Int. J Med. Pharm. Res.
E-ISSN: 2958-3683 | **P-ISSN**: 2958-3675
Available on: https://ijmpr.in/

International Journal of
Medical and Pharmaceutical Research

ORGINAL ARTICLE **OPEN ACCESS**

Lymph node cytology Demystified: The Sydney System Lexicon.

Dr. Anshu Kumar[1], Dr. Kempula Geethamala[2], Dr. Rekha M Haravi[3]

[1]Postgraduate, Dept of Pathology, Belagavi Institute of Medical Sciences, Belagavi
[2]Associate Professor, Dept of Pathology, Belagavi Institute of Medical Sciences, Belagavi
[3]Professor and Head, Dept of Pathology, Belagavi Institute of Medical Sciences, Belagavi

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*Corresponding Author:

Dr. Anshu Kumar
Postgraduate, Dept of Pathology, Belagavi Institute of Medical Sciences, Belagavi

Received: 09-06-2025
Accepted: 22-07-2025
Available Online: 14-08-2025

A B S T R A C T

Introduction-Lymph node cytology has been a cornerstone in the diagnostic evaluation of various lymphadenopathies. However, the absence of a universally accepted classification system has led to inconsistencies in reporting, diagnostic ambiguity and challenges in clinical management decisions. The Sydney system of classification, a comprehensive framework designed to standardise the reporting using clear categories and criterion can enable the pathologists to provide more reliable and uniform reports. **Aims and Objective-** To classify the lymph node cytology lesions according to Sydney system of classification and to analyse the risk of malignancy in each category. **Material and method-** This is a 1.5 years single institute retrospective study done in department of Pathology. Cytology slides of lymph node lesions were retrieved and classified according to the Sydney classification. Histopathological correlation was made where ever possible. Statistical analysis was done using SPSS software. **Results**- A total 210 lymph node cytology lesions were classified by Sydney system of classification which showed Benign category (L2) was the commonest (56.2%) followed by malignant category(L5) which was 33.8%. Other categories were Inadequate (L1) 5.7%, AUS/ALUS (L3) 1%, Suspicious (L4) 3.3%. 26 cases had histopathological correlation. Diagnostic accuracy of 100% and both L4 and L5 category showed 100% risk of malignancy. **Conclusion**- This retrospective study classified 210 lymph node FNAs using The Sydney System. It found male predominance and cervical nodes as the most common site. Crucially, the study demonstrated a 100% diagnostic accuracy and 100% risk of malignancy for suspicious (L4) and malignant (L5) categories, highlighting The Sydney System's vital role in standardizing reporting and guiding patient management, despite a limited number of histopathological correlations.

Keywords: Lymph node, Sydney system of classification, cytology, lymphadenopathy.

INTRODUCTION

Lymph nodes, as vital components of the lymphatic system, are critical to our immune response and their enlargement, or lymphadenopathy, often signals underlying infectious or neoplastic conditions.[1] While biopsy and histopathological examination remain the gold standard for definitive diagnosis, fine needle aspiration cytology (FNAC) of lymph nodes has become a cornerstone in the initial diagnostic evaluation, serving as an invaluable screening tool. [1,2]Historically, the absence of a standardized classification system for lymph node cytology led to inconsistent reporting and diagnostic ambiguities, complicating clinical management. This critical gap was addressed in 2019 at the 20th International Congress of Cytology in Sydney, where an international panel proposed The Sydney System—a standardized, category-based reporting system subsequently endorsed by both the International Academy of Cytology (IAC) and the European Federation of Cytology Societies (EFCS). This comprehensive framework classifies aspirates into five distinct categories based on specific cytological features, enabling pathologists to provide more reliable and uniform reports that directly enhance patient care.[1-7] This study aims to classify lymph node samples using The Sydney System and determine the probability of malignancy within each diagnostic category.

OBJECTIVES OF THE STUDY

1. To classify lymph node samples according to the diagnostic categories of The Sydney System.

2. To determine the probability of malignancy associated with each diagnostic category of The Sydney System.

MATERIALS AND METHODS

This is a retrospective study spanning for 1.5 year period. The study was carried out within the Department of Pathology at Belagavi Institute of Medical Sciences, Belagavi, Karnataka. All available cytology slides pertaining to lymphnode fine needle aspirations performed during the study period were retrieved from the departmental archives. Each retrieved slide was then meticulously re-evaluated and classified according to the established criteria of The Sydney System. (Table 1)[7]

Table 1- The Sydney System classification of lymphnode cytology

Category	The Cytomorphologic Features
L1: Inadequate/Insufficient	Scant cellularity; extensive necrosis; technical limitations that cannot be overcome.
L2: Benign	Suppurative and granulomatous inflammation; heterogeneous lymphoid population with small lymphocytes predominating, and often germinal centers with dendritic cells and tangible body macrophages.
L3: Atypical (cells) undetermined significance / atypical lymphoid (cells) of uncertain significance (ALUS/AUS)	Heterogeneous lymphoid population, features suggest a reactive process, follicular lymphoma cannot be excluded; excess of large cells (centroblasts or immunoblasts) or immature small lymphoid cells or cases where the atypical cells are not lymphoid cells.
L4: Suspicious	Small and/or medium-sized, monomorphic atypical lymphoid cells suspicious of lymphoma, but the cytomorphology alone is not sufficient; polymorphous lymphoid smears, few Hodgkin- or Reed–Sternberg-like cells are detected; large cell or Burkitt lymphomas scantly cellular; smears in which atypical cells suspicious for metastasis are detected, but are too scant to be diagnostic.
L5: Malignant	Non-Hodgkin lymphoma (NHL); Hodgkin lymphoma (HL): appropriate cellular background and diagnostic Hodgkin and Reed–Sternberg cells; metastatic neoplasms.

To ascertain diagnostic accuracy, histopathological correlation was performed for all cases where corresponding biopsy or surgical excision specimens were available. The histopathological diagnoses served as the gold standard against which the Sydney System cytological classifications were compared. Cases without available histopathological follow-up were included in the overall cytologic classification analysis but excluded from the diagnostic accuracy calculations.

Statistical Analysis

All collected data were compiled and subjected to statistical analysis using SPSS software (Statistical Package for the Social Sciences), version 29 . The primary focus of the statistical analysis was to determine various parameters of diagnostic accuracy, including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall diagnostic accuracy, for the Sydney system classification system.

RESULTS

Of the 210 lymph node FNAs performed during the study, the majority of patients were male (65%), resulting in a male-to-female ratio of 1.85:1.

Table 2- Gender distribution of Lymphnode lesions

Sex	Frequency	Percentage
Male	137	65
Female	73	35
Total	210	100

The patients' ages ranged from under 1 year to 90 years. The most common age group undergoing lymph node FNA was 1-10 years (18%), followed by 21-30 years (16.6%), and 51-60 years (15.7%).

Table 3- Age distribution of Lymphnode lesions

Age	Frequency	Percentage
< 1 Year	2	0.9
>1- 10 Years	38	18.0
11- 20 Years	30	14.2
21- 30 Years	35	16.6
31- 40 Years	23	10.9
41- 50 Years	16	7.6

51- 60 Years	33	15.7
61- 70 Years	19	9.0
71-80 Years	11	5.2
> 80 Years	3	1.4
Total	210	100

Left-sided lymph nodes were most frequently aspirated (44.7%, n=94). Right-sided lymph nodes accounted for 40.9% (n=86) of the cases, while bilateral involvement was observed in 14.2% (n=30) of the patients.(Table 4)

Table 4- Distribution of lymphnode lesions according to laterality

Laterality	Frequency	Percentage
Left	94	44.7
Right	86	40.9
Bilateral	30	14.2
Total	210	100

In the present study, the cervical region was the most frequent site, accounting for 69.6% (n=146) of aspirations. Submandibular lymph nodes were the next most common at 10% (n=21), followed by inguinal at 5.7% (n=12), occipital at 4.7% (n=10), and supraclavicular at 3.8% (n=8). Axillary lymph nodes constituted 3.3% (n=7) of cases, with other locations making up the remaining 2.8% (n=6).(Table 5)

Table 5- Distribution of lymphnode lesions according to location

Location	Frequency	Percentage
Cervical	146	69.6
Axillary	7	3.3
Inguinal	12	5.7
Occipital	10	4.7
Supraclavicular	8	3.8
Submandibular	21	10
Other	6	2.8
Total	210	100

Among the cytological diagnoses, reactive lymphadenitis was the most common finding, accounting for 35.2% (n=74) of cases. Metastatic squamous cell carcinoma followed as the second most frequent diagnosis at 23.3% (n=49), with tuberculous lymphadenitis also being significant at 16.6% (n=35). A small percentage, 5.7% (n=12), were deemed inadequate for opinion. Other diagnoses included acute suppurative lymphadenitis (4.2%, n=9), metastatic carcinoma (3.8%, n=8), suspicious for malignancy (3.3%, n=7), non-Hodgkin lymphoma (2.3%, n=5), Hodgkin lymphoma (2%, n=4), lymphoproliferative disease (1.9%, n=4), chronic lymphadenitis (1%, n=2), and large cell metastatic deposits (0.5%, n=1).(Table 6)

Table 6- Lymphnode lesions on cytology

Cytological Diagnosis	Frequency	Percentage
Inadequate For Opinion	12	5.7
Reactive Lymphadenitis	74	35.2
Acute Suppurative Lymphadenitis	9	4.2
Chronic Lymphadenitis	2	1
Tuberculous Lymphadenitis	35	16.6
Lymphoproliferative Disease	4	1.9
Suspicious For Malignancy	7	3.3
Non Hodgkin Lymphoma	5	2.3
Hodgkin Lymphoma	4	2
Metastatic Squamous Cell Carcinoma	49	23.3
Large Cell Metastatic Deposits	1	0.5
Metastatic Carcinoma	8	3.8

Based on The Sydney System classification, Category L2 (Benign) was the most common finding, encompassing 118 cases (56.2%). This category primarily included reactive lymphadenitis (35.2%) and tuberculous lymphadenitis (16.6%). Category L5 (Malignant) was the second most prevalent, comprising 71 cases (33.8%), largely attributed to metastatic

squamous cell carcinoma (23.3%) and metastatic carcinoma (3.8%).Category L1 (Inadequate) included 12 cases (5.7%) that showed only hemorrhagic material without lymphoid cells. Category L4 (Suspicious for Malignancy) accounted for 7 cases (3.3%), while Category L3 (Atypical Lymphoid Cells of Undetermined Significance) contained 2 cases (1%).(Table 7)(Fig 1-6)

Table-7: The Sydney system classification of lymphnode lesions

Categories	Frequency	Percentage
Inadequte (L1)	12	5.7
Benign (L2)	118	56.2
AUS / ALUS (L3)	2	1
Suspicious (L4)	7	3.3
Malignant (L5)	71	33.8
Total	210	100

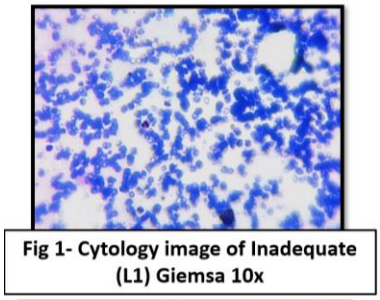

Fig 1- Cytology image of Inadequate (L1) Giemsa 10x

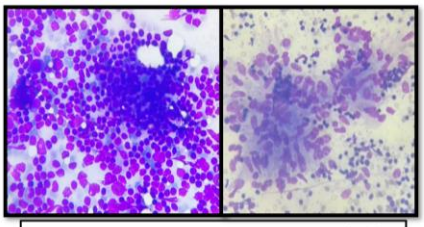

Fig 2- Cytology image of Benign (L2) Giemsa 10x

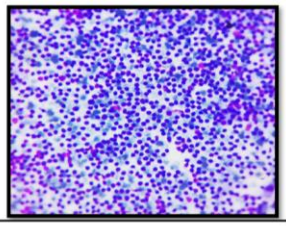

Fig 3- Cytology image of AUS / ALUS (L3) Giemsa 10x

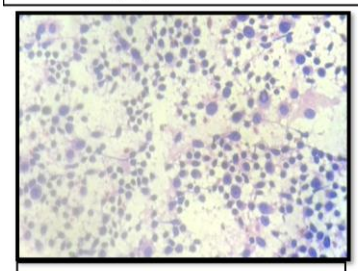

Fig 4- Cytology image of Suspicious (L4) Giemsa 10x

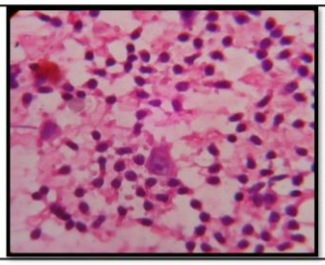

Fig 5- Cytology image of Malignant-Hodgkin lymphoma (L5) H & E 10x

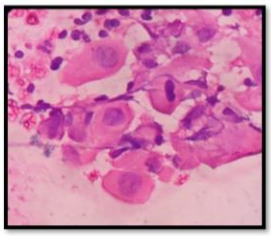

Fig 6- Cytology image of Metastasis (L5) SCC - H & E 10x

Histopathological correlation was available for 26 cases (12.3%) from the study's cytology diagnoses. Of these, one case classified as benign on cytology was confirmed as Actinomycosis of the foot with reactive hyperplasia of inguinal lymphnode through histopathology. Additionally, one case cytologically categorized as suspicious for malignancy was histopathologically confirmed as metastatic squamous cell carcinoma. From the 71 cases in Category L5 (Malignant), 24 were definitively confirmed as malignant upon histopathological examination. Statistical analysis revealed a 100% risk of malignancy (ROM) for both Category L4 (Suspicious for Malignancy) and Category L5 (Malignant). Conversely, Category L2 (Benign) demonstrated a 0% ROM.(Table 8)(Fig 7-12)

Table8: Distribution of cytohistologically correlated cases for benign and malignant lesion in each category of Sydney system with calculation of ROM (n=26)

Sydney System	Histopathological Correlation	ROM
Benign (1/118)	Reactive Lymphoid Hyperplasia	0%
Suspecious (1/7)	Metastatic Carcinoma (SCC)	100%
Malignant (24/71)	Malignant (22-SCC+ 1CA Breast+ 1-HL)	100%
Total	26	

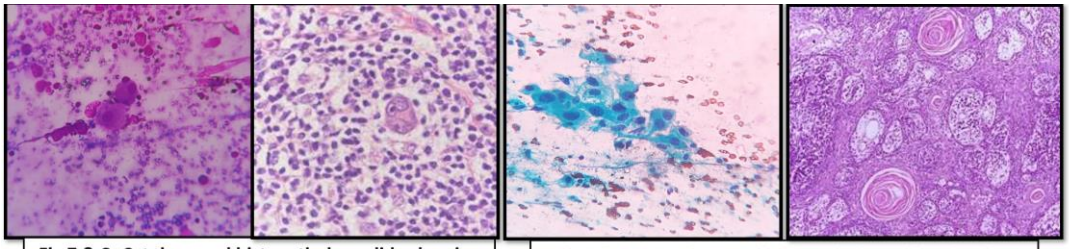

Fig 7 & 8- Cytology and histopathology slide showing Hodgkin lymphoma.

Fig 9 & 10- Cytology and histopathology slide showing squamous cell carcinoma

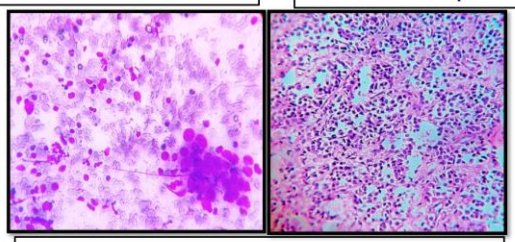

Fig 11 &12- Cytology and histopathology slide showing ductal carcinoma breast

In this study, while sensitivity, specificity, diagnostic accuracy, positive predictive value (PPV), and negative predictive value (NPV) were all found to be 100%, it's crucial to note that these high percentages are based on a very limited number of cases with histopathological correlation. Only 26 (12.3%) out of the total cases underwent this gold-standard confirmation, which does not fully represent the overall diagnostic performance.(Table 9)

Table-9: Diagnostic reliability of cytodiagnosis using Sydney system of classification.

Parameter	**Percentage**
Sensitivity	100
Specificity	100
Positive predictive value	100
Negative predictive value	100
Diagnostic accuracy	100

DISCUSSION

Lymphadenopathy represents a common and often diagnostically challenging clinical presentation, indicative of conditions spanning inflammatory, reactive, and neoplastic etiologies. Fine needle aspiration (FNA) stands as a crucial initial diagnostic tool for assessing lymph node enlargements, offering significant advantages in terms of rapidity and patient tolerance.[7-9] Despite its widespread adoption, the absence of a globally recognized, standardized system for reporting lymph node cytopathology has historically led to considerable diagnostic ambiguity and inconsistencies across different laboratories and clinicians. It was this recognized need for greater uniformity and clarity in reporting that critically informed the development and subsequent endorsement of The Sydney System for Classification and Reporting of Lymph Node Cytopathology.[7-12]

In the present study, a predominance of male patients underwent lymph node FNA. Consistent with findings from Nidhi S et al., Sreelekshmi et al., and Gupta P et al..However, this contrasts with the study by Vigliar et al., which reported a majority of female patients (57.7%).(Table 10)

Table-10: Comparison of gender distribution of lymphnode FNAC cases among various studies

Study	**Percentage**
Nidhi S et al[2]	62
Sreelekshmi et al[3]	55.60
Gupta P et al[4]	66.7
Vigliar et al[6]	57.7- Females
Present study	65

Consistent with findings from Sreelekshmi et al. and Gupta et al., cervical lymph nodes were the most frequent site of aspiration in the current study. Similarly, Nidhi et al. also identified cervical lymph nodes as the predominant site in their study, although specific numerical data were not provided.(Table 11)

Table-11: Comparison of location of lymphnode FNAC cases among various studies

Study	Location (Cervical LNs)
Nidhi S et al[2]	Cervical
Sreelekshmi et al[3]	57.60 %
Gupta P et al[4]	66.8 %
Present study	69.6 %

In this present study, the most prevalent age group undergoing lymph node FNA was found to be 1-10 years and 21-30 years. This contrasts with findings from other studies; Nidhi S et al. identified 11-20 years as the most common age group, while Sreelekshmi et al. reported a peak in the 51-60 years age range.(Table 12)

Table-12: Comparison of age wise distribution of Lymphnode FNAC cases among various studies

Study	Age
Nidhi S et al[2]	11-20 (24%)
Sreelekshmi et al3	51-60 (42%)
Gupta P et al[4]	38.19+-19.1 years
Present study	>1-10 (18%) 21-30 (16.6%)

The cytological diagnosis distribution in the present study aligns broadly with trends observed in other research, yet also highlights some regional variations. Reactive lymphadenitis, at 35.2%, consistently emerged as a predominant benign cause of lymphadenopathy, a finding seen in various other studies where it often constitutes a significant portion of non-neoplastic diagnoses like Nidhi et al study found 30% and Sreelekshmi et al 37.2%. Similarly, tuberculous lymphadenitis was a notable entity in this study (16.6%), reflecting its continued prevalence in endemic regions; other studies from such areas report higher frequencies, sometimes as high as 39.7% or even 45%.

Regarding malignant conditions, metastatic squamous cell carcinoma was the most common malignancy in the current study at 23.3%, with overall metastatic carcinoma contributing 27.6% (23.3% + 3.8% + 0.5% for large cell metastatic deposits). This is comparable to other studies that frequently identify metastatic carcinoma as a leading malignant diagnosis, with percentages ranging from around 10% to over 20%. Lymphomas, including Non-Hodgkin Lymphoma (2.3%) and Hodgkin Lymphoma (2%), collectively accounted for 4.3% of diagnoses in this study. This proportion for lymphomas vary considerably across studies, often depending on the demographic and referral patterns, with some reporting higher rates 7% or more in some referral centers, while others are lower (0.3%).[2-7] The "inadequate for opinion" rate of 5.7% in the current study falls within the acceptable range reported in literature, which can vary from 3% to 30% depending on factors like aspirator experience and sampling technique.[7-12]

An analysis of lymphadenopathy distribution according to The Sydney System across various studies reveals that the Benign (L2) category consistently represents the largest proportion of diagnoses. In the present study, L2 cases constituted 56.2% of the total, a figure closely comparable to findings by Rivas HE et al.[5] (57.3%) and Sreelekshmi et al.[3] (63.60%). Nidhi S et al.[2] similarly reported a high number of benign cases, with L2 accounting for 84% of their diagnoses, further underscoring the prevalence of benign conditions in lymph node aspirates.(Table 13)

Table 13. Correlation of distribution of lymphadenopathy according to Sydney system of classification among various studies

Study	Category
Nidhi S et al.[2]	Benign L2- 84
Sreelekshmi et al.[3]	Benign L2- 63.60
Rivas HE et al.[5]	Benign L2- 57.3
Present study	Benign L2- 56.2

The diagnostic efficacy of The Sydney System for lymph node cytology, as measured by sensitivity, specificity and Risk of Malignancy (ROM) across its categories, demonstrates considerable variability when compared across different studies. The present study reported exceptionally high performance, with 100% sensitivity, specificity, and ROM for L4 (Suspicious) and L5 (Malignant) categories, alongside 0% ROM for L2 (Benign). While these results appear highly favourable, it is crucial to recognize that they are derived from a very limited subset of cases with histopathological correlation, which might not fully reflect real-world diagnostic nuances.

In contrast, other studies provide a broader spectrum of diagnostic outcomes. Nidhi S et al.[2] reported a sensitivity of 61.53% and specificity of 92.59%, with their ROMs showing a gradual increase from 16.67% for L2 to 50% for L4 and 87.5% for L5. Sreelekshmi et al.[3] and Vigliar E et al.[6] both presented strong performance, with sensitivities of 95.65% and 98.47%, and specificities of 96.29% and 95.33%, respectively. Notably, these two studies also reported similar ROMs for L2 (0% and 1.92%), and consistently 100% for L4 and L5, aligning more closely with the present study's ROMs. Rivas HE et al.[5] showed slightly lower figures, with a sensitivity of 78.5% and specificity of 82%, alongside an L2 ROM of 3% and 100% for L4 and L5.

These discrepancies in diagnostic metrics underscore the influence of various factors, including the study's design, patient demographics, the prevalence of different lymph node pathologies and crucially, the proportion of cases subjected to histopathological follow-up.[7,8](Table 14)

Table 14. Comparison Of Statistical Parameters with Other Studies

Study	Sensitivity	Specificity	ROM
Nidhi S et al.[2]	61.53%	92.59%	16.67%-L2 50%-L4, 87.5%-L5
Sreelekshmi et al.[3]	95.65%	96.29%	0%- L2 100%-L4 and L5
Rivas HE et al.[5]	78.5%	82%	3%-L2 100%-L4 and L5
Vigliar E et al.[6]	98.47%	95.33%	1.92%-L2 100%- L4 and L5
Present Study	100%	100%	100%-L4 and L5 0%-L2

CONCLUSION

While acknowledging the limited number of cases with histopathological correlation, this study reaffirms that male patients with cervical lymphadenopathy constitute the most common demographic presenting for lymph node FNA, with the Benign (L2) category of The Sydney System being the most frequently encountered diagnostic group. Crucially, the observed 100% Risk of Malignancy (ROM) for both L4 (Suspicious) and L5 (Malignant) categories, along with a diagnostic accuracy of 100 percent, in this study underscores the significant diagnostic power inherent in The Sydney System Lexicon for lymph node cytology. By providing a standardized framework that categorizes lymphadenopathy based on specific cellular features, this lexicon enables pathologists to deliver precise diagnoses and ensures uniform, consistent reporting. This standardization plays a pivotal role in guiding appropriate clinical treatment strategies, marking a significant leap forward in diagnostic pathology.

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