Original Article

DOI: 10.7860/JCDR/2023/66170.18666

Pathology Section

# Burden of Anaemia and its Impact on Lymphoma Patients in Southern Rajasthan, India: A Cross-sectional Study

GULSHAN KUMAR MUKHIYA[1], GEETA W MUKHIYA[2], PRUTHVI PATEL[3], REETI POKAR[4], ARPAN PATEL[5], DILSHANO THAIYAM[6], KHUSHI MUKHIYA[7]



## ABSTRACT

**Introduction:** The frequency of lymphoma is progressively rising. A key clinical feature of lymphoid malignancies is anaemia. The impact of anaemia goes beyond physical symptoms and can negatively affect functional capacity and Quality of Life (QoL). The presence of anaemia has been identified as a predictive factor for event-free and disease-free survival in patients diagnosed with lymphoma and is regarded as a significant unfavourable predictor for treatment results.

**Aim:** To investigate the prevalence and impact of anaemia in naive lymphoma patients.

**Materials and Methods:** This hospital-based, cross-sectional study was conducted in the Department of Pathology at Geetanjali Medical College and Hospital, Udaipur, Rajasthan, India, from January 2019 to December 2022. A total of 66 patients diagnosed with lymphoid malignancies were included in the study. Various parameters of lymphoma cases were assessed to determine the presence of anaemia and its association with demographic features, disease stage, and haematological indices. Statistical analysis was carried out using Statistical Package for Social Sciences (SPSS) version 20.0 The Pearson's Chi-square test was used to analyse the difference in the prevalence of anaemia in different groups.

**Results:** The mean age of the study patients was 47.35±20.60 years. The present study included 66 patients with lymphoid malignancies and revealed a high incidence of anaemia among them, with 38 (57.58%) cases presenting with anaemia. There was a male predominance, with 52 (78.79%) out of 66 patients male. Out of the total number of patients, 36 (54.55%) were classified as having stage I and stage II disease, while 30 (45.45%) had stage III and stage IV based on age, Ann Arbor staging, extranodal involvement, Lactate Dehydrogenase (LDH) level, and lymphoma prognostic score. Differentiation between anaemic and non anaemic patients was made by statistical analysis. Based on the findings from the complete blood count, the patients were categorised according to the severity and type of anaemia. It was determined that 38 out of 66 patients, accounting for 57.58%, had anaemia.

**Conclusion:** Anaemia was more prevalent in younger patients and females. Microcytic hypochromic anaemia and Anaemia of Chronic Disease (ACD) were the most common types observed. Anaemia was associated with bone marrow infiltration and advanced disease stages. The present study emphasised the importance of early diagnosis and appropriate management of anaemia in lymphoma patients, as it can negatively impact treatment outcomes and reduce QoL.

**Keywords:** Hodgkin's lymphoma, Lymphoid malignancies, Non Hodgkin's lymphoma

## INTRODUCTION

The frequency of lymphoma is progressively rising. The incidence of Non Hodgkin's Lymphoma (NHL) has been on the rise in recent decades, and within the category of B-cell lymphomas, the most frequently diagnosed type is Diffuse Large B-cell Lymphoma (DLBCL) [1]. A key clinical feature of lymphoid malignancies is anaemia, as it is a significant consequential and frequent problem in these patients. Various studies have reflected the prevalence of anaemia, be it 26% in Chronic Lymphocytic Leukemia (CLL), 49% in NHL, and 37.4% in Hodgkin's Lymphoma (HL) during diagnosis in patients affected with these disorders [2,3]. The impact of anaemia goes beyond physical symptoms and can negatively affect functional capacity and QoL [4,5]. Furthermore, it is important to recognise that anaemia has been consistently linked to a negative prognosis and increased mortality rates [6,7].

Anaemia is a significant adverse prognostic factor for the outcome of treatment, especially when there is bone marrow involvement. Furthermore, anaemia in patients with lymphoma can manifest with various symptoms including shortness of breath, cardiovascular complications, reduced performance status, impaired cognitive function, and fatigue. These symptoms can significantly impact the overall well-being and QoL of these individuals [8]. The presence of anaemia has been identified as a predictive factor for event-free and disease-free survival in patients diagnosed with lymphoma. Moreover, persistent anaemia after chemotherapy is strongly associated with the risk of disease relapse [9,10].

The development of anaemia in lymphoma patients is attributed to multiple mechanisms, which may occur in isolation or combination. These mechanisms comprise nutritional deficiencies, Anaemia of Chronic Disease (ACD), bone marrow infiltration, Autoimmune Haemolytic Anaemia (AIHA), and blood loss [11]. It has been identified that several inflammatory mediators, including Interleukin 1 (IL-1), Interleukin 6 (IL-6), gamma interferon, and Tumour Necrosis Factor (TNF), can hinder erythropoiesis. Increased levels of cytokines such as IL-6 are known to elevate hepcidin levels, leading to restricted iron absorption, resulting in ACD, which can manifest with characteristic symptoms [12-14].

According to a study conducted by Tisi MC et al., elevated IL-6 levels were identified as a significant factor contributing to the development of anaemia in patients with DLBCL. Anaemia in patients with lymphoma can also be attributed to abnormal iron utilisation, inappropriately low serum erythropoietin levels, and a decreased response of the bone marrow to erythropoietin, leading to impaired production of red blood cells [15]. In various types of cancer, there is significant evidence that the systemic immune response of the host is an independent and reliable prognostic factor. ACD is the primary type of anaemia in lymphoma, which worsens the burden of the disease. Secondary anaemia due to marrow involvement, vitamin

B12 deficiency, Iron Deficiency Anaemia (IDA), and haemolytic anaemia are also commonly observed in these patients [8]. Severe anaemia in advanced stages is often associated with a poor prognosis, decreased survival rates, and diminished QoL [11,16]. In developing countries, a significant number of lymphoma patients are diagnosed with anaemia, often caused by bone marrow involvement, and are at advanced stages of the disease [8,11].

The average life longevity and well-being of lymphoma affected patients can be improved by treating anaemia through the diagnosis of the type and severity of anaemia based on simple blood testing. Therefore, it is essential that anaemia is identified and treated in all lymphoma patients initially. The aim of the present study was to determine the prevalence of anaemia in naive lymphoma patients and its association with haematological indices, disease stage, and demographic features.

## MATERIALS AND METHODS

A cross-sectional study was undertaken at the Department of Pathology at Geetanjali Medical College and Hospital, Udaipur, Rajasthan, India, spanning from January 2019 to December 2022. The study involved a total of 66 lymphoma patients based on tissue biopsy and Immunohistochemistry (IHC). Following approval from the Institutional Ethical Committee (IEC) (GU/HREC/EC/2022/2159), the study included patients who had accessible pretreatment tissue biopsies, marrow specimens, complete blood count data, and IHC results available.

**Inclusion criteria:** All biopsy samples of lymphoma patients that were received by the pathology department throughout the designated study period were included in the study.

**Exclusion criteria:** Patients with impaired kidney function (serum creatinine >2 mg/dL), individuals who had undergone blood transfusions or received iron, folic acid, or vitamin B complex supplements within the preceding two weeks, patients with relapsed disease, and those who had received prior treatment were excluded from the study.

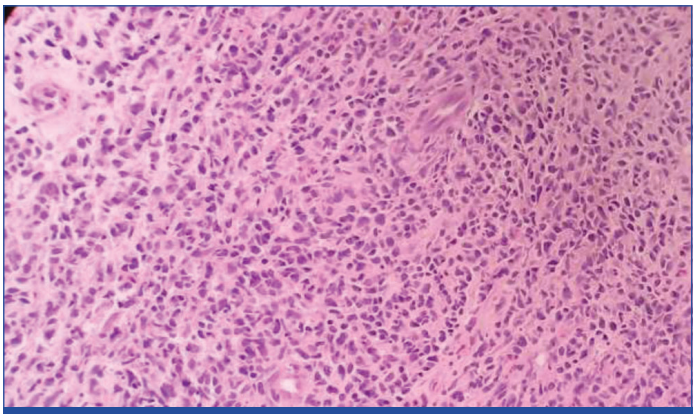
### Study Procedure

In patients with a confirmed diagnosis of lymphoma, various parameters including demographic features, complete haemogram, red cell indices {such as Mean Corpuscular Volume (MCV), Mean Corpuscular Haemoglobin (MCH), Mean Corpuscular Haemoglobin Concentration (MCHC), Red blood cell Distribution Width (RDW)}, reticulocyte count, Direct Coombs Test (DCT), biochemistry (including renal and liver function tests, LDH, iron profile, Total Iron Binding Capacity (TIBC), ferritin, vitamin B12, folic acid, erythropoietin levels), and bone marrow aspirate/biopsy were assessed to determine the presence of anaemia and other relevant parameters. The assessment was made by comparing the obtained values with the age-specific normal ranges as described in the 10$^{th}$ edition of Practical Haematology by Lewis SM et al., [17]. The peripheral blood film for diagnostic purposes was stained using Leishman stain, and a manual differential count was conducted for each patient. According to the World Health Organisation (WHO), anaemia is defined as mild when Haemoglobin (Hb) levels are between 11.0-12.9 g/dL for men and 11.0-11.9 g/dL for women, moderate (Hb level 8-10.9 g/dL), and severe when Hb level is less than 8 g/dL [18]. Vitamin B12 deficiency was defined as serum B12 levels below 160 pg/mL, and folate deficiency was defined as folate levels below 3 ng/dL [17]. The presence of Autoimmune Hemolytic Anemia (AIHA) was determined by a positive DCT along with evidence of haemolysis observed on the peripheral smear (such as spherocytosis, agglutination, or polychromasia).

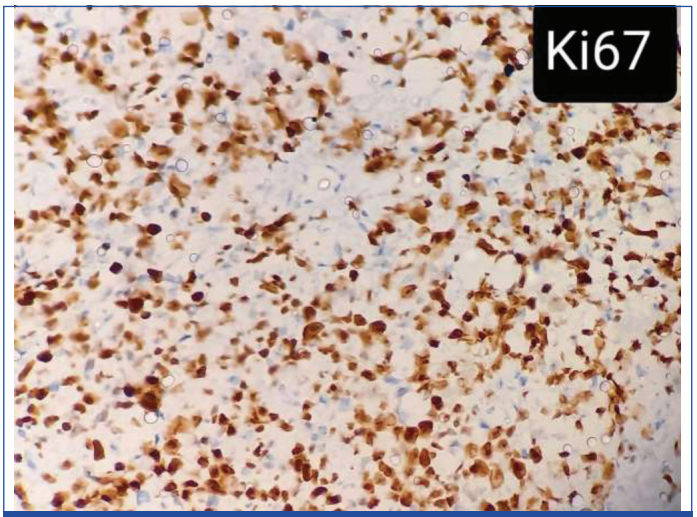
In all cases, relevant tissue biopsy slides stained with Haematoxylin and Eosin stain (H&E), as well as IHC interpretation, were carefully examined by an expert pathologist. The categorisation of lymphoma according to WHO classification was determined based on the IHC findings using immature and mature B and T cell markers like Cluster of Differentiation 34 (CD34), Terminal Deoxynucleotidyl Transferase (TdT), CD3, CD5, CD10, CD23, CD43, CD103, BCL6, Sig, clg, Multiple Myeloma oncogene-1 (MUM1), Cyclin D1, etc., [Table/Fig-1-6] [19].

## STATISTICAL ANALYSIS

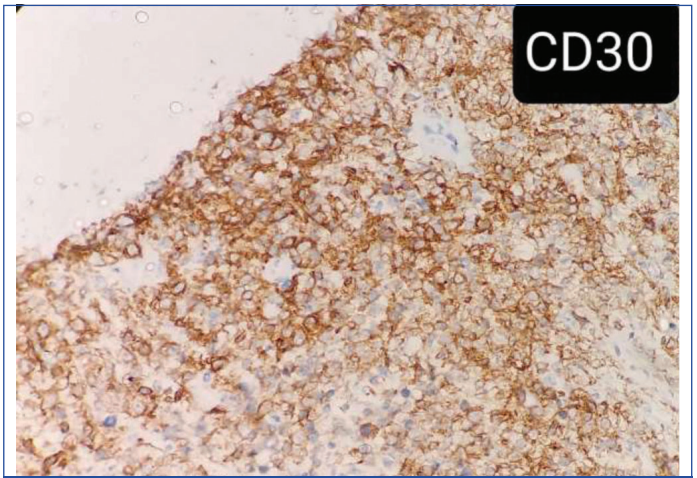
Statistical analysis was carried out using SPSS software version 20.0. (Chicago, IL, USA). Continuous variables were stated as mean±Standard Deviation (SD), and categorical variables were computed as frequencies (n) and percentages (%). The frequency of anaemia was calculated using the simple prevalence formula as the number of patients in each diagnosis divided by the total number of cases. The Pearson's Chi-square test was used to analyse the difference in the prevalence of anaemia in different groups.



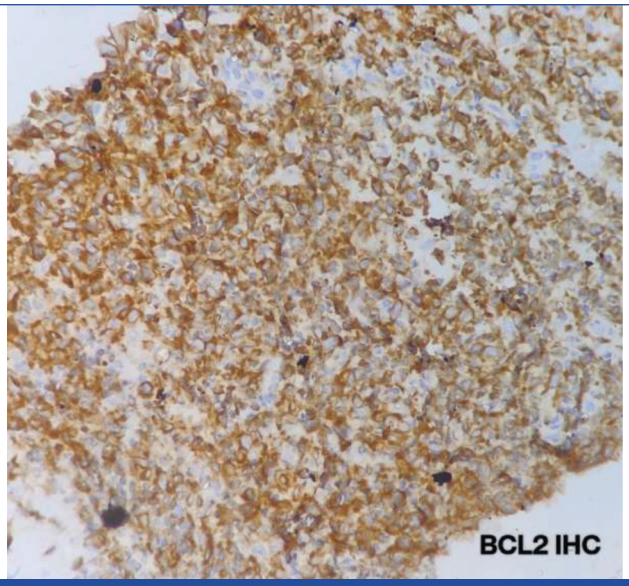
**[Table/Fig-1]:** Hodgkin's lymphoma (H&E stain X100).



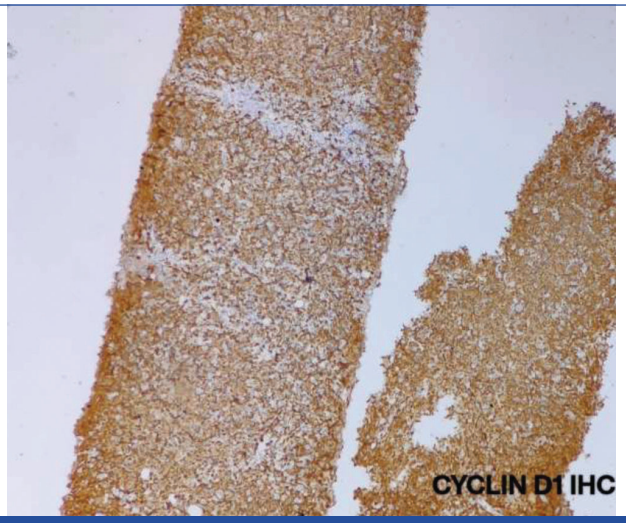

**[Table/Fig-2]:** Diffuse Large B-cell Lymphoma (DLBCL): positive staining for Ki67 in more than 70% of the malignant lymphoid cells (Ki67 IHC).



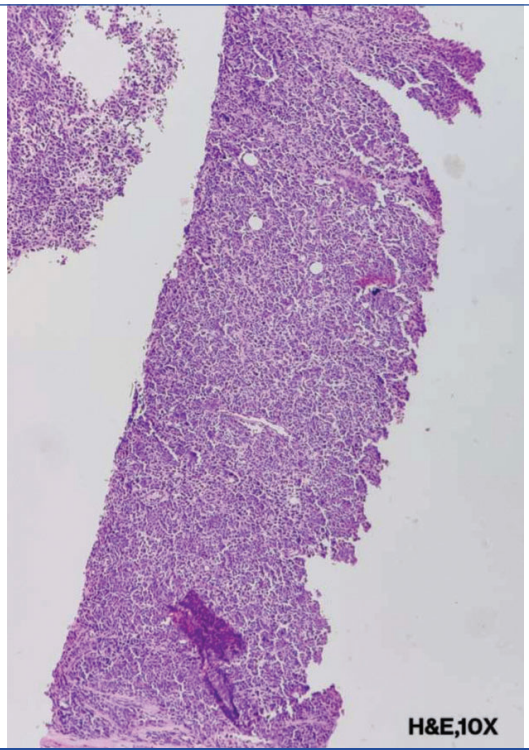

**[Table/Fig-3]:** Classical Hodgkin's lymphoma: Reed-Sternberg (RS) cells showing positive stain for CD30.




**[Table/Fig-4]:** Diffuse large B-cell lymphoma: positive staining for B-cell Lymphoma-2 (BCL-2, IHC, X200).




**[Table/Fig-5]:** Mantle cell lymphoma: positive staining for Cyclin D1 (Cyclin D1 IHC scanner view).




**[Table/Fig-6]:** Non Hodgkins lymphoma: showing complete effacement of lymphoid architecture (H&E X10).

## RESULTS

A total of 66 patients diagnosed with lymphoid malignancies were included in the study conducted during the designated period. The average age of the patients was 47.35±20.60 years. Out of the total 66 patients, 44 patients (66.67%) were below the age of 60 years, while 22 patients (33.33%) were 60 years or older. In terms of gender distribution, there was a male predominance, with 52 out of 66 patients (78.79%) being male. Among all the 66 patients, 36 (54.55%) were classified as having stage I and II disease, while 30 (45.45%) had higher stages, i.e., stage III and IV.

Based on the findings from the complete haemogram, the patients were categorised according to the severity of anaemia. Among the 66 lymphoma patients, it was determined that 38 of them, accounting for 57.58%, had anaemia based on their Hb levels. The Hb levels of the lymphoma patients ranged from 4.3 g/dL to 15.9 g/dL, with an average of 10.85±2.70 (mean±SD). Out of the total 66 patients, seven patients (10.66%) had mild anaemia, 26 patients (39.4%) had moderate anaemia, and 5 patients (7.6%) had severe anaemia, while 28 patients (44.42%) did not have anaemia [Table/Fig-7].

| Parameters | | Frequency (n) | Percentage (%) |
|---|---|---|---|
| Grades of anaemia (n=38) | No anaemia | 28 | 42.4 |
| | Mild | 7 | 10.6 |
| | Moderate | 26 | 39.4 |
| | Severe | 5 | 7.6 |
| Types of anaemia (n=38) | Dimorphic | 6 | 15.79 |
| | Macrocytic | 2 | 5.26 |
| | MCHC | 17 | 44.74 |
| | NCNC | 13 | 34.21 |

**[Table/Fig-7]:** Types and grading of anaemia (N=66).
MCHC: Microcytic hypochromic; NCNC: Normocytic normochromic

Upon further analysis, it was observed that the incidence of anaemia was higher in females, with 9 (64.29%) out of 14 female patients being anaemic, compared to 29 (55.77%) out of 52 male patients. This indicates a higher prevalence of anaemia among females [Table/Fig-8].

| Parameters | | Total n (%) | Anaemia | | p-value |
|---|---|---|---|---|---|
| | | | Yes n (%) | No n (%) | |
| Age (in years) | ≤60 | 44 (66.67) | 26 (59.09) | 18 (40.91) | 0.860 |
| | >60 | 22 (33.33) | 12 (54.55) | 10 (45.45) | |
| Gender | Male | 52 (78.79) | 29 (55.77) | 23 (44.23) | 0.789 |
| | Female | 14 (21.21) | 9 (64.29) | 5 (35.71) | |
| Ann arbor stage | I-II | 30 (45.45) | 15 (50) | 15 (50) | 0.375 |
| | III-IV | 36 (54.55) | 23 (63.89) | 13 (36.11) | |
| International prognostic Index | 0-II | 36 (54.55) | 16 (44.44) | 20 (55.56) | 0.034 |
| | III-IV | 30 (45.45) | 22 (73.33) | 8 (26.67) | |
| PLT (/µL) | 150-450 | 45 (68.18) | 25 (55.56) | 20 (44.44) | 0.827 |
| | ≤150 or ≥450 | 21 (31.82) | 13 (61.9) | 8 (38.1) | |
| ALC (/mm$^3$) | ≤600 | 4 (6.06) | 2 (50) | 2 (50) | 0.837 |
| | ≥600 | 62 (93.94) | 36 (58.06) | 26 (41.94) | |
| TLC (/µL) | ≤12000 | 51 (77.27) | 33 (64.71) | 18 (35.29) | 0.062 |
| | ≥12000 | 15 (22.73) | 5 (33.33) | 10 (66.67) | |
| Extranodal involvement | Absent | 13 (19.70) | 8 (61.54) | 5 (38.46) | 0.992 |
| | Present | 53 (80.30) | 30 (56.60) | 23 (43.40) | |
| Haemoglobin | Mean±SD | | 8.95±1.77 | 13.43±1.034 | <0.001 |

**[Table/Fig-8]:** Characteristics of lymphoma patients presenting with anaemia.
PLT: Platelet; ALC: Absolute lymphoid count; TLC: Total leucocyte count (N=66)

Furthermore, upon analysing the results, it was found that anaemia was more prevalent among younger patients (age <60 years)

compared to older patients (age >60 years). Among the participants, 44 (66.67%) patients in the younger age group experienced anaemia, whereas 22 (33.33%) in the older age group were affected by anaemia. The bivariate Chi-square test was conducted, and the results are presented in [Table/Fig-8]. The analysis revealed that anaemic lymphoma patients did not show a statistically significant association with age (p=0.860), sex (p=0.789), Ann Arbor stage (p=0.375), abnormal platelet count (p=0.827), or absolute lymphocyte count less than 600/mm$^3$ (p=0.837). Significant differences were noted in the levels of Hb between lymphoma patients with and without anaemia (p<0.001).

There was variability in the grading of anaemia across all types of lymphoma as shown in [Table/Fig-7]. Microcytic hypochromic anaemia was identified as the leading cause of anaemia in the present study, observed in 17 cases (44.74%), followed by anaemia of chronic disorder in 13 cases (34.21%). Dimorphic anaemia and purely megaloblastic anaemia accounted for 6 (15.79%) cases and 2 cases (5.26%), respectively. In 42.42% of patients, the Hb levels were within the normal range, indicating the absence of anaemia. Among the 66 patients, 13 showed malignant lymphoma cell infiltration in the bone marrow. Out of these 13 patients, only 8 (61.54%) had moderate anaemia, while the remaining patients did not have any type of anaemia [Table/Fig-9]. In the present study, majority of the patients were diagnosed with DLBCL 34 (51.52%), and more than 50% of them exhibited varying degrees of anaemia (55.88%). Among the patients with Hodgkin lymphoma, all of them presented with different degrees of anaemia, as indicated in [Table/Fig-9].

| Parameters | | % of cases with anaemia n (%) |
|---|---|---|
| Bone marrow infiltration | Seen | 8/13 (61.54) |
| | Not seen | 30/53 (56.60) |
| Ann Arbor stage | I-II | 15/30 (50.00) |
| | III-IV | 23/36 (63.89) |
| International prognostic index | 0-II | 16/36 (44.44) |
| | III-IV | 22/30 (73.33) |
| Diagnosis | Anaplastic large cell lymphoma | 1 (100) |
| | Burkitt's | 1 (100) |
| | Diffuse large B-cell lymphoma | 19/34 (55.88) |
| | Follicular lymphoma | ½ (50) |
| | Hodgkin lymphoma | 5/5 (100) |
| | Lymphoblastic lymphoma | ½ (50) |
| | Marginal zone lymphoma | 0 |
| | PTCL | 1 case (100) |
| | T-cell lymphoblastic lymphoma | 2/4 (50) |
| | Others | 6/14 (42.86) |
| PLT | Normal (150-450) | 25/45 (55.56) |
| | Low or elevated (<150 or >450) | 13/21 (61.90) |

**[Table/Fig-9]:** Distribution of anaemia cases according to various parameters (n=66).
PLT: Platelet; PTCL: Percutaneous T-cell lymphoma

Patients with advanced International Prognostic Index (IPI) scores exhibited anaemia in 73.33% of patients. In the present study, authors found that anaemia was present in all cases of Anaplastic Large Cell Lymphoma (ALCL), Burkitt Lymphoma (BL), HL, and Peripheral T-cell lymphoma (PTCL). Additionally, a relatively high prevalence of anaemia, i.e., 55.88%, was observed in DLBCL cases [Table/Fig-8,9].

## DISCUSSION

Anaemia is a common issue among cancer patients, particularly prevalent among those with lymphoma. Evidence suggests that in lymphoma patients, anaemia is a significant prognostic factor that can negatively impact therapy outcomes and increase mortality rates [6,7,11]. In addition to affecting survival, anaemia can significantly reduce the QoL in these patients, leading to symptoms such as fatigue, shortness of breath, cardiovascular complications, cognitive impairment, and a decline in overall performance status. In the present study, a high incidence of anaemia (57.58%) among patients with lymphoid malignancies were observed. Anaemia was more frequently observed in women compared to men (64.2% vs 55.7%) [20]. Finding of the current study may be attributed to the higher prevalence of anaemia among women in the general population.

The present study showed the prevalence of anaemia in patients with DLBCL and HL was 55.8% and 100%, respectively. Similar findings have been reported by others, with anaemia rates ranging from 32% to 49% in NHL and a prevalence of 37.4% in HL [3,6,21,22]. In addition to its impact on survival and poor prognosis, anaemia also significantly compromises the QoL of patients. A survey conducted by the European Cancer Anaemia Survey (ECAS) revealed that nearly 39% of lymphoma patients enrolled in the study had anaemia. Interestingly, a relatively low percentage (47.3%) of anaemic patients in the survey received treatment for their anaemia, highlighting the crucial importance of early identification and appropriate management of anaemia in lymphoma patients [7,23].

In the present study, out of the total 66 lymphoma patients, more than half of them (38 cases, 57.58%) presented with anaemia. This prevalence of anaemia is slightly higher than the findings reported by Yasmeen T et al., from Pakistan and Ghosh J et al., from India, who observed a prevalence of 42.4% and 45%, respectively [8,11]. Similarly, other authors such as Moullet I and Morrow TJ et al., reported prevalence rates of 32% and 35.3% [6,24]. These variations in prevalence may be attributed to factors such as socioeconomic conditions and accessibility to healthcare. The presence of untreated anaemia among a significant proportion of the population can have a considerable impact on their overall health status. The present study demonstrated a higher incidence of lymphoma in males, with 52 cases (78.79%), compared to females with 14 cases (21.21%). This finding aligns with a previous study conducted by Bukhari U et al., which also reported a higher incidence of lymphoma in males (69%) compared to females (31%) [25]. Interestingly, despite the higher incidence of lymphoma and a larger male population in present study, anaemia was more common in females. This observation may be attributed to menstrual blood loss experienced by young females in the reproductive age group [11,24]. In lymphoma patients, anaemia can arise from various factors occurring simultaneously. The most prevalent cause of anaemia in the present study was microcytic hypochromic anaemia resulting from iron deficiency, accounting for 17 cases, 44.74% of cases. This finding contrasts with the results of a study conducted by Yasmeen T et al., in which anaemia of chronic disorder was identified as the predominant cause of anaemia [8]. These variations in findings may be attributed to differences in patient populations and the underlying characteristics of the disease.

Anaemia of chronic disorder observed in 13 cases, 34.21% of lymphoma patients in present study, emerged as the second most common cause of anaemia. The development of this type of anaemia in lymphoma patients may be attributed to mechanisms such as increased levels of inflammatory cytokines, impaired production of erythropoietin, and bone marrow erythroid hypoplasia, resulting in decreased red cell survival. These findings are consistent with those of a separate study, reinforcing the understanding of anaemia in the context of lymphoma [6,26,27].

In the present study, a significant association between the presence of anaemia in lymphoma patients and a high prognostic score was noted. (p=0.034). This finding aligns with the results of a study conducted by Hardianti MS et al., suggesting a consistent relationship between anaemia occurrence and prognostic scores

in lymphoma patients [28]. The systemic circulation of lymphoma patients may exhibit increased production of IL-6, which in turn stimulates the overproduction of hepcidin. Increased levels of hepcidin can lead to the retention of iron in macrophages and iron-absorbing enterocytes, as well as hinder the release of iron from the reticuloendothelial system and liver. This process can result in the sequestration of iron and contribute to the development of iron-deficiency anaemia. In the present study, 44.74% of patients with iron-deficiency anaemia was found [14,29].

Hohaus S et al., conducted a study involving patients older than 45 years of age and observed higher levels of hepcidin associated with anaemia [14]. However, in the present study, authors did not find a significant impact of age on the occurrence of anaemia in lymphoma patients. Interestingly, anaemia was more frequently observed in younger patients compared to older patients, which aligns with the findings of a previous study involving DLBCL patients that also found no association between the age group above 60 years and anaemia (p=0.860). In the present study, there was no significant correlation found between the presence of extranodal involvement and multiple extranodal sites with the incidence of anaemia in lymphoma patients (p=0.992). This finding indicates that these factors may not play a significant role in contributing to the development of anaemia in lymphoma patients, as observed in the present study. These findings align with the results reported by Hardianti MS et al., and Guney N et al., [28,30].

Furthermore, our study did not reveal a significant correlation between anaemia and abnormal platelet count (either low $<150\times10^9$/L or elevated $>450\times10^9$/L) (p=0.827). This contrasts with the findings of Hardianti MS et al., who found a significant association between anaemia and abnormal platelet count [28]. In the present study, lymphocytopenia was evident in a minority of patients (4 cases; 6.06%). However, we did not observe a significant correlation between lymphocyte count and the presence of anaemia. This finding diverges from the results reported by Hardianti MS et al., and Ray-Coquard I et al., who identified lymphocytopenia as a protective factor against anaemia in lymphoma [28,31]. It is worth noting that the lack of agreement in findings may be attributed to the limited sample size in the present study.

### Limitation(s)

The study was conducted at a single centre, which could introduce referral bias and limit the generalisability of the findings to the broader population. As it was a retrospective study, not all patients underwent the necessary tests to fully characterise the underlying cause of anaemia, particularly in terms of assessing the haemolytic profile.

## CONCLUSION(S)

The findings of the present study highlights the significant prevalence and impact of anaemia in newly diagnosed lymphoma patients. The presence of anaemia not only signifies a poor prognosis and reduced survival but also negatively affects the patient's QoL. It is crucial to promptly identify, investigate, and treat anaemia in all lymphoma patients upon presentation. To further enhance our understanding and improve patient outcomes in lymphoma, future research should focus on predicting and addressing the causes of anaemia, including examining cytokine levels that contribute to its pathogenesis. Given the multifactorial nature of anaemia in patients with lymphoid malignancies, a thorough investigation of its underlying causes is essential for effective management. Moreover, careful monitoring of lymphoma patients is warranted to ensure timely intervention and optimal management of anaemia. By effectively addressing anaemia, the overall management of lymphoma can be enhanced and provide better care, particularly for anaemic patients.

## REFERENCES


[1] Lee SJ, Suh CW, Lee SI, Kim WS, Lee WS, Kim HJ, et al. Clinical characteristics, pathological distribution, and prognostic factors in non Hodgkin lymphoma of Waldeyer's ring: Nationwide Korean study. Korean J Intern Med. 2014;29(3):352. Doi: 10.3904/kjim.2014.29.3.352.

[2] Agrawal N, Naithani R, Mahapatra M, Panigrahi I, Kumar R, Pati HP, et al. Chronic lymphocytic leukemia in India-a clinico-hematological profile. Hematology. 2007;12(3):229-33.

[3] Birgegård G, Gascón P, Ludwig H. Evaluation of anaemia in patients with multiple myeloma and lymphoma: Findings of the European Cancer Anaemia Survey. Eur J Haematol 2006;77(5):378-86.

[4] Ludwig H, Strasser K. Symptomatology of anaemia. Semin Oncol. 2001;28(2 Suppl 8):07-14.

[5] Cella D. Factors influencing QoL in cancer patients: Anaemia and fatigue. Semin Oncol. 1998;25(3Suppl 7):43-46.

[6] Moullet I, Salles G, Ketterer N, Dumontet C, Bouafia F, NeidhartBerard EM, et al. Frequency and significance of anaemia in nonHodgkin's lymphoma patients. Ann Oncol. 1998;9(10):1109-15.

[7] Hasenclever D, Diehl V. A prognostic score for advanced Hodgkin's disease. International Prognostic Factors Project on Advanced Hodgkin's Disease. N Engl J Med. 1998;339(21):1506-14.

[8] Yasmeen T, Ali J, Khan K, Siddiqui N. Frequency and causes of anaemia in Lymphoma patients. Pak J Med Sci. 2019;35(1):61-65. https://doi. org/10.12669/pjms.35.1.91.

[9] Troppan KT, Melchardt T, Deutsch A, Schlick K, Stojakovic T, Bullock MD, et al. The significance of pretreatment anaemia in the era of R-IPI and NCCN-IPI prognostic risk assessment tools: A dual center study in diffuse large B-cell lymphoma patients. Eur J Haematol. 2015;95(6):538-44. Doi: 10.1111/ejh.12529.

[10] Hong J, Woo HS, Kim H, Ahn HK, Sym SJ, Park J, et al. Anaemia as a useful biomarker in patients with diffuse large B-cell lymphoma treated with R-CHOP immunochemotherapy. Cancer Sci. 2014;105(12):1569-75. Doi: 10.1111/cas.12544.

[11] Ghosh J, Singh RK, Saxena R, Gupta R, Vivekanandan S, Sreenivas V, et al. Prevalence and aetiology of anaemia in lymphoid malignancies. Natl Med J India. 2013;26(2):79-81.

[12] Mamus SW, Beck-Schroeder S, Zanjani ED. Suppression of normal human erythropoiesis by gamma interferon in vitro. Role of monocytes and T lymphocytes. J Clin Invest. 1985;75(5):1496-503. Doi: 10.1172/JCI 111853.

[13] Means RT, Dessypris EN, Krantz SB. Inhibition of human erythroid colony-forming units by interleukin-1 is mediated by y-interferon. J Cell Physiol. 1992;150(1):59-64. Doi: 10.1002/jcp.1041500109.

[14] Hohaus S, Massini G, Giachelia M, Vannata B, Bozzoli V, Cuccaro A, et al. Anaemia in Hodgkin's Lymphoma: The role of interleukin-6 and Hepcidin. J Clin Oncol. 2010;28(15):2538-43. https://doi. org/10.1200/jco.2009.27.6873.

[15] Tisi MC, Bozzoli V, Giachelia M, Massini G, Ricerca BM, Maiolo E, et al. Anaemia in diffuse large B-cell non-Hodgkin lymphoma: the role of interleukin-6, hepcidin and erythropoietin. Leuk Lymphoma. 2014;55(2):270-75. Doi: 10.3109/10428194.2013.802314.

[16] Shi H, Jiang Y, Cao H, Zhu H, Chen B, Ji W. Nomogram based on systemic immune-inflammation index to predict overall survival in gastric cancer patients. Dis Markers. 2018;2018:1787424.

[17] Lewis SM, Bain BJ, Bates I. Practical Hematology. Tenth Edition, Philadelphia: Churchill Livingstone; 2009: Pp. 14-17.

[18] Nutritional anaemias. Report of a WHO scientific group. Geneva, World Health Organization, 1968. (WHO Technical Report Series, No. 405). Available at: http://whqlibdoc.who.int/trs/WHO_TRS_405.pdf.

[19] Swerdlow SH, Compo E, Harris NL, Joffe ES, Pileri SA, Stein H, Thiele J (Eds): WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (Revised 4th edition). IARC: Lyan 2017. pp. 11-12.

[20] International Institute for Population Sciences (IIPS) and Macro International. National Family Health Survey (NFHS-3), 2005-06, Vol. II, India. Mumbai: IIPS; 2007.

[21] Conlan MG, Armitage JO, Bast M, Weisenburger DD. Clinical significance of hematologic parameters in non-Hodgkin's lymphoma at diagnosis. Cancer. 1991;67(5):1389-95.

[22] Bloomfield CD, McKenna RW, Brunning RD. Significance of haematological parameters in the non-Hodgkin's malignant lymphomas. Br J Haematol. 1976;32(1):41-46.

[23] Naoum FA. Iron deficiency in cancer patients. Rev Bras Hematol Hemoter. 2016;38(4):325-30. Doi: 10.1016/j. bjhh.2016.05.009.

[24] Morrow TJ, Volpe S, Gupta S, Tannous RE, Fridman M. Anaemia of cancer in intermediate-grade non-Hodgkin's lymphoma. Southern Med J. 2002;95(8):889-96.

[25] Bukhari U, Jamal S, Lateef F. Non Hodgkin lymphoma-A study. Pak Oral Dental J. 2015;35(3):412-15.

[26] Zucker S. Anaemia in cancer. Cancer Invest. 1985;3(3):249-60. Doi: 10.3109/07357908509039786.

[27] Faquin WC, Schneider TJ, Goldberg MA. Effect of inflammatory cytokines on hypoxia-induced erythropoietin production. Blood. 1992;79(8):1987-94.

[28] Hardianti MS, Rizki SHM, Arkananda H, Dhyanti AL, Setiawan SA, Indrawati, et al. Anaemia in lymphoma patients in Indonesia: The prevalence and predictive factors. Asian Pac J Cancer Biol. 2021;6(4):235-41.

[29] Gomes MM, Oliva T, Pinto A. Autoimmune hemolytic anaemia and hodgkin's disease: An unusual paediatric association. Case Rep Pediatr. 2016;2016:4598587. https://doi.org/10.1155/2016/4598587.

[30] Guney N, Soydinc HO, Basaran M, Bavbek S, Derin D, Camlica H, et al. Serum levels of interleukin-6 and interleukin-10 in turkish patients with aggressive non-Hodgkin's lymphoma. Asian Pac J Cancer Prev. 2009;10(4):669-74.

[31] Ray-Coquard I, Cropet C, Van Glabbeke M, Sebban C, Le Cesne A, Judson I, et al. Lymphopenia as a prognostic factor for overall survival in advanced carcinomas, sarcomas, and lymphomas. Cancer Res. 2009;69(13):5383-91.

**PARTICULARS OF CONTRIBUTORS:**
1. Associate Professor, Department of Nephrology, Geetanjali Medical College and Hospital, Udaipur, Rajasthan, India.
2. Professor, Department of Pathology, Geetanjali Medical College and Hospital, Udaipur, Rajasthan, India.
3. Postgraduate, Department of Pathology, Geetanjali Medical College and Hospital, Udaipur, Rajasthan, India.
4. Postgraduate, Department of Pathology, Geetanjali Medical College and Hospital, Udaipur, Rajasthan, India.
5. Intern, Department of Pathology, Geetanjali Medical College and Hospital, Udaipur, Rajasthan, India.
6. Intern, Department of Pathology, Geetanjali Medical College and Hospital, Udaipur, Rajasthan, India.
7. MBBS Student, Department of Medicine, AIIMS, Udaipur, Rajasthan, India.

**NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:**
Dr. Geeta W Mukhiya,
19, Ashirwad Nagar, Shobhagpura, Udaipur-313001, Rajasthan, India.
E-mail: mukhiyageeta@gmail.com

**PLAGIARISM CHECKING METHODS:** [Jain H et al.]
- Plagiarism X-checker: Jul 11, 2023
- Manual Googling: Aug 17, 2023
- iThenticate Software: Oct 02, 2023 (13%)

**ETYMOLOGY:** Author Origin

**EMENDATIONS:** 8

**AUTHOR DECLARATION:**
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Jul 10, 2023**
Date of Peer Review: **Aug 15, 2023**
Date of Acceptance: **Oct 04, 2023**
Date of Publishing: **Nov 01, 2023**