

Association of symptom characteristics and comorbid conditions with viral RNA positivity of Covid-19 patients in Kasaragod district in Kerala, India: A retrospective cohort study

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ABSTRACT

Background. Symptoms of Covid-19 are known to be non-specific ranging from asymptomatic cases to severe illness affecting multiple organ systems. The duration of viral RNA positivity and transmission varies in individuals. We describe the association between symptom characteristics and comorbid conditions with viral RNA positivity of SARS-CoV-2 affected individuals.

Methods. We conducted a record-based retrospective cohort study of 179 patients found to be positive for Covid-19 in Kasaragod district in Kerala. We included details of all patients found positive during the initial phases of the pandemic and recorded details regarding symptoms, duration of viral RNA positivity and the occurrence of transmission. The data were analysed using SPSS.

Results. Any symptom was present in 68%. Fever (43%) was the most common symptom while 50% had at least one respiratory symptom. Increased duration of viral RNA positivity was found to be associated with presence of comorbid conditions. The majority of individuals who

transmitted disease (75%) had some symptom, predominantly a respiratory symptom.

Conclusion. Respiratory symptoms are seen in half of the patients and viral RNA positivity was for a longer duration in patients with comorbid conditions.

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INTRODUCTION

SARS-CoV-2 virus predominantly affects the respiratory system and produces symptoms ranging from mild upper respiratory discomfort to severe pneumonia.^{1–4} Although a majority of the infected persons are reported to be asymptomatic, a quarter to half of the patients develop clinical symptoms. It spreads through respiratory droplets produced during coughing, sneezing and spitting or through direct contact. The median incubation period of the disease is estimated to be 5 days with an incubation period ranging from 2 to 14 days. About 97% of patients who develop symptoms will do so within 13.5 days.⁵

The median duration for reverse transcription polymerase chain reaction (RT-PCR) negativity of Covid-19 virus from the day of onset of symptoms was 19–20 days.⁶ The days of viral RNA shedding of the SARS-Cov-2 virus may contribute to improve the infection prevention and control strategies and to develop policies for follow-up testing of positive people.

The symptoms of Covid-19 are known to be non-specific with a wide range from asymptomatic patients to severe illness. Several epidemiological studies have been conducted to understand the clinical manifestations of the disease.^{7–9}

As SARS-CoV-2 continues to spread through community transmission, it is important that we continue to expand our knowledge about its natural history and transmission. Various combinations of symptoms need to be identified to help in improving screening guidelines in the community. Kasaragod district had the highest number of cases in the state of Kerala and was one of the first hot spots in India during this pandemic. We did this study to understand the pattern and distribution of clinical symptoms and factors associated with the duration of viral RNA positivity among SARS-CoV-2-positive patients in Kasaragod district, Kerala.

METHODS

This was a record-based, retrospective cohort study at the

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district Corona Control Unit at Kasaragod district in Kerala, India. Data were collected from the case records of Covid-19-positive patients admitted in Kasaragod district from 31 January 2020 to 10 May 2020. The data were collected after obtaining permission from district health authorities. No sampling was done and all patients in this phase of the pandemic were recruited via census sampling.

A patient who tested positive for SARS-CoV-2 by RT-PCR was included as a study participant. The period of viral RNA positivity was defined as from the day of onset of first symptom till the first negative RT-PCR result. If the patient was asymptomatic, the period between the day of first positive result and first negative result was used as the period of viral RNA positivity. As RT-PCR was repeated every 2–3 days, there was only a negligible chance of variation in this period.

We extracted demographic data including age and gender, clinical characteristics including all symptoms, details of comorbid conditions, duration of hospital stay and period of viral RNA positivity. We further categorized patients based on their clinical symptoms to category A, B and C as per the guidelines issued by the Government of Kerala.¹⁰ Category A patients were those with low-grade fever, mild sore throat, cough, rhinitis or diarrhoea. Category B patients included those with high-grade fever and/or severe sore throat, cough or category A patients with one or more of the following conditions: (i) lung, heart, liver, kidney or neurological disease, blood disorders, uncontrolled diabetes, cancer or HIV-AIDS; (ii) long-term steroid use; (iii) pregnancy; and (iv) age >60 years. Category C patients included those with (i) breathlessness, chest pain, drowsiness, fall in blood pressure, haemoptysis, cyanosis with red flag signs; (ii) children with ILI (influenza-like illnesses) with red flag signs; and (iii) somnolence, high/persistent fever, inability to feed well, convulsions, dyspnoea/respiratory distress, etc. and worsening of underlying conditions.

The reported symptoms were further categorized based on organ system affected as generalized symptoms, respiratory symptoms or gastrointestinal symptoms. Additionally, the underlying comorbid conditions were also recorded.

The details were entered in Microsoft Excel and statistical analysis was done using Statistical Package for Social Sciences 16.0 (SPSS Inc. Released 2007. SPSS for Windows, Trial Version 16.0. Chicago, SPSS Inc). Clinical symptoms and their combinations were expressed as proportions. Mean with standard deviation (SD) were provided for quantitative variables, including period of viral RNA positivity. Odds ratio with confidence interval was estimated for finding the association between symptom combinations and independent variables such as gender and comorbid conditions. Mann–Whitney U-test was used to find the association with period of viral RNA positivity. Clearances were obtained from the district health authorities and institutional human ethics committee of the Central University of Kerala (IHEC No: CUK/IHEC/2020/04) for conduct of the study.

RESULTS

The mean (SD) age of participants ($n=179$; 72.6% men) was 33.6 (3.9) years. Among the 179 patients, 122 (68%) had at least one symptom in the period preceding diagnosis while the remaining 57 (32%) were asymptomatic before and during the illness. The majority of patients presented with either fever or respiratory symptoms. Generalized symptoms such as fever, fatigue, myalgia and headache were reported in 77 (43%), 25 (14%), 28 (15.6%) and 25 (14%) patients, respectively. Ninety patients (50%) had

at least 1 respiratory symptom while 19 patients (11%) had at least 1 gastrointestinal symptom. Vomiting, diarrhoea and abdominal discomfort were the gastrointestinal symptoms experienced by the patients. Anosmia, which has been reported around the world as a specific symptom of Covid-19, was present in 16 patients (9%).

None of the patients belonged to category C, while 57 (31.8%) belonged to category B and 122 (68.2%) to the mild or asymptomatic category A. The most prevalent comorbid condition was diabetes mellitus (8%) followed by hypertension (6%) and cardiovascular diseases (2.2%). Thirty-two (18%) participants had at least one comorbid condition (Table I).

The presence of any generalized or respiratory symptom was higher in category B patients. They were also more likely to report generalized symptoms such as fever (OR 3.79), fatigue (OR 6.05), myalgia (OR 4.29) headache (OR 9.67) and respiratory symptoms such as running nose (OR 3.01), sore throat (OR 2.79) and cough (OR 3.48; Table II).

As the median duration of viral RNA positivity was found to be 12 days, it was taken as the cut-off for determining the association with exposure variables. The presence of various symptoms was found to have no association with increased viral RNA positivity. However, presence of comorbid conditions led to a significantly higher duration of viral RNA positivity (OR 2.78). Gender and nature of contact/transmission also showed no significant association (Table III).

Among the 179 study subjects, 20 patients transmitted the disease while 159 did not. The 20 individuals, who transmitted the disease, spread it to 69 individuals including one super spreader event. Among those who transmitted, 15 (75%) were symptomatic and 13 had respiratory symptoms. Of the 122 patients who were symptomatic, only 14 (12%) transmitted the disease while among the 90 patients who had respiratory symptoms, only 13 (14.4%) transmitted the disease. Of the 20 individuals who transmitted the disease, viral RNA positivity was <12 days in 12 (60%), and >12 days in 8 (40%).

DISCUSSION

We present the distribution of symptoms among Covid-19-positive patients in Kasaragod district, which was India's first hot spot. The study population was predominantly young with one-third belonging to the age group of 25–34 years and one-fifth to 35–44 years. The mean age of the participants was lower than that reported elsewhere.⁹ This may be because a higher proportion of younger men work in the Gulf countries and the Gulf-returnees constituted the majority of the study participants. A majority of the participants were men (72.6%) and this was due to the fact that most were expatriates, who were returning to the country and the majority of emigrants in general are men.

Our study documents a higher proportion of symptomatic patients (68%) compared to similar studies in other parts of India.^{11,12} However, this is lower than the 80% symptomatic patients reported from Wuhan.⁸ The higher proportion of symptomatic patients may be due to the meticulous documentation of even minor symptoms in a newly emerging disease. Nearly 70% belonged to category A and the rest to category B. The absence of individuals belonging to category C indicates that this was one of the initial cohorts of SARS-CoV-2-infected individuals. Although most cases reported in China and Italy were mild in nature, there were substantially moderate illness.^{9,13} Severe illness was reported among older patients in other countries. However, the predominantly younger patients

TABLE I. Baseline characteristics of the study participants (n=179)

Characteristics	n (%)
<i>Age (years)</i>	
≥18	20 (11.2)
18–24	22 (12.3)
25–34	62 (34.6)
35–44	38 (21.2)
45–54	23 (12.8)
55–64	9 (5.0)
65–74	4 (2.2)
75–84	1 (0.6)
<i>Gender</i>	
Men	130 (72.6)
Women	49 (27.4)
<i>Generalized symptoms</i>	
Fever	77 (43.0)
Fatigue	25 (14.0)
Myalgia	28 (15.6)
Anosmia	16 (8.9)
Loss of taste sensation	14 (7.8)
Headache	25 (14.0)
Individuals with any one of the above generalized symptoms	94 (52.5)
<i>Respiratory symptoms</i>	
Running nose/rhinitis	30 (16.8)
Sore throat	62 (34.6)
Cough	57 (31.8)
Breathlessness	3 (1.7)
Haemoptysis	1 (0.6)
Individuals with any one of the above respiratory symptoms	90 (50.3)
<i>Gastrointestinal symptoms</i>	
Vomiting	2 (01.1)
Diarrhoea	11 (06.1)
Abdominal discomfort	11 (06.1)
Individuals with at least one of the above gastrointestinal symptoms	19 (10.6)
<i>Symptomatic/asymptomatic</i>	
Individuals having at least one symptom	122 (68.16)
Asymptomatic	57 (31.84)
<i>Comorbid conditions</i>	
Hypertension	10 (5.6)
Diabetes mellitus	15 (8.4)
Cardiovascular disease	4 (2.2)
Stroke, chronic obstructive pulmonary disease, asthma,	1 (0.6)
chronic kidney disease, thyroid disease, psychiatric illness,	1 (0.6)
rheumatoid arthritis	1 (0.6)
	4 (2.2)
	1 (0.6)
<i>Other conditions</i>	
Pregnancy	6 (3.4)

captured during the early phase of the pandemic could have resulted in no cases being reported with category C illness.

In our study, fever was the predominant symptom (43%), followed by sore throat (34.6%) and cough (31.8%). The findings are consistent with other studies conducted in northern parts of India.^{11,12} Nearly one-third of the study participants reported cough as a symptom in both these studies. However, one study reported nearly half of the patients having fever, while the other reported only about one-sixth patients having fever. However, the presence of symptoms had no association with the duration

of viral RNA positivity. This is consistent with international studies which report presence of various symptoms even after cessation of viral RNA shedding. However, fever and breathlessness were reported to be absent at the time of cessation of viral RNA shedding.¹⁴ Even though the disease presentation in our study was milder, patients in category B reported a higher likelihood for both generalized and respiratory symptoms than category A patients. This is expected as categorization of patients is based on presence/severity of symptoms. However, the absence of a significant association for the gastrointestinal symptoms points to its lower utility in categorization and identification of patients. Rigorous case identification and prompt treatment could be another reason that severe cases were not reported. The case detection was adequate due to slow progression of the disease.

The median duration of 12 days for cessation of viral RNA shedding was in the intermediary range compared to similar Indian studies. However, these studies had reported a similar proportion of about 18% of patients having comorbid conditions as in our study.^{11,12} Even then, the presence of comorbid conditions is associated with increased duration of positivity. This is consistent with large international studies, which point to bad prognosis in the presence of comorbid conditions.^{15,16} Prolonged viral shedding was found to be associated with hypertension.¹⁷ The occurrence of chronic diseases such as diabetes mellitus, hypertension and chronic obstructive pulmonary disease will increase mortality.¹⁶ Additionally, multiple illnesses in individuals accentuates the risk of a poor outcome in those affected with Covid-19.¹⁸ Symptomatic patients tend to have a longer duration of viral RNA positivity.¹⁷ The presence of symptoms, predominantly respiratory in three-quarters of those who transmitted indicates the need to focus more on those with symptoms for lowering community transmission of SARS-CoV-2 virus. The increased duration of viral shedding associated with comorbid conditions poses a greater risk. Hence, management of symptomatic patients with comorbid conditions should become the focus for reducing mortality, decreasing transmission and preventing collapse of the health system during the Covid-19 pandemic.

Conflicts of interest. None declared

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TABLE II. Distribution of symptoms among Covid-19 patients based on the symptom category

Symptoms	Category A, n (%)	Category B, n (%)	Odds ratio (95% CI)	p value*
<i>Generalized symptoms</i>				
Fever	40 (32.8)	37 (64.9)	3.79 (1.96–7.36)	<0.001
Fatigue	8 (6.6)	17 (29.8)	6.06 (2.43–15.11)	<0.001
Myalgia	11 (9)	17 (29.8)	4.29 (1.85–9.94)	0.001
Anosmia	8 (6.6)	8 (14)	2.33 (0.83–6.55)	0.157
Loss of taste sensation	7 (5.7)	7 (12.3)	2.30 (0.77–6.90)	0.143
Headache	6 (4.9)	19 (33.3)	9.67 (3.60–25.97)	<0.001
Individuals with at least one of the above generalized symptoms	54 (44.3)	40 (70.2)	2.96 (1.52–5.79)	0.001
<i>Respiratory symptoms</i>				
Running nose/rhinitis	14 (11.5)	16 (28.1)	3.01 (1.35–6.72)	0.009
Sore throat	33 (27)	29 (50.9)	2.79 (1.45–5.38)	0.002
Cough	28 (23)	29 (50.9)	3.48 (1.78–6.79)	<0.001
Breathlessness	2 (1.7)	1 (1.8)	1.07 (0.10–12.08)	1.0
Haemoptysis	0	1	–	
Individuals with at least one of the above respiratory symptoms	51 (41.8)	39 (68.4)	3.02 (1.55–5.86)	0.001
<i>Gastrointestinal symptoms</i>				
Vomiting	1 (0.8)	1 (1.8)	2.16 (0.13–35.17)	1.0
Diarrhoea	6 (4.9)	5 (8.8)	1.86 (0.54–6.37)	0.506
Abdominal discomfort	6 (4.9)	5 (8.8)	1.86 (0.54–6.37)	0.506
Individuals with at least one of the above gastrointestinal symptoms	10 (8.2)	9 (15.8)	2.10 (0.80–5.49)	0.191

* Chi-square test CI confidence interval

TABLE III. Factors associated with the duration of viral RNA positivity

Factor	Days of viral RNA positivity		Odds ratio (95% CI)	p value*
	≤12 days†	>12 days		
<i>Gender</i>				
Men	67 (72.8)	63 (48.5)	Reference	1.0
Women	25 (27.2)	24 (27.6)	1.02 (0.52–1.97)	
<i>Type of cases</i>				
International traveller	50 (54.3)	58 (66.7)	Reference	0.096
Local transmission	42 (45.7)	29 (33.3)	0.60 (0.33–1.09)	
<i>Generalized symptoms</i>				
Not present	45 (52.9)	40 (47.1)	Reference	0.765
Present	47 (26.3)	47 (26.3)	1.13 (0.63–2.02)	
<i>Presence of comorbid conditions</i>				
No	82 (55.8)	65 (44.2)	Reference	0.018
Present	10 (31.3)	22 (68.8)	2.78 (1.23–6.27)	
<i>Presence of generalized symptoms</i>				
No	45 (48.9)	40 (46)	Reference	0.765
Present	47 (51.1)	47 (54)	1.13 (0.63–2.02)	
<i>Respiratory symptom</i>				
No	48 (52.2)	41 (47.1)	Reference	0.551
Present	44 (47.8)	46 (52.9)	1.22 (0.68–2.20)	
<i>Gastrointestinal symptom</i>				
No	81 (88)	79 (90.8)	Reference	0.631
Present	11 (12)	8 (9.2)	0.75 (0.29–1.95)	

* Chi-square test † Cut-off is taken based on the median days of viral RNA positivity CI confidence interval

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