How to Cite:
Jasim, Z. Q., & Hadi, A.-H. A. (2022). Evaluation of some hematological criteria in lung cancer patients. *International Journal of Health Sciences*, *6*(S6), 2801–2813. https://doi.org/10.53730/ijhs.v6nS6.9971

Evaluation of some hematological criteria in lung cancer patients

Zahraa Qais Jasim
University of Kufa, Najaf, Iraq
*Corresponding author email: qzahraa1997@gmail.com

Abdul-Hadi Abbas Hadi
University of Kufa, Najaf, Iraq
Email: Abdulhadi.alibraheemi@uokufa.edu.iq

***Abstract*---**Lung cancer is one of the most commonly diagnosed diseases in both men and women and the leading cause of cancer-related death worldwide. This study aims to investigate the effect of lung cancer on the role of some hematological criteria in patient serum. There were fifty (50) lung cancer patients (males and females) and forty (40) healthy subjects in the present study. The levels of some hematological parameters that include erythrocyte indices [red blood cell (RBCs) count, hemoglobin (Hb), hematocrit (HCT), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), and red cell distribution width (RDW)], leukocyte indices [total white blood cell (WBCs) count, neutrophil percentage (%), lymphocyte percentage (%)], and thrombocyte indices [platelet count and mean platelet volume (MPV)] was recorded. In general, the levels of all hematological criteria in the serum of lung cancer patients were significantly different ($p<0.05$) from those of the control groups. In conclusion, hematological measurements can provide important prognostic information for patients with lung cancer, and they are simple and readily available at medical centers.

***Keywords*---**hematological criteria, clinical features, lung cancer, Iraqi patients, prognostic biomarkers.

Introduction

Cancer is a group of diseases distinguished by the uncontrolled growth and spread of abnormal cells. It can result in death if the spread is not contained. Cancer is the sixth leading cause of death in the world, causing more deaths than HIV/AIDS, tuberculosis, and malaria combined. Today, it is the second-leading

cause of death (after cardiovascular disease) in the world (ACS, 2018). Lung cancer is the most prevalent cancer in terms of incidence and mortality among men, while among women it has the third highest incidence and is second in terms of mortality after breast cancer. In the USA, the life-time risk of developing lung cancer is 8% in men and 6% in women (Wild, 2014; Hom *et al.,* 2015). In developed nations, lung cancer incidence and mortality rates are the highest. In contrast, it is estimated that lung cancer rates in underdeveloped regions, such as Central and South America and most of Africa, are lower (Sartorius & Sartorius, 2016). The World Health Organization (WHO) predicts that lung cancer death rates will continue to rise, primarily due to a rise in global tobacco use, especially in Asia (Cruz *et al.,* 2011).

There has been a steady rise in the number of lung cancer cases in Iraq in recent years. According to the Iraq Cancer Board (ICB), bronchial and lung cancer were the second most common cancers in Iraq in 2018. It contributes about 8.19% to both genders; in males it was 5.81% and in females it was 2.38%. It was noted that the highest annual estimate of death was due to bronchi and lung cancer (15.82%) among all cancer cases recorded this year (ICB, 2018). On the other hand, a complete blood count (CBC) is a blood test requested by a physician or other medical practitioner that provides information about the cells in the human blood, including erythrocytes, leukocytes, and thrombocytes (NIH, 2018). CBC is the most frequently requested test by physicians and is used to diagnose anemia, infection, different hematological malignancies, states of low or high platelet count, and therapy response (Jacob, 2016). In fact, the CBC parameters are a routine test and have been considered as predictive factors in patients with lung cancer (Saravia *et al.,* 2017).

Consequently, investigating the continuous changes in CBC indices during cancer growth may provide significant information on anticipated therapeutic efficacy, thereby aiding doctors in the creation of new treatment regimens (Rojko *et al.,* 2020). The current study aims to evaluate the levels of some erythrocyte, leukocyte, and thrombocyte indices in the serum of patients with lung cancer. In addition, the purpose of this research is to investigate the prognostic value of these criteria and the possibility of using them as helpful factors in the initial diagnosis of this cancer.

Materials and Methods

This research was conducted in Department of Laboratory Investigations/Faculty of Science/University of Kufa. All samples were taken from patients at the oncology unit of the AL-Imam Al-Hussein Center for Tumors and Hematology in the province of Karbala between 1/11/2021 and 1/1/2022. The current investigation included only Iraqi patients with lung cancer, as proven by histopathology report. This study included fifty (50) lung cancer patients (male and female) and forty (40) healthy participants. Specialist physicians examined and diagnose all of the patients. The patients and healthy groups were questioned about their age and smoking habits. In addition, informed consent was obtained from the subjects. The project has received approval from the scientific ethics committee. This study included male and female patients with lung cancer who

were separated into subgroups based on gender, age, smoking status, and histological type. 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%
Smoking status:		
Smokers	38	76%
Non-smokers	12	24%
Histopathological type:		
Non-small lung carcinoma (NSCLC)	36	72%
Small cell lung carcinoma (SCLC)	14	28%

The samples were collected from healthy volunteers who had no history of chronic diseases or acute infections. For hematological assessment, the venous blood was taken from the cubital vein of resting patients and a healthy group in the morning using a disposable syringe. One ml of each blood sample was placed in an EDTA tube for measurement of hematological parameters (erythrocyte, leukocyte, and thrombocyte indices) (Rojko *et al.,* 2020). The routine automated method for the complete blood count (CBC) was used to determine the hematological parameters (erythrocyte, leukocyte, and thrombocyte indices). With automated systems, erythrocyte indices like RBCs, Hb, and MCV are directly measured and, from these, the other variables, HCT, MCH, and MCHC, are calculated (Waterbury, 1997).

The hematological parameters that were measured in this study by a hematology analyzer (UrIit-3000plus) included RBCs count, Hb value, HCT level, MCH, MCHC, MCV, RDW, WBCs count, neutrophil (%), lymphocyte (%), platelet count, and MPV. Statistical analyses were conducted using the Social Sciences Statistical Package (SPSS, version 23). Through using independent t-test, a comparison of multiple groups was performed. In statistical analysis, the mean-standard deviation was utilized. In all tests, a probability of $p<0.05$ was considered significant.

Results and Discussion

In the present study, the concentrations of some hematological parameters in the serum of lung cancer patients and healthy individuals were determined, and the

diagnostic significance of these criteria was evaluated. The findings of this study showed a significant decrease ($p<0.05$) in some hematological values of patients with lung cancer, including RBCs count, Hb value, HCT level, when compared with the control group. On the other hand, the data showed that lung cancer patients had a significant increase ($p<0.05$) in MCH, MCHC, MCV, and RDW. Table 2.

Table 2
Hematological Criteria in serum of lung cancer patients and control groups

Parameter	Lung cancer Patients (n=50)		Healthy control (n=40)	
	Males	Females	Males	Females
Red blood cell count (RBCs) (million/mm^3)	3.66±0.98*	3.32±0.66*	5.08±0.3	4.58±0.39
Hemoglobin value (g/dl)	10.38±1.76*	10.02±1.51*	13.79±0.58	12.76±0.54
Hematocrit value (%)	33.04±6.41*	31.16±4.81*	40.82±1.61	38.48±1.60
Mean corpuscular hemoglobin (pg/cell)	30.02±2.43*	29.99±2.51*	28.41±0.98	28.34±0.74
Mean corpuscular hemoglobin concentration (g/dl)	34.35±2.00*	33.76±1.33*	33.20±0.46	32.78±0.46
Mean corpuscular volume (pg/cell)	88.94±4.79*	88.70±5.63*	85.73±3.41	84.51±2.79
Red cell distribution width (%)	15.15±1.97*	15.82±2.15*	11.79±0.50	11.96±0.52

Anemia is defined as a condition of decreased red blood cell (RBC) mass resulting in decreased levels of HCT and Hb (Pirker *et al.,* 2003). Cancer-related anemia is caused by a decrease in erythropoiesis, which is caused by a number of things, including malnutrition, poor intestinal absorption and metabolism, chronic inflammation, getting older, and an advanced stage of cancer (Gilreath *et al.,* 2014). Chemotherapy and radiation therapy can cause myelosuppression, relative erythropoietin deficiency, abnormal bone marrow response, functional iron deficiency, nutritional deficiencies, bleeding, hemolysis, cytokines, and other things that can lead to anemia in lung cancer patients (DeRienzo & Saleem, 1990; Groopman & Itri, 1999; Harrison *et al.,* 2000).

Peripheral tissue cells secrete hepcidin in lung cancer patients, which, unlike hepcidin produced by the liver, is thought to act primarily locally. As a result of inflammation, the liver secretes more hepcidin, which reduces ferroportin expression throughout the body. Cancer-induced hepcidin secretion affects iron

absorption and recycling, limiting circulating iron levels and leading to anemia and decreased erythropoiesis (Torti *et al.,* 2018). Cancer cells can produce inflammatory cytokines such as interleukin-6 (IL-6), which can cause anemia both directly and indirectly by inhibiting erythropoiesis (Yamaji *et al.,* 2004). Proinflammatory cytokines, particularly IL-6, promote changes in erythroid progenitor proliferation, erythropoietin production, and circulating erythrocyte survival. Cancer-related anemia is common in patients with advanced disease and advanced age (Madeddu *et al.,* 2018). Furthermore, oxidative stress has been linked to red blood cell survival and may be a potential mechanism of action for RDW (Semba *et al.,* 2010).

Anemia is regarded as a side effect of chemotherapy. However, numerous cancer patients have anemia even before they begin treatment (Macciò *et al.,* 2015). This type of anemia is caused by an impaired marrow response to erythropoietin, as well as a relative inadequacy of erythropoietin production in lung cancer chemotherapy and radiation therapy (Dowlati *et al.,* 1997). Anemia is also linked to a higher rate of cancer recurrence and a shorter survival time after radiotherapy. This could be because the tumors are more aggressive or there are more of them, not because of the anemia. There is some evidence that hypoxia in tumor cells, which could be made worse by anemia, may make them less sensitive to radiation (Shafiq & Venkateshiah, 2011). On the other hand, a comprehensive review of the literature on the relationship between anemia and survival showed that anemia is a strong predictor of poorer survival in cancer patients and that the relative risk of death increased by 19% in anemic lung cancer patients (Caro *et al.,* 2001).

The level of anemia in patients is reflected by hemoglobin, which is a significant CBC measure. It is reported that patients with malignancies had significantly lower hemoglobin than patients with benign disorders. The serum hemoglobin levels of the patients did not differ significantly between NSCLC and SCLC or between the various clinical stages (Milman & Pedersen, 2002). In a previous study, Gislason and Nõu (1985) recorded that nine percent of the patients with bronchial carcinoma were anaemic, with hemoglobin lower than 11 g/liter. In another study, NSCLC patients who had low hemoglobin levels, high leukocyte counts, BMI <18.5 kg/m2, and TNM Stage IV disease had poor prognosis, significantly worse time to progression (TTP), and overall survival (OS) (Mandrekar *et al.,* 2006). Likewise, Zhang *et al.* (2018) found that NSCLC patients with low hemoglobin had a worse prognosis. Chen *et al.* (2017) found that smoking status, disease type, and TNM stages were linked with hemoglobin in male patients but not in female patients.

Hemoglobin and ferritin are both blood proteins related to iron. Lee *et al.* (2019) discovered a negative correlation between serum ferritin and hemoglobin. In advanced NSCLC patients, the serum ferritin level was increased as the hemoglobin level declined, and correlation analysis demonstrated a strongly negative association between hemoglobin and ferritin. This situation is distinct from iron-deficiency anemia, in which both ferritin and hemoglobin simultaneously drop. Similarly, a large observational study found an adverse relationship between lung cancer patients' hemoglobin and ferritin levels (Macciò *et al.,* 2015). It has been observed that anemia and low hemoglobin levels can

produce hypoxia, which can accelerate tumor progression and increase malignant cell resistance to chemotherapy and radiotherapy by promoting the development of multidrug resistance (Milane *et al.,* 2011; Li *et al.,* 2016).

According to Wu *et al.* (2020), in patients with SCLC, a low hemoglobin-to-red blood cell distribution width ratio (HRR) was related to lower OS and progression-free survival (PFS) and may be a useful prognostic indicator. In addition, HRR may be a more trustworthy determinant of lung cancer prognosis. RDW is a metric typically provided on hematology analyzers. This metric is the most frequently reported index of red cell volume change and can be used to identify mild levels of anisocytosis (Constantino, 2013). In recent years, it has been determined that variations in RDW are associated with the inflammatory condition of the body, which has been proven to influence the formation of malignancies. Therefore, researchers investigated the connection between RDW and the prognosis of certain cancerous tumors and found that a high RDW is related to a poor prognosis (Wu *et al.,* 2020).

Gan *et al.* (2019) demonstrated that patients with lung cancer with higher RDW values had poorer prognosis and lower survival rates than those with lower RDW values. In addition, RDW is an indirect indicator of malnutrition in lung cancer patients. Furthermore, oxidative stress is associated with red cell survival and may represent a potential mechanism of action of RDW (Semba *et al.,* 2010). In one study, the data of lung cancer patients was evaluated by Koma *et al.* (2013); their findings revealed that high levels of RDW are connected with advanced disease stage and predict a poor prognosis for the patients. Similarly, Ichinose *et al.* (2016) found that older NSCLC resection patients with a high RDW score were more likely to get sick and less likely to live. As shown in Table 2, the present study revealed a significant elevation in the total white blood cells and neutrophils in lung cancer patients compared to healthy subjects, while there was a significant decrease in lymphocytes. Our findings are consistent with those of other studies (Mandrekar *et al.,* 2006; Wong *et al.,* 2019; Rojko *et al.,* 2020).

Recent research has identified inflammation as one of the indicators of the immune condition of the host. Inflammation promotes cancer cell proliferation and survival, angiogenesis, and tumor metastasis, thereby playing a crucial role in the development and progression of diverse cancers (Mantovani *et al.,* 2008). Wong *et al.* (2019) found an association between increased total WBC count and increased lung cancer risk. Neutrophil fractions, which are vital components of the innate immune response, were primarily responsible for this association. A high leukocyte count, especially when granulocytes predominate, is frequently attributed to a bacterial infection. Other causes, such as advanced cancer, bleeding, and corticosteroid use, also must be considered (Shafiq & Venkateshiah, 2011).

Mandrekar *et al.* (2006) demonstrated that the prognosis for Stage IV NSCLC patients with a high WBC count was particularly dismal. This could be caused by a higher number of tumor cells in the bone marrow, a possible subclinical infection, or the effect of a chemokine or cytokine released by the tumor but not yet described. Different cytokines and chemokines produced by tumor cells attract leukocytes. The inflammatory component of a neoplasm may contain

neutrophils, macrophages, and dendritic cells, among other leukocyte subtypes. All of these cells produce cytokines, as well as cytotoxic mediators such as reactive oxygen species and soluble mediators such as tumor necrosis factor-alpha (TNF-α) and interleukins (Unal *et al.,* 2013). Neutrophils are the most prevalent subset of leukocytes in the blood. Recent evidence suggests that neutrophils play an important role in inflammation caused by cancer and help predict the outcome of cancer in humans (Donskov, 2013).

In patients with advanced NSCLC, Paesmans *et al.* (1995) found an independent relationship between a high neutrophil count and poor survival. Teramukai *et al.* (2009) indicated a link between the number of neutrophils in the blood before treatment and a low chance of survival for people with advanced NSCLC who were getting chemotherapy. Previous studies have reported that lymphocyte count is an independent prognostic factor in patients with NSCLC. Lymph invasion and NSCLC recurrence were also linked to lower lymphocyte counts (Kobayashi *et al.,* 2012; Zhang *et al.,* 2013). Lymphocytes play a significant role in tumor-related immunology, and lymphopenia has been associated with a poor prognosis in NSCLC. Cho *et al.* (2019) studied the impacts of lymphopenia on OS and PFS in immunotherapy-treated patients and observed that lymphopenia within 0–2 months of immunotherapy initiation was associated with significantly inferior OS and PFS. Multiple studies have demonstrated that the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are associated with the prognosis of lung cancer patients and are valuable predictive markers for treatment (Kang *et al.,* 2014; Russo *et al.,* 2018; Liu *et al.,* 2019; Russo *et al.,* 2020; Shoji *et al.,* 2020).

Elevated NLR is associated with systemic and local inflammation that not only provides a favorable microenvironment for tumor invasion and metastasis but also suppresses the host immune system (Luo *et al.,* 2015). It is hypothesized that inflammation is linked to the prognosis of SCLC, and that NLR or PLR may be useful markers of the inflammatory process (Rojko *et al.,* 2020). An elevated NLR at the time of diagnosis was associated with a poor performance status, an advanced disease stage, and a low response rate. OS and PFS were worse in the group with a high NLR. These findings suggest that the NLR may reflect tumor burden and aid in evaluating treatment response and monitoring the recurrence or progression of SCLC (Kang *et al.,* 2014). Increased preoperative NLR is linked to a higher stage, but it is still a predictor after total resection for NSCLC. It could be used as a biomarker to identify people with stage I disease who are at a high risk of mortality (Sarraf *et al.,* 2009).

This study's findings revealed a significant increase in platelet count and MPV in patients with lung cancer in comparison with control groups (Table 2). The findings of our study are in agreement with those obtained by other investigations (Omar *et al.,* 2016; Zhu *et al.,* 2019; Rojko *et al.,* 2020). Also, having a high number of platelets has been linked to the progression of other cancers, such as rectal cancer (Andronic *et al.,* 2019) and breast cancer (Ali *et al.,* 2020). Platelets play an important role in clotting and inflammation, and stimulated platelets have been related to an increased risk of cancer through a variety of pathways (Zhu *et al.,* 2019). PLR has been studied as an inflammatory marker since platelet activation is increased by proinflammatory cytokines and has a role in neutrophil

recruitment (Ghasemzadeh & Hosseini, 2013; Kang *et al.,* 2014). Platelets can produce platelet-derived growth factor (PDGF), platelet factor 4 (PF4), and thrombospondin (Kaplan *et al.,* 1979; Dubernard *et al.,* 1997). The factors have been demonstrated to increase hematogenous tumor dissemination, tumor cell adhesion and invasion, and angiogenesis. They also play a key role in cancer progression (Qian & Tuszynski, 1996).

Platelet count and leucocyte count had a significant positive correlation, and they also correlated to survival at a significant level (Gislason and Nõu, 1985). So, thrombocytosis is associated with poor cancer prognosis, suggesting a potential role for platelets in the pathogenesis of the disease (Ali *et al.,* 2020). Certain hematologic abnormalities have been linked to a poor prognosis in lung cancer patients. Lung cancer patients have been documented to develop thrombocytosis, leukocytosis, and anemia. Anemia can have a weakly unfavorable effect on tumor radiosensitivity, although tumor-related thrombocytosis and tumor-related leukocytosis have prognostic value (Shafiq & Venkateshiah, 2011). Zhu *et al.* (2019) propose a causative association between higher platelet count and lung cancer risk, which contributes to a better understanding of lung cancer etiology as well as possible evidence for anti-platelet therapies in lung cancer prevention.

The studies indicate a considerable role for platelets in lung carcinogenesis. Platelets may be involved in the lungs' defensive and physiological immunological responses as well as inflammatory lung diseases, according to new research (Middleton *et al.,* 2016). As a result, a higher platelet count may have a biological link to an increased risk of lung cancer. (Gong *et al.,* 2012) found that lung adenocarcinomas and squamous cell carcinomas have higher levels of p-selectin than healthy people. P-selectin is an essential adhesion protein that is found on the surface of activated platelets. Multivariate analysis showed that there was a strong link between OS rates and PLR and response to chemoradiotherapy. Patients with NSCLC can get important prognostic information from their PLR and NLR measurements before treatment. Unal *et al.* (2013) found that evaluating the two parameters together gives a more accurate prognostic assessment of patients with NSCLC.

The MPV also contributes to the early identification and prognosis of lung cancer (Zhu *et al.,* 2019). In one study, PLR and NLR levels were much greater in lung cancer patients than in healthy people, although there was no statistically significant correlation between MPV, NLR, and PLR with histological subgroups and TNM stages (Kemal *et al.,* 2014). It has been reported that MPV affects the prognosis of advanced NSCLC patients. NSCLC patients with high MPV levels had bone metastases following first-line treatment, a poor prognosis, and many metastatic sites upon diagnosis. This study found that NSCLC patients with high MPV had a poor prognosis. Hence, an increased MPV level can be utilized to predict poor overall survival in NSCLC patients (Omar *et al.,* 2016).

Conclusion

According to the findings of the current study, the levels of studied hematological criteria in the serum of lung cancer patients differed significantly from those of healthy individuals. This study's parameter measurements can provide important

prognostic information regarding the progression of lung cancer and may aid in evaluating the treatment response. Also, it's easy to make them and you can find them in labs and medical facilities.

Acknowledgments

We are grateful to the Department of Laboratory Investigations staff as well as all those who assisted us at the Faculty of Science and University of Kufa. We would like to thank everyone at the Al-Hussein Teaching Hospital Center For Tumors in the province of Karbala, particularly the laboratory staff, for their ongoing assistance. We never forget to thank the patients who donated blood, and we pray that Allah will help them get well and live a long time.

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