,

tailoring the health experience and, in turn, improving the patient's satisfaction and HRQoL.

Overall, considering the wide plethora of symptoms considered, PASC-C operationalizes the recommendations for the detection of all physiological or clinical outcomes provided by the international Delphi consensus study regarding a core outcome set to assess within the clinical population who recovered from COVID-19 condition [42]. Although this tool has been developed and tested with patients suffering from COVID-19 during the initial phases of pandemic in Italy, it is still valid and useful for the detection of symptoms related to COVID-19 condition. Indeed, literature showed as COVID-19 sequelae are significantly persistent over time, with only slight differences between waves [43]. PASC-C is also in line with both the core symptoms deserving attention worldwide [42] and the call for action for the development of a core outcome measurement set (COMS) which has to be updated according to the emerging findings of literature [44].

STRENGTHS AND LIMITS

One of the strengths of the study is the proposal of a new handy tool which may be considered a promising multidimensional clinical tool, leading to multidisciplinary management of Long COVID symptoms, as recommended by NICE [8]. Although other studies are requested, this checklist might be widespread in primary care and support the early detection of COVID-19 sequelae in order to propose tailored interventions, optimize healthcare costs and improve patients' quality of life and satisfaction. Indeed, it can be used by all professionals, despite the specialties and the geographical origin of the patient, in order to quickly take care of the patient through a tailored approach over time.

However, this study has to be considered as a pilot study aimed to present initial attempts for assessing the clinical feasibility of a new clinical tool. Our intent is to catch the attention of the scientific community for developing possible international collaborations to corroborate and improve this checklist. Consequently, this study has some pitfalls which deserve to be declared. Firstly, data could not be generalized, since the sample is small and was enrolled in four different centers affiliated to the same Institute (ICS Maugeri). These centers are all located in Lombardy, a region highly impacted by the pandemic and, as a consequence, able to provide informative data and experiences regarding the short- and long-term care of COVID-19 patients. However, it is necessary to bear in mind that the sample is unbalanced considering the prevalence of males, the geographic region, the high rate of hospitalizations compared to non-hospitalizations during COVID-19 disease, and the high incidence of comorbidities in patients' anamnesis. Secondly, the time spans of the clinical check-ups and consequently of the phone interviews have varied widely within the sample, ranging from 1 to 2 years. Thirdly, PASC-C deserves to be further investigated to assess its feasibility and validity in clinical and research contexts. Fourthly, the patient's adherence to suggested checkups should be also assessed and monitored over time.

FUTURE DEVELOPMENTS

This research project is a pilot study for the validation of PASC-C, as it seems to be feasible and promising for the effective identification and monitoring of Long COVID patients. Further studies should replicate this research and extend it on a large scale to other national and international hospitals and healthcare centers, to consolidate results. With further studies the hope is to provide a tool for promoting tailored treatments, and rehabilitation programs that could be commonly shared among the clinical community. This issue is indeed a global healthcare challenge that needs clinical tool to adequately taking care of the patients over time.

CONCLUSIONS

Although the pandemic seems to be reaching its end, several patients worldwide are still struggling with Long COVID syndrome. This chronic and disabling condition leads to a heterogenous complex of clinical manifestations, and knowledge in literature is in its early stages. To date, there is still consensus on the necessity to assess and monitor core set of Long COVID symptoms to improve the quality and efficacy of care provided. The aim of this study has been to investigate physical, psychological, and cognitive symptoms after

1-2 years from COVID-19 acute infection, contributing to shed light on the existing controversial literature. The symptoms assessed by PASC-C are in line with the core outcome set to monitor in patients recovered from COVID-19 condition, thus this tool can be considered valid and useful in the present healthcare scenario.

The findings showed as it is crucial to identify Long COVID patients, in order to take care of their chronic and disabling conditions, adopting tailored diagnostic and care programs, based on a multidisciplinary approach.

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Conflict of interest statement

The Authors declare no conflict of interest.

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