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SEX, BRINKMAN INDEX, AND PLEURAL GLUCOSE LEVELS AS PREDICTORS OF PLEURODESIS OUTCOME IN MALIGNANT PLEURAL EFFUSION: EVIDENCE FROM RSUD JENDERAL AHMAD YANI METRO (2023–2024)

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ABSTRACT

Advanced cancer often causes malignant pleural effusion (MPE), which causes dyspnea and lowers quality of life. Pleurodesis is the conventional palliative treatment, however results vary. We examined the relationship between sex, smoking (Brinkman Index), and pleural glucose and pleurodesis success. RSUD Jenderal Ahmad Yani Metro, Lampung, did an observational analytic study from July 2023 to July 2024. Six of 38 adenocarcinoma-related MPE patients were eliminated, leaving 32 eligible for bleomycin pleurodesis. Complete reaction (CR), partial response (PR), or failure were outcomes. Chi-Square tests examined predicted factors and pleurodesis results. Pleurodesis success is substantially linked with sex ($p = 0.042$), Brinkman Index ($p = 0.027$), and pleural hyperglycemia ($p < 0.001$). CR rates were greater in women (53.8%) than men (15.8%). Pleural glucose >60 mg/dL strongly predicted success, but lower Brinkman Index values improved results. Conclusion: Sex, smoking, and pleural glucose may predict adenocarcinoma-related MPE pleurodesis outcomes. Pleural adhesion improved with female sex, decreased smoking burden, and increased pleural glucose, suggesting their participation in treatment.

Keywords: Adenocarcinoma; Brinkman Index; Glucose; Malignant pleural effusion; Pleurodesis; Sex

АБСТРАКТ

Распространённый рак часто вызывает злокачественный плевральный выпот (ЗПВ), который вызывает одышку и снижает качество жизни. Плевродез является традиционным паллиативным лечением, однако результаты варьируются. Мы изучили взаимосвязь между полом, курением (индекс Бринкмана), уровнем глюкозы в плевре и успешностью плевродезиса. RSUD Jenderal Ahmad Yani Metro, Лампунг, провел наблюдательное аналитическое исследование с июля 2023 года по июль 2024 года. Шесть из 38 пациентов с МПЭ, связанным с аденокарциномой, были исключены, оставив 32 подходящими для плевродезиса блеомицином. Полная реакция (ПР), частичный ответ (ЧО) или неудача были результатами. Тесты хи-квадрат исследовали предсказанные факторы и результаты плевродезиса. Успех плевродезиса существенно связан с полом ($p = 0.042$), индексом Бринкмана ($p = 0.027$) и плевральной гипергликемией ($p < 0.001$). Уровни CR были выше у женщин (53,8%), чем у мужчин (15,8%). Плевральный глюкоза >60 мг/дл сильно предсказывал успех, но более низкие значения индекса Бринкмана улучшали результаты. Заключение: Пол, курение и уровень глюкозы в плевральной жидкости могут предсказать результаты плевродезиса при МПЭ, связанном с аденокарциномой. Плевральное сращение улучшилось при женском поле, уменьшенной нагрузке от курения и повышенном уровне глюкозы в плевре, что указывает на их участие в лечении.

Ключевые слова: Аденокарцинома; Индекс Бринкмана; Глюкоза; Злокачественный плевральный выпот; Плевродез; Пол

INTRODUCTION

Advanced cancer patients with thoracic and extrathoracic malignancies often suffer from malignant pleural effusion (MPE), a major cause of morbidity. One-third to half of MPE patients are lung cancer, particularly adenocarcinoma, which often causes recurrent dyspnea, limited functional ability, repeated hospitalizations, and poor quality of life. Recent breakthroughs in pleural illness management have broadened MPE therapy choices, however pleurodesis remains a popular ultimate operation for expanding lungs. Despite these advances, many patients still fail pleurodesis, underlining the need for accurate treatment success predictions.¹⁻⁴ Pleurodesis induces adhesion between the visceral and parietal pleura through a complex inflammatory and fibrotic process, thereby preventing recurrent pleural fluid accumulation. Successful pleurodesis depends on multiple factors, including adequate lung re-expansion, pleural tumor burden, inflammatory activity, and the biochemical characteristics of pleural fluid. Previous studies have suggested that pleural fluid biomarkers such as pH, glucose, lactate dehydrogenase (LDH), protein, and albumin levels may reflect the biological condition of the pleural space and influence pleurodesis outcomes. However, the predictive value of these markers remains inconsistent across different patient populations and pleurodesis techniques.⁵⁻⁸

Among the available biomarkers, pleural glucose has attracted particular interest because it reflects both tumor metabolic activity and pleural membrane integrity. Low pleural glucose concentrations have been associated with increased malignant cell burden, impaired pleural transport, and an unfavorable pleural microenvironment. A previous study involving patients undergoing bleomycin pleurodesis demonstrated that pleural glucose was independently associated with pleurodesis outcomes and could predict treatment failure with high sensitivity and

specificity. Similarly, other investigators reported that higher pleural glucose levels were associated with increased rates of successful chemical pleurodesis.^{6,7}

In addition to pleural fluid biomarkers, patient-related characteristics may also influence pleurodesis efficacy. Biological sex has been shown to affect inflammatory and immune responses, which play a crucial role in pleural adhesion formation. Furthermore, chronic cigarette smoking may impair mesothelial repair, increase oxidative stress, alter fibroblast activation, and reduce the effectiveness of pleural fibrosis. Nevertheless, evidence regarding the influence of sex and cumulative smoking exposure on pleurodesis outcomes remains limited, and most studies have focused primarily on biochemical markers rather than integrating clinical and behavioral factors.^{2,8-10}

Many research have examined biochemical predictors of pleurodesis success, although Southeast Asian data is limited. Most published research have examined diverse malignancies, but adenocarcinoma-related MPE is scarce. No Indonesian study has examined the relationship between sex, Brinkman Index smoking exposure, and pleural glucose levels in bleomycin-treated adenocarcinoma-related MPE patients. This study addressed this information gap and provided evidence for more customized patient assessment before pleurodesis.

MATERIALS AND METHODS

Study Design and Setting

This prospective observational study was conducted at the Department of Pulmonology and Respiratory Medicine, RSUD Jenderal Ahmad Yani Metro, Lampung, Indonesia, between July 2023 and July 2024. The study aimed to evaluate the association of sex, smoking exposure measured by the Brinkman Index, and pleural glucose levels with pleurodesis outcomes among patients with adenocarcinoma-related malignant pleural effusion (MPE).

Study Population and Sampling

The study included adult adenocarcinoma-related MPE patients who underwent bleomycin pleurodesis. All eligible patients presenting throughout the study were recruited using sequential sampling until the goal sample size was reached. Eligibility was assessed in 38 cytologically confirmed adenocarcinoma-related MPE patients. Six patients were omitted due to missed inclusion criteria or inadequate clinical and laboratory data. The final analysis included 32 patients. Inclusion criteria were: Age ≥ 18 years, Cytologically confirmed malignant pleural effusion caused by adenocarcinoma, No prior chemotherapy before pleurodesis, Eastern Cooperative Oncology Group (ECOG) Performance Status ≤ 2 , Complete lung re-expansion confirmed by chest radiography following pleural drainage, Availability of pleural fluid glucose measurements before pleurodesis.¹² Exclusion criteria were: Trapped lung or persistent lung atelectasis, History of pulmonary tuberculosis, Chronic obstructive pulmonary disease (COPD), Diabetes mellitus, Autoimmune disease, Incomplete clinical, radiological, or laboratory data.

Study Variables. The primary outcome variable was pleurodesis response, categorized as complete response (CR), partial response (PR), or failure. Independent variables included: Sex (male or female), Smoking exposure assessed using the Brinkman Index, and Pleural glucose level.

Pleurodesis Procedure. All patients underwent tube thoracostomy and pleural drainage before pleurodesis. Following complete drainage and radiological confirmation of lung re-expansion, bleomycin 15 mg diluted in 100 mL of sterile normal saline was instilled through the chest tube. The chest tube was clamped for approximately two hours, during which patients were encouraged to change positions periodically to facilitate homogeneous distribution of the

sclerosing agent. Drainage was subsequently resumed according to institutional protocol.¹³

Pleural Fluid Analysis. Pleural fluid samples were collected aseptically through the chest tube immediately before pleurodesis. Samples were transported directly to the clinical pathology laboratory and processed on the same day. Pleural glucose concentrations were measured using the glucose oxidase-peroxidase enzymatic method with an automated chemistry analyzer (Roche Cobas® 6000, Roche Diagnostics, Mannheim, Germany). Based on previous studies evaluating pleurodesis outcomes, pleural glucose levels were categorized as 60 mg/dL and ≤ 60 mg/dL.^{6,7}

Outcome Assessment. Patients were followed for 30 days after pleurodesis. Clinical symptoms and chest radiographs were evaluated at follow-up visits. Complete Response (CR) is complete absence of recurrent pleural effusion and no pleural-related symptoms; Partial Response (PR) is minimal recurrent pleural effusion without the need for additional pleural intervention; Failure is recurrent symptomatic pleural effusion requiring repeat thoracentesis, chest tube insertion, or other pleural procedures.^{2,3,13,14}

Data Collection. Demographic characteristics, smoking history, clinical findings, pleural fluid analysis results, and pleurodesis outcomes were obtained from medical records and standardized research data collection forms.

Statistical Analysis. Data analysis was performed using SPSS Statistics version 21.0 (IBM Corp., Armonk, NY, USA). Categorical variables were presented as frequencies and percentages. Associations between sex, smoking exposure, pleural glucose levels, and pleurodesis outcomes were analyzed using the Chi-square test. Because several contingency table cells contained expected frequencies below five, Fisher's Exact Test was applied whenever Chi-square assumptions were violated.

Statistical significance was defined as a two-tailed p-value <0.05.

Ethical Considerations. This study was approved by the Health Research Ethics Committee of the Faculty of Medicine, University of Lampung (Approval No.833/UN26.18/PP.05.02.00/2023).

Written informed consent was obtained from all participants before enrollment. All procedures were conducted in accordance with the ethical principles of the Declaration of Helsinki.¹¹

RESULT

A total of 38 patients with cytologically confirmed adenocarcinoma-related malignant pleural effusion were screened during the study period. Six patients were excluded because they did not meet the eligibility criteria or had incomplete clinical data. Consequently, 32 patients were included in the final analysis.

Table 1. Respondents' Characteristics and Corelation Between Pleurodesis Response, Demographic Characteristic & Pleural Glucose Level.

Demographic Characteristics & Pleural Glucose Level.				
Variable	Pleurodesis (n=32)			p-value
	Complete Response (%)	Partial Response (%)	Failed (%)	
Age:				
- <40 years (n=1)	0	1 (100)	0	1.000
- ≥40 years (n=31)	10 (32.3)	13 (41.9)	8 (25.8)	
Sex:				
- Female (n=13)	7 (53.8)	5 (38.5)	1 (7.7)	0.044
- Male (n=19)	3 (15.8)	9 (47.4)	7 (36.8)	
Occupation:				
- Construction Worker (n=5)	0	3 (60)	2 (40)	0.273
- Teacher (n=2)	1 (50)	0	1 (50)	
- Housewife (n=5)	3 (60)	2 (40)	0	
- Farmer (n=12)	5 (41.7)	5 (41.7)	2 (16.7)	
- Mechnic (n=3)	1 (33.3)	0	2 (66.7)	
- Grocery Seller (n=2)	0	2 (100)	0	
- Civil Servant (n=1)	0	0	1 (100)	
- Driver (n=2)	0	2 (100)	0	
Smoking (Brinkman Index):				
- Non-Smoker (n=12)	7 (53.8)	4 (33.3)	1 (8.3)	0.0021
- Mild (n=2)	1 (50)	0	1 (50)	
- Moderat (n=4)	0	4 (100)	0	
- Heavy (n=14)	2 (14.3)	6 (42.9)	6 (42.9)	
Glucose:				
- ≥60 (n=16)	7 (43.8)	8 (50)	1 (6.3)	0.0001
- <60 mg/dl (n=16)	3 (18.8)	6 (37.5)	7 (43.8)	

A total of 32 patients with adenocarcinoma-related malignant pleural effusion who underwent bleomycin pleurodesis were analyzed. Most participants were older than 40 years (31 patients, 96.9%), with only one patient (3.1%) younger than 40 years. In the >40-year group, pleurodesis success was achieved in 74.2%, while the single patient aged <40 years also demonstrated a successful outcome. Female patients accounted for 40.6% (13 cases), while males represented 59.4% (19 cases). Pleurodesis success was

higher among females (92.3%) compared with males (63.2%).

With respect to occupation, farmers represented the largest subgroup (37.5%), followed by construction workers and housewives (15.6% each). Outcomes varied by occupation: housewives and grocery sellers achieved 100% success, farmers 83.3%, construction workers 60%, mechanics 33.3%, and civil servants 0%. Regarding smoking history, 37.5% of patients were non-smokers, of whom 91.7% achieved pleurodesis success.

Moderate smokers achieved the highest success rate (100%), while mild smokers had a 50% success rate.

The cohort's 43.8% heavy smokers had the lowest success rate (42.9%). Table 1 shows the relationships between demographics, smoking, pleural glucose, and pleurodesis results. Sex significantly affected pleurodesis results (Fisher's Exact Test, $p = 0.044$). Female patients had more full responses (53.8%) and fewer treatment failures (7.7%). Brinkman Index smoking exposure was also connected with pleurodesis results (Fisher's Exact Test, $p = 0.021$). Non-smokers had the highest complete response rate (53.8%), while heavy smokers had the lowest (14.3%) and highest failure rate (42.9%). Pleural glucose levels significantly correlated with pleurodesis results (Fisher's Exact Test, $p < 0.001$). Pleural glucose levels >60 mg/dL were associated with 95.0% complete and partial response and 5.0% treatment failure. However, 58.3% of patients with pleural glucose levels ≤ 60 mg/dL had therapeutic failure. No significant connection was found between age (1.000) or occupation (0.273) and pleurodesis outcomes. These findings imply that sex, smoking exposure, and pleural glucose level predict pleurodesis outcomes, but age and occupation do not.

DISCUSSION

This study evaluated the association of sex, smoking exposure measured by the Brinkman Index, and pleural glucose levels with pleurodesis outcomes among patients with adenocarcinoma-related malignant pleural effusion undergoing bleomycin pleurodesis. The principal findings demonstrated that female sex, lower cumulative smoking exposure, and higher pleural glucose levels were significantly associated with more favorable pleurodesis outcomes. In contrast, age and occupation were not significantly associated with treatment response. These findings suggest that both patient-related characteristics and pleural fluid biomarkers may influence the success of pleurodesis in patients with malignant pleural effusion.¹⁻⁴

Sex was significantly associated with pleurodesis outcomes in the present study ($p = 0.044$). Female patients achieved a substantially higher complete response rate and a lower treatment failure rate compared with male patients. Sex has not been extensively studied as a significant factor of pleurodesis success, but biological differences in immunological and inflammatory responses may explain this. Women produce more inflammatory mediators involved in tissue healing and fibrosis due to stronger innate and adaptive immune responses than men, according to experiments. Because pleurodesis requires a regulated inflammatory reaction and pleural fibrosis, these sex-related changes may help female patients with pleural symphysis. Women's adenocarcinoma often has a smaller cumulative smoking burden and different molecular features that may affect pleural disease behavior and treatment response.^{2,8-10}

Smoking exposure assessed using the Brinkman Index was also significantly associated with pleurodesis outcomes ($p = 0.021$). Non-smokers demonstrated the highest complete response rate, whereas heavy smokers exhibited the highest treatment failure rate. Cigarette smoke contains numerous oxidants and toxic compounds that promote chronic inflammation, oxidative stress, endothelial dysfunction, and impaired tissue repair. Long-term tobacco exposure may disrupt mesothelial cell integrity and interfere with fibroblast activation, both of which are essential for successful pleural adhesion formation. Furthermore, smoking has been associated with impaired wound healing and dysregulated extracellular matrix remodeling, potentially reducing the effectiveness of pleurodesis. Although previous studies have focused primarily on biochemical markers of pleural fluid, the present findings suggest that cumulative smoking exposure may represent an additional clinically relevant factor influencing pleurodesis outcomes.^{8-10,17,18}

High pleural glucose levels were found to be the best predictor of pleurodesis outcomes ($p < 0.001$). Patients with pleural glucose levels above 60 mg/dL had significantly better results than those with glucose levels below 60 mg/dL. Only 5.0% of patients with higher glucose levels failed treatment, compared to 58.3% of those with lower glucose. Pleural glucose indicates malignant cell metabolism and membrane function, making this conclusion biologically credible. Pleural glucose levels below normal are linked to tumor burden, poor transport, tissue hypoxia, and increased glucose consumption by malignant and inflammatory cells. These circumstances may create an unfavorable pleural milieu that inhibits fibroblast growth and fibrosis, limiting pleurodesis success. Poor pleurodesis results may be caused by significant malignant involvement altering pleural physiology and membrane transport.^{5-7,15,16}

Previous research have linked greater pleural glucose levels to effective pleurodesis. Pantazopoulos et al. found that pleural glucose predicted chemical pleurodesis result using a cut-off value similar to the present investigation. Alsayed et al. found that chemical pleurodesis increased pleural glucose, pH, and LDH and decreased them. Indonesian patients also showed a correlation between pleural fluid biochemistry and pleurodesis results.^{6,7,23} Age was not significantly associated with pleurodesis outcomes ($p = 1.000$). Although malignant pleural effusion predominantly affects older adults, successful pleurodesis appears to depend more on local pleural conditions, lung re-expansion, tumor burden, and biological characteristics of the pleural space than on chronological age alone. Similar observations have been reported in previous studies, where age was not identified as an independent determinant of pleurodesis success.^{2-4,19}

The findings of this study have potential clinical implications. Sex, smoking history, and pleural glucose level are routinely available parameters that can be obtained without additional cost or specialized testing.

Incorporating these variables into pre-procedural assessment may help clinicians identify patients who are more likely to respond favorably to pleurodesis and facilitate individualized treatment planning. In resource-limited settings, simple biomarkers such as pleural glucose may be particularly valuable because they are inexpensive, widely available, and easily integrated into routine clinical practice.^{1-3,6}

Note certain restrictions. One site and a small sample size may limit the study's generalizability. Second, observational design cannot infer causality. Third, tumor molecular characteristics, pleural fluid pH, LDH, and protein content were not predictive. The small sample size prevented multivariable analysis, hence residual confounding cannot be excluded out. To determine if these factors independently predict pleurodesis surgical outcomes, multicenter research with bigger populations is needed.

CONCLUSION

This study demonstrated that Sex, smoking exposure measured by the Brinkman Index, and pleural glucose levels were significantly associated with pleurodesis outcomes in patients with adenocarcinoma-related malignant pleural effusion undergoing bleomycin pleurodesis. Female sex, lower cumulative smoking exposure, and pleural glucose levels >60 mg/dL were associated with more favorable treatment outcomes, while pleural glucose demonstrated the strongest association with pleurodesis success. These findings suggest that readily available clinical and pleural fluid parameters may provide useful information for pre-procedural assessment and patient selection for pleurodesis. Further multicenter studies with larger sample sizes are needed to validate these findings and clarify their prognostic significance.

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DECLARATIONS

All authors contributed equally to the conception and design of the study, data collection, data analysis, interpretation of results, and manuscript preparation. All authors have read and approved the final version of the manuscript.

The authors declare no conflict of interest related to this study. No additional information is available for this paper

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