Original Article

The Role of Chemotherapy Status, Absolute Lymphocyte Count and Neutrophil Lymphocyte Ratio as Biomarkers of Candidiasis in Lung Cancer Patients

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Abstract

Background: Gradually, fungal infections are growing and have become a medical concern. Candida species are one of the most common pathogens in immunocompromised patients, such as those with lung cancer causing invasive fungal disease. Early diagnosis of candidiasis is critical for patient care in lung cancer patients. Anti-mannan IgM and IgG biomarkers are used to diagnose candidiasis. This study aims to determine the relationship between chemotherapy status, absolute lymphocyte count, and neutrophil-lymphocyte ratio to antimannan IgM and IgG.

Methods: A correlative analytic cross-sectional study was conducted on 37 lung cancer patients with positive candida sputum cultures in Dr. Saiful Anwar Malang Hospital. The 37 patients were examined for total lymphocyte level, neutrophil-lymphocyte ratio, anti-mannan IgM, and IgG. Data analysis used a contingency coefficient to determine the relationship between chemotherapy status, absolute lymphocyte count, and neutrophil-lymphocyte ratio to anti-mannan IgM and IgG.

Results: This study showed a positive correlation between chemotherapy status with anti-mannan IgM and IgG, although insignificant (P>0.05). However, there was a significant correlation between total lymphocytes and anti-mannan IgG (P=0.0001) and between neutrophil-lymphocyte ratio and antimannan IgM (P=0.004).

Conclusion: The study revealed that chemotherapy status, absolute lymphocyte count, and neutrophil-lymphocyte ratio could be a biomarker of candidiasis, so lung cancer patients with a history of chemotherapy, lymphopenia, and increased neutrophil-lymphocyte ratio should consider receiving antifungals earlier.

Keywords: antimannan antibodies, candidiasis, lung cancer

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INTRODUCTION

Fungal infections are gradually increasing and have become a widespread concern in the medical world, where candida species are primary pathogens of invasive fungal diseases. More than 400,000 people annually experience life-threatening candida infections.[1] The incidence of pulmonary candidiasis varies and increases in patients with high risks such as malignancy, broad-spectrum antibiotics, chemotherapeutic agents, organ transplants, implanted invasive medical devices, and parenteral nutrition.[2]

Immune status in fighting candida infection is influenced by many factors, including age, underlying disease, chemotherapy status, lymphocyte count, neutrophil count, and others.[3] In lung cancer patients, immunosuppression and gastrointestinal mucosa disorders occur, which play an essential role in the risk of candidiasis.[4] Chemotherapy agents in cancer also cause a decrease in the function of the body's immune system through the release of calreticulin (CALR), chemokine ligand 10 (CXCL 10), high mobility group box 1 (HMGB1), and cell stress. This will trigger the process of apoptosis, autophagy, and disruption of T-cell priming.[5]

Lymphocytes and neutrophils play a role in the innate and adaptive immune system. Lymphocyte cells play an essential role in the production of T-cells

in cellular immunity and the production of B cells in humoral immunity. A decrease in the absolute number of lymphocytes that occurs in people with immunocompromised will reduce antigen presentation, thereby reducing immunoglobulin production.[3,4] Neutrophils are the first leukocytes to migrate from the blood to sites of injury or infection to kill pathogens and remove debris. An increase in the neutrophil-lymphocyte ratio indicates an inflammatory response in the body.[3]

The diagnosis of candidiasis is challenging because there are no specific clinical signs and symptoms. Early diagnosis of candida infection is essential in determining early management and management of patients to reduce mortality.[1] There are several non-culture biomarker tests in diagnosing candidiasis, one of which is the detection of anti-mannan antibodies against candida. The examination of anti-mannan IgM and IgG has a sensitivity of 40%-70% and a specificity of 50%-80%.[6]

This study aims to determine the correlation between chemotherapy status, absolute lymphocyte count, and neutrophil-lymphocyte ratio to anti-mannan IgM and IgG in immunocompromised patients such as lung cancer in terms of helping candidiasis management earlier.

METHODS

The method in this study used a cross-sectional design, where the data source was obtained from collecting lung cancer patients at Dr. Saiful Anwar Malang. Samples were obtained using consecutive sampling in the inpatient room of Dr. Saiful Anwar Malang Hospital. The inclusion criteria included inpatients aged >18 years with underlying lung cancer disease who had established pathological anatomy in both non-small lung cancer and small cell lung cancer and patients with candida infection as evidenced by positive candida sputum culture. The exclusion criteria in this study were all lung cancer patients with non-candidal sputum culture. The sample size used in this study was 37 patients who met the inclusion and exclusion criteria.

The operational standards at Dr. Saiful Anwar Malang Hospital carry out routine blood tests and candida sputum culture. Meanwhile, an anti-mannan IgM and IgG examination was conducted in the Physiological Laboratory of the Faculty of Medicine, University of Brawijaya, Malang using the Human Candida Albicans ELISA kit, BT-Lab brand. Data analysis used correlative analysis between Absolute Lymphocyte Ratio (ALC), Neutrophil Lymphocyte Ratio (NLR), and chemotherapy status with IgM and IgG anti mannan.

The statistical test uses a contingency coefficient where the value of $P<0.05$ with 95% CI. This research has received ethical approval from the health research ethics committee of Dr. Saiful Anwar Malang Hospital with number 400/205/K.3/302/2020.

RESULTS

The distribution of research data is shown in Table 1.

Table 1. Characteristics of Research Data

Characteristics	n	%
Gender		
Male	27	73.0
Female	10	27.0
Age		
18–45 years old	6	16.2
46–59 years old	16	43.2
60–74 years old	11	29.7
75–90 years old	4	10.8
Histopathological Distribution		
Adenocarcinoma	24	64.9
Squamous carcinoma	6	16.2
Adenosquamous carcinoma	3	8.1
Small cell carcinoma	3	8.1
Undifferentiated cell	1	2.7
Chemotherapy status		
Negative	18	48.6
Positive	19	51.4
Absolute lymphocyte count		
<1200 cell/µL	22	59.5
>1200 cell/µL	15	40.5
Neutrophil lymphocyte ratio		
>3.53	15	40.5
<3.53	22	59.5
Anti manan IgM antibodies		
Positive	22	59.5
Negative	15	40.5
Anti manan IgG antibodies		
Positive	5	13.5
Negative	32	85.5

The majority are male, as many as 27 people (73.0%), with the middle age range (46-59 years) having the most significant number of 16 people (43.2%). Based on the histopathological picture of lung cancer, the distribution of the study was bronchogenic, primarily adenocarcinoma in several 24 people (64.9%), while based on chemotherapy status, out of 37 study samples, 19 of them (51.4%) had undergone chemotherapy or received at least two cycles of chemotherapy. The rest, as many as 18 patients (48.6%), had never undergone chemotherapy.

Tables 2 and 3 describe the correlation analysis between Absolute lymphocyte count (ALC), Neutrophil lymphocyte ratio (NLR), and chemotherapy status for anti mannan IgM and IgG for candida. In this study, there was no significant correlation between ALC and anti-mannan IgM with a weak correlation strength (*P*=0.314; r=0.163), but there was a significant correlation with IgG with a robust correlation strength (*P*=0.314; r=0.613).

Table 2. ALC contingency coefficient test, NLR, chemotherapy status with IgM anti-mannan

Characteristics	IgM		r	*P*
	Positive	Negative		
Absolute lymphocyte count				
<1200 cell/µL	4 (80.0%)	18 (56.2%)	0.163	0.314
>1200 cell/µL	1 (20.0%)	14 (43.8%)		
Neutrophil lymphocyte ratio				
>3.53	5 (100.0%)	10 (31.3%)	0.432	0.004
<3.53	0 (0.0%)	22 (68.7%)		
Chemotherapy status				
Negative	3 (60.0%)	15 (46.9%)	0.089	0.585
Positive	2 (40.0%)	17 (53.1%)		

In the statistical test between NLR and IgM anti-mannan, there was a significant correlation with a moderate correlation strength (*P*=0.004; r=0.432), but no significant correlation was found with IgG anti-mannan with a weak correlation strength (*P*=0.156; r=0.227).

This study showed a statistically insignificant correlation between chemotherapy status and IgM anti-mannan with feeble strength (*P*=0.585; r=0.089). Besides, there was no statistically significant correlation with IgG anti-mannan with weak correlation strength (*P*=0.156; r=0.227).

Table 3. ALC contingency coefficient test, NLR, chemotherapy status with IgG anti-mannan

Characteristics	IgG		r	*P*
	Positive	Negative		
Absolute lymphocyte count				
<1200 cell/µL	20 (90.9%)	2 (13.3%)	0.613	0.0001
>1200 cell/µL	2 (9.1%)	13 (86.7)		
Neutrophil lymphocyte ratio				
>3.53	11 (50.0%)	4 (26.7%)	0.227	0.156
<3.53	11 (50.0%)	11 (73.7%)		
Chemotherapy status				
Negative	13 (59.1%)	5 (33.3%)	0.245	0.124
Positive	9 (40.9%)	10 (66.7)		

DISCUSSION

Lung cancer is histologically divided into two types, namely Non-Small Cell Lung Cancer (NSCLC) (85%) and Small Lung Cell Cancer (SCLC) (15%), where NSCLC is divided into adenocarcinoma (38.5%), squamous carcinoma (20%) and large cell carcinoma (2.9%). Epidemiology of lung cancer is expected in the male sex and over 40 years of age.[7] In lung cancer, there are disturbances in antigen recognition, the energy of cytotoxic T cells, and activation of inflammatory inhibitory cells. In addition, in lung cancer, there is also an increase in the number of neutrophils caused by the production of GM-CSF, G-CSF, IL-1, and IL-6.[8]

In this study, 37 patients were diagnosed with candidiasis based on clinical features and positive candida sputum culture. Some patients in this study have negative IgM and IgG anti mannan; we assume immunocompromised patients, such as lung cancer, cannot form an adequate immune system.

This study found a positive correlation between chemotherapy status and anti-mannan IgM and IgG, although it had a weak correlation strength. Traktama and Sufiawati, in their research, stated that chemotherapy in cancer patients was a predictor of the risk of candida Albicans infection.[9] In chemotherapy, immunogenic cell death occurs by releasing calreticulin, CXCL 10, HMGB1, and cell stress, thereby reducing the humoral immune response.[5] There was no significant correlation found in this study, which could be due to not considering the type of chemotherapy and how long the respondent received chemotherapy agents.

This study also found a positive correlation between ALC and anti-mannan IgM and IgG. Shimizu et al mentioned a negative correlation between lymphocyte levels and candida mannan serum levels. In another study, Koga et al showed that normal lymphocyte status would decrease serum levels of Human 1,3-β-D-Glucan by 0.015 pg/dl.[10]

IgM plays a role in inhibiting the adhesion and filamentation of candida yeast cells. In contrast, IgG anti-mannan plays a role in initiating the complement system and increasing phagocytosis. Lymphocyte cells play an essential role in the specific immune system, producing T cells and B cells in humoral immunity. A decrease in the total lymphocyte count will reduce antigen presentation so that immunoglobulin production decreases.[11]

This study positively correlates NLR and anti-mannan IgM and IgG. Meshall et al mentioned NLR as a prognostic factor for various infections (bacterial, fungal, and viral).[11] Neutrophils are the first leukocytes to migrate from the blood to sites of injury or infection. The increase in NLR is an inflammatory response due to the infection process. The presence of a fungal infection will initiate the formation of antibodies as a humoral immune response.[12]

LIMITATION

This study has some limitations, including not conducting a specific analysis of other candidiasis risk factors, not analyzing clinical data, radiological features, and lung cancer progression rates, and not analyzing chemotherapy history, duration, and chemotherapy agents.

CONCLUSION

This study concludes that chemotherapy status, absolute lymphocyte count, and neutrophil lymphocyte ratio play a role in influencing the formation of anti-mannan IgM and IgG against candidiasis. Patients with immunocompromise, such as lung cancer, who have undergone chemotherapy, lymphocytopenia, and increased NLR tend not to form anti-mannan antibodies, so it is recommended to be given antifungals earlier.

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CONFLICT OF INTEREST

None.

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