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Brief Communication

Clinical and Laboratory Factors Associated with Symptom Development in Asymptomatic COVID-19 Patients at the Time of Diagnosis

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ABSTRACT

In preparation for the surge of coronavirus disease 2019 (COVID-19), it is crucial to allocate medical resources efficiently for distinguishing people who remain asymptomatic until the end of the disease. Between January 27, 2020, and April 21, 2020, 517 COVID-19 cases from 13 healthcare facilities in Gyeonggi province, Korea, were identified out of which the epidemiologic and clinical information of 66 asymptomatic patients at the time of diagnosis were analyzed retrospectively. An exposure-diagnosis interval within 7 days and abnormal aspartate aminotransferase levels were identified as characteristic symptom development in asymptomatic COVID-19 patients. If asymptomatic patients without these characteristics at the time of diagnosis could be differentiated early, more medical resources could be secured for mild or moderate cases in this COVID-19 surge.

Keywords: COVID-19; SARS-CoV-2; Asymptomatic; Symptom development; Medical resource allocation

Coronavirus disease 2019 (COVID-19) originated in China in 2019 and soon became a pandemic [1]. However, newly developed COVID-19 vaccines have been distributed globally in early 2021 to manage the ongoing pandemic [2]. Asymptomatic patients were rapidly diagnosed in Korea through aggressive tracing and testing during the early phase of this pandemic [3]. Early identification of asymptomatic patients from mild or moderate cases

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Conflict of Interest
No conflicts of interest.

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is important while preparing to control this pandemic surge for efficient management of medical resources. People who remain asymptomatic until the end of the disease, if predicted in advance will help them isolate through home management [4] and not in a healthcare facility. For this reason, it is imperative to understand the clinical and laboratory factors associated with symptom development in asymptomatic patients at the time of diagnosis.

Between January 27, 2020, and April 21, 2020, 517 COVID-19 cases, from 13 healthcare facilities in Gyeonggi province, Korea was identified out of which 72 (13.9%) was found to be asymptomatic at the time of diagnosis. All confirmed patients were admitted and isolated during the early phase of the pandemic. Clinical information through medical records, including vital signs, laboratory results, and daily attending doctor and nurse progression notes using standardized uniform case record form, was retrospectively reviewed by the researchers thoroughly at each facility. This study was approved by the Institutional Ethics Review Board of Seoul National University Bundang Hospital (No. B-2005-612-108). The median age of 72 asymptomatic cases was 50.5 years [interquartile range (IQR), 28 - 61 years]. Six cases were under the age of 18 and hence, were excluded from this study. Among the 66 patients, 38 (57.6%) were over 50 years old and 24 (46.4%) had one or more underlying diseases. Exposure dates were confirmed in 39 (59.1%) cases and 33 (50.0%) asymptomatic patients who developed symptoms during hospitalization. The median duration of isolation was 10 days (IQR, 6 - 16 days).

Patients who were asymptomatic till the end of the disease were defined as 'asymptomatic group' and patients who developed symptoms during the illness were defined as 'pre-symptomatic group'. Out of the patients whose exposure date was confirmed, 17 (51.5%) were asymptomatic till the date of discharge, while 22 (66.6%) developed clinical symptoms during hospitalization. The median age of the asymptomatic and the pre-symptomatic groups was 50 years (IQR, 28.5 - 59.5) and 54 years (IQR, 39.5 - 64.5), respectively. The total number of male patients in the asymptomatic and the pre-symptomatic groups were 15 (45.5%) and 9 (27.3%). The laboratory test results revealed a significantly decreased initial hemoglobin level (g/dL) (13.5 ± 1.4 *vs.* 14.2 ± 1.3) and a significantly increased aspartate aminotransferase (AST) level (IU/L) (30.3 ± 11.6 *vs.* 24.6 ± 6.5) in the pre-symptomatic group compared to the asymptomatic group (P = 0.037 and 0.021, respectively). Chest X-ray showing abnormal findings were detected in 8 (26.7%) cases of the asymptomatic group and in 5 (18.5%) cases in the symptomatic group. The disease was diagnosed 7 days following exposure in 15 (88.2%) and 8 (36.4%) patients of the asymptomatic and pre-symptomatic groups, respectively (P = 0.001). Detailed demographics and clinical presentation of the patients are listed in **Table 1**. There was no significant difference in cycled-time value of real time reverse transcription polymerase chain reaction (RT-PCR) between the two groups (**Fig. 1**).

Table 1. Clinical characteristics and laboratory findings of asymptomatic COVID-19 patients at the time of diagnosis

Variables	Total (n = 66)	Asymptomatic group (n = 33)	Pre-symptomatic group (n = 33)	*P*-value
Age, median (IQR), years	51.5 (30.5, 61.2)	50 (28.5, 59.5)	54 (39.5, 64.5)	0.325
Age-group, years				0.455
18 - 49	28 (42.4)	16 (48.5)	12 (36.4)	
Over 50	39 (57.6)	17 (51.5)	21 (63.6)	
Male, n (%)	24 (36.4)	15 (45.5)	9 (27.3)	0.125

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Table 1. (Continued) Clinical characteristics and laboratory findings of asymptomatic COVID-19 patients at the time of diagnosis

Variables	Total (n = 66)	Asymptomatic group (n = 33)	Pre-symptomatic group (n = 33)	*P*-value
No. of Underlying medical conditions, n (%)				0.609
None	42 (63.6)	22 (66.7)	20 (60.6)	
1	13 (19.7)	7 (21.2)	6 (18.2)	
Over 2	11 (16.7)	4 (12.1)	7 (21.2)	
Underlying medical conditions, n (%)				
Diabetes mellitus	8 (12.1)	5 (15.2)	3 (9.1)	0.708
Hypertension	17 (25.8)	6 (18.2)	11 (33.3)	0.159
Smoking	6 (9.1)	5 (15.2)	1 (3.0)	0.197
Symptoms, n (%)				N/A
Fever (>37.5°C)	14 (21.2)	-	14 (42.4)	
Cough	8 (12.1)	-	8 (24.2)	
Rhinorrhea/Nasal obstruction	6 (9.1)	-	6 (18.2)	
Diarrhea	6 (9.1)	-	6 (18.2)	
Sore throat	5 (7.6)	-	5 (15.2)	
Hyposmia	4 (6.1)	-	4 (12.1)	
Myalgia	4 (6.1)	-	4 (12.1)	
Nausea/Vomiting	4 (6.1)	-	4 (12.1)	
Headache	3 (4.6)	-	3 (9.1)	
Sputum	3 (4.6)	-	3 (9.1)	
Dyspnea	3 (4.6)	-	3 (9.1)	
Change in mental status	1 (1.5)	-	1 (3.0)	
Chest pain	1 (1.5)	-	1 (3.0)	
Abdominal pain	1 (1.5)	-	1 (3.0)	
Initial laboratory findings				
WBC (/mm^3, mean ± SD)	6,232.7 ± 2,406.9	6,222.1 ± 2,260.6	6,243.7 ± 2,585.4	0.971
Neutrophil, increased (>74%)	11 (16.6)	5 (15.2)	6 (18.2)	0.751
Neutrophil, without increased (≤74%)	54 (83.4)	28 (84.8)	25 (75.8)	
Lymphocyte, decreased (<18%)	13 (20.0)	6 (18.2)	7 (21.2)	0.764
Lymphocyte, without decreased (≥18%)	52 (80.0)	27 (81.8)	25 (75.8)	
Hemoglobin (g/dL, mean ± SD)	13.9 ± 1.4	14.2 ± 1.3	13.5 ± 1.4	**0.037**[a]
Anemia, hemoglobin <12g/dL (%)	5 (7.7)	1 (3.0)	4 (12.5)	0.197
Platelet (10^3/mm^3, mean ± SD)	246.4 ± 76.3	259.1 ± 66.5	232.8 ± 84.1	0.161
Albumin (g/dL, mean ± SD)	4.3 ± 0.7	4.3 ± 0.7	4.2 ± 0.5	0.596
Blood Urea Nitrogen (mg/dL, mean ± SD)	12.4 ± 4.7	11.8 ± 3.8	13.0 ± 5.4	0.295
Creatinine (mg/dL, mean ± SD)	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.1	0.612
AST (IU/L, mean ± SD)	27.4 ± 9.7	24.6 ± 6.5	30.3 ± 11.6	**0.021**[a]
ALT (IU/L, mean ± SD)	28.9 ± 27.0	23.6 ± 10.5	34.5 ± 36.5	0.114
Abnormal LFT, AST or ALT >50 (%)	7 (10.8)	0 (0)	7 (21.2)	**0.005**[a]
Bilirubin, total (mg/dL, mean ± SD)	0.5 ± 0.3	0.5 ± 0.2	0.5 ± 0.3	0.560
C-reactive protein (mg/dL, mean ± SD)	0.9 ± 2.6	0.3 ± 0.8	1.4 ± 3.5	0.094
Normal CRP, <0.5mg/dL (%)	54 (83.1)	29 (87.9)	25 (78.1)	0.339
Initial chest X-ray findings, n (%)				0.464
Normal	44 (66.7)	22 (73.3)	22 (81.5)	
Abnormal	13 (19.7)	8 (26.7)	5 (18.5)	
Time from exposure to diagnosis, median (IQR), days	8 (3, 14)	13.5 (7.25, 14.0)	4 (1.0, 13.3)	0.055
Time from exposure to diagnosis-group, n (%)				**0.001**[a]
Within 7 days	16 (41.0)	2 (11.8)	14 (63.6)	
After 7 days	23 (59.0)	15 (88.2)	8 (36.4)	
Time from admission to discharge, median (IQR), days	10 (6.0, 16.0)	9 (5.0, 16.0)	10.5 (9.0, 17.0)	0.981

Patients who were asymptomatic to the end of disease were defined as 'Asymptomatic group' and patients who developed symptoms during the illness were defined as 'Pre-symptomatic group'.
[a]Indicates statistical significance.
COVID-19, coronavirus disease; IQR, interquartile range; N/A, not applicable; WBC, white blood cell; SD, standard deviation; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LFT, liver function test; CRP, C-reactive protein.

Variables such as AST and exposure-diagnosis interval displayed P <0.1 in the univariate analysis. Other important risk factors including age, neutrophilia, lymphopenia, hypertension, diabetes mellitus, and smoking were included in the multivariate Cox regression model (**Table 2**) [5, 6].

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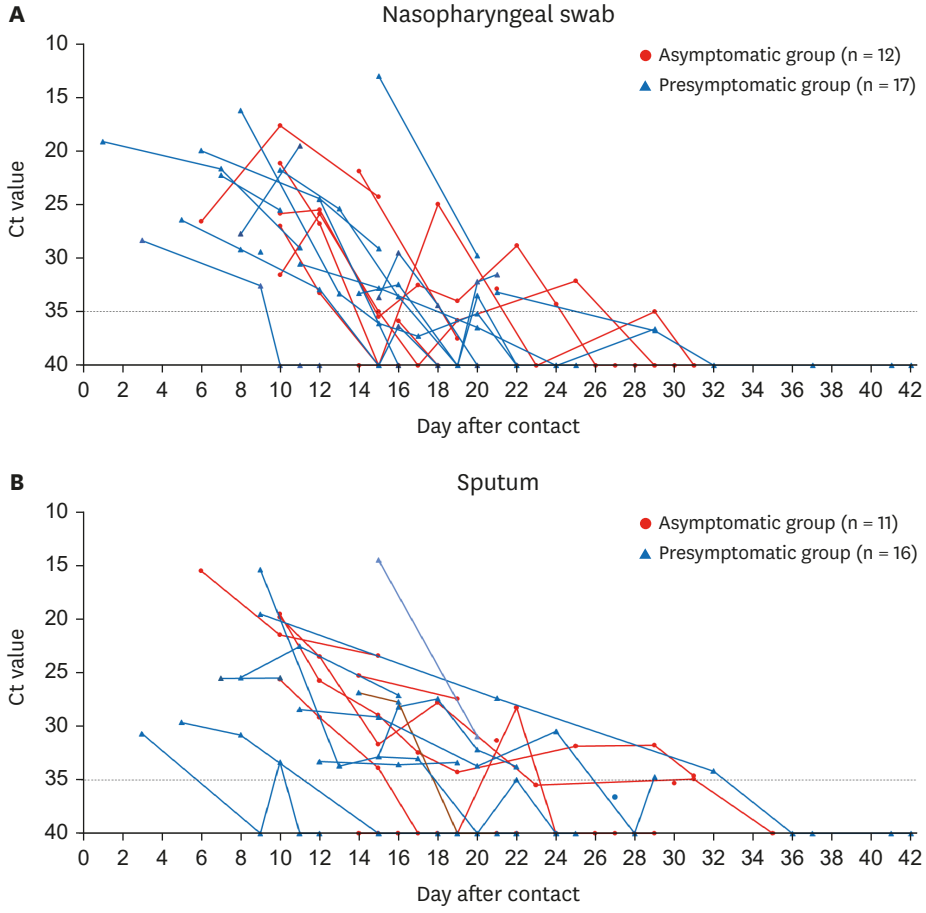

Figure 1. Trends of cycled-time value of SARS-CoV-2 real time RT-PCR between asymptomatic and presymptomatic group.
SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; RT-PCR, reverse transcription polymerase chain reaction; Ct-value, cycled-time value.

The results showed that exposure-diagnosis interval within 7 days [hazard ratio (HR), 4.334; 95% confidence interval (CI), 1.453 - 12.931; $P = 0.009$] and AST over 50 IU/dL (HR, 16.804; 95% CI, 2.667 - 105.900; $P = 0.003$) were clinical and laboratory factors associated with symptom development in the asymptomatic group at the time of diagnosis.

It could be assumed that no clinical symptoms developed 7 days after exposure. This exceeded the known serial interval and median incubation period [7]. In other words, the median of 13.5 days after exposure in the asymptomatic group was nearly up to maximum incubation period. We assumed that the incubation period would be extended due to low inoculum exposure in asymptomatic groups, which were all contact traced and diagnosed under self-isolation after close-contact or overseas arrival at the early phase of pandemic, rather than just delayed diagnosed with barely recognizable symptoms. Furthermore, a normal AST level at the time of diagnosis could predict an asymptomatic state until discharge. Previous studies have reported elevated levels of hepatic enzymes in severe COVID-19 infections [8], indicating that the disease is a systemic inflammatory response and not limited to the lungs. Therefore, it might be possible that the host inflammatory reaction did not occur excessively in asymptomatic patients [9].

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Table 2. Clinical and laboratory factors associated with symptom development in asymptomatic COVID-19 patients at the time of diagnosis

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P*-value	HR	95% CI	*P*-value
Age, group (<50 *vs.* ≥50)	0.680	0.327 - 1.418	0.304	0.364	0.125 - 1.059	0.064
Gender (male *vs.* female)	1.799	0.829 - 3.906	0.137			
Time from exposure to diagnosis-group (within 7 days *vs.* after 7 days)	2.277	0.935 - 5.548	**0.070**[a]	4.334	1.453 - 12.931	**0.009**[a]
Underlying medical conditions						
Diabetes mellitus	0.513	0.156 - 1.690	0.272			
Hypertension	1.054	0.497 - 2.234	0.891			
Smoking	0.574	0.077 - 4.257	0.587			
WBC						
Neutrophil (>74%, increased *vs.* without increased)	0.505	0.175 - 1.459	0.207			
Lymphocyte (<19%, decreased *vs.* without decreased)	0.528	0.199 - 1.397	0.198			
Hemoglobin (<12 g/dL, decreased *vs.* without decreased)	0.690	0.162 - 2.935	0.615	0.372	0.109 - 1.271	0.115
Platelet (<150 × 10^3/μL, decreased *vs.* without decreased)	1.248	0.374 - 4.162	0.718			
Albumin (<3.5 g/dL, decreased *vs.* without decreased)	1.880	0.226 - 15.630	0.559			
Blood Urea Nitrogen (>22.0 mg/dL, increased *vs.* without increased)	0.904	0.313 - 2.616	0.853			
Creatinine (>1.2 mg/dL, increased *vs.* without increased)	1.183	0.408 - 3.428	0.757			
AST (>50 IU/L, increased *vs.* without increased)	8.001	1.787 - 35.821	**0.007**[a]	16.804	2.667 - 105.900	**0.003**[a]
ALT (>50 IU/L, increased *vs.* without increased)	2.159	0.856 - 5.443	0.103			
Bilirubin, total (1.2 mg/dL, increased *vs.* without increased)	1.203	0.163 - 8.888	0.856			
C-reactive protein (>0.5 mg/dL, increased *vs.* without increased)	0.782	0.296 - 2.065	0.619			
Initial chest X-ray findings, (abnormal *vs.* normal)	0.650	0.261 - 1.620	0.355			

[a]Indicates statistical significance.
COVID-19, coronavirus disease; OR, odds ratio; CI, confidence interval; HR, hazard ratio; WBC, white blood cell; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

This study has several limitations. First, a thorough epidemiological investigation capability must be supported to determine the prognosis for the disease by exposure date. Therefore, it might be difficult to apply this result to other countries where epidemiological investigation capabilities are insufficient. Second, since this study took place in the early phase of the pandemic, the number of asymptomatic patients was inadequate and different variants of the virus were not considered. A systematic observational study involving a large number of asymptomatic patients amid the Delta variant surge is needed in the future. Third, all clinical information and laboratory results were obtained at the time of hospital admission; thus, the gap between exposure and diagnosis might have varied individually. Fourth, most of the asymptomatic patients or those with mild symptoms were recently admitted to community treatment centers [10] that were unable to host blood tests; hence, an increase in unknown exposure would be a drawback to clinical application.

This study suggested that COVID-19 patients with exposure-diagnosis intervals over 7 days and normal AST levels on admission could remain asymptomatic through the end of the disease. During the disease surge, if people with these characteristics would be treated through home management or community treatment centers and not in healthcare facilities, more medical resources could be reserved for patients with mild or moderate symptoms.

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