PILOTing towards a RAPID predictor of mortality for infectious pleural effusions

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The RAPID score can estimate short-term mortality in patients with pleural infections and should be considered the "gold standard" for outcomes assessment in this population https://bit.ly/31XctMK

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Depending on the imaging modality used, between 19% (with chest radiographs) [1] and 54% (with ultrasound) [2] of patients with community-acquired pneumonia have an accompanying pleural effusion. Most previous studies on parapneumonic effusions have focused on the necessity of fluid drainage [3, 4], with less attention being paid to the prognostic aspects. However, pleural infection (a term indistinctly used for parapneumonic effusions and empyemas) remains a serious condition associated with significant healthcare resource utilisation that portends a non-negligible mortality. In a large Danish registry of 6878 hospitalised patients with empyema the crude 30-day mortality was about 10%, though it ranged from 1.2% in those younger than 40 years to 20.2% in those aged ⩾80 years [5]. Supportively, in two large series of patients with pleural infections, the reported 30-day mortality rate was roughly 14% [6, 7]. Generally, figures for long-term prognosis are worse, with an observed 3-month and 1-year mortality of 23% and 42%, respectively, in an Australian series of 561 adults with culture-positive pleural infections, two-thirds of which were hospital-acquired [8]. Moreover, a recent systematic review totalling 227 898 patients with pleural infections found the median prevalence of pre-existing comorbidities (mainly respiratory and cardiac diseases) to be as high as 72%, while the median length of hospital stay was 19 days [9].

In community-acquired pneumonia, two validated clinical prediction rules for prognosis are commonly used, namely the Pneumonia Severity Index (PSI) and CURB-65 (confusion, urea, respiratory rate, and age ⩾65 years). Both predict all-cause mortality at 30 days, but the former has higher discriminative power and is, therefore, recommended over the latter [10]. PSI assigns 10 points to the predictor variable "pleural effusion", since its independent association with mortality was demonstrated, and later replicated [11]. Can these scoring systems help to forecast a poor outcome in patients with parapneumonic effusions? The answer is elusive as hardly any publication addressing this question exists. In one retrospective study of 421 cases of complicated parapneumonic effusions PSI risk classes IV–V (*i.e.* >90 points) and CURB-65 ⩾2 points were identified as significant predictive factors for 30-day mortality (respective odds ratios of 4.7 and 5.5) [6]. Conversely, in a series of 4771 patients with pneumonia the electronic version of CURB-65 underestimated 30-day mortality when applied to the 690 who exhibited pleural effusions (7% predicted *versus* 14% actual) [7].

In 2014, Rahman *et al.* [12] developed a prognostic model to specifically assist in predicting 3-month mortality in patients with pleural infections at the time of their presentation. The model, known as RAPID (Renal function, Age, Purulence, Infection source, Dietary factors), was derived using data from the MIST1

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clinical trial [13] and validated on the MIST2 cohort [14]. With the exception of non-purulent fluids, items that make up the RAPID model have a rational link with poor outcomes. Thus, it is expected that renal dysfunction, ageing, hospital-acquired infections and malnutrition negatively impact survival. RAPID scores 0 to 2 were classed as low risk, 3 to 4 as medium risk, and 5 to 7 as high risk of mortality at 3 months. The scoring system was accurate for prognosticating short-term mortality (area under the curve of 0.88 for the derivation cohort), but not surgical referrals. Subsequent to this pivotal research, a few retrospective studies have supported the RAPID score as a robust prognostic tool (table 1) [15–18], even for long-term mortality up to 5 years [15]. However, it can be argued that, to some extent, the RAPID model reflected the unique patient populations enrolled in the clinical trials from which it was generated, rather than the somewhat different features of real-world patients. In this sense, the study of Corcoran *et al.* [19] in this issue of the *European Respiratory Journal* is uniquely relevant, in that it prospectively validates the performance characteristics of the RAPID scoring system in an observational cohort of 542 patients with pleural infections. Patients were recruited in four countries, and adherence to local protocols for pleural infection management was permitted, resulting in an investigation that faithfully reflected clinical practice. The study, under the acronym of PILOT (Pleural Infection Longitudinal Outcome Study), demonstrated that each 1-point increase on the RAPID scale was associated with an increase in 30-day mortality. The sum of this and previous studies on the subject, totalling 1453 patients with pleural infections, show that 3-month mortality rates are 11.8% overall and for those within RAPID low, medium and high-risk categories 1.9%, 11.7% and 35.6%, respectively (table 1).

In the PILOT study, the authors used the concordance (C) statistic, a global measure of model discrimination, to assess the ability of the RAPID score to predict deaths. It was found that the C statistic for prediction of short-term mortality was 0.78, thus indicating a good to strong predictive capacity (0.5 implying random concordance and 1 perfect concordance). C statistic is equivalent to the area under the receiver operating characteristic curve, but it has limitations, particularly for time-to-event data [20]. The C statistic is only a measure of discrimination, not calibration (*i.e.* how accurately the model's predictions match overall observed event rates), so it should be supplemented with other statistical and clinical measures. For instance, using both the positive predictive value and 1 minus negative predictive value can give information on what the patient's chances are of having an event (*e.g.* death), despite the model predicting they will or will not have one. Also, the Hosmer–Lemeshow statistic, though imperfect, is a means to assess model calibration.

Examining the possible outcomes of pleural infections not only gives patients an indication of what the future may hold, but can also theoretically help physicians make the right treatment decisions. Do patients in a RAPID high-risk category warrant more invasive initial therapy? Presumably, in patients with poor prognosis more efficient or invasive therapies, such as surgery, need to be discussed. However, the risk of death is not necessarily the same as the need for surgery. In fact, patients with a high RAPID risk score are not often good candidates for such procedures by virtue of their underlying fitness. On the other hand, conservative management, which includes prompt use of antibiotics [21] and intrapleural therapies, cures nearly 90% of the cases without rescue surgical interventions [22]. Whether RAPID score should be used to guide the care of patients with pleural infections needs to be specifically addressed in future clinical trials. Even if this prognostic data does not actually assist in the selection of appropriate therapy, it can help in counselling a concerned patient or relative about the expected future course of the illness. What

TABLE 1 Studies reporting mortality of pleural infections by RAPID risk categories

Study	Patients n	Mortality at 3 months		
		RAPID score 0–2	RAPID score 3–4	RAPID score 5–7
Rahman *et al.* [12], 2014				
Derivation cohort	358	1%	12%	51%
Validation cohort	191	3%	9%	31%
White *et al.* [15], 2015	187	1.5%	17.8%	44.7%
Wong and Yap [16], 2016	77	2.9%	27.6%	28.6%
Touray *et al.* [17], 2018	98	5.3%	8.3%	22.6%
Corcoran *et al.* [19], 2020	542	2.3%	9.2%	29.3%
TOTAL	1453[#]	1.9%	11.7%	35.6%

[#]: of this total number of patients, 625, 564 and 264 belonged to the low-, medium- and high-risk RAPID (Renal function, Age, Purulence, Infection source, Dietary factors) categories, respectively.

can be substantiated so far is that the RAPID tool is simple, easily applicable at the bedside and accurate enough to be considered the "gold standard" for outcome assessment in patients with pleural infections.

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