Impacts on post-COVID-19 sequelae: A Systematic review

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ABSTRACT

Concerns on whether or not coronavirus disease 2019 (COVID-19) can cause long-term impact are rising since many aspects of the disease are still under investigation. This systematic review was carried out to recognize the post-COVID-19 sequelae infection in various body systems and to analyze the comorbidities in survivors who suffered long-term impacts. The choice of words used to search is “post-COVID-19,” “COVID-19,” and “SARS-CoV-2 infection.” A total of 1,282 articles were extracted. Reports suggested that a wide range of sequelae were faced by the survivors which affected various systems, mainly the respiratory, gastrointestinal, nervous, cardiovascular, and musculoskeletal systems, while rarely affect other systems such as the endocrine, vascular, renal, and urogenital systems. Comorbidities are involved in determining the harshness of sequelae and the persistence of symptoms of post-severe acute respiratory syndrome coronavirus-2 infection. COVID-19 survivors may present with different symptoms and conditions that vary from mild symptoms to severe and rare conditions. It is crucial to understand the sequelae of post-COVID-19 for prevention and help to establish pandemic control strategies and rehabilitation needs.

INTRODUCTION

A cluster of cases with pneumonia caused by an unspecified etiology was detected in Wuhan, Hubei Province, China, in December 2019 (Fiani et al., 2020; Guan et al., 2020). The pathogen was then identified as a novel enveloped virus, the positive-stranded beta coronavirus that was first named the 2019-novel coronavirus as per the World Health Organization (WHO). Later, the Coronavirus Study Group at its International Committee came forward to name it severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2). Finally, the WHO officially called the disease coronavirus disease 2019 (COVID-19) (Guo et al., 2020). In March 2020, after its global spread, the WHO declared COVID-19 a pandemic because of its rapid transmission rate, increasing mortality rate, and limited treatment options (Fiani et al., 2020; Halpin et al., 2020). As of October 23, 2020, there have been 41,712,300 laboratory-confirmed cases detected worldwide, with at least 1,137,400 deaths reported. The number of COVID-19 cases is exponentially increasing with a low to moderate mortality rate internationally (Fiani et al., 2020). Now, seven human coronaviruses have been identified, among which are the two most recognized coronaviruses, SARS-CoV and the Middle East respiratory syndrome-CoV (MERS-CoV), both of which had outbreaks in 2003 and 2012, respectively (Chang et al., 2020).

SARS-CoV-2 and SARS have similar signs and symptoms and structural homology leading many scientists to assume that a person infected with SARS-CoV-2 can have abnormal symptoms like SARS (Vitti-Ruela et al., 2020). Several studies highlighted that long-term sequelae were observed in those who survived SARS and other viral infections such as infectious mononucleosis and measles (Yelin et al., 2020). Therefore, concerns on whether or not COVID-19 can cause long-term impact are rising since any aspect of the disease is still under investigation. Several studies that have been done found some possible sequelae for COVID-19: pulmonary sequelae, musculoskeletal sequelae, neurological sequelae, cardiac sequelae, and cardiovascular sequelae (Fiani et al., 2020; Halpin et al., 2020).

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sequelae, and psychological sequelae (Biehl and Sese, 2020; Disser et al., 2020; Fiani et al., 2020; Frija-Masson et al., 2020; Mitrani et al., 2020). It is from the WHO that a person with COVID-19 usually takes from 2 to 6 weeks to recover, but for some people, symptoms may reoccur in weeks or months, although they are not infectious to others during this period. Those symptoms include cough, congestion in-breath, loss of taste and smell, abdominal pain, headache, and diarrhea (Tenforde et al., 2020). Some of the risk factors attributed to the long-term symptoms are older age, high blood pressure, obesity, and mental health conditions (Sudre et al., 2020).

Although there are many studies to further understand the nature of this disease, there is still much with very limited information, especially when it comes to sequelae of post-COVID-19 infection. Hence, with all the evidence provided through researches, we would like to compile all the information on post-COVID-19 infection sequelae with the following questions for this systematic review.

1. Do all COVID-19 cases cause post-COVID-19 sequelae?
2. What are the sequelae of post-COVID-19?
3. What are the systems involved in post-COVID-19 sequelae?
4. What are the comorbidities that post-COVID-19 patients have?

METHODS

Search strategy

We searched the literature in October 2020 to find the published articles that analyzed the post-COVID-19 sequelae. A systematic literature search using Cochrane Library, PubMed, ProQuest, and Springer on published articles reported the post-COVID-19 sequelae. The search was under the preferred reporting items for systematic reviews and meta-analyses (PRISMA) 2009 criteria checklist. The search terms used were “COVID-19” or “SARS-CoV-2 infection” or “post-COVID-19 consequences” or “sequelae” or “survivor.” The search terms used in this review were broad to enclose all possibilities for various studies applied. The combination of keywords from the four databases mentioned identified 414 references, 226 references, 423 references, and 219 references, respectively. Microsoft Excel was used to create a library of references collected from the databases. A total of 1,282 references were downloaded and exported to Microsoft Excel. 31 duplicates were detected and removed. Some searches were found through cross-referencing the published papers and taken outside the mentioned databases. We followed nil restrictions with the date of publication.

Inclusion and exclusion criteria

Inclusion criteria:
1. Full-text articles.
2. English language articles.
3. Articles from the mentioned databases.
4. Article on post-COVID-19 sequelae in adults.

Exclusion criteria:
1. Articles on post-COVID-19 sequelae in children.
2. Articles on post-COVID-19 sequelae in pregnant mothers.

3. Animal studies.

Primary identification, eligibility criteria, and study selection

Articles with titles and abstracts which did not fit our main scope were eliminated. Any articles that were not full-text were excluded. After all full-text articles were gathered, the eligibility of each article was further assessed according to the criteria stated earlier. Such process of study selection was done separately with the workload divided equally between four researchers. The title with abstract followed by the full-text review was carried out through four independent researchers, and the end number of articles collected by the researchers was added up during the final process of data selection. Any differences between the researchers were discussed thoroughly to reach a mutual agreement and were reviewed by a fifth reviewer. The final analysis of the total articles combined had to be relevant and answer the research questions as stated before. After excluding the full-text article irrelevant to the topic of studies, 36 full-text English articles were selected for the qualitative analysis. In this systematic review, other than clinical trials, we also included clinical and narrative reviews together with case reports and letters to the editor. Data from relevant studies were extracted, organized, and summarized according to the research questions.

RESULTS

Study characteristics

The flowchart for the article searches and the screening process of this study is shown in Figure 1. Of 1,328 studies retrieved from the databases, 1,251 duplicates were removed, and 130 unique articles were selected. After further curation and application of the exclusion criteria, 94 articles were excluded. Finally, 36 relevant studies were selected.

Presence of post-COVID-19 infection sequelae

Prevalence of patients with post-COVID-19 sequelae was found in 11 articles out of 36 involved in the study. In total, 1,520 survivors were included in this study, from whom 877 (57.7%) survivors were seen having post-COVID-19 sequelae. Most studies reported more than 50% in the prevalence of post-COVID-19 sequelae in survivors, as shown in Table 1. Only one study did not report any comorbidities in their patients (Chang and Park, 2020), whereas the rest of the studies reported comorbidities in patients with heart disease, hypertension, lung disease, and diabetes mellitus being recorded in almost all articles. Only two studies did not report any lung disease among their patients (Huang et al., 2020a, 2020b; Zhao et al., 2020).

Systems involved and consequences in COVID-19 survivors

From 36 articles included in the study, 11 articles reported post-COVID-19 sequelae among the survivors. Four articles recorded sequelae involving the respiratory system: with an impaired capacity of diffusion and ventilator defects (Mo et al., 2020), with pulmonary fibrosis (Zhao et al., 2020), with vocal fold paresis and paralysis (Helding et al., 2020), and with pulmonary fibrosis (Kamal et al., 2020). Nervous system involvement was found in studies (Chang and Park, 2020; Chaumont et al., 2020; Lahiri and Ardila, 2020), all of which reported obsessive-compulsive disorder and stroke, cognitive
Figure 1. The PRISMA flow diagram.

Table 1. The prevalence of patients with post-COVID-19 sequelae.

| Author                        | Prevalence of patients with post-COVID-19 sequelae | Age (median), year | Comorbidities                                                                 |
|-------------------------------|-----------------------------------------------------|--------------------|--------------------------------------------------------------------------------|
| (Carfi et al., 2020)          | 125 (87.4%) out of 143 survivors                    | 51.5               | Hypertension (35%)                                                             |
|                               |                                                     |                    | Thyroid disease (18.2%)                                                        |
|                               |                                                     |                    | chronic obstructive pulmonary disease (COPD) (9.1%)                            |
|                               |                                                     |                    | Diabetes (7%)                                                                  |
|                               |                                                     |                    | Chronic heart disease (4.9%)                                                    |
|                               |                                                     |                    | Active cancer (3.5%)                                                            |
|                               |                                                     |                    | Atrial fibrillation (2.8%)                                                      |
|                               |                                                     |                    | Heart failure (2.8%)                                                            |
|                               |                                                     |                    | Kidney failure (2.1%)                                                           |
|                               |                                                     |                    | Stroke (1.4%)                                                                  |
| (Xiong et al., 2020)          | 267 (49.6%) out of 538 survivors                    | 52.0               | Hypertension (15.2%)                                                           |
|                               |                                                     |                    | Diabetes mellitus (7.4%)                                                        |
|                               |                                                     |                    | COPD (4.1%)                                                                     |
|                               |                                                     |                    | Coronary heart disease (3.3%)                                                   |
|                               |                                                     |                    | Chronic kidney disease (2.2%)                                                   |
|                               |                                                     |                    | Carcinoma (0.9%)                                                               |

Continued
| Author                     | Prevalence of patients with post-COVID-19 sequelae | Age (median), year | Comorbidities                                                                 |
|----------------------------|---------------------------------------------------|--------------------|-------------------------------------------------------------------------------|
| (Chang and Park, 2020)     | 13 (20.3%) out of 64 survivors                    | 57.8               | —                                                                             |
| Korea                      |                                                   |                    | Hypertension (23.1%)                                                          |
|                            |                                                   |                    | Coronary artery disease (7.7%)                                                  |
|                            |                                                   |                    | Asthma                                                                         |
|                            |                                                   |                    | Diabetes                                                                        |
|                            |                                                   |                    | Dementia                                                                        |
|                            |                                                   |                    | Stroke                                                                          |
|                            |                                                   |                    | Atrial fibrillation                                                            |
| (Fumagalli et al., 2020)   | 10 (76.9%) out of 13 survivors                    | 57.8               | BMI > 30 kg/m² (29%)                                                           |
| Italy                      |                                                   |                    | Cardiovascular disorder (26.8%)                                                 |
|                            |                                                   |                    | Pulmonary disorder (15.2%)                                                      |
|                            |                                                   |                    | Diabetes mellitus (10.9%)                                                       |
| (Vaira et al., 2020)       | 10 (7.2%) out of 138 survivors                    | 51.2               | Hypertension (23.6%)                                                           |
| Italy                      |                                                   |                    | Diabetes (8.2%)                                                                |
|                            |                                                   |                    | Liver disease (5.5%)                                                            |
|                            |                                                   |                    | Lung disease (2.7%)                                                             |
|                            |                                                   |                    | Heart disease (2.7%)                                                            |
|                            |                                                   |                    | Cerebrovascular disease (2.7%)                                                   |
|                            |                                                   |                    | Kidney disease (1.8%)                                                           |
|                            |                                                   |                    | Solid tumor (0.9%)                                                              |
| (Mo et al., 2020)          | 51 (47.2%) out of 110 survivors                   | 49.1               | Diabetes (26%)                                                                 |
| China                      |                                                   |                    | Pulmonary disease (8%)                                                          |
|                            |                                                   |                    | Myocardial infarction (8%)                                                      |
| (Wong et al., 2020)        | 59 (75.6%) out of 78 survivors                    | 62                 | Hypertension (8%)                                                              |
| Canada                     |                                                   |                    | Diabetes (26%)                                                                 |
|                            |                                                   |                    | Pulmonary disease (8%)                                                          |
|                            |                                                   |                    | Myocardial infarction (8%)                                                      |
| (Huang et al., 2020a)      | 15 (58%) out of 26 survivors                      | 38                 | Hypertension (10.9%)                                                           |
| China                      |                                                   |                    | Diabetes mellitus (3.64%)                                                       |
|                            |                                                   |                    | Cardiovascular disease (3.64%)                                                   |
| (Zhao et al., 2020)        | 39 (70.9%) out of 55 survivors                    | 47.7               | Hypertension (7.7%)                                                            |
| China                      |                                                   |                    | Diabetes (5.2%)                                                                |
|                            |                                                   |                    | Rheumatoid arthritis (1.4%)                                                     |
|                            |                                                   |                    | Dyslipidemia (1.4%)                                                             |
|                            |                                                   |                    | Hypothyroidism (1%)                                                             |
|                            |                                                   |                    | Asthma (1%)                                                                     |
|                            |                                                   |                    | Peptic ulcer (0.7%)                                                             |
|                            |                                                   |                    | Arrhythmia (0.7%)                                                               |
|                            |                                                   |                    | Other conditions (10.2%)                                                        |
| (Kamal et al., 2021)       | 256 (89.2%) out of 287 survivors                  | 32.3               | Hypertension (1.5%)                                                            |
| Egypt                      |                                                   |                    | Coronary heart disease (5.9%)                                                   |
|                            |                                                   |                    | Diabetes mellitus (4.4%)                                                        |
|                            |                                                   |                    | Lacunar infarction (2.9%)                                                       |
|                            |                                                   |                    | Pulmonary tuberculosis (5.9%)                                                    |
|                            |                                                   |                    | Emphysema (4.4%)                                                                |
|                            |                                                   |                    | Asthma (1.5%)                                                                   |
|                            |                                                   |                    | Myocarditis (1.5%)                                                              |
| (Liu et al., 2020)         | 32 (47.1%) out of 68 survivors                    | 44.3               | Coronary heart disease (5.9%)                                                   |
| China                      |                                                   |                    | Diabetes mellitus (4.4%)                                                        |
|                            |                                                   |                    | Pulmonary tuberculosis (5.9%)                                                    |
|                            |                                                   |                    | Emphysema (4.4%)                                                                |
|                            |                                                   |                    | Asthma (1.5%)                                                                   |
impairment and premature onset of dementia, posttraumatic stress disorder, memory deficit, and frontal syndrome, respectively, as shown in Table 2.

**Symptoms in COVID-19 survivors**

**Respiratory symptoms**

Table 3 showed that seven out of eight articles recorded more than three respiratory symptoms experienced by COVID-19 survivors, except for Wong et al. (2020) that showed only two respiratory symptoms, which were cough (23%) and dyspnea (50%). Goertz et al. (2020) and Carfi et al. (2020) recorded that all five respiratory symptoms were present in survivors. Among the five symptoms, the prevalence of dyspnea in an article by Goertz et al. (2020) was the highest (71.0%).

**Cardiovascular-related symptoms**

Based on Table 4, Xiong et al. (2020) recorded that all four symptoms were present in COVID-19 survivors. Among the four symptoms, chest tightness was the highest.

**Psychological symptoms**

As shown in Table 5, 6 out of 36 articles in the study mentioned survivors of COVID-19 were having psychological symptoms during some period after becoming free from the virus. Two articles stated that more than three psychological symptoms were experienced by the survivors. Meanwhile, only articles by Xiong et al. (2020) stated that the survivors experienced somnipathy which is 17.7% of the population study. Among the six articles, anxiety was the highest symptoms percentage reported compared to the other symptoms.

**Neurological symptoms**

Of the 36 articles, 7 articles mentioned the prevalence of neurological symptoms in COVID-19 survivors occurring around 3 countries. Headache was the highest neurological symptom reported, as shown in Table 6.

**Musculoskeletal symptoms**

As shown in Table 7, 6 articles from a total of 36 showed the prevalence of musculoskeletal symptoms in survivors of COVID-19. The most important symptom reported in all the articles was myalgia. Meanwhile, Goertz et al. (2020) reported having three musculoskeletal symptoms, which are myalgia, arthralgia, and also skin rashes, with a percentage of 2% among the population study.

**Gastrointestinal symptoms**

Table 8 shows a total of four articles indicating the prevalence of gastrointestinal symptoms experienced by COVID-19 survivors. Survivors experienced three symptoms such as diarrhea, nausea, and vomiting. All the articles revealed survivors experienced diarrhea post-COVID-19. On the contrary, only one article found that survivors experienced abdominal pain with a prevalence of 3% (Daher et al., 2020).

| Author                | Systems involved          | Sequelae                                      |
|-----------------------|---------------------------|------------------------------------------------|
| (Mo et al., 2020) China | Respiratory system        | Impairment of diffusion capacity              |
|                       |                           | Restrictive ventilatory defects               |
| (Zhao et al., 2020) China | Respiratory system        | Pulmonary fibrosis                            |
| (Helding et al., 2020) United States | Respiratory system        | Vocal fold paresis and paralysis              |
| (Kamal et al., 2021) Egypt | Nervous system            | Obsessive-compulsive disorder                 |
|                       |                           | Stroke                                        |
|                       | Respiratory system        | Pulmonary fibrosis                            |
|                       | Endocrine system          | Diabetes mellitus                             |
|                       | Renal system              | Renal failure                                 |
| Cardiovascular system | Cardiovascular system     | Myocarditis                                   |
|                       |                           | Arrhythmia                                    |
| (Huang et al., 2020a) China | Cardiovascular system     | Myocardial edema                              |
|                       |                           | Myocardial fibrosis                           |
|                       |                           | Decreased right ventricle function            |
| (Lahiri and Ardila, 2020) Russia | Nervous system            | Cognitive impairment                          |
|                       |                           | Premature onset of dementia                   |
| (Chang and Park, 2020) Korea | Nervous system            | Posttraumatic stress disorder                 |
| (Chaumont et al., 2020) France | Nervous system            | Memory deficit                                |
|                       |                           | Frontal syndrome                              |
| (Savastano et al., 2020) Italy | Vascular system           | Microvascular retinal impairment              |
| (Carfi et al., 2020) Italy | Multisystem               | Sicca syndrome                                |
Other symptoms

Table 9 shows a total of six articles that reported other symptoms, which are loss of smell (anosmia) and taste (ageusia), loss of hair (alopecia), and problems related to the eyes in post-COVID-19 survivors. Carfi et al. (2020) and Goërtz et al. (2020) reported the survivors had experience with ageusia, anosmia, and...
eye problems, while Akter et al. (2020) and Xiong et al. (2020) reported the survivors experienced only alopecia.

Table 10 shows case reports reported on post-COVID-19 sequelae along with their age and comorbidities. Nine out of 10 articles (81.8%) revealed the nervous system was involved as a sequela of COVID-19, followed by the urogenital and respiratory systems with 1 article each (9.1%). Out of all the articles, only four studies reported patients with no comorbidities, while the remaining articles reported various comorbidities. The most prevalent comorbidities reported were diabetes mellitus, hypertension, and asthma (25%), followed by hypothyroidism (16.7%), and obesity, ischemic heart disease, cardiomyopathy, small fiber neuropathy, and orthostatic hypoperfusion syndrome (8.3%). The youngest patient reported to have a sequela was 21 years old, and the oldest was 76 years old. Both of them involved the nervous system with encephalomyelitis and posthypoxic myoclonus, respectively.

**DISCUSSION**

Though there was limited information on COVID-19 disease and its sequelae, reports on post-COVID-19 sequelae have emerged. This study identified 36 relevant articles, although we cannot rule out that there were other reports that our research may have missed, from which we can conclude that there was indeed the presence of post-COVID-19 sequelae where the systems involved differ between each patient although not all patients who survived COVID-19 experience persistent symptoms nor develop sequelae.

From our study, we found that 57.7% of survivors had developed post-COVID-19 sequelae. Kamal et al. (2021) reported the highest prevalence of post-COVID-19 sequelae, 89.2%, while Vaira et al. (2020) had the lowest, 7.2%. 11 case reports showed 12 patients who had developed post-COVID-19 sequelae, while the rest of the studies reported on different symptoms developing post-COVID-19. Researchers suggested the range of symptoms may develop from acute viral infection/after some time after infection. During other coronaviruses infection outbreaks, such as the SARS-CoV epidemic in 2003 and MERS-CoV in 2012, sequelae were reported through several studies (Chan et al., 2003; Park et al., 2018; Troyer et al., 2020). A few studies also found that the most common symptoms patients may have post-COVID-19 include fatigue, dyspnea, cough, arthralgia, and chest pain (Banda et al., 2020; Carfi et al., 2020; Keefe and Cellai, 2020) with more serious complications such as myocardial inflammation, pulmonary function abnormalities, acute kidney injury, memory impairment, depression, and anxiety (Banda et al., 2020; Huang et al., 2020b; Peleg et al., 2020; Puntmann et al., 2020).

There was a limited amount of research that emphasized the sequelae of COVID-19 to our knowledge (Mo et al., 2020). The previous study stated that about 90% of COVID-19 survivors along with post-COVID-19 sequelae also have other symptoms such as pulmonary fibrosis, stroke, and renal failure, which may vary from a mild to severe scale (Kamal et al., 2021). From this research, we found that many sequelae arise post-COVID-19 in
Table 8. Prevalence of gastrointestinal symptoms in COVID-19 survivors.

| Author | Diarrhea | Nausea | Vomiting | Abdominal pain |
|--------|----------|--------|----------|---------------|
| (Goertz et al., 2020) | Present (10%) | Present (12%) | Present | — |
| (Daher et al., 2020) | Present | Present (6%) | — | Present |
| Germany | (9%) | — | — | (3%) |
| (Carfi et al., 2020) | Present | — | — | — |
| Italy | (2%) | — | — | — |
| (Liu et al., 2020) | Present (7.4%) | Present (5.9%) | Present (5.9%) | — |
| China | — | — | — | — |

Table 9. Prevalence of other symptoms in COVID-19 survivors.

| Author | Ageusia | Anosmia | Eye problems | Alopecia |
|--------|---------|---------|--------------|----------|
| (Goertz et al., 2020) | Present (11%) | Present (13%) | Present (12%) | — |
| Netherlands and Belgium | — | — | — | Present (8.8%) |
| (Akter et al., 2020) | — | — | — | — |
| Bangladesh | — | — | — | — |
| (Daher et al., 2020) | Present (9%) | Present (12%) | — | — |
| Germany | — | — | — | Present (28.6%) |
| (Xiong et al., 2020) | — | — | — | — |
| China | — | — | — | — |
| (Carfi et al., 2020) | Present (13%) | Present (17%) | Present (13%) | — |
| Italy | — | — | Present (4.4%) | — |
| (Liu et al., 2020) | — | — | — | — |
| China | — | — | — | — |

different systems. Most of our findings showed that COVID-19 survivors had lung-related sequelae. Previous studies showed pneumonia in survivors with coronavirus resulted in damaged lungs. The common sequelae were impaired lung function, which may last for months or years (Mo et al., 2020). We also discovered that survivors experienced vocal fold paresis and paralysis, which was caused by a short period of intubation and injury to the vagus nerve (Helding et al., 2020). Other than that, cardiovascular sequelae such as myocarditis, arrhythmia, and myocardial edema were recorded in two articles. In a recent study, myocardial edema was the major image manifestation noted. Two mechanisms are probably involved in post-COVID-19 myocardial sequelae. First, myocardial inflammation can be caused directly through the angiotensin-converting enzyme 2 (ACE2) receptor binding domain of spike protein-coding S, which is similar to SARS-CoV-2 and SARS-CoV. Second, cytokine storm by the immune response may cause indirect injury (Kamal et al., 2021).

COVID-19 survivors could develop neurological sequelae, and acute respiratory distress syndrome (ARDS) was the main pulmonary manifestation. It was found that there was sufficient evidence where a significant percentage of ARDS survivors also have cognitive impairment in the long term. There was a decline in higher brain functions following ARDS due to several factors. One of the notable factors was the blood–brain barrier acute injury responsible for cognitive impairment after recovering ARDS in COVID-19 survivors (Lahiri and Ardila, 2020).

From 36 articles included in the study, a total of 22 articles reported the system involved in post-COVID-19 sequelae among the survivors. The most affected system reported in 13 articles on post-COVID-19 sequelae was the nervous system. Nervous system involvement was found in Chang and Park (2020); Chaumont et al. (2020); Kamal et al. (2021); and Lahiri and Ardila (2020), all of which reported obsessive-compulsive disorder and stroke, cognitive impairment and premature onset of dementia, posttraumatic stress disorder, memory deficit and frontal syndrome, respectively. The uncertainties of the etiology of these neurological symptoms should be further assessed. Some of the symptoms recorded are unclear, especially lack of consciousness, headache, and dizziness. These symptoms may be developed because of respiratory failure with extreme hypoxia. The day immune condition triggered by the infection, especially the abnormally high inflammation known as the cytokine storm, could result in other symptoms. Cytokine storms with acute neurovascular pathologies were seen in COVID-19 patients without vascular risk factors. Meanwhile, four articles recorded sequelae involving the respiratory system (Mo et al., 2020), pulmonary fibrosis (Zhao et al., 2020), vocal fold paresis and paralysis (Helding et al., 2020), and pulmonary fibrosis (Kamal et al., 2021). Infection with SARS-CoV-2 causes fibroproliferation that brings massive damage to the alveolar epithelial and endothelial cells. This may impose chronic alveolar remodeling and result in lung fibrosis or pulmonary hypertension (Frija-Masson et al., 2020). Infection with SARS-CoV-2 causes a strong and seemingly uncontrolled inflammatory
The long-term effects of COVID-19 might be due to persistent viral infection with low levels of viral shedding, delayed immune reaction, latency, or the presence of virus in reservoir organs or tissues (Jamiolkowski et al., 2020). SARS-CoV-2 also appears to be able to reinfect (To et al., 2021) and have the potential to precipitate new diseases (Kamal et al., 2021). Researches indicating the presence of sequelae even in asymptomatic cases suggest that mass screening and treatment may be needed without any biases. These recent findings urge further and in-depth research in measuring the symptom duration, fluctuation, overall functionality, and quality of life of survivors in comparison to the preinfection state (Perego et al., 2020).

**CONCLUSION**

Based on this systematic review, there was indeed presence of post-COVID-19 sequelae where a wide range of systems are involved, which differ between each patient. Comorbidities play a role in determining the severity of sequelae and the persistence of symptoms after SARS-CoV-2 infection. However, our review also suggests that those without any preexisting illness may also develop some degree of sequelae. COVID-19 survivors may present with different symptoms and conditions that vary from mild symptoms to severe and rare conditions. It is crucial to understand the sequelae of post-COVID-19 for prevention and help to establish pandemic control strategies and rehabilitation needs.

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**Table 10. Case report on post-COVID-19 sequelae.**

| Author | Age, year | Comorbidities | System involved | Sequelae |
|--------|-----------|---------------|-----------------|----------|
| (Sarma and Bilello, 2020) United States | 28 | Hypothyroidism | Nervous system | Transverse myelitis |
| (Lim et al., 2020) United Kingdom | 55 | None | Nervous system | Dysexecutive syndrome |
| (Shoar et al., 2020) Iran | 44 | None | Urogenital system | Sexual dysfunction (anorgasmia) |
| (Zoghi et al., 2020) Iran | 31 | Mild exertional asthma | Nervous system | Encephalomyelitis |
| (Baghbanian and Namazi, 2020) Iran | 53 | Diabetes mellitus, hypertension, ischemic heart disease | Nervous system | Longitudinally extensive transverse myelitis |
| (Novak, 2020) United States | 64 | Hypothyroidism, small fiber neuropathy, orthostatic hypoperfusion syndrome | Central nervous system | Exacerbation of orthostatic cerebral hypoperfusion syndrome and small fiber neuropathy |
| (Carroll et al., 2020) United States | 69 | Diabetes | Central nervous system | Refractory status epilepticus |
| (Koumpa et al., 2020) United Kingdom | 45 | Asthma | Nervous system | Sudden onset sensorineural hearing loss |
| (Le et al., 2020) United States | 41 | Obese, cardiomyopathy, diabetes mellitus type 2, hypertension | Nervous system | Brachial plexopathies |
| (Ros-Castelló et al., 2020) Spain | 72 | Hypertension and asthma | Nervous system | Posthypoxic myoclonus |
Clinical characteristics of Post-COVID-19 inflammatory syndrome

Residual clinical damage

Follow up of Persistent symptoms 3 months after a SARS-CoV-2 infection:

Mixed central and peripheral nervous system disorders in severe SARS-CoV-2 infection. J Neurol, 2020; 287(10):1030–9.

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