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Picking the winners: outcome prediction in pleural disease

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MAIN TEXT
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The burden imposed on patients and healthcare providers by pleural disease is ever growing; the available data suggest that globally around 1 in every 300 people is affected on an annual basis, with the reported incidence of a number of common pleural conditions seen to be increasing [ref]. This rising caseload is particularly evident in the context of malignant pleural effusion (MPE), with an estimated 175,000 new cases every year in the United States alone; and an expectation that patient numbers will continue to grow given the increasing prevalence of cancer in an ageing population [ref]. Furthermore, the range of diagnostic and therapeutic interventions available to patients with pleural disease and their physicians [ref] means that identifying those individuals most likely to benefit from a particular treatment is becoming ever more important in an era of personalised medicine.

Despite this growing need, a common theme across the most frequently seen pleural conditions continues to be the lack of robust tools available to predict key clinical outcomes; for example, prolonged air leak and future recurrence in spontaneous pneumothorax, or morbidity and mortality from pleural infection. In this issue of *Respirology*, Leemans *et al* [ref] present data from a cohort of patients with malignant pleural disease with the aim of addressing another important question: how can we identify those patients with MPE in whom an attempted pleurodesis is likely to be unsuccessful?

Published data from randomised studies suggest that talc pleurodesis is successful in 70-80% of patients with MPE [ref]; and clinical research has preferentially focused on how this might be improved. There is ongoing interest in whether the means by which talc is introduced to the pleural space (i.e. thoracoscopic poudrage vs. slurry instillation via chest tube) might impact on treatment efficacy, following a large randomised trial [ref] showing a trend towards superiority of poudrage, and with a further randomised trial powered to provide a definitive answer to this question close to completion [ref]. Other work has looked at whether alternative sclerosant agents might prove superior to talc [ref] with little evidence of improved outcomes thus far.

However, instead of looking for marginal gains in the proportion of patients with MPE who will have a successful pleurodesis, we may be better served by seeking to understand the characteristics of those individuals in whom pleurodesis fails. Given the efficacy and acceptability of alternative strategies for the management of MPE [ref], having a robust means of identifying which patients with MPE would be better served by opting for an indwelling pleural catheter as a first-line intervention has obvious advantages.

The subset of patients with MPE who would immediately benefit from such a predictive model are those with unexpandable lung, reported to be around 30% of the MPE population [ref] and in whom pleurodesis is automatically precluded. Previously published data [ref] have shown a potential role for thoracic ultrasound (TUS) as a means of predicting the presence of unexpandable lung prior to pleural intervention, utilising either speckle-tracking imaging and/or motion (M-) mode TUS. This allows the operator to identify tissue strain and lung movement characteristics respectively that are associated with cardiac pulse transmission through lung tissue, and which potentially vary according to whether the atelectatic lung underlying an effusion is free or not. Leemans *et al* [ref] present data from a subset of their patients ($n = 30$) in whom M-mode TUS evaluation was performed prior to medical thoracoscopy; by using a cut-off of 2 mm for lung excursion with cardiac pulse transmission, they report a sensitivity of 91% and specificity of

88% for the detection of unexpandable lung. Whilst these data are encouraging and appear to replicate previous findings, a degree of caution is required given the small patient numbers and the fact that the authors chose to use a different cut-off value for the detection of unexpandable lung using M-mode TUS than that proposed elsewhere (2 vs. 0.8 mm) [ref]. Further prospective validation of M-mode TUS as a diagnostic technique for the identification of unexpandable lung is needed before its uptake as part of the routine evaluation of patients with MPE can be considered.

Leemans *et al* [ref] also describe the characteristics associated with pleurodesis failure in their wider patient population ($n = 155$). Of these, a prolonged interval (defined as >38 days) between first thoracentesis and subsequent pleurodesis; the presence of pleural adhesions at thoracoscopy; and the macroscopic extent of pleural involvement by malignant disease were all found to be predictive of subsequent pleurodesis failure. All these observations appear biologically plausible, and may be interlinked. Repeated pleural intervention and/or a delay in definitive treatment (i.e. pleurodesis) for MPE may promote the formation of fibrinous adhesions and septations within the pleural space [ref], thereby impacting on the ease with which fluid can be drained and the lung expanded. The macroscopic extent of malignant pleural involvement is likely to involve both parietal and visceral surfaces, with infiltration of the latter inevitably impacting on lung expansion.

The authors' finding that pleurodesis failure was also a marker of reduced survival with MPE (HR 0.52; 95% CI 0.30 to 0.91; $p = 0.02$) is an interesting one, and given their other observations would appear to fit with a recently published randomised trial of intrapleural fibrinolytics in septated MPE [ref] where median survival was less than two months. It is easy to extrapolate from these findings as to how TUS might inform outcome prediction and treatment choice in patients with MPE. There is robust data demonstrating the efficacy of TUS at identifying pleural adhesions and septations [ref], alongside features such as pleural nodularity and thickening seen in malignant disease [ref] without the need for thoroscopic examination. In conjunction with a validated M-mode marker of unexpandable lung, clinicians might in the future be able to guide patients towards or away from an attempt at drainage and/or pleurodesis at initial presentation with the application of a simple non-invasive ultrasound.

In conclusion, the work by Leemans *et al* whilst retrospective both adds to the evidence base and encourages further thought on how best to manage patients with MPE. As with other areas of pleural disease, further prospective and robustly designed research is needed to better define the characteristics of this population that will ultimately impact on clinical outcomes that are important to both patients and clinicians.