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A Longitudinal Study On Changes in Clinical, Laboratory, Radiological and Psychological Parameters in Covid-19Recovered Patients following Up in a Tertiary Level Covid Hospital In Eastern India

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Abstract:
Background: *After recovery from COVID infection; post covid-19 ("long COVID") may occur which presents as a multisystem disease. After starting post-COVID outpatient (OPD) clinic at Medical College, Kolkata, we found significant proportions of patients were returning to seek medical attention due to prolonged COVID symptoms. Prompted by these observations we aimed to analyse post- COVID symptoms in a systematic manner to manage these symptoms better.*
Materials and Methods*: This study was conducted in a longitudinal and observational manner.All patients who followed up in post-COVID OPD at Medical College, Kolkata were assessed were asked to follow up every month.148 eligible patients were enrolled after selecting according to inclusion & exclusion criteria. Their OPD treatment records were analysed for clinical, laboratory, radiological and psychological parameters.*
Results*: Mild and moderate disease was present in 40.54% subjects each; whereas severe disease was present in18.92% subjects. Amongst co-morbidities hypertension (42.57%) was leading followed by diabetes (35.14%). When compared at 1 month and 6 months; shortness of breath, vertigo, anosmia, chest pain abdominal discomfort, leg swelling, throat pain, headache, myalgia - these symptoms completely resolved at 6 months but weakness, cough, fatigue, chest discomfort, anorexia did not completely subside. Asymptomatic patients were almost doubled on at 6 months as compared to 1 month (34% vs 67%). Longest duration of persistent symptoms was weakness, followed by fatigue and anorexia. At 6-month post-COVID period there is 9.62% increase in diabetic patients and 17.46% increase in hypertensive patients. Depression and anxiety were very high in early Post COVID (1 month) as compared to late post COVID (6 months) period. Mean of CRP normalised (<6 mg/l) around 3rd month of post COVID period. Mean of D-dimer normalised (<500 ng/ml) at 3rd month of post COVID period (irrespective of NOAC prescription). Normalised mean D-dimer values (<500 ng/l) at 4 months of post-COVID period were found in NOAC prescribed patients. Mean of CT Severity Score <5/25 became after 1 month of follow up.*
Conclusion: *So, symptoms continue to persist even after 6 months of COVID recovery which contribute to significant morbidity.*
Key Word*: Post-COVID; CRP; D-dimer; co-morbidity; Depression*

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I. Introduction

Number of COVID-19 cases infections sharply increased since first reported case in December 2019, in Wuhan China [1].Several waves of coronavirus virus infections have hit different countries all around the globe since then [2]. We started operating post-COVID outpatient (OPD) clinic once weekly at Medical College, Kolkata from the month September, 2020. In this clinic we asked COVID-19 recovered patients to follow up regularly. After initial few months of following these COVID recovered patients we found significantproportions of patients were returning to seek medical attention due to prolonged COVID symptoms or new onset of symptoms. Data regarding longitudinal health-related symptoms is small and most available data are based on hospitalised patients.After a relatively mild acute illness Post-acute covid-19 ("long COVID") may occur which presents as a multisystem disease. Some may show delay in improvement of COVID-19 symptoms. Such patients can be divided two groups; those who may have serious sequelae (i.e.,

thromboembolic complications) and those having a non-specific clinical symptom; like, fatigue and breathlessness [3].Post COVID period can be divided in two phases according to duration from onset from symptoms. Post-acute covid-19 and Chronic covid-19 extending beyond three weeks and beyond twelve weeks respectively. [4] Roughly 10% of subjects experience prolonged illness after covid-19 [5]. These patients recover spontaneously with holistic support, rest and symptomatic treatment in most of the cases.An US study revealed that only 65% of people had returned to their previous level of health within 14-21days after a positive COVID test [6]It is hard to predict why some people's recovery or return to normal life is prolonged. Persistent viraemia due to weak or absent antibody production, relapse or re-infection, deconditioning, and mental health related factors such as post-traumatic stress disorders may all contribute to such prolonged recovery [7]. Long term respiratory, musculoskeletal, and neuropsychiatric sequelae have been found for other corona virus diseases like SARS and MERS and these havepathophysiological similarity with post-acute covid-19 [8]. Mild cases of COVID-19 may be associated with long term symptoms like cough, lowgrade fever or fatigue [4, 9] Other documented symptoms are shortness ofbreath, chest pain, headaches, neuro-cognitive problems, musclepains and weakness, gastrointestinal symptoms, metabolic disruption (such as poor control of diabetes), thrombo-embolic conditions, and anxiety, depressionand other mental health conditions [4,10]Prompted by observing different symptoms, signs, laboratory and radiological parameters in post-COVID clinic at Medical College, Kolkata, we aimed to analyse post- COVID symptoms in a systematic mannerso that managing these symptoms in long duration would be helpful.

II. Materials And Methods

Study design, Subjects and Settings: This study was conducted in a longitudinal and observational manner.All patients who followed up in post-COVID OPD at Medical College, Kolkata were assessed on clinical, laboratory, radiological and psychological parameters and they were asked to follow up every month since discharge for next one year. We analysed eligible patients who followed up at desired intervals and they were followed up for significant changes in aforementioned parameters.

Human Subjects Protection: The study was approved by the Institutional Ethics Committee (IEC), Medical College, Kolkata (Ref No: MC/KOL/IEC/NON-SPON/832/10/2020dated:09/10/2020).

Data Collection:148 eligible patients were enrolled after selecting according to inclusion & exclusion criteria. Their OPD treatment records were analysed for clinical, laboratory, radiological and psychological parameters. They were managed and followed up according to current post-COVID management protocol in India [11]. Records were analysed for monthly clinical, laboratory, radiological and psychological parameters. Data collected were be analysed according to standard statistical methods.

Study population:COVID-19 recovered subjects following up in post COVID OPD at Medical College & Hospital, Kolkata.

Inclusion Criteria:

a) Patients fulfilling criteria of defined population
b) Patients >12 years of age
c) COVID RT-PCR or RAT positive report during COVID illness

Exclusion Criteria:

a) Pregnant women
b) Lactating women
c) Paediatric patients (<12 years of age)

STUDY DEFINITIONS:

*Covid-19 infection:*a patient hospitalized with a positive sars-cov-2 reverse transcriptase polymerase chain reaction (RT-PCR) or rapid antigen test (RAT) from a nasopharyngeal swab or other respiratory sample.

*Post covid period:*A COVID-19 infected patient who recovered from covid infection (of any severity) and has been discharged from hospital or declared cured from home isolation (repeat COVID test not required unless indicated by national treatment protocol)

Clinical parameters monitored: Detailed clinical history during acute COVID and post COVID period, through clinical examination (including Blood pressure, Pulse rate, Temperature, SpO2, Respiratory Rate, Single breath count, 6- minute walk test, DASS-21 scale, chest & cardiac auscultations) of subjects in post-COVID clinic.

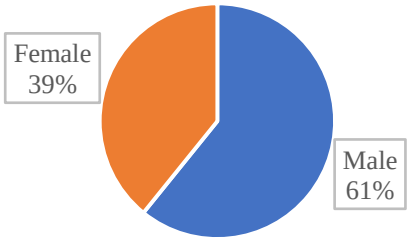
Laboratory, radiology and other parameters monitored: Laboratory results analysed were Haematology data (White blood cell count, neutrophil, lymphocyte and platelet count and erythrocyte sedimentation rate [ESR]); immunological and biochemical inflammatory markers (IL-6, C-reactive protein [CRP], D-dimer, Ferritin, LDH Procalcitonin, blood urea, creatinine, SGPT, SGOT, Bilirubin, P-Time/INR, serum electrolytes); radiology data (Chest X-ray findings, HRCT Thorax- CT severity index), spirometry with broncho-dilator reversibility, Electrocardiogram, Echocardiography.

Data analysis:
Data were tabulated and analysed according to appropriate statistical methods.

III. Result

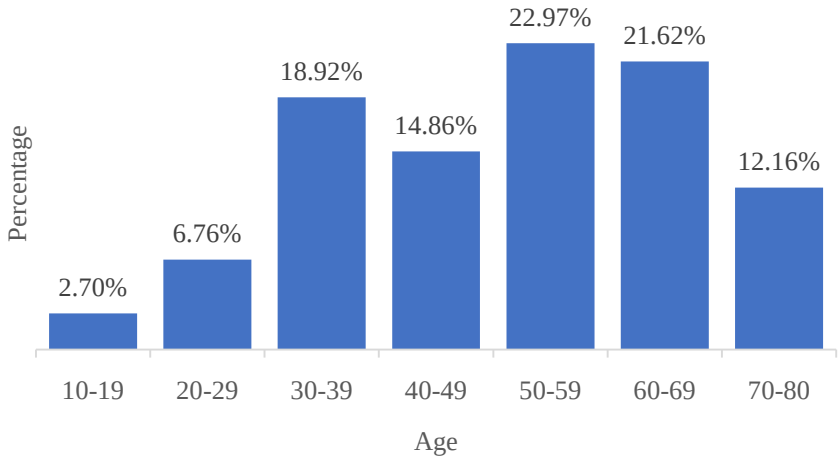
This study included 148 recovered COVID-19 subjects who followed up at Post-COVID-OPD clinic at Medical College & Hospital, Kolkata. 90 of them were males (60.81%) and 58 females (39.19%). [Figure 1]

Figure 1: Gender Distribution



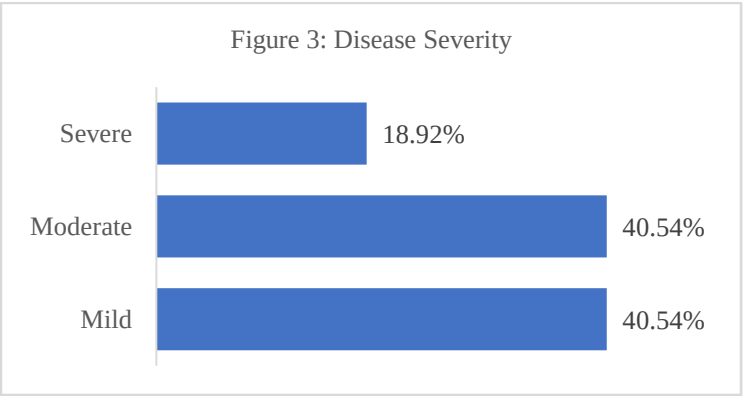
Age of the subjects expressed as Mean ± SD was 50.34 ± 16.02. Age more than 60 years were around 33% and 40-60 years of age was around 37%. [Figure 2]

Figure 2: Age Distribution



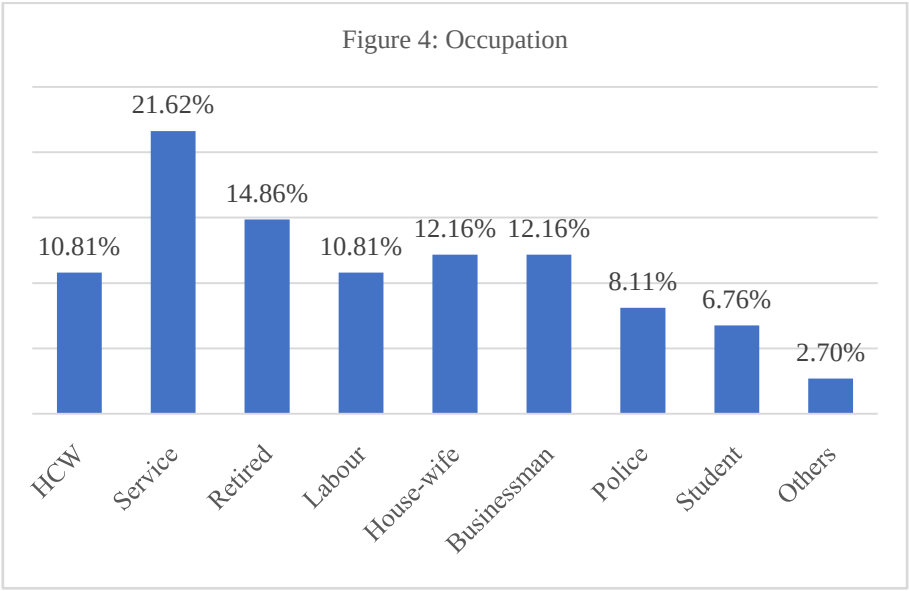
There was not much mean age difference in male and females (Male: 51.53 ± 16.20, Female: 48.48 ± 15.71). 118 (79.73%) subjects came from urban areas. Amongst the followed-up patients 48 (32.43%) had also simultaneous one or more COVID infected person in family residing together. Hospitalised patients (136) were majority (91.89%) at follow up clinic. Rest was managed at home isolation. Mild and moderate disease was present in 60 (40.54%) subjects each; whereas severe disease was present in only 28 (18.92%) subjects. [Figure 3]

Figure 3: Disease Severity



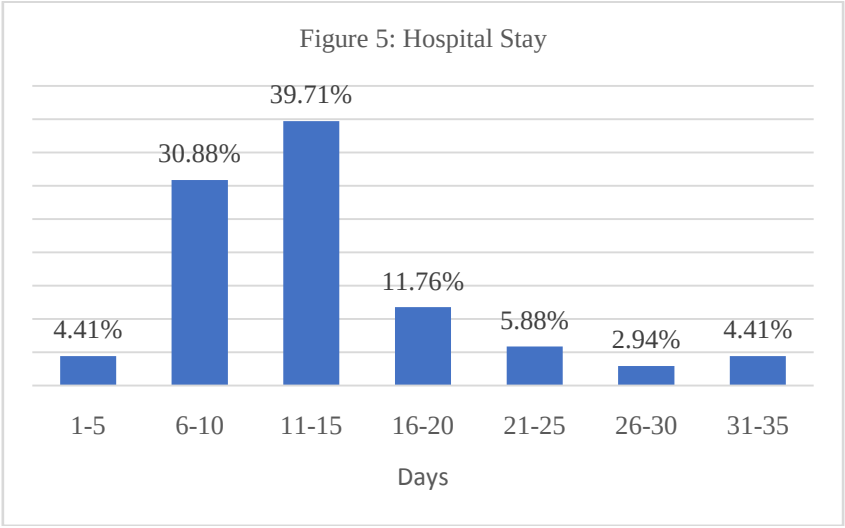
Analysis of occupation of subjects showed only 16 (10.81%) were healthcare worker.Amongstother occupations; service (21.62%) & retired (14.86%) were major groups. [Figure 4]

Figure 4: Occupation



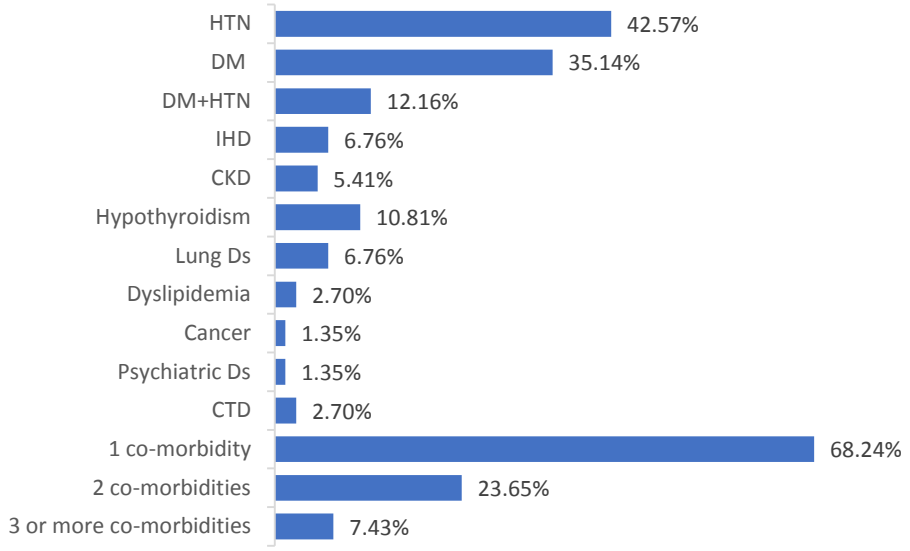
Mean hospital stay duration amongst followed-up subjects was 13.44 ± 6.30 days. Hospital-stay more than 20 days required in 13% of subjects. [Figure 5]

Figure 5: Hospital Stay



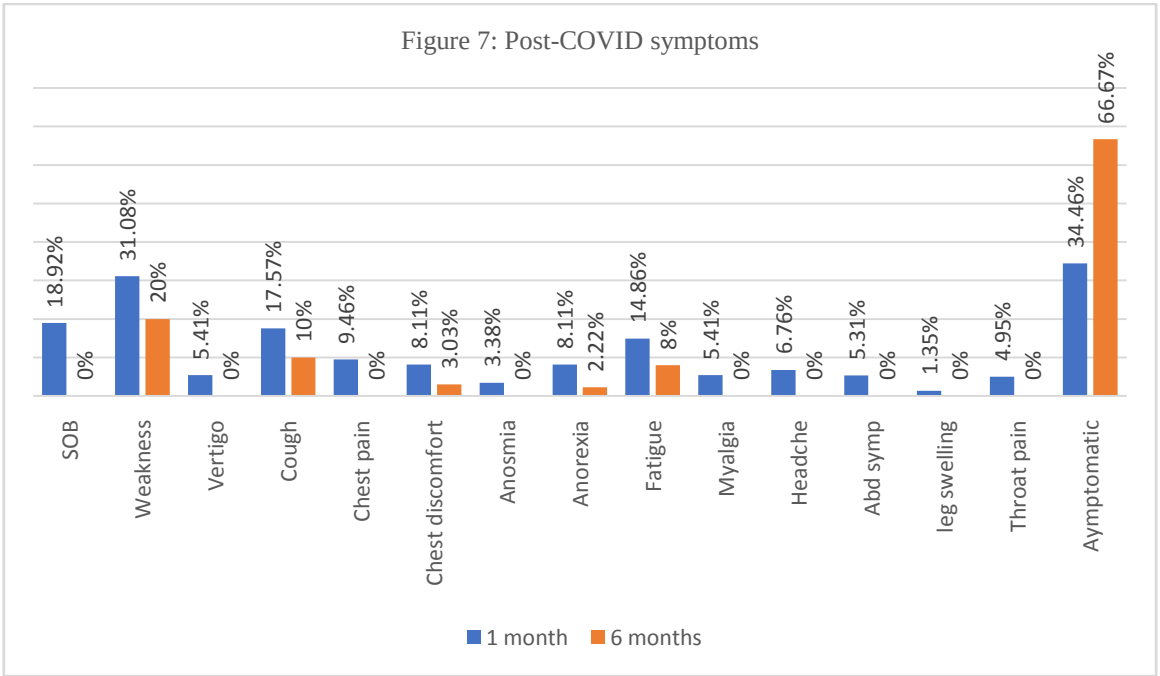
COVID pneumonia was present in 87(58.78%) of subjects. Amongst co-morbidities hypertension (42.57%) was leading followed by diabetes (35.14%) and Diabetes + Hypertension (12.16%). 1 co-morbidity was present in 68.24% of subjects, 2 co-morbidities & ≥3 co-morbidities were present in 23.65% and 7.43% subjects respectively. [Figure 6]

Figure 6: Co-morbidities



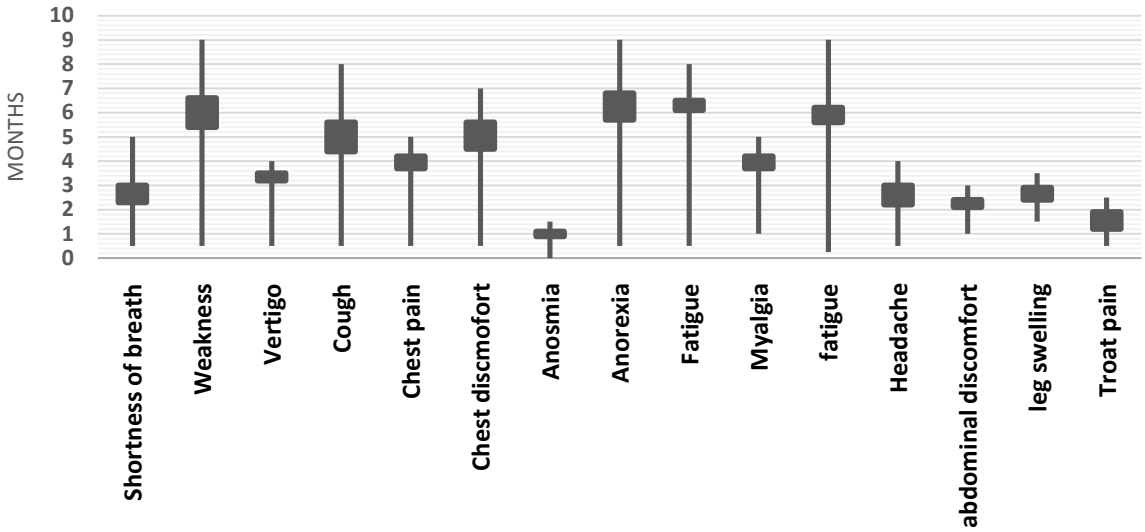
9.46% of subjects were smoker and 6.76% of subjects were alcoholic. Amongst post COVID symptoms when compared at 1 month and 6 months; shortness of breath, vertigo, anosmia, chest pain abdominal discomfort, leg swelling, throat pain, headache, myalgia these symptoms completely resolved at 6 months. Whereas weakness, cough, fatigue, chest discomfort, anorexia did not completely subside at 6 months follow up though their occurrence decreased significantly. Number of Asymptomatic patients were almost doubled on at 6 months as compared to 1 month follow up (34% vs 67%). [Figure 7]

Figure 7: Post-COVID symptoms



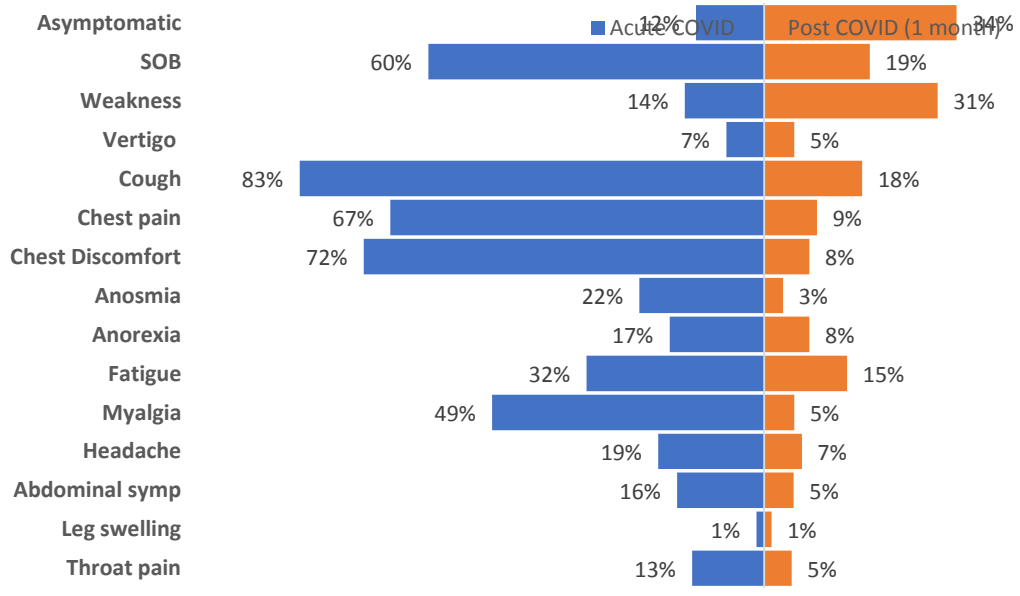
If we follow post-COVID symptoms' timeline longest duration of persistent symptoms were weakness, followed by fatigue and anorexia. And anosmia, headache, abdominal discomfort, leg swelling, throat pain lasted for brief period in post-COVID subjects. [Figure 8]

Figure 8:Post-COVID Symptom Timeline



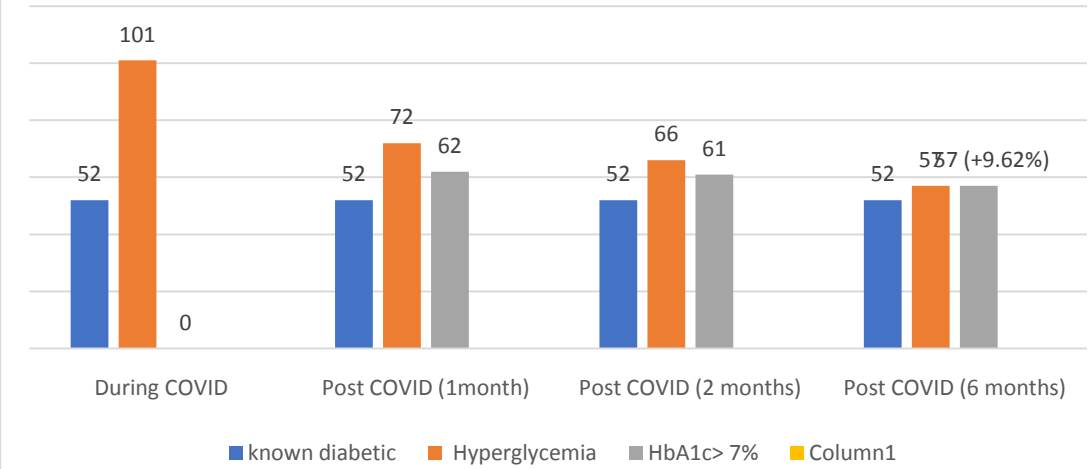
Cough, chest pain, chest discomfort, shortness of breath, myalgia were major complaints in acute COVID period; but in 1month of post COVID state these symptoms were significantly resolved. [Cough (83% vs 18%), chest pain (67% vs 9%), chest discomfort (72% vs 8%), myalgia (49% vs 5%)]. Complaints of weakness significantly increased in post-COVID (1 month period). (14% vs 31%). Asymptomatic patient increased to almost three times in 1 month after COVID recovery. (12% vs 34%). Anosmia also improved significantly in 1month after COVID infection (22% vs 3%). [Figure 9]

Figure 9: Acute and Post COVID (1month) symptom comparison



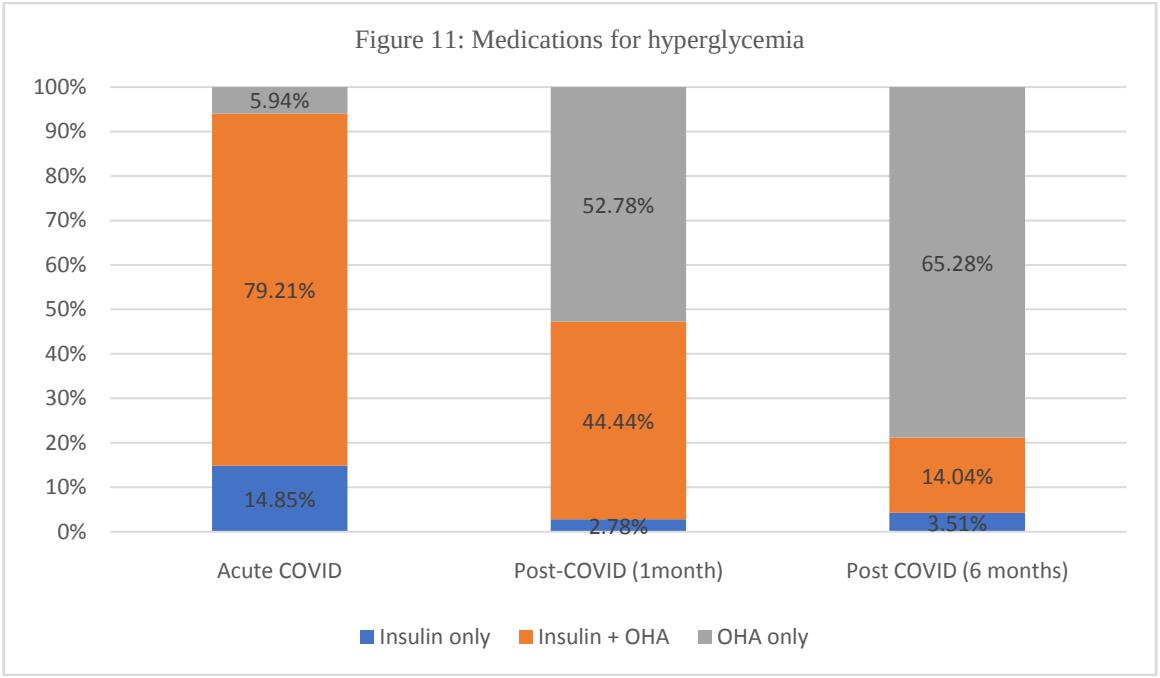
During Acute COVID infection hyperglycaemia were noted in 101 patients amongst them only 52 were originally known diabetic. But during follow up at post COVID clinic at 1-, 2- & 6-months Hyperglycaemia were noted in 72, 66 & 57 patients only. At the end of 6-month post- COVID follow up HbA1C> 7% was noted in 57 patients amongst them 52 were known diabetic at the time of COVID-19 infection. So, at 6-month post-COVID period there is 9.62% increase in diabetic patients. [Figure 10]

Figure 10:New onset Diabates



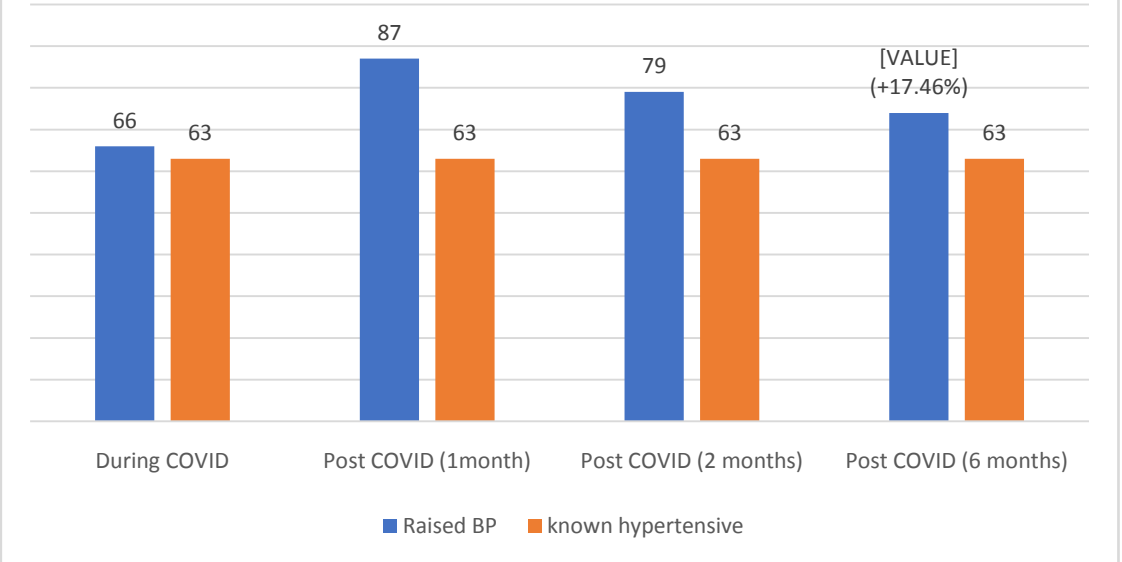
We analysed drugs required for controlling sugar during acute COVID, post- COVID at 1 month & 6 months period and was observed that majority (79.21%) of patients required insulin + oral hypoglycaemic agents (OHAs) during acute COVID. And in post-COVID period at 1 month insulin + OHAs were required in 44.44% of patients whereas OHAs only required in majority (52.78%) of patients. At 6 month follow up of post-COVID period majority (65.28%) of patients required OHAs only. [Figure 11]

Figure 11: Medications for hyperglycemia



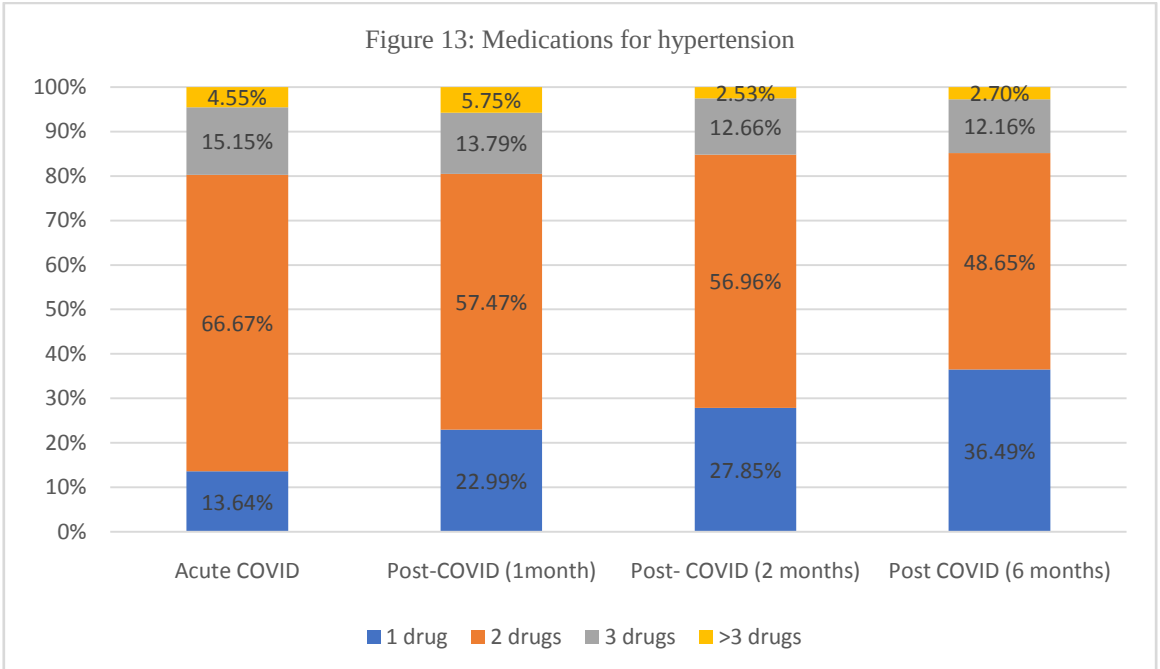
During Acute COVID infection raised blood pressure (SBP≥ 140 mm of Hg or DBP≥ 90) was noted 66 patients amongst them 63 were previously known hypertensive. But during follow up at post COVID clinic at 1- , 2- & 6-months raised BP were noted in 87, 70 & 74 patients only. So, at 6-month post-COVID follow up period there is 17.46% increase in hypertensive patients. [Figure 12]

Figure 12:New onset Hypertension

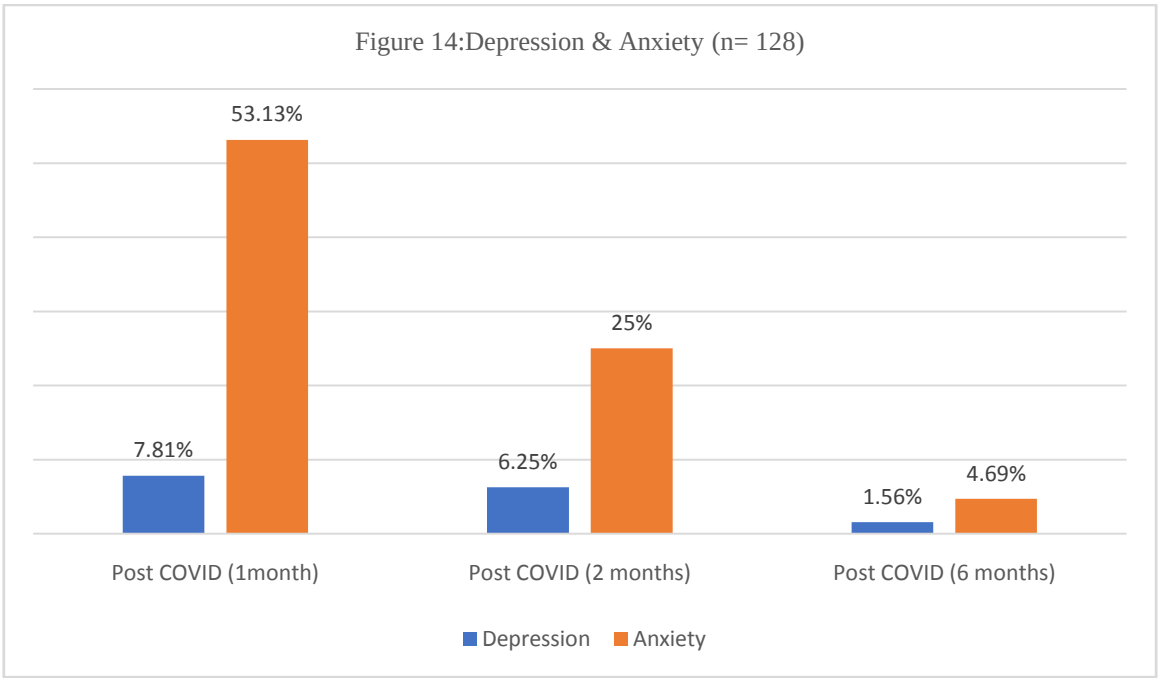


We analysed drugs required for controlling blood pressure during acute COVID, post- COVID at 1 month, 2 months & 6 months period and it was observed that majority (66.67%) of patients required two antihypertensives during acute COVID. And in post-COVID period at 1 month, 2 months & 6 months period requirement of two drugs reduced to 57.47%, 56.96% & 48.65% respectively. Whereas only one antihypertensive requiring subject increased significantly if we compare 1 month & 6 month follow up period (22.99% vs 36.49%). [Figure 13]

Figure 13: Medications for hypertension



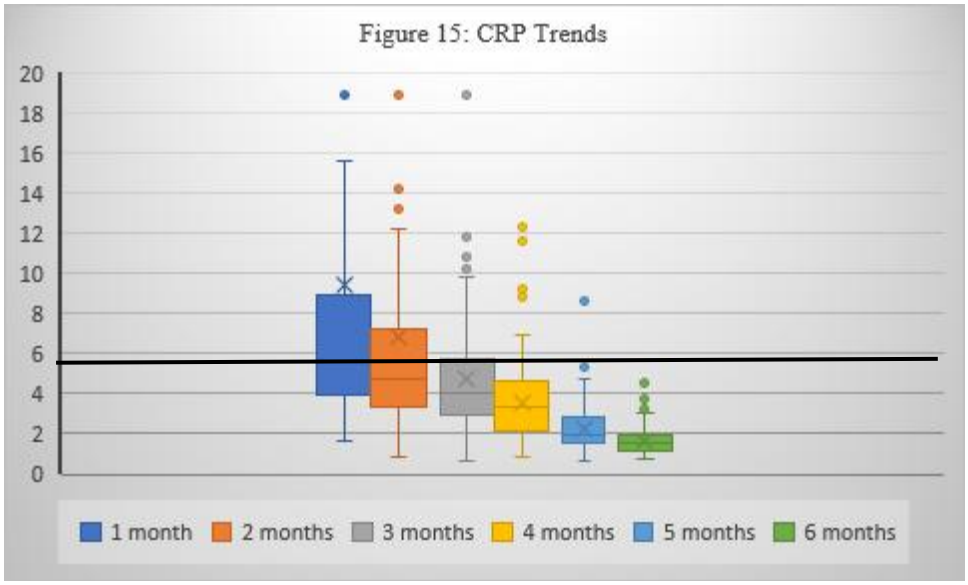
Depression and anxiety (Assessed via DASS-21 scale) were very high in early Post COVID (1 month) as compared to late post COVID (6 months) period [Figure 14]



Trends of CRP were analysed every month till 6-month post-COVID follow up period. Mean of CRP normalised (<6 mg/l) around 3rd month of post COVID follow up. [Table 1 & Figure 15]

Table 1: Summary of CRP values in post COVID period

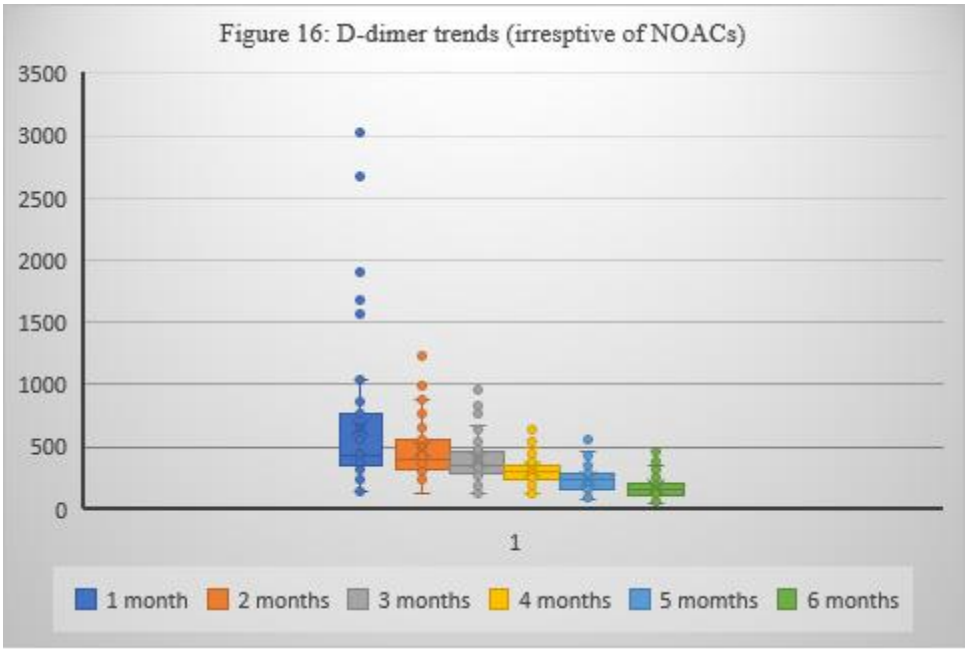
Time	Mean	Standard deviation	Maximum	Minimum
1 month	9.46	13.11	70.4	1.67
2 months	6.88	7.87	56.8	0.8
3 months	4.72	3.23	22.6	0.6
4 months	3.59	1.97	12.3	0.8
5 months	2.28	1.16	8.86	0.6
6 months	1.65	0.68	4.5	0.7



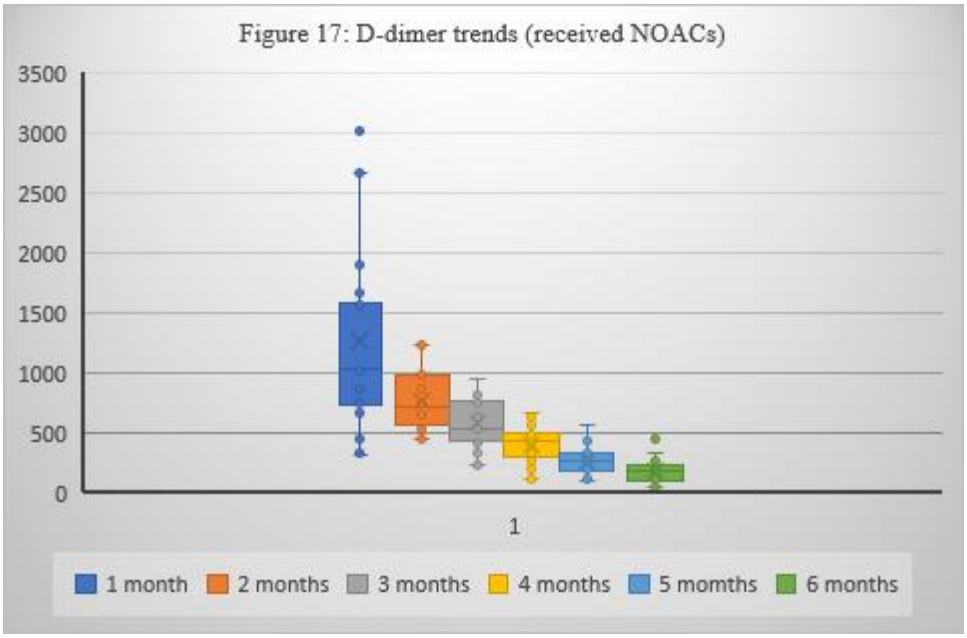
Trends of D-dimer [irrespective of Novel Anticoagulant (NOAC) prescription] were analysed every month till 6-month post-COVID follow up period. Mean of D-dimer normalised (<500 ng/ml) at 3rd month of post COVID follow up. [Table 2 & Figure 16]

Table 2: Summary of D-dimer values in Post COVID period (irrespective of NOACs)

Time	Mean	Standard deviation	Maximum	Minimum
1 month	663.19	553.45	3019	149.9
2 months	484.18	239.62	1244	123
3 months	406.61	174.98	956	123
4 months	317.71	174.98	556	122
5 months	233.77	87.99	567	76
6 months	168.62	75.22	457	50



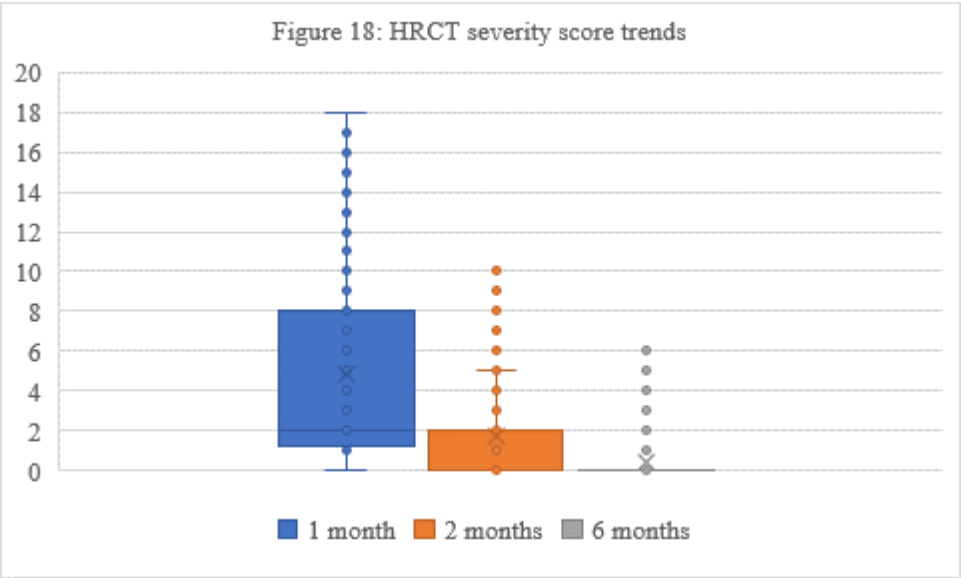
On the other hand, persons who presented with more than twice the upper normal range of D-dimer (>1000 ng/l) or with D-dimer in between 500-1000 ng/l with rising trend in subsequent follow up; were prescribed novel anticoagulants (NOACs) at post-COVID OPD. These subgroups of patients showed normalised mean D-dimer values (<500 ng/l) at 4 months of post-COVID period. [Figure 17]



Trends of HRCT CT (CTSS) severity score were analysed at 1 month, 2 month & 6 months post-COVID follow up period. Mean of CTSS <5/25 became after 1 month of follow up period at post-COVID OPD. [Table 3 & Figure 18]

Table 3: HCRT severity score values

Time	Mean	Standard deviation	Maximum	Minimum
1 month	4.83	4.58	18	0
2 months	1.74	2.82	10	0
6 months	0.43	1.13	6	0



IV. Discussion

This study analysed 148 recovered COVID-19 subjects who followed up at Post-COVID-OPD clinic at Medical College & Hospital, Kolkata. Majority (60.81%) of them were males. Subjects with age more than 60 years were around 33% and 40-60 years of age were 37%.79.73% of subjects were resident of from urban areas. Amongst the followed-up patients 32.43% had also simultaneous one or more COVID infected persons in family residing together.Hospitalised patients were majority (91.89%) at follow up clinic. Rest was managed at home isolation. Mild and moderate disease was present in 40.54% subjects each; whereas severe disease was

present in only 18.92% subjects.Analysis of occupation of subjects showed only 10.81% were healthcare worker.

Mean hospital stay duration amongst followed-up subjects was 13.44 ± 6.30. Hospital-stay more than 20 days required in 13% of subjects.COVID pneumonia was present in 87(58.78%) of subjects. Amongst co-morbidities hypertension (42.57%) was leading followed by diabetes (35.14%) and Diabetes + Hypertension (12.16%). 1 co-morbidity was present in 68.24% of subjects, 2 co-morbidities & ≥3 co-morbidities were present in 23.65% and 7.43% subjects respectively.9.46% of subjects were smoker and 6.76% of subjects were alcoholic.

Amongst post-COVID symptoms when compared at 1 month and 6 months; shortness of breath, vertigo, anosmia, chest pain abdominal discomfort, leg swelling, throat pain, headache, myalgia - these symptoms completely resolved at 6 months.Whereas weakness, cough, fatigue, chest discomfort, anorexia did not completely subside at 6 months follow up though their occurrence decreased significantly. Number of Asymptomatic patients were almost doubled on at 6 months as compared to 1 month follow up (34% vs 67%). In post-COVID symptoms' timeline longest duration of persistent symptoms were weakness, followed by fatigue and anorexia. And anosmia, headache, abdominal discomfort, leg swelling, throat pain lasted for brief period in post-COVID subjects.Cough, chest pain, chest discomfort, shortness of breath, myalgia were major complaints in acute COVID period; but in 1month of post COVID state these symptoms were significantly resolved. Complaints of weakness significantly increased in post-COVID (1 month period).Asymptomatic patient increased to almost three times in 1 month after COVID recovery.Anosmia also improved significantly in 1month after COVID infection.Halpin et al[12] showed thatpost Covid- fatigue was the most common symptom by 72% of subjects in ICUand 60.3% of subjects in general ward. The next most commonsymptoms were breathlessness. CarfiAet al[13] found that high proportion of individuals still reported fatigue, dyspnoea, joint pain, and chest pain.

Our study showed that at 6-month post-COVID period there is 9.62% increase in diabetic patients.In post-COVID period at 1 month insulin + OHAs were required in 44.44% of patients whereas OHAs only required in majority (52.78%) of patients. At 6 month follow up of post-COVID period majority (65.28%) of patients required OHAs only.

At 6-month post-COVID follow up period there is 17.46% increase in hypertensive patients.And in post-COVID period at 1 month, 2 months & 6 months period requirement of two drugs reduced to 57.47%, 56.96% & 48.65% respectively. Whereas only one antihypertensive requiring subject increased significantly if we compare 1 month & 6 month follow up period (22.99% vs 36.49%).

Depression and anxiety (Assessed via DASS-21 scale) were very high in early Post COVID (1 month) as compared to late post COVID (6 months) period.

Mean of CRP normalised (<6 mg/l) around 3rd month of post COVID follow up.Mean of D-dimer normalised (<500 ng/ml) at 3rd month of post COVID follow up (irrespective of NOAC prescription).On the other hand, persons who were prescribed NOACs due to indications at post-COVID OPD. showed normalised mean D-dimer values (<500 ng/l) at 4 months of post-COVID period.

Mean of CT Severity Score <5/25 became after 1 month of follow up period at post-COVID OPD. Pan F[14] et al showed that lung abnormalities on chest CT showed greatest severity at 10 days after onset of COVID symptoms.

V. Conclusion

This study concluded that many symptoms persist in post-COVID period and some new symptoms may appear. There is also newly onset diabetes and hypertension at 6-month post-COVID follow up period. Certain inflammatory biomarkers like C-reactive protein, D-dimer may take few months to normalise. And significant proportion of patients suffer from anxiety and depression. CT changes also take about a month to normalise. More researches with larger number of sample size in this subject of post-COVID symptoms are needed to manage these symptoms efficiently.

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