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ORIGINAL ARTICLE

Clinicohematological profile and treatment outcomes of Hodgkin's Lymphoma- a single center experience from Pakistan.

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ABSTRACT… Objective: To evaluate the epidemiological and clinical characteristics, along with treatment outcomes of Hodgkin's lymphoma patients in Pakistan. **Study Design:** Prospective Cross Sectional study. **Setting:** National Institute of Blood Diseases and Bone Marrow Transplantation (NIBD), Karachi, Pakistan. **Period:** January to December 2024. **Methods:** This was a cross sectional study comprising 22 patients diagnosed with HL as per WHO Classification who presented at National Institute of Blood Diseases and BMT Karachi Pakistan from January to December 2024. The quantitative variables were represented as mean (SD), while nominal variables were presented as frequency and percentages by using SPSS 25 version and STATA 15 version. The Kaplan Meier analysis and log rank test was done for survival analysis. **Results:** A total of 22 HL patients were included in the study. The mean age of the study participants was 31.7±18.7 years. In the study, 63.6% of the patients were male, while 36.4% were female. B symptoms were present in 86.4% of the patients. Hepatomegaly, was noted in 27.3, while splenomegaly, was observed in 45.5% of patients. The Hb level in the cohort was above 10.5 g/dl in the majority (63.7%), while 36.3% had anemia. LDH is a marker of tissue damage, and in this cohort, 63.7% of patients had LDH levels higher than 220 U/L, indicating ongoing cellular breakdown or tissue damage. The site of tissue diagnosis in the study primarily involved cervical lymph nodes (72.8%), followed by Axillary (13.7%) and inguinal (9.1%) lymph nodes. The 90 months overall survival in 22 patients was 73.5%. **Conclusion:** The present study revealed the detailed clinical hematological and treatment outcome of HL patients in Pakistan. However, multicenter studies with larger sample size are needed to validate the findings and enhance treatment strategy especially for relapse patients.

Key words: Clinico-hematological Characteristics, Hodgkin's Lymphoma (HL), Overall Survival, Treatment.

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INTRODUCTION

Hodgkin's lymphoma (HL) is a rare malignancy accounting for 0.4% of newly diagnosed cancer cases and 0.2% cancer related deaths worldwide annually.[1] However, in the recent years there has been a rise in the incidence rates and a shift in epidemiological trends with increasing rates observed among females, younger patients and the Asian population.[2]

Remarkable variations in the incidence, histological subtypes, and mortality rates have been reported across different geographical regions. While higher incidence rates are noted in developed countries, contrarily, mortality rates are higher in Asian countries.[2,3] Several etiological and prognostic factors have been implicated in the pathogenesis and clinical diversity of the disease including genetic factors, environmental influences, and/or the interaction of these two elements.

Genome wide association studies have identified human leukocyte antigen (HLA) and non-HLA loci associated with the risk of developing HL and have also proposed immune dysregulation and infections as key regulators in the pathogenesis.[4,5] Viral infections such as Epstein-Barr virus (EBV) and human immunodeficiency virus (HIV) are associated with the development of HL by causing deoxyribonucleic acid (DNA) damage. Environmental determinants of disease burden include exposure to ionizing radiation, alcohol use, obesity, hypertension, smoking as well as socioeconomic status.[2,6,7] While these factors have been extensively studied in western populations, there is still a need for further research in developing countries.

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With the recent advancements in treatment strategies and introduction of new drugs such as check point inhibitors there has been substantial improvement in the treatment outcomes.[8,9] However due to disease heterogeneity, differing patient characteristics and, the challenges faced in low socioeconomic countries such as Pakistan, treatment outcomes are not as favorable as in the developed world. Additionally, there is limited published data on the clinico-pathological features and treatment outcomes of HL patients in our country.

This study was aimed to evaluate the epidemiological and clinical characteristics, along with treatment outcomes of Hodgkin's lymphoma patients presenting at one of referral hematology center in Pakistan, in order to highlight the disease characteristics indigenous to our population.

METHODS

This was a cross sectional study comprising patients diagnosed with HL as per WHO Classification, including both newly diagnosed and relapse/ refractory cases who presented at National Institute of Blood Diseases and Bone Marrow Transplantation (NIBD-BMT), Karachi Pakistan from January to December 2024 after institutional review board approval (NIBD/IRB- 281/01-2025). A total of 22 patients (aged 12 years and above) were enrolled, including 13 treatment-naive, and 9 with relapse/ refractory disease (who had received primary treatment from some other center at Pakistan). The study was approved by the hospital institutional review board. Demographic variables like age, gender, Eastern Cooperative Oncology Group (ECOG) performance status (PS), physical examination, fever (>38.6°C), weight loss (>10% of body weight in 6 months), Ann Arbor stage, and existing comorbidities were documented.

Imaging was performed using whole-body fluorodeoxyglucose (FDG) positron emission tomography (PET) preferentially or computerized tomography (CT) neck, chest, abdomen and pelvis with contrast in cases of non availability of PET imaging. Bone marrow (BM) biopsy was performed in patients who had CT imaging instead of PET scan. Baseline complete blood count (CBC), renal, hepatic profile, lactate Dehydrogenase (LDH), viral markers, Echo and pulmonary function tests (PFTs) were performed as part of pre treatment evaluation.

The disease staging and prognostication was performed as per British journal of hematology (BJH) guidelines into early stage (Stage I and II) and advanced stage (Stage III and IV) disease. Early stage was further classified into favorable and unfavorable risk group as per European organization for research and treatment for cancer (EORTC). The Hodgkin International Prognostic Index [IPI] on the basis of the following criteria [i.e., Hemoglobin (Hb), age, gender, disease stage, white blood counts (WBC), absolute lymphocyte count(ALC), and serum albumin were calculated for patients with advanced stage disease.

All treatment naïve patients received 6 cycles of ABVD (Adriamycin, bleomycin, vinblastine, and dacarbazine) as the standard regimen. None of the patient received radiotherapy due to non availability at the institute. Relapse/ refractory patients were offered salvage regimen (ICE/DHAP/BV-B) as per availability and patients who underwent remission were consolidated with autologous stem cell transplant (ASCT). Response assessment was done via PET scan at two time points, interim imaging (after 2 cycles) and end of treatment. Patients were then followed up 6 monthly via CT imaging. Comprehensive physical examination and blood counts were performed on follow-up visits every 3 months.

Statistical Analysis

The quantitative variables were represented as mean, standard deviation (SD), while nominal variables were presented as frequency and percentages. The Shapiro-wilk test for normality evaluation of quantitative variable was utilized. To evaluate the differences in alive and dead patients two independent sample t-test for numeric variables Fisher Exact test for nominal variables were applied. Kaplan Meier curves and log rank test was done for survival analysis. SPSS 25 version and STATA 15 version were utilized for statistical test and presentation of data. The p-value equal or <0.05 was considered statistically significant.

RESULTS

A total of 22 HL patients were included in the study. The mean age of the study participants was 31.7±18.7 years. In the study, 63.6% of the patients were male, while 36.4% were female. Co-morbidities were present in 18.1% of the participants. The mean (SD) follow up was 29 (24) months. The most commonly affected region by lymphadenopathy was the cervical region, with 77.3% of patients presenting with cervical lymphadenopathy. With respect to infection at the time of presentation, 91% of the cohort did not present with an infection, however 9% of patients had infection at presentation. B symptoms were present in 86.4% of the patients. Hepatomegaly, was noted in 27.3, while splenomegaly, was observed in 45.5% of patients.

The Hb level in the cohort was above 10.5 g/dl in the majority (63.7%), while 36.3% had anemia. LDH is a marker of tissue damage, and in this cohort, 63.7% of patients had LDH levels higher than 220 U/L, indicating ongoing cellular breakdown or tissue damage. The site of tissue diagnosis in the study primarily involved cervical lymph nodes (72.8%), followed by axillary (13.7%) and inguinal (9.1%) lymph nodes. The various clinical characteristics at disease presentation are depicted in Table-I and Figure-1.

(%): Percentage, BM: Bone Marrow, cHL: Classical Hodgkin's Lymphoma, CT: computed tomography, LDH Lactate Dehydrogenase, LTF: Lost to follow up, MCHL: Mixed Cellularity-Hodgkin's Lymphoma, N/A:Not Available, n:Number, NSHL: Nodular Sclerosis Hodgkin's Lymphoma, PET-CT: Positron Emission Tomography-Computed Tomography, WBC: White Cells Counts

The demographics, hematological characteristics and diagnosis methods were compared in dead and alive patients but no significant results were established. (Table-II)

FIGURE-1.

Flow chart showing outcome of patients with HL.

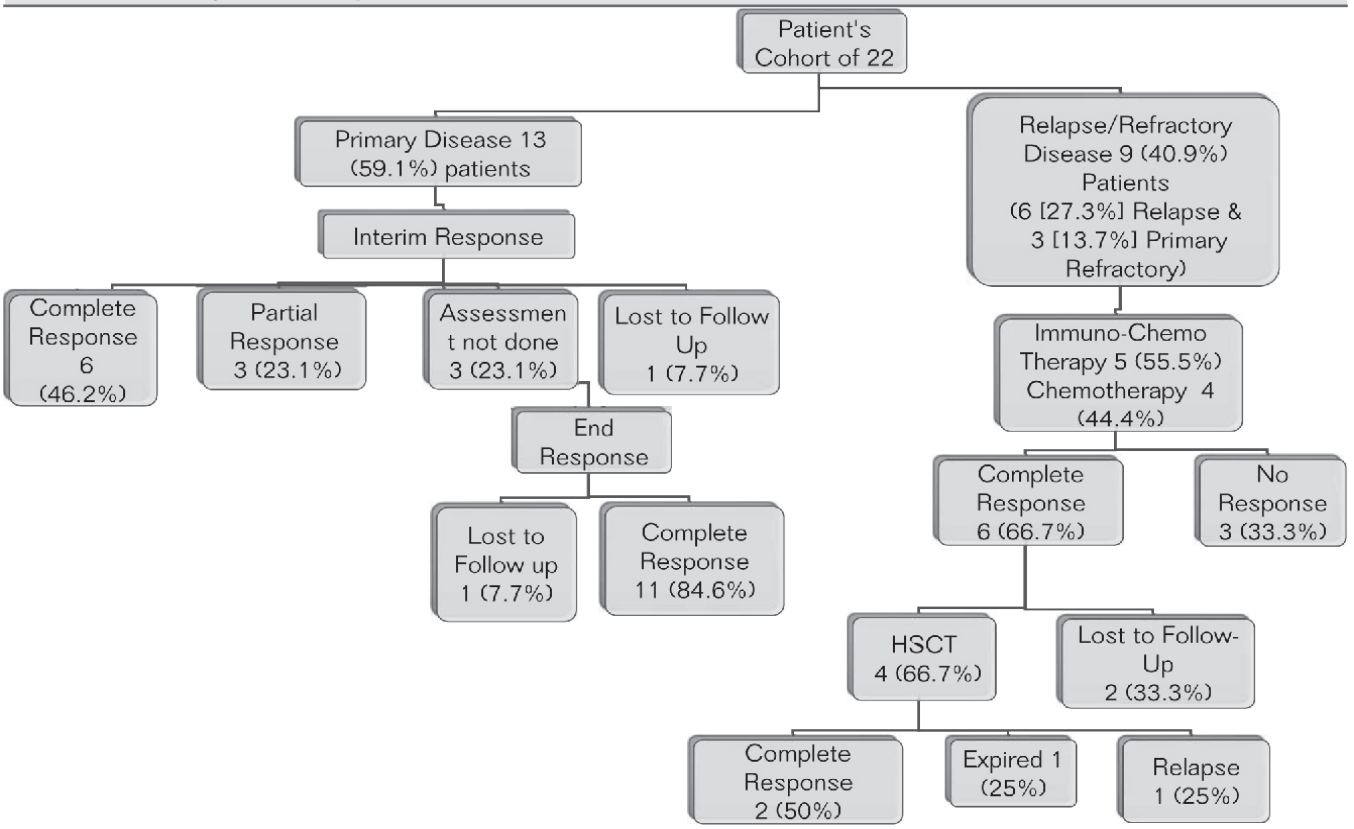


TABLE-I		
Clinical characteristics of HL patients at presentation, treatment and response:		
Age	Mean (SD)	31.7 (18.7)
Gender	Female, n(%)	8 (36.4)
	Male, n(%)	14 (63.6)
Co- Morbidity	No n(%)	18 (81.9)
	Yes n(%)	4 (18.1)
Physical Examination lymphadenopathy	Inguinal lymph node n(%)	1 (4.6)
	Cervical lymph node n(%)	17 (77.3)
	Cervical lymph node, inguinal lymph node n(%)	1 (4.6)
	Axillary lymph node, cervical lymph node n(%)	1 (4.6)
	Axillary lymph node n(%)	1 (4.6)
	Axillary, inguinal, cervical n(%)	1 (4.6)
Infection at presentation	No n(%)	20 (91)
	Yes n(%)	2 (9)
B symptoms	No n(%)	3 (13.7)
	Yes n(%)	19 (86.4)
Hepatomegaly	No n(%)	16 (72.8)
	Yes n(%)	6 (27.3)
Splenomegaly	No n(%)	12 (54.6)
	Yes n(%)	10 (45.5)
Hemoglobin (g/dl)	<10.5 n(%)	8 (36.4)
	>10.5 n(%)	14 (63.7)
WBC (10^9/L)	<15 n(%)	21 (95.5)
	>15 n(%)	1 (4.6)
Platelet (10^9/L)	<150 n(%)	2 (9.1)
	>150 n(%)	20 (91)
LDH	N/A	6 (27.3)
	<220 n(%)	2 (9.1)
	>220 n(%)	14 (63.7)
Urea	<50 n(%)	20 (91)
	>50 n(%)	2 (9.1)
Creatinine	<1.2 n(%)	22 (100)
	>1.2 n(%)	0 (0)
Liver function	Normal n(%)	21 (95.5)
	Abnormal n(%)	1 (4.6)
Site of tissue diagnosis	Axillary lymph node n(%)	3 (13.7)
	Cervical lymph node n(%)	16 (72.8)
	Inguinal lymph node n(%)	2 (9.1)
	Mediastinal lymph node n(%)	1 (4.6)
cHL subtype	N/A n(%)	9 (41)
	MCHL n(%)	4 (18.2)
	NSHL n(%)	9 (40.9)
BM biopsy	Not done n(%)	15 (68.2)
	Done n(%)	7 (31.9)
BM involvement biopsy (n=7)	No n(%)	4 (18.2)
	Yes n(%)	3 (13.7)
Ann-Arbor Stage	2B n(%)	4 (18.2)
	3A n(%)	2 (9.1)
	3B n(%)	11 (50)
	4B n(%)	5 (22.8)
Status at the time of 1st visit	Primary disease n(%)	13 (59.1)
	Relapse n(%)	6 (27.3)
	Primary refractory n(%)	3 (13.7)
Primary Disease (n=13)		
End of Treatment Response Assessment by (n=13)	PET-CT n(%)	11 (84.7)
	CT n(%)	1 (7.7)
	LTF n(%)	1 (7.7)
Relapse	Yes n(%)	2 (15.4)
	No n(%)	7 (53.8)
	LTF n(%)	4 (30.8)
Final Outcome	Alive n(%)	19 (86.4)
	Death n(%)	3 (13.6)

TABLE-II

Comparison of HL patients' characteristics and final outcome:

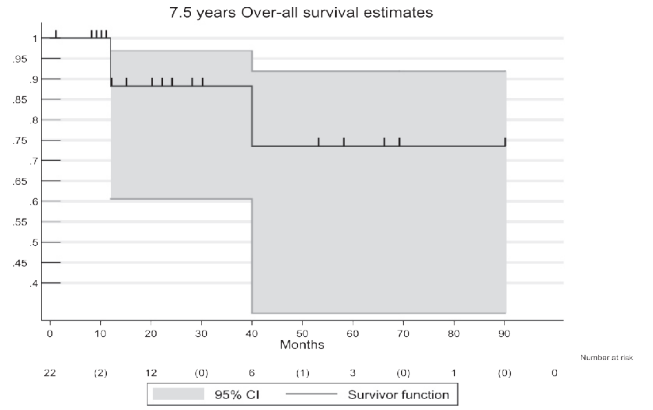
Parameters		Alive (n=19)	Died (n=3)	P-Value
		N (%)	N (%)	
Age	Mean (SD)	31.58 (19.07)	32.67 (20.3)	0.77
Follow up		30 (25)	21 (16)	0.74
Gender	Female	8 (42.1)	0 (0)	0.27
	Male	11 (57.9)	3 (100)	
Co- Morbidity	No	15 (78.9)	3 (100)	1.00
	Yes	4 (21.1)	0 (0)	
Platelets (10^9/L)	<150	2 (10.5)	0 (0)	1.00
	>150	17 (89.5)	3 (100)	
LDH	not available	5 (26.3)	1 (33.3)	1.00
	<220	2 (10.5)	0 (0)	
	>220	12 (63.2)	2 (66.7)	
Urea	<50	17 (89.5)	3 (100)	1.00
	>50	2 (10.5)	0 (0)	
Creatinine	<1.2	19 (100)	3 (100)	1.00
	>1.2	0 (0)	0 (0)	
Liver functions	Normal	19 (100)	2 (66.7)	0.14
	Abnormal	0 (0)	1 (33.3)	
B symptoms	No	3 (15.8)	0 (0)	1.00
	Yes	16 (84.2)	3 (100)	
Infection(s)at presentation	No	18 (94.7)	2 (66.7)	0.26
	Yes	1 (5.3)	1 (33.3)	
Physical Examination lymphadenopathy	Inguinal lymph node	1 (5.3)	0 (0)	0.56
	Cervical lymph node	15 (78.9)	2 (66.7)	
	Cervical lymph node, Inguinal lymph node	1 (5.3)	0 (0)	
	Axillary lymph node, cervical lymph node	1 (5.3)	0 (0)	
	Axillary lymph node	1 (5.3)	0 (0)	
	Axillary, inguinal, cervical lymph nodes	0 (0)	1 (33.3)	
Hepatomegaly	No	14 (73.7)	2 (66.7)	1.00
	Yes	5 (26.3)	1 (33.3)	
Splenomegaly	No	9 (47.4)	3 (100)	0.20
	Yes	10 (52.6)	0 (0)	
Hemoglobin (g/dl)	<10.5	8 (42.1)	0 (0)	0.27
	>10.5	11 (57.9)	3 (100)	
WBC (10^9/L)	<15	18 (94.7)	3 (100)	1.00
	>15	1 (5.3)	0 (0)	
cHL subtype	Not available	9 (47.4)	0 (0)	0.36
	MCHL	3 (15.8)	1 (33.3)	
	NSHL	7 (36.8)	2 (66.7)	
Site of tissue diagnosis	Axillary Lymph node	2 (10.5)	1 (33.3)	0.64
	Cervical lymph node	14 (73.7)	2 (66.7)	
	inguinal lymph node	2 (10.5)	0 (0)	
	Mediastinal lymph node	1 (5.3)	0 (0)	
Status at the time of 1st visit	De novo primary disease	13 (68.4)	0 (0)	0.08
	Relapse	4 (21.1)	2 (66.7)	
	Primary refractory	2 (10.5)	1 (33.3)	

(%): Percentage, cHL: Classical Hodgkin's Lymphoma, LDH Lactate Dehydrogenase, LTF: Lost to follow up, MCHL: Mixed Cellularity Hodgkin's Lymphoma, N/A:Not Available, n:Number, NSHL: Nodular Sclerosis Hodgkin's Lymphoma.

The 90 months overall survival in 22 patients is 73.5%. (Figure-2)

FIGURE-2

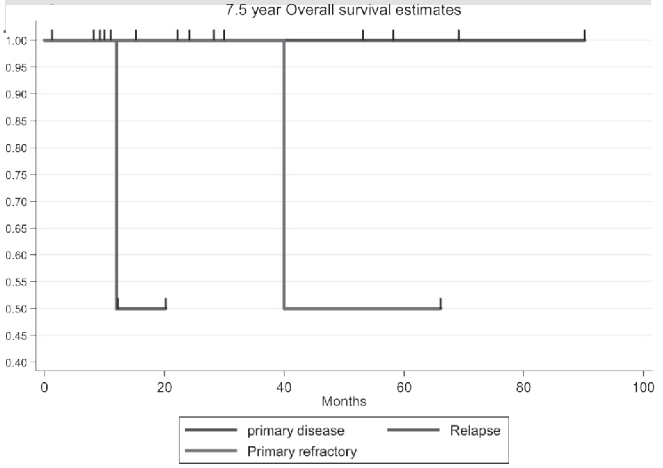
The overall survival of HL patients (n=22).



The 90 months overall survival in primary disease patients was 100%, as 13 (100%) patients were alive at the time of end of the study, while in relapse and refractory group median survival was 12 months and 44 months respectively. (Figure-3) This difference was statistically significant, (log rank test p-value 0.02).

FIGURE-3

The overall survival of relapse/refractory and primary HL



In Relapse/Refractory patients, survival was 0% with a median survival of 12 months in males, while the female patients' consistently demonstrated 100% survival across all groups with a p-value of 0.09. (Table-III)

TABLE-III

Comparison of OS and RFS:

Characteristics		OS (n=22)	P-Value	RFS (n=13)	P-Value	Relapse/Refractory Patients OS (n=9)	P-Value
Gender	Male	53.30%	0.12	80%	0.4	0% (Median=12 Months)	0.09
	Female	100%		0% (Median=Ninety Months)		100%	
B- Symptoms	No	100%	0.6	0% (Median=Ninety Months)	0.7	100% (11 Months Follow Up)	-
	Yes	70%		86%		35.70%	
LDH	<220	100%	0.8	0% (Median=Ninety Months)	0.74	66%	0.8
	>220	68.20%		80%		37.50%	
IPI Score	1			0% (Median=Ninety Months)	0.8		
	3			67%			
Albumin	<4			0% (Median=Ninety Months)	0.48		
	>4			100%			
Stage	Early			100%	0.56		
	Advanced			0% (Median=Ninety Months)			

DISCUSSION

HL is a rare hematological neoplasm, with a diverse clinical and pathological profile depicting variation in the incidence, age, gender distribution and morphology subtypes across the globe. There is a varying age distribution with a documented bimodal peak reported in the western population.[10-12] The first peak is usually around 15-30 years, whereas second peak is around the age of 50-60 years. However, most of the studies done in Asian population reported increased incidence in the younger population.[13,14] Similarly, our study also reported an increased incidence among the younger population.

The reason could be the reduced average life expectancy in this region and socioeconomic and environmental factors, being the reason of this variation from developed world. The gender distribution as reported from the regional data corresponds with increase male to female ratio.[15,16] In this study, we also reported similar finding of male predominance. This could be attributed to the gender discrimination still being prevalent in this part of world and lack of proper care and medical facilities for female population of our society.

The subtype of CHL reported in studies from Pakistan revealed mixed cellularity (MCHL) as a major subtype.[17] Similar findings were reported from India, with MCHL entity in their cohort.[18] Nodular sclerosis (NSHL), being the predominant histological variant in the USA and Europe. Our study population reports an increase incidence of NSHL, which is in contrast with the local data. One of the possibilities of this difference could be the unavailability of histological sub typing in nearly half of our patients.

A pivotal aspect in disease management is accurate staging and prognostication, which guides towards a better disease management plan. Our study population incorporates imaging via PET CT scan and bone marrow biopsy was done in patients who underwent CT imaging instead of PET (i.e. 31.9%).

Our study demonstrates an increased incidence of advanced stage disease (53.8%).Literature have reported similar findings of higher advanced stage diseases prevalence in multiple cohorts.[19,20] The high prevalence of tuberculosis in our region contributes to the misdiagnosis and delayed referral of these patients highlighting the importance of timely diagnosis with proper excision biopsy, and need for the incorporation of better primary care facilities and robust referral system.

ABVD and Escalated BEACOPP have been two chemotherapeutics options utilized in frontline setting for the management of HL worldwide.[21] For limited stage disease, 2-4 cycles of ABVD as per EORTC H10 approach whereas Escalated BEACOPP x 2 plus ABVD X 2 can be used according to GHSG HD17 approach. Number of cycles is guided on the basis of Interim PET imaging. For Advanced stage disease, RATHL approach, starting with ABVD 2 cycles followed by Interim imaging and decision to step down treatment with omission of bleomycin (AVD x 4) or escalation to Escalated BEACOPP is planned. HD 18 approach utilizes Escalated BEACOPP in frontline. Recent updated guidelines from NCCN and American Journal hematology have recommended Brentuximab Vedotin - AVD / Nivolumab – AVD in front line setting for advanced stage disease.[22] Our institutional practice favors ABVD in frontline setting due to familiarity with regimen, good tolerance and mostly outpatient management. In relapse/refractory setting in our cohort, nearly half of our patients receive platinum based regimen, and half of them were able to get immune chemotherapy combinations. We were able to arrange immunotherapy in collaboration with a patient access program, therefore financial burden was minimized. Such programs hold crucial importance as they provide an opportunity for under privileged patients to have an access to recommended line of treatment strategies.

In our cohort, the overall survival (OS) was found to be 73.5%. The 90 months OS in patients who presented with primary disease patients was 100% as all the patients were alive at the time of end of the study. However, in patients with relapse and refractory disease, the OS was 0 % with median survival of 12 months and 44months respectively. The OS reported in our study was comparable to reported national and regional data.[14,23,24] Majority of patients presenting with de novo primary disease were young to middle age which could be the reason

for better OS. A major determinant of better reported outcome could be the absence of infection at disease presentation, as the infection is associated with poor outcomes; its absence allows patients to have better tolerance of treatment. Nevertheless, the poor OS in relapse/refractory patients is in concordance with dismal outcome reported previously. Moreover, we compared different prognostic factor's impact on OS and RFS but none of them was found to have a significant p value. The standard of care for relapse and refractory disease is salvage chemotherapy followed by autologous stem cell transplant (ASCT). In majority of patients, ASCT was hampered on account of financial constraints, limited number of transplant centers in the country and delayed referrals. Therefore, the key lies in early identification of relapse and provision of salvage regimen, and ASCT as soon as remission is achieved.

The study highlights the outcome of HL from a single center in a developing country. However, our study had certain limitations including cross sectional study design from single center, small sample size and unavailability of radiotherapy. Nevertheless, the study demonstrated treatment outcomes at one of the referral hematology center. Previous national studies have reported the demographic characteristics of the disease, however, scarce literature is available on the treatment outcomes and relapse/refractory cases from our region and therefore this was one of the study's strength.

Careful selection of primary treatment regimen keeping in view patient and disease related factors and provision of timely referral system in case of relapse/refractory disease to hematologists is pivotal for definitive management in HL. This requires awareness and collaborative strategies between hematologists, oncologists and referring physicians on the national level. Moreover, in future larger prospective multicenter studies are needed to highlight disease biology and its treatment implications in our part of the world.

CONCLUSION

The study demonstrates the clinical features, demographics and treatment outcomes of HL highlighting the need for careful patient and treatment selection at disease presentation. For relapse/refractory disease timely referral to the hematologist and transplant center is crucial to improve treatment and disease outcomes. In future, larger multicenter national collaborative studies are needed to establish robust outcome inference at national scale.

Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of NIBD Research Ethics Committee. (NIBD/IRB- 281/01-2025).

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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6	**Laraib Majeed:** Data collection.
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8	**Nida Anwar:** Concept of study, final approval.