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Lymphocyte Level at Diagnosis in Hodgkin lymphoma: Could It be an Indicator of the Stage at Initial Diagnosis?

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ABSTRACT

Introduction: Despite the existence of standard risk classification systems and effective treatment approaches, 34% to 37% of advanced-stage Hodgkin lymphomas (HLs) either relapse or progress. Our goal in our study was to show the relationship between initial lymphocyte count and stage, while examining their effects on prognosis. The initial lymphocyte count, which is proven in advanced stage patients, could be an important factor in terms of showing the prognosis in the early stage.

Materials and Methods: Our study included 190 patients diagnosed with HL in our hospital between January 2010 and September 2020. HL subtypes, diagnosis stages, presence of bulky or mediastinal masses, lymphadenopathy areas, and demographic data of patients, such as age and sex. The aim was to obtain a cutoff in the statistical analysis performed to explore the relationship between lymphocyte level and stage, which is the main hypothesis of the study.

Results: Of the 190 patients evaluated, 77 were female (40.5%) and 113 were male (59.5%). To obtain a cutoff in terms of lymphocyte level and stage relationship, a value of 2380/mm3 and below was found to be associated with stage 3-4 disease with a sensitivity of 86.44% and a specificity of 33.3% (AUC: 0.613 (0.539-0.682), p<0.007).

Conclusion: This result can be improved in combination with conventional imaging methods used for staging purposes. Further studies may shed light on staging and especially the diagnosis of advanced stage disease with high sensitivity.

Keywords: Hodgkin lymphoma; Lymphocyte; Stage; Prognosis

INTRODUCTION

Hodgkin lymphoma (HL), formerly called as Hodgkin's disease, is a rare monoclonal lymphoid hematologic malignancy with high cure rates [1]. It has been divided into two different subgroups: classical Hodgkin (cHL) and nodular lymphocyte-predominant Hodgkin lymphoma (NLP-HL). These two diseases differ in terms of clinical picture and pathology. cHL accounts for approximately 95% of all HL and is divided into four subgroups: nodular sclerosing (NSHL), lymphocyte rich (LRHL), mixed cellular (MCHL) and lymphocyte depleted (LDHL) [1, 2].

HL usually occurs in the cervical lymph nodes and it is more common in young adults. Pathology includes nonneoplastic inflammatory cells and large uninucleated neoplastic Hodgkin (Reed-Sternberg) cells. A nonneoplastic T-cell increase is observed around this area[1]. HL has a good overall prognosis, with a cure rate of approximately 80% [1]. It is a rare malignancy with an estimated incidence rate of 2.6 cases per 100000 in the United States[1,3]. Most

affected patients are between the ages of 20 and 40 years, have a bimodal distribution, and have a second peak at 55 years and older. NSHL is more common in young adults, while MCHL tends to affect older adults.

The current gold standard for advanced stage risk stratification in HL is the International Prognostic Score (IPS) [4]. Despite the existence of standard risk classification systems and effective treatment approaches, 34% to 37% of advanced-stage HLs relapse or progress[5]. Therefore, for prognosis and early prediction of the stage, it is necessary to develop new easily usable parameters. Many studies have been conducted with the aim to determine the prognosis and estimation of the stage of this type of lymphoma consisting of different morphological features. In conclusion, studies on the tumor microenvironment and host immunity suggest that changes in lymphocyte ratio and subtypes constitute a new research subject. At this point, absolute monocyte count (AMC) and absolute lymphocyte count (ALC) are indicated as prognostic factors [6–8]. Similarly, developed parameters like the neutrophil-lymphocyte ratio are also used in determining prognosis [9].

Our goal in our study was to determine the relationship between initial lymphocyte count and stage and to examine their effects on prognosis. The initial lymphocyte count, which is proven in advanced stage patients, could be an important factor in terms of showing the prognosis in the early stage.

MTERIALS AND METHODS

Our study included 190 patients diagnosed with HL in our hospital between January 2010 and September 2020. We recorded HL subtypes (NSHL, MCHL, LDHL, LRHL, NLP-HL), diagnosis stages, presence of bulky or mediastinal masses, lymphadenopathy areas (cervical, thoracic, abdomen, pelvis), and demographic data of patients, such as age and sex.

Patients with liver, spleen and bone marrow involvement were documented with positron emission tomography/computed tomography (PET/CT) imaging at initial diagnosis. The presence of definite involvement was confirmed by bone marrow biopsy in patients with bone marrow involvement. The recorded data were compared statistically with both the response status on interim PET/CT and mortality and progression. The patient group with a response was evaluated using the “PET 5-Point Scale (Deauville Criteria)” in Lugano criteria [10] and those with at least Deauville 3 responses were accepted as responders.

Within the entire patient group, the stage was divided into two separate subgroups: stages 1-2 and stages 3-4. The quantitative data that could be associated with the stage subgroups of the patients were analyzed statistically. The analysis aimed to obtain a cutoff in the statistical analysis performed to reveal the relationship between lymphocyte level and stage, the main hypothesis of the study.

Statistical analysis

The data analysis was performed using the SPSS 25 package software. The frequency and percentage values of qualitative variables and mean and standard deviation values of quantitative variables are reported. The chi-square test was used to compare two qualitative variables. Independent sample t tests were used to compare qualitative variables with two categories and quantitative variables. ROC analysis was used to control the use of lymphocyte values in defining stage values. The study considered a type I error rate of 0.05.

RESULTS

Of the 190 patients evaluated, 77 were female (40.5%) and 113 were male (59.5%). When evaluated in terms of histological subtype, 133 patients (70%) were diagnosed with NSHL. A total of 118 of the patients (62.1%) had stage 3-4 disease. While 21 of the patients (11.1%) had a bulky mass at the time of diagnosis, 46 (24.2%) had a mediastinal mass. Splenic involvement was detected by PET/CT in 49 patients (25.8%), while 11 patients (5.8%) had liver involvement. Lymphoma involvement was detected by bone marrow biopsy in nine (11.5%) of 78 patients (41.1%) with PET/CT bone marrow involvement (Table 1).

Regarding mortality and affecting factors, only a high leukocyte count at initial diagnosis and advanced age were associated with mortality (Tables 2 and 3).

According to the evaluation of the relationship between disease parameters at initial diagnosis and response, the presence of a mediastinal mass at the time of diagnosis was a significant negative indicator in terms of response (p=0.004) (Tables 4 and 5). Considering the relationship of the data with progression, the presence of a bulky mass at the time of diagnosis was a significant indicator for progression, albeit low (p=0.047) (Tables 6 and 7).

Evaluation of the stage and diagnosis parameters showed that lower hemoglobin, lymphocyte, albumin and higher sedimentation and LDH at initial diagnosis were associated with stage 3-4 disease (p=0.001, 0.001, 0.01, 0.001, 0.013; respectively) (Table 8). To obtain a cutoff in terms of lymphocyte level and stage relationship, a value of 2380/mm^3 and below was associated with stage 3-4 disease with a sensitivity of 86.44% and a specificity of 33.3% (AUC: 0.613 (0.539-0.682), p<0.007) (Table 9).

Table 1: Demographic data, initial stages, involvement sites, final state

	n	%
Sex		
Female	77	40.5
Male	113	59.5
Disease subtype		
MC	36	18.9
NS	133	70
LR	7	3.7
LD	1	0.5
NLP	13	6.8
Stage		
Stage 1-2	72	37.9
Stage 3-4	118	62.1
Bulky mass		
(-)	169	88.9
(+)	21	11.1
Mediastinal mass		
(-)	144	75.8
(+)	46	24.2
Cervical LAP		
(-)	39	20.5
(+)	151	79.5
Thoracic LAP		
(-)	77	40.5
(+)	113	59.5
Abdominal LAP		
(-)	98	51.6

(+)	92	48.4
Pelvic LAP		
(-)	150	78.9
(+)	40	21.1
Splenic involvement		
(-)	141	74.2
(+)	49	25.8
Hepatic involvement		
(-)	179	94.2
(+)	11	5.8
IPS		
0	22	11.6
1	50	26.3
2	51	26.8
3	39	20.5
4	16	8.4
5	9	4.7
6	3	1.6
PET/CT-Bone marrow involvement		
(-)	112	58.9
(+)	78	41.1
Proven bone marrow involvement by biopsy		
(-)	69	88.4
(+)	9	12.6
Response		
(-)	11	5.8
(+)	179	94.2
Progression		
(-)	172	90.5
(+)	18	9.5
Final state		
Exitus	25	13.2
Alive	165	86.8

****MC:** Mixed cellular, **NS:** Nodular sclerosing, **LR:** Lymphocyte rich, **LD:** Lymphocyte depleted, **NLP:** Nodular lymphocyte predominant, **LAP:** Lymphadenopathy, **IPS:** International prognostic score, **PET/CT:** Positron emission tomography/computed tomography

Table 2: Comparison of mortality and qualitative variables

Sex		Exitus	Alive	Total	Chi-square	p
Female	n	7	70	77	1.323	0.250
	%	9.10%	90.90%	100.00%		
Male	n	18	95	113		
	%	15.90%	84.10%	100.00%		
Disease subtype						
MC	n	3	33	36	4.326	0.359
	%	8.30%	91.70%	100.00%		
NS	n	22	111	133		
	%	16.50%	83.50%	100.00%		
LR	n	0	7	7		
	%	0.00%	100.00%	100.00%		
LD	n	0	1	1		
	%	0.00%	100.00%	100.00%		
NLP	n	0	13	13		
	%	0.00%	100.00%	100.00%		
Stage						
Stage 1-2	n	7	65	72	0.762	0.383
	%	9.70%	90.30%	100.00%		
Stage 3-4	n	18	100	118		
	%	15.30%	84.70%	100.00%		
Bulky mass						
(-)	n	23	146	169	0.032	0.857
	%	13.60%	86.40%	100.00%		
(+)	n	2	19	21		
	%	9.50%	90.50%	100.00%		
Mediastinal mass						
(-)	n	23	121	144	3.168	0.075
	%	16.00%	84.00%	100.00%		
(+)	n	2	44	46		
	%	4.30%	95.70%	100.00%		
Cervical LAP						
(-)	n	4	35	39	0.113	0.737
	%	10.30%	89.70%	100.00%		
(+)	n	21	130	151		
	%	13.90%	86.10%	100.00%		

Thoracic LAP						
(-)	n	12	65	77	0.358	0.55
	%	15.60%	84.40%	100.00%		
(+)	n	13	100	113		
	%	11.50%	88.50%	100.00%		
Abdominal LAP						
(-)	n	13	85	98	0.002	0.964
	%	13.30%	86.70%	100.00%		
(+)	n	12	80	92		
	%	13.00%	87.00%	100.00%		
Pelvic LAP						
(-)	n	17	133	150	1.387	0.239
	%	11.30%	88.70%	100.00%		
(+)	n	8	32	40		
	%	20.00%	80.00%	100.00%		
	n	25	165	190		
	%	13.20%	86.80%	100.00%		
Splenic involvement						
(-)	n	20	121	141	0.216	0.642
	%	14.20%	85.80%	100.00%		
(+)	n	5	44	49		
	%	10.20%	89.80%	100.00%		
Hepatic involvement						
(-)	n	24	155	179	0	1
	%	13.40%	86.60%	100.00%		
(+)	n	1	10	11		
	%	9.10%	90.90%	100.00%		
IPS						
0	n	3	19	22	7.751	0.207
	%	13.60%	86.40%	100.00%		
1	n	5	45	50		
	%	10.00%	90.00%	100.00%		
2	n	5	46	51		
	%	9.80%	90.20%	100.00%		
3	n	4	35	39		
	%	10.30%	89.70%	100.00%		
4	n	4	12	16		
	%	25.00%	75.00%	100.00%		
5	n	3	6	9		

	%	33.30%	66.70%	100.00%		
6	n	1	2	3		
	%	33.30%	66.70%	100.00%		
PET/CT-Bone marrow involvement						
(-)	n	13	99	112	0.291	0.589
	%	11.60%	88.40%	100.00%		
(+)	n	12	66	78		
	%	15.40%	84.60%	100.00%		
Proven bone marrow involvement by biopsy						
(-)	n	24	157	181	0	1
	%	13.30%	86.70%	100.00%		
(+)	n	1	8	9		
	%	11.10%	88.90%	100.00%		
Response						
(-)	n	3	8	11	0.936	0.333
	%	27.30%	72.70%	100.00%		
(+)	n	22	157	179		
	%	12.30%	87.70%	100.00%		
Progression						
(-)	n	21	151	172	0.688	0.407
	%	12.20%	87.80%	100.00%		
(+)	n	4	14	18		
	%	22.20%	77.80%	100.00%		

****MC:** Mixed cellular, **NS:** Nodular sclerosing, **LR:** Lymphocyte rich, **LD:** Lymphocyte depleted, **NLP:** Nodular lymphocyte predominant, **LAP:** Lymphadenopathy, **IPS:** International prognostic score, **PET/CT:** Positron emission tomography/computed tomography

Table 3: Comparison of mortality and quantitative variables

	Status	**Mean**	**SD**	**T**	**p**
Age	Ex	49.88	20.18523	2.111	**0.044***
	Alive	41.0303	14.55579		
Initial hemoglobin	Ex	11.456	2.48748	-1.357	0.177
	Alive	12.1236	2.26328		
Initial albumin	Ex	3.826	0.76324	-1.203	0.239
	Alive	4.0194	0.63648		
Initial leukocyte	Ex	12232.4	7205.428	2.631	**0.009***
	Alive	9154.752	5144.653		
Initial lymphocyte	Ex	1690	1024.699	-0.708	0.480
	Alive	1830	904.5663		
Initial sedimentation	Ex	59.3182	41.60859	1.416	0.159
	Alive	47.8722	33.98338		
Initial LDH	Ex	240.24	126.3472	0.659	0.511
	Alive	227.4259	83.83945		

SD: Standard deviation, **Ex:** Exitus, **LDH:** Lactate dehydrogenase

Table 4: Comparison of response and qualitative variables

	Sex	**Response (-)**	**Response (+)**	**Total**	**Chi-Square**	**p**
Female	n	4	73	77	0.085	0.771
	%	5.20%	94.80%	100.00%		
Male	n	7	106	113		
	%	6.20%	93.80%	100.00%		
Disease subtype						
MC	n	1	35	36	3.458	0.514
	%	2.80%	97.20%	100.00%		
NS	n	9	124	133		
	%	6.80%	93.20%	100.00%		
LR	n	1	6	7		
	%	14.30%	85.70%	100.00%		
LD	n	0	1	1		
	%	0.00%	100.00%	100.00%		
NLP	n	0	13	13		
	%	0.00%	100.00%	100.00%		
Stage						
Stage 1-2	n	4	68	72	0	1
	%	5.60%	94.40%	100.00%		
Stage 3-4	**n**	7	111	118		
	%	5.90%	94.10%	100.00%		
Bulky mass						
(-)	**n**	10	159	169	0.048	0.826
	%	5.90%	94.10%	100.00%		
(+)	**n**	1	20	21		
	%	4.80%	95.20%	100.00%		
Mediastinal mass						
(-)	**n**	4	140	144	8.241	**0.004***
	%	2.80%	97.20%	100.00%		
(+)	**n**	7	39	46		
	%	15.20%	84.80%	100.00%		
Cervical LAP						
(-)	**n**	4	35	39	0.913	0.339
	%	10.30%	89.70%	100.00%		
(+)	**n**	7	144	151		

	%	4.60%	95.40%	100.00%		
Thoracic LAP						
(-)	**n**	7	70	77	2.532	0.112
	%	9.10%	90.90%	100.00%		
(+)	**n**	4	109	113		
	%	3.50%	96.50%	100.00%		
Abdominal LAP						
(-)	**n**	5	93	98	0.012	0.914
	%	5.10%	94.90%	100.00%		
(+)	**n**	6	86	92		
	%	6.50%	93.50%	100.00%		
Pelvic LAP						
(-)	**n**	10	140	150	0.386	0.534
	%	6.70%	93.30%	100.00%		
(+)	**n**	1	39	40		
	%	2.50%	97.50%	100.00%		
Splenic involvement						
(-)	**n**	8	133	141	0	1
	%	5.70%	94.30%	100.00%		
(+)	**n**	3	46	49		
	%	6.10%	93.90%	100.00%		
Hepatic involvement						
(-)	**n**	11	168	179	0.033	0.856
	%	6.10%	93.90%	100.00%		
(+)	**n**	0	11	11		
	%	0.00%	100.00%	100.00%		
IPS						
0	**n**	2	20	22	3.258	0.767
	%	9.10%	90.90%	100.00%		
1	**n**	3	47	50		
	%	6.00%	94.00%	100.00%		
2	**n**	2	49	51		
	%	3.90%	96.10%	100.00%		
3	**n**	3	36	39		
	%	7.70%	92.30%	100.00%		
4	**n**	0	16	16		

	%	0.00%	100.00%	100.00%		
5	**n**	1	8	9		
	%	11.10%	88.90%	100.00%		
6	**n**	0	3	3		
	%	0.00%	100.00%	100.00%		
PET/CT-Bone marrow involvement						
(-)	**n**	7	105	112	0	0.992
	%	6.30%	93.80%	100.00%		
(+)	**n**	4	74	78		
	%	5.10%	94.90%	100.00%		
Proven bone marrow involvement by biopsy						
(-)	n	11	170	181	0.001	0.975
	%	6.10%	93.90%	100.00%		
(+)	n	0	9	9		
	%	0.00%	100.00%	100.00%		

****MC:** Mixed cellular, **NS:** Nodular sclerosing, **LR:** Lymphocyte rich, **LD:** Lymphocyte depleted, **NLP:** Nodular lymphocyte predominant, **LAP:** Lymphadenopathy, **IPS:** International prognostic score, **PET/CT:** Positron emission tomography/computed tomography

Table 5: Comparison of response and quantitative variables

	Response	**Mean**	**SD**	**T**	**p**
Age	(-)	39.3636	12.90948	-0.618	0.538
	(+)	42.3687	15.80529		
Initial hemoglobin	(-)	12.3818	2.32156	0.513	0.608
	(+)	12.0145	2.30164		
Initial albumin	(-)	4	0.42426	0.047	0.963
	(+)	3.9929	0.66659		
Initial leukocyte	(-)	12440	6513.018	1.788	0.075
	(+)	9382.704	5441.869		
Initial lymphocyte	(-)	1848.182	1390.423	0.136	0.892
	(+)	1809.33	888.3412		
Initial sedimentation	(-)	58.1667	45.89735	0.613	0.541
	(+)	49.1477	34.90051		
Initial LDH	(-)	295.3636	155.7172	1.485	0.167
	(+)	225	83.65316		

****SD:** Standard deviation, **Ex:** Exitus, **LDH:** Lactate dehydrogenase

Table 6: Comparison of Progression and Qualitative Variables

Sex		**Progression (-)**	**Progression (+)**	**Total**	**Chi-square**	**p**
Female	n	69	8	77	0.011	0.918
	%	89.60%	10.40%	100.00%		
Male	n	103	10	113		
	%	91.20%	8.80%	100.00%		
Disease subtype						
MC	n	33	3	36	2.406	0.675
	%	91.70%	8.30%	100.00%		
NS	n	119	14	133		
	%	89.50%	10.50%	100.00%		
LR	n	6	1	7		
	%	85.70%	14.30%	100.00%		
LD	n	1	0	1		
	%	100.00%	0.00%	100.00%		
NLP	n	13	0	13		
	%	100.00%	0.00%	100.00%		
Stage						
Stage 1-2	n	65	7	72	0	1
	%	90.30%	9.70%	100.00%		
Stage 3-4	n	107	11	118		
	%	90.70%	9.30%	100.00%		
Bulky mass						
(-)	n	156	13	169	9.394	**0.047***
	%	92.30%	7.70%	100.00%		
(+)	n	16	5	21		
	%	76.20%	23.80%	100.00%		
Mediastinal mass						
(-)	n	134	10	144	3.302	0.069
	%	93.10%	6.90%	100.00%		
(+)	n	38	8	46		
	%	82.60%	17.40%	100.00%		
Cervical LAP						
(-)	n	34	5	39	0.244	0.621
	%	87.20%	12.80%	100.00%		

(+)	n	138	13	151		
	%	91.40%	8.60%	100.00%		
Thoracic LAP						
(-)	n	71	6	77	0.161	0.688
	%	92.20%	7.80%	100.00%		
(+)	n	101	12	113		
	%	89.40%	10.60%	100.00%		
Abdominal LAP						
(-)	n	90	8	98	0.151	0.697
	%	91.80%	8.20%	100.00%		
(+)	n	82	10	92		
	%	89.10%	10.90%	100.00%		
Pelvic LAP						
(-)	n	138	12	150	1.08	0.299
	%	92.00%	8.00%	100.00%		
(+)	n	34	6	40		
	%	85.00%	15.00%	100.00%		
Splenic involvement						
(-)	n	129	12	141	0.236	0.627
	%	91.50%	8.50%	100.00%		
(+)	n	43	6	49		
	%	87.80%	12.20%	100.00%		
Hepatic involvement						
(-)	n	162	17	179	0	1
	%	90.50%	9.50%	100.00%		
(+)	n	10	1	11		
	%	90.90%	9.10%	100.00%		
IPS						
0	n	21	1	22	3.755	0.674
	%	95.50%	4.50%	100.00%		
1	n	44	6	50		
	%	88.00%	12.00%	100.00%		
2	n	47	4	51		
	%	92.20%	7.80%	100.00%		
3	n	35	4	39		
	%	89.70%	10.30%	100.00%		
4	n	15	1	16		

	%	93.80%	6.30%	100.00%		
5	n	8	1	9		
	%	88.90%	11.10%	100.00%		
6	n	2	1	3		
	%	66.70%	33.30%	100.00%		
PET/CT-Bone marrow involvement						
(-)	n	101	11	112	0	1
	%	90.20%	9.80%	100.00%		
(+)	n	71	7	78		
	%	91.00%	9.00%	100.00%		
Proven bone marrow involvement by biopsy						
(-)	n	165	16	181	0.57	0.45
	%	91.20%	8.80%	100.00%		
(+)	n	7	2	9		
	%	77.80%	22.20%	100.00%		

****MC:** Mixed cellular, **NS:** Nodular sclerosing, **LR:** Lymphocyte rich, **LD:** Lymphocyte depleted, **NLP:** Nodular lymphocyte predominant, **LAP:** Lymphadenopathy, **IPS:** International Prognostic Score, **PET/CT:** Positron emission tomography/computed tomography

Table 7: Comparison of progression and quantitative variables

	Progression	Mean	SD	T	p
Age	(-)	42.8779	15.49617	1.874	0.063
	(+)	35.6667	15.93369		
Initial hemoglobin	(-)	12.0494	2.25221	0.252	0.801
	(+)	11.9056	2.77096		
Initial albumin	(-)	3.995	0.66218	0.116	0.908
	(+)	3.975	0.60718		
Initial leukocyte	(-)	9280.14	5070.73386	-1.432	0.169
	(+)	12231.11	8587.37232		
Initial lymphocyte	(-)	1775.814	850.18466	-1.113	0.28
	(+)	2153.333	1411.999		
Initial sedimentation	(-)	48.2199	34.02522	-1.436	0.153
	(+)	62.3571	45.27456		
Initial LDH	(-)	228.7041	91.06902	-0.201	0.841
	(+)	233.2222	85.64946		

****SD:** Standard deviation, **Ex:** Exitus, **LDH:** Lactate dehydrogenase

Table 8: Comparison of stage and quantitative variables

	Stage	Mean	Sd	T	p
Age	Stage 1-2	41.2639	14.88547	-0.64	0.523
	Stage 3-4	42.7627	16.11745		
Initial hemoglobin	Stage 1-2	13.1139	2.04611	5.416	**<0.001***
	Stage 3-4	11.378	2.19997		
Initial albumin	Stage 1-2	4.2101	0.51104	3.903	**<0.001***
	Stage 3-4	3.8612	0.70014		
Initial leukocyte	Stage 1-2	9575.556	4894.11486	0.032	0.974
	Stage 3-4	9550.034	5913.69011		
Initial lymphocyte	Stage 1-2	2030	945.62894	2.596	**0.010***
	Stage 3-4	1678.305	880.93317		
Initial sedimentation	Stage 1-2	35	30.64761	-4.229	**<0.001***
	Stage 3-4	58.4063	35.06012		
Initial LDH	Stage 1-2	209.2	74.60575	-2.521	**0.013***
	Stage 3-4	241.0684	96.92805		

****SD:** Standard deviation, **Ex:** Exitus, **LDH:** Lactate dehydrogenase

Table 9: ROC analysis of the lymphocyte cutoff for 2380/mm^3

	AUC (%95 CI)	SE	p	Cutoff
GS: Imaging results	0.613(0.539-0.682)	0.042	**0.007***	≤2380

***AUC:** Area under the curve, **CI:** Confidence interval, **GS:** Gold standard

DISCUSSION

The histological distinguishing feature of cHL is that Reed Sternberg cells comprise approximately 2% of the environment alongside the other tumor microenvironment. Studies have shown that the background referred to as the tumor microenvironment has a significant effect on prognosis[11]. Tumor-infiltrating lymphocytes and tumor-infiltrating macrophages are reported to be prognostic factors for survival in patients [11–13]. It has long been known that the initial lymphocyte count has a prognostic role in cHL, and lymphopenia (<600 cells/mm3 or<8% leukocytes) is also associated with adverse survival outcomes[12,14]. In our study, we aimed to reveal the factors affecting prognosis, response and progression in the Hodgkin group and to create a new field in terms of scoring at the time of diagnosis, revealing the relationship between lymphocyte count at the time of diagnosis and stage. A study conducted in 2015[14] examined the data of 1450 patients with a diagnosis of cHL to verify whether AMC and lymphocyte-monocyte ratio (LMR) at initial diagnosis are valid prognostic parameters in cHL. Similarly, another study conducted in 2012[15] revealed the effect of the ALC/AMC ratio obtained by using the initial lymphocyte level. A total of 113 NLP-HL patients were able to demonstrate its effect on overall survival (OS) with a sensitivity of 70% and a specificity of 84% for the ALC/AMC ratio, with a cutoff set at 2.1. In this study, there was a statistically significant correlation between the decrease in the ALC/AMC ratio and the decrease in OS. In another study conducted in 2012[16], involving 476 patients with cHL, a value of 0.91 was identified as a cutoff value that can be used for OS with a sensitivity of 90% and a specificity of 79%.

In light of this information, the rates including low lymphocyte level and absolute lymphocyte count show the relationship between OS and PFS. In our study, we aimed to prove the relationship between initial low lymphocyte count and stage, in addition to our Hodgkin data. Accurate evaluation of the stage in patients with HL is critical for the selection of the appropriate treatment. FDG-PET scanning has emerged as an important tool for staging patients with HL, contributing significantly to staging information obtained using other standard radiographic methods[17]. In a study discussing PET/CT and staging sensitivity, the sensitivity of FDG PET in detecting all known pathological lymph nodes was 83% for peripheral lymph nodes, 91% for thoracic lymph nodes and 75% for abdominal and pelvic lymph nodes. In the current study, old and traditional staging procedures and FDG PET showed the same tumor stage in a total of 26 patients. However, FDG PET never missed tumor masses >1 cm [17].

A study conducted in 2017 [18] compared PET/CT with PET/magnetic resonance (PET/MRI). It examined 68 studies with HL or NHL, finding that PET/CT and PET/MRI were correlated significantly (Spearman rho correlation coefficient, 0.842; p<0.001). The present study could not show a more sensitive result, yet it showed similar sensitivities. In another study comparing diffusion-weighted MRI (DW-MRI) and PET/CT[19], the sensitivity and specificity for lymph node involvement in DWI-MRI were 89.9% and 93.8%, respectively, while the sensitivity and specificity were 93.8% and 86.9% for FDG-PET. Regarding extranodal involvement, the sensitivity and specificity were 88.5% and 99.3% for DWI and 92.3% and 92.7% for FDG PET, respectively. The sensitivity of both methods for nodal (p=0.06) and extranodal involvement (p=0.66) did not differ significantly.

The current approach to HL should include personalized treatment. Many HL patients can be treated with standard therapy, which exposes them to the risk of potential long-term complications. The factors that determine patients with a low or high risk of relapse can therefore be most useful in optimizing treatment based on the patient's expected clinical outcome. This approach aims to avoid overtreatment of some patients and undertreatment of others. Prognostic factors for early-stage HL have been identified, including the presence of a large mediastinal mass, an increased sedimentation rate, involvement of multiple nodal sites, extranodal involvement, age of 50 years, or massive splenic disease[20]. A different prognostic scoring system has been developed for advanced stage HL by the International Prognostic Factor Project [4]. The present study defined seven variables:

being over 45 years of age, the presence of stage IV disease, being male, leukocyte count ≥15.000, lymphocyte count <600, albumin <4.0 g/dL and hemoglobin <10.5 g/dL. The 5-year PFS was 42% in patients with five or more factors, while the 5-year PFS was 84% in patients without negative prognostic factors.

In addition to sensitive and proven imaging methods, our study was conducted to be applicable to all patients and to be combined with standard imaging methods. Estimating advanced stage patients with the lymphocyte cutoff value that we obtained is important in terms of creating personalized treatment options. The most significant limitation of our study is that it could not be applied to HL subgroups and was not evaluated for the detection of stage 3-4 disease in combination with PET/CT.

CONCLUSION

In conclusion, our study found that a cutoff value of 2380/mm^3 for initial lymphocyte count with a sensitivity of 86.44% and specificity of 33.3% was associated with stage 3-4 disease in all HL patients in terms of initial lymphocyte count and stage relationship. This result can be improved in combination with conventional imaging methods used for staging purposes. Further studies may shed light on staging, particularly the diagnosis of advanced stage disease with high sensitivity.

Abbreviations

HL: Hodgkin lymphoma
cHL: Classical Hodgkin lymphoma
NLP-HL: Nodular lymphocyte-predominant Hodgkin lymphoma
NSHL: Nodular sclerosing Hodgkin lymphoma
LRHL: Lymphocyte-rich Hodgkin lymphoma
MCHL: Mixed cellular Hodgkin lymphoma
LDHL: Lymphocyte-depleted Hodgkin lymphoma
IPS: International prognostic score
AMC: Absolute monocyte count
ALC: Absolute lymphocyte count
PET/CT: Positron emission tomography/computed tomography
LMR: Lymphocyte-monocyte ratio
OS: Overall survival
PET/MRI: PET/magnetic resonance
DW-MRI: Diffusion-weighted MRI

Ethics approval and consent to participate

Ethical committee approval was received (Approval date and number: 2.10.2020/2528). The patients and control subjects provided their consent prior to the study. The experimental procedures were based on the Declaration of Helsinki and relevant institutional regulations.

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We respectfully remember all the colleagues we lost during the fight against COVID-19.

CONFLICT OF INTEREST

None to declare.

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