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The differences of *Candida sp*. colonization profiles in the sputum of lung cancer and pulmonary tuberculosis patients

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ABSTRACT

Background: The fungal infection is a worldwide health problem triggered by the increasing number of antibiotic and immunosuppressant drug usage, indwelling catheter procedures, and immunocompromised patients. Lung fungal infection is a disease caused by colonization or the fungal infection hypersensitivity reaction. Lung cancer and lung tuberculosis (TB) are chronic diseases that can lead to an immunocompromised state and induce the colonization of *Candida sp* in the respiratory tract. Patients contracted with these diseases tend to colonize Candida sp. in their respiratory tract, which may develop to pulmonary candidiasis with worse prognostic. Thus, this study aimed to understand the difference of *Candida sp* colonization profile in the sputum of Lung cancer and lung TB patients.

Method: This study was an observational study with a cross-sectional approach using 60 consecutively determined samples, where 30 samples were from each lung cancer and lung tuberculosis group. The data were analyzed by using SPSS 25 sav. For numeric variables, we used unpaired t-test analysis, meanwhile the categoric variables such as the laboratory, microscopic, and sputum culture test results; and compared the result statistically using *Chi-Square analysis* to compare the *Candida sp* colonization profile in both groups.

Results: We found that 80% of the lung cancer patient and 87% of lung TB patients had positive results on *Candida sp* culture, which is dominated by Candida albicans. We observed higher WBC value and hyphae of *Candida* in the lung TB patient group. There was a significant difference in the sensitivity of *Candida albicans* isolate against Amphotericin B, and *non-Candida albicans* isolate against Fluconazole and Micafungin in the lung cancer and lung TB patients group. The sensitivity value of Gram assessment was 40% with 90% specificity.

Conclusion: *Candida albicans* were mostly found among lung cancer and lung TB patients. There were significant differences in the WBC value and antifungal sensitivity test results in *Candida albicans* isolates against Amphotericin B and *non-Candida albicans* isolates against Fluconazole and Micafungin in lung cancer lung TB patients.

Keywords: *Candida sp*, sputum, lung cancer, pulmonary TB
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INTRODUCTION

Pulmonary fungal infection/ pulmonary mycosis dysfunction in the pulmonary or airway system results from the fungal infection, colonization, or hypersensitivity reaction. Recently, the number of pulmonary mycoses has increased in concordance with the number of immunocompromised patients and those with risk factors or underlying diseases like chronic pulmonary diseases.[1] The preceding pulmonary diseases found on most pulmonary mycoses cases are TB infection, cavitating pulmonary TB, wide pulmonary fibrosis, bronchiectasis, pulmonary and thorax cavity malignancies, chronic obstructive pulmonary disease (COPD) asthma.[2]

Mucosal *Candida* is one of the potential pathogens for pulmonary mycoses in patients with bronchopulmonary diseases. One research report about the presence of candida infection secondary to lung TB, following the increment of broad-spectrum antibiotic and immunosuppressive agent usage, and coinfection of lung TB and HIV pandemic.[3] Other studies stated that the number of *Candida sp.* collected from lung cancer and lung TB patients were 80% and 89% accordingly.[4]

Both lung cancer and lung TB are chronic pulmonary diseases with immunocompromised status. Patients contracted with these diseases tend to colonize *Candida sp.* in their respiratory tract, which may develop to pulmonary candidiasis with worse prognostic. In sum, to understand the difference in the *Candida sp.* colonization profile of lung cancer and lung TB patients, so the result of this study could be used as a consideration to give initial treatment in patients with

lung cancer or lung TB to inhibit the development of life-threatening invasive candidiasis. Thus, this study was aimed to understand the difference of *Candida sp* colonization profile in the sputum of Lung cancer and lung TB patients.

METHODS

This research is an observational study with the cross sectional approach. The technique of collecting samples was simple random sampling. The populations of this study were the lung cancer and lung TB patients who have been diagnosed by clinical, microbiological, and radiological approaches. At the same time, 30 patients from each lung cancer and lung TB group were taken as a research subject. Samples were then sputum from lung cancer and lung TB patients submitted to clinical microbiology laboratory Saiful Anwar Hospital from a certain period according to the researcher's criteria.

Lung cancer and lung TB patients (≥ 18 y.o) had been clinically diagnosed and had complete medical data. Meanwhile, the lung cancer who got steroids 1week prior to data collection and lung TB with HIV were excluded. The result from Gram assessment, fungal culture, and antifungal sensitivity test on *Candida* from patient's sputum was collected from Clinical Microbiology Laboratory Saiful Anwar Hospital. Supporting data about the subjects were completed from the patient's medical records. Moreover, this study was accepted by the Ethical Committee of Saiful Anwar Hospital Malang.

Sputum Evaluation

We used spontaneous or NaCl 3% Nebulized induced sputum from patients. The gram staining procedure was performed following the sputum collection using crystal violet, Lugol, alcohol and safranin.[5] Clinical Microbiology Residents performed the Gram assessment. The quality of the sputum should have epithelial cells <10/lpf and WBC>10/lpf to be used in this study. The assessment component to assess *Candida* was budding cells. Pseudohyphae or hyphae. The fungal culture was performed on Sabouraud Dextrose Agar incubated at 30°C and 25°C[5] (Leber). The identification of positive candida culture was completed by using Vitek 2. Both positive results from Gram assessment and candida culture were considered candida colonization.

Statistical Analysis

Chi-Square analysis was performed to compare the data of *Candida sp.* colonization in lung cancer and lung TB patient group. Any differences with a p-value < 0.05 were considered statistically significant. The software to analyze the data was using SPSS 25. sav. For categoric variables, we used a chi-square analysis. Meanwhile, for the numeric variables, we used unpaired t-test analysis. The sensitivity and specificity of Gram assessment were done to analyze the Gram assessment of *Candida sp.* colonization on sputum samples.

RESULT

Characteristic of The Subjects

The characteristic of a patient with lung cancer and lung TB is described in Table 1. There were 60 patients involved in this study, with 30 patients in each lung cancer and lung TB group. The average age of lung cancer patients was 55 y.o ranging from 36-76 years old. At the same time, the average age in the lung TB group was 42 years old, ranging from 18-70 years old. Most of the subjects were categorized as "other" in the job criteria, described as farmers, housewives, college students, and unemployed. There was a significant difference in sex, age, and job between the lung cancer and lung TB group with a p-value <0.05 (Table 1).

Characteristics of The Laboratory Test Result

According to the laboratory test, lung cancer (53%, 13%) or lung TB (50%, 10%) had normal leukocyte counts and lymphocyte counts, respectively. Moreover, neutrophil seems higher in both diseases. In the bivariate analysis, we found a significant relationship between lung cancer and TB with neutrophils (p=0.004) and NLR (p=0.035) (Table 2).

Characteristics of Bacterial Sputum Culture

The list of normal flora and pathogen bacteria isolate that grow in culture media from patients' sputum is shown in Figure 1. According to the sample, we found that the most bacteria that exist were CONS, *Streptococcus sp* either lung TB or lung cancer. Meanwhile, we could not find *Bbronchiseptica, A.dentrificans, S. maltophilia, S. paucimobilis, Prettgerri,* and *E. faecalis* in a lung cancer patient we found it in a patient with lung TB sample even though it was just one. In the Lung TB specimen, we could find *E.aerogenes* only.

Table 1. Characteristics of the subjects

		Lung Cancer n=30	Lung TB n=30	P Value
Sex				
	Male	25 (83%)	16 (26.7%)	**0.012*[a]**
	Female	5 (17%)	14 (23.3%)	
Age (y.o)				
	Average	55.97	42.67	**0.000*[b]**
	Deviation standard	11.79	14.79	
	Median	56.0	43.5	
	Range (min-max)	30 - 76	18 - 70	
Job				
	Government employee	5 (17%)	0 (0%)	**0.000*[a]**
	Private employee	1 (3%)	18 (60%)	
	Other (farmer, housewife)	24 (80%)	12 (40%)	

Note: *Significant relationship with p<0.05. [a]using chi-square test analysis, [b]using T test analysis

Characteristics of Sputum Gram Assessment

The characteristic of sputum Gram assessment in lung cancer and lung TB is shown in Table 3. There was a significant difference in WBC value among lung cancer and lung TB patients with a p-value <0.05. In contrast, there was no significant difference in epithelial cell value, budding cell, pseudohyphae/hyphae, and Gram assessment score. There was no significant difference between lung cancer and lung TB in *Candida* culture isolates with a p-value >0.05 (Table 3).

Characteristics of *Candida* culture Assessment

There were 10 Candida species in lung TB groups and 8 Candida species in the lung cancer group (Figure 2). The most common candida species was found in lung cancer and lung TB specimen was *C.albican*.

Characteristics of *Candida* antifungal sensitivity test

There was no significant difference in antifungal Fluconazole, Voriconazole, Caspofungin, Micafungin, and Flucytosine resistance among *Candida albicans* isolates with p-value >0.05. At the same time, there was a significant difference in Amphotericin B resistance with a p-value <0.05 (Table 4). There was no significant difference in antifungal Voriconazole, Caspofungin, Amphotericin B, and Flucytosin resistance among *Non-Candida albicans* isolates with a p-value >0.05. In contrast, there was a significant difference in Fluconazole and Micafungin resistance with a p-value <0.05.

Sensitivity Value of Sputum Gram Stain

The sensitivity and specificity values from the Gram assessment were 40% and 90%, respectively. In comparison, Positive Predictive Value and Negative Predictive Values were 95% and 23% accordingly. There was a significant difference in the Candida colonization profile among lung cancer and lung TB patients specifically on age, job, gender, neutrophil level, neutrophil to lymphocyte ratio, WBC in sputum, antifungal sensitivity in *Candida*

Table 2. The laboratory test result

Type	Standard	Lung cancer n=30	Lung TB n=30	P-value
Leukocyte	Leukopenia (<4700)	4 (13%)	3 (10%)	0.837
	Normal (4700 - 11300)	16 (53%)	15 (50%)	
	Leukocytosis (>11.300)	10 (33%)	12 (40%)	
Neutrophil	Neutropenia (<51)	3 (10%)	1 (3%)	**0.004*[a]**
	Normal (51-67)	10 (33%)	1 (3%)	
	Neutrophilia (> 67)	17 (57%)	28 (93%)	
Lymphocyte	Lymphopenia (< 25)	22 (73%)	27 (90%)	0.098
	Normal (25 - 33)	4 (13%)	3 (10%)	
	Lymphocytosis (> 33)	4 (13%)	0 (0%)	
NLR	Neutrophile to Lymphocyte Ratio (mean ±std. dev)	6.59±6.85	12.03±10.54	**0.035*[a]**

Note: * Significant with p<0.05. [a]using chi-square test analysis

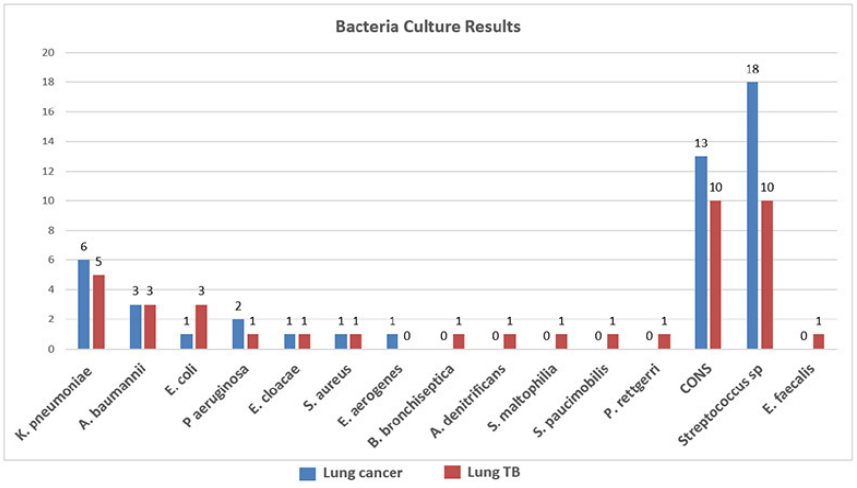

Figure 1. The list of bacteria isolates

Table 3. Result of Gram Assessment and Culture of *Candida*

		Lung Cancer n=30	Lung TB n=30	P Value
Epithelial Cell value				1.0
	Low (1+ - 2+)	20 (67%)	20(67%)	
	High (3+ - 4+)	10 (33%)	10 (33%)	
WBC value				**0.039***
	Low (1+ - 2+)	19 (63%)	11 (37%)	
	High (3+ - 4+)	11 (37%)	19 (63%)	
Positive *Budding Cell*		8 (27%)	13 (43%)	0.176
Negative *Budding Cell*		22 (73%)	17 (57%)	
Positive pseudohyphae/ hyphae		5 (17%)	6 (20%)	0.739
Negative pseudohyphae /hyphae		25(83%)	24 (80%)	
Positive Gram assessment		8 (27%)	13 (43%)	0.176
Negative Gram assessment		22 (73%)	17 (57%)	
Positive *Candida* culture		24 (80%)	26 (87%)	0.488
Negative *Candida* culture		6 (50%)	4 (13%)	

Note: * Significant with p<0.05 using chi-square test

albicans isolates, and antifungal sensitivity in *non-Candida albicans* isolates (Table 5).

DISCUSSION

This study finding was in line with the previous study, which stated that cancer patient was mostly male.[6] Moreover, most TB patients were also male.[7,8] For a female patient who contracted from TB, this might be caused by the low economic status since most were farmers, and some were unemployed.

From laboratory examination, we found that 40% of lung TB 33% of lung cancer patients had leukocytosis. We also observed neutropenia in 93% of lung TB and 33% lung cancer patients. Moreover, 90% of lung TB and 73% of lung cancer patients had lymphopenia. The neutropenic condition in most lung TB patients represented a worse immune status than lung cancer patients.[9] Leukocytosis, neutrophilia, and lymphopenia were the most common abnormalities found among lung TB patients during blood examination.[10] The low lymphocyte number inpatient might increase the pathogenicity of *Candida* colonization following the reduction in immune response since with lower immune response, the growth of *Candida* will increase.

In contrast, a strong immune response will prevent the adhesion of *Candida* cells to the host's epithelial cells.[11,12] The lymphopenia state could also impact the humoral immune system by decreasing antibody production.[13] Without adequate protection from the immune system, *Candida* could be infectious to the host cells.[14,15] This study found an increase in neutrophile to lymphocyte ratio (NLR) in both groups. A high NLR level represented a worse prognosis in lung cancer patients.[16] A high level of neutrophile count among lung TB patients resembles a persistent inflammation, or there might be a failure in the process of bacteria elimination, and these showed a worse prognosis.[17,18] A disturbance in the immune system caused by *M. tuberculosis* infection might lead to neutrophilia.[10] An increase in NLR level in patients showed a worse prognosis in lung TB and lung cancer patients.

We found pathogen bacteria in patient culture among 53% of lung cancer and 47% of lung TB patients. This result showed a higher number than the previous study, which reported a 36% positive pathogen bacteria culture among lung cancer patients.[19] The number of bacterial coinfections in lung TB without HIV patients in Cambodia was 28.5%.[20] Candida colonization in the respiratory tract could increase the risk of bacterial coinfections since Candida colonization would induce an immune response that inhibits the antibacterial action and allow the pathogen bacteria to invade and infect the host cells.[21] *Candida* colonization on the respiratory tract was common among lung TB patients, especially if there were an imbalance in normal flora.[22] When there is a depletion of normal flora bacteria, *Candida* will replace it.[23]

In our examination of the WBC profile on the patient sputum, we found that lung TB patients showed a higher level of WBC than lung cancer patients. A low or absence of WBC in the sputum assessment indicates that there might be colonization or contamination of the sample.[5] We found a higher level of WBC in lung TB patients' samples, which might be induced by ongoing TB infection or neutropenia condition in most TB patients.

The positive Gram assessment results among lung cancer and lung TB patients were 27% and 43%, respectively. These positive results could not determine whether these patients were under infection or colonized by the *Candida*.[24] The diagnosis of invasive candidiasis could only be determined by pathological tissue

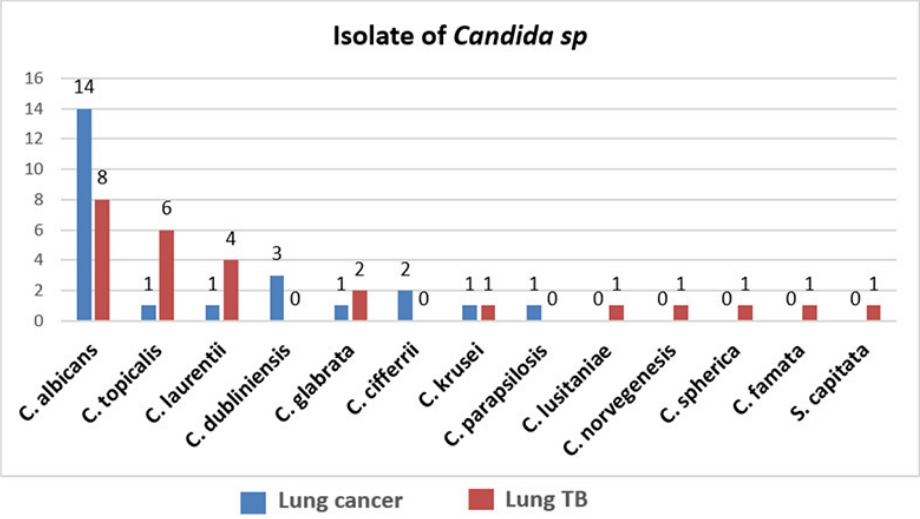

Figure 2. Isolates of *Candida sp*

Table 4. Profile of Antifungal resistance in *Candida albicans* isolates

	Candida albicans			*Non-Candida albicans*		
Type of Antifungal	**Lung cancer n=14**	**Lung TB n=8**	**P value**	**Lung cancer n=10**	**Lung TB n=18**	**P value**
Fluconazole	0	0	1.0	9 (90%)	7 (39%)	**0.009**[a*]
Voriconazole	0	0	1.0	9 (90%)	12 (67%)	0.172
Caspofungin	0	1 (13%)	0.176	5 (50%)	8 (44%)	0.778
Micafungin	0	1 (13%)	0.176	4 (40%)	14 (79%)	**0.046**[a*]
Amphotericine B	0	2 (25%)	**0.049**[*a]	8 (80%)	12 (67%)	0.454
Flucytosin	0	0	1.0	1 (10%)	7 (39%)	0.105

Note: * Significant with p<0.05. [a]Using chi-square test analysis

assessment.[25] The higher level of positive Gram assessment result among lung TB patients might be due to higher Candida density in lung TB patients' sputum. We found hyphae formation in 17% of lung cancer patients and 20% of lung TB patients from Gram assessment. Under microscopic observation, the formation of pseudohyphae/ hyphae indicated the *Candida* infection rather than just *Candida* colonization.[3,26] Morphological changes from budding cells to hyphae acted as a virulence factor in *Candida*. These changes only occur in the host's low immune status condition.[27] When in hyphal form, *Candida* will become more invasive than in budding cells form.[28] Therefore, these patients required more attention to prevent the late diagnosis of invasive candidiasis that can worsen the patient's condition.[29]

We found *Candida sp* isolates on 80% of lung cancer patients and 86% of lung TB. This result was similar to a previous study that reported that *Candida sp* isolate could be observed on 80% of lung cancer and 89% of lung TB patients.[4] *Candida sp* tend to colonize in the respiratory tract of lung TB patients than in lung cancer patients. Candida colonization could be used to identify the severity of the disease and mark any immune system dysregulation.[21,30] Some chemotherapy agents can also affect both healthy and immune cells.[31] Therefore, this condition can facilitate *Candida* colonization in lung cancer patients.

Candida albicans isolate is more frequently observed in the lung cancer patient group (47%) than in the lung TB patient group (27%). While the *non-Candida albicans* isolate is mostly found in the lung TB patient group (60%) than in the lung cancer patient group (33%). *Candida* species were mostly found among lung TB patients. The high number of *non-Candida albicans* isolates among lung TB patients was parallel with the increasing number of non-Candida albicans infections in this last decade.[32]

Table 5. Profile of Candida colonization in lung cancer and lung TB patients

Characteristics	Lung Cancer (n=30)	Lung TB (n=30)	P value
Male gender	25 (83%)	16 (53%)	**0.012*** [a]
Average age	55.97±11.79	42.67±14.79	**0.000*** [a]
Job government employee	5 (17%)	0 (0%)	**0.000*** [a]
Private employee	1 (3%)	18 (60%)	**0.000*** [a]
Leukocytosis	10 (33%)	12 (40%)	0.837
Neutrophilia	17 (57%)	28 (93%)	**0.004*** [a]
Lymphopenia	22 (73%)	27 (90%)	0.098
Neutrophile to Lymphocyte ratio	6.59±6.85	12.03±10.54	**0.035*** [a]
Culture with positive bacterial coinfection	16 (53%)	14 (47%)	0.707
Low epithelial cells value	20 (67%)	20 (67%)	1.0
High WBC value	11 (36%)	19 (63%)	**0.039*** [a]
Positive *Budding Cell* value	8 (26%)	13 (43%)	0.176
Positive finding of hyphae	5 (17%)	6 (20%)	0.739
Positive Gram assessment	8 (27%)	13 (43%)	0.176
Positive Candida culture	24 (80%)	26 (86%)	0.488
Candida albicans isolates	14 (47%)	8 (27%)	0.131
Non-Candida albicans isolates	10 (33%)	18 (60%)	0.131
Candida albicans resistance to Amphotericine B	0%	2/8 (25%)	**0.049*** [a]
Non-Candida albicans resistance to Fluconazole	9/10 (90%)	7/18 (39%)	**0.009*** [a]
Non-Candida albicans resistance to Micafungin	2/10 (40%)	14/18 (79%)	**0.046*** [a]

Note: * Significant with p<0.05. [a]Using chi-square test analysis

The presence of *non-Candida albicans* should be more noticed to prevent the conversion from colonization to becoming infectious.[33]

The number of *non-Candida albicans* isolates were mostly found in *Candida* culture among lung TB patient group. The number of *non-Candida albicans* isolates were also increased in patient with symptomatic lung disease.[3] There was also a shift in the number of *non-Candida albicans* isolates in nosocomial infection cases, which reached 63%, while Candida albicans caused the rest.[34] This trend should raise awareness since antifungal sensitivity might shift as many *non-Candida albicans* have intrinsic resistance to many antifungals.

The *Candida albicans* isolates of lung cancer patients showed higher sensitivity to antifungals than the lung TB group. An earlier study showed that the number of *Candida albicans* that show resistance against Fluconazole and Amphotericin B was 23% and 8%, respectively.[34] This condition might be caused by less antifungal usage among lung cancer patients and a shorter hospitalization period which can minimize the possibility of getting infected or colonized by antifungal *Candida albicans* strain.

The *non-Candida albicans* isolates from lung cancer patients showed more resistance against Fluconazole, Voriconazole, Caspofungin, and Amphotericin B. In contrast, the isolates from lung TB patients were resistant against Micafungin and Flucytocin. A notable resistance level of *non-Candida albicans* against Fluconazole might be induced by massive usage of Fluconazole as a routine therapy to treat fungal infection.[3,34] Following the Azole exposure, some *non-Candida albicans* might become high-level resistance and turn into multidrug resistance. It was known that intrinsic resistance against Fluconazole in some *non-Candida albicans* might contribute to this antifungal resistance among *non-Candida albicans* group.[35]

We can utilize the antibiotic stewardship program to prevent the massive, irrational, and inappropriate dosing of antifungal usage in hospitals or communities. We also must minimize the patient's risk of developing

invasive candidiasis by managing their predisposing factors.[36-38] Azole's long duration and frequent formulation The medical staffs should perform a patient-to-patient transmission prevention strategy. The microbiologist must be aware when dealing with Candida isolate from sputum and be more considerate in suggesting antifungal therapy. We should pay more attention if we find *Candida* colonization in the respiratory tract to prevent invasive candidiasis.[4] Candida Colonization Index assessment must be performed as early detection of invasive candidiasis.

The sensitivity value of Gram assessment in detecting *Candida* was 40% compared to *Candida* culture as the gold standard. At the same time, the specificity value was 90%. This result was similar to the previous study where the Gram assessment had a 9-39% sensitivity value and specificity value >90%.[39] With a low sensitivity value on Gram assessment, any absence of microbes observed on Gram assessment does not indicate a sterile sample.

There were some limitations in this study. One of them is consecutively sampled patients, which may confound the severity of the patient and the WBC value in the sputum. Other limitations are low numbers of subjects and sputum collection that was done by the patient themselves. It may contaminate the sample with saliva. The antifungal resistance pattern in this study also could not be used in clinical practice since the sample size was less than 30 because of the limited patients involved in this study.

CONCLUSION

Candida albicans were mostly found among lung cancer and lung TB patient groups. There was a significant difference in WBC value in the sputum and antifungal sensitivity test of *Candida albicans* isolates against Amphotericin B and *non-Candida albicans* against Fluconazole and Micafungin in both patient groups.

DISCLOSURES

Conflicts of interest

No conflicts of interest regarding the manuscript

Funding

No funding was received in this study.

Ethical Statement

Ethics approval was granted by Dr. Saiful Anwar Hospital, Malang through the following document number 400/091/K.3/302/2021

Author contribution

All authors contributed, read, and approved this final manuscript.

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