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Study of Extrapulmonary Manifestations of COVID-19 patients

DR AMIT KUMAR[1], DR ANKIT KUMAR[2], DR AKSHIT GARG[3], DR APOORV PRATAP SINGH[4] DR JAIDEEP SINGH[5]

[1](Associate professor, department of medicine, subharti medical college, Meerut)

[2](JR3, department of medicine, subharti medical college, Meerut)

[3](Senior Resident, department of medicine, subharti medical college, Meerut)

[4](Assistant Professor, department of medicine, subharti medical college, Meerut)

[5](Senior Resident, department of medicine, subharti medical college, Meerut)

Abstract

Aim: To study extrapulmonary manifestations in COVID-19 patients.

Material and methods: The present retrospective study was conducted among 200 COVID positive patients in the department of medicine, CSS Hospital, Subharti Medical College, Meerut. COVID-19 was diagnosed on the basis of the WHO interim guidance. Patients' diagnosis was identified along with the co-morbidity (if present). Laboratory investigations comprised of CBC and serum albumin detection. Extrapulmonary manifestations were defined as patients having predominantly neurological, gastrointestinal (GI), cardiovascular, cutaneous, and uncommon respiratory symptom such as hemoptysis either concomitant with typical respiratory symptoms or as the sole manifestation.

Results: Fever was most frequent complain (n=97, 48.5%), followed by cough (n=76, 38%) and dyspnea was present in 51 subjects (25.5%). The most common respiratory symptoms was dyspnea (n=64, 32%). The most common cardiovascular symptoms was Dyspnea on exertion (n=54, 27%), followed by Palpitations (n=29, 14.5%). The most common GIT Symptoms was diarrhea (n=34, 17%), followed by Vomiting (n=13, 6.5%) and only 8 subjects (4%) reported abdominal pain. Dermatological symptoms were shown in 5 (2.5%) subjects. The most common musculoskeletal Symptoms was fatigue (n=103, 51.5%), followed by Myalgias (n=11, 5.5%) and Joint/Back Pain (n=4, 2%).

Conclusion: Patients with COVID-19 require long-term follow-up even after recovery for observation and management of their post-COVID ailments. During the ongoing COVID-

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19pandemic, most health facilities are overloaded. Hence, arranging follow-up for patients can be a challenge. Therefore, a comprehensive rehabilitation program is essential for such patients during hospitalization and discharge.

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Introduction:

The coronavirus disease 2019 (COVID-19) is a global emergency due to a beta coronavirus called severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2)[1]. COVID-19 first emerged in China in December 2019 as a respiratory infectious epidemic. Strikingly, within 3 months of its outbreak, COVID-19 had rapidly spread worldwide like no unprecedented infection, infecting 1.2 million persons and claiming 70,000 deaths. Consequently, WHO declared this highly contagious and potentially fatal communicable disease a pandemic on March 3, 2020[2].

This pathology is mainly transmitted through droplets into the air from infected patients (during coughing, sneezing, and speaking) or contact with contaminated surfaces. Aerosol transmission is also possible in case of protracted exposure to elevated aerosol concentrations in closed spaces[3]. Once the pathogen (SARS-CoV-2) enters the human body, it invades the alveoli and links to the angiotensin-converting enzyme 2 (ACE2) receptor of type 2 pneumocytes through their spike protein. Diverse manifestations of the disease are due to the direct effects of the virus or inflammatory mediators especially IL1, IL6, and TNF-alpha. SARS-CoV-2 induces an alveolar-interstitial inflammation with a high risk of acute pulmonary edema or acute respiratory distress syndrome. It is worth to mention that the pathogenesis of COVID-19 also entails a systemic inflammation with several consequences[4].

The incubation period of the virus varies from 2 to 14 days[5] and the major symptoms of the disease include fever (88.7%), cough (67.8%), fatigue (38.1%), sputum production (33.4%), shortness of breath (18.6%), sore throat (13.9%), and headache (13.6%). Asymptomatic and mild cases represent 81% of cases of COVID-19, and severe cases account for 14% and critical cases 5% of all infected patients[4]. Vulnerable groups include patients with advanced age, hypertension, diabetes, obesity, cancer, pregnancy, and chronic kidney disease[1,4]. Severe complications of the disease are due to multiple systemic involvements[6].

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Researchers have sought to better understand the interactions of COVID-19 with all the various cells and organs of the body. However, with an extensive literature search, to the best of our knowledge, there is no Indian study available on the diverse aspects of the disease. We propose this study to illustrate the various interactions of COVID-19 as a systemic disease whose implications need to be considered in the management of infected critically ill patients in challenged-resource settings. The aim of the study was to evaluate the extrapulmonary manifestations of COVID-19 patients.

Material and method:

Study design: The present retrospective study evaluated the COVID positive patients.

Study population: COVID positive patients, of both genders were recruited for the study.

Setting: The study was conducted in the department of medicine, CSS Hospital, Subharti Medical College, Meerut.

Study period: The study was done from December 2020 to March 2022.

Ethical consent: Informed consent of all participants was obtained after explaining the purpose of the study. Permission to carry out the study was obtained by Institutional Ethical Committee of CSS Hospital, Subharti Medical College, Meerut.

Sample: The study sample comprised of 200 COVID positive patients who were sequentially allocated into study based on their criteria for fulfilling eligibility criteria.

Inclusion criteria: All Covid 19 positive patients.

Exclusion criteria: Subjects having following characteristics were excluded from the study:

i. Chronic liver disease
ii. Nephrotic syndrome
iii. Patients who have not given written informed consent

COVID-19 was diagnosed on the basis of the WHO interim guidance. A questionnaire will be prepared to collect the patient's demographic profile. Patients date of admission and discharge was recorded along with the outcome. Patients' diagnosis was identified along with the co-morbidity (if present). Laboratory investigations comprised of CBC and serum albumin detection.

Extrapulmonary manifestations were defined as patients having predominantly neurological, gastrointestinal (GI), cardiovascular, cutaneous, and uncommon respiratory

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symptom such as hemoptysis either concomitant with typical respiratory symptoms or as the sole manifestation.

Statistical analysis: Data so collected was tabulated in an excel sheet, under the guidance of statistician. The means and standard deviations of the measurements per group were used for statistical analysis (SPSS 22.00 for windows; SPSS inc, Chicago, USA).

Results: In the present trial, of the total 200 subjects included in study, there was a male predominance (n=127, 63.5%) over females (n=73, 36.5%). The male female ratio was 1.73:1. Maximum patient belongs to >60-year age group (n=62, 31%), followed by 51-60 years age group (n=52, 26%), 41 (20.5%) subjects were in 41-50 years age group, 28 (14%) subjects were in 31-40 years age group. Of the total 200 subjects, 59 subject (29.5%) had history of smoking and alcohol consumption history was given by 44 (22%) patients. Maximum patient (n=123, 61.5%) had mild symptoms of COVID, followed by subjects who showed moderate symptoms (n=59, 29.5%) of COVID and least no. of patient had severe symptoms (n=18, 9%) of COVID. (Table 1)

Table 1: Gender, age, deleterious habits and COVID severity distribution among the study subjects

Gender	**N=200**	**%**
Male	127	63.5
Female	73	36.5
Age Group (in years)	**N**	**%**
18-30	17	8.5
31-40	28	14
41-50	41	20.5
51-60	52	26
>60	62	31
Age in years, Median (IQR)	61 (47-78)	
Deleterious Habits		
Smoking	59	29.5
Alcohol	44	22
COVID Severity		
Mild	123	61.5
Moderate	59	29.5
Severe	18	9
Total	200	100

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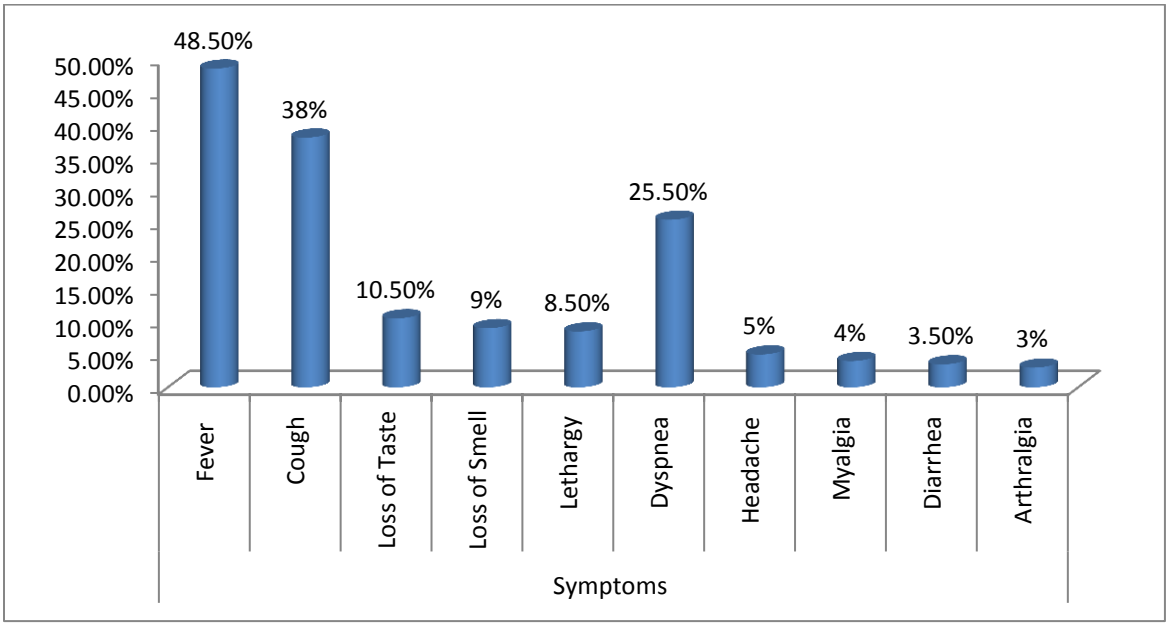
Fever was most frequent complain (n=97, 48.5%), followed by cough (n=76, 38%), dyspnea was present in 51 subjects (25.5%), 21(10.5%) patient complain of loss of taste sensation, 18 (9%) patient had loss of smell, complain of lethargy was by 17 (8.5%) subjects, headache by 10 (5%), myalgia by 8 (4%), diarrhea by 7 (3.5%) and whereas only 3% (n=6) had complain of arthralgia. (Graph 1)



Graph 1: Symptoms among the study subjects at presentation

Temperature>38^0 C, oxygen saturation<90%, received supplemental oxygen at triage, respiratory rate>24 breath/min and heart rate>100 beats/min was reported among 48.5%, 16.5%, 28.5%, 21.5% and 52% of the subjects respectively in this study. (Table 2)

Table 2: Vitals of patients

Parameters	N	%
Temperature>38^0 C	97	48.5
Oxygen Saturation<90%	33	16.5
Received Supplemental Oxygen at Triage	57	28.5
Respiratory Rate>24 Breath/min	43	21.5
Heart Rate>100 Beats/min	104	52

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The most common respiratory symptoms were dyspnea (n=64, 32%), followed by cough (n=23, 10.5%), 4 (2%) patient complained of rhinitis, 3 patient complained of sore throat, and only 2 subjects had complained of sputum production. The most common Cardiovascular Symptoms was Dyspnea on exertion (n=54, 27%), followed by Palpitations (n=29, 14.5%), 13 subjects complained of chest pain and only 6 complained of Orthopnea (table 3).

Table 3: Respiratory, Cardiovascular, Neurological symptoms among the study subjects

Respiratory Symptoms	**N**	**%**
Cough	23	10.5
Dyspnea	64	32
Rhinitis	4	2
Sore Throat	3	1.5
Sputum production	2	1
Cardiovascular Symptoms		
Chest pain	13	6.5
Palpitations	29	14.5
Dyspnea on exertion	54	27
Orthopnea	6	3
Neurological Symptoms		
Anosmia	43	21.5
Dysgeusia	24	12
Headache	8	4
Vertigo	2	1
Confusion	7	3.5
Abnormal body moment (seizure)	1	0.5
Weakness of limb (Stroke)	0	0
Memory Loss	0	0

The most common GIT Symptoms was diarrhea (n=34, 17%), followed by Vomiting (n=13, 6.5%). The most common psychiatry symptoms were insomnia (n=54, 27%) as shown in table 4.

Table 4: GIT and Psychiatry symptoms among the study subjects

GIT Symptoms	**N**	**%**
Diarrhea	34	17
Vomiting	13	6.5

Pain abdomen	8	4
Psychiatry Symptoms		
Depression	9	4.5
Insomnia	54	27
Anxiety	8	4
Substance use	0	0

The dermatological symptoms were shown in 5 (2.5%) subjects. The most common musculoskeletal symptoms were fatigue (n=103, 51.5%), followed by myalgias (n=11, 5.5%) and joint/back pain (n=4, 2%). Other complications which were noticed post COVID included Ophthalmological problems (n=12, 6%), fever (n=16, 8%) and weight loss (n=9, 4.5%). (Table 5)

Table 5: Dermatological, musculoskeletal and other symptoms among the study subjects

Symptoms	**N**	**%**
Dermatological	5	2.5
Musculoskeletal Symptoms		
Fatigue	103	51.5
Myalgias	11	5.5
Joint/Back Pain	4	2
Other Symptoms		
Ophthalmological	12	6
Fever	16	8
Weight Loss	9	4.5

Discussion: At the time of the visit, a high percentage of patients complained of 1 or more persistent symptoms. Similar findings have been observed in recent studies, based on face-to-face reviews or telephone/web surveys, on both COVID-19 inpatient and outpatient populations (Carfì A et al., 2020; Tenforde MW et al., 2020).

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In the present trial, of the total 200 subjects included in study, there was a male predominance (n=127, 63.5%) over females (n=73, 36.5%). The male female ratio was 1.73:1. This can be justified because male member of the family has to go out for work more when compared with female subjects. The results were in accordance to result of Mahmud R et al., (2021), performed a study on 355 subjects and found that ratio of male and female patients was 1.4:1. According to findings of Spinicci M et al., (2021), of the total 100 subjects included in study 41% were females and rest were male subjects. In a study done by Blomberg, B et al., (2021)51% (160/312) were women and rest were male subjects.

In present study, the median age of the study population was 61 years (interquartile range (IQR) 47–78 years). Maximum patient belongs to >60-year age group (n=62, 31%) and least number of patients were in 18–30-year age group (n=17, 8.5%). This may be because aged people have less immunity towards diseases and they can readily catch any viral infection. These findings were in accordance to result of Spinicci M et al., (2021) who found that median age 67.5 years [interquartile range {IQR} 56–78.5] In a study done by Blomberg, B et al., (2021) the median age of the study population was 46 years (interquartile range (IQR) 30–58 years). But according to study of Mahmud R et al., (2021) the mean (SD) age of the study patients in was 39.8 (13.4) years.

Of the total 200 subjects, 59 subject (29.5%) had history of smoking and alcohol consumption history was given by 44 (22%) patients. These findings were not in accordance with findings of Abdelrahman MM et al., (2021), who found that in their study population Active smoker were only 6 (3.5%) subjects, Non-smokers were 151 (87.8%) and X-smoker were15 (8.7%). However, study on specific COVID-19 association with pneumonia by Liu et al (2020) indicated that the history of smoking was a risk factor of disease progression after controlling for age, maximum body temperature at admission, respiratory failure, albumin, C-reactive protein.

Fever was most frequent complain (n=97, 48.5%), followed by cough (n=76, 38%), dyspnea was present in 51 subjects (25.5%), 21(10.5%) patient complain of loss of taste sensation, 18 (9%) patient had loss of smell, complain of lethargy was by 17 (8.5%) subjects, headache by 10 (5%), myalgia by 8 (4%), diarrhea by 7 (3.5%) and whereas only 3% (n=6) had complain of arthralgia. According to findings of Mahmud R et al., (2021) post-viral fatigue was the most prevalent feature (117 [33%]). Other features included persistent cough (8.5%), post-exertional dyspnea (7%), headache (3.4%), vertigo (2.3%), and sleep-related disorders (5.9%).

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Blomberg, B et al., (2021) found that in 272 patients' fatigue was most common (90%, 244/272), followed by cough (71%), headache (64%), myalgia (58%), whereas only 21% had fever. According to findings of Xiong Q et al., (2021),152 (28.3%) reported physical decline or fatigue. Most patients who reported these symptoms improved, but 35survivors reported no improvement. A total of 127 survivors (23.6%) complained of excessive sweating. Twenty-four patients reported significant myalgia. Forty-one patients (7.6%) reported joint pain, most commonly in the knee joint (29 cases) but also in the elbow, ankle, wrist and spinal joints. Twenty-five patients (4.6%) complained of chilliness, such as not being able to face cold air, which they did not notice until they were discharged from the hospital. Abdelrahman MM et al., (2021) found in their study that, Fatigue, dyspnea, and depression were the most common persistent symptoms representing 37.3%, 22%, 22% respectively. In study done by Spinicci M et al., (2021) the more frequent symptoms were fatigue (46%), dyspnea (30%), insomnia (26%), anosmia (20%), and dysgeusia and palpitation (15%).

The most common respiratory symptoms were dyspnea (n=64, 32%), followed by cough (n=23, 10.5%), 4 (2%) patient complained of rhinitis, 3 patient complained of sore throat, and only 2 subjects had complained of sputum production. Abdelrahman MM et al., (2021) found in their study that, as regards the respiratory system, they noticed that dyspnea, dry cough (8.1%), and chest pain were the most frequent persistent complaint. Blomberg, B et al., (2021) found that in 272 patients, dyspnea was present in (55%) of the subjects. Cough and respiratory distress can be explained by persistent squeal lung damage.

In present study, the most common cardiovascular symptoms were Dyspnea on exertion (n=54, 27%), followed by Palpitations (n=29, 14.5%), 13 subjects complained of chest pain and only 6 complained of Orthopnea. According to findings of Mahmud R et al., (2021) post-exertional dyspnea was present in 7% of the subjects. Studies have shown that cardiac injury is a common condition among hospitalized patients and is associated with a higher risk of in-hospital mortality (Fried JA et al., 2020; Shi S et al., 2020). This may be related to angiotensin-converting enzyme 2 (ACE2) acting as the receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (South AM et al., 2020). In the study done by Xiong Q et al., (2021)70 survivors (13%) reported significant cardiovascular symptoms 3 months after discharge. Of the 60 people who reported significantly higher resting heart rates than before they had COVID-19, 45 (75%) had resting heart rate increases during their hospitalization that were

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still present. Twenty-six patients (4.8%) said they occasionally had palpitations. Notably, seven patients said they had recently been diagnosed with high blood pressure and they now require blood pressure lowering drugs. Abdelrahman MM et al., (2021) found in their study that, chest pain was complain of 7.6% subjects.

Epidemic diseases have a psychological impact on both infected and noninfected persons (Shanafelt T et al., 2020). Both the infected and noninfected population might be susceptible as a result of certain experiences, such as widespread anxiety, social isolation, stress in healthcare and other essential workers, unemployment and financial difficulties (Shanafelt T et al., 2020). The most common neurological Symptoms was Anosmia (n=43, 21.5%), followed by Dysgeusia (n=24, 12%), headache was reported by 8 (4%) subjects, confusion by 7 (3.5%) subjects, vertigo by 2 (1%) patient and only one subject (0.5%) reported abnormal body moment (seizure). The most common psychiatry symptoms were insomnia (n=54, 27%), followed by depression (n=9, 4.5%) and anxiety (n=8, 4%). In study done by Spinicci M et al., (2021) neurological disorders included mental confusion (10%), peripheral neuropathies (5%), and vertigo (3%). Furthermore, 4% of patients had psychological symptoms, such as anxiety and depression. According to findings of Mahmud R et al., (2021) headache was present in 3.4% subjects, vertigo in 2.3% patients, and sleep-related disorders were recorded in 5.9% patients. In study done by Xiong Q et al., (2021) found that 17.7% of COVID-19 patients had a major mental disorder characterized by sleep disorders. Only a small number of people showed symptoms such as depression and anxiety. Abdelrahman MM et al., (2021) found in their study that, insomnia was present in 13.4% subjects, headache in 10.5% subjects, forgetting things was symptom in 9.9% subjects.

The most common GIT Symptoms was diarrhea (n=34, 17%), followed by Vomiting (n=13, 6.5%) and only 8 subjects (4%) reported abdominal pain. According to study done by Mahmud R et al., (2021) diarrhea was present in 23 (6.5%) subjects and vomiting was complain of 17 (4.8%) subjects.

Dermatological symptoms were shown in 5 (2.5%) subjects. The most common musculoskeletal Symptoms was fatigue (n=103, 51.5%), followed by Myalgias (n=11, 5.5%) and Joint/Back Pain (n=4, 2%). According to study done by Spinicci M et al., (2021), fatigue was present in 46% subjects, hair loss in 8% subjects, myalgia was present in 4% of subjects. Abdelrahman MM et al., (2021) found in their study that, Joint pain (12.2%), alopecia (10.5%). Mahmud R et al., (2021) found in their study that fatigue, persistent cough, exertional dyspnea,

sleep disorders, and headache or vertigo were observed in 70%, 18%, 15%, 13%, and 12% cases, respectively. The reason for the dominance of fatigue was mostly unexplained.

Limitations: There are still many facts that we do not know about COVID-19 due to gaps in knowledge; therefore, many studies are underway to better understand this virus. This study has several limitations. Firstly, it was a single-center study. Moreover, the follow-up period for patients was limited. More representative findings could be obtained if all cases could be followed up for a longer period. Moreover, the effect size of most associated variables was small. A larger sample size is required to determine a strong association. The data in this analysis was based on the report from a single state in India and may not necessarily represent the whole population of India. Future studies may also confirm the real frequency of unusual symptoms reported in our study and may provide new insights into their pathogenesis.

Conclusion: Patients with COVID-19 require long-term follow-up even after recovery for observation and management of their post-COVID ailments. During the ongoing COVID-19pandemic, most health facilities are overloaded. Hence, arranging follow-up for patients can be a challenge. However, a significant population in the post-COVID state needs continuous monitoring. Patients presenting with respiratory distress, patients with lethargy, and patients with a disease for a prolonged duration require special attention in the post COVID-19 state. The most common early clinical sequelae in COVID-19 survivors include physical decline/fatigue, fever, cough, dyspnea, dyspnea on exertion, Anosmia, Insomnia, Fatigue, palpitations and alopecia. There is a high percentage of patients who complained of persistent symptoms after recovery from COVID-19. Fatigue and headache are the most common persistent symptoms. Age is considered a risk factor for persistent symptoms. Hence a comprehensive rehabilitation program is essential for such patients during hospitalization and discharge.

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