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Prognostic significance of elevated D-dimer level in classical Hodgkin's Lymphoma

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Abstract:

BACKGROUND: Hodgkin lymphoma (HL) is an aggressive B-cell lymphoma, considered one of the most curable hematological malignancies. Hasenclever International Prognostic Score was designed to predict 5-year freedom from the progression of HL. D-dimer is a fibrin degradation element, validated as a standard test in suspected thrombotic disorders. Elevated D-dimer levels were found also in a number of cancers. Its role in the prognosis of these cancers as well as in the mechanism of tumor development is still debated.

OBJECTIVES: The aim of this study was to assess the reliability of D-dimer level in relation to clinical presentations, standard prognostic markers, and early outcomes in patients with classical HL.

PATIENTS AND METHODS: This is a prospective cohort study enrolled 25 adult patients with newly diagnosed classical HL during a period of 1 year from different hematology centers in Iraq. In addition to clinical parameters, each patient had performed D-dimer assay by the expert specialist at the start of treatment and after the end of delete courses of chemotherapy cycles.

RESULTS: An elevated mean D-dimer level was observed (1568.9 ± 1365.73 ng/mL). The stage of the disease showed a significant difference among the patients' groups ($P = 0.042$). In addition, the mean D-dimer was significantly different between chemotherapy responders and nonresponders ($P = 0.004$). Only D-dimer showed a significant association as a univariate predictor to prognosis ($P = 0.003$).

CONCLUSION: There is significant a negative strong correlation in mean D-dimer values and the outcome (i.e., mean D-dimer significantly decrease with increased response).

Keywords:

D-dimer, Hodgkin lymphoma, prognosis, response rate

Background

Hodgkin lymphoma (HL) accounts for 79,990 new cases (0.4% of all new tumors) and 26,167 deaths (0.3% of all cancer deaths) in 2018 globally.[1]

The incidence rate in 2018 was 1.65/100,000 for Iraq, 1.85/100,000 for Jordan, and similarly for Saudi Arabia, and 1.39/100,000 for Iran.[2] In general, the incidence of HL was slightly lower in Middle East countries than in the United States.[3]

HL has a bimodal age presentation, occurs mainly between (20 and 34) years and after 55 years with slightly male predominance. The male-to-female ratio is about (1.3:1).[4,5]

An international effort established seven prognostic factors in 1998 that reliably predict the success rate of therapy in people with locally severe or advanced-stage HL was published.[6] Hasenclever International Prognostic Score (IPS) was designed to predict 5-year freedom from progression (FFP), including age >45 years, male, hemoglobin (Hb) <10.5 g/dl, white blood count (WBC) ≥15.000/µl, lymphocyte count <600/µl or <8% of total WBC, and

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albumin <4.0 g/dl. It is concluded that each adverse prognostic factor will reduce the predicted rate of FFP and overall survival (OS) by approximately 8%.[7] In addition, there are other prognostic factors which may reflect disease control with therapy such as erythrocyte sedimentation rate, number of lymph node regions, and the presence of large mediastinal lymphadenopathy, which are specifically used in early-stage disease.[8] Recently, an interim positron emission tomography scan shows a prognostic significance and may affect the decisions for further therapies.[9]

D-dimer is a special antigen obtained from the breakdown of the cross-linked fibrin factor XIIIa. The D-dimer antigen is obtained from fibrin degradation produced by thrombin, factor XIIIa, and plasmin actions.[10]

There are many conditions that can cause raised D-dimer levels including pregnancy, malignancy, trauma, inflammation, postsurgery, hepatic impairment, and heart disease as well as in hospitalized patients.[11-13] Interestingly, patients with an unexplained rise in D-dimer and a negative Doppler study were significantly associated with an increased risk for malignancy.[14]

The D-dimer assay is considered a sensitive assay in many disease processes that cause intravascular or extravascular injury through infection, inflammation, malignancy, or trauma.[15]

A high D-dimer in patients with systemic lupus erythematosus suggests a greater risk of thrombosis.[16]

Recently, during the COVID-19 pandemic, D-dimer was found to be commonly elevated in relation to severity and thus adopted as a reliable prognostic marker for in-hospital mortality for COVID-19 patients.[17]

An elevated D-dimer was considered to have a poor prognosis in many solid tumors such as colorectal cancer, melanoma, esophageal squamous cell carcinoma as well as hematological neoplasms such as acute myeloid leukemia, and lymphoma.[18]

The aim of the study was to assess the reliability of D-dimer level in relation to clinical presentations, standard prognostic markers, and early outcomes in patients with classical HL.

Patients and Methods

This is a prospective cohort study that included registered data of HL over the period from November 2019 to January 2021, from Hematology Centers in Iraq. Twenty-five patients with newly diagnosed classical HL were enrolled into the study.

All data were taken from patient registry files concerning the diagnosis and treatment protocols details in addition to patient data (age, gender of patients, and performance status), histopathological diagnosis (morphology and immunohistochemistry), clinical presentation, B symptoms, staging, IPS, extranodal involvement, initial laboratory parameters (WBC, lymphocyte count, lymphocyte percentage, Hb, and albumin), and early disease outcome.

The duration of follow-up for each patient has been defined from diagnosis up to the interim evaluation or the end of treatment and the end of the study. This study was approved by review ethical committee of Iraq council for medical specialization. All patients were informed about the study and written consent was taken from all patients prior to enrollment.

Exclusion criteria include relapsed cases, active infection, known congenital thrombophilia, thromboembolic event within 3 months, an underlying inflammatory disease, connective tissue disease or stroke, active peptic ulcer, severe untreated hypertension, neurosurgery within 6 months, pregnancy within the prior 6 months, and concurrent anticoagulant treatment.

D-dimer was measured for each patient before starting the treatment or after the first ABVD standard cycle. It is performed by specialist technician at a private medical specialized laboratory considering normal level below 500 ng/mL.

Statistical analysis was done using software version 25.0 (SPSS, Chicago, Illinois, USA). (2018-12-20). Interpretation for descriptive analysis was carried out for demographic and other parameters. Comparative analysis was done for responsive and nonresponsive patients. The primary endpoints are the association and correlation of D-dimer with prognosis factors and IPS in predicting the prognosis of HL.

Results

The mean age of the study sample is 33.32 ± 17.87 years. The mean albumin is 3.7 ± 0.9 g/dl, the mean of Hb is 10.86 ± 1.8 g/dl, while the mean total WBC count is 11.35 ± 8.25 × 10^3/µl [Table 1 and Figure 1].

The majority of patients are in Stage IV (40%). More than two-thirds of the patients experienced B symptoms (68%) and more than two-thirds (64.7%) were responsive to treatment [Table 1].

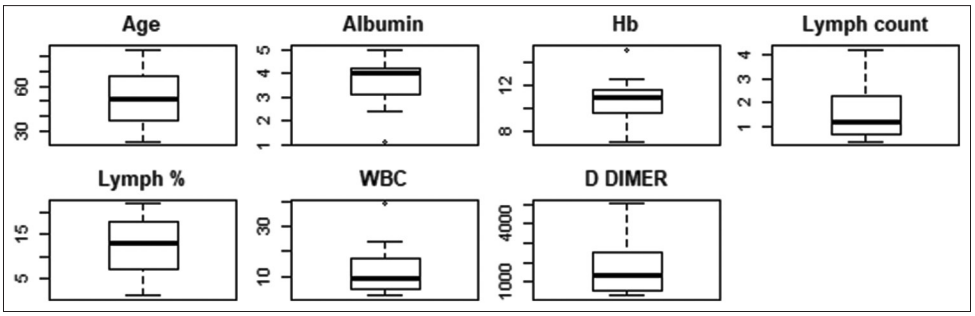

Figure 1: Descriptive analysis for demographic and baseline characteristics. Hb: Hemoglobin, WBC: White blood count

Table 1: Descriptive analysis for demographic and baseline characteristics

Variable	Category	Frequency (%)
Sex	Female	12 (48)
	Male	13 (52)
IPS	0	3 (12)
	1	5 (20)
	2	4 (16)
	3	3 (12)
	4	6 (24)
	5	4 (16)
B symptoms	No	8 (32)
	Yes	17 (68)
Stage	1	2 (8)
	2	8 (32)
	3	5 (20)
	4	10 (40)
Response*	No response	6 (35.3)
	Response	11 (64.7)

*Eight patients were not assessed at the end of the study. IPS: International Prognostic Score

Table 2: Association and correlation of D-dimer with standard prognosis risk factors

Variable	Parameter	D dimer (ng/mL), mean±SD	Spearman correlation coefficient	*P*
Age (years)	>45	2153.3±1651.4	0.20781	0.237
	<45	1384.5±1256.9		
Stage	Stage III and IV	2280.6±1345.2	0.83789	<0.001
	Stage I and II	501.6±221.1		
Sex	Male	1787.9±1382.8	0.25537	0.416
	Female	1331.9±1365.8		
WBC (μL)	≥15,000	1617.4±1675.0	−0.1482	0.915
	<15,000	1550.2±1281.3		
Lymphocyte (%)	<8	2036.7±1461.1	0.24708	0.295
	>8	1387.1±1324.7		
Albumin (g/dL)	<4	2228.5±1397.9	0.62176	0.017
	>4	960.2±1050.0		
Hb (g/dL)	<10.5	2049.9±1390.9	0.45291	0.155
	>10.5	1248.4±1295.6		

SD: Standard deviation, WBC: White blood count, Hb: Hemoglobin

An elevated mean D-dimer level was observed (1568.9 ± 1365.73 ng/mL).

D-dimer showed a weak relationship with increasing age above 45 years, and similarly, with advanced stage disease [Table 2], but negative relationship with increasing total WBC ≥15.000/μl as well as lymphocytes percent unlike the low albumin level that showed a strong relationship and a significant association with D-dimer [Table 2].

Concerning factors affecting response, it is found that the stage of the disease showed a significant difference among the groups (P = 0.042). In addition, the mean D-dimer was significantly different between the two groups [no response = 3130.2 ± 1476.0, response = 996.9 ± 1092.8, P = 0.004, Table 3].

Area under the curve for D-dimer (90.9%) was suggestive of better prognostic utility than IPS (76.5%) [Figure 2].

Logistic regression suggested that only D-dimer showed significant association as univariate predictor to prognosis [P = 0.003, Figure 3] while both albumin (P = 0.140) and Hb (P = 0.080) showed nonsignificant association.

Discussion

It is found that only D-dimer shows a significant association as univariate predictor to prognosis (P = 0.003); where its levels are higher in patients with HL compared with the reference levels in agreement to what suggested by Siddiqui *et al*.[19]

Similarly, Poletaev *et al*. adopted that D-dimer was higher in 33% of HL patients who performed hemostatic assessment on diagnosis and after the six cycles of chemotherapy.[20]

Ay *et al*. assessed the prognostic value of D-dimer in relation to OS and mortality risk in 1178 patients with malignancy participating in the Vienna Cancer and Thrombosis Study.[21]

The results appeared that high level of D-dimer was associated with dismal OS and increased mortality risk in malignant patients.[21]

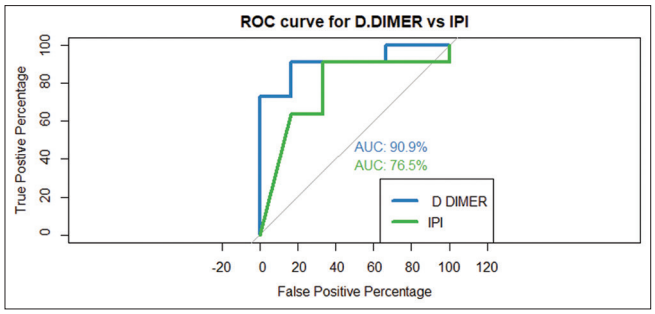

Figure 2: ROC curve comparing D-Dimer and IPS in HL patients. ROC: Receiver operating characteristic, IPS: International Prognostic Score, IPI: International Prognostic Index, HL: Hodgkin lymphoma, AUC: Area under the curve

Table 3: Comparison of baseline characteristics between responders and nonresponders

Label	Levels	Frequency (%)		*P*
		Nonresponse	Response	
Age (years)	>45	4 (66.7)	9 (81.8)	0.916
	<45	2 (33.3	2 (18.2)	
Stage	Stage III and IV	6 (100.0)	4 (36.4)	0.042
	Stage I and II	0	7 (63.6)	
Sex	Male	4 (66.7)	4 (36.4)	0.492
	Female	2 (33.3)	7 (63.6)	
WBC (μL)	≥15,000	5 (83.3)	7 (63.6)	0.768
	<15,000	1 (16.7)	4 (36.4)	
Lymphocyte (%)	<8	3 (50.0)	2 (18.2)	0.413
	>8	3 (50.0)	9 (81.8)	
Albumin (dL)	<4	5 (83.3)	3 (27.3)	0.088
	>4	1 (16.7)	8 (72.7)	
Hb (g/dL)	<10.5	4 (66.7)	2 (18.2)	0.142
	>10.5	2 (33.3)	9 (81.8)	
D-Dimer (ng/mL)	Mean±SD	3130.2±1476.0	996.9±1092.8	0.004
B symptoms	No	3 (50.0)	4 (36.4)	0.258
	Yes	3 (50.0)	7 (63.6)	
IPI	0	0	2 (18.2)	0.074
	1	0	5 (45.5)	
	2	1 (16.7)	1 (9.1)	
	3	0	0	
	4	4 (66.7)	1 (9.1)	
	5	1 (16.7)	2 (18.2)	

SD: Standard deviation, WBC: White blood count, IPI: International Prognostic Index, Hb: Hemoglobin

In regard to HL, the area under the curve for D-dimer (90.9%) was prognostically significant compared with than that of the IPS (76.5%).

This prognostic implication had adopted also by Bi *et al*.[22] who analyses its value in newly diagnosed natural killer/T-cell lymphoma patients, and found that higher level of D-dimer associated with more adverse clinical characteristics, such as low-performance status, B symptoms, advanced stage diseases, elevated lactate dehydrogenase, number of involved lymph node regions, more extranodal involvement, and higher International Prognostic Index and natural killer/T-cell lymphoma prognostic index ratings.[22]

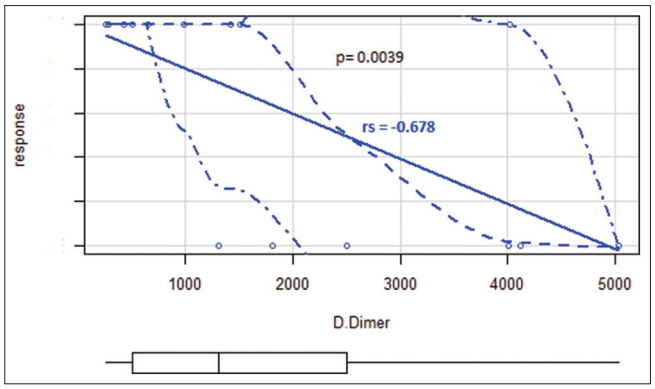

Figure 3: Correlation curve for D-dimer between the two study groups

Conclusions

Concerning the outcome of treatment, there is a significant negative correlation in mean Ddimer values and the outcome (i.e., mean Ddimer significantly decreases with increased response).

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Nil.

Conflicts of interest

There are no conflicts of interest.

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