RESEARCH ARTICLE

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Characteristics of Asymptomatic COVID-19 In SARS-COV-2 Vaccine Trial Screening Participants

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Abstract:

Introduction: We conducted a Phase I SARS-CoV-2 vaccine trial in March 2022. During the screening, we identified a significant number of asymptomatic COVID-19 cases among the candidate participants. We aimed to highlight the clinical characteristics among these asymptomatic individuals as compared to subjects negative for SARS-CoV-2.

Methods: This observational study was conducted during participant screening for a Phase I SARS-CoV-2 vaccine trial in Jepara and Mranggen districts in Central Java, Semarang, Indonesia. Participants who reported no symptoms associated with COVID-19, confirmed by physical examinations, were included. Data on laboratory markers were documented. An asymptomatic case was defined as showing no clinical symptoms and signs of SARS-CoV-2 infection with a positive SARS-CoV-2 RT-PCR result. Individuals who tested negative for SARS-CoV-2 were included for comparison. A chi-square test was employed to assess the differences between the two groups, with a *p*-value <0.05 is considered significant.

Results: A total of 219 participants were screened and included. One hundred and six participants (48.4%) had positive SARS-CoV-2 RT-PCR results, with mean Ct values of 28.29 +/- 6.74 for the helicase gene. There was no significant difference in demographic characteristics, physical examination, and laboratory findings (*p*-value >0.05) among individuals with positive and negative SARS-CoV-2.

Conclusion: In our vaccine trial screening phase, almost half were ineligible due to having asymptomatic SARS-CoV-2 infections. In addition, it is necessary that people with asymptomatic COVID-19 infection still need to be concerned because they have the same transmission potential.

Keywords: Asymptomatic COVID-19, Screening, Vaccine trial, Indonesian population, SARS-CoV-2, COVID-19 infection.

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1. INTRODUCTION

COVID-19 has spread rapidly worldwide [1]. To prevent the spread of infection, the Indonesian government has implemented several policies, including physical distancing, large-scale social restrictions, and a social safety net [2]. According to the WHO, until November 2022, there have been millions of confirmed cases and hundreds of thousands of deaths worldwide, including in Indonesia [3]. The Indonesian government continues to take steps to prevent the spread of the virus by developing a domestic COVID-19 vaccine. Since November 2021, PT Bio Farma (a pharmaceutical company under the Ministry of State-owned Enterprises in Indonesia) has started the manufacturing process of a recombinant protein subunit vaccine for COVID-19 through clinical trials over the country [4].

Patients with COVID-19 commonly have a series of symptoms such as fever, cough, fatigue or myalgia, diarrhea, shortness of breath, anorexia, and headache [5–7]. But asymptomatic cases have also been found [8]. According to WHO interim laboratory testing guidelines for a suspected patient with COVID-19, an asymptomatic patient showed a positive real-time polymerase chain reaction (RT-PCR) and a high-intensity contact history with a COVID-19 case [9]. Studies showed that asymptomatic cases had a similar viral load to the symptomatic patient, so close contacts are equally susceptible to transmission of both asymptomatic and symptomatic instances [10]. Asymptomatic or mild COVID-19 infections are frequently experienced by young persons individuals and adults in middle age with individual functional statuses and no underlying disease [11, 12]. However, given the length of sickness in the asymptomatic group was strongly connected with patient age, symptoms are more likely to appear during the course of the disease in older asymptomatic individuals [13].

The increasing evidence of asymptomatic infections of COVID-19 needs to be a concern because the person with asymptomatic infections mainly do not seek medical assistance even though they can still transmit the virus to others [11]. Early identification of the infected person is essential to cut off the route of COVID-19 transmission and assist medical professionals in facilitating appropriate corrective actions and reducing COVID-19 mortality [12, 14]. The purpose of this study is to know the traits of the COVID-19 asymptomatic patient in vaccine clinical trial subjects to help identify and develop the mitigation strategy to decrease the transmission of this clinical feature.

2. METHODS

2.1. Study Design

This is a sub-study of the Phase 1 Clinical Trial of PT Bio Farma vaccine research in collaboration with the Medical Faculty of Universitas Diponegoro, Semarang, Central Java, Indonesia. This observational study was conducted between February and March 2022 at Pecangaan Public Health Centre in Pecangaan District, Jepara Regency, and Mranggen I Public Health Centre in Mranggen District, Demak Regency, Central Java, Indonesia.

Each participant filled out a questionnaire that was adapted from the Indonesian Ministry of Health to screen for COVID-19, which included demographic data, comorbidities, and a list of symptoms that had been present. The data was obtained from the medical report and compiled for participants with positive and negative results of COVID-19 RT-PCR. The participant's medical history was known through a physical examination carried out by an internist. Nasal and oral swab samples have been used to confirm COVID-19 using RT-PCR tests. An asymptomatic infection was defined as the absence of COVID-19-related symptoms and a positive RT-PCR test. The Medical Faculty Universitas Diponegoro, Semarang, Health Research Ethical Committee approved the study protocol, getting the following ethics code number: 24/EC/KEPK/FK-UNDIP/I/2022.

2.2. Study Population

The study comprised all patients (18-70 years old) who underwent health screening as part of the Phase I Clinical Trial of the Bio Farma vaccine research and underwent physical examination, blood laboratory testing, and PCR SARS-CoV-2 testing for COVID-19. Infections with COVID-19 in the past (based on anamnesis), medical comorbidities such as uncontrolled hypertension, diabetes mellitus, cardiovascular disease, and cancer, and insufficient medical reports were among the exclusion criteria.

2.3. Outcomes and Measurement

The collected data included demographic characteristics such as region of residence, age, gender, education, and occupation. The physical examination data included blood pressure and body mass index (BMI), which is computed as weight (Kg)/height(m^2). In clinical trials for preventative vaccines, healthy adult and adolescent volunteers underwent laboratory tests following Food and Drug Administration (FDA) guidelines for the toxicity grading system [15]. The laboratory data included in this study were hemoglobin (Hb), leukocyte and thrombocyte count, neutrophil-to-lymphocyte ratio (NLR), absolute lymphocyte count (ALC), blood glucose, total cholesterol, aspartate transaminase (AST), alanine aminotransaminase (ALT), ureum, and creatinine. The inflammatory cytokine used interleukin-6 (IL-6) value. SYSMEX XS-500i, INDIKO, and Cobas analyzer were used to get the hematological parameters, clinical chemistry parameters, and IL-6 value, respectively. The laboratory test was conducted in the Diponegoro National Hospital's central laboratory in Semarang.

2.4. Statistical Analysis

Quantitative variables were provided using mean, standard deviation (SD), as well as the median and interquartile range (IQR), much as categorical data were described using frequency (%). The chi-square test was

used to examine the association between two classified variables. A *p*-value of less than 0.05 was considered statistically significant. The SPSS version 25 statistical software was used for all calculations.

3. RESULTS

In this study, 219 participants were enrolled. The majority of participants were male (63.5%). Most participants with positive PCR SARS-CoV-2 results were less than 60 years old (89.6%), with a mean age of 40 years, ranging from 18-70 years old. All participants reported no symptoms associated with COVID-19 according to the screening record form and physical examination. Based on the result of the RT-PCR test, 106 (48.4%) participants were categorized as having positive PCR SARS-CoV-2 results, and 113 (51.6%) had negative results. The average cycle threshold (Ct) values in COVID-19-positive cases were 28.29 ± 6.74 (min 12.70, max 37.87) for the helicase gene and 29.71 ± 6.29 (min 15.00, max 38.00) for RNA-dependent RNA polymerase (RdRp) gene. Participants who lived in Mranggen Demak had a higher positive PCR SARS-CoV-2 percentage (58.5%) than patients residing in Jepara (41.5%). It might be because Mranggen was an industrial area and the

majority of participants occupation in this study were formal workers (61.9%), such as factory workers, private employees, traders, and teachers, who have a greater risk of person-to-person transmission than non-formal workers (3.5%). Most educated participants with positive PCR SARS-CoV-2 results were in elementary school (30.2%), while the majority of participants with negative PCR SARS-CoV-2 results finished their education in junior high school (31.9%). The participants' characteristics are presented in Tables **1** and **2**. PCR SARS-CoV-2 positive participants with high blood pressure (28.3%) were lower than those with negative results (66.4%). Meanwhile, from the BMI results, most participants with positive PCR SARS-CoV-2 results had a BMI over 22.9 kg/m2 or included overweight BMI (51.9%). Blood glucose examination showed that most participants with positive PCR SARS-CoV-2 results had normal blood glucose (89.6%), but the high total cholesterol was higher (59.4%) among participants with positive results. According to the *chi-square* test, there was no significant difference between PCR SARS-CoV-2 results with the demographics characteristics and physical examination results (*p*-value >0.05).

Table 1. Characteristics of asymptomatic COVID-19 participants.

Characteristics		Positive PCR	Negative PCR
		n = 106 (48.4%)	n = 113 (51.6%)
Region of Residence	Pecangaan district, Jepara regency	44 (41.5%)	61 (54.0%)
	Mranggen district, Demak regency	62 (58.5%)	52 (46.0%)
Gender	Male	61 (57.5%)	78 (69.0%)
	Female	45 (42.5%)	35 (31.0%)
Education	No School	1 (0.9%)	3 (2.7%)
	Not Pass Elementary School	14 (13.2%)	17 (15.0%)
	Elementary School	32 (30.2%)	30 (26.5%)
	Junior High School	27 (25.5%)	36 (31.9%)
	Senior High School	27 (25.5%)	24 (21.2%)
	Diploma/Academy	0 (0%)	3 (2.7%)
	Bachelors	5 (4.7%)	0 (0%)
Unemployed Occupation	Housewife	8 (7.5%)	3 (2.7%)
	University Student	0 (0%)	3 (2.7%)
	No Job	24 (22.6%)	23 (20.4%)
Employed Occupation	Formal Occupation	70 (61.9%)	83 (73.5%)
	Non-formal Occupation	4 (3.5%)	1 (0.9%)

Note: Data are n/N(%), where N is the total number of participants with available data. PCR = polymerase chain reaction for SARS-CoV-2.

Table 2. Baseline clinical data and laboratory of asymptomatic COVID-19 participants.

Characteristics	Positive PCR		Negative PCR	
	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)
Age (years)	40.3 ± 13.7	39.5 (18.0 – 68.0)	40.1 ± 13.8	39.0 (18.0 – 70.0)
Physical Examination Results				
BMI (kg/m^2)	24.2 ± 5.0	23.2 (14.4 – 36.7)	23.0 ± 4.0	23.1 (15.2 – 33.7)
Systolic Blood Pressure (mmHg)	132.5 ± 21.7	130.0 (90.0 – 214.0)	133.1 ± 20.7	130.0 (94.0 – 202.0)

(Table 2) contd.....

Characteristics	Positive PCR		Negative PCR	
	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)
Diastolic Blood Pressure (mmHg)	81.7 ± 11.6	80.5 (60.0 – 126.0)	81.7 ± 12.5	81.0 (60.0 – 133.0)
Laboratory Characteristics				
Blood Glucose (g/dL)	129.5 ± 72.4	103.5 (75.0 – 448.0)	115.5 ± 52.6	100.0 (66.0 – 409.0)
Total Cholesterol (d/dL)	216.9 ± 47.3	206.0 (128.0 – 370.0)	207 ± 39.1	208.0 (123.0 – 329.0)
AST (µ/L)	34.7 ± 21.4	29.0 (17.0 – 161.0)	31.3 ± 12.5	28.0 (17.0 – 93.0)
ALT (µ/L)	32.4 ± 28.1	24.0 (8.0 – 182.0)	31.3 ± 22.8	23.0 (9.0 – 128.0)
Ureum (mg/dL)	25.7 ± 8.7	23.5 (11.0 – 65.0)	24.1 ± 7.5	24.0 (10.0 – 44.0)
Creatinine (mg/dL)	1.0 ± 0.3	1.0 (0.5 – 1.9)	1.1 ± 0.3	1.1 (0.6 – 2.5)
Hemoglobin (mg/dL)	14.5 ± 1,7	14.4 (8.4 – 18.2)	14.9 ± 1.9	14.9 (8.8 – 23.1)
Leukocyte (mg/dL)	8.3 ± 2.2	8.2 (4.0 – 15.3)	9.1 ± 2.3	8.8 (4.2 – 15.6)
Thrombocyte (mg/dL)	285.9 ± 87.6	276.0 (123.0 – 593.0)	276.1 ± 71.9	267.0 (131.0 – 445.0)
Neutrophils	54.9 ± 10.9	55.0 (29.0 – 88.0)	58.5 ± 9.7	57.0 (30.0 – 80.0)
Lymphocyte	32.9 ± 8.9	33.0 (6.0 – 53.0)	30.7 ± 8.1	31.0 (13.0 – 52.0)
NLR	2.0 ± 1.6	1.6 (0.5 – 14.7)	2.1 ± 1.0	1.8 (0.6 – 6.1)
ALC	2647.8 ± 785.9	2600.0 (516.0 – 4646.0)	2713.8 ± 742.9	2666.0 (1218.0 – 5460.0)
IL-6 (pg/mL)	3.8 ± 4.1	2.8 (<1.5 – 20.7)	2.6 ± 2.7	2.1 (<1.5 – 10.8)

Note: Data are mean ± SD or median (IQR). PCR = Polymerase Chain Reaction. SD = Standard Deviation. IQR = Interquartile Range. BMI = Body Mass Index. AST = Aspartate Transaminase. ALT = Alanine Aminotransaminase. NLR = Neutrophil-to-Lymphocyte Ratio. ALC = Absolute Lymphocyte Count. IL-6 = Interleukin-6.

As for laboratory findings in participants with positive PCR SARS-CoV-2, the result showed leukocytosis in 13 participants (12.3%) with a mean of 8.3 mg/dL, thrombocytosis in 15 participants (14.2%) and 48 participants (45.3%) had hemoglobin level out of normal range. Inflammatory markers showed participants with positive PCR SARS-CoV-2 results; there were only 7 participants (6.6%) with high NLR and 2 patients (1.9%) with high ALC. In addition, IL-6 results in participants with positive PCR showed increased levels in 15 patients (14.2%), while the other 91 participants (85.8%) had normal IL-6 levels. There was no strong evidence for the association between PCR SARS-CoV-2 results and hemoglobin level (*p*-value=0.810), leukocyte count (*p*-value=0.077), thrombocyte count (*p*-value=0.427), NLR (*p*-value=0.889), ALC (*p*-value=0.142), AST (*p*-value=0.771), ALT (*p*-value=0.680), ureum (*p*-value=0.301), creatinine (*p*-value=0.084), and IL-6 (*p*-value=0.218). The bivariate analysis is presented in Table **3**.

Table 3. Analysis study between the characteristics with PCR SARS-CoV-2 results.

Variables		PCR Results				Total	*p*-value
		Positive (N=106)		Negative (N=113)			
		n	%	n	%		
Demographic Characteristics							
Region	Pecangaan Jepara	44	41.5%	61	54.0%	105	0.065
	Mranggen, Demak	62	58.5%	52	46.0%	114	
Age	≥60 years	11	10.4%	10	8.8%	21	0.701
	<60 years	95	89.6%	103	91.2%	198	
Sex	Female	45	42.5%	35	31.0%	80	0.078
	Male	61	57.5%	78	69.0%	139	
Occupation	Unemployed	28	26.4%	33	29.2%	61	0.822
	Formal job	76	71.7%	77	68.1%	153	
	Non-formal job	2	1.9%	3	2.7%	5	
Physical Examination Result							
BMI	Underweight (<18.5 kg/m^2)	12	11.3%	17	15.1%	29	0.714
	Normal (18.5 – 22.9 kg/m^2)	39	36.8%	39	34.5%	78	
	Overweight (>22.9 kg/m^2)	55	51.9%	57	50.4%	112	
Blood Pressure	≤ 140/90 mmHg	76	71.7%	75	33.6%	151	0.395
	> 140/90 mmHg	30	28.3%	38	66.4%	68	
Laboratory Characteristics							

(Table 5)contd.....

Variables		PCR Results				Total	*p*-value
		Positive (N=106)		Negative (N=113)			
		n	%	n	%		
Blood Glucose	≤ 200 mg/dL	95	89.6%	108	95.6%	203	0.091
	> 200 mg/dL	11	10.4%	5	4.4%	16	
Total Cholesterol	≤ 200 mg/dL	43	40.6%	47	41.6%	90	0.877
	> 200 mg/dL	63	59.4%	66	58.4%	129	
Hb*	Abnormal	48	45.3%	53	46.9%	101	0.810
	Normal	58	54.7%	60	53.1%	118	
Leukocyte	≤ 11x10^3 /µL	93	87.7%	89	78.8%	182	0.077
	> 11x10^3 /µL	13	12.3%	24	21.2%	37	
Thrombocyte	≤ 400x10^3 /µL	91	85.8%	101	89.4%	192	0.427
	> 400x10^3 /µL	15	14.2%	12	10.6%	27	
NLR	≤ 3.53	99	93.4%	105	92.9%	204	0.889
	> 3.53	7	6.6%	8	7.1%	15	
ALC	≤ 1000x10^3 /µL	104	98.1%	113	100.0%	217	0.142
	> 1000x10^3 /µL	2	1.9%	0	0.0%	2	
High AST*	No (Normal)	76	71.7%	79	69.9%	155	0.771
	Yes (Abnormal)	30	28.3%	34	30.1%	64	
High ALT*	No (Normal)	82	77.4%	90	79.6%	172	0.680
	Yes (Abnormal)	24	22.6%	23	20.4%	47	
High Ureum	No (6 – 24 µ/L)	105	99.1%	113	100.0%	218	0.301
	Yes (<6 µ/L and >24 µ/L)	1	0.9%	0	0.0%	1	
High Creatinine*	No (Normal)	86	81.1%	101	89.4%	187	0.084
	Yes (Abnormal)	20	18.9%	12	10.6%	32	
High IL-6*	No	91	85.8%	103	91.2%	194	0.218
	Yes	15	14.2%	10	8.8%	25	

Note: p-values less than 0.05 considered statistically significant.*Normal Hb: male 12.0 – 15.5 g/dL, female 13.5 – 17.5 g/dL. Normal AST: male <35µ/L, female <31µ/L. Normal ALT: male <41µ/L, female <39µ/L. Normal Creatinine: male 0.74-1.35 mg/dL, female: 0.59-1.04 mg/dL. Reference value IL-6 ≤7 pg/mL.

4. DISCUSSION

This study found that the percentages among the positive and negative PCR SARS-CoV-2 results in the asymptomatic participants were not too different. Based on the results of the RT-PCR SARS-CoV-2 examination, it was found that the mean Ct-values in participants with positive PCR results were included in a medium level of viral load based on the study of Magleby *et al.* [16]. In a previous study, Gulbudak *et al.* studied Ct-value patients and found that the RdRp gene Ct-value in asymptomatic patients was significantly higher than in symptomatic patients [17]. However, the participants in this study were healthy asymptomatic patients, so there was no data regarding Ct-values in participants with symptoms related to COVID-19. Another study found a similar viral load detected both in an asymptomatic and symptomatic patient, which suggests the transmission potential of an asymptomatic or mild symptomatic patient [18]. The result of this study should be a concern due to the high percentage of asymptomatic participants, but it has potential transmission and risk for other asymptomatic communities [13, 19]. Prior studies demonstrated that in COVID-19 patients, Ct values could not be used as the only indicator of disease severity. Clinicians should evaluate additional clinical parameters in addition to Ct values, such as age, co-morbidities, and laboratory data [20].

Based on the region of residence in this study, there were slightly more positive PCR SARS-CoV-2 results in participants residing in the Mranggen district, Demak, than in the Pecangaan district, Jepara regency. This could be because both Demak and Jepara are industrial areas, so the population's mobility is quite high, and many residents work in the public sector. We also suggest that one of the reasons for the high percentage of asymptomatic participants with positive PCR results in this study was related to the spread of the omicron variant in Indonesia since December 2021 [21]. Omicron has a substantially greater rate of asymptomatic carriage than another variant of concern, according to a prior study, and is probably a significant contributor to the variant's rapid and widespread global spread [22]. Additionally, investigations have shown that SARS-CoV-2 infections that are asymptomatic or barely symptomatic are likely ignorant of their infectious status, which can lead to outbreaks and continuous rapid person-to-person transmission [19].

The result revealed that the majority of the subjects worked in occupations such as factory workers, private employees, traders, and teachers, where these jobs have relatively high mobility. Previous studies showed that occupation does not impact the virus's ability to spread in the community [23]. However, there was a more

significant risk of COVID-19 infection among critical professionals, particularly those in social and educational fields [24]. Furthermore, Yanik *et al.* studied occupational characteristics correlated with COVID-19 infection among people in the United Kingdom and discovered that the probability of COVID-19 infection was higher in jobs that did not allow for remote work [25].

The laboratory findings in this study showed no significant differences between the positive and negative PCR results. This follows other studies that found no significant difference in laboratory results with the symptoms experienced in patients with COVID-19 infection [10, 13]. The previous study showed a patient with infected COVID-19 usually has a normal leukocyte count [26–28], leukocytosis, and lymphopenia [7, 26, 27] but among the study's asymptomatic subjects, these changes were uncommon. It has been known that elevated NLR and decreased ALC in a patient with COVID-19 are correlated with severity and reliable indicators of death as an outcome of COVID-19 disease [29, 30]. Increased IL-6, a marker of inflammation, has been linked to a higher risk of mortality in individuals with severe symptoms [31]. However, in this study, these indicators could not be used as a comparison because the participants tested were healthy, asymptomatic participants. There was no further follow-up regarding the participant's condition.

5. LIMITATIONS

This study has several limitations. First, laboratory parameters used were based on FDA toxicity guidelines for clinical trials, so some laboratory parameters could not be evaluated in this study. Second, there is a possibility of information or recall bias where the subject does not provide truthful data about the condition and symptoms experienced correlated with COVID-19 because they want to participate in clinical trials. Third, follow-up was not carried out on the subject, so whether any symptoms and kinetic profile of laboratory parameters developed afterward was not known. The Indonesian government should consider current findings when formulating COVID-19 patient testing, tracing, and treatment policies. Even though subjects are asymptomatic, the transmission of viruses still occurs with the same risk as symptomatic patients. Therefore, further extensive screening is needed with the participation of the government to reduce morbidity and mortality due to COVID-19, especially in Indonesia.

CONCLUSION

In this vaccine trial screening phase study, we found that almost half of the participants were ineligible due to having asymptomatic SARS-CoV-2 infection. Meanwhile, from the characteristics and laboratory findings, we found no significant relationship with the PCR results in the participants of this study. Even so, it is necessary that people with asymptomatic COVID-19 infection still need to be concerned because they have the same transmission potential as symptomatic ones.

LIST OF ABBREVIATIONS

BMI	=	Body Mass Index
FDA	=	Food and Drug Administration
NLR	=	Neutrophil-to-lymphocyte Ratio
ALC	=	Absolute Lymphocyte Count
AST	=	Aspartate Transaminase
ALT	=	Alanine Aminotransaminase

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The Medical Faculty Universitas Diponegoro, Semarang, Health Research Ethical Committee approved the study protocol, getting the following ethics code number: 24/EC/KEPK/FK-UNDIP/I/2022.

HUMAN AND ANIMAL RIGHTS

No animals were used in this research. All procedures performed in studies involving human participants were in accordance with the ethical standards of institutional and/or research committee and with the 1975 Declaration of Helsinki, as revised in 2013.

CONSENT FOR PUBLICATION

Informed consent was obtained from all participants.

STANDARDS OF REPORTING

STROBE guidelines were followed.

AVAILABILITY OF DATA AND MATERIALS

The data and supportive information is available within the article.

CONFLICT OF INTEREST

There are no conflicts of interest for the authors.

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