Pleural infection is increasing in incidence in both pediatric and adult populations and is currently estimated to affect > 65,000 patients per year in the United States and in the United Kingdom. These infections carry a significant health burden: (1) Mortality is between 10% and 20%, (2) approximately one-third fail medical management and require surgical drainage, (3) 25% of patients require a hospital admission lasting > 1 month, and (4) health-care costs are estimated at around $5,000 (US dollars) per patient, which equates to approximately $320 million US dollars per year (United Kingdom and United States).

Standard treatment of pleural infection involves appropriate antibiotics and drainage of infected pleural fluid/pus with an intrapleural catheter. More complex surgical drainage techniques (eg, video-assisted thoracoscopic surgical drainage, open thoracotomy with decortication, rib resection, and open drainage) are advocated in patients with a poor response to initial treatment. A large cohort of 4,424 cases and other small surgical series suggest effective surgical drainage may be associated with improved outcome in selected patients. Early surgical intervention may, thus, be appropriate for high-risk patients. Although surgery has been advocated as initial treatment of all patients with pleural infection, evidence to support the unselected use of surgery in all patients is lacking. Two moderate-sized pediatric clinical trials...
showed no clinical benefit and greater cost from this approach,12,22 and two small adult randomized trials did not use robust outcome methodologies.23,24 Surgical thoracic procedures are associated with anesthetic and perioperative risks,25 and thornotomy causes substantial postoperative pain26 up to 3 years after operation.27

Thus, surgery is a vital treatment option in pleural infection, but one that may be best used in selected patients. Evidence from a randomized placebo-controlled trial28 suggests that a combination of intra-pleural DNase and fibrinolytic improves radiology and may be associated with reduced hospital stay, reduced infection, and reduced surgical rates. 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 outcomes. To date, there are no robust validated methods for selecting high-risk patients at presentation in pleural infection.

A cohort study in which clinical care was based on structured treatment guidelines9 in 85 sequential patients assessed whether the generally accepted baseline predictors reliably identified patients at high risk. Only pleural fluid purulence had predictive power for a poor outcome, and this was insufficiently sensitive and specific to be of clinical value.9 This finding was later confirmed in a second study,29 in which predictors of residual pleural scarring were identified, although this was not associated with clinical disability.

Thus, the traditionally used predictors of outcome in pleural infection have not been borne out in clinical studies specifically designed to assess their use. This study was conducted to derive a clinical risk score using baseline characteristics able to predict poor outcome, and then to validate this prediction model in a subsequent cohort of patients with pleural infection.

**Materials and Methods**

This study used data from two randomized trials of intrapleural agents for the treatment of pleural infection10,16 diagnosed according to identical and standard clinical criteria (described here). The initial model derivation was conducted using baseline clinical and outcome data from the first Multicenter Intrapleural Sepsis Trial (MIST1) (ISRCTN39138989),16 a placebo-controlled randomized trial assessing the use of intrapleural streptokinase that recruited 454 patients from 54 UK centers from 2002 to 2004. The derived model was then separately validated using baseline clinical and outcome data from the subsequent MIST2 trial (ISRCTN57454527),28 a randomized-controlled trial assessing the use of intrapleural DNase and tissue plasminogen activator in which 210 patients were recruited from 11 UK centers between 2005 and 2008, demonstrating a significant improvement in the primary outcome measure (radiographic improvement) for the combination treatment compared with placebo. Full trial details and protocols are available with the original publications10,16 and included protocol recommendations on type and duration of antibiotic therapy and intrapleural catheter use.

Patients in both studies were included if they had clinical evidence of infection and fulfilled any of the following criteria: pleural fluid that was macroscopically purulent, positive result on culture for bacterial infection, positive result for bacteria on Gram staining, or pleural fluid that had a pH of <7.2 (measured using blood gas analyzer). Evidence of infection was assessed by the recruiting physician on the basis of fever and elevated serum inflammatory markers such as C-reactive protein or WBC count. Study exclusion criteria for both studies were identical and are listed in e-Appendix 1.

The outcomes used in the model construction and derivation phase of the study were those considered clinically important: mortality at 3 months post-randomization, hospital stay from randomization to discharge to home/convalescent care, and requirement for surgical intervention at 3 months. For model selection, the outcome of mortality at 3 months was considered decisive.

**Data Analysis**

Model selection was undertaken using the MIST1 cohort (in 411 of 454 [90.5%] patients in whom baseline data of potential predictive value were present to find variables predictive of a poor clinical outcome; see e-Table 1 for a full list of variables considered). Backward selection with a P value of .05 was used to find variables associated with mortality at 3 months, surgical intervention at 3 months, and hospital stay; with a separate model used for each outcome. Surgery and time in hospital were also assessed in patients who were younger than 70 years of age to assess for a differential age effect. A subset of variables shown to be predictive of poor outcome was chosen to form the basis of the risk score. Variables were chosen based on the strength of association, clinical plausibility, and ease of data collection at baseline for a potential predictive model. Effects of intrapleural treatments (streptokinase or tissue plasminogen activator/DNase) were not modeled as baseline covariates were likely to be well balanced.
between treatment arms (due to randomization), therefore, preventing bias by ignoring treatments and allowing more generalizable results. Multiple imputation using chained equations\(^3\) was used for patients with missing baseline variables, and 10 imputations were used. Fractional polynomials were used for continuous predictors.\(^4\) Risk stratification according to the model was planned in to low, intermediate, and high groups, with the lowest risk groups acting as the baseline comparator.

The risk score derived from the MIST1 cohort was validated using patients from the MIST2 cohort. This was achieved by classifying MIST2 patients into low-risk, intermediate-risk, and high-risk groups according to the risk score derived from MIST1 and assessing mortality and surgery at 3 months and time to discharge within these groups. Overall survival was assessed using a Cox model. Missing baseline variables used in calculating the risk score were handled using sensitivity analyses, assuming best-case and worst-case scenarios for each missing variable.

Ethical and regulatory approval for each study was obtained before recruitment commenced and each trial was registered (MIST1 [MREC 98/5/61] and MIST2 [04/mre5/5]). For full details of registration, chest tube treatment, and antibiotic management, please see the original publications.\(^10,28\)

**Results**

**Patients and Data Completeness**

The trial flowchart combining patients from both studies is presented in Figure 1. The baseline demographic, clinical, and microbiologic characteristics of participants in the combined trial populations and degree of data completeness for the purpose of this study are presented in Table 1. Mortality at 3-month data (primary outcome) were available in 617 of 621 patients (99%), and secondary outcomes (surgery at 3 months and hospital stay from randomization) were available in 614 of 621 patients (99%) and 617 of 621 patients (99%), respectively. Derivation of the predictive model was conducted in 411 of 454 patients, and validation of the model was undertaken in 191 of 210 patients (91%).

**Predictive Modeling**

Parameters selected and predictive of the specified outcomes using the MIST1 dataset (n = 411) are summarized in e-Table 1. 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, the presence of joint disease as a comorbidity, diastolic BP (>70 mm Hg), and albumin level > 27 g/L were associated with a decreased risk of mortality at 3 months.

The only variable predictive of surgery at 3 months was age > 70 years, associated with a decreased chance of surgery. Initial drain insertion conducted by a radiologist and serum albumin level > 27 g/L were associated with a decreased length of hospital stay. Urea level > 8 mM, hospital-acquired infection, and the presence of cardiac disease as a comorbidity were associated with increased length of stay.

**Creation of a Predictive Model**

On the basis of the results described previously, renal profile (urea/age/purulence of pleural fluid/infection source (hospital vs community), and dietary factors (albumin) at baseline were used as predictors to form a scoring system (renal, age, purulence, infection source, and dietary factors [RAPID]). Other variables (e-Table 1) predictive of outcome were not included from the predictive modeling stage to maintain a clinically applicable and practical scoring system (Table 2). As the mortality ORs were higher for age and renal profile, these were given a score out of 3 in the final scoring system. To aid clinical use of the RAPID score, patients were stratified according to score into low-risk (score 0-2), medium-risk (score 3-4), and high-risk (score 5-7) groups (Table 2). The estimated ORs from each individual parameter derived in the prediction model are presented in Table 3.

Using the derived RAPID risk categorization (low/medium/high) in the MIST1 cohort, mortality at 3 months in the low-risk (reference) group was 1% (one of 186), compared with 12% (14 of 121) in the medium-risk group (OR, 24.4; 95% CI, 3.1-186.7; \(P = .002\)) and 51% (26 of 51) in the high-risk group (OR, 192.4; 95% CI, 25.0-1480.4; \(P < .001\)). For overall survival, the hazard ratio was 11.87 in the medium-risk group (95% CI, 4.16-33.85; \(P < .001\)), and 48.27 in the high-risk group (95% CI, 16.98-137.20; \(P < .01\)).

Median time to hospital discharge in the low-risk group was 10 days (IQR, 7-16), compared with 15 days (IQR, 10-30) in the medium-risk group (\(P < .001\)), and
18 days (IQR, 9-26) in the high-risk group ($P < .001$). Data on missing variables and sensitivity analyses are presented in e-Table 2. These analyses demonstrated no important differences using best-case or worst-case scenarios in the predictive outcomes.

Model Validation Results (MIST2 Cohort)

Assessment of the RAPID score in the MIST2 cohort demonstrated albumin (OR, 2.8; 95% CI, 1.1-7.0; $P = .04$) and urea (OR for highest category, 3.96; 95% CI, 1.7-9.4; $P = .002$) as significant predictors of mortality at 3 months. Age (OR for highest category 4.66, $P = .07$), infection source (OR, 1.71; $P = .41$), and purulence (OR, 2.05, $P = .22$) also showed strong effects but did not reach statistical significance (e-Table 3).

Validation of the risk categorization in the MIST2 cohort demonstrated mortality of 3% (three of 97) in the low-risk (reference) group, 7% (six of 65) in the medium-risk group (OR, 3.2; 95% CI, 1.2-8.5; $P = .04$) and 28% (nine of 29) in the high-risk group (OR, 14.1; 95% CI, 3.5-56.8; $P < .001$) (Table 4). For each patient can obtain a score from 0 to 7. RAPID = renal, age, purulence, infection source, and dietary factors.
Table 3—Parameter Estimates Predicting Mortality at 3 Mo From the MIST1 (n = 408) Cohort Using the Individual Variables in the RAPID Score

<table>
<thead>
<tr>
<th>Variable</th>
<th>Died 3 Mo (%)</th>
<th>OR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50 (ref)</td>
<td>1/125 (1)</td>
<td>n/a</td>
<td>n/a</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>50-70</td>
<td>7/142 (5)</td>
<td>6.81</td>
<td>3.0-15.3</td>
<td></td>
</tr>
<tr>
<td>≥ 70</td>
<td>41/141 (29)</td>
<td>25.63</td>
<td>6.5-100.8</td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td></td>
<td></td>
<td></td>
<td>.008</td>
</tr>
<tr>
<td>≥ 27 (ref)</td>
<td>15/207 (7)</td>
<td>n/a</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>&lt; 27</td>
<td>26/155 (17)</td>
<td>2.25</td>
<td>1.2-4.1</td>
<td></td>
</tr>
<tr>
<td>Urea</td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>&lt; 5 (ref)</td>
<td>6/184 (3)</td>
<td>n/a</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>5-8</td>
<td>5/104 (5)</td>
<td>2.68</td>
<td>1.6-4.7</td>
<td></td>
</tr>
<tr>
<td>≥ 8</td>
<td>33/99 (33)</td>
<td>6.53</td>
<td>2.3-18.5</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td></td>
<td></td>
<td></td>
<td>.03</td>
</tr>
<tr>
<td>Community (ref)</td>
<td>36/338 (10)</td>
<td>n/a</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Hospital</td>
<td>12/46 (26)</td>
<td>2.87</td>
<td>1.1-7.3</td>
<td></td>
</tr>
<tr>
<td>Purulence</td>
<td></td>
<td></td>
<td></td>
<td>.04</td>
</tr>
<tr>
<td>Purulent (ref)</td>
<td>37/338 (11)</td>
<td>n/a</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Nonpurulent</td>
<td>12/70 (17)</td>
<td>2.61</td>
<td>1.0-6.7</td>
<td></td>
</tr>
</tbody>
</table>

(ref) refers to the reference category for each parameter. Although the presence of joint disease was significantly associated with outcome, the numbers of patients with joint disease (10%) was small, the predictive value of this parameter poor (OR, 0.23; 95% CI), and this parameter had poor biologic plausibility; this was not, therefore, included in the final model. See Table 1 and 2 legends for expansion of abbreviations.

overall survival, the hazard ratio was 4.69 in the medium-risk group (95% CI, 1.27-17.34; P = .02) and 17.37 in the high-risk group (95% CI, 4.94-61.02; P < .001). Overall mortality is presented as survival curves in Figure 2.

For hospital stay, the median time to hospital discharge in the low-risk group was 7 days (interquartile range [IQR], 6-13), compared with 10 days (IQR, 8-13) in the medium-risk group (P = .42), and 15 days (IQR, 9-28) in the high-risk group (P = .08).

Sensitivity analyses were conducted and are presented in e-Table 4, demonstrating no important differences using best-case or worst-case scenarios. The receiver operating characteristics analysis for mortality at 3 months according to the RAPID score demonstrated an area under the curve (AUC) of 0.88 (95% CI, 0.84-0.93) for the derivation cohort and an AUC of 0.80 (95% CI, 0.69-0.82) for the validation cohort (Fig 3) and for surgery at 3 months, an AUC of 0.36 (95% CI, 0.28-0.43) for the derivation cohort and an AUC of 0.50 (95% CI, 0.39-0.61) for the validation cohort (Fig 4).

Table 4—Mortality by RAPID Risk Category in the MIST1 and MIST2 Cohorts

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Mortality at 3 Mo (%)</th>
<th>OR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIST1 (n = 411)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk, score 0-2 (ref)</td>
<td>1/186 (1)</td>
<td>n/a</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Medium risk, score 3-4</td>
<td>14/121 (12)</td>
<td>24.41</td>
<td>3.14-186.65</td>
<td>.002</td>
</tr>
<tr>
<td>High risk, score ≥ 5</td>
<td>26/51 (51)</td>
<td>192.40</td>
<td>25.01-1480.41</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>MIST2 (n = 191)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk, score 0-2 (ref)</td>
<td>3/97 (3)</td>
<td>n/a</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Medium risk, score 3-4</td>
<td>6/65 (9)</td>
<td>3.19</td>
<td>0.77-13.23</td>
<td>.11</td>
</tr>
<tr>
<td>High risk, score ≥ 5</td>
<td>9/29 (31)</td>
<td>14.1</td>
<td>3.50-56.78</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

(ref) refers to the reference category for each cohort. See Table 1 and 2 legends for expansion of abbreviations.

To our knowledge, this is the first prognostic risk model for patients with pleural infection derived from data obtained from one cohort that has then been validated in a second cohort. Of 22 baseline characteristics recorded at the time of initial presentation, five were strongly independently associated with poor outcome.

The risk model developed gave more weighting to both age and urea in light of their high ORs for mortality, with the other three variables scoring the same. Each patient’s RAPID score, therefore, ranged between 0 and 7, with low-risk patients (scoring 0-2) having a 1% to 3% mortality at 3 months compared with 31% to 51% for high-risk patients (scoring 5-7). This risk stratification at baseline, if validated in prospective studies, 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.

Unsurprisingly, there are similarities with the widely used CURB-65 (confusion, urea, respiratory rate, BP, age ≥ 65 years) risk model, used for adults presenting to hospital with community-acquired pneumonia. Markers of poor outcome (confusion, urea ≥ 8 mM, respiratory rate ≥ 30 breaths/min, low BP, and age ≥ 65 years) are similar to those found in our study in patients with pleural infection. Low albumin was also identified as a risk factor of poor outcome in the CURB-65 study. However, this variable was not included in the final model, due to concerns that this test is not routinely available. Although it may be suggested that the RAPID score may simply reflect the CURB-65 score in these patients, it is increasingly recognized that pleural infection and pneumonia are different biologic...
patients not being offered surgical treatment. Further investigation of this potential signal is now required.

A British Thoracic Society retrospective study on pleural infection found initial pleural fluid results were not predictive of poor outcome. Low albumin was, however, associated with increased mortality. Fluid purulence has been highlighted previously as a possible predictor of poor outcome. In our study, we found the opposite to be the case, with nonpurulence being a significant risk of poor outcome. Although this seems counterintuitive, it may be explained by the authors’ clinical observation that frankly purulent effusions tend to have fewer loculations and, therefore, may be more likely to drain than nonpurulent highly loculated collections.

Pleural infection remains common with studies reporting sharp increases in incidence; its associated mortality and morbidity remain high and have not improved over recent decades. There is some evidence that delays in prompt and appropriate treatment subsequently result in more invasive interventions, leading to a more prolonged in-hospital recovery and poorer outcomes. The RAPID score should help the clinician identify those likely to have a poor outcome at presentation; high-scoring patients, scoring 5 to 7, have at least a 30% chance of dying in the following 12 weeks. It also informs the clinician of the increased likelihood of a prolonged hospital stay. These patients are likely to be best served by addressing their nutritional status immediately and consideration given to whether earlier more definitive surgical management is appropriate. Although it has been shown that delay in surgical referral can result in video-assisted thoracoscopic surgery needing to be converted to thoracotomy and more formal decortication, this needs to be the subject of specific further studies.

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.

Figure 3. A and B, ROC analysis for the derived RAPID score in the (A) MIST1 and (B) MIST2 cohorts for the outcome of mortality at 3 mo. ROC = receiver operating characteristic. See Figure 1 and 2 legends for expansion of other abbreviations.
There were some limitations in the development of the prognostic model. Previous research has shown that prognostic models developed on small datasets using backward selection methods tend to overstate the effect size of the variables included in the model. However, the effect size for individual variables is not used to calculate the RAPID score, as all variables are assigned the same score (with the exception of the age and urea variables). And, in spite of these limitations, validation of the RAPID score using the MIST2 dataset did find the chosen model to be predictive of poor outcome. A further potential limitation is the recruitment of patients for this study from randomized trials with specific inclusion and exclusion criteria, which is not ideal for the development of prognostic models. However, the inclusion and exclusion criteria in the MIST1 and MIST2 studies closely reflect the normal population of pleural infection, and this is, therefore, not likely to be an unrepresentative sample. As the MIST1 and MIST2 studies were conducted within the United Kingdom, there are potential limitations in the application of this risk score, specifically to the prediction of need for surgical intervention, in health-care settings where surgical referral practice is different. Specific and local studies are needed to test this potential issue.

A further large prospective validation study is now required to evaluate whether RAPID is a reliable and sensitive clinical prediction model of poor outcome in pleural infection. This would then enable clinicians to target aggressive and more expensive therapies to patients with the poorest outcomes in pleural infection.

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REFERENCES