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REVIEW

Risk Scores in Pleural Infection – Comprehensive Review Article

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Abstract

Purpose of Review Pleural infection is associated with high morbidity and mortality rates. Approximately 30% of patients fail treatment, and either die or require surgery. Accurate risk stratification is crucial to identify patients at risk of poor outcomes and to guide timely intervention. This review evaluates validated risk scores in pleural infection and highlights emerging prognostic tools.

Recent Findings The RAPID risk score, a validated prognostic risk model in pleural infection, stratifies patients into low, intermediate and high-risk groups, with associated 3-month all-cause mortality of ~3%, 9%, and 31% respectively. It also predicts hospital stay, requirement for escalation of treatment (Intrapleural Enzyme Therapy and surgery), and hospital costs. Emerging pleural fluid biomarkers such as Plasminogen Activator Inhibitor-1 (PAI-1) and soluble urokinase Plasminogen Activator Receptor (suPAR) have shown potential prognostic value. Elevated PAI-1 levels have been associated with prolonged hospital stay and increased 12-month mortality rate, whereas high suPAR has been correlated with the need for treatment escalation. Furthermore, pleural fluid microbiology and sonographic findings of septations have shown association with adverse clinical outcomes.

Summary The RAPID risk score is the most reliable and validated framework for clinical risk stratification in pleural infection. Future research should evaluate its integration into decision-making for treatment to optimise patient outcomes and reduce healthcare costs. Future models incorporating biomarkers, imaging, and microbiology may increase the prognostic value and clinical utility but will require prospective evaluation.

Keywords Pleural infection · RAPID risk score · Risk stratification · Intrapleural enzyme · Therapy · Surgery · Microbiology

Introduction

Although pleural infection is an ancient disease, it continues to pose significant clinical challenges, with rising global incidence [1] and persistently high morbidity and unchanged mortality rates mortality over last two decades, particularly among people with multiple comorbidities and the elderly population [2]. The disease remains associated with high morbidity, prolonged hospital stay and increasing surgical intervention [2–6]. It encompasses complicated parapneumonic effusion and empyema, affecting 80,000 patients annually in the United Kingdom (UK) and the United States of America (USA) combined [2]. Pleural infection is a serious disease and associated with poor outcomes; all comer mortality is approximately 20% [3–6].

The standard treatment of pleural infection involves a combination of antibiotics and chest drain insertion into the chest cavity to drain the infected pleural fluid.

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Approximately 30% of patients experience treatment failure, often necessitating escalation to either intrapleural enzyme therapy (IET) or surgical intervention [5]. IET fails in 20% of patients [5] and is associated with a 4.1% risk of bleeding, most of which can be managed conservatively [7]. Delays in recognising those at risk of treatment failure or surgical intervention may contribute to poor outcomes [8]. Hence, there is a need for tools enabling the identification of patients at risk of deterioration and requiring more aggressive treatment, and those who are less likely to deteriorate, and who thus may require less intervention.

Risk stratification scores are fundamental in clinical research and patient outcomes. The primary objectives of risk stratification are to improve patient outcomes, optimise resource allocation, provide guidance for further diagnostic tests and best intervention at the right time and for the right patient to reduce health care costs. Such scores frequently rely on prognostic models derived from clinical, radiological and biological parameters. The development of prognostic tools conventionally follows a systematic approach encompassing derivation, internal and external validation, and subsequent implementation studies, which assess the clinical utility and effectiveness of adopting risk-based strategies. While derivation and validation studies are abundant in the literature, high-quality impact studies demonstrating the practical benefits of risk stratification remain relatively scarce [9]. In pleural infection, identifying patients at higher risk of mortality, or those at risk of treatment failure he may require additional treatment or surgical intervention, is crucial to guide early intervention, optimise resource allocation, and improve clinical outcomes.

There is a paucity of validated risk stratification tools in pleural infection. The RAPID score, comprising renal function, age, purulence of pleural fluid, infection source, and dietary factors (albumin), is currently the most rigorously validated and extensively studied prognostic model. It potentially offers a pragmatic approach to stratifying mortality risk at the time of presentation and has demonstrated utility in predicting hospital length of stay and the likelihood of requiring treatment escalation, including surgical intervention and intrapleural enzyme therapy [10, 11].

Beyond the RAPID score, there are no other validated scores to predict outcomes from pleural infection. However, there are certain pleural fluid biomarkers, including plasminogen activator inhibitor, PAI-1 [12] and soluble urokinase plasminogen activator inhibitor, suPAR [13], as well as pleural fluid microbiology results [14], which have been associated with clinical outcomes and may predict the need for invasive intervention. In addition, thoracic ultrasound findings [15] and the nature of pleural fluid (e.g., purulence fluid) have also been suggested as potential predictors of clinical outcomes [4] and delay in surgical intervention [16, 17].

RAPID Score Derivation and Validation

The original RAPID score was retrospectively derived (in 450 patients) and validated (in 230 patients) using randomised trial data in pleural infection with identical recruitment criteria, demonstrating that 5 parameters, which are all collected at baseline in routine care, were independently associated with all-cause mortality at 3 months [10, 11]. The score parameters and risk categories are summarised in Table 1, and as below include two blood test results (which are routinely collected in all hospitals for all patients with this condition), one pleural fluid result (always taken to diagnose pleural infection), and two demographic factors.

A total score of 0 to 7 is assigned, and categorisation of patients into low-risk (RAPID score 0–2), medium-risk (RAPID score 3–4) and high-risk (RAPID score 5–7) groups were associated with mortality at 3 months of 3%, 9% and 31%, respectively, in retrospective validation [10].

Table 1 The RAPID risk stratification score, using baseline clinical characteristics in patients with pleural infections [9]

Clinical Variable	Categories	Points
Renal (Serum urea)	< 5.0 mmol/L	0
	5.0–8.0 mmol/L	1
	>8.0 mmol/L	2
Age	< 50 years	0
	50–70 years	1
	>70 years	2
Purulence of fluid	Purulent	0
	Non-purulent	1
Infection source	Community-acquired	0
	Hospital-acquired	1
Dietary (Serum albumin)	>27 g/L	0
	≤ 27 g/L	1

Prospective Validation

The RAPID risk score was prospectively validated in the PILOT study [11], in which 551 patients with pleural infection were recruited and treated as per standard protocol. The study.

demonstrated robust prediction of 3-month mortality, with relatively narrow confidence intervals across each RAPID category (Table 2):

- Low-risk mortality: 5/222 (2.3%, 95% CI 0.9 to 5.7%).
- Medium-risk mortality: 21/228 (9.2%, 95% CI 6.0 to 13.7%).
- High-risk mortality: 27/92 (29.3%, 95% CI 21.0 to 39.2%).

The RAPID risk score C-statistic to predict mortality at 3 months was 0.78 (95% CI 0.71–0.83), which implies a good to strong predictive capacity (0.5 implying random concordance and 1 perfect concordance) [18]. Beyond mortality rate prediction, the score showed prognostic utility, extending to other clinical outcomes including length of hospital stay (LOS); in the low risk group, median LOS was 11 days (interquartile range (IQR) 6–21), medium risk group 13 days (IQR 7–25), and high-risk group 18 days (IQR 10–27), which was statistically significant ($p = 0.003$). Additionally, the RAPID score was associated with pulmonary function recovery at three months, with higher risk categories associated with significantly reduced forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) values at follow-up (p-values 0.001 and 0.002 respectively), underscoring the score's utility in predicting long-term functional outcomes [11].

In further, external work assessing the health economic prediction of the RAPID score, Touray et al. [19] reported that higher RAPID score group was associated with markedly higher healthcare utilisation. Median hospital costs increased progressively across risk groups (low: US $19,909; medium: US $36,317; high: US $43,384), which correlated with longer hospital stay (10, 21, and 19 days, respectively). These findings highlight the ability of the RAPID risk score to predict not only mortality risk but also healthcare cost, reinforcing its potential value in clinical decision-making and health-economic planning.

In summary, the RAPID score represents the only validated prognostic tool in pleural infection and has consistently demonstrated robust discrimination for all-cause mortality across diverse cohorts of patients worldwide. Its key strength lies in the simplicity and availability of its variables, allowing rapid bedside application and enabling standardised risk stratification in both clinical practice and research.

Biomarkers in Pleural Infection

Biomarkers are defined as "characteristics that are objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" [20]. A diverse array of biomarkers within pleural fluid have been investigated, producing variable results concerning their clinical significance and potential application. For decades, international guidelines have consistently endorsed the use of pleural fluid pH as a surrogate marker to guide intervention strategies, such as chest drain insertion, with a commonly adopted cutoff value of 7.20. However, despite its widespread clinical use, pleural fluid pH has never been prospectively validated as a definitive predictor of patient outcomes [2, 21, 22]. This threshold was originally proposed by Light and colleagues in 1980 [23, 24]. Although pleural fluid pH remains a cornerstone in initial management decisions, evidence suggests that it does not reliably predict critical clinical outcomes such as mortality rates or the development of loculations. Recent research has identified two promising novel entities: soluble urokinase plasminogen activator receptor (suPAR) and plasminogen activator inhibitor-1 (PAI-1). These have shown potential in enhancing prognostic assessment and guiding therapeutic interventions, and have the advantage of being specific to the pathobiology of pleural infection [8, 25].

Plasminogen Activator Inhibitor-1 (PAI- 1)

Plasminogen activator inhibitor-1 (PAI-1) is a serine protease inhibitor (serpins) that plays a crucial regulatory role in the plasminogen/plasmin system [26]. PAI-1 is synthesised as a 45-kDa single-chain glycoprotein comprising

Table 2 Clinical outcomes (3 - Mortality rate and hospital stay) by RAPID risk categories [10]

Risk group	RAPID score	3–month mortality *n*/*N* (%)	Median Hospital stay, days (IQR)
Low	0–2	5/222 (2.3%)	11 (6–21)
Moderate	3–4	21/228 (5.7%)	13 (7–25)
High	5–7	27/92 (29.3%)	18 (10–27)

IQR interquartile range. Higher RAPID risk scores indicate greater mortality and prolonged hospital stay

379 or 381 amino acids, as determined by the presence of alternative cleavage sites for signal peptidases [27]. They are expressed by different cells in different tissues [28, 29], regulated by various factors, including growth factors, inflammatory cytokines, hormones, glucose, and endotoxins [30, 31]. Since its discovery, considerable research has been directed towards elucidating the pathophysiological role of PAI-1 in both humans and diverse animal models of disease. A correlation has been demonstrated between PAI-1 and a range of pathologies, including cardiovascular disease, metabolic disturbances, the process of ageing, cancer, tissue fibrosis, inflammation, and neurodegenerative disease.

Bedawi et al. [12] reported a prospectively collected cohort of 214 patients with pleural infection, demonstrating that pleural fluid plasminogen activator inhibitor-1 (PAI-1) levels were strongly associated with both the presence ($p < 0.001$) and severity ($p = 0.003$) of sonographic septations. Elevated PAI-1 concentrations correlated with prolonged hospital stay ($p = 0.048$) and increased 12-month mortality ($p = 0.003$). In contrast, the presence of septations alone on thoracic ultrasound was not independently predictive of clinical outcomes. These novel findings highlight the important of PAI-1 as potential biomarker to stratify patients with pleural infection, but further prospective validation is required.

Soluble Urokinase Type Plasminogen Activator (suPAR)

Urokinase-type plasminogen activator (uPA) receptor is a glycosylphosphatidylinositol-anchored glycoprotein that is expressed by many hematopoietic, connective tissues, and epithelial cells, in particular during physiologic and pathologic tissue remodelling processes, including peripheral blood mononuclear cells (PBMCs), neutrophils and endothelial cells [30, 31]. The uPA-uPAR system seems to stimulate several immunological functions like.

cell-associated fibrinolysis and subsequent reduction of fibrin associated inflammation [32].

The main component of the uPA system is a proteinase, uPA receptor (uPAR) and an inhibitor. It is worth noting that the uPA system is involved in pericellular proteolysis, cell migration and tissue remodelling [33]. suPAR is the soluble form of uPAR and is a glycoprotein with a molecular weight of 55–60 kDa. Under normal physiological conditions, uPAR and uPA are predominantly expressed by neutrophils, monocytes, macrophages and activated T cells, and the serum concentration of suPAR is relatively stable throughout the day [34, 35]. However, it has been demonstrated that, upon activation of inflammatory cells by cytokines, uPAR expression increases, resulting in increased serum levels of suPAR [36]. SuPAR serum concentrations have been demonstrated to increase in cases of inflammatory and infectious diseases, including arthritis, liver fibrosis, HIV infection, bacterial infection and malaria [34]. This increase is an indication of immune system activation.

Arnold et al. [12] conducted a single-centre prospective cohort study, including 93 patients with parapneumonic effusions and 47 control subjects (malignant and transudative pleural effusion). Pleural fluid suPAR levels were substantially higher in loculated versus non-loculated parapneumonic effusions (median: 132 ng/mL vs. 22 ng/mL, $p < 0.001$), and suPAR showed superior predictive accuracy for subsequent chest tube insertion (AUC = 0.93, 95% CI: 0.89–0.98), compared with pleural fluid pH (AUC 0.82; 95% confidence interval, 0.73–0.90). Moreover, suPAR could more accurately predicted the need for intrapleural fibrinolysis or thoracic surgery, with an AUC of 0.92 versus 0.76 when compared with combined conventional biomarkers (pH, glucose, lactate dehydrogenase). However, no association with mortality was reported in this study.

Microbiology in Pleural Infection

Identifying the causative organism is important in management of pleural infection. However, the yield from the conventional pleural fluid culture results is low at only 30–40%. This increases to 60% when pleural fluid is inoculated into blood culture bottles [32]. Pleural biopsy can increase the yield by 25% further [33]. An alternative approach is the use of nucleic acid amplification testing to detect bacterial DNA/RNA which has the potential to detect multiple organisms, and specifically those that are too fastidious to grow [34]. In previous retrospective studies, the 16 S ribosomal RNA PCR has shown potential for detecting pathogens from patients with pleural infection despite negative conventional pleural fluid culture [35, 36].

Knowledge of the pathogens not only inform antibiotic choices but is also fundamental in predicting clinical outcomes. The bacteriology data from MIST–1 study has demonstrated important prognostic associations. Patients with positive pleural fluid culture, particularly non streptococcal isolates, were associated with prolonged hospital stay. Additionally, there was a higher mortality rate among those with Staphylococcus aureus [6]. Microbiology data from a prospective multicentre randomised controlled trial of pleural infection (MIST–2) demonstrated that in 191 patients, the culture was positive in 32% and 12.4% from pleural fluid and blood, respectively. Those with negative pleural fluid microbiology were less likely to die at 3 months (OR 0.1, 95% CI 0.04 to 0.14, $p < 0.01$). In contrast, patients with positive blood culture had higher mortality (OR 3.5, 95% CI 0.88 to 11.60, $p = 0.05$ and OR 3.2, 95% CI 0.79 to 10.91,

$p = 0.08$ when adjusted for treatment effect). Positive blood cultures were associated with longer hospital stay (coefficient 6.3, $p = 0.03$). Those with positive cultures from either pleural fluid or blood were more likely to require surgical intervention [37].

The largest microbiological study to date (TORPIDS) utilised next-generation sequencing (NGS) to identify pathogens, and findings support the correlation between pathogen and clinical outcomes. In particular, the presence of anaerobic bacteria and members of the Streptococcus anginosus group was associated with improved survival, whereas in contrast, a predominance of bacteria from the Enterobacteriaceae and Staphylococcus groups correlated with increased risk of mortality [14]. Overall, these findings highlight the role of pathogen identification as a potential element that could be incorporated in a risk stratification model for prediction of the clinical outcomes.

Pleural Fluid Appearance and Clinical Outcomes

Davies et al. [13] assessed the outcomes in a prospective study of 85 patients with confirmed pleural infection; all patients were treated with standard care, including antibiotics and chest tube drainage, followed by surgical intervention in cases of treatment failure. They reported that the presence of non-purulent pleural fluid group was the only clinically useful predictor of successful medical treatment; 29 (40%) with non-purulent pleural fluid had successful treatment compared to 10 (77%) in the purulent fluid ($p < 0.02$) [13]. The absence of purulence demonstrated a high positive predictive value (PPV) of 93% for successful non-surgical management. Conversely, the presence of purulence had limited utility in predicting treatment failure, with a PPV of only 26%. These findings are in keeping with the RAPID score, in which the presence of purulent pleural fluid has been demonstrated to be associated with improved clinical outcomes [10]. This observation may be explained by the fact that purulent effusions are more likely to be effectively drained, thereby achieving source control.

Thoracic Ultrasound

In patients with pleural infection, thoracic ultrasound plays a pivotal role in understanding the nature of the pleural effusion, particularly in the evaluation of the fibrin deposition and the.

presence of fibrinous septation in the pleural cavity [38]. Bedawi et al. provided evidence from baseline thoracic ultrasound assessments in the prospectively collected PILOT study cohort, demonstrating a significant association between the presence of ultrasound-detected septations and subsequent use of intrapleural enzyme therapy (IET). Among 368 patients with septated effusions, IET was administered in 72 cases (19.6%), compared to only 9 cases (9.6%) among 94 patients with non-septated effusions ($p = 0.023$) [12]. However, the rates of surgery within 12 months was not statistically different (16.8%–26.1%). In addition, mortality (at 3 and 12 months), readmission rates within 12 months and length of hospital stay did not differ significantly between groups. In contrast, two small retrospective studies reported that the presence of septations is associated with poor clinical outcomes and the requirement for more invasive intervention [15, 39]. However, these studies are limited by the nature of the retrospective design and small sample sizes, which increases the risk of bias and limits the reliability and generalizability of findings.

Other Risk Factors

The Pneumonia Severity Index (PSI) and CURB-65 (confusion, urea, respiratory rate, and age ≥ 65 years) are two robustly validated clinical prediction scores have been used to predict all-cause 30- day mortality in patients with pneumonia [40]. Notably, in the PSI score, pleural effusion is assigned a weight of 10 points implying its independent correlation with increased risk of mortality. This association has been supported by a retrospective study of 421 patients with complicated parapneumonic effusion, which demonstrated that PSI risk classes IV–V (i.e. >90 points) and those with a CURB-65 score ≥ 2 points were significant predictors of 30-day mortality, with respective odds ratios of 4.7 and 5.5 [41].

However, there are limitations to using these studies in patients with pleural infection; for instance, in a large cohort study involving 4,771 pneumonia patients, the electronic implementation of the CURB-65 score substantially underestimated the observed 30-day mortality among the subset of 690 patients with pleural effusion, predicting a mortality rate of 7% compared to the actual rate of 14% ($P < 0.001$) [15].

Conclusions

In pleural infection, the RAPID score is the only validated risk prediction tool, incorporating age, serum albumin, and blood urea to predict mortality risk. The recent British Thoracic Society recommends its use to stratify patients and support discussions about treatment options. RAPID has the potential to personalise treatment and identify high-risk patients for earlier intensive treatment strategies and avoid unnecessary invasive intervention for the low risk group; however, data on clinical utility with its use are currently

lacking. The NIHR-funded RAPTOR-feasibility trial is the first study attempting to evaluate RAPID-guided treatment and will inform design and methodology for future definitive trials.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Human and Animal Rights All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

Competing interests The authors declare no competing interests.

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