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Lactate Dehydrogenase-to-Albumin Ratio (LAR) as a Prognostic Marker in Egyptian Patients with Advanced Classical Hodgkin Lymphoma

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ABSTRACT

Background: Classical Hodgkin lymphoma (cHL) is a malignancy with a high likelihood of successful treatment when detected at an early stage. In advanced-stage disease there is high rate of becoming refractory or developing relapse following first line treatment. Traditional factors for identifying high-risk HL patients are currently less predictive in the era of PET-adapted strategies and novel therapies.

Objectives: This study aimed to evaluate LAR as a simple, low-cost laboratory prognostic marker in Egyptian patients with advanced cHL.

Patients and methods: An open-label prospective study was conducted on 50 participants with stage III/IV cHL. Participants were assigned to have Doxorubicin, Bleomycin, Vinblastine, and Dacarbazine (ABVD). Univariate analysis of prognostic factors was done. LAR was calculated at baseline, and its predictive value for progression was assessed.

Results: High LAR (>8) was significantly associated with disease progression (AUC=0.82, p<0.001). Participants with high LAR had shorter PFS (HR=2.8, 95% CI: 1.4–5.6, p=0.003).

Conclusion: LAR is a promising prognostic bio indicator for determining high-risk individuals who may benefit from intensified therapy.

Keywords: Hodgkin Lymphoma, ABVD, LAR, PET/CT.

INTRODUCTION

Hodgkin lymphoma (HL) is a kind of malignancy that is arising from germinal centre B-lymphocytes. It is subdivided into classical Hodgkin lymphoma (cHL) type, which represents 95% of histopathology of HL cases (with four histological subtypes nodular sclerosis, mixed cellularity, lymphocyte-rich, and lymphocyte-depleted and nodular lymphocyte-predominant HL) [(1)].

Around two-thirds of HL patients are younger individuals of working age, while the remaining one-third are older adults over the age of 55 [(2)] . In USA, approximately 8570 new patients were diagnosed with HL of which 96 % had cHL [(3)]. In Egypt, lymphoma is regarded to be the most prevalent blood cancer in adults accounting for approximately 18.4% of all new cancer cases. Non-HL (NHL) represents 76.6% and HL represents 23.4% of the cases [(4)]. Seventy percent of patients who are newly diagnosed with advanced stage HL are expected to achieve cure following treatment with Doxorubicin, Bleomycin, Vinblastine, and Dacarbazine (ABVD). This protocol is considered as the established standard treatment in the United States [(5)].

About 24% to 39% of patients with advanced HL are refractory or develop relapse after receiving frontline treatment with ABVD [(6)]. Aiming to improve survival, the Hodgkin Disease 15 trial (HD15) studied an alternative treatment protocol for patients with advanced cHL using six cycles of escalated Bleomycin, Etoposide, Doxorubicin, Cyclophosphamide, Vincristine, Procarbazine, and Prednisolone (eBEACOPP), with a reported 5-year progression-free survival (PFS) of 80%, this was associated with grade 3 or 4 neutropenia in 22 % of the patients, secondary malignancy was documented in 2.4% and infertility in about 3% of the patients. In addition to about 4% treatment-related mortality, which was concerning [(7)].

Traditional factors for identifying high-risk HL patients are currently less predictive in the era of PET-adapted strategies and novel therapies. There is still a pressing need for additional prognostic markers to more accurately identify patients at higher probability of reoccurrence before deciding for first-line therapy for advanced cHL especially in developing countries [(8)].

Lactate dehydrogenase (LDH), present in blood cells and lymphoid tissue, has traditionally served as a prognostic marker in hematologic malignancies as part of the International Prognostic Index [(9)].

Recent evidence suggests that the lactate dehydrogenase-to-albumin ratio (LAR) provides a more precise prognostic indicator for overall survival (OS) than LDH alone in patients with solid tumors, including colon, esophageal, colorectal, and pancreatic cancers [(10)].

The aim of this investigation was to determine the prognostic value of LAR as an emerging biomarker that could enhance risk stratification and guide treatment choice in patients with advanced cHL.

PATIENTS AND METHODS

This open-label, prospective clinical study included 50 treatment-naïve patients aged 18 to 60 years with late-

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stage cHL, conducted at the Clinical Oncology Department of Helwan University Hospitals between March 2023 and February 2025.

Inclusion criteria: encompassed ECOG performance status ≤ 2, CD30-positive cHL as per WHO classification, and Ann Arbor stage III or IV disease.

Exclusion criteria: included nodular lymphocyte predominant Hodgkin lymphoma, non-Hodgkin lymphoma, cerebral or meningeal involvement, prior oncologic treatment within 12 weeks of randomization, seropositivity for HIV, hepatitis B or C, and known organ failure.

Methods:

All enrolled patients with histopathologic confirmation of classical Hodgkin disease underwent baseline: Full labs including CBC, LDH (U/L), serum albumin (g/L), liver enzymes, renal function tests and virology lab, pulmonary function test, echocardiography and whole-body (FDG)-PET scan. LAR was calculated for each patient through dividing baseline LDH (U/L) by albumin level (g/L). Then the patients were assigned to receive ABVD drug regimen that is composed of Doxorubicin: 25 mg/m^2; Bleomycin: 10 units/m^2; Vinblastine: 6 mg/m^2; Dacarbazine: 375 mg/m^2 by IV infusion on days 1 and 15 of every 28-day cycle. PET/CT reassessment was done after 2 cycles. Then patients continued to total 6 cycles. Follow up was continued till two years from the beginning of treatment.

Two-year progerssion-free survival (PFS) was evaluated from the day of first cycle till 2 years in relation to LAR to assess its prognostic value.

Ethical approval:

Ethical approval was granted by the Helwan University Institutional Review Board, and documented consent was gathered from all participants in accordance with the Declaration of Helsinki guidelines for human research.

Statistical Analysis:

Data were gathered from historical records, clinical exams, lab tests, imaging, and treatment outcomes, then coded and analyzed in Microsoft Excel before import into SPSS version 26.0. Qualitative data were expressed as counts and percentages, while quantitative data were determined via range, mean, standard deviation (SD), median, and interquartile range (IQR). The Shapiro-Wilk test assessed normality. Statistical tests included Chi-square for qualitative associations, and independent or paired t-tests for comparing quantitative groups, with significance set at $p < 0.05$. Diagnostic performance was evaluated via ROC curves. Kaplan-Meier survival analysis estimated PFS and OS, with Cox regression used to identify significant predictors. PFS was determined from therapy onset to disease advancement, relapse, death, or last follow-up, and OS from therapy start to death or last follow-up, with data censored for patients still alive.

RESULTS

This study included 50 participants with advanced cHL. Seventeen participants were males while 13 participants were females. The mean age of participants was 24.8 ± 6.02 years. As for histopathological subtype, nodular sclerosis comprised 70% of patients **(Table 1)**.

Table (1): Descriptive data of the included participants

	ABVD (n = 50)	
	No.	**%**
Sex		
Male	29	58
Female	21	42
Age (years)		
Min. – Max.	19.0 – 40.0	
Mean ± SD.	26.10 ± 5.74	
Median (IQR)	25.0 (22.0 – 30.0)	
Weight (kg)		
Min. – Max.	58.0 – 97.0	
Mean ± SD.	76.40 ± 10.12	
Median (IQR)	75.5 (70.0 – 84.0)	
Height (cm)		
Min. – Max.	160.0 – 185.0	
Mean ± SD.	168.5 ± 7.92	
Median (IQR)	167.0 (162.0 – 175.0)	
BMI (kg/m^2)		
Min. – Max.	20.10 – 31.80	
Mean ± SD.	26.80 ± 2.75	
Median (IQR)	26.5 (24.8 – 28.7)	
ECOG score		
0	25	50.0
1	23	46.0
2	2	6.0
Histopathology (HP) type		
Nodular sclerosis	35	70.0
Mixed cellularity	12	24.0
Lymphocyte predominant	3	6.0
Lymphocyte depleted	0	0.0
PET/CT stage		
Stage III	27	54.0
Stage IV	23	46.0
IPS ≤2	33	66.0
≥3	17	34.

ECOG: Eastern Cooperative Oncology Group Score.
PET/CT: Positron Emission Tomography/ Computarized Tomography.

Univariate Cox regression analysis for prognostic factors associated with PFS showed that elevated LDH level, increased LAR and PET/CT stage IV were linked with a significantly higher probability of disease advancement **(Table 2)**.

Table (2): Univariate COX regression analysis for laboratory investigations and prognostic factors affecting progression free survival

Variables	P	HR (LL – UL 95%C. I)
Haemoglobin	0.300	0.750 (0.435 – 1.293)
Platelets	0.909	1.000 (0.996 – 1.005)
TLC	0.135	1.164 (0.954 – 1.422)
Albumin	0.137	0.325 (0.074 – 1.430)
LDH	**0.012***	1.007 (1.002 – 1.013)
LDH/ Albumin Ratio	**0.003***	1.292 (1.090 – 1.531)
PET/CT stage		
Stage III		1.000
Stage IV	**0.045***	3.311 (1.029 – 10.653)
Age (years)	0.440	0.963 (0.875 – 1.060)
Sex		
Female		1.000
Male	0.451	0.668 (0.234 – 1.908)

*: Significant

Receiver Operating Characteristic (ROC) curves was used for analysis of LDH and LAR value in predicting disease progression in ABVD Arm of the study. Both curves trend upwards and to the left, indicating a positive association between the markers and the likelihood of progression. A higher level of LAR curve could have a better discriminatory ability in predicting progression than LDH alone **(Table 3 and Figure 1)**

Table (3): Prognostic performance for LDH and LAR to predict progression

	AUC	p	95% C.I	Cutoff	Sensitivity	Specificity	PPV	NPV
LDH	0.730	**0.032***	0.539 – 0.920	**>300**	71.43	62.50	62.5	71.4
LAR	0.790	**0.007***	0.620 – 0.961	**>8#**	85.71	75.0	75.0	85.7

*: Significant

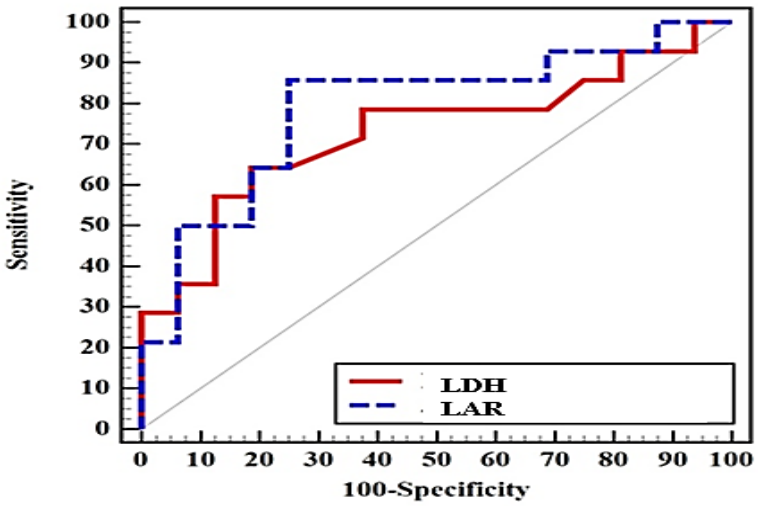

Figure (1): ROC curve for LDH and LAR to predict disease progression

The curve in figure 2 shows PFS of patients based on their LAR values. PFS with LAR ≤ 8 is higher than patients with LAR > 8.

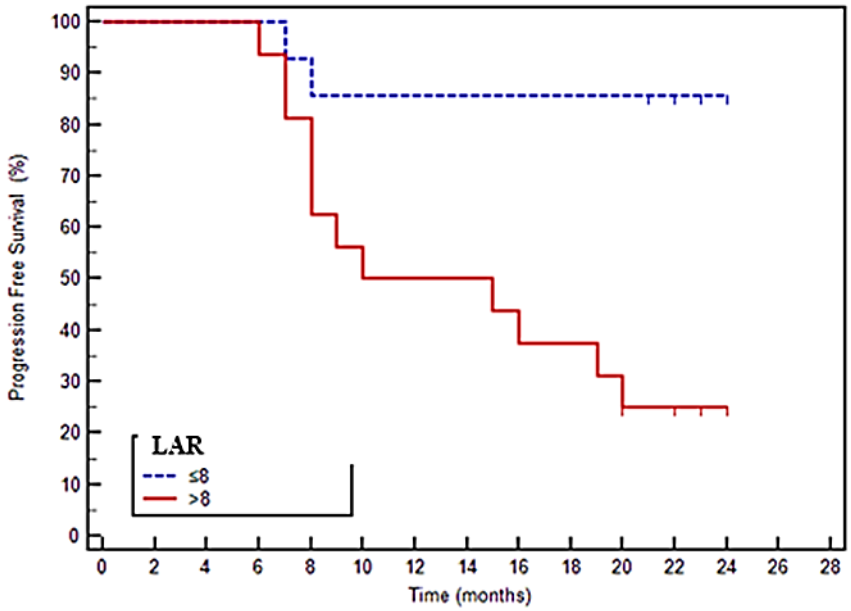

Figure (2): Kaplan-Meier survival curve for LAR with progression free survival

Figure (2) and Table 4 illustrates significant difference in PFS in patients with LAR ≤ 8 vs higher. Patients with lower LAR had a higher proportion of progression-free at 1 year and the end of the study.

Table (4): Kaplan-Meier survival table for LAR with disease progression

ABVD	Mean	Median	% 1 year	% End of study	Log rank	
					χ^2	p
LAR						
≤ 8	21.643	–	85.7%	85.7%	**9.865***	**0.002***
> 8	14.313	10.0	50%	25%		

*: Significant

DISCUSSION

This study showed that variation of sex was not associated with statistical effect on PFS. This is contradictory to **Radkiewicz *et al.*** [11] publication who retrospectively included 1789 male and 1504 female patients with cHL between 2000–2019. They reported significant survival disadvantage in males compared to females. The lack of significant effect of male sex on PFS in our study may be attributable to the small sample size.

In the current study nodular sclerosis represented the most frequent histopathological subtype with 35 (70 %) patients followed by 12 (24%) patients had mixed cellularity then 3 (6%) patients had lymphocyte predominant subtype. None of the patients had lymphocyte depleted subtype. This is similar to a study by **Rose *et al.*** [12] including 727 patients with cHL. The reported histological subtypes were nodular sclerosis (72%), mixed cellularity (19%), classical not otherwise specified (5%), lymphocyte-rich (3%), and lymphocyte-depleted (0.7%) subtypes.

In our study histopathological subtype didn't show significant impact on PFS. The results are aligned with **Konkay *et al.*** [13] who recruited a total of 195 patients of cHL. The specific histologic subtypes did not correlate with differences in PFS.

In the current study haemoglobin level had no statistically significant impact on PFS. These findings are matched with results from an investigation by **Cellini *et al.*** [8] that encompassed 274 participants of HL. The results showed that haemoglobin levels did not significantly affect PFS (HR 3.23).

In this study, there was no significant link among TLC and PFS. This is contradictory to **Yoruk *et al.*** [14] who investigated the adverse prognostic factors in 52 paediatric patients with advanced HL. They found that leucocytosis is a negative risk factor for relapse.

This study didn't show a significant impact of albumin on PFS. These results were in agreement with a study by **Maddi *et al.*** [15] including 195 patients with advanced stage cHL, serum albumin did not influence PFS. This study showed a significant impact of LDH on PFS (HR: 1.007 (1.002 – 1.013) with p: 0.012). Similarly, **Elleithy *et al.*** [16] study included 76 patients with cHL and reported that elevated LDH level was significantly linked with worse PFS and OS (P:0.045).

In this study LAR had a significant impact on PFS (HR: 1.292 (1.090 – 1.531), p: 0.003). The multivariate Cox regression analysis postulated that >8 was the cutoff value between higher and lower risk patients for our study.

These findings are consistent with a **Reyes-Pérez *et al.*** [(10)] study including 44 patients. Twenty-six cases, (59.1%) of them had advanced stage cHL. LAR proved to be a strong prognostic marker for OS, with a hazard ratio (HR) of 10.524 ($P < 0.05$). The multivariate Cox regression analysis suggested a higher cutoff value of >12.5 indicating that participants with a LAR ≤12.5 had better 3-year OS relative to those with an LAR >12.5.

These differences in cutoff values and the focus on OS versus PFS reflect the variability in prognostic markers across different studies and patient populations. However, this highlights the potential value of LAR as a simple, low-cost laboratory assessment that could be validated for prognostic stratification for patients with cHL.

In contrast to a study by **Tóthfalusi *et al.*** [(17)] including 35 patients with HL, the LAR was not a significant prognostic determinants for OS or PFS. This could be explained by including patients with all stages of HL not only patients with an advanced stage.

Strengths of this investigation encompass that it is a prospective study with a standard chemotherapy regimen used for all patients and no patients with chronic inflammatory or autoimmune disease were included.

Limitation of this investigation encompass that it is a single-center study, its relatively dimensioned sample size and short follow-up for OS analysis.

CONCLUSION

In conclusion, LAR is a promising low cost, easily calculated biomarker for progression risk in patients with advanced cHL. However, further validation in larger cohorts is needed.

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REFERENCES

1. Rossi D, Steidl C. (2020): What have we learnt from genomics and transcriptomics in classic Hodgkin lymphoma. In: Anas Younes AE, editor. Hodgkin lymphoma: a comprehensive overview: Springer. p. 87-96. https://www.google.com.eg/books/edition/Hodgkin_Lymphoma/vwTaDwAAQBAJ?hl=en&gbpv=1

2. Ferlay J, Colombet M, Soerjomataram I *et al.* (2021): Cancer statistics for the year 2020: An overview. Int J Cancer., 15:132-93.

3. Siegel R, Giaquinto A, Jemal A (2024): Cancer statistics, 2024. CA Cancer J Clin., 74:12-49.

4. Gad Allah H, ElAzzazi M, Elafifi A *et al.* (2014): Treatment outcome in Egyptian lymphoma patients, 2-year results, single-center experience. Egypt J Haematol., 39:209-16.

5. Entrop J, Weibull C, Smedby K *et al.* (2023): Reproduction patterns among classical Hodgkin lymphoma survivors treated with BEACOPP and ABVD in Sweden, Denmark and Norway-A population-based matched cohort study. Int J Cancer, 153:723-31.

6. Salama M (2020): General overview and incidence. In: Kremyanskaya Marina MES, Teruya-Feldstein Julie, editor. Atlas of Diagnostic Hematology E-Book. p.490-500. https://www.google.com.eg/books/edition/Atlas_of_Diagnostic_Hematology_E_Book/7nH6DwAAQBAJ?hl=en&gbpv=0

7. Taparra K, Liu H, Polley M *et al.* (2020): Bleomycin use in the treatment of Hodgkin lymphoma (HL): toxicity and outcomes in the modern era. Leukemia & lymphoma, 61:298-308.

8. Cellini A, Cavarretta C, Angotzi F *et al.* (2024): Baseline prognostic predictors in classical Hodgkin lymphoma: a retrospective, single-center analysis on patients treated with PET/CT-guided ABVD. Front Oncol., 14:141-63.

9. Xie Z, Zhou H, Wang L *et al.* (2022): The significance of the preoperative lactate dehydrogenase/albumin ratio in the prognosis of colon cancer: a retrospective study. PeerJ., 10:130-13.

10. Reyes-Pérez E, Flores-Cuevas L, Martínez-Mier G *et al.* (2023): Predictive value of the lactate dehydrogenase-to-albumin ratio (LAR) in classical Hodgkin's lymphoma. Annals of Blood, 8:32-54.

11. Radkiewicz C, Bruchfeld J, Weibull C *et al.* (2023): Sex differences in lymphoma incidence and mortality by subtype: A population-based study. Am J Hematol., 98:23-30.

12. Rose A, Grajales-Cruz A, Lim A *et al.* (2021): Classical Hodgkin lymphoma: clinicopathologic features, prognostic factors, and outcomes from a 28-year single institutional experience. Clin Lymphoma Myeloma Leuk., 21:132-8.

13. Konkay K, Paul T, Uppin S *et al.* (2016): Hodgkin lymphoma: A clinicopathological and immunophenotypic study. Indian J Med Paediatr Oncol., 37:59-65.

14. Yoruk M, Mutus H, Timur C *et al.* (2019): Prognostic factors and outcome of ABVD chemotherapy in childhood Hodgkin Iymphoma: A single center experience. Ann Med Res., 15:24-36.

15. Maddi R, Linga V, Iyer K *et al.* (2015): Clinical profile and outcome of adult Hodgkin lymphoma: Experience from a tertiary care institution. Indian J Med Paediatr Oncol., 36:255-60.

16. Elleithy M, Mustafa M, Mohamed D *et al.* (2017): Hodgkin lymphoma: A retrospective clinical and pathological analyses with correlation to treatment outcome. Egypt J Hosp Med., 69:2346-54.

17. Tóthfalusi D, Dobó B, Borics F *et al.* (2025): Impact of comorbidities on prognosis and treatment outcomes in elderly patients with Hodgkin lymphoma. Clin Pract., 15:12-65.