Original Article

Cancer Ratio Diagnostic Test For Malignant Pleural Effusion Patients Treated At Persahabatan Hospital Jakarta, Indonesia

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Abstract

Background: Rapid diagnostics of exudative pleural effusion should be able to rule out tuberculosis (TB) as the causative agent. Cancer ratio, a ratio between serum lactate dehydrogenase (LDH) and pleural fluid adenosine deaminase (ADA), of >20 is predictive for malignant pleural effusion (MPE). This study aimed to observe the diagnostic values and to determine the diagnostic cut-off point of cancer ratio for MPE in a country with a high TB burden such as Indonesia. **Methods:** This prospective cross-sectional study involved 65 subjects with exudative pleural effusion suspected of malignancy and treated at Persahabatan Hospital Jakarta, Indonesia. **Results:** Cancer ratio >20 had a sensitivity of 61.82%, specificity of 80%, positive predictive value (PPV) of 94.44% and negative predictive value (NPV) of 27.59%. The cancer ratio cut-off points of >26 showed sensitivity and specificity of 0.43 (95%CI 0.31-0.55) and 0.9 (95%CI 0.82-0.97) respectively. The area under the curve (AUC) of 0.76 indicated good accuracy. The positive likelihood ratio (PLR) was found to be 4.36 (95%CI 3.43-5.29), while the negative likelihood ratio (NLR) at this cut-off point was 0.22 (95%CI 0.13-0.33). Moreover, the PPV and NPV were found to be 0.96 (95%CI 0.91-1) and 0.22 (95% CI 0.12-0.32) respectively. **Conclusion:** Based on its high specificity, PPV and PLR, cancer ratio cut-off point of >26 was found highly predictive of malignancy in patients with exudative pleural effusion in a country with high TB burden.

Keywords: adenosine deaminase; cancer ratio; lactate dehydrogenase; malignant pleural effusion

Introduction

Pleural effusion is an indicator of an underlying disease process which may originate intrapulmonary or extrapulmonary and can also be acute or chronic. Exudative pleural effusions are usually seen in three conditions particularly cancer, tuberculosis (TB) and para-pneumonic effusions. The complaint of malignant pleural effusion (MPE) include dyspnea, cough, weight loss and chest pain. In addition, pleural effusion in the chest x-ray with negatively proven TB infection and/ or cancer are also considered as the presenting complaints of MPE. The MPE is diagnosed on the basis of clinical findings, imaging support and pleural fluid examination including its analysis and cytology. The main problem in diagnosing MPE is the etiology and the underlying primary tumor which contributes to the complexity in MPE management.[1,2]

Initial step for the diagnosis of MPE is to confirm whether the fluid is exudate based on the Light's criteria i.e. (1) protein ratio > 0.5; (2) LDH ratio > 0.6; (3) effusion LDH level > 2/3 upper limit of serum LDH reference range and primary tumor in the lung or other organs. Further tests include biochemical analysis of cell count, glucose, hydrogen potential (pH), adenosine deaminase (ADA), cytology and cultures of Mycobacterium tuberculosis (MTb). This is followed by pleural biopsy if these biochemical results are inconclusive. To date, reliable

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biochemical markers for MPE diagnosis are not available Increase in serum lactate dehydrogenase (LDH) is observed in various clinical conditions such as hemolysis, cancer, sepsis, humanimmunodeficiency virus (HIV) infection and so on. Whereas extremely high serum LDH values are used as diagnostic marker for conditions like sepsis and malignancy.[3-7]

A study by Verma *et al.*[7] identified MPE by assessing the cancer ratio by comparing serum LDH and pleural fluid ADA values. Cancer ratio of ≥20 was found highly predictive of malignancy. The etiological diagnosis of pleural effusion in Indonesia is often given differential diagnosis of TB which causes morbidity reports of TB to be quite high. Cause of pleural effusion should be identified as soon as possible to determine the next step of management. Based on these investigations, this study aimed to evaluate the role of cancer ratio screening for detecting MPE in suspected patients.

Methods

This was a diagnostic study with prospective cross-sectional design. The sample selection was carried out through consecutive sampling technique. The target population included adult patients (≥18 years) who were eligible for the diagnostic criteria of suspected MPE and who attended the polyclinic and/or emergency room and/or were admitted to the wards at Persahabatan Hospital Jakarta from March to June 2019. Whereas, patients with comorbidities which could generate pleural effusions such as TB, heart failure, chronic renal failure, liver disease and those who had received radiotherapy to the thoracic region or chemotherapy were excluded from the study.

Patient sample collection

After obtaining informed consent from each patient who met the inclusion criteria of this study, pleural fluid and biopsy samples were obtained from them by thoracocentesis and pleural biopsy respectively. The cancer ratio and anatomic pathology results were then evaluated and analyzed to determine the diagnostic value by statistical analysis.

Ethical Clearance

This study had received ethical approval from the Institutional Review Board of the Faculty of Medicine Universitas Indonesia (Ethical Clearance No: KET-308/UN2.F1/ETIK/PPM.00.02/2019).

Statistical analysis

Statistical analysis was performed using GraphPad Prism 6.0 (GraphPad Software, La Jolla, CA). Values were compared using a two-tailed Student's t-test. Categorical variables were analyzed using 2x2 chi square test. Differences between the means were considered statistically significant at $P < 0.05$.

Results

In total, there were 65 subjects recruited in this study having suspected MPE with exudative pleural effusions. Out of these 28 (43.1%) were males and 37 (56.9%) were females. The mean ± standard deviation (SD) of the age of all patients was 56.77±10.24. History of all participants was taken followed by their physical and radiological examinations, pleural punctures (thoracocentesis), pleural biopsy and/or other diagnostic procedures. The radiological examination included thoracic ultrasound, chest X-ray (CXR) and chest CT scan. Pleural fluid samples were examined for pleural fluid analysis, ADA and cytology while pleural biopsy samples were examined for tissue histology. The cancer ratio was calculated based on the comparison of serum LDH with pleural fluid ADA.

Based on anatomic pathology examination, total 59 (90.8%) subjects had the identified pleural effusion etiology whereas the remaining subjects (n=6, 9.2%) had inconclusive causes of pleural effusion. Distribution of subjects with respect to the exudative pleural effusion etiology can be seen in Fig 1.

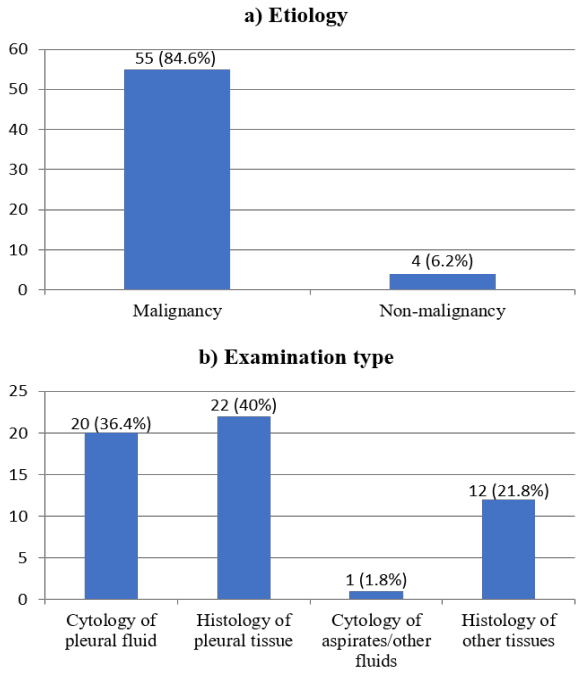

Figure 1: Distribution of subjects based on pleural effusion etiology (a) and anatomic pathology examination (b)

Anatomic pathology examination of pleural fluid and/or tissue and of other fluids/aspirates or other tissues showed the types of malignancy causing exudative pleural effusion. The most frequent type of intrathoracic malignancy causing MPE in this study was found to be adenocarcinoma, while that of of extrathoracic malignancy was breast cancer. The distribution of malignancy types which caused exudative pleural effusions in this study are shown in Fig 2.

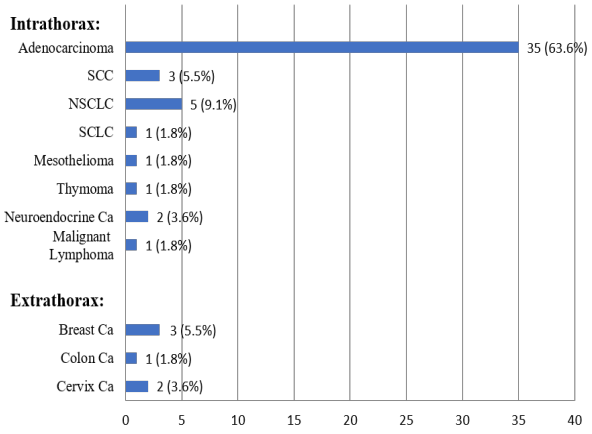

Figure 2: Types of malignancy causing malignant pleural effusion (MPE)

The relationship between the results of anatomic pathology based on the categorical variables of pleural fluid analysis can be seen in table 1. No significant relationship was observed between pleural effusion color, clarity, blood clots and the results of anatomic pathology. Based on the results of macroscopic examination, it was found that most of the pleural fluid in EPG patients at the Friendship Hospital was red an cloudy.

Table 1: Anatomic pathology results based on macroscopic pleural fluid

Variables	Negative		Positive		OR (95%CI)	P value
	n	%	n	%		
Fluid color						
Red	7	10.8	28	43.1	N/A	0.049
Xanthous	2	3.1	23	35.4		
Brown	0	0	4	6.2		
White	1	1.5	0	0		
Clarity						
Clear	2	3.1	8	12.3	1.47	0.645
Cloudy	8	12.3	47	72.3	(0.26-8.21)	
Blood clot						
Yes	1	1.5	6	9.2	1.10	0.932
No	9	13.8	49	75.4	(0.12-10.28)	

N/A: not applicable

The anatomic pathology results based on the characteristics of numerical variables are shown in Table 2.Significant correlation was found between pleural fluid cell count in the negative and positive anatomic pathology group (535 cells/µL vs 1064 cells/µL, *P*=0.037). Moreover, significant difference was also observed between pleural fluid ADA values in both these groups (38.7 U/L vs 12.5 U/L, *P*=0.005). In addition, cancer ratio in the negative and positive anatomic pathology groups was also found significant (5.42 vs 23.8, *P*=0.009). No significant difference was found with respect to the serum LDH values in MPE and non-MPE however, pleural fluid ADA values were found significantly lower in MPE as compared to non-MPE.

Table 2: Anatomic pathology results based on numerical variables

Variables	Non-MPE Median (min-max)	MPE Median (min-max)	P value
Age	54 (26 – 79)	59 (39 – 79)	0.223
Volume estimation	1400 (800 – 2000)	1200 (600 – 2000)	0.194
Pleural fluid (PF) analysis			
Cell count	535 (107 – 2768)	1064 (107 – 8362)	0.037
%PMN	17.5 (2 – 59)	16 (1 – 98)	0.848
%MN	82.5 (41 – 98)	84 (2 – 99)	0.848
pH of PF	8.0 (8.0 – 8.5)	8.0 (7.0 – 8.5)	0.848
PF protein	4.4 (2.2 – 6.9)	4.6 (2.9 – 5.6)	0.467
Serum protein	6.5 (5.8 – 7.9)	6.6 (5 – 66)	0.971
PF glucose	90.5 (8 – 224)	79 (4 – 294)	0.935
Serum glucose	117.5 (90 – 286)	120 (64 – 277)	0.567
PF LDH	443 (86 – 2089)	442 (135 – 5759)	0.525
Serum LDH	235 (161 – 1236)	303 (103 – 1494)	0.187
PF ADA	38.7 (12 – 108)	12.5 (2.5 – 139)	0.005
Cancer ratio	5.42 (1.49 – 105)	23.8 (1.21 – 121)	0.009

PF: pleural fluid

Serum LDH and pleural fluid ADA in MPE were found to have an inverse or reciprocal correlation (R^2=0.048) (Fig 3). Correlation between the two variables using Spearman test showed that there was a weak correlation (r=-0.272) led by number of extreme values of the two variables, nevertheless, it was significant (*P*=0.028).

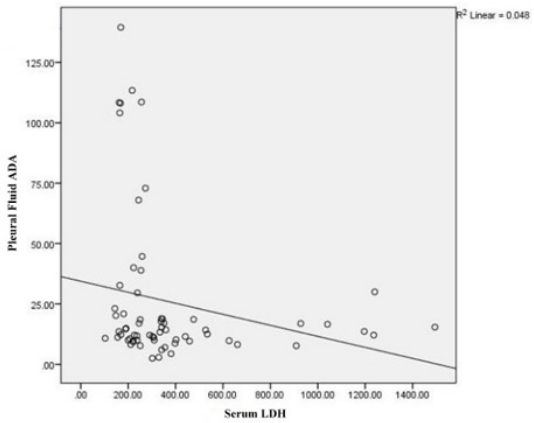

Figure 3: Scatter plot chart of the correlation between serum lactate dehydrogenase (LDH) and pleural fluid adenosine deaminase (ADA) on malignant pleural effusion (MPE) (r=-0.272) and (P=0.028).

The area under the curve (AUC) of receiver operating curve (ROC) describes how well a diagnostic test can be applied. The greater the AUC value or the closer to number 1, the better the quality of the test. In the present study, the area of AUC to cancer ratio was 0.760 (0.573-0.947) with 95% confidence interval (CI)(Fig 4). Diagnostic test for cancer ratio was performed using a 2x2 table calculated on the basis of anatomic pathology as the gold standard. The comparison of results of diagnostic test using cancer ratio and anatomic pathology examination as the gold standard are shown in Table 3. Cancer ratio ≥20 can be used for the diagnosis of MPE; such as sensitivity, specificity, PPV, NPV, positive and negative LR (Table 3). The diagnostic values of cancer ratio ≥20 in patients with MPE as a whole are described in Table 4. The diagnostic test value of cancer ratio ≥26 at Persahabatan Hospital Jakarta with anatomic pathology as the gold standard are shown in Table 5.

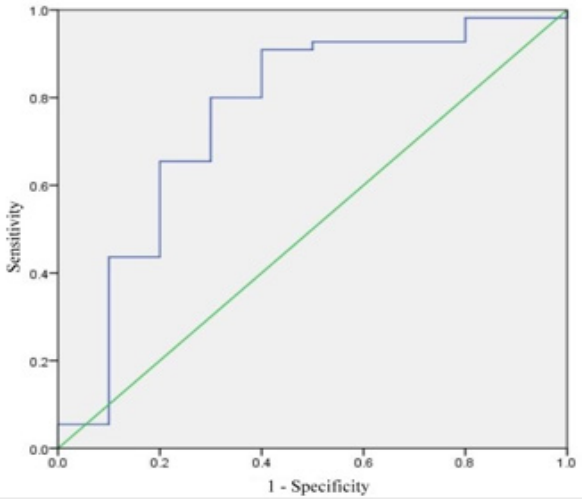

Figure 4: Cancer ratio ROC curve

Table 3: Cancer ratio examination results compared with anatomic pathology as the gold standard

Cancer ratio examination	Anatomic pathology examination		Total
	Positive	Negative	
>20	34	2	36
<20	21	8	29
Total	55	10	65

Table 4: Diagnostic values of cancer ratio >20

Sensitivity	61.82%
Specificity	80%
Positive Predictive Value (PPV)	94.44%
Negative Predictive Value (NPV)	27.59%
Positive Likelihood Ratio (Positive LR)	3.1
Negative Likelihood Ratio (Negative LR)	0.48

Table 5: Diagnostic values of cancer ratio >26

Parameters	Value	95%CI
Sensitivity	43%	31.5 – 55.7
Specificity	90%	82.7 – 97.3
Positive Predictive Value (PPV)	96%	91.2 – 100
Negative Predictive Value (NPV)	22%	12.3 – 32.7
Positive Likelihood Ratio (Positive LR)	4.363	3.43 – 5.29
Negative Likelihood Ratio (Negative LR)	0.229	0.13 – 0.33

Discussion

Gender

Among all study participants, 53.8% were females with MPE in the exudative pleural effusion group while 30.8% were males. Other studies also reported greater proportion of females with MPE as compared to males.[8,9] Lung cancer study in women pointed out that there were differences in risk factors, histology and pathophysiology as compared with men.[10] However, in this study, this difference could be due to the consecutive sampling technique in which the subjects collected were mostly women.

Age

In this study, most of the subjects with exudative pleural effusions were aged ≥40 (96.9%), whereas only 3.1% subjects were <40 years old. The median age of study subjects with proven MPE was 59 years (39-79 years). These results corresponded with a study which revealed that majority of MPE patients were in the 50–70 year age group with a mean age of 58.8 years (32-85 years).[11] Perez Warnisher *et al.*[12] in 2016 reported that adenocarcinoma was a predominant histology finding in both sexes of all ages. Malignancy can be considered as an age-related disease because most of the risk of malignancy increases with age. Certain similar biological mechanisms which regulate aging can also be involved in the pathogenesis of age-related diseases such as cancer, however, there are many factors which influence the onset of malignancy at an early or young age. These include genetic factors and/or race, environmental factors and even the cancer histology.[13] In the present study, some types of MPE were developed from metastasis of primary tumors such as lymphoma, which mostly affected young people.

Anatomic Pathology Results

A retrospective study conducted on patients with pleural effusions reported that a total of 70 out of 110 patients had malignant pleural effusions based on anatomic pathology results. About 45.7% of the diagnosis was established on the basis of pleural fluid cytology results, whereas, 40% was based on pleural tissue histology results using thoracoscopy method guided by video or video-assisted thoracoscopy (VATS). The rest

of the diagnosis was based on radiological assessment as it was not evident from anatomic pathology. Closed pleural biopsy in this study was not performed. Most of the subjects had anatomic pathology of adenocarcinoma (35.7%) followed by mesothelioma (24.3%) and metastatic breast cancer (10%). On the other hand, squamous cell carcinoma (SCC) was diagnosed in less than 10% of patients while the rest included small cell lung carcinoma (SCLC), lymphoma and metastasis of gastrointestinal malignancy.[14] Another study found that malignant cells were detected in 53.73% of cases with pleural fluid cytology and pleural tissue histology. However, despite the presence of primary tumor in 46.27% of cases, no malignant cells could be detected in pleural fluid or pleural tissue.[15] In addition, adenocarcinoma was reported as the most common (52%) type of cancer cell found in MPE, both in pulmonary and metastasis-extrapulmonary origin.[8]

Mechanism of pleural effusion which develop in patients with malignancy is one of determinants for the presence or absence of malignant cells in the fluid. Pleural effusions which are formed due to implantation of tumors on the pleural surface or as a result of direct tumor infiltration of the pleura tend to have malignant cells in the effusion. On the other hand, pleural effusions due to tumor metastasis are generated by embolization of tumor cells to visceral pleura or distant hematogenous spread of the tumor to parietal pleura. Deposits of tumor cells scatter along the parietal pleural membrane and clog the lymphatic stomata causing the blockage of pleural fluid drainage.[16-18] In a study, malignant cells were not found in about 25% of MPE cases, hence the diagnosis was established based on the presence of primary cancer in the lung or other organs and this condition was named as PPE.[16] In this study, adenocarcinoma, of both pulmonary and metastasis-extrapulmonary origin, was found to be the most common type present in 63.6% of MPE cases. It is likely that in this study, MPE was caused by lymphohaematogenic invasion than direct spread of cancer cells to the pleural surface.

Serum LDH: Pleural Fluid ADA (Cancer Ratio)

Microbiology and analysis, ADA and cytology of pleural fluid are routine initial examinations performed on patients with exudative pleural effusions. These tests are followed by pleural biopsy if biochemical results are inconclusive.[7,19] In the current study, serum LDH was found increased in MPE while pleural fluid ADA was found relatively low. However, contrasting results were observed in TB pleural effusion i.e. low serum LDH and high pleural fluid ADA. Low ADA levels are often acknowledged as an indicator of MPE. Due to these reciprocal alterations in biochemical analysis, a ratio of diagnostic power was developed which could determine MPE in an effective, timely, generalizable and generally applicable manner.[20]

The ADA level in MPE is known to be low, hence, it is inappropriate to use it to diagnose MPE due to lack of biochemical association whereas LDH has been proven to be high in malignancies. Therefore, the combination of these two markers as a cancer ratio to develop MPE predictors was evaluated using negative and positive correlation on malignancy. This ratio was found significantly higher in MPE group as compared to TB and parapneumonic effusion groups. Such markers can not only provide an early signal to MPE but also potentially serve as an early warning for patients with no malignant cell according to cytological findings.[7,19]

Serum lactate dehydrogenase

Although serum LDH level in this study did not differ significantly between pleural effusions due to malignancy and non-malignancy, yet its values in MPE tended to be higher than those in non-malignant effusions. Serum LDH is a cellular enzyme that increases in response to tissue injury in a non-specific manner. Elevated serum LDH is found in a variety of clinical conditions, however, highly elevated serum LDH might be a marker of specific diagnostic group. Its diagnostic and prognostic role had previously been studied and reported as a poor prognostic marker in sepsis and also cancer patients.[7,21]

Increase of serum LDH in malignancy occurs due to distinctive glycolysis used for energy by tumor cells and oxidative phosphorylation. Additionally, it also has a role in the generation pathway of adenosine triphosphate (ATP). High level of glycolysis is required for cell growth because it is capable of producing ATP faster than oxidative phosphorylation. As tumor cells grow rapidly, thus, they need more ATP to promote cell growth and glycolysis should be able to meet the ATP demand. Consequently, serum LDH increases in patients with malignancy.[19,22] Its diagnostic potential as a biomarker for MPE has not been reported. The correlation between elevated serum LDH and MPE have been explained by some studies which were consistent with other studies which also reported correlation between serum LDH and cancer.[22]

Pleural fluid adenosine deaminase

Based on the results of this study, the median pleural fluid ADA value in MPE was found quite lower i.e. 12.5 U/L as compared to non-malignant pleural effusions (38.7 U/L). Statistically significant correlation was found between ADA value and malignancy, however, the diagnostic test results achieved an AUC value of ADA <0.7, hence it was not analyzed any further. This was in accordance with the results of another study which reported significantly higher level of ADA activity in pleural fluid in TB pleurisy (110.6±35.2 U/L) than in pleural fluid due to malignancy (17.5±8,4 UL).[23]

Adenosine deaminase is an enzyme which catalyzes the conversion of adenosine and deoxyadenosine into ino-

sine and deoxyinosin in the purine degradation pathway. Their quantity is increased in immature and undifferentiated T-lymphocytes after mitogenic and antigenic stimulation. Activity of ADA is ten times greater in lymphocytes than in erythrocytes and also greater in T-lymphocytes than in B-lymphocytes. This activity varies during T-cell differentiation with a significant increase in levels in immature or undifferentiated state. Increased ADA activity in MPE has been associated with a cluster of differentiation 8 (CD_8) predominance whereas in TB, the increase in ADA was accounted due to a gradual increase in cluster of differentiation 4 (CD_4) blastogenesis after mycobacterial antigenic stimulus.[24,25]

A study reported high percentage of T-lymphocytes in MPE either in vivo or in vitro but upon stimulation by nonspecific mitogens such as phytohemagglutinin (PHA) or concanavalin A (Con-A), the capacity of these cells became lower or even zero. Conversely, in TB or parapneumonic effusions, T-lymphocytes reacted intensely to specific and nonspecific mitogens. Consequently, these cells, especially in TB pleurisy, would undergo intense and accelerated blastogenesis after antigenic stimulation of mycobacteria and there would also be a significant increase in the CD_4 subpopulation. This rise in CD4 cells indicated that ADA synthesis was associated with lymphocytic proliferation and differentiation processes. Baganha *et al.*[23] elucidated that increased ADA activity in TB pleurisy appeared to be associated with an increase in CD_4 lymphocytes whereas its decrease in MPE was correlated with a higher and lower percentage of CD_{11} and CD_4 T-cells respectively.

Diagnostic Test of Cancer Ratio

In accordance with a study by Verma *et al.*[7], cancer ratio cut-off point of >20 could be applied to decide whether the exudative pleural effusion etiology was malignant or not. Therefore, the present study conducted a diagnostic test of the cut-off point by analyzing patients with suspected MPE prospectively. Few years back, a group of researchers obtained the cancer ratio cut-off point >20 with sensitivity and specificity of 95% (95% CI, 0.87-0.98) and 85% (95% CI, 0.68-0.94), respectively. The positive and negative likelihood ratios (LR) obtained were 16 and 0.13 respectively with area of AUC of 0.81.[7,19] In the present study, cancer ratio of >20 was found to have a good diagnostic accuracy i.e. its sensitivity was found to be 61.82% and specificity was 80%. In addition, PPV of 94.44% and NPV of 27.59% were also observed. Patients with MPE were found to have a 3.1-fold probability of cancer ratio >20 as compared to those without MPE. Moreover, 0.48-fold probability of cancer ratio ≤20 was found in patients with MPE as compared to those without MPE.

This study attempted to find a better cut-off point which could be applied to patients with suspected MPE at Persahabatan Hospital as a national respiratory referral center hospital that represents Indonesia. To date, there has been no stipulated method to be complied to determine the cut-off point accurately. The cut-off point was chosen by the clinician after carefully considering which diagnostic value is useful. Although cut-off point >20 gave good results, yet the cut-off point finally accepted for cancer ratio in diagnosing MPE at Persahabatan Hospital Jakarta was ≥26. This is because it had higher specificity (90%), PPV (96%) and positive LR (4.363) than other cut-off points. Clinically, positive predictive value is more important in diagnosing a disease than sensitivity. If the cancer ratio is ≥26 then there would be 96% certainty that the etiology of exudative pleural effusion in these patients was due to malignancy.

In conclusion, the cancer ratio cut-off point of ≥26 in patients with exudative pleural effusion can be used to detect MPE with a diagnostic power that can establish MPE in an effective, efficient, timely and generally applicable manner.

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Disclosure

The authors declare that they have no conflicts of interest relevant to the subject of this manuscript.

References

1. Light RW. The undiagnosed pleural effusion. Clin Chest Med. 2006; 27(2): 309-19. doi: https://doi.org/10.1016/j.ccm.2005.12.002.
2. Psallidas I, Kalomenidis I, Porcel JM, Robinson BW, Stathopoulos GT. Malignant pleural effusion: from bench to bedside. Eur Respir Rev. 2016; 25(140): 189-98. doi: https://doi.org/10.1183/16000617.0019-2016.
3. Azfar Ali H, Lippmann M, Mundathaje U, Khaleeq G. Spontaneous hemothorax: a comprehensive review. Chest. 2008; 134(5): 1056-65. doi: https://doi.org/10.1378/chest.08-0725.
4. Light RW. Clinical practice. Pleural effusion. N Engl J Med. 2002; 346(25): 1971-7. doi: https://doi.org/10.1056/nejmcp010731.
5. Light RW, Erozan YS, Ball WC, Jr. Cells in pleural fluid. Their value in differential diagnosis. Arch Intern Med. 1973; 132(6): 854-60. doi: https://doi.org/10.1001/archinte.1973.03650120060011.
6. Light RW, Macgregor MI, Luchsinger PC, Ball WC, Jr. Pleural effusions: the diagnostic separation of transudates and exudates. Ann Intern Med. 1972; 77(4): 507-13. doi: https://doi.org/10.7326/0003-4819-77-4-507.

7. Verma A, Abisheganaden J, Light RW. Identifying Malignant Pleural Effusion by A Cancer Ratio (Serum LDH: Pleural Fluid ADA Ratio). Lung. 2016; 194(1): 147-53. doi: https://doi.org/10.1007/s00408-015-9831-6.
8. Wu SG, Yu CJ, Tsai MF, et al. Survival of lung adenocarcinoma patients with malignant pleural effusion. Eur Respir J. 2013; 41(6): 1409-18. doi: https://doi.org/10.1183/09031936.00069812.
9. Jeba J, Cherian RM, Thangakunam B, George R, Visalakshi J. Prognostic Factors of Malignant Pleural Effusion among Palliative Care Outpatients: A Retrospective Study. Indian J Palliat Care. 2018; 24(2): 184-8. doi: https://doi.org/10.4103/ijpc.ijpc_183_17.
10. North CM, Christiani DC. Women and lung cancer: what is new? Semin Thorac Cardiovasc Surg. 2013; 25(2): 87-94. doi: https://doi.org/10.1053/j.semtcvs.2013.05.002.
11. Agrawal A, Tandon R, Singh L, Chawla A. Clinico- pathological profile and course of malignant pleural effusion in a tertiary care teaching hospital in western U.P. with special reference to lung cancer. Lung India. 2015; 32(4): 326-30. doi: https://doi.org/10.4103/0970-2113.159551.
12. Perez Warnisher MT, Melchor R, Rio M, et al. Differences according to age and sex among patients with malignant pleural effusion as a presentation form of cancer. Eur Respir J. 2016; 48(suppl 60): PA3395. doi: https://doi.org/10.1183/13993003.congress-2016.PA3395.
13. White MC, Holman DM, Boehm JE, Peipins LA, Grossman M, Henley SJ. Age and cancer risk: a potentially modifiable relationship. Am J Prev Med. 2014; 46(3 Suppl 1): S7-15. doi: https://doi.org/10.1016/j.amepre.2013.10.029.
14. Bikmalla S, Khalil M, Ganaie M, Haris M. Characteristics of malignant pleural effusions. Review of one-year data from a large tertiary centre. Eur Respir J. 2013; 42(Suppl 57): P2931. Available from: http://erj.ersjournals.com/content/42/Suppl_57/P2931.abstract.
15. Cobanoglu U, Kemik O, Celik S, Sayir F. A novel approach for preventing recurrence of malign pleural effusion: early phase pleurodesis. Arch Med Sci. 2018; 14(6): 1404-15. doi: https://doi.org/10.5114/aoms.2017.72543.
16. Putnam JB, Jr. Malignant pleural effusions. Surg Clin North Am. 2002; 82(4): 867-83. doi: https://doi.org/10.1016/s0039-6109(02)00036-1.
17. Sahn SA. The pathophysiology of pleural effusions. Annu Rev Med. 1990; 41: 7-13. doi: https://doi.org/10.1146/annurev.me.41.020190.000255.
18. Andrews CO, Gora ML. Pleural effusions: pathophysiology and management. Ann Pharmacother. 1994; 28(7-8): 894-903. doi: https://doi.org/10.1177/106002809402800715.
19. 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). Can Respir J. 2016; 2016: 1-6. doi: https://doi.org/10.1155/2016/7348239.
20. Wang J, Liu J, Xie X, Shen P, He J, Zeng Y. The pleural fluid lactate dehydrogenase/adenosine deaminase ratio differentiates between tuberculous and parapneumonic pleural effusions. BMC Pulm Med. 2017; 17(1): 168. doi: https://doi.org/10.1186/s12890-017-0526-z.
21. Trédan O, Ray-Coquard I, Chvetzoff G, et al. Validation of prognostic scores for survival in cancer patients beyond first-line therapy. BMC Cancer. 2011; 11: 95. doi: https://doi.org/10.1186/1471-2407-11-95.
22. Füssenich LM, Desar IM, Peters ME, et al. A new, simple and objective prognostic score for phase I cancer patients. Eur J Cancer. 2011; 47(8): 1152-60. doi: https://doi.org/10.1016/j.ejca.2010.12.028.
23. Baganha MF, Pêgo A, Lima MA, Gaspar EV, Cordeiro AR. Serum and pleural adenosine deaminase. Correlation with lymphocytic populations. Chest. 1990; 97(3): 605-10. doi: https://doi.org/10.1378/chest.97.3.605.
24. Helmy NA, Eissa SA, Masoud HH, Elessawy AF, Ahmed RI. Diagnostic value of adenosine deaminase in tuberculous and malignant pleural effusion. Egypt J Chest Dis Tuberc. 2012; 61(4): 413-17. doi: https://doi.org/10.1016/j.ejcdt.2012.08.004.
25. Jiménez Castro D, Díaz Nuevo G, Pérez-Rodríguez E, Light RW. Diagnostic value of adenosine deaminase in nontuberculous lymphocytic pleural effusions. Eur Respir J. 2003; 21(2): 220-4. doi: https://doi.org/10.1183/09031936.03.00051603.