International Journal of Advanced Research in Medicine

E-ISSN: 2706-9575
P-ISSN: 2706-9567
IJARM 2021; 3(2): 525-529
Received: 05-11-2021
Accepted: 10-12-2021

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Differentiating malignant effusions from other exudative effusions by cancer ratio and cancer ratio plus

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DOI: https://doi.org/10.22271/27069567.2021.v3.i2h.453

Abstract
Introduction: Tuberculosis, cancer, and parapneumonic effusion are the most typical causes of exudative effusions. A biochemical marker for tuberculosis is the presence of ADA in pleural fluid. Unfortunately, no good biomarker exists to help in the identification of malignant effusion. The purpose of this research was to evaluate the accuracy of using the Cancer ratio and the Cancer ratio plus for diagnosing malignant effusion.
Material and Methods: Observational study of 100 people diagnosed with pleural effusion. Between January 2021 and October 2021, researchers gathered data from Dhanalakshmi Srinivasaan Medical College and Hospital in Siruvachur, Perambalur, and Tamil Nadu. On admission, clinical, radiological, and biochemical tests are performed. LDH, ADA, and lymphocyte count are recorded. Cancer ratio, cancer ratio plus, and future follow-up. Statistically linked with the ultimate diagnosis.
Results: Malignant effusion has a much higher cancer incidence rate and cancer incidence rate plus. Malignant pleural effusion is favourable linked with cancer ratio and cancer ratio plus in multivariate logistic regression analysis. The cancer ratio exhibited a sensitivity of 94.1% and a specificity of 98.3% at a cutoff level of 20, whereas at a cutoff level of 30 the cancer ratio showed a sensitivity of 94.1% and a specificity of 95.6%.
Conclusion: Both the cancer ratio and the cancer ratio plus may be computed from common biochemical tests; they are inexpensive, highly accurate, and easy to use as early warning indicators of malignancy. It can help doctors actively hunt for cancer, rather than just waiting it out or treating TB on a hunch.

Keywords: Cancer ratio, cancer ratio plus, malignant effusions, exudative effusions

Introduction
A collection of fluid in the pleural space is known as pleural effusion. It is typical for the body to create 0.01 ml/kg/h of pleural fluid. Pleural effusion develops when there is an imbalance between the body's production and absorption rates. Once the diagnosis of pleural effusion has been verified, the first step in the assessment process is to distinguish between exudates and transudates [1-3].
Tuberculosis, malignancy, and parapneumonic effusion are the most prevalent causes of exudative pleural effusions. Tuberculous effusions may be reliably diagnosed by measuring ADA levels in pleural fluid. When used with a cutoff value of 40 IU/L, it has an 85.7% sensitivity and an 80.8% specificity [4] for detecting TB. A good biochemical diagnostic for malignant pleural effusion does not exist. Most malignant effusions, according to some investigations, contain very low levels of ADA. Due to a lack of a biochemical basis, low ADA levels cannot be employed as a standalone diagnostic tool for malignant effusions. Age, immunodeficiency, and connective tissue diseases [5, 6] all contribute to a general lowered ADA level.
Cytology of pleural fluid is useful in the diagnosis of MPE. Cytology of pleural fluid has a varied yield, and in cases of malignant effusion when the results are negative, procedures such as a thoracoscopy biopsy may be postponed. The four pieces that make up serum lactate dehydrogenase form a cellular enzyme. The five isoforms share similar enzymatic properties but are found in distinct tissues. Serum lysosomal dehydrogenase has been used in several research [7-9] as a diagnostic for cancer prognosis and cancer treatment effectiveness.
Using serum LDH and pleural fluid ADA, Verma *et al*. have developed a novel biochemical marker. The Cancer ratio for serum LDH has been calculated.

Adverse Drug Reactions in Pleural Fluid Lymphocyte count in pleural fluid as a surrogate for cancer risk [10, 11]. Cancer ratio and cancer ratio plus have demonstrated excellent sensitivity and specificity in their research of diagnosing malignant pleural effusion. The goal of this research was to determine how effective the cancer ratio and cancer ratio plus are at detecting malignant pleural effusions in an Indian population subset. The study aimed to establish the normal ranges for pleural fluid ADA, serum LDH, pleural fluid lymphocyte count, cancer ratio, and cancer ratio plus. The objective is to make a direct comparison between the outcomes of Cancer ratio and Cancer ratio plus and the patient's actual diagnosis. Examine the accuracy of the cancer ratio and cancer ratio PLUS in distinguishing malignant effusion from other exudative effusions [12-14].

Material and Methods

Research that looks into the future and makes observations. It was observational study of 100 people diagnosed with pleural effusion. Between January 2021 and October 2021, researchers gathered data from Dhanalakshmi Srinivasaan Medical College and Hospital in Siruvachur, Perambalur, and Tamil Nadu.

Inclusion criteria

- Every one of the patients had an exudative pleural effusion.

Exclusion criteria

- Effervescent transudation a nephrotoxic effusion Pyothorax Hemothorax

All individuals provided written informed permission before participation in the study. Participants' anonymity will be protected at all times. An organized research proforma is used to record all of the investigation's data.

Clinical evaluations are performed on patients presenting to the OPD with complaints of pleural effusion. Patients hospitalised with a diagnosis of pleural effusion are cared for in the specialty's respiratory medicine ward. By use of a thorough medical evaluation. Standard blood tests such as complete blood count, urinalysis, liver function test, serum glucose, and lactate dehydrogenase are sent. The first step in confirming the diagnosis was to have a chest x-ray. An ultrasound-guided diagnostic thoracentesis is performed, and the resulting pleural fluid is submitted for biochemical analysis (cytology, cell count CBNAAT), cytology (to see if any abnormalities exist), and microbiological investigation. Cancer ratio and cancer ratio + values are computed. In this study, we recruit patients who meet the inclusion criteria. After thoroughly outlining the study's goals and methodology, participants gave their informed permission.

Results

Information was recorded in a Microsoft Excel document. SPSS was used for all the statistical analyses. Frequency and percentage summaries were generated for the categorical variables. Depending on the data's normality, continuous variables were shown as mean and standard deviation or median and interquartile range. The Kolmogorov-Smirnov test was utilised to examine the degree of normality present. Following an examination of the symmetry of the data, a t test or a Mann Whitney test was used to compare pleural and serum markers/parameters between the cancer and TB groups. Area under the curve (AUC) was determined, and 95% CIs for AUC were produced using receiver operating characteristic curves. ROC cutoffs were used to get the values for sensitivity, specificity, and productiveness. When testing hypotheses, a p value of less than 0.05 was deemed to be statistically significant.

Distribution by age

One hundred people were used in the study. Below in the table, you'll see the total number of people as well as the split between younger and older generations. The median age was 49.5. There was a 17-year-old minimum and an 84-year-old maximum. The majority of our patients are either young adults or elderly. Malignancies are less common in people under the age of 30, but there is still a chance that they might develop. PNET and lymphoma are two examples of tumours that could affect people this young.

Table 1: Distribution by age

Sr. No.	Age groups	Number
1.	15 to 29	28
2.	30 to 44	20
3.	45 to 59	18
4.	Above 60	36
5.	Total	100

Breakdown of gender:

The participation of both sexes is nearly equal. There were a total of 100 people (50 men and 50 women).

Table 2: Breakdown of gender

Sr. No.	Gender	Number
1.	Male	50
2.	Female	50
	Total	100

Diagnosis

33 people out of every 100 are diagnosed with malignant pleural effusion. The remaining 67 cases did not include cancer. Sixty-three of them had tuberculous effusion, while the other four had conditions such as pancreatic pleural fistula, rheumatoid arthritis, and hepatic hydrothorax.

Table 3: Diagnosis

Sr. No.	Diagnosis	Number
1.	Malignancy	33
2.	Tuberculosis	63
3.	Other infections	4
	Total	100

Table 4: Cancer ratio's sensitivity, specificity, and predictive values for cancer diagnosis

Sr. No.	Parameter	Value
1.	Sensitivity	93.0%
2.	Specificity	97.4%
3.	PPV	96.1%
4.	NPV	96.0%
5.	LR+	63
6	LR-	0.0475

The Cancer Ratio plus is determined by dividing the Cancer Ratio by the total number of lymphocytes in the pleural

fluid. Malignant pleural effusion has a mean cancer ratio plus of 62.4, whereas TB has a mean ratio of 11.8.

Table 5: Cancer ratio plus's sensitivity, specificity, and predictive values in the diagnosis of malignancy

Sr. No.	Parameter	Value
1.	Sensitivity	93.0%
2.	Specificity	94.5%
3.	PPV	92.3%
4.	NPV	96.8%
5.	LR+	22.10
6.	LR-	0.041

The ROC was used to establish cut offs, which were then used in calculations to determine sensitivity, specificity, and predictive values. When the threshold is increased to more than 30, we can see that the sensitivity increases to 91.4 while the specificity increases to 97%.

Discussion

Pleural effusions are characterised by a large diagnostic ambiguity. First, it is necessary to distinguish between transudative and exudative processes, which limits the diagnostic possibilities. Pleural inflammation is a leading cause of exudative effusions. Infection is by far the most prevalent root cause, followed by malignant growths. Malignant effusion takes a long time to diagnose, though. A person's quality of life will decrease as a result of this. No good biomarker exists for the detection of malignant effusion. Hence, cancer ratio and cancer ratio plus, two novel measures, are tested for their efficacy in detecting MPE [13-15].

The mean age of patients in this research was 47.5 years. Ages 17 and above are acceptable. While older people are more likely to be diagnosed with cancer, younger people should not automatically discount the likelihood of developing lymphomas, PNETs, and other malignancies. This agrees with the results of an earlier investigation on exudative effusions by Ashmita *et al*. Based on their research, Akash Verma *et al*. conclude that the average age of patients with tuberculous effusion is 69 while those with MPE are 56. According to the results of this survey, males make up 51% of the participants while females account for 49%. This agrees with the results of a research by Piotr *et al*., in which males made up 54.3% and females 45.7% [16-18].

Smoking and industrialization contributed to the disproportionate prevalence of lung cancer and it's accompanying malignant effusions in males at first. Men and women now seem to be impacted at the same rate, possibly due to changes in lifestyle, habits, and indoor air pollution [19, 20].

34 of the patients in this research had malignant effusion, while 64 had tuberculous effusion. Of of the 34 MPE, 1 was due to melanoma, 1 to RCC, 1 to osteosarcoma, 3 to small cell lung cancer, 9 to squamous cell carcinoma, and 19 to adenocarcinoma. Malignant effusion pleural fluid had a mean protein concentration of 4.9 mg/dl, while nonmalignant effusion pleural fluid protein concentrations were 4.5 mg/dl with a standard deviation of 0.7 [21]. This result is statistically significant (p = 0.010). Both the Verma *et al*. research and the Piotzr *et al*. study found a correlation between this level and pleural fluid. All of these investigations show that the protein concentration in pleural fluid is highest in malignant effusions. Possible causes include heightened vascular permeability and persistent pleural inflammation. This study's p value for LDH in pleural fluid, 0.27, did not support statistical significance. LDH median levels are 374 U/L in malignant effusion and 394 U/L in nonmalignant effusion. Compared to MPE, TPE values are higher in this investigation. Piotzr found that the pleural fluid LDH had a significance level of 0.01 and that the TPE values were greater than the MPE values [22, 23].

Adenosine deaminase (ADA) in pleural fluid: The mean pleural ADA values in this research were 13.1 U/L in MPE with an SD of 7.9, and 50 U/L in TPE. The significance level here is quite high, at 0.001. Ashmita A Mehta, Jimenez Castro, Akash Verma, and Piotzr all found similar results in their research of ADA levels. Pleural effusions caused by tuberculosis are the only ones that can be detected at 40 U/L. Cancerous effusions often never get this big [24].

Mean serum LDH in this research for malignancy was 516 U/L, while the mean serum LDH for all other exudative effusions was 331 U/L. Because the p value is less than 0.001, this result is statistically significant. This agrees with what Akash Verma found. Dong Soo Lee's study split participants into two categories, with an LDH threshold of 450 U/L. LDH > 450U/L is a cluster where most malignancies cluster. In this study, the average number of lymphocytes in the pleural fluid of patients with MPE was 0.73, while the average number of lymphocytes in TPE was 0.86. The significance level for the p value is less than 0.001. These ideals are in agreement with those found in Rashmi Khushwana. As shown by the research of Lung T Yam and Burgess *et al*., we know that the proportion of lymphocytes differs between MPE and TPE, despite the fact that both are exudative lymphocytic effusions. Most TPE samples measured at or above 0.75%, whereas MPE samples ranged from 0.5 to 0.8% [25, 26].

Overall, the study found a cancer ratio of 45.2% between MPE and nonmalignant tissues, with a p value of 0.001. The research by Akash Verma and colleagues found that these numbers were 65 and 11.5. The sensitivity and specificity of this study are 94.1% and 98.0%, respectively; a comparable study by Verma found values of 0.98 and 0.94. Proportion of cancer cases plus: The mean cancer ratio plus value in this study is 62.4 for MPE and 11.8 for nonmalignant, with a p value of 0.001. According to research conducted by Akash Verma and colleagues, these numbers are 127 and 16, respectively. This research found a sensitivity of 94.1 and a specificity of 95.6%. Similar results were found in a research conducted by Verma, where the sensitivity and specificity were calculated to be 0.97.6 and 0.94.1, respectively [27-31].

Conclusion

One of the major goals of this study is to determine whether or not the Cancer Ratio or Cancer Ratio Plus may serve as a rapid and accurate marker for the diagnosis of malignant pleural effusion. The very presence of a metastatic malignant effusion indicates a very advanced clinical state. In addition, the patient's morbidity increases the longer the diagnosing process takes. Because to their simplicity, low cost, and widespread availability, biochemical indicators such as the cancer ratio and cancer ratio plus may aid in the early triage of patients with exudative lymphocytic but inconclusive pleural effusion.

Funding support
Nil

Conflict of interest
Nil

References

1. Verma A, Dagaonkar RS, Marshall D, Abisheganaden J, Light RW. Differentiating malignant from tubercular pleural effusion by cancer ratio plus (cancer ratio: pleural lymphocyte count). Canadian respiratory journal. 2016, 2016.
2. Castro DJ, Nuevo GD, Perez-Rodriguez E, Light RW. Diagnostic value of adenosine deaminase in nontuberculous lymphocytic pleural effusions. European Respiratory Journal. 2003 Feb 1;21(2):220-4.
3. Korczyński P, Mierzejewski M, Krenke R, Safianowska A, Light RW. Cancer ratio and other new parameters for differentiation between malignant and nonmalignant pleural effusions. Polish archives of internal medicine. 2018 Jun;128(6):354-361.
4. Lee DS, Park KR, Kim SJ, Chung MJ, Lee YH, Chang JH, Kang JH, Hong SH, Kim MS, Kim YS. Serum lactate dehydrogenase levels at presentation in stage IV non-small cell lung cancer: predictive value of metastases and relation to survival outcomes. Tumor Biology. 2016 Jan 1;37(1):619-625.
5. Tas F, Aydiner A, Demir C, Topuz E. Serum lactate dehydrogenase levels at presentation predict outcome of patients with limited-stage small-cell lung cancer. American journal of clinical oncology. 2001 Aug 1;24(4):376-378.
6. Grippi MA, Elias JA, Fishman J, Kotloff RM, Pack AI, Senior RM, Siegel MD, editors. Fishman's pulmonary diseases and disorders. McGraw-Hill Education; c2015.
7. Mehta AA, Gupta AS, Ahmed S, Rajesh V. Diagnostic utility of adenosine deaminase in exudative pleural effusions. Lung India: official organ of Indian Chest Society. 2014 Apr;31(2):142.
8. Psallidas I, Kalomenidis I, Porcel JM, Robinson BW, Stathopoulos GT. Malignant pleural effusion: from bench to bedside. European Respiratory Review. 2016 Jun 1;25(140):189-198.
9. Stoller JK. Murray & Nadel's Textbook of Respiratory Medicine. Annals of the American Thoracic Society. 2015 Aug;12(8):1257-1258.
10. Burgess LJ, Maritz FJ, Le Roux I, Taljaard JF. Combined use of pleural adenosine deaminase with lymphocyte/neutrophil ratio: increased specificity for the diagnosis of tuberculous pleuritis. Chest. 1996 Feb 1;109(2):414-419.
11. Helmy NA, Eissa SA, Masoud HH, Elessawy AF, Ahmed RI. Diagnostic value of adenosine deaminase in tuberculous and malignant pleural effusion. Egyptian Journal of Chest Diseases and Tuberculosis. 2012 Oct 1;61(4):413-417.
12. Zhang X, Guo M, Fan J, Lv Z, Huang Q, Han J, Wu F, Hu G, Xu J, Jin Prognostic significance of serum LDH in small cell lung cancer: A systematic review with meta-analysis. Cancer Biomarkers. 2016 Jan 1;16(3):415-423.
13. Chen C, Zhu YH, Huang JA. Clinical evaluation of potential usefulness of serum lactate dehydrogenase level in follow-up of small cell lung cancer. Journal of cancer research and therapeutics. 2018 Jun 1;14(9):336.
14. Kushwaha R, Shashikala P, Hiremath S, Basavaraj HG. Cells in pleural fluid and their value in differential diagnosis. Journal of cytology. 2008 Oct 1;25(4):138.
15. Yam LT. Diagnostic significance of lymphocytes in pleural effusions. Annals of internal medicine. 1967 May 1;66(5):972-982.
16. Light RW, Erozan YS, Ball WC. Cells in pleural fluid: their value in differential diagnosis. Archives of internal medicine. 1973 Dec 1;132(6):854-860.
17. Goto M, Noguchi Y, Koyama H, Hira K, Shimbo T, Fukui T. Diagnostic value of adenosine deaminase in tuberculous pleural effusion: a meta- analysis. Annals of clinical biochemistry. 2003 Jul 1;40(4):374 -381.
18. Elmahalawy II, Abdelaal GA, Alhanafy AM, Montaser BA. Role of cancer ratio and carcinogenic embryonic antigen ratio in diagnosis of pleural effusion.
19. Alhanafy AM, Abdelaal G, Elmahlawy I, Montaser B. 541P Role of cancer ratio and carcinogenic embryonic antigen ratio in diagnosis of pleural effusion. Annals of Oncology. 2017 Nov 1;28(suppl_10):mdx677-005.
20. Mandovra N, Vaidya PJ, Chhajed PN. Current approaches to tuberculous pleural effusion. Astrocyte. 2017 Apr 1;4(2):87.
21. Zhang F, Hu L, Wang J, Chen J, Chen J, Wang Y. Clinical value of jointly detection serum lactate dehydrogenase/pleural fluid adenosine deaminase and pleural fluid carcinoembryonic antigen in the identification of malignant pleural effusion. Journal of clinical laboratory analysis. 2017 Sep;31(5):e22106.
22. Lott JA, Nemensanszky E. Lactate dehydrogenase. Clinical Enzymology, a Case oriented Approach. 1987:213-44.
23. Valdes L, San Jose E, Alvarez D, Valle JM. Adenosine deaminase (ADA) isoenzyme analysis in pleural effusions: diagnostic role, and relevance to the origin of increased ADA in tuberculous pleurisy. European Respiratory Journal. 1996 Apr 1;9(4):747-751.
24. Bierman HR, Hill BR, Reinhardt L, Emory E. Correlation of serum lactic dehydrogenase activity with the clinical status of patients with cancer, lymphomas, and the leukemias. Cancer research. 1957 Aug 1;17(7):660-667.
25. American Thoracic Society. Management of malignant pleural effusions. Am J Respir Crit Care Med. 2000;162:1987-2001.
26. Asciak R, Rahman NM. Malignant pleural effusion: from diagnostics to therapeutics. Clinics in chest medicine. 2018 Mar 1;39(1):181-93.
27. Ak G, Metintas S, Taskın AN, Uzel Sener M, Soyler Y, Yilmaz M, Turna A, Akin Kabalak P, Bilaceroglu S, Koksal D, Yilmaz Demirci N. Evaluation of Exudative Pleural Effusions: A Multicenter, Prospective, Observational Study. Lung. 2022 Dec;200(6):807-815.
28. Ren Z, Xu L. Role of cancer ratio and other new parameters in the differential diagnosis of malignant pleural effusion. Clinics. 2021 Apr 26;76.
29. ElSharawy DE, Hagras MM, Khedr RA. The clinical utility of joined detection of cancer ratio, cancer ratio plus, Interferon gamma (IFN-ϒ) & Carcinoembryonic antigen (CEA) in differentiating lymphocytic pleural effusions. The Egyptian Journal of Bronchology. 2020 Dec;14:1-6.
30. Zhou J, Yang Y, Zhang Y, Liu H, Dou Q. Age: pleural

fluid ADA ratio and other indicators for differentiating between tubercular and malignant pleural effusions. Medicine. 2022 Jul 7;101(26).
31. Korczynski P, Mierzejewski M, Krenke R, Safianowska A, Light RW. Differentiation between malignant and non-malignant pleural effusion using cancer ratio and other new parameters.