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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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.

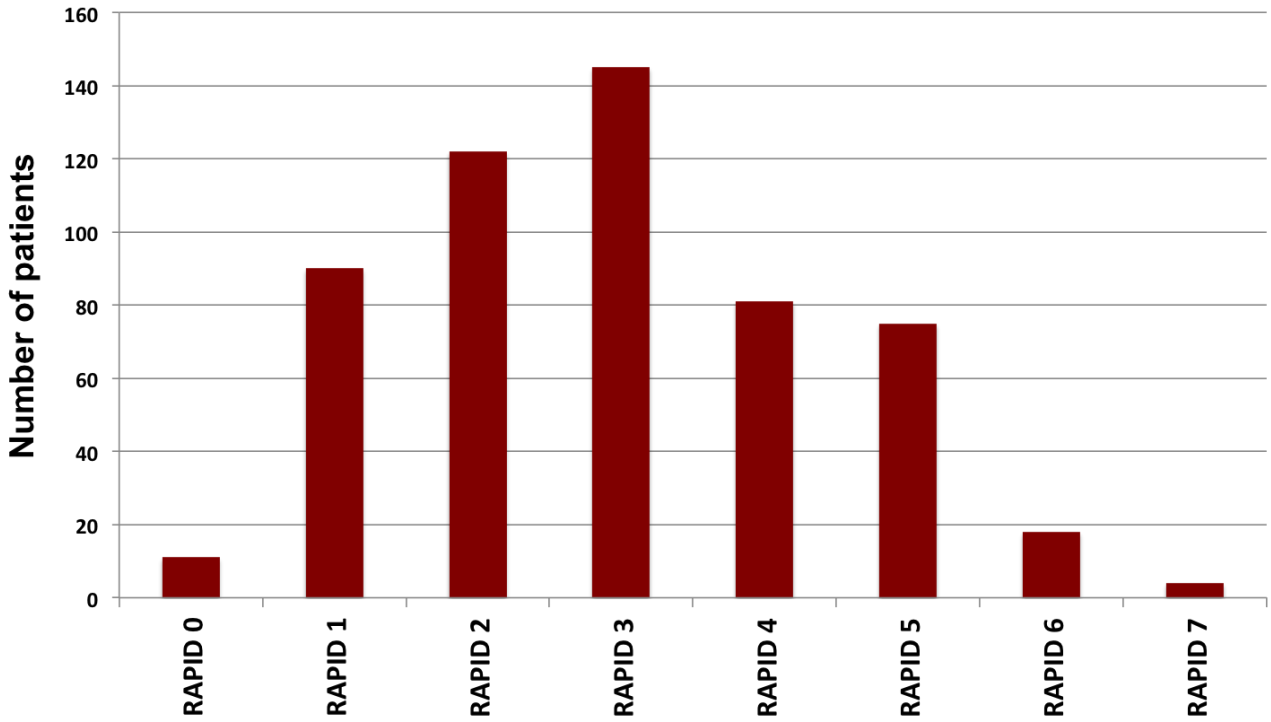
Study funding and support

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.

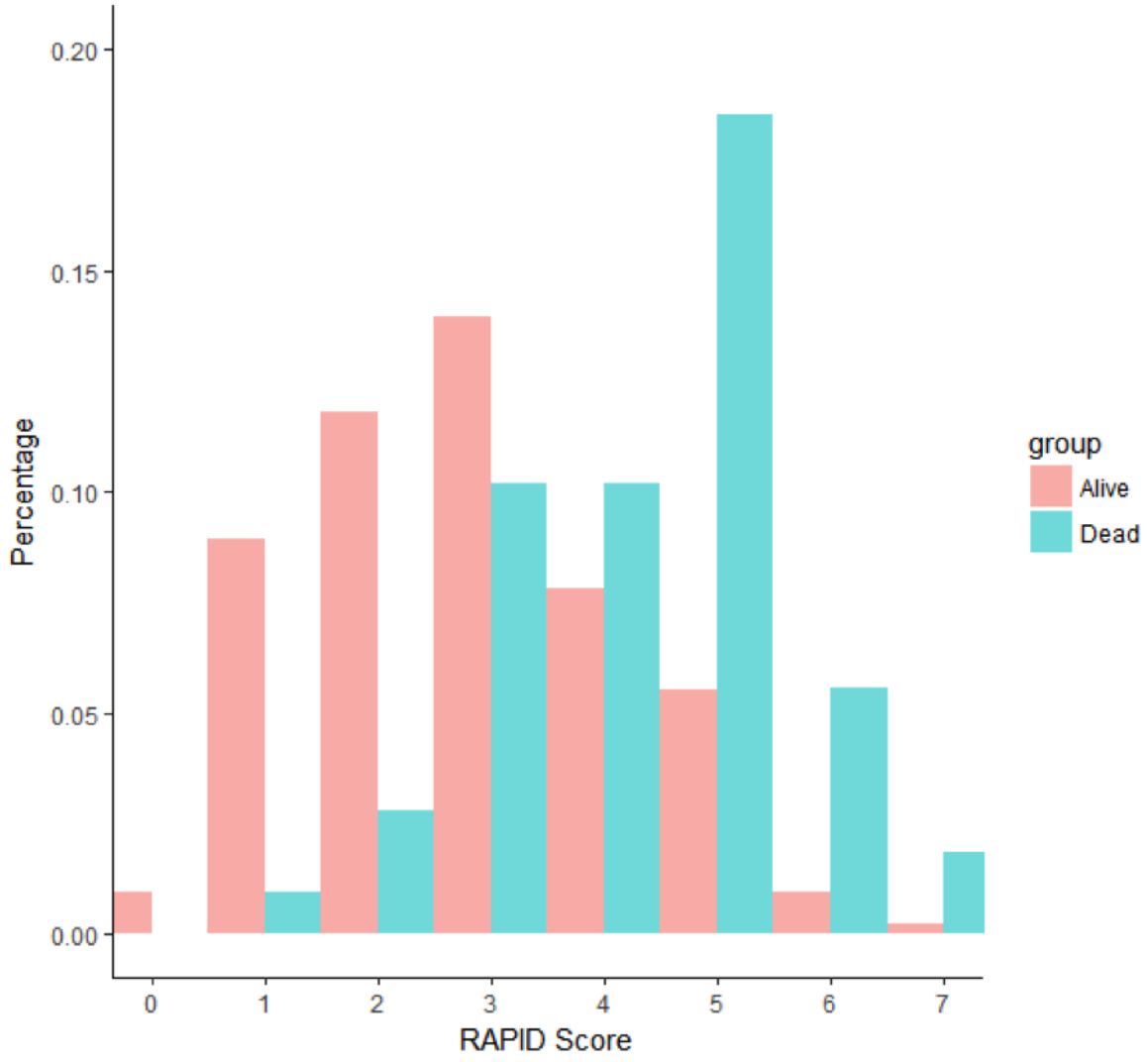
SUPPLEMENTARY RESULTS

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)

PILOT STUDY GROUP MEMBERSHIP LIST

The members of the PILOT Study Group were:

Study Steering Committee

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