Wasit Journal for Pure Science

Journal Homepage: https://wjps.uowasit.edu.iq/index.php/wjps/index
e-ISSN: 2790-5241 p-ISSN: 2790-5233

Clinical value of Hemoglobin in Combination with Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio as a Prognostic Factor in Advanced Lung Cancer

Noor Hameed Hanoush[1]*, Abdul Rahman Mohammed Geeran[2], Rashied Mohammed Rashied[3]

[1]University Of Anbar, College of Science, Department of Biology, Al-Anbar, IRAQ

[2]University Of Anbar, College of Medicine, Microbiology, Al-Anbar, IRAQ

[3]University Of Anbar, College of Science, Department of Biology, Anbar, Al-Anbar, IRAQ

*Corresponding Author: Noor Hameed Hanoush

DOI: https://doi.org/10.31185/wjps.382
Received 20 April 2024; Accepted 02 Jun 2024; Available online 30 Jun 2024

ABSTRACT: The absence of effective prognostic factors for assessing the survival outlook of patients with lung cancer has not significant improvement. Thus, this study aims to investigate the potential of a combination of serum haptoglobin (Hp), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) in blood as reliable prognostic markers for lung cancer patients. There were 62 lung cancer patients (male and female) at an advanced stage (stage III and IV) with an age mean of (65.25) years, and 62 healthy participants with an age mean of 64.27 years. The levels of some hematological parameters were estimated by a hematology analyzer. Heptoglobin level was evaluated in serum by ELISA technology. There was a significant increase in the mean of haptoglobin, NLR, and PLR in SCLC (3.43 ±0.16, 2.47±0.88, and 221 ±23.21, respectively) and NSCLC groups (3.64 ±0.09, 3.68±1.3, and 210.26±12.6, respectively) compared with the control group. Haptoglobin, NRL and PRL did not differ significantly between SCLC and NSCLC. The results indicate that the mean haptoglobin, NLR, and PLR were significantly increased in the lung cancer group in contrast to controls and also showed a positive association with the severity of the disease, where they increased in patients at stage IV and receiving chemotherapy for 2 months. This makes them possible markers for prognostic advanced lung cancer and predictive responses to chemotherapy in lung cancer patients.

Keywords: Haptoglobin, neutrophil-to-lymphocyte ratio, Lung cancer, Prognostic.

1. INTRODUCTION

Lung cancer is the predominant form of malignancy worldwide accounting for approximately 13% of all cancerians. Furthermore, lung cancer accounts for one-third of all cancer-related deaths, particularly in men [1]. In recent years, the frequency of instances of lung cancer in Iraq has steadily increased [2]. The Iraq Cancer Board (ICB) reported that bronchial and lung cancer were the second most prevalent cancers in Iraq in 2018 [3]. Inflammatory responses have a major role in the initiation and development of tumors as well as the prognostic value of inflammatory markers [4]. Several parameters are used to quantify inflammation, such as Haemoglobin, Platelet-Lymphocyte Ratio (PLR), and Neutrophil-to-Lymphocyte Ratio (NLR) [2]. Haptoglobin is an acute-phase plasma glycoprotein. It is mainly made in the liver and also by other tissues, such as the spleen, lung, kidney, adipose tissue, and skin [5].

The primary biological role of haptoglobin is to bind to free haemoglobin (Hb), which helps prevent the loss of iron and the resulting kidney damage after intravascular hemolysis [6]. Following more than 60 years of study, HP is known

to be a multifunctional protein that regulates many different processes, including angiogenesis, immunological responses, reverse cholesterol transport and prostaglandin synthesis [7]. Elevated levels of haptoglobin have been demonstrated in lung cancer, bladder cancer, leukaemia, and breast cancer [6]. Numerous studies involving lung cancer patients have revealed an elevated haptoglobin level among those affected patients [8, 9]. This aimed that haptoglobin is closely related to lung cancers and can be a serum biomarker to diagnose of lung cancers. Furthermore, studies have demonstrated a correlation between elevated haptoglobin levels in the blood and advanced TNM stages as well as distant metastasis in non-small cell lung cancer (NSCLC) [9].

The complete blood count (CBC), on the other hand, is a blood test that a doctor orders that gives details on the many types of human blood cells, such as thrombocytes, leukocytes, erythrocytes, PLR, and NLR [10]. As a matter of fact, the CBC values are a standard examination that have been found to be predictive in individuals with lung cancer [2]. Consequently, studying the evolving CBC indices during the course of cancer progression may yield important insights into the expected effectiveness of treatments, assisting medical professionals in developing novel treatment strategies [11]. This study aims to evaluate the level of haptoglobin, NLR, and PLR parameters in advanced lung cancer patients, investigate the prognostic value of these parameters, and explore the possibility of using them as helpful factors in the first diagnosis of lung cancer from healthy individuals.

2. MATERIALS AND METHODS

The current research was conducted at Anbar Cancer Center in the province of Anbar between 1/12/2022 and 30/12/2023. This study included 62 lung cancer patients at an advanced stage (stage III and IV) (35 male and 27 female) with an age mean (65.25) years, and 62 healthy participants (34 male and 28 female) with an age mean of 64.27 years. The oncologist diagnoses and examined all of lung cancer patients. All participants were questioned about their age, smoking state, and cancer history. The informed consent was taken from all participants. The research protocol has received approval from the research Ethics Committee of college of Medicine in University of Anbar (Certificate No: 123 on November 23, 2023). Tumor staging was based on the 8th edition of the staging criteria issued by the International Association for Lung Cancer Study [12].

Inclusion criteria were patients with advanced-stage lung cancer, those without other cancer types, those without treatment for cancer or receiving treatment for at least 2 months, and those without acute infection at sampling time.

2.1 Sample collection and blood analysis:

About 5 ml of blood samples were collected from patients and control and 2 ml were put into an EDTA tube to estimate CBC parameters, and 3 ml were placed in the plain tube and left to clot for 30 min at 25 ^{o}c then were centrifuged at 4000 rpm for 10 min, the separated sera stored at (-20^{o}C) until assayed for the evaluation of haptoglobin by ELISA technology according to manufacturer instructions. Kits were supplied by ELK biotechnology company/ China (Catalog Number. ELK1054). The hematological markers that were estimated in this research by a haematolgy analyzer (UrIit-3000plus) involved Hb value, RBCs count, HCT level, WBCs count, lymphocyte (%), neutrophil (%), and platelet count. PLR is determined by dividing the platelet counts to lymphocyte counts. While NLR is determined by dividing the total number of neutrophils by the total number of lymphocytes [13].

2.2 Statistical analysis:

The SAS (2018) software was utilized to analyze the impact of different variables on the research parameters. Statistical means were compared using the T-test and the least significant difference (LSD) test. A chi-square test (0.05 and 0.01 likelihood) was used to assess the different types of lung cancer, sex, smoking, and lung cancer stages statistically [14].

3. RESULTS

3.1 Baseline patient and control characteristics

The basic clinical characteristics of the patients and control are shown in **Table 1**. There are no significant differences between patients and control according to age and BMI value, the mean age was (65.25 ±0.82) years in the lung cancer group and (64.27 ±2.30) years in control. While, the mean BMI was (26.60 ±0.43) in lung cancer and (24.82 ±1.48) in control. The male percent (56.5%) is more than the female percent (43.5%) in the patient group, also in the control male percent (54.8%) was more than the female percent (45.2%).

Smoking histories were noted in 77.4% in patients and 37% in control. There are active smokers with percent 64.58% in lung cancer and 56.00% in control.

Table 1. shows Baseline patients and control characteristics.

Characteristics		Patients NO. (62)	Control NO. (62)	T-test	P-value
Age Mean ± SE		65.25 ±0.82	64.27 ±2.30	3.236	0.053
BMI Mean ± SE		26.60 ±0.43	24.82 ±1.48	1.244 **	0.0088
Sex (M/F) No (%)		35/ 27 (56.5%) / (43.5%)	34/ 28 (54.8%)/(45.2%)	-	0.051/ 0.063
Smoking (smoker/no smoker) No (%)		48/14 (77.4%)/(22.58%)	23/39 (37%)/(63%)	-	0.0001 **/ 0.0093 **
Sub-type of Smokers	**Previous**	17 (35.40%)	11 (44.00%)		0.026 *
	Active	31 (64.58%)	14 (56.00%)		0.031*
P-value		0.0062 **	0.033 *		
* (P≤0.05), ** (P≤0.01).					

NO: Number, SE: Stander error, M= male, F=female, BMI=body mass index.

3.2 Lung cancer type and stage in patients group

Diagnoses of lung cancer included: 11 (17.74%) patients with advanced small cell lung cancer and 51 (82.25%) with advanced non-small cell lung cancer. These patients distributed according to lung cancer stages, a higher percentage of patients (56.45%) in stage IV compared to stage III (43.54%), as indicated in the **Table 2**.

Table 2. Patients' distribution according to lung cancer types and stage**s.**

Characteristics		Patients NO. (62)	P-value
Lung cancer type	**SCLC (No / %)**	11 / (17.74%)	0.0013 **
	NSCLC (No / %)	51 / (82.25%)	
Stages of lung cancer No (%)	**III**	27/ (43.54%)	0.014 *
	IV	35/ (56.45%)	
* (P≤0.05), ** (P≤0.01).			

NO: Number, NSCLC=non-small cell lung cancer, SCLC=small cell lung cancer**.**

3.3 Determination of Complete Blood Count (CBC)

Table 3 indicates the level of Hb, PCV, WBC, RBC and PLT in lung cancer patients and control. There was a significant decrease (P ≤0.05) in the level of Hb in NSCLC and SCLC (10.42 ±0.18 and 10.27 ±0.24) respectively, compared with control (12.79 ±0.09). Also, PCV showed a significant decrease in NSCLC and SCLC (35.35 ±0.56 and 34.53 ±0.89) respectively, compared with the control (43.42 ±0.41). WBC mean in the SCLC group was significantly increased (8.47 ±0.24) $x10^9$ compared with other groups. There was a significant decrease in the mean RBC in NSCLC and SCLC (4.21 ±0.19 and 3.88 ±1.05, respectively) $x10^{12}$ compared with control (5.1 ±0.09) $x10^{12}$. While PLT showed a significant increase in SCLC (266.1±15.03) $x10^9$ and NSCLC (253.26 ± 11.5) $x10^9$ compared control group (228.97 ± 8.99) $x10^9$. There was a significant increase of neutrophils in NSCLC and SCLC (5.1 ± 0.18 and 6.4 ± 4.23) $x10^9$ respectively, compared with control (3.6 ±3.45) $x10^9$. While lymphocytes were significantly decreased in NSCLC and SCLC (1.9 ± 4.5 and 1.4 ± 3.61) $x10^9$ respectively, compared with control (3.21 ± 2.8) $x10^9$.

Table 3. Blood Hematological Parameters in Patients with Lung Cancer Compared to Control.

Parameters	NSCLC	SCLC	Control	LSD value	P-value
	Mean ± SE				
Hb (g/dl)	10.42 ±0.18 [a]	10.27 ±0.24 [a]	12.79 ±0.09 [b]	0.550 **	0.0001
PCV (%)	35.35 ±0.56 [a]	34.53 ±0.89 [a]	43.42 ±0.41 [b]	1.819 **	0.0001
WBC ($x10^9$)	7.33 ±0.24 [a]	8.47 ±0.39 [b]	5.66 ±0.27 [c]	0.856 **	0.0016
RBC ($x10^{12}$)	4.21 ±0.19 [a]	3.88 ±1.05 [b]	5.1 ±0.09 [c]	1.425 *	0.030
PLT ($x10^9$)	253.26 ±11.5 [a]	266.1±15.03 [a]	228.97 ±8.92 [b]	23.98 **	0.0001
Neutrophil ($x10^9$)/l	5.4 ± 5.2[a]	6.4 ± 4.23[a]	3.6 ± 3.45[b]	0.679*	0.01
Lymphocyte ($x10^9$)/l	1.9 ± 4.5[a]	1.4 ± 3.61[a]	3.21 ± 2.8[b]	0.431*	0.019

This means having with the different letters in the same row differed significantly.
** (P≤0.01).

SE: Stander error, Hb: haemoglobin, PCV: packed cell volume, WBC: white blood cell, RBC: Red blood cell, PLT: platelet, SCLC: small cell lung cancer, NSCLC: non-small cell lung cancer.

3.4 Determination of prognostic indicators

There was a significant increase in the mean of haptoglobin in SCLC and NSCLC groups (3.43 ±0.16 and 3.64 ±0.09) respectively, compared with the control group (1.92 ±0.08). NLR mean was a significant increase in NSCLC and SCLC (2.47±0.88 and 3.68±1.3) respectively, compared with control (1.14 ± 0.87). Also, PLR was a significant increase in SCLC (221 ±23.21), followed by NSCLC (210.26±12.6) compared with control (68.7±13.38), as shown in **Table 4**.

Table 4. prognostic parameters of lung cancer patients and control groups

Parameters	NSCLC	SCLC	Control	LSD value	P-value
	Mean ± SE				
Haptoglobin (ng/ml)	3.64 ±0.09 a	3.43 ±0.16 a	1.92 ±0.08 b	0.314 **	0.0001
NLR	2.47 ± 0.88[a]	3.68 ± 1.3[a]	1.14 ± 0.87[b]	1.17**	0.001
PLR	210.26 ± 12.6[a]	221 ± 23.21[a]	68.7 ± 13.38[b]	1.56**	0.001

Means with different letters in the same row were significantly different. ** (P≤0.01).

NLR, neutrophil /lymphocyte ratio; PLR, platelet/lymphocyte ratio, SCLC: small cell lung cancer, NSCLC: non-small cell lung cancer.

3.5 Influence of Stage in prognostic indicators of patients with advanced Lung cancer:

Table 5 shows the levels of haptoglobin, NLR, and PLR in stages of lung cancer. The mean of haptoglobin show significant increase at stage IV (4.32 ±0.12) compared to stage III. The mean of NLR and PLR were exhibited a significant increase at stage IV (4.21 ± 1.2 and 220 ± 21.14, respectively) compared with stage III.

Table 5. Effect of Stages in prognostic indicators in patients.

Parameters	Mean ± SE		LSD value	P-value
	Stage III	Stage IV		
Haptoglobin (ng/ml)	3.12 ±0.15 [b]	4.32 ±0.12 [a]	0.471 **	0.0001
NLR	2.84 ± 0.68[a]	4.21 ± 1.2[a]	1.34**	0.0001
PLR	205.16 ± 12.6[a]	220 ± 21.14[b]	1.45**	0.0001

Means with different letters in the same row were significantly different. ** (P≤0.01).

SE: Stander error, NLR, neutrophil /lymphocyte ratio; PLR, platelet/lymphocyte ratio.

3.6 Effect of chemotherapy period in prognostic indicators of patients

Lung cancer patients are divided into three groups depending on receiving chemotherapy period. The mean of haptoglobin, NLR, and PLR show a significant increase in patients who received chemotherapy for 2 months (3.87 ±0.23, 4.21 ± 1.2 and 225 ± 21.14, respectively) compared to patients who received chemotherapy for 1 month and patients not receiving therapy, as shown in **Table 6.**

Table 6. Effect of chemotherapy in prognostic indicators of lung cancer group.

Group	Mean ± SE		
	Haptoglobin (ng/ml)	NLR	PLR
No therapy (46)	2.72 ±0.22 ^{c}	2.84 ± 0.68^{a}	190.26 ± 12.6^{a}
Receiving chemotherapy for 1 month (10)	3.10 ±0.11 ^{b}	3.14 ±0.23 ^{b}	215.5 ±0.87^{b}
Receiving chemotherapy for 2 months (6)	3.87 ±0.23 ^{a}	4.21 ± 1.2 ^{c}	225 ± 21.14^{c}
LSD value	0.471 **	0.557 **	1835**
P-value	0.0001	0.0004	0.0001

Means with different letters in the same column were significantly different. ** (P≤0.01).

SE: Stander error, LSD: Least significant difference, NLR, neutrophil /lymphocyte ratio; PLR, platelet/lymphocyte ratio.

3.7 Correlation coefficient between parameters in study groups

As shown in the **Table 7** there were significant and negative correlations between Hb with haptoglobin (r= -0.32, p=-0.0076; figure 1 A) in lung cancer patients. While, haptoglobin with NLR (0.41, p=0.0001; figure2 A),and haptoglobin with PLR (052, p=0.0001; figure 3 A) show significant and positive correlations in lung cancer groups. All of the parameter correlations in the control group were not significant.

Table 7. Correlation coefficient among studies parameters in healthy group and patients

Parameters	Lung cancer patients		Healthy group	
	Correlation coefficient-r	P-value	Correlation coefficient-r	P-value
Hb and Haptoglobin	-0.32 **	0.0076	0.26 NS	0.124
NLR and Haptoglobin	0.41 **	0.0001	0.35 NS	0.061
PLR and Haptoglobin	0.52 **	0.0001	0.30 NS	0.081

NS: Non-Significant, * (P≤0.05), ** (P≤0.01),

NLR, neutrophil /lymphocyte ratio; PLR, platelet/lymphocyte ratio.

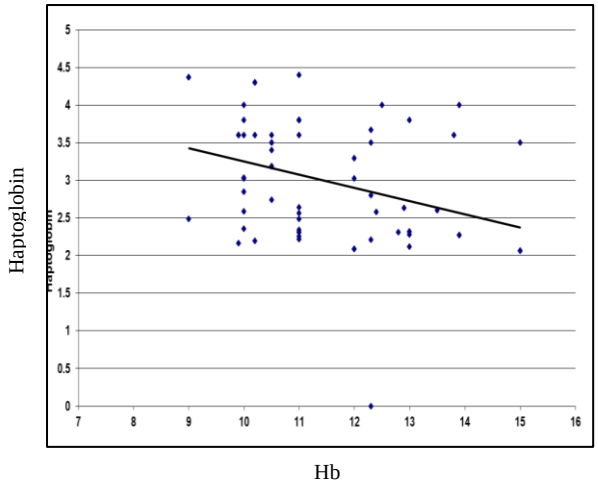

Figure 1(A). Relationship between Hb and Haptoglobin in Lung cancer patients.

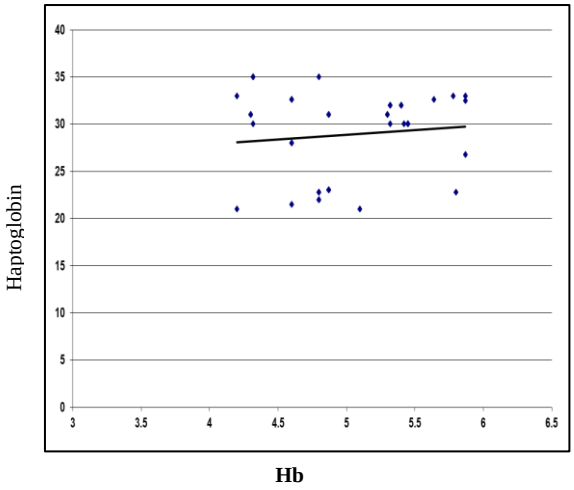

Figure 1(B). Relationship between Hb and Haptoglobin in control.

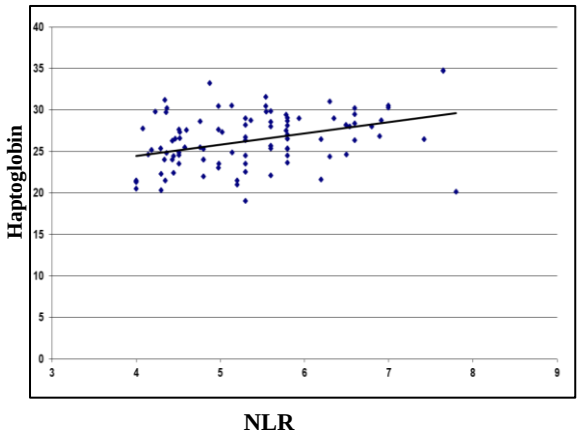

Figure 2(A). Relationship between NLR and Haptoglobin in Lung cancer patients.

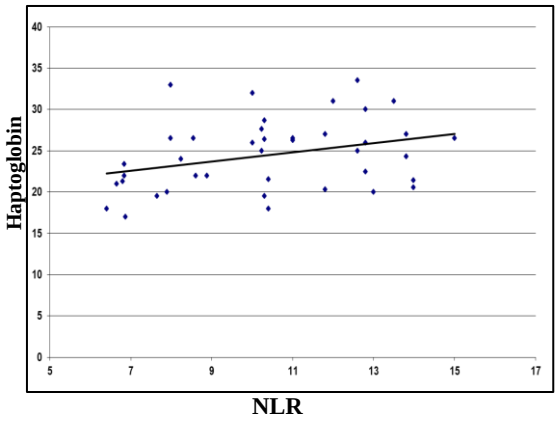

Figure 2 (B). Relationship between NLR and Haptoglobin in control.

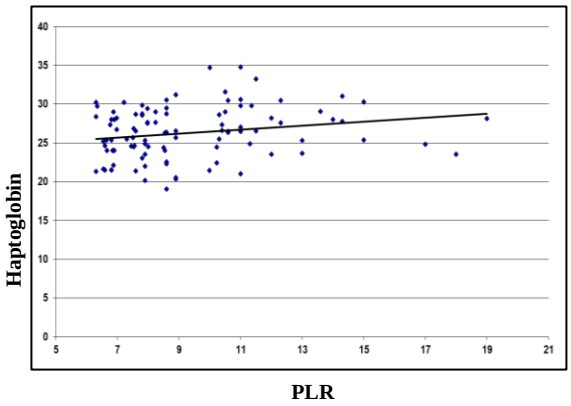

Figure 3(A). Relationship between PLR and Haptoglobin in Lung cancer patients.

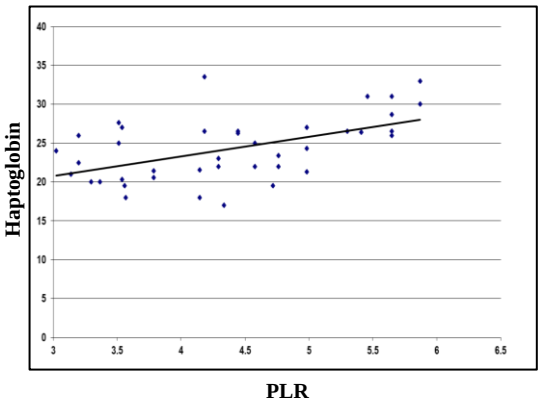

Figure 3(B). Relationship between PLR and Haptoglobin in control

4. DISCUSSION

Anaemia is described as a state where there's a reduction in red blood cells (RBC), leading to lower levels of PCV and Hb. Anaemia is very common in cancer patients because inhibition of erythropoietin synthesis and bone marrow infiltration, which is caused by poor metabolism, cancer at advanced stages, and chronic inflammation [2, 13].

Researchers have recently focused on the impact of anaemia on cancer patients' prognosis and quality of life. The body produces more hypoxic cells when haemoglobin (Hb) concentration decreases, and hypoxic environments reduce tumor cells' susceptibility to chemotherapy and radiation [15]. Tumor growth and resistance to chemotherapy can result from the hypoxia-induced production of invasive tumor cells [13]. However, many cancer patients already suffer from anaemia before starting treatment [16]. This type of anaemia is primarily caused by a compromised marrow response to erythropoietin and a relative inadequacy of erythropoietin production, particularly in lung cancer patients [2].

our results show that the Hb, PCV, RBC and Lymphocyte levels were decreased in lung patients. Likewise, results by Jasim & Hadi, [2] and Wu et al. [13] indicated that Hb, PCV, and RBC levels were a significant decrease in lung cancer patients**.** our results agree with Rojko et al. [11] who found significantly decreasing lymphocyte count, and significantly increasing neutrophil count levels in all lung cancer patient subgroups, irrespective of histopathological type and metastatic site. Liu et al. [17] discovered that non-small cell lung cancer (NSCLC) patients with reduced haemoglobin levels experienced a poorer prognosis.

Neutrophils are essential for the growth and progression of tumors, as well as for the invasive nature of cancer cells [18]. Meanwhile, lymphocytes contribute to immune regulation, identifying and eliminating residual malignant cells and micro-metastases. They serve as reliable defenders against cancer, with high lymphocyte counts being a favourable factor for survival in various human cancers [19]. Our results align with previous studies [11, 17, 20], which found that lung cancer patients had much higher levels of neutrophils and total white blood cells than healthy individuals did, but significantly lower levels of lymphocytes.

In recent decades, there hasn't been a significant improvement in the overall survival time for lung cancer. One key factor is the lack of reliable biomarkers [21]. Although haptoglobin has been noted for its anti-inflammatory and tumor angiogenesis properties, its potential as a tumor biomarker hasn't been widely acknowledged [8, 21]. Our study revealed that serum haptoglobin levels were notably higher in both SCLC and NSCLC patients compared to healthy individuals. Our findings concur with those of Lu et al. [22] and Hoagland et al. [23], who also noted elevated serum haptoglobin levels in NSCLC patients compared to healthy controls, particularly in association with the NSCLC stage.

These findings are consistent with those of Wang et al. [8], who found that patients with lung cancer had significantly greater haptoglobin levels than both benign lung disease and normal control subjects ($p<0.01$). Another study showed a correlation between high haptoglobin levels and poor overall survival, suggesting that it could serve as an independent prognostic factor for non-small cell lung cancer [22].

Our findings strongly indicate that serum haptoglobin, easily assessed using commercially available kits in standard clinical biochemistry laboratories, and could be a valuable biomarker for diagnosing and prognosing lung cancer. This suggests that developing new biomarkers for diagnosing and prognosing lung cancer could help improve clinical care lung cancer detection and prognosis assessment might help physicians treat patients more clinically. Patients with higher serum haptoglobin levels tended to have worse prognoses, indicating that serum haptoglobin could serve as a useful clinical serological biomarker for diagnosing, monitoring progression, and evaluating prognosis in lung cancer [21, 22]**.**

Furthermore, combining haptoglobin with NLR and PLR can improve diagnostic ability and might be used as a potential therapeutic target for the treatment of lung cancer. NLR and PLR values were determined using routine CBC [13], which shows a systematic inflammatory response [16]. These results showed that NLR and PLR were greater in lung cancer patients than in healthy individuals, supporting the idea that NLR and PLR play a part in the lung cancer progression. A previous studies concluded that, individually, the neutrophil-to-lymphocyte ratio demonstrates higher sensitivity and negative predictive value, while the platelet-to-lymphocyte ratio shows a better specificity and positive predictive value in distinguishing metastatic disease and node positivity [24]. The combination of NLR and PLR yields the highest accuracy in predicting advanced disease across all malignancies [25]. Elevated NLR indicates an imbalance in inflammatory pathways, characterized by an increase in neutrophil count or a decrease in lymphocyte count. This explains why cases with elevated NLR had higher rates of recurrence and metastasis as well as shorter survival periods [26]. Similarly, high PLR reflects either an increase in platelet count or a decrease in lymphocyte count, and may reflect a balance between tumor development and tumor suppression [27].

This is the first study to correlate NLR and PLR to the lung cancer stage. The NLR and PLR values were found to be higher at an advanced stage compared to the initial stage in this study. This finding consistent with the hypothesis that platelets have a significant impact on the progression of tumors [1]. Before starting treatment, patients with lung cancer can obtain crucial prognostic data from their PLR and NLR measures [2].

5. CONCLUSION

This study indicates that the mean haptoglobin, NLR, and PLR were significantly increased in patients with lung cancer in contrast with controls and also showed a positive association with the severity of the disease, where they increased in patients at stage IV and receiving chemotherapy for 2 months. This makes them possible markers for prognostic advanced lung cancer and predictive responses to chemotherapy in lung cancer patients. These results show that combination detection of Hp, NLR, or PLR is helpful to the diagnosis of lung cancer; this combination detection has greatly increased compared with Hp, NLR, or PLR single detection.

6. Acknowledgement

We are thankful for all individuals who participated in this study.

REFERENCES

[1] H. Haryati and H. Diany, "Platelet-to-Lymphocyte Ratio (PLR) Profile and Neutrophil-to-Lymphocyte Ratio (NLR) in Lung Cancer Patients in Ulin General Hospital Banjarmasin 2017-2018," *Berkala Kedokteran*, vol. 16, no. 1, pp. 25-34, 2018.

[2] Z. Q. Jasim and A.-H. A. Hadi, "Evaluation of some hematological criteria in lung cancer patients," *International Journal of Health Sciences*, vol. 6, no. S6, pp. 2801-2813, 2022.

[3] Iraqi Cancer Board (ICB), "Iraq Cancer Registry for 2018 report," Ministry of Health and Environment, Iraq, 2018.

[4] G. Wu, Y. Yao, C. Bai, J. Zeng, D. Shi, X. Gu and Y. Song, "Combination of platelet to lymphocyte ratio and neutrophil to lymphocyte ratio is a useful prognostic factor in advanced non-small cell lung cancer patients," *Thoracic cancer*, vol. 6, no. 3, pp. 275-287, 2015.

[5] S. M. Kang, H. J. Sung, J. M. Ahn, J. Y. Park, S. Y. Lee, C. S. Park and J. Y. Cho, "The Haptoglobin β chain as a supportive biomarker for human lung cancers," *Molecular BioSystems*, vol. 7, no. 4, pp. 1167-1175, 2011.

[6] M. K. Tveitarås, F. Selheim, K. Sortland, R. K. Reed and L. Stuhr, "Protein expression profiling of plasma and lungs at different stages of metastatic development in a human triple negative breast cancer xenograft model," *PLoS One*, vol. 14, no. 5, p. e0215909, 2019.

[7] A. Shah, H. Singh, V. Sachdev, J. Lee, S. Yotsukura, R. Salgia and A. Bharti, "Differential serum level of specific haptoglobin isoforms in small cell lung cancer," *Current proteomics*, vol. 7, no. 1, pp. 49-56, 2010.

[8] B. Wang, Y. J. He, Y. X. Tian, R. N. Yang, Y. R. Zhu and H. Qiu, "Clinical utility of haptoglobin in combination with CEA, NSE and CYFRA21-1 for diagnosis of lung cancer," *Asian Pacific journal of cancer prevention*, vol. 15, no. 22, pp. 9611-9614, 2014.

[9] T. Chen, C. He, M. Zhang, X. Li, X. Liu, Y. Liu and Z. Li, "Disease-specific haptoglobin-β chain N-glycosylation as biomarker to differentiate non-small cell lung cancer from benign lung diseases," *Journal of Cancer*, vol. 10, no. 23, pp. 5628, 2019.

[10] National Institutes of Health (NIH), "National Cancer Institute-NCI Dictionary of Cancer," 2018.

[11] L. Rojko, Z. Megyesfalvi, E. Czibula, L. Reiniger, V. Teglasi, Z. Szegedi and Moldvay, "Longitudinal analysis of complete blood count parameters in advanced-stage lung cancer patients," *Thoracic Cancer*, vol. 11, no. 11, pp. 3193-3204, 2020.

[12] P. Goldstraw, K. Chansky, and J. Crowley, "The IASLC lung cancer staging project: Proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer," *J Thorac Oncol*, vol. 11, pp. 39–51, 2016.

[13] F. Wu, S. Yang, X. Tang, W. Liu, H. Chen, and H. Gao, "Prognostic value of baseline hemoglobin-to-red blood cell distribution width ratio in small cell lung cancer: A retrospective analysis," *Thoracic Cancer*, vol. 11, no. 4, pp. 888-897, 2020.

[14] SAS. 2018**.** Statistical Analysis System, User's Guide. Statistical. Version 9.6th ed. SAS. *Inst. Inc. Cary*. N.C. USA.

[15] X. Ke, C. Chen, Y. Song, Q. Cai, J. Li, Y. Tang and D. Liu, "Hypoxia modifies the polarization of macrophages and their inflammatory microenvironment, and inhibits malignant behavior in cancer cells," *Oncology Letters*, vol. 18, no. 6, pp. 5871-5878, 2019.

[16] F. D. Celik, C. Varim, A. Demirci, S. Yaylaci, I. Hacibekiroglu and C. Bilir, "The Significance of Hemogram Parameters for Diagnosis, Prognosis and Treatment of Lung Cancer," *Eurasian Journal of Medical Investigation*, vol. 5, no. 2, p. 159, 2021.

[17] J. Liu, S. Li, S., Zhang, Y. Liu, L. Ma, J. Zhu and Y. Cheng, "Systemic immune-inflammation index, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio can predict clinical outcomes in patients with metastatic non-small-cell lung cancer treated with nivolumab," *Journal of Clinical Laboratory Analysis*, vol. 33, no. 8, pp. 1-8, 2019.

[18] F. Karadeniz, Y. Karadeniz, and E. Altuntaş, "Systemic immune-inflammation index, and neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios can predict clinical outcomes in patients with the acute coronary syndrome," *Cardiovasc J Afr*, vol. 34, pp. 1-7, 2023.

[19] S. R. Thottuvelil, M. Chacko, A. R. Warrier, M. P. Nair and A. K. Rajappan, "Comparison of neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII) as marker of adverse prognosis in patients with infective endocarditis," *Indian Heart Journal*, vol. 75, no. 6, pp. 465-468, 2023.

[20] J. Y. Y. Wong, B. A. Bassig, E. Loftfield, W. Hu, N. D. Freedman, B. T. Ji and Q. Lan, "White blood cell count and risk of incident lung cancer in the UK Biobank," *JNCI Cancer Spectrum*, vol. 4, no. 2, pp. 1-9, 2019.

[21] H. Zhang, D. Li, Z. Lai, J. Zhou, J., Zhang and Z. Li, "Serum immunoinflammatory-related protein complexes as personalized biomarkers for monitoring disease progression and response to treatment in lung cancer patients," *Clinica Chimica Acta*, vol. 533, pp. 53-62, 2022.

[22] J. Lu, Y. Wang, M. Yan, P. Feng, L. Yuan, Y. Cai and L. Li, "High serum haptoglobin level is associated with tumor progression and predicts poor prognosis in non-small cell lung cancer," *Oncotarget*, vol. 7, no. 27, pp. 41758, 2016.

[23] L. F. Hoagland, M. J. Campa, E. B. Gottlin, J. E. Herndon and E. F. Patz Jr, "Haptoglobin and posttranslational glycan-modified derivatives as serum biomarkers for the diagnosis of nonsmall cell lung cancer," *Cancer*, vol. 110, pp. 2260-2268, 2007.

[24] X. Zhu, H. Song, Y. Chen, F. Han, Q. Wang and Y. Cui, "Neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in blood to distinguish lung cancer patients from healthy subjects," *Disease Markers*, 2020.

[25] M. Ye, X. Qian, X., Guo, H. Wang, Q. Ni, Y. Zhao and L. Zhang, "Neutrophil-lymphocyte ratio and platelet-lymphocyte ratio predict severity and prognosis of lower limb arteriosclerosis obliterans," *Annals of Vascular Surgery*, vol. 64, pp. 221-227, 2020.

[26] H. Zhao, W. Li, X. Le, Z. Li and P. Ge, "Preoperative neutrophil-to-lymphocyte ratio was a predictor of overall survival in small renal cell carcinoma: an analysis of 384 consecutive patients," *BioMed Research International*, vol. 2020, Article ID 8051210, 2020.

[27] G. A. Siregar and D. Irwansyah, "Comparison of platelet to lymphocyte ratio between degrees of the Barcelona clinic liver cancer on hepatocellular carcinoma patients at Haji Adam Malik General Hospital," *Open Access Macedonian Journal of Medical Sciences*, vol. 7, no. 20, pp. 3451-3454, 2019.