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ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Effect of Fluid Biochemistry on Bleomycin Pleuredesia in Non-mesothelioma Malign Pleural Effusions

Mezotelyoma Dışı Malign Plevral Efüzyonlarda Sıvı Biyokimyasının Bleomisin Plöredezisine Etkisi

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ABSTRACT

Aim: Malignant pleural effusions (MPE) often signal terminal-stage malignancy, with limited survival and quality of life prospects. This study aimed to evaluate whether fluid biochemistry influences recurrence after bleomycin pleurodesis in patients diagnosed with MPE through VATS pleural biopsy and fluid cytology.

Material and Method: A total of 23 patients diagnosed with MPE due to primary lung carcinoma or pleural metastasis, and treated with bleomycin pleurodesis at our institution, were included. All diagnoses were confirmed via VATS pleural biopsy.

Results: The mean age of patients with recurrence was 52.5 years. Their mean pleural fluid values were: LDH 569.75 U/L, pH 7.5, protein 4.53 g/dL, glucose 81 mg/dL, and albumin 3.13 g/dL. The average drainage time was 10.5 days. Recurrence occurred in 20% of men and 12.5% of women, with a 20% recurrence rate on the right side and 12.5% on the left. Recurrence in pulmonary adenocarcinoma patients was 33.3%, while the overall recurrence after bleomycin pleurodesis was 17.4%. General anesthesia had a higher recurrence rate (25%) compared to local anesthesia (9.1%).

Conclusion: Recurrent pleural effusion in MPE presents a clinical challenge. VATS is a crucial tool in diagnosing and managing MPE. Bleomycin is readily available for pleurodesis in our country, but the treatment should be personalized to balance quality of life and hospitalization time. International guidelines offer valuable insights but need to be adapted to individual cases.

Keywords: Malignant pleural effusions, video-assisted thoracoscopic surgery, quality of life, adenocarcinoma, pleurodesis

ÖZ

Amaç: Malign plevral efüzyonlar (MPE), genellikle terminal evredeki kontrolsüz malign hastalığı işaret eder ve bu hastalarda yaşam süresi ve yaşam kalitesi genellikle sınırlıdır. Bu çalışmada, VATS plevra biyopsisi ve sıvı sitolojisi ile MPE tanısı konmuş hastalarda, bleomisin plöredezisi sonrası sıvı biyokimyasının rekürrens gelişimini etkileyip etkilemediğini araştırmayı amaçladık.

Gereç ve Yöntem: Kurumumuzda VATS plevra biyopsisi ile MPE tanısı konan ve bleomisin ile plöredezi uygulanan 23 hasta çalışmaya dahil edildi. Primer akciğer karsinomu ve plevral metastaza bağlı MPE tanısı almış ve bleomisin ile plöredezi yapılmış hastalar çalışmaya alındı.

Bulgular: Rekürrens görülen hastaların ortalama yaşı 52,5 idi. Ortalama plevra sıvısı değerleri: LDH 569,75 U/L, pH 7,5, protein 4,53 g/dL, glukoz 81 mg/dL ve albümin 3,13 g/dL olarak saptandı. Ortalama drenaj süresi 10,5 gündü. Erkeklerde rekürrens oranı %20, kadınlarda %12,5 idi. Sağ tarafta rekürrens oranı %20, sol tarafta %12,5 olarak bulundu. Pulmoner adenokarsinom tanısı alanlarda rekürrens oranı %33,3 iken, bleomisin ile plöredezi sonrası genel rekürrens oranı %17,4 idi. Genel anestezi uygulananlarda rekürrens oranı %25, lokal anestezi uygulananlarda ise %9,1 olarak tespit edildi.

Sonuç: MPE'da rekürren plevral efüzyon tanı ve uzun dönem yönetimi açısından zorluklar oluşturur. VATS, malign efüzyonların tanı ve tedavisinde önemli bir rol oynar. Bleomisin, malign efüzyonlarda ülkemizde kolay erişilebilir bir ajandır. Klinik yaklaşım, yaşam kalitesi ve hastanede geçirilen süre dikkate alınarak bireyselleştirilmelidir. Uluslararası kılavuzlar klinik karar vermede önemli rol oynasa da, takip ve tedavi bireysel hasta özelliklerine göre belirlenmelidir.

Anahtar Kelimeler: Malign plevral efüzyonlar, video yardımlı torakoskopik cerrahi, yaşam kalitesi, adenokarsinom, plöredez

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INTRODUCTION

Malignant pleural effusions (MPE) are often indicative of uncontrolled terminal-stage malignant disease. Therefore, survival and quality of life after them are not promising. One of the most common causes of exudative effusions encountered in the clinic is malignant pleural effusions. The presence of malignant pleural effusion indicates advanced-stage disease. The mean survival after diagnosing malignant pleural effusion is 3–12 months. However, survival varies depending on the organ of origin of the primary tumour, histological type and the stage of the disease. Lung cancer has the shortest survival, while ovarian cancer has the longest survival (1).

The most common findings in patients with malignant pleural effusion are shortness of breath and cough. These occur in more than 50% of patients. The severity of dyspnea depends on the amount of effusion. Since pleural metastasis is often an indicator of advanced disease, patients may experience fatigue, loss of appetite, and significant weight loss. Chest pain may occur due to metastatic parietal pleura, ribs, or chest wall involvement. Approximately 25% of patients are asymptomatic. In physical examinations, decreased breath sounds due to pleural effusion are frequently observed (2).

Chest X-ray indicates the amount and location of pleural fluid and can be between 500 and 4000 millilitres of liquid. While the fluid is below 500 ml in 10% of the cases, there is massive pleural effusion in the other 10% (3). Thorax computed tomography (CT) is required in malignant pleural effusions. Computed tomography provides information about whether the MPE is loculated, the status of the primary disease, and the anatomy of other organs within the thorax. Pleural thickening, atelectasis in the parenchyma, solitary or multiple nodules, hilar or mediastinal lymphadenopathy, lymphangiitis carcinomatosis, lytic or sclerotic lesions on the ribs, and pericardial effusion can be observed (4). Positron emission tomography (PET–CT) is frequently used to detect metastatic findings in other organs (5).

Malignant pleural effusions are almost always exudate. There is usually lymphocyte predominance. Protein concentration is around 4 g/dl and can vary between 1.5 and 8.0 g/dl. Malignant effusions can be serous, serosanginous or hemorrhagic. The average erythrocyte count is around 40.000/mm3. An excessively hemorrhagic (>100.000 mm3) effusion should be interpreted in favour of malignancy (6).

Malignant pleural effusions are an indicator of poor prognosis and are the second most common cause of exudative pleural fluid encountered in clinical practice. The aim of MPE management is palliation and relieving symptoms. The treatment approach should remain minimally invasive and avoid repetitive procedures as much as possible. In case of recurrent fluids, repeated thoracentesis, pleurodesis with tube thoracostomy, pleurodesis with a permanent tunnelled catheter, thoracoscopy and video-assisted thoracoscopic surgery (VATS) may be preferred depending on the clinic. In MPE, the recommended method is to choose talc as a sclerosing agent and apply it with VATS (7). Within the scope of this research, we aimed to elucidate whether fluid biochemistry affected the development of recurrence after bleomycin pleurodesis in patients diagnosed with MPE by VATS pleural biopsy and fluid cytology.

MATERIAL AND METHOD

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Ethics committee approval was granted from our institution on 04/06/2024 with protocol number 2024–312, and informed consent was obtained from all participants.

A total of 23 patients who were diagnosed with MPE as a result of VATS pleural biopsy in our institution between January 2018 and June 2023 and underwent pleurodesis with bleomycin were enrolled in the study. Among 200 patients whose pleural effusion was determined to be exudate by thoracentesis and who underwent VATS biopsy between these dates, 23 patients who were diagnosed with MPE due to primary lung carcinoma and pleural metastasis and developed pleurodesis with Bleomycin were included in the study (**Figure 1, Figure 2**). Recurrence was defined as the detection of pleural effusion on the chest X-ray taken during the first-month outpatient follow-up after the chest tube was removed in patients who underwent pleurodesis with bleomycin, specifically if the effusion was detected on the same side (**Figure 3**).

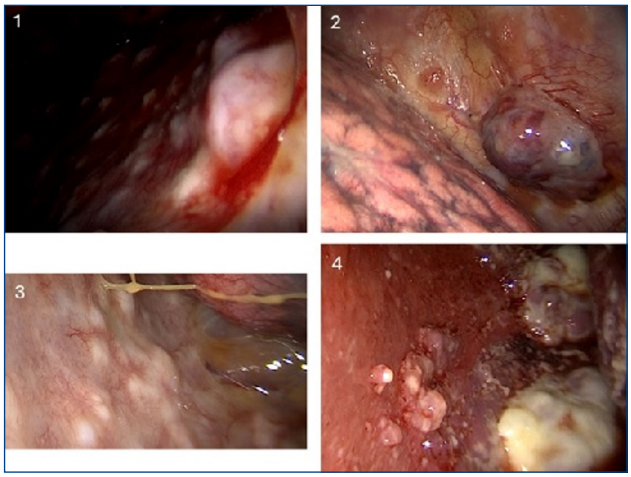

Figure 1: (1) Adenocarcinoma in the parietal plavra , (2) Adenocarcinoma nodüle in the parietal pleura, (3) Adenocarcinoma in the parietal pleura, (4) Adenocarcinoma sarcomatoid type in te parietal pleura

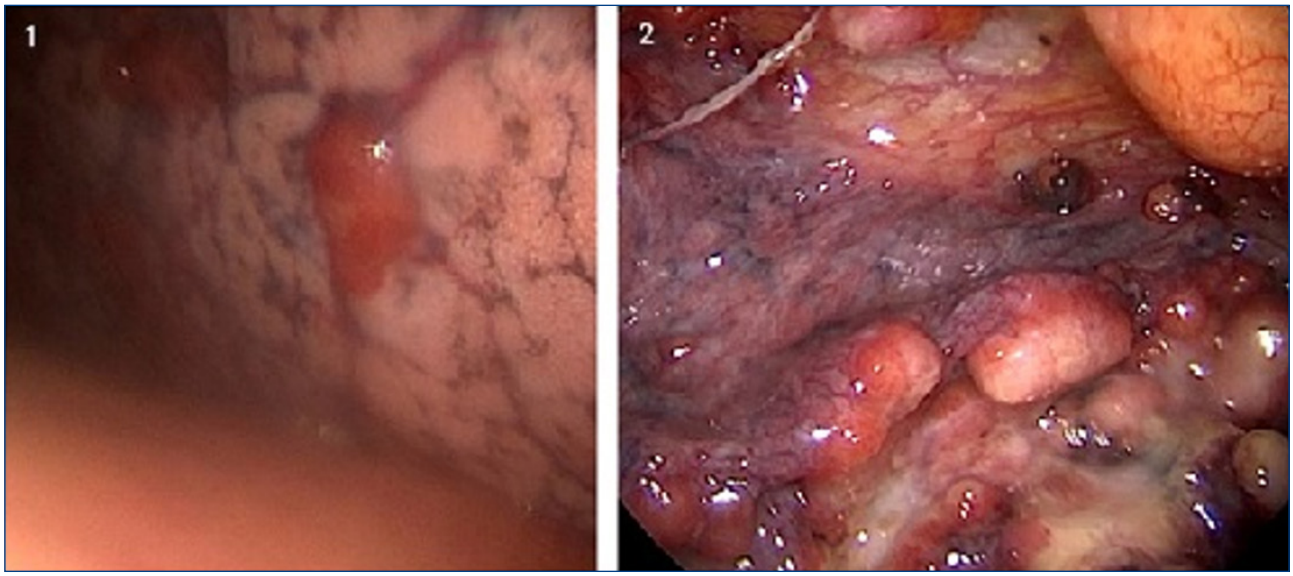

Figure 2: (1) Renal cell carcinoma of the visceral pleura, (2) Renal cell carcinoma metastasis in the parietal pleura

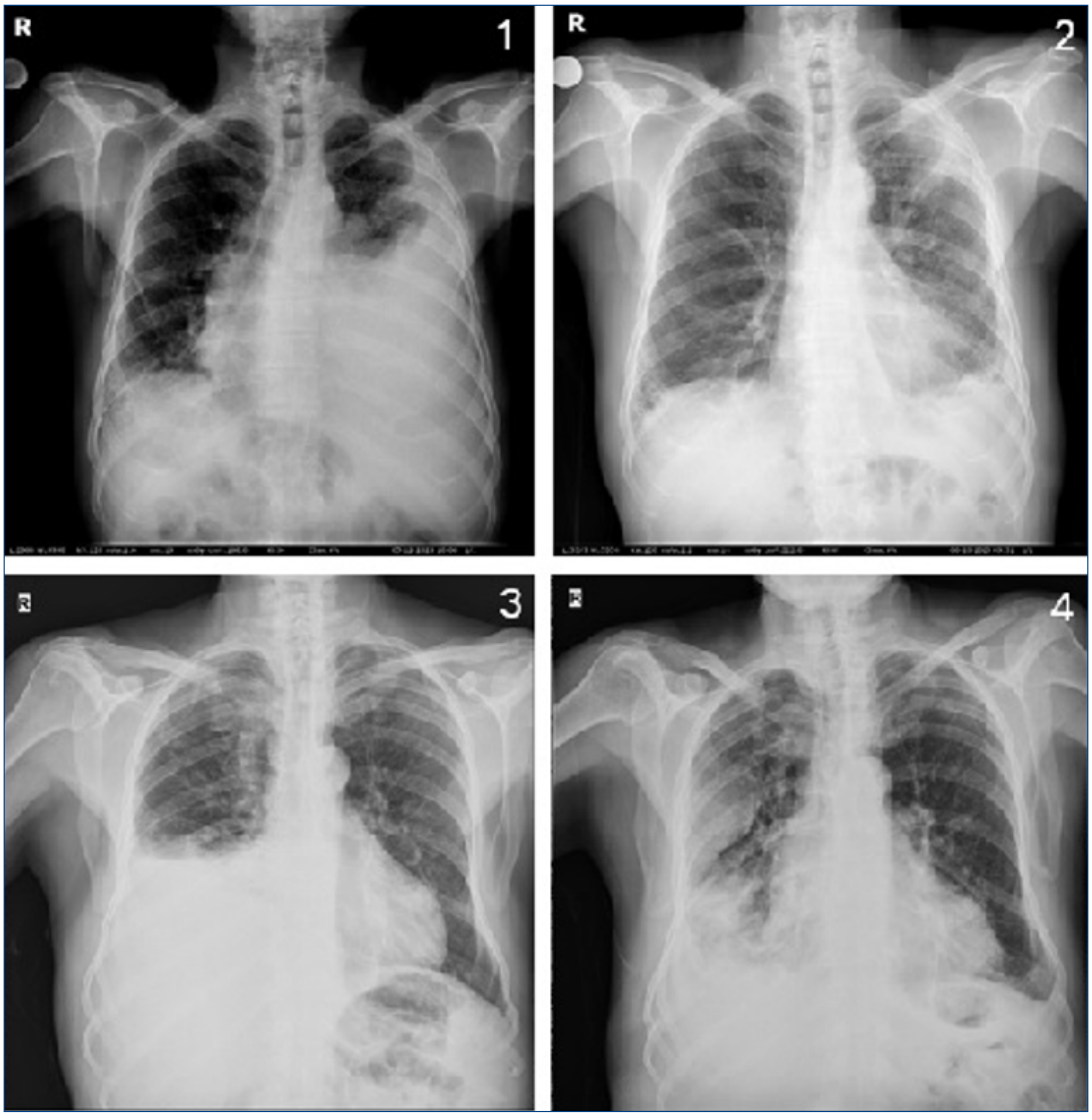

Figure 3: (1) The pre-operative X-ray of a 74-year-old male adenocarcinoma patient, (2) The post-operative X-ray of a 74-year-old male adenocarcinoma patient, (3) The pre-operative X-ray of a 75-year-old male renal cell carcinoma, (4) The post-operative X-ray of a 75-year-old male renal cell carcinoma patient,

Mesotheliomas and benign effusions were excluded from the study. All patients had unilateral fluid. All patients underwent thoracentesis before the operation. VATS pleura biopsy pathologies, fluid cytology, biochemistry results of fluids, and patient information were examined retrospectively.

Statistical Analysis

Patient data collected within the scope of the study were analysed with the IBM Statistical Package for the Social Sciences (SPSS) for Windows 29.0 (IBM Corp., Armonk, NY) package program. Frequency and percentage for categorical data and mean and standard deviation for continuous data were given as descriptive values. For comparisons between groups, the "Independent Sample T-test" was used for two groups, and the "Pearson Chi-Square Test" was used to compare categorical variables. Binary Logistic Regression Analysis (BLRA) examined independent risk factors. The results were considered statistically significant when the p-value was less than 0.05.

RESULTS

Risk factors affecting recurrence were examined with Binary Logistic Regression Analysis. When the model was examined univariately, variables such as age, thoracentesis (T)-LDH, T-Ph, T-Protein, T-Glucose, T-Albumin, and number of days of follow-up with drains, gender, localisation, and type of anaesthesia were not found as statistical risk factors on recurrence (p>0.050).

The mean age of those with recurrence was 52.5, the mean T-LDH value was 569.75 U/L, the mean T-PH value was 7.5, the mean T-protein value was 4.53 g/dL, the mean T-glucose value was 81 mg/dL, the mean T-albumin value was 3.13 g/dL, and the mean number of days we monitored with drains was found to be 10.5 (**Table 1**).

Table 1. Investigation of risk factors affecting recurrence by Binary Logistic Regression Analysis

	Recurrent effusion		Univariate	
	No	Yes	OR (95% CI)	p-value
Age	62.68±12.72	52.5±6.25	0.897 (0.767-1.048)	0.172
T-LDH	879.11±919.78	569.75±137.11	0.999 (0.997-1.001)	0.514
T-PH	8±0.29	7.5±0.5	0.015 (0-3.46)	0.130
T-Protein	4.31±0.93	4.53±0.6	1.33 (0.384-4.613)	0.653
T-Glucose	111.59±95.73	81±12.99	0.995 (0.978-1.011)	0.519
T-Albumin	2.71±0.82	3.13±0.32	2.055 (0.402-10.511)	0.387
Drain day	9.26±6.16	10.5±4.36	1.035 (0.87-1.232)	0.695
Gender				
Male	12 (80)	3 (20)	1.75 (0.151-20.231)	0.654
Female	7 (87.5)	1 (12.5)	Reference	
Localization				
Right	12 (80)	3 (20)	1.75 (0.151-20.231)	0.654
Left	7 (87.5)	1 (12.5)	Reference	
Primary diagnosis				
Pulmonary adenocarcinoma	6 (66.7)	3 (33.3)	---	---
Squamous cell lung cancer	1 (100)	0 (0)	---	---
Small cell lung cancer	1 (100)	0 (0)	---	---
Breast cancer	2 (100)	0 (0)	---	---
Renal cell carcinoma	1 (100)	0 (0)	---	---
Tubal serous carcinoma	0 (0)	1 (100)	---	---
None	8 (100)	0 (0)	---	---
Adenocarcinoma	0 (0)	1 (100)	---	---
Pre-operative diagnosis				
Adenocarcinoma	6 (75)	2 (25)	---	---
Small cell lung cancer	1 (100)	0 (0)	---	---
Malignity	1 (100)	0 (0)	---	---
Breast cancer	2 (100)	0 (0)	---	---
Renal cell carcinoma	1 (100)	0 (0)	---	---
Squamos cell lung cancer	1 (100)	0 (0)	---	---
Tubal serous carcinoma				
None				
Post-operative diagnosis				
Adenocarcinoma	0 (0)	1 (100)	---	---
Adenocarcinoma metastasis	1 (100)	0 (0)	---	---
Pulmonary adenocarcinoma	6 (75)	2 (25)	---	---
Pulmonary adenocarcinoma infiltration	4 (80)	1 (20)	---	---
Squamos cell lung cancer	1 (100)	0 (0)	---	---
Small cell lung cancer	4 (100)	0 (0)	---	---
Breast cancer metastasis	1 (100)	0 (0)	---	---
Metastasis	1 (100)	0 (0)	---	---
Renal cell carcinoma metastasis	1 (100)	0 (0)	---	---
Pleurodesis				
Bleomycine	19 (82.6)	4 (17.4)	---	---
Anesthesia				
General anesthesia	9 (75)	3 (25)	3.333 (0.292-38.082)	0.333
Local anesthesia	10 (90.9)	1 (9.1)	Reference	

The recurrence rate in men was 20% and 12.5% in women. While the recurrence rate was 20% on the right side and 12.5% on the left. The recurrence rate in patients whose primary diagnosis was pulmonary adenocarcinoma in 33.3% of the cases. The recurrence rate in patients who underwent pleurodesis with bleomycin was 17.4%. The recurrence rate was 25% in those with general anesthesia (GA) as the type of anesthesia applied. This rate was 9.1% in those with local anesthesia (LA) (**Table 1**).

DISCUSSION

Medical thoracoscopy and video-assisted thoracoscopic surgery enabled a large pleural surface area to be evaluated and large tissue samples to be taken. In addition to having high diagnostic value, they provide the opportunity to perform diagnosis, drainage and pleurodesis in a single procedure. Diagnostic success in malignant pleural effusions with thoracoscopy is over 90%, sensitivity is 100%, and operative mortality is below 0.5% (8). VATS has increasingly replaced thoracotomy. The effectiveness of VATS in the diagnosis and management of malignant pleural effusions has been emphasized once again in this study. The minimally invasive nature of VATS, along with its advantages of shortening hospital stay and reducing postoperative pain, contributes to improving quality of life in the treatment of malignant pleural effusions.

VATS biopsy and pleurodesis are typically performed under general anesthesia using double-lumen intubation. However, these procedures can also be carried out with single-lumen intubation or under sedation with local anesthesia, depending on the patient's condition and the surgeon's preference (9). In the study, we made the procedure more feasible for patients by applying local anesthesia to those who were not suitable for general anesthesia. As a result, the recurrence rate of 25% in patients who received general anesthesia suggests that local anesthesia should be preferred as a less invasive option in the treatment of MPE. According to the results of our study, we found that local anesthesia can increase the success of pleurodesis with a lower risk of complications. Therefore, this information will be important in clinical practice.

In the multicenter Cancer and Leukemia Group B (CALGB) study, VATS was 82% successful after 30 days of follow-up in patients with over 90% lung expansion, while the success rate of talc administered as a slurry via tube remained at 67%. In addition to providing tissue diagnosis, VATS increases success in sclerosis by removing adhesions and loculations and visualising the pleural surfaces (10). On the other hand, in the study of Yim et al. (11), no significant difference was found between the two techniques. Publications stating that the patient's manoeuvres/rotations (lateral decubitus, prone, supine and reverse lateral decubitus positions) to ensure a uniform distribution after talc is given in the form of slurry do not change the result and are not recommended (12).

Surgical options such as video-assisted thoracoscopic partial pleurectomy were compared to 'physician-performed' talc pleurodesis in the MesoVATS study (n=175 mesothelioma patients). VATS was associated with longer hospital stays, was more expensive and associated with more complications without any difference in fluid control or quality of life. There is insufficient evidence as to whether surgical pleurodesis or decortication is better than talc slurry pleurodesis, and it suggests that, in selected patients considered fit enough for both modalities and where accessibility is not a barrier, both techniques should be discussed to individualize treatment choice (13).

Although the exact mechanism of action is unknown, chemical pleurodesis is understood to generate an inflammatory reaction leading to fibrosis and symphysis between the parietal and visceral pleural layers. Elayouty et al. (14) mentioned in their comparative study that bleomycin resulted in effective pleurodesis in (89%). Mesothelial cells are the main structural axis of pleurodesis. Another important factor involved in angiogenesis is VEGF. This inflammatory mediator is secreted by a wide range of cells in the pleural cavity, including mesothelium, inflammatory and cancer cells (15). Vascular endothelial growth factor is released during inflammatory pleural processes. Higher VEGF concentrations have been observed in complicated pleural effusions and pleural empyema. Pleural thickening, low pH and glucose levels correlate with VEGF secretion into the pleural cavity (18). There is no data on pH's influence on VEGF production (16). In our study, the recurrence rate in patients who underwent pleurodesis with bleomycin was found to be 17.4%, which is consistent with the rates reported in the literature and supports the efficacy of this agent.

Factors associated with decreased survival in patients newly diagnosed with MPE include low pleural fluid (PF) pH, low pleural fluid glucose, high pleural fluid neutrophil count, elevated lactate dehydrogenase (LDH), a high serum neutrophil-to-lymphocyte ratio, primary malignant cell type, and poor performance scores (therefore indicating worse functional status) (17,18). Prognostic scores based on readily available clinical testing can help guide clinical decisions in the treatment of MPE. Both the LENT (lactate dehydrogenase, ECOG, neutrophil-to-lymphocyte ratio, and tumour type) and PROMISE scoring systems have been validated as risk stratification scores to predict survival and help guide clinicians in the care of patients diagnosed with MPE (19,20).

As reported previously, MPE with neutrophilic inflammation (elevated neutrophil percent of cell count, LDH, and total protein) found within the pleural space may be associated with decreased survival after index thoracentesis. In contrast, PF lymphocytosis is associated with improved survival (21). Neither neutrophil nor lymphocyte counts remained significantly associated with survival in multivariate regression modelling. These findings are consistent with studies evaluating the serum neutrophil to lymphocyte ratio, in which patients with MPE and a higher neutrophilic ratio had decreased survival (22). Conversely, improvement in survival reported in MPE patients with high PF lymphocyte count is thought to be the exact mechanism behind the improvement in survival in patients with elevated tumour-infiltrating lymphocytes (23). In our study, age, thoracentesis (T)-LDH, T-Ph, T-Protein, T-Glucose, T-Albumin, and number of days of follow-up with drains, gender, localisation, and type of anaesthesia were not found as statistical risk factors on recurrence.

One of the limitations of this study is the relatively small sample size. Additionally, the lack of long-term outcome evaluation has resulted in a gap in data regarding the quality of life of patients following pleurodesis. In future studies, larger sample sizes and long-term outcome assessments will contribute to determining the best approach for the treatment of malignant pleural effusion.

In conclusion, VATS and bleomycin pleurodesis are proven, reliable, and accessible methods in the treatment of malignant pleural effusion. However, treatment should be tailored to each patient, taking into account factors such as quality of life and length of hospital stay. Our study emphasizes the need for patient-specific decisions in determining the methods to be used in MPE treatment.

CONCLUSION

This study highlights the effectiveness of VATS and bleomycin pleurodesis in the management of malignant pleural effusion (MPE). Our findings demonstrate that these methods are reliable, with low recurrence rates, especially when local anesthesia is used as a less invasive alternative for patients unsuitable for general anesthesia. The results also suggest that tailoring treatment plans to individual patient needs, with a focus on improving quality of life and reducing hospital stay, is essential. Future studies with larger sample sizes and long-term follow-up are necessary to further refine treatment strategies and optimize outcomes in MPE management.

Abbreviations

BLRA: Binary Logistic Regression Analysis, **CALGB**: Cancer and Leukemia Group B Study, **CT**: computed tomography, **GA**: general anaesthesia, **LA**: local anesthesia, **LDH**: lactate dehydrogenase, MPE: malignant pleural effusions, SCLC: small cell lung cancer, **PET–CT**: positron emission tomography, **PF**: pleural fluid, **RCC**: renal cell carcinoma, **SPSS**: Statistical Package for the Social Sciences, **VATS**: video-assisted thoracoscopic surgery

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethical approval for the study was obtained from Selçuk University Local Ethics Committee (Date: 04/06/2024 Decision No: 2024-312).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

AI Statement: The authors used AI and AI-assisted Technologies (Grammarly and MS Word Editor) in the writing process. These technologies improved the readability and language of the work. Still, they did not replace key authoring tasks such as producing scientific or medical insights, drawing scientific conclusions, or providing clinical recommendations. The authors are ultimately responsible and accountable for the contents of the whole work.

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