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Persistent Dyspnea after Recovery from COVID-19: Two Case Reports from Bangladesh

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Abstract

Globally, millions of documented SARS-CoV-2 infections with hundreds of thousands of deaths already reported. The majority of the fatal events have been reported in adults older than 70 years and those who have multiple co-morbidities. Despite the misery fatality of the virus, a significant number of peoples recovered from critical conditions also. Mild cases improved significantly with symptomatic management with strict maintenance of isolation. Therefore, many people believed that COVID-19 is a short-term illness, mild cases recovered completely within 2 weeks and severe or critical illness may require 3-6 weeks for complete recovery. However, the latest issue coming forward is delayed recovery in the surviving patients from severe or moderate COVID presenting with multisystem complications. We reported two cases of post COVID complications, newly named as "long COVID syndrome". We described the common symptoms two patients experienced following recovery from acute phase of COVID-19 and how they were managed. We also discussed on the pathogenesis and management plan of common symptoms persisting after recovery of COVID-19. [*Bangladesh Journal of Infectious Diseases, June 2021;8(1):42-49]*

Keywords: Long COVID syndrome; post COVID dyspnea; post COVID fatigue; pulmonary rehabilitation

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Introduction

In the early stages of the COVID-19 pandemic, post COVID complications were not well identified and so there were no specific or definitive recommendation to combat the difficulties that patients feel after recovery from the acute disease. In course of time, the issue of persisting symptoms even after recovery from the acute phase has come to light. It is already a huge burden and challenge to all the physicians to manage millions of patients presenting with multiple symptoms following acute recovery. The slow pace of recovery leading to the extended duration of persistence of symptoms, has come to be known as post COVID or long COVID syndrome[1]. Long COVID syndrome may be a multi factorial disease usually occurring following a severe COVID-19 but sometimes may occur following a relatively mild disease[2].

Long COVID syndrome is usually defined as persisting symptoms particularly breathlessness and fatigue beyond 12 weeks[3].Usually around 10.0% patients suffering from COVID-19 remain unwell beyond 3 weeks and a smaller portion for more than months[4]. A current study found that 65.0% of people had returned to their previous level of health after 21 days of a positive result with mild to moderate complications like pneumonia[5]. Post COVID symptoms widely varied. It may be associated with most commonly cough, low grade fever, muscle pains, weakness, fatigue. All of the symptoms present in a relapsing and remitting pattern[5]. Other reported symptoms include breathlessness during rest or after mild exertion, chest pain, headaches, neurocognitive difficulties, gastrointestinal disturbance, poor control of diabetes, depressive illness and other mental health disorders[6]. Some degree of breathlessness is common after COVID pneumonia but severe breathlessness is rare. Pulse oximeter have been extremely important device for care of the patients and recommended as part of assessment of post COVID patients with dyspnea[7].

Case Presentation 1

A 42-year-old male without any co-morbidities admitted into district hospital on 11 July ,2020 with the complains of high-grade fever, cough for 6 days and shortness of breath for 2days later found positive for corona on RT-PCR test by nasopharyngeal swab. On admission, his vital status was stable but oxygen saturation on pulse oximeter found 90%, immediately he was put on supplemental oxygen support. He was going on with conventional symptomatic treatment, subsequently within few days his condition deteriorates with further desaturation (oxygen saturation fall up to 84%) and he was put on high flow nasal cannula requiring more than 20 l/min oxygen in the later weeks. His initial High resolution CT scan of chest showed multifocal ground glass density areas intermixed with irregular attenuated areas, crazy paving, sub-segmental consolidation and fibrotic bands were seen in at multiple segments of both lings involved 65.0% to 70.0% of the lung volume (Figure IA, IB).

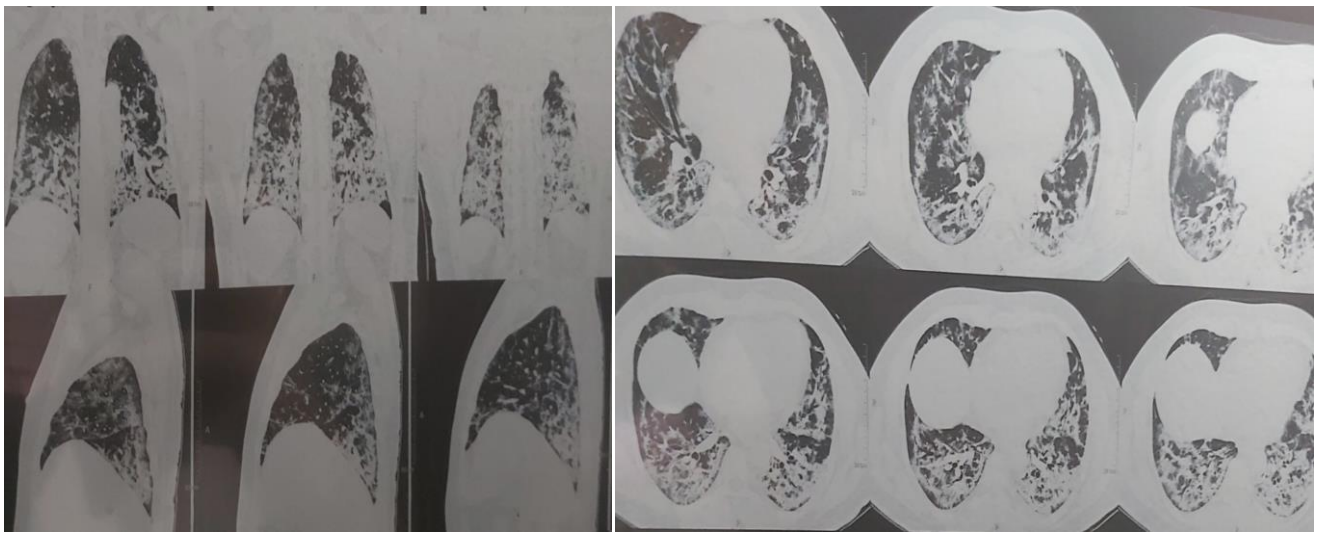

Figure IA and IB): CT-Scan of Chest Showing Extensive Bilateral Pneumonia Involving Both Lungs (Case 1)

Laboratory investigations in multiple days were shown in *table1*. After 10 days hospital stay his condition was improved clinically with prophylactic antibiotic meropenem 1gm 8 hourly, unfractionated heparin, enoxaparin 60 mg 12 hourly, two dose of IL-6 inhibitor, tocilizumab, intravenous steroid

methylprednisolone500mg daily along with other symptomatic drugs. On day 17, he was discharged from hospital after consecutive two negative nasopharyngeal swab for corona and radiological improvement in several chest radiography (Figure IIA, IIB).

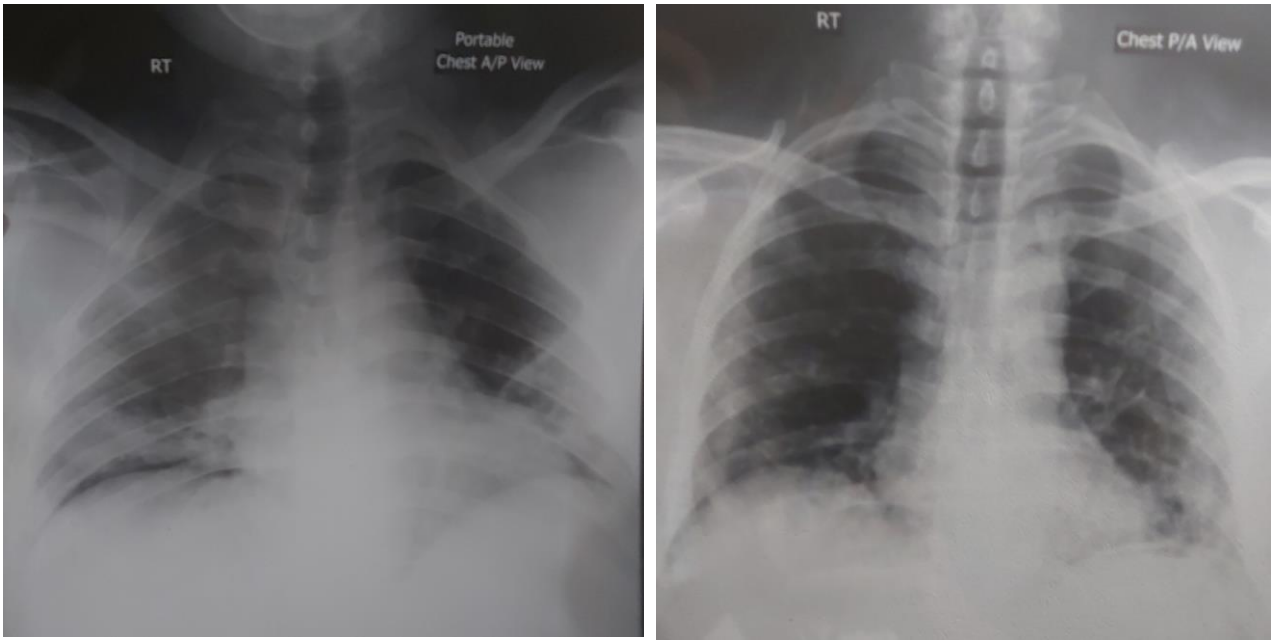

Figure II (IIA and IIB): Showing Serial X ray Chest of the Case 1 shows slow improvement of the lung parenchyma

On 6th August, during quarantine period at home he again developed fever as well as shortness of breath with desaturation below 90% and re-admitted in same hospital. Radiological and laboratory survey showed nothing significant rather the similar findings before. After 5 days symptomatic treatment and continuous oxygen supplementation his condition improved and on 11th August, he was discharged again from hospital though further RT-PCR nor performed this time. Though the patient feels severe fatigue and anorexia in his home, but his saturation was remained more than 92 % all the time with episodic oxygen support in home set up. 23rd August, after 12 days of second time discharge, he again developed respiratory distress and got admitted in the hospital. This time physicians thoroughly searched for any co-infection or re infection. RT-PCR was done again but came negative. However, found everything normal rather some fibrosis was seen in chest radiography. Eventually, he was treated symptomatically with addition of anti-fibrotic drug, pirfenidone801mg 8hourly and mucolytic N-acetylcysyeine600 12 hourly. On 30th August he was finally discharged from the hospital with the advice of continuous oxygen support 3-6L/min. The patient went on continuous oxygen support (3-6L/min) for last 1 month in home set up without further deterioration or any new complications. Till 10 October, he needs episodic supplemental oxygen for maintaining oxygen saturation level above 93%. Moreover, still he felt severe fatigue, occasional feverish, headache and sometimes abdominal discomfort. His normal daily activities were hampered severely. He could not join to his work despite several times negative result for corona. He was put on pulmonary rehabilitation with respiratory exercise, good nutrition and psychological counseling. Despite all of these efforts, it was difficult for the physicians to improve the patient.

Table: 1: Laboratory Parameters of Case 1 on Different Time During His Treatment

Measurement (Reference range)	**Day 1**	**Day 8**	**Day 17**
Hemoglobin (Male 11-16gm/dl)	10.9gm/dl	10.2mg/dl	10.6mg/dl
Erythrocyte Sedimentation rate (ESR)(0-15 mm in 1st hour)	55mm in 1st hour	87mm in 1st hour	70mm in 1st hour
Total White blood cell count (WBC)(4000-11,000/cmm)	23,400/cmm	18,700/cmm	11,100/cmm
Neutrophils (Differentials) (40-75%)	88%	79%	69%
Lymphocytes (Differential)	8%	14%	15%
Haematocrit (37-47%)	36%	35.7%	35.9.8%

Platelet Count (150,000-400,00/cmm	340.000/cmm	290,000/cmm	190,000/cmm
Sodium(135-145nmol/L)	136.0nmol/L	138nmol/L	134nmol/L
Potassium (3.5-5.0nmol/L)	3.60nmol/L	4.5nmol/L	4.2nmol/L
Chloride(98-107nmol/L)	106nmol/L	109nmol/L)	119nmol/L)
Serum Calcium (8.1-10.4mg/dl)	6.4mg/dl		
Serum creatinine (0.5-1.2mg/dl)	1.2mg/dl	1.0mg/dl	1.0mg/dl
Blood urea nitrogen (BUN)(6.0-21mg/dl)	12.7mg/dl		
Total Billirubin (0.2-1.2mg/dl)	1.2mg/dl	1.3mg/dl	1.3mg/dl
Blood Urea(10-50mg/dl)	34mg/dl		
Prothrombin time (Control 13.sec)	17.0 sec	14.0sec	14.0sec
Alanine aminotransferase (Female up to 32 U/L)	14U/L		
C reactive protein (less than 6mg/L)	87mg/l	43.6mg/l	32mg/l
D-dimer (<0.5 mg/ml)	2.69 mg/l	1.1mg/l	0.6mg/l
Activated plasma thromboplastin time (APTT)(25-35)		Control:32 Patient:21	Control:32 Patient:21
Troponin I(<0.1ng/ml)	<0.01ng/ml		
Serum Ferritin (Adult Female 15-120ng/ml)	1000ng/ml	732ng/ml	322ng/ml
N terminal Pro BNP (<300pg/ml HF unlikely)	410pg/ml		
Lactate dehydrogenase (200-400U/L)	565U/L		
Serum Procalcitonin (<0.1ng/ml)	<0.05ng/ml		
Thyroid stimulating hormone (TSH)(0.3-5.05µIU/ml)	4.50µIU/ml		
Malarial Parasite	Not found		
NS1 antigen and ICT for Dengue	Negative		
Electrocardiogram (ECG)	Normal		
Sero immunological Test for Salmonella, Brucella and Ricketssia	Not significant		
Blood culture	No growth		
Serum Cholesterol(<200mg/dl)	280mg/dl		
Serum Triglycerides(<150mg/dl)	232mg/dl		
High density lipoprotein (HDL)(>80mg/dl)	40mg/dl		
Low density lipoprotein (LDL)(100-130mg/dl)	152mg/dl		

Case Presentation 2

A 50 years old male health worker, obese, hypertensive and smoker, was admitted into a district hospital on 12 August, 2020 with the complaints of high-grade fever for 5days, cough and respiratory distress for 3days.On admission he was found hypoxic with oxygen saturation88% on room air. Immediately he was put on supplemental oxygen and found positive on nasopharyngeal swab for COVID-19. His immediate chest x-ray showed bilateral pneumonitis. High resolution Computed Tomography (HRCT) done on following day showed multifocal ground glass opacity, sub-segmental consolidation involving both lungs which was approximately 55-60% of the lung volume (Figure IIIA, IIIB) and serial laboratory investigation findings on (Table 2).

His was treated with antiviral Remdesivir, prophylactic antibiotic ceftriaxone, low molecular weight heparin, intravenous corticosteroid dexamethasone along with other symptomatic drugs. He needed continuous supplemental oxygen with a non-rebreather mask 12 to 15l/min. After 5 days further deterioration occurred and as no clinical improvement was observed, he was given 2 unit of convalescent plasma. On day 19, his

condition improved clinically as well as on radiological follow up. He was discharged with the advice of home isolation. On home isolation his general condition did not improve, he had continuous complaints of fatigue, breathlessness on little effort, difficulties in vision later diagnosed as uveitis by ophthalmologist. On day 29, he again developed high grade intermittent fever along with breathlessness and was again admitted in the hospital. His radiological follow up (Figure IVA, IVB) showed scattered pulmonary fibrosis. He was dependent on continuous oxygen supplementation along with intravenous steroid, (dexamethasone) for relieving his distress. He could not do his normal activities without oxygen support. After 7 days on day 36, he was discharged with home oxygen support and monitoring with pulse oximetry, oral corticosteroid and with antifibrotic drug pirfenidone. After 14 days of second discharge (on day 48) during his follow-up in the outpatient department he complained of severe fatigue, swelling of his face, muscle weakness, inability to stand from the sitting position. Then dose of steroid was tapered with supplemental oxygen in home set up.

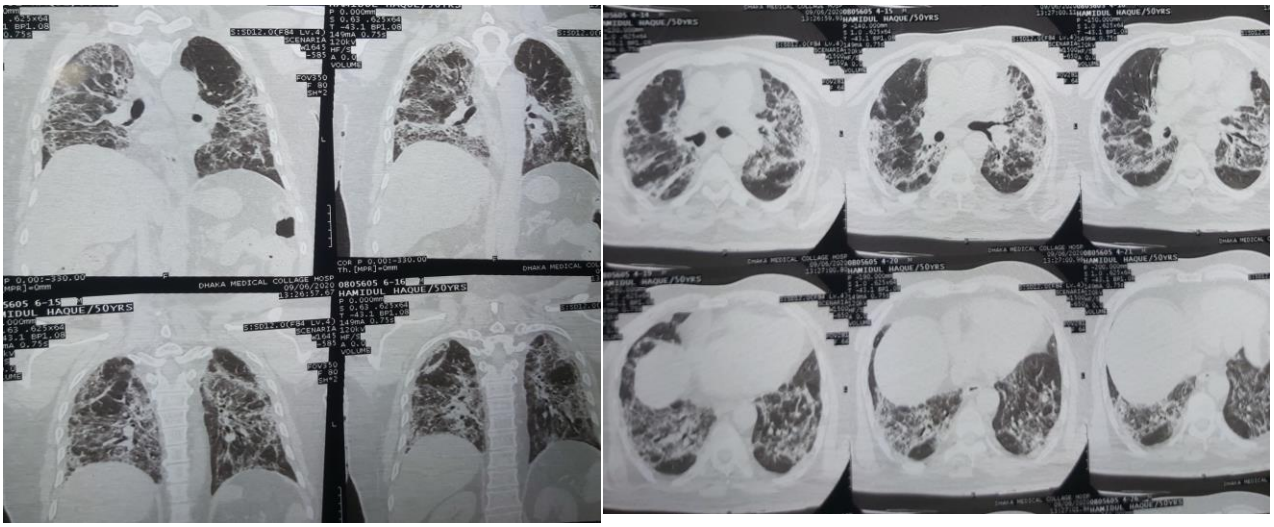

Figure IIIA and IIIB): Showing extensive bilateral pneumonia of both lungs on HRCT of chest of Case 2

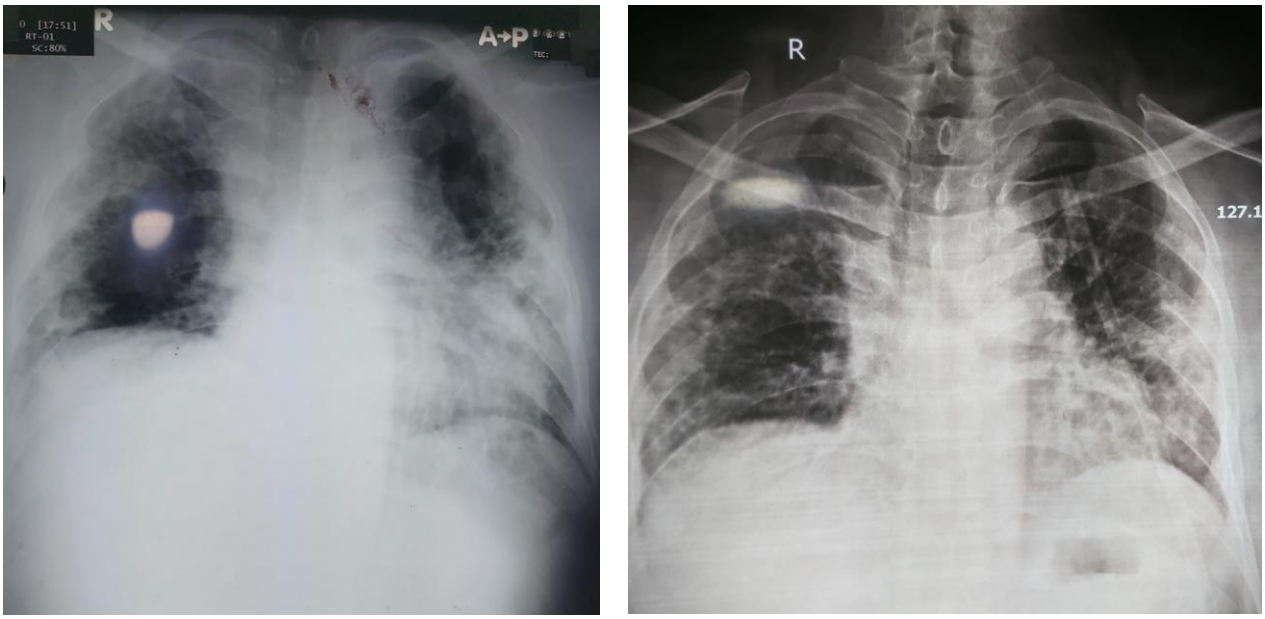

Figure IVA and IVB: Serial follow up Chest X ray of case 2 showing gradual improvement of pneumonia

On tapering of steroid, he again developed respiratory distress and again had to start intravenous steroid, bronchodilator along with other drugs. Till 15 September, 2020 his condition was not improved, he felt breathlessness on little effort, cannot do his normal activities with fatigue and weakness were not improved, but his vision was improved. He also felt anxious, frightened about his

illness hampering his sleep but his appetite was improved. He was on intermittent supplemental oxygen, low dose steroid, inhaled bronchodilators and on other drugs without any new cardiopulmonary complications (Figure V).

Figure V: The picture of the patient shows moon like, puffy, plethoric face with periorbital swelling suggestive of iatrogenic Cushing syndrome due to long term corticosteroid intake

Table 2: Laboratory parameters of Case 2 in different times during his treatment

Measurement (Reference range)	**Day 1**	**Day 9**	**Day 23**
Haemoglobin (male 11-16 gm/dl)	11.4gm/dl	11.6gm/dl	11.2gm/dl
ESR (0-15 mm in 1st hour)	102mm in 1st hour	60mm in 1st hour	68 in 1st hour
WBC (4000-11,000/cmm)	7,100/cmm	12,000/cmm	11,400/cmm
Neutrophils (Differentials) (40-75%)	70%	75%	78%
Lymphocytes (Differential)	10%	07%	06%
Haematocrit (37-47%)	38.2%		
Platelet Count (150,000-400,00/cmm	93000/cmm	140.000/cmm	1650.00/cmm
Sodium(135-145nmol/L)	132.0nmol/L	137.0nmol/L	130.0nmol/L
Potassium (3.5-5.0nmol/L)	4.50nmol/L	4.20nmol/L	3.90nmol/L
Chloride (98-107nmol/L)	106nmol/L	106nmol/L	106nmol/L
Serum Calcium (8.1-10.4mg/dl)	7.4mg/dl	6.8mg/dl	6.6mg/dl
Serum creatinine (0.5-1.2mg/dl)	1.2mg/dl	1.2mg/dl	1.0mg/dl
BUN (6.0-21mg/dl)	22.7mg/dl	20.2mg/dl	18.2mg/dl
Total Bilirubin (0.2-1.2mg/dl)	1.0mg/dl	1.2mg/dl	1.6mg/dl
Blood Urea (10-50mg/dl)	34mg/dl	29mg/dl	37mg/dl
Prothrombin time (Control 13.sec)	13.0 sec	19.0 sec	11.0 sec
Alanine aminotransferase (Female up to 32 U/L)	28U/L	27U/L	31U/L
CRP (<6mg/L)	122mg/l	98mg/l	36mg/l
D-dimer (<0.5 mg/ml)	3.50 mg/l	1.60 mg/l	0.85 mg/l
APTT (25-35)			
Troponin I (<0.1ng/ml)	<0.01ng/ml	<0.01ng/ml	<0.01ng/ml
Serum Ferritin (Adult Female 15-120ng/ml)	1211ng/ml	543ng/ml	400ng/ml
N terminal Pro BNP (<300pg/ml HF unlikely)	165pg/ml	240pg/ml	156pg/ml
Lactate dehydrogenase (200-400U/L)	365U/L	432U/L	234U/L
Serum Procalcitonin (<0.1ng/ml)	<0.05ng/ml	<0.05ng/ml	<0.05ng/ml
TSH (0.3-.05µIU/ml)	1.50µIU/ml		
Malarial Parasite	Not found		
NS1 antigen and ICT for Dengue	Negative	Negative	Negative
Electrocardiogram (ECG)	Left ventricular hypertrophy		
Triple Ag test	Not significant		
Blood culture	No growth		No growth
Serum Cholesterol (<200mg/dl)	280mg/dl		
S. TG	434mg/dl		

(<150mg/dl)			
HDL (>80mg/dl)	53mg/dl		
LDL (100-130mg/dl)	182mg/dl		
Serum Cortisol (6-23microgm/dl	5.1microgm/dl (Day 40)		

Low density lipoprotein=LDL; High density lipoprotein=HDL; Serum Triglycerides=S. TG; Sero immunological Test for Salmonella, Brucella and Rickettsia=Triple Ag test; Thyroid stimulating hormone=TSH; Activated plasma thromboplastin time=APTT; C reactive protein=CRP; Blood urea nitrogen=BUN; Total White blood cell count=WBC; Erythrocyte Sedimentation rate=ESR

Discussion

There are many literatures published on presenting symptoms of COVID-19. However, exploration of symptoms persisting after recovery, worsening after recovery or newly developing after microbiological normalization is still very limited. During SARS and MERS, following acute infection, prolonged respiratory, neurological, psychiatric complications have been observed and described in many publications[8-9]. One publication showed that after the acute SARS episode some patients, many of whom were healthcare workers, went on to develop a chronic fatigue syndrome and myalgic encephalomyelitis-like illness which prevented them from returning to work for up to nearly 20 months[10]. We reported two patients recovered from acute COVID-19, presenting with persistent post COVID symptoms, one of whom was a health care worker. One study from Italy found that in patients who had recovered from COVID-19, 87.4% reported persistence of an at least one symptom[11]. Most common post COVID symptoms are chronic cough, breathlessness, fatigue, chest pain with some serious complications like ventricular dysfunction, dysrhythmias, neurological complications like ischemic stroke, seizures, encephalitis, major psychiatric illness and thromboembolism. Chronic cough is defined as persistence of cough for more than eight weeks[11]. Breathlessness is also common in post COVID patients, it was found that 43.4% of the patients suffering from COVID-19 complained of persistent dyspnea during their post-COVID-19 follow up[11]**.** Both of the patients reported by us had persistent post-discharge breathlessness, which is consistent with the previous findings. Fatigue is another common complaint in patients recovered from acute illness. Significant proportion (53.1%) of patients following COVID-19 experience severe fatigue and weakness[12-13]. Both of our patients complained of persisting fatigue, which hampered their daily activities**.**

There are several hypotheses published in different papers regarding pathogenesis of long COVID syndrome. Most of them mentioned that persistent viremia or delayed viral clearance may be due to weak immunity of the host or absence of innate immunity response to produce antibody[14-15]. Some have mentioned relapse or re-infection as a possibility and some have mentioned mental factors such as post-traumatic stress as a contributing factor[16-17]. Besides, the symptoms after discharge may also be the sequalae of organ damage in the acute phase. So, an important distinction should made between symptoms due to persistent inflammation in the convalescent phase of the disease or sequalae of organ damage particularly acute lung injury resulting in pulmonary fibrosis, kidney injury resulting in chronic kidney disease[13]. In a study conducted on patients recovered from COVID-19, most common post COVID symptoms were dyspnea and fatigue[11]**.** Pulmonary improvement almost always lags behind the microbiological clearance[14]. Persistence of lung fibrosis may cause significant dyspnea in most of the patients. Post infection fatigue is associated with several immune factors. Two previous study found that post infection outcomes were impacted by polymorphisms in IFN-gamma+874 T/A and the IL-10-592C/A. The changes were thought to impact the severity of the illness and cytokine productions[14]. Furthermore, the second case report by us also presented with swelling of his face along with severe fatigue. This may also be due to iatrogenic Cushing's syndrome.

The management of symptoms after the first three weeks is currently based on limited evidence[18]. Persistent cough can be managed by simple breathing control technique exercise, it normalizing breathing patterns and increasing strength of the diaphragm including other respiratory muscles resulting reduced airway irritation, decreasing fatigue and improve breathing and with some simple cough suppressant if there is no superadded infection or other complications[19]. The target range of oxygen saturation is 94.0% to 98.0% and below this level requires supplementary oxygen[20-21]. Self-monitoring of oxygen may be useful for the assessment and reassurance of the patients with persistent respiratory difficulties in the post-acute phase or later[14]. Every patient with lung involvement should be provided with a pulse oximeter and given full instructions for how to use it and how to monitor oxygen with it[14]. Though we cannot find any pharmacological or non-pharmacological treatment recommendation published recently for the management of post COVID fatigue. However, in one study we found

regular aerobic exercise significantly reduce fatigue[22] and another recommendation from Stanford-Hall statement described that after recovery from mild illness, low level stretching and strengthening before targeted cardiovascular sessions, persistent symptoms such as fatigue, cough, breathlessness; limit activity to 60% maximum heart rate until 2-3 weeks after symptoms resolve for sports person returning to exercise[18]. It also defined pulmonary rehabilitation as "a multidisciplinary intervention based on personalized evaluation and treatment which includes, but is not limited to, exercise, training, education and behavioral modification designed to improve the physical and psychological condition of people with respiratory disease"[18].

Conclusion

Post COVID symptoms and complications newly named long COVID syndrome is a crucial issue now for millions of patients recovered from acute infection. So, clinicians and researchers should focus on the continued monitoring of the patient after discharge for long lasting problems or new onset of symptoms presented by the patient. However, urgent recommendation and guidelines is needed for management to be published, for follow up and rehabilitation of such patients.

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