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Review

Beyond COVID-19 and SARS-CoV-2, cardiovascular outcomes of “long covid” from a pathological perspective – a look back and road ahead

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ABSTRACT

With the decrease in severity of COVID-19 there is a sense of relief in the general population. However, there has been an increased incidence of cardiovascular and other organ complications post-infection, which have raised concerns about long COVID. The term “long COVID” was first used by Perego on social media to denote the persistence of symptoms weeks or months after initial SARS-CoV-2 infection and the term ‘long haulers’ was first described by Watson and by Yong to identify post-COVID conditions. There has been an increased incidence of sudden cardiac death and MI post-COVID-19 in healthy individuals, sports persons and prominent movie stars. Potential mechanisms contributing to the pathophysiology of post-acute COVID-19 may include 1) Damage to tissues and cells that are important for blood flow, so clotting of blood is increased. 2) Persistence of fragments of virus or its sub-particles/ protein material in a wide range of body sites and, 3) an immune system gone haywire. As the majority of countries across the globe are easing coronavirus precautionary measures, there is an urgent need by health care organizations and policymakers worldwide to generate awareness by educating the public at large, about the ill effects of long-COVID and varied types of post-acute sequelae of COVID-19.

1. Introduction

1.1. The alarm

While the severity of COVID-19 seemed to be decreasing worldwide giving a sense of relief to the health care community, hospitals and policymakers, at this juncture a critical study, published in “Nature Medicine” Journal on 22 May 2022, has analyzed data of 1,54,000 US veterans with SARS-CoV-2 infection. It has reported that in the year 2022, after recovering from the acute phase of illness the patients have increased risk of multiple cardiovascular problems, including heart muscle inflammation, abnormal heart rhythm, strokes, blood clots, myocardial infarction, and heart failure. What was more alarming from the findings of this study was that increased risk was present even among those who were not hospitalized after the acute COVID-19 infection. They further observed that even those people who were previously healthy, did not have high BMI, were not obese, did not smoke, and did

not have kidney disease or diabetes had a higher risk of heart problems post COVID-19 infection [1].

There have been recent findings of increased incidence of heart-related morbidity and mortality including fatal myocardial infarction and sudden death among young athletes, movie stars and individuals with a healthy lifestyle, who had a recent history of COVID-19 infection even with mild symptoms. It has raised genuine concerns about the current limits of our knowledge and understanding regarding the potentially high-risk and occult prevalence of COVID-19 heart manifestations [2]. COVID-19 has tested the knowledge of humankind and has shown how the desire of society to return to pre-pandemic “normal” can clash with science.

The results of another study done by Ziyad Al-Aly and published in “Nature” showed that individuals who survive for 4 weeks or more after COVID-19 diagnosis have an increased risk of death and are more likely to use health care resources, as well as a substantial burden of health loss, that includes both pulmonary as well as extra-pulmonary organs

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[3]. So a long-term approach to patient care in the post-COVID-19 setting is very important and needs to be holistic with the participation of multidisciplinary teams.

1.2. The science behind long-COVID

A long-lasting disorder that does not resolve over many months (persisting for at least more than 4–8 weeks), arising following infection with SARS-CoV-2 (virus that causes COVID-19), has been termed “long-COVID”, “post COVID-19 condition” “post-acute sequelae of COVID-19” (PASC) or post-acute sequelae SARS-CoV-2 infection. It may impact as many as 40% of COVID-19 survivors [4,5]. The World health organization defines Post COVID-19 condition or long COVID as “the illness that occurs in people who have a history of probable or confirmed SARS-CoV-2 infection; usually within three months from the onset of COVID-19, with symptoms and effects that last for at least two months. The symptoms and effects of the post-COVID-19 condition cannot be explained by an alternative diagnosis.” [6] The term long COVID was first used by Perego on social media to denote the persistence of symptoms weeks or months after initial SARS-CoV-2 infection and the term ‘long haulers’ was first described by Watson and by Yong to identify post-COVID conditions [7]. Long COVID has proved difficult to study and define, not only because the array and varied severity of symptoms makes it hard to objectify but also because of the fact that there is no specific timeline which can be drawn to define the occurrence of symptoms.

An important observation made by researchers regarding long COVID is that the symptoms fluctuate, and people often go through phases of feeling better before relapsing [8]. Nalbandian et al. reviewed nine studies related to the prevalence of “long COVID” and found that between 32.6% and 87.4% of patients reported at least one symptom persisting after several months [9]. Long COVID seems to be more commonly observed in females as compared to males. Post-acute sequelae of COVID-19 are being diagnosed equally in patients who developed severe acute COVID-19, and also in those patients who experienced only mild symptoms or asymptomatic cases. Evans and her PHOSP-COVID colleagues found little relationship between the severity of the acute phase, or levels of organ damage, and the severity of long COVID [10]. However, in a recent study published in Nature, the authors found that the frequency of long COVID exhibit a graded increase in severity of the spectrum of the initial acute phase of COVID-19 (from asymptomatic or symptomatic non-hospitalized, to hospitalized individuals to those admitted to ICU) [11].

An extensive list of symptoms in varying combinations and severity has been reported by a survey of thousands of people which includes shortness of breath, fatigue, dry cough, headache, muscle aches, insomnia, palpitations, chronic rhinitis, dysgeusia, chills, sore throat and cognitive dysfunctions. Athena Akrami with her team found 205 different symptoms in a study in an international cohort of more than 3500 people [12].

Potential mechanisms contributing to the pathophysiology of post-acute COVID-19 may include 1) damage to the tissues and cells that are important for blood flow and clotting of blood is increased. Also, there may be an increased incidence of circulating minute blood clots/ amyloid micro clot formation, due to acute viral infection or fueled by its aftermath, which might lead to micro-infarcts in various organs including the heart 2.) Persistence of fragments of virus or its sub-particles/ protein material in a wide range of body sites, especially nerves and other tissues like the heart, which may keep on hurting chronically, 3.) an immune system gone haywire and attacking the rest of the body, hence the proposition that long COVID could be an auto-immune condition [13,14]. Most of the studies conclude that there are multiple mechanisms at work that lead to long COVID, so there are different and varied clinical presentations.

A significant increase in the level of dysregulated molecules (α (2)-antiplasmin, various fibrinogen chains, as well as serum amyloid A

(SAA)) was seen in supernatant and micro-clots in acute COVID-19 as well as Long COVID/PASC by a research team of South Africa, and they propose that it might be because of the prolonged inflammatory status in long COVID/PASC [13]. So the suspected symptoms caused due to long-COVID may be caused by the inflammatory molecules trapped inside the tiny blood clots.

1.3. Nature of the previous coronavirus and its latest counterpart: is there any difference?

Respiratory tract infections are the main pathology of the previous seven coronaviruses known to infect humans, without prominent involvement of the heart. However, the coronavirus (SARS-CoV-2) which led us to the current devastating pandemic has shown significant infection of the heart in addition to the lung and can lead to necrosis of myocytes mimicking heart attack, and myocarditis (inflammation of the heart), blood clot, heart failure due to muscle dysfunction and arrhythmias.

The Middle East respiratory syndrome (MERS; caused by MERS-CoV) can very occasionally cause inflammation of the myocardium and very few case reports of cardiac involvement in patients with SARS (caused by SARS-CoV) have been documented [15]. The four “common cold” human coronaviruses—H CoV-229E, H CoV-NL63, H CoV-OC43, and H CoV-HKU1—have not shown any involvement in the heart [16].

The level of organ damage experienced by younger healthy adults and children with long COVID is a major concern, since the development of long COVID could greatly impact the future quality of life by predisposing otherwise healthy people to chronic ailments.

1.4. The beginning

In the early days of the pandemic, most of the autopsy studies have shown minimal to negligible direct viral cytopathic changes on the myocytes: this could be due to limited samples examined. Then in March 2020, a case series from Wuhan, China was published in which researchers studied 41 patients with COVID-19 which showed five patients (12%) had a myocardial injury with elevated levels of high-sensitivity cardiac troponin I [17]. Later in May 2020, a meta-analysis of six published studies from China found that 8% of patients with COVID-19 had associated cardiac injury [18].

1.5. The first significant “bugle” of myocardial involvement

As the cases started increasing, it became clear that Coronavirus was wreaking havoc on the heart. In the beginning, troponin levels were reported to be significantly high in patients suffering from COVID-19, which alarmed clinicians and it was taken as an indicator of cardiac injury. Early reports from China showed that 7–20% of patients suffering from COVID-19 had increased levels of cardiac biomarkers or electrocardiographic (ECG) abnormalities indicating underlying myocardial injury [19]. A retrospective study published from Wuhan, China, of 416 COVID-19 hospitalized patients found that 20% had an underlying myocardial injury; these patients had a much higher mortality rate (51%) as compared to patients without cardiac injury (5%) [20].

In hospitalized patients with COVID-19, acute heart failure, arrhythmias, and blood clots began to be commonly encountered. Myocarditis began to be identified as an important cardiovascular complication at autopsy, especially in patients with high viral loads and mononuclear cell infiltrates [21–23] One study suggested that up to 7% of the deaths were caused due to myocarditis in COVID 19 patients [24]. Soon it was observed that acute myocarditis presents across a variable range of clinical severity with increased serum troponin values, in patients with COVID-19 infection.

1.6. The backstage to cardiac involvement

In a systematic review of 316 cases of cardiac autopsy taken from 41 studies, Roshdy et al. found a wide range of cardiac abnormalities including gross pathology or histology in almost all cases, myocyte or ventricular wall hypertrophy was seen in 85 cases (26.8%) and fibrosis in 72 cases (22.8%). They noted acute myocardial ischemia in 25 cases either in the form of acute myocardial infarction (MI) (n = 11) or microscopic evidence of acute or early ischemia (n = 14). Also, fibrin micro-vascular thrombi were identifiable in 27 cases. They also noted that many studies reported the presence of SARS-CoV-2 within the myocardium using different techniques in 50 of 105 hearts (47%) [25]. In a study of 50 cases of a cardiac autopsy by Sang J C et al., they observed myocardial fibrosis in 80.0%, hypertrophy in 72.0%, and microthrombi in 66.0% of cases. A review cohort consisting of 50 studies including 548 hearts was observed by Raghd Almamoulouk and his colleagues. They noted that the most prevalent acute cardiovascular findings were myocardial necrosis (median: 100.0%; IQR, 20–100%; the number of studies = 9; the number of patients = 64) and myocardial oedema (median: 55.5%; IQR, 19.5–92.5%; the number of studies = 4; the number of patients = 46). The most prevalent chronic changes were myocyte hypertrophy (median: 69.0%; IQR, 46.8–92.1%) and fibrosis (median: 35.0%; IQR, 35.0–90.5%). SARS-CoV-2 was detected in the myocardium with a median prevalence of 60.8% (IQR 40.4–95.6%) [26].

There are several studies demonstrating that SARS-CoV-2 binds to ACE2 receptors with greater affinity compared to SARS-CoV. This may partially explain the increased affinity of SARS-CoV-2 in different organs including the heart of patients getting infected with the coronavirus [27–29].

Multiple mechanisms have been shown to have a role in the pathogenesis of multi-organ injury in response to infection with SARS-CoV-2 including direct viral toxicity, dysregulation of the immune response, endothelial cell damage and thrombo-inflammation, and dysregulation of the renin-angiotensin-aldosterone system (RAAS) [30]. There is significant tropism of SARS-CoV-2, to organs other than the lungs, including the heart, kidneys and liver, as has been demonstrated by various studies. In a study from Germany by Puelles and his team, copies of the virus were detected in the heart of 16 of 22 (72.7%) patients who died of COVID-19 [31]. In another autopsy series of 39 patients dying from COVID-19, the virus was documented in 24 of 39 patients (61.5%), whereas 31% had a high viral load above 1000 copies in the heart [32]. Besides directly infecting heart muscle cells, the viral entry has been documented in the endothelial cells that line the blood vessels to the heart and interstitial cells or macrophages invading the myocardial tissue [32].

SARS-CoV-2 in cardiac tissue does not lead to an obligatory inflammatory reaction consistent with clinical myocarditis, it may lead to other long-term consequences [32]. Many potential indirect effects have been observed including secondary immune response to the infected heart and endothelial cells (endothelitis). Juan A Pérez-Bermejo and his team from the USA observed, the exposure of human induced pluripotent stem cell (iPSC) derived heart cells to SARS-CoV-2 and found active infection and marked transcriptomic and morphological hallmark of damage, particularly in cardiomyocytes. Transcriptomic disruption of structural proteins was directly associated with the adverse morphologic features, which consisted of a specific myofibrillar fragmentation and numerous iPSC-cardiomyocytes lacking nuclear DNA. Similar sarcomeric disruption, as well as cardiomyocytes without DNA staining, has also been observed from human autopsy specimens in patients of COVID-19 infection. They raised concerns that these striking cytopathic effects may adversely lead to long-term consequences on the COVID-19 heart [33].

Other indirect effects on the heart which can lead to long-term consequences include, dysregulation of the renin-angiotensin-aldosterone system that modulates blood pressure, downregulation of

ACE2 and activation of a proinflammatory response involving platelets, neutrophils, macrophages, and lymphocytes, with the release of cytokines and a prothrombotic state. A propensity for clotting, both in the microvasculature and large vessels, has been reported in multiple autopsy series and young COVID-19 patients presenting with strokes.

There has been an increased incidence of microvascular and large vessel clot formation, especially in young COVID-19 patients with strokes. These blood clots can block microcapillaries thereby inhibiting oxygen exchange in various organs including the heart leading to late cardiovascular pathologies. Pretorius E. and her colleagues at Stellenbosch University observed from their study that plasma samples from Long COVID/PASC patients still contain large anomalous (amyloid) deposits (micro clots). They further showed that these micro clots in both acute COVID-19 and Long COVID/PASC plasma samples were resistant to fibrinolysis (compared to plasma from controls and T2DM), even after trypsinization. It was only after the second round of trypsinization that, the persistent pellet deposits (micro clots) were solubilized. They also detected various inflammatory molecules that were markedly increased in both the supernatant and trapped in the solubilized pellet deposits of acute COVID-19 and Long COVID/PASC as compared to controls, especially $\alpha(2)$ -antiplasmin ($\alpha(2)AP$), various fibrinogen chains, as well as Serum Amyloid A (SAA) [34]. The persistence of micro clots in long-COVID/ PASC patients might have a significant role in sudden cardiac death and other morbidities associated with the heart.

A study was published in 2015 in JAMA, performed by Corrales-Medina et al., on the association between hospitalization due to pneumonia and subsequent risk of cardiovascular disease. The investigators followed-up of 591 pneumonia cases (community-based cohorts: Cardiovascular Health Study) over 10 years and found that 206 developed cardiovascular diseases (CVD) events during this period. CVD risk among pneumonia cases compared with controls was highest during the first year after hospitalization and remained significantly higher than that among controls throughout 10 years [35]. Similarly COVID-19 associated pneumonia and pneumonitis may also indirectly increase the risk of cardiovascular disease in the patients over some time, this association also has to be studied in detail.

1.7. Bumpy Road ahead for cardiac manifestations of long COVID

There was an increased incidence of sudden cardiac death and MI post-COVID-19 in healthy individuals, sports persons and prominent celebrities, most of them young and healthy who had suffered from mild manifestations of COVID-19. Since these were widely reported from different parts of the globe on news and social media platforms, it led researchers to thoroughly investigate possible causes.

Researchers soon noted that not only symptomatic people with active infection but also those who were asymptomatic had heart-wrecking effects of COVID-19. In a large-scale study, published in Nature Medicine by researchers at the Veterans Affairs (VA) St Louis Health Care System, long-term cardiovascular outcomes of COVID-19 were analysed from data of nearly 154 000 US veterans with SARS-CoV-2 infection and this showed a very grim picture. They found that within a year after recovering from the acute phase of illness, patients had increased risks of several cardiovascular problems, including heart muscle inflammation, abnormal heart rhythms, myocardial infarction, blood clots, strokes, and heart failure. The increased risk was even more evident among those who weren't hospitalized with acute COVID-19. In the 12 months follow up period, it was estimated that for every 1000 people, COVID-19 was associated with an extra 45.29 incidents of cardiovascular condition, as compared to the control group. There were, 23.48 incidents of major adverse cardiovascular events (MACEs), including myocardial infarction and stroke, 19.86 incidents of dysrhythmias, including 10.74 incidents of atrial fibrillation, 12.72 incidents of other cardiovascular disorders including 11.61 incidents of heart failure and 3.56 incidents of non-ischemic cardiomyopathy, 9.88

cases of thromboembolic disorders, consisting of 5.47 incidents of pulmonary embolism and 4.18 incidents of deep vein thrombosis, 7.28 incidents of ischemic heart disease including 5.35 incidents of acute coronary disease, 2.5 incidents of angina, 2.91 incidents of myocardial infarction, 5.48 incidents of cerebrovascular disorders, including 4.03 incidents of stroke and 1.23 incidents of inflammatory disease of the heart or pericardium, including 0.98 incidents of pericarditis and 0.31 incidents of myocarditis. There were increased risks of post-COVID complications which did not have any correlation with age, race, sex, obesity, smoking, hypertension, diabetes, chronic kidney disease, hyperlipidemia, and pre-existing cardiovascular disease. Patients with more severe diseases (determined by whether they recuperated at home, were hospitalized, or were admitted to the intensive care unit) had higher risks.

In July 2020, Puntmann and his team described the outcomes of cardiovascular Magnetic Resonance Imaging in patients who recently recovered from COVID-19. They observed that, high-sensitivity troponin T (hsTnT) was detectable (greater than 3 pg/mL) in 71 patients recently recovered from COVID-19 (71%) and significantly elevated (greater than 13.9 pg/mL) in 5 patients (5%). More alarming and eye opener was the finding that of the 100 people studied, 78 had some kind of heart irregularity around two months after infection — and 60 showed signs of ongoing myocardial inflammation, some of whom were even asymptomatic [36].

1.8. How are children facing long COVID

Globally it has been observed that children are at a higher risk of SARS-CoV-2 infection, although the severity of the disease is mild in most of them. This is not just due to a lack of approved vaccines for children aged 0–4 years but only a few countries allowing vaccination for children aged 5–11 years, difficulties in practicing social distancing among children because of their schooling and less effectiveness of the vaccine, specifically against the Omicron variant of SARS-CoV-2 [37, 38]. In certain European countries, up to 58% of all children have had laboratory-confirmed infection. After the acute phase of SARS-CoV-2 infection, children can also develop long COVID symptoms. The most common, post Covid condition/ long COVID symptoms observed in children are headache (3–80%), fatigue (3–87%), sleep disturbance (2–63%), concentration difficulties (2–81%), and abdominal pain (1–76%) [37].

Professor Berg and his team did a nationwide survey-based study in Denmark to study long COVID symptoms in SARS-CoV-2-positive children aged 0–14 years. Their study group comprised SARS-CoV-2-positive children by PCR test aged 0–14 years (cases) and matched controls from Danish national registers. Cases and controls were selected between Jan 1, 2020, and July 12, 2021. Responses to the survey were received from 10 997 (28.8%) of 38 152 cases and 33 016 (22.4%) of 147 212 controls. For their study, they further divided both cases and controls into three age groups. They investigated the prevalence of long-lasting symptoms, the duration and intensity of symptoms, quality of life, number of sick days and absences from daycare or school, and psychological and social outcomes. They noticed cases had higher odds of reporting at least one symptom lasting more than 2 months than did the controls in all three age groups. They concluded that children with a confirmed history of SARS-CoV-2 infection between 0 and 14 years of age had prevalent long-lasting symptoms compared to the control group [39].

Another study from Germany by Martin Roessler and colleagues titled “Post COVID-19 in children, adolescents, and adults: results of a matched cohort study including more than 150,000 individuals with COVID-19” showed that for all health outcomes combined, incidence rates (IRs) in the COVID-19 cohort were significantly higher than those in the control cohort in both children/adolescents. They used overall, 96 pre-defined health outcomes which were aggregated into 13 diagnosis/symptom complexes and three domains (physical health, mental health,

and physical/mental overlap domain) [40]. A sample-based observation from the United Kingdom showed the prevalence of persistent symptoms lasting ≥ 4 weeks in children during the second and third U.K. wave of the COVID-19 pandemic was 1.7% overall, and 4.6% among children with a definite history of SARS-CoV-2 infection [41]. Long COVID must also be recognized as an alarming condition in children, and the need of the hour is a multi-disciplinary long COVID clinic for children as has been advocated for adults.

1.9. Vaccination and long COVID, it is protective. Think again!

Vaccination has a definite role in markedly decreasing the severity of COVID-19 and this has been proven without any doubt. Whether vaccine has a role in long COVID patients, including those with breakthrough infections, is however a matter of debate.

In the beginning, multiple smaller studies and one comparatively larger study found that vaccination has significant protection against long COVID [42,43]. The larger study by Michela Antonelli et al. found after analyzing the data of a cohort of 1.2 million UK smartphone users, who self-reported their condition, that two doses of a COVID-19 vaccine halved the risk of long COVID. This came as a relief for vaccinated people in which the severity of breakthrough infection was markedly reduced.

However soon after it was found in a large-scale study of more than 13 million people published in “Nature Medicine” on 25 May 2022, that vaccination against SARS-CoV-2 lowers the risk of long COVID after infection by only about 15%. The authors of this study also found that there was no difference in type or severity of long COVID symptoms in unvaccinated SARS-CoV-2 infected patients and those having a breakthrough infection [1].

1.10. The pandemic seems to be dwindling but not the suffering

As the majority of countries worldwide are easing coronavirus precautionary measures, there is an urgent need by health care organizations and policymakers to generate awareness by educating the public at large, about the ill effects of long-COVID and varied types of post-acute sequelae of COVID-19. This is important as it may affect vital organs like the heart and brain. Cardiac conditions need special attention, as there has been an increasing incidence of sudden cardiac death, myocarditis, stroke and myocardial infarction, especially in healthy individuals and sports persons who had a definite history of suffering from even mild COVID-19 in the recent past.

Even if we are vaccinated shall we need to protect ourselves from re-infection? This is an important question because due to widespread vaccination, the severe manifestations of COVID-19 have decreased drastically and people have started considering it at par with the usual flu and mild infective condition /pneumonia. How much vaccination can prevent the long-term complication of COVID-19 is still unclear, as the long COVID condition is prevalent in people who suffered from mild symptoms/ were asymptomatic and those who had severe COVID-19.

Nephrologist Ziyad Al-Aly at VA Saint Louis Health Care System in St Louis, Missouri, whose ground-breaking research published in Nature journal along with his colleagues, regarding “long COVID-19 after breakthrough SARS-COV-2 infection” has aptly said, “ We collectively dropped the ball on COVID-19” and “ I believe we are about to drop the ball on long COVID” [1]. COVID-19 proved to be a devastating multi-systemic disorder [44,45]. So, it is now high time that attention should be focused on long COVID, as the majority of long COVID patients are young adults and a significant population of children. So the risk of unproductivity, morbidity and mortality should not be forgotten as a huge population world over has already been infected by SARS-CoV-2. Let’s not drop the ball on long COVID.

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Conflict of Interest

We want to certify that there is no conflict of interest for the manuscript titled "Beyond COVID-19 and SARS-CoV-2, cardiovascular outcomes of "long covid" from a pathological perspective – a look back and road ahead", further there is no conflict of interest among authors.

References

- Z. Al-Aly, B. Bowe, Y. Xie, Long COVID after breakthrough SARS-CoV-2 infection, *Nat. Med.* 28 (7) (2022) 1461–1467, <https://doi.org/10.1038/s41591-022-01840-0>.
- Gelber J. Think Covid-19 Can't Harm Healthy, Young Athletes? Think Again. (<https://www.theguardian.com/sport/2020/dec/14/covid-19-effects-on-athletes-keyon-tae-johnson>). Accessed on: 26 July 2022.
- Z. Al-Aly, Y. Xie, B. Bowe, High-dimensional characterization of post-acute sequelae of COVID-19, *Nature* 594 (7862) (2021) 259–264, <https://doi.org/10.1038/s41586-021-03553-9>.
- M. Marshall, The four most urgent questions about long COVID, *Nature* 594 (7862) (2021) 168–170, <https://doi.org/10.1007/s11606-022-07443-2>.
- A.D. Proal, M.B. VanElzakker, Long COVID or post-acute sequelae of COVID-19 (PASC): an overview of biological factors that may contribute to persistent symptoms, *Front. Microbiol.* 12 (2021), 698169, <https://doi.org/10.3389/fmicb.2021.698169>.
- World Health Organization. Coronavirus disease (COVID-19): post COVID-19 condition. ([http://who.int/news-room/questions-and-answers/item/coronavirus-disease-\(covid-19\)-post-covid-19condition](http://who.int/news-room/questions-and-answers/item/coronavirus-disease-(covid-19)-post-covid-19condition)). (Accessed on: July 28 2022).
- A.V. Raveendran, R. Jayadevan, S. Sashidharan, Long COVID: an overview, *Diabetes Metab. Syndr.* 15 (3) (2021) 869–875, <https://doi.org/10.1016/j.dsx.2021.04.007>.
- N. Ziauddeen, D. Gurdasani, M.E. O'Hara, et al., Characteristics and impact of Long Covid: findings from an online survey, *PLOS ONE* 17 (3) (2022), e0264331, <https://doi.org/10.1371/journal.pone.0264331>.
- A. Nalbandian, K. Sehgal, A. Gupta, et al., Post-acute COVID-19 syndrome, *Nat. Med.* 27 (4) (2021) 601–615, <https://doi.org/10.1038/s41591-021-01283-z>.
- R.A. Evans, H. McAuley, E.M. Harrison, et al., Physical, cognitive, and mental health impacts of COVID-19 after hospitalization (PHOSP-COVID): a multicenter, prospective cohort study, *Lancet Respir. Med.* 9 (11) (2021) 1275–1287, [https://doi.org/10.1016/S2213-2600\(21\)00383-0](https://doi.org/10.1016/S2213-2600(21)00383-0).
- Y. Xie, E. Xu, B. Bowe, et al., Long-term cardiovascular outcomes of COVID-19, *Nat. Med.* 28 (2022) 583–590, <https://doi.org/10.1038/s41591-022-01689-3>.
- H.E. Davis, G.S. Assaf, L. McCorkell, et al., Characterizing long COVID in an international cohort: 7 months of symptoms and their impact, *E Clin. Med.* 38 (2021), 101019, <https://doi.org/10.1016/j.eclinm.2021.101019>.
- E. Pretorius, M. Vlok, C. Venter, et al., Persistent clotting protein pathology in Long COVID/Post-Acute Sequelae of COVID-19 (PASC) is accompanied by increased levels of antiplastin, *Cardiovasc. Diabetol.* 20 (1) (2021) 172, <https://doi.org/10.1186/s12933-021-01359-7>.
- E.J. Topol, COVID-19 can affect the heart, *Science* 370 (6515) (2020) 408–409, <https://doi.org/10.1126/science.abe2813>.
- T.Y. Xiong, S. Redwood, B. Prendergast, M. Chen, Coronaviruses and the cardiovascular system: acute and long-term implications, *Eur. Heart J.* 41 (19) (2020) 1798–1800, <https://doi.org/10.1093/eurheartj/ehaa231>.
- G.P. Otieno, N. Murunga, C.N. Agoti, K.E. Gallagher, J.O. Awori, D.J. Nokes, Surveillance of endemic human coronaviruses (HCoV-NL63, OC43 and 229E) associated with childhood pneumonia in Kilifi, Kenya, *Wellcome Open Res.* 5 (2020) 150, <https://doi.org/10.12688/wellcomeopenres.16037.2>.
- D. Wang, B. Hu, C. Hu, et al., Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China, *JAMA* 323 (11) (2020) 1061–1069, <https://doi.org/10.1001/jama.2020.1585>.
- B. Li, J. Yang, F. Zhao, et al., Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China, *Clin. Res. Cardiol.* 109 (5) (2020) 531–538, <https://doi.org/10.1007/s00392-020-01626-9>.
- M. Nishiga, D.W. Wang, Y. Han, D.B. Lewis, J.C. Wu, COVID-19 and cardiovascular disease: from basic mechanisms to clinical perspectives, *Nat. Rev. Cardiol.* 17 (9) (2020) 543–558, <https://doi.org/10.1038/s41569-020-0413-9>.
- S. Shi, M. Qin, B. Shen, et al., Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China, *JAMA Cardiol.* 5 (7) (2020) 802–810, <https://doi.org/10.1001/jamacardio.2020.0950>.
- K. Liu, Y.Y. Fang, Y. Deng, et al., Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province, *Chin. Med. J. (Engl.)* 133 (9) (2020) 1025–1031, <https://doi.org/10.1097/CM9.0000000000000744>.
- Z. Xu, L. Shi, Y. Wang, et al., Pathological findings of COVID-19 associated with acute respiratory distress syndrome, *Lancet Respir. Med.* 8 (4) (2020) 420–422, [https://doi.org/10.1016/S2213-2600\(20\)30076-X](https://doi.org/10.1016/S2213-2600(20)30076-X).
- Y. Liu, Y. Yang, C. Zhang, et al., Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury, *Sci. China Life Sci.* 63 (3) (2020) 364–374, <https://doi.org/10.1007/s11427-020-1643-8>.
- Q. Ruan, K. Yang, W. Wang, L. Jiang, J. Song, Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China, *Intensive Care Med.* 46 (5) (2020) 1–3, <https://doi.org/10.1007/s00134-020-05991-x>.
- A. Roshdy, S. Zaher, H. Fayed, J.G. Coghlan, COVID-19 and the heart: a systematic review of cardiac autopsies, *Front. Cardiovasc. Med.* 7 (2020), 626975, <https://doi.org/10.3389/fcvm.2020.626975>.
- R. Almamlouk, T. Kashour, S. Obeidat, et al., COVID-19-Associated cardiac pathology at the postmortem evaluation: a collaborative systematic review, *Clin. Microbiol. Infect.* 28 (8) (2022) 1066–1075, <https://doi.org/10.1016/j.cmi.2022.03.021>.
- D. Wrapp, N. Wang, K.S. Corbett, et al., Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation, *Science* 367 (6483) (2020) 1260–1263, <https://doi.org/10.1126/science.abb2507>.
- Q. Wang, Y. Zhang, L. Wu, et al., Structural and functional basis of SARS-CoV-2 entry by using human ACE2, 894-904.e9, *Cell* 181 (4) (2020), <https://doi.org/10.1016/j.cell.2020.03.045>.
- C. Lei, K. Qian, T. Li, et al., Neutralization of SARS-CoV-2 spike pseudotyped virus by recombinant ACE2-Ig, *Nat. Commun.* 11 (1) (2020) 2070, <https://doi.org/10.1038/s41467-020-16048-4>.
- H. Li, L. Liu, D. Zhang, et al., SARS-CoV-2 and viral sepsis: observations and hypothesis, *Lancet* 395 (10235) (2020) 1517–1520, [https://doi.org/10.1016/S0140-6736\(20\)30920-X](https://doi.org/10.1016/S0140-6736(20)30920-X).
- V.G. Puelles, M. Lütgehetmann, M.T. Lindenmeyer, et al., Multiorgan and renal tropism of SARS-CoV-2, *N. Engl. J. Med.* 383 (6) (2020) 590–592, <https://doi.org/10.1056/NEJMc2011400>.
- D. Lindner, A. Fitzek, H. Bräuninger, et al., Association of cardiac infection with SARS-CoV-2 in confirmed COVID-19 autopsy cases, *JAMA Cardiol.* 5 (11) (2020) 1281–1285, <https://doi.org/10.1001/jamacardio.2020.3551>.
- J.A. Perez-Bermejo, S. Kang, S.J. Rockwood, et al., SARS-CoV-2 infection of human iPSC-derived cardiac cells reflects cytopathic features in hearts of patients with COVID-19, *Sci. Transl. Med.* 13 (590) (2021) eabf7872, <https://doi.org/10.1126/scitranslmed.abbf7872>.
- E. Pretorius, M. Vlok, C. Venter, et al., Persistent clotting protein pathology in Long COVID/Post-Acute Sequelae of COVID-19 (PASC) is accompanied by increased levels of antiplastin, *Cardiovasc. Diabetol.* 20 (2021) 172, <https://doi.org/10.1186/s12933-021-01359-7>.
- V.F. Corrales-Medina, K.N. Alvarez, L.A. Weissfeld, et al., Association between hospitalization for pneumonia and subsequent risk of cardiovascular disease, *JAMA* 313 (3) (2015) 264–274, <https://doi.org/10.1001/JAMA.2014.18229>.
- V.O. Puntmann, M.L. Carerj, I. Wieters, et al., Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19), *JAMA Cardiol.* 5 (11) (2020) 1265–1273, <https://doi.org/10.1001/jamacardio.2020.3557>.
- P. Zimmermann, L.F. Pittet, N. Curtis, How common is long COVID in children and adolescents? *Pedia Infect. Dis. J.* 40 (12) (2021) e482–e487, <https://doi.org/10.1097/INF.0000000000003328>.
- Hansen C.H., Schelde A.B., Moustsen-Helm I.R., et al. Vaccine Effectiveness against SARS-CoV-2 Infection with the Omicron or Delta Variants Following a Two-Dose or Booster BNT162b2 or mRNA-1273. *MedRxiv*. <https://doi.org/10.1101/2021.12.20.21267966>.
- K. Schønning, R.B. Dessau, T.G. Jensen, et al., Electronic reporting of diagnostic laboratory test results from all healthcare sectors is a cornerstone of national preparedness and control of COVID-19 in Denmark, *APMIS* 129 (7) (2021) 438–451, <https://doi.org/10.1111/apm.13140>.
- M. Roessler, F. Tesch, M. Batram, et al., Post COVID-19 in children, adolescents, and adults: results of a matched cohort study including more than 150,000 individuals with COVID-19, *MedRxiv* (2021), <https://doi.org/10.1101/2021.10.21.21265133>.
- Faith Miller, Vincent Nguyen, Annalan M.D. Navaratnam, Madhumita Shrotri, Jana Kovar, Andrew C. Hayward, Ellen Fragaszy, Prevalence of persistent symptoms in children during the COVID-19 pandemic: evidence from a household cohort study in England and Wales *medRxiv*. 2021. <https://doi.org/10.1101/2021.05.28.21257602>.
- S. Reardon, Long COVID risk falls only slightly after vaccination, huge study shows, *Nat* (2022), <https://doi.org/10.1038/d41586-022-01453-0>.
- M. Antonelli, R.S. Penfold, J. Merino, et al., Risk factors and disease profile of post-vaccination SARS-CoV-2 infection in UK users of the COVID Symptom Study app: a

- prospective, community-based, nested, case-control study, *Lancet Infect. Dis.* 22 (1) (2022) 43–55, [https://doi.org/10.1016/S1473-3099\(21\)00460-6](https://doi.org/10.1016/S1473-3099(21)00460-6).
- [44] A. Singh, S. Zaheer, N. Kumar, T. Singla, S. Ranga, Covid19, beyond just the lungs: A review of multisystemic involvement by Covid19, *Pathol. Res. Pract.* 224 (2021), 153384, <https://doi.org/10.1016/j.prp.2021.153384>.
- [45] V. Thakur, R.K. Ratho, P. Kumar, S.K. Bhatia, I. Bora, G.K. Mohi, S.K. Saxena, M. Devi, D. Yadav, S. Mehariya, Multi-organ involvement in COVID-19: beyond pulmonary manifestations, *J. Clin. Med* 10 (3) (2021) 446, <https://doi.org/10.3390/jcm10030446>.