in vivo *35*: 2391-2398 (2021)
doi:10.21873/invivo.12516

Systemic Inflammatory Response to Different Sclerosing Agents as a Predictor of Pleurodesis Outcome

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Abstract. *Background/Aim: The objectives of this study were to evaluate systemic inflammation using different sclerosing agents and to estimate the prediction of systemic inflammation for the efficacy of pleurodesis. Patients and Methods: Ninety-six patients with recurrent and symptomatic malignant pleural effusion were enrolled in this retrospective study. We used serum C-reactive protein (CRP) levels, serum leukocyte counts and neutrophil-to-lymphocyte ratios (NLRs) as parameters of systemic inflammatory reactions. Evaluations of these parameters were performed before and 24 h after pleurodesis. Results: Pleurodesis was successful in 81 (84.4%) patients. The non-graded talc induced the highest changes in serum CRP levels, total white blood cell and neutrophil counts compared to other agents, while mitoxantrone induced the lowest. Graded talc and bleomycin induced the same levels of changes in serum CRP levels and serum leukocyte counts. The change in serum NLR was the same for all agent groups. Logistic regression confirmed that a change in serum CRP levels [odds ratio (OR)=0.92, p=0.002] and previous chemotherapy (OR=3.31, p=0.012) were independent predictors of pleurodesis efficacy. Conclusion: Pleurodesis agents induced a systemic inflammatory response at different levels. The change in serum CRP levels could be useful for predicting the success of pleurodesis.*

Approximately half of all patients with metastatic cancer develop malignant pleural effusion (MPE), which is likely to lead to a significant reduction in their quality of life, secondary to symptoms such as dyspnoea and cough (1). The main goals of MPE treatment are to decrease symptoms and improve quality of life (2). Pleurodesis with chemical agents is the most commonly used treatment for MPE (3). Talc is the most frequently used sclerosing agent (4). Nevertheless, talc pleurodesis can manifest some severe complications, such as hypoxia and acute respiratory distress syndrome (5-9). These complications are less frequent after the use of talc with large particles (10-13). Other agents, such as tetracycline derivates, silver nitrate, povidone-iodine, mitoxantrone, doxycycline and bleomycin have also been used, with variable efficacy and safety (14). The search for the most effective and safe agent for chemical pleurodesis is ongoing (15).

Pleurodesis involves the induction of acute pleural inflammation, which, if sufficiently intense, progresses to pleural fibrosis that obliterates the pleural cavity and prevents the reaccumulation of fluid (16). The inflammatory mechanisms involved in this process are not yet fully understood. The manifested inflammatory reaction can be divided into a systemic and local response. The intensity of inflammatory activity in the pleural cavity may predict the efficacy of pleurodesis (17). However, there is a lack of research comparing systemic inflammation induced by different sclerosing agents.

The objectives of this study were to evaluate the systemic inflammation induced by different sclerosing agents in patients with MPE and to predict systemic inflammation in order to determine pleurodesis efficacy.

Patients and Methods

Study population. A total of 96 consecutive patients who underwent chemical pleurodesis for recurrent and symptomatic MPE in our department from January 2014 to July 2020 were retrospectively selected. Patients with trapped lung, loculated pleural effusion or active pleural or systemic infection were excluded from the study.

All methods were carried out in accordance with the Declaration of Helsinki. The study was approved by the Vilnius Regional Biomedical

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Key Words: malignant pleural effusion, pleurodesis, systemic inflammation, predictive factor.

Table I. *Characteristics of the patients according to pleurodesis agents.*

Characteristics	Non-graded talc (N=30)	Graded talc (N=26)	Bleomycin (N=24)	Mitoxantrone (N=16)	*p*-Value
Age, years	64.5±10.2	68.4±5.5	64.5±14.9	67.0±8.1	0.437
Gender, %					0.271
Male	40.0	53.8	50.0	25.0	
Female	60.0	46.2	50.0	75.0	
Primary cancer, %					0.167
Lung	40.0	43.8	50.0	43.8	
Breast	20.0	13.9	8.3	12.5	
Others	40.0	42.3	41.7	43.7	
LENT score categories, %					0.064
Low or moderate risk	30.7	28.6	21.4	19.3	
High risk	20.0	25.0	30.0	25.0	
Previous chemotherapy, %	86.7	53.8	75.0	62.5	0.056
Previous thoracentesis, number	1.5±1.9	1.2±0.7	1.6±1.3	1.9±1.7	0.491
Total amount of PF, litres	3.7±2.0	3.2±1.1	3.3±2.4	3.9±1.6	0.547
Positive PF cytology, %	71.4	69.2	83.3	62.5	0.501
CRP level, mg/l	24.0±22.7	36.4±38.4	40.1±30.4	33.6±31.4	0.263
WBC count, per mm^3	7.1±3.1	6.6±1.9	7.1±2.9	6.8±2.9	0.944
Neutrophil count, per mm^3	5.0±2.7	4.5±1.6	5.0±2.9	5.1±2.8	0.860
Lymphocyte count, per mm^3	1.3±0.5	1.2±0.6	1.2±0.4	0.9±0.3	0.062
Monocyte count, per mm^3	0.6±0.2	0.7±0.2	0.6±0.3	0.6±0.2	0.146
NLR	4.1±2.5	4.3±2.4	4.7±3.1	7.7±9.2	0.059
Efficacy of pleurodesis, %	93.3	88.5	88.3	62.5	**0.046**
Side effects of pleurodesis, %					
Oxygen desaturation or respiratory failure	6.7	3.8	4.2	0.0	0.094
Fever	32.1	28.6	26.8	25.9	0.267
Chest pain	22.5	20.2	19.8	21.4	0.462

Data are presented as the means±standard deviation (%) or number (%). Significant values are shown in bold. PF, Pleural fluid; CRP, C reactive protein; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio.

Ethics Committee (no. 158200-13-652-210), Vilnius, Lithuania. Written informed consent for participation was obtained from each patient.

Data collection. Data relating to demographic characteristics, pleural fluid parameters and blood sample evaluations were obtained from the medical records. Performance status (PS) was estimated using the Eastern Cooperative Oncology Group (ECOG) scale (18). The prognosis of patients was determined using the LENT (pleural fluid lactate dehydrogenase, ECOG PS score, neutrophil-to-lymphocyte ratio and tumour type) scoring system (19). We used serum C-reactive protein (CRP) levels, white blood cell (WBC) counts, neutrophil, lymphocyte counts, monocyte counts and the neutrophil-to-lymphocyte ratio (NLR) as surrogate markers for systemic inflammation. Serum leukocyte and CRP evaluations were performed immediately before and 24 h after pleurodesis. The efficacy of pleurodesis was evaluated 30 days after the procedure according to Paladine's criteria (20) as follows: complete response (no pleural effusion detected); partial response (minimal pleural fluid detected without the need for repeat thoracentesis or drainage); no response (reaccumulation of pleural fluid causing symptoms or requiring additional pleural procedures). Complete and partial responses were defined as successful pleurodesis.

Pleurodesis technique. A dose of 5 grams of sterile, non-graded talc (Gintarine vaistine, Lithuania), 60 mg of bleomycin (Medac, Germany) or 40 mg of mitoxantrone (Baxter, Germany) in 100 ml of normal saline was instilled after pleural drainage. A dose of 4 grams of sterile, graded talc (Steritalc® F4, Novatech, France) was applied thoracoscopically (poudrage). A chest tube (24F) was clamped for 4 hours and only afterwards connected to the gravity drainage. The drainage systems were removed when the daily pleural fluid drainage volume was less than 100 ml.

Statistical analysis. Chi-squared test, Fisher's exact test, and one-way analysis of variance (ANOVA) followed by the *post hoc* least significant difference (LSD) test were used for comparison between the pleurodesis treatment groups. Binary logistic regression analysis was performed to determine which independent factors had a significant impact on the success of pleurodesis. Receiver operating characteristic (ROC) curve analysis was used to estimate the sensitivity and specificity of the parameters and cut-off value. A p-Value <0.05 was defined as statistically significant. The data were analyzed using SPSS version 21.0 (IBM Corp., Armonk, NY, USA).

Results

Basic characteristics of the study population. Forty-two (43.7%) patients were male and 54 (56.3%) were female.

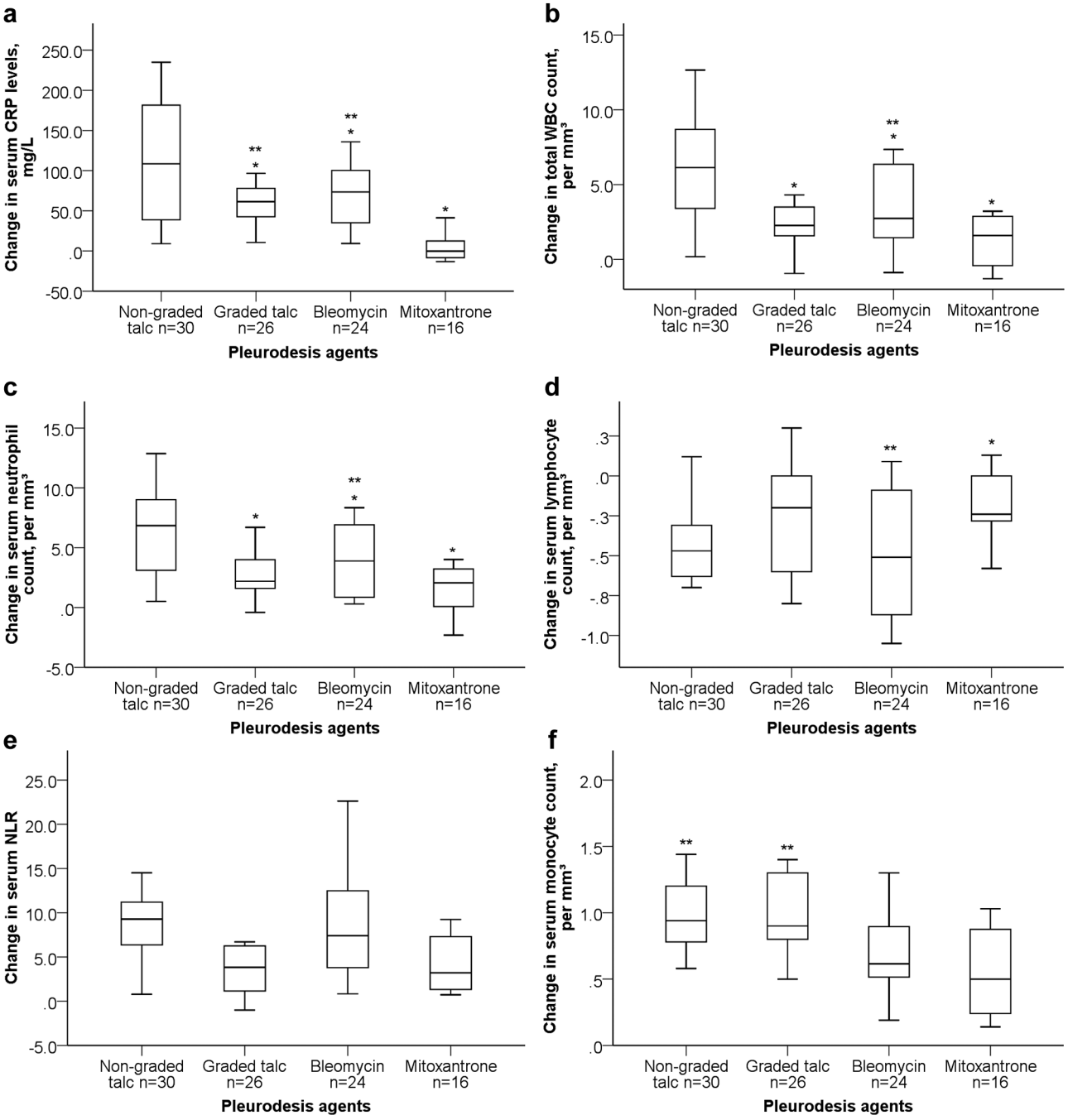

Figure 1. *Changes in serum CRP level. (a), total WBC count (b), neutrophil count (c), lymphocyte count (d), monocyte count (e) and the NLR (f) 24 h after pleurodesis. Data are shown as the minimum, maximum, median, and first and third quartiles. Significant differences of p<0.05 vs. *Non-graded talc, **Mitoxantrone. CRP, C reactive protein; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio.*

The median patient age was 64 years (ranging from 44 to 85 years). The characteristics of the population according to pleurodesis agents are shown in Table I. The majority (87.5%) of patients had LENT scores ≤2 (low or moderate risk), and just over half (54.2%) of the patients had an ECOG PS of 2-3. The primary cancers were lung cancer (41.7%), breast (13.5%), ovarian (10.4%), gastrointestinal (8.4%), lymphoma (8.3%), kidney (6.3%), uterus (2.1%), and others (9.4%). No one had malignant mesothelioma. The results of the pleural fluid cell block were positive in 72.3%

Table II. *Patient characteristics according to the efficacy of pleurodesis at 30 days.*

Characteristics	Successfull pleurodesis (N=81)	Failed pleurodesis (N=15)	*p*-Value
Age, years	66.1±10.1	65.2±11.5	0.766
Gender, %			0.051
Male	48.1	20.0	
Female	51.9	80.0	
Primary cancer			0.586
Lung	84.4	15.6	
Breast	92.9	7.1	
Others	81.1	18.9	
LENT score categories, %			0.090
Low or moderate risk	90.1	73.3	
High risk	9.9	26.7	
Previous chemotherapy, %	75.3	46.7	0.053
Previous thoracentesis, number	1.4±1.4	1.8±1.6	0.308
Total amount of PF, liters	3.4±1.6	3.8±2.5	0.456
Positive PF cytology, %	73.4	66.7	0.753

Data are presented as the means±standard deviation (%) or number (%). PF, Pleural fluid.

Table III. *Patient characteristics according to the efficacy of pleurodesis at 30 days.*

Characteristics	Successfull pleurodesis (N=81)	Failed pleurodesis (N=15)	*p*-Value
CRP at baseline, mg/dl	32.1±30.4	37.7±34.7	0.564
CRP 24 h after pleurodesis, mg/dl	120.5±72.4	50.6±51.4	**<0.001**
CRP change, mg/dl	79.7±55.8	12.8±16.1	**<0.001**
WBC count at baseline, per mm^3	6.5±2.6	8.7±2.7	0.090
WBC count 24 h after pleurodesis, per mm^3	10.5±4.7	10.8±3.5	0.760
WBC count change, per mm^3	3.9±3.4	2.1±2.8	**0.040**
Neutrophil count at baseline, per mm^3	4.5±2.3	6.8±2.7	0.060
Neutrophil count 24 h after pleurodesis, per mm^3	8.6±4.3	9.1±3.3	0.616
Neutrophil count change, per mm^3	4.1±3.5	2.3±2.7	0.057
Lymphocyte count at baseline, per mm^3	1.2±0.5	1.1±0.3	0.174
Lymphocyte count 24 h after pleurodesis, per mm^3	0.9±0.4	0.9±0.3	0.832
Lymphocyte count change, per mm^3	–0.3±0.3	–0.2±0.3	0.226
Monocyte count at baseline, per mm^3	0.6±0.2	0.6±0.2	0.432
Monocyte count 24 h after pleurodesis, per mm^3	0.8±0.4	0.7±0.5	0.833
Monocyte count change, per mm^3	0.2±0.4	0.1±0.3	0.260
NLR at baseline	4.6±4.8	6.6±2.7	0.120
NLR 24 h after pleurodesis	11.0±6.3	11.0±3.7	0.997
NLR change	6.3±7.1	4.5±3.1	0.371

Data are presented as the means±standard deviation (%) or number (%). Significant values are shown in bold. CRP, C reactive protein; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio.

of cases. All other cases of malignant pleural effusion were diagnosed via pleural biopsy.

The efficacy and side effects of pleurodesis. Pleurodesis was successful (39.6% and 44.8% for complete and partial responses, respectively) in 81 (84.4%) patients. Talc was the most effective (91.1%, p=0.046) agent compared to other sclerosing agents (bleomycin 88.3% and mitoxantrone 62.5%). The difference in the response rates of non-graded talc and graded talc was nonsignificant (93.3% *vs*. 88.5%). We found no significant differences in the incidence of fever, chest pain, oxygen desaturation or respiratory failure between pleurodesis agents. In addition, pleural empyema, wound infection or death were not reported in any patients.

Systemic inflammatory response. The changes in serum CRP levels, total WBC, neutrophil and lymphocyte counts, monocyte counts and the neutrophil-to-lymphocyte ratio at 24 h after pleurodesis are presented in Figure 1.

The non-graded talc induced the largest changes in serum CRP levels, total WBC and neutrophil counts compared to other agents, while mitoxantrone induced the smallest changes. Graded talc and bleomycin induced changes in serum CRP levels and total WBC, neutrophil, granulocyte, lymphocyte, and monocyte counts to the same extent. The change in serum NLR was the same for all agent groups.

Predictors of pleurodesis success. The characteristics of the patients according to the efficacy of pleurodesis at 30 days are presented in Table II. The serum inflammatory marker dynamics according to the efficacy of pleurodesis at 30 days are presented in Table III. All variables with a p-value of 0.2 or less according to the efficacy of pleurodesis were entered into binary logistic regression analysis (Table IV). The regression model was statistically significant (χ^2=45.7, p<0.001) and correctly predicted 95.5% of cases. Nagelkerke's R^2 statistic was 0.71, which indicates that the regression model is good for predictive analytics. Binary logistic regression confirmed that a change in serum CRP levels [odds ratio (OR)=0.92; 95% confidence interval (CI)=0.88-0.96, p=0.002] and previous chemotherapy (OR=3.31; 95% CI=2.12-4.21, p=0.012) were independent predictors of pleurodesis efficacy. ROC curve analysis revealed that a change in serum CRP levels 24 h after pleurodesis at a cut-off value of 47 mg/L yielded 68.8%

Table IV. *Logistic regression analysis for pleurodesis success.*

Characteristic	OR (95% CI)	*p*-Value
Gender (male *vs*. female)	0.06 (0.01-16.12)	0.328
Previous chemotherapy (yes *vs*. no)	3.31 (2.12-4.21)	**0.012**
LENT score categories (low or moderate risk *vs*. high risk)	0.27 (0.04-1.52)	0.137
CRP 24 h after pleurodesis	0.91 (0.81-1.03)	0.150
CRP change	0.92 (0.88-0.96)	**0.001**
WBC count at baseline	0.03 (0.01-14.09)	0.256
WBC count change	0.03 (0.01-13.61)	0.254
Neutrophil count at baseline	2.11 (1.18-3.77)	**0.011**
Neutrophil count change	1.53 (1.02-2.29)	**0.039**
Lymphocyte count at baseline	0.23 (0.01-2.40)	0.193
NLR at baseline	1.02 (0.91-1.15)	0.724

Significant values are shown in bold. CRP, C reactive protein; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio; CI, confidence interval.

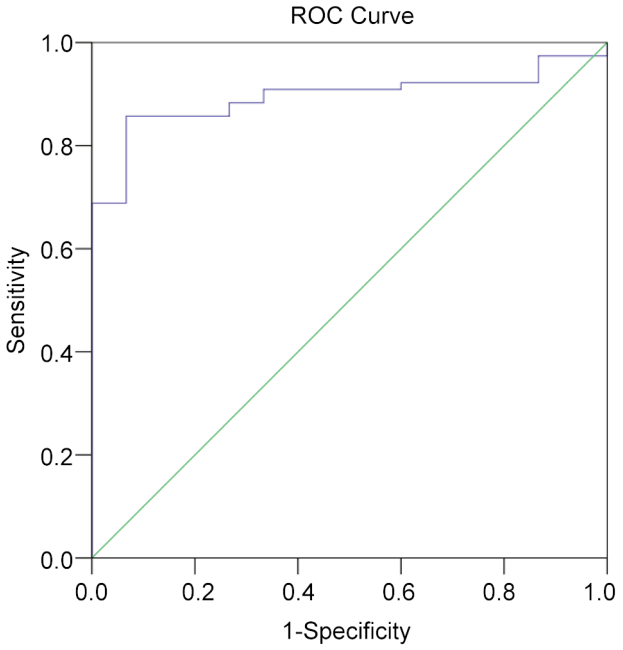

Figure 2. *ROC curve of the relationship between CRP and success of pleurodesis. (AUC=0.89, p=0.002). ROC, Receiver operating characteristic; CRP, C reactive protein; AUC, area under the curve.*

sensitivity and 93.3% specificity in identifying successful pleurodesis (Figure 2).

Discussion

We investigated the systemic inflammatory reaction in patients with MPE following the administration of different chemical agents into the pleura and the predictive factors related to the efficacy of pleurodesis in this study. For pleurodesis to be successful, several conditions have to be considered. A tight and complete apposition between the visceral and parietal pleura is required (21, 22). For these reasons, patients with trapped lungs and loculated effusion were excluded from the study.

Among the various pleurodesis agents currently available, talc is the most commonly used sclerosing agent (23, 24). The efficacy of talc in the control of MPE was found to be superior to that of bleomycin and mitoxantrone in our study. The frequency of successful pleurodesis with the non-graded talc and graded talc was similar, which is in accordance with previous studies (1, 10, 11, 25). We found no significant differences in the incidence of side effects with different agents.

Previous chemotherapy was an independent predictor of pleurodesis efficacy in our study. The statement of the European Respiratory Society (ERS) and the European Association for Cardio-Thoracic Surgery (EACTS) summarises the evidence regarding the management of MPEs. The statement concludes that at present, there is no robust evidence to support the use of oncological therapies as an alternative to standard palliative procedures for MPE management, although further research is required (26).

The intensity of the systemic inflammatory response was quantified by monitoring serum total WBC, the neutrophil, lymphocyte, and monocyte counts, as well as the NLR and CRP levels. Our findings indicate that all pleurodesis agents produced an acute systemic inflammatory response in the first 24 h of the procedure. An increase in total serum WBC, the neutrophil count and CRP levels and a decrease in the lymphocyte count 24 h after pleurodesis were observed. The non-graded talc induced the greatest systemic inflammatory response (the highest changes in serum CRP levels, total WBC and neutrophil counts) compared to other pleurodesis agents. Similar findings have been confirmed by previous studies (6, 10, 25, 27).

It is interesting that graded talc and bleomycin induced the same intensity of systemic inflammation, which was more pronounced than that of mitoxantrone in our study. The precise mechanism of action of bleomycin and other antineoplastic agents is not fully understood. Forty-five percent of an intrapleural dose of bleomycin is absorbed into the systemic circulation (28). Accordingly, it may remain in the pleural space only for a short period. One possible advantage of mitoxantrone over bleomycin is that mitoxantrone binds to the membranes of mesothelial cells and is therefore likely to remain longer in the pleural space (29). However, in contrast to previous studies (30, 31), in the current study, the efficacy of mitoxantrone in controlling MPE was the lowest, compared to other agents. In addition, mitoxantrone induced the lowest systemic

inflammatory response (change in serum CRP level) compared to other agents.

Different studies have addressed the predictors of success of pleurodesis for MPE in different clinical settings (17, 32, 33). However, there have been contradictory results. A meta-analysis of 42 studies demonstrated that the strongest predictors of pleurodesis success were higher pleural fluid pH, smaller volume of effusion before pleurodesis and full lung re-expansion after effusion drainage (34). Higher pleural fluid glucose, lower LDH, lower pleural tumour burden, and shorter duration of tube drainage seem to favour pleurodesis success. However, data from these studies were limited by statistical heterogeneity (34). It is not known how well serum biomarkers correlate with pleural inflammation.

Our data indicate a clear positive correlation between the change in serum CRP levels at 24 h after pleurodesis and the outcome of pleurodesis. The change in serum CRP levels at a cut-off value of 47 mg/L yielded moderate sensitivity and high specificity for successful pleurodesis.

We found only one study that reported similar findings (35). In this study, a post hoc analysis from the TIME 1 trial was undertaken to establish predictors of pleurodesis success. A total of 320 patients with a diagnosis of MPE who underwent pleurodesis were included. Mercer *et al*. (35) concluded that inflammation may be a factor in pleurodesis success, as patients with a greater increase in CRP (mean difference: 19.2 mg/l; 95% CI=6.2-32.0 mg/l, p=0.004) were more likely to have successful pleurodesis. In this study however, only talc was used for pleurodesis. Some patients with unexpandable lungs were also included, which may explain the lower success rate of talc pleurodesis than that observed in our study (81.4% *vs*. 93.3% for non-graded talc and 88.5% for graded talc).

Mercer *et al*. (35) incrementally increased the cut-off value of CRP to assess its potential association with pleurodesis success. Using a CRP cut-off of ≥30 mg/l, 84.7% of patients in the pleurodesis success group met this criterion, compared with 72% in the pleurodesis failure group (χ^2=4.62, p=0.032). Although that study showed a statistically significant difference in the change in CRP between the groups, there was no specific cut-off value that could be used to predict pleurodesis success.

Finding biomarkers that predict pleurodesis success can be clinically useful. Our data support the hypothesis that higher levels of systemic inflammation are associated with pleurodesis success. We found that changes in serum CRP can predict pleurodesis success. We did not determine a CRP cut-off value specific to each pleurodesis agent due to the small group sizes. However, this information could be used to plan future research. An indwelling pleural catheter (IPC) is increasingly used as a therapeutic option in patients with MPE (36). The mechanisms underlying pleural inflammation and spontaneous pleurodesis after IPC placement are poorly understood. The pleural fluid cytokines profile may be associated with the outcome of pleurodesis induced by IPCs (37). Pleurodesis stimulates a massive local rise in many pro-inflammatory cytokines (*e.g*. interleukin-8) (38-40). It is possible that the measurement of these mediators in blood may better reflect the intensity of pleural inflammation and may be associated with the outcome of pleurodesis (16, 40, 41). Another limitation of this study is its retrospective design. Nevertheless, the study population was typical of that seen in everyday practice.

In conclusion, the results of this study demonstrate that pleurodesis agents induce a systemic inflammatory response at different levels. Changes in serum CRP levels at 24 h after pleurodesis could be useful for predicting the success of pleurodesis for patients with MPE. These results should be validated in a prospective study in the future.

Conflicts of Interest

The Authors explicitly state that there are no conflicts of interest in connection with this article.

Authors' Contributions

Rolandas Zablockis designed the study, collected and analysed data, wrote the paper; Edvardas Danila critically reviewed the manuscript; Vygantas Gruslys performed the study and critically reviewed the manuscript; Giedrė Cincilevičiūtė performed the study and critically reviewed the manuscript.

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Received March 22, 2021
Revised April 18, 2021
Accepted April 20, 2021