Original Article

Clinical profile and outcomes of asymptomatic *vs.* symptomatic travellers diagnosed with COVID-19: An observational study from a coastal town in South India

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SUMMARY   Despite the high number of coronavirus disease-19 (COVID-19) cases from India, there are few reports from India describing the clinical epidemiology of COVID-19. This study aimed to describe the clinical/epidemiological characteristics and outcomes of asymptomatic *vs.* symptomatic COVID-19 patients. This was a retrospective chart review of all admitted patients with COVID-19 above 18 years with a history of travel within one month of the admission. The patients were categorized into asymptomatic and symptomatic. The symptomatic patients were further classified into mild, moderate and severe. The demographic profile, risk factors, clinical features, laboratory parameters, treatment details and outcome of all patients were recorded. The clinical and laboratory parameters were compared between symptomatic patients and asymptomatic patients. Of the 127 recruited patients, 75 were asymptomatic. Of the 52 symptomatic patients, 41 patients were classified as a mild illness. The mean age of the patients was 44.5 ± 15 years. A total of 73 patients had one or more risk factors. The male patients were more commonly found to be symptomatic compared to female patients. Neutrophil-lymphocyte ratio, C-reactive protein and lactate dehydrogenase were significantly elevated in symptomatic patients. A total of five individuals required supplemental oxygen therapy, and one of them required mechanical ventilation. All the patients had favourable outcomes. Asymptomatic and mild illness form a significant proportion of positive patients and have excellent outcomes without therapeutic interventions.

Keywords   Pregnancy, household contact, COVID-19, Presymptomatic, asymptomatic, transmission, SARS-CoV-2

1. Introduction

Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), the causative agent of coronavirus disease-19 (COVID-19) is peculiar in terms of transmission dynamics and clinical manifestations despite its genetic relatedness to other coronaviruses (*1*). The virus multiplies in the upper respiratory tract, and the peak viral load is reached even before the symptom onset. As a result, asymptomatic individuals can also transmit. In those who are symptomatic, the manifestations range from mild to severe, requiring intensive care. Studies have shown that the proportion of asymptomatic and mild illness is significantly higher and a tiny proportion of individuals develop a severe disease (*2-4*). Therefore, predictive scores based on comorbidities and laboratory parameters have been suggested to identify those individuals that require higher levels of care (*5*). The treatment for COVID-19 has also been continuously evolving with many of the proposed drugs failing to show benefits in randomized controlled trials (*6*).

Despite the high number of cases, there are relatively fewer reports from India describing the clinical epidemiology of COVID-19. Most of the reports are from tertiary care hospitals that often underestimate the actual proportion of asymptomatic/mild illness as only symptomatic individuals with more distressing symptoms are predominantly admitted in the hospital. Similar to other parts of the globe, the initial cases in

India were from the travellers. As per the regulations, testing and hospital-based treatment (irrespective of symptoms) were recommended for all travellers in the early part of the pandemic. It was hypothesized that the study of a cohort of travellers with COVID-19 would represent a distinct cohort. Therefore, this study aimed to describe the clinical-epidemiological characteristics and outcomes of hospitalized COVID-19 patients with travel history.

2. Materials and Methods

The study was a retrospective chart review conducted at Dr TMA Pai Hospital, Udupi (dedicated COVID-19 centre under public-private partnership) after taking permission from the Institute's Ethics Committee. The study was registered with the Clinical Trials Registry of India. The clinical case records of all admitted patients above 18 years with COVID-19 (based on real-time reverse-transcriptase polymerase chain reaction assay) between 1st of May, 2020 and 10th of July, 2020 were screened for eligibility. Those with a history of travel (international/national/state) within one month of the admission were included. After recruitment, the data was entered into a pre-defined case record form. The patients will be categorized into following categories: asymptomatic (No symptoms through-out the course), presymptomatic (No symptoms at the time of swab but developed symptoms later) and symptomatic (symptoms at the time of swab). The symptomatic patients were further categorized into mild, moderate and severe (Table 1). All patients were managed according to the institution protocol that was regularly updated. Routine investigations were done in all the patients - complete blood count (CBC), liver function tests (LFT), renal function tests (RFT), C-reactive protein (CRP) and lactate dehydrogenase (LDH). Ferritin and d-dimer were done on a case to case basis. Asymptomatic patients with mild disease were managed conservatively. They were not given any antivirals, steroids or immunomodulators. Those patients with moderate/severe disease were treated with supplemental oxygen therapy, hydroxychloroquine, low molecular weight heparin and steroids. Awake prone positioning was administered in all patients requiring oxygen. Those who did not respond to oxygen therapy were managed with non-invasive ventilation and mechanical ventilation. Two negative swabs were mandatory for discharge as per the state guidelines in the early part of the study period. The following details were recorded: the demographic profile, risk factors for severe disease (age > 60 years, hypertension, diabetes, chronic kidney disease, chronic lung disease, coronary artery disease, immunosuppression), clinical features, laboratory parameters, Chest X-Ray findings, treatment details and outcome. Based on an online web calculator, the patients were categorized into low (0.7% probability), medium (7.3% probability) and high risk (59.3% probability) of acquiring critical (mechanical ventilation/intensive care/death) illness (5).

Data analysis: continuous data were presented as either mean with standard deviation (SD) or median with interquartile range (IQR) depending on the data distribution. The frequency of categorical variables was expressed in numbers and percentage. The clinical and laboratory parameters were compared between symptomatic patients and asymptomatic patients. Chi-square test was used for categorical variables, and independent *t*-test was used for quantitative variables. A *p*-value of less than 0.05 was considered significant. All analyses were done using SPSSv26.

3. Results

Of the 127 patients, 75 were asymptomatic, and 52 were symptomatic (Table 1). The median duration of illness at admission in the 52 symptomatic patients was 4 (IQR 2.25-6.75) days. The demographic details are summarized in Table 2. The mean age of the patients was 44.5 (SD-15) years. The risk factors for severe disease are summarized in Table 3. A total of 73 patients had one or more risk factors for severity. The median duration from the day of swabbing to admission was 4 (IQR 2-7) days. The clinical features of symptomatic patients are summarized in Table 4. The median duration of illness from travel to admission was 9 (IQR 6-18) days. The mean pulse rate at presentation was 88.8 (SD-14.3) per minute. The mean respiratory rate at presentation was 18.6 (2.9) per minute. The mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) at presentation were 126.9 (SD-18.5) millimetre (mm) of mercury (Hg) and 81.3 (SD-11.3) mm of Hg respectively. The mean saturation (SpO2) was 97.8 (1.8) %. A total of seven patients had Chest X-ray infiltrates (including two patients who were diagnosed with tuberculosis).

Table 1. Breakup of travellers admitted with COVID-19

Staging	Symptoms	Clinical signs of pneumonia	Oxygen Saturation (SpO$_2$) & Respiratory rate (RR) cut off	Number (Percentage)
Asymptomatic	No	No	-	75 (59%)
Mild	Yes	No	RR < 24/min	41 (36.2%)
Moderate	Yes	Yes	RR 24-30/min or SpO$_2$ 90-94%	2 (1.6%)
Severe	Yes	Yes	RR > 30/min, SpO$_2$ < 90%	3 (2.4%)

Table 2. Demographic details of the patients

Demographic details	Frequency (n = 127)	Percentage
Month of Admission		
May	41	32.3%
June	73	57.5%
July (till the 10th of July)	13	10.2%
Travel		
International	12	9.5%
National	107	84.2%
State	8	6.3%
History of contact with a positive patient	11	8.7%
Age		
18-30 years	27	21.2%
31-40 years	34	26.8%
41-50 years	16	12.6%
51-60 years	27	21.2%
> 60 years	23	18.1%
Occupation		
Unemployed	9	7%
Home-maker	35	27.6%
Hotel employee	22	17.3%
Manual labour	6	4.7%
Health care worker	4	3.1%
Student	4	3.1%
Others	47	37%

The laboratory parameters of the admitted patients have been summarized in Table 5. A total of two patients had leucopenia, while five patients had leucocytosis. A total of seven patients had thrombocytopenia. Neutrophil-lymphocyte ratio (NLR) was more than 3 in 31 patients. CRP was elevated (> 5 mg/L) in a total of 46 patients. LDH was elevated (> 280 U/L) in a total of 46 patients. Bilirubin was elevated (> 1.2 mg/dL) in four patients. Aspartate transaminase (AST) (> 40 U/L) and alanine transaminase (ALT) (> 40 U/L) were elevated in 18 and 21 patients respectively. Alkaline phosphatase (ALP) (> 105 U/L) was elevated in 23 patients. Creatinine was elevated (> 1.2 mg/dL) in five patients. Ferritin was done in 76 patients, and the median ferritin value was 202 (95.4-424.5) nanogram per millilitre. D-dimer was done in 56 patients with a median value of 0.3 (0.2-0.48) mcg/mL. D-dimer (> 0.5 mcg/mL) was elevated in 13 patients.

On comparing the clinical and laboratory manifestations of symptomatic *vs.* asymptomatic patients, male patients were more commonly symptomatic than female patients (Table 6). Platelet count, CRP, LDH, AST and ALT were significantly higher in symptomatic

Table 3. Risk factors in patients diagnosed with COVID-19

Clinical details	Total number of patients (127)		Total symptomatic (52)		Moderate/Severe (5)
	Frequency	Percentage	Frequency	Percentage	
Number of risk-factors					
0	52	40.9%	24	46.1%	3
1	39	30.7%	14	26.9%	2
2	19	15%	7	1.9%	0
More than equal to 3	17	13.4%	7	1.9%	0
Risk factors					
Age > 60 years	23	18.1%	9	17.3%	1
Hypertension	40	31.5%	17	32.7%	1
Diabetes mellitus	39	30.7%	16	30.8%	1
Pregnancy	14	11%	2	3.8%	0
Coronary artery disease	6	4.7%	2	3.8%	0
Chronic lung disease	4	3.1%	4	7.7%	0
Human immunodeficiency virus infection	2	1.6%	0	0%	0

Table 4. Clinical features of patients with COVID-19

Clinical details	Frequency	Percentage of total (n = 127)	Percentage of symptomatic (n = 52)
Fever	19	15%	36.5%
Cough	30	23.6%	57.7%
Sore throat	9	7%	17.3%
Rhinitis	6	4.7%	11.5%
Dyspnoea	6	4.7%	11.5%
Headache	3	2.4%	5.8%
Myalgia	2	1.6%	3.8%
Loss of taste	3	2.4%	5.8%
Loss of smell	1	0.8%	1.9%
Chest discomfort	1	0.8%	1.9%
Tachycardia (> 100 per minute)	25	19.7%	48%
Bradycardia (< 60 per minute)	3	2.4%	5.8%
Tachypnoea (> 20 per minute)	31	2.4%	59.6%
Hypotension	0	0%	0%
Hypoxia (< 94%)	5	3.9%	9.6%

Table 5. Laboratory parameters of patients diagnosed with COVID-19

Laboratory parameters	Mean (Standard deviation)	Median (Inter Quartile range)	Reference range
Total leucocyte count (/mcL)	7,300 (2300)		4,000-11,000
Neutrophil-lymphocyte ratio		2.3 (1.7-3.8).	1-3
Platelet count at admission (lakhs/mcL)	2.98 (1.08)		1.5-4
C-reactive protein (mg/L)		3 (1-10.5)	0-5
Lactate dehydrogenase(U/L)	283.4 (106.4)		125-220
Bilirubin (mg/dL)		0.5 (0.3-0.6)	0.3-1.2
Aspartate transaminase (U/L)		23 (18-30.7)	0-40
Alanine transaminase (U/L)		22 (16-32)	0-40
Alkaline phosphatase (U/L)	83.6 (25)		35-105
Creatinine (mg/dL)	0.81 (0.23)		0.7-1.2

Table 6. Asymptomatic *vs.* symptomatic COVID-19

Parameters	Asymptomatic (n = 75)	Symptomatic (n = 52)	p-value
Sex			0.004
Male (n = 84), %	42 (50%)	42 (50%)	
Female (n = 43), %	33 (77%)	10 (23.2%)	
Number of comorbidities, n (%)			0.589
0 (n = 52), %	28 (53.8%)	24 (46.1%)	
1 (n = 39), %	25 (64.1%)	14 (35.9%)	
> 1 (n = 36), %	22 (61.1%)	14 (38.9%)	
Hypertension, n (%) (n = 40), %	23 (57.5%)	17 (42.5%)	0.809
Angiotensin receptor blocker (n = 15), %	9 (60%)	6 (40%)	0.937
Diabetes (n = 39), %	23 (59%)	16 (41%)	0.990
Pregnancy (n = 14), %	12 (85.7%)	2 (14.3%)	0.03
Age > 60 years (n = 23), %	14 (60.9%)	9 (39.1%)	0.84
Mean total leucocyte count in /mcL (Standard deviation)	7460 (2243)	6973 (2294)	0.877
Median neutrophil lymphocyte ratio (Inter-quartile range)	2.3 (1.7-3.6)	2.4 (1.7-3.8)	0.850
Mean platelet in lakhs/mcL (Standard deviation)	2.8 (1.6)	3.2 (1.2)	0.04
Median C-reactive protein in mg/L (Inter-quartile range)	2 (1-5)	7 (1.2-51.2)	0.001
Mean Lactate dehydrogenase in U/L (Standard deviation)	253 (67)	315 (138)	< 0.001
Median Aspartate transaminase in U/L (Inter-quartile range)	21 (16-25)	27.5 (20.2-44)	< 0.001
Median Alanine transaminase in U/L (Inter-quartile range)	18 (14-27)	28 (20.2-48.7)	0.001
Mean Alkaline phosphatase in U/L (Standard deviation)	82.8 (24)	83.9 (26.3)	0.813
Mean Bilirubin in mg/dL (Standard deviation)	0.5 (0.2)	0.6 (0.3)	0.109
Mean Creatinine in mg/dL (Standard deviation)	0.8 (0.2)	0.9 (0.2)	0.384

patients than asymptomatic patients (Table 6).

A total of five individuals required oxygen. The day of oxygen requirement from the day of onset of illness ranged from 6-10 days. Two of these patients developed acute respiratory distress syndrome (ARDS) in the disease course, and one of them required mechanical ventilation. The risk of developing critical illness according to the COVID GRAM calculator was as follows: low (n = 61), moderate (n = 63) and high risk (n = 3). Of the five patients who eventually required oxygen, three were categorized as high risk while the other two were classified as moderate risk (*5*).

A total of 15 hypertensive patients were on angiotensin receptor blockers. The number of patients who were given hydroxychloroquine (HCQ), low-molecular-weight heparin, steroids and antibiotics (ceftriaxone) was 5, 5, 2 and 5, respectively. All patients recovered eventually and were discharged. The mean duration of admission was 10.6 (SD-4.7) days. Repeat polymerase chain reaction assay (PCR) to demonstrate negativity was done in 64 patients, and the mean duration from the first positive swab to the first negative swab was 15.3 (SD-5.5) days. This period was significantly different between the asymptomatic and symptomatic group (16.2 *vs.* 13.6 days, *p*-value-0.04).

4. Discussion

Asymptomatic transmission of COVID-19 was initially described in household contacts of positive patients from China (*7-9*). The percentage of asymptomatic COVID-19 in positive patients from China ranged from 1.2-11% (*10-13*). However, the rate of individuals with asymptomatic COVID-19 depends highly on the testing strategies as asymptomatic individuals are unlikely to report to the hospital. In estimates derived after statistical modelling from individuals evacuated from China or individuals trapped in the Diamond Princess cruise, the proportion of asymptomatic cases ranged from 17.9% to 30.8% (Table 7) (*3,4*). In our cohort,

Table 7. Studies on transmission dynamics of SARS-CoV-2

S.N	Author Details	Type of study	Population and Sample size	Results
1	Bai *et al.*, China	Familial cluster		5 patients infected from one asymptomatic patient
2	Zhang *et al.*, China	Familial cluster		4 patients infected from one asymptomatic patient
3	Luo Y *et al.*, China	Familial cluster		4/5 household contacts of a symptomatic physician were positive but asymptomatic
4	NCPERE team, China	Retrospective review of records	72,314 patients (including positive and suspected)	1.2% asymptomatic
5	Wang *et al.*, China	Retrospective review of records	1,012 non-critically ill positive patients	3% asymptomatic
6	Dong *et al.*, China	Retrospective review of records	2,135 positive paediatric patients	4.4% asymptomatic
7	Zhu *et al.*, China	Meta-analysis	3,062 positive patients	11% asymptomatic
8	Nishiura *et al.*, Japan	Statistical modelling	565 evacuated individuals (9 symptomatic positives, 4 asymptomatic positives)	Asymptomatic proportion- 31%
9	Mizumoto *et al.*, Japan	Statistical modelling	634 positive in Diamond princess cruise	Asymptomatic proportion- 18%
10	Hu *et al.*, China	Case series	24 asymptomatic positive patients at presentation	21 % eventually developed symptoms (presymptomatic)
11	Meng *et al.*, China	Case series	58 asymptomatic positive patients at presentation	28% eventually developed symptoms (presymptomatic)
12	An *et al.*, China	Case series	25 asymptomatic patients at presentation	36% eventually developed symptoms (presymptomatic)
13	Zhou *et al.*, China	Case series	13 asymptomatic patients at presentation	23% eventually developed symptoms (presymptomatic)
14	Samsami *et al.*, China	Case series	8 asymptomatic patients at presentation	25% eventually developed symptoms (presymptomatic)
15	Kimball *et al.*, USA	Outbreak	76 exposed patients (23 positives)	56% asymptomatic at presentation (77% of which were presymptomatic)
16	Arons *et al.*, USA	Outbreak	76 exposed patients (48 positives)	56% asymptomatic at presentation (89 % of which were presymptomatic)

because all travellers were screened irrespective of the symptoms and were admitted irrespective of the severity, the percentage of asymptomatic individuals was higher (59%).

It is pertinent to distinguish individuals who remain asymptomatic throughout and individuals who are asymptomatic at presentation but develop symptoms later (presymptomatic). The proportion of presymptomatic individuals in patients who are asymptomatic at presentation varies from 21-89% (Table 7) (*14-20*). In our study, the number of presymptomatic individuals was only three. The ability of an asymptomatic or a presymptomatic individual to transmit infection was initially questioned. Still, it was found in an outbreak from a skilled nursing facility in the USA, that viral load in all three groups (symptomatic, presymptomatic and asymptomatic) were equally high. Of the 24 specimens collected from presymptomatic individuals, 17 specimens were also viable on culture. In another study of 2001 contacts of 157 symptomatic and 146 contacts of 30 asymptomatic cases, infection rates were 6% and 4% respectively (*21*). The difference in infectivity of symptomatic and asymptomatic cases was found to be statistically insignificant by the authors.

The spectrum of symptomatic patients with COVID-19 ranges from mild to severe. In a large report from China, the proportion of mild patients among all symptomatic patients was 81%. The risk factors for severe disease in patients with COVID-19 ranges from cardiovascular disease, diabetes mellitus, hypertension, chronic lung disease and immunosuppressive conditions. In a study, the mean number of comorbidities in patients who died was 2.7 (*25*). In another study, the mortality rate was significantly higher in those with comorbidities than those without comorbidities (*26*). Similar to our study, male sex was associated with more severe illness (*27,28*). Older age has also been associated with severe disease and mortality (*25,29*). Infection with respiratory viruses (influenza, SARS-CoV-1) has shown to affect pregnant women disproportionately in terms of increased severity and adverse outcomes (*30*). The data on the effect of this virus on maternal and fetal well-being is still evolving. The percentage of asymptomatic pregnant patients ranges from 23 to 33%, while the percentage of severe pregnant patients ranges from 5% to 14% (*31-34*). In our series, a total of 14 patients in various trimesters of pregnancy were identified. Except for two pregnant patients who had a mild illness, all the other patients were asymptomatic (86%). In a case-control study by Li *et al.*, maternal complications were higher in pregnant women with suspected/confirmed COVID-19 compared to controls (pregnant women without COVID-19) (Table 8) (*35*). Like our study, high NLR, thrombocytopenia, transaminitis, raised

Table 8. Maternal and foetal outcomes of COVID-19 cases

S.n	Author Details	Type of study	Population and Sample size	Results
1	Breslin *et al.*, USA	Case series	43 COVID-19 positive pregnant patients	33% asymptomatic at presentation. 9% severe and 5% critical
2	Ferrazzi *et al.*, Italy	Case series	42 COVID-19 positive pregnant patients	37% required oxygen support (*21*)
3	Yang *et al.*	Review of published cases	114 COVID-19 positive pregnant women	5% of the patients had severe/critical illness
4	Yan *et al.*, China	Case series	116 COVID-19 positive pregnant patients	23% were asymptomatic at presentation, while 7% had severe symptoms
5	Li *et al.*, China	Case-control study	Cases- Pregnant women with COVID-19, Controls- Pregnant patients without COVID-19	Maternal complications were higher in cases

inflammatory marker, raised troponin and raised d-dimer are associated with poorer outcomes (*36-38*).

The most common initial symptoms in patients with COVID are fever, cough, myalgia, rhinitis, diarrhoea, loss of smell and taste (*26*). It is pertinent to note that even though several guidelines include fever as the entry criteria for suspicion, it is present only in 31-46% of the patients in various studies. Similar results were noted in our research as well (*26,39*). The smell and taste alterations in COVID are more subjective than objective, thereby explaining the wide range of prevalence (5 to 98%) in various studies (*40,41*). Most patients with mild symptoms at onset recover without any further progression. A fraction of these patients may develop dyspnea. Like our study, the mean duration of dyspnea development ranges from 5-8 days (*42,43*).

Compared to other studies that report the case-fatality in the range of 1-12%, our outcome was excellent despite our restricted use of antivirals (*22-24*). This could have been because of many reasons. Those patients who were relatively healthy would have decided to travel, and therefore, our cohort may have been healthier at baseline than other hospital cohorts. Since this was the beginning of the pandemic, all patients were tested and were admitted in an institutional setting. This would have led to the inclusion of more asymptomatic patients leading to early identification of worsening and prompt management. Also, because it was the early part of the pandemic, the hospital resources (human resources and beds) were adequate to manage these patients in the best possible manner.

Apart from the limitations associated with the study's retrospective nature, the discharge criteria changed in the middle of the study period. Consequently, time to negativity could not be calculated in all the patients.

The possibility of transmission from asymptomatic cases which form a significant proportion of total positive patients but are missed on symptom-based screening calls for adherence to preventive measures such as physical distancing, frequent handwashing, wearing of masks in the community and universal masking. Since patients with asymptomatic and mild illness have excellent outcomes without any therapeutic interventions, unnecessary and unproven medications

should be avoided in such patients. These patients can also be managed in-home isolation (with monitoring) to decrease the burden on tertiary care hospitals.

Acknowledgements

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