Research Article

Long-Term Sequelae of COVID-19: A Six-Month Follow-Up Study at a Tertiary Care Centre in South Kerala

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A B S T R A C T

Background: COVID-19, emerging in December 2019, has manifested as a significant global health concern. While its acute phase is extensively documented, the long-term effects post-recovery remain less understood, particularly in specific regions such as Kerala, India. This study investigates the prolonged complications encountered by COVID-19 survivors from a tertiary care centre in South Kerala.

Objectives: This research aimed to determine the prevalence and clinical characteristics of post-COVID complications among survivors in South Kerala.

Method: A prospective observational study was conducted from March 2021 to September 2022, involving 184 participants who recovered from COVID-19. All participants were over 18 years of age and had confirmed COVID-19 recovery. Data collection involved interviews and examinations using a validated questionnaire one month post-recovery, continuing monthly for six months. Data on medical history, symptoms, and clinical investigations were gathered, followed by statistical analysis using SPSS 2.0.

Results: The cohort consisted of 184 participants, with an average age of 51.5 years and 52.2% male. Among them, 46.2% had mild COVID-19, 36.4% moderate, and 17.4% critical illness. Co-morbidities were prevalent: hypertension (35.9%), diabetes (35.3%), and coronary artery disease (10.9%).At one month post-recovery, 69% experienced post-COVID complications, with fatigue (43.5%) being most common. By six months, complications reduced to 22.8%, showcasing the importance of supportive care in recovery.

Conclusion: This study underscores the necessity for continuous medical support and monitoring of COVID-19 survivors to manage long-term health challenges effectively. Identifying post-COVID symptoms enables healthcare providers to customise follow-up care, highlighting the need for evidence-based guidelines to address post-COVID syndrome.

Keywords: COVID-19, South Kerala, Post-COVID Complications, Survivors

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Introduction

The World Health Organization (WHO) highlights the ongoing threat of emerging viral diseases. Over the past two decades, outbreaks like severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002–2003 and the H1N1 influenza pandemic in 2009 have occurred.[1] COVID-19, identified in December 2019, marks the third and largest coronavirus outbreak of the century. Initially causing concern with cases of aggressive pneumonia in Wuhan, China, COVID-19 swiftly spread globally.[2] India reported its first case on January 30, 2020, and authorities officially declared the outbreak in India on March 24, 2020.[3–5] The pandemic has since escalated with over 66 million confirmed cases and 6,692,538 deaths worldwide, making India the second most affected country after the USA.[3] Kerala has reported over 884,242 cases, with 808,377 recoveries and more than 3,587 deaths as of January 2021.[6]

The clinical spectrum of COVID-19 ranges from asymptomatic to severe presentations, with symptoms like fever, cough, and fatigue being common.[7]

The natural history of post-COVID-19 in a community population remains a research question. Understanding of post-COVID syndrome is limited. Definition of 'POST COVID SYNDROME' has defined post-acute COVID-19 as symptoms extending beyond three weeks from the onset of first symptoms and chronic COVID-19 as extending beyond twelve weeks of onset.[8]

Some patients experience persistent symptoms post-recovery, including anosmia, dyspnoea, and fatigue.[9] Reports suggest up to 10% of patients remain unwell beyond three weeks, with various symptoms persisting for months.[10] Researchers have a limited understanding of the post-COVID syndrome, which entails symptoms extending beyond three weeks, with fatigue, dyspnoea, cough, arthralgia, and cognitive impairment as commonly reported symptoms.[11–13] Researchers have also documented complications such as myocarditis, lung fibrosis, and neurological sequelae.[8,14] Management of post-COVID syndrome lacks definitive evidence-based guidelines, with holistic approaches often recommended. Studies investigating post-COVID syndromes in Kerala are limited, underscoring the need for further research to address this gap in understanding.

Objective

To determine the prevalence and clinical profile of post-COVID complications of COVID-19 disease among survivors of COVID-19 infection in a tertiary care centre in South Kerala.

Methodology

After obtaining ethical approval from a tertiary care centre in South Kerala, a prospective observational study was conducted from March 2021 to September 2022. A prior study guided in calculating the sample size, assuming 72.8% of the patients experienced fatigue as a persistent symptom.[15] Using the formula n = (Z1- α/2)2p (1-p) /d2, the sample size calculated was 76.

The study involved 184 participants in total. Patients who recovered from COVID-19 illness, meeting the inclusion and exclusion criteria, participated in the study after giving informed consent.

Inclusion Criteria

- Patients more than 18 years of age
- Patient who had recovered from COVID-19 infection with laboratory evidence

Exclusion Criteria

- Patients who did not receive laboratory confirmation of COVID-19
- Patient unwilling to participate

Patients were interviewed by the investigator through telephone or direct consultation using a peer-validated questionnaire developed by the investigator. For a detailed evaluation, a physician other than the investigator examined the patients. Complications were identified and categorised. The subjects were followed up again at six months through a telephonic interview or physical consultation.

Statistical Analysis

SPSS version 2.0 was the statistical tool used to analyse the data. The study population's baseline characteristics were analysed using descriptive statistics. We reported the frequency of post-COVID complications as a percentage with a 95% confidence interval.

Results

Basic Characteristics of the Participants

The ages of patients in the study ranged from 21 to 89 years. Most patients (21.7%) were in the 51–60 age group, while fewer patients were in the over 70 age group. Of the sample, 88 participants (47.8%) were females, and 96 (52.2%) were males.

Regarding COVID-19 severity, 46.2% of patients had a mild disease, 36.4% had a moderate disease, and 17.4% had a critical disease. The prevalence of co-morbidities among the patients was as follows: hypertension in 35.9%, diabetes mellitus in 35.3%, coronary artery disease (CAD) in 10.9%, chronic obstructive pulmonary disease (COPD) in 9.8%, dyslipidaemia in 8.7%, hypothyroidism in 7.6%, chronic kidney disease (CKD) in 4.3%, and other conditions in 8.2%.

Among the 184 patients, 35 had asymptomatic COVID-19 infection and received no treatment. Of the remaining patients, 49 received supportive measures with or without antibiotics, 8 received heparin with symptomatic treatment,

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38 received steroids, heparin, and symptomatic treatment, and 54 received steroids, heparin, and Remdesivir with symptomatic treatment.

Post-COVID Complications

Persistent Symptoms

At four weeks, the most common persistent symptom was fatigue (43.5%), followed by exertional dyspnoea (29.9%). Other symptoms reported included sleep disturbances (20.7%), anxiety (12.5%), myalgia/ arthralgia (11.4%), and hair loss (9.2%). The last reported symptom was the persistence of fever, found in 1.1% of cases.

Over the subsequent months, the majority of patients recovered from these symptoms. By the end of 6 months, only 42 patients (22.8%) still experienced persistent post-COVID symptoms. Fatigue remained the most commonly reported symptom at six months (20.5%), followed by exertional dyspnoea (17.4%). Table 1 depicts the persistent symptoms among survivors at the end of one month and six months. The percentage distribution of the persistence of symptoms serially across one to six months is depicted in Figure 1.

Observed Post-COVID Complications

Among 184 COVID survivors, 127 participants (69.0%) developed post-COVID complications by the end of one month, as shown in Figure 2.

The study categorised post-COVID syndrome into cardio-vascular, pulmonary, neuropsychiatric, musculoskeletal, metabolic, endocrinological, dermatological, peripheral vascular, and multi-systemic involvement. Figure 3 shows the percentage distribution of complications in the study population at the end of 1 month.

The most common pulmonary symptom observed was exertional dyspnoea, followed by dyspnoea at rest. Among the 68 patients who had pulmonary complications, 19 (27.9%) showed radiological evidence of post-COVID pulmonary fibrosis at the end of one month. Neurological symptoms included fatigue, headache, loss of smell and taste, memory loss, inability to concentrate, and focal weakness. Three patients experienced transient ischaemic attacks, and one patient suffered a posterior circulation stroke. Twenty percent of participants reported experiencing sleep disturbances. Among those with musculoskeletal complications, the most common symptom was arthralgia/ myalgia, affecting 11.4% of patients.

Two patients presented with unilateral limb oedema secondary to deep vein thrombosis. Among the 184 participants, 143 had D-dimer assessed at admission and after one month. At admission, 57 patients had normal D-dimer levels, while 86 had elevated D-dimer levels. After one month, among the 57 patients who initially had normal D-dimer levels, 12 experienced an increase in D-dimer levels, whereas the remaining 45 continued to have normal levels. Conversely, of the 86 patients who initially had elevated D-dimer levels, D-dimer levels normalised in 38 patients by the end of one month, while 48 patients continued to have elevated levels, as depicted in Table 2.

Table 1.Percentage Distribution of Symptoms in the Study Population at 1 Month and 6 Months

Persistent Symptoms	At One Month		At Six Months	
	Frequency	Percentage	Frequency	Percentage
Tiredness/ fatigability	80	43.50	38	20.52
Exertional dyspnoea	48	26.00	32	17.40
Uncontrolled blood sugars	45	24.50	19	10.26
Sleep disturbances	38	20.70	19	10.30
Anxious about health	23	12.50	10	5.40
Myalgia/ arthralgia	21	11.40	12	6.52
Hair loss	17	9.20	15	8.15
Chest pain	15	8.20	0	0.00
Dyspnoea at rest	12	6.50	4	2.20
Depression/ mood changes	12	6.50	6	3.24
Headache	11	6.00	1	0.54
Loss of smell and taste	11	6.00	2	1.08
Memory loss	10	5.40	8	4.34
Inability to concentrate	9	4.90	1	0.54
Needle pain in arms and legs	6	3.30	2	1.08
Palpitation	9	4.90	2	1.08
Blackouts/ syncope	5	2.70	0	0.00

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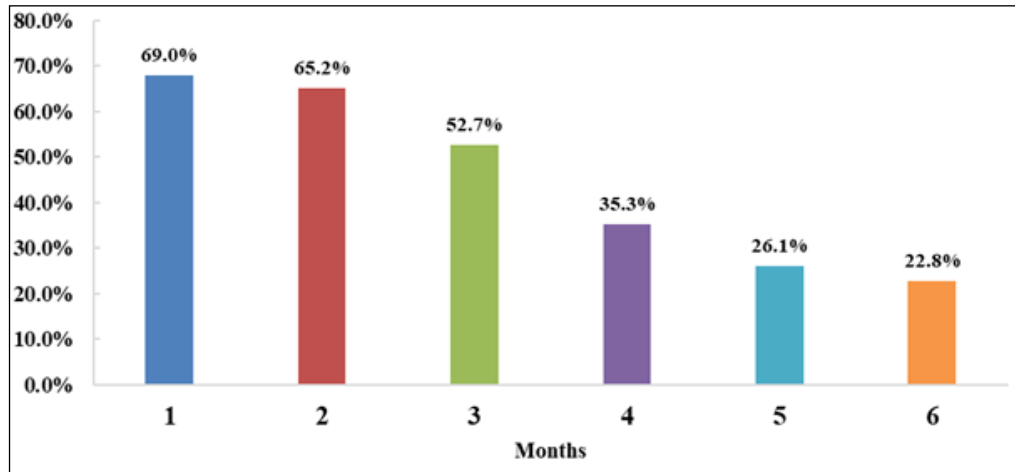| Skin rashes | 5 | 2.70 | 0 | 0.00 |
Focal weakness	4	2.20	0	0.00
Unilateral leg oedema	2	1.10	1	0.54
Persistent fever	2	1.10	0	0.00

Figure 1.Percentage Distribution of Persistence of Symptoms Serially Across One to Six Months
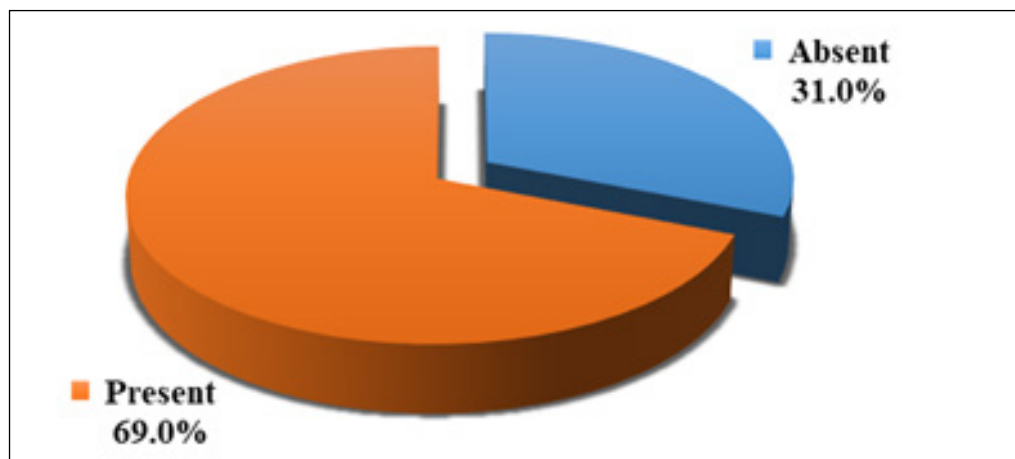

Figure 2.Frequency of Post-COVID Complications at the End of One Month
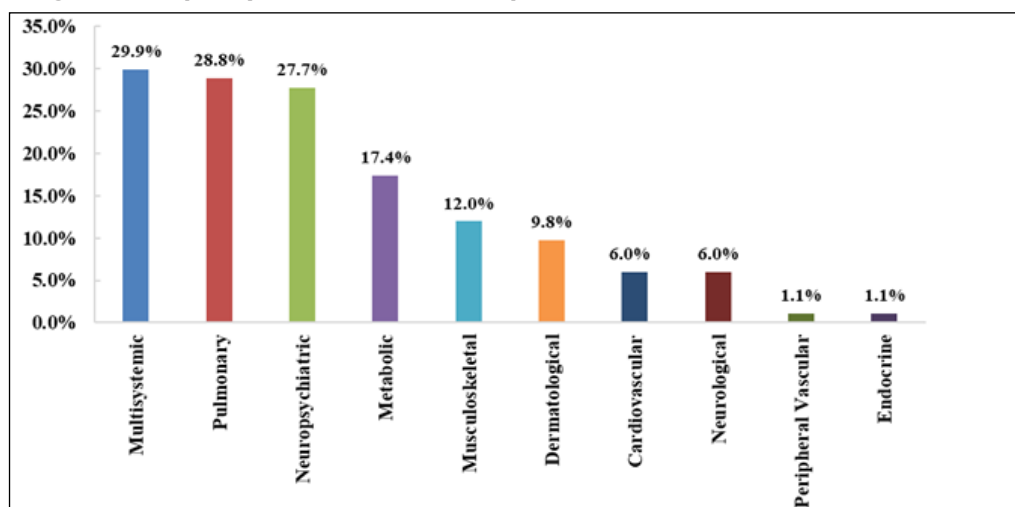

Figure 3.Percentage Distribution of Post-COVID Complications at the End of One Month

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Table 2.Persistence of D-Dimer Elevation at the End of 1 Month

D-Dimer at Admission	D-Dimer at 1 Month		Total	p Value
	Normal n (%)	Abnormal n (%)		
Normal	45 (78.9)	12 (21.1)	57	
Abnormal	38 (44.2)	48 (55.8)	86	0.000
Total	83 (58.0)	60 (42.0)	143	

Discussion

The COVID-19 pandemic is one of the greatest threats faced by the world in recent times. The study found prolonged symptoms among COVID-19 survivors at the end of one month progressively declined at six months.

Though the study included patients above 18 years, most participants were in the 51–60 age group. The study population had an equitable gender distribution. The majority of patients studied were COVID-19 survivors of mild illness.

The study highlighted that over half of the participants had underlying co-morbidities, with hypertension, diabetes, and coronary artery disease being the most prevalent. This pattern indirectly reflects the lifestyle changes and diseases in the community.

Among 184 participants, 69% experienced persistent or new symptoms beyond four weeks. These findings align with a study by Del Rio et al., which reported that 64% of COVID-19 survivors still had symptoms three months post-discharge.[16]

In patients with post-COVID syndrome, multisystemic involvement was noted in 29.9% of the study, followed by pulmonary manifestations in 28.8% and neuropsychiatric manifestations in 27.7%. According to a prospective study by Devis et al., 70% of 201 patients showed damage to at least one organ, with 29% experiencing multi-organ damage.[17] In a follow-up study of 536 participants over one year, the same research group found that 59% had damage to a single organ, while 27% had damage to multiple organs.[18]

Potential mechanisms contributing to the pathophysiology of post-acute COVID-19 include virus-specific pathophysiological changes, immunologic aberrations and inflammatory damage in response to the acute infection, and expected sequelae of post-critical illness.[19]

Initially, the most frequently reported symptom was fatigue, followed by exertional dyspnoea, sleep disturbances, anxiety, myalgia/ arthralgia, and hair loss. As time progressed, many patients recovered from these symptoms. By the end of six months, only 22.8% of patients still had persistent post-COVID symptoms, with fatigue and exertional dyspnoea being the most common at this stage.

Similar to the study findings, fatigue emerged as the most commonly reported symptom across multiple studies at six months: the COVID Symptom Study app and the National Coronavirus (COVID-19) Infection Survey from the UK noted its prevalence.[20] Additionally, Jacobs et al. reported that 55% of post-COVID-19 patients in the USA experienced persistent fatigue, while 50.6% had myalgia and 45.3% suffered from shortness of breath.[21]

In patients with pulmonary complications, exertional dyspnoea was the predominant symptom, followed by dyspnoea at rest. In the post-acute COVID-19 Chinese study, approximately one-quarter of patients had a median 6-minute walking distance lower than the reference values at six months.[22] Decreased diffusion capacity has consistently been reported as the predominant physiological impairment in post-acute COVID-19 cases, with the severity of the initial illness directly correlating with the extent of this decrement.[23] COVID-19 autopsy studies have observed all stages of diffuse alveolar damage, including organising and focal fibroproliferative patterns that appear later in the disease progression.[13]

Pulmonary vascular microthrombosis and macrothrombosis have been found in 20% to 30% of COVID-19 patients, indicating multiple mechanisms contributing to pulmonary manifestations in post-COVID Syndrome.[24]

Regarding cardiovascular symptoms, the study identifies exertional dyspnoea as the most common symptom, followed by palpitations, chest pain, dyspnoea at rest, and syncope. Research of post-acute COVID-19 patients in China reported ongoing palpitations and chest pain in 9% and 5% of participants, respectively, six months after discharge.[23] Autopsy studies involving 39 COVID-19 cases detected the virus in the heart tissue of 62.5% of patients. Findings suggest that direct viral inflammation may contribute to myocarditis, potentially leading to cardiomyocyte death and disruption of essential cell-to-cell adherence proteins.[25]

The study found neurological symptoms such as fatigue, headache, loss of smell and taste, memory loss, inability to concentrate, and focal weakness. Sleep disturbances and anxiety were the major complaints among psychiatric symptoms, with depression being the least reported.

As per literature, COVID-19 survivors often report a post-viral syndrome characterised by chronic malaise, diffuse myalgia, depressive symptoms, and non-restorative sleep.[26] Loss of taste and smell may persist in about one-tenth of

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patients up to six months after other symptoms resolve. Cognitive impairment has also been observed, with or without fluctuations, including symptoms like brain fog affecting concentration, memory, receptive language, and executive function.[26] Anxiety, depression, and sleep difficulties were reported by roughly a quarter of patients in the Chinese study on post-acute COVID-19 during the 6-month follow-up. Approximately 30% of hospitalised COVID-19 patients reported clinically significant PTSD symptoms.[27]

The pandemic's profound socioeconomic disruption has had a significant impact on mental health. Factors such as isolation, mobility restrictions, fear of infection, financial losses, and stigma have all contributed to neuropsychiatric manifestations.[28]

Metabolic complications included uncontrolled blood sugars in 24.5% of individuals. According to the literature, diabetic ketoacidosis (DKA) has been observed in patients without known diabetes mellitus, occurring weeks to months after COVID-19 symptoms have resolved.[29] Use of steroids for moderate and severe COVID-19 pneumonia may worsen the underlying glycaemic status, increasing the susceptibility to secondary infections and vascular complications. Two individuals were observed to have transient thyroiditis.

Among patients with musculoskeletal complications, arthralgia/ myalgia was the most frequently observed symptom. As per the literature, central factors contributing to post-COVID fatigue and myalgias include decreased neurotransmitter levels, reduced neuronal excitability, inflammation, and inhibition in motor neuron unit firing. Additionally, metabolic factors such as vitamin D deficiency, anaemia, and underlying chronic diseases have been identified as contributors to prolonged fatigue.[26]

Hair loss was observed as the most frequent dermatological complication in our study, affecting 9.2% of patients. This condition was predominant, similar to findings in approximately 20% of patients from China, where hair loss was noted. This type of hair loss, known as telogen effluvium, can occur due to viral infection or the associated stress response.[21]

The study found that 42% of individuals had elevated D-dimer levels by the end of one month. Two patients developed deep vein thrombosis, and one suffered from a posterior circulation stroke. Retrospective data indicate that the incidence of venous thromboembolism (VTE) in the post-acute COVID-19 phase is generally less than 5%.[27] According to a single-centre report involving 163 U.S. patients who did not receive post-discharge thromboprophylaxis, there was a 2.5% cumulative rate of thrombosis within 30 days post-discharge, including cases like segmental pulmonary embolism, intracardiac thrombus, thrombosed arteriovenous fistula, and ischaemic stroke.[28]

Unlike the consumptive coagulopathy seen in disseminated intravascular coagulation, COVID-19-associated coagulopathy is marked by a hyperinflammatory and hypercoagulable state. This likely explains the disproportionately high prevalence (20–30%) of thrombotic complications compared to bleeding complications observed in acute COVID-19.[29,30]

Conclusion

This study provides important insights into the long-term effects of COVID-19 on survivors. At one month post-recovery, 69% of participants experienced post-COVID complications, with this figure decreasing to 22.8% at six months. The most common symptoms reported were fatigue and exertional dyspnoea, persisting throughout the one-month and six-month follow-up periods. Multisystemic involvement was the most prevalent, followed by pulmonary and neuropsychiatric manifestations. These findings highlight the necessity for continued medical support and monitoring of COVID-19 survivors to address and manage prolonged health issues effectively.

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