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Original Article

The Prognostic Value of Pretreatment Serum LDH at Diagnosis in Patients with Hodgkin Lymphoma

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Abstract *- Background: Lactate dehydrogenase (LDH) is a marker for lymphoma whose prognostic significance is well established for both indolent and aggressive non-Hodgkin lymphomas but has not been well studied in predicting prognosis in patients with Hodgkin lymphoma. This prompts us to study the prognostic value of LDH in Hodgkin Lymphoma. Aim of the study: We studied the correlation between pre–treatment serum LDH and prognosis (OS, PFS and mortality) in Hodgkin lymphoma patients in our center, Lattakia –Syria. Patients and Methods: This was a retrospective study conducted at University Tishreen Hospital in Lattakia City, Syria, over a period of five years. 208 patients were enrolled in the study. We analyzed recorded data from the patient's files: medical history, full physical examination, complete blood count, AMC, ALC, LMR, erythrocyte sedimentation rate, liver function tests, serum LDH, and serum Albumin. , histological type, radiological investigations, bone marrow biopsy, staging, spread of disease, Mediastinal bulky mass and international prognostic factors IPS. Patients or their guardians provided written informed consent to participate in the study. Then, we evaluated the prognostic value of pretreatment serum LDH in patients with Hodgkin's Disease through a study of overall survival (OS), progression–free survival rate (PFS) and rate of deaths. Results: Pre-treatment serum LDH of more than 480 u/ml is an important indicator of the severity of Hodgkin lymphoma. It is highly associated with advanced stage, presence of B symptoms, and bulky mediational mass. It is also highly correlated with bad international prognostic factors (IPS) of Hodgkin lymphoma. The independent prognostic factors in multivariate analysis were high pretreatment serum LDH and low LMR, which are strongly associated with poor prognosis for patients. Our study revealed that pretreatment serum LDH > 480 was associated with a decrease in OS rates (78.5%) versus (92.3%) in the LDH group ≤480 (p-value=0.004). It was also associated with a decrease in PFS rate (63.1%) versus(81.1%) in the LDH group ≤480 (p-value=0.005). We observed an increase in mortality rate in the LDH group > 480 (21.5%) versus (8.4%) in the LDH group ≤ 480 with a statistical difference (p-value=0.008). Conclusion: pretreatment serum LDH > 480 Un is an important indicator of the severity of Hodgkin lymphoma and an independent prognostic factor for (OS, PFS and mortality) rate.*

Keywords *- LDH, Hodgkin lymphoma, Prognosis, PFS and OS.*

1. Introduction

Hodgkin's lymphoma (HL) is a B-cell lymphoma that comprises 1% of all cancer cases and 14% of all lymphoma cases [1, 2]. The World Health Organization (WHO) classification distinguishes two biologically and clinically distinct entities: nodular lymphocytic predominant HL (NLPHL) and classical HL. Classical HL accounts for 95% of all HL cases [3, 4]. HD is a curable disease. An appropriate therapy scheme, chosen in compliance with prognostic factors, is a very important condition for cure [5]. Cure rates approach 80-90% of patients, and HL is among the neoplastic diseases with the best long-term outcome after cytotoxic treatment [6]**.** The prognostic factors can be divided into factors related to the disease, factors related to the patient and therapy [6]. A number of prognostic factors have been identified for both early- and advanced-stage HL patients. The major prognostic factors are the presence of bulky Mediastinal disease, high Erythrocyte Sedimentation Rate (ESR), age, the number of lymph nodes involved, and the presence of extranodal disease [7]. The "International Prognostic Factors Project on Advanced Hodgkin's Disease" assessed the primary care treatment results and prognostic factors in 5141 advanced-stage HL cases from 23 centers. This study suggested that seven parameters had prognostic significance in this patient group. These were age, sex, stage IV disease, low albumin level (<4.0 g/dL), anemia (<10.5 g/dL), leukocytosis (>15000/mm3) and lymphopenia (<600/mm3). A number of prognostic factors were defined for early- and advanced-stage HL cases, with bulky disease, ESR, LDH, hemoglobin and serum albumin levels, presence of "B" symptoms, age and extra lymphatic involvement being the most significant [8].

Hodgkin's disease (HD) can cause anemia, leukocytosis, neutropenia, eosinophilia, lymphocytopenia and thrombocytosis. The prognosis of Hodgkin's lymphoma depends on the clinical role of the disease (dissemination and extension of the disease), the type and histological classification of the disease based on the biopsy cytological examination. Blood laboratory parameters such as

sedimentation rate (ESR), serum copper, alkaline phosphatase (ALP), serum lactate dehydrogenase (LDH), serum iron, zinc, transferrin titer and serum ferritin are all laboratory parameters that can help in predicting disease prognosis [9-12]. Several studies have shown that elevated serum LDH is indicative of solid tumors and highly malignant lymphomas and is associated with a poor prognosis [13]. Some studies also showed that serum LDH and alkaline phosphatase are strong prognostic factors in Hodgkin's lymphoma [14]. We studied the correlation between pre–treatment serum LDH and prognosis (OS, PFS and mortality) in Hodgkin lymphoma patients in our center a Lattakia –Syria.

2. Patients and Methods

This was a retrospective study conducted at University Tishreen Hospital in Lattakia City, Syria, over a period of five years from 2011 -2015. 208 patients (85 female, 123 male) were enrolled in the study. Inclusion criteria were newly diagnosed patients of Hodgkin lymphoma aged more than 14 years who were admitted to our center of chemotherapy. We analyzed recorded data from the patient's files: medical history, full physical examination, complete blood count, AMC, ALC, LMR, erythrocyte sedimentation rate, liver function tests, serum LDH, and serum Albumin. , histological type, radiological investigations, bone marrow biopsy, staging, spread of disease, Mediastinal bulky mass and international prognostic factors IPS. Patients or their guardians provided written informed consent to participate in the study. The sample is divided into two groups according to pre-treatment Serum LDH: LDH > 480 (65 pts.) and LDH ≤ 480 (143 pts.). Then, we evaluated the prognostic value of pretreatment serum LDH in patients with Hodgkin's Disease through a study of overall survival (OS), progression–free survival rate (PFS) and rate of deaths.

Overall survival (OS) was calculated from the date of diagnosis to the date of death, whatever the cause or to the date of the final study(5 years), and the progression–free survival rate (PFS) was calculated from the date of starting treatment to the date of disease progression or relapse after the therapeutic response during the 5 years.

We used frequencies and percentages for qualitative variables and measures of central tendency for quantitative variables. The initial variables were tested using the log-rank test, and groups were compared using the log-rank test. Results were statistically significant when p-value <0. 05. The program (IBM SPSS statistics) version19 was adopted to calculate statistical transactions and analyze results.

3. Results

208 cases (123 males 59,10%, 85 females 40,90%) of newly diagnosed Hodgkin lymphoma were admitted to the center according to inclusion criteria in the study. The age of the study sample patients ranged from 14 to 79 years, and the median age of the study sample was 31.5 years.

Table 1. Distribution of a sample of 208 Hodgkin lymphoma patients according to histological type

Classical histological type	Number	Percent
Nodular sclerosis	136	65.4%
Mixed cellularity	65	31.3%
Lymphocyte - Rich	5	2.4%
Lymphocytic depletion	2	1%
Total	208	100%

We note from the previous table that the predominant classical histological pattern is Nodular sclerosis, representing 65.4% of the studied sample.

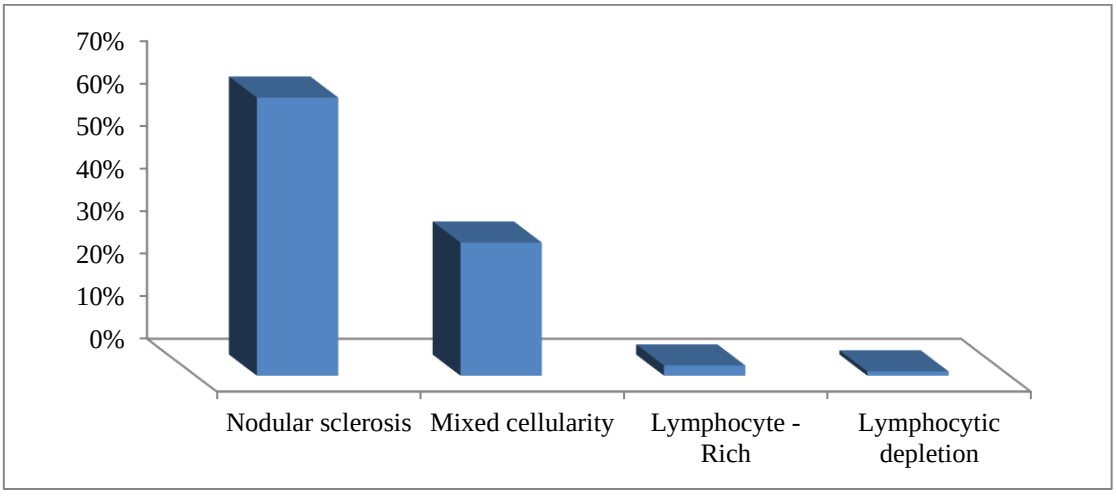

Fig. 1 Distribution of a sample of 208 Hodgkin lymphoma patients according to histological type

Table 2. Distribution of a sample of 208 Hodgkin lymphoma patients according to stage of the disease

Stage of disease.	Number	Percent
Stage I	12	5.8%
Stage II	92	44.2%
Stage III	69	33.2%
Stage IV	35	16.8%
المجموع	208	100%

We note from the previous table that 44.2% of the studied sample were Stage II and 33.2% in Stage III.

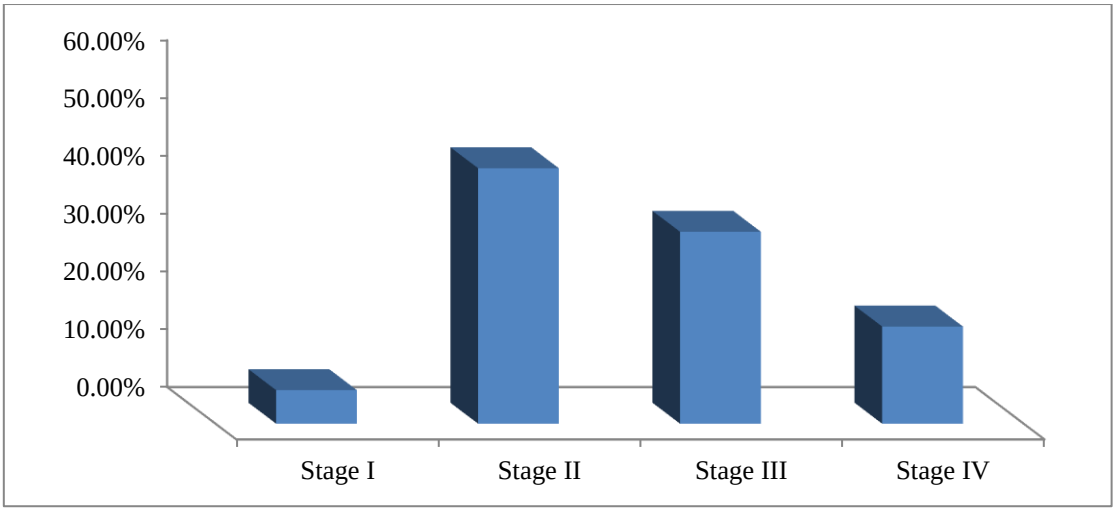

Fig. 2 Distribution of a sample of 208 Hodgkin lymphoma patients according to stage of the disease

Table 3. Distribution of a sample of 208 Hodgkin lymphoma patients, according to the progression of the disease

progression of the disease	Number	Percent
Advance	180	86.5%
Limited	28	13.5%
total	208	100%

We note from the previous table that 86.5% of the studied sample were in the advanced stage.

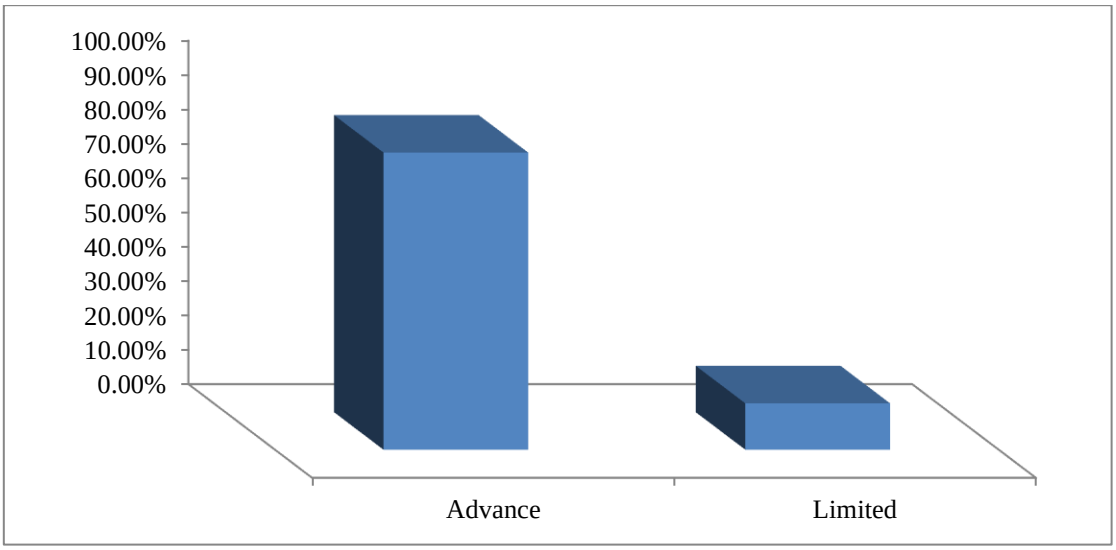

Fig. 3 Distribution of a sample of 208 Hodgkin lymphoma patients, according to disease progression

Table 4. Distribution of a sample of 208 Hodgkin lymphoma patients according to the presence of symptoms of B symptoms

B symptoms	Number	Percent
A	36	17.3%
B	172	82.7%
total	208	100%

We note from the previous table that 82.7% of the studied sample showed general symptoms.

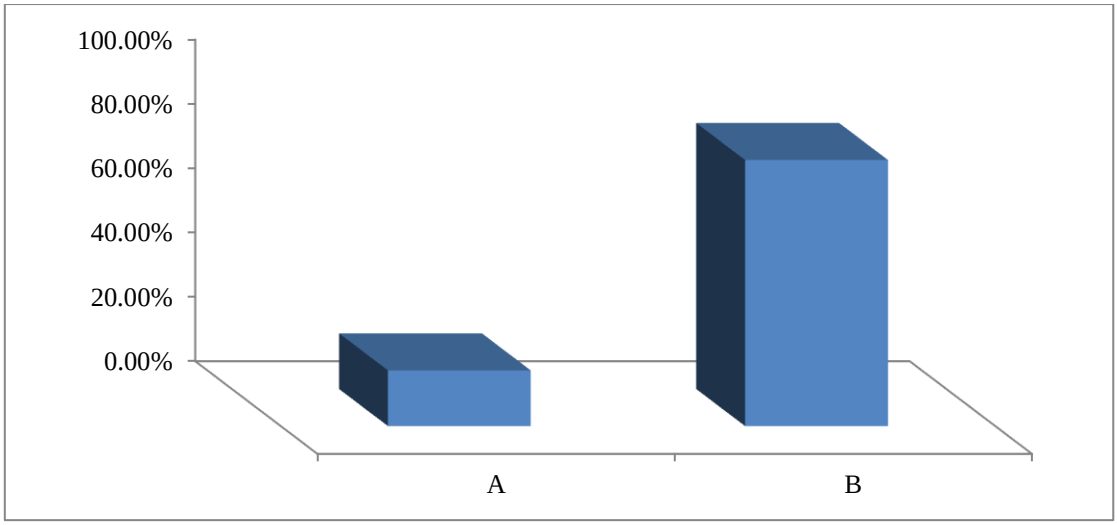

Fig. 4 Distribution of a sample of 208 Hodgkin lymphoma patients according to the presence of symptoms of B symptoms

Table 5. Distribution of a sample of 208 Hodgkin lymphoma patients according to the presence of a Mediastinal mass and its size.

Mediastinal mass	Number	Percent
Absent	111	53.4%
Present Bulky≥10 <10	 22 75	 10.6% 36.1%
total	208	100%

We note from the previous table that the Mediastinal mass was found at 46.7% of the studied sample, and Bulky disease was 10.6%.

Table 6. Distribution of a sample of 208 Hodgkin lymphoma patients according to the type of treatment used

Type of treatment	Number	Percent
Chemotherapy	117	56.3%
Radio- chemotherapy	91	43.7%
Total	208	100%

We note that the combined chemotherapy with radiotherapy represented 43.7% of the studied sample.

Table 7. Distribution according to IPS risk factors in a sample of Hodgkin lymphoma patients

IPS	Number	Percent
Sex (male)	123	59.1%
Age (years) >45 ≤45	 56 152	 26.9% 73.1%
Serum albumin) 60 pts(4≥ <4	 61 99	 38.1% 61.9%
HB >10.5 10.5≤	 131 77	 63% 37%
WBC >15000 ≤15000	 55 153	 26.4% 73.6%
ALC 600≥ <600	 205 3	 98.6% 1.4%
Stage IV	35	16.8%

Table 8. Distribution differences between the two groups of Hodgkin lymphoma patients according to demographic Variables.

Demographic Variables	LDH>480(65)	LDH≤480(143)	P-value
sex male female	42(64.6%) 23(35.4%)	81(56.6%) 62(43.4%)	0.2
Age	30[14 - 79]	32[14 - 72]	0.7
Histological type NS MC LR LD	20(30.8%) 44(67.7%) 0(0%) 1(1.5%)	45(31.5%) 92(64.3%) 5(3.5%) 1(0.7%)	0.4

We note no statistically significant differences between the two groups of Hodgkin lymphoma patients according to gender, age and histological type.

Table 9. Distribution differences according to laboratory findings between the two groups of Hodgkin lymphoma patients

Laboratory Findings	LDH>480(65)	LDH≤480(143)	P-value
WBC	12910.7±5969.5	10894.4±5162.8	0.01
ANC	10451.4±5656.1	8903.2±8757.6	0.1
ALC	1782.1±851.8	2011.9±1148.8	0.1
AMC	537.1±406.8	419.7±366.5	0.04
LMR	5.5±5.7	8.5±10.4	0.02
HGB	10.7±1.7	11.3±1.9	0.02
PLT	338.3±117.4	316.1±135.5	0.2
ALB	3.5±0.7	3.7±0.7	0.04

We note statistically significant differences between the two groups of Hodgkin lymphoma patients according to all laboratory findings except platelet count, ANC and ALC. The LDH group >480 was associated with a greater increase in AMC and WBC and a greater decrease in ALB, HGB, and LMR**.**

Table 10. Distribution differences according to the presence of general B symptoms and the presence of Mediastinal mass between the two groups of Hodgkin lymphoma patients

	LDH>480(65pts)	LDH≤480(143 pts)	P-value
B-symptoms A B	 4(6.2%) 61(93.8%)	 32(22.4%) 111(77.6%)	0.004
Mediastinal mass Absence Present Bulky≥10 <10	 25(38.5%) 40(61.5%) 10(15.4%) 30(46.1%)	 86(60.1%) 57(39.9%) 12(8.4%) 45(31.5%)	0.006 0.04

We note that there are statistically significant differences between the two groups of Hodgkin lymphoma patients according to the presence of B- symptoms, where we found B- symptoms in 93.8% of the LDH>480 groups. According to the presence of Mediastinal mass and its size, there were statistically significant differences; it was the highest with LDH>480.

Table 11. Distribution differences according to stage of disease and treatment regimen between two groups of Hodgkin lymphoma

	LDH>480(65)	LDH≤480(143)	P-value
Staging Stage I Stage II Stage III Stage IV	 1(1.5%) 16(24.6%) 33(50.8%) 15(23.1%)	 11(7.7%) 76(53.1%) 36(25.2%) 20(14%)	 0.0001
Disease progression	63(96.9%)	117(81.8%)	0.003

Advance Limited	2(3.1%)	26(18.2%)	
treatment chemotherapy radiochemotherapy	 38(58.5%) 27(41.5%)	 79(55.2%) 64(44.8%)	 0.6

We note that there are statistically significant differences between the two groups of Hodgkin lymphoma patients according to the stage of the disease and its progression, where the advanced disease stage in the LDH>480 group represented 96.9%, as well as for the stage. There were no differences between the two groups according to the treatment method**.**

Table 12. Univariate cox-regression analysis of demographic variables for OS and PFS in a sample of Hodgkin lymphoma patients

Demographic Variables	n	OS				PFS			
		HR	CI	P-value	Median	HR	CI	P-value	Median
sex female male	85 123	1 1.7	]0.7 – 3.6[	0.1	6.2 6	1 1.6	]0.3 – 3.5[	0.2	5.4 5
Age(years) ≤45 >45	152 56	1 0.5	]0.2 – 1.9[	0.2	6.4 6.1	1 0.4	]0.2 – 1.5[	0.3	5.7 5.2

We note that there is no effect of gender as well as age on survival rates of OS and PFS, but OS and PFS were higher in females than males and at ages less than 45 years.

Table 13. Univariate cox-regression analysis of laboratory findings for OS and PFS

	n	OS				PFS			
		HR	CI	P-value	Median	HR	CI	P-value	Median
WBC ≤15000 >15000	153 55	1 2.5	] 1.1– 5.4[	0.01	6.4 5.8	1 2.3	]1.1– 5.1[	0.02	5.4 4.7
ALC 600≥ <600	205 3	1 3.1	]0.3– 8.9[	0.04	6.3 5.2	1 3.1	]0.9– 6.4[	0.02	5.3 3.6
AMC >720 ≤720	176 32	1 2.7	]0.4– 5.6[	0.02	6.3 6.2	1 2.5	]0.1– 6.7[	0.03	5.2 5.3
LMR 2.9≥ <2.9	148 60	1 2.5	]1.2– 5.7[	0.001	6.2 5.3	1 2.4	]0.1– 1.8[	0.003	5.3 4.7
Serum albumin 4≥ <4	61 99	1 1.3	]0.1– 1.9[	0.04	6.2 5.9	1 1.2	]0.1– 1.7[	0.01	5.4 4.8
HB >10.5 10.5≤	131 77	1 2.4	]1.1– 4.9[	0.02	6.3 6	1 2.3	]1.1– 4.9[	0.02	5.4 5
LDH ≤480 >480	143 65	1 2.8	]1.2– 5.7[	0.01	6.3 5.6	1 2.5	]1.2– 7.5[	0.04	5.3 4.4

We noted an effect on OS and PFS with significant statistical differences for high white blood cell count, absolute monocyte count, low absolute lymphocyte count, LMR, albumin, hemoglobin, and high LDH.

Table 14. Univariate cox-regression analysis for OS and PFS disease stage and treatment type

		OS				PFS			
	n	HR	CI	P-value	Median	HR	CI	P-value	Median
Staging		1 1.2	]0.7– 1.9[						
Stage I	12	1	]1.2–		6.9	1			7
Stage II	92	3	1.7[	0.09	6.3	0.1	]0.05– 1.1[	0.9	6.1
Stage III	69	1.2	]1.2–	0.04	6.1	1.2	]0.1– 1.6[	0.04	6
Stage IV	35	3	1.8[	0.02	5.4	1.4	]0.1– 1.8[	0.02	5
Bulky		1							
>10	75	1.2	]0.4–		6.3	1			5.2
≤10	22	2	3.9[	0.6	5.5	1.1	]0.3– 3.5[	0.8	4.6
treatment									
chemotherapy	117	1	]0.1–		6.4	1			5.5
Combined	91	1.4	1.8[	0.01	6	1.3	]0.1– 1.7[	0.01	5.1

We noted an effect of both stage III and stage IV effects of the disease and the presence of combined radiochemotherapy on OS and PFS.

Table 15. Prognostic factors associated with OS and PFS among Hodgkin lymphoma patients in multivariate analysis

	OS			PFS		
Prognostic factors	HR	P-value	CI	HR	P-value	CI
LMR	2.1	0.02	[1.3– 6.2]	2.3	0.01	[1.2– 6.3]
LDH	2.5	0.02	[0.9 – 5.6]	3.1	0.003	[1.06 – 8.9]

We noted that the prognostic factors associated with OS and PFS in patients with Hodgkin lymphoma in multivariate analysis were high LDH and low LMR, which are strongly associated with poor prognosis for patients.

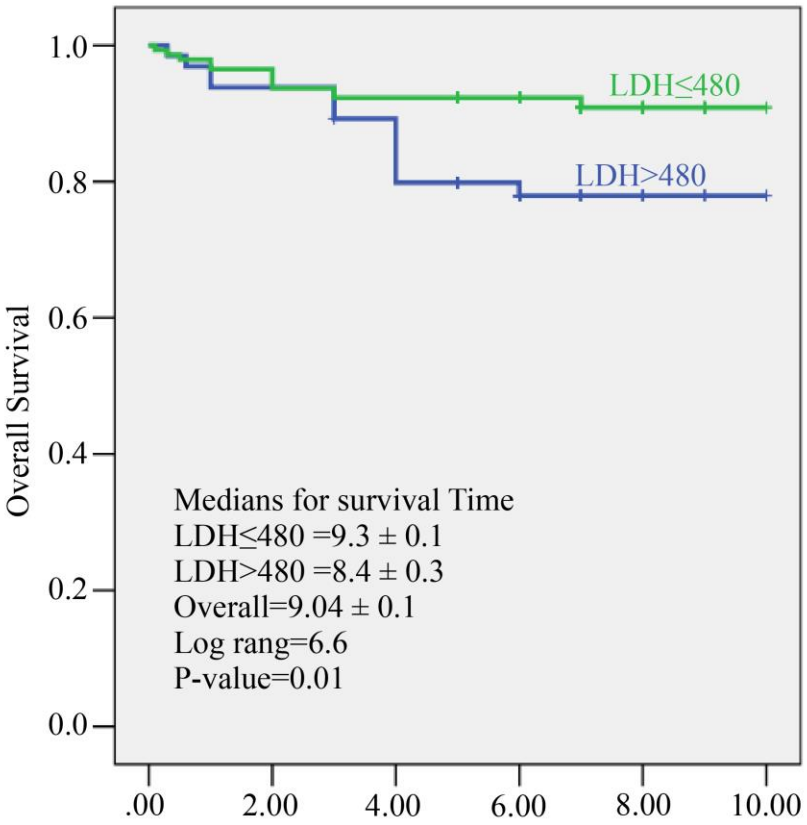

Fig. 5 OS in a sample of Hodgkin lymphoma patients according to pretreatment serum LDH

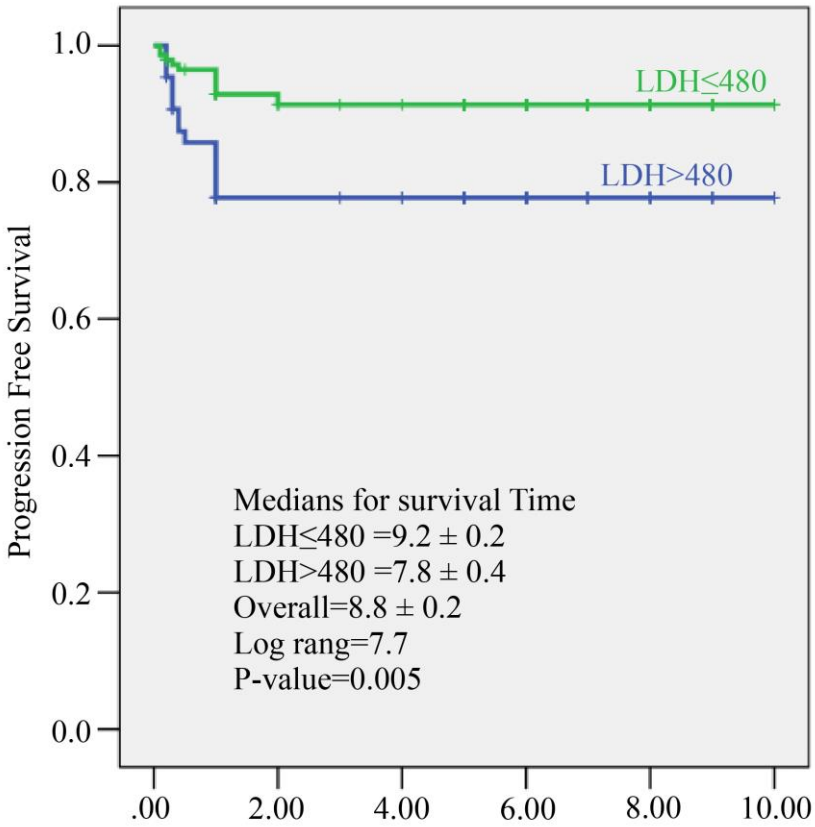

Fig. 6 PFS in a sample of Hodgkin lymphoma patients according to pretreatment serum LDH

3.1. OS and PFS of Sample Study

The overall survival (OS) rate over five years was 88% (183 patients), and (25 pts.) 12% of the sample developed the first event during the five years. With LDH values > 480, OS rates decreased by 78.5% versus 92.3% with LDH≤480 (p-value=0.004). The PFS rate over five years was 75.5% (157 patients), and 51 patients (24,5%) developed the first event during the five years. With LDH values > 480, there was a decrease in PFS rates of 63.1% versus 81.1% with LDH≤480 (p-value=0.005). The number of deaths in the LDH group > 480 was (14 cases, or 21.5%), versus (12 cases, or 8.4%) in the LDH group ≤ 480 with a statistical difference, (p-value=0.008).

4. Discussion

The sample was distributed according to pretreatment serum LDH as follows: LDH > 480 in 31, 25% (65/208pts), LDH ≤ 480 in 68, and 75% (143/208pts). Pre-treatment serum LDH of more than 480 u/ml is an important indicator of the severity of Hodgkin lymphoma. It is highly associated with advanced stage, presence of B symptoms, and bulky mediational mass. It is also highly correlated with bad international prognostic factors (IPS) of Hodgkin lymphoma. The overall survival (OS) rate for five years was 88%. The PFS rate for five years was 75.5% (157 patients). Death occurred in 26 cases (12.5 %). Our study showed that the prognostic factors in univariate analysis of Hodgkin's lymphoma were high white blood cell count, high absolute monocyte count, low absolute lymphocyte count, LMR, albumin, hemoglobin, high pretreatment LDH, stage III and stage IV of disease, as well as the presence of combined radiochemotherapy. There is no effect of gender and age on OS and PFS survival rates. At the same time, the independent prognostic factors in multivariate analysis were high pretreatment serum LDH and low LMR, which are strongly associated with poor prognosis for patients. Our study revealed that pretreatment serum LDH > 480 was associated with a decrease in OS rates (78.5%) versus (92.3%) in the LDH group ≤480 (p-value=0.004). It was also associated with a decrease in PFS rate (63.1%) versus(81.1%) in the LDH group ≤480 (p-value=0.005). We observed an increase in mortality rate in the LDH group > 480 (21.5%) versus (8.4%) in the LDH group ≤ 480 with a statistical difference (p-value=0.008). This agrees with a *meta-analysis* of 76 studies involving 22 882 patients with solid tumors in order to assess the prognostic effect of serum LDH. They found a consistent impact of elevated LDH on survival HR (1.7) among various disease subgroups, mainly in advanced disease stages.

High serum LDH was also associated with a reduced PFS in 13 trials. The effect on OS was the greatest in melanoma and renal cell carcinoma other than metastatic (castration-resistant) prostate cancer [15, 16]**.** Similarly, *Saadettin Kılıckap et al.* reported high serum LDH levels among patients with poor prognostic factors such as the "B" symptoms, bulky disease and extranodal involvement. In addition, other factors with prognostic significance, such as serum albumin and haemoglobin, agree with the results of our study; we revealed that The LDH group >480 was associated with a greater increase in AMC, WBC, a greater decrease in ALB, HGB, LMR, the presence of B-

symptoms, presence of Mediastinal mass and advanced disease [17]. LDH concentrations in human serum during cancer can reflect the cells' metabolic activity and avid glucose uptake. Tumor hypoxia induces the expression of a hypoxia-inducible factor (HIF), a transcription factor that initiates angiogenesis [18]. High pre-treatment serum LDH levels have been found to predict the response to anti-angiogenetic agents. Scartozzi et al. examined this predictive role in two papers, demonstrating that in cases with high serum LDH, bevacizumab achieves a higher RR in colorectal cancer. In hepatocellular carcinoma treated with sorafenib, LDH levels seem to predict clinical outcomes in terms of PFS and OS [19].

Tumor cells may produce LDH to respond to the increase of lactic acid, resulting in an oxidative, reductive reaction to become pyruvic acid. High LDH level describes high aggressiveness and proliferation of the tumor cells. Therefore, LDH level in lymphoma is a cell turnover marker and correlates with tumor burden. Several studies showed a correlation between LDH level and therapy response. High LDH level often provides less response to therapy, relapses, and metastasis [20-23].

5. Conclusion

Pretreatment serum LDH is an important indicator of the severity of Hodgkin lymphoma and an independent prognostic factor for (OS, PFS and mortality) rate.

Declarations

Ethics Approval and Consent to Participate

Written consent was obtained from the patients to participate in the study. Our institutional ethics committee in the faculty of medicine- Tishreen University approved our study.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Authors' Contributions

Corresponding author analyzed and interpreted the patient data.

Abbreviations

LDH: Lactate Dehydrogenase
HL: Hodgkin's Lymphoma
WHO: World Health Organization
NLPHL: Nodular Lymphocytic Predominant Hodgkin's Lymphoma
NSHL: Nodular Sclerosing Hodgkin's Lymphoma
LRHL: Lymphocyte-rich HL Hodgkin's Lymphoma
MCHL: Mixed Cellularity Hodgkin's Lymphoma
LDHL: Lymphocyte Depletion Hodgkin's Lymphoma
IPS: International Prognostic Factors
ESR: Erythrocyte Sedimentation Rate
WBC: White Blood Cells Count
ANC: Absolute Neutrophils Count
ALC: Absolute Lymphocytes count
AMC: Absolute Monocytes Count
LMR: Lymphocytes Monocytes Ratio
HGB: Blood Hemoglobin Concentration
PLT: Platelets Count
ALB: Serum Albumin HL: Non -Hodgkin's lymphoma
OS: Overall Survival
PFS: Progression-Free Survival

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