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Quantifying T-Regulatory Cells and Their Clinicopathological Relevance in Hodgkin Lymphomas

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ORIGINAL STUDY

Quantifying T-regulatory cells and their clinicopathological relevance in Hodgkin lymphomas

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Abstract

Introduction: **Regulatory T cells (Tregs) constitute a distinct subset of lymphocytes recognized for their ability to dampen immune responses. The significance of Tregs as prognostic indicators in individuals with lymphoma has sparked ongoing debates. Therefore, this study was undertaken to enumerate and correlate the clinicopathological findings of Tregs in Hodgkin lymphomas (HLs).**

Methodology: **This hospital-based prospective observational study included a total of 50 participants. All the enrolled participants were divided into cases (all biopsy/immunophenotypically proven cases of Hodgkin's lymphoma, n = 30) and controls (healthy individuals, n = 20). Clinico-demographic details were recorded and compared. Samples collected from the patients were tagged with specific antibody and fluorochrome combinations and analyzed on flow cytometry.**

Results: **In the present study, significantly higher lactate dehydrogenase levels were observed in both HL (1013.75 ± 692.85) compared with the control group (249.58 ± 56.84). A significant difference was noted in the hematological and immunological parameters among groups. Treg% of CD4 T cells was positively correlated with disease-stage lactate dehydrogenase levels and International Prognostic score, while negatively correlated with absolute lymphocyte count (ALC) and platelet count. The Treg % of ALC showed significant negative correlations with ALC. The Treg% of CD4 demonstrated excellent discriminatory power (area under the curve = 0.984) with a high sensitivity of 0.983, outperforming Treg% of ALC (area under the curve = 0.610) in distinguishing HL from control patients.**

Conclusion: **Elevated Tregs levels are indicative of a more favorable prognosis among individuals with HL. Tregs can potentially serve as a valuable prognostic biomarker for patients diagnosed with lymphoma.**

Keywords: Flow cytometry, Hodgkin lymphoma, Lymphoma, Non-Hodgkin lymphoma, T-regulatory cells

1. Introduction

Hodgkin lymphoma (HL), a B-cell-origin lymphoid tumor, is classified according to the 5th edition of the WHO Classification of Hematolymphoid Tumours (5th WHO-Hem), released online in August 2022 [1,2]. This condition primarily affects young adults aged 20−35 [3,4], with its description dating back to 1832 by Thomas Hodgkin, who observed cases characterized by aberrant lymph node and spleen involvement not attributed to a common virus [5]. Geographical variations exist in the prevalence of different subtypes, with non-Hodgkin lymphoma (NHL) being more common in Asia, while HL remains relatively uncommon [6]. In 2020, the United States reported 85 720 newly diagnosed lymphoma cases and 20 910 fatalities [7], emphasizing the ongoing threat and need for improved prognostic indicators. Immune components play pivotal roles in tumor progression, either promoting or inhibiting it. Immunosuppressive cells, including myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs), can dampen antitumor immunity by inhibiting T-cell and natural killer cell activity [8]. Tregs, a subset of CD4+ T cells comprising 1−4% of circulating CD4+ lymphocytes, specialize in immune suppression, regulating undesirable immune responses to self-antigens and foreign antigens within immune tolerance [8]. Research indicates that elevated tumor-infiltrating

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Tregs are associated with poor prognosis in many solid tumors, such as breast cancer, ovarian carcinoma, and hepatocellular carcinoma, consistent with their immunosuppressive and tumor-promoting properties. Intriguingly, the opposite effect has been observed in certain solid tumors like colorectal cancer, esophagal carcinoma, and head and neck cancer. The prognostic significance of Tregs in lymphoma remains debatable, with several studies suggesting a favorable prognosis [9]. Nevertheless, many studies have raised doubts about the association between Tregs and lymphoma outcomes [9,10]. Around 90% of HL patients can be treated with conventional chemotherapy, often combined with radiation therapy. However, relapse rates vary, ranging from 10 to 15% in early-stage (I–II) with a fair prognosis to 30–40% in late-stage disease. Unfortunately, HL remains a deadly disease, and only 20% of refractory or relapsed patients following first–line combination chemotherapy respond to typical second-line regimens. Moreover, radio-/chemotherapy carries the risk of hazardous side effects, including the development of subsequent neoplasms. Therefore, less-toxic and more effective treatment approaches are urgently needed for nonresponsive or relapsed HL patients [11]. In light of these challenges, this study seeks to elucidate the critical role of T cells, especially Tregs, in lymphoma, focusing on HL, to determine their clinical significance as potential prognostic markers and therapeutic targets.

2. Materials and methods

This prospective observational study was conducted at the Department of Pathology, King George's Medical University, Lucknow, for 2 years. The study included Hodgkin's lymphoma cases based on biopsy and immunophenotypic confirmation, adhering to the World Health Organization (WHO) criteria, incorporating morphology and applicable flow cytometry assessments. Patients visiting the department for diagnostic evaluation were considered for inclusion as cases (n = 30), while a control group (n = 20) comprised healthy individuals. Exclusion criteria encompassed patients unwilling to participate in the study, cases with insufficient diagnostic material, and those currently undergoing chemotherapy. Detailed clinical and demographic information was collected and compared between the two groups. Venipuncture was performed to obtain blood samples for a complete blood count and flow cytometry analyses (BD FACSCalibur). Additionally, hematological and immunological parameters were meticulously documented and subjected to comparative analysis. A correlation analysis was conducted to provide comprehensive insights into the role of Tregs in Hodgkin's lymphoma. The area under the curve (AUC) was employed as a statistical tool to facilitate an in-depth evaluation of the presence and significance of Tregs in the context of Hodgkin's lymphoma within our study population.

2.1. Statistical analysis

The statistical analysis was carried out using SPSS version 23. To evaluate the differences in CD4 Treg levels between the HL group and the normal control group, appropriate statistical tests, such as *t*-tests or χ^2 tests, were employed. The correlation between Treg levels in HL patients and various quantitative clinical features was assessed through the Spearman correlation test. Statistical significance was established at a *P* value below 0.05.

3. Results

In the HL group, a substantial proportion of patients were aged within the 3–14-years age range, while most individuals in the control group fell into the 45–54 age group. Males predominated in both groups (Table 1). Most cases were classified as stage-I lymphoma within the HL group (Fig. 1). Notably,

Table 1. Demographic parameters of enrolled patients among both groups (N = 50).

Age (y)	Hodgkin lymphomas (*N* = 30) [*n* (%)]	Controls (*N* = 20) [*n* (%)]	*P* value
3–14	17 (56.67)	3 (15.00)	
15–24	8 (26.67)	3 (15.00)	
25–34	0	2 (10.00)	
35–44	2 (6.67)	2 (10.00)	X = 19.87 ***P* = 0.0029***
45–54	0	4 (20.00)	
55–64	2 (6.67)	6 (30.00)	
65–75	1 (3.33)	0	
Sex			
Female	11 (36.67)	7 (35.00)	X = 0.01447 *P* = 0.9043
Male	19 (63.33)	13 (65.00)	

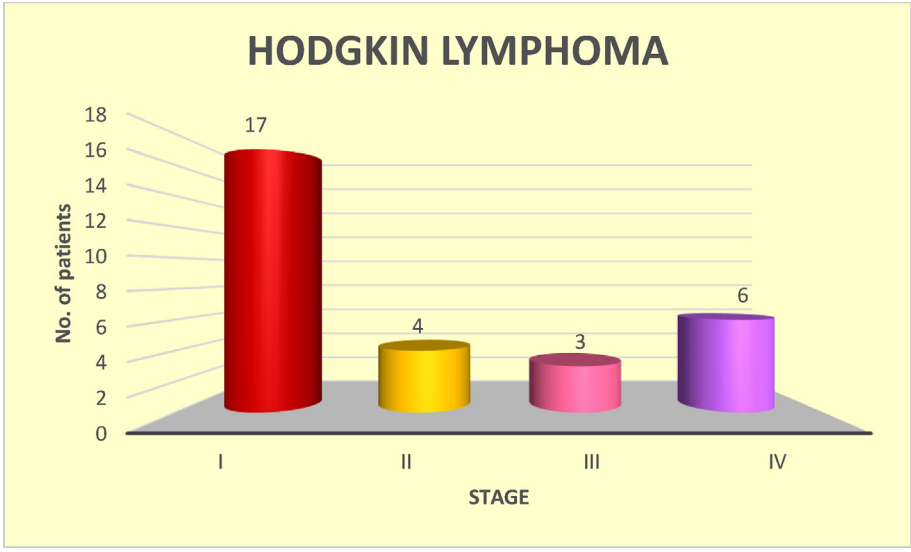

Fig. 1. Lymphoma stage of the enrolled cases.

HL patients exhibited markedly higher levels of lactate dehydrogenase (LDH) [1013.75 ± 692.85] compared with the control group [249.58 ± 56.84], suggesting LDH as a potential differentiator between lymphoma patients and healthy counterparts. Approximately 70% of HL patients had an International Prognostic Score (IPS) of 1, while an Eastern Cooperative Oncology Group (ECOG) score of 2 was prevalent in this group (63.33%) (Figs. 2 and 3). Nodal lymphomas were predominant in 86.67% of HL cases, with limited bone marrow involvement (13.33%) (Figs. 4 and 5). Symptoms were reported in 83.33% of HL patients, while 16.67% remained asymptomatic. Concerning hematological parameters, HL patients exhibited significantly lower levels compared with the control group (Table 2). These findings underscore significant disparities in hematological parameters between HL patients and the control group. Moreover, the HL group exhibited a higher proportion of Treg% of absolute lymphocyte count (ALC) and CD4 than the controls, signifying potential immunological distinctions between lymphoma types (Table 3). Correlation analyses revealed that the Treg percentage of CD4 T cells positively correlated with LDH levels and IPS score. Conversely, it exhibited negative correlations with ALC and platelet levels (Table 4). The AUC for Treg% of CD4 was notably high at 0.984, with a

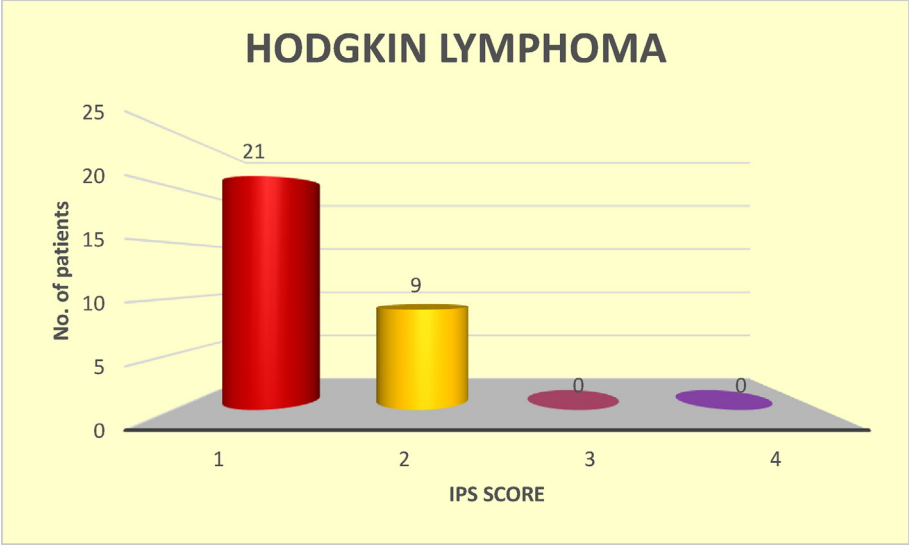

Fig. 2. International Prognostic Score of the enrolled patients with Hodgkin lymphoma.

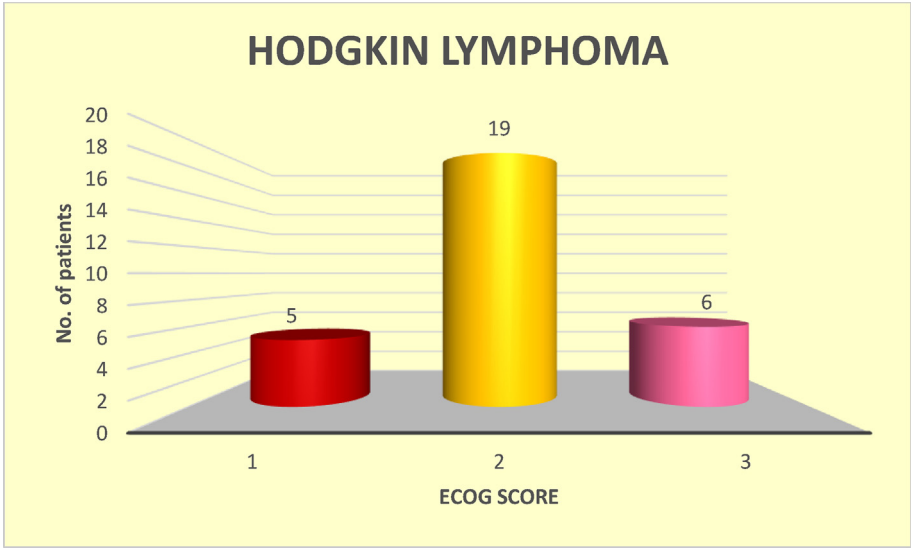

Fig. 3. ECOG score of the enrolled patients with Hodgkin lymphoma. ECOG, Eastern Cooperative Oncology Group.

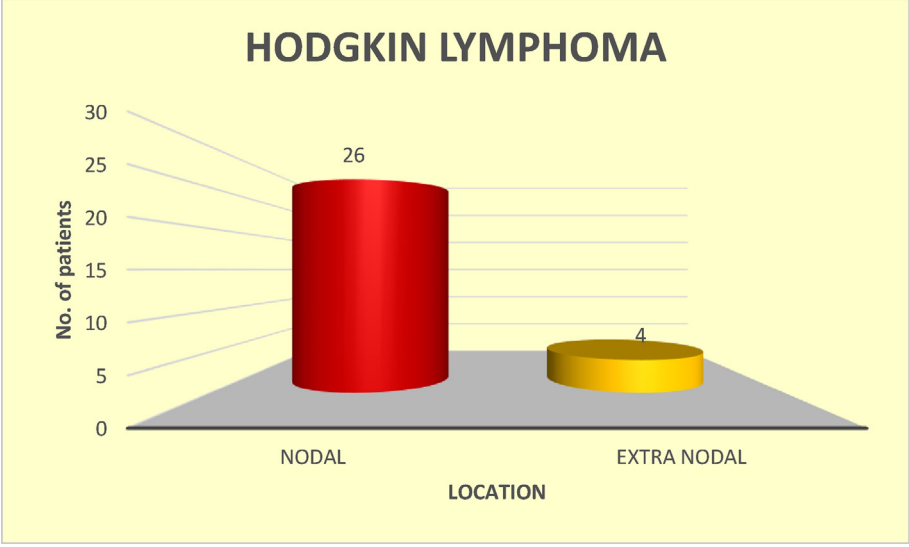

Fig. 4. Location of lymphoma in patients with Hodgkin lymphoma.

cutoff value of 6.17, sensitivity of 0.983, and a 1-specificity of 0.345. Similarly, the AUC for Treg % of ALC was 0.610, with a cutoff value of 1.765, sensitivity of 0.707, and a 1-specificity of 0.483. Both parameters exhibited significant discriminatory power, with Treg% of CD4 displaying superior discriminatory ability in distinguishing between HL and control patients (Table 5).

4. Discussion

In the current study, most HL cases were in the 3–14 age range (56.67%) and 15–24 years (26.67%), while the control group was mostly aged 55–64 years (30.00%) and 45–54 years (20.00%). The age difference was statistically significant ($P < 0.0001$*). Both HL (63.33%) and control groups (65.00%) were predominantly males, consistent with previous studies [12,13]. In the present study, most HL cases (56.67%) had stage-I lymphoma, followed by stage-IV lymphoma (20.00%). This was in accordance with other studies [13,14]. On the contrary, Greaves et al. [15] reported most HL patients had advanced stages (IIB-IV), while Nakayama et al. [16] found stages III sand II were common in their study. In the present study, higher LDH levels in HL [1013.75 ± 692.85] versus controls [249.58 ± 56.84] suggest LDH as a potential lymphoma marker [12,14]. Elevated LDH is

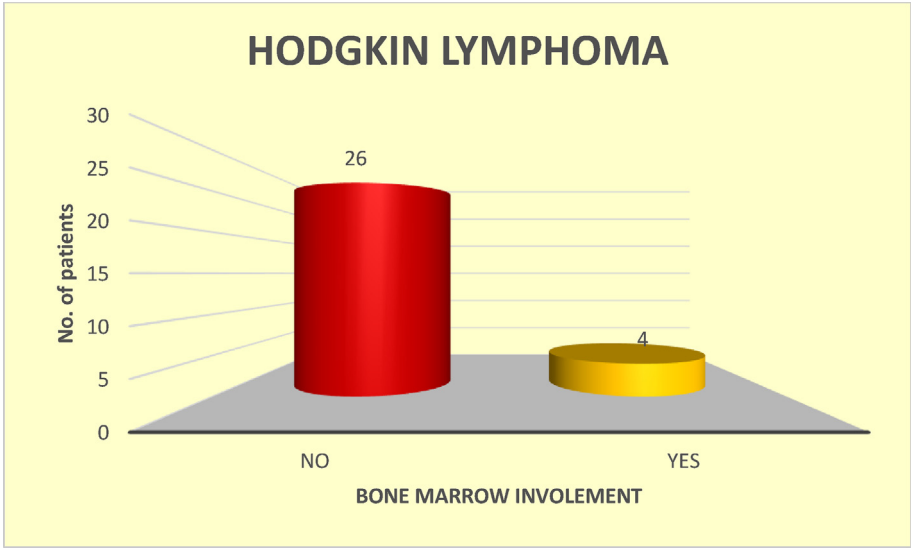

Fig. 5. Bone marrow involvement in patients with Hodgkin lymphoma.

Table 2. Hematological parameters of enrolled patients among both groups.

Hematological parameters	Hodgkin lymphoma		Control		*P* value
	Mean	SD	Mean	SD	
HB (Gm%)	9.63	2.14	13.874	1.04	F = 11.91 ***P* < 0.0001***
TLC (/micL)	10424.48	4221.88	14124.21	6522.34	F = 2.774 ***P* = 0.0069***
ALC (/micL)	1844.83	755.02	9278.48	2311.02	F = 17.04 ***P* < 0.0001***
PLATELETS/LACS/mic/l	2.49	1.30	6.21	3.79	F = 5.185 ***P* < 0.0001***

TLC, total leukocyte count.

Table 3. Immunological markers of enrolled patients among both groups.

Immunological marker	Hodgkin lymphoma		Control		*P* value
	Mean	SD	Mean	SD	
Lymphocytes	6130.55	2630.70	8950.60	1992.51	F = 5.425 ***P* < 0.0001***
CD4	365.82	80.91	893.65	219.71	F = 12.63 ***P* < 0.0001***
TREG	129.26	85.08	97.59	37.58	F = 2.292 ***P* = 0.0246***
TREG% OF CD4	0.15	0.04	0.05	0.01	F = 16.88 ***P* < 0.0001***
TREG% OF ALC	2.14	0.95	0.73	0.34	t = 9.557 ***P* < 0.0001***

Table 4. Spearman correlation analysis of the various parameters with Treg% of CD4 and ALC.

Spearman correlation	Treg% of CD4	Treg% of ALC
	Spearman r	
STAGE	0.307	0.214
LDH	**0.451***	**−0.231**
IPS SCORE	**0.476***	**−0.377***
ECOG SCORE	0.104	0.111
LOCATION	0.313	−0.048
BM INVOLMENT	0.336	−0.032
TLC (/micL)	0.330	−0.059
ALC (/micL)	**−0.425***	**−0.425***
PLAT/LACS/micL	−0.274	−0.155

* = *P* less than 0.05; ** = *P* less than 0.0001.
ECOG, Eastern Cooperative Oncology Group; TLC, total leukocyte count.

Table 5. Receiver operating characteristic analysis of the Treg% of CD4 and ALC between Hodgkin and control patients.

Area under the curve		
	Treg% of CD4	Treg% of ALC
Area	0.984	0.610
Std. error	0.009	0.052
P value	**<0.0001***	**0.041***
95% Confidence interval		
Lower bound	0.967	0.507
Upper bound	1.000	0.713
Cutoff	6.17	1.765
Sensitivity	0.983	0.707
1-Specificity	0.345	0.483

unfavorable in various cancers, impacting prognosis, particularly in prostate, lung, renal cell, nasopharyngeal, and gastric cancers. LDH levels are crucial for melanoma survival [17]. LDH (EC 1.1.1.27) is involved in anaerobic metabolism, converting lactate to pyruvate and impacting cancer growth [18]. Staging alone does not predict prognosis for some lymphomas. The IPS helps classify patients as high or low risk, but it applies to a limited number of lymphoma subtypes due to their heterogeneity [19]. In this study, 70% of HL cases had an IPS score of 1, and 30% had a score of 2. In the HL group, most patients had an ECOG score of 2 (63.33%), while 20.00% had a score of 3, and 16.67% had a score of 1. Mei M et al. [20] reported that ECOG scores of 3–4 were associated with lower survival rates. Similarly, in pediatric patients in India, ECOG scores of 3 and 4 predicted worse outcomes for event-free survival and overall survival [21]. In this study, the majority of HL cases had nodal involvement (86.67%), while other studies [12] found higher rates of extranodal involvement (54% and 42.7%). In this study, 83.33% of HL cases had symptoms, while others [12,13] found a higher proportion of asymptomatic patients. Probably due to abnormal endogenous cytokines, symptomatic patients had a lower survival rate. Intriguingly, men were more likely to exhibit symptoms, and patients with advanced-stage were most likely to exhibit symptoms [22]. In the study, HL patients had slightly lower mean hemoglobin levels [9.63 ± 2.14 gm%] than the control group [13.874 ± 1.0 gm%]. Van Belle SP [23] reported that the patients with bone marrow involvement had a higher incidence of anemia. In patients with subdiaphragmatic Hodgkin's disease, lower Hb levels, low albumin levels, older age, symptoms, and specific histology independently predicted poorer overall survival [24]. In this study, the HL group had a higher mean total leukocyte count (TLC) (/micL) [10424.48 ± 4221.88] than the control group [14124.21 ± 6522.34], but a lower mean ALC (/micL) [1844.33 ± 755.02 vs. 9278.48 ± 2311.02]. Mean lymphocyte levels were higher in the control group [8950.60 ± 1992.51] than in the HL group [6130.55 ± 2630.70]. Treg% of ALC was higher in the HL group compared with the control group [25]. The HL group had the lowest mean platelet count [2.49 ± 1.30] compared with the control group [6.21 ± 3.79], with statistically significant differences in all hematological parameters [14]. All histologic subgroups also showed a high frequency of lymphocytopenia. The mean CD4 level in the HL group was 365.82 ± 80.91, with substantially higher Treg% of CD4 in both groups (HL: 0.15 ± 0.04, Control: 0.05 ± 0.01). A lower current CD4 cell count was associated with a higher risk of HL [26]. In this study, Treg cell levels were higher in HL [129.26 ± 85.08] compared with the control group [97.59 ± 37.58]. Tregs play a significant role in cancer, promoting tumor progression and inhibiting antitumor activity. Tregs are found to be higher in cancer patients compared with healthy individuals, but their prognostic significance varies [27]. Tregs generally predict poor prognosis in cancer, but some studies suggest a more favorable outcome with higher Treg numbers and activity [28]. Treg percentages increase in advanced disease and poorer prognosis, correlating with tumor burden [14,29]. Tregs have an immunosuppressive effect on antitumor T-cell responses in lymphoma [30]. The role of Tregs in B-cell lymphoma is complex, with the potential to inhibit or favorably influence lymphoma growth [31]. High infiltration of Tregs is associated with enhanced survival in follicular lymphoma and classical HL [32]. Due to the direct suppression of B-cell lymphoma cells by tumor-infiltrating Tregs, it was believed that the role of tumor-infiltrating Tregs in B-cell-malignant lymphomas differed from that of solid non-lymphoid tumors [32]. In this study, there is a statistically significant positive correlation between LDH levels and Treg% of CD4 (Spearman $r = 0.451$, $P < 0.05$), as well as IPS score and Treg% of CD4 (Spearman $r = 0.476$, $P < 0.05$). Conversely, there is a significant negative correlation between ALC (/micL) and Treg% of CD4 (Spearman $r = -0.425$, $P < 0.05$), indicating an inverse relationship. Additionally, there is a significant negative correlation between IPS score and Treg% of ALC (Spearman $r = -0.377$, $P < 0.05$), indicating that as IPS score increases, Treg% of ALC tends to decrease. Similarly, another study found a positive correlation of Treg with IPS ($r = 0.492$, $P = 0.024$) and LDH ($r = 0.436$, $P = 0.048$). Also, they reported a negative correlation with ALC ($r = -0.615$, $P = 0.003$) [33]. Hus I et al. [14] also discovered an inverse correlation between the percentages of circulatory Th17 and Treg cells, which may be due to the effect of malignant B cells on T-cell differentiation, which inhibits Th17 and promotes Tregs. Another study discovered that the level of LDH greater than 320 U/l, the clinical stage of lymphoma, and age had a significant prognostic impact on achieving complete remission [34]. In addition, in BM trephine biopsies, there was no correlation between the topographic distribution of Tregs, which is an important prognosticator in other B-cell malignancies, and the pattern of BM myeloma cell infiltration [35]. However, there was a significant correlation between the number of extranodal sites and the total number of sites involved. The lymphocyte count did not correlate

significantly with age, granulocyte count, and number of affected sites [36]. It is also possible that the correlation between lymphocyte count and prognosis is nonlinear, with patients with very low or very high lymphocyte counts having a worse prognosis than the group with an intermediate lymphocyte count [37]. In this study, we evaluated the discriminatory power of Treg% (percentage of regulatory T cells) in CD4+ cells and Treg% of ALC for distinguishing between HL and control groups. Treg % in CD4+ cells demonstrated an AUC of 0.984, with a cutoff value of 6.17, sensitivity of 0.983, and 1-specificity of 0.345. On the other hand, Treg% in ALC had an AUC of 0.610, with a cutoff value of 1.765, sensitivity of 0.707, and 1-specificity of 0.483. Both markers displayed significant discriminatory power, but Treg% in CD4+ cells exhibited higher discriminative ability than Treg% in ALC in distinguishing between HL and control patients.

4.1. Conclusion

According to the results of this study, it has been noted that Tregs promote tumor growth. The changes observed in T-cell subsets in the peripheral blood of HL patients could be attributed to the presence of malignant cells. However, it is also possible that there exists a complex system of reciprocal feedback between Tregs and tumor cells. Moreover, higher baseline frequencies of LDH, lymphocytes, and Treg cells in patients who later responded to immunochemotherapeutic may indicate their predictive value and potential role in supporting disease control. This study had several limitations, such as the results were limited to a single tertiary care hospital with a limited sample size that may not be generalized for all settings. Hence, it cannot be incorporated into the larger population. Although Tregs are associated with poor prognosis, establishing a cause-and-effect relationship between Tregs and lymphoma progression requires further investigation. Factors such as prior treatment, patient comorbidities, and disease stage may influence Treg levels, making it challenging to isolate the direct impact of Tregs on lymphoma progression. Henceforth, further research on the enumeration and correlation of the clinicopathological findings of T-regulatory cells in HLs would be essential for the understanding, especially in introducing novel targeted therapies that were demonstrated to influence T-cell populations.

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None.

Consent

As per international or university standards, the authors have collected and preserved written participant consent.

Ethical approval

As per international or university standards, the author(s) has collected and preserved written ethical permission.

Conflicts of interest

Conflict of interest—All authors declare no conflict of interest.

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