What might COVID-19 Patients Experience after Recovery? A Systematic Review

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Abstract

Objectives: To determine post-COVID-19 complications after recovery and investigate the reported cases of re-infection. Methods: The researchers systematically reviewed three databases: PubMed, Google Scholar, and Word Health Organization (WHO) COVID-19 database looking for studies reported post-COVID-19 complications and COVID-19 reinfection. The search was conducted between November 21, 2020 and January 14, 2021. Inclusion criteria were articles written in English and had primary data. The studies reported the complications of COVID-19 after full recovery were included. Case reports were only included in the COVID-19 reinfection section. Results: The review included 69 studies related to post-COVID-19 complications and 13 case studies related to COVID-19 reinfection. Thirty-six studies reported post-cure respiratory complications including dyspnea to residual pulmonary fibrosis. Cardiac symptoms were reported in nine studies including palpitation, chest pain and diastolic dysfunction. Neurological complications included post-traumatic stress syndrome (PTSD), anxiety, depression, memory issues, insomnia and sleeping disturbance, cognitive impairments, and stigma. Gastrointestinal symptoms included nausea, vomiting, diarrhoea, and acute liver injury. Physical decline was the most common symptom reported in the musculoskeletal complications. Thirteen cases COVID-19 reinfection from nine countries were reported. Four patients had severe symptoms in the second infection while the symptoms of nine patient ranged from mild to moderate. The time taken for the reinfection ranged from 26 days to 145 days. Conclusion: COVID-19 may cause several types of complications after recovery. Lung abnormalities, neurological complications, and exercise intolerance were frequently identified complications among COVID-19 survivors. Reinfection can occur among COVID-19 survivors. Thus, COVID-19 may need long-term follow-up and should take preventive measures to prevent the reinfection.

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Results: The review included 69 studies related to post-COVID-19 complications and 13 case studies related to COVID-19 reinfection. Thirty-six studies reported post-cure respiratory complications including dyspnea to residual pulmonary fibrosis. Cardiac symptoms were reported in nine studies including palpitation, chest pain and diastolic dysfunction. Neurological complications included post-traumatic stress syndrome (PTSD),

anxiety, depression, memory issues, insomnia and sleeping disturbance, cognitive impairments, and stigma. Gastrointestinal symptoms included nausea, vomiting, diarrhoea, and acute liver injury. Physical decline was the most common symptom reported in the musculoskeletal complications. COVID-19 reinfection was reported in 13 studies from nine countries. Four patients had severe symptoms in the second infection while the symptoms of the others ranged from mild to moderate. The time taken for the reinfection ranged from 26 days to 145 days.

Conclusion: COVID-19 may cause several types of complications after recovery. Shortness of breath, psychiatric symptoms and exercise intolerance were frequently identified complications among COVID-19 survivors. Thus, COVID-19 patients may need long-term follow-up. Reinfection can occur among COVID-19 survivors; hence, they should take preventive measures to avoid the reinfection.

Keywords: COVID-19 complications, Post COVID-19, COVID-19 relapse, Long COVID-19, COVID-19 reinfection.

How did you gather, select and analyze the information you considered in your review?

- The researchers systematically reviewed three databases: PubMed, Google Scholar, and Word Health Organization (WHO) COVID-19 database
- Inclusion criteria were articles written in English and had primary data related to post-COVID-19 complications and reinfection.
- Initially, all studies were screened using the titles and the abstracts. Then, full texts of the selected abstracts were evaluated to ensure that they meet the review inclusion criteria.

What is the 'take-home' message for the clinician?

COVID-19 patients may experience post cure complications which need long-term monitoring and may need management.

Reinfection can occur among COVID-19 survivors; hence, they should be advised to take preventive measures against the reinfection.

Introduction

At the end of 2019, a series of pneumonia cases emerged in Wuhan, China due to severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) virus. Thereafter, coronavirus disease 2019 (COVID-19) was declared a pandemic by the WHO on March 11th 2020[1]. As of March 5, 2021, the number of the confirmed COVID-19 cases has reached 116 million including around 2.57 million deaths worldwide[2]. The main clinical characteristics of COVID-19 ranged from minor symptoms which include headache or dizziness, diarrhoea, nausea and vomiting to moderate symptoms that include fever, cough, myalgia or fatigue, and/or dyspnoea. Sore throat, congestion or runny nose, loss of taste, or smell was reported in some cases recently. However, some cases developed complications such as RNAemia (SARS-COV-2 viral load), acute respiratory distress syndrome, acute cardiac injury, secondary infection, sepsis, septic shock, and multiple organs failure[3-6].

Patient recovery presents an additional challenge, which is the follow-up of those patients. Studies have shown that the virus-specific antibodies IgG and IgM, and the neutralizing serum antibodies declined during the convalescent phase (1-2 months post-recovery) especially in patients who were asymptomatic amid their infection episode[7] .Therefore, these studies expected that reinfection with COVID–19 may occur for a second time after recovery [7, 8]. In South Korea, 116 patients were retested positive after complete recovery from COVID–19[9]. Moreover, reinfection has been identified in a plethora of cases in China, France, and Iraq[101112].

Another key question after recovery is the potential long-term complications due to COVID–19 infection. It is paramount to assess the long term consequences of COVID–19, as some survivors have been complaining of limitation in physical function, that involved general weakness and/or shortness of breath[13], while other suffer from psychological complications such as post-traumatic stress disorder (PTSD) [14]. In addition, while screening the psychiatric symptoms of 402 survivors, high rates of PTSD (28%), anxiety (42%), depression (31%), and insomnia (40%) were self-rated as symptoms. Although the score is significantly higher in the

patients with a positive previous history of psychiatric disorders, follow-up after the recovery from COVID–19 is needed[15]. Many studies reported post-COVID-19 complications; thus, this review intended to compile and categorize all these findings to identify the most common post COVID-19 complications which would need monitoring and may need management. Additionally, some people may still not believe in the COVID-19 reinfection, so this review intended to collect cases from all around the world to confirm this reality.

The aims of this review were to determined post COVID–19 complications after complete recovery and review the reported reinfection COVID-19 cases.

Methods

Data sources and search strategy

The search of this review was conducted by two specialist pharmacists and included studies available in three data bases: PubMed, Google Scholar, and WHO COVID-19 databases (from Global research on coronavirus disease (COVID-19)). The review included search for two topics: Post-COVID-19 complication and COVID-19 reinfection.

The search for studies including post-COVID-19 complications started from November 21, 2020 through January 7, 2021. The keywords included ("Post COVID-19 discharge" OR "post COVID-19 follow-up" OR "COVID-19 long-term complications" OR "post COVID-19 complications" OR "COVID-19 survivors" OR "Long COVID).

In addition, a second search strategy included "COVID-19 reinfection" in PubMed, Google Scholar, and WHO COVID-19 databases. The search of this keyword was from January 1, 2021 to January 14, 2021.

Inclusion and Exclusion criteria

The studies were deemed eligible if they reported adult patients with post-COVID-19 complication. In other words, the symptoms should be identified after one or more negative COVID–19 polymerase chain reaction (PCR) tests among previously confirmed cases. In addition, the review included studies dealing with COVID–19 -related complications among both hospitalized and non-hospitalized patients. Only research studies with primary data and written in English were included while articles without empirical data or with secondary data such as reviews, commentaries, editorial, reports, and case reports were excluded (Figure 1). For this first search (post-COVID-19 complications), the researchers excluded case-studies since they are less generalizable.

Initially, all studies were screened using the titles and the abstracts. At this stage, all the abstracts that reported post-COVID-19 follow-up were included. Then, full texts of the selected abstracts were evaluated to ensure that they meet the inclusion criteria of the review. Ultimately, after excluding the irrelevant articles according to the exclusion criteria, a total of 69 studies were included (Figure 1).

Microsoft Excel was used for data extraction. The information of the included studies dealing Post-COVID complications were summarized in supplementary 1. The included information was the study title, authors' names, country, study design, follow-up onset, follow-up duration, objective, and main outcomes. The review focused on the study countries since there may be different strains/variant of SARS-2 virus which can vary across countries.

On the other hand, studies on COVID-19 reinfection represented a small proportion of the COVID-19 literature and most of them were case-report. Therefore, we included primary studies and case reports which are written in English. The studies were included if they reported patients with a confirmed diagnosis of COVID-19 followed by one or more of the followings: confirmed negative RT–PCR-test, then a confirmed diagnosis of COVID-19 for the second time. Out of 204 screened articles, 13 studies were included (Figure 2).

Results

The literature review identified 3,274 titles (PubMed (n=1598), Google Scholar (n=1566), and WHO COVID-19 database (n=110)), of which 69 met the inclusion criteria (Figure 1). The included studies were from 15 countries across five continents (Europe (32), Asia (23), North America (11), Australia (2) and Africa (1)). Of the included studies, 45 involved post-hospital discharge follow-up, 7 post home recoveries follow-up, and the follow-up of the rest of studies was from the onset of the symptoms. The longest follow-up duration was 140 (IQR 105-160) days from the initial diagnosis (Supplementary 1).

Regarding the COVID-19 reinfection, 204 studies were identified from the three search engines (PubMed (n=16), Google Scholar (n=168), and WHO COVID-19 database website (n=20)), of which 13 met the inclusion criteria (Figure 2). All the included data were case reports (with one patient) except for two studies in Iraq and in Bangladesh that included 26 patients and 3 patients respectively. The time between the first and second infection ranged from 26 to 145 days (Table 2). The included studies had different designs: prospective cohort studies (30), retrospective cohort studies (11), cross-sectional (17), retrospective and prospective (1), longitudinal study (3), observational (2), case-control (1), qualitative (semi-structured interviews) (2), and case series (2).

Respiratory Sequelae

Thirty-six studies from 15 different countries reported respiratory complications among COVID-19 survivors[16-51]. The duration of the follow-up ranged from 6 weeks to 4 months post hospital discharge [30, 38, 4231](Table 1). Worsened breathlessness / dyspnoea is one of the common reported symptoms post COVID-19 infection [23, 26, 27, 31, 33, 40, 47]. According to the results reported in a British study, 29 (42.6%) and 21 (65.6%) patients who discharged from ICU and ward respectively suffered from moderate to severe breathlessness for several weeks post-discharge[16], while a prospective study reported significant breathlessness among 64% of the survivors up to 3 months post-discharge[35]. An Italian study revealed that 54 (29.2%) of survivors experienced shortness of breath (SOB) and tachypnoea[21]. Similarly, a Chinese study and a Saudi study revealed that 115 (21.4%) of the survivors had tachypnoea even after mild activity, and 48.8% had difficulty of breathing that impedes them from completing a 6-minute walk test [23, 31] . These symptoms are common among obese patients, ICU survivors, senior survivors, and patients with previous respiratory diseases[16]. In addition, cough is a persisting symptom in a plethora of survivors. Besides excessive sputum, the cough may be accompanied by throat pain[17, 43].

Lung function abnormalities were measured in several studies through measuring Forced expiratory volume in 1 second (FEV1), Forced vital capacity (FVC), the maximal expiratory flow at 50 % of the forced vital capacity (MEF50), MEF25, and maximal mid-expiratory flow (MMEF)[25, 35]. In a retrospective multi-centre study , out of 55 patients, 14 (25.45%) survivors had abnormalities that presented in total lung capacity (TLC) , FEV1 and FVC[25]. In a British study , 60% of the survivors had reported some persistent abnormalities in the lung parenchyma through lung magnetic resonance imaging (MRI) at 2-3 months post discharge[35]. Furthermore, abnormal FEV1 (<80%) or FEV1/FVC < 70% , MEF 50, MEF 25, MMEF 75/25 were presented in 52.17%, 72.73% ,and 45.45% of cases who had previously moderate/sever COVID-19[44].

Lung fibrosis which was presented as interstitial thickening (27.3%) and crazy paving (ground-glass opacities with superimposed interlobular septal thickening and intralobular septal thickening) (5.5%) as reported in some of 55 survivors after three months of discharge[25]. Residual ground glass opacity (GGO) was common in some survivors. According to an Iranian study , 54.5% patients had GGO and 31.8% had mixed GGO and sub-pleural parenchymal band[39]. Additionally, two studies reported 86% and 48% of the survivors had residual GGO respectively [32, 33]. In addition, fifth of the participants had parenchymal bands that may indicate the progression of fibrosis [42]. Lung high-resolution computed tomography (HRCT) was performed for 21 survivors post 3 months of discharge, Five of them revealed abnormalities, 2 patients with local GGO, and 3 patients with local GGO and fibrosis [43]. CT-chest scans of recovered patients (asymptomatic, moderate, or severe) revealed a residual lesion in the lung or sub-pleural lesions after 3 months post hospital discharge. Furthermore, fibrous strip and thickening of the adjacent pleura were presented in patients who recovered from severe infection[51]. This study also revealed a correlation between the presence of differential metabolites such as homotyrosine, lactoylglutathione, indolelactate in the recovered patients and the residual

lesions in the lung[51]. Other studies reported complications including abnormal diffusion / pleural diffusion, pulmonary embolism, and pneumonia[18, 31, 40, 44, 52] .

Cardiovascular sequelae

Cardiac symptoms were reported among COVID -19 survivors. In a longitudinal study , out of 538 survivors, 70 (13%) survivors underwent some cardiovascular related symptoms post discharge that involved high resting heart rates (n=15), palpitations (n=26), elevation in the blood pressure level (n=7) ,in which some patients started taking antihypertensive agent[23]. Similarly, out of 26 survivors pericardial chest pain 3 (12%), chest tightness 6 (23%), and palpitation 23 (88%) were reported.[53]. These cardiopulmonary symptoms were reported in three other studies among patients after COVID-19 infection[20, 34, 43] .

T2 signal and positive late gadolinium enhancement (LGE) on analysing COVID-19 survivors were observed in 58% patients; 54% of patients presented with myocardial oedema in which 50% of survivors had positive LGE and 50% had pericardial effusion[53]. Furthermore, high sensitivity Troponin T values ($>$ 3 pg/ml) were reported in 71% survivors in a German study; most of 78 survivors who had presented with abnormal CMR findings: raised myocardial native T1 (n=73), raised myocardial native T2 (n=60), myocardial LGE (n=32), and pericardial enhancement (n=22). Additionally ischemic type patterns of myocardial LGE presented in 12 patients, and 3 patients suffered from severe abnormalities such as elevated hsTnT, native T1, native T2 measures , LEG ,and left ventricular ejection fraction less than 50%[54]. In an Australian study , trans-thoracic echocardiography during two follow-up visits revealed a high rate of diastolic dysfunction 60% and 55% ;besides pulmonary hypertension and pericardial effusion[46].

According to an Italian study, on nailfold videocapillaroscopy (NVC) examination of recovered patients after approximately one month of hospital discharge, 46.3% of 54 survivors were presented with some non-specific patterns of capillary abnormalities in more than two fingers, which involved enlarged capillaries (85.2%), meandering capillaries (81.4%), and pericapillary oedema (70.4%). Furthermore, hemosiderin deposits resulted from micro-haemorrhage and micro-thrombosis were revealed in 11.1% survivors[55]. The duration of follow-up ranged from 47 days to 3 months post hospital discharge[34, 53].

Nervous system Sequelae

Twenty-eight studies from 12 countries reported psychological and neurological complications among COVID-19 survivors[15, 16, 21, 23, 28-30, 32, 36, 38, 50, 56-71]. The duration of follow-up ranged from two weeks to 4 months post hospital discharge[56, 61] (Table 1). Post-traumatic stress disorder (PTSD) is deemed one of the common psychological complications among COVID-19 survivors[15, 16, 58]. Two studies have evaluated the PTSD according to post-traumatic stress disorder checklist-5 (-5)[15, 58]. A Korean study reported that 20.3% of the patients have PTSD (-5 score of [?]33),and an Italian study reported 12.9% have PTSD after COVID-19, and there is an inverse correlation between the duration of hospitalization with -5[15]. In addition, based on a cross-sectional study results, 46.9% of intensive care unit (ICU) survivors complained of PTSD, and 23.5% of hospital admitted survivors had the same mental sequelae[16]. The main feature regarding PTSD is that it is more prevalent among women compared to men, among the young population of COVID-19 survivors, and among people with a history of psychological diseases[15, 21, 56] .

Depression and anxiety are other common symptoms among COVID-19 survivors. In a Chinese study, out of 126 survivors 22.2% reported anxiety and 38.1 % reported depression[56]. Furthermore, while the severity of anxiety reported by old-survivors was lower compared to the young-survivors, there was no difference in the severity of depression symptoms according to the patient age[56]. In a Chinese study, out of 538 COVID-19 survivors , 23(4.3%) reported depression and loss of interest in things around them[23]. An Irish study reported 35.5% of patients who discharged from ICU had moderate to severe anxiety and depression during the follow-up[68]. The severity of depression and anxiety in COVID-19 survivors were evaluated using the Patient Health Questionnaire-9 (PHQ-9) and self-reported by the Anxiety Screening Scale (GAD-7) and their scores were 4.20$\pm$3.98 and 4.28$\pm$4.05 respectively [57]. Using the same screening scales, in another study , 50 recovered patients reported anxiety with intensity varied between mild (30 cases), moderate (12 cases), moderately severe (5 cases) ,and severe anxiety (3 cases)[50].

Memory problems were reported in two studies[16, 62] . In a British study , new or worsened memory problems were reported in 17.6% of ICU survivors vs 18.8% of the ward survivors[16]. A Spanish study reported 12.3% of patients had memory complaints that ranged from moderate (38%) to sever impairment for the immediate verbal memory, while for delayed memory, 11.8% COVID-19 survivors had moderate and 2.8% had sever impairment[62]. In addition, moderate (34.6%) and severe (8.4%) deficit in semantic verbal fluency were reported in and the survivors,[62]. Insomnia, sleeping disorder, stigma and concentration problems are also reported among survivors[16, 21, 23, 29, 59] .

Musculoskeletal sequelae

Musculoskeletal symptoms including myalgia and joint pain were reported among COVID-19 survivors in twenty-three studies[16, 17, 20, 22, 24, 27-31, 33, 35, 36, 41, 63, 65, 66, 70, 72-77]. The duration of follow-up ranged from 35 days to 3 months post hospital discharge[41, 63]. Fatigue was reported in the 12 studies among COVID-19 survivors. In a Chinese study which followed 337 patients , fatigue or myalgia were reported in 6 patients of 44 patients[17]. Fatigue and physical decline were reported among COVID-19 survivors in different countries: in China (48%), Italy (51%), and Netherlands (87%)[22, 24, 27]. According to another Chinese study which followed 538 patients , although 152 (28.3%) of 267 survivors presented with physical decline, only 35 of them reported no improvement[23]. Fatigue was reported in 30% of the survivors for 125 days post symptoms onset, and the intensity of fatigue was ranged from mild to very severe (100% vs 94.5%) when measured using Utrecht Symptom Diary (USD)[74].

Myalgia was presented in recovered patients. According to the studies in Germany, the U.S., and China, myalgia was reported in 5 of 33, 39 of 77, and 24 of 267 recovered patients respectively[23, 30, 41]. Pain was presented in 49.6% out of 115 survivors that was usually in shoulder (29%), chest (23%), lower limb (9%) ,and the back (13%), and joint pain (7.9%) especially in the knee[23, 36]. In two studies in the U.S. generalized pain was reported in 64% survivors, 50.6% of the survivors had muscular pain and 54.7% reported joint pain at day 35 post hospital discharge [41, 63].

Gastrointestinal tract sequelae

Gastrointestinal symptoms were reported in four studies as a persistent symptoms post COVID-19 recovery[19, 25, 30, 35] . Nausea, vomiting, and diarrhoea were persisted in some COVID-19 survivors after full recovery. Nausea may remain to the 4^{th} week after hospital discharge[19].

According to a British study, acute liver injury with non-specific pattern in blood tests persisted till 2-3 months in 11% of 18 patients who had seen with acute injury during infection. However, another study reported 10% of 52 survivors had signs of liver injury on MRI demonstrated by the increase in the iron corrected liver T1[35].

Urinary system sequelae

Residual renal impairment was reported in a prospective study , 3% (2 of 58) patients after 2-3 month post hospital discharge, although they had no kidney injury prior COVID-19[35].

Miscellaneous symptoms

Headache, weight loss, alopecia, sore throat, loss of taste/smell, voice/swallow abnormalities, fever, and malnutrition were also reported among COVID-19 survivors. The duration of follow-up ranged from 7 days to 125 days from the onset of symptoms[17, 75]

Headache was the commonly reported symptom; the reported intensity of headache was mild-moderate among the respondents[19, 25, 75] . Weight loss was reported in an Italian study , in which 29% of survivors lost $> 5\%$ of their initial body weight[78]. In addition, it was reported [?] 5% of weight loss that persisted for 2 month in some survivors [48]. Alopecia was presented in two studies 28.6% and 8.8% of COVID-19 survivors, and it was common in women more than men. However, hair loss was improved in 30 recovered patients after 3 months of discharge[23, 72] . Sore throat was reported in three studies[17, 19, 72] . Voice and swallow abnormalities were reported in 61% of survivors according to a British study[79]. Mild to moderate loss of

taste and mild loss of smell persisted till day 30 and day 60 after the initial symptoms in 15% and 25% of survivors respectively[75, 79]. Transient fever was reported among 8.4 % survivors at the first and second week post hospital discharge[19]. Malnutrition was reported in 62.7% of survivors according to an Italian study [21].

Hospital readmission

According to a case series of 370 patients, five survivors were readmitted to the hospital because of the cough, pneumonia, and lumbar disease without positive SARS-COVID-19 infection[50]. Furthermore, 22 recovered patients were re-hospitalized again because of persistent COVID-19 symptoms, pneumonia, and pulmonary embolism[18].

Reinfection

The screening of 204 studies revealed that only 13 case reports from 9 countries studied COVID-19 reinfection[80-92]. Most of the reported cases included patients presented with typical COVID-19 symptoms at the time of reinfection. At reinfection time, eight patients presented with mild COVID-19 symptoms[81, 83, 84, 86, 88-90], two patients presented with moderate COVID-19 symptoms[85, 91], and four patients with severe COVID-19 symptoms [80, 82, 87, 89]. However, one patient was asymptomatic at the time of the supposed reinfection[92]. Besides the clinical symptoms of COVID-19, positive COVID-19 PCR test revealed the reinfection in the 13 case reports. The longest period taken for reinfection was 145 days post recovery[89]. All patients survived the relapse in the 13 cases. Another Italian study reported positive COVID-19 PCR test among 22 patients during their follow-up visit [24]. A Chinese study reported that 14.5% of the survivors of mild and moderate symptoms during the course of the disease had re-positive PCR-test during the follow-up period (14 days)[93]. (Table 2)

Discussion

This review assembled data that involved the reported complications following COVID-19 infection among survivors, and the reported reinfection cases after full recovery. The collected data included recovered patients who were either hospitalized or non-hospitalized during their course of infection. The identified complications involved respiratory, neurological/mental, cardiovascular, gastrointestinal tract, urinary tract, musculoskeletal, and miscellaneous complications. However, the key impairments were pulmonary consequences, psychological problems, and exercise intolerance.

Respiratory problems are one of the frequently reported issues among COVID-19 survivors. They include breathlessness, dyspnoea, tachypnoea and cough. Abnormalities in diffusion capacity for carbon monoxide (DLCO) and TLC were detected among COVID-19 survivors. Thus, they demonstrated the abnormal parenchymal diffusion that persisted in some recovered patients for up to 6 months post infection[44]. In addition, reduction in lung function based on FEV1 measurements may prove the restrictive lung disease that persisted in COVID-19 survivors[35]. HRCT findings in some studies revealed the lesions of GGO and interstitial thickening in survivors three months post-hospital discharge[25, 94]. These observations are reminiscent of the previous SARS that cause residual GGO, intralobular and interlobular septal thickening after 84 months post recovery[95]. However, the recovery and stability of pulmonary lesions were observed among recovered patients on an annual follow-up that had lasted for 15 years after SARS infection[96]. Therefore, the respiratory consequences of COVID-19 may need longer time to be revealed.

Neurological complications of COVID-19 included some psychological problems such as PTSD, depression, anxiety, sleep disturbance, insomnia, and memory problems. These complications ranged from 12.9% to 46.9% among COVID-19 survivors. These mental issues were also reported among 79.64 (+-22.34) of Middle East Respiratory Syndrome (MERS) survivors after 14 months of hospital discharge[97]. Another study also reported 70% of patients with MERS infection experienced psychological symptoms such as insomnia, depression, impaired memory, disorientation, and hallucination during hospitalization[98]. Anxiety, depressive mood, and suicidal behaviour among SARS patients were demonstrated as a result of hospital isolation, quarantine, and the severity of symptoms[99]. Furthermore, depressive disorders and PTSD had persisted for one year in patients after 7 days or more of mechanical ventilation in medical or surgical ICU [100]. Thus,

neurological/mental complications may develop after most severe respiratory viral infection: COVID-19, MERS and SARS.

Reduction in exercise tolerance, muscles pain, and joints pain are the musculoskeletal consequences among COVID-19 survivors. Fatigue and exercise intolerance may be due to the pulmonary complications and the shortness of breath that unable some of the survivors from completing the 6-minute walk test[31]. Reduced exercise capacity and myalgia were reported among acute respiratory distress syndrome ARDS survivors within 6 to 24 months after ICU discharge because of mono-neuropathies with focal changes, myopathies, and chronic neurological changes[101]. In addition, hospitalization for long period and pulmonary disease have deemed the reasons for reducing the functional capacity among young ARDS survivors after 6 months of ICU discharge[102].

Nausea, vomiting, and diarrhoea are among the gastro-intestinal symptoms post COVID-19 infection. In addition, acute liver injury was reported. Previous studies on SARS had showed an active viral replication in both the small and large intestine among SARS patients, thus based on the high culture yielded from the intestinal tract, it was suggested that the intestinal tract was the primary targeted organ[103]. According to Lei Pan et al, the higher the severity of COVID-19, the more pronounced gastro-intestinal tract (GIT) symptoms; however, some patients had GIT symptoms without respiratory symptoms during the course of infection[104]. Acute liver injury in demonstrated as a result of direct viral hepatitis or as a result of taking anti-viral medicine through the course of treatment, besides the inflammatory reaction in the body[105]. GIT symptoms and acute liver injury were reported among MERS and SARS patients during the course of the disease Residual renal impairment was one of the complications of COVID-19. Kidney injury was reported as a result of the inflammatory response (inflammatory cytokine release) against the viral infection, hyper coagulation state, and angiotensin pathway activation[106]. Renal injury was reported in 42.9% of MERS patients[107]

Regarding COVID-19 reinfection, all the reported studies based on the reoccurrence of positive PCR-test after full recovery. However, RNA detection in the sample does not demonstrate the presence of active infection[108]. Human coronavirus reinfection was reported, but the symptoms were milder than the first infection[109]. Studies on the profile of antibodies against SARS infection had shown that both IgG and IgM increased dramatically on day 15 after onset of symptoms, and then it declined until day 720. Thus, SARS patients may have a protection against recurrent infection up to 2 years[110]. Therefore, it is crucial to differentiate between the second infection and the complications that may be developed after the course of treatment.

At this stage we cannot conclude the long-term complications and residual dysfunctions especially in the pulmonary and neurological systems. We need to follow-up the lung abnormalities for at least 1 year after cure as well as the psychological symptoms.

Conclusion: COVID-19 may cause several types of complications after recovery (testing negative PCR). Shortness of breath, psychiatric symptoms and exercise intolerance were frequently identified complications among COVID-19 survivors. Reinfection can occur among COVID-19 survivors. Thus, COVID-19 patients may need long-term follow-up and should take preventive measures to prevent the reinfection.

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Table 1: Post COVID-19 complications reported in the included studies

Complications	**Symptoms**	**Number of reported studies**	**Countries of the reported studies**	**Follow-up duration**
Respiratory complications	1-Breathlessness/dyspnea/ tachypnea 2- Cough 3-Lung function abnormalities (|FEV1, |FEV1/FVC, 4-pulmonary fibrosis Interstitial thickening crazy paving 5-Residual ground glass opacity 6- Abnormal diffusion 7-Pulmonary embolism 8-Pneumonia	36 studies	10 Chinese, 1 Egyptian, 1 German, 6 British, 3 Italian 3 Netherlanders, 1 Saudi, 1 Belgian, 3 U.S., 1 Australian, 1 French, 1 Belgian&Netherlanders 1 Canadian, 1 Iranian, 1 Spanish, and 1 Norwegian	6 weeks post hospital discharge [30, 38, 42] 4 months post hospital discharge[31]
Cardiovascular complications	1-| resting rates 2-Palpitation 3-Elevation in the blood pressure 4-Pericardial chest pain 5- Chest tightness 6- T2 signal and positive late gadolinium enhancement (LGE) 7-Myocardial edema 8-Pericardial effusion 9-Diastolic dysfunction 10-Pulmonary hypertension 11-Non-specific patterns of capillaries abnormalities 12-Hemosiderin deposits 13- Cardiac arrhythmias	9 studies	3 Chinese, 2 U.S., 2 Italian, 1 Australian, and 1 German	47 (36-58) days [53] 3 months post hospital discharge [34]

Complications	**Symptoms**	**Number of reported studies**	**Countries of the reported studies**	**Follow-up duration**
Nervous system complications	1-Post traumatic stress disorder 2-Depression 3-Anxiety 4-Memory problems: Immediate verbal memory, delayed memory, semantic verbal fluency 5-Insomnia 6-Sleeping disturbance 7-Cognitive impairment & concentration problem 8-Stigma	28 studies	5 Chinese, 1 Egyptian, 7 British, 1 German, 3 Italian, 2 Netherlanders, 1 Irish, 1 Spanish, 2 Korean, 1 Bangladesh, 3 U.S., and 1 Indian	14 days post hospital discharge [56] 4 months post hospital discharge [61]
Musculoskeletal complications	1- Generalized pain 2. Joint pain 3. Muscles pain 4- Fatigue/physical decline	23 Studies	1 Egyptian, 1 German, 8 British, 2 Chinese, 1 Italian, 1 Saudi, 1 Belgium, 3 U.S., 1 Bangladesh,1 Indian, 2 Netherlanders&Belgian, and 1 Faroe Island	35 days post hospital discharge [41]. 3 months post discharge [63]
Gastrointestinal complications	1-Nausea, vomiting, and diarrhoea 2-Acute liver injury	4 studies	1 U.K, 1 German, and 2 Chinese	1 month post hospital discharge [19] 3 month post hospital discharge[35]
Urinary system complications	Residual renal impairment	1 study	1 British	3 months post hospital discharge [35]
Miscellaneous complications	Headache, weight loss, alopecia, Loss of taste, loss of smell, sore throat, voice and swallow abnormalities, and malnutrition.	17 studies	1 Italian, 2 British, 5 Chinese, 1 Australian, 1 Mexican, 1 Helsinki, 1 Egyptian, 1 Bangladesh, 1 Netherlanders+ Belgian, 1 Faroe Island, 1 French, and 1 Indian	7.5 days (IQR, 6–13)[17] 125 (17, 45-153) days days post onset of symptoms [75]

Complications	Symptoms	Number of reported studies	Countries of the reported studies	Follow-up duration
Re-addmission	Pneumonia, pulmonary embolism, Lumbar puncture,and cough without Positive COVID-19 reinfection.	3 studies	2 Chinese, and 1 U.S.	22 days (20-30 days)[50] 80 days (IQR, 68 84) days[18]

Table 2: The studies covered the reinfection cases of COVID-19

Author name	Country	Number of patients	Diagnostic confirmation	Severity of symptoms	Time of reinfection	Main Findings
Lubana Akram et al [81]	Bangladesh	1	Negative RT-PCR test after 15 days from the first infection, followed by positive RT-PCR test.	Mild	30 days from the initial infection	Although the patient was infected after the exposure to a confirmed COVID-19 patient, it is still unclear whether it is reinfection or he did not recovered from the previous infection. Corona virus antibodies test is required
fatih levent et al [82]	Turkey	1	Negative RT-PCR test after 30 days from the first infection, followed by positive RT-PCR test.	Sever	45 days from the first infection	Acute heart failure secondary to severe mitral regurgitation and left ventricular systolic dysfunction happened after second COVID-19 infection.

Rohit Sharma et al[83]	Qatar	1	Negative RT-PCR test after 3 weeks from the first infection, followed by positive RT-PCR test.	Mild	86 days after first infection	IgM and IgG were positive during the second infection. Asymptomatic COVID-19 infection may predispose reinfection.
Shahid A. Mohammed et al[84]	USA	1	Two subsequent negative RT-PCR test followed by positive RT-PCR	Mild	97 days post hospital discharge	IgG antibody test was positive during the second infection.
Jair Munoz Mendoza et al[80]	USA	1	Negative RT-PCR test followed by positive RT-PCR	Sever	2 months after the first infection	The ESRD patient was previously tested positive for IgG antibodies but he was asymptomatic.
Belén Prado-Vivar et al [85]	Ecuador and South America	1	Negative RT-Negative RT-PCR test followed by positive RT-PCR	Moderate	1 month	Both IgG and IgM were positive during the second infection. The second infection happened 2 days after a contact with patient with confirmed infection. The symptoms were more sever than the initial infection.

Sayyed Reza Ahmadi et al [86]	Iran	1	Two subsequent negative RT-PCR test followed by positive RT-PCR	Mild	3 months after first infection	IgG and IgM were negative although RT-PCR was positive during the second infection.
Nicole M. Duggan et al [87]		1	Two subsequent negative RT-PCR test followed by positive RT-PCR	Sever	48 days after the first infection	After a prolonged ICU stay due to COVID -19 infection on the first presentation , one week later he returned with a second infection.
Muhammad Hanif et al [88]	Pakistan	1	Two subsequent negative RT-PCR test followed by positive RT-PCR	Mild	2 months after the first infection	The patient was reinfected post exposure to patient with confirmed COV-19
Islam, Jubaidul et al[89]	Bangladesh	3	negative RT-PCR test followed by positive RT-PCR	Sever Mild Mild	145 days 96 days 37 days	inflammatory markers for COVID-19 were significantly increased in all cases
Ayad M. Ali et al [90]	Iraq	26	negative RT-PCR test followed by positive RT-PCR	Mild	26 to 138 days after recovery	25 patients had negative IgG and only one patient was IgG-positive

Nawfal Rasheed Hussein et al[12]	Iraq	1	Two subsequent negative RT-PCR test followed by positive RT-PCR	Moderate	7 weeks	Reinfection was associated with increased symptoms, antiviral treatment was required.
Vered Nachmias et al[92]	Israel	1 patient	Negative RT-PCR test followed by positive RT-PCR	A symptomatic	3 months	The second episode happened after exposure to patient with confirmed infection. Although she had no symptoms , she was tachycardiac

Figures legends:

Figure 1: Flow chart for literature search regarding post COVID-19 complications

Figure 2: Flowchart for literature search regarding COVID-19 reinfection

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