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

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JPC, NAM and NMR designed the study. JPC, IP, FP, CFK, TS, CD, IF, RH, AW, AES, JH, JAK, HS, NJD, MH, EHB, CFE, JP, TB, LY, FM, BK, AHT, GH, GW, DDF, MH, MM, AG, MS, ZP, LD, NDP, JS, NRW, RJH, NAM and NMR recruited study patients. SG, GSC and LMY performed the statistical analysis and model validation. MD, RS, ELH, AS, BR and RFM supported the study management team including data entry. IP, JPC, SG, NAM, RFM and NMR wrote the first version of the manuscript. All authors subsequently revised and approved the final version of the manuscript for submission.

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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 (RAPID - Renal (urea), Age, fluid Purulence, Infection source, Dietary (albumin)) in adults with pleural infection.

Methods

Prospective observational cohort study recruiting 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 of 546 (99.3%) patients recruited. Overall mortality was 10% (54/542) at 3 months and 19% (102/542) at 12 months. The RAPID risk category predicted mortality at 3 months; low-risk (RAPID score 0-2) mortality 5/222 (2.3%, 95%CI 0.9 to 5.7), medium-risk (RAPID score 3-4) mortality 21/228 (9.2%, 95%CI 6.0 to 13.7), and high-risk (RAPID score 5-7) mortality 27/92 (29.3%, 95%CI 21.0 to 39.2). C-statistics for the score at 3 and 12 months were 0.78 (95%CI 0.71 to 0.83) and 0.77 (95%CI 0.72 to 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 and United Kingdom (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 unchanged over the last 20 years. Morbidity is significant, with 25% of patients requiring hospital admission for more than 1 month, and 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 & 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 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 anesthetic mortality (20), conversion to thoracotomy (21-23), and long-term pain in up to 5% (24, 25).

A newer semi-invasive strategy for pleural infection is the combined use of intrapleural tPA and DNase given via 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; results from these studies are not robust though given their retrospective designs. Only one study (30) has derived and retrospectively validated a clinical prediction rule in pleural infection (the RAPID score) in which baseline serum urea (Renal), patient age (Age), pleural fluid purulence (Purulence), infection source (community- versus healthcare-acquired Infection), and serum albumin (Dietary) were independently associated with mortality at three months. Categorisation of patients into low- (RAPID score 0-2), medium- (RAPID 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 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 three months (primary outcome), mortality at 12 months, medical treatment failure and need for surgical intervention based on objective criteria, length of hospital stay, and lung function at three months (secondary outcomes).

METHODS

Study design

The Pleural Infection Longitudinal Outcome Study (PILOT) 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 (UK, USA, 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 pH ≤7.2 (measured in a blood gas analyser) or low glucose level (≤3mmol/L or ≤55mg/dL) in a patient with clinical evidence of infection, **OR**
5. Contrast-enhanced 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:

1. Age less than 18 years,
2. No pleural fluid available for analysis,
3. Previous pneumonectomy on the side of pleural infection,
4. Expected survival of less than three 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) pre-defined in the original paper (30) for the purposes of analysis. Individual patients did not have the 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 (see online supplement) 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 wherever possible at baseline, and the size of the pleural collection and extent of any septations scored (see online supplement for ultrasound scoring methodology). Spirometry was conducted at discharge from hospital, and at three months.

Medical treatment failure and surgical referral

As not all patients with pleural infection are 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 three to five days post-study inclusion and recorded on the case report forms (CRF) (see online supplement). 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 meeting minimum objective criteria (see online supplement). 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 were followed up for 12 months; at three 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 (see online supplement),
- Lung function at three 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 to 7), and in each of the three risk categories (low, medium, and high). Discrimination was assessed using the C-statistic (32), and calculated separately for individual values of the RAPID score (0 to 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) with 30% mortality; and high-risk (5-7; 8% of patients) with 70% mortality (30). As a point estimate for the difference between low- 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 over-optimistic, and would not

exclude a minimum clinically significant difference, a minimum significant difference to detect mortality was fixed at 15%, i.e. low-risk mortality 15%, medium-risk 30% - with an unchanged (4:1) ratio of low- to medium-risk patients. Using these data, this study required 500 analyzable 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 participant recruitment commencing.

RESULTS

Patients

In total 551 participants were recruited. Five withdrew consent for use of their data during follow up; 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 three months) was available for 542/546 (99.3%) study participants. At baseline missing prediction score parameters were: urea 21/546 (3.8%); age 9/546 (1.6%); pleural fluid purulence 6/546 (1.1%); infection source 3/546 (0.5%); and albumin 29/546 (5.3%). The RAPID score was well distributed across the study population (see online supplement) in both those who survived and those that died.

Primary endpoint

Mortality at three months was 54/542 (10.0%) and was strongly associated with the RAPID score; mortality increasing with each incremental rise in RAPID score (Figure 2). Analysis of patients according to their RAPID risk category (low, medium, and high) showed an increase in three month mortality according to risk category; low-risk (RAPID score 0-2) mortality was 5/222 (2.3%, 95% CI 0.9 to 5.7), medium-risk (RAPID score 3-4) mortality 21/228 (9.2%, 95% CI 6.0 to 13.7), and high-risk (RAPID score 5-7) mortality 27/92 (29.3%, 95% CI 21.0 to 39.2). The hazard ratio for mortality at three months (with low-risk as the comparator) for medium-risk was 3.2 (95% CI 1.7 to 9.1, $p<0{\cdot}001$), and for high-risk was 11.4 (95% CI 6.1 to 21.2, $p<0{\cdot}001$).

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 at three and 12 months was 0.78 (95% CI 0.71 to 0.83) and 0.77 (95% CI 0.72 to 0.82) respectively. Sensitivity and specificity for the primary endpoint at each incremental level of the RAPID score is detailed in the online supplement.

Secondary endpoints

12-month mortality

Mortality at 12 months was 102/542 (18.8%) patients. The 12-month mortality increased according to RAPID risk category; low-risk (RAPID score 0-2) mortality was 6.1% (95% CI 3.5 to 10.2), medium-risk (RAPID score 3-4) mortality 18.0% (95% CI 13.6 to 23.3), and high-risk (RAPID score 5-7) mortality 49.9% (95% CI 39.8 to 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 (IQR 7–23 days). The median length of hospital stay was significantly associated with baseline RAPID risk category (Table 3).

Medical treatment failure

The failure of initial medical treatment was assessed in those with complete data, and occurred in 158/472 (33.5%) patients; this 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 online supplement and were not significantly different according to RAPID risk category.

Need for surgical intervention within 12 months

Overall, surgical intervention was required by 86/550 (15.6%) patients. 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 done in 68.9% of low-risk, 31.5% of medium-risk, and 28.6% of high-risk patients.

Lung Function at three months

Lung function data were available in 154/540 (28.5%) patients only, limiting any detailed analysis. Significantly better lung function was observed in those in the low-risk RAPID category; 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 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 (fall in C-statistic from 0.82 to 0.69 in those with previous antibiotics) (see online supplement).

Use of intrapleural fibrinolytic therapy

82/546 (15.0%) patients were prescribed intrapleural fibrinolytic therapy by their responsible clinical team as part of their treatment for pleural infection. 62/82 (75.6%) patients received

alteplase and dornase alfa; 20/82 (24.4%) patients received streptokinase. There were no significant differences between the population of patients who received intrapleural fibrinolytics and those who did not with respect to baseline demographics or RAPID risk categorisation (Table 4). Whilst there was a significant difference in three-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 C-statistic 0.73 in those receiving intrapleural fibrinolytics and 0.78 in those who did not at 12-month follow-up (Table 5).

DISCUSSION

Results of the Pleural Infection Longitudinal Outcome Study (PILOT) 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 three-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 management of pneumonia (34, 35). The fact that the RAPID score is strongly predictive of outcome in a study that 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 the RAPID risk categorisation in PILOT is remarkably similar to that seen in the original study (30) in which the RAPID score was first derived, then retrospectively validated. Three month mortality in the original study by risk group (low, medium, and high) was 3%, 9% and 31% respectively, and in PILOT was 2.3%, 9.3% and 30.8%. The PILOT study population mirrors that seen in other multicentre randomised studies with a similar 'all-comers' mortality of 20%, and surgical intervention rate of 16% (10, 11).

Our results suggest a linear relationship between the RAPID score and three month mortality following diagnosis of pleural infection, with scores ≤1 associated with 1.9% mortality and scores ≥6 associated with 35% mortality. It is not clear why all the parameters used in RAPID predict mortality so precisely; associations with increasing age, blood urea, and serum albumin are likely to identify a more frail population, and one in whom uncontrolled infection has resulted in a catabolic state.

We postulate that the association of mortality with healthcare-acquired pleural infection is a result of more resistant organisms (36, 37) and potentially more co-morbid illness. An explanation for why non-purulent pleural fluid is associated with increased mortality remains unclear. 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 simply reflect 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 three 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 among 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, by extension, would 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 (19.1% of patients) than high-risk (5.9% of patients) group. In the high-risk group only one in three patients who objectively had failed medical treatment then underwent surgery; 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 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 randomized 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 among younger individuals, with fewer co-morbidities than seen in unselected patient populations with pleural infection (10, 11). These results inform a pressing need for randomized studies in pleural infection, 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 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 lack of drainage. For example, this 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;

these findings require further exploration. The true value of ultrasound assessment of the infected pleural space needs further study. Considering fluid septation in isolation ignores other sonographic features that may impact on outcome such as the size of a collection, presence of multiple locules of fluid, or pleural thickening.

15% of patients recruited to this study 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 three-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 randomized 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 balanced risks of mortality exist in study groups, and should also inform research assessing the safety and efficacy of new treatment paradigms – whether this is 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 clinical meaningful 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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CONTRIBUTORS STATEMENT

JPC, NAM and NMR designed the study. JPC, IP, FP, CFK, TS, CD, IF, RH, AW, AES, JH, JAK, HS, NJD, MH, EHB, CFE, JP, TB, LY, FM, BK, AHT, GH, GW, DDF, MH, MM, AG, MS, ZP, LD, NDP, JS, NRW, RJH, NAM and NMR recruited study patients. SG, GSC and LMY performed the statistical analysis and model validation. MD, RS, ELH, AS, BR and RFM supported the study management team including data entry. IP, JPC, SG, NAM, RFM and NMR wrote the first version of the manuscript. All authors subsequently revised and approved the final version of the manuscript for submission. Further details relating to membership of the PILOT Study Group can be found in the online supplement.

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FIGURE LEGENDS

Figure 1: Flow chart describing the movement of patients through the study.

Figure 2: Three month mortality according to RAPID score at baseline.

Figure 3: Kaplan-Meier graphs censored for loss to follow up according to baseline RAPID risk category; based on a single representative imputed dataset. Low risk = RAPID score 0 to 2; medium risk = RAPID score 3 to 4; high risk = RAPID score 5 to 7. Shaded areas represent 95% confidence intervals for survival at each point.

TABLES

Parameter	Measure		Score
Renal	Urea (mmol / L)	<5.0	0
		5.0 to 8.0	1
		>8.0	2
Age	<50 years		0
	50-70 years		1
	>70 years		2
Purulence of fleural fluid	Purulent		0
	Non-purulent		1
Infection source	Community Acquired		0
	Hospital Acquired		1
Dietary factor	Albumin (g / L)	>27.0	0
		<27.0	1
Risk category	**Score 0-2**		**Low risk**
	Score 3-4		**Medium risk**
	Score 5-7		**High risk**

Table 1. The RAPID risk prediction score, using baseline clinical parameters in patients with pleural infection (30)

Variable	
Demographic characteristics	
Age, years - mean (SD)	60 (18)
Male - no. (%)	385/545 (71%)
Source of infection - no. (%)	
Community-acquired	286/545 (52%)
Healthcare-acquired	259/545 (48%)
Poor dental hygiene - no. (%)	100/545 (18%)
Small (<15F) chest tube - no. (%)	309/445 (70%)
Antibiotic use before diagnosis - no. (%)	117/545 (21%)
Pleural fluid characteristics	
Pleural fluid purulence - no. (%)	222/545 (41%)
Gram stain or culture positivity - no. (%)	334/545 (61%)
pH - median (IQR)	7.0 (6.8-7.2)
LDH (U/L) - median (IQR)	1968 (946-5009)
Coexisting illness – no. (%)	
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%)

Table 2. Baseline characteristics of PILOT study participants

Outcome	RAPID Risk category			Statistical comparison
	Low N=188	**Medium N=199**	**High N=85**	
12 month mortality (% (95% CI))	6.1 (3.5 to 10.2)	18.0 (13.6 to 23.3)	49.9 (39.8 to 60.0)	HR (versus low) Medium 3.2 (1.7 to 9.1), p<0.001 High 11.4 (6.1 to 21.2), p<0.001
Length of hospital stay (days) (median (IQR))	11 (6 to 21)	13 (7 to 25)	18 (10 to 27)	Mann Whitney p=0.003
Failure of initial medical treatment (no, %, 95% CI)	66 (35.1%) (28.3 to 41.9)	70 (35.2%) (28.5 to 41.8)	22 (25.9%) (16.6 to 35.2)	χ^2 3df = 2.68 p=0.26
Surgical intervention (no, %, 95% CI)	36 (19.1%) (13.5 to 24.8)	31 (15.6%) (10.5 to 20.6)	5 (5.9%) (0.9 to 10.9)	χ^2 3df = 7.991 p=0.02
FEV1 at 3 months (L) (median (IQR))				
- **overall pop[n]**	2.4 (2.0 to 3.1) (n = 44)	2.0 (1.6 to 2.4) (n = 53)	1.9 (1.5 to 2.3) (n = 20)	Krusakal-Wallis p<0.001 (calculated for overall pop[n] only)
- **non-surgical**	2.3 (2.0 to 3.1) (n = 40)	2.0 (1.6 to 2.4) (n = 46)	1.9 (1.5 to 2.3) (n = 19)	
- **surgical**	2.7 (2.0 to 3.0) (n = 4)	1.9 (1.3 to 2.3) (n = 7)	2.3 (2.3 to 2.3) (n = 1)	
FVC at 3 months (L) (median (IQR))				
- **overall pop[n]**	3.5 (2.5 to 4.1) (n = 44)	2.8 (2.2 to 3.4) (n = 53)	2.8 (2.1 to 3.3) (n = 20)	Krusakal-Wallis p=0.002 (calculated for overall pop[n] only)
- **non-surgical**	3.5 (2.5 to 4.1) (n = 40)	2.8 (2.3 to 3.4) (n = 46)	2.6 (2.0 to 3.2) (n = 19)	
- **surgical**	3.6 (2.7 to 4.1) (n = 4)	3.4 (1.7 to 3.5) (n = 7)	3.5 (3.5 to 3.5) (n = 1)	

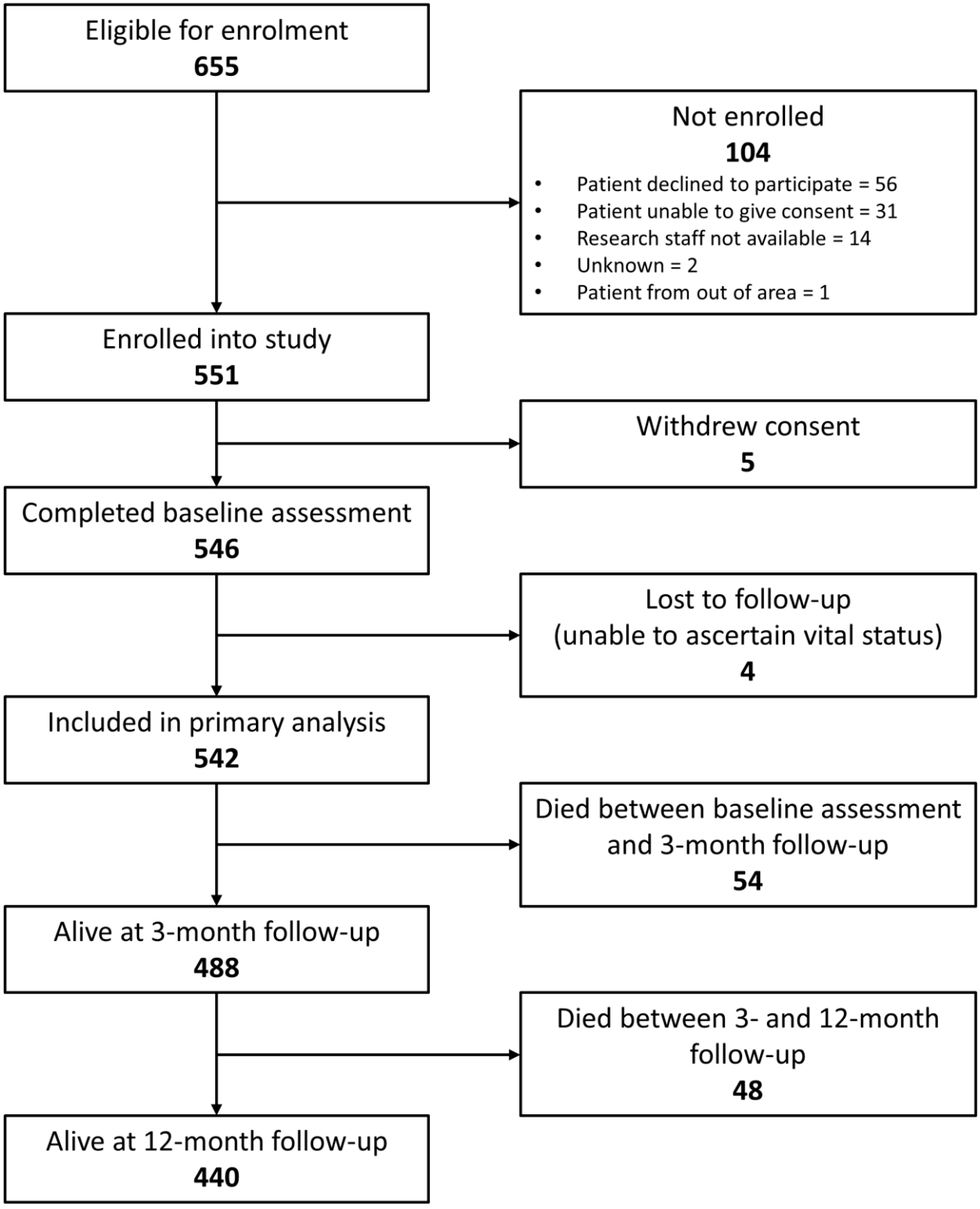
Table 3. Secondary outcomes according to baseline RAPID risk category. Lung function was available in 154 patients (FEV_1) and 155 patients (FVC). Analysis of 12 month mortality was based on multiple imputation: all other analyses were based on complete case data.

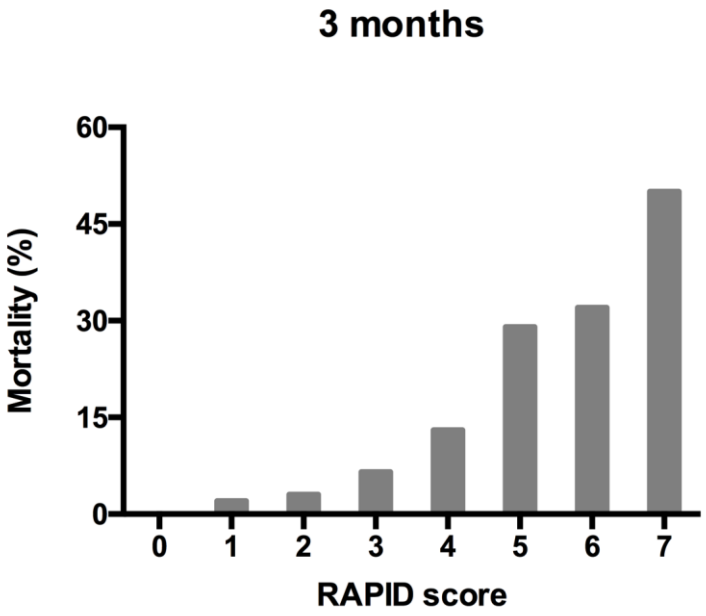
Demographic characteristics	No intrapleural fibrinolytic therapy N = 464	Intrapleural fibrinolytic therapy N = 82	Statistical comparison
Age, years - mean (SD)	60.0 (17.2)	56.7 (15.6)	unpaired t-test p=0.11
Male - no. (%)	320/464 (69%)	65/82 (79%)	χ^2 1df = 3.08 p=0.08
Source of infection - no. (%)			
Community-acquired	409/461 (89%)	75/82 (91%)	χ^2 1df = 0.30
Healthcare-acquired	52/461 (11%)	7/82 (9%)	p=0.58
RAPID risk category			
Low	159/401 (40%)	29/71 (41%)	χ^2 2df = 0.36
Medium	168/401 (42%)	31/71 (44%)	p=0.84
High	74/401 (18%)	11/71 (15%)	

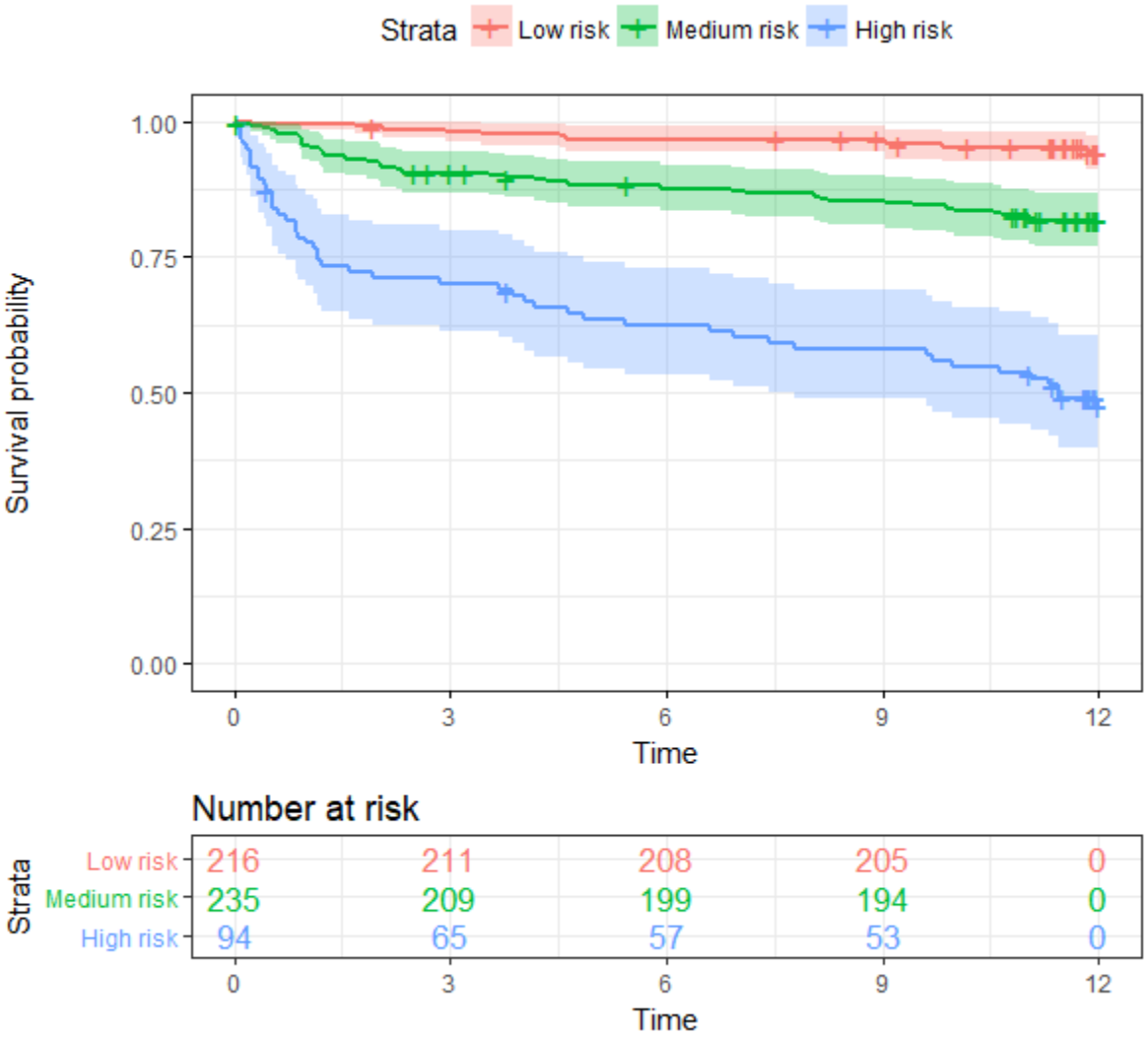
Table 4. Baseline characteristics of study participants who did and did not receive intrapleural fibrinolytic therapy

	No intrapleural fibrinolytic therapy N = 464	**Intrapleural fibrinolytic therapy N = 82**	**Statistical comparison**
3-month mortality - no. (%)	54/464 (11.6%)	0/82 (0%)	Fisher's exact test p=<0.001
3-month C-statistic (95% CI)	0.78 (0.71 to 0.83)	n/a	
12-month mortality - no. (%)	90/464 (19.4%)	12/82 (14.6%)	Fisher's exact test p=0.36
12-month C-statistic (95% CI)	0.78 (0.71 to 0.83)	0.73 (0.57 to 0.84)	

Table 5. Three- and 12-month mortality and RAPID risk prediction model performance in study patients who did and did not receive intrapleural fibrinolytic therapy


Eligible for enrolment
655
Not enrolled
104
Patient declined to participate = 56
Patient unable to give consent = 31
Research staff not available = 14
Unknown = 2
Patient from out of area = 1
Enrolled into study
551
Withdrew consent
5
Completed baseline assessment
546
Lost to follow-up
(unable to ascertain vital status)
4
Included in primary analysis
542
Died between baseline assessment and 3-month follow-up
54
Alive at 3-month follow-up
488
Died between 3- and 12-month follow-up
48
Alive at 12-month follow-up
440


3 months
Mortality (%)
60
45
30
15
0
0
1
2
3
4
5
6
7
RAPID score


Strata
Low risk
Medium risk
High risk
Survival probability
1.00
0.75
0.50
0.25
0.00
0
3
6
9
12
Time
Number at risk
Strata
Low risk 216 211 208 205 0
Medium risk 235 209 199 194 0
High risk 94 65 57 53 0
0
3
6
9
12
Time

ERJ Original Research Submission - ONLINE SUPPLEMENTARY INFORMATION

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

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Trial registration number:

ISRCTN 50236700

SUPPLEMENTARY METHODS

1. **Chest tube drainage, antibiotic treatment, and other investigations**
2. **Suggested study criteria for referral for surgical intervention**
3. **Study criteria for medical treatment failure**
4. **Thoracic ultrasound scoring methodology**
5. **Study Delivery, Funding and Support**

SUPPLEMENTARY RESULTS

1. **Distribution of the RAPID score across the recruited population**
2. **Documented reasons for failure of initial medical treatment**
3. **Performance of the RAPID score by pre-specified subgroup analysis**
4. **Sensitivity and specificity for primary outcome using each level of the RAPID score**

PILOT STUDY GROUP MEMBERSHIP LIST

SUPPLEMENTARY METHODS

1. Chest tube drainage, antibiotic treatment, and other investigations

Chest-tube drainage and antibiotic therapy

If deemed to be clinically indicated by the responsible local clinical team, chest tube size and insertion method were at the discretion of the local study investigator according to local treatment and procedural guidelines. Smaller bore drains (<15Fr) were to be flushed regularly with sterile water or saline to maintain patency, and thoracic suction used where available. Fixation of the drain to the chest wall using sutures and dressings was advised to avoid early unintentional dislodgement.

All patients received intravenous antibiotics initally which were chosen by the managing clinician (usually the local study investigator) in line with up-to-date evidence on the modern microbiology of pleural infection (see, for example, references 15, 34, 35 in the main manuscript) and local microbiological advice. Empiric antibiotic regimens according to the likely source (community vs. healthcare-acquired) of infection were suggested in a study-specific protocol - for example, co-amoxiclav or a third-generation cephalosporin +/- metronidazole in community-acquired pleural infection; or a carbapenem with anti-pseudomonal activity plus vancomycin in healthcare-acquired infection.

Antibiotic treatment was changed according to pleural fluid and/or blood culture and sensitivity results where available. Intravenous antibiotics were changed to oral consolidation therapy by the local study investigator and/or responsible clinician based on the clinical response to treatment. Empiric oral antibiotic consolidation regimens were suggested in a study-specific protocol; for example, co-amoxiclav +/- metronidazole in community-acquired infection; or a fluoroquinolone

+/- clindamycin in healthcare-acquired infection. It was suggested that antibiotic treatment should be continued for a minimum of two weeks and up to six weeks (see reference 15 in the main manuscript) at the discretion of the local study investigator and according to clinical response; however, no minimum treatment duration of intravenous or oral antibiotics was mandated.

Other treatments and investigations

Repeat radiology and blood markers of infection were measured at the discretion of the local study investigator according to local best practice. As a minimum expectation, blood markers (including peripheral blood white-cell count and CRP) were conducted at baseline and prior to discharge, or at the point of referral for surgery if appropriate. The use of intrapleural therapeutic agents (fibrinolytic +/- DNase therapy) was at the discretion of the local study investigator and based on local guidelines, with their use recorded on the study Case Report Forms (CRFs). Thromboembolism prophylaxis whilst undergoing inpatient treatment for pleural infection was recommended in the study protocol, and was in accordance with local best practice.

As a minimum expectation, a chest radiograph was conducted at study entry, at discharge from hospital, and prior to referral for surgery if appropriate. Thoracic CT scans and ultrasound were recommended during treatment and according to clinical need. Thoracic ultrasound was conducted wherever possible at baseline, and septations scored (please see later for ultrasound scoring methodology); and during the inpatient admission and/or follow-up thereafter as deemed appropriate by the local study investigator. Spirometry was conducted at discharge from hospital, and at 3 months.

2. Suggested study criteria for referral for surgical intervention

There are no agreed criteria on which to base surgical referral decisions for patients with pleural infection in current treatment guidelines (see references 14, 15 in main manuscript), or relating to the optimal timing of surgery in those patients who are failing "medical" treatment. This can lead to variation in local practice and decision making, the reasons for which might not always be clear without appropriate documentation in study CRFs. Guidance was therefore provided to all local study investigators on suggested criteria for referral for surgical intervention which included minimum objective criteria with the reasons for surgical referral to be documented on the CRFs. This guidance was based on recommendations made in published guidelines (see references 14, 15 in main manuscript), recognising these were based on expert consensus. The minimum expected criteria for referral for surgical intervention were <u>all</u> of the following:

1. At least 48 hours of medical treatment (including intercostal drainage of pleural collection and intravenous antibiotic therapy), unless significant clinical instability requiring more urgent intervention as judged by the local study investigator and/or responsible senior clinician. Reasons for an "early" decision to refer for surgery were recorded on the CRFs.
2. Persisting evidence of sepsis, as demonstrated by clinical indicators (ongoing fever, or inflammation on blood indices), despite medical treatment as outlined above.
3. A significant residual pleural fluid collection felt to be to contributing to the detriment of the patient and persisting sepsis as judged by the local study investigator and/or responsible senior clinician.

The final decision on whether or not to refer for surgical intervention for a patient's pleural infection remained with the local study investigator and/or responsible senior clinician, regardless

of the suggested minimum study criteria, in order to best replicate usual local clinical practice and in keeping with the observational nature of the study.

3. Study criteria for Medical Treatment Failure

The failure of medical treatment in pleural infection is most commonly marked by referral for surgical intervention in usual clinical practice. However, as not all patients with pleural infection are considered fit enough to undergo surgical intervention, objective criteria for "medical treatment failure" were recorded for all study participants in order to minimise the risk of any cases being otherwise missed. These were measured at 3-5 days post-study inclusion, and recorded on the CRFs as follows:

- The presence of a residual and clinically significant pleural collection as judged by the local study investigator, based on current radiology (chest radiograph, ultrasound, and/or CT); plus at least one of the following:
    1) Clinical evidence of ongoing sepsis as demonstrated by factors such as otherwise unexplained persistent fever, tachycardia and/or hypotension;
    2) A serum CRP that has failed to fall by more than or equal to 50% compared to the baseline value prior to initiation of medical treatment for pleural infection;
    3) A lack of significant response in the peripheral blood white-cell count as judged by the local study investigator since the initiation of medical treatment for pleural infection.

The question of whether or not medical treatment had failed had to be completed for all study participants between 3 and 5 days post-study inclusion; however, medical treatment failure could

also be documented by the local study investigator at any point during a study participant's treatment for their pleural infection up to and including 3-month follow-up. Local study investigators also had the option of documenting a free-text reason in the study CRFs as to why they felt medical treatment had failed in the event that the pre-specified criteria were not sufficient.

4. Thoracic ultrasound scoring methodology

Thoracic ultrasound was recommended at the time of initial chest tube insertion and during subsequent treatment according to clinical need. All patients underwent ultrasound assessment prior to pleural intervention by a respiratory or other physician holding Royal College of Radiology Thoracic Ultrasound level I competence or above. The size of the pleural effusion (small = visible in one rib space; moderate = two to three rib spaces; large ≥ four rib spaces), fluid echogenicity, and average number of septations per image field of view were recorded. Each effusion was categorized based on the initial sonographic findings into one of the following groups: non-septated; mildly septated (<2 septations per field); moderately septated (2-4 septations per field); or severely septated (>4 per field). Visual scales of ultrasound pictures were included on the study CRFs to guide clinicians as to which score to use.

5. Study Delivery, Funding and Support

Study delivery

The study was coordinated by the Oxford Respiratory Trials Unit to standards of Good Clinical Practice, supervised by an independently chaired Study Steering Committee. Safety monitoring was risk assessed and not considered required, due to the observational nature of the study.

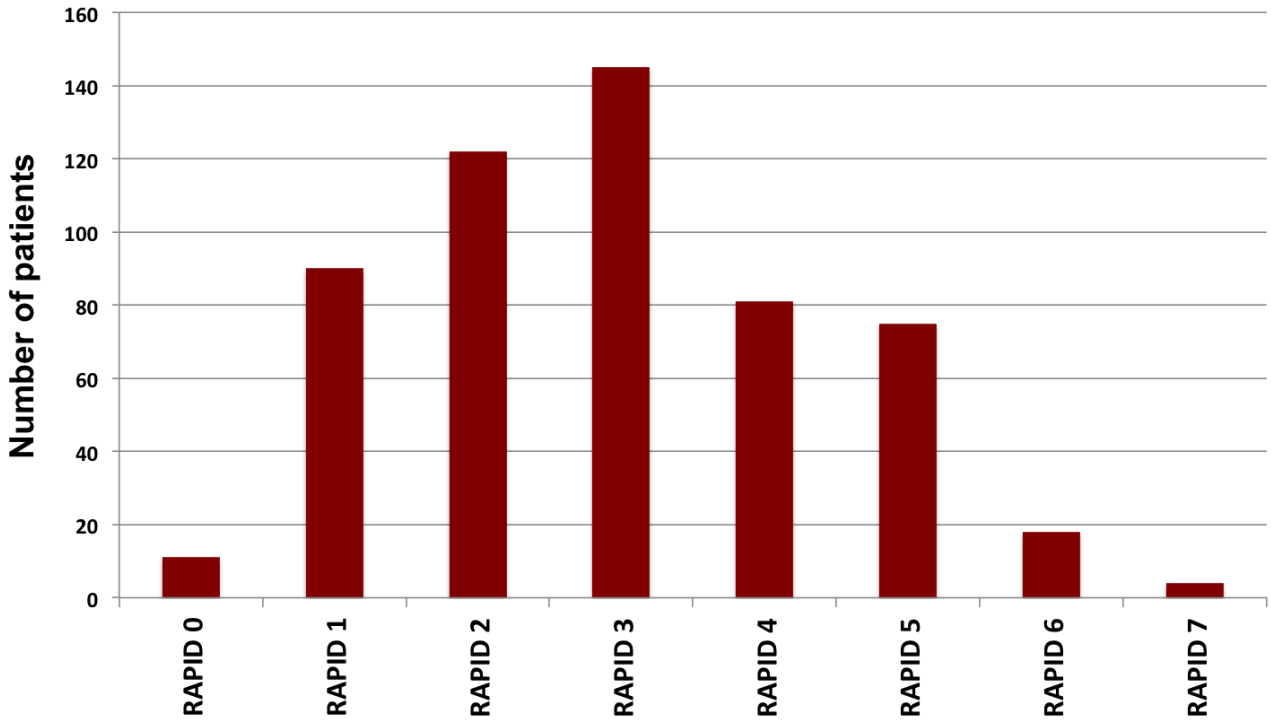
Study funding and support

The study was funded by the UK Medical Research Council (grant number G1001128). NMR was funded by the Oxford NIHR Biomedical Research Centre. Neither organization had influence on the design, conduct, or analysis of the study, or the decision to publish.

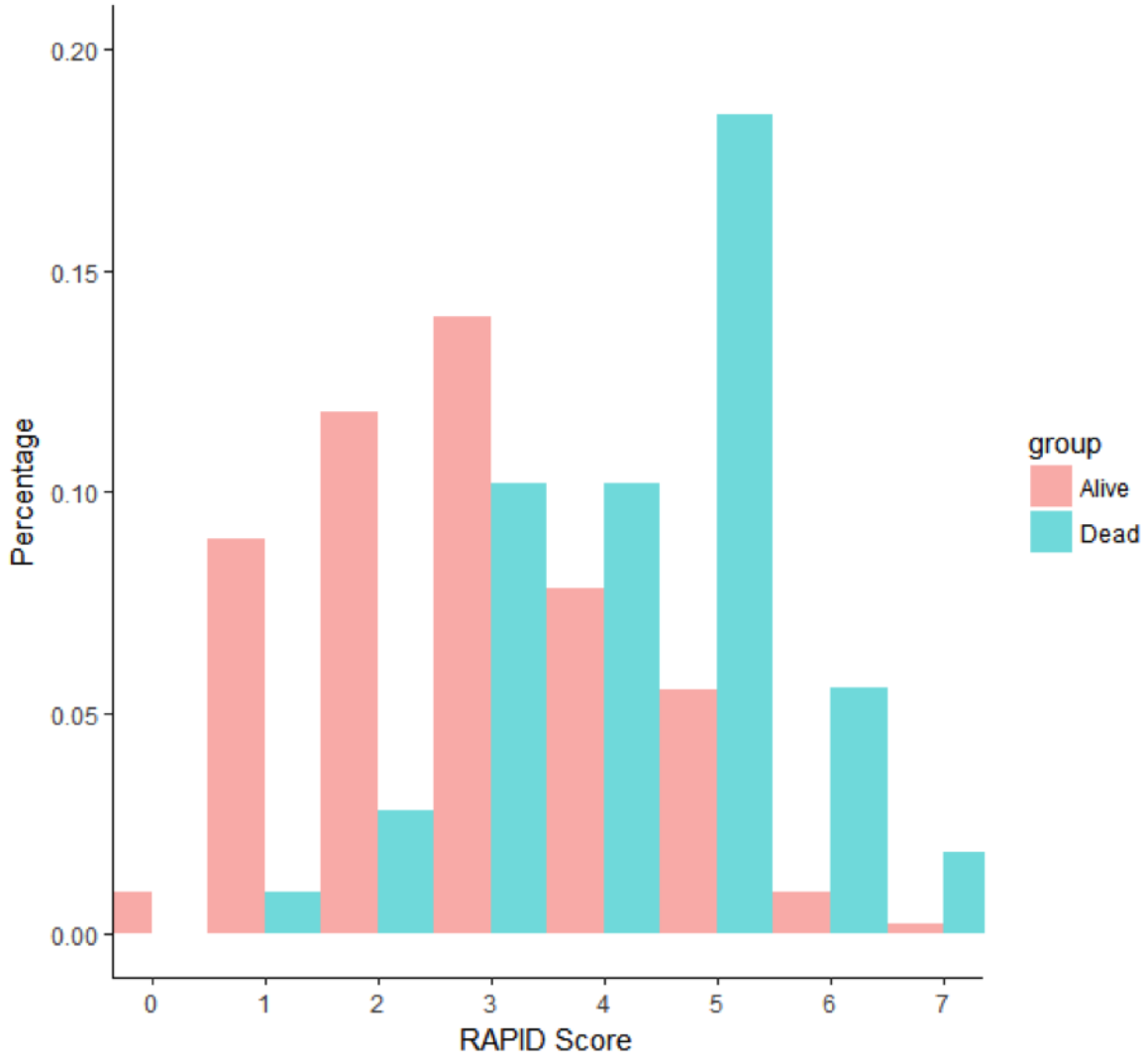
SUPPLEMENTARY RESULTS

1. Distribution of the RAPID score across the recruited study population

The RAPID score was well distributed across the study population as below, with an approximate 2:2:1 split for low-, medium-, and high-risk RAPID category patients.



The distribution was well spread according to the primary outcome measure (death at 3 months) as below:



2. Documented reasons for failure of initial medical treatment

The individual criteria which were met to classify a patient as having "failed medical treatment" are summarised in the table below – individual patients could have more than one reason for failure.

Reason	Low risk (n=188)	Medium risk (n=199)	High risk (n=85)	Total (n=472)
Physiological instability secondary to pleural infection	9	13	3	25
Clinical evidence of on-going sepsis	20	32	5	57
Failure of inflammatory markers or WCC to improve sufficiently	27	36	14	77
Clinically significant residual collection	46	50	15	111
Other	6	5	4	15

4. Performance of the RAPID score by pre-specified subgroup analysis

Subgroup	Number in group	Number died (%)	C-statistic (95% CI)
Ultrasound septation score			
Non-septated	80	10 (12.5)	0.87 (0.76, 0.94)
Mild	63	11 (17.5)	0.84 (0.69, 0.92)
Moderate	112	10 (8.9)	0.81 (0.67, 0.90)
Severe	122	10 (8.2)	0.64 (0.46, 0.78)
WHO performance status			
0	289	15 (5.2)	0.79 (0.66, 0.88)
1	104	10 (9.6)	0.69 (0.52, 0.82)
2 to 4	75	25 (33.3)	0.70 (0.57, 0.81)
On site thoracic surgery			
Yes	262	29 (11.1)	0.75 (0.64, 0.83)
No	207	21 (10.1)	0.82 (0.72, 0.88)
Prior antibiotic use			
Yes	285	30 (10.5)	0.82 (0.75, 0.87)
No	160	17 (10.6)	0.69 (0.54, 0.81)

4. Sensitivity and specificity for primary outcome (mortality at 3 months) using each level of the RAPID score

RAPID score	Sensitivity (95% CI)	Specificity (95% CI)
1	1.00 (1.00, 1.00)	0.02 (0.01, 0.03)
2	0.98 (0.94, 1.00)	0.20 (0.16, 0.23)
3	0.93 (0.85, 0.98)	0.43 (0.39, 0.48)
4	0.72 (0.59, 0.83)	0.70 (0.66, 0.74)
5	0.52 (0.39, 0.65)	0.86 (0.83, 0.89)
6	0.13 (0.06, 0.22)	0.98 (0.96, 0.99)
7	0.04 (0.00, 0.09)	1.00 (0.99, 1.00)

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