



The Relationship of Serum Zinc Levels and Clinicopathological Characteristics in Individuals with Lung Cancer

Haryati^{1*}, Nugroho Eko Prasetyo², Eviriana R. Simarmata³,
Mual Bobby Enrico Parhusip³, Fidyah Rahmadhany Arganita¹, Adhwa Humaira⁴

¹Department of Pulmonology and Respiratory Medicine,
Faculty of Medicine, Lambung Mangkurat University, Banjarmasin

²Department of Pulmonology and Respiratory Medicine,
dr. H. Andi Abdurahman Noor Hospital, Tanah Bumbu

³Department of Pulmonology and Respiratory Medicine, dr. Doris Sylvanus Hospital, Palangkaraya

⁴Faculty of Medicine, Lambung Mangkurat University, Banjarmasin

Corresponding Author:

Haryati | Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Lambung Mangkurat University, Banjarmasin | haryati@ulm.ac.id

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Abstract

Background: Lung cancer is one of the main contributors to malignancy and leads to the patient's death. The immune system, genetics, and inflammation affect lung cancer progression. Zinc (Zn) is an essential mineral; a Zn deficiency increases the tumor suppressor's expression, damaging deoxyribonucleic acid (DNA) repair ability in tumor growth. The study focused on establishing a relationship between serum Zn levels and lung cancer patients' clinicopathologic characteristics.

Method: Thirty-five patients diagnosed with lung cancer were part of the study. The study collected clinicopathological data and serum Zn levels at the initial diagnosis. Serum Zn insufficiency is characterized by a below 80 µg/dL serum Zn level.

Results: The median Zn level in our study was 65 µg/dL (range=56.5-73 µg/dL). Serum Zn deficiency was observed in 91.4% of patients, particularly those who had a smoking history, advanced stage, or had hypoalbuminemia. The low-level group exhibited significantly lower albumin concentrations (3.06 g/dL vs. 3.66 g/dL; P=0.024) than the normal group.

Conclusion: Most patients with lung cancer at initial diagnosis had a deficiency in Serum Zn, which was associated with hypoalbuminemia.

Keywords: clinicopathological characteristic, hypoalbuminemia, lung cancer, serum Zn level

INTRODUCTION

The International Agency for Research on Cancer (IARC) projects reported that in 2020, 19.3 million new cases of cancer globally, resulting in approximately 10 million deaths linked to

cancer. In Indonesia, the increasing trend in cancer incidence is evident, with over 1.3 million cases treated in 2016 alone.¹ According to data from the Global Cancer Observatory, there were an anticipated 396,914 new cancer diagnoses in

Indonesia in 2020, with a corresponding death toll of 234,511. As per the 2018 Riset Kesehatan Dasar (RISKESDAS) report by Indonesia Basic Health Research, the country's cancer prevalence has increased from 1.4 per 1000 people in 2013 to 1.8 per 1000 people in 2018.²

Lung cancer, accounting for approximately 1.8 million fatalities and 2 million diagnoses globally, is the leading contributor to death due to cancer. Lung cancer is one of the common cancer diagnoses for both men and women. There is a global increase in lung cancer cases attributed to the growing availability of tobacco and industrial development in developing nations.³ One of the most critical factors related to this increase in morbidity and mortality was the parallel increase in cigarette consumption after World War II.⁴

Tobacco use is considered the most significant lung cancer risk, with 80-90% of the total number of cases in the world related to cancers emitted as primary or secondary smoke. However, it is not the only risk factor.⁴ Previous research has established that certain external factors, diet, and exercise can impact the likelihood of developing lung cancer. Nevertheless, specific concentrations of trace elements like zinc (Zn) and copper may impact lung cancer progression.⁵

Zinc is crucial in controlling different physiological and biochemical conditions in organisms. It is pivotal in preserving cell membrane integrity and protein, carbohydrate, and lipid metabolism. It also supports the immune system, wound

healing, and various biological processes linked to growth and development. Zinc deficiency impacts many hormones' physiological and biochemical levels.⁶

Zinc ions play a role in structural and regulatory proteins, such as transcription factors, and are involved in forming "Zn fingers" that enable transcription factors to bind to deoxyribonucleic acid (DNA). When Zn ions interact with these biological systems, they form a pool involved in the specific functions of the proteins present. Given the numerous functions carried out by this component, it is crucial in safeguarding against tumor initiation and promotion. However, the mechanism of this function remains not fully understood.⁷

There is an increasing amount of evidence suggesting a connection between Zn deficiency and cancer. Multiple epidemiological studies have suggested that a lack of Zn raises the chances of developing cancer. Research has linked Zn deficiency with larger tumor size and advanced tumor stage among individuals with head and neck cancer.^{8,9}

According to the findings of a meta-analysis conducted by Wang et al, blood Zn levels were found to be considerably lower in lung cancer patients in contrast to levels found in controls.⁵ The antitumor activity of Zn involves several functions, including DNA damage and repair, oxidative stress, immune function, and inflammation. Insufficient Zn levels may alter the antioxidant defense mechanism and hinder the immune system's function.⁸

While there have been studies indicating reduced Zn concentrations in the serum of patients suffering from several kinds of cancers, there is an inconsistency in the results. Moreover, there appears to be a gap in research regarding the relationship between Zn status and lung cancer in developing countries such as Indonesia. This study intended to explore the prevalence of serum Zn insufficiency in patients diagnosed with lung cancer and assess the relationship between clinicopathological characteristics and the patient's blood Zn levels.

METHOD

Cross-sectional research was undertaken with 35 participant patients at the Doris Sylvanus Hospital in Palangkaraya from January to April 2023. The study's criteria for inclusion were patients with lung cancer diagnosis, aged 18 or older, who had not undergone surgery, radiation, or chemotherapy, and who were willing to participate by signing an informed permission form. The exclusion criteria encompassed any other form of malignancy and any medical problems that are known to impact anemia, such as individuals with existing or previous hematology-related conditions, chronic renal disease, and chronic liver disease. This research received permission from the Ethics Committee of Doris Sylvanus Hospital No. 784.1/UM-TU/RSUD/01-20.

Age, gender, smoking history used Brinkman index, height, body weight (BW),

body mass index (BMI), main symptoms, clinical stage, metastasis, and histology were analyzed as patient characteristics. Leucocyte, hemoglobin level, thrombocyte, total lymphocyte counts (TLC), absolute neutrophil count (ANC), neutrophil-lymphocyte ratio (NLR), C-reactive protein (CRP), albumin (Alb), and serum level of Zn were among the laboratory parameters measured. As per Japan's Practical Guidelines for Zn Deficiency, Zn concentration in the serum below the 80 µg/dL threshold indicates a serum Zn deficiency. Serum Zn levels were categorized into "deficient" and "normal" groups.

Variables that adhered to a normal distribution were represented using means and standard deviations. In contrast, medians and interquartile ranges represented variances that deviated from a normal distribution. The mean values of the patient groups were compared using the student t-test or Mann-Whitney U test for continuous data. The Fischer exact test is used to identify any significant differences among categorical variables. Statistical analysis was performed using SPSS 22 software, and statistical significance was assessed at a significance level of $P > 0.05$.

RESULTS

Table 1 shows the clinical features of the 35 individuals diagnosed with lung cancer. The study sample consisted of eight female and 27 male participants, with a median age of 60. The median Zn level

was 65 µg/dL, ranging from 56.5 to 73 µg/dL. Eight of the patients were non-smokers, whereas 27 had a smoking history.

Table 1. The Clinical Features Exhibited by Individuals Diagnosed with Lung Cancer

Variable	n = 35
Age (years), median (range)	60 (53-68)
Sex	
Male	27 (77.1%)
Female	8 (22.9%)
History of smoking	
Smoker	27 (77.1%)
Brinkman Index <600	18 (66.7%)
Brinkman Index ≥600	9 (3.3%)
Non-Smoker	8 (22.9%)
Main Symptom	
Cough	13 (37.1%)
Shortness of breath	9 (25.7%)
Chest Pain	13 (37.2%)
Body Mass Index (kg/m ²)	
<18.5	24 (68.6%)
≥18.5	11 (31.4%)
Pathology	
Adenocarcinoma	19 (54.3%)
Squamous cell	13 (37.1%)
SCLC	3 (8.6%)
Stage	
<IV	6 (17.1%)
≥IV	29 (82.9%)
Metastasis	
No metastasis	6 (17.1%)
Intrathoracic metastasis	27 (77.2%)
Extrathoracic metastasis	2 (5.7%)
Laboratory parameter	
Hemoglobin (g/dl), median (IQR)	11.7 (10.2-13)
Leucocyte (uL), median (IQR)	12330 (8460-16320)
ANC (/mm ³), median (IQR)	8340 (6000-13630)
TLC (/mm ³), median (IQR)	1787 (1337-2384)
Thrombocyte (x10 ⁹ /L mg/dl), median (IQR)	375 (279-465)
CRP (mg/dL), median (IQR)	87.77 (16.53-116.23)
Albumin (g/dL), median (IQR)	3 (2.8-3.42)
Zn level (µg/dL), median (IQR)	65 (56.5-73)

Note: SCLC=Small Cell Lung Cancer; ANC=Absolute Neutrophil Count; TLC=Total Lymphocyte Count; CRP=C-Reactive Protein; IQR=interquartile range

Table 2. The Clinical Presentation of the Patient Diagnosed with Lung Cancer is Determined by Analyzing the Serum Zn Levels

Variable	Serum Zn level		P
	Low level (n=32) ($< 80\mu\text{g/dL}$)	Normal level (n=3) ($\geq 80\mu\text{g/dL}$)	
Age, median (range), years	58.88 \pm 9.8	59.33 \pm 2.08	0.937 ^a
Sex			0.124 ^y
Male	26	1	
Female	6	2	
History of smoking			0.124 ^y
No	6	2	
Yes	26	1	
Brinkman Index			1.000 ^y
<600	9	0	
≥ 600	17	1	
Body mass index			0.190 ^y
< 18.5	8	2	
≥ 18.5	24	1	
Pathology			0.500 ^y
Adenocarcinoma	16	3	
Squamous cell	3	0	
SCLC	13	0	
Stage			1.000 ^y
<IV	6	0	
\geq IV	26	3	
Metastasis			1.000 ^y
No	7	0	
Yes	25	3	
ANC (/mm ³)	8460 (5995-12479)	6936 (6723-10983)	0.724 ^β
TLC (/mm ³)	1767 (1351-2482)	1860 (1555-1970)	0.953 ^β
NLR	3.89 (3.44-8.13)	3.5 (3.33-3.5)	0.859 ^β
CRP (mg/dL)	90.61 (18.06-118.12)	61.9 (38.94-81.23)	0.680 ^β
Albumin (g/dL)	3.06 \pm 0.43	3.66 \pm 0.31	0.024 ^{a*}
Zn level ($\mu\text{g/dL}$) (median)	63.5 (35-79)	101 (89-105)	

Note: *significant $P < 0,05$; ^aStudent T-test; ^βMann Whitney; ^yFisher exact; ANC=Absolute Neutrophil Count; TLC=Total Lymphocyte Count; NLR=Neutrophil Lymphocyte Ratio; CRP=C-Reactive Protein

Thirteen patients experienced the main symptom of coughing, nine patients experienced shortness of breath, and another thirteen patients claimed chest pain. As much as 68.6% of patients were underweight with a BMI < 18.5 . Three

individuals were found to have small cell lung cancer (SCLC), thirteen with squamous cell carcinoma, and nineteen with adenocarcinoma. Our studies reported most patients at stage IV, with 27 having metastasis intrathoracic and 2

having metastasis extrathoracic.

Thirty-two patients were affected by serum Zn deficiency, accounting for 91.4% of the total cases. The clinical features of lung cancer patients based on their serum Zn levels are detailed in Table 2. The median blood Zn level in the low-level group was 63.5 µg/dL, with a range of 35–79 µg/dL. In the normal-level group, the median serum Zn level was 101 µg/dL, with a range of 89–105 µg/dL.

Individuals who have a smoking background, high Brinkmann index, at stage IV, and with metastasis showed predominantly low Zn levels. Compared to the normal group, the albumin levels in the low-level group were significantly lower (3.06 g/dL vs. 3.66 g/dL; $P=0.024$). There were no notable variations between the two groups regarding age, sex, smoking history, Brinkman index, BMI, pathological type, stage, metastasis, ANC, TLC, NLR, and CRP.

DISCUSSION

We discovered that 91.4% of the patients with lung cancer had low serum Zn ($< 80\mu\text{g/dL}$). Several studies conducted in recent years have provided evidence that Zn shortage and lung cancer are related to one another. According to Wang et al, in European and Asian populations, lung cancer patients showed significantly lower serum Zn levels compared to controls.⁵

According to Bai et al, there is a possibility that Zn could be used to help prevent lung cancer. Research has indicated that elevated levels of Zn in the

bloodstream may decrease the likelihood of developing lung cancer by potentially affecting telomere events and the expression of specific oncogenes.¹⁰

Lung cancer is considered predominantly a smoking-related disease, similar to our research finding that most of our patients were smokers (77.1%) and had low levels of Zn serum compared to non-smokers, especially in the high Brinkman index. In the present study, the median serum Zn levels at initial lung cancer diagnosis were 65 (56.5-73) µg/dL, and the majority were in an advanced stage. Compared to the average of 87.5 ± 11.2 (65-110) µg/dL, the serum Zn levels in individuals with lung cancer were 22.5 µg/dL lower than the reference value for a healthy human body.¹¹

Similar to recent meta-analyses by Wang et al, blood zinc levels were considerably lower in patients than in control. Meanwhile, Zhang et al discovered that patients with lung cancer had a significantly higher serum copper/zinc ratio (indicating low zinc levels) than patients with healthy controls; additionally, patients with advanced lung cancer had a significantly higher ratio than those with early-stage lung cancer.¹² The decreased Zn consumption may have diminished Zn levels in individuals with lung cancer. Nevertheless, animal and human bodies can regulate Zn levels within a wide range of Zn intake, ensuring homeostasis. The ability to change may be altered when a cancer progresses.¹³

Moreover, in the process of cancer progression, tissue injury is recognized to

release naturally occurring substances from white blood cells called polymorphonuclear leukocytes. As a blood result, Zn levels decrease, and the liver absorbs more Zn. The increased uptake from the bloodstream can be attributed to lung cancer cells having a significantly greater Zn metabolism requirement than healthy cells.¹³

Reduced levels of Zn in the blood might occur due to ongoing inflammation, a common characteristic of lung cancer. The diminished involvement of Zn in the immune system and antioxidant response can expedite cancer progression if there is a decrease in Zn levels. It could potentially result in a self-perpetuating cycle.¹³

Increased endogenous and external oxidative insults can harm the lungs. Numerous investigations have shown a clear correlation between redox imbalance, both locally and systemically expressed, and lung cancer. A physiological imbalance favoring oxidants (free radicals or reactive species) over antioxidants can lead to oxidative stress, a phenomenon or disease that affects cells.¹⁴

Telomeres, consisting of repeating DNA sequences, are highly conserved structures at the distal ends of eukaryotic chromosomes. Telomeres keep chromosomal ends from breaking down and fusing, crucial for preserving structural integrity and genetic stability.^{15,16}

According to reports, telomere shortening has been linked to inflammation and oxidative stress. Life expectancy was significantly reduced by telomere shortening, which raised the risk of age-

related chronic illnesses and even malignancies. Zn is a vital trace mineral in food with potent anti-inflammatory and antioxidant effects. Though the fundamental process remains unclear, there are a few plausible hypotheses. Zn may promote genomic integrity, lower oxidative stress and inflammatory reactions, and increase telomerase activity to sustain telomere length.¹⁵

This investigation also revealed a strong positive association between serum albumin and Zn levels. Albumin is essential for the systemic distribution of Zn since it is the primary carrier of Zn in plasma.¹⁷ Albumin binds around 80% of blood Zn; a positive correlation exists between albumin and serum Zn levels. Additionally, hypoalbuminemia makes less Zn bound to albumin in the blood, which increases Zn excretion in the urine.¹⁸

Meanwhile, tumor necrosis factor might make the microvasculature more permeable, facilitating more albumin transcapillary transit. In the initial stages of cancer, there is usually a mild or no decrease in the albumin levels. However, as the disease progresses, there is a significant fall in albumin levels, which can be used as reliable indicators of the prognosis of cancer.^{19,20}

This study also comes with limitations. The research was conducted in one center with a limited sample, and underlying health conditions that could potentially impact the levels of trace elements, like infectious diseases, were not considered. Therefore, it is necessary to

conduct larger multicenter studies to confirm our findings.

CONCLUSION

Based on this study, it can be concluded that individuals diagnosed with lung cancer often have low levels of Zn in their bodies. Furthermore, much data indicates a strong connection between the amounts of Zn in the blood and serum albumin levels. Insufficient nutrition at the time of diagnosis may have influenced this outcome. Further investigation is required to authenticate and revise our conclusions regarding patients with lung cancer.

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