Original Article

Carcinoembryonic Antigen (CEA) and Cancer Antigen 125 (CA-125) as Diagnostic Biomarkers for Malignant Pleural Effusion

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Abstract

Background: The etiology of pleural effusion is very important in malignant pleural effusion management and prognosis. Pleural fluid cytology examination is a simple diagnostic tool and has been widely used to differentiate the etiology of pleural fluid with high specificity albeit its relatively low sensitivity. The use of tumor markers for malignant pleural effusion in Indonesia is still sparse. This study was intended to determine the sensitivity and specificity of CEA and CA-125 examinations in diagnosing malignant pleural effusion.

Method: This was an observational analytic study with a cross-sectional approach to find the diagnostic value of CA-125 and CEA of pleural fluid in malignant pleural effusion. Subjects were patients with suspicion of malignant pleural effusion who underwent treatment in the emergency room, polyclinic, and inpatient ward at RSDM from October - November 2022.

Results: CEA value with a cutoff of ≥32.00 had a sensitivity of 83.3%; specificity of 87.8%; PPV of 90.9%; NPV of 77.8% with an accuracy of 85.0% (P=0.001), a CA-125 value with a cutoff of >152.40 had a sensitivity of 83.3%; specificity 81.3%; PPV 87.0%; NPV 76.5%; with an accuracy of 82.5% (P=0.001). An increase in CEA and CA-125 signified a significant risk of malignant pleural effusion (P<0.05). Patients with increased CEA and CA-125 had 105 times the risk of developing malignant pleural effusion.

Conclusion: CEA ≥32.00 and CA-125 >152.40 are potential biomarkers to predict malignant pleural effusion with CEA having better specificity than CA-125.

Keywords: CA-125, CEA, lung cancer, malignant pleural effusion

INTRODUCTION

Pleural effusion often presents as a diagnostic challenge for medical doctors. Differentiating exudates from transudates has always been the main concern in the diagnostic process which requires physical chemistry evaluation from the fluid sample and the biochemical parameters such as total protein, lactate dehydrogenase (LDH), bilirubin, and cholesterol. Determining the exudative or transudative nature of the pleural fluid paves a long way in diagnosing the causative disease.[2]

Pleural effusion may appear benign or malignant and each form has its different management system and prognostic value. Pleural fluid cytology has a high sensitivity for detecting the presence of malignant cells in lung cancer (79.0%), but the result is prone to false negatives when pleural thickening is present and the invasive procedure of sample collection can be uncomfortable for the patients.[3]

Tumor markers hold a promising future as an alternative to pleural fluid cytology for differentiating pleural effusion etiology. These prospective markers include carcinoembryonic antigen (CEA), cancer antigen 125 (CA-125), cancer antigen 15-3 (CA 15-3), cancer antigen 19-9 (CA 19-9), cancer antigen 72-4 (CA 72-4), cytokeratin 19 fragments 21-1 (CYFRA 21-1), neuron-specific enolase (NSE), and squamous cell carcinoma antigen (SCCA). However, the clinical value of tumor markers in pleural effusion fluids has not been widely discovered.[4]

Pleural effusions which are benign in nature are twice as common as their malignant counterpart which has multiple manifestations and origins, presenting themselves as a diagnostic challenge. A negative cytologic examination often requires more procedures to confirm the etiology of a pleural effusion.

Multiple studies by Yataco in 2005,[5] Rasyid in 2012,[6] and Halim in 2009[7] reported the use of tumor markers as alternative diagnostic methods. Tumor markers had previously been mostly used for cancer patient screening, prognostic evaluation, and treatment monitoring. Due to the sheer amount of research on the use of tumor markers in malignant pleural effusion patients, more study is needed.

This study aimed to explore the sensitivity and specificity of CEA and CA-125 in diagnosing malignant pleural effusion. Hoped to establish CEA and CA-125 as additional and rapid diagnostic tools for patients with suspected pleural effusion and no malignant cell found in pleural fluid cytology or histopathological examinations, therefore minimizing the need for invasive procedures.[7]

METHOD

This study is an analytical observational study with a cross-sectional approach conducted by dr. Moewardi Regional Hospital, Surakarta from October-November 2022 to test the diagnostic performance of CEA and CA-125 in predicting malignant pleural fluid. The examination referred to as the gold standard is pleural fluid cytology, i.e. positive histopathological finding of malignant cells in pleural fluid. This study has been approved by dr. Moewardi Regional Biomedical Research Ethics Committee as stated in ethical clearance letter number 1.239/IX/HREC/2022.

Subjects in this study were patients who were undergoing treatment in the hospital's emergency room, clinic, and ward. Pleural exudative fluid was taken from patients with suspected malignant pleural effusion at the dr. Moewardi Regional Hospital Clinical Pathology Laboratory and a pleural fluid cytology

examination were done at the dr. Moewardi Regional Hospital Pathologic Anatomy Laboratory in October 2022.

The sample size was counted using the sample size formula for the diagnostic study with a 95% confidence interval (CI). The minimum sample size was intended for patients with positive diagnoses according to the gold standard. Based on the calculation, required a minimum of 26 subjects. Study subjects were enrolled using consecutive sampling methods, in which eligible subjects were recruited until the bare minimum was met.

Eligible subjects in this study were adult patients above 18 years old, who had exudative pleural effusion, suspected of malignant pleural effusion from one or more of the following criteria: thorax x-ray or computed tomography (CT) scan which showed pleural effusion with a description of lung tumor or metastasis, thorax x-ray or CT scan which showed massive pleural effusion with or without lung tumor or metastasis, and thoracentesis which produced yellow or serosanguinous fluid.

Excluded patients with pneumonia and lung tuberculosis, pleural effusion patients with transudative fluid, comorbidities such as renal failure, heart failure, cirrhosis, and pancreatitis, patients with other malignancies outside of the lung, and pleural fluid analysis determined as invalid due to volume being too small or decontamination.

Used 2x10 cc of the pleural fluid sample through thoracentesis for CEA and CA-125 examination. The pleural fluid was then sent to the clinical pathology laboratory to be stored in an aliquot at -20°C.

The samples were then centrifuged at 2000 rotations per minute (rpm) for 10 minutes. CEA examination was done using Cobas ® E411 from F. Hoffmann-La Roche AG through the electrochemiluminescence immunoassay (ECLIA) principle.

CA-125 examination was done through enzyme-linked immunosorbent assay (ELISA) using mini VIDAS from bioMérieux SA which used a strip reagents system with enzyme-linked fluorescent assay (ELFA) principle for 1 hour. Hemoglobin, leukocyte, platelet, and lymphocyte extraction was done using Mindray BC 1800 for 10 seconds.

Descriptive analysis to see the characteristics of the samples based on their malignancy status. Continuous variables such as CA-125, CEA, and pleural fluid cytology values were analyzed through the Kolmogorov-Smirnov normality test based on their average and deviation standard value. Normally distributed data would be analyzed through an independent t-test, while unevenly distributed data would be analyzed through the Mann-Whitney test.

Also conducted area under curve (AUC) analysis for CEA and CA-125 to determine the cut-off use with the best sensitivity, specificity, and performance value. Diagnostic tests for CEA and CA-125 would be done using a 2x2 table to determine their sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

RESULTS

Obtained 40 eligible patients during the study mostly consisting of males (58.3%) in the malignant group. The number of male and female patients in the non-malignant group were even (50.0%). Chi-square analysis revealed no significant differences among the study groups based on gender. Most subjects in the malignant group had mass in their radiologic examination (66.7%) while in the non-malignant group, only 6 patients had mass (37.5%).

Table 1. Subjects Characteristics

Variables	Malignant (n=24)	Benign (n=16)	P[a]
Gender			
Male	14 (58.3%)	8 (50.0%)	0.604
Female	10 (41.7%)	8 (50.0%)	
Radiologic findings			
Mass	16 (66.7%)	6 (37.5%)	0.069
No mass	8 (33.3%)	10 (62.5%)	

Note: [a]Chi-square result

The average age was 54.67±13.58 years old for the malignant group with a median of 55.00 years old and 54.00±13.87 years old for the non-malignant group with a median value of 57.50 years old.

Mean and median CEA value was found to be higher in the malignant group than in the non-malignant group [198.08±119.66 vs 24.04±39.74 and 267.65 (1.80-318.60) vs 14.00 (0.10-157.20), respectively]. The difference in the CEA value was found to be statistically significant (P<0.001).

The mean and median CA-125 value in the malignant group [340.86±150.85 and 416.15 (37.43-508.40)] was also found to be higher than the non-malignant group [116.00±62.64 and 122.70 (26.10-219.90)]. Found that the difference in CA-125 value was statistically significant (P<0.001).

Conducted ROC analysis to figure out the optimum cut-off point for CEA and CA-125. An AUC value of 0.845 with a cut-off value ≥32.00 was found for CEA with 83.3% sensitivity, 87.8% specificity, 90.9% PPV, 77.8% NPV, and 85.0% accuracy (P≤0.001).

Table 2. Subjects Characteristics

Variables	Malignant (n=24)	Benign (n=16)	P
Age			
Mean±SD	54.67 ±13.58	54.00 ±13.87	0.881[b]
Median (min-max)	55.00 (25.00-76.00)	57.50 (24.00-70.00)	
CEA			
Mean±SD	198.08 ±119.66	24.04 ±39.74	<0.001*[c]
Median (min-max)	267.65 (1.80-318.60)	14.00 (0.10-157.20)	
CA-125			
Mean±SD	340.86±150.85	116.00±62.64	<0.001*[c]
Median (min-max)	416.15 (37.43-508.40)	122.70 (26.10-219.90)	

Note: SD= standard deviation; min= minimum value; max= maximum value; *P<0.05; [b]normally distributed data, comparative analysis through independent t-test; [c]uneven distributed data, comparative analysis through Mann-Whitney test

Table 3. Odds Ratio Analysis for CEA and CA-125

	Malignancy		OR (95% CI)	PPV (%)	NPV (%)	P
	Malignant (n=24)	Benign (n=16)				
CEA						
≥32.00	20 (83.3%)	2 (12.5%)	35.00 (5.62-218.11)	90.0	77.8	<0.001*
<32.00	4 (16.7%)	14 (87.5%)				
CA-125						
≥152.40	20 (83.3%)	3 (18.8%)	21.67 (4.15- 113.02)	87.0	76.5	<0.001*
<152.40	4 (16.7%)	13 (81.3%)				

Note: CEA=carcinoembryonic antigen; CA-125=cancer antigen-125; OR=odds ratio

This result showed that CEA ≥32.00 manifested a malignant pleural effusion. ROC analysis for CA-125 revealed an AUC of 0.870 using a cut-off value >152.40 with 83.3% sensitivity, 81.3% specificity, 87.0% PPV, 76.5% NPV, and 82.5% accuracy (P≤0.001). This demonstrated that CA-125 >152.40 marked a possible malignant pleural effusion.

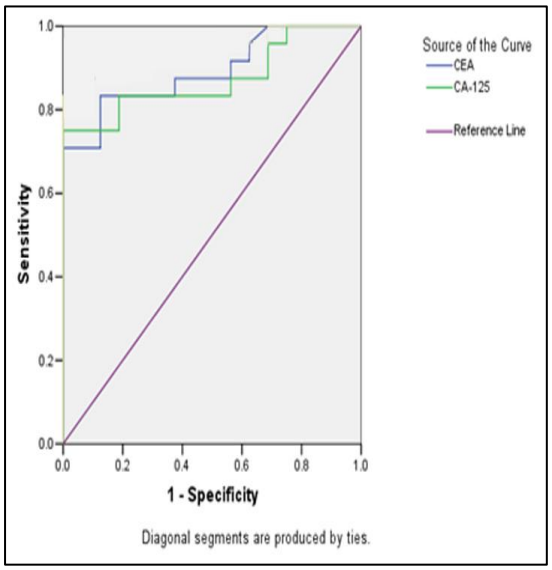

Figure 1. ROC Analysis for CEA and CA-125

Founded that patients with CEA ≥32.00 were 35 times more likely to develop malignant pleural effusion (OR=35.00; 95% CI=5.62-218.11; P≤0.001) and patients with CA-125 ≥152.40 were 21.67 times more likely to have malignant pleural effusion (OR=21.67; 95% CI=4.15-113.02; P≤0.001).

DISCUSSION

Carcinoembryonic antigen is an underutilized biomarker to detect lung cancer prognosis and its use is still debatable.[8] The value of CEA often recedes after birth and it is not uncommon for healthy adults to have little to no CEA. Blood, pleural fluid, cerebrospinal fluid, and peritoneal fluid may serve as samples for CEA examination. A high CEA value may indicate a certain type of cancer including lung cancer.[9] A previous study by Sun et al in 2020 stated that CEA is significantly raised in lung cancer compared to healthy subjects and subjects with benign lung tumors.[10]

Most patients in this study were male (58.3%) compared to female (41.7%). Data from GLOBOCAN 2020 stated that 1,435,943 males had lung cancer compared to 770,828 females.[11] Another hospital-based study from 100 hospitals in Jakarta also showed that lung cancer is the most common disease in men, the 4th most common disease in females, and the main cause of mortality in males and females.[12]

The risk of developing lung cancer increases along with age. Lung cancer may appear at a younger age, but it is unlikely to develop in people aged below 40 years old. The risk of lung cancer increases per year after 40 years old.[13] In this study, it is found that the average age of patients suffering lung malignancy is 54.67±13.58 conforming to the age at risk for lung cancer being above 40 years old. Elderly people tend to have shorter telomeres which contributes to DNA damage and hence, cancer development.[14]

Invading cancer cells often cause CEA estuary in the pleural space, therefore making it a good biomarker for malignant pleural effusion. Our study revealed that malignant pleural effusion patients had a significantly higher CEA than benign pleural effusion patients (P≤0.001). This finding is similar to a study by Cheng and colleagues in 2021 which stated that CEA performed well as a diagnostic marker for malignant pleural effusion with a sensitivity and specificity ratio of 80%:92%.[15]

CA-125 also known as mucin-16 (MUC16) is a protein that is coded by the MUC16 gene in humans. CA-125 is mostly found on the surface of the ovary, inflammatory cells, and non-inflammatory cells. The proliferation of these cells causes CA-125 to be released. CA-125 itself has been commonly used as a specific marker for ovary tumors.[16]

Our study obtained a significant difference in CA-125 value between the malignant and benign groups where the malignant pleural effusion patients had a higher value than the benign ones (P≤0.001). The same result was presented in a study by Shalaby and colleagues in 2015 which showed that pleural fluid CA-125 had a sensitivity of 99% and 78% specificity. This study found CA-125 in malignancy and lung tuberculosis patients and therefore could be utilized in diagnosing malignant cases.[16]

Another study by Zhang and colleagues in 2020 found that biomarkers from pleural fluid samples were superior to pleural fluid cytology in figuring malignant pleural fluid, with CEA being the most effective indicator for lung cancer associated with malignant pleural effusion at the cut-off point of 5.23 ng/ml.[17]

Another previous study by Sthaneshwar and colleagues in 2002 found another cut-off point for CEA and CA-125 in differentiating malignant pleural effusion from benign pleural effusion. These cut-off points were 5.1 ng/ml and 1707 IU/ml, respectively. The study obtained a 64% sensitivity and 98% specificity for CEA, while CA-125 had 36% sensitivity and 94% specificity.[17]

The subjects of this study have different types of lung malignancy and were diagnosed at different stages at the time of study. Hence, there is an overlooked potential that certain patients may have different possibilities of malignant cells being present in pleural fluid as well as having increased CEA and/or CA-125. Also unable to investigate any possible underlying causes of the pleural effusion besides malignancy. This study did not include patients with transudative pleural effusion, therefore the

results from this study may not apply to transudative pleural effusion patients. Subjects in the benign pleural effusion were also not differentiated based on the etiology of the pleural effusion due to the low number.

CONCLUSION

A high CEA (≥32 µg/L) and/or CA-125 (>152.40) may present as a diagnostic predictor for malignant pleural effusion. CEA had a better sensitivity, specificity NPV, and PPV than CA-125.

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REFERENCES

1. Mercer RM, Corcoran JP, Porcel JM, Rahman NM, Psallidas I. Interpreting pleural fluid results. Clinical Medicine. 2019;19(3):213–7.
2. Pairman L, Beckert LEL, Dagger M, Maze MJ. Evaluation of pleural fluid cytology for the diagnosis of malignant pleural effusion: a retrospective cohort study. Intern Med J. 2022;52(7):1154–9.
3. Loscalzo J, Kasper DL, Longo DL, Fauci AS, Hauser SL, Jameson JL. Harrison's Principles of Internal Medicine. 18th ed. New York: The MacGraw-Hill Companies; 2012. 2178–2181 p.
4. Yataco JC, Dweik RA. Pleural effusions: evaluation and management. Cleve Clin J Med. 2005;72(10):854–6.
5. Rasyid A. Anatomi Fisiologi Pleura dan Mekanisme Efusi. Bandung: Divisi Pulmonologi Departemen Ilmu Penyakit Dalam RSMH; 2012.
6. Sudoyo AW. Buku ajar ilmu penyakit dalam. 4th ed. Jakarta: Departemen Ilmu Penyakit Dalam FKUI ; 2006. 2331–2336 p.
7. Grunnet M, Sorensen JB. Carcinoembryonic antigen (CEA) as tumor marker in lung cancer. Lung Cancer. 2012;76(2):138–43.
8. MedlinePlus. CEA Test [Internet]. Bethesda (MD): National Library of Medicine (US). 2023. Available from: https://medlineplus.gov/lab-tests/cea-test/#:~:text=A%20CEA%20test%20is%20mostly,after%20it%20has%20been%20diagnosed.
9. Sun J, Chen X, Wang Y. Comparison of the diagnostic value of CEA combined with OPN or DKK1 in non-small cell lung cancer. Oncol Lett. 2020;20(3):3046–52.
10. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209–49.
11. Kementrian Kesehatan RI. Pedoman Pengendalian Faktor Risiko Kanker

Paru. Jakarta: Kementrian Kesehatan RI; 2018.

12. Taufik FF, Susanto AD, Simarmata E, Faisal H, Jusuf A. Faktor risiko kanker paru. In: Jusuf A, editor. Dasar-dasar diagnosis kanker paru. Jakarta: UI Press; 2017. p. 11–2.
13. de Groot PM, Wu CC, Carter BW, Munden RF. The epidemiology of lung cancer. Transl Lung Cancer Res. 2018;7(3):220–33.
14. Cheng C, Yang Y, Yang W, Wang D, Yao C. The diagnostic value of CEA for lung cancer-related malignant pleural effusion in China: a meta-analysis. Expert Rev Respir Med. 2022;16(1):99–108.
15. Shalaby AEDO, Moussa HAA, Nasr AS, Abdel Samad MN. A study of CA-125 in patients with pleural effusion. Egyptian Journal of Bronchology. 2015;9(3):283–6.
16. Zhang H, Li C, Hu F, Zhang X, Shen Y, Chen Y, et al. Auxiliary diagnostic value of tumor biomarkers in pleural fluid for lung cancer-associated malignant pleural effusion. Respir Res. 2020;21(1):284.
17. Sthaneshwar P, Yap SF, Jayaram G. The diagnostic usefulness of tumour markers CEA and CA-125 in pleural effusion. Malays J Pathol. 2002;24(1):53–8.