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THE PROGNOSTIC VALUE OF PERIPHERAL BLOOD ABSOLUTE LYMPHOCYTE TO MONOCYTE RATIO AT DIAGNOSIS IN HODGKIN'S LYMPHOMA PATIENTS

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ABSTRACT

Determination of prognostic factors in Hodgkin's Lymphoma patients plays an important role in reducing intensive chemotherapy, decreasing economic costs, and improving the outcome of the patients. We conducted this study to determine the prognostic value of [lymphocyte/monocyte ratio (LMR)] in Classical Hodgkin's Lymphoma patients (cHL) [trying to establish a relationship between it, overall survival (OS) & progression free survival (PFS)]. Also, we wanted to study the relationship between LMR and other variables such as age, sex, histological type, white blood cells, absolute lymphocyte count, absolute monocyte count, hemoglobin, serum albumin, Ann Arbor Staging, B-Syptoms, early or advanced stages, bulky mediastinal mass, type of primary treatment if chemotherapy alone or radiochemotherapy and the effect of these variables on OS and PFS. A retrospective study included 242 patients with cHL admitted to the center of radiochemotherapy in Tishreen University Hospital in Lattakia from January 2011 to December 2015. We monitored the patients until 1st September 2020. An LMR at diagnosis of 2.9 or more was the best cut-off value for survival. In univariate analysis, patients with LMR < 2.9 had inferior OS and PFS. LMR had an important prognostic value in patients with limited or advanced stages. In multivariate analysis, LMR was an independent prognostic factor for survival and to predict clinical outcomes in patients with classical Hodgkin's lymphoma. In conclusion, LMR provides a simple model to assess clinical outcomes in cHL

KEYWORDS: Hodgkin Lymphoma, Absolute lymphocyte count, Absolute monocyte count, Prognostic factors.

INTRODUCTION

Hodgkin lymphoma (HL) is the most common subtype of lymphoid neoplasm in patients younger than 40 years old. Despite modern treatment strategies improved overall survival (OS); approximately 20% of patients with classical Hodgkin lymphoma (cHL) will develop relapsed/refractory disease and will die.[1] The International Prognostic Score (IPS) uses seven prognostic factors to predict clinical outcomes in patients with newly diagnosed classical Hodgkin's lymphoma. However, the IPS only applies to patients with advanced stage disease,[2] but it does not fully reflect all the biologic spectrum of cHL and is less suitable for patients with limited stage disease[3] [i.e., stages I and IIA, without constitutional symptoms and no bulky disease (i.e. not ≥ 10 cm in diameter)]. Pathologically, cHL is characterized by the presence of a small number of diagnostic Reed-Sternberg cells in a background of reactive inflammatory cells composed of lymphocytes, neutrophils, macrophages, eosinophils, plasma cells, fibroblasts and collagen fibers.[4] Tumor-associated macrophages (TAMs) are derived from circulating monocytes and are recruited to the tumor site by soluble tumor-derived chemotactic factors.[5,6] Because TAMs originate from circulating monocytes, it is not surprising that the absolute monocyte count (AMC) or LMR may influence TAM content.[4] Recently, the peripheral blood absolute lymphocyte count (ALC)/absolute monocyte count (AMC) ratio at diagnosis in cHL patients was reported to be a prognostic factor for clinical outcomes.[7] How the peripheral blood AMC, LMR, and TAM content may interact with one another in cHL patients in conjunction with clinical outcome is unknown at the present.

We, therefore, studied the role of (LMR-DX), as a simple biomarker combining an estimate of host immune homeostasis [i.e., absolute lymphocyte count (ALC)/tumor- infiltrating lymphocytes][8,9] and tumor microenvironment [i.e., absolute monocyte count (AMC)/tumor-associated macrophages], on clinical outcomes in patients with cHL.[2] Major efforts have been also made to avoid possible overtreatment and potential long-term toxicity in younger patients and to identify patients requiring more aggressive therapy in order to avoid the development of refractory disease. In this regard, to define a scoring system that could stratify patients, and possibly even predict outcome, would be both helpful and practical to apply in daily practice.[10]

MATERIALS AND METHODS

We carried out a retrospective study of 242 patients with cHL who were admitted to the center of chemoradiotherapy in Tishreen University Hospital in Lattakia, between January 2011 and December 2015. We followed up the patients until 1st September 2020. Exclusion criteria were: Patients diagnosed with nodular lymphocyte predominant Hodgkin's lymphoma; age less than 14 years; previous history of malignancy, transplantation, or immunosuppression; positive for anti-HIV; and lack of laboratory data and follow-up information. Clinical characteristics were obtained from medical records. Patients or their guardians provided written informed consent to participate in the study. Routine follow-up imaging analyses were performed every 3 months for the first 2 years, then every 6 months for the next 3 years, and then annually or whenever clinically indicated. The ALC and AMC were obtained from the CBC examined at the time of the cHL diagnosis. The LMR was calculated by dividing the ALC by the AMC from the CBC.

End-points

The primary end-point of this study was to determine the prognostic value of LMR in Classical Hodgkin Lymphoma (studying the relationship between LMR, overall survival and progression-free survival from the moment that classical Hodgkin's lymphoma was diagnosed). The secondary end-point was to determine whether LMR has a prognostic value on clinical outcomes in patients with limited or advanced stage at diagnosis. Limited-stage was defined as stage IA and IIA, without B-symptoms and absence of bulky disease defined as any mass of 10 cm or more in diameter.

Prognostic Factors

The prognostic factors evaluated in the study included: age > 45 years, male gender, albumin <4 g/dl, white blood cell count > 15,000/µl, ALC < 600/µl or < 8% of white cell count, hemoglobin ≤ 10.5 g/dl, stage IV, primary treatment (chemotherapy plus radiation versus chemotherapy alone), limited versus advanced disease, AMC at diagnosis, LMR at diagnosis, histopathology type, bulky medistinal disease and B- Syptoms.

Response and Survival

The OS was defined as the time from the first day of diagnosis to the date of death or date of interrupted follow-up. PFS was defined as the time from cHL diagnosis to the time to progression, relapse from complete response, death as a result of any cause, or last follow-up.

Statistical analysis

OS and PFS were analyzed using the approach of Kaplan and Meier. Differences between survival curves were tested for statistical significance using the two-tailed log-rank test. The Cox proportional hazard model was used for the univariate and multivariate analyses to evaluate the variables under the prognostic factors' section to assess their impact on overall survival and progression-free survival. The choice of the best cutoff values of AMC-DX and the LMR ratio for assessing survival was based on their utility as a marker for the clinically relevant binary outcome of death/survival using the receiver operating characteristics curves (ROC) and area under the curve (AUC). Chi-square tests were used to determine relationships between categorical variables. The binary clinical outcome (death/survival) was established at 5 years after diagnosis. Patients were classified as "alive/censored" when the follow-up time was greater than 5 years and "death" for patients known to have died before this time point. All statistical analyses were performed using the IBM statistics (version20). The results were considered to be statistically significant when p-value < 0.05.

RESULTS

Patients' characteristics

Our study included 242 cHL patients, males were 141 patients (58.3%) and females were 101 patients (41.7%). The male to female ratio was 1.4:1. The median age at diagnosis was 31 years (range, 14-79 years). The distribution of additional baseline characteristics is presented in (Table 1). We recorded the death of 28 patients (11.6%) who died due to relapse/progression of lymphoma. The estimated 5-year OS rate was 88.4% and 5-year PFS was 75.6%.

Table 1: Demographic and clinical characteristics of patients.

Characteristic at diagnosis	No. of patients (%)
Age, median (range, years)	31 (14 – 97)
Male gender	58.3%
Histologic subtype	
Nodular sclerosis	65.2%

Mixed cellularity	30.2%
Lymphocyte-rich	2.9%
Lymphocyte-depleted	1.7%
Not classifiable	6.2 %
Ann Arbor stage	
I	5%
II	44.2%
III	33%
IV	17.8%
Stage (limited versus advanced)	
Limited	13.2%
Advanced	86.8%
B symptoms present	82.2%
Primary treatment	
Chemotherapy	59.1%
Chemoradiotherapy	40.9%
Mediastinal bulky disease	
≥10cm	9.9%
< 10cm	34.7%

Cut-off values for absolute monocyte count at diagnosis, ratio of absolute lymphocyte count to absolute monocyte count for survival analysis

The ROC curves of the LMR according to survival were generated to determine the appropriate cut-off value. For all patients, the area under the curve for the LMR was recorded as 0.62[95% confidence interval (CI): 0.4 to 0.7]. An LMR value of 2.9 corresponded to the maximum joint sensitivity and specificity on the ROC curve for all patients (74% sensitivity and 76% specificity). An AMC-DX of 720 cells/mL or more had an AUC of 0.66 [95% confidence interval (CI): 0.4 to 0.6] with a sensitivity of 73% and specificity of 74%.

Comparison of patients with LMR values ≥ 2.9 to those with values < 2.9

Characteristics are summarized according to whether patients presented with an LMR of 2.9 or more versus less than 2.9 in (Table 2). In this study, 70 patients (28.92%) had an LMR < 2.9, and 172 patients (71.08%) had an LMR ≥ 2.9. Higher numbers of patients in the group with LMR greater or equal to 2.9 had an albumin concentration of 4 g/dL or more (P=0.001). Fewer patients in the group with LMR of 2.9 or more presented with an ALC less than 600 cells/mL or less than 8% of the white blood cells (P=0.01), hemoglobin ≤ 10.5 g/dl (P=0.02), white blood cells > 15000×10^9 (P=0.0001) and also fewer numbers come with advanced stage (P=0.02), have B- Syptoms (P=0.006) and bulky medistinal mass (P=0.04). No difference between the groups was observed regarding age (P=0.07), male gender (P=0.6), chemotherapy regimens (P=0.7), Ann Arbor Staging (P=0.6) and histopathological type (P=0.7).

Table 2: Characteristics of the patients divided according to LMR ratio ≥ 2.9 versus < 2.9.

Characteristics	LMR ≥ 2.9 (N =172)	LMR < 2.9 (N =70)	P- value
At diagnosis Age, years, median (range)	29 [14-65]	32 [14-79]	0.06
Gender Male Female	99(57.56%) 73(42.44%)	42(60%) 28(40%)	0.6
Histology			
Nodular sclerosis	109 (63.4%)	48 (68.6%)	
Mixed cellularity	54 (31.4%)	19 (27.1%)	0.7
Lymphocyte-depleted	6 (3.5%)	2 (2.9%)	
Lymphocyte-rich	3 (1.7%)	1 (1.4%)	
Stage			
I	10(5.8%)	2(2.9%)	
II	77(44.8%)	30(42.9%)	0.6
III	54(31.4%)	26(37.1%)	
IV	26(15.15%)	17(24.29%)	
Stage			
Limited	28(16.3%)	4(5.7%)	0.02
Advanced	144(83.7%)	66(94.3%)	

Mediastinal bulky disease			
≥10cm	13(17.33%)	11(33.33%)	0.04
< 10cm	62(82.67%)	22(60.67%)	
Treatment			
Chemotherapy	103(59.9%)	40(57.1%)	0.7
Chemotherapy and radiation	69(40.1%)	30(42.9%)	
IPS risk factors			
Age in years > 45	48(27.9%)	12(17.1%)	0.07
≤ 45	124(72.1%)	58(82.9%)	
Albumin (g/dL)(N =174) ≥ 4 < 4	54(45%) 66(55%)	14(25.9%) 40(74.1%	0.001
Hemoglobin (g/dL) > 10.5 ≤ 10.5	115(66.9%) 57(33.1%)	36(51.4%) 34(48.6%)	0.02
White blood cell count×$(10)^9$ > 15 ≤15	33(19.2%) 139(80.8%)	31(44.3%) 39(55.7%)	0.0001
Absolute lymphocyte count×$(10)^9$ ≥ 600 < 600	171(99.4%) 1(0.6%)	66(94.3%) 4(5.7%)	0.01
Male	99(57.56%)	42(60%)	0.6
Stage 4	31(18%)	12(17.1%)	0.6

LMR denotes absolute lymphocyte count/absolute monocyte count at diagnosis; IPS: International Prognostic Score.

Prognostic significance of LMR

For patients, those with LMR < 2.9 had a significantly lower survival compared with those with LMR ≥2.9 (5-year OS: 81.4% vs 91.9%, p = 0.03; and 5-year PFS: 67.1% vs 79.1%, p = 0.04) (Fig .1). In Univariate Analysis, Patients with an AMC- DX of 720 cells/mL or more had inferior overall survival and progression-free survival compared with patients with an AMC-DX of less than 720 cells/mL [overall survival: median 6.1 years versus 6.4 years P=0.03]; [progression-free survival: median 4.9 years versus 5.3 years, P=0.03]. Patients with an LMR of 2.9 or more had superior overall survival and progression-free survival compared with patients with an LMR less than 2.9 [overall survival: median 6.4 years versus 5.9 years, 5-year overall survival rates of 91.9% versus 81.4%, p=0.03; progression-free survival: median 5.5 years versus 4.7 years, 5-year progression-free survival rates of 79.1% versus 67.1%, P=0.04]; Neither age nor gender of patients was predictive of overall survival or progression-free survival compared with the other prognostic factors studied (Table 3). In Multivariate Analysis, LMR remained an independent prognostic for overall survival and progression-free survival (Table 3).

Table 3: Univariate and multivariate analysis for overall survival (OS) and progression-free survival (PFS).

Covariate	Univariate analysis					
	OS			PFS		
	HR	95%CI	P value	HR	95%CI	P value
Age (>45years)	0.6	[0.2-1.7]	0.8	0.4	[0.2-1.5]	0.3
Male	0.7	[0.3-1.5]	0.3	0.6	[0.2-1.5]	0.4
WBC (> 15) ×10^9	2.5	[1.2-5.3]	0.01	2.3	[1.1-5.2]	0.01
ALC-DX cells/mL < 600	4.2	[1.1-8.9]	0.004	3.1	[0.9-6.4]	0.002
AMC-DX cells/mL ≥ 720	2.1	[0.3-8.9]	0.03	2.5	[0.9-7.1]	0.03
LMR < 2.9	2.6	[1.2-5.4]	0.001	2.4	[0.1-1.8]	0.003
Albumin (< 4) g/dL	1.6	[0.1-1.9]	0.04	1.7	[0.1-1.7]	0.01
Hemoglobin g/dL (≤ 10.5)	2.4	[1.1-4.9]	0.02	2.3	[1.1-4.9]	0.02
Bulky disease (≥ 10cm)	1.9	[0.3-4.6]	0.03	1.6	[0.4-2.7]	0.04
Stage 4	1.3	[1.2–1.8]	0.02	1.4	[0.1–1.8]	0.02

CT and RT versus CT alone	1.4	[0.1–1.8]	0.01	1.3	[0.1–1.7]	0.01
Covariate	Multivariate Analysis					
	OS			PFS		
	HR	95%CI	P value	HR	95%CI	P value
LMR < 2.9	2.3	[1.2-6.3]	0.01	2.1	[1.3– 6.2]	0.02

ALC-DX: absolute lymphocyte count at diagnosis; AMC-DX: absolute monocyte count at diagnosis; LMR: lymphocyte count/ monocyte count ratio, CT: chemotherapy; RT: radiation; WBC: white blood cell count.

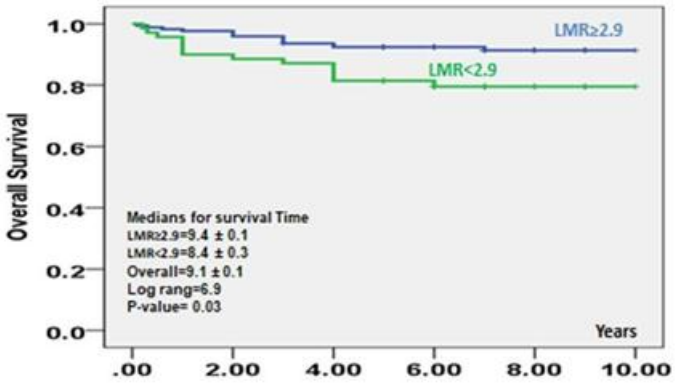
Survival based on the ratio of absolute lymphocyte count to absolute monocyte count at diagnosis by limited/advanced stage at diagnosis

Patients with an LMR of 2.9 or more had superior clinical outcomes compared with patients with an LMR Less than 2.9 regardless of limited stage (5-year overall survival rates of 100% versus 75%, p=0.007) or advanced stage (5-year overall survival rates of 90.3% versus 80.3%, p=0.4) (Table 4).

Table 4: Clinical outcomes based on the LMR at diagnosis according to patients'stage at diagnosis.

	Advanced stages		Limited stages	
	OS	P-value	OS	P-value
LMR ≥ 2.9	90.3%	0.04	100%	0.007
LMR < 2.9	80.3%		75%	

A



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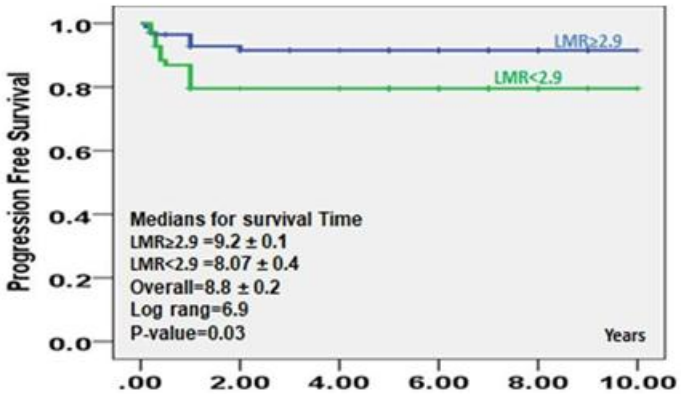

Figure 1: Comparison of the survival using the cutoff value of 2.9 for LMR at diagnosis. (A): Overall survival and (B) progression-free survival.

DISCUSSION

Recently, the AMC and ALC/AMC ratio at diagnosis (LMR) have been used as prognostic factors to identify high-risk patients with lymphoma.[11,12,13] Although the differentiation between cut off values reported in the various studies, similar results were obtained by different working groups, indicating that monocytosis or lymphopenia at diagnosis has an adverse impact on survival in patients with HL.

The LMR representing a surrogate biomarker for the interaction between host immunity and tumor microenvironment has been reported to predict clinical outcomes, specifically PFS and OS in cHL. We, therefore, studied the LMR as representative markers of the interaction between tumor burden, host immunity, and tumor microenvironment to further stratified clinical outcomes in cHL. To support the hypothesis that the LMR can further stratified PFS and OS in cHL patients, it was necessary to demonstrate that the LMR was an independent predictor of PFS and OS. By univariate analysis, we determined that patients presenting with an AMC-DX of 720 cells/µL or more had an inferior survival of OS and PFS. LMR of 2.9 or more was associated with superior overall survival and progression-free survival. By multivariate analysis, LMR remained an independent prognostic factor for survival when compared to these prognostic factors. Furthermore, patients in the group with an LMR less than 2.9 tended to have adverse features, including advanced stage (i.e., tumor burden), suggesting an impact of host immunity (i.e., ALC) versus tumor microenvironment (i.e., AMC) on tumor growth control. Our results also demonstrated that a lower LMR was associated with worst prognostic factors such as a hemoglobin level of less than 10.5 g/dl, a WBC count of more than15,000 cells/mm^3, and an albumin level of less than 4 g/dl. A limitation of the IPS scoring system is that it only applies to patients with advanced stage classical Hodgkin's lymphoma and not to those with limited stage disease. We, therefore, investigated the prognostic value of LMR to assess survival in patients with limited and advanced stage disease. The LMR was able to discriminate clinical outcomes not only in patients with limited or advanced stage disease. In our study a low LMR was associated with the OS and PFS outcomes. In comparison with global studies, Porrata et al. used the cutoff of 1.1, and LMR was an independent prognostic factor for OS and PFS in a series of 476 patients with classical HL.[7] In a Korean analysis of 312 patients with classical HL, the cutoff of 2.9 was used, and LMR correlated with OS, but not event-free survival.[4] In this study, LMR was also negatively, albeit moderately, correlated with TAM content, estimated by immunohistochemistry. The largest series of HL patients that has been analyzed for the prognostic impact of AMC and LMR ratio was recently reported by Tadmor et al.[10] Data on 1,079 patients treated with ABVD (43%) or BEACOPP-like CT (29%) were initially presented in abstract form by Sacchi et al., and the cutoff of 1.5 was proposed.[10] The adverse prognostic effect of LMR, 1.5 was independent of IPS or CT regimen used. Strength of our study, the LMR combines the clinical surrogate biomarkers for the inflammatory, pathological biomarkers – tumor-infiltrating lymphocytes and tumor- associated macrophages – which directly affect the biology of classical Hodgkin's lymphoma. Secondly, LMR is a simple, easily determined clinical biomarker that can be used to assess the clinical outcome in limited and advanced stages of classical Hodgkin's lymphoma. Thirdly, we report the clinical value of a single biomarker (LMR) to assess clinical outcomes in classical Hodgkin's lymphoma based on a widely available, inexpensive, routine clinical test: the complete blood count.

A major limitation of this study is that formal investigations of the tumor microenvironment in this population were not performed. Future researches should correlate the peripheral blood absolute lymphocyte count and monocyte count with microenvironmental data. Other limitations of this study include the retrospective nature of it and the short follow-up period of some recent cases. Further studies, including prospective clinical trials, are required to investigate the effect of the LMR on clinical outcomes, and to confirm the present findings. In conclusion, LMR is a single, low cost, predictive biomarker for clinical outcomes in classical Hodgkin's lymphoma.

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