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Diagnostic accuracy of cancer ratio and other new parameters in differentiating malignant from benign pleural effusions

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Abstract

Differentiation of malignant from benign pleural effusions is challenging in clinical practice due to limitations in the cytologic analysis. The combination of pleural fluid biomarkers has previously been used to predict malignant pleural effusion (MPE). We have conducted a prospective observational study to assess the diagnostic potential of cancer ratio [(CR) serum lactate dehydrogenase (sLDH): pleural fluid adenosine deaminase (pADA)], CR plus (CR: pleural lymphocyte count), sLDH: pleural lymphocyte count, and age: pADA in differentiating malignant effusions from benign ones. Prospective data from patients evaluated for exudative pleural effusions in the pulmonary medicine department at our institute over 12 months were collected. All subjects underwent thoracentesis, and if the results were inconclusive, they underwent invasive diagnostic testing for confirmation. They were divided into MPE and non-MPE groups for analysis. Pleural fluid biomarker ratios were calculated and compared between both groups, and receiver operating characteristic curves were generated. We included 120 subjects: 59 were diagnosed with MPE, and 61 had benign effusion (46 tubercular and 15 parapneumonic). The mean (standard deviation) age of the study population [64 (53.3%) males] was 52.4 (14.5) years. CR, CR plus, and age: pADA were significantly higher in the MPE group compared to the benign group. The sLDH: lymphocyte count was similar between both groups. Age: pADA ratio and CR performed best, with areas under the curve of 0.99 [95% confidence interval (CI), 0.97-1.0] and 0.97 (95% CI, 0.94-1.0) respectively. A higher age: pADA level was associated with a malignant etiology of effusion (adjusted odds ratio 12.27, 95% CI 2.37-63.54) on multivariate analysis. At a cut-off of 2, age: pADA ratio provided 96.6% sensitivity, 93.4% specificity, with a positive likelihood ratio of 14.7. Age: pADA and CR are promising diagnostic indices for differentiating MPE and non-MPE with high sensitivity and specificity. The diagnostic accuracy of CR plus and sLDH: lymphocyte ratio is inferior to that of CR and age: pADA.

Key words: malignant pleural effusion, cancer ratio, adenosine deaminase, lactate dehydrogenase.

Introduction

Pleural effusion is a common clinical entity encountered in the clinical practice of general physicians and pulmonologists. History and clinical examination help narrow down the differential diagnoses. Thoracentesis and pleural fluid analysis are the initial diagnostic steps in the evaluation of effusion. Effusions are classified as exudative or transudative based on the biochemical analysis using Lights criteria [1]. The causes of exudative pleural effusion are numerous, with tuberculosis, parapneumonic and malignant effusions (MPE) being the most common [2]. Further diagnosis of an exudative effusion requires additional testing of the pleural fluid, which include culture sensitivity, adenosine deaminase level (ADA), acid fast bacilli, GeneXpert MTB/RIF and malignant cytology. For patients where pleural fluid analysis cannot definitively establish a diagnosis, medical thoracoscopy guided pleural biopsy or closed pleural biopsy becomes necessary [3].

Distinguishing between malignant and tuberculous exudative effusions is challenging in daily clinical practice. The paucibacillary nature of tubercular effusions and the low yield of cytology in malignant effusions are significant hurdles. Additionally, the widely used biomarker pleural fluid ADA level for tuberculosis has its limitations [4,5]. In tuberculosis endemic regions, many patients of undiagnosed pleural effusion are erroneously diagnosed and treated with empirical anti-tuberculous therapy. This misdiagnosis deprives patients from appropriate treatment, as the underlying condition remains unidentified [6].

Pleural fluid biomarkers are minimally invasive and can suggest a specific diagnosis before proceeding with invasive diagnostic tests. Low levels of pleural fluid ADA (pADA) are used as a surrogate indicator of malignant effusion while awaiting the cytology results. However, there is insufficient data on the true diagnostic performance of this relationship. Several pleural fluid tumor markers including carcino-embryonic antigen (CEA), cytokeratin 19 fragments, cancer antigen 125, have been evaluated previously. Lack of validated studies and standardized laboratory analytic methods limit their implementation in clinical practice [7].

The pleural fluid biomarkers are combined to improve the accuracy of diagnostic tests. Serum lactate dehydrogenase (sLDH) is raised in MPE whereas pADA and lymphocyte count remain comparatively low. In comparison, serum LDH is low in tubercular effusion whereas pADA and lymphocyte count are raised. This reciprocal relationship between serum LDH, pADA, and pleural lymphocyte count has gained interest in recent times in differentiating MPE from benign effusions. Cancer ratio [CR, serum LDH: pleural ADA ratio] at a cut-off level of > 20 was highly predictive of MPE in patients with lymphocyte predominant exudative pleural effusion [8]. This ratio when combined with pleural lymphocyte count, termed as cancer ratio plus [CR plus] further shown to enhance the specificity. LDH: pleural lymphocyte count has also been shown to be higher among MPE subjects [9]. The best cut-off values for CR and CR plus have not been established. The inclusion of age into these biomarkers has also been studied, as the incidence of malignancies increase with age. Age: pADA level has shown to have good performance in predicting MPE [10]. The addition of pleural CEA to these ratios increased the diagnostic efficacy in subjects with MPE [11].

The present study aimed to evaluate the performance of CR, CR plus, age: ADA, and sLDH: pleural lymphocyte count in differentiating malignant from non-malignant pleural effusions.

Materials and Methods

Study design, setting, and participants

The current study was a prospective observational study conducted between January 2022 to December 2022 in the department of respiratory medicine at our institute. All subjects aged 18 years or more with exudative pleural effusions who underwent pleural fluid analysis were enrolled. Written informed consent was obtained from all study participants or their next to kin to participate in the study. The study protocol has received approval from the Institutional ethical committee (EC/NIMS/3025/2022). We have reported the study according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Variables and data sources

Demographic and clinical details of the participants were recorded. All patients underwent pleural fluid investigations, which included cell count, cell type, biochemical analysis [protein, glucose, LDH levels], ADA levels and fluid for malignant cytology. In cases suspected of infectious etiology, the pleural fluid was tested for microbiologic cultures and GeneXpert MTB/RIF. Serum was tested for LDH and protein levels. The diagnosis of malignancy was confirmed either by fluid cytology, pleural biopsy or biopsy from another metastatic/primary site. The diagnosis of tubercular effusion was confirmed by pleural fluid biochemical analysis (ADA level > 70 U/L or lymphocytic effusion with ADA of 40-70 U/L and clinical suspicion) or identification of acid fast bacilli (AFB) or positive GeneXpert MTB/RIF in pleural fluid/sputum/bronchoalveolar lavage or granulomatous inflammation on pleural biopsy. The parapneumonic effusion was confirmed by isolation of microorganism on fluid culture or response to antibiotic therapy.

We analysed the effects of following laboratory ratios in determining the accuracy of identifying malignant pleural effusion.

1) The ratio between sLDH and pADA: this was called as CR
2) The ratio of cancer ratio to the percentage of differential pleural lymphocyte count: this was called as CR plus
3) Age to pADA ratio
4) Ratio of sLDH and differential pleural lymphocyte count

Statistical methods

For statistical analysis, data were entered into a Microsoft excel spread sheet and then analysed by SPSS (version 27.0; SPSS Inc., Chicago, IL, USA). The data was described using counts and proportions for categorical data and Mean + standard deviation (or Median with Interquartile range if non-parametric distribution) as appropriate for continuous data. The normality of the data was assessed by Kolmogorov-Smironov and Q-Q plots. Categorical data was analysed using chi-square test. Numerical data between the groups was compared using Student's t test or Mann Whitney U test based on the data distribution.

A multivariate binomial logistic regression analysis was performed to assess the factors which predict the likelihood of malignant etiology. We entered relevant variables for the multivariate analysis (gender, symptom duration, fever, cancer ratio, cancer ratio plus, and age/ADA levels) to calculate the adjusted odds ratio. We used the receiver operating characteristic (ROC) curves to determine the performance of the biomarker ratios. The area under the ROC curve (AUC) was used to quantify the performance of these ratios. The best cut-off value was described using the Youden's J statistic which is calculated as: sensitivity + specificity - 1. The sensitivity, specificity, positive and negative predictive value of the best cut-off with their 95% confidence intervals (CI) was then calculated. *P*-value ≤ 0.05 was considered statistically significant.

Results

During the study period, 120 patients with exudative pleural effusion were enrolled. The mean (SD) age of the study population [64 (53.3%) males] was 52.4 (14.5) years. The mean (SD) duration of clinical symptoms was 33.8 (26.1) days. Out of 120 cases, 59 (49.2%) were diagnosed with malignant etiology, while 61 (50.8%) were diagnosed with non-malignant etiology. The most common sites of primary were the lung (n= 38) and breast (n=10). Other primary sites included the cervix (n=2), neuroendocrine tumour (n=2), and one each in the thyroid, kidney, ovary, synovial sarcoma, and ependymoma. In two cases, no primary site of malignancy was identified. Among non-malignant effusions, 46 (38.3%) cases were of tubercular etiology, while 15 (12.5%) cases were parapneumonic effusions. The method for diagnosing all types of effusions is detailed in the flow chart shown in Figure 1. All non-malignant effusions were followed up in our clinic for six months and showed clinical improvement with antimicrobial therapy. Effusions with an underlying malignant etiology were referred to the oncology center at our institute. The baseline clinical and pleural fluid characteristics are shown in Table 1.

Comparison of characteristics of MPE group and non-MPE groups (Table 2)

The mean age (*56.8 vs 48.2 years, $p<0.01$*) and symptom duration (*40.2 vs 27.6 days, $p<0.01$*) were higher in MPE group. MPE group had more female population compared to non-malignant group. All the clinical symptoms were similar between the two groups, except for fever, which was more common in the non-MPE group *[48 (78.7%) vs 19 (32.2%), $p<0.01$]*. Patients with MPE had less protein, LDH, ADA level, and cell count in their pleural fluid; however, they had a higher glucose, CR, CR plus, and age: pADA than non-MPE patients (Table 2). The sLDH: lymphocyte count ratio was similar between the two groups. On multivariate analysis, higher age: pADA level was associated with malignant etiology of pleural effusion (aOR 12.27, 95% CI 2.37 -63.54).

ROC curves were calculated for CR, CR plus, sLDH: lymphocyte count, and age: pADA (Figure 2). Age: pADA ratio and CR performed best with an AUC of 0.99 (95% CI, 0.97-1.0) and 0.97 (95% CI, 0.94-1.0) respectively. CR plus performed good with an AUC of 0.89 (95% CI, 0.84-0.95) while sLDH: lymphocyte count ratio performed poorly (Table 3).

The best cut off values for the various ratios for differentiating malignant from non-malignant effusions are determined using Youden's statistic (Table 4). CR at a cut-off of 10 offered 93.2 % sensitivity, 95.1 % specificity, 94.8% positive predicted value, and 93.5% negative predicted value. At a cut-off of 15, cancer ratio plus provided 83.1 % sensitivity, 72.1 % specificity, 74.2 % positive predicted value, and 81.5 % negative predicted value. At a cut-off of 2, age: pADA level ratio provided 96.6 % sensitivity, 93.4 % specificity, 93.4 % positive predicted value, and 96.6 % negative predicted value. At a cut-off of 450, sLDH: lymphocyte count provided 50.8 % sensitivity, 57.4 % specificity, 53.6 % positive predicted value, and 54.7 % negative predicted value.

Discussion

The present study was done to evaluate the diagnostic utility of various biomarkers (CR, CR Plus, age: pADA ratio and sLDH: Pleural lymphocyte count) to discriminate MPE from non-malignant pleural effusions. We found that CR, CR plus and age: pADA ratio were significantly higher in MPE and were useful in differentiating malignant from benign effusions. Among them, age: pADA ratio had the highest accuracy followed by CR, in predicting MPE. The cutoffs obtained in our study were 2 for age: pADA and 10 for CR. Addition of pleural lymphocyte count to CR did not increase the accuracy.

Serum LDH is a ubiquitous cellular enzyme that rises non-specifically after tissue damage. It is elevated in various inflammatory conditions, severe sepsis and malignancies. The elevation in malignancy is related to the tumour burden and metastatic spread. This is due to predominant dependence of cancer cells on glycolytic pathway for metabolism, and LDH facilitates glycolysis [12]. The level of sLDH varies in different types of primary malignancies, being highest in hematologic malignancies, and also changes with the stage of malignancy. Moreover, sLDH levels vary in cases of hemolysed samples during laboratory analysis. We did not find any difference of sLDH values between both the groups. This parameter varied differently across previous studies, with some studies showing higher sLDH in malignant effusions [10,13] while some showing no difference [14,15].

ADA is an enzyme which catalyses the conversion of adenosine to inosine. It is produced by lymphocytes, neutrophils, monocytes, and macrophages. ADA is utilised primarily for its negative predictive value in regions with low tuberculosis prevalence. In areas of high tuberculosis prevalence, no ADA level can reliably exclude TPE. The level of ADA is higher in tubercular effusion than other exudative effusions. It is also elevated in parapneumonic effusions, empyema, rheumatoid arthritis, and occasionally in malignancies (lung cancer, mesothelioma and lymphoma) [16]. In our study, ADA levels were significantly lower in MPE compared to benign effusions, consistent with previous studies. Subjects with pleural tuberculosis comprised the majority of the benign effusion group.

In our study, CR at a cut-off of 10 showed 93.2% sensitivity, 95.1% specificity with 94.8% positive predicted value, and 93.5% negative predicted value. It performed best with an AUC of 0.97 (95% CI, 0.94-1.0). The initial study on CR by Akash verma et al, reported good sensitivity and specificity (98% and 94% respectively) similar to us but with a cut off of 20 [8]. The cut-offs for CR have varied in previous studies, ranging from 10 to 22. The largest study till date on CR which included 987 subjects with 318 being MPE showed sensitivity and specificity of 94% and 73% at a cut off > 10 [17]. The results of our study are concordant with a recent meta-analysis on CR which reported pooled sensitivity and specificity of CR was 0.96 and 0.88 respectively with an AUC of 0.98 [18]. However a recent study that included patients with heart failure in the control group, in contrast to other studies that used tuberculosis and pneumonia as controls, reported limited accuracy of CR [15].

In our study, CR Plus at a cut off of 15, showed sensitivity, specificity and AUC of 83.1%, 72.1% and 0.89 respectively. Initially this ratio was shown to increase the specificity of CR by addition of pleural lymphocyte count [9]. The performance of this ratio is inconsistent across previous studies; the largest study by Gayaf et al showed 82.2 % sensitivity and 45.8 % specificity [13]. In another study, CR has been shown to have better accuracy than CR plus [19]. The summary of previous studies on CR and CR plus are summarized in the *Supplementary Table 1*. The variable performance of these ratios is likely due to differences in inclusion criteria and characteristics of the study population. Across different studies, the differences in sLDH and pleural fluid lymphocyte count between groups varied, whereas pADA consistently showed lower levels in MPE compared to controls.

The diagnostic accuracy of this LDH: lymphocyte count ratio for discriminating MPE from benign effusions is found to be low; these findings are consistent with previous studies [9,13]. We did not find any difference of this parameter between MPE and non MPE groups, unlike other studies. This is likely due to the smaller difference in pleural fluid lymphocyte counts observed in our cohort.

The diagnostic accuracy of CR decreased with increasing age, showing that CR may not be a reliable marker of MPE in older patients [15]. Patients with MPE were older than those with non-malignant PE, and their pleural fluid ADA levels were lower. It was expected that the ratio of age and ADA would increase the differentiation between the two groups and enhance diagnostic performance. In our study this ratio had highest accuracy compared with other ratios in differentiating effusions, similar to one of the subgroups in a study by Ren Z et al [20]. In a Chinese study [14], the sensitivity and specificity at a cut-off of 2.6 were found to be 81.5% and 97.8% respectively; in a polish study [10], these values were 93.2% and 71.2% (Table 5). There are also certain limitations of ADA which influence the interpretation of the ratio, including factors such as timing of fluid sampling in the disease course, age and smoking status [4].

These ratios can aid in assessing the likelihood of a malignant etiology in undiagnosed exudative effusions. Similar to ADA levels, these ratios that include ADA are expected to have higher positive predicted value in TB-endemic regions than non-endemic regions. However, they have performed well in previous studies conducted across all regions, regardless of TB endemicity. They could be particularly useful in identifying patients who require definitive diagnosis, rather than initiating empirical anti-tuberculous therapy in TB-endemic regions. . Nevertheless, signs of malignancy should not be overlooked during the clinical examination, regardless of the fluid analysis findings.

Our study has a few limitations. This is a single centre observational study with a small sample size. Our cohort of non MPE primarily included parapneumonic and tubercular effusions; other causes of benign exudative effusion were not represented. In cohort of MPE, 9 cases did not have proven malignancy in pleural fluid or pleural tissue, as biopsy from other accessible sites was preferred. These effusions could probably represent a para malignant etiology. However, a pleural biopsy would have given us a better information on the true nature of the effusion. Additionally, confounding factors that influence serum LDH levels, such as reliability of values on single-time measurement, underlying connective tissue diseases and other inflammatory conditions were not explored. These ratios also inherently lack practical implications for management, particularly in cases of malignant effusions.

Conclusions

Age: pleural fluid ADA and CR are promising diagnostic indices for differentiating MPE from benign effusions, showing high sensitivity and specificity, particularly with a high positive likelihood ratio. The diagnostic accuracy of CR plus and sLDH: lymphocyte ratio is inferior to CR and age: pADA. Further studies involving larger-scale cohorts from multiple centres are needed to validate the findings of our study.

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Online supplementary material

Supplementary Table 1. Characteristics of the studies investigating the diagnostic accuracy of cancer ratio and cancer ratio plus in differentiating MPE from benign pleural effusions.

Table 1. Baseline characteristics of the study population (n=120).

Variables	**Values**
Age in years, mean (SD)	52.4 (14.5)
Male gender, n (%)	64 (53.3)
Duration of symptoms in days, mean (SD)	33.8 (26.1)
Complaints, n (%)	
Breathlessness	110 (91.7)
Cough	109 (90.8)
Chest pain	73 (60.8)
Fever	67 (55.8)
Anorexia	78 (65)
Loss of weight	56 (46.7)
Hemoptysis	4 (3.3)
Comorbidities, n (%)	
Hypertension	38 (31.7)
Diabetes Mellitus	37 (30.8)
Smoking	26 (21.7)
Alcoholism	42 (35)
Diagnosis of pleural effusion, n (%)	
Malignant effusions	59 (49.2)
Non-malignant effusions	61 (50.8)
Tuberculosis	*46 (38.3)*
Parapneumonic	*15 (12.5)*
Pleural fluid and serum analysis, Median (range)	
Total cell count, (cells/mm^3)	500 (20-10000)
Lymphocytes, (%)	*70 (5-100)*
Polymorphs, (%)	*30 (0-95)*
Pleural fluid protein, (g/dl)	4.8 (2.9-7.4)
Pleural fluid LDH, (U/L)	407 (19-40190)
Pleural fluid glucose, (mg/dl)	87.5 (1-255)
ADA level, (U/L)	28.2 (2.1-407.3)
Cancer ratio	9.1 (0.14-289.04)
Cancer ratio plus	18.82 (1.4-963.33)
Age: pleural fluid ADA	2.03 (0.07-23.33)
Serum LDH: pleural lymphocyte count	432.77 (163.33-7700)
Serum protein, (ref: 6-8 g/dl)	6.7 (5.3-9.1)
Serum LDH, (ref: 125-220 U/L)	243 (129-1725)

SD-standard deviation; LDH-Lactate dehydrogenase; ADA-Adenosine deaminase; ref-Reference range.

Table 2. Comparison of characteristics among malignant and non-malignant effusion groups.

Variable	Malignant effusions (n=59)	Non-malignant effusions (n=61)	P value	aOR (95% CI)
Age in years, mean (SD)	56.8 (11.1)	48.2 (16.2)	<0.01	-
Male gender, n (%)	24 (40.7)	40 (65.6)	<0.01	0.08 (0.01- 1.16)
Duration of symptoms in days, mean (SD)	40.2 (30.8)	27.6 (18.9)	<0.01	1.01 (0.97-1.04)
Smoking, n (%)	11 (18.6)	15 (24.6)	0.43	-
Clinical symptoms, n (%)				
Cough	53 (89.8)	56 (91.8)	0.71	-
Chest pain	39 (66.1)	34 (55.7)	0.25	-
Breathlessness	54 (91.5)	56 (91.8)	0.96	-
Fever	19 (32.2)	48 (78.7)	<0.01	0.28 (0.02-3.11)
Hemoptysis	3 (5.1)	1 (1.6)	0.29	-
Anorexia	39 (66.1)	39 (63.9)	0.8	-
Weight loss	33 (55.9)	23 (37.7)	0.05	-
Pleural fluid and serum analysis, Median (range)				
Pleural protein, (g/dl)	4.6 (2.9 - 7.4)	5.2 (3.2-6.8)	0.03	-
Pleural LDH, (U/L)	347 (87- 4540)	459 (19-40190)	0.04	-
Pleural glucose, (mg/dl)	97 (2 - 255)	72 (1-251)	<0.01	-
ADA, (U/L)	12 (2.1-35)	60.8 (12.8-407.3)	<0.01	-
Cancer ratio	23.97 (6.26-289.04)	4.2 (0.14 - 36.98)	<0.01	1.11 (0.97-1.26)
Cancer ratio plus	42.11 (8.43-963.33)	6.77 (1.4 -259.3)	<0.01	0.99 (0.97- 1)
Age: pleural fluid ADA	4.69 (1.57- 23.33)	0.77 (0.07-3.9)	<0.01	12.27 (2.37- 63.54) *
Serum LDH: Lymphocyte count	451.42 (178-7700)	396.92 (163.3 - 7600)	0.96	-
Total cell count, (cells/mm^3)	400 (30-3200)	700 (20-10000)	<0.01	-
Lymphocytes, *(%)*	70 (1-100)	80 (5-100)	0.4	-
Polymorphs, *(%)*	30 (0-90)	20 (0-95)	0.4	-
Serum protein, (g/dl)	6.6 (5.3-9.1)	6.7 (5.3-8.7)	0.59	-
Serum LDH, (U/L)	244 (156 -1725)	240 (129-625)	0.13	-

SD-standard deviation; LDH-Lactate dehydrogenase; ADA-Adenosine deaminase. Chi-square test is used for comparison of categorical variables. Mann Whitney U test is used for all continuous variable except age and symptom duration, where Student's test is used for analysis. *p-value < 0.05.

Table 3. Area under the curve (AUC) values of various ratios.

Biomarker ratio	AUC	SE	95% CI	P value
Cancer ratio	0.97	0.016	0.94 – 1.0	<0.01
Cancer ratio plus	0.89	0.029	0.84 - 0.95	<0.01
Age: pleural fluid ADA	0.99	0.008	0.97 – 1.0	<0.01
Serum LDH: pleural lymphocyte count	0.49	0.053	0.39 - 0.6	0.962

LDH-Lactate dehydrogenase; ADA-Adenosine deaminase.

Table 4. Performance characteristics of the best cut-offs different ratios in differentiating malignant effusions from non-malignant effusions

Biomarker ratio	Sensitivity	Specificity	PPV	NPV	PLR	NLR
Cancer ratio *Cut off >10*	93.2 (86.8 - 99.6)	95.1 (89.7 - 1.00)	94.8 (89.1 - 1.00)	93.5 (87.4 - 99.7)	18.95 (6.27-57.26)	0.07 (0.03-0.18)
Cancer ratio plus *Cut off > 15*	83.1 (73.5 - 92.6)	72.1 (60.9 - 83.4)	74.2 (63.7 - 84.8)	81.5 (71.1 - 91.8)	2.98 (1.96-4.53)	0.23 (0.13-0.42)
Age: pleural fluid ADA *Cut off >2*	96.6 (92 - 1)	93.4 (87.2 - 99.6)	93.4 (87.2 - 99.7)	96.6 (92 - 1)	14.73 (5.71-38.04)	0.04 (0.01-0.14)
Serum LDH: pleural lymphocyte count *Cut off >450*	50.8 (41.5 - 60.2)	57.4 (48.2 - 66.5)	53.6 (43.9 - 63.2)	54.7 (45.7 - 63.6)	1.19 (0.81-1.75)	0.86 (0.61-1.2)

LDH-Lactate dehydrogenase; ADA-Adenosine deaminase; PPV-Positive predictive value; NPV-Negative predictive value; PLR-Positive likelihood ratio; NLR- Negative likelihood ratio. All values are expressed as percentage with 95 % confidence intervals.

Table 5. Characteristics of the studies investigating the diagnostic accuracy of age: pleural fluid ADA for MPE

Author	Year	Study design	Subgroups	MPE	Controls	Cut -off	Sensitivity	Specificity	PLR	NLR	AUC
Korczynski et al[10]	2018	Retrospective	Nil	74	66	2.62	93.2	71.2	3.24	0.10	0.847
Zhou et al[14]	2022	Prospective	Nil	90	130	2.65	81.5	97.8	36.69	0.19	0.916
Ren et al[20]	2021	Retrospective	Age ≤ 50 years	9	80	3.2	88.9	100	-	0.11	0.987
			Age > 50 years	91	39	6	81.3	89.7	7.93	0.21	0.855
Present study	2024	Prospective	Nil	59	61	2	96.6	93.4	14.73	0.04	0.99

MPE- Malignant pleural effusion; PLR-Positive likelihood ratio; NLR- Negative likelihood ratio; AUC- Area under the curve.

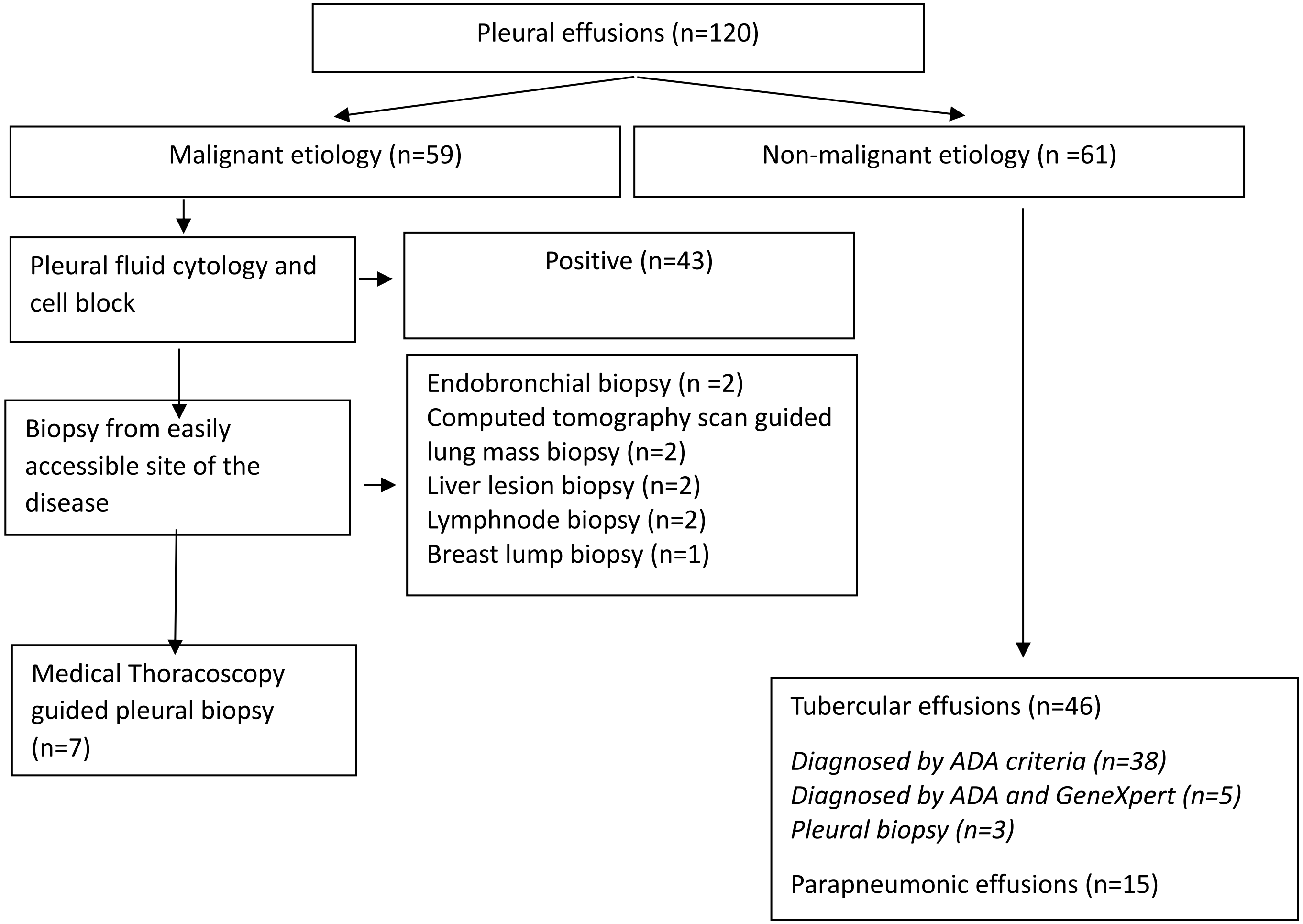

Figure 1. Flow chart showing the mode of diagnoses in all subjects.

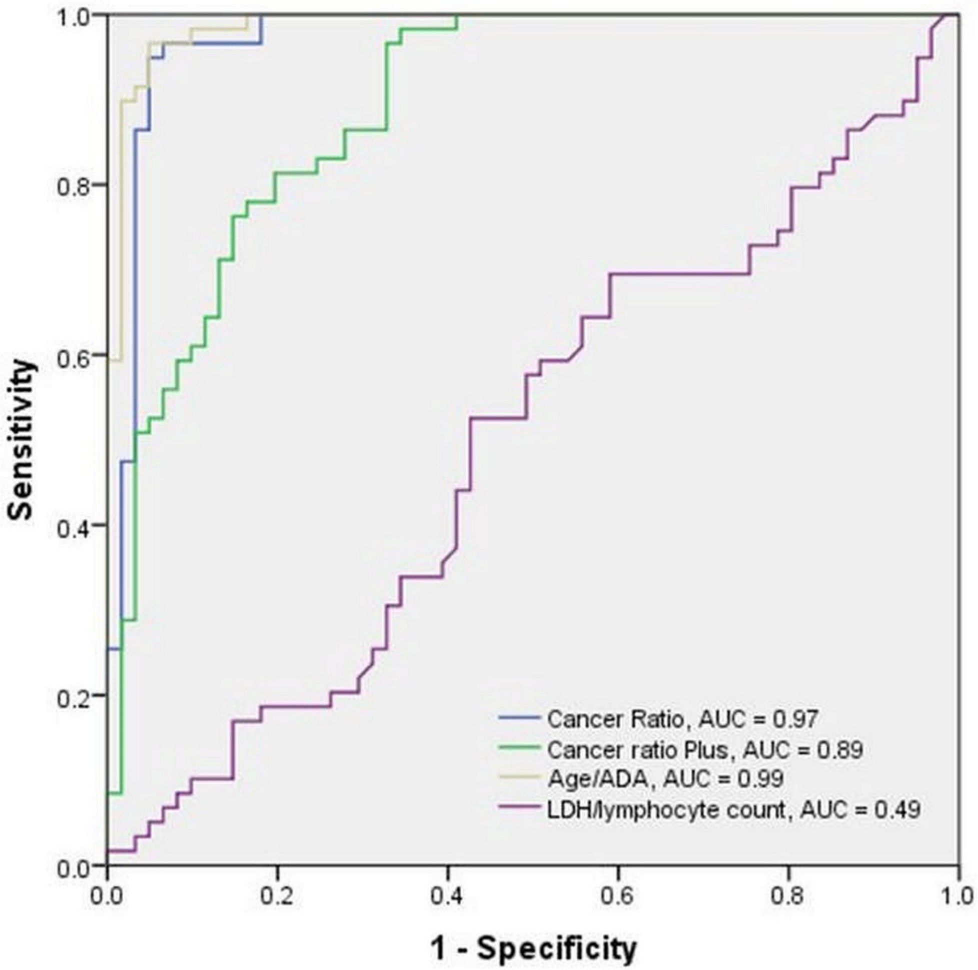

Figure 2. Receiver operating characteristic curves of CR, CR plus, age: pADA, and sLDH, pleural lymphocyte count.