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Assessment of iron status markers in patients with lung cancer

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Abstract---Lung cancer is one of the most diagnosed diseases in men and women and is the leading cause of cancer-related mortality worldwide. The purpose of this study is to examine the impact of lung cancer on the role of iron status markers in patient serum. The present study included fifty (50) lung cancer patients (males and females) and forty (40) healthy subjects. The levels of iron status markers that include iron, ferritin, transferrin, transferrin saturation (TS%), total iron binding capacity (TIBC), and unsaturated iron binding capacity (UIBC) were estimated in the serum of lung cancer patients, as well as the value of interleukin 6 (IL-6) were recorded. Generally, the results of the present study revealed significant differences ($p < 0.05$) in the levels of iron status markers and IL-6 in the serum of lung cancer patients in comparison with the control groups. The findings of this study suggest that these indicators play an important role in lung cancer at multiple levels and that the specific activity of these biomarkers may be relevant as an independent predictor of lung cancer disease progression.

Keywords---iron status markers, interleukin 6, lung cancer, Iraqi patients, prognostic biomarkers.

Introduction

Cancer is a condition that is characterized by unregulated cell growth and proliferation in which cells have eluded the body's usual growth control mechanisms and developed the ability to divide continuously. It's a multistep process that needs the accumulation of numerous genetic alterations with time (CCA, 2021). According to the American Cancer Society, there were 2.1 million cases of lung cancer in 2018, accounting for approximately 12% of all cancer

cases. Lung cancer is a major cause of cancer-related mortality among men worldwide and the second-leading cause among women, with an expected 1.8 million deaths in 2018, accounting for one in five cancer deaths (ACS, 2018). Worldwide, lung cancer is the most prevalent cancer in terms of incidence and mortality among men, while it ranks third in terms of incidence among women and second in terms of mortality after breast cancer (Mustafa *et al.*, 2016). The World Health Organization (WHO) predicts that lung cancer mortality rates will continue to rise, primarily due to a rise in global tobacco use, especially in Asia (Duma *et al.*, 2019).

In Iraq in 2018, bronchus and lung cancers accounted for 8.19% of cancers in both genders, 5.81% in males and 2.38% in females. Lung cancer is the most prevalent cancer in terms of incidence and mortality among men (ICB, 2018). Lung cancer can result from many causes, including modifiable and unmodifiable risk factors. Some risk factors, such as smoking, are modifiable. Others, such as an individual's age or family history, cannot be altered (ACS, 2019). On the other hand, iron (Fe) is a necessary component of numerous major metabolic pathways. It is essential for the delivery of oxygen to all cells and is involved in oxidation–reduction reactions and the proliferation of cells (Toyokuni, 2009). So, iron is very important for making hemoglobin, and some compounds that are related to iron, like ferritin, transferrin, and IL6, play important roles in iron storage, transport, and keeping the amount of iron in the body within normal limits (Chen *et al.*, 2019; Sukiennicki *et al.*, 2019).

The ferritin level serves as a diagnostic indicator for iron-deficiency anemia. Previously, serum ferritin has been proposed as a tumor marker for the diagnosis of cancers (Cazzola *et al.*, 1985). Besides, IL-6 facilitates a number of physiological processes by acting as a hepatocyte-stimulating factor and inducing acute-phase protein synthesis (Mihara *et al.*, 2012). Upon returning to the literature, we have found that the studies that have been completed on the relationship of iron status to the lung cancer are few and almost non-existent in Iraq, so this study has been designed to evaluate iron status markers and some hematological parameters in patients with lung cancer. In fact, we think that these criteria can be helpful factors in the initial diagnosis of this cancer, as well as in managing, follow-up, presentation, and treatment of the disease.

Materials and Methods

This investigation was conducted in the advanced research laboratory of the Department of Laboratory Investigations/Faculty of Science/University of Kufa. All of the samples were collected from patients at the oncology unit of the AL-Imam Al-Hussein Center for Tumors and Hematology in Karbala province between 1/11/2021 and 1/2/2022. In the current study, only Iraqi patients diagnosed with lung cancer, verified by histopathology report, were included. This study investigates fifty (50) lung cancer patients (male and female) and forty (40) healthy participants. All the patients were examined and diagnosed by specialist physicians, and the study excluded all cases that did not have a histological report. The patients and healthy groups were exposed to questioners about age and smoking. In addition, participants were informed of the study and consent was obtained. The project was approved by the scientific ethical committee. The

patients with lung cancer in this study involved males and females who were divided into subgroups according to gender, age, histopathological type, and smoking status. Table 1.

Table 1
Frequency of clinical features of lung cancer patients

Features	Number	Percentage %
Lung cancer group	50	55.56%
Control group	40	44.44%
Gender:		
Males	30	60%
Females	20	40%
Age (year):		
≤ 50	22	44%
> 50	28	56%
Histopathological type:		
1. Non-small lung carcinoma (NSCLC):	36	72%
Adenocarcinoma	29	58%
Squamous cell carcinoma	4	8%
Large cell carcinoma	3	6%
2. Small cell lung carcinoma (SCLC)	14	28%
Smoking status:		
Smokers	38	76%
Non-smokers	12	24%

The samples were collected from healthy volunteers who had no history of chronic diseases or acute infections. The ages of the healthy subjects selected in this study were identical with the ages of the patients. In order to measure iron status indicators and IL-6 in blood serum, five ml of blood was put in glass tubes without anticoagulant at room temperature for one hour. After clotting, the serum samples were isolated by centrifuge and transported into Eppendorf tubes by micropipette and stored in freezing conditions at -20°C until they were analyzed (Koh *et al.*, 2012; Guo *et al.*, 2020). A kit for determining the human ferritin level in the serum was provided by Snibe Diagnostic/China. This kit has been developed for the quantification of ferritin in the human serum. The test was performed using the fully-automated chemiluminescence immunoassay (CLIA) analyzer MAGLUMI.

The value of transferrin was calculated according to the following equation: Transferrin (mg/dl) = $0.8 \times \text{TIBC} - 43$ (Sukiennicki *et al.*, 2019). The TS % was calculated using the following equation: $\text{TS\%} = \frac{\text{serum iron}}{\text{TIBC}} \times 100$ (Miya *et al.*, 2018). A kit for determining the human TIBC level in the serum (Ferene method) was provided by DIRUI/China. The level of UIBC was calculated according to the following equation: $\text{UBIC} = \text{TIBC} - \text{serum iron}$ (Sukiennicki *et al.*, 2019). Using an Enzyme-Linked Immunoassay (ELISA) kit supplied by Bioassay

Technology Laboratory (China), the serum IL-6 concentration was determined. This sandwich kit enables for the quantitative detection of human IL-6. Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS, version 23). A comparison between several groups was made using the independent t-test. The mean±standard deviation was used in the statistical analysis. A probability of <0.05 was considered significant for all tests.

Results and Discussion

In the present study, we determined the concentrations of iron status biomarkers and IL-6 in the serum of lung cancer patients and healthy individuals and evaluated the diagnostic significance of these criteria. The findings of this study revealed an reduction the levels of iron, transferrin, TS%, TIBC, and UIBC that is statistically significant ($p<0.05$) in the sera of patients with lung cancer disease when compared with healthy subjects. In contrast, the ferritin level of lung cancer patients was significantly elevated ($p<0.05$). Table 2.

Table 2
Iron status markers and IL-6 in serum of lung cancer patients and control groups

Parameter	Lung cancer patients (n=50)	Healthy control (n=40)
Iron ($\mu\text{g/dl}$)	15±15.94*	36±18.16
Ferritin (ng/ml)	327.07±181.42*	101.39±64.58
Transferrin (mg/dl)	109.63±37.43*	203.38±24.43
TS (%)	20.54±7.45*	26.11±5.06
TIBC ($\mu\text{g/dl}$)	188.86±45.32*	307.97±30.54
UIBC ($\mu\text{g/dl}$)	150.72±40.69*	227.59±28.25
IL-6 (pg/ml)	35.04±11.60*	3.83±1.36

Iron is an important trace element in the body, and its deficiency or excess triggers a wide array of biological processes. Several malignant tumors, including the lung cancer, are closely associated with iron dysregulation. Emerging evidence suggests that iron plays an especially important role in lung cancer (Kuang & Wang, 2019). In this study, the serum iron levels of lung cancer patients have been significantly lower than those of healthy individuals. These findings are in agreement with those obtained by other investigations (Milman *et al.*, 1991; Milman *et al.*, 1993; Knekt *et al.*, 1994; Milman and Pedersen, 2002; Erbaycu *et al.*, 2007; Guo *et al.*, 2020). Contradictory results have been recorded by Sukiennicki *et al.* (2019), who found an increase in iron levels in the sera of lung cancer patients (Sukiennicki *et al.*, 2019). Also, Stevens *et al.* (1988) found that

the serum iron was slightly higher in lung cancer patients compared to controls, but this increase was not statistically significant.

There is no obvious explanation for the discrepancies between the studies regarding the correlation between the serum iron and/or iron parameters and lung cancer. This could be attributed to variations in study size and design, as well as the sensitivity of the techniques for measuring these parameters in the serum (Sukiennicki *et al.*, 2019). On the other hand, there are emerging biomarkers that must be taken into account. The ferroportin/hepcidin regulatory axis is one of the most essential recent discoveries in iron homeostasis. The ferroportin–hepcidin axis controls intestinal iron absorption and iron recycling (Nemeth *et al.*, 2004). In addition to the systemic regulation of cell iron by serum ferroportin–hepcidin levels, Xiong *et al.* (2014) suggest that the intracellular iron of tumor cells may also be regulated by the ferroportin–hepcidin axis. So, focusing on iron metabolic pathways could lead to new ways to diagnose and treat lung cancer.

The available data suggest that the low serum iron is due to the fact that the release of iron from the reticuloendothelial system (RE-cells) is impaired in malignancies (Lipschitz *et al.*, 1971; Lee, 1983). According to Nemeth (2010), an elevated hepcidin value in the patients with advanced lung cancer is the leading cause of the serum iron deficiency because it can sequester iron in reticuloendothelial macrophages. It is believed that the inflammatory mediators encourage the production of hepcidin, which inhibits the secretion of iron from macrophages into the blood by restricting the activity of transferrin, resulting in an increase in serum ferritin and a decline in serum iron (Ganz & Nemeth, 2012). In addition, the inflammation is another topic worthy of discussion. C-reactive protein (CRP) is an acute-phase protein regarded as a prognostic marker of inflammation that has been linked to iron stores in the body (Fonseca-Nunes *et al.*, 2014).

Guo *et al.* (2020) have found that the level of CRP was higher in people with lung cancer, and that the level of CRP was much higher in people with advanced disease than in people with early disease. They also found that serum iron level was inversely related to CRP level. The iron accumulation in the inflammatory tumor due to the production of several inflammatory cytokines was also thought to be related to the low serum iron level in these patients (Chen *et al.*, 2019). Therefore, anemia is thought to be a direct reflection of the decreased level of serum iron in advanced-stage lung cancer patients since a considerable quantity of iron in the body is absorbed by the active metabolism of tumor cells, which exacerbates anemia and worsens the prognosis (Yovino *et al.*, 2005). Another study has revealed that the iron levels have increased in the lung cancer patients getting chemotherapy from day two of treatment (Miya *et al.*, 2018). During the chemotherapy, erythropoiesis may take in less iron, which may increase the expression of hepcidin and stop interleukin 6 (IL-6) from working through a negative-feedback mechanism (Ochiai *et al.*, 2014).

Ferritin is a significant iron reserve that is mostly found in bone marrow, liver, and spleen (Yang *et al.*, 2020). This thing was first found to be a protein that stores iron and keeps the balance of iron in the body. The ferritin level is used to

diagnose iron-deficiency anemia (Lee *et al.*, 2019). It is commonly known that malignancies have elevated serum ferritin levels; hence, this indication may be used to aid in the detection of cancerous tumors (Lee *et al.*, 2019). In addition, a higher serum ferritin value was an independent predictor of a poor survival result in advanced lung cancer patients (Lee *et al.*, 2017). In a previous study, it has been found that lung cancer patients have a much poorer survival rate with serum ferritin levels of > 300 microgram/liter (Milman & Pedersen, 2002). Our results have revealed that the levels of the serum ferritin have been considerably greater in lung cancer patients than in healthy participants. This finding is in line with data reported by recent studies that found a positive association between increased serum ferritin and disease incidence (Wang *et al.*, 2018; Sukiennicki *et al.*, 2019; Guo *et al.*, 2020).

Shi *et al.* (2014) have observed that the ferritin level in the serum of patients with advanced NSCLC was greater than that in healthy individuals, and that the effect of platinum chemotherapy in patients who had high serum ferritin levels was worse than that in patients with normal ferritin levels. In another study, Kakari *et al.* (1991) have found that the serum ferritin levels of people with lung cancer were statistically significantly higher than those of people in the control group. However, there was no significant difference in the serum ferritin levels of people with benign lung disease. According to Milman & Pedersen (2002), even after adjusting for the performance status, age, sex, TNM stage, and histological tumor type, an elevated ferritin level was a significant predictive predictor. Serum ferritin levels and the chance of survival in people with primary lung cancer are linked in a way that is clinically significant.

More serum ferritin is generated in the presence of tumors, resulting in the elevated serum ferritin levels in patients (Yang *et al.*, 2020). In addition, there is evidence that the serum ferritin concentration in malignancies increases in parallel with the tumor mass (Milman *et al.*, 1991). Previous work has shown that serum ferritin levels are proportional to tumour stage, not only in lung cancer (Gropp *et al.*, 1977). Regarding the cancer mechanism, a study has found that high serum ferritin is caused by inflammation and oxidative stress rather than iron overload (Kukulj *et al.*, 2010). It is assumed that higher serum ferritin levels in patients with non-small cell lung cancer (NSCLC) are due to inflammation and not iron overload (Ashmawi *et al.*, 2015). Anemia and significant alterations in iron metabolism are caused by infection or inflammation, and serum ferritin increases with infection (Thurnham *et al.*, 2010; Righetti *et al.*, 2013).

The sources of serum ferritin are currently unknown; however, hepatocytes and macrophages are reported to release serum ferritin (Cohen *et al.*, 2010). Tumor-associated macrophages (TAM) play a significant role in tumor growth via direct mechanisms to secrete procarcinogenic chemicals and indirect mechanisms of iron binding and ferritin release (Orlandi *et al.*, 2014). These results may explain why the level of the serum ferritin is much higher when there is inflammation and why there is a strong link between serum ferritin and CRP levels (Lee *et al.*, 2019). Generally, the serum iron and ferritin levels are typically correlated with the stage of lung cancer. In the later stages of lung cancer, serum iron levels are lower, serum ferritin levels are greater, and CRP levels are up. Inflammation may play a

significant influence on lung cancer patients' blood iron and ferritin levels (Guo *et al.*, 2020).

The transferrin functions to maintain cellular proliferation by providing iron for processes that have yet to be defined (Dowlati *et al.*, 1997). A recent study demonstrated that the difference in transferrin level was significant, and its level was lower in the patients with chronic obstructive pulmonary disease (COPD) diagnosed with lung cancer (Brzóska *et al.*, 2018). Furthermore, the results obtained by Chen *et al.* (2017) revealed a correlation between serum transferrin levels and tumor stage in male patients and between transferrin levels and menopausal status in female patients. It is believed that chronic inflammations, which frequently precede certain malignancies, cause diminished liver transferrin synthesis and poor tissue iron consumption (Knekt *et al.*, 1994). Besides, raised IL-6 levels have been associated with a decreased serum level of transferrin in patients with advanced lung cancer (Songür *et al.*, 2004).

Sukiennicki *et al.* (2019) found that there was no significant difference in TS between lung cancer control subjects. However, there was a negative link between TS and lung tumor stage, which verifies the association between low iron levels and advanced lung malignancies. Additionally, it is believed that high TS is not necessarily caused by an iron deficiency but could possibly be secondary to other illnesses (Knekt *et al.*, 1994). Concerning the TIBC, our observation is consistent with results that are obtained by Knekt *et al.* (1994), who found that TIBC was considerably lower in patients with lung cancer than in controls. In recent work, Brzóska *et al.* (2018) reported that the lower TIBC index in COPD with lung cancer subjects was significantly different to that of the COPD group. On the other hand, Sukiennicki *et al.* (2019) found that lung cancer patients had significantly higher mean TIBC than their controls, but there was no significant difference in UIBC between the two groups.

TIBC varies inversely with iron stores. However, the relationship may be less accurate in individuals with an iron excess than in those with normal or depleted iron stores. Hence, TIBC has been used as an indicator for body iron levels (Knekt *et al.*, 1994). In a clinical study, Miya *et al.* (2018) found that the saturation ratio of TIBC went up in lung cancer patients getting chemotherapy, while the saturation ratio of UIBC went down a lot. The statistical analysis in this study pointed out a significant elevation in the serum IL-6 values of patients with lung cancer when compared with healthy individuals. (Table 2). Consequently, our results confirmed the findings observed in previous reports (De Vita *et al.*, 1998; Songür *et al.*, 2004; Koh *et al.*, 2012; Siagian *et al.*, 2021; Kaanane *et al.*, 2022).

The IL-6 is a well-documented cytokine that has a significant role in numerous chronic inflammatory disorders (Kang *et al.*, 2020). It is a major cytokine that is known to affect immune response and is expressed in tumor-infiltrating cells (Wang *et al.*, 2014). The IL-6 facilitates the differentiation of B-cells into immunoglobulin-secreting cells and is reported to be a proliferative factor in some tumors (Yamaji *et al.*, 2004). It is a T-cell costimulatory signal factor that lung cancer stem cells directly target. As a cytokine that is made by lung cancer cells in large amounts, IL-6 is important in a number of biological processes, such as the growth, spread, invasion, and metastasis of tumors (Tang *et al.*, 2018). The

lung cancer-associated IL-6 upregulates hepcidin, hence lowering ferroportin and iron outflow. Transferrin receptor 1 (TFR1) and lipocalin-2 (LCN2) increase in the lung cancer, resulting in an increase in the iron import (Kuang & Wang, 2019).

The IL-6 is a powerful inducer of the synthesis of the hepcidin, a crucial iron metabolism regulator. An increase in the hepcidin can decrease iron levels, resulting in anemia. In addition, greater hepcidin levels are linked to more aggressive disease (Ganz, 2003; Wrighting and Andrews, 2006; Chen *et al.*, 2014). Pine *et al.* (2011) have discovered that increased IL-6 levels in lung, prostate, colorectal, and ovarian cancers were linked to cancer diagnosed within two years of blood collection. Songür *et al.* (2004) found that most people with advanced NSCLC have high levels of serum IL-6 at the time of their first diagnosis. This is linked to malnutrition, poor performance, an acute phase response, and a short life span.

In another study, the IL-6 levels have been found to be high in the majority of patients with lung cancer, but also dropped after a year of monitoring, particularly in individuals who responded to treatment (Sasaki *et al.*, 1996). Also, lung cancer patients had elevated levels of serum IL-6, which has been linked to a condition of systemic inflammatory response (Dowlati *et al.*, 1999). Tekpli *et al.* (2013) have concluded that the epigenetic alterations play a role in regulating the expression of IL1B, IL6, and IL8. Given that the production of these cytokines plays various functions in chronic inflammation, which may be associated with a greater susceptibility to carcinogenesis or tumor growth, this characteristic is critically significant. In the previous report, the mean IL-6 levels were greater than those of the controls. Patients with metastatic tumors reported elevated levels compared to those with localized illness. An increase in IL-6 levels was associated with the development of the tumor. Patients who responded to treatment exhibited lower serum IL-6 concentrations than those who did not. Thus, the authors propose that the serum IL-6 concentrations may serve as a predictive indicator in the NSCLC, as patients with elevated IL-6 levels have a poorer clinical prognosis (De Vita *et al.*, 1998). Finally, Koh *et al.* (2012) have found that the serum IL-6 is produced from overexpressed the IL-6 in the malignant cells itself in many cases of NSCLC. The expression of IL-6 in cancerous tissue was linked with the levels of serum IL-6, the development of the tumor, and OS in the NSCLC.

Conclusion

The results of the present study showed significant differences in the levels of iron status markers and IL-6 in the serum of patients with lung cancer compared with the healthy individuals. The measurements of the biomarkers that are used in this work can provide important prognostic observations of the malignant progression of this disease and may help in assess the treatment response and predicting recurrence. The changes in the iron, ferritin, and IL-6 values are more sensitive markers for the detection and prognosis of the lung cancer. Also, they are easy to make and can be found in the laboratories and health centers.

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