

Post Covid-19 Syndromes, The Timeline of Covid

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Author's Contribution

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^{1,2,4} Analysis/Interpretation/Discussion
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Abstract

Introduction: Novel corona virus has claimed significant mortality and morbidity. Timeline of long-term complications and effects on humanity are yet to be explored.

Objective: To evaluate the spectrum of post Covid syndromes amongst Covid survivors.

Materials and Methods: This cross-sectional study was conducted at Medicine Dept. RIHS Islamabad after ethical approval. 195 recovered COVID cases were selected and followed 3 months over a year. Inclusion criteria: Age >12 years, both genders, Covid PCR +ve >4 weeks earlier. Exclusion criteria: Malignancies, pregnancy, recurrent Covid and that lost follow-up. Patients were evaluated for new onset generalized symptoms, respiratory, cardiovascular, neurological, hematological, gastrointestinal, dermatological and genitourinary supported by relevant investigations. Data analyzed by SPSS-22 with significant $p < 0.05$.

Results: Amongst 195 cases, 102(52.3%) males and 93(47.7%) females, mean age was 42.35 ± 14.31 years, mean duration since Covid recovery 32 ± 24.47 weeks. There was history of mild COVID in 89(45.6%), moderate 71(36.4%), severe 32(16.4%) and life threatening 02(01%) having significant association with increased mean age and female gender ($p < 0.05$). ninety four (48.2%) cases had post COVID syndromes. persistent fatigue (58), fever (29), myalgia's (27), dyspnea (26), persistent cough (19), weight loss/gain (18), smear positive TB (2), bronchitis (7), asthma exacerbations (3) and pleural effusion (1). X-ray findings showed lung fibrosis in 12, ground glass appearance 10. Spirometry showed reduced exercise capacity in 11. Anemia in 11, leukopenia 02, thrombocytopenia 02, pancytopenia 01 case. In CVS, retrosternal chest pain in 11, orthopnea/PND 05, myocarditis/myocardial fibrosis 04, pericardial effusion 01, new onset hypertension 03, worsened hypertensive control 02, palpitations 10 and POTS 03. Regarding ENT, sinusitis in 12 and mucor-mycosis 03. Reduced GFR 05 and COVAN 01. New onset diabetes 05, worsened diabetic control 06, bone-demineralization 03 and thyroiditis 01. Persistent diarrhea 06, IBS 04, gastritis 08, esophagitis 06, GERD 11. Seven of 93 females reported menstrual irregularities. Hair loss 15, rash 07. headache in 23, anxiety 17, disturbed sleep 14, depression 09, peripheral neuropathy 03, CVA 03, amnesia and PTSD 03 each. 03 cases expired with cardiopulmonary arrest.

Conclusion: Post COVID syndrome observed in half of Covid survivors. The respiratory, cardiovascular, dermatological, neuropsychiatric and generalized symptoms were frequent. Authors suggest follow-up of Covid survivors. The clinical evaluation and timely management may improve quality of life and morbidity amongst survivors.

Keywords: COVID-19. Post Covid Syndromes, Long Covid syndrome, Covid complications, Persistent post-Covid syndrome (PPCS), Myocarditis. Lung Fibrosis.

Introduction

Corona virus disease, the Covid-19 is a pandemic. The causative agent is SARS corona virus i.e., SARS COV-2). The symptomatology involves varying grades of fever, cough and fatigue in **mild** cases and shortness of breath and respiratory failure needing ventilatory support in **moderate, severe** and **critical** cases.^{1,2} The Post-Covid syndrome is also termed as long Covid that might include general myalgia, diffuse myalgia, persistent fatigue, dry skin, difficulty in reading, increased anxiety, depression, insomnia, and nonrestorative sleep which continue for 12 months and are not explained by alternate diagnosis. It also includes the generalized or systemic, medical, psychological and cognitive manifestations. These include pulmonary, cardiac, vascular fibrosis and persistent immunosuppression. There is higher mortality, morbidity and impaired quality of life due to fibrosis of organs and vasculature. Currently we are experiencing the pandemic and its long-term effects.

It mainly involves respiratory system but, in some cases, multi-system involvement may occur including gastro-intestinal, cardiovascular, central nervous system, musculoskeletal etc. Most of the patients of Covid-19 recover without complications, but in some cases symptoms like cough, SOB, fatigue, GERD, depression, anxiety and other bacterial/viral/fungal infections may persist for several months post recovery.³ These patients may present with certain symptoms long after recovery from Covid-19. This presentation of multiple symptoms and diseases is grouped as post Covid syndromes (PCS).⁴

Post Covid syndrome leads to multiple consultations and hospitalizations, thus causing significant morbidity and anxiety. Hence, it is important to categorize the most common post Covid syndromes along with their relevance and significance in terms of patient care; so that proper diagnosis and management of post Covid syndromes can be carried out.

There are some studies done earlier and certain studies are ongoing regarding Post Covid syndrome but little information we get from these, as multiple new symptoms and diseases are continuously emerging after Covid-19 and they are still to be studied and explored.

In Pakistan cases of Covid-19 are still occurring but not much studies regarding post Covid syndrome are done in our country yet. A study from Agha Khan University Hospital Karachi focusses on the neurological manifestations as post Covid syndrome.⁵

However, we need to study the variety of the systemic manifestations of Covid syndrome in our region. We are facing lot of symptoms and diseases after Covid-19 infection which is wrongly associated with other diseases, these points out the necessity to study this syndrome thoroughly.

The objective of this study is to assess which symptoms and organ dysfunction are commonly occurring and persisting after Covid19 infection. The data will be helpful to study, analyze and compare the trends of post Covid manifestations in our cases. This may help us to create better awareness among health care professionals to identify, investigate and manage post Covid syndromes. This may also help to avoid misdiagnosis, over or under management of such cases and improvement in morbidity and mortality. Our main focus is to assess the symptoms and organ dysfunction associated with post COVID-19 syndrome. Our objective is to assess the signs, symptoms and complications which persist after COVID-19 infection beyond 4 weeks after recover along with the organ dysfunction caused by it.

Materials and Methods

This observational study was conducted at Dept. of Medicine, Rawal Institute of Health Sciences Islamabad after ethical approval from ethics review committee (ERB#RIHS-REC/081/21). 200 cases of confirmed COVID (PCR +ve cases initially) who were declared PCR -ve and recovered were selected and followed over a period of one year. Study was conducted from Feb. 2021-Feb.2022.

Inclusion criteria: Adult cases of age ≥ 18 years of both the genders that had PCR +ve report at least >4 weeks before presentation.

Exclusion criteria: Diagnosed malignancies, <1 month of disease, pregnant women and cases with recurrent Covid were excluded. Patients were followed over a period of one year at 3 months' intervals.

The demographic data and contact details were documented. 19 cases lost follow-up and were excluded. Total 195 cases were finally included. Specially designed proforma was used for data collection. Patients were inquired about generalized symptoms (fever, malaise, weight loss), followed by systemic inquiry addressing respiratory, cardiovascular, neurological, hematological, musculoskeletal, gastrointestinal, dermatological and genitourinary. Relevant investigations performed accordingly in each case. New onset manifestations

post-Covid infections were documented and pre-existing diseases excluded.

Data was analyzed by SPSS version-22. Frequencies and percentages calculated for qualitative variables (gender, disease severity, symptoms, signs, complications). Mean and standard deviation calculated for quantitative variables (i.e., age, duration since recovery from COVID). Chi-square test applied to study association of frequency of post-COVID syndromes with gender and disease severity. P-value <0.05 considered as statistically significant.

Results

Amongst 195 cases that participated in this research, there were 102(52.3%) males and 93(47.7%) females. The mean age of the study participants was 42.35±14.31 years (range 14-75). Mean duration since recovery from Covid was 32±24.47 weeks (range 04-96). In terms of Covid severity, there was history of mild Covid in 89(45.6%), moderate in 71(36.4%), severe in 32(16.4%) and life threatening in 02(01%) cases.

There was significant association of severity of COVID with the mean age; that was found to be lower in mild to moderate as compared to severe COVID ($p < 0.0001$). With respect to gender, males had higher frequency of mild COVID and female had higher frequency of moderate to severe COVID ($p = 0.039$).

When inquired about various symptoms and signs of post COVID syndrome, 94(48.2%) cases had post COVID syndromes and 101(51.8%) cases had no syndrome. The generalized symptoms were inquired and 58 cases had persistent fatigue, 29 cases had fever, 27 had myalgia's, 13 cases had weight loss, 05 had weight gain, persistent loss of taste in 05 and recurrent bacterial infections in 07.

Regarding respiratory system, 26 had dyspnea, 19 had persistent cough, 12 had lung fibrosis, 11 had reduced exercise capacity, 07 had bronchitis, 03 case had asthma exacerbations, 02 cases were found to have smear positive TB (TB re-activation), and 01 case had pleural effusion. While, 141 out of 195 cases reported no respiratory symptoms after recovery. Regarding the X-ray findings, 178 cases had no residual findings, 12 cases had lung fibrosis, 10 cases had ground glass

appearance and 01 case developed bilateral pleural effusions.

In cardiovascular system, 11 cases reported retrosternal chest pain, palpitations in 10 cases, 05 reported orthopnea and PND, myocarditis in 02, myocardial fibrosis in 02, pericardial effusion in 01, new onset hypertension in 03, worsening of hypertensive control in 02, and postural orthostatic tachycardia syndrome (POTS) in 03 cases. Thromboembolism was observed in 05 cases; limb ischemia in 02, DVT in 02 and pulmonary embolism in 01. 175 cases had no cardiovascular complications or symptoms. Variety of neuro-psychiatric symptoms were seen that included headache in 23 cases, anxiety symptoms in 17, disturbed sleep in 14, depression in 09, CVA in 03 cases (02 cases with ischemic infarct and 01 case with intracranial bleed), limb ischemia in 02, peripheral neuropathy in 03 cases, short term memory loss in 03 and PTSD in 03 cases. 157 cases were free from such symptoms. 03 cases expired and had cardiopulmonary arrest during the post Covid follow-up period.

Regarding ear, nose, throat (ENT) symptoms, sinusitis was observed in 12, persistent loss of taste in 05 and mucor-mycosis in 03 cases. 183 cases had no ENT complaints. 02 cases had rapid deterioration of vision. In the Renal system, reduced GFR was observed in 05 cases and Covid associated nephropathy (COVAN) in 01 case/ dialysis. New onset diabetes was seen in 05 cases, worsening of diabetic control seen in 06 cases, progressive bone-demineralization in 03 cases and thyroiditis in 01 case. Persistent diarrhea in 06 cases, 04 cases diagnosed as inflammatory bowel syndrome (IBS), 08 had gastritis, 06 had esophagitis, 11 had GERD and 01 had hepatitis. 170 had no GI symptoms. 07 out of 93 females reported menstrual irregularities. Dermatological complaints were hair loss in 15 cases, rash in 07 cases. 176 cases had no such complaints.

Hematological laboratory findings based on complete blood picture showed anemia in 11 cases, leukopenia in 02, thrombocytopenia in 02 and pancytopenia in 01 case. 181 cases had no hematological residual abnormality.

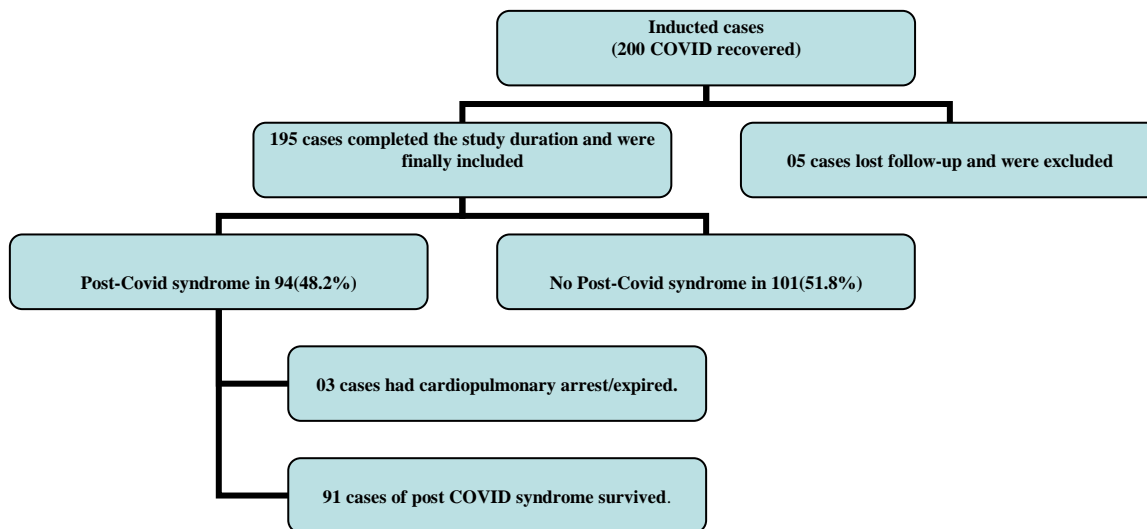


Figure 1: Flow chart representing the frequency of post Covid syndromes in Covid survivors (n=195)

Table 2: Presenting the demographic variables with respect to the severity of Covid in Covid survivors indicted in study for evaluation of post-Covid syndromes (n=195)

Variables	Amongst All n=195	Mild n=89	Moderate n=71	Severe n=32	Life threatening n=2	p-value
Age	42.35±14.31 (14-75)	36.03±13.08 (14-74)	46.65±13.20 (20-75)	53±11.44 (27-89)	42.5±17.67 (30-55)	<0.0001
Weeks Since recovery	32±24.47 (04-96)	29±21.99 04-96	34.45±26.72 (04-96)	35.94±24.7 (04-75)	25.5±31.82 (04-48)	<0.0001
Gender						
Males	102(52.3%)	55(53.9%)	35(34.3%)	10(9.8%)	01(01%)	0.039
Females	93(47.7%)	34(36.6%)	36(38.7%)	22(23.7%)	01(1.1%)	

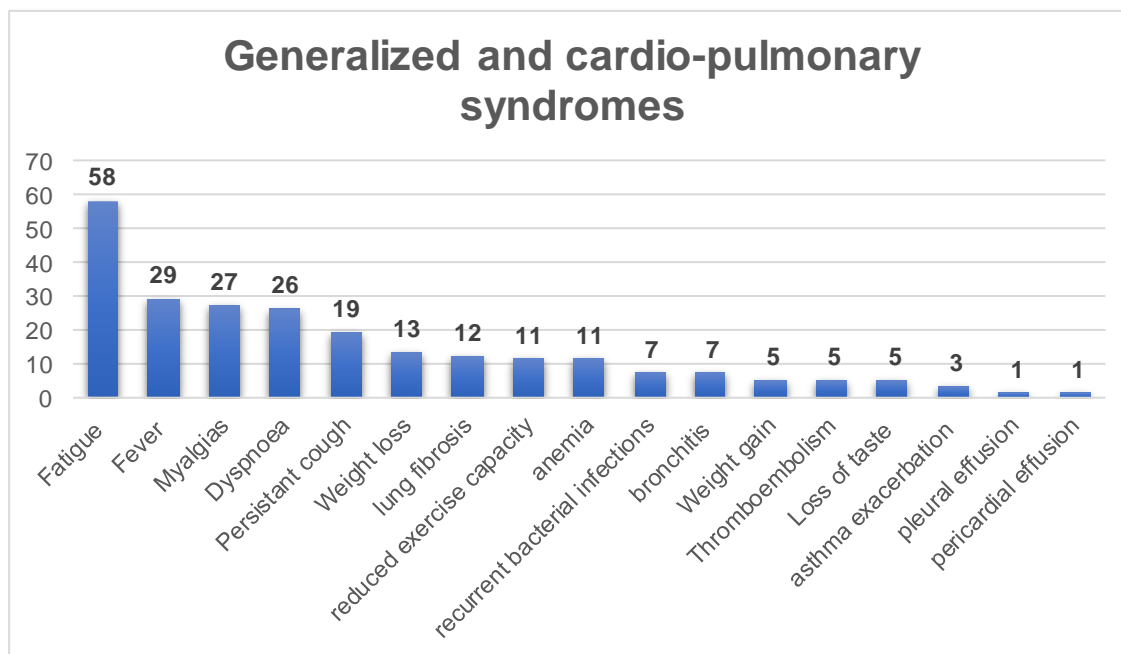


Figure 2: Bar graph presenting the frequencies of generalized and cardio-pulmonary syndromes observed in recovered cases of Covid (n=195)

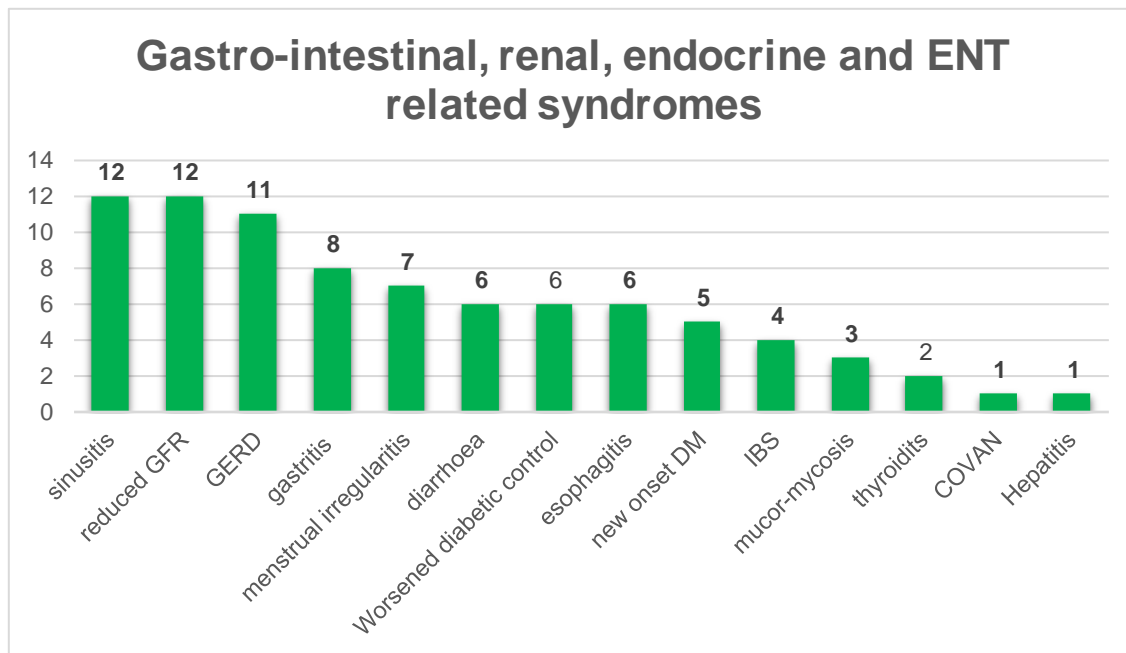


Figure 3: Bar graph presenting frequencies of Gastro-intestinal, renal and ENT related syndromes in recovered cases of Covid (n=195)

Discussion

In this study almost half (48.2%) of the cases had various post COVID syndromes. The exact prevalence of Post-acute and Post-chronic COVID-19 Syndrome is not known. In a smartphone-based study in UK, it was concluded that ten percent of COVID survivors remained symptomatic beyond three weeks, and few were unwell beyond several months.⁶ A US based study concluded that only 65% of Covid survivors resumed their normal health status after two to three weeks.⁷ The mean duration since Covid recovery was thirty-two weeks. Generally mild to moderate COVID-19 patient improve within 7 to 14 days whereas severe to critical COVID-19 patients take > three weeks to recover. However, certain COVID-19 patient's symptoms persist for several weeks to months.⁸ A patient-led research from USA found that significant numbers of COVID recovered patients are facing the symptoms after 2-weeks of recovery. This two-week duration is claimed to be the complete recovery period for mild cases. These long-term after effects are now given the label of Long COVID.⁹

COVID-19 has been a 'novel' unknown, unseen disease and its long-term complications are yet to be observed. The pathophysiology is still unclear and is possibly multifactorial involving multiple systems in

the form of systemic inflammatory or compensatory anti-inflammatory response syndrome, also called as SIRS and CARS. This triggers various levels of cytokine release storm. Persistent cytokine storm leads to hypoxia, hypo-perfusion, hypercoagulable state, multiorgan failure, septic shock and death.¹⁰

The study participants were comparable with respect to gender. However, female gender was associated with disease severity. Most cases were younger or middle-aged (30 to 55 years), i.e., the working age group. The increased outdoor activity, public interaction or job requirements could be the reason for this increased risk. The younger people are found to have lesser complications;¹¹ however, they may be source of COVID transmission to elderly and kids.

COVID-19 infection could lead to several systemic complications. In this study > half cases had persistent fatigue, 1/4th had fever, myalgia and dyspnea. Regarding the BMI, 18 cases reported significant weight changes. Disease related ill health, loss of taste may lead to weight loss, the dietary reasons, caloric rich diet to overcome the weakness, lack of physical activity due to outdoor restrictions or the use of corticosteroids could be the reason for weight gain. Di Flippo et al reported that 20-30% cases have >5% weight loss during COVID infection.¹² Same author found fluctuations in weight and abdominal adiposity in COVID survivors.¹³ Covid plus syndrome (comorbid)/pre-existing condition damage the body response due to poor nutrition. Many people

during their illness quit their proper health diet and hydration.

Nineteen cases had persistent cough. Studies have demonstrated that patients may suffer cough for several weeks to months post-COVID. Certain mechanisms are implicated for this cough. These include the vagal sensory nerve directed pathways of neurotropism, neuro-inflammation, and neuroimmunomodulation. These may lead to a cough hypersensitivity state.¹⁴ Other respiratory symptoms included bronchitis, asthma exacerbations, smear positive tuberculosis (< 10 cases each). Regarding tuberculosis, CDC states that the COVID-19 and tuberculosis have certain similarities in the presenting symptoms. The exposure to both of these diseases may occur concurrently. Certain co-morbid conditions contribute to poor outcomes both in Covid and tuberculosis. The COVID-19 PCR positivity doesn't exclude tuberculosis. Certain regions of Pakistan are considered as high burden settings. In case of high clinical suspicion, patient should be screened for TB as well. Additional risk factors for tuberculosis in post COVID cases are suppressed immunity, use of corticosteroids or missed diagnosis.¹⁵

We observed only one case of pneumo-mediastinum plus pneumo-pericardium; and one case of pleural effusion. Woon et al found low incidence (7%) of pleural effusion in COVID cases that was exudative, lymphocytic. Effusions occurred after a week of illness in critical cases and was associated with multisystem inflammatory syndrome (MIS).¹⁶

Regarding imaging, the X-ray findings showed lung fibrosis in 12 cases, ground glass appearance in 10. Spirometry showed reduced exercise capacity in 11 cases. X ray imaging is cost effective, safe and feasible; however, it may miss several findings. Hence CT scan is recommended imaging of choice. Sattar et al concluded that serial chest X rays may be helpful to grade the Covid severity and to monitor the clinical course of disease.¹⁷ Via artificial intelligence, the scoring software's for COVID X rays have been developed, these save time as well as provide the standardization of scoring.¹⁸

The laboratory investigations showed anemia (11), leukopenia (02), thrombocytopenia (02) and pancytopenia (01) case. We may infer that there were non-significant hematological manifestations in post COVID cases.

Neurologically, when the inflammatory markers (cytokines) enter across the blood-brain-barrier (BBB) leading to condition called as brain fog.¹⁹ We found CVA in three cases, this is rarely observed but a serious

complication with significant morbidity. In CVS, retrosternal chest, palpitations, orthopnea/PND, myocarditis/myocardial fibrosis and pericardial effusion were observed in <10 cases. The new onset hypertension seen in 03, worsened hypertensive control in 02 and POTS in 03. Thromboembolism, limb ischemia, DVT and pulmonary embolism in 01.

ENT manifestations were sinusitis and mucor-mycosis. Regarding renal complications, reduced GFR and COVAN were seen, though rare. The endocrinological findings were new onset diabetes, worsened diabetic control, bone-demineralization and thyroiditis. Garg et al found variety of derangement in endocrine system post Covid, i.e., hypothalamic pituitary axis, beta cell dysfunction/apoptosis, autoimmune destruction of thyroid gland.²⁰

GI symptoms were persistent diarrhea, IBS, gastritis, esophagitis, and GERD. Seven of 93 females reported menstrual irregularities. Hair loss seen in 15 and rash in 07. We may conclude that GI and dermatological manifestations were rare. Three cases expired with cardiopulmonary arrest in the post COVID follow-up.

MIS-A can be very serious having continuous fever PLUS more than one of these symptoms: epigastric pain, red eye, loose stools, dizziness or vertigo, cutaneous rash, nausea, vomiting, etc. Many patients missed to have acute myocardial infarction, myocarditis, angina, apprehension, palpitation etc. Multisystem inflammatory syndrome as well as thrombotic phenomena which cause wide range of its implication like stroke, limb ischemia, DVT, renal thrombosis, mesenteric ischemia, vasculitis, auto immune syndrome, (new onset of diabetes), rheumatoid arthritis etc. Symptoms may persist for longer duration, particularly fatigability, shortness of breath and cognitive decline. Patients may complain of inability to concentrate, impaired memory, confusion and lack of clarity, as well as psychological effects. These complaints may manifest during the Covid infection and persist or may appear after recovery from Covid. These symptoms may wax and wane in a remitting relapsing way in subsequent Covid waves.

The COVID-19 isn't a mere acute infectious disease, rather it should be considered as a complicated disease process. Covid does have various complications and long-term after-effects, particularly involving the lungs. Hence, the management of covid sequelae needs to be monitored and continued after recovery in the follow-ups. Authors suggest that further research is required to study the contributory risk factors for these complications. This can guide us how to intervene and manage for better outcome in the post

Covid phase. There are several unanswered questions about the pathophysiology of Covid. The dedicated centers or hospitals for Covid may be helpful to generate further data regarding the recovered cases in the follow-up assessment.

Hence, there is a need for structured and properly designed follow-up of Covid survivors regarding the sequelae and complications after recovery. Patients suffer from the poor quality of life, physical and psychological morbidity/disability and mortality because of these complications. There is need for mental support in addition to physical health support. Further research, monitoring, awareness and education are required. We anticipate that as we study Covid for longer time duration, we will be able to have better understanding of post-COVID sequelae. The finding may vary amongst the diverse settings and populations. Eventually, we may need 5 to 10-years for better understanding. The Covid survivors need multi-disciplinary approach to provide primary care, specialized rehab, social support, psychosocial and mental health professionals.

Conclusion

Post COVID syndrome is frequently observed (half of recovered cases) with significant burden of generalized symptoms. The respiratory, cardiovascular, dermatological and neuropsychiatric symptoms were frequent in our cases. Authors suggest to follow-up and screen recovered Covid cases for post COVID syndromes. The clinical evaluation, appropriate investigations and timely management may improve the quality of life and morbidity amongst survivors.

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