VOLUME - 12, ISSUE - 03, MARCH - 2023 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

General Medicine

"PROSPECTIVE OBSERVATIONAL STUDY TO DETERMINE VARIOUS CLINICO-BIOCHEMICAL PARAMETERS IN DEVELOPMENT OF LONG COVID"

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ABSTRACT Long COVID-19 describes illness in people who have recovered from covid-19, still report lasting effects or having unusual symptoms for longer period. It is affected by various comorbid conditions and the biochemical parameters at the time of presentation. This is a Prospective observationsl study conducted at tertiary care hospital in south India. RT PCR confirmed cases were followed on 14, 30, 90 and 180 day's post-discharge telephonically or in person. **Results** Long-COVID symptoms observed among 55.32% of the study samples. Most symptoms distributed around 30th day of follow-up. Fatigue was the longest symptoms observed (48.9%). Breathlessness (34%), stroke (4.3%), seizure (1.4%), GBS (2.1%) cases respectively. Hypertensive cases account 36.2%, Type 2 DM (29.1%). CAD (10.6%), CCF (7.1%), Asthma/COPD (19.9%/5.7%). Hb, PCV, serum protein, albumin level was lower and increase in TLC, N/L ration, BUN, PT and APTT noted in long covid cases. **Conclusion** Prevalence of long COVID was 55.32%. Fatigue was the predominant long covid symptom. Stroke/seizure/GBS/delirium were the least but serious manifestations of long COVID Age morethan 50, males affected more. Patients with HTN, TYPE 2DM, CAD, CCF, asthma/COPD developed more long COVID symptoms. Anaemia, hypalbuminaemia, neutrophilia, increased N/L ratio, elevated SGOT/SGPT on day of admission had higher risk for long COVID.

KEYWORDS : Long Covid -19, Post COVID, N/L ratio

INTRODUCTION

The world has been the stage for a new coronavirus, officially named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The long-term impact of COVID-19 is still under investigation. "Long COVID-19" is a term being used to describe illness in people who have either recovered from covid-19 but are still reporting lasting effects of the infection or have had the usual symptoms for far longer than would be expected. Scientific evidence suggests the possibility of a high residual viral load of SARS-CoV-2 in convalescent patients.[1] Post-acute covid-19 ("long COVID-19") seems to be a multisystem disease.

They continue to cripple the lives of the people who have recovered from COVID-19. Most common longterm symptoms includes chronic cough, low grade fever, and fatigue, all of which may relapse and remit. Other reported symptoms include shortness of breath, chest pain, headaches, neurocognitive difficulties, muscle pains, weakness, gastrointestinal symptoms, rashes, metabolic disruption.[4]. There are multiple reports on the increasing incidence of thrombotic complications in patients with COVID-19.[2] Neurological complications in COVID-19 include cerebrovascular event, altered mental status and encephalopathies. Increased suicidal ideation, behavioral disorders, post-traumatic stress disorder, anxiety, depression, pain disorder, panic disorder, obsessive compulsive disorder, and sleep disorders are few of the major neuropsychiatric manifestations.[3] The present study is undertaken with an aim of assessing the various clinico biochemical parameters contributing for development of long COVID-19.

METHODOLOGY

This is a prospective observational study. Data for the present study will be obtained from all the patients admitted with COVID-19 during the study period. Study period was 18 months (February 2021– August 2022). Patients more than 18 years of age, patients who are willing to give written informed consent, Patients who are willing for follow-up after Patients treated for COVID-19. Patients of age less than 18 years. Patients not willing to give written consent. According to proforma, detailed history will be taken regarding age, gender, history of any underlying medical conditions along with blood investigations on day of admission. This will be followed by details about treatment and response to treatment.

These cases will be followed up at various time intervals such as after 14 days, 30days, 90 days and 180 days for any development of long COVID-19 manifestations through telephonically or in person and severity will be noted. The sample size was determined by using the formula $N=Z^2 P(1-P)/d^2$. In this α was 0.05, Z was 1.96 (at 95% confidence level), and the estimated acceptable margin of error for proportion d was 0.05. Based upon the previous study on Long COVID, the prevalence of psychological co-morbidities was estimated to be around 10%.[10] Based on the above formula sample size was estimated to be a minimum of 141. The P-value <0.05 will be considered as statistically significant. The parameters studied in this study are various post covid manifestations and clinicobiochemical parameters in the development of Long covid.

RESULTS

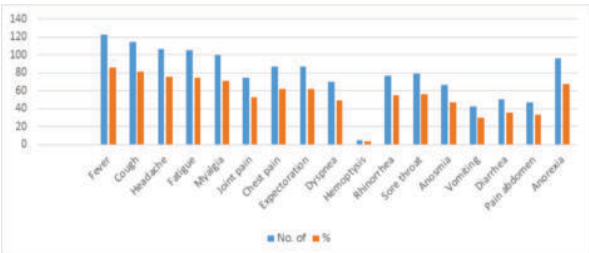

Figure 1: Frequency distribution of major post COVID syndrome from day 14 to day 180

Table 1: Distribution of gender among the study population

Gender	No. of Patients (N)	Percentage population (%)	Prolonged COVID symptoms	
			Present N (% out of 141 samples)	Absent N (%)
Female	50	35.5	23 (16.3%)	27 (19.1%)
Male	91	64.5	55 (39%)	43 (30.5%)
Total	141	100.0	78 (55.32%)	63 (44.68%)
	p<0.0001 (Student t test)		p 0.0006 (Chi square test)	

p 0.0745 Chi square test

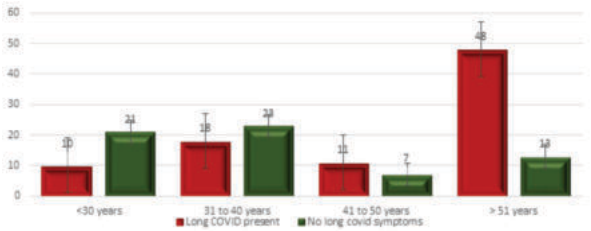

Figure 2: Bar diagram illustrating the distribution of age

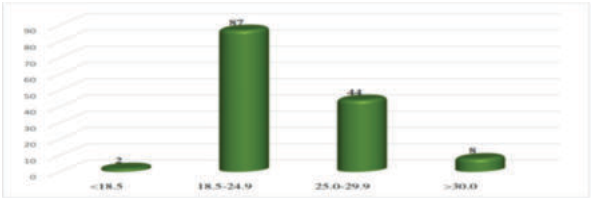

Fig No 3: Distribution of BMI

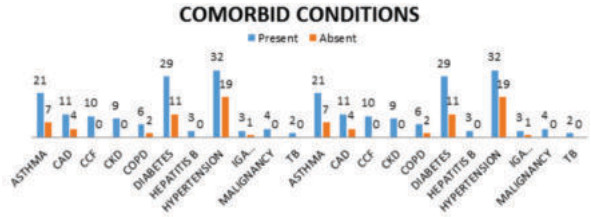

Fig 4: Comorbid conditions, p <0.0001

Table 2: Biochemical parameters based on the severity of the disease

Variables	Long COVID symptoms		Total	P Value
	Absent	Present		
HB	13.6±1.55	10±2.77	12.83±2.22	0.002**
PCV	39.66±3.92	33.19±7.5	37.83±5.93	0.008**
TLC	7018.1±2856.21	22316.8±61325.62	10915.67±26301.66	0.047*
N/L RATIO	3.02±2.21	9.25±9.22	6.06±6.46	<0.001**
MCV	85.71±10.82	83.57±11	84.37±11.36	0.509
PLATELET	2.08±0.67	2.21±0.94	2.15±0.8	0.675
Bilirubin(T)	0.69±0.23	0.62±0.27	0.74±1.02	0.583
Bilirubin(D)	0.34±0.19	0.29±0.19	0.37±0.78	0.680
SGOT	37.9±17.12	38.24±41.36	41.4±29.87	0.271
SGPT	38.62±16.85	41.68±50.26	43.28±44.09	0.468
ALP	64.86±24.19	87.24±30.98	77.95±35.94	<0.001**
GGT	38.17±10.81	52.6±30.61	49.08±51.88	0.101
PROTEIN	6.66±0.74	6.51±0.62	6.6±0.74	0.685
ALBUMIN	3.45±0.4	2.83±0.7	3.17±0.66	<0.001**
GLOBULIN	3.45±0.41	3.62±0.36	3.53±0.56	0.352
BUN	10.51±1.78	20.82±18.24	16.36±21.57	0.025*
Creatinine	0.73±0.2	1.5±1.74	1.62±5.65	0.219
SODIUM	134.91±4.93	133.88±3.7	133.7±11.32	0.490
Potassium	4.11±0.33	3.91±0.54	4.12±0.61	0.114
PT	13.17±13.64	12.38±1.66	12.38±8.79	0.630
APTT	24.57±1.73	28.17±7.86	26.4±5.95	0.008**

Fig 1 illustrates various long covid symptoms observed during the study and the maximum symptoms observed during day 30 of the follow up. Table 2 illustrates the distribution of gender among the study population. Male patients were comparatively higher compared to the female patients with the statistically significant difference. Overall prevalence of Prolonged COVID symptoms was 78 (55.32%) with the p value of 0.0745, which had no significance. But of those who developed complications, the gender distribution was 55 (39%) among men and 23 (16.3%) among women, which had statistically higher number of male patients. The average age of the recruited study was 45.45±17.27 years with the statistically significant higher prevalence of elderly patients aged >51 years accounting for about 43.3%. 62 (62%) were aged less than 40 years. Prevalence of Prolonged COVID symptoms or sequelae was significantly higher among the patients aged more than 41 years with significant p values. Fig no 2 illustrates the distribution of BMI among the study population. 87/141 (61.7%) were found with BMI 18.5 to 24.9 followed by 44 (31.2%) were between 25 to 29.9. 8 (5.7%) were with BMI more than 30 and only two patients were found to be having less than 18.5. Patients with BMI between 25 to 30 had significant number of population with Prolonged COVID symptoms compared to those with lesser BMI. 108/141(76.59%, p <0.0001) patients were presented with substance abuse. Of which 63/108 (44.7%) and 45/108 (31.9%) were chronic alcoholic and smokers. Hence the long COVID symptoms were significantly high among those with habitual substance abuse. Majority of the patients had history of HTN in past which accounted for about 36.2% of the study samples, followed by Type 2 DM among the 41 (29.1%) of the subjects. 15 (10.6%) had previous history of coronary vascular disease and 10 (7.1%) with congestive cardiac failure. Patients with known case of Asthma and COPD were about 28 (19.9%) and 8 (5.7%) respectively. Nine patients each had diagnosed with IgA nephropathy and Chronic Kidney disease (CKD). Previous history of tuberculosis was found among 5 (3.5%) of the patients. 6 (4.3%) and 3 (2.1%) were with history of malignancy and hepatitis B respectively. Total number of samples here seems more.

This is because most of the elderly patients were presented with more than one comorbid condition. Out of 141 patients, 30 (21.2%) were already on steroid medication for different conditions and the 6 (4.3%) patients were on immunosuppressants. Prevalence of study population with this drug history were found to be having higher number of long and post COVID symptoms. Table no 8 shows abnormal vital parameters observed among the recruited study samples. 76 (53.9%) were observed to be presented with tachycardia followed by tachypnoea among 58 (41.3%) and 53 (39%) with hypoxia. But the average values were under normal limits. Which are mentioned in the table 10A. The average variation in vital parameters had significant changes among the patients with long COVID 19 symptoms. 58/141 (41.1%) each had found with mild to moderate severity and the rest 25 (17.7%) of the patients were with severe COVID changes based on the clinical and radiological criteria. Table 2 illustrates the average value of biochemical parameters observed between the patients with post COVID symptoms and those who did not develop any long term COVID symptoms. We could observe from the above table that, the Hb, PCV, serum protein and albumin level were significantly lower among the patients presented with long COVID sequalae. There was statistically significant increase in TLC, N/L ration, BUN, PT and aPTT among these patients. Most of the clinical symptoms had been distributed in higher number around 30th day of follow up compared to other days.

DISCUSSION

The present study was conducted to analyse the various clinicobiochemical parameters at the time of diagnosis of covid 19 in the development of Long COVID. Fatigue was the longest symptoms observed which was accounted for about 69/141 (48.9%) of the study population. Followed by breathlessness among (48/141) 34% patients. This in consistent with the results reported by Pooya AA et al.[5] Their study also reported hair loss in 102 (2%) similar to the present study in which 3 (2.1%) had developed hair loss. In our study almost 9 (6.4%) had developed AKI at 14th day follow up then 4 (2.8%) and 2 (1.4%) at 30th day and 180th day follow up respectively but, in their study, only one patient had AKI. Also, Lopez-Leon Set al in their meta-analysis found that 5 most common manifestations of Long COVID-19 were fatigue among 58%, headache in 44%, attention disorder in 27%, hair loss in about 25% and dyspnea 24% of the study population[6]. The reason for breathlessness as the commonest finding

could be due to the COVID 19 infection leading to pulmonary complications such as chronic cough, fibrotic lung disease, bronchiectasis, and pulmonary vascular disease. Moriguchi T et al[7]and Lu et al[8] has discussed in their study that CSF of few patients showed neuro-invasive features and the possible disruption to micro-structural and functional brain integrity in patients recovered from COVID-19. This could be the reason behind the 4.3% (6/141) of our study population developing stroke, 2 (1.4%) seizure, 3 (2.1%) GBS, one each had developed depression, delirium, mood disorder as the long COVID manifestations. Varatharaj A et al [9] also had observed the similar findings in their study and had been mentioned these symptoms as "brain fog", the collective CNS symptoms of lack of attention, concentration and cognitive blunting.

The present study found that there was significantly increased fatigue score among those with long covid 19 than without. Similar to this, Van Herck M et al also had reported the significantly increased median fatigue and mental wellbeing scores as the disease progressed.[10] Blomberg B et al[11] also reported that there was comparatively higher fatigue score among those with higher COVID antigens which directly associates with the prolongation of disease in their study. Another study by Praksh J et al, an Indian study had observed significantly high magnitude of depression, anxiety and stress among the patients with long covid as the present study.[12] We observed that proportion of male patients were comparatively higher compared to the female patients with the statistically significant difference. Of the 141 patients recruited in the study, prolonged COVID symptoms was observed among 78 (55.32%) of the study samples with the p value of 0.0745, which had no significance. This is almost same as the prevalence of post COVID symptoms observed by Peghin M et al[13] in which it was 40.2% (241/599) of the recruited study population. Whereas in study conducted Pooya AA et al[5], they found that 57% of participants among long follow up (6 – 12 months) and 66% in short follow up (3 – 6 months) group still had clinical complaints of COVID 19, the prevalence of which is little higher than ours. In contrast to our findings, Sudre CH et al found that only 13.3%, 4.5% and 2.3% had found to be having symptoms lasting for >28 days, >8 weeks and >12 weeks in their study period. But of those who developed complications, the gender distribution was 55 (39%) among men and 23 (16.3%) among women, which had statistically higher number of male patients. Contrary to our findings, Peghin M et al[13] had higher prevalence of female patients and also the proportion of long COVID was higher among these. The average age of the recruited study was 45.45±17.27 years with the statistically significant higher prevalence of elderly patients aged >51 years accounting for about 43.3%. Pooya AA et al also observed the similar distribution of age among their study population with the average age of the 52±15 years.[5] 62 (62%) were aged less than 40 years. Prevalence of Prolonged COVID symptoms or sequelae was significantly higher among the patients aged more than 41 years with significant p value of <0.05. This could be increased associated risk factors such as the comorbid conditions and the elderly patients who will be having physiological variations such as the lack of immunity, reduced renal clearance and the reduced pulmonary function. Similar to our study, Sudre CH et al[14] also observed higher number of elderly male patients with long COVID and no changes in prevalence with respect to gender. Another study by Tenforde M.W et al,[15] also reported the similar finding as the present study with statistically significant long COVID among elderly patients, >50 years (47%). In our study, patients with BMI between 25 to 30 had significant number of populations with Prolonged COVID symptoms compared to those with lesser BMI. This could be due because of increased number of overall populations were found to be under this range of BMI. Otherwise, we did not observe much correlation between BMI and the long COVID symptoms. Whereas in Sudre CH et al,[14] the patients with BMI >30 and <25 were found to be presented with long COVID symptoms. Similar to our observations, Tenforde M.W et al[15] also found higher prevalence of long COVID among the patients with BMI >30. 108/141(76.59%) patients were presented with substance abuse with significant p value of p <0.0001. Of which 63/108 (44.7%) and 45/108 (31.9%) were chronic alcoholic and smokers. Hence the long COVID symptoms were significantly high among those with habitual substance abuse.

Majority of the patients had history of HTN in past which accounted for about 36.2% of the study samples, followed by Type 2 DM among the 41 (29.1%) of the subjects. 15 (10.6%) had previous history of coronary vascular disease and 10 (7.1%) with congestive cardiac failure. Patients with known case of Asthma and COPD were about 28 (19.9%) and 8 (5.7%) respectively. The patients with known comorbid conditions had significantly higher prevalence of long COVID symptoms than without. In the present study, 30 (21.2%) were already on steroid medication for different conditions and the 6 (4.3%) patients were on immunosuppressants. Prevalence of study population with this drug history were found to be having higher number of long and post COVID symptoms. In our study, the Hb, PCV, serum proteins, albumin level were significantly lower among the patients presented with long COVID symptoms and significant increase in TLC, N/L ratio, BUN, PT and aPTT among these patients. There are not much studies which has explained or observed the biochemical markers in predicting the long COVID. Of the few studies, Ramírez-TruqueM et al[16] has reported that neutrophilia, thrombocytopenia, hypoalbuminemia, the elevation of liver enzymes, creatinine and elevated nonspecific inflammatory markers such as C-reactive protein (CRP) and Interleukin 6 (IL-6) at the time of admission were observed among the patients with long COVID, this finding is comparable with our findings too.

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