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 throughout 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.

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).

| Staging   | Symptoms | Clinical signs of pneumonia | Oxygen Saturation (SpO2) & 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 SpO2 > 90-94%                            | 2 (1.6%)            |
| Severe    | Yes      | Yes                         | RR > 30/min, SpO2 < 90%                                  | 3 (2.4%)            |

Table 1. Breakup of travellers admitted with COVID-19
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 patients. The clinical details and frequency of occurrence are given in Table 4. The percentage of total and symptomatic patients have been calculated. The percentage of moderate/severe patients is also given in Table 4.
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 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)              | 2.3 (1.7-3.8)                 | 4,000-11,000   |
| Neutrophil-lymphocyte ratio           |                           | 3 (1-10.5)                   | 0-5            |
| Platelet count at admission (lakhs/mcL)| 2.98 (1.08)               |                               | 1-3            |
| C-reactive protein (mg/L)             |                           | 5.0 (0.3-0.6)                | 0.3-1.2        |
| Lactate dehydrogenase(U/L)            | 283.4 (106.4)             |                               | 125-220        |
| Bilirubin (mg/dL)                     |                           | 25 (18-30.7)                 | 0-40           |
| Aspartate transaminase (U/L)          |                           | 22 (16-32)                   | 0-40           |
| Alanine transaminase (U/L)            |                           | 83.6 (25)                    | 35-105         |
| Alkaline phosphatase (U/L)            |                           | 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 (60.99%)           | 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/ml (Standard deviation) | 2.8 (1.6)             | 3.2 (1.2)            | 0.04    |
| Mean 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 |
| Mean Aspartate transaminase in U/L (Inter-quartile range) | 21 (16-25)            | 27.5 (20-22-44)      | < 0.001 |
| Mean Alanine transaminase in U/L (Inter-quartile range) | 18 (14-27)            | 28 (20-24-87)        | 0.001   |
| Mean Alkaline phosphatase in U/L (Standard deviation) | 82.8 (24)             | 83.9 (263)           | 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   |
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 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 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)                                        |
| 5   | Wang et al., China      | Retrospective review of records    | 1,012 non-critically ill positive patients                                                 |
| 6   | Dong et al., China      | Retrospective review of records    | 2,135 positive paediatric patients                                                       |
| 7   | Zhu et al., China       | Meta-analysis                       | 3,062 positive patients                                                                  |
| 8   | Nishiura et al., Japan  | Statistical modelling              | 565 evacuated individuals (9 symptomatic positives, 4 asymptomatic positives)            |
| 9   | Mizumoto et al., Japan  | Statistical modelling              | Asymptomatic proportion- 18%                                                             |
| 10  | Hu et al., China        | Case series                         | 634 positive in Diamond princess cruise                                                   |
| 11  | Meng et al., China      | Case series                         | 24 asymptomatic positive patients at presentation                                        |
| 12  | An et al., China        | Case series                         | 58 asymptomatic positive patients at presentation                                        |
| 13  | Zhou et al., China      | Case series                         | 25 asymptomatic patients at presentation                                                  |
| 14  | Samsami et al., China   | Case series                         | 13 asymptomatic patients at presentation                                                  |
| 15  | Kimball et al., USA     | Outbreak                            | 8 asymptomatic patients at presentation                                                   |
| 16  | Arons et al., USA       | Outbreak                            | 76 exposed patients (23 positives)                                                        |
|     |                         |                                    | 76 exposed patients (48 positives)                                                        |

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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

Authors gratefully acknowledge the Department of Health and Family Welfare, Udupi District, Government of Karnataka for granting permission to undertake the study.

Funding: None.

Conflict of Interest: The authors have no conflicts of interest to disclose.

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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 |

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Received August 10, 2020; Revised February 9, 2021; Accepted February 26, 2021.

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Released online in J-STAGE as advance publication February 28, 2021.