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# The correlation between Candida colonization index and risk factors of invasive candidiasis among patients in intensive care unit

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## ABSTRACT

**Background:** Invasive candidiasis is frequently found among patients hospitalized in intensive care units (ICU) due to immunocompromised state and performed the invasive procedure. To simplify invasive candidiasis screening, the Candida colonization index (CCI) was performed on the patients. But the implication of the CCI towards the risk factors of invasive candidiasis has never been evaluated before. Hence this study aims to evaluate the correlation between the CCI and invasive candidiasis risk factors and antifungal therapy.

**Methods:** During this study, CCI was collected from routine clinical culture results of the ICU patients while information regarding risk factors was obtained from routine follow-ups conducted on patients in the ICU. This study showed a significant correlation between the CCI, and several risk factors of invasive candidiasis, such as sequential organ failure assessment (SOFA) score, number of invasive medical instruments, and Candida score.

**Results:** These results support the hypothesis that proposes a certain correlation between CCI and risk factors of invasive candidiasis. There is also a significant correlation between antifungal therapy and the prevalence of Candida non-albicans colonization.

**Conclusion:** This study also supports the hypothesis that proposes shifting in the distribution of Candida species causing invasive candidiasis from *Candida albicans* to Candida non-albicans due to misappropriate use of antifungal therapy.

**Keywords:** Candida colonization index, candidiasis, invasive, intensive care unit.

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## INTRODUCTION

Invasive candidiasis is the most frequent fungal nosocomial infection in intensive care unit (ICU) ward, especially among immunocompromised patients.<sup>1</sup> Centers of Disease Control and prevention (CDC) reported around 25,000 cases of invasive candidiasis every year, while in Indonesia certain studies mentioned 12.3% cases of invasive candidiasis in tertiary hospitals.<sup>2</sup> *Candida albicans* is the most frequent candida-causing invasive candidiasis followed by *Candida parasilosis*, *Candida krusei*, and *Candida auris*. But during the last decade, there is a shift in the distribution of Candida species that cause invasive candidiasis from *Candida albicans* to Candida non- albicans due to extensive empiric antifungal therapy.<sup>3</sup>

Invasive candidiasis is caused by the rapid growth of *Candida* sp. due to normal

flora imbalance in the human body. Several risk factors involved are previous empiric antibiotic therapy, immunosuppressant administration, invasive procedure, total parenteral feeding, gastrointestinal surgery history, and long ICU ward hospitalization.<sup>1,4</sup> To simplify invasive candidiasis assessment and prediction, there are several scoring systems made hence antifungal therapy could be administered earlier. The most popular scoring system for invasive candidiasis is Candida colonization index (CCI). CCI determines Candida colonization as the most important risk factor of invasive candidiasis among critically ill patients. CCI compares the number of body parts colonized by *Candida* sp. with the total number of examined body parts. Specimens from parts of the body that can be used to assess the CCI include throat

swabs, perineal swabs, rectal swabs, axilla swabs, sputum, and urine.<sup>1,5</sup>

This study aims to assess the CCI of the patients in the ICU ward and its correlation with invasive candidiasis risk factors and antifungal therapy. This study also evaluates the species of colonizing Candida among the patients in the ICU ward.

## METHODS

### Patients enrollment

This study was performed in October 2022 for a full month. Enrolled patients for this study were selected among the patients in the ICU ward who have been hospitalized for at least 5 days. Clinical information of each patient regarding the risk factor of invasive candidiasis (such as antifungal or antibiotic therapy, invasive procedure,

history surgery, sepsis diagnosis, sequential organ failure assessment (SOFA) score, etc.) were obtained through routine follow-up during the study period.

### Specimen collecting procedure

The specimen was collected from patients in the ICU ward of dr. Saiful Anwar Hospital during the study period in October 2022. There are 5 types of collected specimens: expectorated sputum, intubation or tracheostomy aspirate, urine from a urine bag, perineal swab, and pharyngeal swab. Then, Gram staining and inoculation on CHROMagar were used to screen the species of colonizing *Candida* sp. If the Gram staining showed budding yeast and hyphae, *Candida* sp. is confirmed. If the *Candida* colony on the CHROMagar showed light green colony growth, *Candida albicans* was confirmed. If the *Candida* colony on the CHROMagar showed metallic blue colony growth, *Candida tropicalis* was confirmed. If the *Candida* colony on the CHROMagar showed brownish-white colony growth, *Candida glabrata* was confirmed. If the *Candida* colony on the CHROMagar showed fuzzy colony growth, *Candida krusei* was confirmed.

### Calculation of the Candida colonization index (CCI)

CCI was calculated by determining the ratio of *Candida* detected specimen(s) obtained from certain patients among total specimens obtained from the mentioned patient. If the ratio was more than or equal to 0.5 while the total specimen number was more than or equal to 4, invasive candidiasis was confirmed. If the total specimen number was 3 and the ratio was more than or equal to 0.3 invasive candidiasis was confirmed.

### Calculation of Candida score

The *Candida* score was calculated by evaluating several risk factors of invasive candidiasis. Sepsis earns 2 points while total parenteral feeding procedure, history of gastrointestinal surgery, or multifocal colonization of *Candida* sp. earns 1 point. The total of earned points is used to determine the risk of invasive candidiasis (more than or equal to 3 total points indicates invasive candidiasis).

### Statistical analysis

Statistical analysis of numerical data was performed using an independent T-test if the distribution is normal. If the distribution is not normal, the statistical analysis was performed using Mann-Whitney. Statistical analysis of categorical data was performed using Pearson Chi-square and logistic regression (if Pearson Chi-square shows significant result).

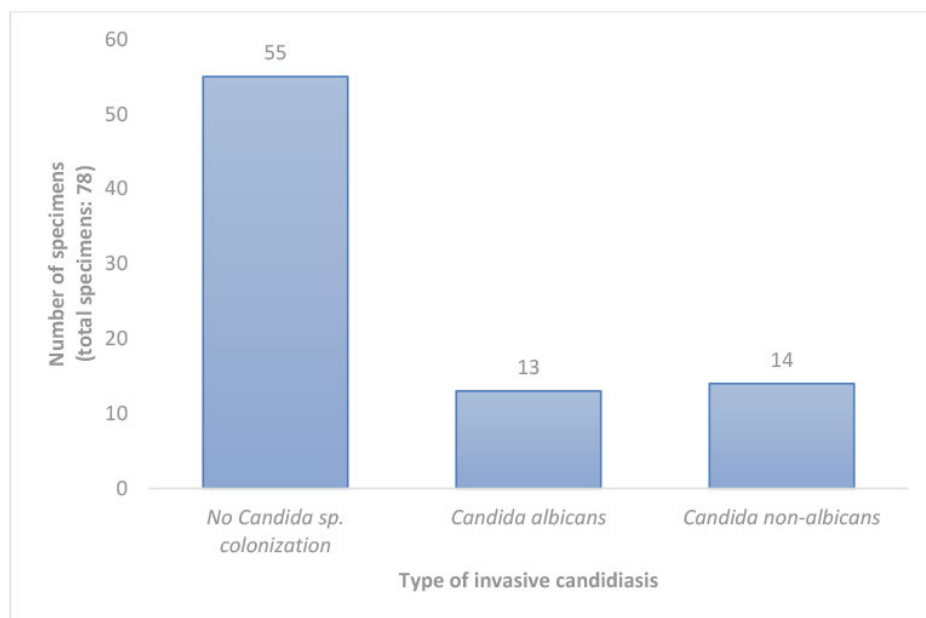
## RESULTS

### Characteristics of patients

During this study, 40 ICU patients were enrolled for specimen collection. Table 1 provides the characteristics of the enrolled patients. Table 1 shows there were more male patients in the ICU ward compared to female patients. Most of the patients in the ICU were 50 up to 59 years old during hospitalization.

**Table 1. Patients characteristics**

Total patients (40 patients)	
Male	26 patients
Female	14 patients
Group of age	
18-29 years old	6 patients
30-39 years old	3 patients
40-49 years old	9 patients
50-59 years old	14 patients
60-65 years old	8 patients



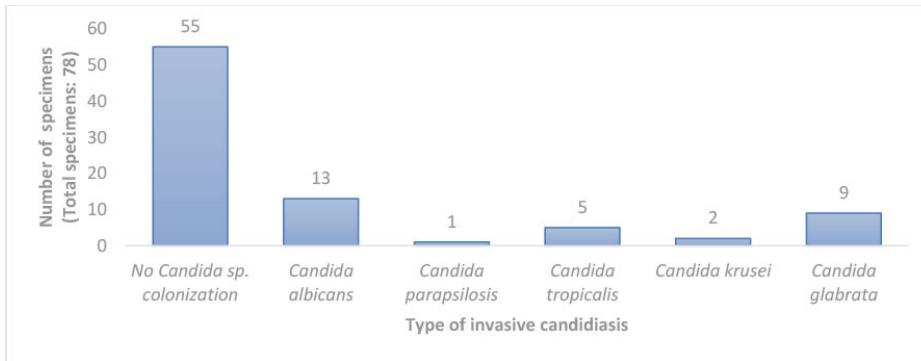
**Figure 1.** Number of specimens with positive results for *Candida albicans* or *Candida non-albicans* (4 specimens showed a positive result for *Candida albicans* and *Candida non-albicans* at once).

### Characteristics of specimens

Figure 1 shows several specimens with positive results either for *Candida albicans* or *Candida non-albicans* compared with specimens with negative results (55 specimens among 78). From this information, we learned that there are 4 specimens with positive results for *Candida albicans* and *Candida non-albicans*. To understand the results for each species of tested *Candida non-albicans*, Figure 2 shows a more detailed graphic.

### Correlation of patient length of stay and Candida colonization index

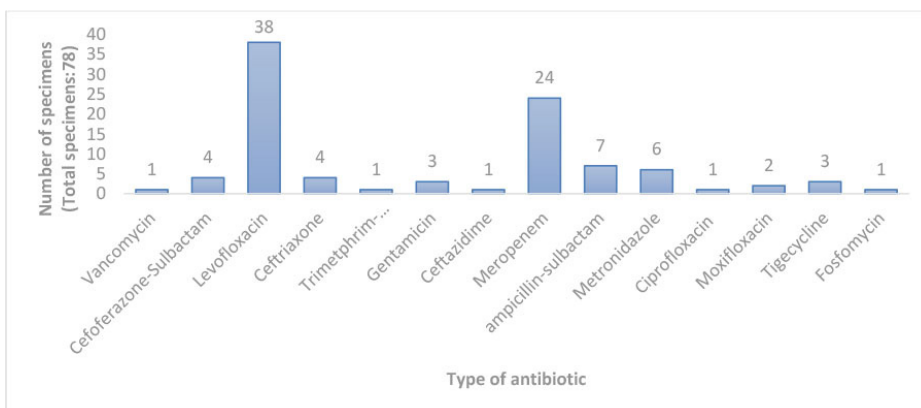
Table 2 shows the distribution of specimens based on the patient's length of stay and *Candida* colonization index. Using Pearson Chi-square analysis, we found no significant correlation between the patient's length of stay and the *Candida* colonization Index with a p-value of 0.914.



**Figure 2.** Number of specimens with positive results for each species of *Candida* fungal.

**Table 2.** Distribution of specimens based on length of stay and CCI

Length of stay	Candida colonization index (CCI)		Total
	Not tend to invasive candidiasis	Tend to invasive candidiasis	
1-7 days	31 (39.7%)	12 (15.4%)	43 (55.1%)
8-14 days	12 (15.4%)	6 (7.7%)	18 (23.1%)
>14 days	12 (15.4%)	5 (6.4%)	17 (21.8%)
<b>Total</b>	<b>55 (70.5%)</b>	<b>23 (29.5%)</b>	<b>78 (100%)</b>



**Figure 3.** Antibiotic therapy in ICU patient.

**Table 3.** Distribution of specimens based on antibiotic therapy and CCI

Antibiotic therapy	Candida colonization index (CCI)		Total
	Not tend to invasive candidiasis	Tend to invasive candidiasis	
Not receiving antibiotic	9 (11.5%)	4 (5.1%)	13 (16.7%)
Receiving antibiotic	46 (59.0%)	19 (24.4%)	65 (83.3%)
<b>Total</b>	<b>55 (70.5%)</b>	<b>23 (29.5%)</b>	<b>78 (100%)</b>

**Table 4.** SOFA score of invasive candidiasis based on CCI

Candida colonization index (CCI)	SOFA score	p-value
Not tend to invasive candidiasis	8.6 ± 0.3	0.013
Tend to invasive candidiasis	1.3 ± 0.5	

### Characteristics of antibiotic administration among the received specimen

Figure 3 shows antibiotic therapy given to patients whose specimens were evaluated

for the presence of *Candida* sp. The most frequent antibiotic given is levofloxacin, followed by meropenem.

### Correlation between antibiotic therapy with the *Candida* colonization index

Table 3 shows the distribution of specimens based on the patient's antibiotic therapy and *Candida* colonization index. Using Pearson Chi-square analysis, we found no significant correlation between the patient's antibiotic therapy and the *Candida* colonization index with a p-value of 0.912.

### Correlation between SOFA scores and *Candida* colonization index

Table 4 shows the SOFA score of each invasive candidiasis group divided based on the *Candida* Colonization Index results. Using Mann-whitney analysis, we found asignificant correlation between the patient's SOFA score and the *Candida* colonization index with a p-value of 0.013.

### Correlation between the number of used invasive medical devices and the *Candida* colonization index

Table 5 shows the number of the invasive medical instrument attached to the patient's body compared to each invasive candidiasis group divided based on the CCI results. Using Mann-whitney analysis, we found a significant correlation between the number of invasive medical instruments and the CCI with a p-value less than 0.001.

### Correlation between the history of gastrointestinal surgery used by the patient and the *Candida* colonization index score

Table 6 shows the distribution of specimens based on the history of gastrointestinal tract surgery and *Candida* Colonization Index. Using Pearson Chi-square analysis, we found no significant correlation between the patient's antibiotic therapy and the *Candida* Colonization Index with a p-value of 0.788.

### Correlation between *Candida* score and *Candida* colonization index

Table 7 shows the distribution of specimens based on the candida score and *Candida* colonization index. Using Pearson Chi-square analysis, we found a significant correlation between the *Candida* score and the *Candida* colonization index with

**Table 5. Invasive medical instrument attached to patient's body compared to CCI**

Candida colonization index (CCI)	Number of invasive medical instruments	p-value
Not tend to invasive candidiasis	4.1 ± 0.1	<0.001
Tend to invasive candidiasis	4.5 ± 0.5	

**Table 6. Distribution of specimens based on history of gastrointestinal surgery and CCI**

History of gastrointestinal tract surgery	Candida colonization index (CCI)		Total
	Not tend to invasive candidiasis	Tend to invasive candidiasis	
Without surgery	49 (62.8%)	20 (25.6%)	69 (88.5%)
With surgery	6 (7.7%)	3 (3.8%)	9 (11.5%)
<b>Total</b>	<b>55 (70.5%)</b>	<b>23 (29.5%)</b>	<b>78(100%)</b>

**Table 7. Distribution of Specimens based on Candida score and CCI**

Candida score	Candida colonization index (CCI)		Total
	Not tend to invasive Candidiasis	Tend to invasive Candidiasis	
<3	48 (61.5%)	0 (0%)	48 (61.5)
≥3	7 (9.0%)	23 (29.5%)	30 (38.5%)
<b>Total</b>	<b>55 (70.5%)</b>	<b>23 (29.5%)</b>	<b>78 (100%)</b>

**Table 8. Correlation of *Candida albicans* confirmed specimens and antifungal therapy**

Antifungal therapy	<i>Candida albicans</i>		Total
	Not confirmed <i>Candida albicans</i>	Confirmed <i>Candida albicans</i>	
Not receiving antifungal therapy	44 (56.4%)	9 (11.5%)	53 (67.9%)
Receiving antifungal therapy	21 (26.9%)	4 (5.1%)	25 (32.1%)
<b>Total</b>	<b>65 (83.3%)</b>	<b>13 (16.7%)</b>	<b>78 (100%)</b>

**Table 9. Correlation of *Candida non-albicans* confirmed specimens and antifungal Therapy**

Antifungal therapy	<i>Candida non-albicans</i>		Total
	Not confirmed <i>Candida non-albicans</i>	Confirmed <i>Candida non-albicans</i>	
Not receiving antifungal therapy	47 (60.3%)	6 (7.7%)	53 (67.9%)
Receiving antifungal therapy	17 (21.8%)	8 (10.3%)	25 (32.1%)
<b>Total</b>	<b>64 (82.1%)</b>	<b>14 (17.9%)</b>	<b>78 (100%)</b>

a p-value less than 0.001. Then, logistic regression was performed to determine the prevalence ratio. The result shows a prevalence risk of 4.286 (2.240-8.198; 95 confidence interval). It means patients with Candida score ≥ 3 are 4.286 times more at risk of invasive candidiasis.

#### Correlation between antifungal therapy and the prevalence of *Candida albicans* and *Candida non-albicans* colonization

Table 8 shows the distribution of confirmed *Candida albicans* specimens among the patients who received antifungal therapy. Using Pearson Chi-square analysis, we found no significant correlation between the *Candida albicans* specimens and the antifungal therapy with a p-value of 0.914.

Table 9 shows the distribution of confirmed *Candida non-albicans* specimens among the patients who received antifungal therapy. Using Pearson Chi-square analysis, we found a significant correlation between the *Candida non-albicans* specimens and the antifungal therapy with a p-value of 0.026. Then, logistic regression was performed to determine the prevalence ratio. The result shows a prevalence risk of 3.686 (1.116-12.178; 95 confidence interval). It means patients who receive antifungal therapy are 3.686 times more at risk of *Candida non-albicans* colonization.

## DISCUSSION

This study's results show no significant correlation between the patient's length of stay and *Candida* colonization index. This result is quite similar to a previous study performed in China in 2020 which stated no significant difference in the patient's length of stay correlated to candidemia incidence.<sup>6</sup> But, once the patient was admitted into ICU, the incidence of candidemia was noticeably higher. It happened because patients in ICU receive different treatments and interventions compared to the patients in the regular ward. In ICU the patients were given the broad spectrum of antibiotics more frequently, attached with a more invasive medical instrument, and in an immunocompromised state.<sup>6</sup>

Interestingly, this study showed a significant correlation between the number of invasive medical and invasive candidiasis incidence. More invasive medical therapy attached to the patient increased the risk factor of invasive candidiasis.<sup>7</sup> *Candida albicans* on the surface of the invasive medical instrument can create a biofilm layer preventing antifungal agents and immune response components such as neutrophils. This increases the risk factor of invasive candidiasis.<sup>6</sup>

This study shows no significant correlation between thy antibiotic therapy and CCI which contradicts the previous study performed in Stockholm, Sweden in 2020. In that study, a broad spectrum of antibiotics was significantly affecting the incidence of invasive candidiasis. It happened because broad-spectrum

antibiotics eliminated the normal flora of the host hence inducing *Candida sp.* overgrowth and transforming *Candida sp.* into pathogenic fungi.<sup>8</sup>

Another significant correlation was shown between the SOFA score and CCI. This study shows higher SOFA score is correlated with a higher CCI. This result is similar to the previous study performed in Rome, Italy in 2011. In that study, sepsis was defined as one of the risk factors for invasive candidiasis.<sup>9</sup> But our study shows no significant correlation between the history of gastrointestinal surgery and CCI. This result is unlike the previous study performed in Italy in 2011 which shows a significant correlation between gastrointestinal surgery and the incidence of invasive candidiasis.<sup>8</sup> Perhaps, our study shows a different result due to the empirical antifungal therapy given to the patient post- gastrointestinal surgery hence decreasing the incidence of invasive candidiasis like the previous study performed by Knitsch and his colleagues in 2015.<sup>10</sup>

Our study also shows a certain correlation between Candida score and CCI. As CCI represents the invasive candidiasis incidence, our study reveals that patients with Candida score  $\geq 3$  are 4.286 times more at risk of invasive candidiasis compared to patients with Candida score  $< 3$ . This supports the certain hypothesis that Candida score is sufficient to detect invasive candidiasis although we suggest CCI as the standard for invasive candidiasis screening because CCI evaluates its component more meticulously.

The most important finding in this study is the fact that there is no significant correlation between antifungal therapy and the incidence of *Candida albicans* colonization but there is a significant correlation between antifungal therapy and the incidence of *Candida non-albicans* colonization. A significant correlation between extensive antifungal therapy for ICU patients and *Candida non-albicans* colonization is proven by a p-value of 0.026 and a prevalence risk of 3.686. It means patients who receive antifungal therapy are 3.686 times more at risk of *Candida non-albicans* colonization. This result is similar to the previous study

performed in Birmingham in 2018. That study stated that there was a shift in *Candida* colonization from *Candida albicans* to *Candida non-albicans*. More colonization of *Candida glabrata* has been found, known for its intrinsic resistance to fluconazole, due to the massive use of empirical antifungal therapy.<sup>3</sup>

## CONCLUSION

From this study, we found that *Candida albicans* is not the most frequent etiology of invasive candidiasis. Several species of *Candida non-albicans* have also become frequent causes of invasive candidiasis. We also found a significant correlation between the CCI which represents the invasive candidiasis state several risk factors of invasive candidiasis, especially the SOFA score that represents sepsis diagnosis, invasive medical instrument, and Candida score. Antifungal therapy has also been proven to be a risk factor for invasive candidiasis caused by *Candida non-albicans*.

## CONFLICT OF INTEREST

The authors affirmed that there were no conflicts of interest in this study.

## FUNDING

The authors were responsible for all research funding without obtaining financial support.

## ETHICAL CLEARANCE

This study has obtained ethical clearance from the Health Research Ethics Commission of General Hospital Dr. Saiful Anwar Malang with reference letter number 400/148/K.3/102.7/2022.

## AUTHOR CONTRIBUTION

All authors contributed equally in this research and publication of this manuscript.

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