



Predicting Outcomes in Patients with Malignant Pleural Effusions

Syed Hamza Abbas¹ · Eleanor K. Mishra¹

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Abstract

Purpose of Review There is limited understanding on predicting clinical outcomes in patients with malignant pleural effusions (MPEs). This review explores recent research in predicting outcomes for patients with malignant pleural effusions, looking at findings in topics such as predicting survival, non-expansile lung, time to next procedure, pleurodesis success, time to IPC removal and symptom benefit.

Recent Findings We show that many tools exist to help guide management of patients in MPEs, with some showing limited results. Much more is now known in areas such as predicting survival, symptom benefit and time to next procedure, whilst other areas of clinical interest require further development before clinical application can be fully realised.

Summary Overall, work predicting outcomes for patients with MPEs shows promise, but more work is required in all areas before these emerging findings can be put into clinical practice to best manage patients.

Keywords Malignant pleural effusion · Survival · Pleurodesis · Indwelling pleural catheter · Non-expansile lung

Introduction

A malignant pleural effusion (MPE) occurs when fluid accumulates in the pleural space due to cancer [1]. Malignant pleural effusions occur at a rate of 70 per 100,000 people a year and have been documented to cost upwards of \$10.1 billion a year in the US alone [2]. Presently, malignant pleural effusions are treated with palliative intent, typically draining off fluid. However, different methods exist, and patient outcomes with malignant pleural effusions vary.

Fundamentally, given the heterogeneous nature of patients presenting with MPEs, there is merit in identifying likely outcomes for MPE patients. This in turn helps guide the best clinical approaches for different types of MPE patients to effectively relieve symptoms, minimise unnecessary procedures and avoid complications. Therefore, clinical scores have been developed to try to predict outcomes for patients with MPE.

Key criteria are used to assess clinical scores. **Discrimination** is the model's ability to differentiate between

individuals who will experience the outcome and those who will not. This is measured using the C-statistic (or area under the receiver operator curve), where 0.5 indicates no better than random chance and 1 means perfect discrimination. As a rule of thumb, C statistics of 0.7–0.8 indicate an acceptable model to use in clinical practice. **Calibration** assesses the agreement between predicted risks and observed outcomes, with a well-calibrated model providing accurate risk estimates across all probabilities. It can be assessed by calibration plots and slopes. **Internal validity** means the model is reliable and robust within the discovery dataset and can be assessed using subsets of data. **External validity** assesses the generalisability of the model beyond the population it was developed on. This is determined by assessing the model in other datasets. Finally, **clinical utility** means that it provides helpful information to guide clinical decision making and improve patient outcomes and is essential if a clinical score will be used in practice.

The purpose of this review article is to explore current literature on variables and clinical scores which predict outcomes in patients with MPEs, using the criteria above. The key outcomes to be discussed are survival, presence of non-expandable lung (NEL), pleurodesis success, time to next procedure and benefit.

✉ Syed Hamza Abbas
syedhamza.abbas@nnuh.nhs.uk

¹ Norfolk and Norwich University Hospital NHS Foundation Trust, Norwich, UK

Predicting Survival

Patients with MPEs have incurable cancer with a poor prognosis. The ability to predicting survival in individual patients with MPEs would be helpful, both to inform patients and guide clinical decision making. The LENT and PROMISE scores are clinical scores which have been developed to predict survival in patients with MPE.

The LENT score uses pleural fluid LDH, ECOG performance status, neutrophil to lymphocyte ratio and tumour type to stratify patients into “low-risk”, “medium-risk” or “high-risk” patients in terms of risk of death [3]. Patients with a low-risk score had a median survival of 319 days, moderate-risk 130 days and high-risk 44 days. Initial derivation demonstrated better discrimination at predicting survival by Kaplan-Meier curve compared to ECOG performance status alone, with a C-statistic of 0.77 (95% CI 0.70–0.84) at 1 month and 0.84 (95% CI 0.79–0.89) at 3 months. A similar score, the GASENT score, uses age, sex, ECOG performance status, neutrophil to lymphocyte ratio and tumour type to stratify patients into the same risk categories and has been shown to perform slightly better in a single centre [4].

The PROMISE score uses haemoglobin, white blood cell count, CRP, ECOG performance status, cancer type, pleural fluid tissue inhibitor of metalloproteinases 1 (TIMP1) levels and previous chemotherapy or radiotherapy to predict prognosis [5]. Given that TIMP1 levels are not routinely available, the PROMISE score can also be conducted without this data (termed clinical PROMISE score). External validation showed C statistics of 0.89 (95% CI 0.84–0.93). This score produces a percentage risk of mortality based on patient factors, which can again be stratified into categories, dividing patients into low mortality (< 25% risk of mortality at 3 months), medium (25–50% mortality), high (50–75% mortality) and very high (> 75% mortality).

External validation has produced conflicting results. Both scores have been externally validated in a single UK hospital demonstrating C-statistics of around 0.8 [6]. However, evaluation in an Asian population undergoing pleuroscopy showed C-statistics of only 0.59 (95% CI 0.52–0.67) for the LENT score and 0.72 (95% CI 0.53–0.63) for the PROMISE score. This study developed an alternative prognostic model, the SELECT score which had a C-statistic of 0.87 (95% CI 0.79–0.95), but this score has not been validated [7].

However, there are key limitations to these scores which reduce their clinical utility. Both LENT and PROMISE scores were developed using datasets which were retroactively available from other studies and not specifically developed to assess survival and therefore could only use variables which were collected in these data sets. This means

they may miss key variables which can predict prognosis as well as underrepresenting some patients with MPE, such as those with a poor performance status. This is evidenced with some studies, such as Mounsey et al. and Ermin et al., which suggest that some potential areas of underrepresentation include specific tumour types and specific mutations within those tumour types [6, 8]. As new therapies make use of these markers for treatment, this may affect prognosis and are yet to be evaluated as part of predicting outcomes in pleural medicine. There is also a failure to demonstrate that different management strategies are optimal in different prognostic groups. These scores have been developed by pleural physicians caring for patients with a wide range of underlying tumour types. However, decisions about systemic anticancer treatment are made by oncologists who specialise in a specific tumour type and therefore are likely to use prognostic scores developed for that tumour type or make decisions based on presence of sensitising mutations.

Other variables have been identified which predict prognosis in patients with MPE which were not considered in the discovery datasets for the PROMISE and LENT scores. Our previous meta-analysis demonstrated that baseline breathlessness was predictive of survival in patients with MPE, in keeping with other morbidities [9]. Further studies include Atasever et al. who demonstrated that SUVpeak values (taken from nuclear medicine studies) was predictive of mortality [10]. Additionally, a systematic review identified 11 other clinical and biological variables associated with survival in these patients [11]. This suggests that dedicated studies may be warranted to better understand prognostic elements of MPEs.

A further limitation of these studies is that they do not provide information on survival in a form which is meaningful to our patients. Most patients will not understand the meaning of a median survival or percentage survival at a certain time point. Exploratory work is required to understand how to make prognostic information available to patients with MPE in a way that enables them to make informed decisions about their treatment options.

In summary, the LENT and PROMISE scores are validated scores which can categorise patients with MPE into different prognostic groups, but their clinical utility is limited at present. Other variables have also been identified which predict survival, but these have not been assessed in multivariate models to determine whether they provide independent prognostic information. Further research may enable the development of more accurate scores, but ultimately these will remain scores which determine average survival in a population rather than precise information for an individual patient.

Predicting Non Expandable Lung

Non-expandable lung (NEL) is where a lung – affected by a pleural effusion – does not re-expand following drainage of the effusion [12]. It affects up to 30% of MPEs [13]. Whilst NEL does not necessarily imply poor symptom control, its presence can impact the management approach. Patients with NEL are likely to fail talc pleurodesis owing to the absence of proximity between visceral and parietal pleura, so IPCs are the preferred treatment option [1, 13, 14]. NEL is usually identified on chest X-ray following drainage of the effusion. Early identification of NEL will determine which patients should be treated with IPCs. Our clinical experience is that patients who experience central chest pain during pleural fluid drainage often have underlying NEL, but the presence of this symptom as a predictive variable has not been formally studied.

Pleural manometry is the measurement of the pressure of the pleural space as pleural fluid is drained and has been used to identify NEL [15]. The Pre-EDIT trial was a feasibility trial of measuring manometry to identify patients with NEL [16]. This study showed that manometry was a viable metric to assess but, as a feasibility study, did not demonstrate if manometry was predictive of NEL. Youssef et al. conducted an observational study, which showed that pleural elastance of > 14.5 kPa was associated with NEL ($p < 0.001$). Whilst manometry has proven to be feasible and predictive, uptake is limited for various reasons. Firstly, manometry requires additional equipment, monitoring, time and requires specialist training to take measurements. Secondly, pleural manometry in MPEs requires drainage of the effusion to take a measurement. Whilst this means that it can identify NEL early, this can paradoxically increase the procedure burden to the patient, as measurement would require a therapeutic aspiration first before performing a definitive procedure such as an IPC or chest drain insertion. Finally, manometry has not been shown to be superior to chest X-ray or symptoms to detect NEL. Therefore, it is not currently used widely to detect NEL.

Thoracic ultrasound has the potential to identify NEL prior to pleural fluid drainage, and hence to reduce the number of procedures patients with MPE will undergo. A recent narrative review showed that an absent sinusoidal sign and reduced atelectatic lung movement on M-mode can predict NEL [17]. Other variables, such as speckle tracking imaging strain analysis, may also be helpful but remain experimental at present.

Other variables have also been investigated to determine whether they can predict NEL. A retrospective cohort study identified that loculated MPE, complete hemithorax opacification, lung cancer and higher effusion: serum LDH were independent predictors of NEL, but these variables have

not been externally validated [18]. A study of the ability of medical thoracoscopists to identify NEL during thoracoscopy using video demonstrated only 12.5% of NEL was correctly identified [19].

To summarise, determination of NEL currently requires drainage of the effusion with assessment of symptoms, chest X-ray or pleural fluid manometry but thoracic ultrasound has the potential to identify NEL prior to drainage. Further work is required to derive and validate effective ultrasound protocols for this indication.

Predicting Time to Next Procedure

MPEs recur at different rates following drainage. Current management of patients with MPE is usually initial therapeutic aspiration followed by a definitive procedure when the fluid reaccumulates. However, patients with rapidly reaccumulating effusions often become breathless rapidly and attend the emergency department where they may have inappropriate procedures [20]. In contrast, patients with slowly reaccumulating effusions may experience unnecessary or cancelled procedures. The ability to predict time to next procedure would enable clinicians to schedule procedures appropriate and inform patients.

The RED score is the first validated score which can predict time to next procedure in patients with MPE undergoing therapeutic aspiration [21]. The RED score uses three easily available clinical variables (respiratory rate, effusion depth measured using ultrasound and dyspnoea measured using a visual analogue scale). Patients with a high RED score are likely to require another procedure within 2 weeks, those with a medium RED score in 2–6 weeks, and those with a low score after 6 weeks or they may not need another procedure. The RED score has moderate discriminatory power, determined by C-statistics of 0.73 (95% CI 0.65–0.82) and 0.75 (95% CI 0.65–0.84) and has been validated internally and externally. It has clinical utility, but further research is needed to determine whether use of the RED score in clinical practice can improve clinical outcomes.

Other studies have also identified variables with predict time to next procedure. Grosu et al. found that size of effusion on chest X-ray, total volume of pleural fluid drained and pleural fluid biochemistry (LDH, total protein and cholesterol) were all predictive of recurrence of pleural fluid [20]. However, attempts to derive a predictive score failed. Fysh et al. also found size of effusion on chest X-ray to predict the need for a definitive procedure, as well as pleural fluid pH [12, 22]. Fjaellegaard et al. demonstrated that daily pleural fluid production as well as size of effusion were predictive of a faster MPE recurrence rate [23]. These findings are consistent with the use of effusion size as a predictive variable in the RED score. However, pleural fluid variables were not

included in the derivation of the RED score, because these can only be determined once the fluid has been drained so cannot be used to determine initial management.

In summary, several clinical variables have been identified which can predict time to next pleural procedure. The RED score is a validated clinical score which can be used to plan further procedures and inform patients. More work is required to determine whether use of the RED score improves clinical outcomes before it is routinely used in clinical practice.

Predicting Pleurodesis Success

Pleurodesis is the permanent apposition of the visceral and parietal pleural, achieved by means of an intercostal chest drain insertion followed by injection of an irritant such as talc after the pleural effusion is completely drained. The introduction of talc causes inflammation between the visceral and parietal pleura, resulting in adhesion to occur [24]. This removes the potential space for a pleural effusion to reaccumulate but failure rates have ranged from 20% [25] to 57% [26]. Success of chemical pleurodesis is usually assessed by the need for further pleural procedures.

A systematic review published in 2020 found that the strongest predictors of pleurodesis success were higher pleural fluid pH, smaller volume of effusion pre-pleurodesis and expandable lung [27]. There was less strong evidence for shorter duration of effusion drainage, higher pleural fluid glucose, lower LDH and lower pleural tumour burden as predictors of pleurodesis success. There is also evidence that a greater inflammatory response to talc is predictive of pleurodesis success, but this can only be determined once talc has been given [28].

To conclude, some variables have been identified which predict the success of talc pleurodesis, but there is currently no score which can predict whether individual patients will achieve pleurodesis. If a score could be validated, it would have significant clinical validity because patients with a high probability of pleurodesis failure would be offered IPC in preference.

Predicting Time to IPC Removal

Indwelling pleural catheters (IPCs) are tunnelled, semi-permanent chest drains which allow pleural fluid drainage as an outpatient. In around half of patients, fluid stops draining over time due to spontaneous pleurodesis and the IPC can be removed [29]. This is important because longer time in situ is associated with a greater risk of infection as well as increased health care costs [30, 31].

Farooq et al. identified that functional status, chemotherapy, radiation post IPC insertion and mean duration of IPC

were all associated with pleurodesis [32]. Interestingly, use of medical thoracoscopy was also statistically significant for increasing the chances of pleurodesis. Key limitations are the single-centre study being performed retrospectively. Similar findings were realised in a small study by Wong et al., who noted that time with IPC was also predictive of pleurodesis, as was absence of NEL and low time between presentation and IPC insertion [33]. Warren et al. found that IPC removal was more likely in patients with breast or gynaecological cancer compared to those with lung or other cancers. Other predictive factors were positive pleural fluid cytology, chest wall irradiation and NEL [34]. Clinicians can decrease time to IPC removal by advising patients to drain frequently (daily) and offering talc pleurodesis via the IPC [35–37].

This data demonstrates some variables which can predict time to IPC removal as well as interventions which can decrease time to IPC removal. However, at present, there is no predictive clinical score which can be used to predict time to IPC removal or which patients would be like to achieve a spontaneous pleurodesis. This would be useful in clinical practice because patients would be more likely to choose IPCs if they knew it would only be present for a limited time.

Predicting Symptomatic Benefit

Patients with MPE have terminal disease and palliation of symptoms are a key goal of treatment. However, studies show that approximately a third of patients do not gain significant relief of their breathlessness following a pleural procedure [9]. The current British Thoracic Society guidelines advise offering interventions to patients with MPE who are likely to benefit, but do not offer guidance as to who will benefit [1].

Some clinical variables have been shown to be predictive of breathlessness relief, defined as a decrease in mean breathlessness of great than the minimal important difference [38]. The PLEASE studies have shown that severity of breathlessness pre-procedure as well as diaphragmatic shape and function predict breathlessness relief [39]. Patients with a low RED score are also unlikely to experience significant relief of breathlessness. This is in keeping with other results, because these patients have low levels of dyspnoea and smaller effusions.

This data demonstrates that some variables have been identified which predict breathlessness relief. However, patient benefit is broader than breathlessness relief alone – other symptoms experienced by patients with MPE include chest discomfort, cough and sleep disturbance. Further research requires a broader definition of benefit but has

significant potential to avoid inappropriate procedures in patients who will not benefit.

Conclusions

We demonstrate that there has been significant research undertaken to enable clinicians to predict outcomes in patients with MPE, particularly survival, presence of NEL, time to next procedure, pleurodesis success and benefit. This research has led to the identification of many predictive variables and the development and validation of various clinical scores. However, use of these scores in clinical practice remains limited, mainly due to a lack of evidence that use of these scores improves clinical outcomes. An ability to predict outcomes in patients with MPE could benefit patients but remains elusive at present.

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 - This analysis helped to identify a predictor for a key outcome of concern for many patients with MPEs – overall survival. It also provides a strong basis to help inform patients about what to expect regarding prognosis.

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- Similar to previous, this study helps to provide important information on a matter very significant to patients during their journey and can therefore help to facilitate conversations with patients about goals of treatment.

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Conflict of Interest:

None to declare.

Data Availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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