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

John P Corcoran* [1,2], Ioannis Psallidas* [1,2], Stephen Gerry [3], Francesco Piccolo [4], Coenraad F Koegelenberg [5], Tarek Saba [6], Cyrus Daneshvar [7], Ian Fairbairn [8], Richard Heinink [9], Alex West [10], Andrew E Stanton [11], Jayne Holme [12], Jack A Kastelik [13], Henry Steer [14], Nicola J Downer [15], Mohammed Haris [16], Emma H Baker [17], Caroline F Everett [18], Justin Pepperell [19], Thomas Bewick [20], Lonny Yarmus [21], Fabien Maldonado [22], Burhan Khan [23], Alan Hart-Thomas [24], Georgina Hands [25], Geoffrey Warwick [26], Duneesha De Fonseka [27], Maged Hassan [1,2], Mohammed Munavvar [28], Anur Guhan [29], Mitra Shahidi [30], Zara Pogson [31], Lee Dowson [32], Natalia D Popowicz [4], Judith Saba [6] , Neil R Ward [7] , Rob J Hallifax [1,2], Melissa Dobson [2], Rachel Shaw [2], Emma L Hedley [2], Assunta Sabia [2], Barbara Robinson [2], Gary S Collins [3], Helen E Davies [33], Ly-Mee Yu [34], Robert F Miller [35], Nick A Maskell [27], Najib M Rahman [1,2,36]

Affiliations:

1. Oxford Centre for Respiratory Medicine, Oxford University Hospitals NHS Foundation Trust, UK
2. Oxford Respiratory Trials Unit, University of Oxford, UK
3. Centre for Statistics in Medicine, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, UK
4. Department of Respiratory Medicine, Sir Charles Gairdner Hospital, Perth, Australia
5. Division of Pulmonology, Department of Medicine, Stellenbosch University, Cape Town, South Africa
6. Blackpool Teaching Hospitals NHS Foundation Trust, UK
7. University Hospitals Plymouth NHS Trust, Plymouth, UK
8. Victoria Hospital, NHS Fife, UK
9. Shrewsbury and Telford Hospital NHS Trust, UK
10. Guy's and St. Thomas' NHS Foundation Trust, London, UK
11. Great Western Hospitals NHS Foundation Trust, Swindon, UK
12. University Hospital of South Manchester NHS Foundation Trust, UK
13. Hull and East Yorkshire Hospitals NHS Trust, UK
14. Gloucestershire Hospitals NHS Foundation Trust, UK
15. Sherwood Forest Hospitals NHS Foundation Trust, Mansfield, UK
16. University Hospitals of North Midlands NHS Trust, UK
17. Institute of Infection and Immunity, St George's, University of London, UK
18. York Teaching Hospitals NHS Foundation Trust, UK
19. Taunton and Somerset NHS Foundation Trust, UK
20. Derby Teaching Hospitals NHS Foundation Trust, UK
21. Division of Pulmonary and Critical Care Medicine, John Hopkins University, Baltimore, Maryland, USA
22. Division of Allergy, Pulmonary and Critical Care Medicine, Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, Tennessee, USA
23. Dartford and Gravesham NHS Trust, UK
24. Calderdale and Huddersfield NHS Foundation Trust, UK

25. Northern Devon Healthcare NHS Trust, UK
26. King's College Hospital NHS Foundation Trust, London, UK
27. Academic Respiratory Unit, University of Bristol, UK
28. Lancashire Teaching Hospitals NHS Foundation Trust, UK
29. University Hospital Ayr, NHS Ayrshire and Arran, UK
30. Buckinghamshire Healthcare NHS Trust, UK
31. United Lincolnshire Hospitals NHS Trust, UK
32. Royal Wolverhampton Hospital NHS Trust, UK
33. University Hospital of Wales, Cardiff, Wales, UK
34. Nuffield Department of Primary Care Health Sciences, University of Oxford, UK
35. Institute for Global Health, University College London, UK
36. Oxford NIHR Biomedical Research Centre

* Joint first authors, with equal contribution to study recruitment and manuscript writing

Correspondence:

Prof Najib M Rahman
Oxford Centre for Respiratory Medicine
Oxford University Hospitals NHS Foundation Trust
Churchill Hospital Site
Oxford
OX3 7LJ
United Kingdom

Email: najib.rahman@ndm.ox.ac.uk; Telephone: +44(0)1865 225256

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.

Funding:

The study was funded by the UK Medical Research Council (MRC), grant number G1001128. NMR is funded by the UK National Institute for Health Research Oxford Biomedical Research Centre Programme. None of the funders had any influence on study design, delivery, analysis, or manuscript preparation.

Short Title / Running Head:

Validation of the RAPID score in pleural infection

Total Word Count:

3378 (excluding abstract, references, and legends)

Conflict of Interest Statement:

None of the authors have any conflicts of interest to declare with respect to the subject of this manuscript.

Trial registration number:

ISRCTN 50236700

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.

Abstract word count: 249

MeSH Key words: Empyema, Pleural; Pleural Effusion; Thoracostomy

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 <u>any</u> 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 powered to assess the impact of intrapleural fibrinolytics on outcomes in pleural infection we cannot draw any conclusions, but alongside previous work (11) this raises the question of whether mortality 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.

ACKNOWLEDGEMENTS

The authors would to thank all members of the University of Oxford Respiratory Trials Unit, the local investigators and their supporting staff who helped conduct the study, and the UK Medical Research Council.

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.

REFERENCES

1. Light RW, Girard WM, Jenkinson SG, George RB. Parapneumonic effusions. Am J Med 1980; 69(4):507-12
2. Desrumaux A, Francois P, Pascal C, Cans C, Croize J, Gout JP, et al. Epidemiology and clinical characteristics of childhood parapneumonic empyemas. Arch Pediatr 2007; 14(11):1298-303
3. Munoz-Almagro C, Jordan I, Gene A, Latorre C, Garcia-Garcia JJ, Pallares R. Emergence of invasive pneumococcal disease caused by nonvaccine serotypes in the era of 7-valent conjugate vaccine. Clin Infect Dis 2008; 46(2):174-82
4. Roxburgh CS, Youngson GG. Childhood empyema in North-East Scotland over the past 15 years. Scott Med J 2007; 52(4):25-7
5. Farjah F, Symons RG, Krishnadasan B, Wood DE, Flum DR. Management of pleural space infections: a population-based analysis. J Thorac Cardiovasc Surg 2007; 133(2):346-51
6. Finley C, Clifton J, Fitzgerald JM, Yee J. Empyema: an increasing concern in Canada. Can Respir J 2008; 15(2):85-9
7. Grijalva CG, Zhu Y, Pekka NJ, Griffin MR. Emergence of parapneumonic empyema in the USA. Thorax 2011; 66(8):663-8
8. Ferguson AD, Prescott RJ, Selkon JB, Watson D, Swinburn CR. The clinical course and management of thoracic empyema. QJM 1996; 89(4):285-9
9. Davies CW, Kearney SE, Gleeson FV, Davies RJ. Predictors of outcome and long-term survival in patients with pleural infection. Am J Respir Crit Care Med 1999; 160(5 Pt 1):1682-7
10. Maskell NA, Davies CW, Nunn AJ, Hedley EL, Gleeson FV, Miller R, et al. U.K. Controlled trial of intrapleural streptokinase for pleural infection. N Engl J Med 2005; 352(9):865-74
11. Rahman NM, Maskell NA, West A, Teoh R, Arnold A, Mackinlay C, et al. Intrapleural use of tissue plasminogen activator and DNase in pleural infection. N Engl J Med 2011; 365(6):518-26
12. Sonnappa S, Cohen G, Owens CM, van Doorn C, Cairns J, Stanojevic S, et al. Comparison of urokinase and video-assisted thoracoscopic surgery for treatment of childhood empyema. Am J Respir Crit Care Med 2006; 174(2):221-7
13. Netten A, Dennett J, Knight J. Unit Costs of Health and Social Care. Canterbury: PSSRU, University of Kent 1999
14. Colice GL, Curtis A, Deslauriers J, Heffner J, Light R, Littenberg B, et al. Medical and surgical treatment of parapneumonic effusions : an evidence-based guideline. Chest 2000; 118(4):1158-71

15. Davies HE, Davies RJ, Davies CW. Management of pleural infection in adults: British Thoracic Society Pleural Disease Guideline 2010. Thorax 2010; 65 Suppl 2:ii41-ii53
16. Angelillo Mackinlay TA, Lyons GA, Chimondeguy DJ, Piedras MA, Angaramo G, Emery J. VATS debridement versus thoracotomy in the treatment of loculated postpneumonia empyema. Ann Thorac Surg 1996; 61(6):1626-30
17. Cunniffe MG, Maguire D, McAnena OJ, Johnston S, Gilmartin JJ. Video-assisted thoracoscopic surgery in the management of loculated empyema. Surg Endosc 2000; 14(2):175-8
18. Podbielski FJ, Maniar HS, Rodriguez HE, Hernan MJ, Vigneswaran WT. Surgical strategy of complex empyema thoracis. JSLS 2000; 4(4):287-90
19. LeMense GP, Strange C, Sahn SA. Empyema thoracis. Therapeutic management and outcome. Chest 1995; 107(6):1532-7
20. Allen MS, Deschamps C, Jones DM, Trastek VF, Pairolero PC. Video-assisted thoracic surgical procedures: the Mayo experience. Mayo Clin Proc 1996; 71(4):351-9
21. Lardinois D, Gock M, Pezzetta E, Buchli C, Rousson V, Furrer M, et al. Delayed referral and gram-negative organisms increase the conversion thoracotomy rate in patients undergoing video-assisted thoracoscopic surgery for empyema. Ann Thorac Surg 2005; 79(6):1851-6
22. Luh SP, Chou MC, Wang LS, Chen JY, Tsai TP. Video-assisted thoracoscopic surgery in the treatment of complicated parapneumonic effusions or empyemas: outcome of 234 patients. Chest 2005; 127(4):1427-32
23. Petrakis IE, Kogerakis NE, Drositis IE, Lasithiotakis KG, Bouros D, Chalkiadakis GE. Video-assisted thoracoscopic surgery for thoracic empyema: primarily, or after fibrinolytic therapy failure? Am J Surg 2004; 187(4):471-4
24. Dajczman E, Gordon A, Kreisman H, Wolkove N. Long-term postthoracotomy pain. Chest 1991; 99(2):270-4
25. Stammberger U, Steinacher C, Hillinger S, Schmid RA, Kinsbergen T, Weder W. Early and long-term complaints following video-assisted thoracoscopic surgery: evaluation in 173 patients. Eur J Cardiothorac Surg 2000; 18(1):7-11
26. Piccolo F, Pitman N, Bhatnagar R, Popowicz N, Smith NA, Brockway B, et al. Intrapleural tissue plasminogen activator and deoxyribonuclease for pleural infection. An effective and safe alternative to surgery. Ann Am Thorac Soc 2014; 11(9):1419-25
27. Luengo-Fernandez R, Penz E, Dobson M, Psallidas I, Nunn AJ, Maskell NA, Rahman NM. Cost-effectiveness of intrapleural use of tissue plasminogen activator and DNase in pleural

infection: evidence from the MIST2 randomised controlled trial. Eur Respir J 2019; 54(2). pii: 1801550

28. Stefani A, Aramini B, della Casa G, Ligabue G, Kaleci S, Casali C, Morandi U. Preoperative predictors of successful surgical treatment in the management of parapneumonic empyema. Ann Thorac Surg 2013; 96(5):1812-9
29. Chen CH, Chen W, Chen HJ, Yu YH, Lin YC, Tu CY, et al. Transthoracic ultrasonography in predicting the outcome of small-bore catheter drainage in empyemas or complicated parapneumonic effusions. Ultrasound Med Biol 2009; 35(9):1468-74
30. Rahman NM, Kahan BC, Miller RF, Gleeson FV, Nunn AJ, Maskell NA. A clinical score (RAPID) to identify those at risk of poor outcome at presentation in patients with pleural infection. Chest 2014; 145(4):848-55
31. Royston P. Multiple imputation of missing values: further update of ice, with an emphasis on interval censor monitoring. Stata Journal 2007; 7:445-64.
32. Pencina MJ, D'Agostino RB Sr. Evaluating discrimination of risk prediction models: the C statistic. JAMA 2015; 314(10):1063-4
33. Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): the TRIPOD statement. Ann Intern Med 2015; 162(1):55-63
34. Lim WS, van der Eerden MM, Laing R, Boersma WG, Karalus N, Town GI, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax 2003; 58(5):377-82
35. Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med 1997; 336(4):243-50
36. Maskell NA, Batt S, Hedley EL, Davies CW, Gillespie SH, Davies RJ. The bacteriology of pleural infection by genetic and standard methods and its mortality significance. Am J Respir Crit Care Med 2006; 174(7):817-23
37. Marks DJ, Fisk MD, Koo CY, Pavlou M, Peck L, Lee SF, et al. Thoracic empyema: a 12-year study from a UK tertiary cardiothoracic referral centre. PloS One 2012; 7(1):e30074
38. Florova G, Azghani A, Karandashova S, Schaefer C, Koenig K, Stewart-Evans K, et al. Targeting of Plasminogen Activator Inhibitor 1 Improves Fibrinolytic Therapy for Tetracycline Induced Pleural Injury in Rabbits. Am J Respir Cell Mol Biol 2015; 52(4):429-37

39. Komissarov AA, Florova G, Azghani AO, Buchanan A, Boren J, Allen T, et al. Dose dependency of outcomes of intrapleural fibrinolytic therapy in new rabbit empyema models. Am J Physiol Lung Cell Mol Physiol 2016; 311(2):L389-99

40. Stewart PS, Costerton JW. Antibiotic resistance of bacteria in biofilms. Lancet 2001; 358(9276):135-8

41. Psallidas I, Kanellakis NI, Bhatnagar R, Ravindran R, Yousuf A, Edey AJ, et al. A pilot feasibility study in establishing the role of ultrasound-guided pleural biopsies in pleural infection (The AUDIO study). Chest 2018; 154(4):766-72

42. Porcel JM, Vives M, Esquerda A, Ruiz A. Usefulness of the British Thoracic Society and the American College of Chest Physicians guidelines in predicting pleural drainage of non-purulent parapneumonic effusions. Respir Med 2006; 100(5):933-7

43. Porcel JM. Minimally invasive treatment of complicated parapneumonic effusions and empyemas in adults. Clin Respir J 2018; 12(4):1361-6

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
- **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)	(calculated for overall pop^n only)
- **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
- **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)	(calculated for overall pop^n only)
- **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