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Original Research Article

Application of the Sydney system for classification and reporting lymph node cytopathology: a retrospective analysis at a tertiary centre

Ashok Teja Kummari[1], Pramod Kumar Pamu[1]*, Krishna Kiran Ganna[1], Param Jyothi[2], Sadashivudu[3]

[1]Department of Pathology, Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India
[2]Department of Pulmonary Medicine, Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India
[3]Department of Medical Oncology, Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India

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***Correspondence:**
Dr. Pramod Kumar Pamu,
E-mail: pramodkumarpamu @gmail.com

ABSTRACT

Background: Lymph node fine needle aspiration cytology (LN FNAC) is a minimally invasive, safe, quick, inexpensive and reliable diagnostic technique for evaluating lymph node (LN) pathologies, but the existing classification systems exhibits inconsistencies leading to diagnostic discrepancies and challenges in interobserver reproducibility. The Sydney system provides a standardised, tiered categorisation to improve diagnostic precision of LN cytopathology. This study aimed to analyse diagnostic performance of the Sydney system and evaluate its applicability in a tertiary care setting.
Methods: The retrospective observational study was conducted at tertiary care institution in India with 630 LN cytopathological cases, reviewed and reclassified using the Sydney system and compared with available histopathological correlations. The risk of malignancy was calculated for each category. Diagnostic performance metrics including sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy were evaluated with 95% CI.
Results: 630 LN FNAC samples were distributed as: L1, 19.7% (n=124); L2, 46.8% (n=295); L3, 1.1% (n=7); L4, 1.3% (n=8); L5, 31.1% (n=196). ROM increased progressively: L1, 0%; L2, 4.8%; L3, 66.7%; L4, 83.3%; L5, 98.5%. Diagnostic performance showed sensitivity 97.30%, specificity 93.02%, PPV 96%, NPV 95.24%, and accuracy 95.73%.
Conclusions: The Sydney system demonstrated high diagnostic accuracy and reliable risk stratification in a tertiary institution, reducing interobserver variability and enhancing patient management. Adoption of the Sydney system is recommended for standardised LN cytology reporting, with potential for ancillary techniques to refine indeterminate categories. This validation in a tertiary care institution supports the global applicability, particularly in high burden environments.

Keywords: Lymph node cytopathology, Sydney system classification, Fine needle aspiration cytology, Risk of malignancy, Diagnostic accuracy

INTRODUCTION

Lymph node (LN) cytology plays a crucial role in the diagnostic evaluation and staging of diverse medical conditions such as infectious diseases, malignancies, and autoimmune disorders.[1] Consequently, lymphadenopathy arises from a spectrum of causes, ranging from benign reactive lymphoid hyperplasia accounting for approximately 90% of cases, to malignant diseases comprising only 10%.[2] Lymph node fine needle aspiration cytology (LN FNAC), a minimally invasive technique offers rapid and cost-effective insights into LN abnormalities and its accurate classification and reporting facilitating appropriate patient management and treatment planning. The diagnostic yield of LN cytology is constrained by the inconsistencies and limitations of the

existing classification systems, leading to significant implications including diagnostic discrepancies, and challenges in interobserver reproducibility, ultimately impacting the patient management.[3] The adoption of a standardised system will have an impact on reducing the diagnostic ambiguities and improve clarity. The Sydney system, representing a comprehensive and tiered diagnostic categorisation for the performance, classification and reporting of LN cytopathology was proposed in 2020.[4] The tiered classification comprises five diagnostic categories: Inadequate, benign, atypical lymphoid cells of undetermined significance, Suspicious, and Malignant. Additionally, a second diagnostic level is included, intended to identify specific diagnostic entities by utilising ancillary testing.[5] Previous applications of the Sydney System demonstrated promising improvements in diagnostic precision and consistency, particularly in differentiating benign from malignant lesions and subclassifying malignancies.[1,3] Validation in diverse clinical settings such as tertiary care centres, encountering a high volume and heterogeneity of LN pathologies is essential to establish the broader applicability and performance of the classification system.

The present retrospective study aims to assess the applicability of the Sydney system and validate it as a robust and reliable tool for the LN cytology classification and reporting, ultimately enhancing patient care and management in the field of LN pathology. We evaluate the diagnostic accuracy, ROM for each category, and assess the interobserver variability, and concordance rates achieved by the system. By reclassifying the cases according to Sydney system, we examine the effectiveness in distinguishing benign and malignant lesions and identifying specific malignancy subtypes. Our findings contribute to evidence supporting the implementation of standardised guidelines for LN cytology reporting in tertiary care institutions and potentially guide future modifications of the Sydney system based on its performance in the specific setting. Ultimately, this analysis underscores the potential of the Sydney system to enhance diagnostic reliability, reduce variability, and optimise patient care in LN pathology.

METHODS

The current retrospective observational study was conducted from January 2019 to December 2021 at the department of pathology, Nizam's institute of medical sciences (NIMS), Punjagutta, Hyderabad, India. The study involved review and reclassification of a total 630 samples including LN FNAC smears and cell block samples in the department of pathology to evaluate the Sydney system classification. LN aspirates from both sexes and all age groups were included in the study and Non LN aspirates were excluded.

Patient demographics, clinical findings, imaging findings and relevant laboratory investigations were obtained from electronic medical records and pathology reports. All samples were independently reviewed by two pathologists blinded to original diagnosis and each other's assessments to analyse the interobserver variability. Cases were reclassified according to the Sydney system categories: (L1) Inadequate/non-diagnostic, (L2) benign, (L3) atypical cells of undetermined significance (AUS), (L4) suspicious for malignancy, and (L5) malignant, with subcategorization where applicable. Ancillary studies, if performed originally were incorporated into the reclassification to align with Sydney system recommendations. Any discrepancies in the classification were resolved through consensus discussion and the concordance with original reports was also evaluated. Based on histopathologic correlation and malignant outcomes, the ROM was assessed for each diagnostic category, determined as the ratio of histologically or clinically confirmed malignant cases to all confirmed cases.

Data were compiled and analysed using Microsoft excel version 2019. Diagnostic performance was evaluated by calculating sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for the Sydney system categories, using histopathological findings as the reference standard in the available cases. True positives were defined as histologically or clinically confirmed malignant lesions with a cytological diagnosis of L5, L4, or L3. Histologically or clinically confirmed benign lesions with a cytological diagnosis of L2 were considered as True negatives. False positives were defined as histologically benign lesions with an L5, L4, or L3 cytological diagnosis. Any histologically malignant lesions with L2 cytological diagnosis are considered as False negatives and L1 cases were excluded from the statistical analysis.

RESULTS

Patient demographics and cytological samples

A total of 630 LN cytopathological cases spanning across all the age groups from 7 years to 93 years (Table 1) were reviewed and reclassified according to the Sydney system (Table 2). The study population with a mean age of 43.2 years indicated a nearly balanced gender distribution with male to female ratio 1:1.05, comprising of 307 males (48.70%) and 323 females (51.30%). The 20% of cases documented clinical features indicating known malignancies, including carcinomas of the breast, thyroid, lung, oral cavity, ovary, penis, and melanoma, as well as hematological malignancies such as chronic myeloid leukemia and lymphomas. The most common aspiration site was the cervical LN (50%), followed by supraclavicular (15%), axillary, inguinal, mediastinal and other sites such as subcarinal, hilar, submandibular, paratracheal, periportal, intra-abdominal, and celiac LNs. Procedures were predominantly conventional FNAC (70%), with ultrasound-guided FNAC (20%), endobronchial ultrasound-guided FNAC, endoscopic ultrasound-guided FNAC and computed tomography-guided FNAC comprising the remainder.

Table 1: Patient demographics.

Age group (in years)	Male		Female		Total	
	N	%	N	%	N	%
≤10	12	48	13	52	25	4
11-30	61	48	65	52	126	20
31-50	123	49	129	51	252	40
51-70	86	49	90	51	176	28
>70	24	48	26	52	50	8
Total patients	307	48.70	323	51.30	630	100

Diagnostic categories

Of the total 630 cases, 124 cases (19.7%) were classified as L1 (Non diagnostic/Inadequate), indicating insufficient material for diagnosis. 46.8% of cases (n=295) were categorized as L2 (Benign) reflecting non-malignant conditions, 7 cases (1.1%) were classified as L3 (AUS/ALUS) and 8 cases (1.3%) as L4 (suspicious for malignancy). 31.1% cases (n=196) were classified as L5 (Malignant).

Table 2: Reclassification according to Sydney system.

Category	Description	N (%)
L1	Non-diagnostic/ inadequate	124 (19.7)
L2	Benign	295 (46.8)
L3	AUS/ALUS	7 (1.1)
L4	Suspicious for malignancy	8 (1.3)
L5	Malignant	196 (31.1)
Total		630 (100)

Histopathological correlation

Histopathological correlation was available with 151 cases of the total 630, where 49% (n=74) were confirmed malignant and 51% (n=77) benign (Table 2). In Category L1, all 34 cases with histopathological follow up were benign, resulting in a 0% (95% CI: 0.00-10.15) ROM. Out of 42 cases in category L2, 40 were found to be benign and 2 malignant, yielding ROM of 4.8% (95% CI: 1.32-15.79). Category L3 included 3 cases, with 1 benign and 2 malignant, corresponding to the ROM of 66.7% (95% CI: 20.77-93.85). Category L4 resulted in ROM of 83.3% (83.33%, 95% CI: 43.65-96.99) with total 6 cases, including 1 benign and 5 malignant cases. 66 cases, with 1 benign and 65 malignant, were categorised into L5, leading to the ROM of 98.5% (95% CI: 91.90-99.73). Chi-square test ($\chi2=133.21$, df=4, $p<0.001$) confirmed a significant association between Sydney System categories and histopathological outcomes.

The L1 category samples (Figure 3), predominantly showed only blood elements, lacking sufficient cellular material for diagnosis. Benign cases (Figure 4) were characterised by a background of necrosis admixed with well-defined aggregates of epithelioid macrophages forming granulomas. Category L4 (Figure 5) displayed singly scattered atypical lymphoid cells, suggesting potential malignancy but lacking definitive features. Malignant cases (Category L5) exhibited highly cellular smears arranged in sheets and clusters, with round to polygonal cells, featuring pleomorphic hyperchromatic nuclei, prominent nucleoli, and moderate cytoplasm, consistent with a malignant diagnosis (Figure 6). IHC markers, such as TTF1, HBME1 and BRAF V600E for thyroid metastases and CEA, Chromogranin for medullary carcinoma, were applied in relevant cases for confirmation of diagnoses.

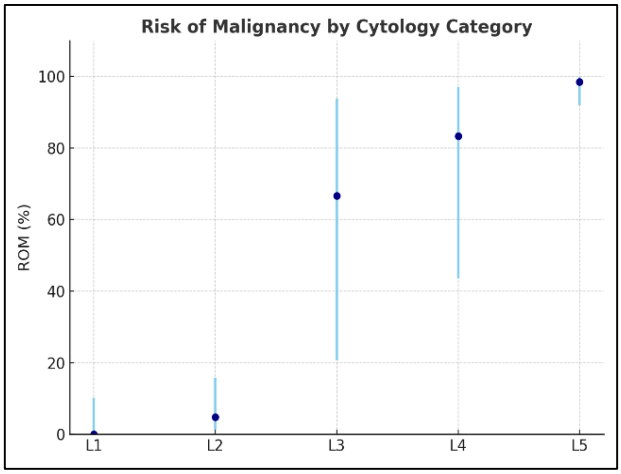

Figure 1: ROM by cytology category.

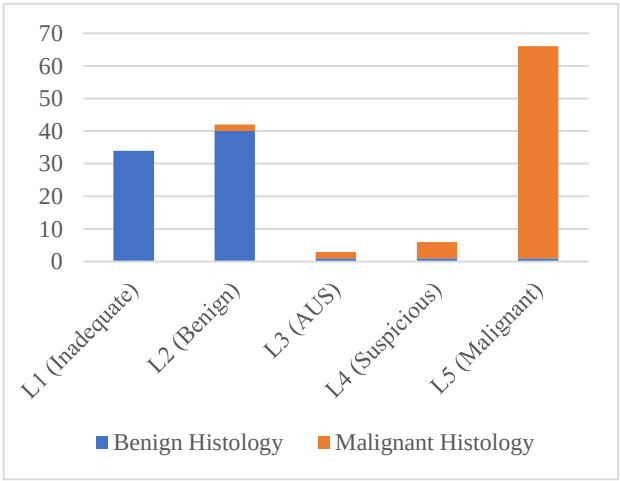

Figure 2: Cytology-histopathology correlation.

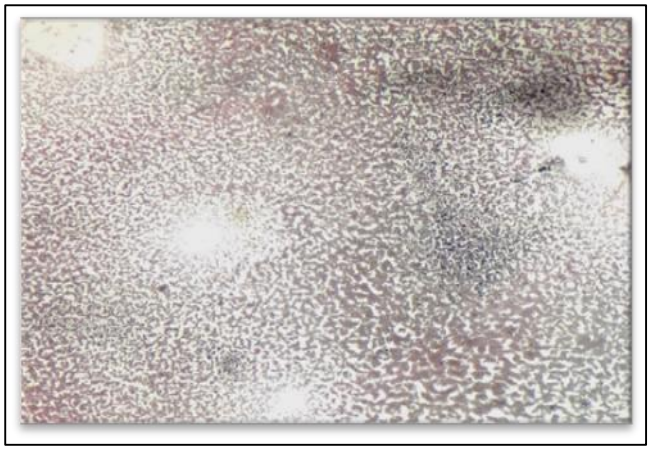

Figure 3: Category L1: non-diagnostic/inadequate

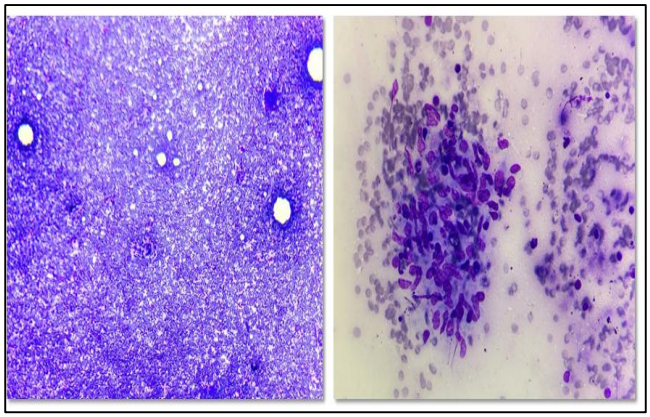

Figure 4: Category L2: benign.

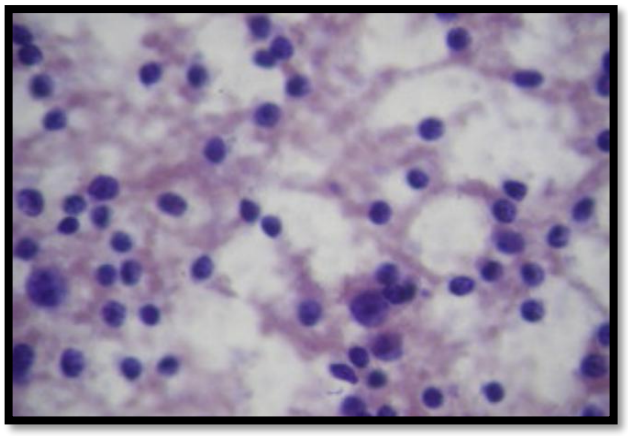

Figure 5: Category L4: suspicious for malignancy

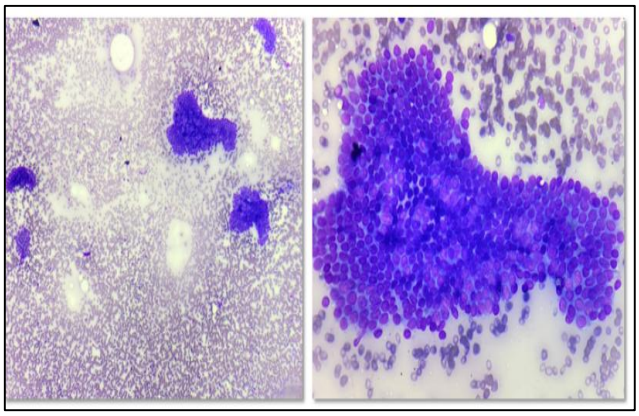

Figure 6: Category L5: malignant.

Table 3: Cytology-histopathology correlation and ROM.

Cytology category	Benign histology	Malignant histology	Total	ROM (%)	95% CI
L1 (Inadequate)	34	0	34	0.00	0.00-10.15
L2 (Benign)	40	2	42	4.76	1.32-15.79
L3 (AUS)	1	2	3	66.67	20.77-93.85
L4 (Suspicious)	1	5	6	83.33	43.65-96.99
L5 (Malignant)	1	65	66	98.48	91.90-99.73
Total	77	74	151		

Statistical analysis

Excluding L1 cases from total cases with histopathological correlation, diagnostic performance was calculated for 117 cases. The diagnostic sensitivity was found to be 97.30% (95% CI: 90.67-99.26) and specificity 93.02% (95% CI: 81.39-97.60). The positive predictive value was 96% (95% CI: 88.89-98.63) and the negative predictive value was 95.24% (95% CI: 84.21-98.68). The diagnostic accuracy achieved was found to be 95.73% (95% CI: 90.38-98.16).

DISCUSSION

Cytological evaluations and reporting rely on standardised systems, such as the Bethesda system for thyroid and the Milan system for salivary gland tumor/nodule cytology. [6] The cytopathological evaluation of LN FNAC has been challenging due to the lack of standardised guidelines and reporting systems, leading to interobserver variability, inconsistent terminology, and communication gaps.[7] The Sydney system is a significant advancement in the standardised reporting of LN FNAC, addressing inconsistencies in the cytopathological interpretations and thereby improving clinical decision making.[8] In the current study, the reclassification of LN aspirates according to the Sydney system revealed that L2 cases predominated in the analysis, followed by L5, L1, L3 and L4. ROM increased progressively across categories, aligning with the tiered design of Sydney system to stratify risk and guide the clinical management. Diagnostic performance

demonstrated high sensitivity, specificity, PPV, NPV and accuracy, underscoring the reliability of the classification system in a high burden, heterogenous setting.

The category distribution in our study population aligns with the patterns observed in prior validations, where L2 and L5 cases predominate, reflecting the binary nature of most LN pathologies.[7,9] The low representation of L3 and L4 is consistent with meta-analytic data, where these groups comprise of <5% of total cases, highlighting the ability of system to minimise diagnostic ambiguities through clear cytomorphological guidelines.[10,11] ROM values from our study are consistent with the hierarchical progression observed in similar studies. ROM for L5 and L4 aligned closely with the study by Gupta et al and the L3 ROM matched in both the studies.[1] A lower ROM for L1 and L2 categories in our study in contrast to similar studies may reflect differences in patient populations, procedural techniques or stringent application of adequacy criteria in the setting.[12] The absence of malignancy in L1 suggests high specificity in identifying inadequate samples. L4 ROM was found to be slightly lower than that of Vigliar et al possibly due to the limited sample size in the indeterminate groups. 66.7% ROM for L3 was found to be similar to 66.6% from the study of Alqaidy et al., and comparable to 58.3% by Vigliar et al and 88.9% by Uzun et al highlighting the diagnostic ambiguity and the need for ancillary testing to refine risk assessment in the category.[3,13,14] The low ROM in L1 and L2 contrasted with higher values in the similar studies, reflecting stricter adequacy criteria or the differences in follow up protocols. The diagnostic performance metrics of sensitivity and specificity in our study closely aligned with similar studies, reflecting the efficacy of standardised reporting.[3,14] PPV, NPV and diagnostic accuracy indicated similar or improved diagnostic performance from other studies.[4,15]

Categories L1, L2, and L5 demonstrated low ambiguity, with cytomorphological features facilitating a clear reporting. The use of ancillary techniques likely contributed to the high diagnostic accuracy, particularly in confirming malignancy in L5 cases. L3 and L4 exhibited higher interobserver variability due to subjective interpretations of atypical lymphoid cells, posing diagnostic challenges which can be mitigated by ancillary techniques. The Chi-square test confirmed a highly significant association between Sydney system categories and histopathological outcomes, supporting the ability to effectively distinguish benign from malignant LN pathologies in our tertiary care setting.

The study limitations include the retrospective design, potentially introducing selection bias and the limited histopathological follow up which can underestimate ROM in non-correlated cases. Future multi centre studies with comprehensive ancillary integration are essential to validate the findings across diverse populations and minimise the variability.

CONCLUSION

In conclusion, the Sydney system effectively standardises LN cytopathology reporting, improving diagnostic accuracy and clinical communication, with a reliable risk stratification. Its implementation offers to reduce the interobserver variability and optimise patient management with broader implications for resource limited settings and global cytopathology practice. Findings of our study validates reliability of the system in diagnosis and its potential to optimise clinical decision making in tertiary care institutions. Despite the limitations in present study, including retrospective design and partial histopathological follow up, this study supports the global adoption of the Sydney system as a standardised framework for LN cytopathology reporting.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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