

Online Appendix D12 BTS Guideline for Pleural Disease

Section D Pleural malignancy

Question D12 Evidence Review and Protocol

D12 For adults with pleural malignancy, does the use of prognostic and predictive scores improve clinical outcomes?

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Question Evidence Review

D12 For adults with pleural malignancy, does the use of prognostic and predictive scores improve clinical outcomes?

Background

Malignant pleural effusions (MPE) are associated with short survival as, with the exception of malignant pleural mesothelioma, they signify advanced or metastatic disease. Numerous other factors, including patient characteristics, pleural fluid parameters and biochemical and haematological values have been shown to be related to clinical outcomes in MPE, however these findings have often lacked validation in independent cohorts. Relating separate findings to each other, and interpreting them in the context of patients, is also often difficult. By combining prognostic factors into validated scoring systems, these may be more clinically useful. This review aims to determine if validated prognostic scores exist for MPE and, if so, their use improves clinical outcomes in adults with MPE (excluding mesothelioma).

Outcomes

Mortality, quality of life, clinical symptoms, pleurodesis rates and need for further intervention

Evidence Review

Of 14 potentially eligible studies identified through the literature search, none compared clinical outcomes in patients who had treatment directed by a prognostic score at baseline compared with those who had treatment directed using standard measures. Two externally validated prognostic scoring systems have been reported for MPE, the LENT¹ and PROMISE² scores, however the impact of these scores on clinical decision making and outcomes other than survival has not been evaluated.

The LENT study combined pleural fluid lactate dehydrogenase (LDH) levels, Eastern Cooperative Oncology Group (ECOG) performance status, serum neutrophil to lymphocyte ratio (NLR) and underlying tumour type emerging into a prognostic score for separating patients into low-, moderate- or high-risk mortality groups.¹ The PROMISE score evaluated seven clinical biomarkers and one pleural fluid biomarker (haemoglobin, C-reactive protein, white blood cell count, ECOG performance status, cancer type, pleural fluid tissue inhibitor of metalloproteinases 1 (TIMP1) concentrations and previous chemotherapy or radiotherapy) to predict absolute risk of death at 3 months. Patients were categorised into one of four categories (<25% absolute risk of death at 3 months, 25% - <50% absolute risk of death at 3 months, 50% - <75% absolute risk of death at 3 months and ≥75% absolute risk of death at 3 months).²

Mortality

Both studies assessed the performance of prognostic scores to predict survival in MPE and data are summarised in [Table D12a](#). Median survival times for the low-, moderate- and high-risk mortality groups in the LENT study were 319 days [228–549] (n = 43), 130 days [47–467] (n = 129) and 44 days [22–77] (n = 31) respectively [interquartile range].^{1,2}

A strength of the LENT score is its use of readily accessible clinical parameters to calculate prognostic group. However, it was developed prior to widespread use of targeted therapies for lung cancer and therefore may underestimate survival in patients with lung cancer and epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) mutations. The introduction of immune checkpoint inhibitors in lung cancer (and other malignancies) may also affect its performance.¹

Quality of life, clinical symptoms and need for further intervention

No data was reported on quality of life, clinical symptoms or need for further intervention.

Pleurodesis rates

PROMISE evaluated clinical and biological factors associated with pleurodesis success but was unable to identify any distinct predictive factors for this outcome.² A second study investigating if pH may be more useful

for predicting pleurodesis failure, showed patients with a pleural fluid pH between 7.0 and 7.2 had a likelihood ratio of 2.59 (95% CI 1.63–4.13) for pleurodesis failure.³

Table D12a: MPE survival prediction using LENT or PROMISE prognostic scores

Prognostic score	Predicted survival			
	1 month	LENT ¹ (AUC) 3 months	6 months	PROMISE ² (C statistic value [95% CI]) <3 months / ≥3 months
LENT (AUC)	0.77	0.84	0.85	
ECOG PS (AUC)	0.66	0.75	0.76	
<i>p</i>	<0.01	<0.01	<0.01	
Internal validation				0.78 [0.72,0.83]
External validation				0.89 [0.84,0.93]

AUC – area under curve; CI – confidence interval; ECOG PS – Eastern Cooperative Oncology Group performance status

Evidence Statements

Two validated prognostic scoring systems, LENT and PROMISE, exist for malignant pleural effusion (**Ungraded**)

LENT and PROMISE provide estimates of survival for patients with malignant pleural effusion, but neither have been assessed in their ability to improve outcomes (**Ungraded**)

Recommendations

No recommendation can be made from the presented evidence.

Good Practice Points

- ✓ Clinicians may consider using a validated risk score for malignant pleural effusion if the information is of use in planning treatments or in discussion with patients
- ✓ Patients with pleural malignancy should be managed in a multi-disciplinary way, including referral to specialist palliative care services where appropriate.

Research Recommendation

- Further research is needed into developing a prognostic score that predicts pleurodesis success and investigating if prognostic scores lead to improved clinical outcomes in patients with malignant pleural effusion

References

1. Clive AO, Kahan BC, Hooper CE, et al. Predicting survival in malignant pleural effusion: development and validation of the LENT prognostic score. *Thorax*. 2014;69(12):1098-1104.
2. Psallidas I, Kanellakis NI, Gerry S, et al. Development and validation of response markers to predict survival and pleurodesis success in patients with malignant pleural effusion (PROMISE): a multicohort analysis. *Lancet Oncol*. 2018;19(7):930-939.
3. Heffner JE, Heffner JN, Brown LK. Multilevel and continuous pleural fluid pH likelihood ratios for evaluating malignant pleural effusions. *Chest*. 2003;123(6):1887-1894.

Question Protocol

Field	Content
Review Question	For adults with pleural malignancy, do prognostic scores improve clinical outcomes?
Type of review question	Intervention review
Objective of the review	To assess whether validated prognostic scoring systems in malignant effusion exist and are helpful
Eligibility criteria – population / disease / condition / issue / domain	Adults (18+) with pleural malignancy (exclude mesothelioma only studies)
Eligibility criteria – intervention(s)	Baseline prognostic scores
Eligibility criteria – comparators(s)	No baseline prognostic scores
Outcomes and prioritisation	Mortality Quality of life Clinical symptoms Pleurodesis rates Need for further intervention
Eligibility criteria – study design	RCTs Prospective comparative studies Case series of >100 patients
Other inclusion /exclusion criteria	Non-English language excluded unless full English translation Conference abstracts, Cochrane reviews, systematic reviews, reviews Cochrane reviews and systematic reviews can be referenced in the text, but DO NOT use in a meta-analysis
Proposed sensitivity / subgroup analysis, or meta-regression	None

Selection process – duplicate screening / selection / analysis	Agreement should be reached between Guideline members who are working on the question. If no agreement can be reached, a decision should be made by the Guideline co-chairs. If there is still no decision, the matter should be brought to the Guideline group and a decision will be made by consensus
Data management (software)	<p>RevMan5 Pairwise meta-analyses Evidence review/considered judgement. Storing Guideline text, tables, figures, etc.</p> <p>Gradeprofiler Quality of evidence assessment</p> <p>Gradepro Recommendations</p>
Information sources – databases and dates	MEDLINE, Embase, PubMed, Central Register of Controlled Trials and Cochrane Database of Systematic Reviews 1966 - present
Methods for assessing bias at outcome / study level	RevMan5 intervention review template and NICE risk of bias checklist (follow instructions in ' <i>BTS Guideline Process Handbook – Intervention Review</i> ')
Methods for quantitative analysis – combining studies and exploring (in)consistency	If 3 or more relevant studies: RevMan5 for meta-analysis, heterogeneity testing and forest plots (follow instructions in ' <i>BTS Guideline Process Handbook – Intervention Review</i> ')
Meta-bias assessment – publication bias, selective reporting bias	GRADEprofiler Intervention review quality of evidence assessment for each outcome (follow instructions in ' <i>BTS Guideline Process Handbook – Intervention Review</i> ')
Rationale / context – what is known	There are currently two validated prognostic scoring systems in the literature – LENT and PROMISE. Little evidence was available on prognostic scores during the production of the BTS Pleural Disease Guideline 2010, so the question will explore if there is new data available