A CLASSIFICATION SYSTEM FOR POST-ACUTE SEQUELAE OF SARS CoV-2 INFECTION

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Abstract
This study aimed to contribute to the development of a research case definition for post-acute sequelae of SARS CoV-2 infection (PASC) using a PASC data set and experiences from case definitions developed for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Our database included patients with PASC who provided self-report symptomology during the onset of infection and the time of survey completion (post-infection). We found that we could distinguish between those with mild, moderate, and severe PASC. Regarding the proportion meeting an ME/CFS case definition, we found 0% in the mildly impaired group, 30.6% to 62.6% in the moderately impaired group, and 74.3% to 89.0% in the severely impaired group. Based on these preliminary data, we propose a 5-part classification system for PASC. Axis 1 involves the variant of the COVID infection and the type of documentation of the infection. Axis 2 involves the time elapsed since infection. Axis 3 involves the type of medical collateral damage to different organs. Axis 4 involves functional impairment classified into three categories: mild, moderate, or severe. Finally, Axis 5 is the identified symptoms. Finally, if the patient has been sick for 6 or more months, it is important to determine whether the person has met the ME/CFS criteria. This proposed 5-part classification system for PASC might bring considerable clarity to diagnosing PASC.

Keywords: PASC, ME/CFS, Classification system

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INTRODUCTION
The coronavirus disease (COVID-19) pandemic was caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The distribution of COVID-19 (data to date: Nov. 23, 2021): 258 million confirmed cases worldwide and 48.7 million in the US; 5.2 million deaths worldwide and 794.9 thousand in the US; 2.3% case fatality rate worldwide and 15.3% in the US [1]. Psychological distress has occurred in the general population owing to changes in routine, access to healthcare, and anxiety about the well-being of friends and family [2, 3, 4]. After infection, symptoms often occur 2-14 days later, and the symptoms can range from mild to severe. The typical symptoms are fatigue, fever or chills, shortness of breath, and the new loss of taste or smell, and can include trouble breathing and persistent pain or pressure in the chest [5, 6, 7, 8, 9, 10]. Although effective vaccines have helped reduce the number of cases of COVID-19 [11], many previously infected with COVID-19 have not fully recovered with persisting and new symptoms [12]. Persisting symptoms...
include but are not limited to fatigue, muscle aches, cardiac issues, and rashes. Newly developed symptoms or complications post-COVID-19 include Guillain-Barré [13], lung scarring, blood clots, renal failure, neurological complications [14], and heart damage [15]. Many have termed the post-COVID-19 infection phenomenon as “long COVID” or “long haul COVID,” and it should not be mistaken as “persisting COVID,” as symptoms in long COVID are present without the presence of the COVID-19 virus itself [16, 17]. In addition, “long COVID” or “long haul COVID” has been referred to by the CDC as post-acute sequelae of SARS CoV-2 infection (PASC). If only 10% develop PASC [18], then of the 48.7 million cases in the US [19], there will be over 4 million individuals affected.

Reviewing past epidemics, such complications of post-infection are common. Islam, Cotler, and Jason [20] reviewed the literature to demonstrate that some people recovering from infection (viral or bacterial) have experienced persisting symptoms or the development of new symptoms from past epidemics such as the Spanish Flu of 1918 [21], SARS [22], Ebolavirus [23], and tick-borne encephalitis [24]. Often, these symptoms can mimic symptoms of other serious, debilitating illnesses such as myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) [25]. Researchers have also found that even people at low-risk can experience PASC. Similar results were found by Tenforde et al. [26] in which 28% of patients screened with no reported chronic illnesses did not return to “usual state of health” within weeks post-positive indication of COVID-19.

Initial reports described post-COVID-19 complications [27]. and Lambert and Survivor Corps [28] found that fatigue was the most reported symptom post-COVID-19 infection, followed by muscle or body aches, shortness of breath, and difficulty concentrating or focusing. Rubin [29] also found that fatigue, shortness of breath, and neurocognitive symptoms were the most significant symptoms in people post-COVID-19, and these findings have now been replicated in other studies [26, 30, 31, 32, 33, 34, 35, 36].

Lopez-Leon et al.’s [37] systematic review of 15 studies that reported on the long-term effects of COVID, involving 47,910 patients, found that 80% of the infected patients developed one or more long-term symptoms, with the five most common symptoms being fatigue (58%), headache (44%), attention disorder (27%), hair loss (25%), and dyspnea (24%). Differences in questionnaires might be responsible for some of these differential outcomes. Sandler et al. [38] reviewed 21 long COVID studies of persistent fatigue and found that measures of fatigue were poorly described, and they suggested the need for using validated measures. These investigators [37] proposed that the label “post-COVID fatigue” should be applied when the fatigue is as follows: “a dominant symptom; chronic; disabling to an extent that it interrupts all or a majority of normal activities (such as work/school attendance, social activities, etc.); persistent for 6 months or more (3 months in children/adolescents); and emerged during confirmed acute COVID-19 (i.e., with a positive severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] test), without symptom free interval since onset.”

Other symptoms have also been reported, such as when Ding and colleagues [39] compared patients with COVID-19 who had pneumonia concurrent with the infection to persons who did not develop pneumonia. The pneumonia group exhibited greater immunological responses (e.g., fever); however, the non-pneumonia group reported greater neurological impairments such as impaired vision, tingling, and numbness, which suggest nerve damage. Furthermore, patients who initially had dyspnea during infection were found to develop long-term symptoms such as anosmia, ageusia, and neurocognitive dysfunction (e.g., loss of memory, confusion) [40].

Mandal and colleagues [41] found that some COVID-19 patients experienced higher levels of certain biomarkers such as d-dimer and C-reactive protein after hospital discharge. Other studies have also found elevated levels of C-reactive protein within patients with PASC [42]. Furthermore, imaging studies revealed that many patients had residual deterioration in the chest. However, it must be noted that chest radiography as a follow-up measure has been demonstrated to be a poor predictor or assessment of PASC [43].

A recent study has found that most PASC symptoms fall into one of seven domains: neurocognitive, autonomic, gastrointestinal, respiratory, musculoskeletal, psychological, and “others” [44]. Similarly, Huang and colleagues [45] identified five symptom clusters for PASC at 61 or more days: chest pain, dyspnea, tachycardia, abdominal pain, and lower-back pain. Another study by Al-Aly, Xie, and Bowe [46] found that people who were not hospitalized in the first 30 days post-infection often developed issues in the following systems after six months: respiratory nervous system, metabolic, cardiovascular, gastrointestinal, psychological, and general well-being. Additionally, these researchers found that some participants indicated less commonly reported post-infection symptoms such as arthritis, skin disorders, and pulmonary embolism.
Despite the emerging literature on PASC, there is little agreement on how to assess, diagnose, and treat people with persisting symptoms post-COVID-19. There is not even a consensus on what to call this recently recognized illness [47, 48]. This is in part because post-COVID-19 complications present a broad and inconsistent spectrum of symptoms amongst many people. Another challenge in defining long COVID is the timeframe of symptom onset or presentation.

**HYPOTHESIS**

The current study aimed to contribute to the development of a research case definition for PASC using some experiences from diagnostics and case definitions from the ME/CFS field. We used a database of patients with PASC who provided self-report symptomology during the onset of infection and the time of survey completion (post-infection). ME/CFS case definitions were applied to the participants of the current study and the distribution of these case definitions were compared to provide a framework for a proposed PASC case definition.

**METHODS**

**Data Collection and Participants**

Two hundred ninety-nine participants who had not recovered from COVID participated in the current study. Participants were recruited through various online platforms such as patient-advocate websites (e.g., social media platforms). Participants were asked to complete two symptom questionnaires at one-time point, with one describing current symptoms and one recounting experiences when initially infected with SARS-CoV-2 from an average of 21.7 weeks prior. The participants were not provided incentives for filling out the questionnaires (For more details, see [49]).

**Ethics Statement**

Participants consented to be part of this study. The study obtained IRB approval from DePaul University on August 21, 2020 (Protocol PF02317PSY-R18).

**MEASURES**

**DePaul Symptom Questionnaire**

Participants filled out the DePaul Symptom Questionnaire (DSQ) [50], a 54-item self-report measure of symptomatology that also has questions regarding demographics, medical, occupational, and social history [51]. This questionnaire was developed and validated over the past decade, and the intention was to provide a psychometrically reliable way to determine whether a person’s self-reported symptoms met the criteria for different ME/CFS case definitions. Participants rated the frequency and severity of various domains of symptoms at two time points: once for the time of COVID-19 infection onset and once for the time of survey completion. Participants rated the frequency of each symptom over the past six months on a 5-point Likert scale with 0=none of the time, 1=a little of the time, 2=about half the time, 3=most of the time, and 4=all of the time. Likewise, participants were asked to rate the severity of each symptom over the past six months on a 5-point Likert scale with 0=symptom not present, 1=mild, 2=moderate, 3=severe, and 4=very severe. Individual scores of symptom domains were reported on a 100-point scale (scores were multiplied by 25 and then the frequency and severity scores were averaged). The DSQ traditionally has seven symptom domains: sleep, post-exertional malaise (PEM), neurocognitive, immune, pain, gastrointestinal, and orthostatic. However, for this study, an eighth domain was added, consisting of symptoms recommended by the Center for Disease Control and Prevention (CDC) [52]. Such symptoms included the loss of hair, loss of taste, loss of smell, shortness of breath, etc. The DSQ has demonstrated excellent psychometric properties [53]. One item on the DSQ measures patients’ level of impairment by answering a 7-point Likert scale item that assesses the severity of participants’ impairment ranging from “bedridden” (e.g., unable to move) to mild impairment. Participants who were bedbound or homebound were classified as “severely impaired.” Those who could work part-time and leave the house but did not have energy for other activities were classified as “moderately impaired.” Participants that responded as fully functional were classified as “mildly impaired.”

**Coronavirus Impact Scale**

Participants were asked to complete the Coronavirus Impact Scale (CIS) [54]. The questionnaire consists of 12 4-point Likert scale questions and one open-ended question that assess how the COVID-19 pandemic has affected various dimensions of a person’s life (e.g., routine, access to medical care, social/family support, etc.). The first eight questions assess the respondents’ experience while the rest ask about extended family members and friends. From this background, we created a CIS summary score by taking the sum of the first eight questions. The instrument has demonstrated good reliability and validity [55].

**Case Definition: ME/CFS Inclusion and Exclusion Criteria**

ME/CFS case definitions were used as they can identify those patients with PASC who have high levels of
persisting symptoms and impairment. Two ME/CFS case definitions both require symptom persistence of six or more months and substantial reduction in functioning. Substantial reduction in function was a self-report item in the DSQ in which persons responded to a binary item: “Since the onset of your problems with fatigue/energy, have your symptoms caused a 50% or greater reduction in your activity level?” The Canadian Consensus Criteria (CCC) [56] also requires the person to experience the following: (1) fatigue, (2) PEM, (3) sleep dysfunction, (4) pain, (5) two or more neurocognitive symptoms, and (6) symptoms that are within two areas of the following domains: autonomic, neuroendocrine, or immune. The IOM is an ME/CFS case definition that requires persons to have PEM, sleep dysfunction, and either neurocognitive dysfunction and/or orthostatic intolerance [57]. Of the two case definitions, the CCC is more restrictive than the IOM.

Statistical Analyses
A one-way analysis of variance (ANOVA) on the summary score and domains of the DSQ at the time of infection (time point 1) across the three impairment groups (mild, moderate, severe) was performed. Post-hoc comparisons were conducted with Bonferroni corrections.

RESULTS
Table 1 shows the percentage of PASC respondents who indicated whether they had mild, moderate, or severe symptoms at the current time. Only seven individuals were only mildly affected, the remainder were about evenly divided among those with severe and moderate functional limitations. Table 2 shows the sociodemographic characteristics of the sample. The sample was in their mid-40s and primarily White and female except for those who were mildly affected, who were 57% men.

DePaul Symptom Questionnaire Outcomes
The ANOVA on the summary score of the DSQ at the time of infection (time point 1) across the three impairment groups (mild, moderate, severe) found a main effect, F(2, 289) = 18.09, p < .001). Post-hoc comparisons with Bonferroni corrections found that the severely impaired group scored significantly higher than both the moderate and mild groups. Moreover, the moderate group scored significantly higher than the mild group. See Table 3 for descriptive and inferential statistics. Comparable results were found at time point 2. Over time, multiple paired-samples t-tests were conducted with an adjusted α = .017 (α = .05/3). The severely impaired participants’ scores significantly improved at time point 2 compared with time point 1, t(135) = 6.17, p < .001. Similar results were found for the moderately impaired group t(146) = 9.88, p < .001.

Another ANOVA conducted on all individual symptom domains across the three groups revealed a main effect of impairment, p < .001. Post-hoc Bonferroni comparisons revealed two patterns of findings across the impairment groups within a domain score at testing time 1. First, the severe group scored significantly higher (i.e., more symptomatic) than both the moderate and mild groups; furthermore, the moderately impaired group reported higher scores than the mildly impaired group. This pattern was observed in the following domains: sleep, neurocognitive, pain, gastrointestinal, orthostatic intolerance, and CDC guidelines. A second pattern was also observed within the PEM, immune, and neuroendocrine domains, as the severely impaired group scored significantly higher than both the moderate and mild groups; however, no significant differences were observed between the moderate and mild group. Again, comparable effects were found at time point 2. Over time, within the severely impaired group, participants reported significant improvement in scores from time point 1 to time point 2 across the following domains: sleep, immune, neuroendocrine, orthostatic intolerance, and CDC guidelines. Within the moderately impaired group, scores significantly improved from time point 1 to time point 2 across all domains except neurocognitive. Within the mildly impaired group, no significant differences were observed between the two time points across any domain.

Coronavirus Impact Scale (CIS)
An ANOVA on the summary score of the CIS across the three impairment groups (mild, moderate, severe) found a main effect, F(2, 280) = 28.10, p < .001. Post-hoc Bonferroni comparisons found that the severely impaired group scored significantly higher than both the moderate and mild groups; furthermore, the moderately impaired group reported higher scores than the mildly impaired group. This pattern was observed in the following domains: sleep, immune, neuroendocrine, orthostatic intolerance, and CDC guidelines. Within the moderately impaired group, scores significantly improved from time point 1 to time point 2 across all domains except neurocognitive. Within the mildly impaired group, no significant differences were observed between the two time points across any domain.

Case Definitions
Two case definitions were applied in the current study: the CCC [56] and the IOM [57]. There were no participants in the mildly impaired group who met either case definition. Within the moderately impaired group, 62.6% of participants met the IOM criteria whereas 30.6% of participants met the CCC. With regards to the severely impaired group, 89.0% of participants met the
IOM criteria, and 74.3% of participants met the CCC. See Table 5 for descriptive statistics of the case definitions across the impaired groups.

DISCUSSION

The principal finding is that those with PASC can be classified into three groups using a simple rating scale. Those in the severe category are more symptomatic than those in the moderate category, and few symptoms are present in those rated as mild. The CIS provided similar results. Overall, we noticed an improvement in symptoms over time. Finally, it is possible to categorize between 74% to 89% of those in the severe group as meeting one of the ME/CFS case definitions. These findings can help clarify several issues relating to a possible case definition or criteria for PASC.

The lack of consistency in symptoms of those with PASC has led many healthcare professionals to not acknowledge the illness, creating stigma and barriers to proper healthcare access [58]. Several others have proposed frameworks for classifying PASC. Greenhalgh and colleagues [59] have labeled symptoms existing for at least three weeks as “post-acute COVID-19.” They suggested that patients experiencing symptoms beyond 12 weeks should be classified as having “chronic COVID-19.” Research by Datta and colleagues [60] has proposed three stages of PASC. The first stage is an acute infection of COVID-19 marked by hallmark symptoms associated with COVID-19 (e.g., dry cough, fever, etc.). Datta et al. [60] then suggested that some may progress into a second stage called “postacute hyperinflammation illness” which has an onset of 2-5 weeks after initial infection. People in this stage experience inflammation marked by certain biological irregularities such as increased troponin, C-reactive protein, and d-dimer levels. Finally, some people may move onto a stage called “late inflammatory and virological sequelae that develops approximately four weeks after initial infection. This stage is again marked by hyperinflammation and is akin to what most people commonly report as PASC.

Sudre and colleagues [61] classified 4,182 patients into five categories based on the duration of symptoms: short COVID (4-8 days), long COVID beyond 28 days, long COVID beyond 56 days, and long COVID beyond 84 days. Fernández-de-las-Peñas and colleagues [44] also proposed a multiphase course for the illness defined by symptom duration post-infection: a transitional phase from infection onset (4-5 weeks), acute post-COVID (phase 1; 5-12 weeks), long-post acute COVID (phase 2; 12-24 weeks), and persistent post-COVID (beyond 24 weeks). Alwan and Johnson’s [62] criteria for PASC include: 1) positive COVID-19 PCR or antigen test, 2) positive COVID-19 antibody test, 3) loss of sense or taste in the absence of any other identified cause, 4) common clinical symptoms and high prevalence of COVID-19 at the time and location of onset, and 5) at least one common clinical symptom and contact of a confirmed case of COVID-19 around the time of onset.”

More recently, the World Health Organization [48] developed a case definition for post COVID-19 condition. Their definition indicates that it “occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include not only fatigue, shortness of breath, and cognitive dysfunction but also others (see Table 3) which generally have an impact on everyday functioning. Symptoms may be new onset, following initial recovery from an acute COVID-19 episode, or persist from the initial illness. Symptoms may also fluctuate or relapse over time.”

A clinical case definition is intended to be very broad so that it can include all those who have the disorder. This is in contrast to a research case definition, which is more restrictive in criteria to identify a more homogeneous sample. Given that the WHO has developed a clinical case definition, it is unclear why three months have to elapse for a person to have the diagnosis. In other words, those patients who continue having symptoms after the first few weeks of COVID-19 infection are left without a diagnosis for several months, and these first few months might be a critical time for a diagnosis that could help patients secure treatment. The next part of the WHO case definition is that the symptoms must last for two months. We know that sometimes symptoms are delayed with long haul COVID, so if symptoms occurred three months past infection, a patient would need to be sick again for two months before being provided a diagnosis and treatment. These guidelines involving time periods are not reflected in multiple other criteria formulas that have been proposed. It would be simpler to just indicate the amount of time that has elapsed since being infected or becoming sick, and anyone with persisting symptoms beyond two weeks would be classified as being as long haul COVID. This would eliminate problems associated with individuals not being able to have a diagnose and treatment at the critical early times in the illness.

More work is occurring regarding postulating physiological similarities between PASC and ME/CFS.
There is a new ICD-10 code for post-COVID conditions: U09.9 (Post COVID-19 condition, unspecified) and also the code for any other conditions (https://www.cdc.gov/nchs/data/announcements/New-ICD-code-for-Post-COVID-Condition-April-2022-final.pdf). In other words, if a person with ME/CFS met the ICD ME code (G93.3), it is not instead of the long COVID code but in addition to it. In a recent study, six months following symptom onset (which is a criterion for case definitions of ME/CFS), an international sample of 3,761 patients with long COVID had somewhat similar symptoms (i.e., fatigue, PEM, and cognitive dysfunction) [65] to those with ME/CFS. Finally, González-Hermosillo et al. [66] examined post-acute COVID-19, and also found fatigue to be the most common symptom affecting 46.9% of the sample and 13% met the IOM criteria for ME/CFS. Finally, Campen et al. [67] found early-onset orthostatic intolerance symptoms among those with PASC, and similar outcomes to patients with ME/CFS.

Based on the prior PASC classification system proposed above and the findings from our study, we propose a 5-part classification system for PASC (a copy can be obtained from the first author). Axis 1 would involve designating the COVID variants such as Alpha, Beta, Gamma, Delta, or Omicron and their documentation (Positive PCR test, Positive antigen result, etc.). Of course, other characteristics of the person would be collected, but these COVID-19 factors would be prominent within the first Axis of a case definition for PASC.

Axis 2 involves the time elapsed since infection. Several prior classifications have been proposed from a few weeks to many months, and we feel that it would be simpler to just indicate the amount of time that has elapsed since being infected or becoming sick. Axis 2 implies that anyone with persisting symptoms beyond two weeks would be classified as PASC, but that as time elapses, as with the current study, it is likely that symptoms will improve for some patients.

Axis 3 involves the type of collateral damage done to different organ areas (respiratory, nervous system, metabolic, cardiovascular, gastrointestinal, etc.). There will be two types of PASC: those that have this type of biological organ documentation versus those where the organ damage is not able to be determined. There will likely be differences between these two groups, as well as differences between those with different types of organ damage.

At present, most classification systems have no differentiation of illness severity by those who have not recovered. Axis 4 involves functional impairment classified into mild, moderate, or severe. Findings from the current study indicate that those in the severe category are more symptomatic than those in the moderate category, and this finding was also supported by our CIS outcomes. This relatively simple rating scale can help differentiate patients into meaningful categories, and while all appear to improve over time, there are also important functional reductions between these groups. Such a relatively simple rating scale could have been proposed to differentiate patients into meaningful categories, as there will be important functional reductions between such groups which will affect healthcare needs for services.

Finally, Axis 5 will determine over 30 possible COVID-19 generated symptoms. The symptoms were taken from multiple surveys [39, 48, 49, 52, 65, 68]. As with the DePaul Symptom Questionnaire, it is useful to document for each symptom a frequency and a severity score. Almost all classification systems do not make this differentiation in the frequency and severity of symptoms. Many of the symptoms, such as fatigue, are common among individuals who have never had COVID-19. So just indicating that a person has a symptom is insufficient for designating at what threshold the symptom needs to exist for it to be considered a problem. A very frequent symptom might not be a problem for the person even if it is rather serious when it occurs, and a very frequent symptom might also be less impactful when the severity of it is minimal. Failing to document these types of frequency and severity differentiations in symptoms makes it considerably more difficult to assess the impact of symptoms. In addition, it is critical to use psychometrically sound questionnaires so that it is more likely that the symptoms will be elicited in similarly by different investigators, thus reducing potential problems for interpreting and comparing the data. Questionnaires also should provide an opportunity to identify unique symptoms experienced that might not be on a particular questionnaire.

This 5-part classification system for PASC would bring considerable clarity to diagnosing patients with PASC. Given the complexities of developing ME/CFS case definitions and an over a 30-year history, those studying PASC can use this experience that has occurred from other post-viral infections [49]. Scientists can use existing ME/CFS criteria to differentiate those with minimal post-viral symptoms, those who might have chronic fatigue and other symptoms but not ME/CFS, and those who met the time and symptom criteria for ME/CFS. The 5-Axis system would allow investigators to collect consistent critical data across samples, which
can be used for basic research to better understand why some individuals recover from COVID-19 and others do not.

Komaroff and Bateman [18] have suggested that PASC may lead to the development of ME/CFS. A study conducted in Latvia by Araja et al. [63] found that some people who first developed COVID-19 and had never been diagnosed with ME/CFS reported symptoms of ME/CFS. The authors posited that there may be an increase of ME/CFS cases by 15% owing to COVID-19 infection. Jason et al. [49] have recently compared a sample of people with ME/CFS to those who had not recovered from COVID-19. Both groups of patients had high rates of PEM, cognitive impairment, and sleep disruptions, which are key features of ME/CFS. The current study now suggests that among the group that is severely impacted, significantly more can be diagnosed with ME/CFS.

A major limitation is the small size of the mild group. Given the mild group's small sample size, no firm conclusions on this grouping can be made. However, those in this group will likely be the least impacted, and by allowing for a mild group in our classification system, it is possible to classify all post COVID-19 individuals who have a persisting symptom, without regard to the severity of it or how long it has persisted. At one point, we deleted the mild group from our analyses, and the findings involving moderate versus severe were the same. We also considered using non-parametric statistics with the three groups, and comparable results were found. Ultimately, we decided to keep all three groups in the study, as we thought the small size of the mild group might be of interest to readers. The fact that so few who describe themselves as long haulers filled out our questionnaire with mild symptoms suggests that although there might be many individuals with lingering PASC symptoms, many who are only mildly impacted may not consider themselves within the long-haul category. However, it is also likely that there are far more individuals within this category who are only minimally affected, but further longitudinal research will be needed to determine whether this is the case. A final limitation is that ME/CFS case definitions require six or more months of symptoms, and as some participants had not been sick for that long, we had to extrapolate that had they been sick for six or more months with those symptoms, they would have met the criteria.

As stated above, a clinical case definition is by very nature broad to include all those with an illness, and the fact that there are currently multiple definitions that have been proposed by different organizations is extremely problematic. A high priority need is to reach a consensus on the case definition of long haul COVID. In this article, we have provided some of the parameters that could be used to classify all patients as well as provide scientists with needed research case definition criteria for classification purposes, but further research with larger samples is needed to replicate our findings. Finally, responder bias is another limitation in our study, and it more adversely affects individuals who may not have access to the internet so they would not be able to respond.

Every disease has a case definition, and these entities are crucial, as they allow patients to have a diagnosis for a constellation of symptoms as well as for scientists who can research those with the illness versus those without the illness. If difficulties occur in arriving at a reliable case definition, there are serious consequences for patients, as they would then be unsure whether or not they have the illness, as well as for scientists, who might then have difficulties in estimating prevalence as well as finding biomarkers. This has occurred for the post-viral illness that is known as ME/CFS. The consequences have been increased stigma for patients as to when patient heterogeneity makes it difficult to identify biomarkers, and when they are not identified, healthcare workers can easily attribute the condition to solely psychiatric reasons [69]. The relevance of ME/CFS takes on even greater importance given recent findings that a PASC-anticipating risk factor at the time of initial COVID-19 diagnosis is the Epstein-Barr virus viremia, which has also been associated with ME/CFS [70].

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**Conflicts of Interests**

All authors have completed the ICMJE Disclosure Form (http://www.icmje.org/disclosure-of-interest/; available on request from the corresponding author). All authors declare that there are no potential conflicts of interest.

**Disclaimer**

No part of this article is copied or published elsewhere in whole or in part.

All primary data and additional information on research methods are available for evaluate on reasonable request.
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Table 1. Item responses, level of impairment, and frequency to the DSQ question: Which statement best describes your fatigue/energy?

| Impairment | Item Response                                                                 | % (n)    |
|------------|-------------------------------------------------------------------------------|----------|
| Severe     | I am not able to work or do anything, and I am bedridden.                     | 3.8 (11) |
|            | I can walk around the house, but I cannot do light housework.                 | 17.9 (52)|
|            | I can do light housework, but I cannot work part-time.                        | 25.2 (73)|
| Moderate   | I can only work part time at work or on some family responsibilities.         | 20.7 (60)|
|            | I can work full time, but I have no energy left for anything else.           | 16.9 (49)|
|            | I can work full time and finish some family responsibilities but I have no   | 13.1 (38)|
|            | energy left for anything else.                                                |          |
| Mild       | I can do all work or family responsibilities without any problems with my    | 2.4 (7)  |
|            | energy.                                                                        |          |

Table 2. Demographic statistics across the three impairment groups

| Demography                  | Mild        | Moderate     | Severe      |
|-----------------------------|-------------|--------------|-------------|
|                             | M (SD)      | M (SD)       | M (SD)      |
| Age                         | 44.43 (12.86)| 44.25 (12.75)| 46.18 (27.35)|
| % (n)                       | % (n)       | % (n)        |             |
| Race                        |             |              |             |
| White/Caucasian             | 85.70 (6)   | 91.20 (134)  | 90.40 (123) |
| Asian or Pacific Islander   | 14.30 (1)   | 04.10 (6)    | 02.20 (3)   |
| American Indian or Alaskan Native | 14.30 (1) | 02.00 (3) | 01.50 (2) |
| Black/African American      | 0 (0)       | 01.40 (2)    | 01.50 (2)   |
| Latinx                      | 14.30 (1)   | 06.80 (10)   | 07.40 (10)  |
| Gender                      |             |              |             |
| Female                      | 42.90 (3)   | 83.00 (122)  | 83.50 (111) |
| Male                        | 57.10 (4)   | 16.30 (24)   | 13.50 (18)  |
| Non-binary                  | 0 (0)       | 00.70 (1)    | 03.00 (4)   |
Table 3. Descriptive and inferential statistics for DSQ scores across symptom domains and timepoints

| Domain     | DSQ Score | Time 1 | Time 2 |
|------------|-----------|--------|--------|
|            |           | M (SD) | M (SD) |
| Total      |           |        |        |
| Severe     | 51.20 (18.62)\(^{ab}\) | 43.73 (15.70)\(^{ab*}\) |
| Moderate   | 41.16 (16.59)\(^{ac}\) | 29.41 (13.41)\(^{ac*}\) |
| Mild       | 21.65 (16.50)\(^{bc}\) | 09.17 (05.69)\(^{bc}\) |
| Sleep      |           |        |        |
| Severe     | 60.14 (25.31)\(^{ab}\) | 49.00 (21.42)\(^{ab*}\) |
| Moderate   | 51.33 (22.77)\(^{ac}\) | 35.98 (19.23)\(^{ac*}\) |
| Mild       | 32.50 (21.98)\(^{bc}\) | 14.29 (08.37)\(^{bc}\) |
| PEM        |           |        |        |
| Severe     | 74.03 (26.44)\(^{ab}\) | 73.04 (20.34)\(^{ab}\) |
| Moderate   | 64.67 (28.67)\(^{a}\) | 51.39 (23.93)\(^{ac}\) |
| Mild       | 30.95 (29.18)\(^{b}\) | 08.93 (10.81)\(^{bc}\) |
| Neurocognitive |     |        |        |
| Severe     | 45.20 (26.09)\(^{ab}\) | 49.43 (20.91)\(^{ab}\) |
| Moderate   | 32.05 (22.98)\(^{ac}\) | 30.92 (20.43)\(^{ac}\) |
| Mild       | 15.55 (19.34)\(^{bc}\) | 08.98 (08.10)\(^{bc}\) |
| Immune     |           |        |        |
| Severe     | 49.11 (23.48)\(^{ab}\) | 24.15 (18.66)\(^{ab*}\) |
| Moderate   | 39.02 (20.49)\(^{a}\) | 15.43 (15.38)\(^{a}\) |
| Mild       | 15.36 (15.03)\(^{b}\) | 00.71 (01.89)\(^{b}\) |
| Neuroendocrine |     |        |        |
| Severe     | 40.70 (20.81)\(^{ab}\) | 27.99 (18.10)\(^{ab*}\) |
| Moderate   | 31.74 (18.58)\(^{a}\) | 15.95 (12.90)\(^{ac}\) |
| Mild       | 11.61 (12.88)\(^{b}\) | 05.80 (07.90)\(^{bc}\) |
| Pain       |           |        |        |
| Severe     | 56.27 (25.64)\(^{ab}\) | 52.20 (21.57)\(^{ab}\) |
| Moderate   | 45.60 (23.28)\(^{ac}\) | 36.83 (21.78)\(^{ac}\) |
| Mild       | 23.21 (19.62)\(^{bc}\) | 11.79 (10.28)\(^{bc}\) |
| Gastrointestinal |     |        |        |
| Severe     | 31.86 (22.42)\(^{ab}\) | 30.24 (19.03)\(^{ab}\) |
| Moderate   | 22.22 (19.12)\(^{ac}\) | 18.06 (15.98)\(^{ac}\) |
| Mild       | 12.14 (15.71)\(^{bc}\) | 04.29 (07.32)\(^{bc}\) |
| Orthostatic |           |        |        |
| Severe     | 52.10 (24.15)\(^{ab}\) | 43.09 (20.71)\(^{ab*}\) |
| Moderate   | 39.81 (22.33)\(^{ac}\) | 26.64 (16.37)\(^{ac}\) |
| Mild       | 20.54 (23.40)\(^{bc}\) | 11.90 (06.22)\(^{bc}\) |
| CDC        |           |        |        |
| Severe     | 40.91 (18.06)\(^{ab}\) | 28.69 (18.90)\(^{ab*}\) |
| Moderate   | 34.57 (19.28)\(^{ac}\) | 20.03 (15.15)\(^{ac}\) |
| Mild       | 22.92 (17.26)\(^{bc}\) | 12.50 (13.98)\(^{bc}\) |

Note: Corresponding letters indicate a significant difference between groups (across columns) within a domain and within a timepoint. * indicate a significant differences between timepoints 1 and 2 within a group (across rows)
Table 4. Summary statistics for the CIS and DSQ at two time points

| Measure       | Impairment | Mild          | Moderate       | Severe         |
|---------------|------------|---------------|----------------|----------------|
|               |            | M (SD)        | M (SD)         | M (SD)         |
| CIS           |            | 06.86 (02.73) | 09.47 (03.78)  | 12.53 (03.58)  |
| DSQ Time 1    |            | 21.65 (16.50) | 41.16 (16.59)  | 51.20 (18.62)  |
| DSQ Time 2    |            | 09.17 (05.69) | 29.41 (13.41)  | 43.73 (15.70)  |

Note: Corresponding letters indicate a significant difference between the groups (across rows). Corresponding numbers indicate significant differences within impairment groups across the two DSQ time points (across columns).

Table 5. Descriptive statistics of the frequency of participants who met case definition(s) within each impaired group

| Impairment | Case Definition |
|------------|----------------|
| IOM        | CCC            |
| % (n)      | % (n)          |
| Severe     | 89.00 (121)    | 74.30 (101)    |
| Moderate   | 62.60 (92)     | 30.60 (45)     |
| Mild       | 0 (0)          | 0 (0)          |
Тұйінделме

Бұл зерттеу PASC мәліметтер жыныстың және миалгиялы энцефаломиелитке (ME/CFS) арналған жағдайларды анықтау тәжірибесін қолданып, SARS CoV-2 (PASC) инфекциясының жедел салдары анықтауға үлес қосуға бә жәғ дайылығын анықтау езірлесіне үлес қосу ұшына бағытталған. Біздің деректер басынан SARS шалдыйқ қан ауқу астанда кіреді, олар инфекцияның басында және тексеруді аяқтау кезінде (инфекциядан кейінгі) бөлігілере тұралы дерbes хабарлары. Біз қызмет, ортасы және ауыр PASC-қа шалдыйқ қан ауқу астанда ажырқа ежелінің әліпнамызбізді білдік. ME / CFS жағдайыны анықтау өсікестігінің пайызына келетін болсақ, біз қызмет бұзылуы бар топта 0%, ортаса бұзылуы бар топта 30,6%-дан 62,6%-ға дейін және ауыр бұзылуы бар топта 74,3%-дан 89,0%-ға дейін таптық. Осындай айтылған мәліметтер негізінде біз 5 ұшылық PASC диагностикалық жүйесін ұсынамыз. 1-ші осіне COVID инфекциясының нұқасысы және инфекция құжаттамасының туры кіреді. 2-ші осіне инфекцияларға сә кіт кісін бұтаң ә тұқымыз кіреді. 3-ші осіне ар тұрлі органдардың қатар жүретін медициналық зақымдану турі кіреді. 4-ші осы кейінгі жасырға жатады, жоғары функционалық бұзылуы бар: қызмет, ортаса және ауыр.

Сонымен, 5-ші осы - анықтауға белгілер. Сондықтан, егер наука 6 немесе одан да ұзақ айлар бойы ауыры, оның ME/CFS әліметдерінің сәйкес көлінетінің анықтау маңызы болып табылады. 5 бөлікtener тураның ұсынылығы жағдай жүйесі PASC диагностикасына айтарлықтай түсінік бере алады.

Тұйін сөздер: PASC, ME/CFS, жағдай жүйесі

Дайындық ұсыны: Джейсон Л.А., Исхам М.И. SARS COV-2 инфекциясының жедел салдарының жағдайы.

Système de classification postéthoriques des infections SARS CoV-2

Звездоюго

Это исследование направлено на то, чтобы внести вклад в разработку определения случаев постострых последствий инфекции SARS CoV-2 (PASC) с использованием набора данных PASC и опыта определения случаев, разработанных для миалгического энцефаломиелита (ME/CFS). В нашем базе данных вошли пациенты с PASC, которые самостоятельно сообщили о симптомах в начале инфекции и во время завершения обследования (постинфекция). Мы обнаружили, что можем различать пациентов с легким, умеренным и тяжелым PASC. Что касается процента соответствия определению случая ME / CFS, мы обнаружили 0% в группе с легкими нарушениями, от 30,6% до 62,6% в группе с средними нарушениями и от 74,3% до 89,0% в группе с тяжелыми нарушениями. На основании этих предварительных данных мы предлагаем 5-балльную диагностическую систему PASC. Ось 1 включает вариант инфекции COVID и тип документации инфекции. Ось 2 включает время, прошедшее с момента заражения. Ось 3 включает тип сопутствующего медицинского повреждения различных органов. Ось 4 включает функциональные нарушения, классифицируемые по трем категориям: легкие, умеренные и тяжелые. Наконец, ось 5 — выявленные симптомы. Наконец, если пациент болен в течение 6 или более месяцев, важно определить, соответствует ли он критериям ME/CFS. Предлагаемая система классификации из 5 частей может внести значительную ясность в диагностику PASC.

Ключевые слова: PASC, ME/CFS, система классификации

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