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Prognostication in malignant pleural effusion: one size does not fit all

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Physicians are poor at predicting survival in patients with malignant pleural effusion (MPE). This is exemplified by the TIME 2 trial [1] where, despite criteria precluding trial entry with an estimated survival of <3 months, 34% of participants died within 90 days. An added complexity is the variation in exercise capacity associated with how effectively the pleural effusion is controlled. The resulting impact a large, undrained effusion has on performance status renders this a poor prognostic indicator. Accurate estimates of prognosis are important to inform discussion with patients and guide management and follow-up strategies. This is of particular significance given the short survival conferred by a diagnosis of MPE, with median survival figures between 3 – 12 months [2].

Until now, two prognostic scores have been reported for use in MPE. The LENT score [3], (combining pleural fluid lactate dehydrogenase (LDH), Eastern Cooperative Oncology Group performance status (ECOG PS), neutrophil: lymphocyte ratio and tumour type) externally validated in 10 studies, categorises patients into low, moderate and high risk groups (median survival 319 days, 130 days and 44 days respectively)[3]. The PROMISE score [4] combines biological (TIMP1 pleural fluid biomarker) and clinical parameters (chemotherapy, radiotherapy, haemoglobin, leucocyte count, C-reactive protein (CRP), ECOG PS and cancer type) to give four risk categories: Group A (lowest risk; <25% 90 day mortality) to D (highest risk; ≥75% 90 day mortality)[4]. A variation of the LENT score (modified LENT) has also been developed in patients with MPE secondary to adenocarcinoma [5].

In a recent publication in Respirology, Quek et al [6] report their evaluation of the LENT, modified LENT and clinical PROMISE scores in an Asian MPE population and report a new score: the SELECT model. Patients were identified from a pleuroscopy database, with data available to calculate LENT and modified-LENT scores in 130 participants and clinical PROMISE score in 57. C-statistics demonstrated that no score was strong at survival prognostication in their patient population. In response, the SELECT model was developed using data from 147 patients in the database. Incorporating readily accessible variables (sex, ECOG PS, leukocyte count, epidermal growth factor receptor (EGFR) mutation, chemotherapy and primary tumour type) patients were stratified into low risk (predicted probability of 90 day mortality ≤10%) and high risk (predicted probability of 90 day mortality >10%) groups. Comparison of the four prognostic scores using logistic regression in 52 patients demonstrated the SELECT model performed better than the LENT and PROMISE scores, but not in comparison to modified-LENT. The authors conclude the SELECT score is accurate at identifying patients with a high probability of survival at 90 days.

The authors address a relevant limitation of the LENT and PROMISE scores; newer targeted cancer therapies confer a survival advantage not accounted for in these prognostic models. With wider access to tyrosine kinase inhibitors for EGFR positive mutations, the LENT and PROMISE scores risk underestimating survival in patients with adenocarcinoma. By incorporating EGFR status, the SELECT prognostic model may now provide a more accurate survival estimate for patients with MPE. Although previous studies have sought to address this issue [5], SELECT is the first prognostic score developed to date from a patient population with different primary cancer types to include EGFR status.

However, external prospective validation in an unselected cohort is essential before the SELECT model is utilized in clinical practice. In contrast to the LENT and PROMISE scores (developed and validated prospectively in 'all comers' with MPE), a significant limitation of the study from Quek et al. is the retrospective design and single-centre evaluation. Patients with a greater level of dependency were under-represented in the authors' analysis of participants undergoing pleuroscopy; 81% of whom had an ECOG status of 0 or 1. Higher risk categories were represented with similarly low numbers; 10 of 130 participants were 'high risk' by LENT criteria and 0 of 57 by PROMISE Group D. Dividing participants into two prognostic groups, the SELECT model may help to distinguish those with a low 90 day mortality, but the real-world utility of a 'high risk' classification (>10% 90 day mortality risk) has yet to be determined.

Notably, the rate of EGFR positive mutation among patients with lung adenocarcinoma in the Asian population studied by Quek et al. was approximately four times that of the UK, Australian and Netherlands based LENT population (56% in the Asian cohort vs 12-15% respectively)[3]. This reflects the findings of previous studies [7, 8], which observe geographical variation in the incidence of EGFR mutation, with highest rates seen in the Asian-Pacific subgroups. Quek et al. highlight how inter-population differences can limit the transferability of a prognostic tool validated in one MPE cohort to another. The authors demonstrate the heterogeneity of the MPE population and subsequently, the importance of understanding local trends.

How should we therefore approach the next patient with a new MPE diagnosis? Survival estimates from prognostic scores are useful to inform discussion and provide some guidance about life expectancy. No model is perfect however and as therapeutic options advance, prognostic scores require adaptation and re-validation to keep up. It is essential to understand the limitations of whichever score is used, considered also in the context of the local population. No score yet offers a survival estimate accurate enough to determine an individualized treatment strategy. Factors such as patient preference and symptom burden should be regarded in equal measure. As our understanding of the complexity of the condition deepens, a universal 'one-size-fits-all' approach to patients with MPE is rendered an outdated concept.

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