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The Difference of Clinical Characteristic COVID-19 patient with Vaccinated and Unvaccinated

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ABSTRACT

Coronavirus disease or COVID-19 was first discovered in Wuhan, China and spreads through respiratory droplet transmission with various clinical characteristics that are often encountered such as fever and cough, shortness of breath, myalgia and nausea/vomiting according to the severity of COVID-19 patients. The severity of clinical characteristics in COVID-19 patients can be influenced by factors of age, comorbidities, gender, immunocompromised status, occupation (healthworkers), and vaccination status. This research is for knowing the differences in the clinical characteristics of vaccinated and unvaccinated COVID-19 patients at University of Muhammadiyah Surakarta students. This study uses an observational analytic study with a cross-sectional approach and was carried out on students at the University of Muhammadiyah Surakarta who were confirmed to have COVID-19 using a google-form questionnaire as primary data. Data were analyzed using chi-square test. The symptoms of COVID-19 such as fever, cough, common cold, myalgia, anosmia or rash did not show a significant difference. Meanwhile, the symptoms of nausea/vomiting were found in individuals who had not been vaccinated more than individuals who had been vaccinated (p = 0.002). There was no significant difference in clinical characteristics of COVID-19 patients who had been vaccinated or had not been vaccinated, except for complaint of nausea/vomiting.

Keywords: clinical characteristics, vaccination, COVID-19

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INTRODUCTION

In 2019, several cases of pneumonia caused unknown etiology emerged in Wuhan, Hubei Province, China, so WHO declared the epidemic disease caused by SARS-CoV-2 called coronavirus disease 2019 (COVID-19). WHO reported the first occurrence of COVID-19 in Indonesia on March 2, 2020 with a total of two cases. Data on March 31, 2020 showed that there were 1,528 confirmed cases and 136 deaths. Some of the symptoms that are often happened by COVID-19 patients include fever, cough (with or without sputum), fatigue, shortness of breath (dyspnea), myalgia (muscle pain),

headache, nausea, vomiting, diarrhea. Health workers who have been vaccinated have a relatively longer time interval or resistance to be infected with COVID-19 than health workers who have not been vaccinated. Health workers who were fully vaccinated were on average infected with COVID-19 at 16 weeks or 4 months after receiving the second dose. Meanwhile, for health workers who have not been vaccinated, on average they are infected with COVID-19 after 3 weeks from the first day of observation, which means that they are infected with COVID-19 much faster (Dhewantara, et al., 2021) .There are differences in the number of deaths of health workers in Turkey, with 2,477,463 (March 2020-January 2021) before being vaccinated and 1,810,366 (1 April-17 May 2021) after being vaccinated (Akpolat and Uzun, 2021). In data from the Weekly Report in New York, 1,271 new Covid-19 hospitalizations (0.17 per 100,000 person-days) occurred among fully vaccinated adults, compared with 7,308 (2.03 per 100,000 person-days).) among unvaccinated adults.

This study aims to determine and analyze the differences and clinical characteristics of vaccinated and unvaccinated Covid-19 patients at University of Muhammadiyah Surakarta students.

METHODS

The type of this research is an observational analytic study with a cross-sectional and was carried out on students of the University of Muhammadiyah Surakarta who were confirmed COVID-19 using a google-form questionnaire and conducted in October - November 2021. Researchers took samples using the total sampling principle. The inclusion criteria used in this study included students from the University of Muhammadiyah Surakarta who were confirmed to have COVID-9 with an age limit of 18-40 years. The research has obtained a permit from the KEPK team, Faculty of Medicine, University of Muhammadiyah Surakarta with number 3834/B.1/KEPK-UMS/XI/2021.

RESULTS AND DISCUSSION

The results of this study indicate that the majority (72.7%) of the respondents in this study have not been vaccinated against covid-19.

Table 1. Characteristics of Research Respondents

Variable	Frequency	Percentage	
Gender			
Man	19	28,8	
Woman	47	71,2	
Age			
18 years old	5	7,6	
19 years old	6	9,1	

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20 years old	20	30,3
21 years old	19	28,8
22 years old	15	22,7
23 years old	1	1,5
Department		
Economics and Business	1	1,5
Pharmaceutical	6	9,1
Physiotherapy	2	3,0
Geography	1	1,5
Nutritional Science	5	7,6
IT	2	3,0
Medical Science	37	56,1
Nursing	3	4,5
Management	1	1,5
Accountancy	1	1,5
English Education	1	1,5
Biology Education	4	6,1
Sport Management	1	1,5
Primary School Teacher	1	1,5
Education		
Total	66	100,0

Table 2. Clinical Characteristic of COVID-19

Variable	Frequency	Percentage	
Symptomatic			
Yes	56	84,8	
No	10	15,2	
Fever			
Yes	52	78,8	
No	14	21,2	
Cough			
Yes	46	69,7	
No	20	30,3	
Common cold			
Yes	42	63,6	
No	24	36,4	
Dyspnea			
Yes	15	22,7	
No	51	77,3	
Nausea/vomiting			
Yes	23	34,8	
No	43	65,2	
Myalgia			
Yes	34	51,5	
No	32	48,5	
Anosmia			
Yes	9	13,6	
No	57	86,4	
Rash			
Yes	2	3,0	
No	64	97,0	

Hospitalized

Variable	Frequency	Percentage
Yes	5	7,6
No	61	92,4
Total	66	100,0

From the table above shows that the majority (84.8%) of the respondents in this study were symptomatic and the most common symptom was fever (78.8%).

Table 3. Vaccination status of COVID-19 Variable

	Frequency	Percentage
Vaccination status		
Vaccinated	18	27,3
Unvaccinated	48	72,7
Total	66	100,0

The table above shows that the majority (72.7%) of the respondents in this study have not been vaccinated.

Table 4. The Difference of Severity Clinical Characteristic in COVID-19 patient

Symptom			Vaccinated		Unvaccinated		P Valu	OR
		•	YES	NO	YES	NO	v am e	OK
Mild sympto	Fever	N(%)	13(25,0 %)	5(35,7%)	39(75%)	9(64,3%)	0,424	0,60 0
m	Cough	N(%)	13(28,3 %)	5(25,0%)	33(71,7 %)	15(75%)	0,785	1,18 2
	Common cold	N(%)	11(26,2 %)	7(29,2%)	31(73,8 %)	17(70,8%)	0,794	0,80
	Nausea/vomitin	N(%)	1(4,3%)	17(39,5 %)	22(95,7 %)	25(60,5%)	0,002	0,0
	Myalgia	N(%)	10(29,4 %)	8(25.0%)	24(70,6 %)	24(75,0%)	0,688	1,2
	Anosmia	N(%)	3(33,3%)	15(26,3 %)	6(66,7%)	42(73,7%)	0,660	1,4 0
	Rash	N(%)	0(0,0%)	18(28,1 %)	2(100,0 %)	46(100,0 %)	0,379	1,0

Symptom	Hospita	ızed	Vaccinated Unvaccinated		Total	
-) <u>F</u>	YES	ИО	, 400,,,,,,,,,		10111	
Mild sympto	om 3	13	4	12	16	
Moderate	1	39	11	29	40	
symptom						

Tabel 5. The Severity of Clinical Characteristic of COVID-19 patient

Unvaccinated COVID-19 patients experienced significantly more nausea/vomiting than vaccinated COVID-19 patients (p = 0.002). Meanwhile, there was no significant difference in symptoms of fever (p = 0.424), cough (p = 0.785), common cold (p = 0.794), shortness of breath/dyspnea (p = 0.952), muscle pain (p = 0.688), anosmia (p = 0.660), or rash (p = 0.379) and hospitalization (p = 0.704) between vaccinated and unvaccinated COVID-19 patients.

This research is relatively in line with a study conducted by Taquet (2021) in the UK. The study, which was a retrospective cohort design involving 10,024 patients, aimed to determine the sequelae of COVID-19 in vaccinated individuals. One of the results of this study shows that individuals who have not received the COVID-19 vaccine will have a 1.03-fold greater risk (HR = 1.03) for experiencing various abdominal complaints (nausea/vomiting/diarrhea) than individuals who have received the vaccine. (Taquet et al., 2021).

Relatively different results were obtained in the study of Antonelli (2021) in England. The study with a case-control involving more than 120,000 people aims to determine the profile of COVID-19 infection in individuals who have received the COVID-19 vaccination. One of the results of this study showed that in individuals aged 18-59 years, only the symptoms of sneezing and shortness of breath were significantly different between individuals who had received the COVID-19 vaccine and those who had not (Antonelli et al., 2021). The difference in the results is thought to be caused by differences in characteristics, especially age, between the research conducted by the researcher and Antonelli's study and the difference in the type/brand of vaccine received between the British and Indonesian people. In theory, most of the clinical characteristics of COVID-19 are similar to other respiratory or viral illnesses, namely

fever, cough, shortness of breath, fatigue, muscle aches, headache, sore throat, loss of smell and taste, and nasal congestion or runny nose. These symptoms can vary between individuals and as the disease progresses. Most COVID-19 patients develop mild (40%) or moderate (40%), approximately 15% develop severe disease requiring oxygen support, and 5% develop critical illness with complications including respiratory failure, ARDS. sepsis and septic shock, thromboembolism, and/or multi-organ failure (Chen et al., 2020). In a study conducted by Guan (2020) showed that patients with comorbidities had a greater severity of disease than those without comorbidities such

as COPD (Chronic Obstructive Pulmonary Disease), hypertension, diabetes, and malignancy and patients with chronic disease. (Guan et al., 2020).

The relative absence of clinical characteristics differences between individuals who have been vaccinated and individuals who have not been vaccinated against COVID-19 is thought to be due to the large number of new variants of SARS-CoV-2. Data are also emerging on the humoral response to the variant of concern (VOC) of COVID-19, with various studies noting decreased virus neutralization in response to natural infection and vaccination (Hoffmann et al., 2020).

For further research to use other research designs that are more appropriate to compare two phenomena in a population, such as case control and cohorts, and use the same number of research subjects in the two groups of research subjects.

CONCLUSION

Coronavirus Disease 2019 (COVID-19) is an infectious disease transmitted by respiratory droplets and mainly attacks the lungs with clinical characteristics such as breath, dizziness, dyspnea, myalgia, nausea/vomiting, diarrhea. There is a difference between the symptoms of nausea and vomiting with vaccination status by COVID-19 patients, while in other symptoms there is no significant difference.

The suggestions that can be followed up based on this systematic review are for students to have themselves vaccinate because this study shows that the number of students who have not been vaccinated is greater than the number of students who have been vaccinated, for health workers to provide appropriate education regarding the signs and symptoms that maybe it will be the same if you experience COVID-19 even though you have been vaccinated and For the Government to urge the public to carry out a full dose of vaccination as an effort to prevent the spread of COVID-19.

REFERENCES

- Aaron Kofman, M., Rami Kantor, M., & Eli Y. Adashi, M. M. (2021). Potential COVID-19 Endgame Scenarios Eradication, Elimination, Cohabitation, or Conflagration? JAMA.com. doi: 10.1001/jama.2021.11042
- Akpolat, T., & Uzun, O. ~. (2021). Reduced mortality rate after coronavac vaccine among healthcare workers. Journal of Infection, 83(2), e20-e21. doi:10.1016/j.jinf.2021.06.005
- Antonelli, M., Penfold, R. S., Merino, J., Sudre, C. H., Molteni, E., Berry, S., . . . Graham, M. S. (2021). Risk factors and disease profile of post-vaccination SARS-CoV-2 infection in UK users of the COVID Symptom Study app: a prospective, community- based, nested, case-control study. The Lancet Infectious Diseases, 1-13. doi:10.1016/S1473-3099(21)00460-6
- Baden, L., Sahly, H. E., B. Essink, K. K., S. Frey, R. N., Diemert, D., Spector, S., . . . Segall, N. (2021). Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. New England Journal of Medicine, 384(5), 403-416. doi: 10.1056/NEJMoa2035389

- Benjamin S. Bleier, M., Murugappan Ramanathan Jr, M., & Andrew P. Lane, M. (2021). COVID-19 Vaccines May Not Prevent Nasal SARS-CoV-2 Infection and Asymptomatic Transmission. Otolaryngology Head and Neck Surgery (United States), 164(2), 305-307. doi: 10.1177/0194599820982633
- Biswas, M., Rahaman, S., Biswas, T. K., Haque, Z., & Ibrahim, B. (2020). Association of Sex, Age, and, Comorbidities with Mortality in COVID-19 Patients: A Systematic Review Meta-Analysis. Karger. doi:10.1159/000512592
- Brosseau, L. M., Escandón, K., Ulrich, A. K., Rasmussen, A. L., Roy, C. J., Bix,
- G. J., . . . Osterholm, M. T. (2021). SARS-CoV-2 Dose, Infection, and Disease Outcomes for COVID-19 – A Review. Oxford University Press for the Infectious Diseases Society of America. doi: 10.1093/cid/ciaa1675
- Burhan, E., Isbaniah, F., Susanto, A. D., Yoga, T. A., soedarsono, Saertono, T. R., & Sugiri, Y. J. (2020). Pneumonia Covid-19 Diagnosis dan Penatalaksanaan. Jakarta: Perhimpunan Dokter Paru Indonesia. ISBN: 978-623-92946-0-7
- Burhan, E., Susanto, A. D., Nasution, S. A., Ginanjar, E., Pitoyo, C. W., Susilo, A., . . . Wulung, N. G. (2020). Pedoman tatalaksana COVID-19 Edisi 3 Desember 2020. Pedoman Tatalaksana COVID-19, 36-37. ISBN: 978-623-92946-0-7
- CDC. (2021). Science Brief: COVID-19 Vaccines and Vaccination.
- Chen, N., Zhou, M., Dong, X., Qu, J., Gong, F., Han, Y., . . . Wang, J. (2020). Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. The Lancet, 395(10223), 507-513. doi: 10.1016/S0140-6736(20)30211-7
- Dan, J. M., Mateus, J., Kato, Y., Hastie, K. M., Yu, E. D., Faliti, C. E., . . . Haupt, S. (2021). Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection. Science, 371(6529). doi: 10.1126/science.abf4063
- Dhewantara, P. W., Ramadhany, R., Hananto, M., Tejayanti, T., Hendarwan, H., & Suryatma, A. (2021). Penularan, Perawatan dan Kematian akibat COVID-19 pada Tenaga Kesehatan di DKI Jakarta, Januari-Juni 2021.
- Dong, Y., Mo, X., Hu, Y., Qi, X., Jiang, F., Jiang, Z., & Tong, S. (2020). Epidemiology of COVID-19 among children in China. Pediatrics, 145(6). doi:10.1542/peds.2020-0702
- Emary, K. R., Golubchik, T., Aley, P. K., Ariani, C. V., Angus, B., Bibi, S., . . . Dold, C. (2021). Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 variant of concern 202012/01 (B.1.1.7): an exploratory analysis of a randomised controlled trial. www.The Lancet.com. doi: 10.1016/S0140-6736(21)00628-0
- Garcia-Beltran, W. F., Lam, E. C., Denis, K. S., Nitido, A. D., Garcia, Z. H., Hauser, B. M., . . . Naranbhai, V. (2021). Multiple SARS-CoV-2 variants escape neutralization by vaccine-induced humoral immunity. medRxiv. doi: 10.1016/j.cell.2021.03.013

- García-Montero, C., Fraile-Martínez, O., Bravo, C., Torres-Carranza, D., Sanchez-Trujillo, L., Gómez-Lahoz, A. M., . . . Bujan, J. (2021). An updated review of sars-cov-2 vaccines and the importance of effective vaccination programs in pandemic times. Vaccines, 9(5), 1-22. doi: 10.3390/vaccines9050433
- Ge, H., Wang, X., Yuan, X., Xiao, G., Wang, C., Deng, T., . . . Xiao, X. (2020). The epidemiology and clinical information about COVID-19. European Journal of Clinical Microbiology and Infectious Diseases, 39(6). doi: 10.1007/s10096-020-03874-z
- Guan, W., Ni, Z., Hu, Y., Liang, W., Ou, C., He, J., . . . Tang, C. (2020). Clinical Characteristics of Coronavirus Disease 2019 in China. New England Journal of Medicine, 382(18), 1708-1720. doi: 10.1056/NEJMoa2002032
- Guan, W.-j., Liang, W.-h., Zhao, Y., Liang, H.-r., & Chen, Z.-s. (2020). Comorbity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. CrossMark. doi: 10.1183/13993003.00547-2020
- Gupta, R. K. (2021). Will SARS-CoV-2 variants of concern . Nature Reviews .doi: 10.1038/s41577-021-00556-5
- Handayani, D., Hadi, D. R., Isbaniah, F., Burhan, E., & Agustin, H. (2020).
- Penyakit Virus Corona 2019. Respir Indo, 40(2), 119-129. doi: 10.26497.jri.v40i2.101
- Health, Washington State Department of; (2021). COVID-19 Cases, Hospitalizations, and Deaths by Vaccination Status.
- Hoffmann, M., Kleine-Weber, H., Schroeder, S., Muller, M. A., Drosten, C., & Pohlmann, S. (2020). SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Elsevier. doi: 10.1016/j.cell.2020.02.052
- Hu, B., Guo, H., Zhou, P., & Shi, Z. L. (2021). Characteristics of SARS-CoV-2 and COVID-19. Nature Reviews Microbiology, 19(3), 141-154. doi: 10.1038/s41579-020-00459-7
- Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., . . . Yu, T. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet, 395(10223), 497-506. doi: 10.1016/S0140-6736(20)30183-5
- Jara, A., Undurraga, E. A., González, C., Paredes, F., Fontecilla, T., Jara, G., . . . Leighton, P. (2021).
 Effectiveness of an Inactivated SARS-CoV-2 Vaccine in Chile. New England Journal of Medicine, 1-11. doi: 10.1056/NEJMoa2107715
- Jarjour, N. N., Masopust, D., & Jameson, S. C. (2021). T Cell Memory: Understanding COVID-19. Cell Press. doi: 10.1016/j.immuni.2020.12.009
- Jin, J.-M., Bai, P., He, W., Wu, F., Liu, X.-F., Han, D.-M., . . . Yang, J.-K. (2020). Gender Differences in Patients With COVID-19: Focus on Severity and Mortality. Frontiers in Public Health, 8, 1-6. doi: 10.3389/fpubh.2020.00152
- Keech, C., Albert, G., Cho, I., Robertson, A., Reed, P., Neal, S., . . . R.E. Haupt. (2020). Phase 1–2 Trial of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine. New England Journal of Medicine, 383(24), 2320-2332. doi:10.1056/NEJMoa2026920

- Kementrian Kesehatan RI. (2020). Pedoman kesiapan menghadapi COVID-19. 0-115.
- Kirtana, J., Kumar, A., Kumar, S. S., Singh, A. K., Sharma, S. H., Shankar, A., . . . Sethi, P. (2020).
 Mild COVID-19 infection-predicting symptomatic phase and outcome: A study from AIIMS,
 New Delhi. J Family Med Prim Care, 5360–5365. doi: 10.4103/jfmpc.jfmpc 1610 20
- Levine-Tiefenbrun, M., Yelin, I., Katz, R., Herzel, E., Golan, Z., Schreiber, L., . . . Kishony, R. (2021). Initial report of decreased SARS-CoV-2 viral load after inoculation with the BNT162b2 vaccine. Nature Medicine, 27(5), 790-792. doi: 10.1038/s41591-021-01316-7
- Li, Y., Tenchov, R., Smoot, J., Liu, C., Watkins, S., & Zhou, Q. (2021). A Comprehensive Review of the Global Efforts on COVID-19 Vaccine Development. ACS Central Science, 7(4), 512-533. doi: 10.1021/acscentsci.1c00120
- Liu, J., Li, S., Liu, J., Liang, B., Wang, X., Wang, H., . . . Guo, C. (2020).
- Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. EBioMedicine, 55. doi: 10.1016/j.ebiom.2020.102763
- Lurie, N., Saville, M., Hatchett, R., & Halton, J. (2020). Developing Covid-19 Vaccines at Pandemic Speed. New England Journal of Medicine. doi: 10.1056/NEJMp2005630
- Maxime Taquet, P., Quentin Dercon, M., & Paul J Harrison, F. (2021). Six- month sequelae of post-vaccination SARS-CoV-2 infection: a retrospective cohort study of 10,024 breakthrough infections. MedRxiv. doi: 10.1016/j.bbi.2022.04.013
- Naserghandi, A., Allameh, S. F., & R.Saffarpour. (2020). All about COVID-19 in brief. New Microbes and New Infections, 35. doi: 10.1016/j.nmni.2020.100678
- Palacios, R., Patiño, E. G., Piorelli, R. d., Conde, M. T., Batista, A. P., Zeng, G., . . . Gast, C. (2020). Double-Blind, Randomized, Placebo-Controlled Phase III Clinical Trial to Evaluate the Efficacy and Safety of treating Healthcare Professionals with the Adsorbed COVID-19 (Inactivated) Vaccine Manufactured by Sinovac PROFISCOV: A structured summary of a. Trials, 21(1), 21-23. doi: 10.1007/s11684-021-0913-y
- Parasher, A. (2021). COVID-19: Current understanding of its Pathophysiology, Clinical presentation and Treatment. Postgraduate Medical Journal, 97(1147), 312-320. doi:10.1136/postgradmedj-2020-138577
- Pascarella, G., Strumia, A., Piliego, C., Buono, R. D., & Costa, F. (2020). COVID-19 diagnosis and management: a comprehensive review. Journal of Internal Medicine(10.1111/joim.13091), 1-15. doi: 10.1111/joim.13091
- Rohde, R. E., & McNamara, R. (2021, July 22). US is split between the vaccinated and unvaccinated and deaths and hospitalizations reflect this divide. doi: 10.1007/s11606-022-08007-0
- Rosenberg, E. S., Holtgrave, D. R., Dorabawila, V., Conroy, M., Greene, D., Lutterloh, E., . . . Zucker, H. A. (2021). New COVID-19 Cases and Hospitalizations Among Adults , by Vaccination Status New York , May 3 July 25 , 2021. US Department of Health and Human

- Services/Centers for Disease Control and Prevention, 70(34). doi : 10.15585/mmwr.mm7034e1
- Russell, M. W., Moldoveanu, Z., Ogra, P. L., & Mestecky, J. (2020). Mucosal Immunity in COVID-19: A Neglected but Critical Aspect of SARS-CoV-2 Infection. Frontiers in Immunology, 11, 1-5. doi: 10.3389/fimmu.2020.611337
- Saeidi, A., Zandi, K., Cheok, Y. Y., Saeidi, H., Wong, W. F., Lee, C. Y., . . . Shankar, E. M. (2018). T-cell exhaustion in chronic infections: Reversing the state of exhaustion and reinvigorating optimal protective immune responses. Frontiers in Immunology, 9, 1-12. doi: 10.3389/fimmu.2018.02569
- Schmidt, M. E., & Varga, S. M. (2018). The CD8 T cell response to respiratory virus infections. Frontiers in Immunology, 9. doi: 10.3389/fimmu.2018.00678