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The association of defective pleural sRAGE production with the recurrence of malignant pleural effusion after Talc pleurodesis

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Symptomatic malignant pleural effusions (MPE) are treated with chemical pleurodesis to prevent recurrence. The serum soluble receptor for advanced glycation end products (sRAGE) has been linked to lung cancer progression but its role in predicting talc pleurodesis failure is unclear. A prospective cohort study was conducted from November 2023 to December 2024, encompassing subjects with confirmed MPE. Pleural fluid samples were collected prior to intercostal drainage (ICD) insertion for the measurement of sRAGE, ADAM10, MMP9, and HMGB1 levels. Participants were monitored for 90-day post-pleurodesis failure, pleural interventions, and survival. Among seventy-three adults (median age 66 [IQR 53–74 years]) with MPE who received pleurodesis, lung adenocarcinoma was the most common. Talc pleurodesis failure (24.7%) was associated with greater pleural fluid output, multiple pleurodesis attempts, longer ICD retention, and lower pH and lymphocyte fraction. Pleural sRAGE and MMP9 levels were significantly diminished ($p = 0.0033$ and $p = 0.029$, respectively), whereas HMGB1 levels were substantially elevated ($p = 0.019$) in the failure cases. Among biomarkers, pleural sRAGE had the most predictive value for talc pleurodesis failure, followed by HMGB1 and MMP9. However, pleural sRAGE and MMP-9 lacked prognostic significance for 90-day mortality. The present study demonstrated that lower pleural sRAGE is a potential predictive biomarker for talc pleurodesis failure despite inferiority to pleural acidity. Imbalance between sRAGE and HMGB1 in MPE may be associated with the underlying mechanism for talc pleurodesis failure.

Keywords HMGB1, Malignancy, Pleural effusion, sRAGE, Talc pleurodesis

Abbreviations

ADAM10	A disintegrin and metalloproteinase 10
HMGB1	High mobility group box-1 protein
MMP9	Matrix metalloproteinase 9
MPE	Malignant pleural effusion
sRAGE	Soluble receptor for advanced glycation end products

Malignant pleural effusion (MPE) develops in 15% of patients with advanced cancer[1]. The majority of patients with MPE are symptomatic and suffer with high recurrent burden after only intercostal drainage (ICD) without any procedure[2]. However, the recurrent rate can be minimized by talc pleurodesis using talc slurry instillation or thoracoscopic talc insufflation, an effective life prolonging therapy for patients that fit the criteria for this intervention[2–5]. Success rates for talc pleurodesis in randomized studies are 70%–80%, with hospitalization requirement[6,7]. Key failure predictors of talc pleurodesis in patients with malignant pleural effusions are essential for making a prudent decision on the procedure. Clinical evaluation of pleural biochemical parameters and malignant tumour diagnosis may not accurately predict post-pleurodesis relapse[4]. Furthermore, a systematic review and meta-analysis has failed to identify effective independent predictors for talc pleurodesis success due to the quality of the evidence[8]. Whether biomarkers related to MPE-driving biological mechanisms can predict talc pleurodesis failure has yet to be identified.

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High mobility group protein 1 (HMGB1) and the receptor for advanced glycation end products (RAGE) axis play a complex role in tumor biology[9]. After the binding to RAGE on the cell membrane, HMGB1 can induce downstream signaling pathways that regulate various cellular functions, including cell proliferation, apoptosis, metastasis, autophagy, and angiogenesis across different malignant tumour types such as lung cancer[9]. The receptor for advanced glycation end products comprises two isoforms, including membrane-bound RAGE and soluble RAGE (sRAGE)[10]. The formation of sRAGE is regulated by the sheddases ADAM10 and MMP9 which proteolytically cleave membrane-bound RAGE to become sRAGE[10,11]. sRAGE acts as a decoy receptor and sequesters HMGB1, interfering with the HMGB1/RAGE axis. Clinically, elevated HMGB1 expression and downregulated RAGE correlates with higher cancer stages and poor prognosis[12,13]. A systematic review and meta-analysis of observational studies indicate the protective effects of sRAGE against the progression of lung cancer[14,15]. In malignant pleural effusion, the balance between sRAGE and HMGB1 production and its role in predicting talc pleurodesis outcome remains unknown, and requires further investigation.

The present study investigated pleural fluid biomarkers of interest in patients with MPE who underwent talc pleurodesis, determined the differences of individual biomarker concentrations in the success and failure groups, and addressed the best predictor among all biomarkers for talc pleurodesis failure.

Methods

Study design

A prospective cohort study was conducted in patients admitted to Siriraj hospital between November 2023–December 2024 for talc pleurodesis to manage symptomatic MPE. Written informed consent was obtained from all participants prior to the enrolment. The study protocol was approved by The Siriraj Institutional Review Board (SIRB) (reference number Si 302/2023).

Participants

Consecutive participants who aged 18 years or older with clinically suspected MPE that necessitated performing talc pleurodesis for symptom alleviation were invited to participate. Subjects qualified for the inclusion criteria of the study if their MPE had been verified histocytologically through biopsy-proven pleural tissues or by the presence of malignant cells in the pleural effusion. Pleural fluid specimens were obtained from recruited subjects before the installation of a chest tube. Patients with MPE underwent either talc slurry through a chest tube or talc poudrage during medical thoracoscopy. The treating physician determined the use of talc slurry or poudrage based on the clinical indication. Exclusion criteria were contraindication to chest tube placement, individuals with trapped lung, poor prognosis (expected survival less than 1 month as judged by treating physician), and patients with non-MPE or exudative pleural effusion with an unresolved cancer diagnosis. This study had been performed in accordance with the Declaration of Helsinki.

Procedures

The management of MPE adhered to the British Thoracic Society recommendations[2]. In participants undergoing thoracoscopy with talc poudrage, all fluid was evacuated during the endoscopic procedure, and a large-bore tube (> 20 F) introduced following the administration of talc powder (4 g) into the pleural cavity. In some cases, pleurodesis was performed by talc slurry via a chest tube. A dose of 4 g of sterile, asbestos-free talc mixed with 90 ml of sterile saline and 10 ml of lidocaine 1% was instilled through the chest drain, which was clamped for 6 h after the procedure. The tube was removed after a minimum of 24 h, upon radiological confirmation of lung re-expansion, and when tube output was below 250 ml per day. A chest radiograph was performed on all study participants promptly after the removal of the chest tube and was subsequently evaluated by the clinical team. If the radiograph was considered satisfactory and the participant had no other significant medical concerns necessitating hospitalization, they were declared medically fit for discharge.

The occurrence of trapped lung following pleural fluid drainage was characterized by the lack of pleural apposition in over two-thirds of the hemithorax on the post-drainage radiograph. In these circumstances, the choice to perform pleurodesis was entrusted to the judgment of the attending physicians.

Data on the length of ICD insertion, total volume of pleural effusion drainage, frequency of talc administration, and definite cancer treatment were collected from all individuals. Two follow-up trial evaluations were conducted at one month and three months following talc pleurodesis. During each visit, patients were interviewed, and their medical records were reviewed. Data on additional ipsilateral pleural interventions was gathered at 1 and 3 months. All participants completed a healthcare usage log on both visits. Any participant requiring further pleural treatments in the ipsilateral hemithorax to alleviate dyspnea, or who exhibited breathlessness and over 50% ipsilateral opacification on chest X-ray, was classified as experiencing talc pleurodesis failure, as previously delineated in the TIME 1 trial[16]. Mortality status was ascertained by accessing participants' medical records.

Outcomes

The primary outcome was the evaluation of biological determinants of talc pleurodesis failure, specifically the baseline levels of pleural sRAGE, HMGB1, ADAM10, and MMP9. A secondary outcome was the assessment of the predictive accuracy of these biological predictors alongside other clinical parameters and biochemical markers from pleural fluid analysis. Additionally, the study aimed to identify independent predictors of failed pleurodesis and to explore clinical and biological factors influencing all-cause mortality.

Pleural fluid assays

During ICD insertion or pleuroscopy, a minimum of 50 ml of pleural fluid was obtained from each individual using a syringe. In all instances, the pleural fluid pH and the concentrations of various biochemical markers, including glucose, lactic dehydrogenase, and total protein, were systematically assessed. A 2-ml pleural fluid

sample was obtained using a heparinized syringe. The pH of the pleural fluid was assessed within 30 min post-thoracentesis using a blood pH/gas analyzer. Fifty milliliters of pleural fluid were centrifuged to isolate cell pellets from the supernatant. Cell pellets were preserved in 5% DMSO, while supernatants were stored at − 80 °C for subsequent analysis.

The LENT score was computed, comprising serum lactate dehydrogenase (LDH), Eastern Cooperative Oncology Group Performance Status (ECOG-PS), blood neutrophil/lymphocyte ratio, and tumor type. The score varies from 0 to 7. Patients are categorized into low-risk (score 0–1), moderate-risk (scoring 2–4), and high-risk (score 5–7) prognosis categories, corresponding to median survival durations of 319, 130, and 44 days, respectively.

Enzyme-linked immunosorbent assays

Pleural sRAGE (MyBiosource Inc, San Diego, CA), HMGB1 (Antibodies.com, Great Shelford, Cambridge), ADAM10 (LLC, St. Louis, MO) and MMP9 (Proteintech Group Inc, Rosemont, IL) concentrations were measured by sandwich enzyme-linked immunoassay according to the manufacturer's protocols. The sensitivity values for sRAGE, HMGB1, ADAM10, and MMP9 were 18.75 pg/mL, 18.75 pg/mL, 37.5 pg/mL, and 16.6 pg/mL, respectively.

Sample size and statistical analysis

Due to the absence of data regarding the relationship between sRAGE and pleurodesis results, we utilized data on the link between pleural fluid pH and successful pleurodesis for sample size calculations. By establishing the standard normal at 1.96, we determined that a sample of 62 patients would yield a minimum of 80% power (1-β) to identify the disparity in pleural sRAGE levels between the failure and successful groups at a two-sided significance threshold of 0.05. Additionally, taking account of a 15% dropout rate, it was anticipated that 74 patients with MPE should be initially enrolled.

Subject characteristics were delineated using descriptive statistics, encompassing frequencies (percentage) for categorical variables, while continuous variables were reported as median and 25–75% interquartile range (IQR), unless specified otherwise. The primary outcome analysis (pleural sRAGE levels between groups) and all secondary outcomes were conducted using a Mann-Whitney U-test because of deviations from normality. Qualitative factors were analyzed using the Fisher exact test. Correlations between pleural fluid biomarkers were analysed using Kendall's tau correlation coefficient. The ROC curve for the cutoff persistent score and long-term outcomes was shown, including AUC, sensitivity, specificity, PPV, and NPV. The affection parameters and pleurodesis outcomes were summarized using Kaplan-Meier curves and compared by the log-rank test and Cox proportional hazards analysis, reported as hazard ratios (95% confidence interval). Multivariable regression analysis was conducted to assess the risk of confounding factors associated with failed talc pleurodesis, utilizing backward stepwise binary logistic regression. In all conducted tests, a two-tailed P-value of less than 0.05 was deemed indicative of statistical significance. All analyses were conducted using the statistical software IBM SPSS, version 29.0. The CONSORT flow diagram was presented in Fig. 1.

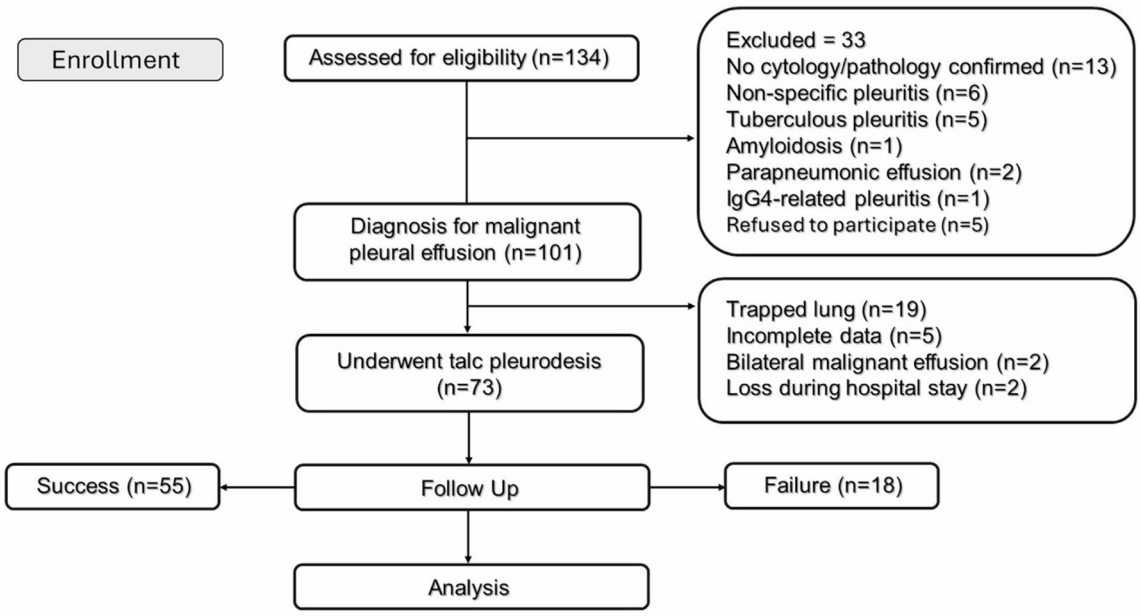

Fig. 1. Flowchart of the inclusion process in this study.

Results

Patient characteristics

A total of 134 patients with clinically suspected MPE were initially enrolled in the study, which took place over a 14-month period from 2023 to 2024. A total of 101 patients had histologically confirmed MPE, determined via pleural cytology or biopsy, 73 were included in the final analysis. The reasons for exclusion are summarized in the flow chart of the study (Fig. 1). Demographic characteristics of the patients are presented in Table 1. Seventy-three eligible patients had a mean age of 66 years (interquartile range [IQR] 53–74) and 50 participants (68.5%) were female. Of all eligible subjects with MPE who underwent talc pleurodesis, 55 (75.3%) responded successfully, while 18 (24.7%) were considered failed responders (Fig. 1). All patients had their primary cancer type specified; 34 patients (46.6%) with lung cancer exhibited adenocarcinoma, and 12 patients (16.4%) had breast cancer. A compendium of the remaining primary cancer types is presented in online supplemental Table S1. Most patients had ECOG-PS of 1 (43.8%) or 2 (28.8%), and most had a LENT score of 3 (35.6%) or 4 (27.4%). Eleven patients (34.3%) had received chemotherapy prior to talc pleurodesis. The success and failure groups were evenly matched for age, body mass index (BMI), various primary cancers, LENT score, ECOG-PS, and talc delivery method. The failure rates of pleurodesis at 1 month were comparable to those at 3 months, being 21.1% and 29%, respectively. The duration until chest tube removal was significantly longer in the failure group compared to the successful group (median duration of 6 days; IQR 3–13 vs. 5 days; IQR 3–6; $p = 0.038$, respectively). Moreover, the failure group had a higher mean (± SD) number of talc pleurodesis (1.4 ± 0.7,

Characteristics	All patients, $N = 73$	Success, $N = 55$	Failure, $N = 18$	P value
Sex, Female (%)	50 (68.5)	36 (65.5)	14 (77.8)	0.393
Age, years	66.0 (53–74)	67.0 (52.5–74.0)	61.5 (54–74)	0.720
Body Weight, kg	55 (48-64.5)	54.3 (48.8–64.1)	59 (48–67)	0.868
Height, cm	158 (150–165)	158 (150–165)	158 (153–165)	1.0
BMI, kg/m^2	23.0 (19.1–24.9)	22.4 (19.1–24.7)	23.3 (19.5–25.8)	0.788
Cancer types				0.277
Lung cancer	34 (46.6)	28 (50.9)	6 (33.3)	
Breast cancer	12 (16.4)	11 (20)	1 (5.6)	
Other solid cancer	24 (32.9)	14 (25.5)	10 (55.6)	
Hematologic	3 (4.1)	2 (3.6)	1 (5.6)	
ECOG PS				0.239
0	4 (5.5)	4 (7.3)	0	
1	32 (43.8)	24 (43.6)	8 (44.4)	
2	21 (28.8)	17 (30.9)	4 (22.2)	
3	13 (17.8)	8 (14.5)	5 (27.8)	
4	3 (4.1)	2 (3.6)	1 (5.6)	
LENT				0.184
1	3 (4.1)	2 (3.6)	1 (5.6)	
2	7 (9.6)	7 (12.7)	0	
3	26 (35.6)	20 (36.4)	6 (33.3)	
4	20 (27.4)	15 (27.3)	5 (27.8)	
5	12 (16.4)	8 (14.5)	4 (22.2)	
6	3 (4.1)	2 (3.6)	1 (5.6)	
7	2 (2.7)	1 (1.8)	1 (5.6)	
Talc delivery method	57 (78.1)	42 (76.4)	15 (83.3)	0.745
Slurry Poundage	16 (21.9)	13 (23.6)	3 (16.7)	
Time of pleurodesis	1.2 ± 0.5	1.1 ± 0.3	1.4 ± 0.7	0.021
Days of ICD	5 (3–7)	5 (3–6)	6 (3–13)	0.038
Pleural fluid release (mL)	2300 (1700–4110)	2200 (1545–3690)	3495 (2470–5470)	0.01
Systemic treatment	48/73 (65.8%)	39/55 (70.9%)	9/18 (50%)	0.105
CMT	32/48 (66.7%)	24/39 (61.5%)	8/9 (88.9%)	
Pre-pleurodesis	11/32 (34.3%)	8/24 (33.3%)	3/8 (37.5%)	
At the time of pleurodesis	21/32 (65.6%)	16/24 (66.7%)	5/8 (62.5%)	
Loss (day)	42 (29–55)	41 (30–59)	49 (30–54)	0.909
Within 30 day	2 (2.7)	2 (3.6)	0	0.155
Within 90 days	20 (27.3)	9 (16.4)	11 (61.1)	< 0.001

Table 1. Patient characteristics in Talc pleurodesis success and failure. Data for continuous and categorical variables are presented as median (interquartile ranges) and numbers (%), respectively. BMI, body mass index; ECOG PS; Eastern Cooperative Oncology Group Performance Score, LENT prognostic score.

$p = 0.021$) and greater pleural fluid outflow than the success pleurodesis counterpart (median fluid volume of 3,495 mL; IQR 2,470-5,470; $p = 0.01$). During the follow-up period, ten patients (55.6%) and eight patients (44.4%) in the failure group required insertion of ICD or thoracentesis for an ipsilateral MPE, respectively. Mortality at 90 days was significantly higher in the failure group compared to the successful group (61.1% vs. 16.4%, $p < 0.001$) (Table 1).

The data regarding EGFR mutations in lung cancer patients revealed that 11 patients (32%) had positive mutations, 15 patients (44%) had negative mutations, and 8 patients (24%) had missing data. Among those with EGFR mutations, nine patients underwent TKI therapy. Furthermore, the subgroup analysis of lung cancer patients with negative EGFR mutations suggested a trend toward the failure of talc pleurodesis ($p = 0.175$).

Pleural fluid biomarkers in successful and failed Talc pleurodesis groups

The pleural fluid pH and lymphocyte percentage were significantly lower in patients who experienced pleurodesis failure compared to those who had successful pleurodesis (median pH of 7; IQR 7-7.5 vs. 7.5; IQR 7.4–7.5; $p < 0.001$ and median percentage of 27.5; IQR 17–48 vs. 42; IQR 23–69; $p = 0.034$, respectively) (Table 2). Pleural fluid levels of sRAGE, ADAM10, MMP9, and HMGB1 were analysed in all the samples (Fig. 2). Pleural sRAGE levels were significantly lower in patients who had unsuccessful pleurodesis compared to those who had successful pleurodesis (median concentration of 651.2; IQR 395.0-805.2 pg/mL versus 1106; IQR 757.6–1584.0 pg/mL) (Fig. 2A, $p = 0.0033$). MMP9 levels were significantly lower in the failure group (median concentration of 7308 pg/mL; IQR 4802–8501 pg/mL versus 8007 pg/mL; IQR 7407–9062 pg/mL) (Fig. 2B, $p = 0.029$), while ADAM10 levels showed only a slight downward trend in the failure group compared to the success group (Fig. 2C, $p = 0.627$). Conversely, HMGB1 levels were markedly higher in the failure group than in the treatment successful group (median level of 738.5 pg/mL; IQR 486.4–2443 pg/mL versus 395.9; IQR 92.2-995.1 pg/mL, Table 2) (Fig. 2D, $p = 0.019$).

We further assessed the predictive effectiveness of these pleural biomarkers in distinguishing between successful and unsuccessful talc pleurodesis. The analysis using the receiver operating characteristic (ROC) curve identified the optimal cutoff for the pleural biomarkers assessed in predicting the failure of talc pleurodesis. A cut-off value of sRAGE below 908 pg/mL was identified as the optimal threshold for differentiation, resulting in a sensitivity of 88.89%, a specificity of 65.45%, and an area under the curve (AUC) of 0.728 (Fig. 3A, $p = 0.0011$). However, the ideal pleural pH threshold of below 7.05, with the AUC of 0.761, a specificity of 100%, and a sensitivity of 66.7%, demonstrated superior prediction accuracy compared to the predictive profile of sRAGE (Fig. 3B, $p = 0.004$). A cut-off value of MMP9 below 7331 pg/mL led to an AUC of 0.672, with a specificity of 78.18% and a sensitivity of 55.56% (Fig. 3C, $p = 0.0208$). The optimal HMGB1 threshold exceeding 544 pg/mL showed a sensitivity of 77.78%, a specificity of 58.18%, and an AUC of 0.683 (Fig. 3D, $p = 0.0088$). The optimal pleural fluid output threshold exceeding 2400 mL showed a sensitivity of 77.8%, a specificity of 61.8%, and an AUC of 0.702 (Fig. 3E, $p = 0.01$). The optimal threshold for a pleural lymphocyte percent of less than 64% demonstrated the lowest predictive efficiency, with a sensitivity of 100%, a specificity of 32.7%, and an AUC of 0.667 (Fig. 3F, $p = 0.017$). Multivariate logistic regression analysis identified pleural pH, sRAGE, HMGB1, absolute lymphocyte counts, and the number of pleurodesis as independent predictors of failed talc pleurodesis (Table 3).

Cellular and biomarker profiles	All patients, $N = 73$	Success, $N = 55$	Failure, $N = 18$	P value
Pleural LDH, U/L	300.0 (212.5–567.0)	294 (212.5–513)	503 (250–979)	0.099
Pleural protein, g/dL	4.8 (4.0-5.3)	4.6 (4–5)	4.5 (4.2–5.3)	0.223
Pleural glucose, mg/dL	99 (83–124)	105 (87–125)	90 (42–115)	0.071
Pleural pH	7.4 (7.3–7.5)	7.5 (7.4–7.5)	7.0 (7-7.5)	< 0.001
Total pleural cell counts	1011 (477–1861)	1011 (580–1935)	994 (470–1583)	0.522
% Pleural neutrophils	4.00 (1–16)	7.5 (2–33)	3 (1-13.5)	0.272
Absolute pleural neutrophil counts	52 (9-208)	35 (8-185)	102 (9-223)	0.420
% Pleural lymphocytes	38 (22–64)	42 (23–69)	27.5 (17–48)	0.034
Absolute pleural lymphocyte counts	361 (140–694)	392 (192–1004)	296 (109–475)	0.077
sRAGE, pg/mL	932.3 (582.0-1521.0)	1106 (757.6–1584.0)	651.2 (395.0-805.2)	0.0033
ADAM10, pg/mL	177.1 (0-987.3)	190.3 (0-1053)	121.8 (0-967.7)	0.627
MMP9, pg/mL	7937 (7147–8979)	8007 (7407–9062)	7308 (4802–8501)	0.029
HMGB1, pg/mL	571.8 (128.6–1492.0)	395.9 (92.2-995.1)	738.5 (486.4–2443)	0.019
Serum LDH, U/L	272 (213–365)	272 (213–353)	267 (212–375)	0.345
Serum Protein, g/dL	7 (6.6–7.5)	7 (6.6–7.6)	7 (6.9-7.0)	0.868
% Peripheral blood neutrophil	71 (66–79)	71 (65–79)	74 (68–82)	0.586
% Peripheral blood lymphocytes	18 (12–29)	19 (14–23)	16 (10–19)	0.384
Peripheral N/L ratio	4.0 (3.0-6.4)	3.9 (2.9–5.8)	4.8 (3.6–8.4)	0.288

Table 2. Pleural fluid profile in Talc pleurodesis success and failure. Data for continuous variables are presented as median (interquartile ranges). Cell counts are expressed as cells/mm^3.

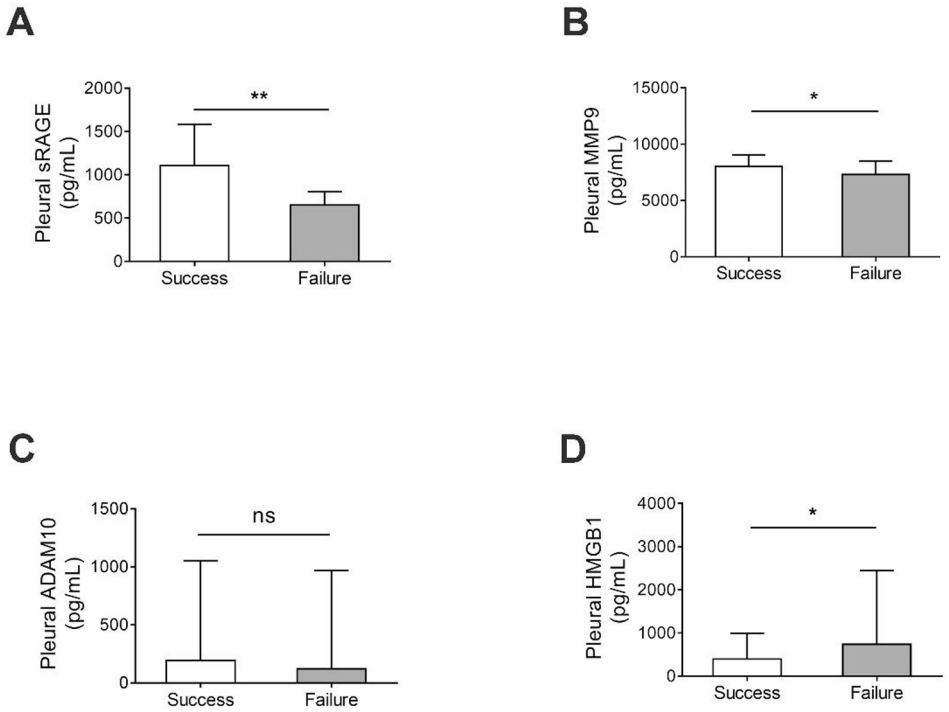

Fig. 2. The comparison of pleural biomarkers in malignant effusions between talc pleurodesis success ($n = 55$) and failure ($n = 18$). The levels of sRAGE (**A**), MMP9 (**B**), ADAM10 (**C**), and HMGB1 (**D**) in both groups were shown. Pleural effusions containing sRAGE, MMP9, and HMGB1 were detectable in all the samples whereas 18 samples of successful pleurodesis and 7 samples of failed pleurodesis were undetectable for ADAM10. Data are shown as median (IQR). $^{*}p \leq 0.05$, $^{**}p \leq 0.01$ as assessed by Mann-Whitney test. Non-significant differences ($p > 0.05$) are stated as ns. *ADAM10* a disintegrin and metalloproteinase 10; *HMGB1* high-mobility group box 1; *MMP9* matrix Metalloproteinase-9; *sRAGE* soluble receptor for advanced glycation end product.

The relationship among mortality, clinical factors, and prognostic biomarkers associated with Talc pleurodesis failure

The mortality rate within 90 days was substantially greater in the pleurodesis failure than success group (61.1% compared to 16.4%, $p < 0.001$). It significantly correlated with poor ECOG-PS, higher LENT prognostic score, increased frequency of pleurodesis, prolonged duration of ICD, and higher levels of pleural protein, peripheral blood neutrophil percentage, and neutrophil-lymphocyte ratio, alongside a reduced percentage of peripheral blood lymphocytes (Tables 4 and 5). Pleural sRAGE and MMP9 levels demonstrated a non-significant negative association with the 90-day mortality rate ($p = 0.083$ and 0.084, respectively). Subgroup analysis revealed that pleural HMGB1 levels were significantly higher in malignancies other than lung adenocarcinoma ($p = 0.034$).

Discussion

This prospective cohort analysis found that 25% of patients with MPE experienced failed talc pleurodesis, which was associated with higher 90-day mortality compared to those who had successful pleurodesis. The group that experienced failed talc pleurodesis exhibited significantly lower levels of pleural sRAGE and MMP9 while showing considerably higher levels of HMGB1 compared to the success group. Additionally, MPE in the failed pleurodesis group had a higher acidity than those in the successful group. Pleural fluid acidity emerged as the most accurate predictor of failed talc pleurodesis, followed by sRAGE, HMGB1, the number of pleurodesis, and absolute lymphocyte counts in the accuracy order. In addition, pleural sRAGE, HMGB1 and MMP-9 lacked prognostic significance in the 90-day mortality.

The effectiveness of talc pleurodesis in this trial was analogous to prior findings[6]. The present study found several laboratory and clinical factors associated with pleurodesis failure, including lower pleural fluid pH, reduced pleural lymphocyte fraction, reduced sRAGE and MMP9 levels, elevated HMGB1, greater fluid output, and prolonged chest tube duration. However, multivariate regression analysis demonstrated that there were only five independent predictors for failed talc pleurodesis including pleural pH, sRAGE, HMGB1, number of pleurodesis, and absolute pleural lymphocyte counts. This data may suggest the presence of pro-tumour-related biological processes that influence the outcomes of pleurodesis.

The failed pleurodesis group had decreased pleural sRAGE levels which resulted in reduced suppression of upregulated HMGB1 pro-tumour effects. The imbalance between sRAGE and HMGB1 expression may be attributed to increased pleural acidity. Prominent pleural acidity may reflect the Warburg effect, which is well-established metabolic hallmark of cancer and characterized by increased glycolysis and lactic acid production despite the presence of oxygen, resulting in a lower pH.[17,18]

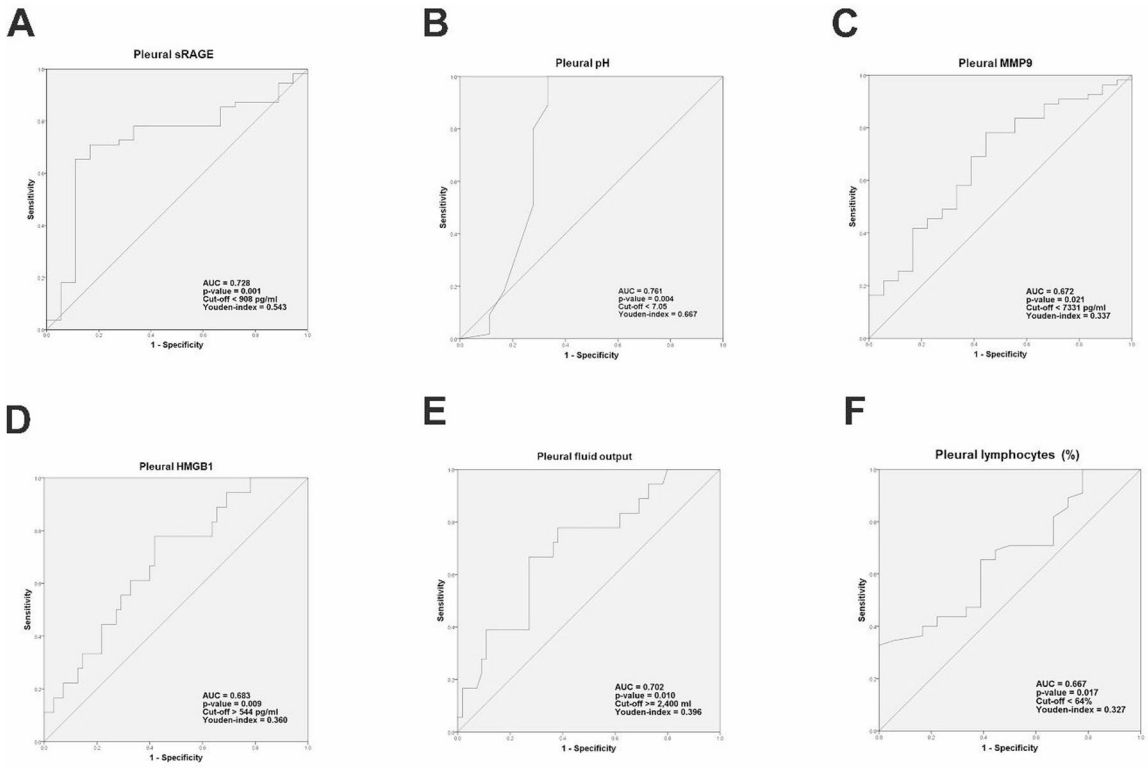

Fig. 3. Predictive analysis for talc pleurodesis failure using ROC curve. The ROC curve evaluated the performance of the predictive model, yielding an AUC of sRAGE (**A**), pH (**B**), MMP9 (**C**), HMGB1 (**D**), Pleural fluid output (**E**), percent of pleura; lymphocytes (**F**) for discrimination. An optimal cutoff values were selected from the highest Youden index to calculate sensitivity and specificity of pleurodesis outcome ($N = 73$).

Predictor	B (Coefficient)	S.E.	Wald	*P* value	OR	95% CI	
						Lower	Upper
Pleural pH	−5.304	1.758	9.005	0.003	0.005	0.000	0.159
Pleural absolute lymphocyte counts	−0.003	0.001	3.804	0.051	0.995	0.995	1.000
Pleural sRAGE	−0.003	0.001	9.044	0.003	0.995	0.995	0.999
Pleural HMGB1	0.001	0.001	6.123	0.013	1.000	1.000	1.002
Number of pleurodesis	2.255	1.072	4.425	0.035	1.157	1.157	77.904

Table 3. Multivariate logistic regression analysis of independent predictors of failed Talc pleurodesis. Backward stepwise binary logistic regression was used for the multivariate analysis.

The reduced levels of sRAGE and MMP9 in the pleurodesis failure group can be attributed to Warburg effects in the pleural fluid microenvironment. Given that pleurodesis failure was associated with lower pleural fluid pH, it is biologically plausible that reduced sRAGE levels are at least partly attributable to the acid microenvironment. The findings were clinically relevant in cases of failed talc pleurodesis, as sRAGE reflected a more acidic pleural microenvironment associated with more advanced disease. Additionally, multivariate regression analysis revealed that sRAGE served as an independent predictor of pleurodesis failure. In this study, although pleural pH demonstrated better predictive accuracy than sRAGE, the clinical significance of sRAGE lies in the fact that one-third of patients with pleural pH above the cut-off point could still benefit from sRAGE measurement.

After adjusting for other variables, including pleural pH, HMGB1 remained independently associated with pleurodesis failure. HMGB1 outweighed the suppressive activity of sRAGE in the talc pleurodesis failure group, and therefore it can freely mediate its pro-tumour effects via the enhancement of tumour invasion, metastasis, and chemoresistance[19]. Furthermore, HMGB1 limits lymphatic clearance, possibly resulting in failed talc pleurodesis[20]. Lastly, given that lung adenocarcinoma predominantly caused primary lung cancer-associated MPE in the present study made HMGB1 function more relevant, as it can inhibit anti-tumoural immunity and facilitate neutrophil extracellular trap-mediated immune evasion in non-small cell lung cancer[21].

Although the current study has demonstrated that the imbalance between sRAGE and HMGB1 may be associated with the underlying mechanism for talc pleurodesis failure in patients with MPE, some limitations must be acknowledged. Firstly, other cancer-associated RAGE ligands, such as the S100 protein, were omitted

Characteristics	All patients, $N=73$	Survivor, $N=53$	Loss, $N=20$	P value
Sex, Female (%)	50 (68.5)	36 (67.9)	14 (70.0)	1.0
Age, year	66 (53–74)	67.0 (53.0–73.0)	61 (54.5, 75.5)	0.990
Body Weight, kg	55 (48-64.5)	56 (48.1–66.0)	54.5 (48.0-59.8)	0.319
Height, cm	158 (150.0-165.0)	159 (150.0-165.0)	158 (153.0-164.0)	0.543
BMI, kg/m^2	23.0 (19.1–24.9)	23.0 (19.4-245.6)	22.8 (18.3–23.7)	0.266
Cancer type				0.295
Lung cancerBreast cancer	34 (46.6) 12 (16.4)	27 (50.9) 10 (18.9)	7 (35) 2 (10)	
Solid cancer	24 (32.9)	13 (24.5)	11 (55)	
Hematologic	3 (4.1)	3 (5.7)	0	
ECOG PS				< 0.01
0	4 (5.5)	4 (7.5)	0	
1	32 (43.8)	29 (54.7)	3 (15)	
2	21 (28.8)	14 (26.4)	7 (35)	
3	13 (17.8)	5 (9.4)	8 (40)	
4	3 (4.1)	1 (1.9)	2 (10)	
LENT				< 0.01
1	3 (4.1)	2 (3.8)	1 (5)	
2	7 (9.6)	7 (13.2)	0	
3	26 (35.6)	24 (45.3)	2 (10)	
4	20 (27.4)	13 (24.5)	7 (35)	
5	12 (16.4)	6 (11.3)	6 (30)	
6	3 (4.1)	1 (1.9)	2 (10)	
7	2 (2.7)	0	2 (10)	
Talc method				0.133
Slurry	57 (78.1)	39 (73.6)	18 (90)	
Poundage	16 (21.9)	14 (26.4)	2 (10)	
Time of pleurodesis	1 (1–2)	1 (1–1)	1 (1–2)	0.005
Days on ICD	5 (3–7)	5 (3–6)	6 (4–12)	0.013
Pleural fluid release (ml)	2300 (1700.0-4110.0)	2280 (1680.0-3680.0)	2835 (1955.0-5855.0)	0.138

Table 4. Patient characteristics in survivor and 90-day mortality groups. Data for continuous and categorical variables are presented as median (interquartile ranges) and numbers (%), respectively. BMI, body mass index; ECOG PS; Eastern Cooperative Oncology Group Performance Score, LENT prognostic score.

Profiles	All patients, $N=73$	Survivor, $N=53$	Loss, $N=20$	P value
Pleural LDH, U/L	300.0 (212.5–567.0)	296 (211.0-548.0)	433 (232.0-567.0)	0.661
Pleural protein, g/dl	4.8 (4.0-5.3)	4.9 (4.4–5.3)	4.0 (3.8–5.1)	0.007
Pleural glucose, mg/dl	99.0 (83.0-124.0)	111.0 (83.0-129.0)	92.0 (78.0-105.0)	0.054
Pleural pH	7.4 (7.3–7.5)	7.5 (7.3–7.5)	7.4 (7.0-7.6)	0.254
Total pleural cell counts	1011.0 (477.0-1861.0)	1099.0 (484.0-1893.0)	963 (582.0-1171.0)	0.630
% Pleural neutrophils	4.00 (1.0–16.0)	3.0 (1.0–15.0)	9.5 (2.0–30.0)	0.238
Absolute pleural neutrophil counts	52.0 (9.0-208.0)	34.0 (8.0-193.0)	102.0 (10.0-214.0)	0.386
% Pleural lymphocytes	38.0 (22.0–64.0)	38.0 (22.0–67.0)	38.0 (21.0–61.0)	0.540
Absolute pleural lymphocyte counts	361 (140.0-694.0)	361 (174.0-788.0)	400 (136.0-585.0)	0.701
sRAGE, pg/ml	932.3 (582.0-1521.0)	1003.7 (649.3–1584)	755.0 (437.5-1162.5)	0.083
ADAM10, pg/ml	177.1 (0.0-987.3)	95.3 (0.0-998.8)	291.7 (21.3-983.2)	0.503
MMP9, pg/ml	7937.0 (7147–8979)	8004.8 (7386-8004.8)	7502.5 (5994.5-8906.2)	0.174
HMGB1, pg/ml	571.8 (128.6–1492.0)	355.4 (112.6-754.9)	841.1 (444.5-2368.4)	0.084
Serum LDH, U/L	272 (213.0-365.0)	254 (213.0-311.0)	315 (213.0-504.0)	0.271
Serum Protein, g/dl	7.0 (6.6–7.5)	7.0 (6.6–7.6)	7.0 (6.6–7.1)	0.333
% Peripheral blood neutrophils	71.0 (66.0–79.0)	70.0 (65.0–76.0)	78.0 (69.0–83.0)	0.024
% Peripheral blood lymphocytes	18.0 (12.0–29.0)	19.0 (14.0–24.0)	14.0 (7.0–19.0)	0.012
Peripheral N/L ratio	4.0 (3.0-6.4)	3.8 (2.7–5.4)	5.8 (3.8–11.0)	0.010

Table 5. Pleural fluid profile in survivor and 90-day mortality groups. Data for continuous variables are presented as median (interquartile ranges). Cell counts are expressed as cells/mm^3.

from our investigation, rendering the exclusion of their role in the current pathway entirely unattainable. Secondly, the concordant correspond among sRAGE, MMP9 and HMGB1 expression in pleural fluid and tissues, including the pleural and serum ratios of these biomarkers, extends beyond this cohort and necessitates additional exploration. Thirdly, the occurrence of the mortality rate during the period of follow up was documented, despite talc pleurodesis success, was potentially attributable to immortal time bias. For implication point of view, the results from this study limit generalisability because patients with non-expandable lung (a major cause of pleurodesis failure) were excluded. In addition, the 90-day mortality may be affected by the heterogeneity of underlying malignancy. However, this cohort investigated the neglected role of the RAGE/HMGB1 axis in the mechanism behind talc pleurodesis failure in symptomatic patients with MPE.

Conclusion

This study found that lower pleural sRAGE is a potential predictive biomarker for talc pleurodesis failure despite inferiority to pleural acidity. Imbalance between sRAGE and HMGB1 in MPE may be associated with the underlying mechanism for failed talc pleurodesis.

Data availability

No data are available. The data are not publicly available due to privacy or ethical restrictions.

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Author contributions

KM is the guarantor. KM: conceptualisation, methodology, validation, investigation, writing, review and editing of manuscript. CK: methodology, validation, investigation, and formal data analysis. CB: methodology, validation and investigation. JA: methodology and investigation. IMA: writing, review and editing of manuscript. All authors contributed to and approved the final manuscript. All authors had final responsibility for the decision to submit for publication. The lead author (KM, the manuscript's guarantor) affirms that this manuscript is an honest, accurate and transparent account of the study being reported.

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Declarations

Competing interests
The authors declare no competing interests.

Ethical approval
This study involves human participants and was approved by the Institutional Review Board of Siriraj Hospital (number of approval: Si 771/2018). Participants gave informed consent to participate in the study before taking part.

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