LYMPHOCYTE-NEUTROPHIL RATIO IN THE DIAGNOSIS OF TUBERCULAR PLEURAL EFFUSION IN A TERTIARY CARE CENTRE: A DESCRIPTIVE CROSS SECTIONAL STUDY

Rajneesh Jha[1], Ram Kumar Mehata[2], Puru Koirala[3]*

Affiliation

1. *Assistant Professor, Department of Internal Medicine, Birat Medical College and Teaching Hospital, Nepal*
2. *Lecturer, Department of Internal Medicine, Birat Medical College and Teaching Hospital, Nepal*
3. *Associate Professor, Department of Internal Medicine, Birat Medical College and Teaching Hospital, Nepal, Nepal*

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**** Corresponding Author***

Dr. Rajneesh Jha
Assistant Professor
Department of Internal Medicine
Birat Medical College and Teaching Hospital, Nepal
Email: jha_rajneesh@yahoo.com
ORCID: https://orcid.org/0000-0003-4921-7801

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ABSTRACT

Introduction

Tuberculosis is a common infection in our community. Tubercular pleural effusion is the second most common form of extrapulmonary tuberculosis. Among the several causes of exudative pleural effusison tubercular remains the most common form in clinical practice. The aim of this study was to evaluate the significance of lymphocyte-neutrophil ratio(LN ratio) in cases of exudative effusion for diagnosis of tubercular effusion.

Methodology

This was a hospital based cross sectional study done in Patients at tertiary care hospital from 1st September 2020 to 1stapril 2021 after taking ethical clearance from institutional reviw committee. Convienience sampling was done. Statistical Analysis of data like percentages and frequencies were used for categorical variables. Mean and SD (standard deviation) were used for describing continuous variables. Inferential statistical tools like Chi-Square test and Student's t-test were used. P-value of <0.05 was considered statistically significant.

Result

out of 200 cases 75% were tubercular pleural effusion and these cases were found have high levels of LN ratio (0.89 ± 0.11 for females and 0.97 ± 0.14 for males) and ADA (137.79 ± 44.61for females and 147.61 ± 51.64 for males) and more than 90% sensitivity and specificity of LN ratio and ADA level.

Conclusion

Exudative pleural fluid L/N ratio >0.75 is an efficient means of diagnosing tuberculous pleural effusion and its combination with ADA level gives us more accuracy and surety about the diagnosis of tubercular pleural effusion.

KEYWORDS

LN ratio, ADA, exudative effusion.

INTRODUCTION

Pleural effusion is defined as the abnormal collection of fluid in the pleural cavity. It is classified into transudates and exudates based on the Light's criteria.[1] Common causes of exudative pleural effusions found in clinical practices are tuberculosis, para pneumonic, malignancy primary or metastasis, associated with collagen vascular disease, liver abscess, subphrenic abscess, pancreatitis.[2] Tuberculous pleural effusion is seen in many cases in our region. Tuberculosis has high prevalence in asian countries like Nepal anad India. It is the one of the most common form of extra pulmonary tuberculosis.[3]

It becomes challenging for a clinician many a times to diffrentiate the causes for pleural effusion. First of all we have to differentiate transudative effusion from exudative effusion. Then it is essential to find out diagnosis for underlying cause of exudative effusion. For this purpose several biochemical parameters like adenosine deaminase (ADA), lactate dehydrogenase (LDH), C-reactive protein (CRP), interferon gamma and procalcitonin levels, have been studied, but its diagnosis is still challenging.[4-6] However adenosine deaminase (ADA) is being frequently used as a diagnostic maker in tuberculous pleural effusion in many centres in our region. ADA derived from the summary receptor operator curve with cut off value >40U/L is found to be more than 90% both sensitivite and specific.[7-8] Lymphocyte-neutrophil ratio (LN ratio) is being investigated as novel inflammatory marker nowadays. The association of lymphocyte-neutrophil ratio and lung cancer has been mostly investigated among studies on lung diseases , and a few studies have investigated its values in the pleural fluid for the differential diagnosis of bacterial pneumonia and tuberculous pleural effusion.[9-10]

Aim of the study was to find out the role of the lymphocyte neutrophil ratio (LNR) which can be easily obtained by determining the total and differential cell counts of pleural fluid for the diagnosis of exudative pleural effusion as tubercular in origin.

METHODOLOGY

It was a single centre hospital based descriptive cross sectional study. It was conducted in Birat medical college and teaching hospital, biratnagar, Nepal from September 1st 2020 to april 1st 2021. The study included 200 patients aged more than 15 years giving consent to be enrolled in the study. Prior to the the study ethical clearance was taken from IRC. Sample size calculation was obtained by using the formula,

Sample Size (N) = $(1.96)^2$ X P (1-P) / M^2

Where, P = Prevalence of the disease in the locality; M = Margin of error (5%) .The prevalence of tuberculous pleural effusion has been reported to be variable in different countries. prevalence varies in asaian and non asian countries. Nepal as an asian country has a higher prevalence reate. Prevalence in asian countries is usually 10-20% by various studies.(11-12) keeping a prevalence of 15%, the sample size was calculated 196. So, sample size of 200 was considered in this study.

Inclusion criteria

- Patients of exudative pleural effusion,
- Age >15years,
- Hemodynamically stable.

Exclusion criteria

- Patients of transudative pleural effusion,
- Age <15years,
- Hemodynamically unstable.

Diagnostic criteria

Light's criteria (1) was used to diagnose exudative pleural effusion. Exudative pleural effusion meets at least one of the following criteria

- Pleural fluid / serum protein >0.5
- Pleural fluid LDH/serum LDH >0.6,
- Pleural fluid LDH > two-thirds of normal upper limit for serum.

Criteria taken for diagnosis of tuberculous pleural effusion[8]

Demonstration of AFB in pleural fluid by AFB stain or Gene Xpert test and / or ADA > 40 U/L and / or L/N ration > 0.75 in pleural fluid.

Imaging

Plain chest X-ray PA view, USG chest and/or CT chest based on afford ability.

Under all aseptic precautions diagnostic thoracocentesis was done, and fluid was sent for analysis of glucose, protein, cytology and cell count, LDH, AFB and gram stain, culture and sensitivity and ADA were done in all cases. Gene Xpert test of pleural fluid was done in selected cases depending upon the availability of test and recommendation by government tuberculosis centre specially in suspected MDR cases and patients who were treated for pulmonary tuberculosis in the past.

In non-tuberculous pleural effusion, evaluation was done for pneumonia, malignancy, metastasis, empyema and rheumatoid pleurisy, liver abscess, pancreatitis. Besides detailed history and clinical examination, the different investigations were carried out like Complete haemogram, ESR, serum Urea, Serum Creatinine, Liver Function Tests, serum ANA, dsDNA, RA factor, serum thyroid function tests, Sputum AFB, Sputum culture and sensitivity depending on the patient history and examination.

The LN ratio was obtained by dividing the absolute lymphocyte count by the absolute neutrophil count. Total and differential counts were obtained from pleural fluid analysis.

Para-pneumonic effusion was diagnosed based on the presence of clinical symptoms cough, fever, dyspnoea and a radiographic pulmonary infiltrate that recovered with use of antibiotics.

Pleural effusion due to lung primary or secondaries was diagnosed when the pleural fluid cytology and/or pleural biopsy findings were positive for malignancy.

Effusion due to connective tissue disorder like Sustemic lupus erythamtosis was defined as effusion in patients

positive for ANA and Anti DsDNA.

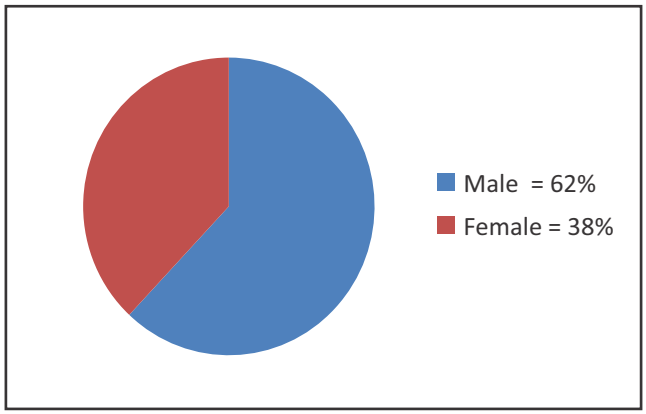
Pleural effusion aasociated with Pancreatitis was diagnosed as cases with raised amylase and ultrasound abdomen showing evidence of pancreatitis.

Pleural effusion associated with rheumatoid arthritis was diagnosed when it had low glucose, low pH, high LDH and patients positive for RA factor and anti ccp.

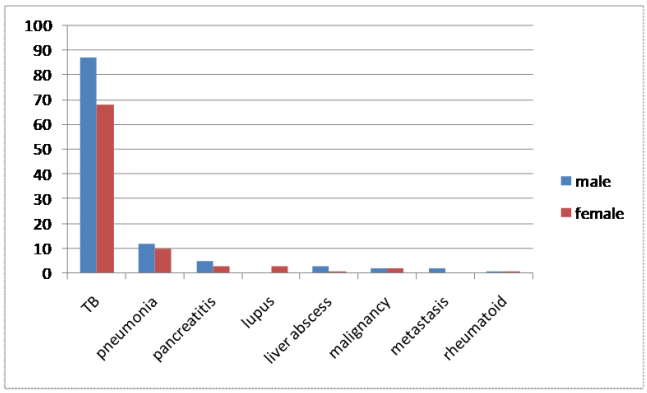
Statistical Analysis of data like percentages and frequencies were used for categorical variables. Mean and SD(standard deviation) were used for describing continuous variables. Inferential statistical tools like Chi-Square test and Student's t-test were used. P-value of <0.05 was considered statistically significant.

RESULTS

A total of 200 patients of exudative pleural effusion were analyzed, out of which 124 (62%) were males and 76(38%)



Out of these 200 patients most of them had pleural effusion due to tuberculosis. Other causes were pneumonia, systemic lupus erythematosis, rheumatoid arthritis, pancreatitis, liver abscess, bronchogenic cancer and metastasis to lungs. Males and females were in almost similar proportion among the different groups (diagram2)



We analysed 200 participant's samples and categorized them into female and male groups so as to further observe the age groups, ADA, LN ratio values. we found different mean values for tuberculous and nontuberculous pleural effusion samples among males and females (table 1).

Table 1:

Variables	Nontuberculous effusion	Tuberculous effusion	P- value
Female			
Age	39.04 ± 13.72	48.55 ± 15.72	N/A
ADA	33.75 ± 14.13	137.79 ± 44.61	0.0001
LN ratio	0.53 ± 0.16	0.89 ± 0.11	0.0001
Male			
Age	40.15 ± 18.24	41.97 ± 13.74	N/A
ADA	37.46 ± 15.50	147.61 ± 51.64	0.0001
LN ratio	0.45 ± 0.16	0.97 ± 0.14	0.0001

When we compared the samples dividing it into two major groups as tuberculous and nontubercoulous we found that most of the tuberculous samples had both ADA>40U/L and LN ratio>0.75 together while most of the nontuberculous samples had both ADA<40U/L and LN ratio<0.75 together.

Table 2:

	Tuberculous (n)	Non-Tuberculous (n)	Total (n)
< 40 U/L ADA and <0.75 LN ratio	0	38	38
> 40 U/L ADA and >0.75 LN ratio	148	3	151
< 40 U/L ADA and >0.75 LN ratio	0	0	0
> 40 U/L ADA and <0.75 LN ratio	2	9	11

Similarly we analysed the ADA levels and LN ratio separately in these two groups and found that maximum number of tuberculous samples had ADA >40U/L and LN ratio >0.75 (tables and diagrams 3 and 4)

Table 3: ADA levels in TB and Non-TB groups

	TB	Non-TB
> 40 U/L	150	12
< 40 U/L	0	38

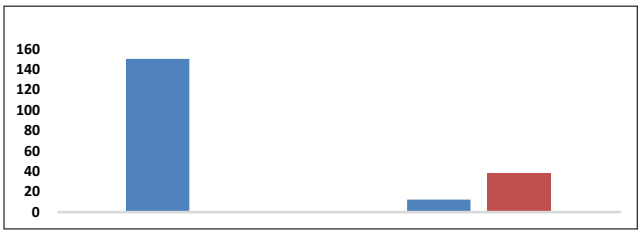
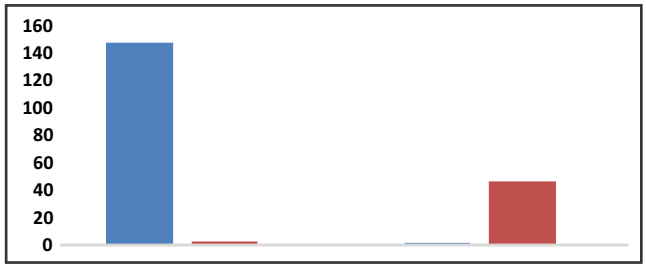


Table 4: LN Ratio in TB and Non-TB groups

	TB	Non-TB
> 0.75 LN ratio	148	3
< 0.75 LN ratio	2	47



We found very high sensitivity, specificity, PPV, NPV of LN ratio in tuberculous pleural effusion (table-5)

Table-5	Sensitivity %	Specificity %	PPV %	NPV %	Disease prevalence
ADA level > 40 U/L	92.6	100	100	76	75
LN ratio > 0.75	98	95.9	98.7	94	75

DISCUSSION

Pleural effusion is common respiratory problem in our clinical practice. Many cases with fever, cough, dyspnoea visiting our outpatient department or admitted in medical ward through emergency are found to have pleural effusion. The most common causes of exudative pleural effusion include pneumonia, tuberculosis and cancer .The diagnostic dilemma many a times alter the course of management. Pneumonia responds to limited course of antibiotics, while tuberculosis needs long term antitubercular drugs according to national tuberculosis program while lung cancer has different protocol like surgery, chemo and radiotherapy. Cases like pleural effusion associated with pancreatitis , rheumatoid arthritis, liver abscess respond only when underlyind causes are treated. Hence diagnosis of exudative pleural effusion is of utmost importance. Although many biochemical parameters, such as adenosine deaminase, lactate dehydrogenase, C-reactive protein, adenosine deaminase, interferon gamma and procalciton in levels, have been studied in the context of the diagnosis of exudative pleural effusion, its diagnosis is still challenging.

As we know prevalence of tuberculosis is high in Nepal[13] and it can present in two forms either pulmonary or extra pulmonary. Tuberculous pleural effusion is one of the most common form of extra pulmonary tuberculosis.[14] Its diagnosis can be done through pleural fluid analysis via thoracocentesis. Different parameters are analysed in pleural fluid like glucose ,protein, cell count, LDH, ADA, malignant cells.[15] Staining is done with AFB stain, Graham stain. Culture is done for bacteria, tuberculosis. PCR is available for different organisms. But among all, lymphocyte-neutrophil ratio (LN ratio) calculated with cell count is simple, inexpensive and quick method to diagnose tuberculous effusion. AFB staining is very less sensitive,[16] culture for tuberculosis is not feasible in all centres, PCR is very expensive, not much sensitive for pleural fluid[17] and also not available in all centres.

In this study, we investigated the cell counts of exudative pleural effusions and these counts' contribution to differential diagnosis by calculating the LN ratio. The pleural fluid LN ratio value was significantly higher in tuberculous effusion compared to nontuberculous effusions. This was similar to the study done by Emet et al.(18)However, LN ratio in malignant, para-pneumonic and other nonmalignant effusions was not significantely different.

In our study, we found that most of the tuberculous pleural effusion samples had both ADA>40U/L and LN ratio>0.75 together while most of the nontuberculous samples had both ADA<40U/L and LN ratio<0.75 together. it shows that LN ratio had important impact on diagnosis of tuberculous pleural effusion besides ADA level. This was similar to the study done by Lesley J. et al.[19]

In this present study, 75% of the pleural effusion cases were tubercular in origin and all of them had ADA level was ≥40U/L which correlates well with the study done by Ocaña let al,[20] in which they stated that adenosine Deaminase level >40 IU/L has very high diagnostic value in pleural effusion.

Similarly, among the tubercular effusion cases 98% had LN ratio >0.75 which correlates well with the study done by luisveldes et al[21] in which they found that more than 95% tubercular effusion had >50%lymphocytes.

Our study shows high sensitivity and specificity of LN ratio similar to ADA . When patients of exudative pleural effusion are evaluated in opd and wards we always send ADA as a diagnostic parameter. With a cut off value of more than 40 IU/ML, exudative pleural effusion are diagnosed as tubercular in origin. Since LN ratio is found to have similar sensitivity and specificity itclarifies that LN ratio has high diagnostic value in assesement of case of tubercular pleural effusion. In country like us where diagnostic parameters like PCR, biopsy, culture, biochemical analysis are not always available in all centres of peripheral and remote areas, LN ratio can be used for simple and easy tool for diagnosis of tubercular effusion and furthermore in the well equipped centres where all diagnostic facilities are available it will be good supportive test for tubercular pleural effusion adding more accuracy with ADA level.

CONCLUSION

From the above discussion, it is concluded that pleural fluid L/N ratio >0.75 is an efficient means of diagnosing tuberculous pleural effusion and its combination with ADA level gives us more accuracy and surety about the diagnosis of tubercular pleural effusion.

LIMITATIONS OF THE STUDY

The sample was taken from a medical college of eastern Nepal, so it may not be totally applicable to other regions . Moreover, larger sample size could have given little different results. Calculation of LNR values seemed to be more helpful in tubercular pleural effusion compared to malignant, para-pneumonic and para-malignant effusions, so the potential use of this formula may be limited to countries with high TB incidence. An additional limitation of our study was that we only used LNR values; adding other parameters, such as, CRP levels, TB IgM to the evaluation could be more helpful for differential diagnosis.

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CONFLICT OF INTEREST

None

FINANCIAL DISCLOSURE

None

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