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PROGNOSTIC VALUE OF LACTATE DEHYDROGENASE (LDH) IN PATIENTS WITH METASTASIS NON-SMALL CELL LUNG CANCER (NSCLC)

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ABSTRACT

Background: Evaluation of the prognostic role of LDH levels In patients with metastatic NSCLC and its role In the response for chemical treatment. **Methods:** The study concluded 75 patients who were conducted to the Oncology Center at Latakia University Hospital between 2023-2024, who were diagnosed with metastatic NSCLC. A detailed medical history was taken with CT scan and histological study results. LDH values were calibrated before and after treatment In the same way. **Results:** The total sample of the study was 75 patients, including (72%) males and (28%) females, with a probability for the age group of 56-65 years, the percentage of smokers in the study sample was 72%. Adenocarcinoma ADC was the most common histological type (60 patients), followed by squamous cell carcinoma (15 patients). When studying the relationship between LDH levels and the histological type of tumor, there were no statistically significant differences (p-value>0.05). The average LDH values were directly proportional to the progression of the brain metastasis in the study patients, with a statistically significant difference (p-value<0.05). **Conclusion**: LDH is a predictive marker In patients with metastatic NSCLC and helps In assessing response and prognosis In patients. In addition, assessment of their response for treatment.

KEYWORDS: LDH, NSCLC, Metastasis.

1. INTRODUCTION

In 2020, the incidence of lung cancer reached 2.2 million cases worldwide, accounting for 11% of all cancer cases and representing the most common cause of cancer-related death.[1] A total of 1.8 million deaths from lung cancer were recorded in 2020, representing 18% of all cancer deaths.[1]

According to the World Health Organization classification in 2021, lung cancer is histologically, immunohistochemically, and microscopically categorized into two main types: Non-small cell lung cancer (NSCLC) and Small cell lung cancer (SCLC).[2]

Lactate dehydrogenase (LDH) is an important enzyme in the anaerobic metabolic pathway. Its function is to catalyze the reversible conversion of lactate to Pyruvate with the reduction of NAD^+ to NADH and in opposite way. The enzyme is found in many living organisms, including plants and animals. It is widely distributed in all tissues and plays an important role in gluconeogenesis and DNA metabolism.[3]

It has several Iso-enzymes ranging from LDH-1 to LDH-5, each with a different expression pattern in body tissues.[4] Typically, normal LDH levels range between 140 and 280 U/L. However, clinical interpretation depends on the patient's signs and symptoms.[5] LDH values can be influenced by chronic diseases whether renal, cardiac, or muscular as well as by some medications. For example, high doses of vitamin C can falsely lower LDH values, whereas the presence of anesthetic agents, Aspirin, alcohol and Procainamide can falsely elevate LDH results.[5,6]

In cancer cells, LDH function, specifically LDHA, is altered compared to normal cells. Cancer cells use LDH to enhance Aerobic Metabolism (Glycolysis, ATP production, and Lactate production) even in the presence of Oxygen. This process is known as Warburg effect.

Tumor markers are measures of biological processes in the body or of the tumor itself, which may indicate the body's response to treatment. They are classified according to their role into prognostic, diagnostic, and predictive markers, and vary in both sensitivity and specificity.[7]

Since elevated LDH levels are an unfavorable prognostic indicator in cancer patients, it has been proposed as a marker of tumor aggressiveness and a predictor of disease course and outcome. This study discusses the importance of LDH as a prognostic marker in patients with NSCLC patients.

2. Significance of the Study

The importance of this research lies in identifying laboratory biomarkers that can aid in predicting disease progression and prognosis. Serum lactate dehydrogenase (LDH) measurement represents a widely available, low-cost, and easily performed laboratory test. It plays a valuable role in the therapeutic and clinical follow-up of patients with non-small cell lung cancer (NSCLC).

3. OBJECTIVES

To evaluate the prognostic value of serum LDH levels in patients newly diagnosed with metastatic non-small cell lung cancer (NSCLC) and its role in predicting response to first-line therapy.

To assess the prognostic significance of LDH values.

- According to radiological response criteria.
- According to tumor histological subtype.
- According to the site of metastases.

4. MATERIALS AND METHODS

This study was conducted at the Oncology Center, Lattakia University Hospital, during the period 2023–2024. The final study sample included 75 patients newly diagnosed with metastatic NSCLC. Patients were stratified into two groups based on their serum LDH levels: normal LDH and elevated LDH.

4.1. Inclusion Criteria

Newly diagnosed metastatic NSCLC prior to initiation of therapy.

4.2. Exclusion Criteria

- Small cell lung cancer.
- Localized NSCLC.
- Comorbid conditions known to elevate LDH levels (hemolytic diseases, hepatic disorders.

5. METHODS

A detailed medical and personal history was obtained for each patient, and the information was recorded in a dedicated study form. All patients underwent a chest X-ray and chest computed tomography (CT) before starting the treatment plan. Serum LDH levels were measured for each patient prior to therapy initiation.

5.1. LDH Assay Procedure

Blood samples (2–3 ml) were collected from each patient into heparin-coated tubes, immediately centrifuged, and the plasma was transferred into storage vials using a micropipette.

The kinetic method was employed for lactate dehydrogenase (LDH) measurement, performed immediately or within 24 hours after sample collection. Samples remained stable for 24 hours at 2–8 °C, and for up to two days at room temperature. Any degree of hemolysis rendered the sample unacceptable for analysis.

The reference range for LDH was **207–417 U/L,** according to the specifications of the device used in this study (Human®).

5.2. Patient Classification

Patients were categorized according to histopathological diagnosis, tumor stage, and TNM classification. The treatment plan for each patient was determined according to tumor stage.

Patients were followed up after the first course of chemotherapy (four doses of the prescribed regimen) to assess treatment response using computed tomography (CT).

6. Statistical Analysis

- **Study Design:** A randomized prospective study.
- **Descriptive Statistics**

1. Graphs and frequency tables were used to describe categorical data.
2. Means, standard deviations, and measures of central tendency were calculated for quantitative data.

- **Inferential Statistics**

1. Continuous variables were analyzed using Microsoft Excel.
2. Mann–Whitney U test was used for comparing mean ranks between study groups.
3. Statistical significance was set at $p \leq 0.05$.

7. RESULTS

7.1. Sample characteristics

Serum LDH levels were measured in all patients enrolled in the study who were diagnosed with non-small cell lung cancer (NSCLC). The sample was divided into two groups based on LDH values, considering levels >400 U/L as pathologically elevated and <400 U/L as within the normal range, according to the device used for the assay. The number of patients in Group A with elevated LDH values was 45, compared to 30 patients in Group B with normal LDH values.

The study included 75 patients, of whom 54 were males (72%) and 21 were females (28%). The ages of patients in Group A ranged from 49 to 75 years, with a mean age of 62.11 ± 6.74 years, whereas in Group B, ages ranged from 48 to 76 years, with a mean of 59.5 ± 7.2 years. The

majority of patients in the total study sample were in the 56–65 age group, accounting for 38 patients (50.67%). A total of 54 patients were smokers, representing 72% of the study population.

Table 1: sample characteristics.

Variables		Group A	Group B
Age (years)	Max	49	48
	Min	75	76
	Mean ± sd	62.11± 6.74	59.5± 7.2
Gender	Male	33 (73.3%)	21 (70%)
	Female	12 (26.7%)	9 (30%)
Smoking	Smoker	32 (71.1%)	22 (73.3%)
	Non-smoker	13 (28.9%)	8 (26.7%)

Table 2: Distribution of the study sample according to pre-treatment LDH values.

		n	Mean	Sd	Min	Max
LDH	**Group A**	**45**	**501.8**	**34.17**	**465**	**597**
	Group B	**30**	**269.43**	**34.7**	**207**	**344**

7.2. Distribution of the study sample according to histopathological findings

According to the histopathological results of the samples, adenocarcinoma (ADC) was the most common cancer type in the sample, recorded in 60 patients (80%), followed by squamous cell carcinoma (SCC) in 15 patients (20%)**.**

Table 3: Distribution of the study sample according to tumor histopathology.

Histopathology	Group A	Group B	Total
ADC	35	25	**60 (%80)**
SCC	10	5	**15 (%20)**

7.3. Correlation between LDH levels and tumor histopathology

LDH levels were measured in both study groups before and after treatment, and these results were compared with the histopathological findings of non-small cell lung cancer (NSCLC).

Table 4: Correlation between LDH levels and tumor histopathology.

			N	Mean	Sd	P-value
LDH	**Group A**	**ADC**	**35**	**506.26**	**36.9**	**0.08**
		SCC	**10**	**486.2**	**14.57**	
	Group B	**ADC**	**25**	**268.12**	**34.3**	**0.12**
		SCC	**5**	**276**	**25.9**	

The results showed that the mean LDH values were comparable between the two histological subtypes of non-small cell lung cancer in the study sample, with no statistically significant differences observed (p-value>0.05). Although the mean LDH level was higher In patients with adenocarcinoma compared to those with squamous cell carcinoma, this increase was not statistically significant.

7.4. Distribution of the sample according to the position of metastases

The study patients were classified into two groups according to the site of metastases: brain metastases and non-brain metastases, as follows.

Table 5: Distribution of the sample according to the position of metastases.

metastases	Patients		Total	LDH mean	p-value
	Group A	Group B			
Brain	**40**	**12**	**52**	**522.5**	**0.0002**
Other	**5**	**18**	**23**	**326**	

7.5. Distribution of the study sample according to post-treatment LDH values

LDH values were evaluated after 4 round of chemotherapy for all patients. We found a significance decrease in LDH values in both groups.

Table 6: Distribution of the study sample according to post-treatment LDH values.

		n	Mean	Sd	Min	Max
LDH	**Group A**	**45**	**468.97**	**37.7**	**420**	**590**
	Group B	**30**	**248**	**30.8**	**210**	**322**

LDH	Before	After	p-value
Group A	**501.8**	**468.97**	**0.0002**
Group B	**269.43**	**248**	**0.015**

8. DISCUSSION

Lung cancer is the leading cause of cancer-related deaths worldwide, with approximately 85% of cases being non-small cell lung cancer (NSCLC).[8] Despite improvements in diagnosis and treatment, the prognosis remains poor, as the 5-year survival rate in NSCLC is less than 15%.[9] Therefore, it is essential to search for prognostic biomarkers for patients. Serum biomarkers play an important role due to several advantages, including their non-invasive nature, and the possibility of rapid and easily repeatable measurements.[10]

Our current study evaluated the prognostic value of LDH in 75 patients diagnosed with metastatic NSCLC. The total study sample consisted of 75 patients, 72% male and 28% female, with the predominant age group being 56–65 years. Smokers accounted for 72% of the study population. According to the histopathological classification, adenocarcinoma (ADC) was the most common type (60 patients), followed by squamous cell carcinoma (SCC) (15 patients). When analyzing the relationship between LDH levels and tumor histology, no statistically significant differences were found (p-value > 0.05). These results are consistent with most global studies, where adenocarcinoma is the most common histological subtype in NSCLC patients.

The sample was classified according to the site of metastases into two groups: brain metastases and non-brain metastases. The majority of patients (70%) had brain metastases. When analyzing the relationship between LDH values and the site of metastases, we found that the mean pre-treatment LDH level was significantly higher in the presence of brain metastases (p-value < 0.05). Therefore, LDH can be considered a prognostic predictive marker whose values increase significantly with brain metastases.

This can be explained by the fact that cancer cells produce lactate via LDH about 40 times more during glycolysis compared to normal cells, which promotes cell proliferation and growth and provides the necessary energy. This feature is more pronounced in metastatic patients, which may explain the elevated LDH with tumor progression.[11] LDH suppresses the function of a subset of T cells (CD8+) and natural killer (NK) cells. In addition, it can promote angiogenesis, as well as cell migration and metastasis through enhanced VEGF expression.[12] Ultimately, this leads to poorer prognosis and reduced survival rates in patients.

- Wang et al. in China (2022)[13] involving 224 patients found a significant decrease in overall survival (OS) in NSCLC patients with brain metastases and high LDH levels compared to those with low or normal LDH levels (P=0.009). The median OS in the two groups ranged from 16 to 33 months.
- Tjokrowidjaja et al. in Australia (2022)[14] including 1,327 advanced NSCLC patients treated with immune checkpoint inhibitors (ICIs) found that elevated pre-treatment LDH was an independent marker of poor prognosis, and that a persistent increase in LDH during treatment was associated with reduced survival.
- Lee et al. in South Korea (2016)[15] conducted a study on 394 patients and found that serum LDH levels were significantly associated with the spread of metastases throughout the body and were an independent prognostic factor for survival in stage IV disease, which is consistent with our findings.
- X. Zheng et al. in China (2016)[16] studied 3,765 patients and found a statistically significant association between elevated LDH levels and reduced survival in NSCLC patients (p = 0.02). Both small cell and non-small cell lung cancer showed a strong association with LDH values (p = 0.00), while our study did not include any patients diagnosed with small cell lung cancer.

9. CONCLUSION

- LDH is a prognostic predictive marker in patients diagnosed with NSCLC, with significantly higher levels in cases with brain metastases. Elevated LDH levels are associated with a poorer response to chemotherapy in metastatic NSCLC patients.
- LDH measurement at the time of NSCLC diagnosis should be performed as an adjunct to investigations for assessing prognosis, survival, and treatment

response. Future studies should include a larger number of lung cancer patients with various subtypes and stages to confirm these results.

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