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Post discharge outcomes of patients with coronavirus disease (COVID-19)

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ABSTRACT

Since WHO declared COVID-19 a pandemic, globally more than 212 milion people were infected and approximately 4.4 milion died (25 August 2021). As the pandemic evolved, it became clear that there are many more things to research and discover about the SARS-CoV-2 infection.

Besides the fact that SARS-CoV-2 primarily affects the respiratory system, more and more articles indicate a systemic involvement which could be responsible for long term consequences.

The aim of this review was to evaluate the long- term signs and symptoms of COVID-19 infection. We looked for information regarding the prevalence and persistence of symptoms associated with COVID-19 infection and the persistence of organ dysfunction beyond the acute phase. We also searched data regarding the impact of the infection on the quality of life, physical, mental and psychosocial function.

Recent studies have shown that some symptoms can persist a long time after the acute episode of COVID-19. Furthermore, organ sequalae can be present after the acute episode. The most common symptoms of "long COVID" are: fatigue and shortness of breath, lack of taste/smell, cough, myalgia and arthralgia, headache. Also, cardiac abnormalities, cognitive impairment, insomnia, anxiety and concentration issues can be present.

Keywords: outcomes in COVID-19, long COVID, persistent symptoms, organ dysfunction after COVID-19

INTRODUCTION

The coronavirus disease of 2019 (COVID-19) is an infection caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and has been declared by World Health Organization (WHO) a global pandemic on 12th of March 2020. Since then, worldwide, more than 209 million were confirmed and 4.4 million have died due to the ongoing pandemic (1).

SARS-CoV-2 primarily affects the respiratory system, being responsible for an atypical pneumonia, which can involve different proportion of the lung parenchyma and it can progress to acute respiratory distress syndrome (ARDS) and respiratory failure at a higher rate than other diseases/infections (2). Secondary, the virus can produce myocardial involvement, acute renal injury, gastrointestinal and hepatobiliary symptoms, hepatocellular injury, hematologic disturbances, dermatologic, neurologic and ophthalmic involvement (3).

Clinical presentation can vary from asymptomatic (17-25%) to severe forms of the disease (15%), needing oxygen support and hospitalization. 5% of the patients develop a critical form of the disease with complications such as respiratory failure, ARDS, sepsis and septic shock, thromboembolism or acute kidney injury or cardiac injury (4). The most common symptoms in hospitalized patients are summarized in Table 1. Among them are: fever or chills, cough, shortness of breath or dyspnea, myalgia, arthralgia, headache, loss of taste/odor,

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odynophagia, runny nose, nausea or vomiting and diarrhea. Additionally, malaise, impaired mind focus, or sputum production may appear (5).

TABLE 1. Clinical manifestation in SARS-CoV-2 infection (5)

Fever	**83,3%**
Chill	**15%**
Dry cough	**60,3%**
Shortness of breath	**24,9%**
Chest pain	**14,9**
Fatigue	**38%**
Myalgia	**28,5%**
Headache	**14%**
Rhinorrhea	**3,5%**
Nausea/vomiting	**3,6%**
Diarrhea	**8,4%**
Sore throat	**12,3%**

As the pandemic evolved, it became clear that there are many more things to research and discover about the SARS-CoV-2 infection. In addition to epidemiological, pathogenesis, clinical presentation and treatment aspects, it is equally important to discuss about post-discharge outcomes, to evaluate the persistent symptoms, quality of life, lung function, cardiac, and neurologic sequelae. At this moment, there are a few studies regarding all of this and much more research is needed, in order to find out which are the long-term consequences of COVID-19 infection (6).

A first step towards fixing this problem was made by National Institute for Health and Care Excellence (NICE), in collaboration with Royal College of General Practitioners and Healthcare Improvement Scotland, who developed a rapid guideline for managing the long-term effects of COVID-19. The guideline defines, for the first time, terms like „post-COVID-19 syndrome" and „long COVID" („signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis) (7).

Literature research was performed in order to determine current knowledge regarding the long-term consequences of COVID-19 infection. A search was conducted using databases such as PubMed, Scopus, Google Scholar, Science Direct, WHO COVID-19 Database. The review took into consideration all the articles published in English, specifically results using search terms such as: "COVID-19", "persistence of symptoms", "post discharge outcomes", "sequelae after COVID-19", "COVID-19 syndrome", "long COVID".

AIM

The aim of this review was to evaluate the consequences of COVID-19 infection in the post-acute period. We looked for information regarding the prevalence and persistence of symptoms associated with COVID-19 infection and the persistence of organ dysfunction beyond the acute phase; we also searched data regarding the impact of the infection on the quality of life, physical, mental and psychosocial function.

PREVALENCE AND PERSISTENCE OF SYMPTOMS AFTER COVID-19

According to NICE guideline, acute COVID-19 is defined as „signs and symptoms of COVID-19 for up to 4 weeks". The persistence of symptoms between 4 and 12 weeks is considered „ongoing symptomatic COVID-19" and persistance after 12 weeks defines „post-COVID-19 syndrome" (5).

Persistent symptoms after infection have been reported mostly in patients with severe and moderate COVID-19, but symptoms were observed in a smaller percentage even in mild forms who did not require hospitalization. The most common symptoms are: fatigue, dyspnea, arthralgias, concentration problems, alopecia, cough, insomnia, anxiety and short-term memory loss (8).

In a cohort study, Huang et al. (6) observed that, after 6 months post discharge, 76% of the patients (1256 of 1655) presented at least one of the symptoms mentioned above, with a higher probability in women. They found fatigue and muscle weakness present in 63% of the participants, sleep difficulties in 26%, anxiety or depression in 23%, hair loss in 23%, smell disorder in 11%, taste disorder in 7%, dizziness in 6%, palpitations in 9%, chest pain in 5% and myalgia in 2% (6).

Patients who needed high-flow nasal cannula, non-invasive mechanical ventilation, extracorporeal membrane oxygenation or mechanical ventilation during hospitalization had more frequently symptoms like pain, discomfort, mobility problems and anxiety than those which did not receive supplemental oxygen. Females were more likely to develop alopecia than men and they developed higher levels of stress anxiety and depression (6).

In another study conducted by Garrigues et al. (9), with 120 respondents (96 in the ward group and 24 in the ICU group), after a period a time of 110.9 days (+/- 11.1), the most persistent common symptoms were: fatigue (55%), breathing problems (42%), loss of memory (34%), concentration problems (28%), sleep disorder (30.8%), loss of hair (20%), cough (16%), anosmia (13.3%) and ageusia (10.8%). There was no statistically significant difference regarding the persistence of symptoms between the two groups (9).

In Table 2 are summarized some publications regarding the persistence of symptoms post-COVID-19 in hospitalized and non-hospitalized subjects.

TABLE 2. Sinthesys of studies which evaluated persistent symptoms after acute SARS-CoV-2 infection

	Study, publication date	No patients included	Gender distribution	Median age	Follow-up period	Symptoms reported after COVID-19 infection
Hospitalised patients	Carfi et al., 2020 (10)	143	Men: 63% Women: 37%	56.5 years	60.3 days	Fatigue – 53.1% Dyspnea – 43.4% Joint pain – 27.3% Chest pain – 21.7%
	Carvalho-Schneider et al., 2021 (11)	150	Men: 44% Women: 56%	49+/-15 years (mean)	60 days	Dyspnea – 7.7% Chest pain – 13.1% Anosmia/ageusia -22.7% Palpitations – 10.9% Arthralgia – 16.3% Flu-like symptoms -21.5% Diarrhea – 33.3%
	Jacobs et al., 2020 (12)	183	Men: 61.5% Women: 39.5%	57 years	35 days	Fatigue - 55% Shortness of breath – 45.3% Cough – 41.8% Lack of taste – 22.8% Muscular pain – 50.6% Diarrhea – 10.9% Lack of smell – 26.2% Headache - 39% Joint pain – 54.7% Confusion – 43.2%
	Mandal et al., 2021 (13)	384	Men: 62% Women: 38%	59.9 years	54 days	Fatigue- 69% Shortness of breath- 53% Cough- 34%
Non-hospitalized	Tenforde et al., 2020 (14)	274	Men: 48% Women: 52%	42.5 years	21 days	Fatigue - 71% Cough - 61% Headache - 61%
	Stavem et al., 2021 (15)	451	Men: 44% Women: 56%	49.7 years	117 days	Dyspnea - 16% Disturbance/loss of smell - 12% Disturbance/loss of taste - 10% Arthralgia - 9% Myalgia - 8% Dry cough - 5% Headache - 5%

ORGAN DYSFUNCTION AFTER COVID-19

Currently there are very few studies concerning organ dysfunction after COVID-19. However, beside the respiratory manifestations, recent studies are showing impact on cardiovascular system, neurological, renal and gastrointestinal complications (3).

In a retrospective cohort study made by National Health Service hospitals in United Kingdom on 47,780 patients discharged alive by 31st of August 2020, an important number of patients has been associated with high risk of readmission and death following discharge (29.4% were readmitted and 12.3% died post-discharge). Age higher than 70 years was associated with a higher risk of post discharge events. Multi-organ dysfunction was described both in intensive care unit (ICU) group (4,745) and in non-ICU patients (43,035), with a higher prevalence of respiratory disease, diabetes, major adverse cardiovascular event and chronic kidney disease in the ICU group (16).

Pulmonary sequelae

The respiratory tract is deeply affected by SARS-CoV-2 due to its tropism for the lung. The virus main receptor is represented by angiotensin converting enzyme 2 (ACE 2) who is well expressed on the apical side of the alveolar epithelial cell type II. After the virus starts to replicate, alveolar injury and interstitial inflammation can occur. The infection can vary from asymptomatic to severe forms with hypoxia (14%) and even critical forms of disease accompanied by shock and multi organ failure (5%) which can lead to death in 2.3% of infected patients (17).

In the acute phase, the infection's main consequence is the interstitial pneumonia, which can be complicated in approximately 5% with ARDS. Regarding the post-acute phase, in a prospective longitudinal study conducted in the Netherlands on 101 participants (27.7% with moderate pneumonia and 72.3% with severe pneumonia), after 6 weeks post-

discharge important limitation of the diffusion capacity was observed. Diffusion capacity with values less than 80% was found in 71.7%, restriction dysfunctionality in 21.2% (total lung capacity <80%) and obstruction (Tiffeneau index <0.7) in 25.7%. The chance of having diffusion capacity limitation was higher for patients with severe pneumonia (18).

Radiological abnormalities such as ground glass, irregular lines and fibrosis can persist up to 3 months or more. Those modifications were observed in a cohort study of 55 subjects who have been evaluated 3 months after discharge. Out of them, 70.91% presented radiological abnormalities on high-resolution computed tomography and 23.64% had bilateral lesions. Furthermore, it was observed that the lower right lobe of the lung was more affected than the left one (41.82% vs. 21.82%). After spirometry was done, lung function abnormalities were found in 25.45%, diffusing capacity of the lungs for carbon monoxide (DLCO) anomaly being more frequent. D-dimer value was corelated with the DLCO impairment (19).

Cardiac sequelae

At this moment, the mechanism of cardiac injury in COVID-19 infection is still uncertain. However, the high cardiac expression of ACE2 receptor on vascular and myocardial tissue may explain one of the multiple pathways – the direct viral mechanism. Cardiac complications may include: myocardial injury and myocarditis, acute myocardial infarction, heart failure and cardiomyopathy, arrhythmias, shock and cardiac arrest and venous thromboembolic events (VTE) (20).

Myocardial injury during or after COVID-19 was first described in China, in a small group of 41 hospitalized patients, from which 5 had elevated cardiac troponin I (cTnI) (21). After that, more studies showed that the injury/damage with an elevated troponin level can vary from 7% up to 17% of all infected (21). Patients admitted in ICU had higher values for myocardial biomarkers (creatine-kinase-MB, cTnI) than those not receiving ICU care, according to a study from Wuhan (21).

Furthermore, arrhythmia risk is increased in patients affected by COVID-19 infection; the implied mechanism could be represented by myocardial inflammation, metabolic dysfunction, myocardial injury, sympathetic activity and treatment adverse reactions, such as QT-prolonging drugs. In a cohort study of 138 hospitalized patients, the cardiac arrhythmia was the second complication after ARDS, 17.6% of the patients developing disorders such as atrial and ventricular fibrillation, conduction block and ventricular tachycardia. The prevalence of arrhythmias was higher in patients requiring ICU admission (44% vs. 7%) (22,23).

Acute coronary syndrome has already been described after viral infections. In 2018, Kwong et al. found a significant association between respiratory infection and acute myocardial infarction in the first 7 days of disease. Influenza incidence ratio were 6.1 compared to other viruses 2.8 (24). At this moment, there are a few cases reported of myocardial infarction in COVID-19 context. Bangalore et al. reported a case series of 18 patients with COVID-19 who had ST-segment elevation; 14 from them had focal ST-segment elevation and 4 diffuse ST-segment elevation (25). Among those with focal modifications, 8 had a reduced left ventricular ejection fraction. Half of the patients underwent coronary angiography and obstructive disease was found in 6 of them (25). In a cohort study, Modin et al. reported that out of 5,119 patients diagnosed with COVID-19, 17 had their first ever acute miocardial infarction (AMI) (26). They also observed that the incidence of AMI was 5 times higher in the first 14 days after diagnosis. The incidence remained statistically significant even after 21 days and up to 31 days after COVID-19 diagnosis (26).

Another cardiovascular-related outcome after COVID-19 is persistent myocardial inflammation and abnormal imaging parameters. In a prospective observational cohort study which included 100 patients who recovered after COVID-19, Puntmann et al. (27) described after a median period of time of 71 days elevated levels of high-sensitivity troponin T (>3 pg/ml) in 71% of the patients and significant levels (>13.9 pg/ml) in 5%. Cardiovascular magnetic resonance was performed at the same time and showed abnormal findings in 78% of the subjects. Among them, imaging studies described decreased left and right ventricular ejection fraction in 6% and respectively 7%, dilated left ventricle in 9% of the patients, pericardial effusion in 20%, increased myocardial native T1 (specific for fibrosis or/and edema) in 73% and increased T2 (specific for edema) in 60%, both of which being corelated with active inflammatory process (27).

Another major cardiovascular event observed after COVID-19 infection is high blood pressure. Hypertension is the most common co-morbidity in COVID-19 patients, its prevalence ranging from 15% to 30%. Hypertension is considered a major risk factor for poor prognosis and death. The exact incidence of new diagnosed hypertension after COVID-19 is unknown, due to lack of data (28).

Late thromboembolic complications

COVID-19 is a viral infection characterized by an increased inflammatory status, endothelial dysfunction and coagulopathy. The mechanisms responsible for the hypercoagulable status are not fully known. It is assumed that inflammatory cy-

tokines (interleukin 6, interleukin 8, and tumor necrosis factor α) associated with hypoxemia leads to endothelial lesions, the main consequence being the increased risk of thrombosis (29,30).

The risk of thromboembolic complications is high in patients with COVID-19, especially in those from ICU units. In an Italian study of 388 patients admitted to an university hospital from Milan, the incidence of venous and arterial thromboembolic events was 8%, with 50% of the events happening in the first day of hospitalization. Out of 388 patients, 4.4% developed venous thromboembolism (VTE), 2.8% pulmonary embolism (PE), 2.5% ischemic stroke, 2.1% disseminated intravascular coagulation and 1.1% myocardial infarction. Due to the thromboembolic risk, all patients hospitalized received prophylactic anticoagulation (31). A high incidence of thromboembolic and hemorrhagic events was reported in critical patients who associated ARDS. Thus, despite thromboprophylaxis, in a multicenter prospective cohort study which included 184 ICU patients from Denmark, the cumulative incidence of thromboembolic events was 31% (VTE 27% and arterial thrombotic events 3.7%); pulmonary embolism was the most common complication (81%) (32). In a systematic review and meta-analysis, conducted by Kunutsor et al., including 35 eligible studies, the pooled incidence for VTE was 18.4% (n = 19 studies), 13.5% for PE (n = 22 studies), and 11.8% for deep vein thrombosis (n= 18 studies). The incidence of arterial and venous thromboembolic disease was 17.8% (9.9-27.4) (33).

At this moment, there are a few data published about long-term thromboembolic events. COVID-19 is associated with thromboembolic complications, especially during hospitalisation, the incidence of VTE after discharge being low. In a retrospective study on 163 patients who did not received anticoagulation on discharge, after 30 days, Patell et al. found a cumulative incidence of thrombosis (venous and arterial events) of 2.5%. The median period of time from discharge to occurrence of the events was 23 days. During the follow-up period, the cumulative incidence of hemorrhage was 3.7% (34). In another study conducted in North Carolina on 447 patients, the incidence of VTE at 30 days after discharge was 2%. The incidence of thromboembolic events was higher in the group of patients discharged without anticoagulation than those who received prophylaxis (2.7% vs. 2.1%). The authors also reported that those requiring ICU treatment had more thromboembolic events than those treated in a non-ICU ward (3.4% vs. 1.1%). Thromboembolic events were represented by splenic and myocardial infarction, pulmonary embolism and ischemic stroke (35).

Neurologic sequelae

The central nervous system and peripheral nervous system seem to be involved in COVID-19 infection, as more and more articles are reporting. It is known that severe acute respiratory syndrome can cause neurological disease, but the mechanisms and pathophysiology are unknown at this moment. In the acute phase of COVID-19, Mao et al. found that 36.4% of patients develop neurological symptoms, with a higher incidence in patients with severe forms of disease (36).

The most common symptoms during acute phase of SARS-CoV-2 infection include dizziness, headache, seizures, anosmia and ageusia, paresthesia and impaired consciousness. Less common, severe neurological involvment have beend described, like encephalopathy, viral encephalitis, hemiplegia, delirium, Guillain-Barré syndrome, myopathy and neuromuscular disorders (37,38). The long-term neurological consequences of SARS-COV-2 reported so far are represented by cognitive deficits, hyposmia/anosmia, poly-neuro/myopathy, ischemic stroke, abnormal reflex status, parkinsonism, limb paresis, muscle atrophy, and physiological tremor (39,40).

Rass et al. reported neurological sequelae 3 months after infection in a prospective multicenter observational study on 135 patients (23% required ICU, 53% regular ward and 24% outpatients) (39). Neurological involvement was documented using neurological examination, 16-item Sniffin-Sticks-test for smelling disturbance, Montreal Cognitive Assessment for cognitive deficits and Hospital Anxiety and Depression Scale, Post-traumatic Stress Disorder Checklist-5 for mental health. After 3 months, 15% of the patients had one or more neurological sequelae which were not present at admission. Complications were noted more frequently in the ICU group than others and were represented by: poly-neuro/myopathy (13%), mild encephalopathy (2%), ischemic stroke (1%) and parkinsonism (1%). Hyposmia/anosmia at 3 months was observed in 17% of the patients, a significantly lower percent compared to the acute phase (44%). Other neurological manifestations detected were: cognitive deficits in 23% of the patients, sleep disturbance in 34%, anxiety and depression in 11%, tremors in 10%, muscle atrophyor limb-paresis in 5% and bradykinesia in 5% (39).

Persistent neurological problems were described even 6 months post-acute infection. In a 6 months follow-up study on 165 patients in Italy, Pilotto et al. found that 40% of the patients had neurological abnormalities. The most prevalent were hyposmia (18%), limb deficits (7.8%), postural tremor (13.8%) and memory and attention complains (31%). All manifestations were more likely to be present in el-

derly patients with comorbidities and longer admission period (40).

Furthermore, more than 27 cases of Guillain-Barré syndrome (GBS) have been described after COVID-19 infection. GBS was most common in elderly with no evidence of SARS-COV-2 in the cerebrospinal fluid, which suggests an inflammatory mechanism responsible for the peripheral nerve involvement (35).

QUALITY OF LIFE, PHYSICAL, MENTAL AND PSYCHOSOCIAL FUNCTION

The COVID-19 pandemic has been associated with decreased quality of life and poor mental health caused by disease, quarantine, social distancing, lockdown, job loss, homeschooling and work from home. The current pandemic has affected young people and elderly equally, causing unprecedented changes in our lives and being responsible for a high rate of morbidity and mortality (41).

Recovery process after COVID-19 infection is complex and needs to take into consideration the disease outcomes such as persistent lung damage, post-traumatic stress disorder (PTSD), anxiety, depression, persistent symptoms, etc. Studies of SARS survivors after 2 years showed important levels of anxiety (30%), depression (33%) and PTSD (39%). Also, the percent of people not returning to work after 2 years was 29.6% from healthcare workers group and 7.1% from non-healthcare workers group (42). In a prospective cohort study, Jacobs et al. (12) analyzed the impact of persistent symptoms after 35 days post-discharge on quality of life, physical and mental health and social active role. They reported that 23.2% of respondents described their quality of life as poor, 27.1% had poor physical health and another 16.9% had poor mental health. Some participants described problems doing everyday activities such as: dressing (3.3%), walking (15.6%), climbing stairs (29.9%), washing dishes (4.4%), meal preparation (6.3%), making the bed (6.2%). After 35 days from discharge, only 29.9% of the participants employed had returned to their job (12).

In a prospective study authored by Taboada et al., 99 ICU patients were evaluated 6 months after infection diagnosis (43). The results showed a decrease in quality of life among 67% patients. This was measured using EQ-5D-3L questionnaire which contains 5 dimensions (mobility, self-care, usual activities, pain and discomfort and anxiety and depression) and a visual analog scale (0 = worst imaginable health and 100 = best imaginable health). The study also evaluated functional status using a post-COVID-19 functional status scale and the results showed that 17.6% of patients were not able to perform all usual activities while 5.5% were facing severe limitations, depending on other person due to significant symptoms (43).

Regarding mental health consequences of COVID-19, it has already been described that a considerable number of patients are confronting PTSD, depression, anxiety, insomnia and obsessive-compulsive symptomatology. In a study that included 144 patients with COVID-19 infection, 34.72% were diagnosed with anxiety and 28.47% of the patients had symptoms of depression. The results showed that patients with severe forms of disease, older age and female gender were more likely to be anxious. On the other hand, age, family infection with SARS-CoV-2 and lack of social support were associated with depression. Risk factors for mental health issues were education background, family member concern or lack of family (44).

Another prospective cohort study, which included 101 COVID-19 survivors, found a median Hospital Anxiety and Depression Scale score of 3.0 for depressive symptoms and 4.0 for anxiety; the score results were higher in patients with severe pneumonia than those with moderate pneumonia. The prevalence of anxiety was 16% and depressive symptoms were present in 12% of the patients (18).

CONCLUSIONS

The ongoing pandemic caused by SARS-COV-2 is still a significant global health concern, causing thousands of deaths every day. There is much more to find out about COVID-19 infection and its consequences.

In this review, we summarized which are the post-discharge outcomes for patients with coronavirus disease. A part of the patients infected with SARS-COV-2 develop post-COVID syndrome which have already been described in the literature.

Post-COVID-19 syndrome is including a persistent symptomatology, prolonged organ dysfunction and changes regarding quality of life, mental health and wellbeing. Persistent symptoms can be found even 6 months after acute infection. The most frequent symptoms reported were fatigue and dyspnea, but cough, sleep difficulties, smell and taste impairment, joint and chest pain, short-term memory loss and concentration problems were also described. The impact of these symptoms is experienced by some patients day by day, physically and mentally, affecting social and professional life, and in same cases even ability to care for themselves.

COVID-19 infection in some high risk categories, such as those with severe forms, or elder patients was correlated with increased risk of hospital readmission and death after discharge. These arguments are supporting the idea of multi-organ dysfunction and long-term sequelae of COVID-19.

Also, due to the increased risk of distant thromboembolic events, long-term anticoagulation could be necessary especially in high-risk patients. Some studies suggest extended anticoagulation prophylaxis for severe forms of COVID-19 after the acute episode, although long term outcomes regarding thromboembolic events are unknown.

There is an alarming impact on quality of life and mental health consequences determined by COVID-19. After an acute episode, many patients face anxiety, depression, insomnia and PTSD.

Considering that the number of infected people is increasing day by day, adding to the 209 million people who have already been infected, greater pressure on health systems can be expected. Also initially unforseen social costs due to long term consequences of COVID-19 become more and more evident.

Finally, more research is needed in order to determine the short and long-term footprints of the COVID-19 infection and also regarding knowledge about diagnosis, treatment and prevention of post-COVID syndrome.

REFERENCES

1. WHO, COVID-19 Dashboard Geneva: World Health Organization 2020. Available at: https://covid19.who.int/ (accessed on 21 of August 2021).
2. Li X, Ma X. Acute respiratory failure in COVID-19: is it "typical" ARDS? *Crit Care.* 2020 May 6;24(1):198.
3. Gupta A, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS, Bikdeli B, et al. Extrapulmonary manifestations of COVID-19. *Nat Med.* 2020 Jul;26(7):1017-1032.
4. World Health Organization. COVID-19 Clinical management. Living guidance. Available at: https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-1.
5. Fu L, Wang B, Yuan T, Chen X, Ao Y, Fitzpatrick T, et al. Clinical characteristics of coronavirus disease 2019 (COVID-19) in China: A systematic review and meta-analysis. *J Infect.* 2020 Jun;80(6):656-665.
6. Huang C, Huang L, Wang Y, Xia Li X, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *The Lancet.* 2021;397(10270):220-232.
7. National Institute for Health and Care Excellence - guideline, COVID-19 rapid guideline: managing the long-term effects of COVID-19. Available at: https://www.nice.org.uk/guidance/ng188 (accessed on 9th of March 2021).
8. National Center for Immunization and Respiratory Diseases (NCIRD), Division of Viral, Post-COVID Conditions: Information for Healthcare Providers. Available at: https://www.cdc.gov/ncird/index.html.
9. Garrigues E, Janvier P, Kherabi Y, Le Bot A, et al. Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. *J Infect.* 2020 Dec;81(6):e4-e6.
10. Carfì A, Bernabei R, Landi F; Gemelli Against COVID-19 Post-Acute Care Study Group. Persistent Symptoms in Patients After Acute COVID-19. *JAMA.* 2020 Aug 11;324(6):603-605.
11. Carvalho-Schneider C, Laurent E, Lemaignen A, Beaufils E, et al. Follow-up of adults with noncritical COVID-19 two months after symptom onset. *Clin Microbiol Infect.* 2021 Feb;27(2):258-263.
12. Jacobs LG, Gourna Paleoudis E, Lesky-Di Bari D, Nyirenda T, et al. Persistence of symptoms and quality of life at 35 days after hospitalization for COVID-19 infection. *PLoS One.* 2020 Dec 11;15(12):e0243882.
13. Mandal S, Barnett J, Brill SE, Brown JS, Denneny EK, et al.; ARC Study Group. 'Long-COVID': a cross-sectional study of persisting symptoms, biomarker and imaging abnormalities following hospitalisation for COVID-19. *Thorax.* 2021 Apr;76(4):396-398.
14. Tenforde M, Kim SS, Lindsell CJ, et al. Symptom Duration and Risk Factors for Delayed Return to Usual Health Among Outpatients with COVID-19 in a Multistate Health Care Systems Network — United States, March–June 2020. Morbidity and Mortality Weekly Report (MMWR). 2020;69(30):993-998.
15. Stavem K, Ghanima W, Olsen MK, Gilboe HM, Einvik G. Persistent symptoms 1.5-6 months after COVID-19 in non-hospitalised subjects: a population-based cohort study. *Thorax.* 2021 Apr;76(4):405-407.
16. Ayoubkhani D, Khunti K, Nafilyan V, Maddox T, Humberstone B, Diamond I, et al. Epidemiology of post-COVID syndrome following hospitalisation with coronavirus: a retrospective cohort. *medRxiv.* 15.01.2021.
17. Gavriatopoulou M, Korompoki E, Fotiou D, Ntanasis-Stathopoulos I, Psaltopoulou T, Kastritis E, Terpos E, Dimopoulos MA. Organ-specific manifestations of COVID-19 infection. *Clin Exp Med.* 2020 Nov;20(4):493-506.
18. van der Sar, van der Brugge S, Talman S, et al. Pulmonary function and health-related quality of life after COVID-19 pneumonia. *Respir Med.* 2021 Jan;176:106272.
19. Zhao Y, Shang Y, Song W, Li Q, Xie H, et al. Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery. *EClinicalMedicine.* 2020;25.
20. Long B, Brady WJ, Koyfman A, Gottlieb M. Cardiovascular complications in COVID-19. *Am J Emerg Med.* 2020 Jul; 38(7):1504-1507.
21. Huang C, Wang Y, Li X, Ren L, Zhao J, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* 2020 Feb 15;395(10223):497-506.
22. Guzik TJ, Mohiddin SA, Dimarco A, Patel V, Savvatis K, et al. COVID-19 and the cardiovascular system: implications for risk assessment, diagnosis, and treatment options, *Cardiovascular Research.* 2020; 116(10):1666-1687.
23. Mitrani RD, Dabas N, Goldberger JJ. COVID-19 cardiac injury: Implications for long-term surveillance and outcomes in survivors. *Heart Rhythm*. 2020;17(11):1984-1990.
24. Kwong JC, Schwartz KL, Campitelli MA, Chung H, Crowcroft NS, et al. Acute Myocardial Infarction after Laboratory-Confirmed Influenza Infection. *N Engl J Med.* 2018 Jan 25;378(4):345-353.
25. Bangalore S, Sharma A, Slotwiner A, Yatskar L, Harari R, Shah B, et al. ST-Segment Elevation in Patients with Covid-19 - A Case Series. *N Engl J Med.* 2020 Jun 18;382(25):2478-2480.
26. Modin D, Claggett B, Sindet-Pedersen C, Lassen MCH, Skaarup KG, et al. Acute COVID-19 and the Incidence of Ischemic Stroke and Acute Myocardial Infarction. *Circulation.* 2020 Nov 24;142(21):2080-2082.
27. Puntmann VO, Carerj ML, Wieters I, Fahim M, Arendt C, et al. Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol.* 2020 Nov 1;5(11):1265-1273.
28. Sardu C, Gambardella J, Morelli MB, Wang X, Marfella R, Santulli G. Hypertension, Thrombosis, Kidney Failure, and Diabetes: Is COVID-19 an Endothelial Disease? A Comprehensive Evaluation of Clinical and Basic Evidence. *J Clin Med.* 2020 May 11;9(5):1417.
29. Costanzo L, Palumbo FP, Ardita G, et al. Coagulopathy, thromboembolic complications, and the use of heparin in COVID-19 pneumonia. *J Vasc Surg Venous Lymphat Disord.* 2020;8(5):711-716.

30. Rieder M, Goller I, Jeserich M, Baldus N, Pollmeier L, et al. Rate of venous thromboembolism in a prospective all-comers cohort with COVID-19. *J Thromb Thrombolysis.* 2020 Oct;50(3):558-566.
31. Lodigiani C, Iapichino G, Carenzo L, et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. *Thromb Res.* 2020;191:9-14.
32. Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res.* 2020 Jul;191:145-147.
33. Kunutsor SK, Laukkanen JA. Incidence of venous and arterial thromboembolic complications in COVID-19: A systematic review and meta-analysis. *Thromb Res.* 2020;196:27-30.
34. Patell R, Bogue T, Koshy A, et al. Postdischarge thrombosis and hemorrhage in patients with COVID-19. *Blood.* 2020 Sep 10;136(11):1342-1346.
35. Eswaran H, Jarmul JA, Shaheen AW. Vascular thromboembolic events following COVID-19 hospital discharge: Incidence and risk factors. *Res Pract Thromb Haemost.* 2021 Feb 8;5(2):292-295.
36. Mao L, Jin H, Wang M, et al. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurol.* 2020 Jun 1;77(6):683-690.
37. Pergolizzi JV Jr, Raffa RB, Varrassi G, Magnusson P, et al. Potential neurological manifestations of COVID-19: a narrative review. *Postgrad Med.* 2021 Jan 11:1-11.
38. Rahman A, Niloofa R, De Zoysa IM, Cooray AD, Kariyawasam J, Seneviratne SL. Neurological manifestations in COVID-19: A narrative review. *SAGE Open Medicine.* January 2020.
39. Rass V, Beer R, Josef Schiefecker A, Neurological outcome and quality of life three months after COVID-19: a prospective observational cohort study. *Eur J Neurol.* 2021 Mar 7.
40. Pilotto A, Cristillo V, Piccinelli SC. Long-term neurological manifestations of COVID-19: prevalence and predictive factors. *medRxiv.* 2020.
41. Ravens-Sieberer U, Kaman A, Erhart M, Devine J, Schlack R, Otto C. Impact of the COVID-19 pandemic on quality of life and mental health in children and adolescents in Germany. *Eur Child Adolesc Psychiatry.* 2021 Jan 25:1–11.
42. Ngai JC, Ko FW, Ng SS, To KW, Tong M, Hui DS. The long-term impact of severe acute respiratory syndrome on pulmonary function, exercise capacity and health status. *Respirology.* 2010;15(3):543-550.
43. Taboada M, Moreno E, Cariñena A, Rey T, Pita-Romero R, et al. Quality of life, functional status, and persistent symptoms after intensive care of COVID-19 patients. *Br J Anaesth.* 2021 Mar;126(3):e110-e113.
44. Kong X, Kong F, Zheng K, Tang M, Chen Y, et al. Effect of Psychological-Behavioral Intervention on the Depression and Anxiety of COVID-19 Patients. *Front Psychiatry.* 2020 Nov 20;11:586355.