

## A STUDY ON USE OF NLR AS A POTENTIAL DIFFERENTIAL DIAGNOSTIC MARKER IN GRANULOMATOUS TB AND NON-TB LYMPHADENITIS

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### Abstract

**Background:** To compare NLR and FNAC reports of cervical lymphadenopathy cases and analyse the association between them. **Material and Methods:** A total 370 cases for FNAC during 2 months study period, of which 60 cases were of cervical lymphadenopathy. Based on inclusion and exclusion criteria we included 43 cases in our study at outpatient and in-patient department, Government Tertiary Care Hospital, Telangana State during the period from 05-12-2023 to 04-02-2024. **Results:** The total 43 cases, 24 were of male patients and 19 were of female patients and Cervical lymphadenopathy included in the study 25 [58.2%] were granulomatous lymphadenitis and 18 [41.8%] were non-granulomatous non-tuberculous lymphadenitis. **Conclusion:** A study population of 43 patients over a period of 02 months. 3 cases were excluded from study due to lack of confirmatory diagnosis. 22 cases were diagnosed as granulomatous TB lymphadenitis upon confirmation by positive AFB staining and/or CBNAAT and 18 cases as non TB lymphadenitis. As ours is a pilot study done on a small sample size, the results obtained call for similar studies on larger sample sizes to establish definitive statistical association.

## INTRODUCTION

Lymphadenopathy (LA) is a pathological process of lymph nodes manifested by abnormally increased size or altered consistency or number.<sup>[1]</sup>

Cervical lymphadenopathy (CLA) refers to swelling of cervical nodal tissue measuring more than 1 cm in diameter. However, palpable supraclavicular nodes of any size are considered abnormal. It is not a disease by itself; rather, it is a sign of an underlying pathology that ranges from a trivial infection to a metastatic malignant neoplasm [malignancies, infections, autoimmune disorders, iatrogenic, and other miscellaneous conditions].<sup>[1]</sup>

Cervical lymphadenopathy could be granulomatous or non-granulomatous. Granulomatous Lymphadenopathy has either infectious or non-infectious causes. Infectious causes can be Suppurative (Tularaemia, Cat-scratch Disease, Yersinia Lymphadenitis) or Non-Suppurative (Tuberculosis, BCG Histiocytosis, Toxoplasmosis). Non-Infectious causes are Sarcoidosis and Sarcoid like reaction.<sup>[2]</sup> Non-granulomatous lymphadenopathy has several causes like Kikuchi-

Fujimoto disease (KFD), Systemic Lupus Erythematosus (SLE), tuberculosis, lymphoma/metastasis and lymph node infarction.

Tuberculosis (TB) is caused by the Mycobacterium tuberculosis complex.<sup>[3]</sup> Worldwide, TB is the 13th leading cause of death and the second leading infectious killer after COVID-19.<sup>[4]</sup> In 2020, an estimated 10 million people fell ill with tuberculosis (TB) worldwide (5.6 million men, 3.3 million women and 1.1 million children) present in all countries and age groups. The total number of incident TB patients (new and relapse) notified during 2021 were 19,33,381 as opposed to that of 16,28,161 in 2020.<sup>[5]</sup> TB is classified as pulmonary, extrapulmonary, or both.<sup>[6]</sup>

Lymph node TB (LNTB, also called TB lymphadenitis) refers to mycobacterial tuberculosis infection of the lymph nodes, and may occur as the sole manifestation of TB infection, or alongside pulmonary or miliary TB and presents as painless swelling of the lymph nodes, most commonly at posterior cervical and supraclavicular sites (SCROFULA).<sup>[6]</sup> LNTB is the most common form of Extra Pulmonary Tuberculosis (EPTB) in India,

accounting for around 35% of EPTB cases. Total estimated incidence of LNTB was 30.8 per 100 000 population in India in 2013.

Care should be taken to identify patients who need to be investigated for LNTB, as there are multiple differential diagnoses for chronic lymphadenopathy.<sup>[7]</sup> Isolated peripheral tuberculous lymphadenopathy is usually due to the reactivation of disease at a site seeded hematogenously during primary tuberculosis (TB) infection, perhaps years earlier.<sup>[8]</sup>

Granulomatous TB lymphadenitis remains both diagnostic and therapeutic challenge because it mimics other pathologic processes and yields inconsistent physical and laboratory findings.<sup>[9]</sup> For example, the differential diagnosis of tuberculosis, creates a challenge due to sarcoidosis also having lung and lymph node involvement, showing granulomatous inflammation in pathological specimens, and similar symptoms such as fever, fatigue, weight loss.<sup>[10]</sup> Also, it is important to differentiate tuberculous from nontuberculous mycobacterial cervical lymphadenitis because their treatment protocols vary. In differential diagnosis of cervical TB lymphadenitis, other granulomatous lymphadenitis should be considered caused by atypical mycobacteria.<sup>[11]</sup>

Diagnosis of cervical TB lymphadenitis includes tuberculin test, Fine needle aspiration cytology (FNAC), AFB staining, and molecular tests such as CBNAAT and PCR which help in early diagnosis.<sup>[11,12]</sup> FNAC is a minimally invasive procedure to assess cervical lymphadenopathy. The sensitivity and specificity of FNAC in the diagnosis of tuberculous lymphadenitis are 88% and 96%, respectively.<sup>[13]</sup> FNAC material is subjected to Ziehl- Neelson (ZN) staining for AFB, to increase diagnostic yield. Sensitivity of ZN staining ranges from 46-78% and specificity is 100%,<sup>[14]</sup> the low sensitivity can be a drawback for clinical suspicion of granulomatous lymphadenopathy.

In FNAC, cyto-diagnosis is done by demonstrating granuloma, epithelioid giant cells with or without caseous necrosis followed by cytological evidence of AFB staining.<sup>[15]</sup> When AFB is negative in presence of epithelioid granulomas patient is advised for further investigations and follow ups,<sup>[16]</sup> which are absent in remote areas and primary health care centres. Frequent aspiration is required if needle has not penetrated till pathological site.

With the above-mentioned minor challenges in early diagnosis of lymphadenopathy, certain haematological parameters have come into pivotal importance in recent time one of which is Neutrophil-lymphocyte ratio(NLR). The NLR is the number of neutrophils divided by the number of lymphocytes. Under physiologic stress, the number of neutrophils increases, while the number of lymphocytes decreases,<sup>[17]</sup> whereas in chronic pathological state like TB it varies. The NLR was found to correlate well with the severity of disease

and outcome, according to Acute Physiology and Chronic Health Evaluation II and Sepsis-related Organ Failure Assessment scores.<sup>[18]</sup> Many publications have been written on the relationship between prognosis and NLR as a marker of inflammation. The value of NLR has been studied in cardiovascular disease, chronic renal disease, malignancies, osteoporosis and Alzheimer's disease. Studies have shown use of NLR for differential diagnosis of patients with pulmonary TB from patients with bacterial community acquired pneumonia.<sup>[19,20]</sup> In a similar way, use of NLR can be studied in subjects presenting with cervical lymphadenopathy for early clinical suspicion of TB.

Early isolation of suspected tuberculosis subjects presenting with cervical Lymphadenopathy, using NLR as differential diagnostic marker at primary health care centre can aid in avoiding a delay in referral to tertiary health care centres for histocytological confirmation.

#### **Aim of The Study**

- Use of NLR as a non-invasive method for differential diagnosis of tuberculous lymphadenitis and Non-tuberculous lymphadenitis, and to assess the chronic inflammatory state of the subject.
- To correlate the NLR values of the subject having an FNAC confirmed report of TB lymphadenitis.
- Use of NLR as a screening parameter for early isolation of TB patients.

## **MATERIALS AND METHODS**

A Observational study and cross sectional study of 60 cases of cervical lymphadenopathy, In our study we included 43 cases, All outpatient and inpatient subjects presenting with cervical lymphadenopathy at Government Tertiary Care Hospital, Hyderabad

#### **Inclusion Criteria**

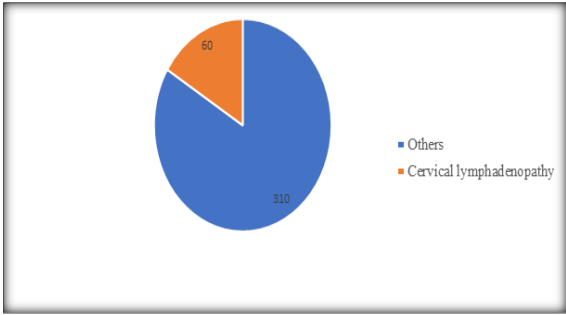
- Patients who are diagnosed with cervical lymphadenopathy and are subjected to FNAC.

#### **Exclusion Criteria**

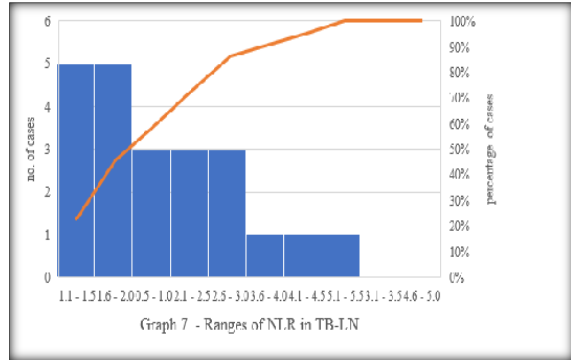
- Subjects with impaired cognition.
- Subjects who are on immunosuppressants and steroid therapy.
- Subjects diagnosed as HIV positive as they show negative results due to decreased sensitivity of T cells.

## **RESULTS**

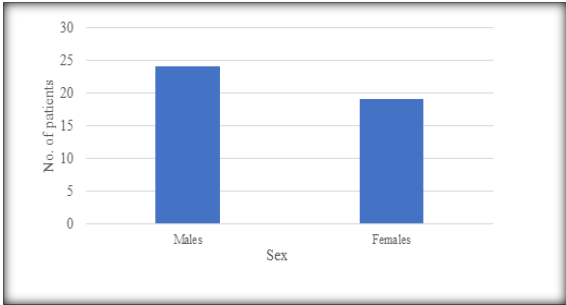
This study was conducted in government tertiary health care centre. We received a total of 370 cases for FNAC during our 2 months study period, of which 60 cases were of cervical lymphadenopathy. Based on inclusion and exclusion criteria we included 43 cases in our study.



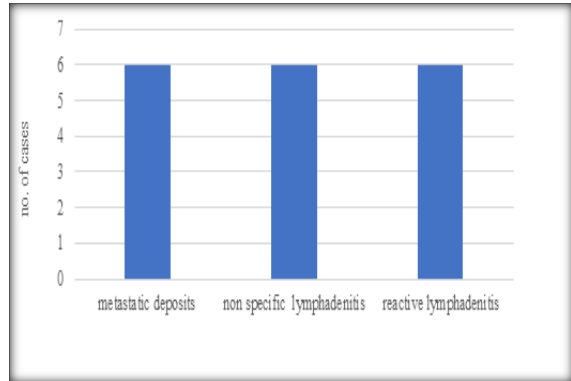
**Figure 1: Case Distribution**



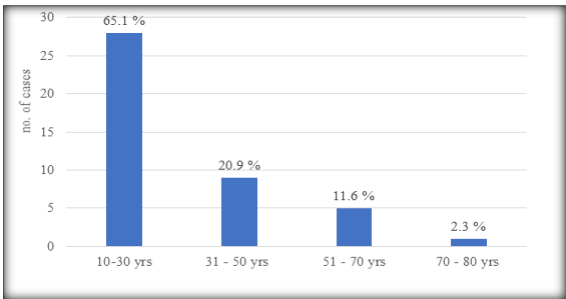
**Figure 6: NLR in TB lymphadenitis**



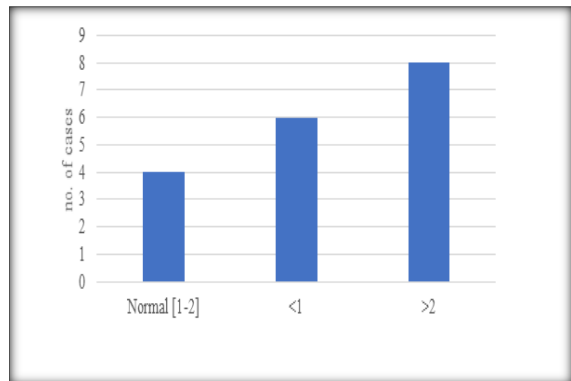
**Figure 2: Sex Distribution**



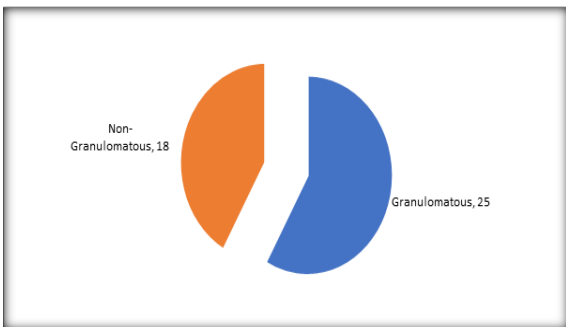
**Figure 7: Non TB lymphadenitis cases**



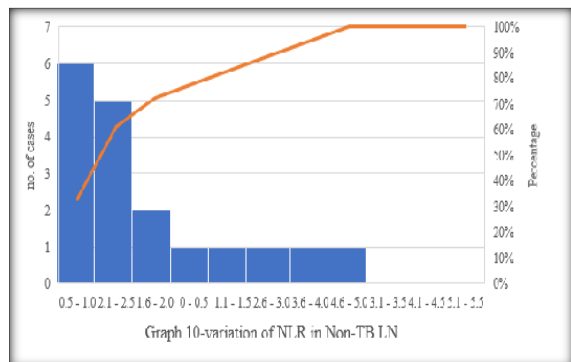
**Figure 3: Age distribution**



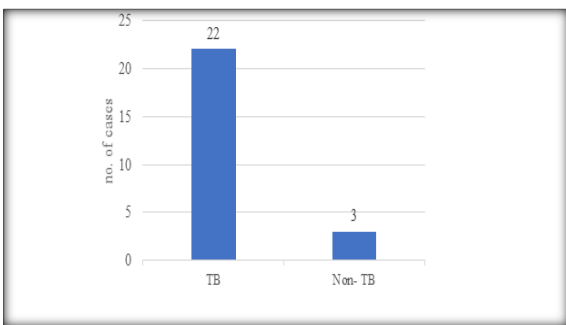
**Figure 8: NLR in Non TBLN**



**Figure 4: Granulomatous Lymphadenitis vs Non-Granulomatous Lymphadenitis**



**Figure 9: Variation of NLR in Non-TB LN**



**Figure 5: Granulomatous TB vs Non-TB**

**Table 1: NLR values in 22 granulomatous TB lymphadenitis cases**

Normal NLR [1-2]	11
NLR <1	2
NLR >2	9

**Table 2: Distribution of TB lymphadenitis cases**

Category	Cytomorphological findings	Cases	NLR		
			<1	N	>2
1	necrosis +inflammatory degenerative material	3	0	2	1
2	Caseous Necrosis+epitheloid histiocytes granuloma	13	2	5	6
3	only epitheloidhistiocytes,granuloma, without necrosis	6	0	4	2

## DISCUSSION

This study was conducted in a Government Tertiary Health Care Center on 43 patients who satisfied the inclusion and exclusion criteria.

Case Distribution shows that 0.16% of FNAC cases were of cervical lymphadenopathy. It proves one of the common clinical presentations in the outpatient department.

Sex Distribution shows the distribution of cases among males and females. In our study 59% of tuberculous lymphadenitis cases were females. These results were similar to the study conducted by Dursun Tatar et al.<sup>[21]</sup> where there was female predominance.

Age Distribution shows 65.1 % of cases are in the range of 10-30 years age group. Moreover, of the 22 cases of tuberculosis in our study maximum cases (16) were in the age group of 10-30 years. These results are comparable to that of a study conducted by Aramide KO.<sup>[22]</sup> Dandapat et al.<sup>[23]</sup> have suggested that TB lymphadenitis is more frequent in females and in the younger age groups because of male-dominated communities, where women experience poorer living conditions.

Granulomatous Lymphadenitis Vs Non Granulomatous Lymphadenitis shows that the frequency of granulomatous lymphadenitis cases presenting as cervical lymphadenopathy is slightly higher than that of non-granulomatous etiology in our study.

Yoon NB, Um SJ et al.<sup>[19]</sup> Role of the neutrophil-lymphocyte count ratio in the differential diagnosis between pulmonary tuberculosis and bacterial community-acquired pneumonia. *Ann Lab Med.* 2013 Mar;33(2):105-10. doi: 10.3343/alm.2013.33.2.105. Epub 2013 Feb 21. PMID: 23482854; PMCID: PMC3589634. This study retrospectively analysed the clinical and laboratory parameters in pulmonary TB and community acquired bacterial pneumonia, and evaluation was done between inflammatory marker NLR and C-reactive protein.

Granulomatous TB Vs Non TB shows 22 (88%), of the 25 granulomatous lymphadenitis cases were diagnosed as TB lymphadenitis. The FNAC reports of the 22 cases diagnosed as TB lymphadenitis had features like epithelioid histiocytes, Langhans giant cells, with or without caseous necrosis and granuloma formation which are highly suggestive of

tuberculous etiology. All these cases were correlated with clinical history (evening rise of temperature, weakness, night sweats, positive history of contact with TB), positive Mantoux test/ PPD test, AFB staining for tuberculous bacilli or CBNAAT. Of 22 cases, 18 cases showed AFB positivity and 4 cases had a CBNAAT positive report.

AFB staining requires specialized reagents and trained personnel for performing the procedure and for interpretation. More over sensitivity rate of ZN staining ranges from 48-76%, which is a drawback.

Of the 3 granulomatous cases of non-tuberculous aetiology, 1 case was signed out as lymphoproliferative disorder and 2 other cases needed further evaluation for confirmatory diagnosis. NLR value of those cases were not included in the study as their underlying etiology might affect our study results.

In our study TB Lymphadenitis cases based on cytomorphology there were 6 cases (46.1%) belonging to category 2 which had NLR of >2, compared to 2 cases (33.33%) belonging to category 3. This indicates that presence or absence of necrosis plays a key role in the variation of NLR. NLR >2 in TB lymphadenitis is result of chronicity of disease in patients. It varies according to immune status of patient, anti-tubercular drug therapy etc.

Non Granulomatous Lymphadenitis, NLR values in 18 non granulomatous, non-lymphadenitis cases and variation of NLR in non-granulomatous are showing results of Non-TB lymphadenitis, in which we had a total of 6 cases with metastatic deposits of epithelial malignancy. Such high number 6/18 (33.3%) can be attributed to study being conducted at a tertiary health care centre, where patients present at a late stage with advanced disease. Whereas, at primary health care centre most of the cases encountered are those with acute and sub-acute presentation.

Berhane M, Melku M, Amsalu A, Enawgaw B, Getaneh Z, Asrie F et al.<sup>[20]</sup> The Role of Neutrophil to Lymphocyte Count Ratio in the Differential Diagnosis of Pulmonary Tuberculosis and Bacterial Community-Acquired Pneumonia: a Cross-Sectional Study at Ayder and Mekelle Hospitals, Ethiopia. *Clin Lab.* 2019 Apr 1;65(4). doi: 10.7754/Clin.Lab.2018.180833. PMID: 30969087. This is a cross-sectional study in which the role of NLR and Erythrocyte Sedimentation Rate [ESR] has been evaluated in the differential diagnosis of



pulmonary tuberculosis and community acquired bacterial pneumonia.

EM Crit A, Farkas J. PulmCrit: Neutrophil-Lymphocyte Ratio (NLR) et al 17: Free upgrade to your WBC [Internet]. EMCrit Project. 2019 [cited 2022 Feb 17]. This article gives an idea how NLR has been gaining attention in recent years across many fields of medicine. It's giving an overview of NLR, its physiological range, and how it varies in various pathological diseases.

All the above cases of squamous cell carcinoma, adenocarcinoma and other epithelial malignancies with NLR values of >2 are indicative of higher grade of tumor with tumor necrosis.

Chi-square test using 2\*2 contingency table is used to determine the statistical significance

	Physiological range NLR	Physiological range NLR	TOTAL
TB	11	11	22
Non-TB	4	14	18
TOTAL	15	25	40

The p-value thus obtained is 0.04 (<0.05) which is statistically significant.

This indicates that the variation of NLR in tuberculous lymphadenitis from physiological to pathological range is significant when compared to that of NLR of Non tuberculous etiology.

## CONCLUSION

- Tuberculosis is one of the highly prevalent diseases in India causing high mortality and morbidity. Due to the absence of adequate infrastructure, resources and facilities to identify Lymph Node Tuberculosis (LNTB) at grass root level there is often delay in diagnosis and initiation of treatment.
- Early identification of patients suspected to have tuberculous lymphadenitis among those presenting with cervical lymphadenopathy at primary health care centres, with the help of NLR as differential diagnostic marker, helps to avoid delay in referral of the patient to higher health care centres for confirmatory diagnosis.
- From our study we conclude that Neutrophil to Lymphocyte Ratio (NLR) a simple, ubiquitous, universally available inflammatory biomarker can be utilised as marker to isolate TB lymphadenitis patients from Non TB lymphadenitis patients.
- This warrants, further studies for identification of simpler and cost-effective tools like NLR in diagnosis of tuberculosis.
- The limitations of this study include the small size of the study population. Validating the findings in larger trials can add to the veracity of results.

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