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Rheumatological Manifestations in Post Covid Patients Attending A Tertiary Care Centre in Kerala

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Abstract

A variety of rheumatological manifestations have been reported in post-COVID patients. With this background, a prospective observational study was conducted to determine the proportion of rheumatological manifestations and their profile in post-COVID patients who had attended the post COVID outpatient department of Govt. T.D. Medical College, Alappuzha. Convenient sampling was used to select 200 post-COVID patients from whom data were collected using a structured proforma after monitoring the patients for the development of rheumatological symptoms, signs, or serological markers over a period of six months via outpatient department visits on or within 1 week of day 30 and again on or within 1 week of day 180.Among the 200 patients, 40% had rheumatological manifestations in the form of arthralgia (40%), swelling (17.5%), tenderness (5.5%), and restricted mobility (5%). On day zero, 19% had painful joints between 1 and 10, 17.5% between 11 and 20, and 4% between 21 and 30. After one month, 17.5% had painful joints between 1 and 10 and 3% between 11 and 20. After six months, 10% had painful joints between 1 and 10. On day zero, 11.5% had swollen joints between 1 and 10, and5.5% between 11 and 20. After one month, 3.5% had swollen joints between 1 and 10. On day zero, 5% had tender joints with restricted mobility between 1 and 10.New-onset rheumatological manifestations are seen in post-COVID patients in the form of arthralgia, arthritis, and positive serum autoimmune markers.

Keywords: COVID arthropathy, post COVID syndrome, post viral arthritis

Introduction

Coronavirus disease 2019 (COVID-19) is an exceedingly contagious viral illness caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease has had a calamitous effect on the world's population size and has led to more than 6 million deaths worldwide. Nevertheless, the management of COVID-19 is restricted by the unending spread of this virus and its variants. [1] The mechanism by which the respiratory and digestive tracts are infected is determined by the distribution of ACE2. SARS and COVID-19 have been found to share similar symptomatologies. A correlation may be established between the onset of acute respiratory distress syndrome and long-term outcomes when intestinal microbiota is detected in lung tissue. [2]

Certain individuals who have been infected with the virus might experience long-term effects from their primary infection, referred to as post-COVID conditions (PCC) or long COVID. Post-COVID conditions have been referred to by many names, including "long COVID, chronic COVID, post-acute COVID-19, long-haul COVID," and so on.[3] The signs and symptoms may last for four or more than four weeks after the acute infection, many of which might be multi systemic.[4] Not different from previously studied viral infections, severe acute respiratory syndrome-associated coronavirus-2 (SARS-CoV-2) has been shown to result in a degree of autoimmunity in patients who are recovering from its effects. The toll-like receptors and complement system are affected, and this leads to the release of a varying degree of inflammatory mediators. New onsets of rheumatic conditions or worsening of previously diagnosed rheumatic conditions have been noticed in people who have recovered from the infection. Better awareness of these manifestations will be crucial to the appropriate management of these patients. [5]

The primary objective of the study is to understand the proportion of rheumatological manifestations in patients who have recovered from COVID 19 attending the post-COVID OPD of Government T.D. Medical College, and the secondary objective is to study the profile of rheumatological manifestations in patients who have recovered from COVID 19 attending the post-COVID OPD of Government T.D. Medical College, Alappuzha. Post-acute COVID-19 is a syndrome that is trademarked by the presence of clinical symptoms that persist beyond four weeks from the onset of acute symptoms.[6]

The post-COVID-19 condition occurs in individuals who have a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the commencement of COVID-19, with symptoms that last for at least 2 months and cannot be authenticated by an alternate diagnosis. The common symptoms comprise fatigue, shortness of breath, cognitive dysfunction, and others, and these have an impact on activities of daily living. Symptoms may be new in onset following primary recovery from an acute episode or might be ones that persist from the initial illness.[7]

The term long COVID was used for the first time by Perego on a social platform to signify the persistence of symptoms after her initial SARS-CoV-2 infection, and the term 'long haulers' was used by Watson and Yong.[8] It is imperative that a distinction be made between symptoms due to persistent chronic inflammation, sequelae of organ damage, and other nonspecific effects from hospitalisation and social isolation.[8] Depending on the duration of symptoms, post-COVID or long-term COVID may be divided into two stages: post-acute COVID when symptoms range beyond 3 weeks but less

than 12 weeks, and chronic COVID when symptoms outspread 12 weeks.[9]

Secondary to any severe infection or trauma, the human body reacts with an overwhelming immune response known as systemic inflammatory response syndrome, which is followed by a protracted compensatory, offsetting anti-inflammatory cascade referred to as compensatory anti-inflammatory response syndrome. There exists a subtle balance between these two, which governs the abrupt clinical outcome and the ensuing prognosis associated with the infection. SARS CoV 2 infection has the potential to cause excessive cytokine release, a phenomenon known as "cytokine storm," in patients with concomitant illnesses. This culminates in acute respiratory distress syndrome, a hypercoagulable state, maladaptation in the angiotensin-converting enzyme 2 pathway, hypoperfusion to the end-organs, septic shock resulting in multiorgan failure, and subsequently death.

A myriad of viruses have been caught up in the pathogenesis of autoimmune diseases, and we assume a similar association with SARS-CoV-2. The virus penetrates various tissues and leads to endotheliitis, triggering vascular manifestations including thrombosis. SARS-CoV-2 stimulates toll-like receptors and the complement system, thereby leading to autoantibody formation. These predispose to systemic autoimmunity. Both connective tissue disorders and reactive arthritis have been reported following COVID. Patients who have recovered from COVID need to be observed for autoantibody production in the background of rheumatic manifestations.[10] The immune system plays a twofold role in COVID-19, such that it is implicated in both the anti-viral response and in the acute progression of the disease, with a dysregulated response that is embodied by the marked cytokine release syndrome, macrophage activation, and systemic hyper inflammation. [11]

Materials & Methods

This prospective observational study was conducted in a tertiary care centre in Kerala, India, from June 2021 to December 2022. Ethical clearance was obtained from the Institutional Ethics Committee (IEC), Govt. T.D. Medical College, Alappuzha (EC 53/2021, Date 26/04/21). Informed consent was obtained from all the participants.

Inclusion Criteria: Post-COVID patients (who were confirmed cases of COVID 19) who attended the post-COVID OPD of Government T D Medical College, Alappuzha, during the study period and who had consented for the study.

Exclusion Criteria: Patients with documented rheumatological diseases like rheumatoid arthritis, SLE, etc. Patients with a documented history of osteoarthritis and patients less than 18 years of age

Sample Size Estimation

As previous studies were not available on the topic during the conception of the idea regarding the study, the sample was calculated using the formula

$$\frac{4PQ}{D^2}$$

where P = prevalence was considered to be 50%. Q is (1-P).

D = absolute precision = 7% of prevalence

The estimated sample size was 200.

Method of Data Collection

Participants were enrolled in my study according to inclusion and exclusion criteria. After obtaining informed and written consent from the patients, the participants were subjected to a detailed history, a clinical examination, and relevant blood investigations.

The participants were tested for acute phase reactants like erythrocyte sedimentation rate (ESR) and C reactive protein (CRP), complete blood count, antinuclear antibody (ANA) by immunofluorescence IF, anti-double stranded DNA (anti-ds DNA), RA factor, and anti-CCP (cyclic citrullinated peptide) antibodies. A detailed history, rheumatological examination, and the above-mentioned laboratory tests were done on the day of reporting and then reassessed (by repeat testing and examination) after 30 days and then again after 180 days. The findings were duly noted.

Statistical Analysis

Data collection was done using a semi-structured proforma, entered in an MS Excel spread sheet, and analysed using IBM SPSS software version 23.0. Data analysis was done using percentages and proportions. The instruments of measurement used were proforma, laboratory investigations, and detailed rheumatological assessments.

Results

Two hundred patients were available for analysis. It was observed that 40% of the subjects had joint pain on day zero, 20.5% after one month, and 10% after six months; 17% had joint swelling on day zero, 4% had joint swelling after one month, and 1% had joint swelling after six months, whereas 5.5% had joint tenderness on day zero and 0.5% after one month; 5% of the total study subjects had joints with restricted mobility, and 0.5% had the same after one month, whereas nobody was found to have joints with deformity. Another observation from the study was that 24.5% had elevated acute phase reactants on day zero, 5.5% after one month, and 0.5% after six months; 4% had thrombocytopenia on day zero and 1% after one month; 8% turned out to have a positive ANA test on day zero and thereafter; and 3.5% had positive anti-ds DNA on day zero and thereafter. Only 1% were found to have RA factor positivity, while nobody was found to have anti-CCP antibody positivity.

Scoring based on joint involvement

Table 1: Scoring based on joint involvement

Joint	Score
Cervicothoracic	1
Lumbosacral	1
Shoulder	2
Elbow	2
Wrist	2
First Metacarpophalangeal (MCP) joint	2
2nd to 5th MCP	2
Proximal interphalangeal (PIP) joints of upper limb	2
Distal interphalangeal (DIP)joints of upper limb	2
Hip	2
Knee	2
Ankle	2
First Metatarsophalangeal (MTP) joint	2
2nd to 5th MTP	2
PIP lower limb	2
DIP lower limb	2

Here, the scores apply to the number of joints affected. Both the right and left sides of the appendicular skeleton have been included, each with a score of one. It is to be noted that the first MCP and MTP have been given a score of 1 each for each limb, whereas the remaining MCP and MTP have been considered a single joint for the purpose and ease of the study. The PIP and DIP have also been grouped together and given a score of one in each limb.

The time distribution of the number of painful joints among the participants was such that on day zero, 61.5%

of the subjects did not have any painful joints, 19% had painful joints between a range of 1 to 10, 17.5% had painful joints between a range of 11 to 20, and 4% had painful joints between a range of 21 to 30. After one month, 79.5% of the subjects did not have any painful joints. 17.5% had painful joints between a range of 1 and 10, and 3% had painful joints between a range of 11 and 20. None of the subjects had more painful joints than 20. After six months, 90% of the subjects did not have any painful joints, whereas 10% had painful joints in a range of 1 to 10.

Table 2: Percentage of time distribution of number of painful joints in post COVID patients

Number of painful joints	On day zero		After one month		After six months	
	N	%	N	%	N	%
Zero	123	61.5	159	79.5	180	90
1-10	38	19	35	17.5	20	10
11-20	35	17.5	6	3		
21-30	4	2				

On day zero, 83% of the subjects did not have any swollen joints; 11.5% had swollen joints in a range of 1 to 10, and 5.5% of the patients had swollen joints in a range of 11 to 20. None of the subjects had swollen joints greater than 20. After one month, 3.5% of the subjects had swollen joints in a range of 1 to 10, whereas 0.5% had swollen joints in a range of 11 to 20. After six months, 1% of the subjects had swollen joints in a range of 1 to 10. On day zero, 5% of the subjects had tender joints in a range of 1 to 10, whereas 0.5% had tender joints in a range of 11 to 20. After one month, 0.5% of the subjects had tender joints in a range of 1 to 10. After six months, 0.5% of the subjects had tender joints in a range of 1 to 10.

3.5% of the subjects had swollen joints in a range of 1 to 10 whereas 0.5% had swollen joints in a range of 11 to 20. After six months 1% of the subjects had swollen joints in a range of 1 to 10. On day zero 5% of the subjects had tender joints in a range of 1 to 10 whereas 0.5% had tender joints in a range of 11 to 20. After one month 0.5% of the subjects had tender joints in a range of 1 to 10. After six months 0.5% of the subjects had tender joints in a range of 1 to 10.

On day zero, 5% of the participants had joints with restricted mobility in a range of 1 to 10, while 0.5% had joints with restricted mobility in a range of 11 to 20. After one month and six months, 0.5% of the subjects had joints with restricted mobility in a range of 1 to 10, whereas none were above 10.

Table 3: Percentage of time distribution of number of swollen joints

Number of swollen joints	On day zero		After one month		After six months	
	N	%	N	%	N	%
Zero	166	83	192	96	198	99
1-10	23	11.5	7	3.5	2	1
11-20	11	5.5	1	0.5	0	0

Table 4: Percentage of time distribution of number of tender joints

Number of tender joints	On day zero		After one month		After six months	
	N	%	N	%	N	%
Zero	189	94.5	199	99.5	199	99.5
1-10	10	5	1	0.5	1	0.5
11-20	1	0.5	0	0	0	0

Table 5: Percentage of time distribution of number of joints with restricted mobility

Number of joints with restricted mobility	On day zero		After one month		After six months	
	N	%	N	%	N	%
Zero	190	95	199	99.5	199	99.5
1-10	9	4.5	1	0.5	1	0.5
11-20	1	0.5	0	0	0	0

Discussion

This was a prospective, observational study with a study population of 200 subjects.

The majority of patients who attended the post-COVID OPD belonged to the age group of 18 to 40 years (54%), followed by the age group of 41 to 60 years (38%). The effect of age on the incidence of COVID-19 complications: a systematic review and meta-analysis done by Socony's Abebaw Tiruneh, Zemenu Tadese Tesema, et al. revealed that older populations are more likely to develop COVID-related complications.[12]

The study included 57% males and 43% females. A prospective study conducted by Francesca Bai, Daniele Tomasoni, et al. observed that the female gender is more associated with post-COVID manifestations.[13]

Among the participants, 42% were diabetic, 19% were hypertensive, and 31% had dyslipidemia. A literature review conducted by Adekunle Sanyaolu, Chuku Okorie, et al. observed that patients with COVID-19 disease who have concomitant illnesses like hypertension or diabetes mellitus have a higher chance of developing complications.[14]

39% of the participants belonged to category A, 52% to category B, and 9% to category C. A study conducted by Janet D. Pierce, Qiuhua Shen, et al. revealed that post-COVID manifestations can occur in any patient who is recovering from or has recovered from COVID 19, irrespective of their category of illness.[15] Among the participants, 45% had received antivirals and 8.5% had received steroids. A study conducted by Nitin Goel and Nitesh Goyal led to the observation that systemic steroids might promote early recovery in a select group of patients.[16] 25% of the participants had post-COVID neurological manifestations, 3.5% had post-COVID cardiovascular manifestations, and 38.5% had lung manifestations. S V Aswathy Raj, Abraham Jacob et al. conducted a study to determine the clinical factors and associated risk factors of post-COVID syndrome in the northern part of Kerala, and the study revealed that most of the patients complained of dyspnea (48%), fatigue (32%), and cough (25.6%). Mental health problems had also been reported in 6% of participants. It was noticed that the respiratory system was commonly involved (61.2%).[17]

In the present study, a rheumatological profile could be detailed based on history, examination, and laboratory investigations. A scoring system was devised to aid in doing the same based on the location and number of joints involved. The same was applied at the point of initial contact and at every point of reassessment.

In the present study a rheumatological profile could be detailed based on history, examination and laboratory investigations. A scoring system was devised to aid in doing the same based on the location and number of joints involved. The same was applied at the point of initial contact and at every point of reassessment.

A serial fall in acute-phase reactants could be made out from the study. The incidence of leucopenia and thrombocytopenia among post-COVID patients was comparable to other studies reviewed.

Mehdi Karimi Shahri, Hamid R. Niazkar et al. conducted a study that suggests that leukopenia and thrombocytopenia are associated with a poor prognosis, with the incidence of thrombocytopenia being 5% to 40%.[18]

There was a gradual and noticeable improvement in symptoms among the participants at every point of contact. The majority of the participants were found to have involvement in a limited number of joints without any large joint or small joint predilection. No conclusions were drawn regarding the pattern and dynamicity of joint involvement.

N. Varghese, V. Salaru, and V. Sadovici-Bobeica conducted a study to establish the pattern of post-COVID arthropathy, and it showed that 43.7% of the patients had peripheral joint involvement in the form of synovitis, 37.5% had enthesitis, 6.25% had isolated axial involvement (sacroiliac joints), and 6.25% had enthesitis along with axial involvement (cervical spine), whereas 6.25% had synovitis along with enthesitis. The distribution of pain was found to be symmetric (71.4%). The majority of the cases of synovitis involved the hands (wrist, MCP, and PIP).[19]

Summary and Conclusion

From the study, it could be concluded that 40% of the patients had musculoskeletal manifestations in the form of pain on day one, which reduced to 20.5% and 10% after one month and six months, respectively. The same pattern was observed in cases of joint swelling, tenderness, and restricted mobility, even though in significantly lower proportions. 19% of the patients had joint involvement ranging from 1 to 10, whereas only 4% had involvement in more than 20 joints. This trend eventually decreased over a period of six months.

Limitations of the Study

The selection of samples was conducted using convenient sampling (non-probability sampling), and this was a single centre-based study. Only the short-term outcomes were analysed in the study. Long-term mortality and morbidity could not be assessed. The possibility of other viral arthritides was not considered during the course of the study. A consensus on how to distinguish post-COVID arthropathy from other causes and types of arthritis could not be reached. Newer treatment modalities and their association with post-COVID rheumatological manifestations could not be studied due to the timeline of the study.

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