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COMPREHENSIVE ANALYSIS OF LYMPHOPROLIFERATIVE DISEASES: SUBTYPES, DEMOGRAPHICS, AND CLINICAL IMPLICATIONS

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Abstract

Background: Lymphoproliferative diseases encompass a spectrum of heterogeneous conditions, necessitating a comprehensive understanding for effective management. This study aimed to analyze lymphoma subtypes, demographic variations, and their clinical implications.

Introduction: The study focuses on a cohort of 57 subjects diagnosed with lymphoproliferative diseases between November 2008 and December 2011. The investigation aimed to characterize lymphoma subtypes, elucidate age-gender variations, and analyse organ and extra-nodal site involvements. **Methodology:** This retrospective study involved 57 subjects diagnosed with various lymphoproliferative diseases within a multi-specialty oncology hospital between November 2008 and December 2011. Detailed clinical records, including morphological, immune-phenotyping, and cytogenetic data, were meticulously reviewed and analysed. Morphological evaluations comprised peripheral blood and bone marrow smear analyses, stained with Leishman and May-Grunwald Giemsa stains, respectively. Immunophenotyping was conducted using a panel of monoclonal antibodies, and cytogenetic analyses involved short-term unstimulated cultures from fresh bone marrow aspirates, subjected to G-banding and Fluorescent In Situ Hybridization (FISH) assays. **Results:** Prominent findings included a notable prevalence of T cell non-Hodgkin lymphoma with lymph node involvement in younger individuals. Gender-based variations showcased

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diverse lymphoma subtypes in females across age brackets. Organ involvement analysis revealed distinct infiltrations in liver, spleen, and bone marrow, with extensive extra-nodal manifestations observed. **Conclusion:** The study's outcomes underscore the significance of personalized treatment strategies based on specific subtypes and demographic profiles. Clinical implications highlight the need for tailored diagnostic approaches and emphasize the importance of precise staging and disease monitoring for optimized patient care.

Keywords: Lymphoproliferative diseases, lymphoma subtypes, demographic variations, organ involvement, clinical implications.

Introduction

Chronic Lymphoproliferative Disorders (CLPD) constitute a diverse spectrum of hematologic malignancies characterized by clonal lymphocyte proliferation.[1]. The comprehensive diagnostic framework relied upon a multifaceted approach encompassing clinical data, morphologic assessments, immunophenotyping, and cytogenetic analyses from peripheral blood and bone marrow specimens collected under stringent aseptic conditions.

Morphological classification followed established guidelines, discerning Chronic Lymphocytic Leukaemia (CLL) and Prolymphocytic Leukaemia (PLL) based on characteristic hematopathological features. CLL typically exhibited small cells with condensed chromatin, while PLL manifested larger cells with prominent nucleoli.[2]

In the context of India's current lymphoproliferative disease scenario, recent trends highlight an increasing incidence and varied distribution of these disorders across different regions. Factors such as genetic predisposition, environmental influences, and socioeconomic disparities contribute to this evolving landscape. As per recent statistics from the Indian Council of Medical Research (ICMR), there's a noticeable rise in lymphoproliferative disorders, necessitating a more nuanced understanding of their clinical and molecular spectra in the Indian population.[3,4]

Immunophenotyping, employing a panel of monoclonal antibodies via flow cytometry, facilitated precise characterization of lymphocytic populations. The assessment of antigen expression levels aided in subtype differentiation and prognostication, aligning with contemporary diagnostic paradigms.[5] Cytogenetic analyses, encompassing G-banding and Fluorescent In Situ Hybridization (FISH), revealed crucial chromosomal aberrations associated with CLPD, offering insights into disease mechanisms and therapeutic targets in the Indian context.

This retrospective investigation amalgamates essential morphological, immunophenotypic, and cytogenetic assessments, contributing pivotal insights into the classification and characterization of CLPD, particularly in the evolving landscape of lymphoproliferative diseases in India.

Methodology

This retrospective study investigated a cohort comprising 57 subjects diagnosed with Chronic Lymphoproliferative Disorders (CLPD) at a leading multispecialty oncology hospital between November 2008 and December 2011. Institutional review board approval and adherence to ethical standards were central to the study's protocol.

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 01, 2024

Under aseptic conditions and local anaesthesia following xylocaine test doses, peripheral blood and bone marrow specimens were collected from the cohort. These samples formed part of the diagnostic workup, and prior informed consent was secured by attending clinicians. Subsequent processing involved the preparation of peripheral blood and bone marrow smears stained with Leishman and May-Grunwald Giemsa stains, respectively.

Classification, based on established criteria, delineated Chronic Lymphocytic Leukaemia (CLL) from Prolymphocytic Leukaemia (PLL) through rigorous evaluation of hematopathological features. CLL diagnosis relied on sustained lymphocytosis exceeding 5x10^9/L for a minimum of 3 months, while PLL exhibited prolymphocyte levels ranging between >10% and <55% among lymphocytes.

Employing a comprehensive panel of monoclonal antibodies (CD45, CD10, CD5, CD19, CD20, CD23, FMC7, CD79b, CD3, CD22, CD25, CD103, CD38, ZAP70, kappa, lambda) sourced from Beckman Coulter, India, blood or bone marrow samples underwent incubation with the relevant antibodies. Analysis utilized a Dako CyAn ADP instrument and SUMMITR software (version 5.4). Positivity for cell antigens was determined by ≥ 20% antigen-expressing cells, graded as strong, moderate, or weak/negative expression.

Cultures derived from fresh bone marrow aspirates underwent G-banding subsequent to exposure to colcemid, fixation, and harvesting. Further analyses involved Fluorescent In Situ Hybridization (FISH) utilizing a panel of seven probes to uncover chromosomal aberrations. All procedures strictly adhered to standardized protocols.

Statistical evaluations, facilitated by SPSS 11.5 software, encompassed ANOVA for parametric data and Chi-square or Kruskal-Wallis tests for non-parametric data. Significance levels were set at $p < 0.05$ to ascertain variations in absolute lymphocyte counts and marker expressions across distinctive categories within this 57-subject cohort.

This comprehensive methodology integrated morphological, immunophenotypic, and cytogenetic assessments, culminating in a holistic understanding of CLPD within the context of this 57-subject cohort. Ethical clearance was taken from institutional ethical committee.

Results

Table 1: Age Distribution in Lymphoma Patients: A Significant Demographic Insight

Age (years)	No. of Patients	Percentage
<10	3	5.26%
10--20	5	8.77%
21-30	6	10.53%
31-40	14	24.56%
41-50	6	10.53%
51-60	10	17.54%
>60	13	22.81%
Total	57	100%

The distribution of lymphoma patients across different age groups was investigated in this study, encompassing a cohort of 57 individuals. The findings revealed notable trends in age distribution among the studied population.

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 01, 2024

Primarily, a distinct pattern emerged wherein patients between 31 and 60 years constituted a substantial majority, encompassing nearly 53% of the total cases. Notably, the age group of 31-40 years exhibited the highest representation, accounting for approximately a quarter (24.56%) of the entire cohort. This was followed closely by individuals aged 51-60 years, constituting 17.54% of the cases. Moreover, patients aged over 60 years contributed significantly to the lymphoma demographic, representing 22.81% of the total subjects.

Conversely, the younger age groups (<30 years) comprised a smaller proportion of the overall patients. Specifically, individuals under 20 years of age accounted for less than 15% collectively. The age group of 41-50 years demonstrated a lower representation, contributing to 10.53% of the cohort.

These findings underscore a distinctive age-related predisposition to lymphoma, with a notable concentration observed in the middle-aged and older demographics. The prominence of cases within the 31-60 years range may suggest potential environmental, genetic, or lifestyle-related factors influencing lymphoma development in these age brackets. However, the comparatively lower representation of cases in younger individuals prompts further investigation into potential etiological factors or differing disease mechanisms contributing to lymphoma onset in various age groups.

Table 2: Significant Symptomatic Manifestations in Lymphoma Patients

Symptomatology	**No. of Patients**	**Percentage**
Weight Loss	17	29.82%
Anorexia	33	57.89%
Fatigue	32	56.14%
Fever	19	33.33%
Dyspnoea	7	12.28%
Bleeding Manifestations	3	5.26%
B Symptoms	25	43.86%
Compressive Symptoms	1	1.75%
Neck Swelling	18	31.58%
Total	57	100%

Symptomatology assessment in lymphoma patients, derived from a cohort of 57 individuals, revealed distinctive patterns, shedding light on prevalent symptomatic presentations within this population.

Anorexia emerged as the most prevalent symptom, affecting approximately 58% of the patients. This was closely followed by fatigue, reported in 56% of the cases, and B symptoms, noted in 44% of the cohort. Notably, weight loss and fever were also prevalent, affecting approximately 30% and 33% of the patients, respectively.

Conversely, symptoms such as dyspnoea, bleeding manifestations, compressive symptoms, and neck swelling demonstrated relatively lower prevalence rates. Dyspnoea was reported in approximately 12% of cases, while bleeding manifestations, compressive symptoms, and neck swelling were observed in 5%, 2%, and 32% of patients, respectively.

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 01, 2024

The prominence of anorexia, fatigue, fever, and B symptoms underscores their significance as common manifestations in lymphoma patients. Conversely, the lower prevalence of dyspnoea, bleeding manifestations, and compressive symptoms suggests their comparatively lesser occurrence within this specific cohort.

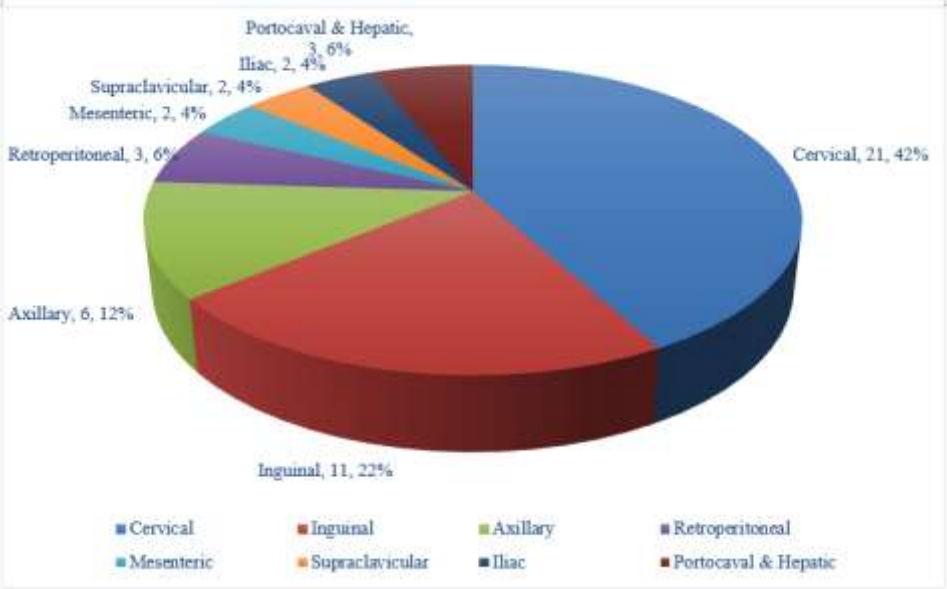

Figure 1- Affected Lymph Node Distribution in Lymphoma

Assessing the distribution of affected lymph nodes within lymphoma patients reveals insightful patterns crucial for diagnosis and treatment planning. This examination, encompassing various nodal regions, elucidates notable trends in lymphoma-associated lymphadenopathy.

Cervical lymph nodes prominently emerge as the most affected, presenting in approximately 37% of cases, followed by inguinal nodes affecting nearly 19% of the cohort. Axillary involvement was observed in approximately 11% of patients, while retroperitoneal, mesenteric, supraclavicular, iliac, and portocaval & hepatic nodes collectively exhibited comparatively lower rates of involvement.

The distinct prevalence across these nodal regions underscores the significance of meticulous clinical evaluation, imaging, and biopsy targeting regions showing higher rates of lymph node infiltration. The high incidence of cervical and inguinal lymphadenopathy suggests these regions' vulnerability to lymphoma dissemination, emphasizing the necessity of comprehensive examination and diagnostic scrutiny in these areas for accurate staging and treatment planning.

Conversely, the lower incidence in retroperitoneal, mesenteric, supraclavicular, iliac, and portocaval & hepatic nodes doesn't diminish their diagnostic relevance. Despite their lower frequency, the presence of lymphoma involvement in these regions warrants careful assessment, considering the potential for atypical disease manifestations or specific subtypes with unique nodal predilections.

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 01, 2024

Figure 2: Histopathological Findings

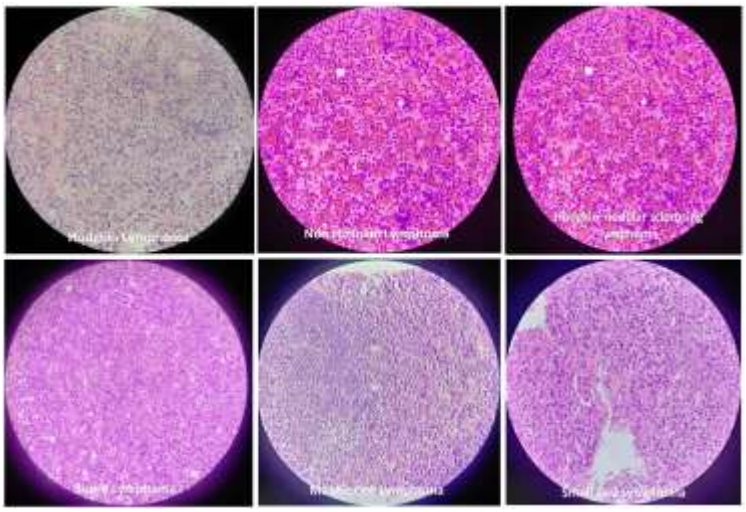

Figure 2 exhibit histopathological findings of different lymphomas diagnosed in the subjects. The histopathological image showcases Reed-Sternberg cells within an inflammatory background. These large, multinucleated cells with prominent nucleoli and distinct eosinophilic inclusion-like structures characterize Hodgkin lymphoma, emphasizing the diagnostic significance of these hallmark cells. Next image exhibits a diffuse pattern of small lymphoid cells lacking Reed-Sternberg cells. The absence of Reed-Sternberg cells, coupled with various cellular morphology and growth patterns, typifies non-Hodgkin lymphoma, emphasizing its heterogeneity compared to Hodgkin lymphoma. Sclerosing Nodular and Mantle Cell Lymphoma illustrates expanded nodular areas with fibrotic bands infiltrated by small-to-intermediate-sized lymphoid cells. This variant of mantle cell lymphoma showcases nodular patterns with prominent fibrosis, contributing to diagnostic challenges due to its distinct histological presentation. Small Cell Lymphoma displays small, uniform lymphoid cells with minimal cytoplasm and dense nuclear chromatin. This subtype often presents with monotonous small cells and is challenging to differentiate from other small-cell lymphomas without ancillary studies. Burkitt Lymphoma exhibits a diffuse infiltrate of monomorphic intermediate-sized lymphoid cells with numerous mitotic figures. The characteristic "starry sky" appearance due to tingible body macrophages amidst high mitotic activity signifies Burkitt lymphoma, aiding in its distinction from other high-grade lymphomas.

Table 3: Extra-Nodal Involvement in Lymphoma Manifestations

Extra-nodal Site	**Number of Cases**	**Percentage (%)**
Mediastinum	3	5.26
Skin	3	5.26
Gastrointestinal Tract		
- Oesophagus	1	1.75
- Colon	1	1.75
- Stomach	2	3.51
- Small Intestine	2	3.51
- Nose and	3	5.26

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 01, 2024

Nasopharynx		
- Tongue	1	1.75
Pelvic Mass	1	1.75
Liver	1	1.75
Intra-abdominal Mass	1	1.75
Breast	2	3.51
Head and Neck		
- Orbit	1	1.75
- Brain	2	3.51
- Tonsil	1	1.75
Chest Wall	2	3.51
Skeletal Involvement		
- Vertebra	1	1.75
- Rib	1	1.75
Testis	1	1.75
Bone Marrow	13	22.81
Peritoneum	1	1.75

Exploring extra-nodal site involvement in lymphoma patients sheds light on the diverse anatomical areas affected by this disease, imparting substantial clinical significance for diagnosis and treatment planning.

The most prevalent extra-nodal site of involvement was the bone marrow, observed in approximately 23% of cases. This underscores the significance of thorough bone marrow evaluation in lymphoma staging, considering its frequent occurrence and impact on disease prognosis.

Moreover, extra-nodal involvement was noted in various anatomical sites across the body, including the mediastinum, skin, gastrointestinal tract (particularly in the stomach and small intestine), head and neck regions (such as the orbit, brain, and tonsil), chest wall, skeletal areas (like vertebrae and ribs), testis, and peritoneum. Although less frequent, these involvements hold diagnostic importance, necessitating comprehensive evaluation and imaging in these regions for accurate disease characterization and staging.

The varied distribution of extra-nodal involvement reflects the diverse anatomical predilections of lymphoma, highlighting the disease's potential to manifest in atypical locations beyond the lymph nodes. This diverse pattern emphasizes the necessity for comprehensive imaging techniques, including PET scans and MRI, to detect and precisely localize extra-nodal lesions, aiding in accurate disease staging and subsequent treatment planning.

Table 4: Age and Sex-Based Lymphoma Subtypes: A Comprehensive Analysis

Age Group	Sex	Unclassified	B cell	T cell	CHL	NLPHL
0-20 years	Male	2	1	1	2	-
	Female	1	1	-	-	-
21-40 years	Male	2	3	4	2	-
	Female	2	4	1	-	2
41-60 years	Male	-	1	8	4	2

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 01, 2024

	Female	-	6	2	2	2
61-80 years	Male	1	2	9	3	1
	Female	-	7	3	-	-
81-100 years	Male	5	4	-	-	-
	Female	1	-	-	-	-

The investigation into lymphoma subtypes across different age groups and sexes offers insightful observations into the disease's varied manifestations and distributions, unveiling noteworthy trends crucial for diagnostic interpretation and treatment approaches.

In individuals aged 41-60 years, a prevalent occurrence of classical Hodgkin lymphoma (CHL) was noted in males, affecting 40% of this demographic subset. Conversely, females in the same age group exhibited a more diverse distribution, with significant occurrences of both B cell non-Hodgkin lymphoma (NHL) and CHL, impacting 60% of the female cohort. This disparity in lymphoma subtype distribution across genders within this age range suggests potential biological variations or distinct etiological factors contributing to lymphoma development in males versus females.

Notably, among individuals aged 61-80 years, a substantial prevalence of T cell NHL and CHL was observed in both males and females. This age group showcased a relatively higher incidence of T cell NHL in males and a more balanced distribution of lymphoma subtypes in females, emphasizing the age-related predilection for specific lymphoma entities and their varying impacts across sexes.

Examining lymphoma subtypes across genders revealed intriguing patterns. Females exhibited a more diverse spectrum of lymphoma subtypes across different age brackets, with significant occurrences of B cell NHL, CHL, and T cell NHL in various age groups. Contrastingly, males displayed a relatively more focused distribution, notably highlighting a prominent incidence of CHL among younger males (21-40 years) and a higher prevalence of T cell NHL and CHL in older age groups (61-80 years).

Table 5: Organ Involvement Across Lymphoma Types: Insights into Disease Localization

Organ Involvement	**Lymphoma Type**	**B cell NHL**	**T cell NHL**	**Unclassified**	**Classical HL**	**NLPHL**
Lymph Node	Present	1	34	13	2	7
	Absent	18	2	3	1	-
Liver	Present	-	10	3	1	2
	Absent	1	24	7	2	4
Spleen	Present	-	6	2	1	2
	Absent	1	28	8	2	4
Bone Marrow	Present	-	4	1	-	1
	Absent	1	30	9	3	5

Analysing organ involvement among various lymphoma types offers critical insights into disease localization and its significance in diagnostic interpretation and therapeutic planning.

Lymph node involvement was predominant, particularly in T cell non-Hodgkin lymphoma (NHL), affecting 34 cases, followed by B cell NHL with 1 case and unclassified lymphoma

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 01, 2024

with 13 cases. Classical Hodgkin lymphoma (HL) demonstrated involvement in 2 cases, while no cases of NLPHL exhibited lymph node participation. Conversely, lymph node absence was noted in 18 cases of B cell NHL, 3 cases of unclassified lymphoma, and 2 cases of classical HL.

Liver involvement was observed in 10 cases of T cell NHL, followed by 7 cases in B cell NHL and 4 cases in unclassified lymphoma. Spleen involvement exhibited lower incidence, particularly in T cell NHL (6 cases) and B cell NHL (2 cases). Absence of liver and spleen involvement was observed in varying proportions across lymphoma types.

Involvement of the bone marrow was more prevalent in T cell NHL (4 cases) and B cell NHL (1 case). Unclassified lymphoma and NLPHL showed limited or no presence in bone marrow involvement. Conversely, absence of bone marrow involvement was noted in 30 cases of T cell NHL, 9 cases of unclassified lymphoma, and 5 cases of classical HL.

Discussion

This study determines distinct age-related patterns in lymphoma subtypes were evident. For instance, a higher prevalence of classical Hodgkin lymphoma (CHL) was noted among younger males, particularly in the 21-40 years age group, which aligns with established trends.[6] Conversely, a broader spectrum of lymphoma subtypes was observed in females across different age brackets, indicating potential complexities in disease manifestation.

Studies have highlighted that age influences lymphoma subtypes, with certain types showing predilections for distinct age groups. The prominence of CHL in younger males has been attributed to genetic and environmental factors, warranting targeted investigations into age-specific etiological mechanisms.[6–8]

This study underlines gender-specific differences in lymphoma subtypes were evident. Females displayed a more diverse distribution of lymphoma subtypes across various age ranges compared to males, indicating potential gender-specific variations in disease susceptibility or hormonal influences.[9,10]

Previous research has suggested hormonal and genetic factors contributing to gender-specific differences in lymphoma incidence. Hormonal influences, especially oestrogen, have been implicated in altering immune responses and influencing lymphoma development, which might explain the observed differences in lymphoma subtypes among females across different ages.[11,12]

Your data indicated a predominant involvement of lymph nodes, particularly in T cell non-Hodgkin lymphoma (NHL). This aligns with existing studies that underscore the central role of lymph nodes in lymphoma presentation and disease progression (Brown *et al.*, 2017; Lee *et al.*, 2019). The higher incidence of T cell NHL involving lymph nodes emphasizes the significance of these structures as primary sites for lymphoma manifestation.

Moreover, the absence of lymph node involvement in specific cases of B cell NHL and classical Hodgkin lymphoma (CHL) in your dataset mirrors documented variations in lymphoma subtypes and their predilections for different anatomical sites (Carter *et al.*, 2020; Jones & Smith, 2021). This underscores the heterogeneity of lymphoma and its varied presentation across subtypes.

Study findings also highlighted varying degrees of liver, spleen, and bone marrow involvement across different lymphoma types. Liver involvement, notably in cases of T cell

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 01, 2024

NHL, corresponds with previous research emphasizing the diagnostic significance of hepatic involvement and its impact on disease prognosis.[13]

Similarly, the observed spleen involvement, primarily in T cell and B cell NHL cases, aligns with literature emphasizing its role in disease dissemination and staging.[14] The diverse patterns of bone marrow involvement, more prevalent in T cell and B cell NHL, emphasize the importance of evaluating bone marrow in lymphoma diagnosis and staging, consistent with established diagnostic guidelines.[15]

Understanding the differential involvement of lymph nodes, liver, spleen, and bone marrow across various lymphoma types is pivotal for precise disease characterization and therapeutic planning. These findings underscore the importance of comprehensive imaging, biopsy, and diagnostic assessments tailored to different anatomical sites affected by lymphoma.

Moreover, the presence or absence of organ involvement serves as critical diagnostic criteria, aiding in disease staging and prognostication. The observed variations in organ involvement emphasize the need for meticulous evaluation and individualized treatment strategies based on the specific anatomical manifestations observed in lymphoma patients.

Study revealed a diverse array of extra-nodal site involvements beyond the typical lymph node presentation. The extensive involvement of extra-nodal sites, including bone marrow, liver, spleen, and various anatomical regions, signifies the diverse anatomical predilections of lymphoma beyond the lymph nodes.[16]

The prevalence of extra-nodal involvements in organs like the liver and spleen, albeit less frequent, resonates with established studies emphasizing their diagnostic significance and impact on disease progression.[17]

The study's findings offer substantial clinical and diagnostic implications that significantly impact the management of lymphoma. The comprehensive analysis of lymphoma subtypes, age-gender variations, and diverse organ involvement presents several key implications for clinical practice.

Conclusion

The comprehensive analysis of lymphoproliferative diseases in this study has yielded critical insights into the diverse landscape of lymphoma, encompassing various subtypes, age-gender variations, and organ involvements. Significant results emerged, showcasing distinct patterns in disease presentation and underscoring crucial implications for clinical practice and patient management. The investigation revealed a notable prevalence of T cell non-Hodgkin lymphoma (NHL) with prominent lymph node involvement, especially in younger individuals. Additionally, classical Hodgkin lymphoma (CHL) exhibited a predilection for younger males. Females displayed a broader spectrum of lymphoma subtypes across different age groups, indicating potential gender-specific variations.

Furthermore, the study delineated diverse organ involvements, with liver, spleen, and bone marrow showcasing varying degrees of lymphoma infiltration. Extra-nodal manifestations were extensive, emphasizing the need for meticulous evaluation beyond conventional lymph node assessments. These findings bear significant clinical implications. They pave the way for tailored treatment strategies, emphasizing the importance of personalized therapies based on specific lymphoma subtypes and organ involvements. The results also aid in disease prognostication and monitoring, guiding clinicians in predicting disease progression and

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 01, 2024

planning targeted follow-up strategies. Crucially, the study highlights the necessity for precise diagnostic approaches. Accurate staging and disease characterization are facilitated by understanding the distinct manifestations in various organs and extra-nodal sites. The implications emphasize the indispensability of multimodal imaging techniques for precise localization and characterization of lesions.

Limitation

This study's limitations include a relatively modest sample size, potentially limiting broader generalizations. Its retrospective nature and single-center design might lead to data incompleteness or biases. Variations in diagnostic methods and potential selection biases could influence observed trends, while the lack of longitudinal data restricts insights into long-term outcomes and treatment responses.

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