

Asymptomatic Coronavirus Disease 2019 (COVID-19) Carriers: Are They Infectious?

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Abstract Coronavirus disease 2019 (COVID-19) is highly contagious in symptomatic patients as it is thought to be transmitted through respiratory droplets. However, it is debatable whether asymptomatic COVID-19 patients are contagious due to lack of data. From 1st March to 15th April 2020, a total of 247 COVID-19 cases were admitted to Tengku Ampuan Afzan Hospital and 1010 close contacts were identified. We studied the epidemiological and clinical outcomes in asymptomatic subjects, as well as estimated the metrics of disease transmission between asymptomatic, symptomatic, and pneumonia subjects. From a total of 125 asymptomatic subjects, majority (n=116, 92.8%) remained asymptomatic upon discharge. Only 9 (7.2%) subjects developed mild symptoms after admission. Seven subjects had abnormal chest radiograph suggestive of pneumonia, and 22 subjects (17.6%) were found to have mild liver impairment. None of the asymptomatic subjects required oxygen support, inotropic support or ICU care during admission. Fifteen second generation COVID-19 cases were found transmitted from the asymptomatic group, with an attack rate of 3.9%, which was statistically significantly lower compared to the symptomatic (7.6%) or pneumonia groups (25.7%, $p < 0.001$). In conclusion, asymptomatic COVID-19 patients show excellent clinical outcome. They are infectious but had a lower transmission risk compared with symptomatic or pneumonia patients.

Keywords: Asymptomatic COVID-19 patients, clinical outcome, Coronavirus disease 2019 (COVID-19), Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), Transmission risk

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1. Introduction

Coronavirus disease 2019 (COVID-19), which was first reported in December 2019 in Wuhan, China, was declared a pandemic disease by the World Health Organization (WHO) on 12 March 2020 [1]. The first COVID-19 case in Malaysia was detected on 25th January 2020 [2]. Following that, there was a massive spike of cases that emerged in March, which was linked to a religious gathering held in Sri Petaling, Kuala Lumpur [3]. Within one month, Malaysia had recorded the largest cumulative number of confirmed COVID-19 infections in Southeast Asia, breaching over 3000 active cases by 3rd April 2020 [1].

COVID-19 is highly contagious in symptomatic patients as it is thought to be transmitted through respiratory droplets [4]. Zou et al [5]. reported that higher viral loads were detected soon after symptoms onset. On the other hand, it is debatable whether asymptomatic

COVID-19 patients are contagious due to a lack of data. To date, there are conflicting data regarding the risk of transmission among asymptomatic patients. In a recent paper, He et al. reported 6 cases that were transmitted from 30 asymptomatic cases in Ningbo, China [6]. Chan et al. reported a case of transmission from an asymptomatic patient to the family members, which led to severe pneumonia [7]. On the other hand, Cheng et al. reported that none of the 9 asymptomatic patients transmitted COVID-19 to others [8].

Prompt public health measures were taken in Malaysia, including intensive surveillance and routine hospitalization for all classes of COVID-19 patients, including asymptomatic individuals [3]. Tengku Ampuan Afzan Hospital (HTAA) is a general hospital and the only hospital designated to treat patients with COVID-19 in Pahang state, with a population of 1.6 million. In this study, we aim to evaluate the outcome of asymptomatic COVID-19 patients. We also want to determine the attack rate of asymptomatic patients compared to patients who are symptomatic with

or without pneumonia. These data are important for better disease control measures.

2. Methods

This is a retrospective study performed at HTAA, Malaysia, from 1st March 2020 until 15th April 2020. A total of 247 adult patients with COVID-19 infection were admitted to HTAA during this period. All patients had tested positive for COVID-19 via laboratory testing with real-time reverse transcriptase polymerase chain reaction (RT-PCR) of respiratory secretions obtained by nasopharyngeal or oropharyngeal swab. All patients had a chest X-ray performed on admission and repeated on a weekly basis as part of the management protocol. Swabs were repeated on day 13 following the last contact and those with negative results were subsequently discharged. We analyzed all asymptomatic patients aged >18 years. Their demographic data, laboratory results, and clinical outcome were reviewed. Those patients who had symptoms after contact but were asymptomatic on admission were excluded (Figure 1).

Thorough contact tracing was implemented by the outbreak investigation team of the Pahang Centers for Disease Control and Prevention (CDC) and District Health Office. Close contacts were identified according to WHO guidelines. The definition involved persons who experienced face-to-face contact within 1 meter and for

more than 15 minutes, direct physical contact or direct care for a patient with probable or confirmed COVID-19, without appropriate proper personal protective equipment, in the 2 days before and 14 days after the onset of symptoms [9]. If the first swab was negative, a second swab was taken 13 days after the last close contact with positive subjects. For the analysis of transmission, data from close contacts were obtained from Pahang Disease Control and Prevention. Close contacts who had multiple contacts with confirmed cases were excluded from analysis because we were not able to ascertain the source of infection. This included group travelers who were travelling with asymptomatic patients, students from boarding schools who stayed together and colleagues who work in the same environment. Attack rate was calculated by the total number of infected close contacts divided by close contacts screened.

For the purpose of comparison, we also analyzed attack rate among those patients who were symptomatic, as well as in those with pneumonia. The definitions are as follows:

(1) Asymptomatic: A person infected with COVID-19 who does not develop symptoms [10].

(2) Symptomatic: a case who had developed signs and symptoms compatible with COVID-19 infection but who does not have clinical or radiological evidence of pneumonia.

(3) Pneumonia: a case infected with COVID-19 who has clinical and radiological confirmation of pneumonia.

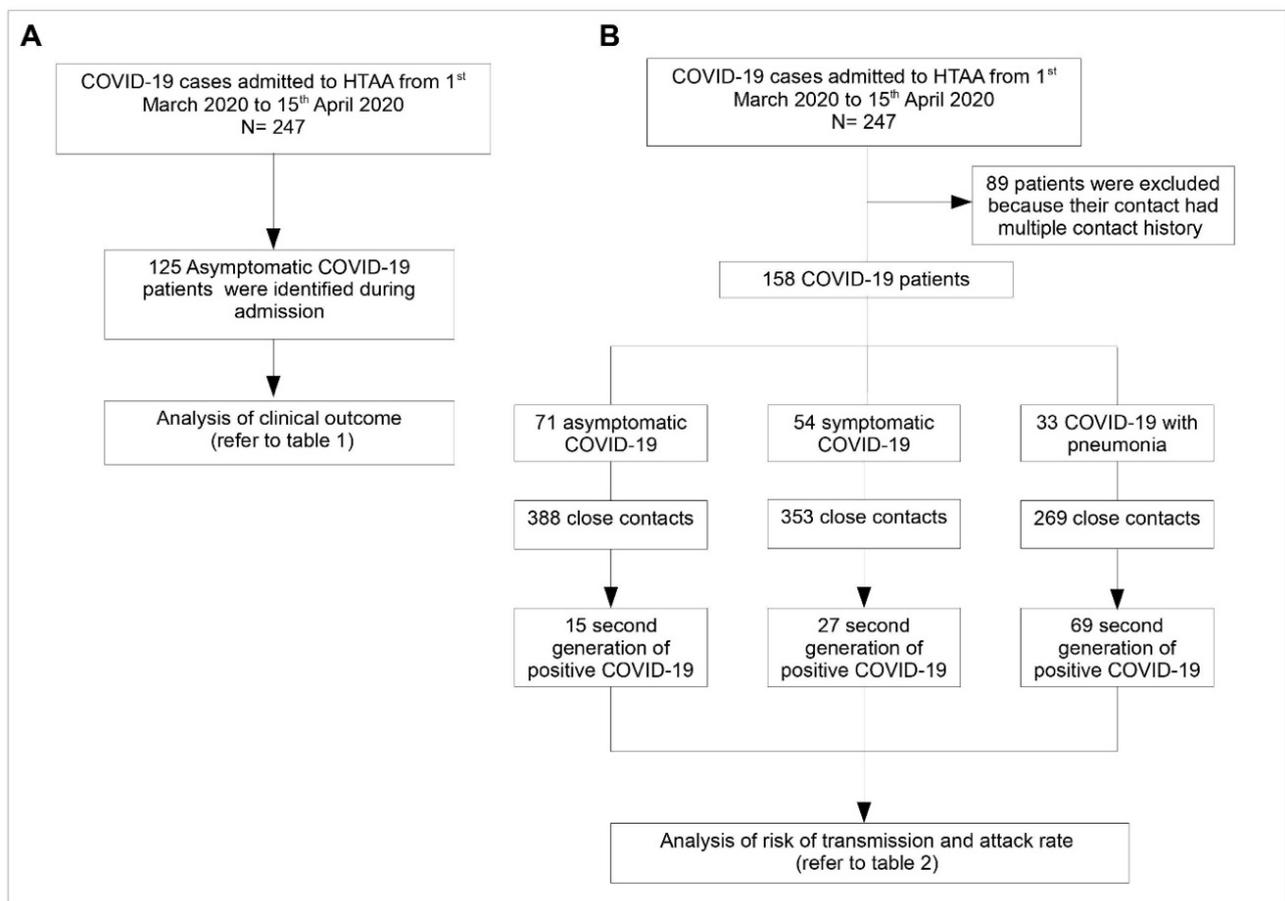


Figure 1. A) Flow chart regarding data collection and clinical outcome analysis of asymptomatic COVID-19 subjects. B) Transmission risk analysis between asymptomatic, symptomatic and pneumonia subjects

3. Results

A total of 247 cases were admitted and 125 subjects who were asymptomatic during laboratory confirmation for SARS-CoV-2 RT-PCR were identified. These included 88 male and 37 female patients, with a median age of 24 years old (ranging from 18 to 62). Comorbidities were identified in 25 cases (20.0%), with hypertension and diabetes mellitus being the most common (Table 1).

Asymptomatic patients were only on supportive treatment. Symptomatic patients were given tablet Chloroquine 500mg BD for 5 days while patients with pneumonia were treated with Lopinavir 200mg /Ritonavir 50mg 2 tablet BD for 7 - 10 days. Of the 125 subjects who were asymptomatic at admission, surprisingly, 116 (92.8%) remained asymptomatic throughout the entire admission period. There were only 9 subjects (7.2%) who developed mild symptoms. Cough (33%) was the most common symptom followed by diarrhea (22%). The interval between last contact with positive COVID-19 patients and symptoms onset was 6-14 days. On admission, all asymptomatic patients underwent a routine chest radiograph, which showed pneumonia in 7 asymptomatic subjects. Notably, none of them required oxygen therapy during admission.

Twenty-two subjects (17.6%) were found to have mild liver impairment, with alanine aminotransferase (ALT) or

aspartate aminotransferase (AST) levels less than 5 times the normal upper limit. None of these individuals developed acute liver failure. There were no cardiac or renal complications in any of the asymptomatic subjects, and none of them required inotropic support or hemodialysis. The majority (92%) of asymptomatic patients exhibited a normal lymphocyte count, with only 8% developing lymphopenia. In addition, 11% had CRP elevated to more than 8mg/L, with the highest CRP level being 31 mg/L. All patients recovered and were discharged from home without requiring oxygen therapy or intensive care.

Of the 247 COVID-19 patients who were admitted to HTAA, 89 patients were excluded from analysis for the reasons explained in the methods section. Overall, 388 close contacts were screen after exposure to 71 asymptomatic patients, and 15 secondary cases of COVID-19 infection were detected, with an attack rate of 3.9% (Table 2). Among these 15 secondary cases, 12 were household contacts and another 3 were friends of asymptomatic patients. Notably, the attack rate of pneumonia patients is 25.7%, which is eight times higher compared with asymptomatic patients. The attack rate of pneumonia patient is statistically significantly higher compared to symptomatic or asymptomatic patients ($p < 0.001$).

Table 1. General characteristics, laboratory data and outcome of asymptomatic COVID-19 patients

Data	Patients by infection classification, No (%)		
	Total (N = 125)	Remains Asymptomatic (n = 116 [92.8%])	Develop Symptoms (n = 9 [7.2%])
Age, median (IQR) years	24 (18-35)	24 (18-35)	19 (18-29)
Sex			
Male	88 (70.4)	82 (65.6)	6 (4.8)
Female	37 (29.6)	34 (27.2)	3 (2.4)
Comorbidities			
Diabetes	6 (4.8)	5 (4.0)	1 (0.8)
Hypertension	12 (9.6)	11 (8.8)	1 (0.8)
Asthma	4 (3.2)	2 (1.6)	2 (1.6)
COPD	1 (0.8)	1 (0.8)	0 (0.0)
CKD	2 (1.6)	2 (1.6)	0 (0.0)
Time interval, median (time), day			
From last contact to positive SARS-CoV-2 RT-PCR result	6 (2.5-1.2)	5.5 (2.0-13.0)	9.0 (4.0-9.0)
From last contact to illness onset ^a	-	-	11.50 (6.00-14.00)
Investigations			
Elevated TWC count ($>11 \times 10^9/L$)	22 (17.6)	20 (16.0)	2 (1.6)
Decreased TWC count ($<4.0 \times 10^9/L$)	2 (1.6)	2 (1.6)	0 (0.0)
Decreased lymphocyte count ($<1.5 \times 10^9/L$)	10 (8.0)	10 (8.0)	0 (0.0)
Elevated CRP($>8mg/L$)	14 (11.2)	12 (9.6)	2 (1.6)
Abnormal chest x ray	7 (5.6)	7 (5.6)	
Liver enzyme alteration			
Mild (ALT/AST ULN -5 x ULN)	22 (17.6)	20 (16.0)	2 (1.6)
Moderate (ASLT/AST 5-10 x ULN)	1 (0.8)	1 (0.8)	0 (0.0)
Marked (ALT/AST $>10 \times$ ULN)	0 (0.0)	0 (0.0)	0 (0.0)
Adverse outcome			
AKI ^b / Dialysis/ Inotropic support/Heart failure / cardiac arrhythmia/ICU admission	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: ALT, Alanine Aminotransferase; AST, Aspartate aminotransferase; CRP, C-Reactive Protein; ICU, Intensive care Unit; SARS-CoV-2-PCR, Severe Acute Respiratory Syndrome Coronavirus Real-time Reverse Transcriptase Polymerase Chain Reaction; ULN, Upper Limit of Normal; WBC, White Blood Cell.

^aIllness onset was defined as the appearance of signs and symptoms compatible with COVID-19 infections.

^bAcute kidney injury was defined according to KDIGO guidelines. [11]

Table 2. Analysis of attack rate between Asymptomatic, symptomatic and pneumonia patients with COVID-19.

Group	1 st generation	Total number of close contacts	Attack rate ^a (%)	Number of close contacts infected (2 nd generation)		Pearson Chi-Square (df)	P-value
				Yes (%)	No (%)		
Asymptomatic	71	388	3.9	15 (3.9)	373 (96.1)	83.262	<0.001
Symptomatic	54	353	7.6	27 (7.6)	326 (92.4)		
Pneumonia	33	269	25.7	69 (25.7)	200 (74.3)		

^aAttack rate: number of infected 2nd generation individuals divided by total number of close contact individuals.

4. Discussion

Our study confirms that asymptomatic adults with COVID-19 have an excellent clinical outcome. None of them required oxygen care, ICU admission or developed organ failure. Among our asymptomatic patients, only 5.6% had abnormal chest radiographs. In comparison with a study performed in Shenzhen, China, looking at 55 asymptomatic patients who were admitted to hospital, reported higher incidence (67%) of pneumonia changes on computerized tomography (CT) scan of the thorax [12]. This may be due to different modalities used for imaging, as CT scans are more sensitive than chest radiographs to detect pneumonia changes. In their study, two patients older than 60 years with comorbidities developed hypoxia requiring oxygen therapy, but none required intensive care and they were discharged well [12]. In our study, there were three patients older than 60 years with comorbidities, none of which required oxygen therapy. More data are needed on the clinical outcome of asymptomatic patients with co-morbidities, especially in the elderly.

Our study confirms that asymptomatic patients can transmit the disease to others, even though the risk of transmission is lower compared to that seen in symptomatic patients as well as in patients with pneumonia. This is consistent with another four case series that reported asymptomatic transmission in China and Germany [13,14,15,16]. In addition, there are a few virological studies that suggest the transmission of COVID-19 from asymptomatic or pre-symptomatic patients [17,18,19,20]. Le et al. reported viral shedding in an asymptomatic patient [19]. However, a positive PCR result reflects only the detection of viral RNA and does not necessarily indicate presence of viable virus [21]. The presence of viable virus is proven by Hoehl et al [17], who managed to isolate a positive culture of SARS-CoV-2 virus from two asymptomatic patients. Both epidemiological and virological reports further support the risk of transmission during the asymptomatic period and more importantly, among patients who are totally asymptomatic, as shown in our study.

This study has several implications for public health disease control measures. One of the most important findings of the current study is that asymptomatic COVID-19 patients contribute to half of the cases in Pahang, and all of them were identified through contact screening. This highlights the fact that comprehensive contact tracing from local health authorities and strict isolation is important to prevent silent transmission from asymptomatic individuals to others. In Malaysia, all COVID-19 confirmed patients are routinely hospitalized, regardless whether they are symptomatic or not. Our study

confirmed that asymptomatic COVID-19 patients had an excellent clinical outcome. Therefore, they may not need to be admitted to hospital, especially to a tertiary care hospital. Furthermore, admitting all asymptomatic COVID-19 individuals could expose healthcare workers to the risk of a potential nosocomial outbreak. Since asymptomatic COVID-19 individuals are infectious, they need to be isolated, either at home or in designated dormitory care, but with immediate access to a hospital if patients develop worsening symptoms. Home isolation may raise compliance issues. The strategy of not admitting them to tertiary care hospitals is to prevent overwhelming healthcare facilities, as this may compromise the care of non-COVID-19 patients.

We have a relatively large cohort of asymptomatic COVID-19 patients which shows good clinical outcomes. However, larger-scale multicenter studies are needed to verify our findings. Secondly, there is still the possibility of missing carriers when screening contacts using pharyngeal swab specimens. We found that most of the close contacts who were infected by asymptomatic patients were household contacts, where it is quite difficult to avoid transmission. However, a few transmission cases were from friends of patients, so it is important to get details of possible modes of transmission between friends. Studies should investigate whether wearing a mask, physical distancing or hand washing can reduce the risk of transmission.

5. Conclusions

In conclusion, asymptomatic COVID-19 patients have excellent clinical outcomes and a lower transmission risk compared to the symptomatic or pneumonia groups. However, the existence of transmission from asymptomatic individuals raises the alarm of prompt public health measures such as comprehensive contact tracing and strict isolation to prevent further spread of the disease.

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Declaration of Conflict of Interest

No conflict of Interest declared.

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