Original Article

Correlation Between Coinfection of Severe and Critically Ill COVID-19 Patients In Intensive Care Unit with Leucocyte, Neutrophil, CRP, Procalcitonin and Length of Stay

Harman Prayitno[1], Yani Jane Sugiri[1], Tri Wahju Astuti[1], Arie Zainul Fatoni[2], Nurima Diyah Puji Hastuti[3]

[1]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Brawijaya University, Dr. Saiful Anwar General Hospital, Malang
[2]Department of Anesthesiology and Intensive Care, Faculty of Medicine, Brawijaya University, Dr. Saiful Anwar General Hospital, Malang
[3]Department of Clinical Microbiology, Faculty of Medicine, Brawijaya University, Dr. Saiful Anwar General Hospital, Malang

Corresponding Author:
Harman Prayitno | Department of Pulmonary and Respiratory Medicine, Faculty of Medicine, Brawijaya University, Dr. Saiful Anwar General Hospital, Malang | Dr.harman.prayitno@gmail.com

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Abstract

Background: Severe or critical COVID-19 infections are linked to admissions in the intensive care unit (ICU), which increases the risk of coinfection and results in a worsened prognosis. This research seeks to evaluate the relationship between bacterial and fungal coinfection in COVID-19 and leukocyte, neutrophil, C-Reactive Protein (CRP), procalcitonin levels, length of stay, and outcome (whether the patient was discharged from ICU to the ward or died).

Method: This research constitutes a retrospective cohort analysis. Data was collected from the medical records of patients admitted to the ICU of Saiful Anwar General Hospital in Malang from August 2020 to August 2021, who tested positive for COVID-19. A total of 352 individuals qualified according to the inclusion criteria.

Results: Coinfection occurred in 22.2% of COVID-19 patients, with bacterial 84.61%, fungal 11.53%, and both bacterial and fungal 3.84%. The average stay for patients without coinfection was 6 days, while it was 13 days for those with coinfection. We also observed a rise in mortality rate for coinfection at 71.8% compared to 31% for non-coinfection. Coinfection with bacterial, fungal, or both types in COVID-19 shows a positive correlation with Leucocyte (P=0.001; r=0.356), Neutrophil (P=0.001; r=0.438), CRP (P=0.003; r=0.164) and Procalcitonin (P=0.001; r=0.192) as well as a positive correlation with the length of stay (P=0.001) and a negative correlation with the outcome (P=0.001).

Conclusion: Coinfection occurred in just about one-fifth of COVID-19 patients. We suggest prescribing antimicrobials only when there is a compelling reason. Timely detection of bacterial and fungal coinfection was essential to identify high-risk patients and determine appropriate interventions to prevent longer hospital stays and reduce mortality.

Keywords: COVID-19, coinfection, length of stay, mortality

INTRODUCTION

In Wuhan, China, around the end of 2019, there was a pneumonia case without a known cause. In certain cases, severe symptoms of respiratory tract infection occur, including acute respiratory distress syndrome (ARDS), acute respiratory failure (ARF), and other serious complications. Later, a new coronavirus was identified by the Chinese Centre for Disease Control and Prevention (CDC) and named 2019 – nCoV by WHO.[1]

The WHO declared the novel coronavirus (COVID-19) outbreak a pandemic on March 11, 2020. In its report, the WHO expressed concern about the spread and severity of the disease. According to the most recent COVID-19 pandemic reports, there have been 3,167,039 deaths and 150,359,096 confirmed cases of the virus worldwide, which is a significant number in many nations, including Indonesia.[2]

Co-infection with SARS-CoV-2 has received less research attention, as most studies focus only on SARS-CoV-2. Coinfections with certain pathogens can also hinder an accurate diagnosis of the disease. In addition to providing information on bacterial and fungal infections, Wang et al offer the most recent SARS-CoV-2 coinfection status in China.[3] The type and prevalence of co-infections in SARS-CoV-2-positive patients remain uncertain.

Bacterial and fungal infections are common complications of viral pneumonia, especially in critically ill patients. Bacterial and fungal coinfections increase the need for intensive care and increase mortality. In influenza patients, bacterial co-infection occurs in ~0.5% of healthy young individuals and at least 2.5% of older individuals.[4]

Several factors increase the risk of developing bacterial and fungal infections in COVID-19 patients. First, the action of SARS-CoV-2 itself causes tissue damage, infection of enterocytes, and changes in intestinal haemostasis. Second, there is an intense release of inflammatory cytokines and dysregulation of the immune system. Thirdly, invasive medical procedures and prolonged hospital stays are associated with patient features and comorbidities (such as chronic obstructive pulmonary disease (COPD), diabetes, chronic renal failure, and immunosuppression). Additionally, the pandemic crisis led to overworked medical staff.[5]

Among hundreds of published articles with clinical data, only a few report secondary infections—mostly without detailed pathogens. Even in studies for which data on secondary infection were available, the rate of antibiotic use (94%-100%) was much higher than the reported incidence of secondary infection (10%-15%). In addition, most current infection control protocols aim to prevent transmission and cross-infection of SARS-CoV-2 without considering the prevention of secondary bacterial or fungal infection.[4]

Researchers are interested in studying co-infections, particularly bacterial and fungal infections in COVID-19, their correlation with the duration of

hospitalization, and clinical outcomes considering the facts.

METHOD

A retrospective cohort study was conducted on patients with severe or critical confirmed COVID-19 cases who were hospitalized in the COVID-19 Intensive Care Unit of RSUD Dr. Saiful Anwar Malang. Ethical clearance has been approved by the ethics committee with the number 400/165/K.3/302/2021.

Inclusion criteria in this study were patients who underwent sputum, blood, or urine culture examination; patients over 18 years old; patients with complete data on sputum culture results and/or blood and/or urine, and laboratory data of leukocytes, neutrophils, C-Reactive Protein (CRP) and procalcitonin. Patients who died before sputum, blood, or urine cultures were performed, as well as those with incomplete medical records, were excluded from the study.

According to the formula, the minimum number of samples was 76 people. In this study, 352 subjects who met the inclusion and exclusion criteria were taken data including data on the history of the course of the disease, epidemiological data, clinical data, supporting examination data both laboratory and radiology from the patient's medical record. Receiver Operating Characteristic (ROC) curve was used to determine the cut-off value of leukocytes, neutrophils, CRP and procalcitonin variables in determining the risk of coinfection.

The data was analysed and processed using IBM SPSS software version 26.0. Numerical data are reported by the mean and standard deviation. Categorical data are reported by percentage. The Kruskal-Walis test was used for analysis of variables and statistical significance was set at $P<0.05$.

RESULT

A total of 352 patients treated in the intensive care unit of Dr. Saiful Anwar Malang from August 2020 to August 2021 met the inclusion and exclusion criteria.

Table 1. Demographic Profile of Research Subjects

Variables	n	%
Age (mean±SD)	53.71±13.9	
Sex		
Male	117	33.2
Female	235	66.8
Co-infection		
Non-Coinfected	274	77.8
Coinfected with other microorganisms	78	22.2
Coinfected with		
Bacterial	66	84.61
Fungal	9	11.53
Fungal and bacterial	3	3.84

In the univariate analysis (Table 1), the mean age of the 352 COVID-19 patients was 53.71 years, with the youngest patient being 21 years old and the oldest being 88 years old. As many as 117 subjects (33.2%) were male and 235 subjects (66.8%) were female.

There were 274 (77.84%) non-coinfected subjects and 78 (22.15%) coinfected subjects out of a total of 352 subjects that matched the inclusion criteria. Out of them, 66 (84.61%) subjects had

bacterial coinfection, nine (11.53%) had fungal coinfection, and three (3.84%) had both bacterial and fungal coinfection.

Overall, there were 105 pathogens found in 78 co-infected patients. Ninety-three (88.57%) of them were bacteria—majorly accounted with gram-negative bacteria (70; 66.66%), followed by gram-positive bacteria (23; 21.90%)—and the remaining 12 (11.42%) were fungi. The most common pathogens identified were *Acinetobacter baumannii* (25), *Klebsiella pneumoniae* (21), and *Enterococcus faecalis* (15). *Candida glabrata* (4/3.80%) was found in most fungal infections, followed by *Candida albicans* (4/3.80%), *Candida tropicalis* (3/2.87%), and *Candida lusitaniae* (1/0.95%).

The test showed a significant difference in neutrophil counts between individuals with COVID-19 who were not coinfected and those who were coinfected, with patients in the coinfected group having median neutrophil counts that were generally higher (median=91.4%) than those in the non-coinfected group (median=82.85%).

The comparison of CRP in COVID-19 patients between the non-coinfected and coinfected groups revealed a significant value of P=0.001. The test revealed a significant difference in CRP levels between the coinfected and non-coinfected groups of COVID-19 patients, with the coinfected group's median CRP tending to be higher (median=10.06 g/mL) than the non-coinfected group's (median=7.26 g/mL).

The comparison of Procalcitonin in COVID-19 patients between the non-coinfected and coinfected groups showed a significance value (P<0.000), which indicated that Procalcitonin in COVID-19 patients between the non-coinfected and coinfected groups had quite difference in medians, where the median Procalcitonin in the coinfected group (median=0.655 ng/ml) tended to be higher than in the non-coinfected group (median=0.3 ng/ml).

Table 2. Correlation of Leukocyte, Neutrophil, CRP, and Procalcitonin Values with Co-infection in COVID-19 in Spearman Correlation Test

		Correlation	Coefficient Correlation	P
Leu	with	Co-infection	0.356	0.0001
Neutrophil	with	Co-infection	0.438	0.0001
CRP	with	Co-infection	0.187	0.001
Procalcitonin	with	Co-infection	0.221	0.0001
Leu	with	Bacterial co-infection	0.354	0.0001
Neutrophil	with	Bacterial co-infection	0.410	0.0001
CRP	with	Bacterial co-infection	0.164	0.003
Procalcitonin	with	Bacterial co-infection	0.192	0.0001
Leu	with	Fungal co-infection	0.028	0.596
Neutrophil	with	Fungal co-infection	0.096	0.074
CRP	with	Fungal co-infection	0.090	0.105
Procalcitonin	with	Fungal co-infection	0.122	0.024
Leu	with	Bacterial and fungal co-infection	0.057	0.290
Neutrophil	with	Bacterial and fungal co-infection	0.071	0.184
CRP	with	Bacterial and fungal co-infection	-0.009	0.876
Procalcitonin	with	Bacterial and fungal co-infection	-0.026	0.630

The tests were followed with a correlation test of the leukocyte, neutrophil, CRP, and procalcitonin levels in COVID-19 coinfection. There are positive correlation results between Leukocytes and Co-infection (P=0.0001), Leukocytes and Bacterial co-infection (P=0.0001), Neutrophils and co-infection (P=0.0001), Neutrophils and bacterial co-infection (P=0.0001), CRP and coinfection (P=0.001), CRP and bacterial co-infection (P=0.003), Procalcitonin and coinfection (P=0.000), Procalcitonin and bacterial co-infection (P=0.0001), Procalcitonin and fungal co-infection (P=0.024).

It indicates that with the higher the leukocytes level, co-infection and bacterial co-infection will be more severe, with the higher the neutrophils level, co-infection and bacterial co-infection will be more severe, with the higher the CRP level, co-infection and bacterial co-infection will be more severe, with the higher the procalcitonin level, co-infection, bacterial co-infection, and fungal co-infection will be more severe.

The study was followed with chi-square test in which was found significant correlation between leukocytes (a category based on the cut-off value of ROC) and coinfection (P=0.0001), neutrophils (a category based on the cut-off value of ROC) and coinfection (P=0.0001), but no significant correlation between neutrophils (a category based on the cut-off value of ROC) and coinfection (P=0.064). The following diagnostic value was thus obtained based on the crosstabs (Table 3).

Table 3. Threshold Values for Leukocytes, Neutrophils, CRP, and Procalcitonin with Coinfection in COVID-19

Values	Coinfected	Non-Coinfected	P
Leu (with ROC cut-off)			
>12485	53 (67.9%)	90 (32.8%)	0.0001
<12485	25 (32.1%)	184 (67.2%)	
Neutrophil (with ROC cut-off)			
>88.2	56 (71.8%)	76 (27.7%)	0.0001
<88.2	22 (28.2%)	198 (72.3%)	
CRP (with ROC cut-off)			
>8.74	46 (59.0%)	129 (47.1%)	0.064
<8.74	32 (41.0%)	145 (52.9%)	
Procalcitonin (with ROC cut-off)			
>19.73	6 (7.7%)	17 (6.2%)	0.639
<19.73	72 (92.3%)	257 (93.8%)	

With a sensitivity value of 71.8%, neutrophils were found to have the greatest sensitivity compared to leukocytes, CRP, and procalcitonin. However, the results of the specificity test showed that the Procalcitonin marker had the highest specificity value of 93.8%, followed by neutrophils at 72.3%, leukocytes with a specificity of 67.2%, and CRP markers with a specificity of 52.9%.

Table 4. Diagnostic Value of Leukocytes, Neutrophils, CRP, and Procalcitonin with Coinfection in COVID-19

Characteristics	Sensitivity	Specificity	PPV	NPV	PPR	Accuray	OR
Leu	67.9%	67.2%	37.1%	88.0%	2.069	67.3%	4.334
Neutrophil	71.8%	72.3%	42.4%	90.0%	2.588	72.2%	6.632
CRP	59.0%	52.9%	26.3%	81.9%	1.253	54.3%	1.616
Procalcitonin	15.8%	93.8%	26.1%	88.9%	2.545	84.3%	2.835

Note: NPV=Negative predictive value; PPV=Positive predictive value; PPR=Positive probability ratio; OR=Odds Ratio

Additionally, as shown in the table above, the positive predictive value (PPV)—i.e., the probability of the subject being co-infected if the result of the diagnostic test is positive—for neutrophils—which is 42.4%—is the highest compared to other test parameters. This indicates that if the diagnostic test results are positive, the person is more likely to be co-infected.

Meanwhile the negative predictive value (NPV)—the probability of the subjects being not coinfected if the results of the diagnostic test are negative—showed the Neutrophil marker as the highest value—which is 90.0%—followed by Procalcitonin at 88.9%, Leukocytes at 88.0%, and the last is CRP, at 81.9%. The probability ratio (LR)—the probability of co-infected subjects getting a positive diagnostic test result—among the 4 markers showed that sequentially, the largest is the Neutrophil—which is 2,588—and Procalcitonin—2,545, followed by Leukocytes with a value of 2,069, and CRP with a value of 1,253.

The prediction accuracy in estimating the possibility of the subjects labelled as non-coinfected or coinfected based on Leukocyte biomarkers is 67.3%. Given the odds ratio of 4.334 (OR>1), it can be inferred that the leukocytes could be a risk factor in determining the status of coinfection, wherein a leukocyte of greater than 12.485, may indicates that the patient has a 4.33 times risk of co-infection compared to patients with Leukocytes value of less than 12485.

As shown in the table above, neutrophils, CRP, and procalcitonin could be risk factors in determining the coinfection status. A neutrophil value of greater than 88.2 may indicate that the patient has a 6.632 times risk of co-infection compared to patients with a neutrophil value of less than 88.2. A CRP value greater than 8.74 may indicate that the patient has a 1.616 times risk of co-infection compared to patients with a CRP value of less than 8.74. A procalcitonin value of greater than 19.73 may indicate that the patient has a 1.260 times risk of co-infection compared to patients with a Procalcitonin value of less than 19.73

The length of hospitalization of non-coinfected patients had a mean value of 6,38 days, less than that of coinfected patients, who had a mean value of 13,47 days.

Table 5. The Correlation between LoH and Coinfection

	LoH (days)	
	Coefficient Correlation	**P**
Bacteria/Fungi	0.382	1.000*

Note: LoH=Length of Hospitalization;
*Spearman correlation test

We could determine a significant correlation between length of hospitalization (LoH) and coinfection status and conclude a significant correlation between LoH and bacterial/fungal (non-coinfection, bacterial, fungal, and fungal + bacteria coinfection). In this study, we found that of 274 non-coinfected patients, 31% died and 69.0% were discharged. Meanwhile, of 78 coinfected patients, 71.8% died and 28.2% were discharged.

Using the Spearman correlation test between the clinical outcomes of patients with coinfection (non-coinfected and

coinfected), we found a significant relationship between the prognosis and coinfected status of the subjects. In other words, co-infection increases the mortality risk in a patient.

In this study, we found that of 274 non-coinfected patients, 31% died, while 69.0% were discharged. Meanwhile, of the 66 patients with bacterial co-infection, 71.2% died and 28.8% were discharged. Of the 9 patients with fungal co-infection, 88.9% died and 11.1% were discharged. As for the 3 patients with fungal + bacterial coinfection, 33.3% died and 66.7% were discharged. There is a significant correlation between patient outcomes and bacteria/fungi (non-coinfection, bacterial, fungal, and fungal + bacterial coinfection). In other words, the presence of bacterial/fungal co-infection (non-coinfection, bacterial coinfection, fungi, and fungal + bacterial coinfection) in patients increases the mortality risk.

DISCUSSION

There were 78 coinfected COVID-19 patients (22.15%) compared to 274 non-coinfected patients (77.85%), with 66 (18,75%) being a bacterial coinfection, nine (2,55%) having a fungal coinfection, and three (0,85%) having both bacterial and fungal coinfection. Previously conducted studies showed varying results of the percentage of coinfection in COVID-19. According to Zhang et al, the percentage of bacterial coinfection in COVID-19 was 7.7% and fungal coinfection was 3.3%. Zhang et al stated that COVID-19 with higher severity had a higher percentage of coinfection—25.5% being bacterial and 10.9% being fungal.[6] This aligns with a study in France, which stated that the percentage of coinfection in COVID-19 patients in the ICU was 19.8%—the among being almost the same as we found in this study.[7]

The median age value in the two groups did not differ, both being 56 years. Oxidation and inflammation processes will increase with age.[8] This could be one of the factors influencing clinical outcomes in COVID-19 infection. However, in this study, we found the median age between the non-coinfected and coinfected groups are the same, thus indicating no statistical difference between the ages of the two groups.

The number of female samples was more than the number of male samples in the two study groups—66.4% against 33.6% in the non-coinfected group and 67.9% against 32.1% in the coinfected group. This contradicts earlier studies that claimed COVID-19 affected men more than women. However, the mechanism that influences this difference is not clear. However, there was no statistically significant difference in terms of gender in the coinfected and non-coinfected groups in this study (P=0.801).[9]

There are no significant characteristics of comorbidities in the two groups—60.6% being non-coinfected and 64.1% being coinfected. A meta-analysis study states that comorbidities increase the severity of COVID-19.[10] Another meta-analysis study conducted in Iran stated that

comorbidities, especially diabetes and hypertension, increase the risk of severity and the possibility of ICU admission up to two times, and cardio-cerebrovascular-related comorbidities could increase it three times.[11] Comorbidities were not confounding factors in this study, as their prevalence did not significantly differ between the two groups.

Gram-negative bacteria made up most of the pathogens in the COVID-19 coinfected group (66.66%), followed by gram-positive bacteria (21.90%) and fungi (11.42%), with *Acinetobacter baumanii* (25), *Klebsiella pneumoniae* (21), and *Enterococcus faecalis* (15) being the most prevalent pathogens. *Candida albicans* (4), *Candida glabrata* (4), and *Candida tropicalis* (3) are the most prevalent fungal pathogens. The characteristics of this pathogen are almost the same as the multicentre cohort study conducted in China with the most pathogens being gram-negative bacteria (50%), followed by gram-positive bacteria (26.92%), viruses (11.54%) and fungi (7,69%) with the most common pathogens being Klebsiella pneumoniae, Enterococcus faecium, Acinetobacter baumannii.[6]

Leukocytes in the coinfected group had a significantly higher value than the non-coinfected group ($P<0.05$). There was also a significant correlation ($r=0.356$, $P=0.0001$) between leukocytes and the presence of coinfection.in line with a prior study by Lv et al, which found that COVID-19 coinfection resulted in considerably greater leukocyte values than non-coinfection.[9]

A study by Silva et al also stated that leukocytes would increase significantly in coinfected COVID-19 patients compared to non-coinfected patients ($P<0.001$).[12] Increased leukocyte values can be caused by infection. The leukocyte value may decrease at the beginning of a severe infection but may increase later on.[13]

This study found significantly higher neutrophil counts in coinfected patients compared to non-coinfected ones. Previous research also indicates that neutrophil levels remain elevated in co-infected COVID-19 patients, even after antibiotic treatment.[14] Our findings confirm that neutrophil count correlates with bacterial coinfection but not with fungal or mixed infections. This aligns with Mason et al, who reported a similar increase in neutrophil levels in bacterial coinfection.[15]

C-Reactive Protein, as a systematic marker for inflammation and tissue damage, is extensively used by clinicians to monitor infections. In this study, we found that CRP had a significant correlation with coinfection status in COVID-19. According to a study by Lv et al, the CRP value in the coinfected group was noticeably greater than the non-coinfected group.[9]

In this study, we also found a significant correlation between CRP values and bacterial coinfection. However, there was no significant correlation between CRP values and either fungal coinfection or a combination of both bacterial and fungal coinfection. This is in accordance with a study by Wang et al who found a significant difference between the CRP values in the

bacterial coinfected and non-coinfected group (P<0.05).[16]

Procalcitonin production is triggered by bacterial toxins and inflammatory cytokines, whose activation and production is inhibited by the large amount of INF-γ produced during viral infection. It is in alignment with our study that procalcitonin levels have a significant correlation with coinfection in COVID-19 infection. A study by Tang et al suggested that in COVID-19 with coinfection, procalcitonin values were found higher than without, which was due to a greater inflammatory response in coinfected rather than non-coinfected patients.[17]

In this study, the average length of hospitalization (LoH) for non-coinfected patients was 6,3773 days and for coinfected patients, it was 13,4675 days. Additionally, there was a strong correlation between the LoH and coinfection status. Coinfection leads to hematological and biochemical imbalances, worsening the general condition and prolonging hospital stay. This is in accordance with a study by Silva et al which stated that coinfection would lead to a longer length of hospitalization and increase the cost of care for COVID-19 patients compared to the non-coinfected group.[12]

A study by Signorini et al, stated that coinfection would lead to a longer LoH in ICU than patients without coinfection (median 15 days vs. 5 days).[18] A study by Zhang et al found that patients without co-infection with COVID-19 had a higher chance of being hospitalized in under 60 days than co-infected patients (P<0.001).[6]

In this study, the mortality rate in the non-coinfected patient was 31%, and 71.8% in the coinfected patient. A significant correlation was found between COVID-19 infection and clinical outcomes. This is in accordance with a study by Silva et al , which stated that coinfection would lead to a longer length of hospitalization and increase the cost of care for COVID-19 patients compared to the non-coinfected group.[12]

Based on a study by Signorini et al, the presence of coinfection will increase the mortality rate within 28 days than in the patients without coinfection (P<0.001). If the mortality rate is differentiated between bacterial coinfection and fungal coinfection, there is a significant increase in mortality rate in bacterial coinfection but not in fungal coinfection.[18] A study by Costa et al stated that coinfection would lead to an increased risk of death in COVID-19 patients compared to the non-coinfected group.[19]

This study has some limitations as it was conducted in a single centre and because of its retrospective nature, data availability was limited to the medical records of the hospital. Other factors, such as standard therapy, disease severity, comorbidities, and mechanical ventilation, may still affect outcomes.

CONCLUSION

In this study, we found a significant increase in leukocyte values, neutrophil values, procalcitonin values, and length of hospitalization in COVID-19 patients with

coinfection. Moreover, there was a significantly higher mortality rate in COVID-19 patients with coinfections.

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