

Abstract

Objectives: Pleurodesis is an important management option to palliate breathlessness in patients with malignant pleural effusion (MPE). This systematic review aimed to examine available literature for studies investigating factors that predict pleurodesis outcome.

Methods: the healthcare databases advanced search (HDAS) Medline and Embase in addition to Cochrane Database of Systematic Reviews were searched on for publications reporting on pleurodesis for MPE in English language. All studies types reporting previously unpublished data on predictors of pleurodesis success were included. 34 studies involving 4626 patients were included in the systematic review. The most common pleurodesis agent used was talc which was used in 27 studies. Meta-analyses demonstrated that the strongest predictors of pleurodesis success were higher pleural fluid pH, smaller volume of effusion pre-pleurodesis and full lung re-expansion post effusion drainage. Shorter duration of tube drainage, higher pleural fluid glucose, lower LDH and lower pleural tumour burden all seem to favour pleurodesis success, but with considerable statistical heterogeneity between studies. Available data do not suggest that chest tube size affects pleurodesis outcome.

Conclusion: Overall, available results are difficult to interpret due to evidence quality. Prospective studies are needed to further explore these factors.

Protocol registration: CRD42018115874 (Prospero database of systematic reviews)

Keywords: pleural disease; mesothelioma; meta-analysis

Article highlights

- Malignant pleural effusion is relatively common and often causes considerable breathlessness.
- Pleurodesis is one of the main management options for recurrent malignant pleural effusion.
- Studies report success rates of pleurodesis in malignant pleural effusion ranging between 60-90%.
- Strong predictors of pleurodesis success include higher pleural fluid pH, smaller volume of effusion pre-pleurodesis and full lung re-expansion post effusion drainage.
- Other potential predictors of pleurodesis success may include shorter duration of tube drainage, higher pleural fluid glucose, and lower pleural fluid LDH but the evidence base is less strong.

1.0 Introduction

Malignant pleural effusion (MPE) is a condition commonly encountered by respiratory physicians. Patients with MPE are usually symptomatic with breathlessness and/or chest pain and almost all patients are offered therapeutic pleural aspiration[1]. In patients with symptomatic benefit and evidence of effusion recurrence, pleurodesis is a main therapeutic option to palliate symptoms from MPE with indwelling pleural catheter (IPC) insertion as the alternative [2]. With the exception of non-expansion of the lung post drainage , there are no clear criteria to favour one choice over the other and the decision is often based on the preference of the patient or clinician [2]. Knowledge of pleurodesis likelihood of success would influence decision making, aiming at more personalized treatment and decisions.

Several studies have compared the efficacy of different agents and methods of pleurodesis. A recent network meta-analysis found that talc poudrage is superior to other agents in terms of efficacy [3]. The majority of randomised studies of pleurodesis focused on the pleurodesis agent, and only a few addressed the effect of different practices associated with the pleurodesis procedure on outcome such as chest tube size, type of analgesia and the routine of drainage before and after pleurodesis [4,5].

Multiple observational studies have examined the effect of other parameters such as pleural fluid biomarkers or primary malignancy on outcome [6,7]. A recent study using mass spectrometry to identify protein signatures related to pleurodesis outcome in MPE samples failed to identify any pattern that significantly correlated with pleurodesis success [8]. Other studies have investigated whether physiological measurements such as pleural manometry [9] or radiological features such as the lack of sonographic pleural sliding could predict pleurodesis outcome [10], but these markers remain exploratory.

This systematic review aimed to examine available evidence on the effect of different parameters (pleural fluid-related, patient-related and procedure-related) on the outcome of

pleurodesis in patients with MPE, and whether there is sufficient evidence to use such parameters to inform clinical decision making in regard to pleurodesis.

2.0 Methods

2.1 Protocol and registration

This study was conducted in accordance with the Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [11]. A protocol was designed and agreed between the authors before the database search was carried out and is registered on the systematic reviews database, Prospero (CRD42018115874).

2.2 Search strategy and screening

Both Embase and Medline databases were searched using the National Institute for Health and Care Excellence (NICE) healthcare databases advanced search (HDAS) online portal (<https://hdas.nice.org.uk/>) in addition to the Cochrane Database for Systematic Reviews. The search was carried out by EH on 12th November 2018 using the following search strategy (for Medline): (((("PLEURAL EFFUSION, MALIGNANT"/ OR ("malign* pleura* effusion*" OR "malignant pleura* mesothelioma*").ti,ab OR (MPE).ti,ab) AND (PLEURODESIS/ OR (pleurodesis OR sclerotherap*).ti,ab)) AND (exp "TREATMENT OUTCOME"/ OR (outcome* OR success* OR fail* OR predict* OR surviv* OR mortalit*).ti,ab)) [Languages English]. The search was repeated on 8th October 2019. The full search strategy for different databases is included in the supplementary material.

Screening the initial list of titles/abstracts returned by the search for inclusion was carried out independently by two reviewers (MH and MG). Disagreement in the inclusion/exclusion decision was settled with discussion and consensus. Screening was performed on the Rayyan desktop and mobile applications [12].

The inclusion criteria for publications were reporting data on the outcome of chemical pleurodesis for malignant pleural effusion in adults in the English language where specific predictors (that were determined pre-hoc) were studied. These predictors are:

- Biomarkers: pleural fluid glucose, LDH, and pH as well as pleural fluid or systemic inflammatory markers

- Procedure- related: chest tube size, volume and duration of drainage of pleural fluid post chest tube insertion, full lung re-expansion post drainage
- Patient-related: primary malignancy, pleural tumour burden, systemic anti-neoplastic treatment

Studies were excluded if the method of pleurodesis was non-chemical (e.g. physical or biological) to avoid combining data resulting from different patho-biological processes. Small case series of less than 20 patients were excluded to avoid the selection bias that characterizes very small series. As a measure of quality control, studies were excluded if the method of determining the outcome of pleurodesis was not clearly reported, or if the study was reported in abstract form only.

2.3 Study selection and risk of bias

MH screened the retrieved full papers against the inclusion and exclusion criteria. All study types were included as long as variables of interest were compared according to the presence of successful or failed pleurodesis. In addition to the quality control measures mentioned above, and as most of the involved studies were observational in nature, the Risk Of Bias In Non-randomized Studies of Exposures (ROBINS-E) tool[13] was used to assess the degree of bias in the included studies. Assessment of publication bias was not feasible due to the small number of studies included in each meta-analysis performed.

2.4 Data extraction

A spreadsheet was used for screening and data extraction from full papers. Two reviewers (MH and MG) independently extracted study-level data to ensure accuracy. Data on different predictors were combined from included studies if similar methods of measurement were used. For data that could not be combined, a narrative synthesis was presented.

2.5 Statistics

All meta-analyses were carried out using the open-source software 'Open meta analyst' (<http://www.cebm.brown.edu/openmeta>). All comparisons were modelled to predict pleurodesis success. A random-effects model was used in all meta-analyses. Heterogeneity was assessed using the I^2 statistics; a value in excess of 50% was used to determine significant statistical heterogeneity.

For quantitative variables, the difference in means with 95% confidence interval (CI) was presented. For studies presenting data as medians and ranges, a formula was used to estimate the mean and standard deviation (SD) [14]. For qualitative variables, the pooled odds ratio (OR) with 95% CI was presented.

3.0 Results

The search strategy returned 1070 titles that were screened against inclusion criteria which resulted in 166 full articles retrieved and reviewed for eligibility. One hundred and thirty two articles were excluded for reasons detailed in the PRISMA flow diagram (figure 1) and 34 reports (on 4626 patients) were included in the synthesis of results [4–7,16–45]. Twenty six articles of those included in the systematic review contributed to the various meta-analyses conducted.

Table one presents a summary of the characteristics of the included studies and reported cohorts. Regarding study type, 19 studies (2601 patients, 56.2%) were retrospective in nature. Five studies (663 patients, 14.3%) were prospective observational. Five studies (419 patients, 9.1%) were biomarker studies while four studies were randomized controlled trials (510 patients, 11.1%) and one study was a patient level meta-analysis (433 patients, 9.3%). Twenty-four studies reported data on patients with MPE secondary to different primaries, while four studies reported on patients with mesothelioma only and one study exclusively involved patients with lung cancer.

The overall success rate of pleurodesis was 80.7%. Talc was the most commonly used agent in 27 studies followed by bleomycin, used in four studies and tetracyclines, used in three studies. Regarding method of delivery, pleurodesis via chest tube was the commonest method and was employed in 15 studies, followed by medical thoracoscopy that was used in ten studies, a mixture of both methods in five studies and video-assisted thoracoscopic surgery (VATS) in four studies.

Regarding bias assessment, 30 of the 34 included studies carried a risk of bias ranging from low to severe risk. The full details of the risk of bias assessment are presented in the supplementary material.

3.1 Biomarkers

3.1.1Pleural fluid glucose

Five studies including 709 participants presented the mean/median glucose level in patients with successful and failed pleurodesis[6,33,34,37,44]. The combined results showed higher glucose levels in favour of pleurodesis success with a mean glucose difference of 36.6 mg/dL (2 mmol/L) (95 CI 16.3 – 56.2 mg/dL), $p < 0.001$, I^2 93%, $p < 0.001$ (figure 2A). The study by Ak et al [26] reported the mean glucose levels without SD and did not find a significant difference according to pleurodesis outcome ($p=0.65$). Two studies attempted to identify a cut-off value to predict pleurodesis failure. Heffner et al[6] reported that a glucose level <72 mg/dL (4 mmol/L) was predictive of pleurodesis failure with an area under the curve (AUC) of 0.66 (95% CI 0.61 – 0.72). Pantazouplos et al[33] found that a glucose level <65 mg/dL (3.6 mmol/L) had an AUC of 0.81 to predict pleurodesis failure with high sensitivity and specificity (90.7% and 76.8%, respectively, $p < 0.001$).

3.1.2 Pleural fluid LDH

Heffner et al[6] presented LDH as a percentage of the upper limit of normal range and showed a significant difference in median percentages, with median LDH% of 85 for the successful group vs. 174 for the failure group ($p = 0.0005$). Meta-analysis of the results from three studies [33,34,37] including 232 participants showed that lower LDH levels were associated with pleurodesis success with a mean difference between the success and failure groups of -728 IU/L (95% CI -1498 – 43, $p=0.064$), I^2 95.5%, $p < 0.001$ (figure 2B). Heffner et al[6] found that a cut-off for LDH% >146 had an AUC of 0.63 (95% CI 0.54-0.71), while Pantazouplos et al[33] found that a cut-off of >300 IU/L had an AUC of 0.61 to predict pleurodesis failure.

3.1.3 Pleural fluid PH

The results from six studies [6,26,33,34,37,45] including 866 participants were combined in meta-analysis (figure 2C) which showed that higher pH was associated with pleurodesis success with a mean difference in pleural fluid pH between the success and failure groups of 0.124 (95% CI 0.107 – 0.140, $p=0.008$), I^2 0%, $p=0.473$. Arellano-Orden et al[40] reported

that successful pleurodesis correlated with pleural fluid pH with a correlation co-efficient (r) of 0.42. Regarding cut-off points, Heffner *et al*[6] reported that a pleural fluid pH value < 7.28 was predictive of failure with an AUC of 0.67 (95% CI 0.62 – 0.71) while Pantazouplos *et al*[33] reported that a pH of <7.32 had an AUC of 0.77 to predict pleurodesis failure.

3.1.4 Markers of inflammation

Three studies [22,24,36] examined the behaviour of blood and pleural fluid inflammatory markers in relation to pleurodesis outcome. Bilgin *et al*[24] found that erythrocyte sedimentation rate and blood C-reactive protein (CRP) values were increased in the postoperative period in patients with successful VATS pleurodesis but not in the failure group. Psathakis *et al*[22] reported that pleural fluid neutrophils rose more profoundly after talc poudrage in the successful pleurodesis group in comparison to the failure group. The study by Habal *et al*[36] found that more pronounced increases in serum white cell count, and pleural fluid and serum CRP were seen in the success group in comparison to the failure group.

3.2 Procedure-related factors

3.2.1 Chest tube size

Data from six studies[5,27,32,39,41,43] including 507 participants were combined into meta-analysis and the resultant pooled OR for pleurodesis success with large bore chest tubes was 1.28 (95% CI 0.80 – 2.06, p 0.298), I^2 0%, p=0.703 (figure 3A).

3.2.2 Volume of fluid drained pre-pleurodesis

Fysh *et al*[31] reported no difference in outcome of pleurodesis in patients with mesothelioma according to size of the effusion pre-drainage. Kennedy *et al*[17] used a chest

X-ray score to quantify effusion size, and reported that patients who had successful pleurodesis had lower mean \pm SD score (and thus smaller effusions) of 3.2 \pm 0.2 vs. a score of 4.2 \pm 0.2 in the failure group ($p=0.005$). Two studies including 214 participants estimated the volume of pleural fluid drained prior to pleurodesis[26,35]. Meta-analysis of their results shows a mean difference of -835 ml (95% CI -1437 - -234, $p=0.006$, I^2 45.9%, $p=0.174$) between the volume of effusion drained in the success and the failure groups respectively (figure 3B). Nohara et al [38] performed a multivariate logistic regression analysis of factors associated with pleurodesis success and found an OR of 0.995 (95% CI 0.992-0.998, $p<0.001$) for volume of drainage in mls.

3.2.3 Duration of drainage pre-pleurodesis

Three studies including 129 participants reported mean duration of effusion drainage (between chest tube insertion and pleurodesis) in patients with MPE [17,26,37]. Meta-analysis showed a mean difference in duration of drainage between the success and failure group of -2.5 days (95% CI -5.4 – 0.3 days, $p=0.079$), I^2 82.1%, $p=0.004$ (figure 3C). Trotter et al[20] reported that prolonged drainage was seen in 1.7% of the successful group and in 23.1% of the failure group, $p=0.0001$.

3.2.4 Lung re-expansion

Four studies[20,26,42,45] including 685 participants examined the effect of full lung re-expansion pre-pleurodesis and success rates of the procedure. The pooled OR of success with full expansion was 5.45 (95% CI 2.06 – 14.44, $p<0.001$), I^2 74.3%, $p=0.009$ (figure 4A). In the multivariate analysis by Nohara et al[38] absence of lung re-expansion had an OR for success of 0.06 (95% CI 0.015 – 0.247, $p<0.001$). In multivariate logistic regression analysis to predict successful pleurodesis, Burgers et al[25] reported that good apposition of the pleura was a good predictor with a p value of 0.03.

3.2.5 Duration of drainage post-pleurodesis

Goodman et al[4] showed in an RCT that removing the tube 24 or 72 hours post talc slurry pleurodesis did not have effect on outcome. In their retrospective study Leemans et al[42]

reported that the median duration of tube drainage following pleurodesis was 4 (3) days in patients with successful pleurodesis in comparison to a median of 5.5 (3) days in the failure group ($p=1.0$).

3.3 Patient-related

3.3.1 Primary malignancy

Sixteen studies including 2329 participants reported the outcome of pleurodesis in different primary tumours causing MPE [7,18,23,26,28,29,31,33,35–38,40,42,44,45]. MPE due to mesothelioma shows the lowest pleurodesis success rate of 71.9%, while MPE secondary to lymphoma and breast cancer have the highest success rates of 88.8% and 87.4% respectively. Table 2 summarizes the success rates of pleurodesis in MPE due to different primaries.

3.3.2 Systemic cancer treatment

The results of four studies[26,32,42,44] including 269 participants were meta-analysed to provide an OR for successful pleurodesis for patients on active systemic treatment. The pooled OR of successful pleurodesis is 3.11 (95%CI 0.77 – 12.54, $p=0.111$), I^2 77.2%, p 0.004 (figure 4B). In the multivariate analysis carried out by Nohara et al[38], treatment with tyrosine kinase inhibitors in patients with MPE due to lung cancer had an adjusted OR of success of 17.24 (95%CI 1.93 – 142.85). In the multi-variate analysis by Burgers et al[25], systemic anti-cancer treatment was the strongest predictor of pleurodesis success with a p value of 0.0001.

3.3.3 Extent of pleural disease burden

Seven studies (7,16,18,19,22,40,42) reported on the effect of pleural disease burden and the outcome of pleurodesis. Five of these studies utilized a score initially suggested in the early 1990s to describe the extent of pleural involvement during medical thoracoscopy with a range from 0-9 (where higher scores correspond to the more extensive

involvement)[16]. Table 3 summarizes the results of these studies which show a general trends towards lower pleurodesis success rates with more extensive pleural involvement. However, the method of defining high versus low disease burden was not uniform.

4 Discussion

This systematic review updates the systematic review carried by Heffner et al[6] in 2000 and widens its scope by examining, besides pleural fluid biomarkers, other patient- and procedure-related factors and their effect on pleurodesis outcome in MPE. The role of the pleurodesis agents was not included among the aims of the current review because a recent and comprehensive Cochrane network meta-analysis has tackled this point and concluded that talc poudrage is superior to all other methods of pleurodesis in MPE.[3]

Looking for factors that predict pleurodesis success, and in particular patient-related factors, is becoming more relevant now due to the availability and widespread use of IPCs for managing MPE. Talc, the most successful pleurodesis agent, is only effective in 70-80% of patients.[3] The availability of robust predictors of pleurodesis success would be a valuable tool for decision making on the best management option for patients with symptomatic MPE.

The data from the current systematic review and meta-analyses support the previously noted strong predictive role of low pleural fluid pH for pleurodesis failure. Lower pleural pH together with higher LDH, which are both associated with worse pleurodesis outcome, probably represent higher catabolic activity in the pleural space and have been both linked with worse survival in patients with MPE.[46]

This systematic review showed that the lack of full lung expansion at pleurodesis also predicts failure. The current British Thoracic Society guidelines suggest that pleurodesis could be attempted in the presence of 50% or more apposition of the two pleural surfaces.[1] However, data from the current review suggest that such degree of re-expansion might be insufficient to warrant offering pleurodesis. Whether patients are on active anti-neoplastic treatment also appears to be associated with pleurodesis success.

Other predictors that emerge from the current systematic review as reasonable predictors of outcome, but with varying degrees of statistical heterogeneity between studies, include

lower pleural fluid glucose, larger size of the pleural effusion pre-drainage and longer duration of drainage pre-pleurodesis which all seemed to be linked to pleurodesis failure.

A few studies included in the current review have reported data to support the notion that patients who mount stronger pleural and systemic inflammation achieve successful pleurodesis.[22,24,36] This has been shown in a recent study that demonstrated that patients with MPE who achieved successful pleurodesis had more pronounced increase in the serum levels of serum C-reactive protein than patients with failed procedure.[47]

The data from this systematic review do not demonstrate a superiority for large-bore chest tube in achieving pleurodesis. This finding reiterates the findings of a recent meta-analysis that included four RCTs and failed to show a significant difference in pleurodesis outcome in patients with MPE who received large-bore vs. small-bore chest tubes [48].

It is argued that the extent of pleural involvement by malignancy could have a bearing on the ability to mount sufficient inflammation and thus achieve pleurodesis. Most of the studies included in the current systematic review that examined the effect of pleural tumour burden and the outcome of pleurodesis reported a negative effect for extensive disease on pleurodesis outcome. The majority of these studies utilized the score suggested by Sanchez-Armengol et al to describe the extent pleural involvement during thoracoscopy.[16] However, there was no specific cut-off agreed to determine high- vs. low-burden disease which led to non-uniform manner of reporting and data that is difficult to combine. Additionally, none of these studies seems to have had a pre-hoc aim of studying this relationship. It is noteworthy that one of the included studies that provided data on the extent of visceral tumour burden in different primaries, found only minor differences in the extent of involvement despite reporting considerable differences in the success rates between different primaries [40], suggesting that the effect of pleural tumour burden is unlikely to be purely mechanical.

Due to the nature and aims of the current systematic review, we did not include mechanistic studies of pleurodesis or studies investigating the role of novel predictors of outcome. Of note, there is interest in exploring the role of ultrasound in the prediction of pleurodesis in

outcome by examining observations such as pleural sliding[10] or pleural fluid characteristics[44] and its relationship to other patho-biological mechanisms affecting pleurodesis outcome such as the fibrinolytic activity of an MPE.[22,49]

It has recently been reported that performing talc pleurodesis via IPCs for patients with MPE can reduce the time to IPC removal by accelerating 'auto-pleurodesis' [50]. Studies reporting the use of this method of pleurodesis has been excluded from this review due to the considerable differences between between this technique and standard pleurodesis which questions the relevance of including this novel method in the current review. It is also important to note that IPCs and their consumables are expensive and not universally available, and thus in most settings simple pleurodesis via chest tube remains the first choice.

Caution is required in interpreting the results of the current review due to various limitations. The majority of the included studies are retrospective in nature with at least moderate risk of bias. Besides the statistical heterogeneity noted in some of the meta-analyses, there is considerable methodological heterogeneity between studies in the execution of pleurodesis and, more importantly, the definition of the outcome. One fifth of the included studies relied on radiology rather symptomatic recurrence to determine failure. Almost half of the studies used a three-tier system (complete success, partial success, failure) to determine outcome, but to mitigate this variation, we combined the data for 'partial' and 'complete' success together as both groups included patients without symptomatic recurrence. Another important limitation is that the majority of analyses retrieved from the included reports were univariate leaving a wide room for confounding that is not accounted for. Both series of medical and surgical pleurodesis were included which is also another source of methodological heterogeneity. Although different pleurodesing agents were used in the included studies, the most widely used agent was talc. Controlling for the agent in the meta-analyses would have been of doubtful meaning because the he numbers of participants for the non-talc studies would be very small for each studied variable

5 Conclusion

There is data to suggest that various patient- and procedure-related factors have bearing on the outcome of pleurodesis in patients with MPE but the calibre of evidence is not uniform for the different variables. There is a strong need to reach an agreement on a standardised means for reporting of outcomes. In addition to the studies currently underway to identify radiological and biological predictors of pleurodesis outcome, further studies are needed to further explore the pathobiological mechanisms of pleurodesis (particularly inflammation and fibrinogenesis/fibrinolysis) with the aim to identify prognostic markers to predict outcome and potentially enhance the efficacy of the procedure. Another area of research should focus on improving the evidence base behind the different practices surrounding the procedure of pleurodesis such as whether suction is applied to chest tubes, the need for flushing of chest tubes post pleurodesis, the clinical/radiological criteria to institute the pleurodesing agent and to remove the chest tube post pleurodesis. |

Author contribution: MH conceived the study. MH and NMR wrote the protocol. EH performed the literature search. MH and MG screened the search results for eligibility and extracted the data. MH performed the statistics and drafted the first manuscript. NMR and RM critically revised the manuscript. All authors reviewed and approved the final manuscript.

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Tables:

Table 1: characteristics of included studies in the systematic review

Author	Year	Study size	Study type	Agent	Primary	Vehicle	%success	Definition of pleurodesis success
Sanchez-Armengol [16]	1993	125	Prospective observational	Talc	miscellaneous	poudrage	0.88	symptomatic recurrence
Kennedy [17]	1994	47	Retrospective case series	Talc	miscellaneous	slurry	0.81	radiological recurrence
Viallat [18]	1996	327	Retrospective case series	Talc and others	miscellaneous	poudrage	0.86	symptomatic recurrence
Heffner [6]	2000	433	Patient-level meta-analysis	Various	miscellaneous	poudrage and slurry	0.82	symptomatic recurrence radiological recurrence
Antony [19]	2004	23	Biomarker study	Talc	miscellaneous	poudrage	0.70	radiological recurrence
Trotter [20]	2005	202	Retrospective case series	Talc	miscellaneous	VATS	0.88	symptomatic recurrence
Kolschmann [21]	2005	85	Retrospective case series	Talc	miscellaneous	poudrage	0.89	symptomatic recurrence
Goodman [4]	2006	41	Randomised trial	Talc	miscellaneous	slurry	0.85	symptomatic recurrence
Psathakis [22]	2006	168	Biomarker study	Talc	miscellaneous	poudrage	0.92	symptomatic recurrence
Debeljack [23]	2006	71	Retrospective case series	Talc	miscellaneous	poudrage and slurry	0.77	symptomatic recurrence
Bilgin [24]	2007	58	Prospective observational	Talc	mesothelioma	VATS	0.74	radiological recurrence
Burgers [25]	2008	75	Retrospective case series	Talc	miscellaneous	slurry	0.71	radiological recurrence
AK [26]	2009	42	Retrospective case series	Talc	mesothelioma	poudrage	0.62	symptomatic recurrence
Aydogmus [27]	2009	73	Retrospective case series	Talc	miscellaneous	slurry	0.82	symptomatic recurrence
Barbetakis [28]	2010	400	Prospective observational	Talc	miscellaneous	VATS	0.85	symptomatic recurrence
Nikbakhsh [29]	2011	50	Prospective observational	Bleomycin	miscellaneous	slurry	0.86	symptomatic recurrence
Bielsa [7]	2011	573	Retrospective case series	talc and doxycycline	miscellaneous	poudrage and slurry	0.86	symptomatic recurrence
Firoozbakhsh [30]	2012	40	Retrospective case series	Bleomycin	miscellaneous	slurry	0.81	symptomatic recurrence
Fysh [31]	2012	165	Retrospective case series	Talc	mesothelioma	various	0.68	symptomatic recurrence
Wajda [32]	2014	28	Retrospective case series	Talc	miscellaneous	slurry	0.71	symptomatic recurrence
Pantazopoulos [33]	2014	162	Retrospective case series	Bleomycin Tetracycline	miscellaneous	slurry	0.65	radiological recurrence
Alsayed [34]	2015	30	Prospective observational	Bleomycin	miscellaneous	slurry	0.57	symptomatic recurrence
Rena [35]	2015	172	Retrospective case series	Talc	mesothelioma	VATS	0.76	symptomatic recurrence
Habal [36]	2015	114	Biomarker study	Talc	miscellaneous	poudrage	0.86	symptomatic recurrence

Shehata [37]	2015	40	Biomarker study	Doxycycline	miscellaneous	slurry	0.63	symptomatic recurrence
Rahman [5]	2015	100	Randomised trial	Talc	miscellaneous	slurry	0.73	symptomatic recurrence
Nohara [38]	2016	94	Retrospective case series	Talc and OK 432	lung	slurry	0.77	symptomatic recurrence
Aktürk [39]	2017	185	Retrospective case series	Talc	miscellaneous	slurry	0.86	symptomatic recurrence
Arellano-Orden [40]	2017	74	Biomarker study	Talc	miscellaneous	poudrage	0.62	symptomatic recurrence
Mendes [41]	2018	61	Retrospective case series	Talc	miscellaneous	slurry	0.87	radiological recurrence
Leemans [42]	2018	155	Retrospective case series	Talc	miscellaneous	poudrage	0.78	symptomatic recurrence
Keeratichananont [43]	2018	110	Randomised trial	Talc and autologous blood	miscellaneous	slurry	0.85	symptomatic recurrence
Hassan [44]	2019a	44	Retrospective case series	Talc	miscellaneous	poudrage and slurry	0.48	symptomatic recurrence
Hassan [45]	2019b	259	Randomised trial	Talc	miscellaneous	poudrage and slurry	0.79	symptomatic recurrence

VATS: video-assisted thoracoscopic surgery

Table 2: Success rate of pleurodesis according to the primary malignancy

Primary	Total number	% success
Lung	799	77.1%
Mesothelioma	764	71.9%
Breast	375	87.4%
Gynaecologic	107	86.9%
GI tumours	101	79.2%
Lymphoma	54	88.8%
Urologic	27	85.1%

GI: gastro-intestinal

Table 3: Summary of the studies reporting on the effect of pleural tumour burden on pleurodesis outcome

Study	Direction of effect
Sanchez-Armengol 1993	In patients with massive visceral pleural burden (score 3), pleurodesis failure in 27% vs. in patients without this degree of burden failure 13% (p=0.28)
Viallat 1996	Massive cancer involvement of pleural cited as main cause of failure (no statistics)
Antony 2004	In success group (16 patients): 2 patients had score of 5 or more, while in failure group (7 patients) all patients had tumour burden score of 6 or more
Psathakis 2006	In the success group mean+SD score for pleural burden was 5.36+1.7, and in the failure group it was 6.2+1.3, p=0.29
Bielsa 2011	In 58 patients with pleural burden score 1-3 success rate was 89.7%, and in 116 patients with score 7-9 success rate was 80.2% (p=0.02). Multivariate analysis including tumour type, high score (>6) had OR of 0.81 (0.68–0.98) for success
Arellano-Orden 2018	Higher visceral pleural tumour burden associated with failure in 53% of patients (p < 0.04)
Leemans 2018	OR of extensive pleural lesions and pleurodesis success 0.17 (95%CI 0.05 – 0.96, p 0.04)

CI: confidence interval; OR: odds ratio

Figure legends

Figure 1: PRISMA flow chart of the systematic review steps

Figure 2: Forest plots of the meta-analyses of effect of pleural fluid biomarkers on pleurodesis success A) Forest plot for pleural fluid glucose level B) Forest plot for pleural fluid LDH level C) Forest plot for pleural fluid pH level

Figure 3: Forest plots of the meta-analyses of effect different procedure-related factors on pleurodesis success. A) Forest plot of the effect of large size chest tubes on pleurodesis success. B) Forest plot of the volume of pleural fluid drainage prior to pleurodesis. C) Forest plot of the duration of pleural fluid drainage prior to pleurodesis.

Figure 4: Forest plots of the meta-analyses of effect different patient-related factors on pleurodesis success. A) Forest plot of the effect of full lung expansion on pleurodesis success. B) Forest plot of the effect of current systemic treatment on pleurodesis success.