



CLINICAL MANIFESTATION OF COVID-19 CO-INFECTION CASE IN BENGKULU CITY

Debie Rizqoh^{1*}, Enny Nugraheni¹, Jusup Endang^{1,2}, Mulya Sundari^{1,2}, Dessy Triana¹, Mardhatillah Sariyanti¹,
Nikki Aldi Massardi¹

¹ Faculty of Medicine, University of Bengkulu, Bengkulu, Indonesia

² M. Yunus Hospital Center, Bengkulu, Indonesia

* Corresponding Author : Email: debierizqoh@unib.ac.id

ABSTRACT

Background: The COVID-19 pandemic is still ongoing, and no one could predict when it would end. In some cases of COVID-19, patients experienced infection by SARS-Cov-2 and other microorganisms, including viruses, bacteria, and fungi. Some researches reports that microbial co-infection of COVID-19 plays an important role in development of SARS-CoV-2 infection by raising the difficulties of diagnosis, treatment, prognosis of COVID-19, and even increasing the disease symptom and mortality. **Objective:** This study aims to determine Co-infection on clinical symptoms and mortality of COVID-19 patients in Bengkulu City, Indonesia. **Methods:** We reviewed and analyzed data on patients with confirmed COVID-19 who were co-infected, including basic information, clinical manifestations, radiological and laboratory examinations, to the final status. **Results:** A total of 105 patients with confirmed COVID-19 participated in this study with various clinical manifestations: mild case (12%), moderate case/ mild pneumonia (52%), severe pneumonia (20%), and critical case (16%). Of the 105 patients, six patients were co-infected with human immunodeficiency virus (HIV) (1 case), Mycobacterium tuberculosis (2 cases), Salmonella thypii (2 cases), bacterial pneumonia, and viral pneumonia (1 case). As many as three of the six patients experienced inferior clinical manifestations and died. **Conclusion:** The co-infection of other microorganisms in COVID-19 can affect the severity and mortality in COVID-19 patients.

Keywords: COVID-19, co-infection, clinical manifestation, mortality.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is still threatening people all around the world. More than a year ago, the Coronavirus Disease 2019 (COVID-19) pandemic is still ongoing worldwide. The number of confirmed cases of COVID-19 is increasing day by day, as are the victims who died. Until April 24, 2021, the number of confirmed positive COVID-19 patients reached more than 90 million people, and the number of deaths reached nearly 2 million worldwide.¹ In Indonesia, COVID-19 cases are also still increasing every day, up to 28. In March 2021, almost 1.6 million people were confirmed positive, and the number of deaths was more than 44,000 from all provinces.²

Bengkulu City is the capital city of Bengkulu Province, Indonesia, which has 373,591 people with 151.70 km².³ On April 22, 2021, confirmed cases of COVID-19 in Bengkulu City reached 3107 people, with a death toll of 93 people.⁴

COVID-19 is caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Cov-2), initially called novel coronavirus 2019 (nCoV-2019), which first caused an outbreak in Wuhan, Hubei Province, China, in December 2019.⁵ This virus infects humans by binding the glycoprotein component of Spike to the angiotensin-converting

enzyme (ACE) receptor, which is also the receptor of the SARS-Cov virus that previously caused the previous epidemic.^{6,7}

Like other coronaviruses, SARS-Cov-2 is transmitted via respiratory droplets and possibly the fecal-oral route. In infection, the median incubation time is about 4-5 days before symptoms, with 97.5% of symptomatic patients showing symptoms within 11.5 days.⁸ Clinical symptoms of COVID-19 generally include fever, cough, myalgia, dyspnoea, or shortness of breath. This disease can cause acute respiratory distress syndrome (ARDS), RNAemia, acute cardiac injury, and secondary infection.⁹ Ground-glass opacity is the most common radiological finding on computed tomography (CT) chest and lymphocytopenia experienced by most patients.¹⁰

Some COVID-19 patients were not only infected by the SARS-CoV-2 virus but also infected by other pathogens. A study report that COVID-19 had co-infection with *Staphylococcus aureus*, *Haemophilus influenzae*, group B streptococci, influenza A virus and influenza B, coronaviruses, and rhinoviruses/enteroviruses.¹¹ Another study found serological cross-reaction and co-infection SARS-CoV-2 with Dengue Virus.¹²



Co-infection is generally related to the need for a higher level of care, increased length of stay, and the onset of acute respiratory distress syndrome. As a result of the co-infection caused greater damage to the immune system. Patients, who are positive for SARS-CoV-2 and other microbes, can be more severe, treatment is more complicated and the treatment cycle is longer in general.¹³

This study aimed to determine co-infection on clinical symptoms and mortality of COVID-19 patients in Bengkulu City, Indonesia.

METHOD

2.1. Research design

The research method was carried out in a quantitative approach. The design of this study used a retrospective study design by collecting medical record data of COVID-19 patients hospitalized at the M. Yunus Hospital and the Harapan and Doa Hospital of Bengkulu City. Sample collected from October 1- November 31, 2020. Baseline information (sex, age, weight, time of diagnosis by SARS-CoV-2 nucleic acid test, date of admission and discharge), clinical manifestations, laboratory and radiologic findings, treatment, outcome, and follow-up data were recorded with standardized data collection forms. All confirmed COVID-19 patients were included in this study, especially for co-infection cases. Coinfection is the simultaneous infection of a host by multiple pathogen species.

The inclusion criteria for the co-infection study are patients with COVID-19 who tested positive for RT-PCR and patients who were also infected with other microbes from other clinical laboratory tests. Exclusion criteria are COVID-19 patients who have other commorbid diseases.

2.2 Laboratory confirmation

Confirmation of COVID-19 was based on a positive result for real-time reverse transcription-polymerase chain reaction (RT-PCR) testing of SARS-CoV-2 in nasopharyngeal swabs by a hospital laboratory.

2.3 Diagnosis Classification

The clinical spectrum of COVID-19 varies from asymptomatic, very mild symptoms to clinical conditions characterized by respiratory failure. In summary, the clinical manifestations that can arise are described in Table 1.

2.2. Statistical Analysis

Categorical data were expressed as a number and percentage, and continuous data were expressed as a median with a range or interquartile.

Tabel 1. Description of Clinical Manifestation type of COVID-19

	Diagnostic criteria
Asymptomatic	The patient does not show any symptoms.
Mild case	Patients with non-specific symptoms include fever, cough, sore throat, nasal congestion, malaise, headache, and muscle aches.
Moderate case/ mild pneumonia	Adolescent or adult patients with clinical signs of pneumonia (fever, cough, dyspnea, rapid breathing) and no signs of severe pneumonia. Children with mild pneumonia have a cough or difficulty breathing and fast breathing.
Severe pneumonia	Adolescent or adult patient with fever or under surveillance for respiratory tract infection, plus one of the following: respiratory rate >30 breaths/minute, severe respiratory distress, or oxygen saturation (SpO ₂) <90% at room temperature. Pediatric patient with cough or difficulty breathing, plus at least one of the following symptoms: oxygen saturation <90%, severe respiratory distress (such as snoring, severe chest indrawing), inability to breastfeed or drink, lethargy or loss of consciousness, or seizures. Another sign of pneumonia in children is tachypnea: >60x/minute (<2 months), >50x/minute (2-11 months), >40x/minute (1-5 years), or 30x/minute (>5 years). Chest imaging showed the presence of severe pneumonia.
Critical case	Those who meet any of the following criteria and require ICU care: Respiratory failure requiring mechanical ventilation (e.g., ARDS, persistent hypoxia that cannot be alleviated by inhalation through nasal catheters or masks) Septic shock Combined with other organs failure



RESULT AND DISCUSSION

The total number of subjects who participated in this study was 105 people. Based on the data obtained, most of the patients were male (58%). Generally, hospitalized patients are over 40 years old (89%) (Table 2). The symptoms that are often encountered in COVID-19 patients include fever (74%), cough (75%), chest tightness (68%), fatigue (42%), and nausea (35%). Some patients also had symptoms of anosmia (7%), age (4%), diarrhea (4%), and unconsciousness (3%).

The most clinical manifestation found was moderate case/mild pneumonia (54/52%) (Figure 1). In hospital, there were not found asymptomatic case. The mild case, severe pneumonia and critical cases respectively reached 13 cases (12%), 21 cases (20%) and 17 cases (16%).

Tabel 2. The essential characteristic of COVID-19 Patients in Bengkulu City

Subject characteristic	n (%)
Sex :	
- Male	61 (58)
- Female	44 (42)
Age :	
- 0 – 17 y	3 (3)
- 18 – 40 y	13 (12)
- >40 y	89 (85)
Clinical Symptoms:	
- Fever	78 (74)
- Cough	79 (75)
- Chest congestion	71 (68)
- Fatigue	44(42)
- Nausea	37 (35)
- Anosmia	7 (7)
- Ageusia	4 (4)
- Diarrhea	4 (4)
- Unconciuous	3 (3)

Of the 105 subjects, six were co-infected with other pathogens, both bacteria, and viruses (Table 3). The bacterial co-infections found included *Salmonella typhi*, *Mycobacterium tuberculosis*, and bacterial pneumonia. Meanwhile, the virus co-infections found were HIV and atypical viral pneumonia. Clinical manifestations The clinical

manifestations of the six patients varied, one mild case, one moderate case/mild pneumonia, two severe pneumonia, and two critical cases. Two of the six patients who were co-infected with critical cases died. One patient's recovery is unknown because the patient was discharged from hospital treatment before being confirmed negative.

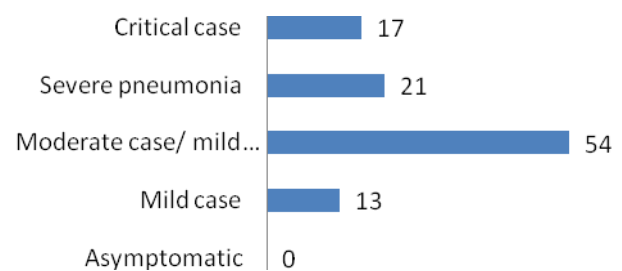


Figure 1. Various cases of COVID-19 clinical manifestation in two hospitals in Bengkulu city, M. Yunus Hospital and the Harapan and Doa Hospital of Bengkulu City.

The co-infection of the SARS-CoV-2 with other microorganisms, such as viruses, bacteria, and fungi, is a crucial factor in COVID-19, and it can raise the difficulties of diagnosis, treatment, the prognosis of COVID-19, and even increase the disease symptom and mortality.(1) A study report that co-infected TB-COVID-19-patients have a low chance to build an immune response to SARS-COV-2.(2). Another study found that 6 of 1103 COVID-19 patients has co-infection with Influenza Virus.(3) Besides, another study said 24 of 116 COVID-19 patients have co-infection with the most common co-infections were rhinovirus/ enterovirus (6.9%), respiratory syncytial virus (5.2%), and non-SARS-CoV-2 Coronaviridae (4.3%).¹

This study has limited reports of co-infection cases of COVID-19. Data on co-infection of COVID-19 patients in Bengkulu City may be incomplete because, generally, patients do not carry out examinations to detect diseases other than COVID-19.



Tabel 3. Profil of COVID-19 Co-infection case in Bengkulu City.

No.	Subject code	Gender	Age (year)	The lowest O ₂ Saturation	Image examination diagnosis	Clinical classification	Co-infection	Outcomes
1.	001	Male	40	95%	bilateral pneumonia, negative cardiomegaly	Moderate case/ Mild pneumonia	<i>Salmonella thypii</i>	Recovery
2.	002	Female	40	95%	no cardiomegaly, bronchitis picture	Mild case	<i>Salmonella thypii</i>	Recovery
3.	020	Male	44	80%	severe pneumonia increases, typical covid	Severe pneumonia	<i>Mycobacterium tuberculosis</i>	Unrecovery
4.	066	Female	50	48%	opacity with minimal infiltrates in the lower field, right lung suggestive of bronchopneumonia	Critical case	bacterial pneumonia, atypical viral pneumonia	Death
5.	069	Male	40	94%	No image examination	Critical case	<i>Mycobacterium tuberculosis</i>	Death
6.	093	Male	45	76%	suggestive of left pneumonia, average cast size	Severe pneumonia	Human Immunodeficiency Virus (HIV)	Recovery

CONCLUSION

Co-infection in COVID-19 patients can affect the clinical manifestations, severity, and mortality of COVID-19 patients. Therefore, supporting examinations to detect other infections in COVID-19 patients need to be carried out so that patients receive better treatment and improve the safety of COVID-19 patients.

Ethical Approval

This research has been approved by Ethical Committee with ethical approval number 189/UN30.4.9/LT/2020.

Conflicts of Interest

The authors declare no conflict of interest.

Funding

This research is supported by a grant from the PNPB Faculty of Medicine, University of Bengkulu. Thank you for the support.

Acknowledgments

This work was supported by the Faculty of Medicine, University of Bengkulu.

REFERENCES

1. WHO. WHO COVID-19 global table data April 3rd 2021 at 3 [Internet]. 2021 [cited 2021 Apr 3]. Available from: <https://covid19.who.int/table>
2. Kemenkes RI. Protokol Tata laksana COVID-19. 2nd ed. Kementerian Kesehatan Republik Indonesia; 2021.
3. Badan Pusat Statistik Kota Bengkulu. Bengkulu Municipality in Figures 2021 [Internet]. Bengkulu: Percetakan Negara Republik Indonesia (PNRI); 2021.
4. Dinas Kesehatan Provinsi Bengkulu. Situasi Terkini Perkembangan COVID-19 [Internet]. 2021. Available from: https://drive.google.com/file/d/1nI6lChzOAJjxopY5CvBf1BDbuX_1TISf/view
5. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health



Debie Rizqoh, Enny Nugraheni, Jusup Endang, Mulya Sundari,
Dessy Triana, Mardhatillah Sariyanti, Nikki Aldi Massardi

- concern. *Lancet*. 2020 Feb 15; 395 (10223): 470-473. doi: 10.1016/S0140-6373(20)30185-9.
6. Del Rio C, Malani PN. COVID-19-New Insights on a Rapidly Changing Epidemic. *JAMA*. 2020 Apr 14; 323(14): 1339-1340. doi: 10.1001/jama.2020.3072
7. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J pat hol*. 2004 Jun 203(2):631-7. doi: 10.1002/path.1570.
8. Tay MZ, Poh CM, Rénia L, Macary PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. *Nat Rev Immunol*. 2020 Jun 20(6):363-374. doi: 10.1038/541577-028-0311-8.
9. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan , China. *Lancet*. 2020 Feb 15;395 (10223):497–506. doi: 10.1016/S0140-6736(20)30183-5
10. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS. China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 2020; 382:1708-1720 DOI: 10.1056/NEJMoa20020322020;
11. Calcagno A, Ghisetti V, Burdino E, Trunfio M, Allice T, Boggione L, Bonora S, Di Perri G. Co-infection with other respiratory pathogens in COVID-19 patients. *Clin Microbiol Infect*. 2021 Feb;27(2):297-298. doi: 10.1016/j.cmi.2020.08.012.
12. Masyeni S, Santoso MS, Dyah P, Wedha DG, Nainu F, Harapan H, et al. International Journal of Infectious Diseases Serological cross-reaction and coinfection of dengue and COVID-19 in Asia : Experience from Indonesia. *Int J Infect Dis [Internet]*. 2021;102:152–4. Available from: <https://doi.org/10.1016/j.ijid.2020.10.043>
13. Chen X, Liao B, Cheng L, Peng X, Xu X, Li Y, Hu T, Li J, Zhou X, Ren B. The microbial coinfection in COVID-19. *Appl Microbiol Biotechnol*. 2020 Sep;104(18):7777-7785. doi: 10.1007/s00253-020-10814-6.
14. Petrone L, Petruccioli E, Vanini V, Cuzzi G, Gualano G, Vittozzi P, et al. International Journal of Infectious Diseases Coinfection of tuberculosis and COVID-19 limits the ability to in vitro respond to SARS-CoV-2. *Int J Infect Dis [Internet]*. 2021;(xxxx):2–7. Available from: <https://doi.org/10.1016/j.ijid.2021.02.090>
15. Ozaras R, Cirpin R, Duran A, Duman H, Arslan O, Bakcan Y, Kaya M, Mutlu H, Isayeva L, Kebanlı F, Deger BA, Bekeshev E, Kaya F, Bilir S. Influenza and COVID-19 coinfection: Report of six cases and review of the literature. *J Med Virol*. 2020 Nov;92(11):2657-2665. doi: 10.1002/jmv.26125.
16. Kim D, Quinn J, Pinsky B, Shah NH, Brown I. Rates of Co-infection Between SARS-CoV-2 and Other Respiratory Pathogens. *JAMA*. 2020 May 26;323(20):2085-2086. doi: 10.1001/jama.2020.6266.