Prospective validation of the RAPID clinical risk prediction score in adult patients with pleural infection: the PILOT study

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This multicentre observational study shows that RAPID score can stratify adults with pleural infection into categories according to increasing risk of 3-month mortality and should inform future research directed at improving outcomes in this population https://bit.ly/37tk2LN

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ABSTRACT

Background: Over 30% of adult patients with pleural infection either die and/or require surgery. There is no robust means of predicting at baseline presentation which patients will suffer a poor clinical outcome. A validated risk prediction score would allow early identification of high-risk patients, potentially directing more aggressive treatment thereafter.

Objectives: To prospectively assess a previously described risk score (the RAPID (Renal (urea), Age, fluid Purulence, Infection source, Dietary (albumin)) score) in adults with pleural infection.

Methods: Prospective observational cohort study that recruited patients undergoing treatment for pleural infection. RAPID score and risk category were calculated at baseline presentation. The primary outcome was mortality at 3 months; secondary outcomes were mortality at 12 months, length of hospital stay, need for thoracic surgery, failure of medical treatment and lung function at 3 months.

Results: Mortality data were available in 542 out of 546 patients recruited (99.3%). Overall mortality was 10% at 3 months (54 out of 542) and 19% at 12 months (102 out of 542). The RAPID risk category predicted mortality at 3 months. Low-risk mortality (RAPID score 0–2): five out of 222 (2.3%, 95% CI 0.9 to 5.7%); medium-risk mortality (RAPID score 3–4): 21 out of 228 (9.2%, 95% CI 6.0 to 13.7%); and high-risk mortality (RAPID score 5–7): 27 out of 92 (29.3%, 95% CI 21.0 to 39.2%). C-statistics for the scores at 3 months and 12 months were 0.78 (95% CI 0.71–0.83) and 0.77 (95% CI 0.72–0.82), respectively.

Conclusions: The RAPID score stratifies adults with pleural infection according to increasing risk of mortality and should inform future research directed at improving outcomes in this patient population.

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Introduction

Pleural infection is common, affecting more than 60 000 patients each year in the United States (US) and the United Kingdom (UK) [1], and is increasing in both paediatric [2–4] and adult [5–7] populations. The condition is associated with poor clinical outcomes; all-comers mortality is around 20% [8–11] and is unchanged over the last 20 years. Morbidity is significant, with 25% of patients requiring hospital admission for more than 1 month, with a median hospital stay of 12–15 days [8–11]. Treatment costs are substantial, with care costing approximately USD 5000 per patient [12, 13], equating to around USD 400 million per annum (UK and US).

Standard ("medical") treatment for confirmed pleural infection includes broad-spectrum antibiotics (until microbiological identification and sensitivities are established) and drainage of infected pleural fluid, usually *via* a chest tube [14, 15]. More invasive treatment is recommended in those with poor initial response [14, 15]. This involves surgical drainage, usually by video-assisted thoracoscopic surgery (VATS), but may require thoracotomy with decortication, rib resection and/or open drainage in more complex cases [5, 16–19]. The unselected use of surgical drainage in all cases of pleural infection cannot be justified, as at least 70% of patients will recover with "medical" treatment alone [10, 11] and surgery is associated with significant morbidity including peri-operative and anaesthetic mortality [20], conversion to thoracotomy [21–23] and long-term pain in up to 5% of patients [24, 25].

A newer semi-invasive strategy for pleural infection is the combined use of intrapleural tissue plasminogen activator (tPA) and deoxyribonuclease (DNase) given *via* a chest tube, which has been shown to improve drainage and potentially reduce hospital stay and surgical requirement [11]. This treatment is now widely used as "rescue" therapy in those failing initial medical treatment [26], but is associated with substantial costs of around USD 1400 per patient [27]. Thus, surgical drainage or combined intrapleural tPA and DNase are potentially useful treatments in pleural infection, but would be best used in selected patients in whom outcomes are poor with standard management.

Several studies have attempted to identify factors associated with poor outcome in pleural infection, suggesting that fluid purulence [9], delayed access to surgery [28] and ultrasound parameters [29] may be associated with poor outcomes; however, results from these studies are not robust given their retrospective designs. Only one study [30] has derived and retrospectively validated a clinical prediction rule in pleural infection, the RAPID (Renal (urea), Age, fluid Purulence, Infection source, Dietary (albumin)) score, in which baseline serum urea, patient age, pleural fluid purulence, infection source (community-acquired infection *versus* hospital-acquired infection) and serum albumin were independently associated with mortality at 3 months. Categorisation of patients into low-risk (RAPID score 0–2), medium-risk (RAPID

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score 3–4) and high-risk (RAPID score 5–7) groups was associated with mortality at 3 months of 3%, 9% and 31%, respectively (table 1) [30].

A robust prediction model for outcome in pleural infection would allow clinicians to risk stratify their patients and would inform further research assessing the use of invasive and/or expensive treatment strategies in higher-risk populations with the goal of improving long-term outcomes. This prospective study was conducted to test the hypothesis that the RAPID score at baseline predicts poor clinical outcome in adults with pleural infection. It evaluated whether the RAPID score could accurately predict mortality at 3 months (the primary outcome), as well as medical treatment failure and length of hospital stay (defined during initial hospital admission), lung function (measured at 3 months), and mortality and the need for surgical intervention based on objective criteria (measured at 12 month follow-up) (the secondary outcomes).

Methods

Study design

The Pleural Infection Longitudinal OuTcome (PILOT) study was a prospective observational cohort study in which adult patients with pleural infection were managed according to published guidelines [14, 15], adapted for usual local practice and conducted in 29 centres in four countries (the UK, the US, Australia and South Africa) that together made up the PILOT study group.

Subjects enrolled

Study entry was offered to all participants fulfilling the entry criteria. Inclusion criteria were consistent with diagnostic criteria for pleural infection from national clinical guidelines [14, 15]. Patients were included if they had a clinical presentation consistent with pleural infection and any of the following criteria: 1. pleural fluid that was macroscopically purulent; or 2. pleural fluid that was positive on culture for bacterial infection; or 3. pleural fluid that demonstrated bacteria on Gram staining; or 4. pleural fluid with a pH $\leqslant$7.2 (measured by blood gas analyser) or low glucose level ($\leqslant$3 mmol·L^{-1} or $\leqslant$55 mg·dL^{-1}) in a patient with clinical evidence of infection; or 5. contrast-enhanced computed tomography (CT) evidence of pleural infection (consolidation of underlying lung with enhancing pleural collection) in a patient with clinical evidence of infection, alongside exclusion of other sources of infection. Evidence of infection was assessed by the recruiting physician on the basis of fever, an elevated peripheral blood white-cell count, or elevated serum inflammatory markers such as C-reactive protein (CRP). Study exclusion criteria were as follows: 1. age <18 years; 2. no pleural fluid available for analysis; 3. previous pneumonectomy on the side

TABLE 1 The RAPID risk-prediction score, using baseline clinical parameters in patients with pleural infection [30]

Parameter	Score
Renal (urea) mmol·L^{-1}	
<5.0	0
5.0–8.0	1
>8.0	2
Age years	
<50	0
50–70	1
>70	2
Purulence of pleural fluid	
Purulent	0
Non-purulent	1
Infection source	
Community-acquired	0
Hospital-acquired	1
Dietary factor (albumin) g·L^{-1}	
$\geqslant$27.0	0
<27.0	1
Risk category	
Low	0–2
Medium	3–4
High	5–7

of pleural infection; and 4. expected survival of <3 months due to co-morbid disease, as judged by the recruiting physician.

RAPID score

The RAPID score [30] at baseline presentation was calculated according to the parameters in table 1. From the derived score, patients were placed in one of three risk categories (low, medium or high) for the purposes of analysis, as pre-defined in the original paper [30]. Individual patients did not have a RAPID score calculated or used to guide their clinical management during the study.

Chest-tube drainage, antibiotic treatment and investigations

All decisions regarding patient management were left to the discretion of the responsible local clinicians, who were asked to follow published national guidelines adapted to their usual practice. Advice for study investigators regarding chest-tube size and insertion method (if deemed clinically appropriate), antibiotic choice and other treatments for pleural infection was also provided in the study protocol (supplementary material) and based on widely available guidelines [14, 15]. Radiological investigations included, as a minimum, a chest radiograph at study entry and at discharge from hospital, and (if appropriate) prior to referral for surgery. Thoracic ultrasound was conducted at baseline wherever possible, and the size of the pleural collection and extent of any septations was scored (the ultrasound scoring methodology can be found in the supplementary material). Spirometry was conducted on discharge from hospital and at 3 months.

Medical treatment failure and surgical referral

As not all patients with pleural infection were considered fit enough to undergo surgical intervention, objective criteria for "medical treatment failure" were recorded in all cases. In brief, this required the presence of a significant residual pleural collection alongside clinical or biochemical features of uncontrolled infection, such as ongoing fevers or persistently elevated inflammatory markers. These criteria were measured at 3–5 days post study inclusion and recorded on a case report form (CRF) (supplementary material). Current treatment guidelines [14, 15] do not describe detailed criteria on which to base surgical referral decisions for patients with pleural infection. Thus, guidance was provided to study investigators on referral for surgical intervention, including on meeting minimum objective criteria (supplementary material). The final decision to refer for surgery and to proceed with any subsequent operative intervention was at the discretion of the responsible local clinicians, with the reasons for surgical referral documented in CRFs thereafter.

Follow-up

All patients underwent follow-up for 12 months, while at 3 months they underwent assessment of the need for further drainage and/or surgical intervention, spirometry and a chest radiograph. Vital status was determined through clinical follow-up and case note review.

Study outcomes

Primary endpoint

The primary outcome was all-cause mortality at 3 months post study entry.

Secondary endpoints

Secondary outcomes were: all-cause mortality at 12 months; duration of hospital (in-patient) stay; need for surgical drainage of infected pleural fluid over 12 months; medical treatment failure, as defined by the study protocol (supplementary material); and lung function at 3 months.

Statistical analysis

Briefly, the description of participants' characteristics, available predictors and missing data were planned. Performance of the RAPID model was assessed with missing data imputed using multiple imputation by chained equations for missing predictors and missing outcomes [31]. All available baseline variables were included in the imputation model. Predictive accuracy of the RAPID model was assessed using a variety of measures including discrimination, sensitivity and specificity for each value of the RAPID score (0–7), and in each of the three risk categories (low, medium and high). Discrimination was assessed using the C-statistic [32] and was calculated separately for individual values of the RAPID score (0–7) and for the three risk categories. The C-statistic was also calculated and reported within pre-defined subgroups to assess consistent performance of the RAPID score. Analysis of secondary outcomes, with the exception of 12-month mortality, was based on complete case data.

Sample size calculation

Sample size calculations were based on the original study (n=450) which provided the derivation and validation datasets for RAPID [30]. In that study, a low-risk score (0–2; seen in 72% of patients) was

associated with no deaths; medium-risk (3–4; 20% of patients) was associated with 30% mortality; and high-risk (5–7; 8% of patients) was associated with 70% mortality [30]. As a point estimate for the difference between low-risk and medium-risk groups, 96 subjects would be needed for this study (90% power, alpha 0.05). As this estimate was retrospectively derived and therefore likely to be over-optimistic, while not excluding a minimum clinically significant difference, a minimum significant difference to detect mortality was fixed at 15% (*i.e.* low-risk mortality 15% and medium-risk mortality 30%, with an unchanged (4:1) ratio of low-risk to medium-risk patients). Using these data, this study required 500 analysable patients (90% power, alpha 0.05) and, allowing for 10% loss to follow-up based on prior experience in carrying out clinical trials of pleural infection [10, 11], a recruitment target of 550 patients was set. This study was reported according to the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) statement [33].

Ethical approval and registration

Ethical and regulatory approval was obtained (Oxford B Research Ethics Committee Reference 13/SC/0204) and the study registered (ISRCTN 50236700) prior to commencing participant recruitment.

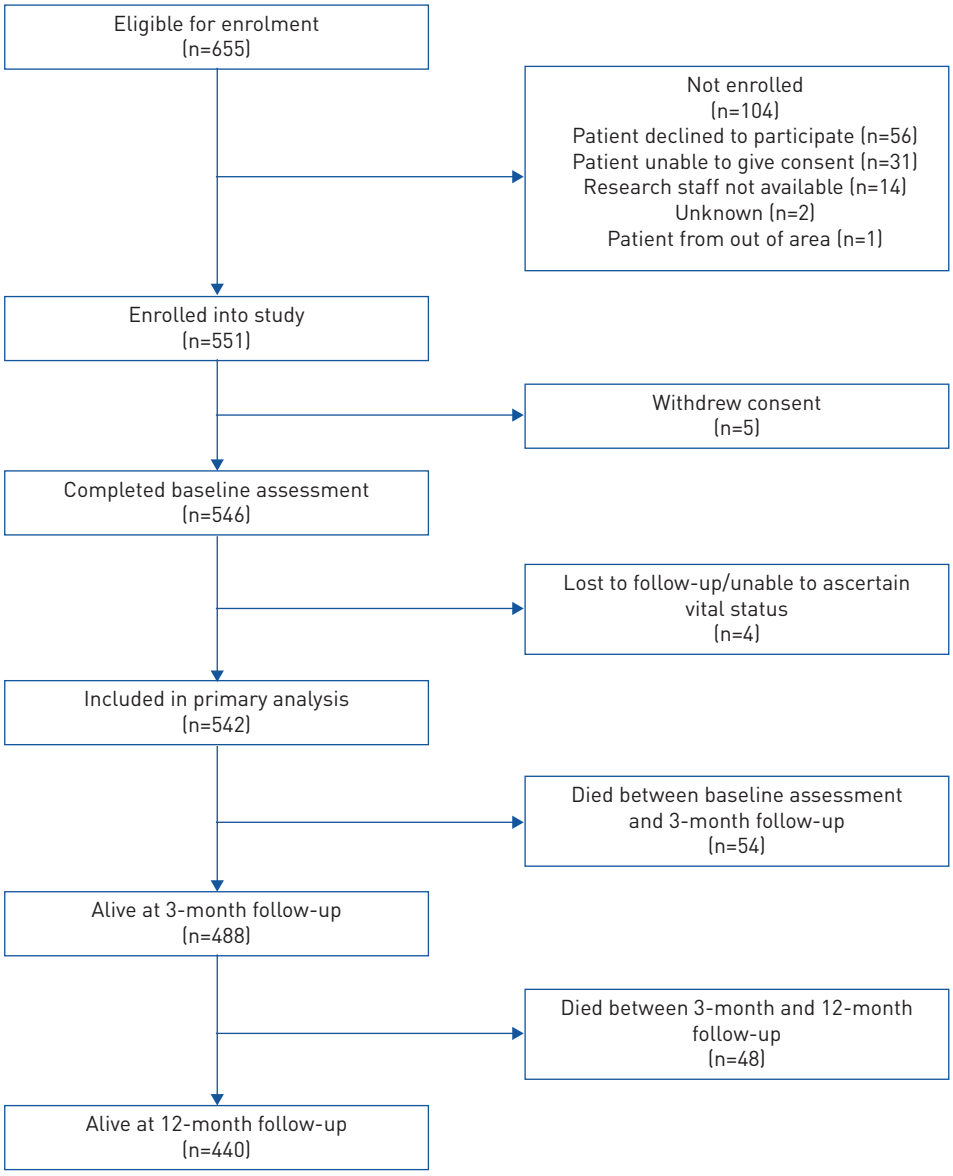

FIGURE 1 Flow chart describing the movement of patients through the study.

Results

Patients

In total 551 participants were recruited. Five withdrew consent for use of their data during follow up and thus 546 were included in the final analysis (figure 1). Baseline characteristics of the study population (table 2) were comparable to previously published studies of pleural infection [10, 11, 30].

Data quality

The primary outcome measure (mortality at 3 months) was available for 542 out of 546 study participants (99.3%). At baseline, missing prediction score parameters were as follows: urea, 21 out of 546 (3.8%); age, nine out of 546 (1.6%); pleural fluid purulence, six out of 546 (1.1%); infection source, three out of 546 (0.5%); and albumin, 29 out of 546 (5.3%). The RAPID score was well distributed across the study population (supplementary material) in both those who survived and those that died.

Primary endpoint

Mortality at 3 months was 54 out of 542 (10.0%) and was strongly associated with the RAPID score, with mortality increasing with each incremental rise in RAPID score (figure 2). Analysis of patients according to their RAPID risk category showed an increase in 3-month mortality according to risk category as follows: low-risk mortality (RAPID score 0–2), five out of 222 (2.3%, 95% confidence interval (CI) 0.9–5.7%); medium-risk mortality (RAPID score 3–4), 21 out of 228 (9.2%, 95% CI 6.0–13.7%); and high-risk mortality (RAPID score 5–7) 27 out of 92 (29.3%, 95% CI 21.0–39.2%). The hazard ratio for mortality at 3 months, with low risk as the comparator, was 3.2 (95% CI 1.7–9.1) for medium-risk and 11.4 (95% CI 6.1–21.2) for high-risk ($p<0.001$ in both cases). The Kaplan–Meier survival plot according to baseline RAPID risk category is shown in figure 3. Discrimination of the predictive capability of the RAPID score for mortality was 0.78 (95% CI 0.71–0.83) at 3 months and 0.77 (95% CI 0.72–0.82) at 12 months. Sensitivity and specificity for the primary endpoint at each incremental level of the RAPID score are detailed in the supplementary material.

TABLE 2 Baseline characteristics of PILOT study participants

Variable	Result
Demographic characteristics	
Age years	60±18
Male sex	385/545 (71)
Source of infection	
Community-acquired	286/545 (52)
Hospital-acquired	259/545 (48)
Poor dental hygiene	100/545 (18)
Small (<15 French) chest tube	309/445 (70)
Antibiotic use before diagnosis	117/545 (21)
Pleural fluid characteristics	
Pleural fluid purulence	222/545 (41)
Gram stain or culture positivity	334/545 (61)
pH	7.0 (6.8–7.2)
LDH units·L^{-1}	1968 (946–5009)
Coexisting illness	
Anticoagulation	259/540 (49)
Asthma	70/543 (13)
Atrial fibrillation	37/543 (7)
Cancer (current)	63/543 (12)
Cancer (previous)	59/543 (11)
COPD	70/543 (13)
Heart disease	47/543 (9)
Interstitial lung disease	10/543 (2)
Liver disease	28/543 (5)
Previous pleural infection	41/543 (8)
Renal	32/543 (6)
Diabetes	77/543 (14)

Data are presented as mean±SD, n/n (%), or median (IQR). LDH: lactate dehydrogenase; COPD: chronic obstructive pulmonary disease; SD: standard deviation; IQR: interquartile range.

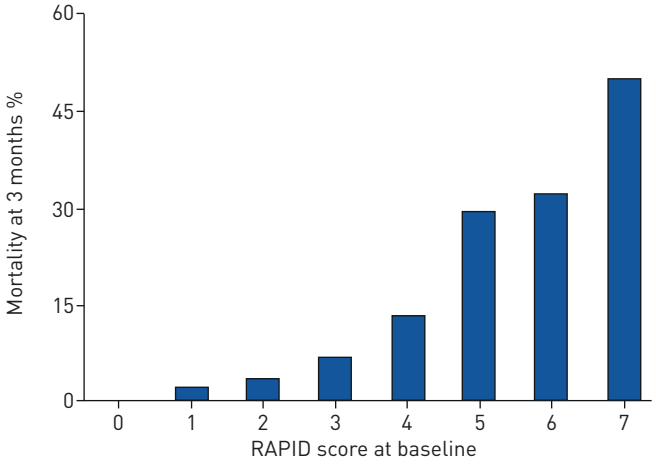

FIGURE 2 Three-month mortality according to baseline RAPID scores.

Secondary endpoints

12-month mortality

Mortality at 12 months was 102 out of 542 patients (18.8%). Twelve-month mortality increased according to RAPID risk category as follows: low-risk mortality (RAPID score 0–2), 6.1% (95% CI 3.5–10.2%); medium-risk mortality (RAPID score 3–4), 18.0% (95% CI 13.6–23.3%); and high-risk mortality (RAPID score 5–7), 49.9% (95% CI 39.8–60.0%). Hazard ratios for mortality, with low-risk as the reference group, are shown in table 3.

Duration of hospital stay

The median length of hospital stay across the study population was 13 days (interquartile range (IQR) 7–23 days). The median length of hospital stay was significantly associated with baseline RAPID risk category (table 3).

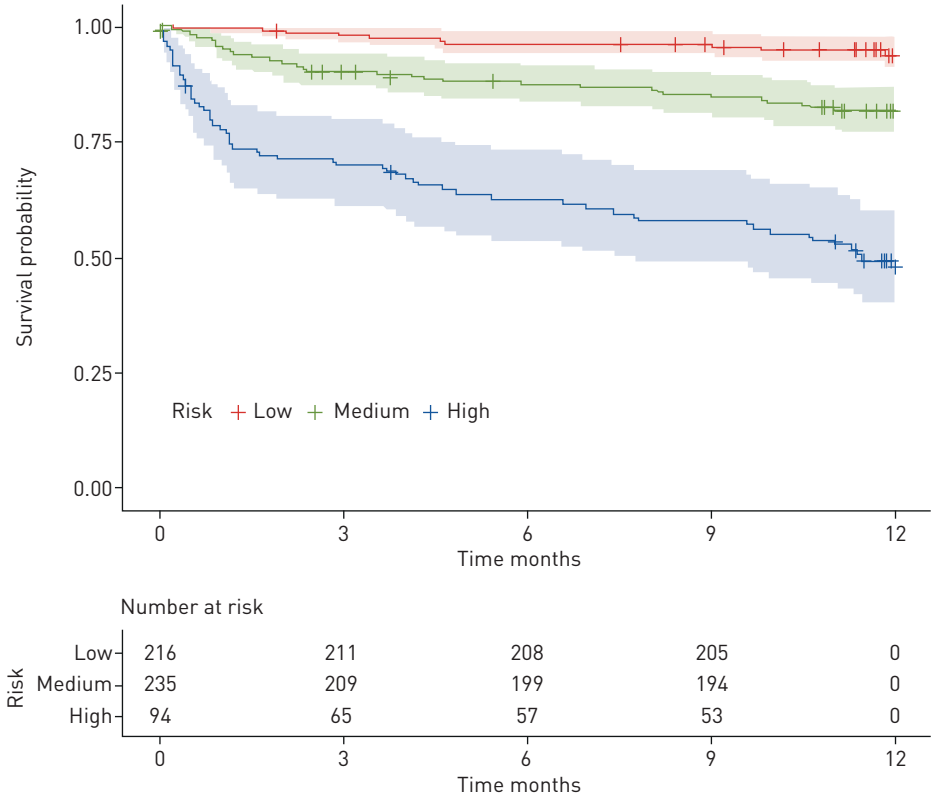

FIGURE 3 Kaplan–Meier graphs censored for loss to follow-up according to baseline RAPID risk category (based on a single representative imputed dataset). RAPID scores are: 0–2 (low risk); 3–4 (medium risk); and 5–7 (high risk). Shaded areas represent 95% confidence intervals for survival at each point.

TABLE 3 Secondary outcomes according to baseline RAPID risk category

Outcome	RAPID risk category			Statistical comparison
	Low (n=188)	Medium (n=199)	High (n=85)	
12-month mortality %	6.1 (95% CI 3.5–10.2)	18.0 (95% CI 13.6–23.3)	49.9 (95% CI 39.8–60.0)	Hazard ratio (medium *versus* low risk) 3.2 (95% CI 1.7–9.1), p<0.001 Hazard ratio (high *versus* low risk) 11.4 (95% CI 6.1–21.2), p<0.001
Median length of hospital stay days	11 (IQR 6–21)	13 (IQR 7–25)	18 (IQR 10–27)	Mann–Whitney p=0.003
Failure of initial medical treatment n	66 (35.1), 95% CI 28.3–41.9	70 (35.2), 95% CI 28.5–41.8	22 (25.9), 95% CI 16.6–35.2	Chi-squared (3df) 2.68, p=0.26
Surgical intervention n	36 (19.1), 95% CI 13.5–24.8	31 (15.6), 95% CI 10.5–20.6	5 (5.9), 95% CI 0.9–10.9	Chi-squared (3df) 7.991, p=0.02
Median FEV_1 at 3 months L				
Overall population	2.4 (IQR 2.0–3.1) (n=44)	2.0 (IQR 1.6–2.4) (n=53)	1.9 (IQR 1.5–2.3) (n=20)	Kruskal–Wallis p<0.001
Non-surgical	2.3 (IQR 2.0–3.1) (n=40)	2.0 (IQR 1.6–2.4) (n=46)	1.9 (IQR 1.5–2.3) (n=19)	
Surgical	2.7 (IQR 2.0–3.0) (n=4)	1.9 (IQR 1.3–2.3) (n=7)	2.3 (IQR 2.3–2.3) (n=1)	
Median FVC at 3 months L				
Overall population	3.5 (IQR 2.5–4.1) (n=44)	2.8 (IQR 2.2–3.4) (n=53)	2.8 (IQR 2.1–3.3) (n=20)	Kruskal–Wallis p=0.002
Non-surgical	3.5 (IQR 2.5–4.1) (n=40)	2.8 (IQR 2.3–3.4) (n=46)	2.6 (IQR 2.0–3.2) (n=19)	
Surgical	3.6 (IQR 2.7–4.1) (n=4)	3.4 (IQR 1.7–3.5) (n=7)	3.5 (IQR 3.5–3.5) (n=1)	

Data is presented as % (95% CI), median (IQR) or n (%), 95% CI. Analysis of 12-month mortality was based on multiple imputation (all other analyses were based on complete case data). CI: confidence interval; IQR: interquartile range; df: degrees of freedom; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity.

Medical treatment failure

The failure of initial medical treatment was assessed in those with complete data and occurred in 158 out of 472 patients (33.5%). It was not significantly different according to baseline RAPID risk category (table 3). The reasons for failure of initial medical treatment, per protocol guidance, are detailed in the supplementary material and were not significantly different according to RAPID risk category.

Need for surgical intervention within 12 months

Overall, surgical intervention was required by 86 out of 550 patients(15.6%). The proportion of patients undergoing surgical intervention was significantly different according to RAPID risk category (table 3), as 19.1% of low-risk patients and 5.9% of high-risk patients underwent surgery. Analysing only those who met criteria for failure of initial medical treatment, there were significant differences in the number of patients undergoing surgery according to RAPID risk category, with surgery performed in 68.9% of low-risk patients, 31.5% of medium-risk patients and 28.6% of high-risk patients.

Lung function at 3 months

Lung function data were available in 154 out of 540 patients (28.5%) only, limiting any detailed analysis. Significantly better lung function was observed in those in the low-risk RAPID category and this was seen in patients managed both medically and surgically (table 3).

Subgroup analyses

Performance of the RAPID score was assessed in four predefined subgroups: ultrasound septation score, World Health Organisation (WHO) performance status, presence of on-site thoracic surgery and prior use of antibiotics. The model performed well in all subgroups, apart from those patients with severe septations on ultrasound (C-statistic 0.87 in the non-septated group, falling to 0.64 in the heavily septated group) or those with prior antibiotic use (C-statistic fell from 0.82 to 0.69 in those with previous antibiotics use) (supplementary material).

TABLE 4 Baseline characteristics of study participants who did and did not receive intrapleural fibrinolytic therapy

Demographic characteristics	Intrapleural fibrinolytic therapy		Statistical comparison
	No (n=464)	Yes (n=82)	
Age years	60.0±17.2	56.7±15.6	Unpaired t-test p=0.11
Male sex	320/464 (69)	65/82 (79)	Chi-squared (1df) 3.08, p=0.08
Source of infection			
Community-acquired	409/461 (89)	75/82 (91)	Chi-squared (1df) 0.30, p=0.58
Hospital-acquired	52/461 (11)	7/82 (9)	
RAPID risk category			
Low	159/401 (40)	29/71 (41)	Chi-squared (2df) 0.36, p=0.84
Medium	168/401 (42)	31/71 (44)	
High	74/401 (18)	11/71 (15)	

Data are presented as mean±SD or n/n (%). df: degrees of freedom; SD: standard deviation.

Use of intrapleural fibrinolytic therapy

Eighty-two out of 546 patients(15.0%) were prescribed intrapleural fibrinolytic therapy by their responsible clinical team as part of their treatment for pleural infection. Of these, 62 out of 82 patients (75.6%) received alteplase and dornase alfa, and 20 out of 82 patients (24.4%) received streptokinase. With respect to baseline demographics or RAPID risk categorisation, there were no significant differences between the patients who received intrapleural fibrinolytics and those who did not (table 4). Whilst there was a significant difference in 3-month mortality between the two patient groups, this was not maintained out to 12-month follow-up (table 5). The RAPID model performed well in both groups, with a C-statistic at 12-month follow-up of 0.73 in those receiving intrapleural fibrinolytics and 0.78 in those who did not (table 5).

Discussion

Results of the PILOT study demonstrate that, at baseline, the RAPID score allows adult patients with pleural infection to be stratified into different categories according to an increasing risk of 3-month mortality. Patients were recruited based on commonly used clinical criteria for the diagnosis of pleural infection, while variables used to calculate the score are easily accessible to clinicians as part of routine clinical care at baseline presentation. As such, the score has clinical applicability in a manner similar to clinical prediction scores used in the management of pneumonia [34, 35]. The fact that the RAPID score is strongly predictive of outcome in a study that has recruited from a large number of centres, varying in size, expertise and geographical location, and despite local variations in clinical practice, further demonstrates its clinical utility.

The performance of RAPID risk categorisation in the PILOT study is remarkably similar to that seen in the original study [30], in which the RAPID score was first derived and then retrospectively validated. Three-month mortality in the original study was 3% for the low-risk group, 9% for the medium risk group and 31% for the high risk group, while in the PILOT study it was 2.3%, 9.3% and 30.8%, respectively. The

TABLE 5 Mortality (3 month and 12 month) and RAPID risk prediction model performance in study patients who did and did not receive intrapleural fibrinolytic therapy

Measure	Intrapleural fibrinolytic therapy		Statistical comparison
	No (n=464)	Yes (n=82)	
Mortality			
3 month	54/464 (11.6)	0/82 (0)	Fisher's exact test p⩽0.001
12 month	90/464 (19.4)	12/82 (14.6)	Fisher's exact test p=0.36
C-statistic			
3 month	0.78 (0.71–0.83)	NA	
12 month	0.78 (0.71–0.83)	0.73 (0.57–0.84)	

Data is presented as n/n (%) or n (95% CI).

PILOT study population mirrors that seen in other multicentre randomised studies with a similar "all-comers" mortality rate of 20% and a surgical intervention rate of 16% [10, 11].

Our results suggest a linear relationship between RAPID score and 3-month mortality following a diagnosis of pleural infection, with scores of one or less associated with 1.9% mortality and scores of six or more associated with 35% mortality. It is not clear why all the parameters used in RAPID predict mortality so precisely; however, associations with increasing age, blood urea and serum albumin are likely to identify a more frail population, one in whom uncontrolled infection has resulted in a catabolic state.

We postulate that the association of mortality with hospital-acquired pleural infection is a result of more resistant organisms [36, 37] and potentially more co-morbid illness. However, it remains unclear as to why non-purulent pleural fluid is associated with increased mortality. Previous clinical didact and a single case series suggest that fluid purulence associates with poor outcome [9]; however, these data were not prospectively derived. A lack of pleural fluid purulence may instead associate with abnormalities in the pleural space, either through increased septation and a more complex pleural space potentially related to deranged fibrinolytic activity [38, 39], or as a marker of poor pleural space neutrophil recruitment and immunity.

The RAPID score appears to associate not only with mortality, but also with length of hospital stay. The score may predict those with pleural infection and complex treatment requirements, or may simply reflect the frailty of the population being treated (with increasing age and co-morbidity being intrinsic to the RAPID score). In this study a majority of deaths occurred within the first 3 months following diagnosis of pleural infection, as in previous studies [9, 10], suggesting that mortality is disease-specific and potentially amenable to improvement.

The RAPID score appears to have validity amongst all subgroups assessed. There was no association between provision of on-site surgical services and RAPID prediction of mortality. Indeed, the proportion of patients who failed initial medical treatment and who would, by extension, be referred for consideration of surgical intervention, was similar across all RAPID groups. Despite this, use of surgical intervention was higher in the low-risk group (19.1% of patients) than in the high-risk group (5.9% of patients). In the high-risk group, only one in three patients who had objectively failed medical treatment then underwent surgery and of these 30% subsequently died. These data might infer that surgical intervention is used most frequently in a low-risk group of patients with pleural infection (where mortality is low) and is avoided in the highest risk group (where mortality is high). This high-risk group commonly includes the elderly, where outcomes from pleural infection are poorest [7].

As this is not a randomised study, it is not possible to speculate if surgical intervention itself is the reason for the lower mortality from pleural infection in the lowest risk group. However, it may be that potentially life-saving surgical treatment is avoided in the highest risk group, despite a similar rate of objective medical treatment failure; a hypothesis lent weight by large surgical case series [5, 37] which show a preference to intervene amongst younger individuals with fewer co-morbidities than seen in unselected patient populations with pleural infection [10, 11]. These results inform a pressing need for randomised studies in pleural infection that are robustly powered to assess the impact of more invasive treatments, including surgical intervention, on mortality and other clinically important outcomes.

Retrospective studies have identified the sonographic presence of septated pleural fluid as a potential predictor of outcome in pleural infection [29]. Ultrasound was not used as part of the RAPID score as these parameters were not available in the derivation and validation datasets used to construct the score [30]. Our results demonstrate that the predictive ability of the RAPID score is reduced in the severely septated group as categorised by ultrasound. Although septations on ultrasound are often used as a surrogate for "non-draining" fluid, in reality they are often communicating spaces within the pleural cavity and their true significance remains unknown. The presence of pleural fluid septations may be a marker for more significant disease, but not necessarily for lack of drainage. For example, they might indicate worsened fibrinolytic activity in the pleural space [38, 39] or deep-seated and biofilm-forming infection [40]. Recent data suggest that bacteria in pleural infection occupy a niche in the pleural lining rather than the fluid itself [41] and we postulate that the presence of septating effusion may facilitate bacterial growth and migration, findings which require further exploration. The true value of ultrasound assessment of the infected pleural space needs further study. Indded, considering fluid septation in isolation ignores other sonographic features that may impact on outcome, such as the size of a collection, the presence of multiple locules of fluid, or pleural thickening.

Of the patients recruited to this study, 15% were prescribed intrapleural fibrinolytic therapy by their responsible clinical team as part of their treatment for pleural infection, a sign of its increasing use as a routine intervention in this population. Our results show the RAPID score performed well in both

patient groups, reflecting the fact that the score was originally developed using data from two randomised studies of intrapleural fibrinolytics [10, 11]. An interesting observation was the significant difference in 3-month mortality favouring those patients who received intrapleural fibrinolytics despite the two groups having similar baseline characteristics, although this difference was not preserved to 12-month follow-up. As this was not a randomised study specifically powered to assess the impact of intrapleural fibrinolytics on outcomes in pleural infection and the way in which fibrinolytics were used varied between centres, we cannot draw any firm conclusions. However, alongside previous work [11], the signal seen in this study raises the important question of whether mortality from pleural infection can be influenced by more invasive treatment and highlights the need for further research in this area of practice.

As this study demonstrates RAPID to be a robust prediction score in pleural infection, how should it be used in practice? The score should be incorporated into future prospective studies of pleural infection to ensure that balanced risks of mortality exist in study groups and it should also inform research assessing the safety and efficacy of new treatment paradigms (*e.g.* the use of less invasive, ambulatory strategies in the low-risk RAPID population [42, 43] or early invasive treatment, such as surgery or intrapleural fibrinolytic therapy, in the high-risk group). Whilst it cannot yet direct clinical care or decision making, the RAPID score may also inform a clinician's evidence-based discussions of the likely outcome from pleural infection at presentation and the balance of risk or benefit from any planned medical or surgical intervention.

Conclusion

The RAPID score uses data routinely available to a clinician at a patient's baseline presentation with pleural infection in order to predict meaningful clinical outcomes. Further studies targeting treatment according to RAPID risk categorisation are now required to better inform the treatment of adults with pleural infection, with the long-term aim of improving outcomes in a condition that continues to be associated with significant morbidity and mortality.

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