Long COVID syndrome (LCS), also known as post COVID-19 condition, occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of symptomatic COVID-19, with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis (1). It is characterized by chronic symptoms of fatigue, weakness, headache, dyspnea, cough, exercise intolerance, cognitive dysfunction, etc. LCS has been reported in about half of adults with COVID-19 (2-6). In a previous study on 4681 adult patients, we observed that 62% of the survivors of COVID-19-related hospitalizations reported symptoms or complaints of LCS (5).

Underpinning mechanisms of LCS are not entirely clear yet. SARS-CoV-2 invades many tissues and causes multi-organ and multi-system damage (7). In addition, psychological factors may contribute to the development of LCS (8). Finally, a previous study showed that immunological dysfunction may persist for months following the initial infection with SARS-CoV-2 (9). Hence, it is plausible to assume that LCS lasts long, at least in some individuals.

In the current longitudinal and follow-up study, we aimed to identify the longevity of the symptoms of adults who reported suffering from LCS in our previous study which was conducted in 2021. The study population included patients who were referred to healthcare facilities (55 centers) in Fars province, Iran.

Materials and Methods: This longitudinal retrospective and follow-up cohort study was conducted on adult patients who were hospitalized with COVID-19. We inquired about their current health status and obtained the information after they consented to participate and answer questions over the phone.

Results: In total, 2383 people participated in the study, 543 of whom (27.3%) reported experiencing symptoms of LCS. Fatigue (12.2%) and exercise intolerance (10%) were the two most common symptoms of persistent LCS. On the other hand, 240 people (12.1%) who did not report any symptoms of LCS in phase 1 of the study reported experiencing problems that are compatible with the diagnosis of LCS. Patients with persistent LCS (long-LCS) had longer hospital stays during their initial illness (7 days vs. 5 days) and were more frequently admitted to ICUs (15.8% vs. 8.9%) compared with those without long-LCS.

Conclusion: More than one-quarter of adults will continue to suffer from the symptoms of long-COVID for more than one year after their initial infection. The scientific community should develop validated measures and biomarkers to objectively diagnose and follow up this condition.

Keywords: Adult, COVID-19, Coronavirus, Long COVID
hospital stay in the initial illness, respiratory problems in
the initial illness, and intensive care unit (ICU) admission
in the initial hospitalization, and age of the patients (5).

**Materials and Methods**

**Participants**

This was a longitudinal retrospective and follow-up
cohort study, conducted on 4681 adult patients with
COVID-19 from our previous study (here called phase 1). For a detailed description of the methodology of
phase one, refer to the work of Asadi-Pooya et al (5). We
selected every other adult patient from our database of
4681 patients (alternate patients in the database sorted
by their phone numbers) from all healthcare facilities (55
centers) in Fars province, Iran.

**Data Collection**

The data of the participants were collected through phone
calls from January to February 2022 (11 months after the
initial study and more than 14 months after their hospital
admission due to COVID-19). We collected the data
based on our predefined case report form (Supplementary
file 1) that was adopted from phase one of the study. We
inquired about their current health status and obtained
the information after they consented orally to participate
in the study and answer the questions. We asked if the
patient has noticed any problems (e.g., muscle or joint
pain, weakness, etc.) during the past week, compared with
their pre-COVID-19 condition. We specifically asked
about their symptoms and complaints during the past
seven days in order to minimize the risk of recall bias. We
defined long-LCS at two levels: with a loose criterion (i.e.,
those who had not reported any symptom and complaint
in phase 1 of the study but had some symptoms and
complaints in the current follow-up study) and with a
strict criterion (i.e., patients who had reported at least one
symptom or complaint in phase 1 of the study and had
the same symptom or complaint in the current follow-up
study).

In the last part of the questionnaire, we asked the
patients to compare their current status (based on five
items) with their pre-COVID-19 condition based on a
5-point Likert scale (1: much worse; 2: somewhat worse;
3: the same as before; 4: somewhat better; 5: much better).
We asked about their ability to perform the activities of
daily living, ability to concentrate and think, ability to
study and read, quality of life, and hope for the future.
We also asked whether the patients experienced another
episode of COVID-19 after the first phase of the study
(self-declared).

We specifically investigated whether patients with or
without each specific symptom or complaint in phase 1 of
the study had the same symptom or complaint in phase
2 of the study. If a specific symptom or complaint was
reported in both phases of the study, it was considered as
true long-long COVID related symptom. However, if a
patient had not reported a specific symptom or complaint
in phase 1 but reported such an issue in phase 2 of the
study, the case was considered as false long-LCS. This
data might help us understand the longevity of the long
COVID symptoms. This is also helpful in recognizing the
challenges in making the diagnosis of LCS with regard to
each specific symptom.

**Statistical Analysis**

Kolmogorov-Smirnov normality test was performed.
Values were presented as mean ± standard deviation
(SD) or median/interquartile range (IQR) (based on
their normality) for continuous variables and as number
(percentage) for categorical variables. Fisher’s exact test,
t test, Mann–Whitney U test, and Bonferroni correction
test were used to analyze the data. A P value (2-sided) of
less than 0.05 was considered statistically significant.

**Results**

We made 4112 phone calls, of which 1419 calls were
not answered, 220 people refused to participate in the
study, and 90 individuals were deceased. A total of 2383
people were included in this study [1226 male (51.4%) and
1157 female (48.6%) participants]. The mean age of
the participants was 53 years (minimum: 19, maximum:
98, median 53, and interquartile range: 23 years). Of the
studied participants, 1502 people (63%) reported having
LCS in phase 1 of the study. In total, 395 people (16.6%)
reported COVID-19 reinfection. One might reasonably
argue that what we observed in phase 2 of the study
with regard to long-LCS could have been influenced by
reinfection, at least in some people. People with a history
of reinfection reported a significantly higher number of
seemingly long-long COVID related symptoms compared
with those who did not experience a reinfection [160:395
(40.5%) vs. 545:1988 (27.4%); P = 0.0001]. Therefore, we
excluded people with a history of COVID-19 reinfection
for the rest of the analyses (2383-395 = 1988).

Table 1 shows the number of participants reporting
LCS and long-long COVID symptoms in phase one and the
current phase of the study. With a loose criterion,
720 individuals (36.2%) reported experiencing symptoms
that are typically compatible with the diagnosis of LCS in
the current study. With a strict criterion, 543 individuals

<table>
<thead>
<tr>
<th>LCS in phase 1 (1236 people)</th>
<th>Long COVID symptoms in phase 2 (720 people)</th>
<th>No long COVID symptoms in phase 2 (516 people)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No LCS in phase 1 (752 people)</td>
<td>Long COVID symptoms in phase 2 (240 people)</td>
<td>No long COVID symptoms in phase 2 (512 people)</td>
</tr>
</tbody>
</table>

LCS: long COVID syndrome
(27.3% of the total population and 43.9% of those with LCS in phase 1) reported experiencing symptoms that are typically compatible with the diagnosis of LCS in the current phase of the study (true long-long COVID). On the other hand, 240 people (12.1%) who did not report any symptoms or complaints of LCS in phase 1 of the study reported experiencing problems that are typically compatible with the diagnosis of LCS (false long-LCS in the current phase of the study).

Table 2 shows the number of true and false long-long COVID symptoms. Fatigue [in 243 people (12.2%)] and exercise intolerance [in 206 persons (10%)] were the two most common symptoms of long-LCS. For none of the symptoms, a longevity of more than one year was observed in more than 50% of those who reported those symptoms in phase 1 of the study. For the following symptoms, a longevity of more than one year was observed in more than 25% of those who reported the same symptoms in phase 1 of the study (i.e., true symptoms of LCS). These symptoms included muscle weakness, joint pain, fatigue, dyspnea, chronic cough, walking intolerance, and exercise intolerance. The ratio of true to false symptoms reported in phase 2 of the study (as an indirect indicator of the reliability of the reported symptom) was 4 or higher (arbitrarily) for the following symptoms: palpitation, excess sputum, loss of smell, diarrhea, and abdominal pain.

Table 3 shows how the patients rated the following items over the past week compared with before their COVID-19 infection (ability to do routine tasks, ability to concentrate and think, ability to study, overall quality of life, and hope for the future) in phases 1 and 2 of the study. The ratings were not significantly different between phase 1 and phase 2 of the study.

Table 4 shows the risk factors associated with long-LCS in univariate analyses. Patients with long-LCS had longer hospital stays during their initial illness (7 days vs. 5 days) and were more frequently admitted to ICUs (15.8% vs. 8.9%) compared with those without long-LCS.

**Discussion**

In the current longitudinal study of adults with COVID-19 (requiring hospitalization), we observed that more than one-quarter of adults will continue to suffer from the symptoms of LCS (true long-LCS) for more than one year after their initial infection. Furthermore, we observed that compared with the initial months after the hospitalization, almost similar percentage of the survivors of symptomatic COVID-19 reported impairment in their ability to do routine daily tasks, ability to concentrate and think, ability to study, and overall quality of life one year (or more) after their hospitalization with the initial infection. In brief, we observed that long COVID could last longer than one year in a substantial number of the survivors of severe COVID-19 (requiring hospitalization).

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**Table 2. Number, Percentage, and Ratio of True and False long-long COVID Symptoms**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Number</th>
<th>Percent</th>
<th>Ratio of True to False Symptoms in Phase 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle weakness</td>
<td>True</td>
<td>155</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>False</td>
<td>272</td>
<td>17</td>
</tr>
<tr>
<td>Myalgia</td>
<td>True</td>
<td>95</td>
<td>384</td>
</tr>
<tr>
<td></td>
<td>False</td>
<td>184</td>
<td>1601</td>
</tr>
<tr>
<td>Joint pain</td>
<td>True</td>
<td>97</td>
<td>353</td>
</tr>
<tr>
<td></td>
<td>False</td>
<td>169</td>
<td>1621</td>
</tr>
<tr>
<td>Fatigue</td>
<td>True</td>
<td>243</td>
<td>594</td>
</tr>
<tr>
<td></td>
<td>False</td>
<td>274</td>
<td>1391</td>
</tr>
<tr>
<td>Sleep difficulty</td>
<td>True</td>
<td>47</td>
<td>261</td>
</tr>
<tr>
<td></td>
<td>False</td>
<td>155</td>
<td>1678</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>True</td>
<td>156</td>
<td>393</td>
</tr>
<tr>
<td></td>
<td>False</td>
<td>208</td>
<td>1587</td>
</tr>
<tr>
<td>Chest pain</td>
<td>True</td>
<td>31</td>
<td>203</td>
</tr>
<tr>
<td></td>
<td>False</td>
<td>94</td>
<td>1780</td>
</tr>
<tr>
<td>Palpitation</td>
<td>True</td>
<td>33</td>
<td>206</td>
</tr>
<tr>
<td></td>
<td>False</td>
<td>76</td>
<td>1774</td>
</tr>
<tr>
<td>Chronic cough</td>
<td>True</td>
<td>47</td>
<td>174</td>
</tr>
<tr>
<td></td>
<td>False</td>
<td>151</td>
<td>1809</td>
</tr>
<tr>
<td>Excess sputum</td>
<td>True</td>
<td>26</td>
<td>105</td>
</tr>
<tr>
<td></td>
<td>False</td>
<td>61</td>
<td>1848</td>
</tr>
<tr>
<td>Loss of smell</td>
<td>True</td>
<td>18</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td>False</td>
<td>82</td>
<td>1887</td>
</tr>
<tr>
<td>Loss of taste</td>
<td>True</td>
<td>4</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>False</td>
<td>64</td>
<td>1917</td>
</tr>
<tr>
<td>Sore throat</td>
<td>True</td>
<td>6</td>
<td>89</td>
</tr>
<tr>
<td></td>
<td>False</td>
<td>47</td>
<td>1892</td>
</tr>
<tr>
<td>Headache</td>
<td>True</td>
<td>36</td>
<td>216</td>
</tr>
<tr>
<td></td>
<td>False</td>
<td>123</td>
<td>1766</td>
</tr>
<tr>
<td>Dizziness/vertigo</td>
<td>True</td>
<td>22</td>
<td>161</td>
</tr>
<tr>
<td></td>
<td>False</td>
<td>80</td>
<td>1821</td>
</tr>
<tr>
<td>Confusion (brain fog)</td>
<td>True</td>
<td>43</td>
<td>234</td>
</tr>
<tr>
<td></td>
<td>False</td>
<td>111</td>
<td>1754</td>
</tr>
<tr>
<td>Excess sweating</td>
<td>True</td>
<td>16</td>
<td>172</td>
</tr>
<tr>
<td></td>
<td>False</td>
<td>63</td>
<td>1808</td>
</tr>
<tr>
<td>Exercise intolerance</td>
<td>True</td>
<td>206</td>
<td>508</td>
</tr>
<tr>
<td></td>
<td>False</td>
<td>198</td>
<td>1476</td>
</tr>
<tr>
<td>Walking intolerance</td>
<td>True</td>
<td>147</td>
<td>401</td>
</tr>
<tr>
<td></td>
<td>False</td>
<td>195</td>
<td>1581</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>True</td>
<td>5</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>False</td>
<td>27</td>
<td>1928</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>True</td>
<td>7</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>False</td>
<td>47</td>
<td>1910</td>
</tr>
<tr>
<td>Anorexia</td>
<td>True</td>
<td>5</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>False</td>
<td>63</td>
<td>1906</td>
</tr>
</tbody>
</table>

**True:** Patients reported a symptom or complaint in phase 1 of the study and also had the same symptom or complaint in the current follow-up study.

**False:** Patients did not report a symptom or complaint in phase 1 of the study but had a symptom or complaint in the current follow-up study.
and could impair physical and mental functions of the affected people substantially.

Our observations that patients with long-LCS had longer hospital stays at the time of their initial illness and were more frequently admitted to ICUs compared with those without long-LCS and also the observations by Sudre et al (2) and Peghin et al (10) that experiencing more symptoms during the first week of illness was associated with LCS may suggest that a more severe COVID-19 causes a more severe immune response and cytokine storm and could impair physical and mental functions of the affected people substantially.

Table 3. Patients’ Rating on the Following Items over the Past Week Compared with before COVID-19

<table>
<thead>
<tr>
<th>Changes of the Items</th>
<th>Much Worse (Phase 1/Phase 2)</th>
<th>Somewhat Worse (Phase 1/Phase 2)</th>
<th>The Same as Before (Phase 1/Phase 2)</th>
<th>Somewhat Better (Phase 1/Phase 2)</th>
<th>Much Better (Phase 1/Phase 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ability to do routine daily tasks</td>
<td>205 (4.4%)</td>
<td>758 (16.3%)</td>
<td>3619 (77.9%)</td>
<td>57 (1.2%)</td>
<td>8 (0.2%)</td>
</tr>
<tr>
<td>Ability to concentrate and think</td>
<td>117 (2.5%)</td>
<td>634 (13.6%)</td>
<td>3869 (83.3%)</td>
<td>22 (0.5%)</td>
<td>4 (0.1%)</td>
</tr>
<tr>
<td>Ability to study</td>
<td>36 (1.8%)</td>
<td>216 (10.9%)</td>
<td>1714 (86.2%)</td>
<td>14 (0.7%)</td>
<td>2 (0.1%)</td>
</tr>
<tr>
<td>Overall quality of life</td>
<td>24 (1.2%)</td>
<td>139 (7.0%)</td>
<td>1799 (90.5%)</td>
<td>14 (0.9%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Hope for the future</td>
<td>168 (3.6%)</td>
<td>634 (13.6%)</td>
<td>3781 (81.4%)</td>
<td>54 (1.2%)</td>
<td>9 (0.2%)</td>
</tr>
<tr>
<td></td>
<td>50 (2.5%)</td>
<td>344 (17.3%)</td>
<td>1545 (77.7%)</td>
<td>17 (1.9%)</td>
<td>7 (0.4%)</td>
</tr>
</tbody>
</table>

Table 4. The Risk Factors Associated with long-LCS in Univariate Analyses

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>Long-LCS, N = 543</th>
<th>No long-LCS, N = 1445</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (female: male)</td>
<td>273: 270</td>
<td>674: 771</td>
<td>0.158</td>
</tr>
<tr>
<td>Age (mean ± SD), years</td>
<td>52 ± 16</td>
<td>51 ± 16</td>
<td>0.325</td>
</tr>
<tr>
<td>Length of hospital stay (median, IQR, days)</td>
<td>7, 6</td>
<td>5, 5</td>
<td>0.0001*</td>
</tr>
<tr>
<td>Respiratory problems at the onset</td>
<td>500 (92.1%)</td>
<td>1275 (88.2%)</td>
<td>0.014</td>
</tr>
<tr>
<td>ICU admission</td>
<td>86 (15.8%)</td>
<td>128 (8.9%)</td>
<td>0.0001*</td>
</tr>
</tbody>
</table>

LCS: long COVID syndrome; SD: standard deviation; IQR: interquartile range; ICU: intensive care unit.

* Significant. After the Bonferroni correction, the significant P value was 0.01.

and could impair physical and mental functions of the affected people substantially.

Our observations that patients with long-LCS had longer hospital stays at the time of their initial illness and were more frequently admitted to ICUs compared with those without long-LCS and also the observations by Sudre et al (2) and Peghin et al (10) that experiencing more symptoms during the first week of illness was associated with LCS may suggest that a more severe COVID-19 at presentation is a significant risk factor for experiencing long-LCS. We can speculate two possibilities for these observations. First, severe COVID-19 causes a more severe immune response and cytokine storm and more organ damage (e.g., to the brain, lungs, and heart) (3-6). Second, severe COVID-19 is usually aggressively treated with more medications (e.g., corticosteroids) and is more often associated with iatrogenic harm (e.g., due to intubation or nosocomial infections) with long-lasting consequences (5).

Previous studies have suggested that differences in the rate of recovery from COVID-19 at cellular and transcriptional levels may explain the persistence of symptoms associated with long-LCS, at least in some cases (11-13). Other authors have suggested that symptoms of long-LCS are probably due to the persistence of endothelial dysfunction (14,15). Finally, many previous studies have shown that the COVID-19 pandemic has had deleterious psychological impacts on all human populations, including those with cured COVID-19 (16-19). Psychiatric problems (e.g., depression) may have significant associations with some of the subjective symptoms that are typically reported by patients with long-COVID and long-LCS (e.g., fatigue, sleep problems, etc) (20). Therefore, it is plausible to assume that long-LCS may have a multifactorial underlying pathophysiology. Future studies should specifically investigate the underlying pathophysiology of long-LCS.

Having said the above, we should be careful about how we define and investigate the symptoms of LCS and long-LCS. In the current study, we observed that one in eight patients reported symptoms that could be considered compatible with what we expect as the usual manifestations of LCS (e.g., fatigue, sleep difficulty, exercise intolerance, etc.), while they had not reported any or such symptoms before and in the early months after their initial infection and hospitalization with SARS-CoV-2. While fluctuation in the severity of symptoms could be expected in LCS, we believe that these symptoms should not be considered as the manifestations of long-LCS and they can easily be pandemic-associated symptoms (e.g., work closures and stay-at-home orders during the pandemic) (21). This significant observation highlights that long-term COVID-19-associated symptoms (LCS and long-LCS) may be difficult to investigate and the scientific community should define both LCS and long-LCS and also propose clear criteria for these conditions in order to facilitate future studies (1). Validated measures and biomarkers should be developed to objectively diagnose and follow up this condition. It is noteworthy to mention that although the prevalence of post Omicron COVID-19 conditions was lower than that of the other strains, further research is needed to investigate the epidemiology of post COVID-19 conditions of Omicron variant and its impacts (22). Clinical management of patients with LCS requires a whole-patient perspective with challenging and time-consuming consultations (23).

Limitations

Selection bias and recall bias are among the most important limitations. Furthermore, the data on long-LCS were not collected prospectively and we cannot
provide any information on the course (e.g., fluctuation in symptoms) of the long-LCS based on the current study. In addition, we did not investigate asymptomatic reinfections in this study. Finally, we did not take any objective measures to study the symptoms and we did not have a control group.

**Conclusion**

We can conclude that more than one-quarter of adults will continue to suffer from the symptoms of long COVID for more than one year after their initial infection. It is plausible to assume that long-LCS has a multifactorial underlying pathophysiology. However, the scientific community needs to develop validated measures and biomarkers to be able to objectively diagnose and follow up this condition.

**Authors’ Contribution**

Conceptualization: Ali A. Asadi-Pooya.
Data curation: Anahita Jafari.
Formal analysis: Seyyed Saeed Mohammadi.
Funding acquisition: Afroz Karimi.
Investigation: Ali A. Asadi-Pooya, Sara Nasiri.
Methodology: Hossein Bayat, Mina Shahisavandi.
Project administration: Ali A. Asadi-Pooya.
Resources: Meshkat Nemati.
Software: Zahra Rahimian.
Supervision: Ali A. Asadi-Pooya.
Validation: Hossein Bayat, Mina Shahisavandi.
Visualization: Ali Akbari, Amir Emami.
Writing–original draft: Ali A. Asadi-Pooya.
Writing–review & editing: Ali A. Asadi-Pooya.

**Competing Interests**

None of the authors has any conflict of interests.

**Ethical Approval**

Ethical Committee of Shiraz University of Medical Sciences, Shiraz, Iran, has approved this study (IR.SUMS.Rec.1399.022; Ethical Approval). None of the authors has any conflict of interests. Writing–original draft: Ali A. Asadi-Pooya. Writing–review & editing: Ali A. Asadi-Pooya.

References


