ORIGINAL ARTICLE

THE ASSOCIATION BETWEEN THE RATIO OF CYTOLOGY VOLUME TO THORACENTESIS VOLUME AND MALIGNANCY DETECTION

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ABSTRACT

Background: Pleural effusion cytology is a primary method to identify malignant pleural effusion. While the volume of fluid submitted for cytology may influence malignancy detection, the relationship between the ratio of cytology fluid volume to thoracentesis volume and malignancy detection remains unclear.
Objective: To assess the association between the ratio of cytology fluid volume to thoracentesis volume and malignancy detection.
Methods: An observational cross-sectional study was conducted at Cipto Mangunkusumo National General Hospital from January 1 to October 31, 2023. Inclusion criteria were patients with suspected malignant pleural effusion who underwent thoracentesis and cytology examination. Exclusion criteria included a history of malignant pleural effusion, more than one cytology examination with discordant results, and incomplete data. Bivariate analysis used the Kruskal-Wallis test, followed by multivariate analysis to control confounders. The optimal fluid ratio cutoff was determined using ROC curve analysis.
Results: Among 174 subjects, malignancy was detected in 26.4% of cases. Adenocarcinoma (25.9%) and breast cancer (12.1%) were the most frequently identified types and primary sites. The AUC was 0.629, with an optimal fluid ratio cut-off of 0.022 (sensitivity 62%, specificity 63%). A fluid ratio <0.022 increased the risk of malignancy detection (PR 1.647; 95% CI: 1.204–2.252; p=0.002). A thoracentesis volume >680 mL with a cytology volume of 15 mL was associated with increased malignancy detection.
Conclusion: There is an association between the cytology fluid volume-to-thoracentesis fluid volume ratio with malignancy detection, which is influenced by the total thoracentesis volume. A fluid ratio <0.022 and thoracentesis volume >680 mL with a cytology volume of 15 mL increase the likelihood of detecting malignancy.

Keywords: fluid volume ratio, cytology, thoracentesis, malignant pleural effusion

ABSTRAK

Latar Belakang: Pemeriksaan sitologi efusi pleura merupakan metode utama untuk mengidentifikasi efusi pleura ganas. Volume cairan pemeriksaan sitologi dapat mempengaruhi temuan keganasan, namun hubungan rasio terhadap volume torakosentesis dengan temuan keganasan belum diketahui.
Tujuan: Mengetahui hubungan rasio volume cairan sitologi dibandingkan volume torakosentesis dengan temuan keganasan.
Metode: Penelitian observasional potong lintang di Rumah Sakit Cipto Mangunkusumo pada 1 Januari–31 Oktober 2023. Kriteria inklusi meliputi pasien dengan kecurigaan efusi pleura ganas yang menjalani torakosentesis dan pemeriksaan sitologi. Kriteria eksklusi meliputi pasien dengan riwayat efusi pleura ganas, riwayat pemeriksaan sitologi >1 kali dengan hasil berbeda antar pemeriksaan, dan data laporan tidak lengkap. Analisis bivariat menggunakan uji Kruskal-Wallis, dilanjutkan analisis multivariat untuk mengontrol variabel perancu. Titik potong rasio diperoleh dari analisis kurva ROC.
Hasil: Dari 174 subjek, proporsi temuan keganasan sebesar 26,4%. Adenokarsinoma (25,9%) dan mammae (12,1%) merupakan jenis dan lokasi keganasan dengan temuan terbanyak. Nilai AUC 0,629 dengan titik potong rasio cairan optimal 0,022 (sensitivitas 62%, spesifisitas 63%). Rasio cairan <0,022 meningkatkan risiko temuan keganasan (PR 1,647; IK 95%: 1,204-2,252; p=0,002). Nilai titik potong volume torakosentesis >680 mL pada volume sitologi 15 mL meningkatkan temuan keganasan.
Kesimpulan: Terdapat hubungan antara rasio volume cairan sitologi terhadap volume torakosentesis dengan temuan keganasan, yang dipengaruhi oleh besarnya volume torakosentesis. Nilai titik potong rasio cairan <0,022 dan volume torakosentesis >680 mL pada volume sitologi 15 mL berhubungan dengan peningkatan temuan keganasan.
Kata Kunci: rasio volume cairan, sitologi, torakosentesis, efusi pleura ganas

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INTRODUCTION

Malignant pleural effusion (MPE) is a common condition frequently found in patients with malignancies, such as thoracic cancers, pleural mesothelioma, or metastases from other organs. This group of diseases is known to have a poor prognosis, with a survival rate ranging from three to twelve months. It is estimated that there are one million cases of MPE annually worldwide, with a projected increasing global healthcare burden.[1,2] While national prevalence data on pleural effusion in Indonesia is currently unavailable, reports indicate that the prevalence of MPE in Indonesia ranges between 42% and 64%, with variation across different healthcare centers.[3]

Pleural fluid cytology is one of the primary methods used to identify MPE. However, its sensitivity varies greatly, ranging from 40% to 87%, although its specificity is high, between 89% and 99%.[4] One of the factors suspected to influence the diagnostic accuracy of this method is the volume of fluid submitted for cytological analysis. Earlier studies found no significant association between the volume of pleural fluid sent for cytology and malignant findings.[5,6] Nevertheless, more recent studies have demonstrated a significant correlation, indicating that the volume of pleural fluid examined may affect cancer detection and diagnosis.[1,7,8] Additionally, current guidelines from the British Thoracic Society explicitly recommend a minimum of 25 mL, and preferably 50 mL, of pleural fluid for cytological examination to improve diagnostic yield for malignancy, although this has not yet been established in an international consensus involving multiple expert societies.[2]

While the volume of pleural fluid submitted for cytology may influence malignancy detection, the relationship between the ratio of cytology sample volume to total thoracentesis volume and malignancy detection remains unknown. To date, no specific studies have investigated the association of this ratio with malignant findings. One study reported that only around 50% of the total drained pleural fluid is submitted for cytological analysis.[9] Previous studies have primarily emphasized the relationship between total thoracentesis volume and diagnostic yield. Although emerging evidence supports the importance of optimal cytology sample volume for improving malignancy detection, the association between the volume ratio of cytology sample to total thoracentesis fluid and malignancy findings has yet to be confirmed. Therefore, this study aims to identify the association between the ratio of pleural fluid volume submitted for cytology to total thoracentesis volume and the detection of malignancy, as well as to determine the optimal cutoff value for this ratio.

METHODS

The study employed a cross-sectional design with retrospective data collection from medical records spanning the period of January to October 2023 at Cipto Mangunkusumo National General Hospital (CMNGH). The inclusion criteria were: (1) patients aged >18 years with pleural effusion who underwent thoracentesis, (2) patients with suspected malignant pleural effusion, and (3) patients who had cytological examination performed following thoracentesis. Subjects were excluded if: (1) they had previously been diagnosed with malignant pleural effusion, (2) they had undergone more than one cytological examination with discordant results, and (3) the thoracentesis or cytology report data were incomplete.

Bivariate analysis was conducted using comparative hypothesis tests for unpaired numerical variables among three groups. ANOVA was used if the data distribution was normal, while the Kruskal–Wallis test was used for non-normally distributed data. In addition, multivariate analysis was performed, controlling for comorbidities as potential confounding variables (chronic kidney disease, heart failure, liver cirrhosis, pulmonary embolism, pulmonary infection). This study also assessed the sensitivity and specificity of the pleural fluid volume ratio using the area under the curve (AUC) derived from the receiver operating characteristic (ROC) curve.

The study received ethical approval from the Health Research Ethics Committee of the Faculty of Medicine, Universitas Indonesia (FMUI) on 15 November 2024 (Reference No.: KET-1725/UN2.F1/ETIK/PPM.00.02/2024) and research site approval from CMNGH (Reference No.: YR.02.01/D.IX.2.3/1610/2024) on 30 December 2024.

RESULTS

A total of 174 subjects were included in this study after applying the predefined inclusion and exclusion criteria (Figure 1). The characteristics of the study population showed a median age of 54 years, with the majority being

female (56.9%). Malignant findings were identified in 26.4% of the subjects. The median volume of pleural fluid obtained through thoracentesis was 650 mL, while the cytology sample volume was consistently 15 mL, in accordance with the cytological examination protocol at CMNGH. The most common comorbidity was pulmonary infection, present in 46.0% of subjects (Table 1). Furthermore, adenocarcinoma was found to be the most prevalent malignancy in this study population (25.9%), followed by squamous cell carcinoma (6.3%) and lymphoproliferative malignancies (5.2%) (Table 2).

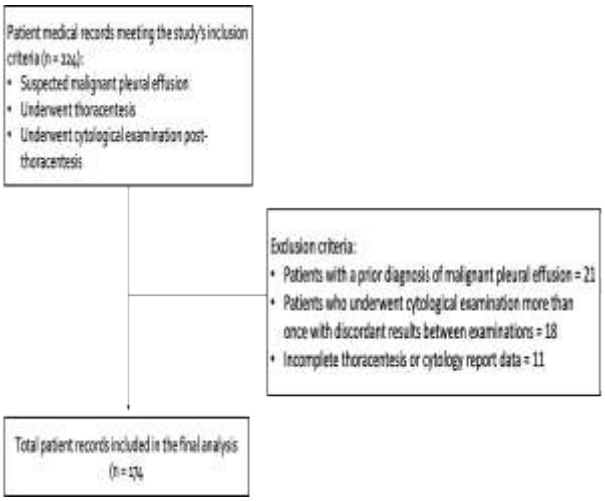

Figure 1. Data Sampling

The analysis revealed a significant association between the ratio of cytology sample volume to total thoracentesis volume and malignancy findings (p = 0.022) (Table 3). The median ratio was lower in the malignant group (0.018) compared to the non-malignant group (0.027). The volume of pleural fluid obtained via thoracentesis showed a significant difference, with a higher median volume in the malignant group (805 mL) compared to the non-malignant (550 mL) and inconclusive groups (725 mL) (p = 0.022). However, the cytology volume remained constant at 15 mL across all groups, and this difference was not statistically significant (p = 1.000).

Table 1. Baseline Characteristics of Study Subjects

Characteristics	N = 174
Demographic Data	
Age, median (IQR)	54 (44 – 62) years
Age, n (%)	
< 60 years	115 (66,1)
>= 60 years	59 (33,9)
Sex, n (%)	
Female	99 (56,9)
Male	75 (43,1)
Comorbodity	
Chronic kidney disease, n (%)	
No	167 (96,0)
Yes	7 (4,0)
Heart Failure, n (%)	
No	172 (98,9)
Yes	2 (1,1)
Liver cirrhosis, n (%)	
No	170 (97,7)
Yes	4 (2,3)
Pulmonary Embolism, n (%)	
No	173 (99,4)
Yes	1 (0,6)
Pneumonia, n (%)	
No	94 (54,0)
Yes	80 (46,0)
Malignancy Findings	
Negative	114 (65,5)
Positive	46 (26,4)
Inconclusive	14 (8,0)
Fluid Volume Data	
Cytology volume, median (IQR)	15 (15 – 15)
Thoracentesis volume, median (IQR)	650 (25,0 – 921,25)
Cytology-to-thoracentesis volume ratio, median (IQR)	0,023 (0,016 – 0,060)

ROC analysis yielded an AUC of 0.629, with an optimal volume ratio cutoff of 0.022, corresponding to a sensitivity of 62% and specificity of 63%. A lower fluid ratio (<0.022) was associated with an increased risk of malignancy detection (Prevalence Ratio [PR] 1.647; 95% Confidence Interval [CI]: 1.204–2.252; p = 0.002) (Table 4). Nonetheless, interpretation of the fluid ratio is heavily influenced by the variability in thoracentesis volumes, as the cytology sample volume is fixed at 15 mL according to CMNGH sampling protocol. Based on the identified cutoff ratio of <0.022 with a constant cytology volume of 15 mL, a thoracentesis volume exceeding 680 mL was found to increase the likelihood of malignancy detection. Both bivariate and multivariate analyses confirmed that potential confounding variables including chronic kidney disease, heart failure, liver cirrhosis, pulmonary embolism, and pulmonary infection, did not significantly affect the association between fluid volume ratio and malignancy findings.

Tabel 2. Malignancy Type

Malignancy Type	N = 174
Adenocarcinoma	
No	129 (74.1%)
Yes	45 (25.9%)
Lymphoproliferative	
No	165 (94.8%)
Yes	9 (5.2%)
Germinal Cell	
No	171 (98.3%)
Yes	3 (1.7%)
Squamous Cell	
No	163 (93.7%)
Yes	11 (6.3%)
Mucoepidermoid	
No	172 (98.9%)
Yes	2 (1.1%)
Sarcoma	
No	171 (98.3%)
Yes	3 (1.7%)
Hepatocellular	
No	172 (98.9%)
Yes	2 (1.1%)
GIST	
No	171 (98.3%)
Yes	3 (1.7%)

DISCUSSION

The prevalence of malignancy findings in this study was 26.4%, which is lower than reported in several previous studies.[3,10–12] This discrepancy may be attributed to differences in population characteristics, examination techniques, and the experience of pathologists. MPE has been known to correlate with advanced cancer stages and a prior history of primary malignancy.[13,14] However, the population in this study consisted of patients with suspected MPE, and the exact staging of the disease was not determined. Additionally, it is known that combining cytological examination with cell block preparation and pleural biopsy provides significantly higher diagnostic accuracy than cytology using smear techniques alone, which was the method employed in this study.[15,16]

Table 3. Comparison of Mean Volumes and Volume Ratios Based on Malignancy Findings

Variable	Malignancy Findings			P Value
	No[b]	Yes[a]	Inconclusive[c]	
Cytology Volume Median (IQR)	15 (15 – 15)	15 (15 – 15)	15 (15 – 15)	1,000
Thoracentesis Volume, Median (IQR)	550 (118,75 – 812,5)	805 (500 – 1012,5)	725 (243,75 – 1050)	**0,022**
Cytology-to-thoracentesis Volume ratio, Median (IQR)	0,027 (0,018 – 0,127)	0,018 (0,015 – 0,030)	0,021 (0,014 – 0,087)	**0,022**

Kruskal-Wallis; Post-hoc Mann-Whitney a and b (p = 0,006); a and c (p = 0,489)

The median thoracentesis volume in this study was 650 mL, while the cytology sample volume was constant at 15 mL, resulting in a median volume ratio of 0.023. Patients with malignant findings had significantly larger thoracentesis volumes than those without malignancy, supporting previous studies indicating that malignant effusions tend to produce larger pleural fluid volumes compared to other etiologies.[1,8,17] This may be due to increased fluid production associated with tumor-related increased permeability or lymphatic obstruction.[18,19]

A lower fluid ratio was observed in the malignant group; however, this is influenced by the larger thoracentesis volumes, while the cytology volume remained constant at 15 mL per CMNGH protocol. ROC analysis demonstrated that the cytology-to-thoracentesis volume ratio had an AUC of 0.629 (p = 0.009), with a cutoff value of 0.022, providing a sensitivity of 62% and specificity of 63% for malignancy detection. Given this cutoff ratio and a fixed cytology volume of 15 mL, the corresponding thoracentesis cutoff volume was calculated at 681 mL, rounded down to 680 mL.

However, it is important to note that in this study, the fluid ratio cannot be fully relied upon as a diagnostic parameter for evaluating MPE, since thoracentesis volume was the more influential variable. This is particularly relevant considering that cytology sample volumes were constant at 15 mL across all subjects. Additionally, the study did not account for residual pleural fluid left during thoracentesis, which may have influenced the findings.

Tabel 4. Cutoff Point Analysis of Fluid Volume Ratio and Malignancy Findings

Characteristics	Malignancy Findings		PR (95% CI)	P Value
	Yes (n=46)	No (n=128)		
Fluid Volume Ratio n (%)				
<0,022	29 (37,18)	49 (62,82)	1,647 (1,204 – 2,252)	**0,002**

≥0,022	17 (17,71)	79 (82,29)

Chi Square

Bivariate analysis indicated that none of the potential confounding variables significantly affected the association between fluid ratio and malignancy findings. Nonetheless, multivariate analysis was performed as these comorbidities may still be clinically relevant confounders. The multivariate model showed no meaningful change in the PR after adjustment for pulmonary infection, liver cirrhosis, heart failure, and chronic kidney disease.

This is the first known study to explore the association between fluid volume ratio and malignancy detection in patients with pleural effusion. Furthermore, this study identified a cutoff value for the fluid ratio, which may serve as a foundation for future research. Several limitations of this study include the single-center subject recruitment, retrospective study design, and the use of consecutive sampling. In addition, no confirmatory diagnostic procedures such as pleural biopsy or primary tumor biopsy were performed. This study also did not account for residual pleural effusion volume that remained undrained during thoracentesis, nor did it consider specific molecular factors that may influence the sensitivity of cytological examination.

CONCLUSION

This study demonstrates a significant association between the ratio of cytology volume to thoracentesis volume and malignancy findings. A fluid ratio below 0.022 and thoracentesis volume greater than 680 mL, with a constant cytology volume of 15 mL, were associated with increased malignancy detection. Further studies are recommended using variable cytology volumes, with confirmation by advanced diagnostics (e.g. immunocytochemistry, pleural biopsy, pleuroscopy, or primary tumor biopsy), and in patients undergoing complete fluid drainage, to generate stronger evidence and clinical recommendations.

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COMPETING INTERESTS

The authors declare no conflict of interest related to this study.

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