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Diagnostic potential of inflammatory markers in tuberculous pleural effusion: a prospective tertiary hospital study

Shashidhar S Vananjakar[1], Prasanna Kumar T[2], Nirantha S P[3], Mohammed Sameer Kundale[4], Sruthy Vijayan[5], Pragati Rao D[6]

ABSTRACT

Introduction

Background and Objectives

India is an endemic country for TB Tuberculosis(TB), with the pleura being the most common extra pulmonary site affected, followed by lymph nodes. Diagnosing EPTB Extrapulmonary Tuberculosis(EPTB)is as crucial as treating it, since many cases are often neglected or improperly managed outside medical college hospitals. The objective of my study is to compare the diagnostic accuracy of the Neutrophil lymphocyte ratio (NLR) with that of isolated pleural fluid ADA Adenosine deaminase(ADA) levels in lymphocyte predominant effusions.

Methods

This is a prospective study conducted after ethical clearance and collected patient data, including demographics, vital signs, laboratory test results, and imaging. Under aseptic conditions diagnostic and and therapeutic pleurocentesis was performed for the patients after their informed consent. Pleural fluid for NLR was compared with standard ADA alone in high pre-test probability (exudative lymphocytic predominant). Patients were followed up after a month of starting ATT (Anti Tuberculosis Treatment), to assess clinical response by repeat imaging.

Results

A total of 54 patients among 80 patients who met the inclusion criteria ,with exudative pleural effusion was included in the study. The mean neutrophil-lymphocyte ratio value was significantly lower in tuberculous pleural effusion. NLR cut off was plotted with Receiver Operating Characteristic (ROC) curve with sensitivity and specificity calculated.

Conclusion

The pleural fluid neutrophil-lymphocyte ratio, which is an inexpensive, reproducible, and easily calculated haematological parameter when tested with ADA, synergistically increases the diagnostic accuracy.

Keywords:Tuberculosis, Pleural effusion, Neutrophils, lymphocytes, Neutrophil, lymphocyte ratio, adenosine deaminase, Receiver Operating Characteristic (ROC) curve.

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1*Corresponding author Shashidhar S Vananjakar*, Department of Respiratory Medicine, M S Ramaiah Medical College and Hospital, Rajiv Gandhi University of Medical Sciences, Bengaluru, India, dr.ssvananjakar@yahoo.com, +91 9740921911; [2]Prasanna Kumar T, Department of Respiratory Medicine, M S Ramaiah Medical College and Hospital, Rajiv Gandhi University of Medical Sciences, Bengaluru, India, prasannakumart@msrmc.ac.in; [3]Nirantha S P, Department of Respiratory Medicine, M S Ramaiah Medical College and Hospital, Rajiv Gandhi University of Medical Sciences, Bengaluru, India, nirantha.sp@gmail.com; [4]Mohammed Sameer Kundale, Department of Respiratory Medicine, M S Ramaiah Medical College and Hospital, Rajiv Gandhi University of Medical Sciences, Bengaluru, India, sameer.kundale@gmail.com; [5]Sruthy Vijayan, Department of Respiratory Medicine, M S Ramaiah Medical College and Hospital, Rajiv Gandhi University of Medical Sciences, Bengaluru, India, sruthy1095@gmail.com; [6]Pragati Rao D, Department of Respiratory Medicine, M S Ramaiah Medical College and Hospital, Rajiv Gandhi University of Medical Sciences, Bengaluru, India, dwarapu.pragati@gmail.com

Conflict of Interest—none | Funding—none

Ethics Approval and Informed Consent:

Data collection began following approval from the Institutional Ethics Committee. Informed consent was obtained from each participant, detailing study procedures and providing a patient information sheet.

INTRODUCTION

In India, the pleura is recognized as the most common site of extrapulmonary tuberculosis (TB), followed by lymph node involvement. When evaluating exudative pleural effusions, the neutrophil-lymphocyte ratio (NLR) and adenosine deaminase (ADA) levels in pleural fluid are essential diagnostic tools. A high NLR typically indicates a parapneumonic effusion (PPE), where neutrophils are predominant, while a lower NLR is more characteristic of tuberculous pleural effusion (TPE) and malignant pleural effusion (MPE), both of which usually display lymphocyte predominance. ADA concentrations exceeding 40U/L are highly sensitive and specific for TPE in effusions where lymphocytes predominate, although some overlap in elevated ADA may be seen in cases of malignancy. Utilizing both NLR and ADA together enhances the clinician's ability to differentiate TPE from PPE and MPE, particularly in lymphocyte-rich exudative effusions. Accordingly, these markers play a critical role in the initial evaluation and management of patients with suspected exudative pleural effusions in regions with a high TB burden. The rationale for this study stemmed from the critical need for accurate diagnosis of extra-pulmonary TB, which is as important as its treatment since many cases remain neglected or improperly managed, particularly outside tertiary medical centers. The main objectives were to compare the diagnostic accuracy of pleural fluid NLR with that of ADA in lymphocyte-predominant exudative effusions, thereby improving recognition and management of tuberculous pleural effusion.

Methods

Objectives of study:

1. Diagnosing EPTB is as crucial as treating it, since many cases are often neglected or improperly managed outside medical college hospitals.
2. The objectives of my study are to compare the diagnostic accuracy of the NLR ratio with that of isolated pleural fluid ADA levels in lymphocyte-predominant exudative effusions.

Source of data:

This prospective study was conducted in the Department of Respiratory Medicine at Ramaiah hospitals, Bengaluru, between August 2022 and July 2023. The study aimed to assess diagnostic markers in patients admitted with pleural effusion. Ethics approval was granted by the Institutional Ethics Committee, and informed consent was obtained from all participants prior to inclusion.

Data collection:

A total of 54 patients were enrolled, with the sample size calculated based on previous literature (Beukes A, et al.). Study participants included adults over the age of 18 years presenting with lymphocyte-predominant exudative pleural effusion, defined as pleural fluid containing more than 50% lymphocytes on total and differential cell count. Patients were further classified based on history, physical examination, and imaging modalities—specifically chest X-ray and chest ultrasonography (USG)—to confirm a diagnosis of tuberculous pleural effusion. Exclusion criteria comprised patients with pleural fluid ADA levels less than 15 IU/L and more than 100 IU/L, those with transudative pleural effusions (classified by Light's criteria), malignant exudative pleural effusions, chylothorax and hemothorax, hemodynamically unstable patients, and individuals unwilling to participate. Additionally, patients with a low pre-test probability for tuberculosis—defined as those lacking classic risk factors or features suggestive of TB—were excluded.

Inclusion criteria :

1. Patients aged > 18 years with lymphocyte-predominant exudative pleural effusion.
2. Patients diagnosed with tuberculous pleural effusion based on history, clinical examination, and appropriate imaging modalities. Ultrasonography of chest and chest x- ray.

Exclusion criteria :

1. Pleural effusions with ADA <15 & >100 IU/L
2. Transudative pleural effusions.
3. Malignant exudative pleural effusions
4. Low pre-test probability patients
5. Chylothorax, hemothorax
6. Patients who are hemodynamically unstable

7. Patients who are unwilling to take part in study.

Clinical information encompassed:

The **chief complaints** represent the patient's primary reasons for seeking medical attention, typically including symptoms such as fever, cough, chest pain, or shortness of breath. A thorough **physical examination**, encompassing both general physical examination (GPE) and systemic assessments, helps identify clinical signs like reduced breath sounds, dullness to percussion, or signs of respiratory distress. These findings guide the need for further **investigations**, which often include radiological imaging such as chest X-rays or CT scans, as well as laboratory tests like pleural fluid analysis, complete blood count, and microbiological studies to aid in diagnosis and management.

Follow-Up

Participants underwent follow-up evaluations after one month to assess the resolution of symptoms and to monitor changes in radiological findings. This structured approach facilitated systematic data collection and ensured adherence to ethical guidelines throughout the study period.

Structured proforma

The study began with the collection of **socio-demographic details** including the participant's name, age, sex, address, educational status, body height, body weight, marital status, comorbidities, and addictive habits. For the **laboratory tests**, relevant investigations such as a complete blood count (CBC), coagulation profile, viral serology, and random blood sugar (RBS) were performed on all patients. **Radiological investigations** included chest X-rays and ultrasound (USG) of the chest to quantify and mark pleural fluid. Diagnostic and therapeutic pleurocentesis, was performed under aseptic conditions. Relevant pleural fluid investigations included biochemical analysis for glucose, protein, ADA, and LDH levels, along with CBNAAT/GeneXpert, acid-fast bacilli (AFB) testing, and routine cell count, cell type analysis, and cytology. Patients meeting the exudative criteria criteria for exudative pleural fluid according to Light's criteria, with lymphocytic predominance, were selected for further evaluation. The **pleural fluid neutrophil-to-lymphocyte ratio (NLR)** was calculated to assess its diagnostic utility. Anti-tuberculosis therapy (ATT) was initiated according to weight band guidelines under the National Tuberculosis Elimination Program (NTEP) for patients with ADA levels > 40 IU/L and based on clinical and radiological diagnoses. Follow-up evaluations were conducted one month later with repeat chest X-rays or USG of the chest to assess the clinical response in patients undergoing ATT.

Study Conduct

Baseline demographic data, including age, sex, address, educational status, height, weight, marital status, comorbid conditions, and addictive habits, were documented on a structured proforma. This was followed by transfer of these details to Microsoft Excel spreadsheets for systematic analysis. Clinical information was thoroughly collected, encompassing each patient's presenting symptoms such as fever, cough, chest pain, and shortness of breath. A detailed general and systemic examination helped note clinical signs like diminished breath sounds or dullness on percussion. Relevant laboratory investigations included complete blood count, coagulation profile, random blood sugar, and viral serology. All patients underwent diagnostic and therapeutic pleurocentesis under aseptic conditions for pleural fluid analysis. The pleural fluid was assessed for biochemistry (glucose, protein, lactate dehydrogenase [LDH], and adenosine deaminase [ADA]), total and differential cell counts, cytology, and microbiology (CBNAAT/GeneXpert and acid-fast bacilli testing). Selection for analysis was based on Light's criteria for exudates and a lymphocyte predominance (>50% lymphocytes).

Anti-tuberculosis therapy was initiated according to the National Tuberculosis Elimination Program (NTEP) guidelines for cases with ADA >40 IU/L and based on clinical and radiological diagnosis. Patients underwent follow-up at one month with repeat imaging (either chest X-ray or USG chest) to assess clinical and radiological response.

STATISTICAL ANALYSIS

For statistical analysis, SPSS version 26.0 software was used to process and interpret the collected data. Quantitative data were summarized using measures such as mean, median, and standard deviation,

selected according to the data's distribution. The information gathered from participants was initially entered into Microsoft Excel spreadsheets to facilitate data management and organization. Graphs and tables were subsequently generated using Microsoft Word and incorporated throughout the study to enhance clarity and effectively present findings. Data were systematically displayed in the form of tables, figures, and graphs wherever appropriate to ensure clear and comprehensive representation of the results.

For statistical analysis, receiver operating characteristic (ROC) curve analysis was employed to determine the diagnostic accuracy of the neutrophil-lymphocyte ratio (NLR) and isolated ADA levels in predicting tuberculous pleural effusion in lymphocyte-predominant exudative effusions. The area under the ROC curve (AUC) was interpreted as follows: an AUC of 0.9-1.0 indicated an excellent test; 0.8-0.9, a good test; 0.7-0.8, a fair test; 0.6-0.7, a poor test; and 0.5-0.6, indicated a failed test.

E. Results:

Table: 1 Baseline characteristics of participants

Parameters	Values
Age (mean)	35 yrs
Lights criteria	Applied (exudative vs transudative)
Pleural fluid analysis	(mean)
Glucose	94 mg/dl
Protein	5.5 g/dl
LDH	374.2 U/L
TC	743.7
Neutrophils	292
Lymphocytes	1098.5
ADA	50.8 IU/L

Figure1: Gender distribution of participants

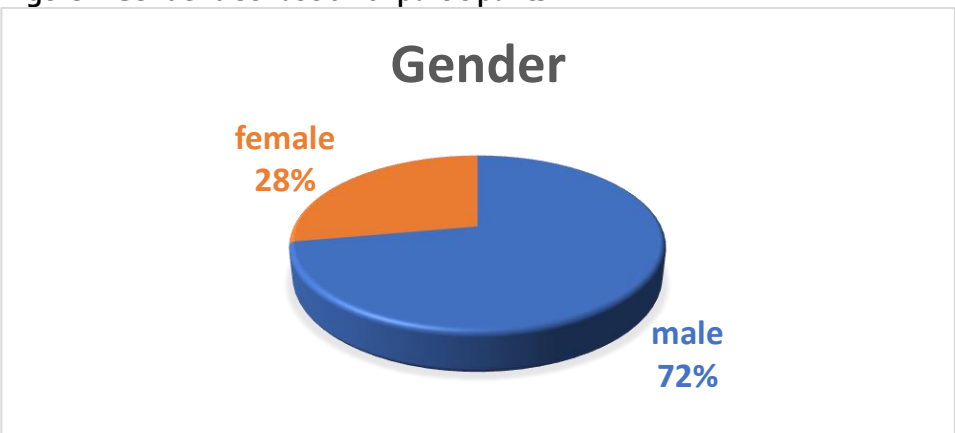


Figure 2: Symptoms of the participants

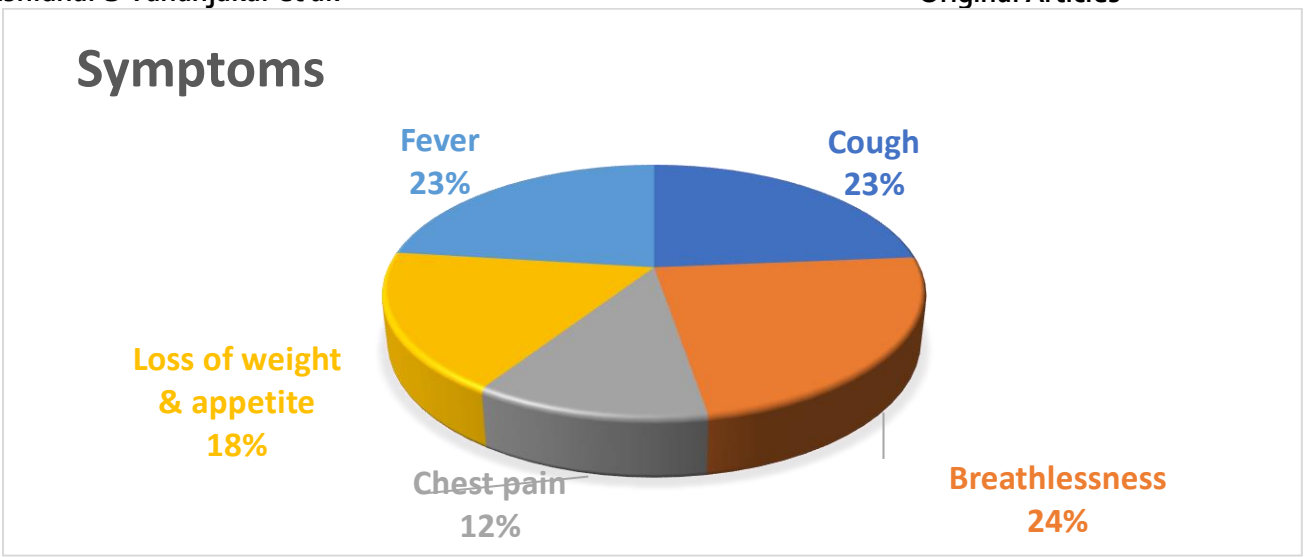
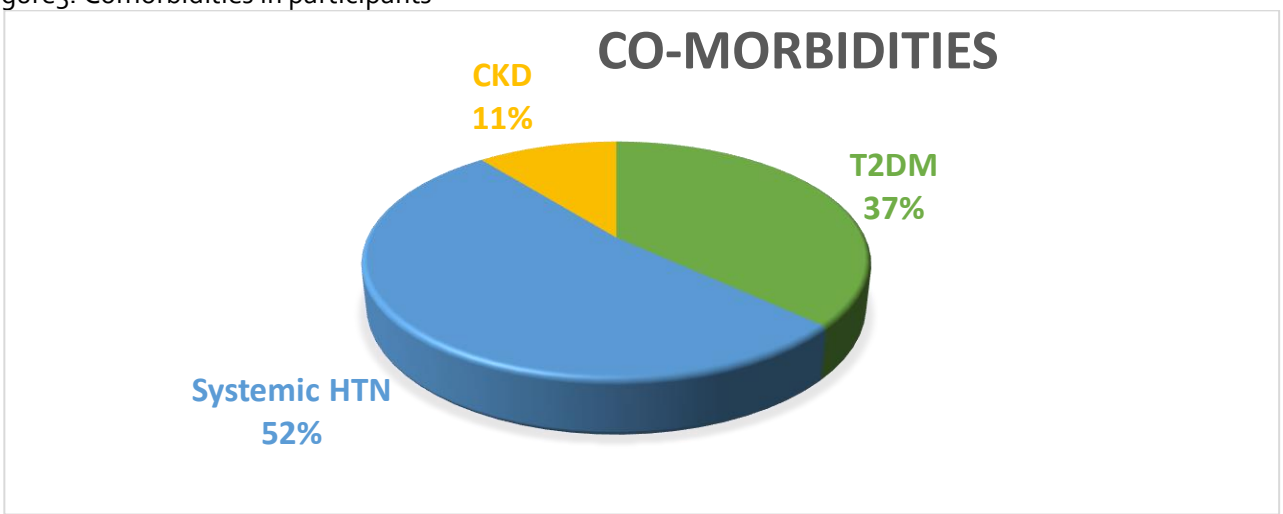


Figure3: Comorbidities in participants



The study included 54 patients with lymphocyte-predominant exudative pleural effusion. The mean age of participants was 35 years. Pleural fluid analysis demonstrated the following mean biochemical parameters: glucose at 94 mg/dL, protein at 5.5 g/dL, and lactate dehydrogenase (LDH) at 374.2 U/L. The total cell count (TC) averaged 743.7 cells/mm³, with neutrophils averaging 292 cells/mm³ and lymphocytes 1098.5 cells/mm³. Adenosine deaminase (ADA) levels averaged 50.8 IU/L, consistent with tuberculous pleural effusion in this high-prevalence setting.Receiver operating characteristic (ROC) curve analysis compared the diagnostic performance of the neutrophil-to-lymphocyte ratio (NLR) with ADA levels. The area under the curve (AUC) for NLR was 0.931, indicating excellent discriminative ability. Using a cut-off value of 0.95 for NLR, the sensitivity was 93.1%, while specificity reached 100%, demonstrating superior diagnostic accuracy. ADA levels also demonstrated high diagnostic value, affirming their role as a cornerstone biomarker for TPE.

ROC curve:

Area under curve for NLR vs ADA – 0.931

Cut off value of NLR = 0.95 (sensitivity 93.1%, specificity =100%)

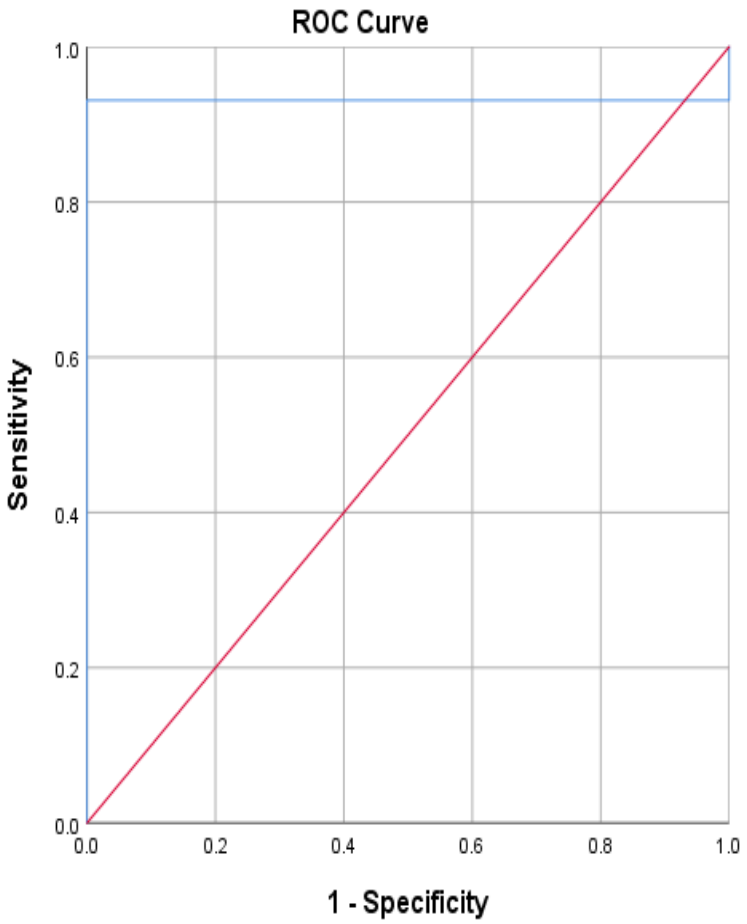


Figure 4: Receiver operating characteristic (ROC) curve comparing neutrophil-to-lymphocyte ratio (NLR) with adenosine deaminase (ADA) for diagnosing tuberculous pleural effusion. Area under the curve (AUC) for NLR = 0.931.

F. Discussion

In this prospective study of patients with lymphocyte-predominant exudative pleural effusion, the neutrophil-to-lymphocyte ratio (NLR) demonstrated excellent diagnostic accuracy for tuberculous pleural effusion (TPE), with an area under the curve (AUC) of 0.931. At an NLR cut-off of 0.95, the sensitivity was 93.1% and specificity was 100%, outperforming ADA alone and highlighting NLR as a valuable rapid diagnostic marker. The study reaffirmed the biochemical profiles previously noted, showing significantly higher LDH in parapneumonic effusions and elevated total protein in TPE. ADA levels averaged 50.8 IU/L, consistent with established diagnostic thresholds for TPE. The combined analysis of NLR and ADA, along with the LDH/ADA ratio, offers enhanced sensitivity and specificity, underscoring their complementary roles in differentiating TPE from parapneumonic and malignant effusions. These findings support prior reports and strengthen the proposition that incorporating NLR into routine pleural fluid analysis can improve early identification and clinical decision-making for TPE. Given the cost-effectiveness and accessibility of these tests, their application is especially relevant in resource-limited, TB-endemic settings. Early and accurate diagnosis supports timely anti-tuberculosis therapy, reducing morbidity and contributing to TB elimination efforts.

G. Conclusion:

In the modern era of **evidence-based medicine,** we have the advanced facilities to investigate and search for relevant literature, allowing for more accurate diagnosis and treatment. It is crucial to correctly diagnose diseases to ensure that appropriate treatments are provided. To further enhance diagnostic capabilities, it is essential to utilize **available**, **acceptable**, and **accessible** investigative modalities, improving both the accuracy and efficiency of the diagnostic process. This study demonstrates that the neutrophil-to-lymphocyte ratio (NLR), with an AUC of 0.931, provides excellent diagnostic accuracy for tuberculous pleural effusion (TPE), exhibiting high sensitivity and perfect specificity at a cut-off of 0.95. When combined with ADA measurement, these markers significantly enhance the diagnostic approach for lymphocyte-predominant exudative pleural effusions. Their use as accessible, cost-effective tools can improve early detection and treatment of TPE, facilitating better patient outcomes and supporting tuberculosis control programs in endemic regions.

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