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A COVID-19 Follow Up Protocol Based on Short and Long Term Clinical Outcomes

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Authors' contributions

This work was carried out in collaboration among all authors. Author HAK searched the literature for relevant articles. Authors HAK and AHB synthesized data from included articles and reviewed the manuscript. Author PAB and VCD significantly contributed to data synthesis and review of manuscript. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Background: Corona virus disease (COVID-19) represents a public health emergency of international concern, with continuously growing number of confirmed and re infected cases.
Main body: Clinical sequels during early COVID-19 convalescence were common**;** it ranges from mild to moderate respiratory illness associated with pulmonary abnormalities; physical, mental and/or other clinical health outcomes. Older people, males and those with underlying medical problems like cardiovascular disease, diabetes, chronic respiratory disease, pregnancy and cancer more likely to develop serious complications and poor outcomes. Later on, Mucormycosis complications have been also reported in many hospitals. These complications are observed at short and long term follow up. Thus, a simple, well inferring easy to perform protocol needs to be in place to follow up COVID discharged patients. This review describes the outcomes/complication associated with COVID 19 and its contributory factors. In its context based on available literature and guidelines the review also proposes a post COVID follow up protocol at 7 days, 1 and 3 months after discharge.
Conclusion: COVID-19 the global health issue is severely associated with pulmonary defects, a long quarantine period/hospitalization stay and a possible reactivation of the virus; potential

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pulmonary, physical and/or psychological outcomes may be anticipated in patients following discharge. Thus, a follow up protocol needs to be implemented at 1 week, 1 and 3 months respectively for the holistic wellbeing of the patient.

Keywords: COVID-19; short- and long-term outcomes; comorbidities; follow-up.

ABBREVIATIONS

ACE : Angiotensin converting enzyme
ARBs : Angiotensin receptor blockers
BMI : Body mass index
BP : Blood pressure
CBC : Complete blood count
CDC-NIH : Center for disease control and national institutes of health
CRP : C-reactive protein
CT : Computed tomography
CTPA : Chest thorax pulmonary angiogram
CVD : Cardiovascular disease
DKA : Diabetic ketoacidosis
DLCO : Diffusing capacity for carbon monoxide
FGR : Fetal growth restriction
FEV1 : Forced expiratory volume
FVC : Forced vital capacity
GGO : Ground glass opacification
GI : Gastro-intestinal
HIV : Human immunodeficiency virus
HRCT : high-resolution computerized tomography
HRQoL : Health related quality of life
ICU : Intensive care unit
LH : Luteinizing hormone
MERS : Middle East respiratory syndrome
MRCD : Medical research council dyspnea scale
PCFS : Post COVID-19 functional status
PE : Preeclampsia
pPROM : Preterm prelabour rupture of membranes
PTB : Pre-term birth
PTSD: Posttraumatic stress disorder
PSI : Pneumonia severity index
QoL : Quality of life
RAAS : Renin angiotensin aldosterone system
SARS : Severe acute respiratory syndrome
TLC : Total leucocyte count
VTE : venous thromboembolism
WHO : World health organization

1. INTRODUCTION

The novel coronavirus pneumonia (SARS-CoV-2) an infectious disease, first reported in Wuhan, China at the end of December 2019 has spread extensively to be labeled as a global pandemic by WHO [1,2]. COVID-19 generally causes respiratory and gastrointestinal infections that might range from mild, self-limiting conditions to more serious disorders, such as viral pneumonia with systemic impairment [3,4]. The overall cumulative COVID-19 hospitalization rate is 156.8 per 100,000, with the highest rates in people aged 65 years and older more so males [5]. Discharge rates of COVID-19 patients stand at 52%, and fatality rate at 5% [6]. Discharge criteria's importantly include few fibrous stripes on chest CT (Computed Tomography) and restoration of immune function [7,8].

Post discharge short- and long-term outcomes including but not limited to physical, pulmonary

and mental health affect quality of life (QoL): WHO estimates three to six weeks for total recovery from COVID 19. The most common symptoms that linger over time include fatigue, cough, shortness of breath, headache, joint pain and some mental consequences [9]. Long term effects are unknown, and researchers are trying to compare it with SARS and MERS-CoV to fully define the longer-term consequences of infection with COVID 19 [10]. Inadequate and scattered literature citing the handling of COVID 19 discharge patients at short and long term is available.

The objective of the present review is to summarize the short- and long-term clinical outcomes of COVID 19 discharged patients researching literature through Centre for Disease Control and National Institutes of Health (CDC-NIH, USA) reports, WHO reports, clinical trials and current PubMed articles and propose a follow up protocol with times lines and investigations to be conducted at follow up visits in line with the documented outcomes and comorbidities affecting those outcomes.

2. Physical Health Outcomes

Physical inactivity is a much-observed sign during COVID 19 recovery which has a strong deconditioning effect on bones, muscles and the cardiovascular system and may potentially increase the risk of injuries related to falls, such as hip fractures [11]. Patients particularly experience fatigue and joint pain at 2 months recovery [12] and 3 months as well [13]. X Wang et al. studied 4 weeks outcomes after discharge on weekly basis. They observed 63 (48.09%) patients had one or more symptoms including fatigue (5.34%), chest tightness (6.11%), chest pain (3.05%), headache (3.82%) and myalgia (0.76%) during the first and the second week after discharge, while at third and the fourth week of discharge, only 18 (13.74%) patients had one or more symptoms with chest tightness (0.76%) and pharyngeal pain (1.53%) [14]. One clinical trial based on cohort observational prospective study is proceeding with 60 participants for 1 year after discharge from a hospital in Switzerland to study long term physical performance and health related quality of life (HRQoL) [15].

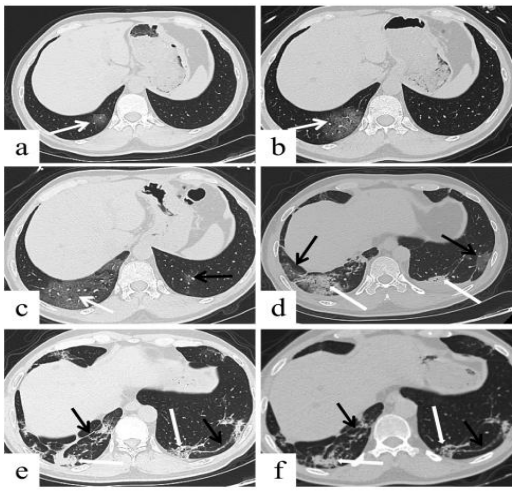

Fig. 1. Male, 48 years, transverse thin-section CT scan shows features at particular days after onset of initial symptoms (a) After 4 days (stage-1): sub pleural GGO (arrow) in the right lower lobe. (b) After 8 days (stage-2): more severe lesions with GGO and crazy-paving pattern (arrow) in the right lower lobe. (c) After 12 days (stage-3): again increased severity of GGO and crazy paving pattern (white arrow) in the right lower lobe, and GGO (black arrow) also appeared in the left lower lobe. (d) After 18 days (stage-4): Consolidation (thick white arrow), accompanied by a small GGO (thin black arrow) in both lower lobes. (e) After 26 days (stage-5): the extent of the lesions was reduced with consolidation (thick white arrow) and linear opacities (thin black arrow) in the right lower lobe, and crazy-paving pattern (thick white arrow) and linear opacities (thin black arrow) in the left lower lobe. (f) After 38 days (stage-6): There was no significant change in the extent and composition of lesions compared with the directly prior CT result [20]

3. Pulmonary Outcomes

COVID-19 infection often leads to a wide range of respiratory dysfunction sequel that requires dedicated follow-up [16,17]. Normal lungs appear black on CT scans, while Covid-19 patients' lungs frequently have lighter grey patches called "ground-glass opacities (GGO)". At a 3-week radiological follow-up more than 40% of patients demonstrated residual abnormalities, including GGO and fibrous stripe as the main CT manifestation [18,19]. The other features such as consolidation, interstitial thickening, bronchiectasis, crazy paving, air bronchogram, irregular interface, coarse reticular pattern, parenchymal band, lymphadenopathy, and pleural effusion, as well as the involving lung lobes were also recorded [13].

One short term observational study on 149 patients in Wuhan, China showed predominant CT scan abnormalities at discharge including GGO, stringy stripe, and solidifying of the adjacent pleura which progressively reduced with time [21]. A 4 week follow-up study on 131 patients showed 48.09% of patients had one or more symptoms including cough (31.3 %), rhinorrhea (0.76%) and dyspnea (7.63%).In the 3rd and 4th week after discharge13.74% of patients had one or more symptoms with the incidence of cough (9.16%) and dyspnea (1.53%) [14]. In a 3 month discharge follow-up study radiological and residual abnormalities of pulmonary function were detected in 25.45% of patients ; which included anomalies in total leucocyte count(TLC),forced expiratory volume(FEV1),forced vital capacity (FVC), Diffusion capacity of the lung for Carbon monoxide (DLCO) and small airway function. Most of diffusion reductions in DLCO indicated pulmonary fibrosis or a late phase in the course of recovery [13]. The radiological changes do not appear to resolve fully in all patients of COVID-19 pneumonia and in some patients, inflammation matures to form residual pulmonary fibrosis [22]. Thus, pulmonary rehabilitation is established as a key management strategy designed to optimize patients' exercise capacity and breathlessness [22].

4. MENTAL HEALTH OUTCOMES

People affected by COVID have been experiencing different degrees of post-traumatic stress disorder (PTSD), anxiety, depression, panic attacks, and insomnia [23]. Apart from physical suffering, patients with COVID-19 have been reported to suffer from great psychological pressure and other health-related problems and may experience fear of severe disease consequences and the contagion as well as fear of recurrence after recovery [24]. Social isolation and quarantine for over 10 days are significant implications for mental health that impact negatively on QoL [25,26,27].Patients surviving COVID-19 are also at high risk for subsequent development of neurological disease particularly Alzheimer's disease [13].

In Shenzen, China, 96 patients were observed for their mental health consequences after discharge for 14 days. The study reported 43.75% suffered from short term mental health consequences which include anxiety, depression and insomnia [23]. Another study from Wuhan, China on 675 patients evaluated at 36.75 days reported mental health consequences [28].One study of France reported dysexecutive syndrome consisting of inattention, disorientation or poorly organized movements amongst 33% patients after discharge [23].At 3 months when 60 patients were evaluated in Fuyang, China, 55% had neurological symptoms like mood change (16.67%), memory loss (2-8.33%), headache (10%), loss of smell (3.33%) and loss of taste, hearing and change in vision (1.67%).These abnormalities were related to disruption of microstructure and functional brain integrity mainly in the central olfactory cortices. Abnormalities in these areas might cause long term neurological symptoms in COVID-19 patients after recovery [29].

These findings suggest that post-COVID hospitalization, particularly for those with severe illness and with family stressors, should receive mental health resources directly after hospital discharge. Previous studies on SARS suggested that people avoid recovered patients due to fear of infection. Thus, fears of discrimination by others are observed more for COVID-19 patients, and the sense of feeling isolated seems to contribute to symptoms of mental illness. But the isolation is central to the quarantine process to reduce COVID-19 transmission. So, finding a way for quarantined patients to remain connected to their loved ones may be crucial for preventing mental health problems [30].

5. OTHER CLINICAL OUTCOMES

Cardiovascular Complications Acute myocardial injury is a common complication among patients hospitalized with COVID-19.

19.7% of patients showed cardiac injury amongst 416 hospitalized patients of COVID-19 accompanied with a greater risk of in-hospital mortality [31]. An increase in inflammation and direct damage to the heart muscle can be responsible in COVID-19 patients for cardiac injury [32]. Patients admitted to intensive care unit(ICU) or having severe/fatal illness have several-fold higher likelihood of troponin elevation which is associated with an increased risk of death [33]. A manifestation of secondary cardiac involvement in COVID-19 is stress-induced cardiomyopathy [34] as well as COVID-19 related myocardial wall edema and thickening of wall resulting in acute myocarditis [35]. Patients hospitalized for COVID-19 are experiencing high rates of blood clots that can cause strokes, heart attacks, lung blockages, and other complications [36,37]. Out of 1412 confirmed COVID patients admitted at our hospital, 24(1.7%) patients (mean age :64 ± 14 years ;males:22 /24) developed cardiovascular complications of which mortality was reported in 79% (19/24). Incidence of sudden cardiac arrest (29%) and atrial fibrillation (21%) were the most common complications accounting for mortality. Also, complications of cardiogenic shock, heart failure, and ventricular tachycardia had poorer outcomes. [Unpublished data]. Other cardiovascular complications observed at our hospital included myocardial infarction (12%), thromboembolic events (8%) and myocarditis (12%) [Unpublished data].

Genital complications A recent study provides insights into diminished male gonadal function on SARS- CoV-2 infection. This study showed that the testosterone to luteinizing hormone (T to LH) ratio in 81 patients with COVID-19 historically reduced in assessment with 100 age- matched healthy corresponding person. This proportion acts as an interpreter of male gonadal function which could be an indicator of diminishing of generative health by SARS- CoV-2 [38].

Pregnancy complications In a discussion about pregnancy and perinatal outcomes of CoV spectrum infections and particularly COVID-19 during pregnancy the following outcomes were observed:

- Preterm birth (PTB; either before 37 or 34 weeks of gestation).
- Preeclampsia (PE).
- Preterm prelabour rupture of membranes (pPROM).
- Fetal growth restriction (FGR).
- Miscarriage
- Cesarean mode of delivery.

Evidence of vertical transmission, defined as the presence of clinical signs of mother-to-child transmission in the antenatal or perinatal period was noted [3]. During the early period of the pandemic, only symptomatic pregnant women for SARS-CoV-2 and newborns of infected mothers were placed in isolation rooms [39]. The risk of severe disease in the pregnant population (8%) compared favorably with the risk reported in the general population of patients presenting with Covid-19 [40]. During pregnancy, women undergo physiological changes that increase their susceptibility to severe respiratory infections and subsequent respiratory failure–a key concern to COVID-19 infections [41].

Mucormycosis complication recent reports have cited mucormycosis, a rare but serious fungal infection caused by a group of molds called mucormycetes with 50% mortality rate in recovered COVID-19 patients. Mucormycosis is not contagious; people can be infected through inhalation of fungal spores from the air, or through a cut, burn or other types of skin injury. The clinical presentation of mucormycosis varies depending on the location of the disease but most specifically, it produces rhino-orbital-cerebral, pulmonary and GI infection. Patients may experience one-sided facial swelling, nasal congestion, headache, fever, swollen eyes, black lesions cough, chest pain, shortness of breath, abdominal pain, gastrointestinal bleeding, nausea, and vomiting etc [42]. According to a state advisory, mucormycosis infects people with a weak immune system and existing illnesses like diabetes or cancer, those who underwent organ transplant, stem cell transplant or people with too much iron deficiency in their body [43,44].

Amanda Ehrenreich and Salil et al documented a case of mucormycosis in combination with COVID-19 infection in a diabetic patient [45,46]. Our hospital has so far treated about 8 cases of mucormycosis [unpublished data].

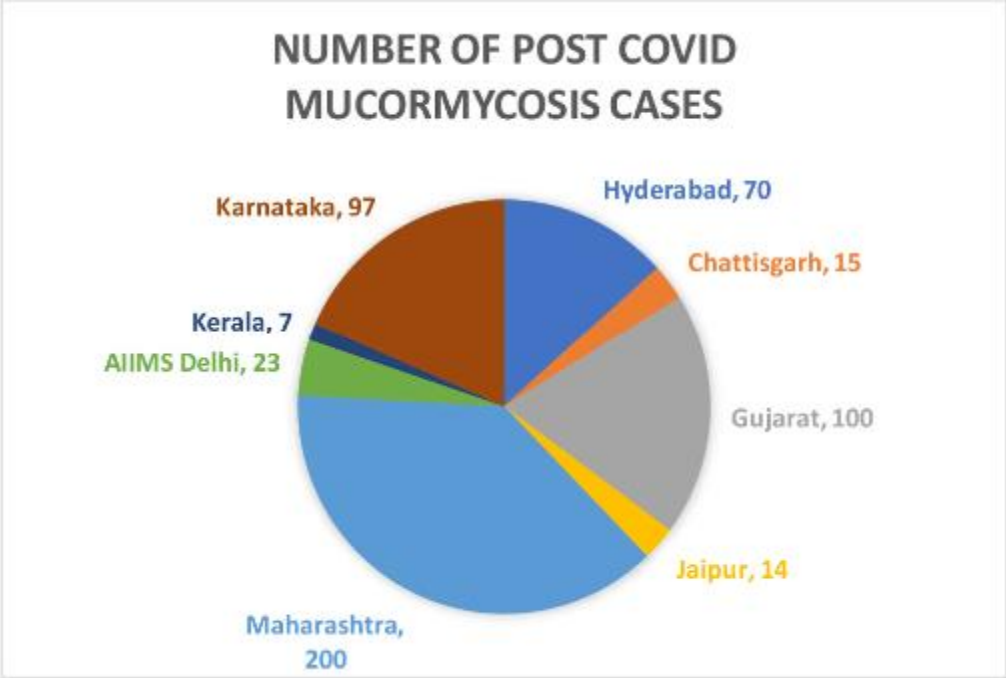

Fig .2. Number of Post COVID Mucormycosis cases reported in India as of 17 May 2021

Figure shows mucormycosis cases after COVID 19 till 17 May 2021 in India. Post-COVID 19 patients who are at an increased risk to develop Mucormycosis are those with a history of poorly controlled diabetes mellitus and the patients who are treated with steroids and other drugs to manage COVID 19 that may reduce their ability to fight environmental pathogens [47].

6. COMORBIDITIES AND OUTCOMES

Diabetes COVID patients with diabetes present with more severe inflammatory responses, acute kidney injury, secondary infection and are at a greater risk of worse prognosis [48,49]in terms of higher mortality rate compared to patients without diabetes or uncontrolled hyperglycemia [50,51,52]. Diabetic patients with COVID-19 infection have a longer length of hospital stay and are at a higher risk to be admitted to ICU during the infection. For diabetes, a meta-analysis of six studies (1527 patients) found the prevalence to be twice as high in the ICU/severe group compared to non-severe COVID-19 patients [16]. On disaggregating this outcome into two (non ICU and ICU admitted), prevalence of diabetes was 1.6 times higher in the ICU group [53]. Diabetes patients with diabetic ketoacidosis (DKA) encountered lower mortality than diabetes patients without DKA [54]. Patient tailored therapeutic strategies, rigorous glucose and lipid observing and suspicious deliberation of drug interactions might help reduce contrary outcomes and improve clinical outcomes [55,56].

Hypertension was a common morbidity in Italian cases, affecting 73.8% of patients, 52% whom were taking ARBs or ACE inhibitors [57]. Due to the theoretical risk of RAAS inhibition in COVID-19 patients, discontinuation of these antihypertensive agents has been recommended. Currently, no evidence indicated ACE-I's or ARB's withdrawal; prevention of infection or impact on clinical outcomes [58,59]. Initial reports from Wuhan, [60,61]. Lombardy, [62,63]. and New York City [64]. identified higher rates of hypertension among severely ill, hospitalized COVID-19 patients. Arterial hypertension is the most frequent co-morbidity seen in patients with COVID-19 [65]. Patients with high BP hold a two-fold increased risk of death from COVID-19 compared to patients without it. Besides it also explains that patients who were not taking medications to control high BP were at an even greater risk of death from COVID-19 [66]. Our study reported prevalence of hypertension 1.5 times higher in the ICU group [53].

Coronary artery disease history is at higher risk of cardiovascular complications and cardiac injury after COVID-19 infection as compared to healthy people [37]. Data analyzed from our

hospital reported higher mortality rate in COVID patients with preexisting CVD (12.16% vs. 3.48%, P <0.0001; Odds ratio 3.83; 95% CI: 4.19 -14.98). In these patients age greater than 65 years increased the mortality risk by 1.76 times and males were 3 times more prone to poorer outcomes. Also, one third of these patients developed cardiovascular complications (1-heartfailure,2-atrial fibrillation, 3- sudden cardiac arrest) which was the cause of death. However, mortality outcomes at one month follow were not affected by preexisting CVD (p= 0.6189). [Unpublished data]

Obesity was considered as a risk factor for increased severity and regularity of patients admitted in intensive care for SARS-CoV-2 infection. Disease severity augmented with BMI [67,68]. A six-times increased risk of severe COVID-19 in patients with a BMI more than 25 kg/m² was reported [69]. People with obesity are often physically inactive, more insulin resistant, and with gut dysbiosis, which might increase the inflammatory response to infection with SARS-CoV-2 [70].

Males Data analysis of our COVID patients highlighted a striking difference between male and female gender regarding disease susceptibility: a male to female ratio of 1:0.39, inclining towards male was observed. This striking difference depicting higher proneness of men to COVID-19 could be related to differences in innate immunity, steroid hormones and factors related to sex chromosomes crucial in the defense against viral infections [53].

The reproductive track is easily affected by corona virus because the blood-testes barrier is not perfect enough to completely isolate virus [71]. Virus-induced testes damage can impair gonadal hormone secretion and spermatogenesis, as seen in human immunodeficiency virus(HIV) or mumps-induced orchitis [72]. The sex-related hormones between reproductive-aged men with SARS-CoV-2 infection and age-matched healthy men, reported significantly increased serum luteinizing hormone (LH) [39]. Diangeng Li study found that SARS-CoV-2 can be present in the semen of patients with COVID-19, and SARS-CoV-2 may still be detected in the semen of recovering patients [73].

Aging itself has been strongly associated with worse outcomes, because of the pathophysiological changes that characterize the respiratory system for e.g., a gradual decrease in the number of cilia and ciliated cells in the airway with aging. As age advances, disruption of both innate and adaptive arms of the immune system has been reported [74]. People with more than 60 years of age showed heavier clinical manifestations, higher severity and longer course of illness compared to those under 60 [75]. Based on current epidemiological data, SARS-CoV2-infected patients aged>80 show a greater risk of death in comparison with younger patients. A age related comparative study reported mortality, the proportion of patients with Pneumonia Severity Index (PSI) grade IV and V ($P < 0.05$), the proportion of multiple lobe involvement ($P < 0.001$) and mechanical ventilation received by elders is significantly higher than those of young and middle aged patients [76]. Another similar study reported that those elderly patients with COVID-19 are more likely to progress to severe disease and its outcomes [77,78].

7. FOLLOW UP PROTOCOL POST COVID-19

Based on the outcomes, contributing comorbidities, guidelines and available assessment scales a short- and long-term follow-up protocol is designed which can put to use. The Medical Research Council Dyspnoea (MRCD) scale [79]. is a simple to use which indicates the extent of breathlessness which affects mobility. The 0-4 stage scale is used alongside the questionnaire to establish clinical grades of breathlessness [80]. The Post COVID-19 Functional Status (PCFS) scale was proposed by WHO to assess functional sequelae upon discharge from the hospital [81,82].

Every hospitalized COVID patient should be followed up for their early, medium and long-term complications after discharge. Based on their physical activity, respiratory functions including breathlessness, oxygen requirements, rehabilitation, palliative care/symptom management and psychosocial needs the follow up protocol should be implemented.

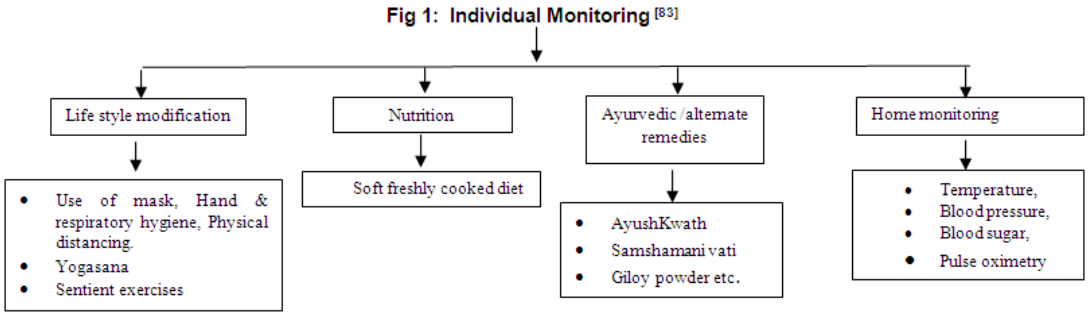

Fig. 3. Individual monitoring

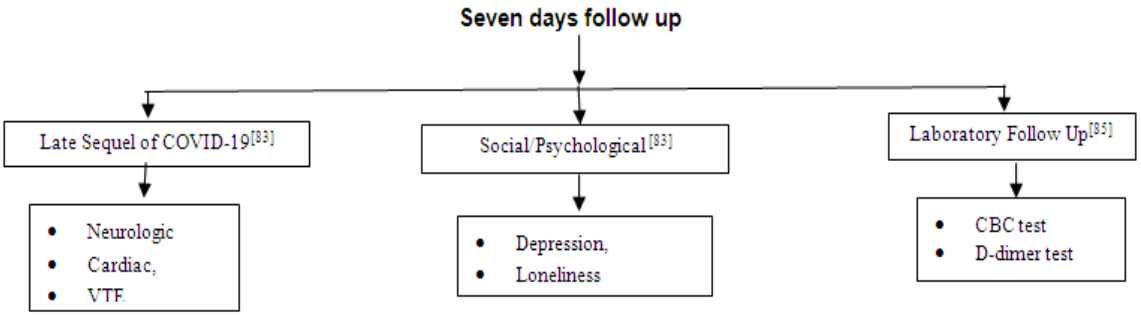

Fig. 4. Seven days follow up

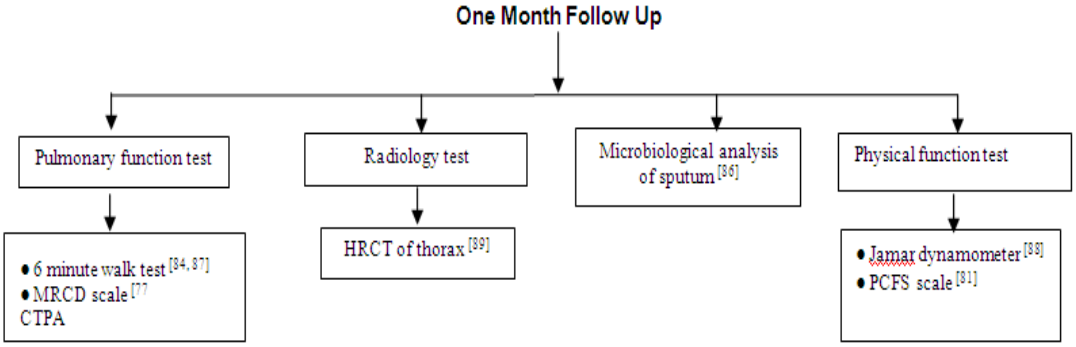

Fig. 5. One Month Follow up

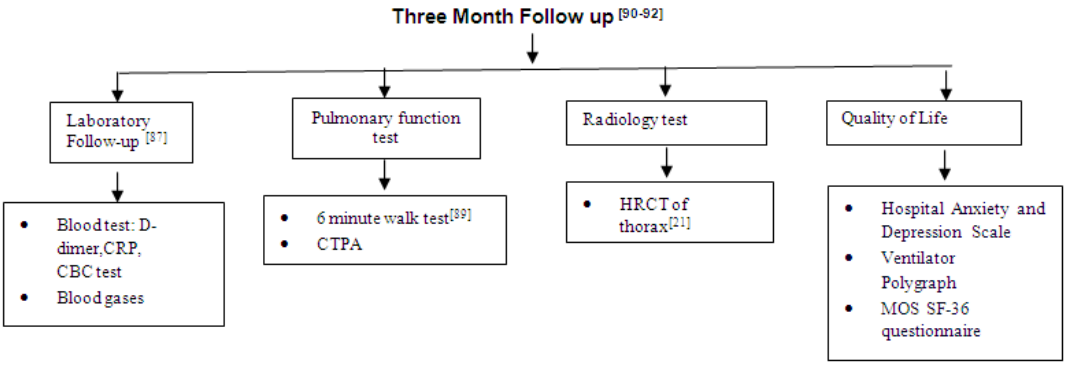

Fig. 6. Three Month Follow up

8. CONCLUSION

COVID-19 the global health issue is severely associated with pulmonary defects, a long quarantine period/hospitalization stay and a possible reactivation of the virus; potential pulmonary, physical and/or psychological outcomes may be anticipated in patients following discharge. Thus, a follow up protocol needs to be implemented at 1 week, 1 month and 3 months respectively for the holistic wellbeing of the patient. Clinical Study for evaluation of short and long term outcomes in COVID-19 patients after discharge can be performed to strengthen this review article. We have already performed one such type of clinical study at our hospital.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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