

# The clinical impact of bacterial co-infection among moderate, severe and critically ill COVID-19 patients in the second referral hospital in Surabaya

*by Try Pudi Asmarawati*

---

**Submission date:** 28-Dec-2022 11:38AM (UTC+0800)

**Submission ID:** 1987014929

**File name:** OVID-19\_patients\_in\_the\_second\_referral\_hospital\_in\_Surabaya.pdf (1.56M)

**Word count:** 8197

**Character count:** 43577



## RESEARCH ARTICLE

**REVISED** **The clinical impact of bacterial co-infection among moderate, severe and critically ill COVID-19 patients in the second referral hospital in Surabaya [version 2; peer review: 2 approved]**

Tri Pudy Asmarawati <sup>1,3</sup>, Alfian Nur Rosyid <sup>2,4</sup>, Satriyo Dwi Suryantoro <sup>1,2</sup>, Bagus Aulia Mahdi <sup>1</sup>, Choirina Windradi <sup>1</sup>, Prastuti Asta Wulaningrum <sup>2,4</sup>, Muhammad Vitanata Arifijanto <sup>1,3</sup>, Bramantono Bramantono <sup>1,3</sup>, Erwin Astha Triyono <sup>1,3</sup>, Musofa Rusli <sup>1,3</sup>, Brian Eka Rachman <sup>1-3</sup>, Erika Marfiani <sup>1-3</sup>, Pepy Dwi Endraswari <sup>2,3,5</sup>, Usman Hadi <sup>1,3</sup>, Kuntaman Kuntaman <sup>3,5</sup>, Nasronudin Nasronudin <sup>1,2</sup>

<sup>1</sup>Department of Internal Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, East Java, 60115, Indonesia

<sup>2</sup>Universitas Airlangga Hospital, Surabaya, East Java, 60115, Indonesia

<sup>3</sup>Dr. Soetomo General Teaching Hospital, Surabaya, East Java, 60286, Indonesia

<sup>4</sup>Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, East Java, 60115, Indonesia

<sup>5</sup>Department of Clinical Microbiology, Faculty of Medicine, Universitas Airlangga, Surabaya, East Java, 60286, Indonesia

**v2** First published: 15 Feb 2021, 10:113  
<https://doi.org/10.12688/f1000research.31645.1>  
 Latest published: 29 Mar 2021, 10:113  
<https://doi.org/10.12688/f1000research.31645.2>

**Abstract**

**Background:** Data on the prevalence of bacterial co-infections among COVID-19 patients are limited, especially in our country, Indonesia. We aimed to assess the rate of bacterial co-infections in hospitalized COVID-19 patients and report the most common microorganisms involved and the antibiotic use in these patients.

**Methods:** This study is a retrospective cohort study, among COVID-19 adult patients admitted to Universitas Airlangga Hospital Surabaya from 14 March-30 September 2020. The bacterial infection is defined based on clinical assessment, laboratory parameters, and microbiology results.

**Results:** A total of 218 patients with moderate to critical illness and confirmed COVID-19 were included in this study. Bacterial infection was confirmed in 43 patients (19.7%). COVID-19 patients with bacterial infections had longer hospital length of stay ( $17.6 \pm 6.62$  vs  $13.31 \pm 7.12$ ), a higher proportion of respiratory failure, intensive care treatment, and ventilator use. COVID-19 patients with bacterial infection had a worse prognosis than those without bacterial infection

59

**Open Peer Review**

**Reviewer Status** ✓ ✓

	Invited Reviewers	
	1	2
<b>version 2</b> (revision) 29 Mar 2021	✓ report	
<b>version 1</b> 15 Feb 2021	↑ report	✓ report

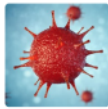
- Fitriana Murriya Ekawati** <sup>id</sup>, Universitas Gadjah Mada, Yogyakarta, Indonesia
- Erni J. Nelwan** <sup>id</sup>, Universitas Indonesia, Jakarta, Indonesia

( $p < 0.04$ ). The empirical antibiotic was given to 75.2% of the patients. Gram-negative bacteria were commonly found as causative agents in this study ( $n = 39$ ; 70.37%).

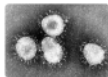
**Conclusion:** COVID-19 patients with bacterial infection have a longer length of stay and worse outcomes. Healthcare-associated infections during intensive care treatment for COVID-19 patients must be carefully prevented.

#### Keywords

Bacterial infection, COVID-19, SARS-CoV-2, antibiotics



This article is included in the **Disease Outbreaks** gateway.



This article is included in the **Coronavirus** collection.

**Corresponding authors:** Tri Pudy Asmarawati ([tpasmarawati@fk.unair.ac.id](mailto:tpasmarawati@fk.unair.ac.id)), Alfian Nur Rosyid ([alfian-n-r-10@fk.unair.ac.id](mailto:alfian-n-r-10@fk.unair.ac.id))

**Author roles:** **Asmarawati TP:** Conceptualization, Formal Analysis, Investigation, Methodology, Project Administration, Writing – Original Draft Preparation, Writing – Review & Editing; **Rosyid AN:** Conceptualization, Investigation, Methodology, Project Administration, Software, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Suryantoro SD:** Conceptualization, Formal Analysis, Investigation, Methodology, Project Administration, Writing – Original Draft Preparation, Writing – Review & Editing; **Mahdi BA:** Data Curation, Formal Analysis, Project Administration, Software, Visualization, Writing – Original Draft Preparation; **Windradi C:** Data Curation, Investigation, Project Administration, Software, Writing – Original Draft Preparation; **Wulaningrum PA:** Methodology, Supervision, Writing – Review & Editing; **Arifijanto MV:** Supervision, Validation; **Bramantono B:** Supervision, Validation; **Triyono EA:** Supervision, Validation; **Rusli M:** Supervision, Validation; **Rachman BE:** Project Administration, Supervision, Validation; **Marfiani E:** Supervision, Validation; **Endraswari PD:** Conceptualization, Data Curation, Resources, Validation; **Hadi U:** Conceptualization, Supervision, Validation; **Kuntaman K:** Conceptualization, Supervision, Validation, Visualization; **Nasronudin N:** Conceptualization, Supervision, Validation

**Competing interests:** No competing interests were disclosed.

**Grant information:** The author(s) declared that no grants were involved in supporting this work.

**Copyright:** © 2021 Asmarawati TP *et al.* This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

**How to cite this article:** Asmarawati TP, Rosyid AN, Suryantoro SD *et al.* **The clinical impact of bacterial co-infection among moderate, severe and critically ill COVID-19 patients in the second referral hospital in Surabaya [version 2; peer review: 2 approved]** F1000Research 2021, 10:113 <https://doi.org/10.12688/f1000research.31645.2>

**First published:** 15 Feb 2021, 10:113 <https://doi.org/10.12688/f1000research.31645.1>

21

**REVISED Amendments from Version 1**

In the introduction, we have emphasized the fact that the research on secondary infection accompanying COVID-19 in Indonesia is still limited and there is no prior investigation linked to this topic ever done before, by adding "Indonesia" in our first sentence of paragraph 2.

We also made minor revisions by correcting the "leukocyte" to "leucocytes" and "leukocytosis" to "leucocytosis"

We also insert citation for SPSS version 24.0

**Any further responses from the reviewers can be found at the end of the article**

**Introduction**

Coronavirus disease (COVID)-19 has experienced an increase in 2,995,758 positive cases and 204,987 deaths in distribution areas of more than 213 countries<sup>1</sup>. In Indonesia, until November 2020, there were 522,581 confirmed cases of COVID-19 with 68,604 active cases, 437,456 recovered cases, and 16,521 (3%) deaths. According to national data, among the total number of cases, East Java is the second-highest prevalence of 60,190 (11.6%). As of November 26, 2020, the cumulative data on confirmed COVID-19 patients in Surabaya were 16,763 with 1204 (7.03%) deaths<sup>1</sup>.

Data regarding secondary respiratory infection in COVID-19 patients are still limited in Indonesia even though the cases distribution is still worldwide. Several reports suggest that secondary infection will impact the patient's survival and increase intensive care unit (ICU) treatment<sup>2</sup>. COVID-19 pneumonia itself is also related to increasing ICU care, secondary infection rate, and higher invasive treatment<sup>3</sup>. Co-infection of SARS-CoV-2 and other microorganisms such as viruses, bacteria, and fungi is an essential factor in COVID-19 treatment since this condition may raise the difficulty in diagnosis, treatment, and the prognosis, also increasing the mortality<sup>4,5</sup>. Upper respiratory tract infection, a typical manifestation of COVID-19, is challenging to differentiate from other causes of pneumonia.

There are various types of co-infection in COVID-19; such as: 1) secondary SARS-CoV-2 following bacterial infection or colonization; 2) mixed infection between viral and bacterial pneumonia infection; 3) secondary bacterial superinfection following SARS-CoV-2 infection. The mechanisms underlying those types of infection are very dependent on the onset and involving complex interactions between three different agents (virus, host, and bacteria). Immune response towards SARS-CoV-2 infection only differs with mixed infection to bacteria or viral pneumonia. Therefore, it could be hypothesized that any co-infection will worsen the outcome and severity of COVID-19<sup>6</sup>.

Although several studies have investigated the epidemiological and clinical characteristic of COVID-19, information regarding SARS-CoV-2 infection with secondary infection are limited<sup>7</sup>. This study aims to describe bacterial co-infection and antibiotic use among patients who confirmed SARS-CoV-2 infection from

moderate to critically ill manifestation in Universitas Airlangga hospital Surabaya.

**Methods****Study design and population**

This study is a retrospective cohort study, total sampling, among COVID-19 adult patients admitted to Universitas Airlangga Hospital Surabaya. This hospital is an academic hospital and also a referral hospital for COVID-19 management in Surabaya, East Java Region. We included cases of moderate to critically ill COVID-19 patients between 14 March and 30 September 2020 that were admitted in the intensive care unit or high-care unit. COVID-19 diagnosis was made based on World Health Organization (WHO) guidelines<sup>8</sup> and the Indonesian Ministry of Health guidelines<sup>9</sup>. Confirmed COVID-19 patients were proven by oropharyngeal and nasopharyngeal swabs SARS-CoV-2 PCR (polymerase chain reaction). Bacterial infection was defined based on clinical assessment, laboratory parameters, and inflammatory parameters (C-reactive protein (CRP) and procalcitonin). Bacterial co-infection of SARS-CoV-2 defines if the culture samples were taken at patient presentation to the hospital or < 48 hours admission, while secondary bacterial infection defined if the culture samples were taken > 48 hours of admission. The bacterial causative agents were extracted from data of microbiology, that were identified by Microbiology automated machine Vitek-2 compact, as a routine procedure in this hospital.

This study was approved by the Ethical Committee of Universitas Airlangga Hospital (171/KEP/2020). Written informed consent was obtained from all participants prior to the start of the study.

**Data collection**

Data were taken from medical records and microbiology reports from the laboratory. Incomplete medical records were excluded. Clinical characteristics were divided according to the severity of the disease. Moderate case definitions are: 1) clinically sign of pneumonia (fever, cough, dyspnea, tachypnea); 2) Oxygen saturation  $\geq 93\%$  free air. Severe case definitions are if there were clinically sign of pneumonia, and one of the following: 1) respiration rate >30 times per minute, or 2) severe respiratory distress, or 3) oxygen saturation < 93% free air. Critically ill cases defined if there were acute respiratory distress syndrome (ARDS), sepsis, and septic shock<sup>10</sup>. Culture examination was performed when there was suspicion of bacterial infection or sepsis. The sample for culture was taken from blood, urine, and respiratory tract.

**Statistical analysis**

Data were analyzed with SPSS version 24.0 (Chicago, IL, USA)<sup>11</sup>. Descriptive statistics included categorical variables reported as number (percentage) and continuous variables as mean (standard deviation). For missing data, we used listwise deletion or univariable and multivariable analysis. Chi-square test and Mann-Whitney test were used accordingly to the type of variable. Categorical variables were shown as number (%) and continuous variables as mean (standard deviation) or median (range) depending on whether the data are normally distributed

or not. Statistical significance was assessed by means of chi-squared for dichotomous variables, or by means of the two independent sample t-test or the Mann-Whitney U test for continuous variable depending on whether the data are normally distributed or not.

## Results

### Patient characteristics

From March 14 until September 30, 2020, a total of 218 patients confirmed for SARS-CoV-2 infection were admitted to Universitas Airlangga Hospital Surabaya from moderate to critically ill condition. Patients characteristic symptoms were defined according to their severity. Clinical characteristics and main comorbidities are detailed in Table 1. The median age of the study subject was 52.45 ( $\pm 14.44$ ) years, and 55.05% of patients were male. According to disease severity, the number of patients with

moderate, severe, and critically ill manifestations were 126 (57.8%), 40 (18.3%), and 52 (23.9%), respectively. Diabetes and hypertension were the most common comorbidity, in 34.4% and 29.9% of patients, respectively. Among all subjects, patients that were critically ill 7.3% manifested respiratory failure ( $p < 0.05$ ), 23% were on a ventilator ( $p < 0.05$ ) and in 7.8% were in sepsis ( $p = 0.006$ ). Critically ill patients had the longest length of stay (mean  $16.89 \pm 9.4$  days). Bacterial infection was confirmed in 43 patients (19.7%); 16 patients were in critically ill condition. Among COVID-19 patients with a bacterial infection, we divided them into two categories, bacterial co-infection (23%) and secondary bacterial infection (77%).

Characteristic symptoms and laboratory result are shown in Table 1. The most common symptoms in all severity were

**Table 1. Baseline Characteristics of Patients.**

	Severity COVID-19 (n=218)						Total (n.%)		p Value
	Moderate		Severe		Critical Ill				
	126		40		52		218	100	
<b>Sex</b>	57.80		18.35		23.85			100	
Male (n=120)	69		27		24		120.00	55.05	0.12
Female (n=98)	57		13		28		98.00	44.95	
<b>Age(Mean/SD)</b>	51.04	15.32	53.50	14.63	55.02	11.65	52.45	14.44	0.21
<b>Comorbidities</b>									
DM (n.%)	41	18.8	11	5	23	10.6	75	34.4	0.2
HT (n.%)	35	16.1	6	2.8	24	11	65	29.9	0.004
Geriatric (> 60 years) (n.%)	31	14.2	12	5.5	16	7.3	59	27	0.63
Heart disease (n.%)	7	3.2	4	1.8	3	1.4	14	6.4	0.83
Stroke (n.%)	7	3.2	1	0.5	3	1.4	11	5.1	0.72
CKD (n.%)	5	2.3	2	0.9	2	0.9	9	4.1	0.95
Smoker (n.%)	5	2.3	2	0.9	0	0	7	3.2	0.1
COPD (%)	1	0.4	0	0	0	0	1	0.4	0.1
Liver disease (n.%)	0	0	0	0	1	0.5	1	0.5	0.2
Respiratory Failure (n.%)	0	0	0	0	43	19.7	43	19.7	<0.05
Ventilator (n.%)	0	0	0	0	23	10.5	23	10.5	<0.05
Sepsis (n.%)	0	0	0	0	17	7.8	17	7.8	0.006
<b>Type of bacterial infection</b>									
< 48 hours (n.%) (Co-infection)	4	1.8	3	1.4	6	2.8	13.0	6.0	0.52
> 48 hours(n.%) (Secondary Infection)	22	10.1	16	7.3	16	7.3	54.0	24.8	
<b>Bacterial Infection (n.%)</b>	15	6.9	12	5.5	16	7.3	43.0	19.7	0.55
<b>Antibiotic use (n.%)</b>	90	41.3	44	20.2	30	13.8	164.0	75.3	

	Severity COVID-19 (n=218)						Total (n.%)		p Value
	Moderate		Severe		Critical Ill				
<b>Symptom and Duration</b>									
Dyspnea (%.days)	19.27	4.00	7.34	6.00	14.68	3.20		41.29	
Fever (%. days)	16.97	6.40	3.21	6.00	2.75	8.80		22.93	
Cough (%.days)	7.34	4.60	3.21	10.60	0.92	3.00		11.47	
Malaise (%. days)	7.34	2.60	0.92	3.50	2.29	6.80		10.55	
Nausea and Vomiting (%. days)	1.38	6.30	0.92	4.00	0.46	7.00		2.76	
Diarrhea (%. days)	0.92	3.50	0	-	0	-		0.92	
Headache (%. days)	0.92	2.00	0	-	0.92	3.00		1.84	
Anosmia (%. days)	0.46	2.00	0	-	0	-		0.46	
Joint pain (%. days)	0.46	4.00	0.46	7.00	0	-		0.92	
Chest pain (%. days)	0.46	2.00	0.92	1.00	0	-		1.38	
Loss of consciousness (%. days)	0	0.00	0.92	1.50	1.84	2.30		2.76	
<b>Vital sign</b>									
Systolic Pressure (mean. SD)	133.5	20.62	125.7	20.1	131.63	27.42			0.161
Diastolic Pressure (mean.SD)	87.9	60.47	78.2	8.6	79.96	13.92			0.104
Respiration Rate (mean. SD)	23.34	3.76	24.73	3.52	28.92	6.4			< 0.05
Temperature (mean.SD)	37.38	4.87	36.88	0.91	36.73	0.75			0.512
Oxygen saturation (mean. SD)	94.2	3.97	88.05	9.5	88.24	11.29			< 0.05
<b>Laboratory</b>									
Leucocyte (10 <sup>3</sup> /uL; mean. SD)	8.52	4.26	10.01	5.78	11.01	6.98			0.014
Neutrophil (%. mean. SD)	69.86	18.98	71.26	23.43	81.16	6.71			0.001
Lymphocyte (%. mean. SD)	16.99	10.32	12.76	8.83	11.86	5.24			0.001
Neutrophil-Lymphocyte Ratio (NLR) (mean. SD)	8.65	30.56	8.15	6.02	8.94	5.44			0.98
Thrombocyte (10 <sup>3</sup> /uL; mean. SD)	260.13	114.39	288.97	137.74	289.46	120.21			0.213
C-Reactive Protein (mg/L; mean. SD)	11.15	29.27	16.6	35.19	23.37	50.1			0.122
Procalcitonin (ng/ml; mean. SD)	0.055	0.18	1.18	6.58	1.62	5.55			0.033
Basal Urea Nitrogen (mg/dl; mean.SD)	16.75	23.2	16.16	11.44	29.35	34.88			0.007
Creatinine (mg/dl; mean. SD)	1.3	2.14	1.72	3.96	1.9	3.3			0.4
Aspartate aminotransferase (u/L; mean. SD)	25.11	28.1	31.78	27	90.9	64.58			0.78
Alanine aminotransferase (u/L; mean. SD)	28.1	43.65	27	34.1	64.58	135.6			0.01
PaO2:FI02 ratio (n=71)(mean. SD)	242.53	70.62	160.67	90.54	132.78	57.031			0.005
<b>Length of stay (mean/SD)</b>	12.97	6.7	15.61	7.1	16.89	9.4	14.12	7.21	0.03
<b>Outcome</b>									
Discharge (n.%)	115	52.7	38	16.4	30	13.8	183.0	82.9	<0.05
Death (n.%)	0	0	2	0.9	19	8.7	21.0	9.6	<0.05

dyspnea, fever, cough, and malaise. In patients who were moderate, severe, and critically ill, symptoms cough (7.34%, 3.21%, 0.92%), fever (16.97%, 3.21%, 2.75%) and dyspnea (19.27%, 7.34%, 14.68%) respectively. Other symptoms recorded were nausea, vomiting, diarrhea, headache, joint pain, chest pain, and loss of consciousness, but only affected the minority of the patients. From vital sign examination, two variables had a significant difference for moderate, severe, and critically ill patients; respiratory rate (23.34, 24.73, 28.92;  $p < 0.05$ ) and oxygen saturation ( $\text{SaO}_2$ ) (94.2, 88.05, 88.24;  $p < 0.05$ ) respectively. Some symptoms vary in duration between groups. Severe patients complained of cough symptoms for an average of 10.6 days, longer than those in the moderate or critically ill group. The duration of fever was almost similar between groups, namely 6–8.8 days.

From the laboratory findings, the mean leucocyte count ( $p = 0.014$ ), neutrophil count ( $p = 0.001$ ), procalcitonin ( $p = 0.033$ ), basal urea nitrogen (BUN) ( $p = 0.007$ ), alanine aminotransferase (ALT) levels ( $p = 0.01$ ) were significantly higher in either severe or critically ill COVID-19 patients than

moderate cases. We also found a lower lymphocyte count ( $p = 0.001$ ) and  $\text{PaO}_2$ :  $\text{FiO}_2$  ratio ( $p = 0.005$ ) in either severe or critically ill COVID-19 patients than moderate cases. The procalcitonin level significantly increased in severe and critical illness conditions. The CRP level also increased but was not statistically significant. The majority of patients (82.9%) were recovered and discharged from the hospital, while 9.6% of the patient died. Most of the patients who died were in critically ill condition at presentation to hospital.

### Bacterial infections

Bacterial infection was confirmed in 43 patients (19.7%) (see Table 2). There were no sex differences between bacterial infection and no bacterial infection patients. Patients with a bacterial infection have an older mean age than no bacterial infection, although, among elderly patients, there were no differences in bacterial infection rate. We documented one patient with chronic obstructive pulmonary disease (COPD) and one with liver disease as a comorbidity, and both of them suffered from bacterial infection. Other comorbidities such as diabetes,

**Table 2.** Comparison of COVID-19 patients who had bacterial infections and without bacterial infections.

	Bacterial Infection		No Bacterial Infection		Total (n.%)		p value
	43		175		218		100
<b>Sex</b>							
Male (n=35)	20	29.85	100	45.90	120.00	75.75	0.21
Female (n=32)	23	34.33	75	34.40	98.00	68.73	
<b>Age(Mean/SD)</b>	55.28	12.98	51.76	14.72	52.45	14.44	0.153
<b>Comorbidities</b>							
HT (n.%)	18	8.30	47	21.60	65.00	29.90	0.054
DM (n.%)	15	6.90	60	27.50	75.00	34.40	0.94
Geriatric (> 60 years) (n.%)	12	5.50	47	21.60	59.00	27.10	0.89
Heart disease (n.%)	4	1.80	10	4.60	14.00	6.40	0.39
CKD (n.%)	2	0.90	7	3.20	9.00	4.10	0.85
Stroke (n.%)	1	0.50	10	4.60	11.00	5.10	0.36
COPD (%)	1	0.50	0	0.00	1.00	0.50	0.043
Liver disease (n.%)	1	0.50	0	0.00	1.00	0.50	0.043
Smoker (n.%)	1	0.50	6	2.80	7.00	3.30	0.42
<b>ICU room (n.%)</b>	22	10.1	14	6.4	36.00	16.50	<0.05
<b>Respiratory Failure (n.%)</b>	14	6.4	29	13.3	43.00	19.70	0.018
<b>Ventilator (n.%)</b>	9	4.1	14	6.4	23.00	10.50	0.013
<b>Sepsis (n.%)</b>	7	3.2	10	4.6	17.00	7.80	0.021
<b>Antibiotic use</b>	36	16.5	128	58.7	164.00	75.20	
<b>Length of stay (mean/SD)</b>	17.6	6.62	13.31	7.12			<0.05
<b>Outcome (between group)</b>							
Discharge (n.%)	35	81.40	148	84.57	183.00	165.97	0.04
Death (n.%)	7	16.28	14	8	21.00	24.28	

hypertension, heart disease, stroke, chronic kidney disease did not differ between the two categories. COVID-19 patients with bacterial infections had a longer hospital length of stay, a higher proportion of respiratory failure, ICU treatment, ventilator use.

Mortality occurs in 16.28% of COVID-19 patients with bacterial infections, higher than those without bacterial infection (8%). Overall, COVID-19 patients with bacterial infection had a worse prognosis than those without bacterial infection ( $p < 0.04$ ).

The empirical antibiotic was given to 75.2% of the patients. Antibiotics used in these patients were quinolones (60.1%), cephalosporins (28.44%), carbapenem (23.85%), and aminoglycosides (4.59%). Quinolone used in these patients was mostly levofloxacin (79.39%), and the others were moxifloxacin (20.61%). The carbapenem used in this study was meropenem. Cephalosporins used were ceftriaxone, ceftazidime, cefotaxime, cefoperazone-sulbactam, and cefuroxime (see Figure 1).

**Pathogens associated with a bacterial infection**

We collected 110 culture samples from suspected bacterial infection patients, consisting of 44 blood samples, nine urine samples, and 57 sputum samples. Among them, bacteria were detected in nine blood cultures, four urine cultures, and 47 sputum cultures. Sputum samples were collected, some from spontaneous sputum (n=47) and the others from endotracheal tube aspirate (n=10). Gram-negative bacteria dominate the culture result (70.37%). Bacteria found in the blood were extended-spectrum  $\beta$ -lactamase (ESBL)-producing *Klebsiella pneumoniae* (2), *Pseudomonas fluorescens* (1), *Pseudomonas putida* (1), *Staphylococcus epidermidis* (2), *Staphylococcus haemolyticus* (1), *Staphylococcus hominis* (2). Bacteria found in urine were ESBL-producing *Escherichia coli* (2), *Enterococcus faecalis* (1), and *Pseudomonas putida* (1). There were 47 isolates found

in sputum cultures, in which six of them were fungi (*Candida spp*). The most frequent bacteria found was *Acinetobacter baumannii* (9), followed by *Klebsiella pneumoniae* (5), *Pseudomonas aeruginosa* (4), *Escherichia Coli* (2), *Enterobacter cloacae complex* (3), and *Staphylococcus haemolyticus* (3) (see Table 3 and Figure 2).

**Discussion**

Our study focuses on bacterial infection results in COVID-19 patients and evaluates their clinical and microbiological features. Clinical characteristics of the study group were described according to disease severity. According to disease severity, the number of patients with moderate, severe, and critically ill manifestations were 126 (57.8%), 40 (18.3%), and 52 (23.9%), respectively. The average age was 52.45 ( $\pm 14.44$ ) years, and 55.05% of patients were male. Other studies regarding the characteristic of hospitalized COVID-19 patients showed various results. Zhou *et al.* reported that the median age of the 191 patients was 56.0 years (18–87 years), and most patients were male<sup>12</sup>. Ly *et al.* reported 354 hospitalized patients, 175 (49.44%) were male, and the median age was 62 years (23–90 years)<sup>13</sup>. A study conducted in Saudi Arabia reported among the 99 hospitalized patients, the median age was 44 years (range 19–87), and the majority were men (66%)<sup>14</sup>. We found that diabetes and hypertension were the most common comorbidity, similar to these other studies<sup>12-15</sup>.

In this study, inflammation signs such as leucocyte count, neutrophil count, procalcitonin in the critically ill group were higher than the others. Lymphopenia in COVID-19 patients occurs through various mechanisms such as direct virus invasion lymphocytes, lymphatic organ destruction, altered inflammatory cytokines production leading to lymphocyte apoptosis, and inhibiting lymphocytes function by metabolic molecules produced by metabolic disorders, such as hyperlactic acidemia<sup>16</sup>.

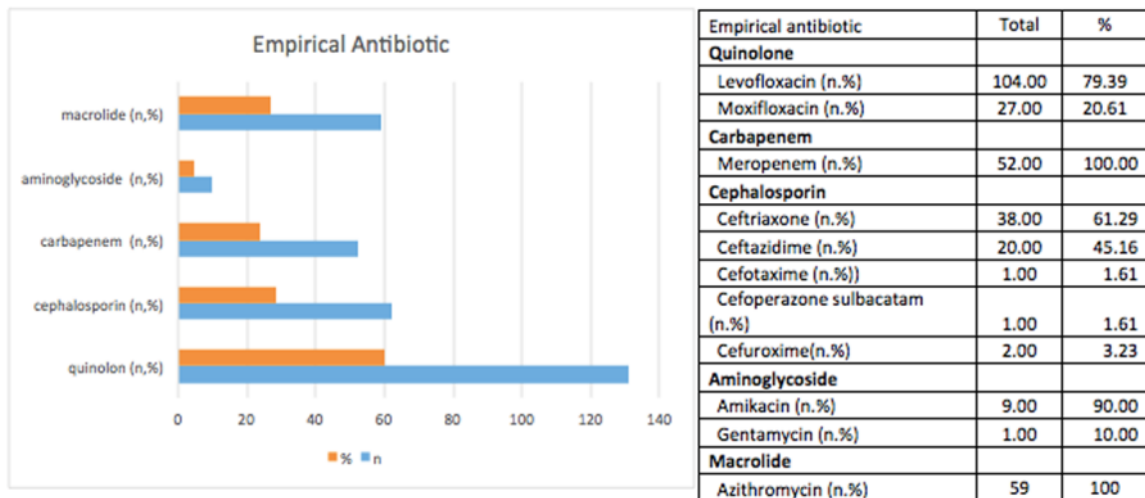


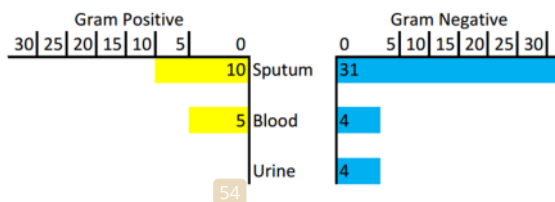
Figure 1. The empirical antibiotic use in study population.



**Table 3. Result of microbiological culture.**

Culture	Number
<b>Sputum</b>	57
Acinetobacter baumannii	9
Candida spp.	6
Klebsiella pneumoniae	5
Pseudomonas aeruginosa	4
Enterobacter doacae complex	3
Staphylococcus haemolyticus	3
Streptococcus mitis / Streptococcus oralis*	3
Escherichia coli	2
Escherichia coli (ESBL)	1
Others	11
No growth	10
<b>Blood</b>	44
Klebsiella pneumoniae (ESBL+)	2
Staphylococcus epidermidis*	2
Staphylococcus hominis*	2
Pseudomonas fluorescens	1
Pseudomonas putida	1
Staphylococcus haemolyticus	1
No growth	35
<b>Urine</b>	9
Escherichia coli (ESBL)	2
Enterococcus faecalis	1
Pseudomonas putida	1
No growth	5

Note : \*, considered as normal flora bacteria.

**Figure 2. Distribution of Gram-positive and Gram-negative bacteria.**

Neutrophil and lymphocyte ratio (NLR) has been proposed as a prognostic marker of severity in various chronic inflammatory

diseases, including cardiovascular diseases and oncological processes<sup>17</sup>.

Our result showed a significant increase of procalcitonin level and a higher proportion of bacterial infection in severe and critically ill COVID-19 patients. This finding is consistent with the study result from Wang *et al.* in elderly COVID-19 patients. They also concluded that bacterial infection was also considered as a predictor of mortality in these patients<sup>18</sup>. Increased procalcitonin level in COVID-19 patients may be associated with the release of some cytokines, especially IL-6. It is established that procalcitonin is a better marker to predict severity, prognosis, or the sepsis course and is also helpful to guide antibiotic usage. Increased procalcitonin in critically ill patients with COVID-19 can represent a bacterial co-infection, and blood cultures for bacteria detection are needed to a prompt response<sup>19</sup>.

In this study, we found that bacterial infection was confirmed in 43 patients (19,7%). The bacterial infection that was detected at patient admission (bacterial co-infection) was 23%, while bacterial infection that occurs late during hospital stay (secondary infection) was 77%. The prevalence of bacterial co-infections in patients admitted to the ICU for acute respiratory failure related to COVID-19 pneumonia is poorly studied<sup>20,21</sup>. In Fu *et al.* study, 13.9% (5 of 36) of the patients in the ICU were diagnosed with COVID-19 and secondary bacterial infection. In another report that was published from a UK secondary care setting, 27 among 836 patients (3.2%) had early confirmed bacterial isolates identified (0–5 days post-admission), rising to 51 cases (6.1%) during the admission. In a study conducted in Shiraz, Iran, in 2009, Hassanzadeh *et al.* suggested that ICU-acquired infections were documented in 51.7% of ICU patients, with a mortality rate of 10.9% (5 patients)<sup>22,23</sup>. Our finding was relatively higher among other studies. The possible explanation is that most of the patients had been treated in hospital for more than two weeks (average 12–17 days). Secondary infections usually correspond with nosocomial or healthcare-associated infections. Nosocomial infections are most commonly correlated with invasive medical devices or surgical procedures. Lower respiratory tract and bloodstream infections have the highest mortality, while urinary tract infections are the most common<sup>24</sup>.

The median length of stay among patients in our study was higher in the bacterial co-infection group rather than non co-infection, with an average of 17.6 and 13.31 days, respectively. This finding is consistent with the result of several studies<sup>22,25</sup>. Sharifpour *et al.* reported that the median length of stay is around 15 days (interquartile range, 2 to 39). A study on respiratory co-infection in patients with pandemic 2009 influenza A (H1N1) virus infection showed that ICU length of stay was three days longer among patients with co-infection. Another study by Zhou *et al.* reported a longer length of stay of 8.0 days (4.0–12.0) of all patients with COVID-19 admitted to their ICU<sup>12</sup>. These findings suggest that the length of ICU stay can be prolonged if patients become co-infected.

The most common bacterial infection in this study was from respiratory tract infection, followed by bloodstream infection and urinary tract infection. The culture result was dominated by gram-negative bacteria (75.68%). This finding is similar to the result from Zhang *et al.* (50%), although they also included virus and fungal cultures<sup>3</sup>. Gram-negative bacteria were reported responsible for more than 30% of healthcare-associated infections, and these bacteria predominate in cases of ventilator-associated pneumonia (47%) and urinary tract infections (45%)<sup>24</sup>. In intensive care units (ICUs), gram-negative bacteria account for about 70% of these types of infections<sup>26</sup>. Gram-negative bacteria are highly efficient at up-regulating or acquiring genes that code for antimicrobial resistance mechanisms, especially in the presence of antibiotic selection pressure. Among gram-negative bacteria, the *Enterobacteriaceae* family being the most commonly found and multidrug-resistant organisms, including *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and extended-spectrum  $\beta$ -lactamase (ESBL)-producing or carbapenemase-producing *Enterobacteriaceae*, are increasingly being reported worldwide<sup>24</sup>. The identification of bacterial infection with gram-negative organisms is more reflected as a complication of ICU care and is not suggested as a specific predilection for co-infections in COVID-19<sup>23</sup>.

*Acinetobacter baumannii* is the most common bacteria found in this study. Several reports regarding bacterial infection in COVID-19 also found a similar result<sup>3,7,9,19,24</sup>. *Acinetobacter baumannii* is the common cause of respiratory tract infection, especially in ICU settings where patients often received mechanical ventilation. Environmental contamination also plays a role in this phenomenon. Our ICUs for COVID-19 patients were set as a large ward consist of 16 beds. Although we already managed the distance between beds for more than 1.5 meters, the inter-patient transmission is hard to avoid. It is crucial to maintain hand hygiene compliance of the staff, strict cleanliness, and disinfection of the hospital environment in the hospital, especially in high-care or ICU setting.

Antibiotic is often given to COVID-19 patients for various reasons. The clinical manifestation on presentation was sometimes challenging to distinguish with bacterial infection<sup>2</sup>. Secondary infection and nosocomial infection are also other considerations in the use of antibiotics. In this study, 75.3% of patients included were given antibiotics. A meta-analysis conducted about bacterial co-infection and secondary infection in COVID-19 patients reported that the majority of patients with COVID-19 received antibiotics (71.9%, 95%CI 56.1 to 87.7%)<sup>27</sup>. Another meta-analysis reported that >90% of COVID-19 patients were given an empirical antibiotic, while the bacterial infection was detected only in 7% of hospitalized patients and 14% of ICU patients<sup>28</sup>. Quinolones (levofloxacin and moxifloxacin) were frequently prescribed, followed by cephalosporins and carbapenems. Indonesian national guidelines for COVID-19 treatment recommend using antibiotics in severe and critically ill patients, especially if there was suspicion of bacterial infection. The empirical antibiotic choice was intravenous azithromycin or levofloxacin<sup>10</sup>. In our hospital, levofloxacin is more feasible than azithromycin, so clinicians prefer to prescribe this drug. In our hospital, antibiotic use usually was decided based on clinical signs and laboratory parameters (leukocytosis, increased CRP, or procalcitonin). Culture examinations were not

routinely performed, preferably in ICU/high-care settings and in patients showing bacterial infection.

The widespread use of antibiotics in this pandemic era raises concern about antimicrobial resistance<sup>4,6</sup>. Although bacterial infection in COVID-19 patients has already been reported in various results, evidence supports the restrictive use of antibiotics. Clinical guidelines and standard testing to diagnose bacterial infection in COVID-19 are not clearly available. The microbiological examination is an important strategy to confirm bacterial infection and decide the antibiotic choice<sup>4</sup>. Sputum, blood culture samples, and also pneumococcal urinary antigen testing should also be performed. Antibiotics should be stopped in patients who represent cultures, and urinary antigen tests show no signs of bacterial pathogens after 48 hours<sup>29</sup>.

39 There are some limitations to our study. First, we only included COVID-19 patients in high-care and intensive care units. In low-care settings, bacterial infection cannot be confirmed due to limited data. Second, we only reported bacterial infection from microbiology results. Virus culture or gene sequencing to detect pathogens is not available in our hospital. Bacterial culture was not performed in all COVID-19 patients, so in a condition where the sign of infection is absent such as in elderly or in immunocompromised patients, the bacterial infection might be underdiagnosed.

## Conclusions

11 Bacterial infection was detected in 19.7% of COVID-19 patients admitted in high-care and intensive care units, predominantly secondary infections. COVID-19 patients who suffered from bacterial infection have a longer length of stay and have higher mortality. The pathogen commonly found in this study was *Acinetobacter baumannii* that yielded from sputum. Increased antibiotic use and multi-drug resistant organism is an emerging problem in this pandemic situation. Infection control practice need to strictly conducted to reduced secondary or healthcare-associated infection

## 18 Data availability

### Underlying data

Dryad: The clinical impact of bacterial co-infection among moderate, severe and critically ill COVID-19 patients in the second referral hospital in Surabaya, <https://doi.org/10.5061/dryad.sxksn0328><sup>30</sup>.

This project contains the following underlying data:

- Baseline characteristics for all patients
- Lab data for all participants

14 Data are available under the terms of the Creative Commons Zero "No rights reserved" data waiver (CC0 1.0 Public domain dedication).

## Acknowledgments

We would like to thank Esthiningrum Dewi Agustin, Jamiatul Khairiyah, Nila Novia Putri, Adhyasta Nata Prawira S for supporting this research.

## References

1. Satuan Tugas Penanganan COVID-19: **Peta Sebaran COVID-19 Satgas Penanganan COVID-19**. 2020.
2. Fattorini L, Creti R, Palma C, et al.: **Bacterial coinfections in COVID-19: an underestimated adversary**. *Ann Ist Super Sanita*. 2020; **56**(3): 359–64. [PubMed Abstract](#) | [Publisher Full Text](#)
3. Zhang H, Zhang Y, Wu J, et al.: **Risks and features of secondary infections in severe and critical ill COVID-19 patients**. *Emerg Microbes Infect*. 2020; **9**(1): 1958–64. [PubMed Abstract](#) | [Publisher Full Text](#)
4. Chen X, Liao B, Cheng L, et al.: **The microbial coinfection in COVID-19**. *Appl Microbiol Biotechnol*. 2020; **104**(18): 7777–85. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
5. Ruuskanen O, Lahti E, Jennings LC, et al.: **Viral pneumonia**. *Lancet*. 2011; **377**(9773): 1264–75. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
6. Bengoechea JA, Bamford CG: **SARS-CoV-2, bacterial co-infections, and AMR: the deadly trio in COVID-19?** *EMBO Mol Med*. 2020; **12**(7): e12560. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
7. Fu Y, Yang Q, Xu M, et al.: **Secondary Bacterial Infections in Critical Ill Patients With Coronavirus Disease 2019**. *Open Forum Infect Dis*. 2020; **7**(6): ofaa220. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
8. Sampieri RH: **Clinical Management of COVID 19**. 2020; **I**: 634.
9. Burhan E, Susanto AD, Nasution SA, et al.: **Pedoman Tatalaksana COVID-19**. 1st. 2020.
10. Burhan E, Susanto AD, Nasution SA, et al.: **Pedoman Tatalaksana COVID-19**. 2nd, Agustus ed. Pedoman Tatalaksana COVID-19. PDPI, PERKI, PAPDI, PERDATIN, IDAI. 2020; 3–6. [Reference Source](#)
11. IBM: **IBM SPSS Statistics for Windows, Version 24.0**. Armonk, NY: IBM Corp.: IBM Corp; 2016.
12. Zhou F, Yu T, Du R, et al.: **Clinical Course and Risk Factors for Mortality of Adult Inpatients with COVID-19 in Wuhan, China: a Retrospective Cohort Study**. *Lancet*. 2020; **395**(10229): 1054–62. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
13. Lv Z, Cheng S, Le J, et al.: **Clinical characteristics and co-infections of 354 hospitalized patients with COVID-19 in Wuhan, China: a retrospective cohort study**. *Microbes Infect*. 2020; **22**(4–5): 195–9. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
14. Barry M, AlMohaya A, AlHijji A, et al.: **Clinical Characteristics and Outcome of Hospitalized COVID-19 Patients in a MERS-CoV Endemic Area**. *J Epidemiol Glob Health*. 2020; **10**(3): 214–221. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
15. Ma S, Lai X, Chen Z, et al.: **Clinical characteristics of critically ill patients co-infected with SARS-CoV-2 and the influenza virus in Wuhan, China**. *Int J Infect Dis*. 2020; **96**: 683–7. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
16. Tan L, Wang Q, Zhang D, et al.: **Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study**. *Signal Transduct Target Ther*. 2020; **5**(1): 33. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
17. Jimeno S, Ventura PS, Castellano JM, et al.: **Prognostic implications of neutrophil-lymphocyte ratio in COVID-19**. *Eur J Clin Invest*. 2021; **51**(1): e13404. [PubMed Abstract](#) | [Publisher Full Text](#)
18. Wang L, He W, Yu X, et al.: **Coronavirus disease 2019 in elderly patients: Characteristics and prognostic factors based on 4-week follow-up**. *J Infect*. 2020; **80**(6): 639–45. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
19. Martins-Filho PR, Tavares CSS, Santos VS: **Factors associated with mortality in patients with COVID-19. A quantitative evidence synthesis of clinical and laboratory data**. *Eur J Intern Med*. 2020; **76**: 97–9. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
20. Contou D, Claudinon A, Pajot O, et al.: **Bacterial and viral co-infections in patients with severe SARS-CoV-2 pneumonia admitted to a French ICU**. *Ann Intensive Care*. 2020; **10**(1): 119. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
21. Zhou P, Liu Z, Chen Y, et al.: **Bacterial and fungal infections in COVID-19 patients: A matter of concern**. *Infect Control Hosp Epidemiol*. 2020; **41**(9): 1124–5. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
22. Sharifipour E, Shams S, Esmkhani M, et al.: **Evaluation of bacterial co-infections of the respiratory tract in COVID-19 patients admitted to ICU**. *BMC Infect Dis*. 2020; **20**(1): 646. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
23. Lansbury L, Lim B, Baskaran V, et al.: **Co-Infections in People with COVID-19: A Systematic Review and Meta-Analysis**. *SSRN Electron J*. 2020. [Publisher Full Text](#)
24. Peleg AY, Hooper DC: **Hospital-Acquired Infections Due to Gram-Negative Bacteria**. *N Engl J Med*. 2010; **362**(19): 1804–13. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
25. Rothe K, Feihl S, Schneider J, et al.: **Rates of bacterial co-infections and antimicrobial use in COVID-19 patients: a retrospective cohort study in light of antibiotic stewardship**. *Eur J Clin Microbiol Infect Dis*. 2021; **40**(4): 859–869. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
26. Gaynes R, Edwards JR, National Nosocomial Infections Surveillance System: **Overview of Nosocomial Infections Caused by Gram-Negative Bacilli**. *Clin Infect Dis*. 2005; **41**(6): 848–54. [PubMed Abstract](#) | [Publisher Full Text](#)
27. Langford BJ, So M, Raybardhan S, et al.: **Bacterial co-infection and secondary infection in patients with COVID-19: a living rapid review and meta-analysis**. *Clin Microbiol Infect*. 2020; **26**(12): 1622–1629. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
28. Lansbury L, Lim B, Baskaran V, et al.: **Co-infections in people with COVID-19: a systematic review and meta-analysis**. *J Infect*. 2020; **81**(2): 266–75. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
29. Sieswerda E, de Boer MGJ, Bonten MMJ, et al.: **Recommendations for antibacterial therapy in adults with COVID-19 - an evidence based guideline**. *Clin Microbiol Infect*. 2021; **27**(1): 61–66. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
30. Asmarawati TP, Rosyid AN, Suryantoro SD, et al.: **The clinical impact of bacterial co-infection among moderate, severe and critically ill COVID-19 patients in the second referral hospital in Surabaya**. *Dryad*. 2021. <http://www.doi.org/10.5061/dryad.sxksn0328>

## Open Peer Review

Current Peer Review Status:  

### Version 2

Reviewer Report 07 April 2021

<https://doi.org/10.5256/f1000research.55357.r82430>

© 2021 Ekawati F. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



**Fitriana Murriya Ekawati** 

Department of Family and Community Medicine, Universitas Gadjah Mada, Yogyakarta, Indonesia

I can see that there are some improvements in the manuscript that the authors have provided. However, I believe the quality can be further improved by accomodating these minor suggestions:

1. Abstract, background, remove "in our country Indonesia" the sentence can be improved as:  
While the prevalence of COVID in Indonesia is high, data on the prevalence of...are limited.
2. The information for the antibiotic selection is already in the heading of "pathogens associated with bacterial infection", I wonder if the last paragraph on the "bacterial infection" can be shifted under the "pathogens" heading?
3. Discussion: what are suggestions for further research raised from this paper? There are some uncertainties mentioned by the authors regarding the use/guideline of antibiotics in COVID. It can be one of them.

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Health service research in LMICs

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

### Version 1

Reviewer Report 23 March 2021

<https://doi.org/10.5256/f1000research.34701.r81317>

© 2021 Nelwan E. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



**Erni J. Nelwan** 

Division of Tropical and Infectious Disease, Universitas Indonesia, Jakarta, Indonesia

A well written article and proper data collection to support the conclusion. From a LMIC like Indonesia, this article shares important findings, since the co-bacterial infection is not more than 20%, higher than reported in IDSA data but lower compared to what had been expected in clinical practice among Indonesian doctors.

Authors might add value by putting a highlight on what is the clinical appearance of the co-bacterial infected vs. the non co-bacterial infected for readers to apply in daily practice.

**Is the work clearly and accurately presented and does it cite the current literature?**

Yes

**Is the study design appropriate and is the work technically sound?**

Yes

**Are sufficient details of methods and analysis provided to allow replication by others?**

Yes

**If applicable, is the statistical analysis and its interpretation appropriate?**

Yes

**Are all the source data underlying the results available to ensure full reproducibility?**

Yes

**Are the conclusions drawn adequately supported by the results?**

Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** tropical medicine and infectious disease

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

Reviewer Report 09 March 2021

<https://doi.org/10.5256/f1000research.34701.r80840>

© 2021 Ekawati F. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



**Fitriana Murriya Ekawati** 

Department of Family and Community Medicine, Universitas Gadjah Mada, Yogyakarta, Indonesia

Thank you very much for the opportunity for reviewing this manuscript. This manuscript has presented interesting findings of bacterial coinfection in COVID-19 patients. Data collected for the research were from patients' medical records in Univ Airlangga hospital in Indonesia. The presentations of Methods, Results, and Discussion in the manuscript are appropriate. However, there are some minor revisions needed, which I believe are beneficial for improving the manuscript:

- Introduction
  - Line 1. I would recommend the authors to improve the first sentence of the first and second paragraph to improve clarity.
  - Are there any prior investigations related to this topic in Indonesia? Please write/present if in the introduction there is any.
    - Methods
  - Just to clarify, so the infection was examined if there is any suspicion of bacterial infection and not a routine examination?
- Results
  - Statistical analysis: SPSS version 24.0 (citation?).
  - Patient characteristic and laboratory findings, is there any table/summary table associated with the patients' leucocyte count, procalcitonin? Please cite/involve the summary table in the main manuscript.
    - Discussion
  - Are there any things that still unknown/need further investigation arising from this research?
  - What are the study implications for further research and practice?
  - I would recommend a language proofreading for this manuscript.

Best wishes to the authors for the manuscript revision.

**Is the work clearly and accurately presented and does it cite the current literature?**

Yes

**Is the study design appropriate and is the work technically sound?**

Yes

**Are sufficient details of methods and analysis provided to allow replication by others?**

Yes

**If applicable, is the statistical analysis and its interpretation appropriate?**

Yes

**Are all the source data underlying the results available to ensure full reproducibility?**

Yes

**Are the conclusions drawn adequately supported by the results?**

Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Health service research in LMICs

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**

Author Response 09 Mar 2021

**Tri Pudy Asmarawati**, Faculty of Medicine, Airlangga University, Surabaya, Indonesia

We firstly would like to thank you for the kindly comprehensive review of our manuscript. Here's to answer and respond to your questions:

1. Introduction

- We believe that there is no prior investigation linked to this topic ever done before in Indonesia

2. Methods

- We clarify that the bacterial culture examination was done on the suspicious patients only.

3. Results

- We have enclosed the leucocyte and procalcitonin data of the patients on the table 1.

4. Discussion

- In the study to come, further investigation can probably be done on the low health-care setting, also bigger concerns on under-diagnosed bacterial co-infection of elderly and immunocompromised patients can be taken into consideration.
- The implication of the study is that we find the bacterial culture examination necessary in the COVID-19 patients management since the bacterial co-infection might worsen the clinical outcome.

Furthermore, we also appreciate your suggestions in order to improve the final quality of this manuscript. We are currently working on the minor revisions, proof-reading, and going to submit the latest version promptly.

**Competing Interests:** No competing interests were disclosed.

Author Response 25 Mar 2021

**Tri Pudy Asmarawati**, Faculty of Medicine, Airlangga University, Surabaya, Indonesia

We have just process revised several points on the manuscript as what the reviewer, named Fitriana Murriya Ekawati, had recommended a couple days ago. We include the latest version of our manuscript down below along with highlighted changes. We also insert our reply to the reviewer, which said:

"We firstly would like to thank you for the kindly comprehensive review of our manuscript. Here's to answer and respond to your questions:

1. Introduction

- We believe that there is no prior investigation linked to this topic ever done before in Indonesia. We added this information in the second and last paragraphs of Introduction

2. Methods

- Yes, the bacterial culture examination was done on the suspicious patients only. Please refer to the last sentence of the paragraph 8 in the Discussion section.

3. Results

- We have enclosed the leucocyte and procalcitonin data of the patients on the table 1 on Result section

4. Discussion

- In the study to come, further investigation can probably be done in the low health-care setting, also bigger concerns on under-diagnosed bacterial co-infection of elderly and immunocompromised patients can be taken into consideration. we added this sentence on the last paragraph of the discussion.

- The implication of the study is that we find the bacterial culture examination necessary in the COVID-19 patients management since the bacterial co-infection might worsen the clinical outcome. Therefore this examination should be conducted when the patient shows signs of infection during the intensive care. We added this sentence in the second paragraph of the introduction.

Furthermore, we also appreciate your suggestions in order to improve the final quality of this manuscript. We are currently working on the minor revisions, proof-reading, and going to submit the latest version it promptly"

Hope this will meet all the requirement and we will receive the final pdf proof soon.

Thanks in advance,  
Tri Pudy Asmarawati and research team

**Competing Interests:** No competing interest were disclosed



The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact [research@f1000.com](mailto:research@f1000.com)

**F1000Research**

# The clinical impact of bacterial co-infection among moderate, severe and critically ill COVID-19 patients in the second referral hospital in Surabaya

## ORIGINALITY REPORT

19%

SIMILARITY INDEX

8%

INTERNET SOURCES

18%

PUBLICATIONS

0%

STUDENT PAPERS

## PRIMARY SOURCES

- 1 "Proceedings of Reanimation 2022, the French Intensive Care Society International Congress", Annals of Intensive Care, 2022  
Publication 1%
- 2 Saif Aldeen AlRyalat, Khaled Al Oweidat, Mohammad Al-Essa, Khaled Ashouri et al. "Influenza Altmetric Attention Score and its association with the influenza season in USA", F1000Research, 2020  
Publication 1%
- 3 Paulo Ricardo Martins-Filho, Carolina Santos Souza Tavares, Victor Santana Santos. "Factors associated with mortality in patients with COVID-19. A quantitative evidence synthesis of clinical and laboratory data", European Journal of Internal Medicine, 2020  
Publication 1%
- 4 Zhimei Zhong, Hongyuan Li, Jieyun Zhu, Pan Ji, Bocheng Li, Jielong Pang, Jianfeng Zhang, 1%

Xiangdong Liang. "Clinical characteristics of 2,459 severe or critically ill COVID-19 patients", *Medicine*, 2021

Publication

---

5

Lorenzo M. Canziani, Serena Trovati, Enrico Brunetta, Amidio Testa et al. "Interleukin-6 receptor blocking with intravenous tocilizumab in COVID-19 severe acute respiratory distress syndrome: A retrospective case-control survival analysis of 128 patients", *Journal of Autoimmunity*, 2020

Publication

---

1 %

6

Abdulaziz Alqahtani, Edrous Alamer, Mushtaq Mir, Ali Alasmari et al. "Bacterial Coinfections Increase Mortality of Severely Ill COVID-19 Patients in Saudi Arabia", *International Journal of Environmental Research and Public Health*, 2022

Publication

---

1 %

7

Hayam Mahmoud, Anwar Ebid, Mohammed Alghamdi, Abeer Ibrahim, Ahmed Almoosa. "Prevalence of Musculoskeletal, Neurological and Physical Disorder After COVID-19 in Saudi Arabia: A Cross Sectional Study", *F1000Research*, 2022

Publication

---

1 %

8

"1-A3: Clinical Respiratory Medicine 1 : Poster Sessions", *Respirology*, 2013.

Publication

1 %

9

Kyungwon Lee. "Further Increases in Carbapenem-, Amikacin-, and Fluoroquinolone-Resistant Isolates of Acinetobacter spp. and P. aeruginosa in Korea: KONSAR Study 2009", Yonsei Medical Journal, 2011

Publication

1 %

10

Anggia Prasetyoputri. "Detection of Bacterial Coinfection in COVID-19 Patients Is a Missing Piece of the Puzzle in the COVID-19 Management in Indonesia", ACS Infectious Diseases, 2021

Publication

<1 %

11

Inass Taha, Yasser Abdou, Ikhlas Hammad, Omnia Nady et al. "Utilization of Antibiotics for Hospitalized Patients with Severe Coronavirus Disease 2019 in Al-Madinah Al-Munawara, Saudi Arabia: A Retrospective Study", Infection and Drug Resistance, 2022

Publication

<1 %

12

Y Yuliani, Putut Har Riyadi, Eko Nurcahya Dewi, Irwandi Jaswir, Tri Winarni Agustini. "Ocimumbasilicum(kemangi)intervention on powder and microencapsulatedSpirulina platensisand itsbioactivemolecules", F1000Research, 2021

Publication

<1 %

13

Internet Source

&lt;1 %

14

Jennifer F. Morton, Laura Myers, Katherine Gill, Linda-Gail Bekker et al. "Evaluation of a behavior-centered design strategy for creating demand for oral PrEP among young women in Cape Town, South Africa", Gates Open Research, 2020

Publication

&lt;1 %

15

[journals.plos.org](https://journals.plos.org)

Internet Source

&lt;1 %

16

[innovareacademics.in](https://innovareacademics.in)

Internet Source

&lt;1 %

17

[www.researchgate.net](https://www.researchgate.net)

Internet Source

&lt;1 %

18

Mohidin Norhani, Yu Chen Low, Mohd-Ali Bariah, Mohamad Shahimin Mizhanim, Arif Norlaili. "Corneal endothelial morphology of healthy myopic Malaysian children of Chinese ethnicity aged 8-9 years and its association with axial length", F1000Research, 2022

Publication

&lt;1 %

19

Bradley J. Langford, Miranda So, Sumit Raybardhan, Valerie Leung et al. "Bacterial co-infection and secondary infection in patients with COVID-19: a living rapid review and

&lt;1 %

meta-analysis", Clinical Microbiology and Infection, 2020

Publication

20

Pant, Narayan Dutt, and Manisha Sharma. "Environmental screening for microorganisms of patient's surrounding as the possible source of nosocomial infections in a hospital in Nepal", Journal of Biomedical Sciences, 2016.

Publication

<1 %

21

Linh Thuy Thi Doan, Huyen Phuc Do, Huong Lan Thi Nguyen, Huong Le Thi, Dung Kim Pham. "Results of early warning indicators for HIV/AIDS in 42 outpatient clinics in 25 northern provinces of Vietnam", F1000Research, 2017

Publication

<1 %

22

Sara Jimeno, Paula S. Ventura, Jose M. Castellano, Salvador I. García - Adasme et al. "Prognostic implications of neutrophil - lymphocyte ratio in COVID - 19", European Journal of Clinical Investigation, 2020

Publication

<1 %

23

[www.jaypeedigital.com](http://www.jaypeedigital.com)

Internet Source

<1 %

24

Adrian J. Brink, Guy Richards, Hafsa Tootla, Elizabeth Prentice. "Epidemiology of Gram-negative bacteria during coronavirus disease

<1 %

2019. What is the real pandemic?", Current Opinion in Infectious Diseases, 2022

Publication

25

Chih-Cheng Lai, Shey-Ying Chen, Wen-Chien Ko, Po-Ren Hsueh. "Increased antimicrobial resistance during the COVID-19 pandemic", International Journal of Antimicrobial Agents, 2021

Publication

<1 %

26

Louise Lansbury, Benjamin Lim, Vadsala Baskaran, Wei Shen Lim. "Co-infections in people with COVID-19: a systematic review and meta-analysis", Journal of Infection, 2020

Publication

<1 %

27

Saber Soltani, Samireh Faramarzi, Milad Zandi, Ramin Shahbahrami et al. "Bacterial Co-infection among COVID-19 patient groups: an update Systematic review and Meta-analysis", New Microbes and New Infections, 2021

Publication

<1 %

28

[link.springer.com](https://link.springer.com)

Internet Source

<1 %

29

Abdul Khairul Rizki Purba, . Mustofa, Indwiani Astuti. "Synergistic interaction between quercetin and doxorubicin on MCF-7 human breast cancer cell line", Journal of thee

<1 %

30

Jackson S. Musuuza, Lauren Watson, Vishala Parmasad, Nathan Putman-Buehler, Leslie Christensen, Nasia Safdar. "Prevalence and outcomes of co-infection and superinfection with SARS-CoV-2 and other pathogens: A systematic review and meta-analysis", PLOS ONE, 2021

Publication

---

<1 %

31

Bradley J. Langford, Miranda So, Valerie Leung, Sumit Raybardhan et al. "Predictors and microbiology of respiratory and bloodstream bacterial infection in patients with COVID-19: living rapid review update and meta-regression", Clinical Microbiology and Infection, 2021

Publication

---

<1 %

32

Meryl B. Kravitz, Elizabeth Yakubova, Nick Yu, Steven Y. Park. "Severity of Sleep Apnea and COVID-19 Illness", OTO Open, 2021

Publication

---

<1 %

33

Shuyan Chen, Qing Zhu, Yanyu Xiao, Chi Wu, Zhaofang Jiang, Lei Liu, Jiuxin Qu. "Clinical and etiological analysis of co - infections and secondary infections in COVID - 19 patients:

<1 %



An observational study", The Clinical  
Respiratory Journal, 2021

Publication

---

34

Yichun Cheng, Ran Luo, Kun Wang, Meng Zhang, Zhixiang Wang, Lei Dong, Junhua Li, Ying Yao, Shuwang Ge, Gang Xu. "Kidney disease is associated with in-hospital death of patients with COVID-19", Kidney International, 2020

Publication

---

<1 %

35

[www.pure.ed.ac.uk](http://www.pure.ed.ac.uk)

Internet Source

---

<1 %

36

K Jayasri, CH Pooja, K Padmaja, P Eswara Prasad. "Review on biochemical alterations in COVID-19 patients", International Journal of Clinical Biochemistry and Research, 2020

Publication

---

<1 %

37

Thomas Lardaro, Alfred Z. Wang, Antonino Bucca, Alexander Croft et al. "Characteristics of COVID - 19 patients with bacterial coinfection admitted to the hospital from the emergency department in a large regional healthcare system", Journal of Medical Virology, 2021

Publication

---

<1 %

38

[pure.eur.nl](http://pure.eur.nl)

Internet Source

---

<1 %

39

Bongyoung Kim, Hyunjoo Pai, Won Suk Choi, Yeonjae Kim, Ki Tae Kweon, Hyun Ah Kim, Seong Yeol Ryu, Seong-heon Wie, Jieun Kim. "Current status of indwelling urinary catheter utilization and catheter-associated urinary tract infection throughout hospital wards in Korea: A multicenter prospective observational study", PLOS ONE, 2017

Publication

&lt;1 %

40

Jacek Dutkiewicz, Barbara Mackiewicz, Marta Lemieszek. "COVID 19 – Possible interrelations with respiratory comorbidities caused by occupational exposure to various hazardous bioaerosols. Part I. Occurrence, epidemiology and presumed origin of the pandemic", Annals of Agricultural and Environmental Medicine, 2020

Publication

&lt;1 %

41

[academic.oup.com](https://academic.oup.com)

Internet Source

&lt;1 %

42

"P1198 - P1459", Clinical Microbiology and Infection, 4/2006

Publication

&lt;1 %

43

Evelien A. N. Oostdijk, Anne Marie G. A. de Smet, Jozef Kesecioglu, Marc J. M. Bonten. "The role of intestinal colonization with Gram-negative bacteria as a source for intensive

&lt;1 %

care unit-acquired bacteremia\*", Critical Care Medicine, 2011

Publication

---

44

Ling Ma, Wenjing Wang, Jehane Michael Le Grange, Xiaorong Wang, Shuaixian Du, Chen Li, Jia Wei, Jin-Nong Zhang. "

<1 %

Coinfection of SARS-CoV-2 and Other Respiratory Pathogens

", Infection and Drug Resistance, 2020

Publication

---

45

Muhammad Ilham Aldika Akbar, Khanizyah Erza Gumilar, Eccita Rahestyningtyas, Manggala Pasca Wardhana et al. "Cohort Study: The Accuracy of Screening Methods of COVID-19 in Pregnancy: Practical Approach in Low Resources Health Services", Cold Spring Harbor Laboratory, 2021

<1 %

Publication

---

46

Waleed Alhazzani, Morten Hylander Møller, Yaseen M. Arabi, Mark Loeb et al. "Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19)", Intensive Care Medicine, 2020

<1 %

Publication

---

47

[christie.openrepository.com](http://christie.openrepository.com)

Internet Source

---

<1 %

48

[www.ejmanager.com](http://www.ejmanager.com)

Internet Source

&lt;1 %

49

"OS18: Interstitial Lung Disease 1",  
Respirology, 2013

Publication

&lt;1 %

50

Alfian Nur Rosyid, Daniel Maranatha.  
"Methacholin Provocation Test in COPD and  
Healthy Smokers", Current Respiratory  
Medicine Reviews, 2018

Publication

&lt;1 %

51

H Andel, M Rab, M Felfernig, D Andel, R Koller,  
L-P Kamolz, M Zimpfer. "The axillary vein  
central venous catheter in severely burned  
patients", Burns, 1999

Publication

&lt;1 %

52

J.T. Thaden, S.A. Maskarinec. "When two for  
the price of one isn't a bargain: Estimating  
prevalence and microbiology of bacterial co-  
infections in patients with COVID-19", Clinical  
Microbiology and Infection, 2020

Publication

&lt;1 %

53

N. Lansac, F. J. Picard, C. Ménard, M.  
Boissinot, M. Ouellette, P. H. Roy, M. G.  
Bergeron. "Novel Genus-Specific PCR-Based  
Assays for Rapid Identification of Neisseria  
Species and Neisseria meningitidis", European

&lt;1 %

54

Robert Root-Bernstein. "Innate Receptor Activation Patterns Involving TLR and NLR Synergisms in COVID-19, ALI/ARDS and Sepsis Cytokine Storms: A Review and Model Making Novel Predictions and Therapeutic Suggestions", International Journal of Molecular Sciences, 2021

Publication

<1 %

55

SY Wong, KH Leong, KS Ng, SH Tan, PLC Lo, K Chan. "An elderly couple with COVID-19 pneumonia treated in Singapore: contrasting clinical course and management", Singapore Medical Journal, 2020

Publication

<1 %

56

[austinpublishinggroup.com](http://austinpublishinggroup.com)

Internet Source

<1 %

57

[eprint.ncl.ac.uk](http://eprint.ncl.ac.uk)

Internet Source

<1 %

58

[files.covid19treatmentguidelines.nih.gov](http://files.covid19treatmentguidelines.nih.gov)

Internet Source

<1 %

59

[researchonline.jcu.edu.au](http://researchonline.jcu.edu.au)

Internet Source

<1 %

60

Rasoul Mirzaei, Pedram Goodarzi, Muhammad Asadi, Ayda Soltani et al.

<1 %

"Bacterial co-infections with SARS-CoV-2",  
IUBMB Life, 2020

Publication

---

61

"Abstracts", *Respirology*, 11/2011

Publication

---

<1 %

62

Elske Sieswerda, Mark G.J. De Boer, Marc M.J. Bonten, Wim G. Boersma et al.

"Recommendations for antibacterial therapy in adults with COVID-19 – an evidence based guideline", *Clinical Microbiology and Infection*, 2020

Publication

---

<1 %

63

Niels Hvidt, Alex Kappel Kørup, Farr Curlin, Klaus Baumann et al. "The NERSH International Collaboration on Values, Spirituality and Religion in Medicine: Development of Questionnaire, Description of Data Pool, and Overview of Pool Publications", *Religions*, 2016

Publication

---

<1 %

64

Ronald A. Seaton, Cheryl L. Gibbons, Lesley Cooper, William Malcolm et al. "Survey of antibiotic and antifungal prescribing in patients with suspected and confirmed COVID-19 in Scottish hospitals", *Journal of Infection*, 2020

Publication

---

<1 %

Exclude quotes      On

Exclude matches      Off

Exclude bibliography      On

# The clinical impact of bacterial co-infection among moderate, severe and critically ill COVID-19 patients in the second referral hospital in Surabaya

---

GRADEMARK REPORT

---

FINAL GRADE

**/100**

GENERAL COMMENTS

**Instructor**

---

PAGE 1

---

PAGE 2

---

PAGE 3

---

PAGE 4

---

PAGE 5

---

PAGE 6

---

PAGE 7

---

PAGE 8

---

PAGE 9

---

PAGE 10

---

PAGE 11

---

PAGE 12

---

PAGE 13

---

PAGE 14

---

PAGE 15

---

PAGE 16

---