Microbiology Section

Clinical Manifestations and Sequelae of COVID-19 in First and Second Wave among Nursing Officers of a Tertiary Care Centre, New Delhi, India

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ABSTRACT

Introduction: There are lot of challenges involved in studying the multiorgan manifestations and sequelae of acute Coronavirus Disease 2019 (COVID-19), that too in face of fighting the pandemic, which has led to fall short of resources and restriction in activities for prevention of transmission. The literature on persisting manifestations and sequelae of COVID-19 in the patients recovered in the first and second waves is scarce.

Aim: To study the presenting and persistent manifestations after acute COVID-19 illness in first and second wave among Nursing Officers (NOs) of a tertiary care Medical Institute.

Materials and Methods: This was a cross-sectional study conducted in Dr. Rajendra Prasad Centre for Ophthalmic Sciences at All India Institute of Medical Sciences, New Delhi, India, from 15th May 2021 to 31st October 2021. Total 103 nurses, who had recovered after testing positive for COVID-19 in the first and second wave were followed-up for persisting symptoms. Statistical analysis was done using Pearson Chi-square test.

Results: Total of 103 subjects were recruited in the study, 36 in the first wave and 67 in the second. Fever (72.82%), bodyache (67.96%) and fatigue (66.99%) were found to be the most common presenting manifestations in the study subjects having mild to moderate COVID-19 infection. Bodyache (p-value=0.048), headache (p-value=0.044) and fatigue (p-value=0.025) were seen in significantly more subjects in second wave as compared to first wave. Persistence of symptoms for more than four weeks was seen in 45.63% subjects. There was no statistically significant difference between persisting symptoms in the two waves, except sleep disturbances which were found to be persisting in significantly more subjects in second wave than those in first wave.

Conclusion: The data of current study will add to the literature of presenting signs and sequelae of coronavirus, and pave the way for more elaborate and multispecialty studies for enhanced understanding of the disease.

INTRODUCTION

Novel Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) has led to a worldwide pandemic of Coronavirus Disease 2019 (COVID-19). Classic cases present with respiratory symptoms and fever. However, wide range of other manifestations including gastrointestinal and neurological involvement has been observed [1]. It has also been observed across the globe that all the symptoms of all patients who suffer from SARS-CoV-2 infection do not get resolved with their recovery from acute infection; there is a subset of patients having persisting symptoms. Sequelae of COVID-19 are the symptoms reported by the patient after recovering from COVID-19, which are not explained by alternative diagnosis. In the absence of universally accepted definition, in mild and moderate COVID-19 cases, signs and symptoms that develop or persist after end of quarantine or discharge are taken as sequelae of COVID-19 [2-5]. While there are a lot of studies unraveling the structure and pathogenicity of SARS-CoV-2 [6-10], and quite a few highlighting the clinical manifestations and complications of COVID-19, not many have looked into the sequelae [10-13].

Due to their proximity to patients, Healthcare Workers (HCWs) including nurses remain at extraordinary risk of acquiring infections; the risk is amplified in the current pandemic due to the fact that HCWs are supposed to be working even when there is lockdown for preventing transmission of infection in populations at large [14-16]. Some studies have looked into sequelae and quality of life after COVID-19 in HCWs [16-18]. Nursing assistance is the cornerstone of all medical care; during the pandemic, nurses are working round

the clock to aid in maintaining the essential healthcare services [18]. Except for one study from India on psychological sequelae of COVID-19 in HCWs including nurses [18], there have been no studies on sequelae of COVID -19 in Nursing Officers (NOs). Despite taking all precautions and maintaining COVID-19 appropriate behaviour, many nursing officers at the centre got infected. The symptomatic NOs were followed-up for the sequelae of COVID-19. This study was aimed to assess the presenting and persistent manifestations of COVID-19 illness in first and second wave, among nursing officers of a tertiary care Medical Institute, Delhi, India.

MATERIALS AND METHODS

This was a cross-sectional study conducted in Dr. RP Centre for Ophthalmic Sciences at All India Institute of Medical Sciences, New Delhi, Delhi, India, from 15th May 2021 to 31st October 2021. Approval of Institute Ethics Committee was obtained before commencement of the study (IEC-230/09.04.2021, RP-02/2021) and the methods were in agreement with the Helsinki Declaration of 1975, as revised in 2000. All the study participants were given an information sheet regarding the study to read, and a written informed consent was obtained for participation in the study.

Inclusion criteria: All nursing officers working in the specialty centre who had recovered after testing positive for COVID-19 in the first wave (March 2020 to February 2021) or second wave (March 2021 to May 2021) were included in the study [13].

Exclusion criteria: The NOs who were asymptomatic, whose COVID-19 test result was indeterminate, or who were tested positive

for COVID-19 from a laboratory not approved by Indian Council of Medical Research (ICMR) were excluded from the study.

As per the guidelines circulated by Ministry of Health and Family Welfare, India, a positive COVID-19 test was defined as a positive result from any Indian Council of Medical Research (ICMR) approved laboratory in India in [19-21]:

- Reverse Transcription-Polymerase Chain Reaction (RT-PCR) or
- Cartridge Based Nucleic Acid Amplification Test (CBNAAT) or
- Rapid Antigen Test (RAT),

The ICMR approval was given to a laboratory after quality assessment of kits and procedures of the laboratory; and all the three tests were considered valid for diagnosing symptomatic cases of COVID-19 [21].

Study Procedure

A proforma regarding their COVID-19 illness to be filled was given to all participants, and the data obtained was entered in Microsoft excel sheets and analysed. The proforma was based on authors' experience with COVID-19 patients, various national grand rounds and daily review meetings and discussions with COVID-19 task force. To decrease the subjective variation of symptoms reported by the participants, the definitions/meanings of all medical symptoms/terms were put on backside of the proforma and the participants were instructed to mark their answers accordingly [22-24]:

- **Weakness/Fatigue:** Sense of a low energy level, or the feeling that near exhaustion is reached after relatively little exertion.
- **Disturbance in sleep:** Difficulty in initiating or maintaining sleep.
- **Stress:** Feeling discomfort/troubled/overwhelmed/threatened by the circumstances and events of day to day life.
- **Breathing difficulty:** Subjective experience of breathing discomfort. Consisting of sensations like feeling suffocated, intense tightening in the chest, air hunger. Sensations may vary in intensity from person to person.
- **Difficulty in concentration:** Not being able to focus on a particular task.
- **Anorexia:** Lack of appetite for food.

The language of proforma was chosen to be English, as it could be understood by all the NOs who hail from different states of the nation.

STATISTICAL ANALYSIS

Statistical analysis was done using Pearson Chi-square test of association and Fischers-exact test using Statistical Package for Social Sciences (SPSS) IBM, statistics for windows, version 21.0, Armonk, NY: IBM Corp statistics. A p-value <0.05 was considered significant.

RESULTS

In the first wave, out of total 225, 36 nursing officers (16%) and in the second wave, 67 out of 190 (35.3%), had mild to moderate symptoms and were positive for COVID-19. This difference in COVID-19 positive cases in the two waves was statistically significant (p-value=0.043). Thus, a total of 103 subjects were recruited in the study, 36 in the first wave and 67 in the second. In the first wave, nine (25%) participants had moderate symptoms and 27 (75%) had mild symptoms. In the second wave three (4.5%) participants had moderate symptoms and 64 (95.5%) had mild symptoms (p-value=0.455).

The age of the participants ranged from 26-60 years (26-59 years in first and 26-60 years in second wave); and the mean age was 41.4 years (42.6 years in first and 40.1 years in second wave). Out of 103, 96 participants were females. The study subjects of the first wave had years of experience ranging from 1-33 years, and those of second wave had experience of 4 months to 36 years.

Duties of the NOs were in Operation Theatres, Wards, Outpatient Departments and Casualty of the Ophthalmic Centre, as well as in COVID-19 care areas of the institute. In the first wave, all 36 of the study subjects were in the ophthalmic centre duty at the time of contracting COVID-19 (positive). In the second wave, 19 out of 67 COVID-19 positive NOs were on COVID-19 duty at the time of becoming COVID-19 positive.

The most common co-morbidity in the study population was hypertension (9, 8.74%). This was followed by diabetes and bronchial asthma, each present in 6 (5.83%) subjects and arthritis and hypothyroidism, each present in 3 (2.91%) of the subjects. There was no statistically significant difference in co-morbidities in the study subjects from first and second waves of COVID-19 [Table/Fig-1].

Co-morbidity	1st Wave (n, %)	2nd Wave (n, %)	Total (n, %)	p-value (Pearson Chi-square test)
Hypertension	3 (8.33%)	6 (8.96%)	9 (8.74%)	0.915
Diabetes	3 (8.33%)	3 (4.48%)	6 (5.83%)	0.426
Bronchial asthma	3 (8.33%)	3 (4.48%)	6 (5.83%)	0.426
Arthritis	1 (2.78%)	2 (2.99%)	3 (2.91%)	0.952
Hypothyroidism	2 (5.56%)	1 (1.49%)	3 (2.91%)	0.242
Obesity	1 (2.78%)	-	1 (0.97%)	0.170
Chronic allergic sinusitis	1 (2.78%)	-	1 (0.97%)	0.170
Depression	-	1 (1.49%)	1 (0.97%)	0.461
Pulmonary tuberculosis	-	1 (1.49%)	1 (0.97%)	0.455

[Table/Fig-1]: Co-morbidities associated with COVID-19 in the two waves.
*p-value <0.05 was considered as statistically significant

[Table/Fig-2] shows the clinical manifestations of COVID-19 in the two waves. Fever was the most common manifestation- present in 75 (72.82%) subjects, followed closely by bodyache and fatigue seen in 70 (67.96%) and 69 (66.99%) subjects, respectively. Other common manifestations were sore throat, cough, headache, dysgeusia, parosmia and weight loss. Diarrhoea, rhinitis and conjunctivitis were less common manifestations. While chest pain, dizziness, gastritis, anorexia and fluctuations in blood pressure were rare (each seen in one study subject). Bodyache (p-value=0.048), fatigue (p-value=0.025) and headache (p-value=0.04) were more common in second wave as compared to first wave. Other

Manifestation	1st Wave (n, %)	2nd Wave (n,%)	Total (n,%)	p-value (Pearson Chi-square test)
Fever	23 (63.89%)	52 (77.61%)	75 (72.82%)	0.136
Bodyache	20 (55.56%)	50 (74.63%)	70 (67.96%)	0.048*
Fatigue	19 (52.78%)	50 (74.63%)	69 (66.99%)	0.025*
Sore throat	17 (47.22%)	42 (62.69%)	59 (57.28%)	0.130
Cough	17 (47.22%)	41 (61.19%)	58 (56.31%)	0.173
Headache	14 (38.89%)	40 (59.70%)	54 (52.43%)	0.044*
Dysgeusia	15 (41.67%)	31 (46.27%)	46 (44.66%)	0.654
Parosmia	14 (38.89%)	30 (44.78%)	44 (42.72%)	0.565
Weight loss	14 (38.89%)	30 (44.78%)	44 (42.12%)	0.565
Diarrhea	9 (25%)	12 (17.91%)	21 (20.39%)	0.394
Rhinitis	6 (16.67%)	13 (19.40%)	19 (18.45%)	0.733
Conjunctivitis	1 (2.78%)	4 (5.97%)	5 (4.85%)	0.472
Any other manifestation (fluctuations in BP, chest pain, dizziness, gastritis, anorexia)	-	1 each (1.49%)	1 each (0.97%)	0.754
Hospitalisation	9 (25%)	3 (4.48%)	12 (11.65%)	0.002*

[Table/Fig-2]: Clinical manifestations of COVID-19 in the two waves.
*p-value <0.05 was considered as statistically significant

manifestations did not show any statistically significant difference. Out of 36, 9 (25%) subjects needed hospitalisation due to moderate symptoms in first wave. Whereas only three out of 67 (4.48%) needed hospitalisation in second wave (p-value=0.002). None of the subjects had severe disease and there was no mortality.

In present study, 7 (6.80%) subjects completely recovered and showed no persistence of symptoms after minimum isolation and resolution of acute phase of COVID-19. One or more symptoms persisting for 1-2 weeks and 2-4 weeks were seen in 26 (25.24%) and 23 (22.33%) subjects, respectively. While 47 (45.63%) subjects reported one or more persistent symptoms for more than four weeks. Of the Postacute Sequelae of COVID-19 (PASC), most common was fatigue seen in 88.35% of subjects; this was followed by sleep disturbance, stress, breathing difficulty, difficulty in concentration and anorexia seen in 57.28%, 54.39%, 50.49%, 41.75% and 36.89% subjects, respectively. The subjects of second wave having disturbance in sleep were significantly more than those of first wave (p-value=0.049); the difference of other sequelae between the two waves did not show any statistical significance [Table/Fig-3].

different degrees of virulence. Clade distribution in India varied over time, with a rise of the G clades from 21.6% in first wave to 46% in March 2021 and an escalation to 82.34% by the end of May 2021 [13]. The G clade has been reported to be associated with a higher viral load than other clades, hence the rapid rising of the G clade in India during the second wave might have played a significant role in augmenting the number of cases and varied manifestations of COVID-19 infection [25]. Bakhshandeh B et al., have interpreted in their review that many factors remain unknown regarding the varied clinical manifestations and outcome of COVID-19, however, host genetic susceptibility, and mutations and genetic variability of the virus have a critical impact on variable clinical features of COVID-19 [26].

In the present study, persistence of symptoms for more than four weeks was seen in 45.63% subjects and fatigue was found to be the most common sequela, persisting in 88.35% of the participants. Significantly greater number of subjects had persisting sleep disturbances in second wave than those of first wave. The present study findings correlate with those of authors from other countries.

Sequelae	Wave	Duration of persistence					p-value (Pearson Chi-square test)
		1-2 weeks (n, %)	2-4 weeks (n, %)	>4 weeks (n, %)	Total patients having COVID-19 Sequelae (n,%)		
Weakness	1st wave	5 (13.89%)	9 (25%)	15 (41.67%)	29 (80.56%)	91 (88.35%)	0.063
	2nd wave	24 (35.82%)	15 (22.39%)	23 (34.33%)	62 (92.54%)		
Disturbance in sleep	1st wave	5 (13.89%)	3 (8.33%)	06 (16.67%)	14 (38.89%)	59 (57.28%)	0.049*
	2nd wave	18 (26.87%)	11 (16.42%)	16 (23.88%)	45 (67.16%)		
Stress	1st wave	10 (27.78%)	2 (5.56%)	05 (13.89%)	17 (47.22%)	56 (54.39%)	0.446
	2nd wave	17 (25.37%)	10 (14.93%)	12 (17.91%)	39 (58.21%)		
Breathing difficulty	1st wave	4 (11.11%)	3 (8.33%)	10 (27.78%)	17 (47.22%)	52 (50.49%)	0.050
	2nd wave	16 (23.88%)	12 (17.91%)	07 (10.45%)	35 (52.24%)		
Difficulty in concentration	1st wave	6 (16.67%)	2 (5.56%)	02 (5.56%)	10 (27.78%)	43(41.75%)	0.175
	2nd wave	16 (23.88%)	11 (16.42%)	06 (8.96%)	33 (9.25%)		
Anorexia	1st wave	6 (16.67%)	4 (11.11%)	01(2.78%)	11 (30.56%)	38 (36.89%)	0.766
	2nd wave	13 (19.40%)	12 (17.91%)	02 (2.99%)	27 (40.30%)		

[Table/Fig-3]: Sequelae of COVID-19 and their duration of persistence in the two waves.
Figures in parentheses indicate percentage
*p-value <0.05 was considered as statistically significant

DISCUSSION

Coronavirus disease 2019, though a respiratory illness, affects almost all systems of the body. A thorough follow-up would thus involve multispecialty clinical examination and investigations. However, with restrictions in outdoor activities and limited medical resources, workup for a complete understanding of all sequelae of COVID-19 may be a remote objective to realise. Hence, authors decided to initiate a follow-up of NOs who had joined back after recovering from COVID-19.

In the present study, with the common denominator of the total nursing officers of the centre, significantly more number of NOs (35.3%) got mild to moderate COVID-19 in the second wave as compared to those in first wave (16%) (p-value=0.043). Fever, bodyache and fatigue were found to be the most common presenting manifestations in the study subjects. Bodyache, fatigue and headache were seen in significantly more subjects in second wave as compared to first wave. Sarkar A et al., in their analysis of SARS-CoV-2 in the two waves in India have observed that emergence of SARS-CoV-2 clade G was one of the prime reasons for the onset of the second wave and associated increase of COVID-19-positive cases in India. Their analysis explored the link between gradual changes in clade distribution due to virus mutations and the emergence of new variants of SARS-CoV-2. Mutations in spike gene, ORF1a, ORF1b, ORF3a, ORF8, N gene, E gene and M gene led to formation of different clades (G, GH, GR, GRY) which had

In a large study from Wuhaan, China, Huang C et al., followed-up 1733 patients recovered from COVID-19 for six months. They found fatigue or muscle weakness (63%) to be the most common persistent symptom, followed by sleep difficulties (26%) and anxiety or depression (23%) [27]. Findings of a multicentric study involving patients' responses from 56 countries have been reported by Davis HE et al., found that fatigue, and memory and cognitive dysfunctions persisted in 89% and 88% of subjects recovered from COVID-19 and approximately 50% of the patients experiencing PASC were still experiencing significant symptom burden after seven months of resolution of acute phase [28].

Tabacof L et al., have reported negative impacts of PASC on physical and cognitive functions in their study population of 156 patients, who sought consultation in a PASC clinic in United States of America. They have found that fatigue was the most common persistent symptom (82%) followed by brain fog (67%) and headache (60%) [29]. In another study from USA, Logue JK et al., have reported that persistent symptoms were present in 30% of the patients recovered from mild COVID-19, and fatigue was the most common persistent symptom [30]. Carfi A et al., from Italy have reported persistence of one or two symptoms in 32%, three or more in 55%, and worsened quality of life in 44.1% of patients after two months of recovery of COVID-19 [31]. In a study from France, Garrigues E et al., have reported that the most frequently reported persistent symptoms at 110 days of

follow-up were fatigue (55%) and dyspnoea (42%); followed by loss of memory (34%), sleep disorders (30.8%) and difficulty in concentration (28%) [32]. In their meta-analysis on PASC, Groff D et al., have found that more than 50% of patients recovered from acute COVID-19 experienced PASC six months post recovery. They found functional mobility impairments, pulmonary abnormalities, and mental health disorders to be the most common sequelae [33].

In their questionnaire based study of persistent symptoms of COVID-19 in 138 Healthcare Workers (HCW), authors from England have observed that 32% of HCWs had one or more persistent symptoms 3-4 months following the acute phase. Fatigue was the most common disabling symptom (39%), followed by mild-to-moderate shortness of breath, anxiety and sleep disturbance [16]. In a study from India on psychological sequelae of COVID-19 in frontline HCWs, it was observed that 69.7% HCWs had higher perceived stress, psychological distress was seen in 53%, and definitive post-traumatic stress disorder was found in 34.8%. Higher perceived stress was seen most commonly in nursing officers (77.7%), followed by postgraduates and interns (70% in each) [18].

Development of sequelae in a subset of patients recovering from acute COVID-19 is multifactoral, having contribution from a range of biological factors which mutually interact in complex ways. While in acute phase, the virus might cause tissue injury in one or more organs leading to chronicity of specific symptoms. There may be persistent reservoirs of SARS-CoV-2 in certain tissues, or there may be re-activation of latent infections under conditions of COVID-19 immune dysregulation. During the illness, there may be interactions of SARS-CoV-2 with host microbiome/virome communities; or the cytokine response to the virus might be interfering with coagulation pathways, nerve signalling and ongoing immune activity in the body. Autoimmunity occurring due to molecular mimicry between pathogen and host proteins may be the reason for persistence of certain manifestations. The varied nature of sequelae and different factors contributing to it suggest that different therapeutic approaches may be required for best management of patients experiencing sequelae of COVID-19 [2].

Limitation(s)

The present study endures many limitations. The follow-up was done based on answers provided by the participants to the questions in the proforma; no follow-up clinical examinations or investigations could be done due to the diversion of resources for COVID-19 care and the requirement of keeping other activities of the institute to a minimum for preventing transmission. There may be potential bias due to self reporting of symptoms by the participants. Also, although all categories of healthcare workers were affected by COVID-19; authors could follow only NOs, as they were supposed to come for work every day and had an understanding of the medical terminology used in the proforma.

CONCLUSION(S)

This study indicates the spectrum of manifestations in mild and moderate cases of COVID-19 and throws light on persistence of symptoms even among those who experienced mild illness. To the best of our knowledge, our study is the first from India comparing the clinical manifestations of COVID-19 and PASC in the first and second wave. The observations and results will add to the literature of presenting manifestations and sequelae of COVID-19, and pave the way for more elaborate and multi specialty studies for enhanced understanding of the disease.

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