Original Article

RELATIONSHIP OF PERIPHERAL BLOOD LYMPHOCYTE/ MONOCYTE RATIO WITH CLASSICAL HODGKIN'S LYMPHOMA STAGE AT THE TIME OF DIAGNOSIS AND ITS UTILITY AS PROGNOSTIC FACTOR

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Abstract:

Introduction: Hodgkin lymphoma, a prevalent neoplasm in our part of the world requires the simplest investigations that can overview prognostic features.The objective of this study is to examine the lymphocyte-monocyte ratio (LMR) in various stages of classical Hodgkin's lymphoma (cHL) as defined by Ann Arbor Staging System and to study the relationship of LMR with the overall survival of the patients.

Materials & Methods: A prospective cohort study was done at the Department of Pathology, King Edward Medical University, Lahore from June 2019 to June 2024. Eighty patients were enrolled after informed consent. Clinical parameters included age, gender, and clinical stage. Laboratory parameters included histology, serum albumin, Hemoglobin (Hb), Total leukocyte count, ALC, and AMC with 3-year overall survival. LMR was calculated from the EDTA sample taken and overall survival in each stage was recorded.

Results: Out of eighty patients, 78.8% were males. The mean age was 40.9±14.8 years. LMR was highest in stage I and lowest in stage IV. Lower LMR was associated with inferior overall survival.

Conclusion: LMR at diagnosis is inversely related to disease stage in cHL and patients with low LMR have a poor disease outcome. This relationship with stage can be used to predict the clinical outcome in patients with cHL in resource limited countries.

Keywords: Classical Hodgkin lymphoma, absolute lymphocyte count, absolute monocyte count, lymphocyte/monocyte ratio, and survival rate.

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INTRODUCTION

The tumor microenvironment plays a pivotal role in the growth and survival of malignant cells.[1]

Classical Hodgkin lymphoma (cHL) is characterized by the presence of neoplastic Reed Sternberg cells in an inflammatory background which represents tumor microenvironment.[2] Of these, lymphocytes and macrophages are associated with clinical outcomes in cHL. Recently, the peripheral blood LMR has gained attention as a predictor of disease outcome in cHL.[3] There is a variation in cut offs of LMR from <1.1 to 1.5 and 2.9 as independent prognostic indicators in quoted literature.[4,5] Moreover, consensus is lacking to incorporate this biological marker (LMR) into currently

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validated prognostic scoring systems along with acceptable risk factors for disease monitoring.

According to a collective cancer registry report from Shaukat Khanum Memorial Cancer Hospital and Research Center 1994-2023, Hodgkin lymphoma is the 6th most common tumor in Pakistan and the commonest malignancy in the pediatric population constituting about 21.6% of all malignancies in the age group < 18 years.[6,7] So far, there has not been any study that has solely explored LMR and its relationship with prognostic factors in cases of classic Hodgkin lymphoma in the setting of our country. Considering this fact, the study was designed and conducted to examine LMR in various stages of Hodgkin's disease and to study its relationship with overall disease survival. The LMR prognostic score, obtained from a globally available test such as complete blood count (CBC) at diagnosis combines an estimate of host immune status and tumor microenvironment. This is one of the easiest and most inexpensive tests ever used in any predictive model.[8] The objective of this study was to examine the lymphocyte monocyte ratio (LMR) in various stages of classical Hodgkin's lymphoma (cHL) as defined by Ann Arbor Staging System and to study the relationship of LMR with the overall survival of the patients.

MATERIALS & METHODS

This prospective cohort study was designed and conducted in the Department of Pathology at King Edward Medical University, Lahore, and included cases from June 2019 to June 2022. Purposive sampling was done. No patients refused their authorization to use their medical records for research and none was lost to follow up. The inclusion criteria was newly diagnosed cases of cHL were enrolled and followed for 3 years. The exclusion criteria was the patients who had received any chemotherapy in the past, history of malignancy or immunosuppression, HIV positivity, or those diagnosed as nodular lymphocyte predominant Hodgkin lymphoma were excluded to minimize selection bias.

Patients were treated with ABVD chemotherapy according to the standard protocol: 2-4 cycles for the early stage and 4-6 cycles for the advanced stage.

The clinical parameters including age, gender, clinical stage, and laboratory parameters including histology, serum albumin, Hemoglobin (Hb), Total Leucocyte Count, (TLC), ALC, AMC, and disease stage were evaluated. The ALC and AMC were obtained from CBC performed at the time of diagnosis and LMR was calculated. The overall survival in each group of the disease was recorded and analyzed. The prognostic factors assessed were age >45 years, male gender, Hb <10.5 g/dL, TLC ≥15 x 109/L, ALC <600 x 109/L, serum albumin <4 g/dL and stage IV (Blombery P and Linch D, 2016)

Statistical analysis was done using SPSS version 23. Frequencies and percentages were calculated for categorical data while mean with standard deviation and median (IQR: Q1-Q3) for quantitative data. Shapiro-Wilk and Kolmogrov Smirnov test was used to assess the normality of quantitative variables. The overall survival (OS) time was defined as the time between the first day of diagnosis and the date of death from any cause.[7] The follow-up period was 3 years. Kaplan and Meier's method was employed for overall survival analysis. Log-rank test was used to analyze the differences between survival curves. The prognostic factors for survival were analyzed through univariate and multivariate Cox proportional hazard models. Chi-squared tests Fisher's exact test or likelihood ratio test were used to determine relationships between categorical variables as appropriate. Independent sample t-test or Mann-Whitney U test was used to determine the difference between continuous variables. All P values are two sided and a P value of

less than 0.05 is considered statistically significant. Receiver Operating Curves (ROC) were generated for LMR. The 1.7 cut off value having the highest AUC (0.77) with a significant P value (0.011) was chosen.

RESULTS

A total of 80 patients were enrolled, 63 (78.8%) were males. The mean age was 40.9± 14.8 years (range 15-75 years). Stage I was seen in 3 (3.8%), stage II in 37 (46.3%), stage III and stage IV each in 20 (25%). Mixed Cellularity was the most common histology 64 (80%), followed by Nodular Sclerosis 12 (15%), Lymphocyte Rich 3 (3.8%) and Lymphocyte Depleted 1 (1.3%). Mean was calculated for CBC parameters with normal distribution whereas median were calculated for the parameters not following normal distribution. The mean Hb was 11±3.5 g/dL. Median TLC was 8.4(6.7-12.7x10^9/L, median platelet count was 222.9(220.4-232.8x10^9/L, median ALC was 1.8(1.2-2.7) x10^9/L, median AMC was 0.4(0.2-0.6) x10^9/Land median serum albumin was 3.7(2.3-6.5g/dL. Mean Hb, TLC and LMR differed significantly between early and advanced-stage disease ($p<0.05$). (Table 1)

Table 1: Difference in mean Hb, TLC, serum albumin and LMR between early and advanced stage disease

Characteristics	Stage I/II	Stage III/IV	P value
Age (years)	41.2±16.3	40.7±13.4	0.881
Gender			
Male	26 (65%)	37 (92.5%)	0.003
Female	14 (35%)	3 (7.5%)	
Median serum albumin (g/dL)	4.1 (2.3-6.8)	3.3 (2.3-6.3)	0.365
Mean Hb (g/dL)	11.9±3.1	10.2±3.7	0.035
Median TLC	8.4 (7.6-13.2)	7.5 (5.8-10.5)	0.025
Mean LMR difference	9.9±1.1	5.6±1.3	<0.001

The characteristics of study population summarized according to LMR ≥1.7versus <1.7 are presented in Table 2. (Table 2)

Table 2: IQR according to LMR

Characteristics	LMR ≥1.7 (N=72)	LMR ≤1.7 (N=8)	P value
Age			
Median (IQR)	38.0 (25.3-50.0)	27.0 (22.8-32.3)	0.170

A higher number of patients in the group with LMR ≥1.7 had ALC ≥ 600x10^9/L ($p=0.042$) and AMC <900x10^9/L ($p=0.001$). No difference was observed regarding age ($p=0.674$), male gender ($p=0.192$), Hb ($p=0.068$), histology ($p=0.107$), stage IV disease ($p=0.085$), TLC ($p=0.143$), platelet count (p+0.640), limited vs advanced stage disease ($p=0.712$) and IPS score≥3 ($p=0.197$). The median survival time was 5.1 years with a range of 3.0 to 5.6 years. In univariate analysis, Hb ≤10.5g/dL, ALC <600 X 10^9/L, AMC ≥ 900 x 10^9/L, LMR ≥ 1.7, and stage IV and IPS index >3 were independent risk factors of poor OS. In multivariate analysis, Hb ≤10.5g/dL, AMC ≥900 X 109/L, stage IV and IPS index ≥3 were independently associated with poor OS. (Table 3)

Table 3: Evaluation of clinic-pathological variations between different stages of Hodgkin's Lymphoma and their relationship in IPSS scoring.

Gender			
Male	55 (76.4%)	8 (100%)	0.192
Female	17 (23.6%)	0 (0%)	
Histology			
Lymphocyte Dominant	01 (1.4%)	1 (12.5%)	0.17
Lymphocyte Rich	03 (4.2%)	0 (0%)	
Mixed Cellularity	59 (81.9%)	5 (62.5%)	
Nodular Sclerosis	09 (12.5%)	2 (25%)	

Hb			
Mean SD	10.8±2.7	9.0±1.4	0.068
Stage			
I	3 (4.2%)	0 (0%)	0.357
II	35 (48.6%)	3 (37.5%)	
III	19 (26.4%)	1 (12.5%)	
IV	15 (20.8%)	4 (50%)	
Limited vs. advanced Disease			
I & II (limited)	37 (51.4%)	3 (37.5%)	0.712
III & IV (advanced)	35 (48.6%)	5 (62.5%)	
TLC			
Median	7.5 (5.7-10)	9.6 (07-17.1)	0.138
Platelets			
Median	220 (146.3-356.8)	344.5 (166.3-459.8)	0.262
IPS			
Age			
>45 years	20 (27.8%)	1 (12.5%)	0.674
<45 years	52 (72.2%)	7 (87.5%)	
Hb g/dL			
≥ 10.5	44 (61.1%)	2 (25%)	0.066
≤ 10.5	28 (38.9%)	6 (75%)	
TLC x 109			
≥ 15	5 (6.9%)	2 (25%)	0.143
≤ 15	67 (93.1%)	6 (75%)	
Platelets x 10^9			
≤ 150	13 (18.1%)	2 (25%)	0.640
≥150	59 (81.9%)	6 (75%)	
ALC x 10^9			
≥ 600	66 (91.7%)	5 (62.5%)	0.042
≤ 600	6 (8.3%)	3 (37.5%)	
AMC x 10^9			
≥ 900	70 (97.2%)	4 (50%)	0.001
≤ 900	2 (2.8%)	4 (50%)	
Stage IV	16 (22.2%)	04 (50%)	0.085
IPS factor index	≥ 3 ≤3	17(23.6%) 55 (76.4%)	0.197

Five patients died of causes other than disease or its treatment. Overall survival (OS) at 5 years for stage I was 91% (88-95%), stage II; 88% (83-90%), in Stage III; 71% (68-75%) and in stage IV; 64% (58-69%).

The LMR correlated significantly with overall survival (p< 0.001). However, there was no significant variation of LMR between different histological subtypes of cHL (p 0.656). Of the studied variables, female gender, early stage of the disease, those with Hb >10.5g/dL, ALC>600 x 10^9/L, AMC<900 x 10^9/L, IPS sore<3 and LMR ≥1.7 had a superior overall survival. **(**Figure 1).

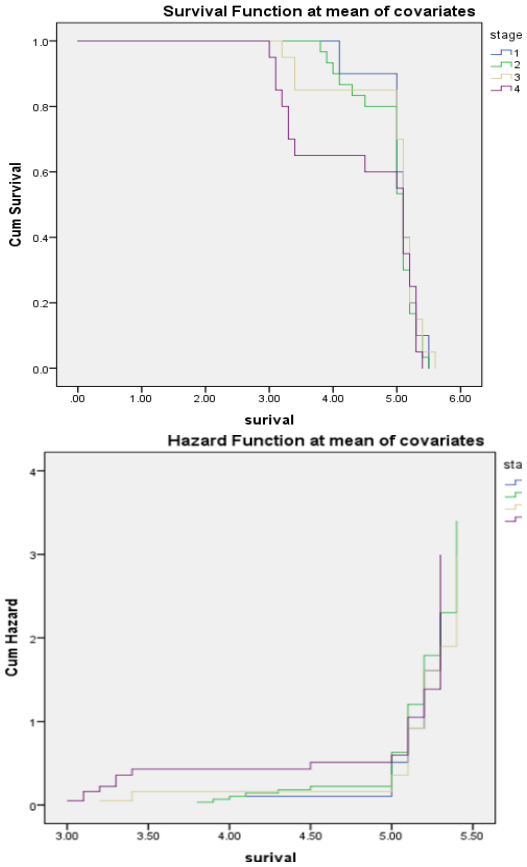

Figure 1: Overall survival in different stages of Hodgkin Lymphoma.

DISCUSSION

The mean age of our patient population was 40.9 years in comparison with 32 years Bolukbasi et al[9] and 36.4 years.[5] This slight difference may be attributed to the late access of the patients to the tertiary care centers in

developing countries either due to lack of awareness, mishandling by quacks or Hakeem, or financial constraints. The majority of our patients were males (78.8%) in contrast to females in the study of Mexico by Perez R et al[10] who found 59% of females and 41% of males to be affected. Male patients were found to be 50% more suffering from cHL (following data from USA.[11] UK cancer registry[12] highlights 58% affected males and 42% affected females. The most common histological pattern in the present study was mixed cellularity (80%) followed by nodular sclerosis (15%). This is similar to another study from Pakistan which mentions 63.8% mixed cellularity followed by 19% nodular sclerosis.[13] While according to another study[14] the most frequent histological pattern was nodular sclerosis (77.4%). This variability is consistent with WHO data on developing vs developed countries. Fifty percent of our patients were at an advanced stage at diagnosis; a pattern consistent with Pakistani data from another study.[15]

B symptoms were seen in 40% and bone marrow was involved in 25% of our patients. According to an Australian study, 44% and 11% had B symptoms and bone marrow involvement respectively.[16]

Serum albumin <4g/dL was seen in 71% of our patients in whereas in a previous study it was 58%.[16]

Bulky disease was seen in 11.3% and LDH was elevated in 15% of our patients. These levels were different from similar previous studies.[17,18]

Our study showed that patients with higher LMR scores were younger and had higher levels of Hb and serum albumin; very similar to a previous study.[20] The findings of study reported Porrata LF et al[20] are similar in terms of younger age and high serum albumin levels; however, they didn't report much difference in Hb values among their patients. A previous study[16] stated that the prognostic value of LMR is particularly significant in nodular sclerosis subtype histology. However, we could not find any statistical difference in LMR between different histological subtypes (p=0.820).

Our study showed that LMR varies inversely with disease stage i-e. LMR decreases as disease advances consistent with the evading of anti-tumor immunity by malignant cells. We found a statistically significant difference in LMR values between early and advanced stage disease (p <0.001). Our study also showed that a lower LMR at diagnosis is an independent prognostic marker associated with overall inferior survival.

Our findings are in consistent with a meta-analysis of eight studies done in 2019.[19] As LMR is associated with the stage of the disease, this can reflect upon prognostic sub grouping of cHL patients even before the results of time consuming staging investigations have been received. This association becomes relevant to predict clinical sequelae in cHL patients in countries such as Pakistan where financial constraints and unequal distribution of standardized diagnostic facilities pose a big hurdle in the delivery of healthcare services across different areas.

CONCLUSION

LMR is inversely related with disease stage at the time of the diagnosis and patients with low LMR have an inferior overall survival. This association can be useful to predict disease course in cHL by utilizing a routinely available and simple test such as CBC without extra financial burden on the patient and compromised health resources in developing countries like Pakistan.

AUTHOR'S CONTRIBUTION

US: Conceptualization
RM: Conceptualization, Formulation of Data Collection Form
HSP: Data Collection, Manuscript Writing
MNK: Review, Manuscript Writing

MTR: Data Collection, Manuscript Writing
MAN: Data Collection, Statical Analysis Assistance

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