What's the Score? Do pleural effusion clinical scoring systems help in management of disease?

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Abstract

Pleural effusion is a common condition, affecting over 3000 people per million population every year. More than 50 causes of pleural effusions are known, including pleural infection and malignant pleural disease. These conditions place a large burden on healthcare systems with one fourth of patients with pleural infection having a length of hospital stay of more than one month. Malignant pleural effusion represents advanced malignant disease with a correspondingly high mortality.

Prognostic models using clinical information in combination with blood or pleural fluid biomarkers predicting survival and other outcome measures are therefore a priority in improving clinical care, and potentially outcomes. Identifying patients with poor prognosis may help to avoid discomfort and unnecessary interventions at the end of their lives, while, on the other hand, individuals with scores predicting a particularly good prognosis might be selected for more aggressive early treatment. Such scores must be based on data representing routine practice in a general hospital and variables chosen based on their clinical availability at clinical decision points (i.e. before treatment is instituted), making the findings widely applicable.

Key words:

Pleural effusion, scores, prognosis, management, pleural infection, malignant, LENT, PROMISE

Introduction

Pleural effusion is a common condition. It affects over 3000 people per million population every year (1). More than 50 causes of pleural effusions are recognised, including conditions such as pleural infection and malignant pleural disease (2). In the United States, 126,825 hospitalisations were shown to be due to malignant pleural effusions in 2012 (3). Malignant pleural effusion represents advanced malignant disease with a corresponding high mortality. Pleural infection is increasing in incidence. One fourth of patients with pleural infection have a length of hospital stay of more than 1 month. Moreover, it has a high mortality of more than 10%. (4)

Treatment of these conditions may cause morbidity and places a large burden on healthcare systems. A prognostic model using clinical information in combination with blood or pleural fluid biomarkers predicting survival and other outcome measures may therefore be important for adequate management (5). Identifying patients with poor prognosis may help to avoid discomfort and unnecessary interventions at the end of their lives (6). It is key that any such score is based on data representing routine practice, and the variables chosen based on clinical availability making the findings widely applicable.

Factors predicting patient-reported outcome measures (PROMs)

Pleural effusions (PE) can profoundly affect the cardiorespiratory system with breathlessness being the most common presentation. It is often debilitating and significantly impairs quality of life. Patient-reported outcome measures (PROMs) indicate a patient's health status or health-related quality of life at a single point in time and are gathered through short, self-

completed questionnaires. They offer the opportunity to improve quality and outcomes of health services, reflecting patients' experiences and views.

Relief of breathlessness often necessitates therapeutic pleural interventions. However, pleural interventions are by nature invasive with associated discomfort, risks of infection, bleeding, pneumothorax and even death. Moreover, the severity of breathlessness often correlates poorly with the size of the PE, and symptom reduction from fluid drainage varies significantly between patients. The provision of a simple scoring system which might predict symptomatic response to pleural intervention is therefore an attractive potential to both clinicians and patients.

Unfortunately, to date there are no clinical scores predicting symptomatic benefit from pleural intervention in patients with pleural effusion, despite pleural interventions to relieve breathlessness being one of the most common procedures conducted in medicine. In a study by Psallidas et al. (7), a correlation between fluid removal and improvement in patients' dyspnoea was identified. However, 14.3% of patients undergoing therapeutic aspiration did not experience a significant change in breathlessness – and it should be noted that all such patients had been “selected” by clinicians as those with the possibility of benefit from a therapeutic procedure. The average fluid drained in patients with a lack of relevant symptomatic benefit was 836 mL, underlining the idea that volume of drainage alone (and therefore size of pre-drainage effusion) may not predict symptom benefit, underlying the potentially complex interaction between pleural fluid presence, physiological change and the symptom of breathlessness.

In this study, the presence of septations was shown to be independently and negatively correlated with improvement in dyspnea (7), where septations were scored as none, 1–2, 3–4 and >5 septations visible in a single ultrasound field at the area of maximum septation. The cause of this association is unclear – but it is unlikely to be related to lack of drainage, given that the amount of fluid drained was not lower in these patients than average. We speculate that septations may be a surrogate marker for unexpandable lung (with the same fibrin driving process occurring in the pleural fluid as on the visceral pleural surface), but this hypothesis is yet to be tested. Interestingly, the recently published TIME 3 trial has shown that the use of urokinase in patients with a septated malignant pleural effusion did improve chest radiograph appearance and mortality but did not affect dyspnea (8). The fact that the radiographs improved with no improvement in measured dyspnoea may be explained by the average survival in these patients being very poor, perhaps suggesting that dyspnoea was multifactorial near the end of life, and could not significantly improve with pleural intervention.

Considering other potential mechanisms of dyspnoea, diaphragm dysfunction is a significant potential association in pleural disease. This can be evaluated by diaphragmatic ultrasound, by measuring diaphragm thickness at end expiration or diaphragmatic thickening fraction (TF). Low TF was shown to be a good predictor of weaning in patients on invasive mechanical ventilation for at least 24 hours. (9). To date, no data exist regarding static or dynamic diaphragmatic dysfunction as predictor of symptomatic benefit after pleural drainage.

Patients in whom an effusion is associated with flattening, inversion or paradoxical motion of the ipsilateral hemidiaphragm on thoracic ultrasound will almost always experience significant

symptomatic benefit from pleural fluid aspiration due to the improvement in respiratory mechanics (10, 11).

Unexpandable lung is a condition where the lung is not able to completely re-expand, even following adequate pleural fluid drainage. This state is thought to lead to persisting dyspnoea, although previous small case series have suggested significant improvement in dyspnoea after drainage despite lack of lung expansion. Knowledge of whether a patient has unexpandable lung before any pleural intervention would help to avoid unnecessary interventions. Ultrasound markers of unexpandable lung have been identified. The degree of lung movement related to the cardiac impulse during a breath hold using M-mode was shown to be significantly diminished in entrapped lung (12). However, as to whether this finding influences symptomatic benefit from large volume aspiration is unknown.

There are therefore a number of baseline parameters commonly measured in pleural disease, which might predict improvement in dyspnoea. The ability to select and limit pleural interventions to patients who are likely to have symptomatic benefit from fluid drainage based on clinical and sonographic findings (or a combination thereof) would represent a major advance in pleural medicine, and studies specifically addressing the above areas are now required.

Malignant pleural effusion and prognosis

Malignant pleural effusion (MPE) is common, affecting 500–700 individuals per million population annually. The estimated annual incidence is of 150 000 in the USA and the incidence is rising (13). MPE represents advanced malignant disease with inherent high

mortality. Guidelines state median survivals of between 3 and 12 months (14). However, with improvements in therapy affecting survival of patients, the burden of malignant pleural effusion is increasing (15, 16).

Interestingly, clinical judgment alone is imprecise for estimation of patient survival. This is highlighted by the ineffective exclusion of study participants with poor prognosis from large clinical trials (17), in which up to 25% of patients did not survive for the required length in inclusion criteria. This suggests that clinicians are poor in predicting prognosis from clinical judgement alone.

Treatment may cause morbidity and necessitate an inpatient stay; hence, a prognostic model using clinical information in combination with blood or pleural fluid biomarkers identifying patients with the poorest prognosis may help to minimise unnecessary interventions and discomfort. This could also be used for other outcome measures e.g. pleurodesis response to and to balance randomisation groups in the clinical trial setting.

Factors predicting survival in patients with malignant pleural effusion

A number of factors may predict survival of patients with malignant pleural disease, including type of primary cancer, histological subtypes, extent of disease, performance status and comorbidities (6, 18, 19, 20, 21). Moreover, several inflammation-based prognostic scoring systems have been developed (22). These include the neutrophil-to-lymphocyte ratio (NLR) and the modified Glasgow Prognostic Score (mGPS) which uses raised circulating C-reactive protein (CRP) and hypoalbuminemia. High blood neutrophil-to-lymphocyte ratio was shown to be associated with a poor prognosis in patients with malignant mesothelioma undergoing systemic therapy (23). Again, in patients with malignant pleural mesothelioma, the mGPS correlated with outcome and sustained neoangiogenesis and increased proliferative index (24).

LENT

The LENT study (6) was performed to gain data on overall survival and survival dependent on underlying cell type for patients with malignant pleural effusion and to identify prognostic indicators of overall survival in unselected patients with malignant pleural effusion. The final aim was to develop and validate a prognostic scoring system to guide clinical management decisions.

Three prospectively collected databases from 3 different countries comprising of patients presenting with their first episode of MPE were used. Data were obtained on 789 patients, all of whom had been followed up for a minimum of 12 months or until death. A prognostic scoring system ('the LENT score') was derived retrospectively from a subset of variables from the 'UK Cohort 1' which represented routine practice in a general hospital making the findings

widely applicable. Variables were chosen based on the dimension of the hazard ratios (HRs) and their clinical availability.

Four variables (pleural fluid LDH, Eastern Cooperative Oncology Group (ECOG) performance score (PS), serum neutrophil-to-lymphocyte ratio (NLR) and tumour type) were selected to be included in a predictive model. The scoring system results in a score range of 0–7. The score proved robust in validation using patients with no missing data for the four variables included from ‘UK Cohort 2’.

Based on the derived LENT score, patients can be divided into low-risk (score 0–1), moderate-risk (score 2–4) and high-risk (score 5–7) prognostic groups at the time of presentation with MPE. Survival analysis of the combined cohorts showed a large spread of survival times, ranging from median survivals of under 50 days in the urological cancer, sarcoma and melanoma groups, compared with 339 days for those patients with mesothelioma. The lung cancer group had a median survival of only 74 days. Although the score was derived retrospectively, it was validated on a separate data cohort and demonstrated to be robust.

The LENT score is the first validated risk stratification system in MPE and is significantly better than ECOG PS at predicting survival. Moreover, it is less subjective than performance status alone, as it relies on readily available tests. Should we thus use the LENT score in predicting survival in all MPE patients at presentation? There is no doubt that this score is clinically highly accessible and appears to be robust - however, the score may not be generalized to all patients with clinically suspected MPE or para-malignant effusions, as it was developed using patients with robust diagnoses of malignant pleural effusion. Secondly, the spread of risk score

categories in real practice requires assessment, and perhaps most importantly, the change in clinical decision making according to the LENT score (e.g. low score results in more aggressive intervention, higher scores result in a more palliative approach) requires prospective assessment with patient centred outcome measures, and this has not occurred to date.

PROMISE

This multicohort study (5) was unique, in that it consisted of a three-step approach (discovery, validation, and prospective assessment) in a single study, and included an unbiased assessment of baseline pleural fluid biological markers. The discovery phase included a biological section (quantitative proteomic analyses of pleural fluid) and a clinical section (identification of prognostic clinical variables in published cohorts comprising patients with stage IV cancer and proven malignant pleural effusion (8, 17, 25)). Based on these findings, a model was developed and validated in two separate cohorts. Finally, the model was prospectively assessed in two independent datasets from ongoing randomised studies in patients with malignant pleural effusion.

The TIME-2 database was used for the discovery phase. Study participants were categorised as having poor (<3 months) or good (≥ 3 months) survival. A total of 25 candidate predictors were assessed, including baseline demographics (age and sex), malignancy type, previous chemotherapy or radiotherapy, severity of illness, serum laboratory values, and pleural fluid proteins. A single upstream regulator protein identified with quantitative proteomic analyses (TIMP1) showed differential expression that was significant between the good and poor survival groups.

A simplified version of the final model was created, that was implementable in real-life practice, while maintaining predictive performance and the ability to calculate absolute risk. All continuous predictors were categorized, which allowed the assignment of points to each category of each predictor. In order to facilitate the pragmatic application of the PROMISE score in every hospital setting, the authors have proposed a clinical PROMISE score with only clinical information and no biological factor, which proved to have a reasonable performance. A simple table was produced to transform the total point scores into an absolute risk.

	Points
(Continued from previous column)	
Biological PROMISE score	
Chemotherapy	
No	0
Yes	3
Radiotherapy	
No	0
Yes	2
Haemoglobin (g/dL)	
>16	0
14–16	1
12–14	2
10–12	3
<10	4
White blood cell count (10 ⁹ cells per L)	
<4	0
4–6.3	2
6.3–10	4
10–15.8	7
>15.8	9
C-reactive protein (IU/L)	
<3	0
3–10	3
10–32	5
32–100	8
>100	10
ECOG performance status	
0–1	0
2–4	7
Cancer type	
Mesothelioma	0
All other types of cancer	5
Lung	6
TIMP1 (ng/mg protein)	
<40	0
40–160	1
>160	2
© 2018 Oxford University. ECOG=Eastern Cooperative Oncology Group. TIMP1=tissue inhibitor of metalloproteinases 1.	
Table 2: Clinical PROMISE score and biological PROMISE score (clinical plus TIMP1)	

The external validation dataset comprised 162 individuals from the SIMPLE study (26) and Oxford Radcliffe Pleural Biobank databases. Discrimination was high and similar for full and simplified PROMISE models – both the clinical and biological PROMISE scores showed good discrimination.

Based on the risk of death by 3 months, the PROMISE score can be classified into four categories. Category A is less than 25%, B is 25% to less than 50%, C is 50% to less than 75% and D is 75% or more. Finally, the clinical and biological PROMISE scores and the LENT score were validated, using complete case data, which included 192 individuals. Kaplan-Meier estimates showed good discrimination of survival for all three models and revealed that PROMISE scores performed better than LENT score despite smaller sample sizes.

Figure 3: Performance of LENT score and PROMISE score in patients with malignant pleural effusion

(A) Kaplan-Meier survival curves from patients with low, medium, and high LENT score. Kaplan-Meier survival curves from patients classified into PROMISE score categories for the clinical (B) and biological (C) PROMISE score.

Individuals with a PROMISE score category A (with <25% absolute risk of death) had a particularly good prognosis, and these patients could be selected for more aggressive pleural and potential oncological or surgical management. In patients with a PROMISE score category

D ($\geq 75\%$ absolute risk of death), it may be reasonable to offer minimally invasive procedures aimed at symptom control (eg, therapeutic aspiration or indwelling pleural catheter insertion), best supportive care, and a strategy to spend as few days as possible in hospital.

The development of the PROMISE score was an important step forward in the precise and personalized management of malignant pleural effusion. It could potentially be used in everyday clinical practice as a method to improve patient management, reduce associated health-care costs, and as an enrichment strategy for future clinical trials. However, as for the LENT score, data showing that use of the score impacts and improves care of quality of life by refining clinical decision making is lacking to date. One potential advantage of the PROMISE score over LENT is that a precise risk of death can be calculated for the individual, which may be helpful for patients.

Factors predicting pleurodesis success in patients with malignant pleural effusion

Malignant pleural effusion (MPE) is associated with a poor prognosis. The presence of malignant cells in the pleural space reflects highly metastatic malignancy irrespective of the primary neoplasm. Most patients will have therapeutic drainage for relief of breathlessness (27). In case of recurrent MPE, patients may be managed with the insertion of an indwelling pleural catheter or chemical pleurodesis. Chemical pleurodesis is most often performed using sterile talc, generating inflammation in the pleural space. This process generates adhesion formation and pleural space obliteration, preventing MPE recurrence (28, 29). A failure rate of 22 % for talc pleurodesis via intercostal chest tube was reported in the TIME2 trial (25).

In a prospective observational cohort pilot study by Corcoran et al. (30) the role of thoracic ultrasound (TUS) in predicting long-term pleurodesis success or failure in malignant pleural

effusion was investigated. Standardized bedside TUS assessment was performed immediately before and 1 day following talc slurry instillation. A total pleural adherence score for the hemithorax was calculated: lung sliding was scored in nine zones (upper, middle, and lower zones in the anterior, lateral, and posterior chest wall) as present (= 0), questionable (= 1), or absent (= 2) (31).

Eighteen patients were included in the study. 83.3% participants reached the 1-month follow-up. Eleven of these 15 patients (73.3%) had successful pleurodesis by this time point.

There was a significant difference between mean total pleural adherence score at day 1 for patients with successful vs failed pleurodesis. Thereby, interrater reliability was good to excellent. None of the 11 participants with a successful pleurodesis at 1-month follow-up suffered delayed failure.

This study shows that TUS can detect early loss of lung sliding due to pleural adhesion formation following talc pleurodesis for MPE, predicting long term pleurodesis success. This hypothesis is currently under assessment in a large randomised trial (SIMPLE) which should definitively answer the question of ultrasound guided pleurodesis and is more than 80% recruited currently (32).

The PROMISE study, while accurately estimating the 3-month mortality in patients with malignant pleural effusion (5), [was not successful in identifying biomarkers of](#) pleurodesis outcomes. In the proteomic analysis, success and failure groups did not have distinct protein profiles. Whether this is related to no proteomic profile being associated with pleurodesis

outcome, or related to degradation of measured markers in historical frozen samples, is not known.

A prognostic model using the combination of clinical data as well as blood and pleural fluid biomarkers that predicts pleurodesis response before the intervention is performed would be of great importance for patient management. PROMISE represents the first such practically applicable tool; however, further studies are now required to fully investigate pleural fluid and clinical parameters prospectively, both to predict pleurodesis and further understand the biological basis of this common treatment.

Factors predicting survival in patients with pleural infection

Pleural effusion may develop in up to 44% of patients with community-acquired pneumonia (33). Pleural infection is increasing in incidence and is currently estimated to affect more than 65,000 patients per year in the United States and in the United Kingdom (4). The median duration of the hospital stay for patients with pleural infection is 12 to 15 days, with 25% of patients having a length of hospital stay of more than 1 month (34, 35). Pleural infection has a high mortality rate of between 10% and 20% (36, 37). The associated health care costs are high with the care of each patient costing approximately \$5,000 (38).

The Standard treatment of pleural infection involves appropriate antibiotics and drainage of pleural fluid. This treatment fails in up to one third of patients, requiring surgical drainage (39). Early surgical intervention including video-assisted thoracoscopic surgical drainage as well as open thoracotomy with decortication may be beneficial for some patients (39, 40, 41, 42). However, these surgical procedures are associated with perioperative risks (43).

Moreover, thoracotomy may cause substantial postoperative pain (44). Evidence from the MIST2 trial, a randomized placebo- controlled trial suggests that a combination of intra-pleural DNase and fibrinolytic improves change in pleural opacity and may be associated with reduced hospital stay and reduced surgical referral (38). However, the drug treatment cost for this intervention is significant.

A reliable and sensitive clinical prediction model of poor outcome in pleural infection would enable clinicians to triage patients in terms of risk and might enable targeting of more aggressive and expensive therapies to patients with the poorest out-comes.

A cohort study in which clinical care was based on structured treatment guidelines assessed whether generally accepted clinical, pleural fluid, and radiological baseline characteristics reliably identified patients at high risk of treatment failure with medical therapy in 85 consecutive patients with pleural infection. The absence of frank pleural fluid (PF) purulence was the only clinically useful predictor of successful outcome with medical therapy. However, the presence of purulent PF did not predict the fail. (45). This finding was later confirmed in a second study where the development of residual pleural thickening (RPT) in patients with parapneumonic effusion was found in 48 of the 348 patients included (13.79%). Among the factors studied, presence of pus in the pleural space was independently associated with the risk of RPT (46).

The goal of a study by Rahman et al. (4) was to develop a clinical risk score in patients with pleural infection using baseline characteristics able to predict poor outcome. Data from two randomized trials of intrapleural agents for the treatment of pleural infection, the MIST1 (34)

and MIST2 trials (38), were analysed. For the initial model derivation, the baseline clinical and outcome data from MIST1 trial were used. This model was then validated using baseline clinical and outcome data from the MIST2 trial.

Poor clinical outcome was defined as mortality at 3 months, surgical intervention at 3 months, and hospital stay. Variables from the MIST1 trial associated with poor outcome were chosen to form the basis of the risk score. Age > 70 years, hospital (as opposed to community acquired) infection, and urea level > 8 mM were all strongly associated with increased mortality at 3 months. Pleural fluid purulence and albumin level > 27 g/L were associated with a decreased risk of mortality at 3 months. The RAPID score (renal, age, purulence, infection source, and dietary factors) was based on these findings with the weight of each variable depending on their mortality OR.

This risk score was then validated using patients from the MIST2 cohort. MIST2 patients were classified into low-risk (score 0-2), intermediate-risk (score 3-4), and high-risk (score 5-7). Mortality and surgery at 3 months and time to discharge within these groups were then assessed.

Table 2—Scoring System (RAPID) Derived From the Initial Prediction Model Using Baseline Characteristics

Parameter	Measure	Score
Renal		
Urea, mM	< 5	0
	5-8	1
	> 8	2
Age, y	< 50	0
	50-70	1
	> 70	2
Purulence of pleural fluid		
Purulent	...	0
Nonpurulent	...	1
Infection source		
Community acquired	...	0
Hospital acquired	...	1
Dietary factors		
Albumin, g/L	≥ 27	0
	< 27	1
Risk categories		
Score 0-2	...	Low risk
Score 3-4	...	Medium risk
Score 5-7	...	High risk

Each patient can obtain a score from 0 to 7. RAPID = renal, age, purulence, infection source, and dietary factors.

Validation of the risk categorization in the MIST2 cohort demonstrated mortality of 3% in the low-risk group, 9% in the medium-risk group and 31% in the high-risk group. For hospital stay, the median time to hospital discharge in the low-risk group was 7 days (IQR, 6-13), compared with 10 days (IQR, 8-18) in the medium-risk group ($p=0.42$), and 15 days (IQR, 9-28) in the high-risk group ($p = 0.08$).

This risk stratification at baseline is a potentially important tool for the treating physician, with the potential to identify those at high risk at presentation, facilitating earlier discussions about aggressive management strategies while the patient is still well enough to receive them.

FIGURE 2. Survival curves for the MIST1 and MIST2 cohort of patients according to the derived RAPID scoring system. RAPID = renal, age, purulence, infection source, and dietary factors. See Figure 1 legend for expansion of other abbreviations.

Patients in the MIST1 and MIST2 studies closely reflect the normal population of pleural infection. Hence the score can be considered as robust and based on a representative sample. Prospective assessment of the score has been conducted in the largest study to date worldwide in pleural infection (PILOT), the results of which should be published in the next 12 months (47).

RAPID therefore appears to be a powerful predictor of outcome - however, there is a potential limitation in the application of this risk score to the prediction of need for surgical intervention, as surgical referral practice varies considerably between healthcare systems.

Factors predicting cardiac origin of exudates

Pleural effusions are a common finding in patients with decompensated heart failure (HF). Performing thoracentesis is unnecessary in most cases. However, the diagnosis of cardiac effusions is not always straightforward, even in the presence of pleural fluid data (48, 49).

According to the Light's criteria, pleural fluid is considered an exudate if any of the following are met (50): (1) ratio of pleural fluid protein to serum protein level > 0.5 ; (2) ratio of pleural

fluid LDH to serum LDH level >0.6 ; (3) pleural fluid LDH level more than two-thirds the upper normal reference serum value. The above criteria were developed in a way to be sensitive for identifying exudates. Therefore, they misdiagnose 15% to 25% of transudates as exudates (51, 52).

However, a study by Romero-Candeira et al. showed a significant superiority of Light's criteria over clinical presumption. In this study, two physicians made an estimation of the characteristics of the effusion (transudate or exudate) based on clinical, radiological and laboratory information before performing pleural tap (53).

It has previously been demonstrated that measurement of the levels of the amino-terminal fragment of pro-brain natriuretic peptide (NT-proBNP) in pleural fluid using a cut-off value of >1500 pg/mL has an accuracy for identifying pleural effusions from cardiac causes of 90% (54). In a study by Porcel et al. (52), the respective median levels of NT-proBNP in pleural fluid and serum were significantly higher in patients with heart failure (6106 pg/mL and 6368 pg/mL) than in patients with effusions from other causes (373 pg/mL and 504 pg/mL, all $P < 0.001$). Multivariate analysis evaluating a range of endpoints – pleural fluid to serum protein ratio < 0.5 , pleural fluid to LDH ratio < 0.6 , pleural LDH lower than two-thirds the upper limit of the reference interval, pleural cholesterol < 45 mg/dL, serum-pleural fluid protein gradient > 31 g/L, serum-pleural fluid albumin gradient > 12 g/L, and pleural and serum NT-proBNP > 1500 pg/mL – indicated that pleural NT-proBNP was the best diagnostic parameter for effusions owing to heart failure. The authors concluded, that pleural NT-proBNP may provide complementary information and reassurance in doubtful cases, especially in patients using diuretics.

The goal of a yet another study by Porcel et al. (49) was to develop an easily applicable score based on the combination of clinical, radiological and pleural fluid biochemical data for the accurate identification of exudative effusions (according to Light's criteria) in the context of heart failure, when natriuretic peptides are not immediately available.

Data of patients who had undergone diagnostic thoracentesis were reviewed retrospectively, if their pleural fluid met Light's criteria for exudates. These data helped to generate a scoring system for discriminating between cardiac and non-cardiac effusions. This score was subsequently validated in an independent sample of patients who were also retrospectively identified at a different hospital.

The diagnosis of heart failure relied on history, physical examination, chest-X ray, echocardiogram and response to diuretics. Alternative diagnoses included definitive diagnosis of malignant effusion, probable malignancy, tuberculous pleuritic, parapneumonic effusions and empyema. A total of 3182 adult patients with exudative pleural effusions were identified to establish the derivation sample. 276 (8.7%) of these patients were found to have a pleura effusion related to heart failure. 9.2% of the 1165 patients constituting the validation sample had pleural effusion of cardiac origin.

The individual findings that increased the probability of cardiac effusions the most were the presence of a bilateral effusion on a chest radiograph (LR = 4.3), a serum to pleural fluid protein gradient > 3.1 g/dL (LR = 3.9), and a pleural fluid LDH concentration < 250 U/L (LR = 3.5). Conversely, the findings that decreased the probability of HF-related effusions the most were a protein gradient ≤ 2.5 g/dL (LR = 0.30), an albumin gradient ≤ 1.2 g/dL (LR = 0.33) and

age < 75 years (LR = 0.34).

Five variables were selected by the logistic regression model and served to generate a scoring system for predicting HF-related effusions: age $\geq$ 75 years (3 points), albumin gradient > 1.2 g/dL (3 points), bilateral effusions on chest radiograph (2 points), pleural fluid LDH < 250 U/L (2 points) and protein gradient > 2.5 g/dL (1 point). Thus, scores ranged from 0 to 11. In the validation sample, a score of 7 or more greatly increased the probability of having a cardiac effusion (LR positive 6.5), whereas a score < 7 decreased this probability (LR negative 0.33). This score exceeded the discriminative capabilities of protein and albumin gradients in isolation.

Overall, the scoring system may represent a useful tool in the identification of cardiac pleural effusions miscategorised by standard criteria, when peptide data are lacking.

However, the score can only be applied to patients for whom a pleural aspiration is performed. (52; 55).

Conclusion

Scores for predicting survival and other outcome measures for the most common pleural diseases based on data representing routine practice and variables chosen based on their clinical availability at clinical decision points (i.e. before treatment is instituted) have recently been developed. Two scores, the LENT score and the PROMISE score have been found to predict survival in patients with malignant pleural effusion, with PROMISE being the first to demonstrate and validate a pleural fluid biological signal. The RAPID score for patients with pleural infection was based on a representative sample of two large studies and prospectively

assessed, the results of which should be published soon; it appears to be a powerful predictor of outcome. Factors predicting clinical benefit from pleural aspiration in symptomatic patients with large pleural effusion (e.g. presence of septations) were identified but await prospective validation.

However, data showing that use of these score impacts and improves care and quality of life by refining individual clinical decision making or that it reduces associated health-care costs is still lacking. Therefore, the use of risk score categories in daily practice with the associated change in clinical decision making according to these scores requires prospective assessment with patient centred outcome measures.

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