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THE CLINICO-BIOCHEMICAL, RADIOLOGICAL AND PULMONARY FUNCTION TEST ABNORMALITIES IN POST COVID-19 POSITIVE PATIENTS

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ABSTRACT
As we battle through the COVID pandemic, the challenging part is to manage COVID-19 sequelae and our objective was to evaluate the clinico-biochemical, radiological and pulmonary function test abnormalities in post COVID-19 positive patients. We conducted a prospective cohort study in 100 COVID-19 RT-PCR positive adult patients (>18 years) from a period of July 2020 to June 2022.Out of the 100 patients, majority came under the 41–60-year group with mean and standard deviation of 50.3 $\pm$ 15.41 and majority were male patients (56%). Significant positive correlation was found with various biomarkers and disease severity - Serum ferritin (r=0.725,0.325, p<0.001), interleukin-6 (r=0.638,0.473, p value<0.001), Lactate dehydrogenase (r= 0.813,0.487, p value<0.001) and D-dimer (r=0.744,0.567, p value<0.001) at 1st, 3rd and 6th month after discharge from the hospital. It was also noted that around 27% of the patients had residual fibrosis 6 months after the covid infection which was statistically significant and had a negative correlation with the spirometry at 1st 3rd and 6th month. It is crucial that we start proactively collecting and analysing data from COVID-19 survivors in controlled studies in order to identify potentially modifiable clinical risk factors or use risk-reduction techniques to help safeguard patients from developing post-COVID pulmonary fibrosis.

KEYWORDS: Post covid fibrosis, COVID-19, CT severity score.

MATERIAL AND METHODS
The Prospective cohort study was conducted in Sir Sunder Lal Hospital, Institute of Medical Sciences, Banaras Hindu University, Uttar Pradesh, India under Department of TB & Respiratory Diseases.

The consent for the evaluation of clinico-biochemical, radiological and pulmonary function abnormalities in post COVID patients was taken. After taking written consent, investigations like COVID-19 panel, Chest imaging and Pulmonary function tests (Spirometry) was done as required. Prior approval was taken from the Institutional Ethical Committee.

After collecting reports during the first, third and sixth month of visit of the patients, appropriate statistical tools were used to evaluate the clinico-biochemical, radiological and pulmonary function parameters and analysis of the data was done.

Study Design	Prospective Cohort study
Study Centre	Sir Sunder Lal Hospital, BHU, Varanasi, Uttar Pradesh, India
Study Population	Adult post COVID patients
Sample Size	100 Post COVID patients
Sample Method	Post covid patients meeting the inclusion criteria
Study Period	July 2020-June 2022

Inclusion criteria

1. Adult aged > 18 years who was tested positive with RT-PCR for COVID -19 infection and became negative.
2. Patients with and without other comorbidities- Diabetes mellitus, Systemic Hypertension, Dyslipidaemia, Coronary artery disease.

Exclusion Criteria

1. Patient not giving Consent.
2. Patients who were diagnosed with other chronic lung abnormalities, like COPD, Asthma, Bronchiectasis, Tuberculosis.
3. Patients who are RT-PCR positive at the time of study.

STASTISTICAL ANALYSIS

Data were recorded on a predesigned proforma and managed on an Excel spreadsheet. Descriptive statistics was done and mean and standard deviation was calculated. A paired t-test and Fisher exact test was used to analyse different parameters. Correlation was assessed using Spearman rank coefficient and statistical significance was accepted at p value <0.05. Statistical analysis was done using the Microsoft Excel and IBM statistical package for the social sciences (SPSS), for Windows, version 23.0(IBM corp, ARMONK, NY).

RESULTS

Table 1: Baseline Characteristics of Patients.

Variable	Subgroup	n (%)
Age(n=100)	20-40	32 (32)
	41-60	41 (41)
	61-80	26 (26)
	>80	1 (1)
Sex(n=100)	Male	56(56)
	Female	44(44)
Clinical features(n=100)	Fever	63(63)
	Cough	84(84)
	Shortness of Breath	76(76)
	Myalgia	56(56)
	Sore-Throat	53(53)
Comorbidities(n=100)	Diabetes	35(35)
	Hypertension	55(55)
	Coronary artery disease	17(17)
	Dyslipidemia	12(12)
Smoking status(n=100)	Yes	44(44)
	No	56(56)

The above table shows the demographic data of the study participants according to the age, gender, clinical features, comorbidities and smoking status. From this table we can see that majority of the patients (41%) come under the 41-60 age group whereas 32% and 26% patients come under 20-40 and 61-80 age group respectively. Mean and standard deviation of the group was 50.3 $\pm$ 15.41. Among the study participants, majority were males (56%) and the most common presenting symptom was dry cough (84%), followed by shortness of breath (76%) and fever (63%). The table shows that the most common comorbidity in affected individuals was hypertension (55%), followed by diabetes mellitus in 35% patients. Another important finding is that 44% of the affected were smokers.

Table 2: Distribution of Serum Ferritin levels among the participants at 1,3,6-month interval.

Ferritin		Increased Group		Normal Group		P-Value
		Mean	SD	Mean	SD	
Female	1st month	506.53	137.44	246.35	41.7	<0.0001*
Male		490.96	80.56	247.27	49.5	
Female	3rd month	438.7	97.29	237.7	47.27	<0.0001*
Male		451.37	75.9	241.3	57.62	
Female	6th month	417.4	24.97	208.15	41.71	<0.0001*
Male		409.6	64.58	207.21	62.06	

The table shows values of serum ferritin at three different period in both males and females, where the mean obtained was statistically significant. (p value <0.05* is taken as statistically significant)

Table 3: Distribution of IL-6 levels among the participants at 1,3,6-month interval.

IL-6	Increased Group		Normal Group		P-Value
	Mean	SD	Mean	SD	
1st month	141.5	135.82	13.36	7.49	<0.0001*
3rd month	100	-	12.41	7.69	<0.0001*
6th month	-	-	8.61	5.56	-

The table shows values of IL-6 at three different period in the participants, where the mean and SD obtained in the first and third month were 13.36 ± 7.49 and 12.41 ± 7.69 respectively which was statistically significant. (p value <0.05* is taken as statistically significant).

Table 4: Distribution of D-Dimer levels among the participants at 1,3,6-month interval.

D-Dimer	Increased Group		Normal Group		P-Value
	Mean	SD	Mean	SD	
1st month	1546.28	1051.61	201.91	89.46	<0.0001*
3rd month	1841	679.1	223.8	107.61	<0.0001*
6th month	1164.83	548.33	172.98	92.6	<0.0001*

The table shows values of D-Dimer at three different period in the patients, where the mean obtained was statistically significant. (p value <0.05* is taken as statistically significant).

Table 5: Comparison of LDH levels among the participants at 1,3,6 month interval.

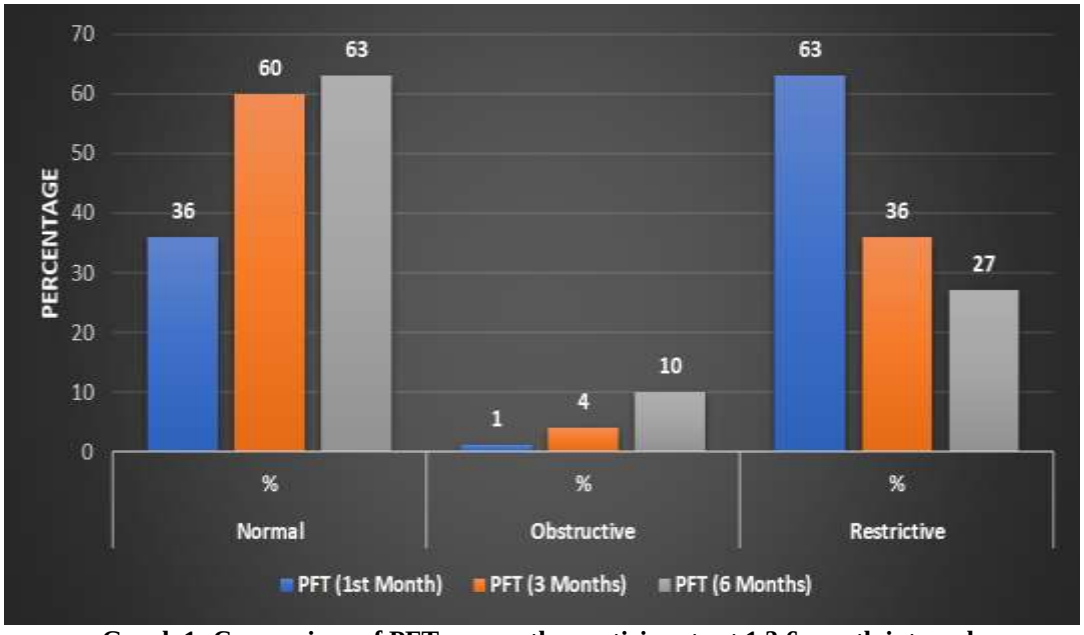
LDH	Increased Group		Normal Group		P-Value
	Mean	SD	Mean	SD	
1st month	554.29	163.06	248.13	53.55	<0.0001*
3rd month	561.14	142.19	244.06	60.49	<0.0001*
6th month	530.53	120.63	208.71	62.17	<0.0001*

The table shows values of LDH at three different period in the patients, where the mean obtained was statistically significant. (p value <0.05* is taken as statistically significant).

Table 6: Distribution of CT severity score among the participants at 1,3,6 month interval.

CTSS	MEAN	SD	F	p
1 Month	10.7	7.1	266.1	0.0001*
3rd Month	5.9	6.9		
6 Months	3.2	4.4		

*P value <0.05 - Statistically Significant



Graph 1: Comparison of PFT among the participants at 1,3,6 month interval.

The graph shows pulmonary function test results of the participants at three different intervals of post covid phase, where it is noticed that 27% of the patients had restrictive abnormality 6 months after the infection and 10% had obstructive PFT. But majority of the patients (63%) recovered after the initial insult.

Table 8: Correlation between biomarkers and disease severity in post covid patients.

Parameters	Correlation	P value
Serum Ferritin and CT severity score at 1st month	r = 0.725	0.000
Serum Ferritin and CT severity score at 6th month	R=0.325	0.0009
IL-6 AND CT severity score at 1st month	R= 0.638	0.000
IL-6 and CT severity score at 6th month	R=0.473	0.000
LDH and CT severity score at 1st month	R= 0.813	0.000
LDH and CT severity score at 6th month	R=0.487	0.000
D-Dimer and CT severity score at 1st month	R= 0.744	0.000
D-Dimer and CT severity score at 6th month	R=0.567	0.000

To assess the correlation between various biomarkers and disease severity, CT severity score was taken as the main parameter. All the four biomarkers showed a positive correlation with the disease severity at 1st and 6th month, which was statistically significant (p value <0.05), as given in the table.

DISCUSSION

The majority of COVID-19 patients ultimately recover, however according to the most recent researches, 10% to 20% of patients may continue to have mid- or long-term consequences after their initial illness. The term "post COVID-19 state" or "long COVID" refers to these effects' combined short- and long-term consequences.[1]

In this prospective cohort study, majority of the patients were male (56%), and 44% were females, out of the 100 study participants who were COVID-19 RT-PCR positive. We found that most patients presented with fever, cough, shortness of breath, myalgia, sore throat out of which dry cough (84%) was the most common symptom followed by shortness of breath (76%) and fever (63%). The findings of our prospective cohort study was similar to the study conducted by Huang et alC[1] first reported the clinical characteristics of 41 patients with COVID-19 in Wuhan city. The results showed that patients clinical manifestations included fever, cough, dyspnea, myalgia, fatigue with diagnostic tests showing lymphopenia, and radiographic abnormalities.

On evaluation of the distribution based on underlying systemic conditions, about 35% with diabetes, 55% shows hypertension, 17% coronary artery disease, 12% dyslipidemia. A number of existing literature suggested that the presence of risk factors, particularly hypertension, diabetes, lung, and coronary artery diseases, carries a poor prognosis, with even worse outcome when multiple risk factors are present.[2]

On comparison of ferritin levels at 1 month, 3rd month and 6th month interval. It was found ferritin levels are increased at 1st month by 53 %, 11% at 3rd month, by 7% at 6 month. The results of our study was similar to study conducted by Hussein et al.[3] It was also observed that there is a positive correlation between serum ferritin levels during the initial as well as the later phase of disease with the disease severity (r=0.725,0.325; p value=0.000) which was statistically significant. Ferritin can serve as a marker for liver damage, serious illness, and course of treatment. Ferritin is an acute phase protein which can be discharged from destroyed hepatocytes. Extra ferritinemia may be caused by impaired liver activity or a metabolic syndrome. Covid-19 patients with abnormal ferritin levels has more risk of liver injury and severe illness, previous studies also found that liver injury is common in covid-19 patients.

On comparison of Interleukin-6 levels among the participants at 1,3,6 month interval it was found to be increased at first month in 19 patients. The findings of our study was similar to the study conducted by Sabaka et al[4] in the role of interleukin-6 as a predictive factor for a severe course of Covid-19. There is a substantial body of evidence linking the IL-6 concentration to the severity of disease and unfavourable outcome of Covid-19. We also found a positive correlation between IL-6 and disease severity at first and 6th month of illness(r=0.638,0.473; p value=0.0009), which was statistically very significant. Han et al[5] examined the predictive value of various cytokines and concluded that IL-6 is the best predictor of severe Covid-19. A metanalysis of 10 studies by Coomes et al[6] concluded that increased IL-6 is highly associated with severe disease.

On comparison of the LDH levels at 1 month, 3rd month and 6th month intervals LDH levels was found to be increased by 53% in 1 month, 13% in 3rd month and by 10 % in 6th month. The findings of our study was similar to study conducted by Martha et al[9] prognostic value of elevated lactate dehydrogenase in patients with COVID-19. There was statistically significant positive correlation between LDH levels at first month and sixth month with CT severity score (r=0.813, 0.487; p value= 0.000) in our study also. The elevated LDH levels was associated with presence of diabetes, this phenomenon might be due to reduced glycogen synthesis, change in glucose oxidative metabolism and elevated whole-body rate of non-oxidative glycolysis. These mechanisms cause elevated

lactate in patients with insulin resistance compared with those without. LDH elevation in patients with COVID-19 indicates lung and tissue injuries. COVID-19 may lead to inadequate tissue perfusion and multiple organ failure due to various mechanisms, including thrombosis, which lead to LDH elevation. Thus, high LDH serves as a biomarker of the disease extent. This study indicated that the association between LDH elevation and poor prognosis was not affected by age, gender, hypertension or diabetes; these factors were known to increase COVID-19 severity and its associated mortality, thus, may confound the association.[7]

Comparison of D-DIMER levels among the participants at 1,3,6 month interval D-DIMER was found to be increased by 45% at 1 month, 9% at 3rd month and by 6% at 6 month. The findings of this were similar to previous study carried out in Dublin, Ireland, which showed elevation of D-dimer in 25.3% of patients after recovery. Our study also revealed a positive correlation between D-dimer levels and disease severity (r= 0.744, 567; p value =0.000), which showed statistical significance. Before the onset of COVID-19 disease, D-dimer was not used as an essential biomarker for the progression of viral or bacterial disease. Due to the intense damage caused by SARS-CoV-2 leading to thrombo-inflammatory complications, D-dimer levels increased and thus D-dimer became an essential biomarker for the hospitalization of the patients.[8]

On Comparison of CT severity among the participants at 1,3,6-month interval, mean at first month was found to be 10.7, at 3rd month was 5.9 and at 6th month 3.2 and difference between the mean at different interval was found to be statistically significant. The CT severity score correlation with all the biomarkers at two different stages of post covid phase also revealed a positive correlation with statistical significance. The findings of our study was similar to study conducted by Saad et al[9] in which CT-SS in patients who developed post-COVID syndrome is significantly higher than in those who did not develop Post-COVID syndrome (P value < 0.001). More than one-third of patients who survived severe coronavirus pneumonia had lung abnormalities resembling fibrosis on a six-month CT scan. Age, acute respiratory distress syndrome, prolonged hospital stays, tachycardia, non-invasive mechanical ventilation, and a higher baseline chest CT score were all linked to these alterations.[10]

Comparison of PFT among the participants at 1,3,6-month interval. PFT at 1st month was normal in 36 patients. There was obstructive defect in 1 patient and restrictive defects in 63 patients. PFT at 6 month was normal in 63, obstructive in 10 and restrictive in 27 patient. Our data suggest that like in cases of other atypical pneumonia, COVID-19 patients' pulmonary function needs to be thoroughly examined. It was observed that pulmonary function tests improved significantly in the first three months, but from three to six months, there was no additional significant improvement. The results of this investigation were comparable to those of the research of Fumagilli et al.[11] The restrictive pattern was present in 10 out of 13 patients who had COVID-19 pneumonia at the time of hospital discharge, suggesting that COVID-19 pneumonia may impair pulmonary function in a way that is clinically significant. Although pulmonary function had improved after 6 weeks, some degree of the restrictive change remained.

Our study had certain limitations

1. Data on functional tests or CT scans prior to admission were not available for assessment of longitudinal changes.
2. Small sample size. However further research is required to evaluate the the clinico-biochemical, radiological and pulmonary function abnormalities in post COVID patients.

CONCLUSION

The clinico-biochemical, radiological and changes in lung function are relatively common after COVID-19 and may persist well up to 6 months after discharge. Most of these abnormalities regressed further between the first month and third month, but showed a significant positive correlation with the disease severity. There is persistence of lung function defects in a group of patients that might be pointing towards post covid fibrosis, one of the more serious and often described sequalae COVID-19. The precise incidence of this sequalae among COVID-19 survivors and its connection to the viral disease are yet to be determined. The data from larger cohorts undergoing longer follow-up are likely to further clarify these results.

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