Patient-reported Outcome of Mild Coronavirus Disease 2019 Infection in Patients diagnosed from a Tertiary Care Center in Kerala: A 1-year Follow-up Study

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Received: 24 October 2022; Accepted: 03 March 2023

Abstract
Background: The coronavirus disease 2019 (COVID-19) infection caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus had a huge burden on asymptomatic or mildly symptomatic persons who may have only briefly been associated with healthcare delivery systems during their illness. The knowledge about patient perception of disease outcomes is important in deciding future programs for dealing with pandemics in the community.

Materials and methods: The objectives of the study were to determine patient-reported outcomes (PROs) 30 days and 1 year after the initial diagnosis of mild COVID-19 infection and to determine any factors associated with PROs. Patients who attended the fever screening clinic and were diagnosed with mild COVID-19 infection were contacted telephonically as they completed 30 days after their initial diagnosis, and their responses to the EuroQol five-dimensions 5-level (EQ-5D-5L) questionnaire were recorded. The patients were again contacted 1 year after the initial diagnosis and the same process was repeated.

Findings: A total of 237 patients were contacted telephonically and 167 patients responded to the call. The domain most affected at 30 days was usual activities, and at 1 year, it was anxiety and depression. The mean utility score at 30 days was 0.9347 and at 1 year was 0.9801. The factors associated with worse utility scores were age >45 years and comorbidities.

Interpretation: There is a significant proportion of patients who had restrictions in performing their usual activities 30 days after a mild COVID-19 infection, whereas the domain which showed the least improvement after 1 year was anxiety or depression. Even mild COVID-19 infection had an impact on the health-related quality of life (HRQOL) of people with the elderly and those with comorbidities affected more.

Introduction
The first official announcement of a novel coronavirus infection outbreak was made by the Chinese government in December 2019.\textsuperscript{1,2} The virus spread across the globe, causing illnesses ranging from asymptomatic or mild respiratory illness to severe pneumonia and acute respiratory distress syndrome, especially in a vulnerable subset of patients with comorbid illnesses. On January 30, 2020, the World Health Organization declared COVID-19 as a public health emergency of international concern and later declared a global pandemic.\textsuperscript{3,4} The disease brought about unparalleled economic, social, and political implications. The world had to adopt previously novel methods to protect the population from the medical and social, and economic effects of the disease. It was also a disease with a huge burden on asymptomatic or mildly symptomatic persons who may have missed or only briefly associated with healthcare delivery systems during the course of their illness. Many people, after initial diagnosis of a mild infection, were referred for home isolation or treatment at home. Mild COVID-19 patients, after their diagnosis from COVID-19 clinics, were often lost to follow-up, especially in middle-income countries like India. And therefore, their disease outcome and the impact of disease on their QOL are poorly defined. The knowledge about patient perception of the disease and its outcomes is also important in deciding future programs for dealing with COVID-19 or other pandemics in the community. Thus, it becomes important to assess the outcomes of various treatment protocols from the point of view of the patient. For this, we are in need of structured and validated questionnaires. Patient-reported outcome measures (PROMs) are validated questionnaires filled by patients describing their perspectives on their physical, mental, and social well-being. PROMs have come to be an important tool in analyzing the fight against COVID-19.\textsuperscript{5} This study chose the EQ-5D-5L questionnaire developed by the EQ Research Foundation. EQ-5D is a standardized measure of health status developed by the EQ Group in order to provide a simple, generic measure of health for clinical and economic appraisal.\textsuperscript{6} Recently, EQ-SD utility score sets have been published for the Indian population.\textsuperscript{7} In this context, the current study focuses on PROs in patients affected by mild COVID-19 disease at 30 days and 1 year after COVID-19 infection.

Materials and Methods
Study Design
The main objectives of the study were:

• Determine patient-reported outcome at 30 days and at 1 year after initial diagnosis of mild COVID-19 infection.

• Determine any factors associated with PROs at 30 days and at 1 year.

Study Subjects and Methods
This is a prospective observational cohort study conducted in a fever screening clinic of a tertiary care institute in Kerala. The study was conducted among patients attending the fever screening clinic during the delta wave of COVID-19 between March and May 2021. Consecutive cases were included in the study. The inclusion criteria were a positive confirmatory test for COVID-19 infection in patients aged 18 years or older in those attending the fever clinic and classified as mild according to the Indian Council of Medical Research (ICMR) guidelines.\textsuperscript{8} The definition of the mild case was COVID-19-positive by a confirmatory test with saturation at room air of 94% or more and a respiratory rate of 24 or more per minute. The patients are admitted to treatment areas or sent on home isolation according to the government guidelines for the same.\textsuperscript{9} Registers are

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How to cite this article: Pallivalappillil L, Chittilapilly SJ, Innies I. Patient-reported Outcome of Mild Coronavirus Disease 2019 Infection in Patients diagnosed from a Tertiary Care Center in Kerala: A 1-year Follow-up Study. J Assoc Physicians India 2023;71(6):20–25.

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maintained in the fever clinic for recording the demographic details, tests performed, and contact details of the patient. In the later part of the study, a monoclonal antibody cocktail of casirivimab and imdevimab therapy was introduced into the treatment protocol for mild COVID-19 infection by the Ministry of Health and Family Welfare, Government of India.9 This data was also recorded in the clinic registers. The screening clinic registers were retrospectively analyzed. Consecutive patients who have completed 30 days after initial diagnosis were called, and a telephonic assessment of patient-reported outcome was done. EQ-SD-5L telephonic assessment questionnaire was used for assessing the outcome. EQ-SD-5L is a standardized measure of health status developed by the EQ Group to provide a simple, generic measure of health for clinical and economic appraisal. The questionnaire was downloaded with permission from the EQ group via email. The questionnaire was not available in the local language of Malayalam. Therefore, to avoid a translational bias, the questionnaire was translated into Malayalam and validated by the second and third authors of the study. The EQ-SD-5L descriptive system comprises the following 5D, each describing a different aspect of health—mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has five response levels of severity—no problems, slight problems, moderate problems, severe problems, and unable to do an activity. There are 3,125 possible health states obtained by combining one level from each dimension, ranging from 11,111 to 55,555.6. The HRQOL of a particular health state, thus measured using EQ-SD-5L descriptive system, is then scored and represented by its utility score. Jyani et al.7 published an Indian utility score set for the EQ-SD-5L scores. This was adopted for creating an EQ-SD summary index for each patient. Therefore, each health state can be assigned a single score, and the scores can be compared or analyzed. The questionnaire was addressed to the patient directly over the phone by the same investigator. The question was asked in vernacular language after validation of translation from the original English version. The respondent is asked to indicate his/her health state, and it was recorded by the investigator by checking the box next to the most appropriate response level of each of the 5D. The same set of patients was contacted telephonically at the completion of 1 year after the initial diagnosis. The same questionnaire was asked to reassess their QOL. All five domains were scored and utility scores were assigned for each patient.

Analysis
A descriptive analysis of the responses in each dimension at 30 days and at 1 year was done. A paired samples t-test was used to compare the mean utility scores at 30 days and 1 year. Independent samples t-test was used to compare the utility scores among various subgroups. A p-value of <0.05 was considered significant. The statistical analysis was done using IBM Statistical Package for the Social Sciences statistics version 26.

The study was approved by the Institutional Ethics Committee of the Amala Institute of Medical Sciences (Ref No 11/IEC/21/AIMS-41 dated 18/02/2021).

RESULTS
A total of 237 consecutive patients were identified from the register of the fever clinic. Demographic data were available for all these patients from the registers. When contacted telephonically, 48 patients did not answer the phone call. A total of 20 patients expressed unwillingness to participate in the study. A total of 167 patients were eligible for analysis at 30 days. At the end of 1 year, 162 patients responded to the phone call.

The demographic data are given in Table 1. The outcome according to hospitalization was as given in Table 2. The percentage of subjects in each of the five categories of the five domains at 30 days follow-up and 1-year follow-up is represented in Figures 1 to 5. The EQ-SD-5L level index was calculated at 30 days and at 1 year. The mean scores at 30 days and one year and the difference in scores are given in Table 3. A paired samples t-test for comparing utility scores at 30 days and 1 year was done, which showed a difference of 0.418 (0.257–0.579) between the 1-year score and the original score indicating significant improvement (Table 4).

Table 1: Demographic data

<table>
<thead>
<tr>
<th>Demographic data</th>
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<tbody>
<tr>
<td>Age in years mean (SD)</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Comorbidities</td>
</tr>
<tr>
<td>Present</td>
</tr>
<tr>
<td>Absent</td>
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</tbody>
</table>

Table 2: 30-day hospitalization data

<table>
<thead>
<tr>
<th>Outcome at 30 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did not require hospitalization</td>
</tr>
<tr>
<td>Hospitalized, ward admission</td>
</tr>
<tr>
<td>Hospitalized, ICU admission</td>
</tr>
<tr>
<td>Death</td>
</tr>
</tbody>
</table>

Fig. 1: Comparison of mobility scores at 30 days and at 1 year
Comparison of the difference in utility scores in persons above vs below 45 years of age showed that those above 45 years of age have a poor improvement in function compared to the younger age-group (Tables 12 and 13) (p-value = 0.003).

**Discussion**

Self-assessment of patient outcomes is central to COVID-19 research and future pandemic planning. We are only beginning to understand the long-term effects of SARS-CoV-2 infection. The symptoms have returned in some patients a few months postrecovery, while others have developed serious conditions such as Kawasaki-like disease. PROs might be used for long-term follow-up to assess the impact on a patient’s QOL and alert physicians to the development of potentially life-threatening complications. India had one of the largest populations of COVID-19-infected patients, and this should have led to a large cohort of patients suffering from various post-COVID-19 manifestations. In order to tackle the enormous surge during the delta wave, the country and the southern state of Kerala used a triaging system by ICMR which classified patients into mild, moderate, and severe infections based on the parameters of respiratory rate and saturation by pulse oximetry. The patients were sent for home isolation and advised to self-monitoring in case of mild infection. Many of these patients did not return to the healthcare system. So, a telephonic follow-up was considered ideal to understand their status both at 30 days and 1 year past diagnosis. The understanding gained by such a study can be used to focus future healthcare strategy planning on targeting this group of patients.

Studies using validated and structured questionnaires to assess the patient’s version of the impact of COVID-19 infection have not been conducted in the South Indian state of Kerala. This is the first such study in this group discussing both short-term and long-term follow-up of this group of patients. Jyani et al. recently published the largest 5L version of the EQ-5D-5L valuation study conducted so far in the world. This is also the first valuation study in South Asia for use in the Indian population. The value set provided by these authors was used in the current study to provide utility scores to compare the EQ-5D-5L scores.

The current study showed that the mean utility score of subjects; 1 year after mild COVID-19 infection [0.9801, standard deviation (SD) 0.1243] was higher than the score; 1 month after diagnosis [0.9347, SD 0.0476]. The scores showed that the subjects’ QOL was improving over the course of 1 year that did not receive it showed a mean improvement in score of 0.0677 among those who did not receive the cocktail and 0.015 in those who did (Table 6). Robust independent samples t-test indicated that the difference is statistically significant (Table 7) (p-value ≤ 0.001). A comparison of people without and with any comorbidities showed that people with any comorbidity had worse QOL utility scores (Tables 8 and 9) (p-value = 0.011). Male gender had worse utility scores, but it was not statistically significant (Tables 10 and 11) (p-value = 0.571).
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as the difference between the two scores was significant \( p\)-value = 0.001, confidence interval (CI) 0.257–0.579.

But when we analyze the health status of the subjects in each of the domains, we can see that the domain most affected in the initial assessment at 30 days was the performance of usual activities. A total of 32% of patients had at least some limitations in usual activities. The reason behind this will have to be assessed by further investigations into people who visited the hospital at this time. We assume that the persistent COVID-19 symptoms may have been perceived as limiting daily activities in this group. At the end of 1 year, this domain showed significant improvement, with only 6% of people reporting at least some problem in performing usual activities. The next domain to be involved was anxiety and depression. A total of 24% of people experienced some severe anxiety or depression in the 1st month. This was interestingly the domain that showed the least improvement, with 17% of people still having at least some anxiety and depression at 1 year. A total of 23% of people also felt pain or discomfort at 1 month. This also showed a trend of persistence at one year since 19% of people had at least some discomfort at 1 year. The rather significant proportion of people with discomfort and anxiety 1 year after an initial diagnosis of mild COVID-19 infection is a significant finding of this study. The reason for this will also have to be analyzed by further clinical examinations and is not possible by telephonic communications alone. Mobility was the domain that was least affected, followed by limitations in self-care. In these two domains, only around 5% of people were affected in the initial 1 month, which came down to 2% at 1 year.

When this is compared to similar studies, we find that gender, occupation, and comorbidities exerted a major influence on EQ-5D scores in another population study from Tamil Nadu, which is a neighboring state of Kerala.\(^\text{10, 11}\) While comparing such data from across the world, we can see that a varying proportion of patients had persistent symptoms post-COVID-19 infection. In a study by Elkan et al.,\(^\text{12}\) it was found that around 56% of patients had one or more persistent symptoms at a 9-month follow-up period. The extent and severity of persistent symptoms during the follow-up period depended on the severity of the COVID-19 infection and the length of the follow-up period. When predominantly outpatients with mild infection were studied by Logue et al.,\(^\text{13}\) it was found that 30% of patients had persistent symptoms at a median follow-up period of 169 days. Rass et al.\(^\text{14}\) reported that every third patient reported a reduction in HRQOL
3 months after COVID-19 diagnosis, and impairments were more prominent in mental than physical well-being. The short form-36 questionnaire (SF-36-item Health Survey), Hospital Anxiety and Depression Scale, and Posttraumatic Stress Disorder Checklist-5 were used in this study. Similar findings were also reported from China in the study by Qu et al. Fatigue is the most common symptom reported in the post-COVID-19 period in various studies around the world. A review by Nandasena et al. found that a large majority of patients at various stages after discharge from the hospital had impacted their QOL. They also propose to study the domains in which the quality was impacted to plan future interventions for these people.

Compared to these cohorts, a lower percentage of patients reported symptoms when assessed by the EQ-5D-5L questionnaire. The varying periods of follow-up make direct comparison difficult.

The persistent symptoms of depression and anxiety warrant the need for psychological evaluation and support in this group of patients. Detailed evaluation will also be needed to analyze the domain of pain and discomfort.

The next objective was to analyze the factors which led to worse utility scores. A subgroup analysis in the current study showed that the presence of any comorbidities, male gender, age >45 years, and use of a monoclonal antibody cocktail was associated with worse utility scores at the end of 1 year. The fact that the monoclonal antibody cocktail was given to the at-risk population with advanced age and multiple comorbidities may be acting as a confounding factor. A study by Chen et al. using SF-36 scores demonstrated a significant difference in HRQOL in patients with COVID-19 and age female sex, obesity, and length of stay associated with negative physical function and mental function. In the meta-analysis by Malik et al., which included a total of 12 studies with 4,828 postacute COVID-19 syndrome patients, it was found that postacute COVID-19 syndrome was associated with poor QOL. Persistent symptoms including fatigue, dyspnoea, anosmia, sleep disturbances, and worse mental health. Intensive care unit (ICU) stay was significantly associated with poor QOL. The meta-analysis by Qu et al. pointed out that in the 38 studies included, fatigue and dyspnoea were the most prevalent symptoms in acute post-COVID-19 and fatigue and sleep disturbance in chronic post-COVID-19 syndrome, respectively. They also opined that the available evidence is generally of poor quality, with considerable risk of bias, and is of observational design.

So, the need for further evaluation of the post-COVID-19 syndrome by a nuanced clinical evaluation is warranted. Our study is probably the first to analyze the chronic post-COVID-19 syndrome in the mild disease group patients and also one of the first to use a structured and validated questionnaire in this particular population of Southern India. The fact that the mild disease group is also not fully back to normal after one year of infection is to be noted and considered for further evaluation. We could concentrate more on the elderly population, male gender, and those with comorbidities to target further studies on the post-COVID-19 state.

The limitations of the study pertain to the nonavailability of the vernacular version of the telephonic questionnaire though we have tried to circumvent this by validating a translation of the questionnaire in Malayalam.
The recall bias of the respondents will have affected some of the data. The number of patients included in this study is also a limiting factor. However, this analysis of the acute and chronic post-COVID-19 state in the mild COVID-19 disease group gives valuable insights into the domains of life affected and will help plan targeted interventions in this group of subjects.

REFERENCES