ORIGINAL ARTICLE

Bacterial and Fungal Coinfections in COVID-19 Inpatients at a Tertiary Hospital in Surabaya, Indonesia, from November 2020 to February 2022

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ABSTRACT

Introduction: After the first discovery of coronavirus disease 2019 (COVID-19) in 2020, the rapid increase of cases beyond China prompted the declaration of a pandemic. Elevated rates of bacterial-fungal coinfection were observed in hospitalized COVID-19 patients. This study aimed to determine the profiles of bacterial and fungal coinfections in COVID-19 patients diagnosed between November 2020 and February 2022 at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.

Methods: This retrospective descriptive study obtained data from medical records and used total sampling to assemble 278 COVID-19 patients who met the inclusion criteria. The evaluated variables were subject characteristics, including age, sex, comorbidities, length of stay, ventilator use, bacterial coinfections, fungal coinfections, and bacterial-fungal coinfections.

Results: The age group of 55–64 years (26.9%) was predominant among the patients, with males (55.4%) outnumbering females. Hypertension was the most prevalent comorbidity (15.8%). The patients were mostly hospitalized for over ten days (66.2%). Eleven patients (4%) were admitted to the intensive care unit, and five patients (1.8%) required mechanical ventilation. The bacterial coinfections were primarily caused by *Streptococcus viridans* (56.6%), found in 145 sputum specimens, followed by *Klebsiella pneumoniae* (23.4%). The predominant isolates in the bacterial-fungal coinfections were *Streptococcus viridans* and *Candida albicans* (24.8%), identified in 125 sputum specimens, followed by Klebsiella pneumoniae and Candida albicans (18.4%).

Conclusion: COVID-19 patients with bacterial-fungal coinfections present certain characteristics, including being male, middle-aged, hypertensive, and hospitalized beyond ten days. *Streptococcus viridans*, *Klebsiella pneumoniae*, and *Candida albicans* are common etiologies in bacterial-fungal coinfections.

Keywords: Coronavirus disease 2019 (COVID-19); coinfection; bacteria; fungi; communicable disease

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Highlights:

1. This study overviews the distribution of patients and causative pathogens associated with bacterial, fungal, and bacterial-fungal coinfections, which have escalated with the rapid rise of coronavirus disease 2019 (COVID-19) hospitalization.
2. Data on the causative pathogens of bacterial-fungal coinfection in COVID-19 patients can be considered in the development of guidelines for empirical therapy in clinical practice.

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INTRODUCTION

The first reported case of the novel coronavirus was identified in China. The World Health Organization (WHO) labeled it a public health emergency of international concern (PHEIC), classifying the epidemic as a pandemic due to the rapid spread of the virus to other nations around the world. From the first verified case of coronavirus disease 2019 (COVID-19) until February 2022, Indonesia has witnessed three waves of COVID-19, each marked by an increase in daily cases. As of February 2022, Indonesia had 5,564,448 confirmed cases of COVID-19 (COVID-19 Task Force, 2022). Surabaya, a city in Indonesia, recorded a total of 104,585 confirmed COVID-19 patients, with 2,683 deaths (COVID-19 Task Force of Surabaya City, 2022). The majority of COVID-19

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patients can develop acute respiratory distress syndrome, which necessitates the use of mechanical ventilators and leads to a high risk of intensive care unit (ICU) admission. Patients in intensive care, particularly those using mechanical ventilators, are more likely to become infected with germs or fungus (Pemán et al., 2020). Bantun (2023) conducted a literature review and found that the rates of coinfection and superinfection by fungi and bacteria in hospitalized COVID-19 patients are relatively high (23.5%).

A previous study showed that 119 patients developed superinfection after 48 hours of hospitalization, with a bacterial or fungal coinfection rate in the ICU reaching 50.42% (Novacescu et al., 2022). Fungal and/or bacterial isolates were detected in 89 samples from severe COVID-19 patients, with 73 (83.14%) resulting in fatalities (Silva et al., 2021). The aim of this study was to determine the profiles of bacterial and fungal coinfections in COVID-19 patients at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. The results of this study are expected to enhance the understanding of bacteria and fungi in order to decrease the incidence and mortality rates caused by COVID-19 infection.

METHODS

This study employed a retrospective descriptive method and obtained data from the medical records of patients diagnosed with COVID-19 (Johnston et al., 2019). A total of 278 COVID-19 patients who met the inclusion criteria were selected using the total sampling technique (Bhardwaj, 2019). The inclusion criteria for this study were patients diagnosed with COVID-19 in the period from November 2020 to February 2022, confirmed by positive reverse transcription polymerase chain reaction (RT-PCR) tests and sputum specimen cultures indicating bacterial and/or fungal coinfection. The test results were identified microbiologically in the Clinical Microbiology Laboratory of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. The characteristics of the subjects were evaluated, encompassing age, sex, comorbidities, length of stay, ventilator use, bacterial coinfections, fungal coinfections, and bacterial-fungal coinfections. The collected data were analyzed using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, N.Y., USA).

RESULTS

This study had 278 patients who met the inclusion criteria as research subjects. The predominant characteristics of the research subjects consisted of individuals aged between 55 and 64 years old (26.9%) and male participants (55.4%). The data on the characteristics of the subjects based on comorbidity history revealed that 85 of the 278 research subjects (30.5%) had no history of comorbidities. Hypertension was the most common comorbidity among patients with a history of comorbidities, accounting for 44 people (15.8%). More than half of the research subjects (66.2%) received treatment for more than ten days. Eleven persons were admitted to the ICU (4%), of which five required ventilators (1.8%). Table 1 presents the detailed characteristics of the research subjects.

Table 2 displays the characteristics of the research subjects categorized by the etiology of the coinfections. According to the results, 145 (52.1%) out of the 278 patients only indicated the presence of aerobic bacterial growth in their sputum specimens. On the other hand, 8 patients (2.9%) exhibited fungal growth, and 125 patients (45%) demonstrated both aerobic bacterial and fungal growth. The primary age group for those with bacterial coinfections was 45–54 years (29%), whereas those with fungal coinfections were predominantly 25–34 years old (50.0%). Most of the patients with both bacterial and fungal coinfections were between 55 and 64 years old (37.6%). In this study, male patients made up 55.4% of the total sample. The majority of the research subjects had no comorbidities, totaling 85 individuals (30.5%). Hypertension was the most common comorbidity observed among the research subjects with bacterial coinfections, affecting up to 25 individuals (17.2%). In patients with bacterial-fungal coinfections, the most common comorbidity was type 2 diabetes mellitus, with as many as 28 individuals (22.4%).

Table 1. Baseline characteristics of the patients (n=278)

Characteristics	n	%
Age		
<5	0	0
5–14	0	0
15–24	18	6.4
25–34	45	16.1
35–44	41	14.7
45–54	68	24.4
55–64	75	26.9
>64	32	11.5
Sex		
Male	154	55.4
Female	124	44.6
Comorbidities		
None	85	30.5
Hypertension	44	15.8
T2DM	43	15.4
Hypertension with T2DM	39	14
HIV/AIDS	10	4
Malignancy	15	5.4
Cardiovascular disease	6	2.1
Renal disease	1	0.3
TB	5	1.8
COPD	1	0.3
Others	29	10.4
LoS		
≤10 days	94	33.8
>10 days	184	66.2
ICU admission		
Yes	11	4
No	267	96
Ventilator use		
Yes	5	1.8
No	273	98.2

Notes: T2DM=type 2 diabetes mellitus; HIV/AIDS=human immunodeficiency virus/acquired immune deficiency syndrome; TB=tuberculosis; COPD=chronic obstructive pulmonary disease; LoS=length of stay; ICU=intensive care unit.

The examination of sputum specimens revealed bacterial growth in 145 patients, indicating the occurrence of bacterial coinfections. *Streptococcus viridans* (56.6%) was the most commonly observed bacterial isolate, followed by *Klebsiella pneumoniae* (23.4%) and coagulase-negative staphylococci (13.8%). *Streptococcus viridans* (56.6%) and coagulase-negative staphylococci (13.8%) were the predominant species among the Gram-positive bacteria associated with the bacterial coinfections. The most frequently observed Gram-negative bacterial species were *Klebsiella pneumoniae* (23.4%) and *Acinetobacter baumannii* (10.3%). Table 3 presents the distribution of the bacterial coinfections among the research subjects.

Table 4 shows the findings on the distribution of fungal coinfections among the research subjects. The table indicated that eight sputum specimens exhibited only fungal growth. The most commonly found fungal species was *Candida albicans* (50%), followed by *Candida tropicalis* (37.5%).

Table 2. Characteristics of the patients according to the coinfecting agents

Characteristics	Bacterial coinfection (n=145)	Fungal coinfection (n=8)	Bacterial-fungal coinfection (n=125)
Age			
<5	0 (0%)	0 (0%)	0 (0%)
5–14	0 (0%)	0 (0%)	0 (0%)
15–24	13 (9.0%)	0 (0%)	5 (4.0%)
25–34	27 (18.6%)	4 (50.0%)	14 (11.2%)
35–44	19 (13.1%)	0 (0%)	22 (17.6%)
45–54	42 (29%)	1 (12.5%)	25 (20%)
55–64	25 (17.2%)	1 (25%)	47 (37.6%)
>64	19 (13.1)	1 (12.5%)	12 (9.6%)
Sex			
Male	73 (50.3%)	5 (62.5%)	76 (60.8%)
Female	72 (49.7%)	3 (37.5%)	49 (39.2%)
Comorbidities			
None	46 (31.7%)	3 (37.5%)	36 (28.8%)
Hypertension	25 (17.2%)	1 (12.5%)	18 (14.4%)
T2DM	15 (10.3%)	0 (0%)	28 (22.4%)
Hypertension with T2DM	22 (15.1%)	1 (12.5%)	16 (12.8%)
HIV/AIDS	4 (2.8%)	0 (0%)	6 (4.8%)
Malignancy	8 (5.5%)	0 (0%)	7 (5.6%)
Cardiovascular disease	4 (2.8%)	1 (12.5%)	1 (0.8%)
Renal disease	1 (0.7%)	0 (0%)	0 (0%)
TB	1 (0.7%)	0 (0%)	4 (3.2%)
COPD	1 (0.7%)	0 (0%)	0 (0%)
Others	18 (12.4%)	2 (25%)	9 (7.2%)
LoS			
≤10 days	47 (32.4%)	3 (37.5%)	44 (35.2%)
>10 days	98 (67.6%)	5 (62.5%)	81 (64.8%)
ICU admission	5 (3.4%)	0 (0%)	6 (4.8%)
Ventilator use	3 (2.1%)	0 (0%)	2 (1.6%)

Notes: T2DM=type 2 diabetes mellitus; HIV/AIDS=human immunodeficiency virus/acquired immune deficiency syndrome; TB=tuberculosis; COPD=chronic obstructive pulmonary disease; LoS=length of stay; ICU=intensive care unit..

Table 3. Distribution of species among the coinfecting bacteria

Bacterial species	n	%
Gram-positive bacteria		
Streptococcus viridans	82	56.6
Corynebacterium pseudodiphtericum	1	0.6
Staphylococcus aureus	6	4.1
CoNS	20	13.8
Gram-negative bacteria		
Acinetobacter baumannii	15	10.3
Klebsiella pneumoniae	34	23.4
Klebsiella ozaenae	3	2.1
Klebsiella aerogenes	2	1.4
Escherichia coli	9	6.2
Pseudomonas aeruginosa	12	8.3
Enterobacter cloacae	11	7.6
Stenotrophomonas maltophilia	4	2.8
Proteus mirabilis	1	0.6

Note: CoNS=coagulase-negative staphylococci.

Table 4. Distribution of species among the coinfecting fungi

Fungal species	n	%
Candida albicans	4	50
Candida tropicalis	3	37.5
Candida famata	2	25
Kodamaea ohmeri	1	12.5

According to Table 5, a total of 125 sputum specimens had bacterial and fungal growth, indicating the occurrence of bacterial-fungal coinfections. The dominating bacterial and fungal species were *Streptococcus viridans* and *Candida albicans* (24.8%), followed by *Klebsiella pneumoniae* and *Candida albicans* (18.4%), and subsequently *Acinetobacter baumannii* and *Candida albicans* (9.6%).

Table 5. Distribution of species among the coinfecting bacteria and fungi

Bacterial and fungal species	n	%
Streptococcus viridans and Candida albicans	31	24.8
Streptococcus viridans and Candida tropicalis	8	6.4
Streptococcus viridans and Candida kruseii	1	0.8
Streptococcus viridans and Candida glabrata	3	2.4
Streptococcus viridans and Candida parapsilosis	1	0.8
Streptococcus viridans and Candida dubliniensis	8	6.4
Streptococcus viridans and Candida famata	3	2.4
Streptococcus viridans and Candida lusitaniae	2	1.6
Acinetobacter baumannii and Candida albicans	12	9.6
Acinetobacter baumannii and Candida glabrata	1	0.8
Acinetobacter baumannii and Candida tropicalis	3	2.4
Klebsiella pneumoniae and Candida albicans	23	18.4
Klebsiella pneumoniae and Candida kruseii	2	1.6
Klebsiella pneumoniae and Candida tropicalis	9	7.2
Klebsiella pneumoniae and Candida dubliniensis	1	0.8
CoNS and *Candida albicans*	7	5.6
CoNS and *Candida tropicalis*	3	2.4
Pseudomonas aeruginosa and Candida dubliniensis	2	1.6
Pseudomonas aeruginosa and Candida albicans	2	1.6
Pseudomonas aeruginosa and Candida tropicalis	2	1.6
Pseudomonas aeruginosa and Candida glabrata	1	0.8
Staphylococcus aureus and Candida albicans	4	3.2
Staphylococcus aureus and Candida dubliniensis	1	0.8
Escherichia coli and Candida albicans	6	4.8
Escherichia coli and Candida tropicalis	2	1.6
Escherichia coli and Candida kruseii	1	0.8
Enterobacter cloacae and Candida albicans	2	1.6
Enterobacter cloacae and Candida tropicalis	2	1.6
Enterobacter cloacae and Candida glabrata	1	0.8

Note: CoNS=coagulase-negative staphylococci.

DISCUSSION

Baseline characteristics of patients with coinfections

The characteristics of the patients indicated that the age group of 55–64 years had the highest coinfection prevalence compared to the other age groups. A meta-analysis conducted by Morovati et al. (2022) revealed that the highest incidence of coinfections was observed in adults over 60 years old, followed by those aged 50 to 60 years old. This suggests that the incidence of coinfection increases with age due to physiological conditions and immunological diseases in older adults. Impairments in the functions of T and B cells, as well as excessive production of type 2 cytokines, can lead to a poor prognosis if virus replication becomes uncontrolled (Zhou et al., 2020). In this study, male participants exhibited a higher prevalence of coinfections than female patients. The immune systems of females and males exhibit distinct responses to viral infections. Females have stronger cellular and humoral immune responses, along with higher immunoglobulin levels compared to males (Butterworth et al., 1967). The levels of cluster of differentiation 3+ (CD3+) and cluster of differentiation 4+ (CD4+) cells, the ratio of CD4+ to cluster of differentiation 8+ (CD8+) cells, and type 1 helper T cells in males are lower than in females (Hewagama et al., 2009). Females exhibited significantly higher mean cluster of differentiation 4 (CD4) and cluster of differentiation 8 (CD8) T cell counts in comparison to males ($p<0.05$). Furthermore, both the absolute and relative ratios of CD3+/CD4+ T lymphocytes were notably greater in females, with p-values of 0.009 and 0.036, respectively (Kokuina et al., 2019; Yonge et al., 2019).

Hypertension was the most common comorbidity among the subjects in this study. This aligns with another study conducted by Richardson et al. (2020), who discovered that hypertension was the predominant comorbidity among COVID-19 patients with coinfections. Obesity and diabetes ranked as the second and third most prevalent comorbidities in the study. Poorly managed blood pressure can interfere with immune system regulation, leading to CD8+ T cell malfunction. CD8+ T cells are unable to effectively combat viral infections and contribute to cytokine overproduction, which increases the risk of adverse outcomes (Suh & Do, 2022). The majority of the subjects in this study had received treatment for more than ten days. Zhang et al. (2020) found that patients who are hospitalized for more than 11 days have an increased risk of acquiring coinfections. In addition, Orsini et al. (2022) discovered that COVID-19 patients suffered coinfections after more than seven days of treatment, implying that hospital-associated infections (HAIs) constitute a considerable proportion of coinfection cases. In this study, five patients necessitated support devices, such as mechanical ventilators. A previous study by Franco et al. (2022) observed that bacterial and/or fungal superinfection occurred in ICU patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, which was primarily related to the duration of mechanical ventilator use, with the risk of superinfection increasing with the duration of mechanical ventilator use. Furthermore, De Francesco et al. (2023) found that hospitalized patients who use mechanical ventilators for one day encounter a raised probability of bacterial and/or fungal superinfection by 2.7 times.

Bacterial species responsible for coinfections

This study identified *Streptococcus viridans* as the most common isolate in COVID-19 patients with bacterial coinfections, followed by *Klebsiella pneumoniae* and coagulase-negative staphylococci. Previously, Wijaya et al. (2022) conducted sputum culture and found that among 204 samples from COVID-19 patients, a majority were identified as normal flora (42.16%). The remaining samples were classified as various bacterial isolates, including *Klebsiella pneumoniae* (22.55%) and *Acinetobacter baumannii* (6.37%). *Streptococcus viridans* bacteria are normal flora in the upper respiratory tract and play an important role in maintaining the health of mucous membranes (Ibrahim, 2015). Another study revealed that bacterial coinfections were present in 43 (19.7%) out of 218 COVID-19 patients treated at Airlangga University Hospital, Surabaya, Indonesia, with *Acinetobacter baumannii* (15.8%) being the predominant bacterial species identified in sputum culture specimens, followed by *Klebsiella pneumoniae* (8.7%) (Asmarawati et al., 2021).

Previous research revealed the presence of up to 109 isolates in sputum specimens, comprising the genera *Streptococcus*, *Rothia*, and *Lactobacillus*, which are part of the normal microflora of human mucous membranes. This might result from inappropriate sputum specimen collection techniques, potentially leading to bacterial contamination from saliva and nasopharyngeal fluid (Maksimova et al., 2022). Coagulase-negative staphylococci are commensals of the upper respiratory tract. These bacteria predominate in microbiological specimens and are regarded as the cause of infection when associated with many medical disorders, such as pneumonia. Mechanical ventilator use and aspiration pneumonia may evolve these bacteria into pathogens (Budayanti et al., 2019). Meanwhile, *Klebsiella pneumoniae* is the most common pathogen detected in SARS-CoV-2 patients, both in and out of the ICU. This phenomenon is induced by the virulence factor possessed by these bacteria, wherein the polysaccharide capsule (PSC) can prevent bacteria from being opsonophagolyzed by polymorphonuclear cells in humans (Yahya, 2022).

Species identified in fungal coinfections

In this study, *Candida albicans* and *Candida tropicalis* were the predominant species in sputum specimens from COVID-19 patients with fungal coinfections. Similarly, Negm et al. (2023) discovered that out of 61 fungal isolates from COVID-19 patients, 13 (70.5%) were identified as *Candida albicans* species. *Candida albicans* was likewise reported as the most commonly detected isolate at 74.36%, followed by *Candida tropicalis* at 15.38% (Khalil et al., 2022). The *Candida albicans* species can be found as commensal or pathogenic microbes in 40–80% of healthy people. However, when the host is immunocompromised, a *Candida albicans* infection may progress to an opportunistic one. Host predisposing variables that may cause the illness include reduced cell-mediated immune responses and changes in mucosal membranes and skin, which serve as the body's protection against foreign substances. Furthermore, the virulence factors of *Candida albicans* contribute to the occurrence of opportunistic infections. These include its ability for morphological dimorphism, transitioning from yeast cells to hyphae, as well as its capacity to produce acid proteases and phospholipases that contribute to fungal pathogenicity. Additionally, the presence of adhesin proteins facilitates the attachment of *Candida albicans* to host cell surfaces (Lestari, 2015).

Candida tropicalis was the second most prevalent fungal isolate in the current study. This is in line with the findings of a prior investigation, which detected Candida tropicalis in 4.6% of severe and critical COVID-19 patients.

This species, despite its limited prevalence, demonstrates a worse prognosis and a higher mortality rate compared to other non-*Albicans Candida* species (Arastehfar et al., 2020). The key determinants for the pathogenicity of this species are virulence factors and host cell immunity. Some Candida tropicalis species generate hyphae more frequently than others in the same environment. The development of Candida tropicalis hyphae is associated with increased pathogenicity (Jiang et al., 2016).

Species involved in bacterial-fungal coinfections

The findings of this study indicated that the predominant bacterial-fungal species in the sputum specimens of COVID-19 patients with bacterial-fungal coinfections were *Streptococcus viridans* and *Candida albicans* (24.8%), followed by *Klebsiella pneumoniae* and *Candida albicans* (18.4%). This demonstrated that *Streptococcus viridans* and *Klebsiella pneumoniae* were the most frequently isolated species in sputum specimens from both patients with bacterial coinfections and those with bacterial-fungal coinfections. *Candida albicans*, a fungal species, prevailed in sputum specimens from both patients with fungal coinfections and those with bacterial-fungal coinfections. Prior research carried out by Rafat et al. (2022) found 15 cases (20.54%) of bacterial and/or fungal coinfections among a total of 73 specimens collected from COVID-19 patients. According to the types of infection, 11 patients (73.34%) exhibited bacterial-fungal coinfections, 2 patients (13.33%) had bacterial coinfections, and 2 patients (13.33%) showed fungal coinfections. The most commonly detected bacterial species was *Klebsiella pneumoniae*, with five cases (38.46%), followed by *Acinetobacter baumannii*, with four cases (30.77%). Meanwhile, the predominant fungal species identified was *Candida albicans*, with eight cases (61.53%), followed by *Candida glabrata*, with three cases (23.08%).

Following the main virus infection, the immune response of the body weakens respiratory tract defense, leaving the patient vulnerable to bacterial and fungal proliferation. The patient's predisposing variables for superinfection include the use of mechanical ventilators and the dysregulation of the host immune system. The interaction between host cells and the virus causes the release of several pro-inflammatory cytokines, including interleukin 6 (IL-6), interleukin 2 (IL-2), tumor necrosis factor alpha (TNF-α), interleukin 4 (IL-4), and interleukin 10 (IL-10). The cytokine release syndrome leads the host to experience immunosuppression and lung tissue destruction, which facilitates the emergence of superinfection (Nag & Kaur, 2021). In addition to the predisposing characteristics of the host, interactions between fungus and bacteria promote biofilm formation. Polymicrobial biofilm arises from interactions between multiple microbial species that create a biofilm community. Infections caused by the factors linked to microbial biofilm formation exhibit a substantially higher mortality rate (70%) compared to those caused by a single microorganism species. Several factors influence bacterial-fungal interactions, including species type, strain, and environmental conditions such as temperature, pH, and glucose levels (Zago et al., 2015; Asih et al., 2023).

This study offers an overview of the baseline characteristics of COVID-19 patients with bacterial, fungal, and bacterial-fungal coinfections, along with the distribution of the causative pathogens. The data presented in this study may assist in formulating guidelines for clinical practice regarding the management and prevention of these coinfections. Nonetheless, this study was limited to the period of November 2020 to February 2022, and it included all coronavirus subtypes. The pre- and post-study periods were not investigated, and no research was undertaken on the predominant pathogen groups during particular waves of the COVID-19 pandemic or on the classification of virus variants. Considering these limitations, further research is required.

CONCLUSION

This study demonstrates that bacterial-fungal coinfections are prevalent in male COVID-19 patients who are middle-aged and hypertensive, particularly those with a length of hospital stay exceeding days. The most common etiological agents of bacterial-fungal coinfections in these patients are *Streptococcus viridans*, *Klebsiella pneumoniae*, and *Candida albicans*.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest in the course of this study.

ETHICS CONSIDERATION

The ethical clearance for this research was obtained from the Health Research Ethics Committee of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, under reference number 2202/120/4/VI/2023 on June 9, 2023.

FUNDING DISCLOSURE

This study did not receive any funding.

AUTHOR CONTRIBUTION

NGS contributed to the conception and design of this study, drafted the article, and collected, assembled, analyzed, and interpreted the data. ADWW and MR drafted the article, participated in its critical revision for important intellectual content, and gave final approval of the article.

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