A clinical score (RAPID) to identify those at risk of poor outcome at presentation in patients with pleural infection.

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ABSTRACT

Background: Pleural infection is associated with a high morbidity and mortality. Development of a validated clinical risk score at presentation to identify those at high risk would enable triage of patients and may help inform early management strategies.

Method: A clinical risk score was derived, based on data from patients entering the multi-centre UK pleural infection trial (MIST1, n=411). From 22 baseline clinical characteristics model selection was undertaken to find variables predictive of poor clinical outcome. The outcomes were mortality at 3 months (primary), need for surgical intervention at 3 months and time from randomisation to discharge. The derived scoring system (RAPID) was validated using patients enrolled in a subsequent UK multi-centre pleural infection trial (MIST2, n=191).

Results: Age, urea, albumin, hospital-acquired infection, and non-purulence predicted poor outcome. Using this (the RAPID) score, patients were stratified into low- (0-2), medium- (3-4) and high-risk (5-7) groups. Using the low-risk group (score 0-2) as a reference, a RAPID score 3-4 and >4 was associated with an odds ratio (OR) of 24.4 (95% CI=3.1-186.7; p=0.002), and 192.4 (95% CI=25.0-1480.4; p<0.001) respectively for death at 3 months. In the validation (MIST2) cohort, a medium-risk RAPID score was non-significantly associated with mortality (OR 3.2, 95% CI=0.8-13.2; p=0.11) and a high-risk score was associated with increased mortality (OR 14.1, 95% CI=3.5-56.8; p<0.001). Duration of hospitalisation was associated with increasing RAPID score: score 0-2, median duration=7, IQR 6 to 13; score>5, median duration=15, IQR 9 to 28, p=0.08.

Conclusion: The RAPID score may permit risk-stratification of patients with pleural infection at presentation and may be useful in guiding initial management.

Abstract word count: 249

INTRODUCTION

Pleural infection is increasing in incidence in both paediatric[1-3] and adult[4-6] populations, and is currently estimated to affect more than 65,000 patients per year in the United States and the United Kingdom[7]. These infections carry a significant health burden; mortality is between 10 and 20%[5,8-10], approximately one third fail "medical management" and require surgical drainage[5,10], 25% of patients require a hospital admission lasting more than one month[10,11] and health care costs are estimated at around US$5000 per patient[12,13] which equates to ~US$320 million per year (UK & US).

Standard treatment for involves appropriate antibiotics and drainage of infected pleural fluid/pus with an intrapleural catheter [11,14]. More complex surgical drainage techniques (e.g. video assisted thoracoscopic surgical (VATS) drainage, open thoracotomy with decortication, rib resection and open drainage[11,14]) are advocated in patients with a poor response to initial treatment. A large cohort of 4,424 cases[5] and other small surgical series[15-19] suggest effective surgical drainage may be associated with improved outcome in selected patients. Early surgical intervention may thus be appropriate for high-risk patients. Although surgery has been advocated as initial treatment for all patients with pleural infection[19-21], evidence to support the unselected use of surgery in all patients is lacking. Two moderate sized paediatric clinical trials showed no clinical benefit and greater cost from this approach[12,22] and two small adult randomised trials did not use robust outcome methodologies[23,24]. Surgical thoracic procedures are associated with anaesthetic and perioperative risks[25], and thoracotomy causes substantial post-operative pain[26] up to 3 years after operation[27].

Thus, surgery is a vital treatment option in pleural infection, but one which may be best used in selected patients. Recent evidence from a randomised placebo controlled trial[28] suggests that a combination of intrapleural DNase and fibrinolytic improves radiology and may be associated with reduced hospital stay, reduced infection and reduced surgical rates. However, the drug treatment cost for this intervention is significant. A reliable and sensitive clinical prediction model of poor outcome in pleural infection would enable clinicians to triage patients in terms of risk, and might enable targeting of more aggressive and expensive therapies to patients with the poorest outcomes. To date, there are no robust validated methods for selecting high risk patients at presentation in pleural infection.

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

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

METHODS

Study design

This study used data from two randomised trials of intrapleural agents for the treatment of pleural infection[10,28] diagnosed according to identical and standard clinical criteria (see below).

The initial model derivation was conducted using baseline clinical and outcome data from the MIST1 trial[10], a placebo controlled randomised trial assessing the use of intrapleural streptokinase which recruited 454 patients from 54 UK centres from 2002 to 2004. The derived model was then separately validated using baseline clinical and outcome data from MIST2[28], a randomised controlled trial assessing the use of intrapleural DNase and tPA, in which 210 patients were recruited from 11 UK centres between 2005 to 2008, which demonstrated a significant improvement in the primary outcome measure (radiographic improvement) for the combination treatment compared to placebo.

Full trial details and protocols are available with the original publications[10,28] and included protocol recommendations on type and duration of antibiotic therapy, and intrapleural catheter use.

Subjects enrolled

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

Study exclusion criteria for both studies were identical and are listed in the online supplement.

Trial outcomes

The outcomes used in the model construction and derivation phase of the study were those considered clinically important: mortality at 3 months post randomisation, hospital stay

from randomisation to discharge to home / convalescent care and requirement for surgical intervention at 3 months. For model selection, the outcome of mortality at 3 months was considered decisive.

Data analysis

Model Derivation

Model selection was undertaken using the MIST1 cohort (in 411 / 454 (90.5%), in patients in whom baseline data of potential predictive value was present to find variables predictive of a poor clinical outcome (see online supplement for a full list of variables considered). Backwards selection with a p-value of 0.05 was used to find variables associated with mortality at 3 months, surgical intervention at 3 months, and hospital stay, with a separate model used for each outcome. Surgery and time in hospital were also assessed in patients who were less than 70 years of age to assess for a differential age effect. A subset of variables shown to be predictive of poor outcome were chosen to form the basis of the risk score. Variables were chosen based on the strength of association, clinical plausibility and ease of data collection at baseline for a potential predictive model. Effects of intrapleural treatments (streptokinase or tPA / DNase) were not modelled as baseline covariates were likely to be well balanced between treatment arms (due to randomisation) therefore preventing bias by ignoring treatments, and allowing more generalisable results. Multiple imputation using chained equations[30] was used for patients with missing baseline variables, and 10 imputations were used. Fractional polynomials were used for continuous predictors[31]. Risk stratification according to the model was planned in to low, intermediate and high groups, with the lowest risk groups acting as the baseline comparator.

Model Validation

The risk score derived from the MIST1 cohort was validated using patients from the MIST2 cohort. This was achieved by MIST2 patients into low, intermediate, and high risk groups according to the risk score derived from MIST1, and assessing mortality and surgery at 3 months, and time to discharge within these groups. Overall survival was assessed using a Cox

model. Missing baseline variables used in calculating the risk score were handled using sensitivity analyses, assuming best and worst-case scenarios for each missing variable.

Ethical Approval and Registration

Ethical and regulatory approval for each study was obtained before recruitment commenced and each trial was registered. For full details of registration, chest tube treatment and antibiotic management, please see the original publications[10,28].

RESULTS

Patients and data completeness

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

Results - Predictive modelling

Parameters selected and predictive of the specified outcomes using the MIST1 dataset (n=411) are summarised in the online supplement. Age >70, hospital (as opposed to community acquired) infection and urea >8mmol/L were all strongly associated with increased mortality at 3 months. Pleural fluid purulence, the presence of joint disease as a comorbidity, diastolic blood pressure (>70mmHg), and albumin >27mmol/L were associated with a decreased risk of mortality at 3 months.

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

Creation of a predictive Model

On the basis of the results above, **R**enal profile (urea) / **A**ge / **P**urulence of pleural fluid / **I**nfection Source (hospital versus community) and **D**ietary factors (albumin) at baseline were used as predictors to form a scoring system ("RAPID"). Other variables (see online supplement) predictive of outcome were not included from the predictive modelling stage to maintain a clinically applicable and practical scoring system (Table 2). As the mortality odds ratios were

higher for Age and Renal profile, these were given a score out of 3 in the final scoring system. To aid clinical use of the RAPID score, patients were stratified according to score in to low-risk (score 0-2), medium-risk (score 3-4) and high-risk (score 5-7) groups (Table 2). The estimated odds ratios from each individual parameter derived in the prediction model are presented in Table 3.

Using the derived RAPID risk categorisation (low / medium / high) in the MIST1 cohort, mortality at 3 months in the low risk (reference) group was 1% (1/186), compared to 12% (14/121) in the medium risk group (OR 24.4, 95% CI 3.1 to 186.7, p=0.002) and 51% (26/51) in the high risk group (OR 192.4, 95% CI 25.0 to 1480.4, p<0.001). For overall survival, the hazard ratio was 11.87 in the medium risk group (95% CI 4.16 to 33.85, p<0.001), and 48.27 in the high risk group (95% CI 16.98 to 137.20, p<0.01).

Median time to hospital discharge in the low risk group was 10 days (IQR 7 to 16), compared with 15 days (IQR 10 to 30) in the medium risk group(p<0.001), and 18 days (IQR 9 to 26) in the high risk group (p<0.001).

Data on missing variables and sensitivity analyses are presented in the online supplement. These analyses demonstrated no important differences using best or worst case scenarios in the predictive outcomes.

Model validation results (MIST2 cohort)

Assessment of the RAPID score in the MIST2 cohort demonstrated albumin (OR 2.8, 95% CI 1.1 to 7.0, p=0.04) and urea (OR for highest category 3.96, 95% CI 1.7 to 9.4, p=0.002) as significant predictors of mortality at 3 months. Age (OR for highest category 4.66, p=0.07), infection source (OR=1.71, p=0.41), and purulence (OR=2.05, p=0.22) also showed strong effects but did not reach statistical significance (see online supplement).

Validation of the risk categorisation in the MIST2 cohort demonstrated mortality of 3% (3/97) in the low risk (reference) group, 9% (6/65) in the medium risk group (OR 3.2, 95% CI 0.8 to 13.2, p=0.11) and 31% (9/29) in the high risk group (OR 14.1, 95% CI 3.5 to 56.8, p<0.001) (Table 4). For overall survival, the hazard ratio was 4.69 in the medium risk group (95% CI 1.27 to 17.34, p=0.02) and 17.37 in the high risk group (95% CI 4.94 to 61.02, p<0.001). Overall mortality is presented as survival curves in Figure 2.

For hospital stay, the median time to hospital discharge in the low risk group was 7 days (IQR 6 to 13), compared with 10 days (IQR 8 to 18) in the medium risk group (p=0.42), and 15 days (IQR 9 to 28) in the high risk group (p=0.08).

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

DISCUSSION

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

The risk model developed gave more weighting to both age and urea in light of their high odds ratios for mortality, with the other three variables scoring the same. Each patients' RAPID score therefore ranged between 0 - 7 with low risk patients (scoring 0-2) having a 1-3% mortality at 3 months, compared with 31-51% for high risk patients (scoring 5-7). This risk stratification at baseline, if validated in prospective studies, is a potentially important tool for the treating physician, with the potential to identify those at high risk at presentation, facilitating earlier discussions about aggressive management strategies while the patient is still well enough to receive them.

Unsurprisingly, there are similarities with the widely used CURB-65 risk model, used for adults presenting to hospital with community acquired pneumonia[32]. Markers of poor outcome (confusion, urea>/=8mmol/L, respiratory rate >/=30/min, low blood pressure and age >/=65[32]) are similar to those found in our study in patients with pleural infection. Low albumin was also identified as a risk factor of poor outcome in the CURB-65 study. However, this variable was not included in the final model, due to concerns that this test is not routinely available. Although it may be suggested that the RAPID score may simply reflect the CURB score in these patients, it is increasingly recognised that pleural infection and pneumonia are different biological and microbiological processes[33], with distinctly different outcomes.

Low albumin and poor nutritional status have long been associated with poor prognosis in pleural infection[11], and age is a strong predictor of poor outcome in pleural infection, with previous series showing a strong correlation between increasing age and mortality [6,8]. In our study, increased age was associated with a lower likelihood of undergoing surgical treatment despite the higher mortality associated with this age group. This may represent a lack of willingness to use surgical intervention in older populations, despite outcomes being worse. The ROC curve analysis demonstrates that while the RAPID prediction rule appears to predict mortality at 3 months (AUC 0.80 in the validation cohort), the predictive power for surgery at 3

months is poor (AUC 0.50), and this may be related to the most ill patients not being offered surgical treatment. Further investigation of this potential signal is now required.

A British Thoracic Society retrospective study on pleural infection found initial pleural fluid results were not predictive of poor outcome. Low albumin was however, associated with increased mortality[8]. Fluid purulence has been highlighted previously as a possible predictor of poor outcome[9]. In our study, we found the opposite to be the case, with non-purulence being a significant risk of poor outcome. Although this seems counter-intuitive, it may be explained by the clinical observation that frankly purulent effusions tend to have fewer loculations and therefore may be more likely to drain than non-purulent highly loculated collections.

Pleural infection remains common with recently reported studies reporting sharp increases in incidence[1,2,6], and its associated mortality and morbidity remain high and has not improved over recent decades[6,11]. There is some evidence that delays in prompt and appropriate treatment subsequently result in more invasive interventions, leading to a more prolonged in hospital recovery and poorer outcomes [14,34]. The RAPID score should help the clinician identify those likely to have a poor outcome at presentation; high scoring patients, scoring 5-7, have at least a 30% chance of dying in the following 12 weeks. It also informs the clinician of the increased likelihood of a prolonged hospital stay. These patients are likely to be best served by addressing their nutritional status immediately and consideration given to whether earlier more definitive surgical management is appropriate. Although it has been shown that delay in surgical referral can result in VATS surgery needing to be converted to thoracotomy and more formal decortication[19,20], this needs to be the subject of specific further studies.

There were some limitations in the development of the prognostic model. Previous research has shown that prognostic models developed on small datasets using backward selection methods tend to overstate the effect size of the variables included in the model[35]. However, the effect size for individual variables is not used to calculate the RAPID score, as all variables are assigned the same score (with the exception of the age and urea variables). And, in spite of the above limitations, validation of the RAPID score using the MIST2 dataset did find the chosen model to be predictive of poor outcome. A further potential limitation is the recruitment of patients for this study from randomised trials with specific inclusion and

exclusion criteria, which is not ideal for the development of prognostic models. However, the inclusion and exclusion criteria in the MIST1[10] and MIST2[28] studies closely reflect the normal population of pleural infection, and this is therefore not likely to be an unrepresentative sample.

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

TABLES

	MIST1 (n=411)		MIST2 (n=210)	
	Result	**Missing (n, %)**	**Result**	**Missing (n, %)**
Baseline Demographics				
Age (mean, SD)	59.7 (17.8)	0 (0)	58.8 (18.1)	0 (0)
Male (n, %)	299 (72.7)	0 (0)	151 (71.9)	0 (0)
Hospital-acquired infection (n, %)	46 (11.3)	4 (1.0)	28 (13.3)	0 (0)
Symptoms >=15 days prior to randomisation (n, %))	200 (49.9)	10 (2.4)	84 (41.0)	5 (2.3)
Drain inserted by a radiologist (n, %)	216 (53.5)	7 (1.7)	Not collected	Not collected
% of hemithorax occupied with pleural fluid (mean, SD)	n/a	n/a	40.5 (23.5)	0 (0)
Loculation (n, %)	Not collected	Not collected	192 (91.4)	0 (0)
Pleural fluid characteristics				
Purulence (n, %)	339 (82.5)	0 (0)	102 (48.6)	0 (0)
Gram stain (n, %)	88 (25.1)	60 (14.6)	10 (4.8)	3 (1.4)
Culture (n, %)	64 (18.2)	60 (14.6)	15 (7.3)	4 (1.9)
Gram stain or culture (n, %)	105 (29.4)	54 (13.1)	21 (10.2)	4 (1.9)
Antibiotics (n, %)	346 (85.2)	5 (1.2)	192 (91.9)	1 (0.5)
Acidic Ph (mean, SD)	6.8 (0.4)	182 (44.3)	6.9 (0.3)	75 (35.7)
Investigations at baseline				
WCC (mean, SD)	15.6 (7.1)	24 (5.8)	15.4 (6.9)	3 (1.4)
CRP (median, IQR)	164 (83 to 244)	81 (19.7)	160 (119 to 220)	14 (6.7)

Urea (median, IQR)	5.1 (3.7 to 8.1)	21 (5.1)	5.0 (3.4 to 7.6)	13 (6.2)
Albumin (mean, SD)	27.7 (6.9)	46 (11.2)	31.5 (7.8)	6 (2.9)
Diastolic BP (mean, SD)	69.9 (11.7)	57 (13.9)	71.2 (11.8)	28 (13.3)
Systolic BP (mean, SD)	124.9 (21.2)	57 (13.9)	126.1 (22.1)	27 (12.9)
Creatinine (median, IQR)	79 (67 to 97)	17 (4.1)	78 (66 to 97)	33 (15.7)
Co-morbid illnesses				
Respiratory problems (n, %)	76 (18.7)	4 (1.0)	51 (28.3)	30 (14.3)
Cardiac problems (n, %)	110 (27.0)	4 (1.0)	56 (30.6)	27 (12.9)
Alcohol problems (n, %)	40 (9.8)	4 (1.0)	23 (12.7)	29 (13.8)
Diabetes (n, %)	43 (10.6)	4 (1.0)	29 (16.0)	29 (13.8)
Neurological problems (n, %)	31 (7.6)	4 (1.0)	21 (11.5)	28 (13.3)

Table 1. The baseline characteristics of the patients in each of the trials, including the amount of missing data for each parameter.

Parameter	Measure		Score
Renal	Urea	<5mmol/L	0
		5-8 mmol/L	1
		>8 mmol/L	2
Age	Age	<50 years	0
		50-70 years	1
		>70 years	2
Purulence of pleural fluid	Purulent		0
	Non-purulent		1
Infection Source	Community acquired		0
	Hospital acquired		1
Dietary Factors	Albumin	> or = 27mmol/L	0
		<27mmol/L	1
Risk categories	Score 0-2		**Low risk**
	Score 3-4		**Medium-Risk**
	Score 5-7		**High Risk**

Table 2. Scoring system ("RAPID") derived from the initial prediction model using baseline characteristics. Each patient can obtain a score from 0 to 7.

	% died 3 months	Odds Ratio	95% CI	p-value
Age (years)				
<50 (ref)	1/125 (1)	n/a	n/a	<0.001
50-70	7/142 (5)	6.81	3.0 to 15.3	
>=70	41/141 (29)	25.63	6.5 to 100.8	
Albumin				
>=27 (ref)	15/207 (7)	n/a	n/a	0.008
<27	26/155 (17)	2.25	1.2 to 4.1	
Urea				
<5 (ref)	6/184 (3)	n/a	n/a	<0.001
5-8	5/104 (5)	2.68	1.6 to 4.7	
>=8	33/99 (33)	6.53	2.3 to 18.5	
Infection				
-community (ref)	36/358 (10)	n/a	n/a	0.03
-hospital	12/46 (26)	2.87	1.1 to 7.3	
Purulence				
-purulent (ref)	37/338 (11)	n/a	n/a	0.04
-non-purulent	12/70 (17)	2.61	1.0 to 6.7	

Table 3. Parameter estimates predicting mortality at 3 months from the MIST1 (n=408) cohort using the individual variables in the RAPID score. "Ref" refers to the reference category for each parameter. Although the presence of joint disease was significantly associated with outcome, the numbers of patients with joint disease (10%) was small, the predictive value of this parameter poor (OR 0.23, 95% CI) and this parameter had poor biological plausibility; this was not therefore included in the final model.

	Mortality at 3 months (%)	OR	95% CI	p-value
MIST1 (n=411)				
Low risk, score 0-2 (ref)	1/186 (1)	n/a	n/a	n/a
Medium risk, score 3-4	14/121 (12)	24.41	3.14 to 186.65	0.002
High risk, score >=5	26/51 (51)	192.40	25.01 to 1480.41	<0.001
MIST2 (n=191)				
Low risk, score 0-2 (ref)	3/97 (3)	n/a	n/a	n/a
Medium risk, score 3-4	6/65 (9)	3.19	0.77 to 13.23	0.11
High risk, score >=5	9/29 (31)	14.1	3.50 to 56.78	<0.001

Table 4. Mortality by RAPID risk category in the MIST1 and MIST2 cohorts. "Ref" refers to the reference category for each cohort.

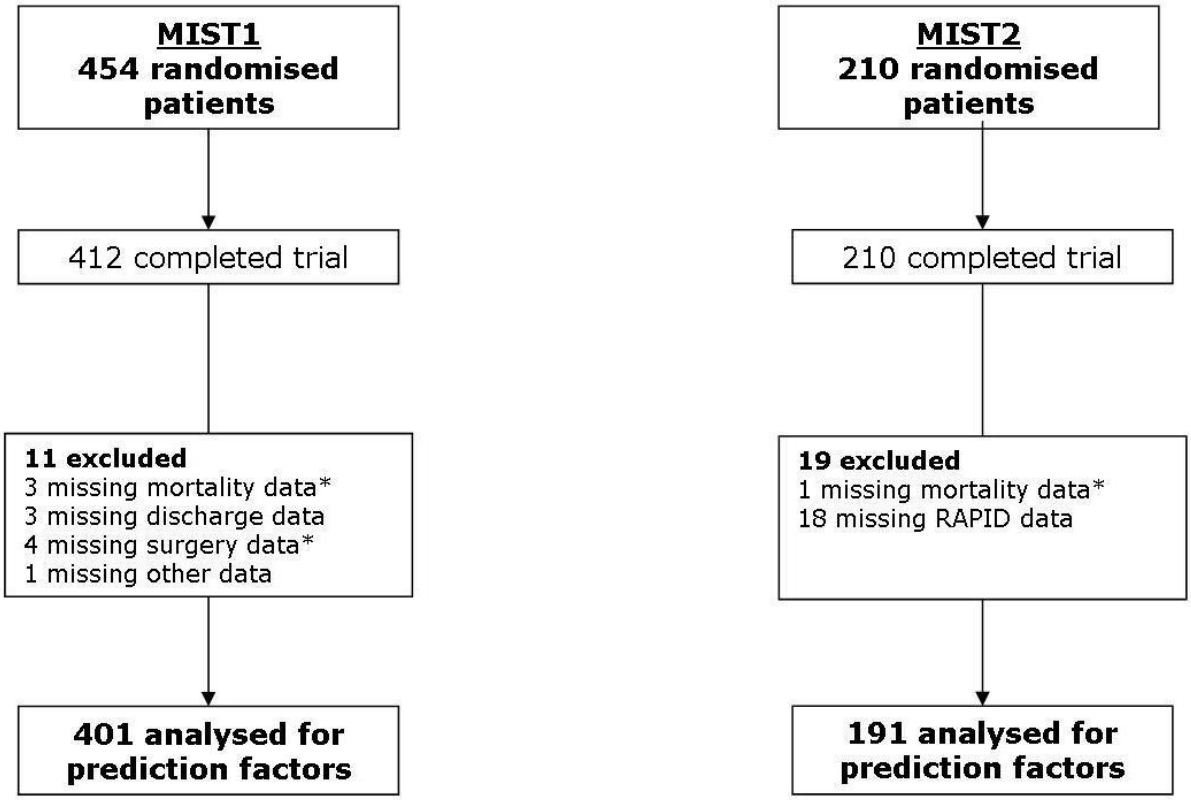

Figure 1 – flowchart of patient numbers in the MIST1 (exploratory) and MIST2 (validation) datasets. * = at 3 months.

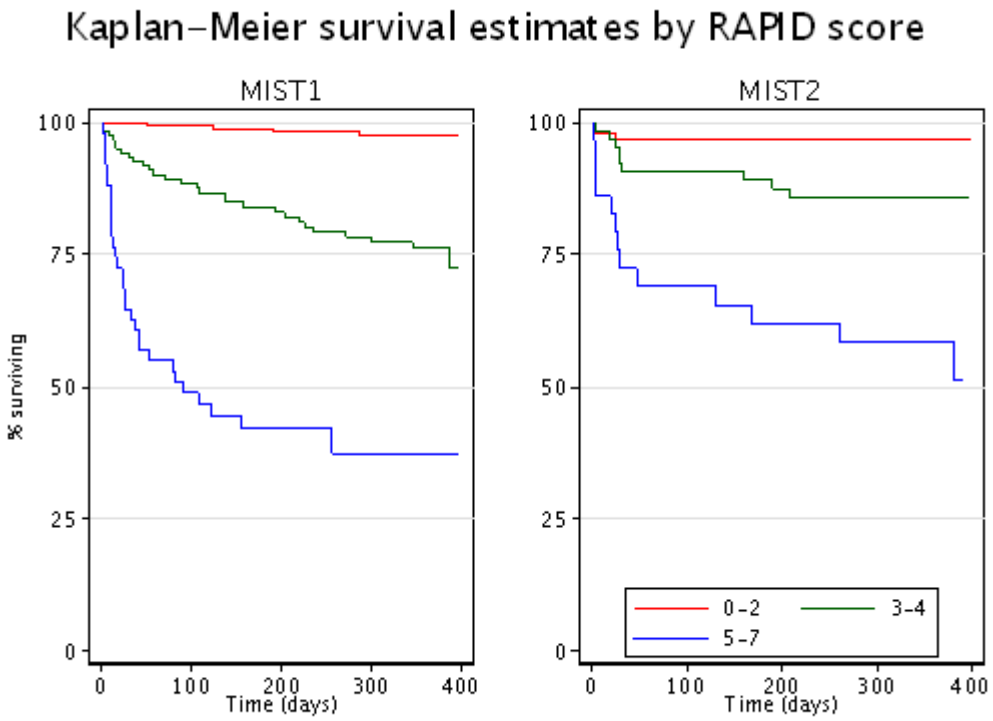

Figure 2. Survival curves for the MIST1 and MIST2 cohort of patients according to the derived RAPID scoring system.

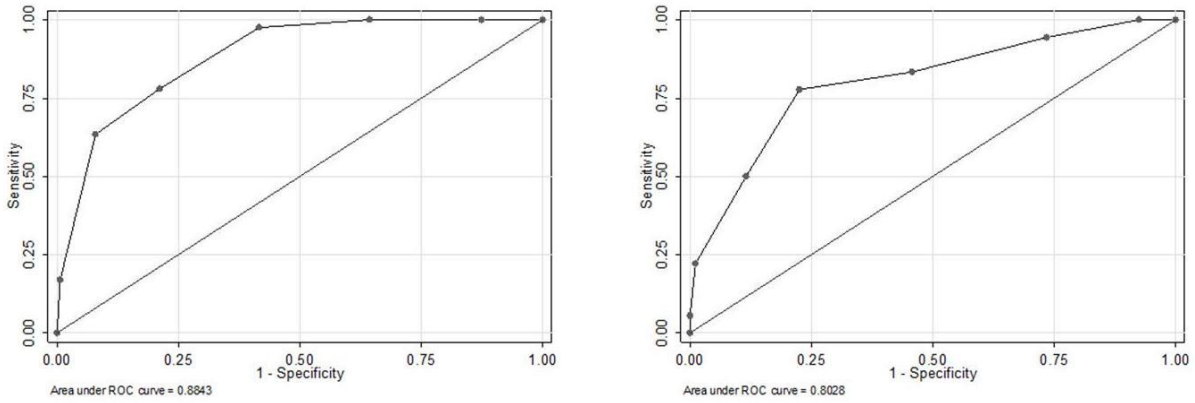

Figure 3. ROC analysis for the derived RAPID score in the MIST1 (left panel) and MIST2 (right panel) cohorts for the outcome of mortality at 3 months.

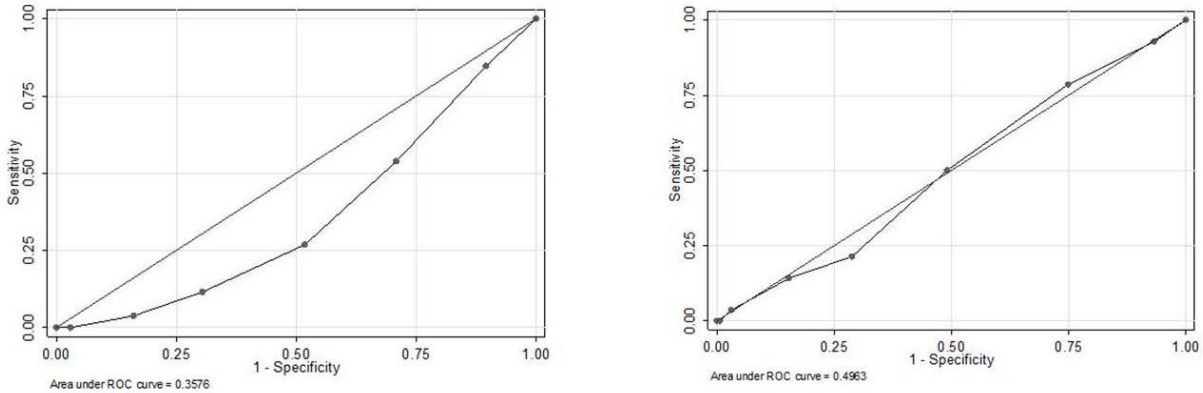

Figure 4. ROC analysis for the derived RAPID score in the MIST1 (left panel) and MIST2 (right panel) cohorts for the outcome of surgery at 3 months.

References

1. Desrumaux A, Francois P, Pascal C, et al. [Epidemiology and clinical characteristics of childhood parapneumonic empyemas]. ArchPediatr 2007;14:1298-303.
2. Roxburgh CS, Youngson GG. Childhood empyema in North-East Scotland over the past 15 years. ScottMedJ 2007;52:25-7.
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. ClinInfectDis 2008;46:174-82.
4. Finley C, Clifton J, Fitzgerald JM, Yee J. Empyema: an increasing concern in Canada. CanRespirJ 2008;15:85-9.
5. Farjah F, Symons RG, Krishnadasan B, Wood DE, Flum DR. Management of pleural space infections: a population-based analysis. JThoracCardiovascSurg 2007;133:346-51.
6. Grijalva CG, Zhu Y, Pekka NJ, Griffin MR. Emergence of parapneumonic empyema in the USA. Thorax 2011;66:663-8.
7. Light RW, Girard WM, Jenkinson SG, George RB. Parapneumonic effusions. AmJMed 1980;69:507-12.
8. Ferguson AD, Prescott RJ, Selkon JB, Watson D, Swinburn CR. The clinical course and management of thoracic empyema. QJM 1996;89:285-9.
9. Davies CW, Kearney SE, Gleeson FV, Davies RJ. Predictors of outcome and long-term survival in patients with pleural infection. AmJRespirCrit Care Med 1999;160:1682-7.
10. Maskell NA, Davies CW, Nunn AJ, et al. U.K. Controlled trial of intrapleural streptokinase for pleural infection. NEnglJMed 2005;352:865-74.
11. 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.
12. Sonnappa S, Cohen G, Owens CM, et al. Comparison of urokinase and video-assisted thoracoscopic surgery for treatment of childhood empyema. Am J RespirCrit Care Med 2006;174:221-7.
13. Netten A, Dennett J, Knight J. Unit Costs of Health and Social Care. In. Canterbuty: PSSRU, University of Kent; 1999.
14. Colice GL, Curtis A, Deslauriers J, et al. Medical and surgical treatment of parapneumonic effusions : an evidence-based guideline. Chest 2000;118:1158-71.
15. Angelillo Mackinlay TA, Lyons GA, Chimondeguy DJ, Piedras MA, Angaramo G, Emery J. VATS debridement versus thoracotomy in the treatment of loculated postpneumonia empyema. AnnThoracSurg 1996;61:1626-30.
16. LeMense GP, Strange C, Sahn SA. Empyema thoracis. Therapeutic management and outcome. Chest 1995;107:1532-7.
17. Podbielski FJ, Maniar HS, Rodriguez HE, Hernan MJ, Vigneswaran WT. Surgical strategy of complex empyema thoracis. JSLS 2000;4:287-90.

18. Cunniffe MG, Maguire D, McAnena OJ, Johnston S, Gilmartin JJ. Video-assisted thoracoscopic surgery in the management of loculated empyema. SurgEndosc 2000;14:175-8.
19. Waller DA, Rengarajan A, Nicholson FH, Rajesh PB. Delayed referral reduces the success of video-assisted thoracoscopic debridement for post-pneumonic empyema. RespirMed 2001;95:836-40.
20. Waller DA, Rengarajan A. Thoracoscopic decortication: a role for video-assisted surgery in chronic postpneumonic pleural empyema. AnnThoracSurg 2001;71:1813-6.
21. Molnar TF. Current surgical treatment of thoracic empyema in adults. EurJCardiothoracSurg 2007;32:422-30.
22. St Peter SD, Tsao K, Harrison C, et al. Thoracoscopic decortication vs tube thoracostomy with fibrinolysis for empyema in children: a prospective, randomized trial. JPediatrSurg 2009;44:106-11.
23. Wait MA, Sharma S, Hohn J, Dal Nogare A. A randomized trial of empyema therapy. Chest 1997;111:1548-51.
24. Bilgin M, Akcali Y, Oguzkaya F. Benefits of early aggressive management of empyema thoracis. ANZJ Surg 2006;76:120-2.
25. Allen MS, Deschamps C, Jones DM, Trastek VF, Pairolero PC. Video-assisted thoracic surgical procedures: the Mayo experience. Mayo ClinProc 1996;71:351-9.
26. Perttunen K, Tasmuth T, Kalso E. Chronic pain after thoracic surgery: a follow-up study. Acta AnaesthesiolScand 1999;43:563-7.
27. Dajczman E, Gordon A, Kreisman H, Wolkove N. Long-term postthoracotomy pain. Chest 1991;99:270-4.
28. Rahman NM, Maskell NA, West A, et al. Intrapleural use of tissue plasminogen activator and DNase in pleural infection. NEnglJ Med 2011;365:518-26.
29. Jimenez CD, Diaz G, Perez-Rodriguez E, Light RW. Prognostic features of residual pleural thickening in parapneumonic pleural effusions. EurRespirJ 2003;21:952-5.
30. Royston P. Multiple imputation of missing values: further update of ice, with an emphasis on interval censor monitoring. . Stata Journal 2007;7:445-64.
31. Royston P, Sauerbrei W. Multivariable model-building. A pragmatic approach to regression analysis based on fractional polynomials for modelling continuous variables. . Chichester: Wily-Blackwell; 2008.
32. Lim WS, van der Eerden MM, Laing R, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax 2003;58:377-82.
33. Lisboa T, Waterer GW, Lee YC. Pleural infection: changing bacteriology and its implications. Respirology 2011;16:598-603.
34. Ashbaugh DG. Empyema thoracis. Factors influencing morbidity and mortality. Chest 1991;99:1162-5.

35. Steyerberg EW, Eijkemans MJ, Harrell FE, Jr., Habbema JD. Prognostic modelling with logistic regression analysis: a comparison of selection and estimation methods in small data sets. Statistics in medicine 2000;19:1059-79.