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## **Comparison of candidemia patient profile in COVID-19 and non-COVID-19 cases in a tertiary hospital in Surabaya, Indonesia**

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**Abstract**--The COVID-19 pandemic has been linked to secondary infections. Candidemia, a fungal healthcare-associated infection, has been described in patients hospitalized with severe COVID-19. Risk factors for developing severe COVID-19 include older age, malignancies, obesity, immunocompromised conditions, and chronic diseases, many of which are also risk factors for candidemia. This study aimed to compare clinical characteristics of candidemia in patients with and without COVID-19. This retrospective study observe patients medical records from 2020 – 2021 at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. A total of 131 candidemia cases (23 COVID-19 patients and 108 non-COVID-19 patients) were included during the study periods. COVID-19 cases had a higher rate of diabetes (60,9%,  $p=0,00$ ), pulmonary disease (87%,  $p=0,00$ ), obesity (34,8%,  $p=0,00$ ), and having urinary catheter (69,6%,  $p=0,00$ ). *Non-albicans candida* was the most common agent of candidemia in non-COVID-19 patients (91,3%,  $p=0,03$ ). The susceptibility of fluconazole (80,6 v 56,5,  $p=0,01$ ), caspofungin (82,4 v 60,9,  $p=0,04$ ), amphotericin B (90,7 v 78,3,  $p=0,03$ ) and flucytosine (92,6 v 73,9,  $p=0,00$ ) were higher in non-COVID-19 patients. Based on the study result, it is important to take measures to prevent the transmission of *Candida* spp. with lower antifungal sensitivity that cause candidemia in COVID-19 patients.

**Keywords**---candidemia, *Candida* sp., COVID-19.

## **Introduction**

Blood stream infections caused by *Candida* are among the most common invasive fungal infections. Candidemia is a severe infection that is associated with high morbidity and mortality, long duration of hospitalization, and increased health costs. Risk factors associated with mortality may differ based on the population at risk, species distribution, and infection management (Todi, 2020; Zhang et al., 2020; Agneli et al., 2021). Most cases of candidemia are healthcare-associated infections. (HAI), common risk factors are the use of a central venous catheter (CVC), abdominal surgery, malignancy, haemodialysis, diabetes, use of immunosuppressant therapy (including corticosteroids), total parenteral nutrition, systemic antibiotic therapy. For non-HAI cases, the main risk factor is the use of injection drugs. In developed countries, *Candida* spp. is a pathogen that causes health-care-associated bloodstream infection ranked third or fourth (Pappas et al., 2018; Aquaresta et al., 2020; Seagle et al., 2021)

In March 2020, WHO announced a global pandemic of Coronavirus disease -19 (COVID-19), a respiratory infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 patients in America who experience severe symptoms, for instance acute respiratory distress syndrome, renal failure, and other complications require intensive care (Seagle et al., 2021). Research by Nucci et al., 2021 in Brazil found an increase in the incidence of candidemia during the COVID-19 pandemic. In this study, it was found that there were differences in the characteristics of candidemia patients with and without COVID-19, such as candidemia patients with COVID-19 had no comorbid malignancy and had no history of surgery, and all of these patients were admitted to the ICU.

The COVID-19 pandemic poses a challenge in the field of health services, coinfection of SARS-CoV-2 and other microorganisms including fungal coinfection, one of which is candidemia. Risk factors for severe COVID-19 include advanced age, malignancy, obesity, immunodeficiency conditions, and chronic diseases including diabetes, some of which are also risk factors for candidemia. In addition, hospitalized COVID-19 patients are also exposed to the hospital environment (use of invasive medical instruments, antibiotic therapy) which are also risk factors for candidemia. So candidemia can be a complication for COVID-19 patients, especially those who are admitted to the ICU or suffer from severe disease. (Song et al., 2020; Asmarawati et al., 2021; Nathania et al., 2021). This study aims to determine whether COVID-19 make a different characteristics for candidemia cases.

## **Method**

### **Data collection**

We retrospectively evaluated the clinical and microbiological data of all candidemia cases in Dr. Soetomo General Academic Hospital, Surabaya, Indonesia from January 2020 to December 2021. Age and gender data,



comorbidities, microbiological and sensitivity data, and patients outcomes were evaluated. A candidemia case is defined as a positive blood culture for any *Candida* species. Blood cultures identification and antifungal sensitivity test were performed using *Vitek*® 2 Compact.

### Study variables

Clinical data, including age at the time of diagnosis, gender, underlying diseases, laboratory results, medical intervention and outcome of 131 patients with candidemia were recorded on standardized forms. Diseases, including diabetes, liver disease, cardiovascular disease, pulmonary disease, renal failure, solid organ malignancy, hematologic malignancy, gastrointestinal disease, neurological disease, HIV (Human Immunodeficiency Virus) status and obesity, were recorded. Predisposing factors that occurred before the onset of candidemia were also collected. These included central venous catheter, urinary catheter, mechanical ventilation, receipt of corticosteroids, hemodialysis, surgical procedures and intensive care unit (ICU) stay. Laboratory data within 7 days before obtaining the first positive blood culture were analyzed.

### Statistical analysis

Statistical analyses were performed by using the IBM SPSS Version 23.0 for windows. Descriptive statistics were presented as frequency and percentages for categorical variables, and medians with quartiles (interquartile range [IQR] 25th–75th percentile) for continuous variables. Categorical variables were compared using Chi-square test or Fisher's exact tests. Student's t test and Mann Whitney U test were used in the comparison of continuous variables for normally distributed and non-normally distributed data, respectively. A p value less than 0.05 was considered statistically significant. Multivariate analyses were performed to identify the independent factors associated with mortality by using logistic regression.

### Ethical Clearance

The Health Research Ethics Committee of the Faculty of Medicine at Universitas Airlangga Surabaya has approved this study for ethical feasibility (No. 0922/LOE/301.4.2/VI/2022).

### Results and Discussion

We observed a total of 131 candidemia cases during the study period, 23 in COVID-19 patients and 108 in non-COVID-19 patients. Most COVID-19 cases were from 45-64 age group meanwhile non-COVID-19 cases were from less than 1 year old age group.

Table 1. Demographic data of COVID-19 and non-COVID-19 candidemia

Characteristic	All (n=131) n(%)	COVID-19 (n = 23) n(%)	Non-COVID-19 (n = 108) n(%)	<i>p</i>
Age				0,00

< 1 year old	35 (26,7)	0 (0,0)	35 (32,4)	
1-18 years old	36 (27,5)	3 (13,0)	33 (30,6)	
19-44 years old	17 (13,0)	4 (17,4)	13 (12,0)	
45-64 years old	30 (22,9)	13 (56,5)	17 (15,7)	
≥ 65 years old	13 (9,9)	3 (13,0)	10 (9,3)	
Sex				0,05
Male	81 (61,8)	10 (43,5)	71 (65,7)	
Female	50 (38,2)	13 (56,5)	37 (34,3)	

In research by Seagle et al. (2021) found the highest number of patients were in the age group 65 years ( $p = 0.03$ ). The large number of elderly patients is probably due to the severity of the illness and the higher risk of COVID-19 complications, resulting in a higher hospitalization rate.

COVID-19 cases had a higher rate of diabetes (60,9%,  $p=0,00$ ), pulmonary disease (87%,  $p=0,00$ ), obesity (34,8%,  $p=0,00$ ), and having urinary catheter (69,6%,  $p=0,00$ ). Meanwhile, non-COVID-19 cases had a higher rate of malignancy (21,3%,  $p=0,01$ ), gastrointestinal disease (47,2%,  $p=0,00$ ), previous hospitalization (18,5%,  $p=0,02$ ), and surgery (31,5%,  $p=0,01$ ).

Table 2. Underlying Conditions of COVID-19 and non-COVID-19 Candidemia

Characteristic	All (n=131) n(%)	COVID-19 (n=23) n(%)	Non-COVID-19 (n=108) n(%)	<i>p</i>	OR (95% CI)
Diabetes	24 (18,3)	14 (60,9)	10 (9,3)	0,00	15,2 (5,3-44,0)
Malignancy	23 (17,6)	0 (0,0)	23 (21,3)	0,01	0,1 (0,0-1,3)
Hematologic	9 (6,9)	0 (0,0)	9 (8,3)	0,36	
Non hematologic	14 (10,7)	0 (0,0)	14 (13,0)	0,13	
Liver disease	7 (5,3)	0 (0,0)	7 (6,5)	0,35	
Chronic kidney disease	16 (12,2)	5 (21,7)	11 (10,2)	0,16	
Pulmonary disease	35 (26,7)	20 (87)	15 (13,9)	0,00	41,3 (10,9-156,3)
Cardiovascular disease	29 (22,1)	4 (17,4)	25 (23,1)	0,55	
Gastrointestinal disease	53 (40,5)	2 (8,7)	51 (47,2)	0,00	0,2 (0,0-0,5)
Neurologic disease	20 (15,3)	4 (17,4)	16 (14,8)	0,75	
HIV	1 (0,8)	0 (0)	1 (0,9)	1,00	
Obesity	9 (6,9)	8 (34,8)	1 (0,9)	0,00	57,1 (6,7-488,9)

Seagle et al. (2021) found that candidemia patients with COVID-19 had lower rates of chronic liver illness, non-haematological malignancies, gastrointestinal disorders, and hepatitis C than patients without COVID-19. Diabetes and obesity are more likely in persons with candidemia who do not have COVID-19. According

to Kayaaslan et al. research from 2021, more chronic lung illnesses were discovered in candidemia patients with COVID-19.

Table 3. Medical Encounters and Medications of COVID-19 and non-COVID-19 Candidemia

Characteristic	All (n=131) n(%)	COVID-19 (n=23) n(%)	Non- COVID-19 (n=108) n(%)	<i>p</i>	OR (95% CI)
Intensive care	54 (41,2)	12 (52,2)	42 (38,9)	0,24	
Urinary catheter	48 (36,6)	16 (69,6)	32 (29,6)	0,00	5,4 (2,0-14,5)
Mechanical ventilation	52 (39,7)	9 (39,1)	43 (39,8)	0,95	
Hemodialysis	14 (10,7)	5 (21,7)	9 (8,3)	0,07	
Previous hospitalization	20 (15,3)	0 (0,0)	20 (18,5)	0,02	0,0 (0,0-0,8)
Central venous catheter	27 (20,6)	6 (26,1)	21 (19,4)	0,57	
Surgery	35 (26,7)	1 (4,3)	34 (31,5)	0,01	0,1 (0,0-0,8)
Laparotomy	23 (17,6)	1 (4,3)	22 (20,4)	0,08	
Antibiotic	83 (63,4)	16 (69,6)	67 (62,0)	0,50	
Antifungal prior culture	8 (6,1)	2 (8,7)	6 (5,6)	0,63	
Systemic corticosteroid	24 (18,3)	7 (30,4)	17 (15,7)	0,14	

In this study, there were no significant differences in all laboratory results variables, candidemia patients both with and without COVID-19 had the same characteristics of WBC, neutrophils, lymphocytes, procalcitonin, C-reactive protein, potassium, sodium and chloride. Kayaaslan et al. (2021) found significantly higher WBC counts, neutrophil counts, urea, creatinine, aspartate aminotransferase, alanine aminotransferase and procalcitonin in candidemia patients with COVID-19. Research by Mastrangelo et al. (2020) also found no difference in the laboratory results of patients with and without COVID-19.

Table 4. Laboratory examinations of COVID-19 and non-COVID-19 candidemia

Parameters	median (IQR <sup>a</sup> )	COVID-19	Non-COVID-19	<i>p</i>
White blood cells (cells x 10 <sup>9</sup> /L)	13,69 (9,87-20,36)	13,7 (10,7-25,9)	13,7 (8,8-20,2)	0,575
Neutrophil (cells x 10 <sup>9</sup> /L)	10,16 (5,21-15,65)	10,4 (8,5-21,7)	10,0 (4,6-15,1)	0,169
Lymphocyte (cells x 10 <sup>9</sup> /L)	1,69 (0,91-3,07)	1,4 (0,8-2,2)	1,9 (1,0-3,3)	0,101
Procalcitonin (µg/ml)	2,11 (0,63-5,62)	0,7(0,3-4,1)	2,2 (0,9-6,7)	0,144
C-reactive protein (g/L)	7,5 (2,3-13,3)	7,1 (1,4-18,0)	7,5 (2,5-12,6)	0,866
Kalium	3,8 (3,2-4,3)	3,9 (3,5-4,6)	3,8 (3,0-4,3)	0,353
Natrium	137 (134-141)	138 (135-143)	137 (134-141)	0,320

Chlorida	100 (96-106)	99 (96-105)	100,5 (95,3-106)	0,708
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<sup>a</sup> IQR: Interquartile range (25% and 75%)

*Candida albicans* is the species most commonly found as the cause of candidemia in all subjects. In cases of candidemia with COVID-19 *C. albicans* was less in number, while *C. krusei* and *C. duobushaemulonii* were more common in non-COVID-19 group. *Non-albicans candida* was the most common agent of candidemia in non-COVID-19 patients (91,3%,  $p=0,03$ ). In the analysis of data for antifungal sensitivity, it was found that the antifungal sensitivity rates of fluconazole, caspofungin, amphotericin B and flucytosine were higher in candidemia patients without COVID-19. Candidemia caused by atypical *Candida* tends to respond poorly to antifungal therapy and can lead to treatment failure (Chen 2019). Research by Kayaaslan et al. (2021) and Seagle et al. (2021) did not find any significant differences in *Candida* that cause candidemia and the results of the sensitivity test. Indrasari et al. (2022) found significant increase of *C. dubliniensis* and *C. albicans* prevalence during COVID-19 pandemic in Dr. Soetomo General Academic Hospital.

Table 5. *Candida* species, antifungal susceptibilities, and clinical outcomes of COVID-19 and non-COVID-19 candidemia

Characteristic	All (n=131) n(%)	COVID-19 (n=23) n(%)	Non-COVID-19 (n=108) n(%)	<i>p</i>
<i>Candida</i> spp.				
<i>C. albicans</i>	36 (27,5)	2 (8,7)	34 (31,5)	0,03
<i>C. tropicalis</i>	32 (24,4)	6 (26,1)	26 (24,1)	0,83
<i>C. parapsilosis</i>	35 (26,7)	4 (17,4)	31 (28,7)	0,27
<i>C. glabrata</i>	10 (7,6)	2 (8,7)	8 (7,4)	0,69
<i>C. krusei</i>	2 (1,5)	2 (8,7)	0 (0,0)	0,03
<i>C. famata</i>	7 (5,3)	2 (8,7)	5 (4,6)	0,61
<i>C. duobushaemulonii</i>	3 (2,3)	3 (13,0)	0 (0,0)	0,01
Other <i>Candida</i> spp.	6 (4,6)	2 (8,7)	4 (3,7)	0,28
Antifungal susceptibilities				
Fluconazole	100 (76,3)	13 (56,5)	87 (80,6)	0,01
Voriconazol	121 (92,4)	21 (91,3)	100 (92,6)	0,72
Micafungin	112 (85,5)	17 (73,9)	95 (88,0)	0,10
Caspofungin	103 (78,6)	14 (60,9)	89 (82,4)	0,04
Amphotericin B	116 (88,5)	18 (78,3)	98 (90,7)	0,03
Flucytosine	117 (89,3)	17 (73,9)	100 (92,6)	0,00
Death	64 (48,9)	10 (47,8)	54 (53,7)	0,57
Hospitalization duration (days) (median, IQR <sup>a</sup> )	34,5 (15,0-51,8)	40 (15,0-46,5)	32,5 (16,5-60,3)	0,96
Time from admission to candidemia (days) (median, IQR <sup>a</sup> )	10,0 (2,0-23,0)	12 (4,0-20,0)	10 (2,0-23,8)	0,99

<sup>a</sup> IQR: Interquartile range (25% and 75%)

The mortality percentage of candidemia patients with COVID-19 in this study was 43.5%, there was no significant difference with the percentage of deaths in patients without COVID-19. Seagle et al. (2021) had a higher mortality percentage in patients with COVID-19 at 62.5%, while the study of Kayaaslan et al. (2021) also had a higher mortality rate in patients with COVID-19 of 87.5%. The median range between patients admitted to hospital and cultured in cases with COVID-19 in this study was 12 (IQR = 4,0-20,0), there was no difference with the median in cases without COVID-19. In the study of Seagle et al. (2021) the median number of days between hospital admission and blood culture was 14 days (IQR = 7-18 days) in patients with COVID-19 while in patients without COVID-19 it was 4 days (IQR = 0-14 days).

Based on a multivariate analysis test with logistic regression to determine the independent risk factors for death in candidemia patients, it is known that candidemia patients are more at risk for death if they have cardiovascular disease, do not receive antifungal therapy, decreased neutrophil, or are treated in the intensive care unit. Kayaaslan et al. (2021) cited corticosteroid therapy, sepsis, and advanced age >65 years as independent risk factors for mortality.

Table 5. Multivariate logistic regression analysis of the risk factors for mortality

Variables	<i>p</i>	OR	CI 95%
Cardiovascular disease	0,00	4,78	1,57-14,54
Antifungal post culture	0,00	0,12	0,05-0,33
Intensive care	0,00	1,09	1,03-1,16
Neutrophil	0,00	0,22	0,09-0,57

## Conclusion

Candidemia patients with COVID-19 were less likely to have certain comorbid disease, recent surgery, and *Candida* spp. with decreased sensitivity were more possibly found as the causative of candidemia. It is important to take measures to prevent candidemia in patients with COVID-19 and its transmission.

## Disclosure

The authors declare that they have no financial or personal conflicts of interests in this work.

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