

## “LONG COVID”: an insight

M.S. AHMAD<sup>1</sup>, R.A. SHAIK<sup>1</sup>, R.K. AHMAD<sup>2</sup>, M. YUSUF<sup>3</sup>, M. KHAN<sup>3</sup>,  
A.B. ALMUTAIRI<sup>4</sup>, W.K.Z. ALGHUYAYTHAT<sup>4</sup>, S.B. ALMUTAIRI<sup>4</sup>

<sup>1</sup>Department of Community Medicine/Public Health, College of Medicine, Majmaah University, Al Majmaah, Saudi Arabia

<sup>2</sup>Department of Applied Medical Science, Buraydah Private Colleges, Buraydah, Saudi Arabia

<sup>3</sup>Department of Clinical Pharmacy, College of Pharmacy, Taif University, Taif, Saudi Arabia

<sup>4</sup>College of Medicine, Majmaah University, Al Majmaah, Saudi Arabia

**Abstract.** – We aimed this systematic review to analyze and review the currently available published literature related to long COVID, understanding its pattern, and predicting the long-term effects on survivors. We thoroughly searched the databases for relevant articles till May 2021. The research articles that met our inclusion and exclusion criteria were assessed and reviewed by two independent researchers. After preliminary screening of the identified articles through title and abstract, 249 were selected. Consequently, 167 full-text articles were assessed and reviewed based on our inclusion criteria and thus 20 articles were regarded as eligible and analyzed in the present analysis. All the studies included adult population aged between 18 and above 60 years. The median length of hospital stay of the COVID-19 patients during the acute infection phase ranged from 8 days to 17 days. The most common prevalent long-term symptoms in COVID-19 patients included persistent fatigue and dyspnea in almost all of the studies. Other reported common symptoms included: shortness of breath, cough, joint pain, chest pain or tightness, headache, loss of smell/taste, sore throat, diarrhea, loss of memory, depression, anxiety. Associated cardiovascular events included arrhythmias, palpitations and hypotension, increased HR, venous thromboembolic diseases, myocarditis, and acute/decompensated heart failure as well. Among neurological manifestations headache, peripheral neuropathy symptoms, memory issues, concentration, and sleep disorders were most commonly observed with varying frequencies. Mental health issues affecting mental abilities, mood fluctuations namely anxiety and depression, and sleep disorders were commonly seen. Further, diarrhea, vomiting, digestive disorders, and Loss of appetite or weight loss are common gastrointestinal manifestations. Therefore, appropriate clinical evaluation is required in long COVID cases which in turn may help us to iden-

tify the risk factors, etiology, and to my help, we treat them early with appropriate management strategies.

*Key Words:*

Long COVID, Long-term COVID-19 effects, Long haulers, Post-COVID syndrome.

### Introduction

In present times, COVID-19 has emerged to be a major pandemic, causing an unparalleled challenge and a constant threat to the human population worldwide with increased morbidity and mortality. The causative agent behind this deadly disease is the novel severe acute respiratory syndrome (SARS) coronavirus 2 (SARS-CoV-2)<sup>1</sup>.

Once exposed, the incubation period of this disease is about 4 to 5 days. WHO reported that the majority of the positive COVID-19 cases (about 80-85%) clinically manifest as a mild or asymptomatic form and therefore may resolve completely within two weeks without any complications mimicking the seasonal flu. The presenting symptoms include fever, throat pain, cough, headache, muscle or body aches, loss of taste or smell, and diarrhea<sup>2</sup>. Whereas, in about 10-15% of cases this infection takes a severe turn and might last till six weeks. Hospitalization and oxygen supplementation might be required in such cases. Only 5% of the affected population presents with the critical illness, affecting lungs and multi-organs, and hereby necessitates ICU admissions and mechanical ventilation<sup>3</sup>.

Although the majority of the positive COVID-19 cases completely recover within 3-4 weeks after

onset of infection, in some patient's prolonged or recurrent symptoms can be seen even after weeks or months post COVID-19 recovery. To date, no recognized term has been given to such long-lasting sequelae of COVID-19 during a post-recovery phase. Various authors have used different names like "long COVID-19", "long haulers", "Long-term COVID-19 effects", "Persistent COVID-19 Symptoms", and "Post COVID-19 syndrome".

In the present systematic analysis, we agreed to use the term "Long COVID" to describe the long-lasting effects of COVID-19. "Long COVID" may clinically present with one or many symptoms of the acute phase infection, however, the appearance of some new symptoms might also be noticed. It's been noticed that usually, patients with post-COVID syndrome have a negative PCR report depicting that although the clinical symptoms might persist the microbial viral load has decreased, and the patient is heading towards clinical recovery<sup>4</sup>.

Long COVID can be further categorized into two stages depending on the duration of prolonged symptoms: First is the 'post-acute COVID' which includes those cases in which symptoms prolong >3 weeks but are < 12 weeks. The second one is the 'chronic COVID' in which symptoms prolong >12 weeks<sup>5</sup>. Although the pathophysiology and etiology of Long-COVID-19 are uncertain, still factors from the acute phase like endotheliopathy, antigen-antibody reactions, and aberrant immune response might elicit secondary responses in the body.

Although worldwide continuous efforts are being directed towards timely diagnosis, explore effective treatment modalities and means of prevention of COVID-19, still, the mystery of long-lasting effects observed in patients with "Long COVID-19" are yet to be explored. Therefore, the primary aim of this systematic review was to analyze and review the currently available published literature related to long COVID, understanding its pattern and predicting the long-term effects on survivors.

## **Materials and Methods**

### ***Study Protocol***

This extensive systematic review was carried out according to the recommendations structured by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

### ***Information Sources and Search Methodology***

We thoroughly searched the following databases: PubMed, Google Scholar, Medline, Web of Science, Scopus and Cochrane Library, Research Gate, EMBASE, and references of the relevant articles; with a rationale to identify research papers on the long-term effects of COVID-19. This anticipated search was accomplished by two independent reviewers, keeping in view the structured format of this systematic review. Our search strategy integrated the terms "COVID-19", "long COVID-19", "post-COVID-19 syndrome", "long-term symptoms", "persistent symptoms" and "chronic COVID syndrome".

### ***Eligibility Criteria***

In the extensive review, PICO model criteria were taken into consideration which included: (1) literature including cases presenting with long-term COVID-19 effects as the Population under study, (2) interventions of this review were studies that primarily focused on the evaluation of long-term COVID-19 symptoms with reported follow-ups (minimum follow up time of 14 days) as well, (3) for comparisons we included studies using a control group or even without it (4) outcome measures included those studies which enumerated and discussed long-term COVID-19 effects. Based on the above-mentioned criteria, we reviewed all the studies and published data till May 2021. The literature published in the English language from academic peer-reviewed journals and meeting the PICO criteria were included.

### ***Exclusion Criteria***

Studies published in a language other than English.

Unpublished reports, case reports, study abstracts, duplicate reporting, coronavirus strains other than COVID-19, and studies that only hypothesize post-COVID-19 sequelae were excluded.

### ***Study Design and Data Collection***

This systematic review lists all observational studies, case-control studies, prospective and retrospective cohort studies. The results of the preliminary search of all the published research were initially screened through their abstracts and title. The research articles that met our inclusion and exclusion criteria were assessed and reviewed by two independent researchers.

The following information was extracted from each included study: authors, year of study, study

setting, participants and their profile, length of hospital stay, ICU and mechanical ventilation, mean follow-up time, and clinical findings. This being a rapid review, therefore the risk of bias associated with the included studies was not assessed. Ethical clearance from the institutional ethical committee was not required as all the data extracted was from already published studies and no patients or the public were directly interviewed or involved in the present research. We did not receive any outside funding for the execution of this study.

## Results

### Study Selection

During the initial data search, we identified 856 records using database search and 32 additional records from some additional sources. After preliminary screening of the identified articles through title and abstract, 249 were selected. Among them, 167 articles were kept after the removal of duplicate ones. Consequently, 167 full-text articles were assessed and reviewed based on our inclusion criteria and thus 20 articles were regarded as eligible and analyzed in the present analysis. Figure 1 represents the criteria for study selection presented in form of a PRISMA flow chart.

### Study Characteristics

The majority of the studies evaluated specific post-COVID 19 infection symptoms and quality of life of these patients through means of telephonic conversations, follow-ups interviews, standard questionnaires, and pulmonary function tests, patient-related outcome measurement information system, standard scoring methods, quality of life assessment parameters, chest CT, MRI, and Spirometry. These studies included data from different parts of the developed countries of the world like the UK/Europe, China, Italy, the Netherlands, France, Canada, and Germany and Europe. We did not find any such study, meeting our inclusion criteria from developing countries like India. The follow-up time observed ranged from a minimum of 2 weeks to a maximum of 6 months. The majority of the studies included mild, moderate, and severe active COVID-19 patients.

All the studies included adult population aged between 18 and above 60 years. Females were observed to be affected more in 10 reviewed stud-

ies<sup>6,8,9,11,12,16,18,19,22,23</sup>, while males predominated in other 10 studies<sup>7,10,13,14,15,17,20,21,24,25</sup>. The median length of hospital stay of the COVID-19 patients during the acute infection phase ranged from 8 days to 17 days (Table I).

### Prevalent Long-Term Effects of COVID 19 Infection

The most common prevalent long-term symptoms in COVID-19 patients included persistent fatigue and dyspnea in almost all of the studies<sup>6,7,8,9,10,11,12,13,18,20,21,22,24,25</sup>. Other reported common symptoms included: shortness of breath, cough, joint pain, chest pain or tightness, headache, loss of smell/taste, sore throat, diarrhea, loss of memory, depression, anxiety. Furthermore, some symptoms observed less frequently were insomnia, palpitations, anorexia, tingling fingertips, skin rashes, and hair loss. In the studied cases, we observed that at least one or more than one symptom was reported, and these reported long-term symptoms were observed in mild and moderate, and severe types of the disease. Although patients with severe illness presented with a higher frequency of these symptoms. Carvalho-Schneider et al<sup>23</sup> mentioned that in their study cohort with mild/moderate cases of COVID-19 patients, approximately 66% presented a minimum of one such symptom. According to an analysis by Lopez-Leon et al<sup>26</sup>, the five commonest post-COVID 19 presentations were: fatigue (58%), headache (44%), attention disorder (27%), hair loss (25%), and dyspnea (24%). (Table II)

In one of the included prospective observational studies, Sudre et al<sup>7</sup> suggested two key models related to clinical symptoms in long COVID cases. The first pattern included clinical symptoms like fatigue and headache along with upper respiratory tract-related symptoms like shortness of breath and cough. The second pattern was related to multi-organ symptoms which manifested as fever and in some cases as gastroenterological events (Table I).

Wang et al<sup>12</sup> revealed a consistent decline in the long COVID-19 symptoms during the 4 weeks follow up during the recovery phase, which included cough (9.16%), chest tightness (0.76%), dyspnea (1.53%), pharyngeal pain (1.53%) and nausea (0.76%). The persistent cough and dyspnea observed in the cohort after discharge were simply mild, causing no inconvenience. Nevertheless, unexpected short-lived fever during second-week follow-ups was seen in 11 patients from their cohort.

**Table I.** Demographic details of the included studies.

S.no	Authors	Year; Place	Type of Study	Number of Patients	Category of Patients	Mean Age	Gender	Mean/Median Length of Hospital Stay	Hospitalised	ICU Admissions	Ventilation
1	Carfi et al <sup>6</sup>	2020; Italy	Case series Observational	143	NA	56.5 years	53 (37%) females	13.5 (SD, 9.7) days;	NA	12.6%	15% noninvasive ventilation 5% invasive ventilation.
2	Sudre et al <sup>7</sup>	2020 UK	Prospective observational cohort study	4182	13.3% had symptoms lasting $\geq 28$ days, 4.5% for $>=8$ weeks 2.3% for $>=12$ weeks	42 Years	28.5% males	NA	13.9%	NA	NA
3	Zhao et al <sup>8</sup>	2020; China	Retrospective multi-center cohort study Chest CT images and pulmonary function	55	Moderate-severe	47.74 years	41.82% female	15.87 $\pm$ 6.84 days	NA	14 patients required additional oxygen therapy	NO
4	Liang et al <sup>9</sup>	2020; china	Prospectively observational study	67	91% : mild/general 9% : severe / critical	41.3 $\pm$ 13.8 years	55: females 21: males	17 days	NA	NA	NA
5	Garrigues et al <sup>10</sup>	2020; France	Prospectively observational study	120	NA	63.2 years	62.5 % males	11.2 days	NA	48	Mechanical ventilation for 14 cases; CPAP for 10 cases; High flow nasal cannula for 7 cases.

Table Continued

**Table 1. (Continued).** Demographic details of the included studies.

S.no	Authors	Year; Place	Type of Study	Number of Patients	Category of Patients	Mean Age	Gender	Mean/Median Length of Hospital Stay	Hospitalised	ICU Admissions	Ventilation
6	Goertz et al <sup>11</sup>	2020 Netherlands	Prospectively observational study	2113	NA	47 years	85% females	NA	112	15	NA
7	Wang et al <sup>12</sup>	2020; China	A prospective cohort study	131	Non-severe (N=62) Severe (N=69)	49 years	45.04% males 54.96% females	15 days	NA	NA	NA
8	Van den Borst et al <sup>13</sup>	2020; Netherlands	A prospective observational study	124	27 with mild 51 with moderate, 26 with severe 20 with critical disease	59 ± 14 years	60% male	8 days	NA	20 cases	NA
9	Hall et al <sup>14</sup>	2020; UK	Retrospective study	200	Moderate to severe cases	54.8±15	61.5 % males	NA	89	77 cases	NA
10	Shah et al <sup>15</sup>	2021; Canada	Prospective cohort study	60	NA	67 years	32% females 68% males	NA	All	NA	NA
11	Ladds et al <sup>16</sup>	2020;	Prospective cohort study	114	Moderate to severe cases	27-73 years	80 females	NA	8	NA	NA
12	Daher et al <sup>17</sup>	2021; Germany	Prospective study	33	Severe disease	64±3 years	33% females	NA	NO	Oxygen supplementation required for 9±1.4 days	NA
13	Galván-Tejada et al <sup>18</sup>	2020; Mexico	Case control study	219	NA	Females 39.14 years Males: 39.1 years	49% males 51% females	NA	NA	NA	NA

Table Continued

**Table 1. (Continued).** Demographic details of the included studies.

S.no	Authors	Year; Place	Type of Study	Number of Patients	Category of Patients	Mean Age	Gender	Mean/Median Length of Hospital Stay	Hospitalised	ICU Admissions	Ventilation
14	Buttery et al <sup>19</sup>	2021; UK	Mixed-methods analysis (quantitative and qualitative)	3290	16.5% completed the survey between 4 and 8 weeks of the onset of their symptoms 21.4% between 8 and 12 weeks 62.1% more than 12 weeks after severe	45-54 years	78% female,	NA	12.7% 87.3% re-mained home	3.3% 33.6%: respiratory support	50.4% required non-invasive support. 10.6% required intubation.
15	Romero-Duarte et al <sup>20</sup>	2021; Spain	Retrospective observational study	797	severe	63.0 years	53.7% males	NA	NA	NA	NA
16	Moreno-Pérez et al <sup>21</sup>	2021; Germany	prospective cohort study	277	Mild (34.3%) Severe (65.7%)	56 years	52.7% males	8.5 days	NA	8.7%	NA
17	Halpin et al <sup>22</sup>	2021; Europe	Service evaluation study	100 total cases Ward:68 ICU:32	NA	W:70.5 years ICU:58.5 years	W:51.5 males ICU:59.4 males	W: 6.5 days ICU:12 days	NA	32	NA
18	Carvalho-Schneider et al <sup>23</sup>	2021; France	Epidemiologic prospective follow-up	150	Mild/moderate COVID-19 (77.3%) Severe COVID-19 (22.7%)	49 ± 15 years.	56% females	NA	35.2%	NA	NA

Table Continued

**Table 1. (Continued).** Demographic details of the included studies.

S.no	Authors	Year; Place	Type of Study	Number of Patients	Category of Patients	Mean Age	Gender	Mean/Median Length of Hospital Stay	Hospitalised	ICU Admissions	Ventilation
19	Bellan et al <sup>24</sup>	2021; Italy	Prospective cohort study	238	Mild to severe cases	61 years	59.7% males	NA	All	11.8%	42.9% received oxygen via nasal cannulae or Venturi masks 20.6% required noninvasive ventilation. 8.8% underwent mechanical ventilation.
20	Huang et al <sup>25</sup>	2021; China	Ambidirectional cohort study	1733	Mild to severe	57 years	52% males	NA	25% admitted to hospital, not requiring supplemental oxygen 68% admitted to hospital, requiring supplemental oxygen 6% admitted to hospital, requiring HFNC or non-IMV or both	4%	1 % admitted to hospital, requiring extracorporeal membrane oxygenation. or invasive mechanical ventilation or both

COVID-19: coronavirus disease 2019

**Pulmonary Symptoms/Dysfunctions**

The presenting pulmonary symptoms included fatigue, dyspnea, cough, discomfort/pain in the chest, decreased diffusing capacity of lungs, and pulmonary fibrosis. One of our studies by Zhao et al<sup>8</sup> on a sample of 55 cases, with a follow-up period of 3 months after discharge observed that 64% cases had persistent

symptoms, 14.5% had exertional dyspnea, 71% cases had some radiologic abnormalities, and 25.4% cases presented with decreased diffusion lung capacity. Van den Borst et al<sup>13</sup> in their study on 124 patients of the mild, moderate and severe type reported decreased lung diffusion capacity in 42% of patients, reduced ground-glass opacification in 99% of cases after the

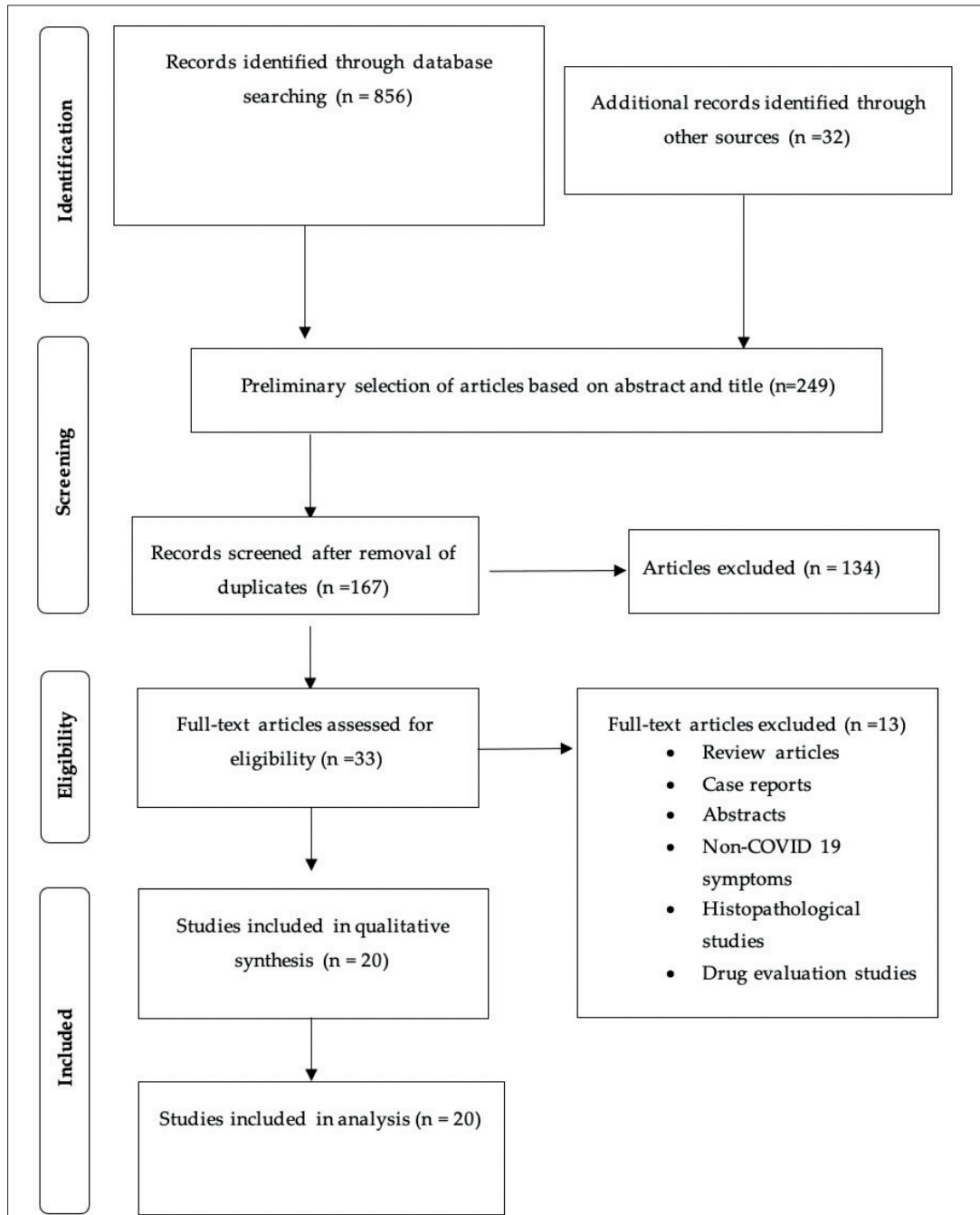


Figure 1. PRISMA Flow chart presenting the criteria for studies selected in the present systematic review.



discharge. Also, 91% of patients had residual pulmonary parenchymal abnormalities which were associated well with the decreased lung diffusion capacity observed in those patients.

In another such by Hall et al<sup>14</sup> on assessment of pulmonary functions based on physiological impairment and patient-reported symptoms at follow-ups of 30 days to 45 days, identified 40% cases with cardio-respiratory cause of breathlessness, 32% cases with parenchymal abnormality, and a few cases of pulmonary embolism and cardiac complications as well. In yet another study, Shah et al<sup>15</sup> studied clinical, radiological, and pulmonary function abnormalities in 60 cases at 12 weeks follow-ups post COVID-19 onset. They reported that 58% of cases from their study group presented with a minimum of one abnormal pulmonary function. Further on imaging studies, 88% of the sample had abnormal chest CT and 45% cases had abnormal total lung capacity specifying a restrictive ventilatory deficit. Also, 11% of cases had airflow obstruction, 55% cases with more than 10% of lung volume affected by either ground glass or reticulation. Moreno-Perez et al<sup>21</sup> assessed the Post-acute COVID-19 syndrome (PCS) in a sample of 277 patients with a follow-up of 14 weeks. Their observations revealed dyspnea and fatigue to be the most common persistent symptoms. 18.9% of cases presented with significant imaging changes, although 52.9% of those cases were without any respiratory symptoms. 58.2% of patients presented with severe pneumonia, 36.6% with mild pneumonia while 37.0% of patients were without any symptoms of pneumonia. On the contrary, 20.7% of cases with respiratory symptoms like cough or dyspnea presented with significant findings on chest imaging, while 14.3% had abnormal pulmonary function tests. Similarly, Romero-Duarte et al<sup>20</sup> in their extensive retrospective 6-month follow-up study on 797 severe COVID-19 cases mentioned that 42% of cases were associated with respiratory dysfunction. Bellan et al<sup>24</sup> observed that Diffusing capacity of the lung for carbon monoxide (DLCO) was decreased to <80% of the expected value in 51.6% patients and further decreased to <60% in 15.5% cases by evaluating lung function anomalies among 219 moderate to severe COVID-19 patients 4 months after discharge. 22.3% of cases presented with the Short Physical Performance Battery [SPPB] score of less than 11, suggesting limited mobility in those patients.

### ***Long-Term Extrapulmonary Manifestations***

As observed, the respiratory system is known to the most frequent organ system affected by the COVID-19 during the acute illness phase and even prolongs in the post-COVID-19 phase after recovery patients. It is now well recognized that apart from pulmonary manifestations, extrapulmonary systems impairments like cardiovascular system, neural system, gastrointestinal and renal system are also considered being affected. Occasionally, some researchers have even reported neuropsychiatric symptoms affecting the well-being and mental health of the individuals, especially ones who were critical and had ICU admissions. In the present analysis we documented the following extrapulmonary manifestations reported by various authors (Table II)

### ***Cardiovascular Complications***

It's well-acknowledged through various research that COVID-19 not only affects the cardiovascular system in its acute phase but can even manifest during the post-recovery phase. Romero-Duarte et al<sup>21</sup> reported 5.8% cases with cardiovascular events mainly arrhythmias, palpitations, and hypotension. Palpitations and Tachycardia in 6.1% of cases were also reported by Sudre et al<sup>7</sup>. Another researcher, Goertz et al<sup>11</sup> observed 32% cases with palpitations and 28% cases with increased HR. Two other such reports by Wang et al<sup>12</sup> and Carvalho-Schneider et al<sup>23</sup> also mentioned palpitations to be observed in their study cohorts. Furthermore, Huang et al<sup>25</sup> from their study reported the incidence of venous thromboembolic diseases along with some cardiovascular and cerebrovascular events. Myocarditis and heart failure are some other cardiovascular events reported in the literature.

### ***Neurological Manifestations***

Numerous recent studies have specified the high incidence of neurological manifestations faced by the patients after COVID-19, during follow-ups. In our analysis, Headache has been reported to be the most common neurological manifestation as reported by Sudre et al<sup>7</sup> (91.2%)<sup>7</sup>, Zhao et al (18.18%)<sup>8</sup>, Goertz et al (38%)<sup>11</sup>, Wang et al<sup>12</sup> (3.82%) and Moreno-Perez et al<sup>16</sup>. Others include Peripheral Neuropathy Symptoms (tingling and numbness), Tinnitus and earache<sup>7</sup>, Memory Issues<sup>7,10,20</sup>, concentration and sleep disorders<sup>10</sup>.

### ***Mental Health***

Buttery et al<sup>19</sup> documented problems like sleep disturbances (46.2%), affected mental abilities

**Table II.** Outcome and clinical symptoms of long Covid-19 infection as reported.

S.no	Authors	Mean follow up duration after onset of covid 19 and completely recovered	Worsened quality of life	Major clinical symptoms	Less common symptoms
1	Carfi et al <sup>6</sup>	60.3 (SD, 13.6) days  12.6%: completely free of any COVID-19-related symptom	44.1%	Fatigue (53.1%) Dyspnea (43.4%) Joint Pain, (27.3%) Chest Pain (21.7%).	Cough Ansomnia Rhinitis Dysgeusia Headache Loss of appetite Sore throat diarrhea
2	Sudre et al <sup>7</sup>	Over a period of 84 days	NA	Fatigue (97.7%) Headache (91.2%) Symptoms (Palpitations, Tachycardia) (6.1%) Memory Issues (4.1%) Tinnitus And Earache (3.6%) Peripheral Neuropathy Symptoms (pins and needles and numbness) (2%)	Diarrhoea Chest Pain skipped meals Unusual Muscle pains Fever Sore Throat, Persistent Cough Loss of smell
3	Zhao et al <sup>8</sup>	64 to 93 days	NA	Gastrointestinal (GI) symptoms (30.91%) lung function abnormalities (25.45%): In abnormal CT manifestations, 30.77% had abnormality in pulmonary function. In Normal CT Group, 12.50% Had Abnormal Lung Function. Headache (18.18%) Fatigue (16.36%) Exertional Dyspnea (14.55%) Cough and sputum (1.81%).	NA
4	Liang et al <sup>9</sup>	3-month follow-up study	NA	20% fever 60% cough 43% increased sputum production 62% chest tightness and palpitations 60% fatigue 26% diarrhea	NA
5	Garrigues et al <sup>10</sup>	110.9 (±11.1) days Completely recovered:69.1%	NA	Fatigue (55%) Dyspnoea (42%) Loss Of Memory (34%) Concentration (28%) Sleep Disorders (30.8%) Loss Of Hair (20%)	Cough Ageusia
6	Goertz et al <sup>11</sup>	79±17 days	NA	Fatigue (87%) Dyspnoea (71%) Headache(38%) Chest tightness (44%) Cough (29%) Muscle pain (36%) Sore throat (26%) Fever (22%) Pain in shoulders (33%) Pain /burning feeling in lungs (24%) Heart palpitations (32%) Increased HR (28%) Dizziness (27%) Burning in trachea (20%)	Ageusia Joint pain Nausea Mucous Sneezing Hot flushes Eye problems Ear pain Vomiting Red spots on toes/feet

**Table II. (Continued).** Outcome and clinical symptoms of long Covid-19 infection as reported.

S.no	Authors	Mean follow up duration after onset of covid 19 and completely recovered	Worsened quality of life	Major clinical symptoms	Less common symptoms
7	Wang et al <sup>12</sup>	4 weeks  Completely recovered: By 1 <sup>st</sup> & 2 <sup>nd</sup> week: 51.91%  By 3 <sup>rd</sup> & 4 <sup>th</sup> week:86.26%	NA	By 2 <sup>nd</sup> week: cough (31.3%), fatigue (5.34%), expectoration (0.76%), chest tightness (6.11%), chest pain (3.05%), palpitation (2.29%), pharyngeal pain (1.53%), nausea (1.53%), inappetence (2.29%), vomiting (0.76%), diarrhea (0.76%), myalgia (0.76%) By 4 <sup>th</sup> week: cough (9.16%), chest tightness (0.76%), dyspnea (1.53%), pharyngeal pain (1.53%) and nausea (0.76%)	Nausea Diarrhoea Myalgia rhinorrea
8	Van den Borst et al <sup>13</sup>	3 months	Health status was generally poor, QoL (72%).	Lung diffusion capacity was below the lower limit of normal in 42% of discharged patients On follow-up CT imaging of discharged patients, 99% of patients. had decreased ground-glass opacities (GGOs); in 1%, GGO was unchanged extent of residual pulmonary parenchymal abnormalities was significantly lower 22% had low exercise capacity 19% low fat-free mass index, 36% problems in mental and/or cognitive function Functional impairment (64%) Fatigue (69%)	NA
9	Hall et al <sup>14</sup>	30-45 days	NA	Persistent interstitial change in 32% patients on CT. 40%, at follow-up with a cardiorespiratory cause of Breathlessness including persistent parenchymal abnormality (64 patients) pulmonary embolism (four patients) cardiac complications (eight patients).	NA
10	Shah et al <sup>15</sup>	12 weeks	NA	At least one pulmonary function variable was abnormal in 58% of patients 45% patients having an abnormal total lung capacity indicating a concurrent restrictive ventilatory deficit. 11% with Airflow obstruction, defined as FEV1 /FVC 55% had >10% of lung volume affected by either ground glass or reticulation. 88% had abnormal imaging on chest CT.	NA
11	Ladds et al <sup>16</sup>	3-4 weeks	NA	Confusing illness, relapsing-remitting symptoms and uncertain prognosis; A heavy sense of loss and stigma difficulty accessing and navigating services; difficulty being taken seriously and achieving a diagnosis possible critical events (e.g. deterioration after being unable to access services).	NA

Table continued

**Table II. (Continued).** Outcome and clinical symptoms of long Covid-19 infection as reported.

S.no	Authors	Mean follow up duration after onset of covid 19 and completely recovered	Worsened quality of life	Major clinical symptoms	Less common symptoms
12	Daher et al <sup>17</sup>	60 days	NA	Anosmia, as well as nausea or vomiting are the two symptoms that present the greatest risk of recurrence in recovered patients, and in particular, dyspnea is a symptom that is only present in recovered patients.	NA
13	Galván-Tejada et al <sup>18</sup>	>12 Weeks	NA	breathing problems (92.1%) fatigue (83.3%), muscle weakness or joint stiffness (50.6%) sleep disturbances (46.2%) problems with mental abilities (45.9%) changes in mood including anxiety and depression (43.1%) cough (42.3%).	Hair loss Loss of appetite or weight loss Anosmia Nightmares
14	Buttery et al <sup>19</sup>	6-month follow-up study	20.1% patients returned to the Emergency Services 4.4% required hospital readmission. 1.0% died during follow-up.	Respiratory (42.0%) Systemic (36.1%) Neurological (20.8%) Mental Health (12.2%) Infectious (7.9%) Reasons of emergency readmission: Fever, dermatological, arrhythmia or palpitations, thoracic pain and pneumonia.	NA
15	Rome-ro-Duarte et al <sup>20</sup>	10–14 weeks  Median of 77 days  Completely recovered: 65.8%	66.9%	58.2% : severe pneumonia 36.6% : mild pneumonia 37.0% without pneumonia, Fatigue (34.8%) Anosmia-dysgeusia, (21.4%) Myalgias-arthralgias (19.6%) Dyspnea (34.4%) Cough (21.3%)  Neurological:11.9% Headache (17.8%) Memory disorders  Spirometry abnormalities:9.3% (mainly obstructive epattern) Imp Lab findngs: lymphopenia and high ferritin and D-dimer levels.	Diarrhoea Skin Features Visual Loss
16	More-no-Pérez et al <sup>21</sup>	48 days	W:22  ICU:17	Fatigue: 72% ICU;60.3% W Breathlessness: 65.6% ICU; 42.6% W Neuropsychological symptoms Speech and swallow problems Nutrition related Continence	NA

*Table continued*

**Table II. (Continued).** Outcome and clinical symptoms of long Covid-19 infection as reported.

S.no	Authors	Mean follow up duration after onset of covid 19 and completely recovered	Worsened quality of life	Major clinical symptoms	Less common symptoms
17	Halpin et al <sup>22</sup>	Mean follow up 32.7 ± 2.5 and 59.7 ± 1.7 days	19.7%	<p><b>D 30:</b> Anosmia/ageusia (40/150) Chets pain (27/150) Flu like symptoms: (54/150) Ferver (76/150) Digestive disorders (26/150) Dysponea (16/150)</p> <p><b>D 60:</b> Anosmia/ageusia (29/150) Chets pain 177/150) Flu like symptoms: (28/150) Ferver (0/150) Digestive disorders (15/150) Dysponea (10/150)</p>	Palpitations Arthralgia Weight loss Cutaneous signs
18	Carvalho-Schneider et al <sup>23</sup>	4 months	Limited mobility score 22.3%  Over all 58.3% with functional impairment	<p>DLCO (Diffusing capacity of lung for carbon monoxide) measurement.: DLCO was reduced to less than 80% of the estimated value in 113 patients (51.6%) and less than 60% in 34 patients (15.5%) Posttraumatic stress symptoms 17.2% 21.0% reported that their tolerance to exercise had worsened Cough:2.5% Dysponea :5.5% Ageusia:5% Anosmia:4.6% Diarrhea:1.3% Arthralgia.:5.9% Myalgia:5.9% Chest pain: 0.</p>	Chest pain
19	Bellan et al <sup>24</sup>	56 days	Reduced QoL, mainly due to decreased mobility in 6 cases	<p>33% had dyspnea 33% had cough, 45% fatigue. 45% Tirednes 15% myalgia Slightly reduced DLCO (77%) 6MWT distance was reduced in most patients without oxygen desaturation. No indicators for depression or anxiety</p>	Rhinorrhea Sore Throat Fever Loss Of Smell
20	Huang et al <sup>25</sup>	186 days	Mobility: problems with walking around:7% Personal care: problems with washing or dishing 1% Usual activity: problems with usual activity”2%	<p>Fatigue or muscle weakness (63%) Pain or discomfort (27%) sleep difficulties (26%) Anxiety or depression (23%) Hair loss 22% Smell disorder 11% Lung function assessment showed that a considerable proportion (22–56% across different severity scales) of participants had a pulmonary diffusion abnormality 6 months after symptom onset. Long-term extrapulmonary organ manifestations: persistent renal dysfunctions, some participants were newly diagnosed with diabetes, and venous thromboembolic diseases, (including cardiovascular and cerebrovascular events) occurred.</p>	Papatations Joint Pain Decreased Appetite Taste Disorder Dizziness Skin Rash Myalgia

(45.9%), mood fluctuations namely anxiety and depression (43.1%) in their study population. Romero-Duarte et al<sup>20</sup> stressed the mental health issues in 12.2% of their study patients. According to Bellan et al<sup>24</sup>, posttraumatic stress symptoms were reported in a total of 17.2% of patients. On the other hand, Shah et al<sup>15</sup> reported issues like loss and stigma, problems in accessing services, and problems in making diagnoses by the professionals. Overall, we observed women to be affected with a greater frequency of anxiety-related disorders, depression, mood fluctuations, and sleep disturbances.

### ***Gastrointestinal Manifestations***

Diarrhea, vomiting, and digestive disorders were the most common encountered symptoms as reported by Zhao et al<sup>8</sup>, Wang et al<sup>12</sup>, Moreno-Perez et al<sup>20</sup>, and Carvalho-Schneider et al<sup>22</sup>. Other authors like Romero-Duarte et al<sup>20</sup> reported systemic involvement of 36.1%, while Buttery et al<sup>18</sup> reported loss of appetite or weight loss from their reports.

### ***Renal Manifestations***

Among renal manifestations in this present analysis, Huang et al<sup>25</sup> reported renal dysfunctions (decreased eGFR) among 35% of the patients at follow-up among patients with non-acute kidney injury, 13% presented with decreased eGFR.

### ***Quality of Life (QOL)***

Moreno-Perez et al<sup>16</sup> mentioned that the quality of life in comparison to those who were without any symptoms post COVID-19 infection showed worsened impact on their quality of life. Carfi et al<sup>6</sup>, Van den Borst et al<sup>13</sup>, Moreno-Perez et al<sup>21</sup>, and Carvalho-Schneider et al<sup>23</sup> specified that 44.1%, 72%, 66.9%, 19.7% of the population respectively in their studies had a worsened/ decreased QOL post-infection. Romero-Duarte et al<sup>20</sup> mentioned 20.3% of patients with decreased quality of life and returning to the Emergency Services. Fever, arrhythmias or palpitations, thoracic pain, and pneumonia were recorded as the most common reasons behind this emergency returning.

## **Discussion**

During these tough pandemic times, millions of people have suffered from post-COVID-19 health consequences. Due to its prolonged implications, various researchers worldwide have em-

phasized a better understanding of the prevalence of these conditions and continuously working towards gathering knowledge of the prolonged post-COVID recovery phase. Presently, there is still a paucity of available data to identify the predictors of the post-recovery phase. The majority of these studies are being survey-based analyses utilizing telephonic conversations, follow-ups interviews, standard questionnaire's pulmonary function tests, standard scoring methods, quality of life assessment parameters, chest CT, MRI, and spirometry to accumulate the long COVID symptoms. It's been suggested that the symptoms observed in "Post-COVID Syndrome" may be associated with the lasting inflammation, effects due to hospitalization or due to ICU admissions or prolonged ventilation, and emotional distress during isolation.

The present systematic analysis suggested a high occurrence of prolonged symptoms in COVID-19 patients, ranging from 4 weeks – 6 months after disease onset. The most common prevalent symptoms were fatigue and dyspnea in almost all of the studies. These symptoms may even be evident after 12 weeks of follow-up following COVID-2 infection. The authors could not find any link between the onset of fatigue and the severity of the disease. Reasons for its occurrence and the other related long-term complications in post-COVID-19 patients are still unknown. Most of the researchers agree that the long-term COVID-19 symptoms are associated with the ability of the virus to initiate an immense inflammatory response referred to as "cytokine storm". Other reported common symptoms included: shortness of breath, cough, joint pain, chest pain or tightness, headache, loss of smell/taste, sore throat, diarrhea, loss of memory, depression, anxiety. Furthermore, some symptoms observed less frequently were insomnia, palpitations, anorexia, tingling fingertips, skin rashes, and hair loss.

Understanding the pathophysiology related to these Long-COVID -19 symptoms seems to be important. This might help us in understanding, predicting, preventing, and treating these consequences related to post COVID-19 infection. Long-COVID-19 is the resultant or more accurately a continuum of the acute disease. The coronavirus (SARS-CoV-2) has a high affinity for angiotensin-converting enzyme-2 (ACE-2) receptors which are commonly found in not only lungs but other organs like the liver, kidneys, and blood vessels. Within the lungs, once the virus attacks the alveolar epithelium, specifically type II pneu-

mocytes cause destruction. This can lead to scarring and pulmonary fibrosis representing the lung damage and such patients clinically are expected to present with long-lasting respiratory symptoms. The endothelium within the capillaries also gets damaged and may elicit an inflammatory response, resulting in the formation of microthrombi and pulmonary consolidation. This leads to alteration of the diffusion capacity of the lung for carbon monoxide (DLCO) in such patients post COVID-19<sup>29,30</sup>.

In one of our reviewed articles by Shah et al<sup>15</sup>, a strong connection was reported between days of oxygen provided to the patient initially during active disease with DLCO-% and total CT score. They thus suggested the importance of follow-ups required in such patients to keep a check on their respiratory complications.

Anosmia and dysgeusia may be explained based on the route of entry of the virus through the nose or throat during the acute phase, resulting in transient damage to the olfactory bulbs. Cases with persistent symptoms may be due to prolonged healing, which varies from person to person<sup>31</sup>.

In the present analysis, we documented the extrapulmonary manifestations including, cardiovascular complications, neurological manifestations, mental health stability, and renal manifestations. The pathophysiology behind these extrapulmonary manifestations in COVID-19 may be attributed to the formation of antigen-antibody complexes during the second or third week after infection, leading to a humoral immune response. Autoimmunity is known to cause organ damage in COVID-19 patients, similar to that seen in various autoimmune diseases<sup>30</sup>.

Associated cardiovascular events as reported by the researchers included arrhythmias, palpitations and hypotension, increased HR, venous thromboembolic diseases, Myocarditis, and acute/decompensated heart failure as well. This could be probably explained through imaging studies that demonstrate damage to the myocardium following the acute phase for few weeks to months during a recovery phase.

Among neurological manifestations: Headache, Peripheral Neuropathy Symptoms, Memory Issues, concentration, and sleep disorders were most commonly observed with varying frequencies. It appears that the virus may not infect the brain and the symptoms are a secondary consequence of cerebral inflammation<sup>32</sup>. Apart from the above-mentioned findings, in one of the published review articles, some serious neurological side

effects like ischemic strokes, encephalitis, cranial neuropathies, ‘brain fog’, seizures and Guillain-Barre syndrome have also been discussed several months following the initial infection<sup>33</sup>.

Mental health issues affecting mental abilities, mood fluctuations namely anxiety and depression and sleep disorders were commonly seen in the study cohorts, specifically in women. This raises an alarm for identifying and improving the mental health of patients’ post-hospitalization. Various factors like isolation at the time of hospitalization and outcome stress of the disease could be aggravating and leading to disturbed mental health<sup>20</sup>. Further, diarrhea, vomiting, digestive disorders, and loss of appetite or weight loss are common gastrointestinal manifestations that could probably be due to adverse drug reactions associated with extensive use of drugs during active COVID-19 treatment.

Reactivation seen in long COVID cases is an additional concern during the follow-ups. The probable reason and mechanisms behind such reactivations are still not clear. Probably it could be due to reactivation of the initial virus or else it could be due to infection from a new viral strain. Another school of thought suggests that the neutralizing antibodies developed during the initial active phase of infection in patients start declining within a period of 2-3 months after infection. Thus, from the above facts, we can suggest that patients with Long-COVID-19 symptoms may act as carriers and thus should be closely observed through repeat tests and timely follow-ups<sup>34,35</sup>.

### **Limitation of the Study**

Despite our efforts and findings, our review has its limitations. Firstly, as this topic is quite new and depends on the methods used by the authors and observations derived from the study population and its self-perception, raises the risk of bias. For the included studies, we did not include the risk of bias assessment. Secondly, some of the included studies centered their focus on only one type (homogenous) of the infected population for COVID-19. Heterogeneity of population is required to obtain better insights, as the disease is a pandemic with increased mortality and severity.

### **Conclusions**

Due to the ongoing recurrence of COVID-19 because of the new waves, Long COVID is a most important health issue affecting the gener-

al population worldwide. A detailed investigation on understanding all the aspects related to long-term COVID-19 consequences is therefore important. To date, doctors and researchers have centered their focus on the ongoing active phase of the disease, which is although mandatory. But persistent monitoring of these patients even after recovery and discharge is required to focus on the long-lasting deleterious effects of COVID-19. Therefore, appropriate clinical evaluation is required in long COVID cases which in turn may help us to identify the risk factors, etiology, and to my help, we treat them early with appropriate management strategies.

### Conflict of Interest

The Authors declare that they have no conflict of interests.

### Acknowledgement

The current research is supported by Taif University Research Supporting Project number (TURSP-2020/293), Taif University, Taif-21944 Saudi Arabia.

### References

- 1) Raveendran AV, Jayadevan R, Sashidharan S. Long COVID: An overview. *Diabetes Metab Syndr* 2021; 15: 869-875.
- 2) Who-China Joint Mission Members. World Health Organization; 2020. Report of the WHO-China joint mission on coronavirus disease 2019 (COVID-19)
- 3) WHO [homepage on the internet]. Coronavirus disease (COVID-19). [updated November 10, 2020]. Available from: <https://www.who.int/news-room/qa-detail/coronavirus-disease-covid-19>.
- 4) Garg P, Arora U, Kumar A, Wig N. The "post-COVID" syndrome: how deep is the damage? *J Med Virol* 2021; 93: 673-674.
- 5) Raveendran A.V. Long COVID-19: challenges in the diagnosis and proposed diagnostic criteria. *Diabetes Metab Syndr* 2020; 15: 145-146.
- 6) Carfi A, Bernabei R, Landi F; Gemelli Against COVID-19 Post-Acute Care Study Group. Persistent Symptoms in Patients After Acute COVID-19. *JAMA* 2020; 324: 603-605.
- 7) Sudre CH, Murray B, Varsavsky T, Graham MS, Penfold RS, Bowyer RC, et al. Attributes and predictors of long-COVID: analysis of COVID cases and their symptoms collected by the Covid Symptoms Study App. *medRxiv* [Preprint]. (2020). doi: 10.1101/2020.10.19.20214494
- 8) Zhao YM, Shang YM, Song WB, Li QQ, Xie H, Xu QF, Jia JL, Li LM, Mao HL, Zhou XM, Luo H. Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery. *EClinicalMedicine* 2020; 25: 100463.
- 9) Liang L, Yang B, Jiang N, Fu W, He X, Zhou Y, Ma WL, Wang X. Three-month Follow-up Study of Survivors of Coronavirus Disease 2019 after Discharge. *J Korean Med Sci* 2020; 35: e418.
- 10) Garrigues E, Janvier P, Kherabi Y, Le Bot A, Hamon A, Gouze H, Doucet L, Berkani S, Oliosi E, Mallart E, Corre F, Zarrouk V, Moyer JD, Galy A, Honsel V, Fantin B, Nguyen Y. Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. *J Infect* 2020; 81: e4-e6.
- 11) Goërtz YMJ, Van Herck M, Delbressine JM, Vaes AW, Meys R, Machado FVC, Houben-Wilke S, Burtin C, Posthuma R, Franssen FME, van Loon N, Hajian B, Spies Y, Vijlbrief H, van 't Hul AJ, Janssen DJA, Spruit MA. Persistent symptoms 3 months after a SARS-CoV-2 infection: the post-COVID-19 syndrome? *ERJ Open Res* 2020; 6: 00542-2020.
- 12) Wang X, Xu H, Jiang H, Wang L, Lu C, Wei X, Liu J, Xu S. Clinical features and outcomes of discharged coronavirus disease 2019 patients: a prospective cohort study. *QJM* 2020; 113: 657-665.
- 13) van den Borst B, Peters JB, Brink M, Schoon Y, Bleeker-Rovers CP, Schers H, van Hees HWH, van Helvoort H, van den Boogaard M, van der Hoeven H, Reijers MH, Prokop M, Vercoulen J, van den Heuvel M. Comprehensive health assessment three months after recovery from acute COVID-19. *Clin Infect Dis* 2020: ciaa1750.
- 14) Hall J, Myall K, Lam JL, Mason T, Mukherjee B, West A, Dewar A. Identifying patients at risk of post-discharge complications related to COVID-19 infection. *Thorax* 2021; 76: 408-411.
- 15) Shah AS, Wong AW, Hague CJ, Murphy DT, Johnston JC, Ryerson CJ, Carlsten C. A prospective study of 12-week respiratory outcomes in COVID-19-related hospitalisations. *Thorax* 2021; 76: 402-404.
- 16) Ladds E, Rushforth A, Wiering S, Taylor S, Rayner C, Husain L, Greenhalgh T. Persistent symptoms after Covid-19: a qualitative study of 114 "long Covid" patients and draft quality principles for services. *BMC Health Serv Res* 2020; 20: 1-3.
- 17) Daher A, Balfanz P, Cornelissen C, Müller A, Bergs I, Marx N, Müller-Wieland D, Hartmann B, Dreher M, Müller T. Follow up of patients with severe coronavirus disease 2019 (COVID-19): Pulmonary and extrapulmonary disease sequelae. *Respir Med* 2020; 174: 106197.
- 18) Galván-Tejada CE, Herrera-García CF, Godina-González S, Villagrana-Bañuelos KE, Amaro JDL, Herrera-García K, et al. Persistence of COVID-19 symptoms after recovery in Mexican population. *Int J Environ Res Public Health* 2020; 17: 9367.
- 19) Tse Y, Darlington AE, Tyerman K, Wallace D, Pankhurst T, Chantziara S, Culliford D, Recio-Saucedo A, Nagra A. COVID-19: experiences of lockdown and support needs in children and young adults



- ts with kidney conditions. *Pediatr Nephrol* 2021; 1-14.
- 20) Romero-Duarte Á, Rivera-Izquierdo M, de Alba IG, Pérez-Contreras M, Fernández-Martínez NF, Ruiz-Montero R, Serrano-Ortiz Á, González-Serna RO, Salcedo-Leal I, Jiménez-Mejías E, Cárdenas-Cruz A. Sequelae, persistent symptomatology and outcomes after COVID-19 hospitalization: the ANCOHVID multicentre 6-month follow-up study. *BMC Med* 2021; 19: 1-3.
  - 21) Fears C, Mahida N, Oppenheim B, Lynch C, Gray J. Journal of Hospital Infection moves to Article-Based Publishing. *J Hosp Infect* 2020; 105: A1.
  - 22) Halpin SJ, Mclvor C, Whyatt G, Adams A, Harvey O, McLean L, Walshaw C, Kemp S, Corrado J, Singh R, Collins T, O'Connor RJ, Sivan M. Post-discharge symptoms and rehabilitation needs in survivors of COVID-19 infection: A cross-sectional evaluation. *J Med Virol* 2021; 93: 1013-1022.
  - 23) Carvalho-Schneider C, Laurent E, Lemaigen A, Beaufile E, Bourbao-Tournois C, Laribi S, Flament T, Ferreira-Maldent N, Bruyère F, Stefic K, Gaudy-Graffin C. Follow-up of adults with noncritical COVID-19 two months after symptom onset. *Clin Microbiol Infect* 2021; 27: 258-263.
  - 24) Blanco JR, Cobos-Ceballos MJ, Navarro F, Sanjoaquin I, Arnaiz de Las Revillas F, Bernal E, Buzon-Martin L, Viribay M, Romero L, Espejo-Perez S, Valencia B, Ibañez D, Ferrer-Pargada D, Malia D, Gutierrez-Herrero FG, Olalla J, Jurado-Gamez B, Ugedo J. Pulmonary long-term consequences of COVID-19 infections after hospital discharge. *Clin Microbiol Infect* 2021; 27: 892-896.
  - 25) Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, Kang L, Guo L, Liu M, Zhou X, Luo J, Huang Z, Tu S, Zhao Y, Chen L, Xu D, Li Y, Li C, Peng L, Li Y, Xie W, Cui D, Shang L, Fan G, Xu J, Wang G, Wang Y, Zhong J, Wang C, Wang J, Zhang D, Cao B. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet* 2021; 397: 220-232.
  - 26) Lopez-Leon S, Wegman-Ostrosky T, Perelman C, Sepulveda R, Rebolledo PA, Cuapio A, Villapol S. More than 50 Long-term effects of COVID-19: a systematic review and meta-analysis. Available at SSRN 3769978. 2021 Jan 1.
  - 27) Lopez-Leon S, Wegman-Ostrosky T, Perelman C, Sepulveda R, Rebolledo PA, Cuapio A, Villapol S. More than 50 Long-term effects of COVID-19: a systematic review and meta-analysis. *medRxiv [Preprint]*. 2021 Jan 30: 2021.01.27.21250617. doi: 10.1101/2021.01.27.21250617.
  - 28) Bellan M, Soddu D, Balbo PE, Baricich A, Zeppegno P, Avanzi GC, Baldon G, Bartolomei G, Battaglia M, Battistini S, Binda V. Respiratory and psychophysical sequelae among patients with COVID-19 four months after hospital discharge. *JAMA Netw Open* 2021; 4: e2036142.
  - 29) Garg S, Garg M, Prabhakar N, Malhotra P, Agarwal R. Unraveling the mystery of Covid-19 cytokine storm: from the skin to organ systems. *Dermatol Ther* 2020; 33: 1385-1389.
  - 30) Garg M, Maralakunte M, Garg S, Dhooria S, Sehgal I, Bhalla AS, Vijayvergiya R, Grover S, Bhatta V, Jagia P, Bhalla A, Suri V, Goyal M, Agarwal R, Puri GD, Sandhu MS. The Conundrum of 'Long-COVID-19': A Narrative Review. *Int J Gen Med* 2021; 14: 2491-2506.
  - 31) Aragão MFVV, Leal MC, Cartaxo Filho OQ, Fonseca TM, Valença MM. Anosmia in COVID-19 associated with injury to the olfactory bulbs evident on MRI. *AJNR Am J Neuroradiol* 2020; 41: 1703-1706.
  - 32) Lyons D, Frampton M, Naqvi S, Donohoe D, Adams G, Glynn K. Fallout from the COVID-19 pandemic - should we prepare for a tsunami of post-viral depression? *Ir J Psychol Med* 2020; 37: 295-300.
  - 33) Nihra V. Living with 'Long COVID-19': The long-term complications and sequelae. *Int J Clin Virol* 2021; 5: 011-021.
  - 34) Shah AK, Raul MU. (RE) currencies in COVID-19: (RE)-activation or (RE)-infection? *J Family Med Prim Care* 2021; 10: 1525-1529.
  - 35) Salehi-Vaziri M, Jalali T, Farahmand B, Fotouhi F, Banifazl M, Pouriayeali MH, Sadat Larijani M, Afzali N, Ramezani A. Salehi-Vaziri M, Jalali T, Farahmand B, Fotouhi F, Banifazl M, Pouriayeali MH, Sadat Larijani M, Afzali N, Ramezani A. Clinical characteristics of SARS-CoV-2 by re-infection vs. reactivation: a case series from Iran. *Eur J Clin Microbiol Infect Dis* 2021; 40: 1713-1719.