Respiratory Research

RESEARCH

Open Access

Prognostic significance of pleural fluid microbiological positivity in pleural infection: a bicentric 10-year retrospective observational study

Charles Wong[1*], Hon Cheung Fan[2], Najib M. Rahman[3,4,5], Jeffrey Chi Chung Wong[1], Hei Shun Cheng[1], Pui Hing Chiu[1], Chun Wai Tong[1], Flora Pui Ling Miu[1] and Loretta Yin Chun Yam[1]

Abstract

Background Despite its heterogeneity, there is currently limited data in pleural infection phenotyping. Using pleural fluid characteristics, pleural infection can be classified into microbiological-positive pleural infection (MPPI) and microbiological-negative pleural infection (MNPI). This study aimed to evaluate the prognostic significance of microbiological positivity in pleural infection, and to evaluate the performance of RAPID (renal, age, purulence, infection source, dietary factor) score in these subgroups.

Methods Consecutive patients hospitalized for pleural infection over a 10-year period in two acute-care hospitals in Hong Kong were evaluated. According to the pleural fluid characteristics, they were classified into MPPI and MNPI, respectively. Survival was evaluated using multivariate Cox regression analysis. Performance of RAPID score to predict mortality at 3-month and 1-year was evaluated using C-statistics.

Results In total, 381 patients with pleural infection were included. They were classified into MPPI ($n=169$) and MNPI ($n=212$), respectively. The MPPI group had more elderly home residence and use of large-bore chest tube, and higher Charlson comorbidity index and RAPID score, compared to the MNPI group. Length-of-stay, the need of surgery and intensive care were similar between the two groups. MPPI was associated with significantly increased risk of mortality (adjusted hazard ratio [aHR] 1.46, 95% CI 1.08–1.98). Three-month mortality was significantly higher in MPPI compared to MNPI (24.9% vs. 10.4%, $p<0.001$; adjusted odd ratio 2.05, 95% CI 1.11–3.80). The trend continued at 1, 3, 5 and 7 years. RAPID score predicted 3-month and 1-year mortality in both groups (C-statistics, MPPI 0.71, 0.75; MNPI 0.84, 0.81). In the MPPI group, presence of *Staphylococcus aureus* (aHR 2.26, 95% CI 1.43–3.57) and *Gram-negative organisms other than Enterobacteriaceae* (aHR 2.00, 95% CI 1.10–3.61) were associated with worse survival, while presence of *Streptococcus anginosus group* was associated better survival (aHR 0.50, 95% CI 0.32–0.78), when compared to their absence.

*Correspondence:
Charles Wong
respirologistlesarch@gmail.com

Full list of author information is available at the end of the article

Conclusions Pleural fluid microbiological positivity is independently associated with increased mortality in patients with pleural infections. This finding should complement the RAPID score in risk stratification and inform future research aimed at improving outcomes in this patient population.

Background

Pleural infection continues to pose a significant healthcare challenge with substantial morbidity and mortality rates. It has a combined incidence of over 80,000 cases per annum in the USA and the UK [1]. Moreover, the incidence has shown an increasing trend, which could be contributed by an ageing population with comorbidities which act as predisposing factors to pleural infection (e.g., diabetes mellitus, neurological conditions causing oropharyngeal aspiration), increased use of sensitive imaging techniques like ultrasound and computed tomography (CT), and increased awareness among clinicians leading to more accurate diagnosis [2]. Pleural infection, when considered as a single disease entity, is associated with worse clinical outcomes when compared to those with uncomplicated parapneumonic effusion (UPPE), including longer hospital stay and increased mortality risk [3]. However, pleural infection has a wide disease spectrum from complicated parapneumonic effusion to empyema [4]. Data regarding the differential outcomes in different phenotypes is limited.

Previous reports suggested that culture positivity in pleural fluid may be associated with worse clinical outcomes in empyema [5–7]. However, the differential outcome of microbiological (including gram staining and/or culture) positivity has not been established in an all-encompassing pleural infection cohort, as previous studies mainly focused on empyema cases, without inclusion of non-empyema pleural infection in their analysis [5–6]. The RAPID (renal, age, purulence, infective source, dietary factor) score has been developed and validated as a prognostication tool in pleural infection [8–13]. Data regarding its performance in specific subgroups, such as microbiological-positive pleural infection (MPPI) and microbiological-negative pleural infection (MNPI), is not reported.

We hypothesized that microbiological positivity in pleural infection is associated with increased mortality. Our study aimed to compare the clinical characteristics and outcomes of patients with MPPI and MNPI. In addition, the prognostic significance of individual microorganism group in MPPI, and the performance of the RAPID score in MPPI and MNPI were evaluated.

Methods

Study design

This was a retrospective observational study which recruited patients in two acute-care hospitals in Hong Kong (Pamela Youde Nethersole Eastern Hospital [PYNEH] and Ruttonjee Hospital [RH]). Adult patients admitted for pleural infection in the two hospitals over a 10-year period (1 January 2011 to 31 December 2020) were identified in a territory-wide healthcare electronic database (Clinical Data Analysis and Reporting System) using the relevant discharge diagnosis codes consistent with parapneumonic effusion and empyema (ICD-9 codes 510.0, 510.9, 511.0 and 511.1). Exclusion criteria included (1) duplicated records, (2) no pleural fluid for analysis, (3) uncomplicated parapneumonic effusion not fulfilling the definition of pleural infection, (4) tuberculous pleuritis, and (5) pleural effusion of other causes.

Patients were included if they had a clinical presentation consistent with pleural infection, and any of the following criteria: (1) pleural fluid that was frank pus; or (2) pleural fluid that was positive on Gram staining or culture for bacteria; or (3) pleural fluid with a pH ≤ 7.2; or (4) pleural fluid with a low glucose level (≤ 2.2 mmol/l) or (5) contrast-enhanced computed tomography (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 [9]. Evidence of infection was assessed by the investigators based on the presence of fever, an elevated peripheral white blood cell (WBC), or elevated serum inflammatory markers such as C-reactive protein (CRP) [9]. As the standard practice in the two participating hospitals, in patients with suspected pleural infection undergoing thoracentesis or drainage, the appearance of pleural fluid was documented routinely (pus or non-pus), and the pleural fluid was sent for gram staining and culture in plain bottle (without the use of blood culture bottle). Other pleural fluid analysis including pleural pH and glucose were arranged at the discretion of treating physician, if fluid volume is adequate.

Definitions of MPPI and MNPI

Included patients were classified into one of the two subgroups according to the following criteria:

1) MPPI was defined by microbiological positivity (Gram stain or culture of microorganisms) in the pleural fluid, regardless of pleural fluid appearance.
2) MNPI was defined by pleural infection without microbiological positivity (Gram stain or culture of microorganisms) in the pleural fluid.

Clinical notes and electronic records of these admission episodes were reviewed. Data on the subject's

demographics, clinical parameters, laboratory parameters, treatments, hospital length-of-stay (LOS), and survival status were collected. Co-morbidities were summarized using Charlson comorbidity index (CCI) [14]. Pleural infection was considered hospital-acquired if the onset occurred over 48 h after hospitalization, patient had been hospitalized within the preceding 4 weeks, or related to an invasive pleural procedure [15]. RAPID score was calculated for each subject according to the original study [8]. Microorganisms isolated in MPPI were classified into one of eight groups according to the TORPIDS study [16]: *Anaerobes*, *Streptococcus (Strep) anginosus group*, *Strep pneumoniae*, *Staphylococcus (S) aureus*, *other Gram-positive*, *Enterobacteriaceae*, *other Gram-negative* and *Fungal*.

Survival time was calculated from the date of pleural infection diagnosis to death. Subjects were censored at the time of data extraction if alive (31 December 2023). Institutional Review Board approval was obtained with a waiver of patient consent for the use of de-identified patient data (HKECREC-2021-084).

Statistical analysis

Descriptive statistics included frequency (percentages) for categorical variables, mean (+/- standard deviation [SD]) or median (inter-quartile range [IQR]) for continuous variables. Parameters of each group were compared using univariate analyses. Between-group comparisons were performed with Mann–Whitney test for continuous variables, and Chi-squared test for categorical variables. Survival analyses were performed using Kaplan-Meier survival curves, multivariate logistic and Cox regression backward selection model. Components of RAPID score (serum urea, age, fluid purulence, infection source and serum albumin) were adjusted in both the multivariate logistic and Cox regression analyses. Concordance (C) statistic was used to evaluate the discriminative ability of the RAPID score in predicting mortality at 3-month and 1-year. The C statistic is a summary measure of a model's accuracy, with a value of 0.5 implying random concordance and 1.0 perfect concordance [17]. *P* values (2-tailed) were considered significant if < 0.05. All statistical analyses were performed using computer programs Statistical Package for the Social Science (SPSS) version 23.0 (IBM Corp., Armonk, NY, USA for Microsoft Windows) and Stata version 14.2 (Texas, USA).

Sample size calculation

Sample size calculation was based on the estimated 90-day mortality difference between MPPI and MNPI. Previous study reported mortality of 27.1% and 10.8% in culture positive and culture negative pleural infection at 30-day, respectively [18]. Assuming a minimum significant difference to detect mortality fixed at 15% at 90-day (with MPPI mortality of 30% and MNPI mortality of 15%), with a 40% prevalence of microbiological positivity in an all-compassing pleural infection cohort [18, 19], this study required 333 analyzable subjects (90% power, alpha 0.05) and, allowing for 10% incomplete data or unanalyzable subjects, a recruitment target of 367 was set.

Results

Study population

Among 681 episodes retrieved from the database, 300 episodes met exclusion criteria and were precluded from further analysis (Fig. 1). A total of 381 patients fulfilled the diagnostic criteria of pleural infection and were included in the analysis. Applying the classification criteria, patients were classified into MPPI ($n = 169$) and MNPI ($n = 212$), respectively. In those with MPPI, microorganisms were identified in pleural fluid in 91 by both gram stain and culture, 73 by culture only, and 5 by gram stain only. The median follow-up time was 8.47 (7.62–9.32) years.

Comparison of clinical characteristics between MPPI and MNPI

Baseline clinical characteristics

Baseline clinical characteristics were summarized in Table 1. Age, sex, ethnicity (Chinese), rate of prior antibiotic use and hospital acquired infection were similar between the two groups. The MPPI group has a higher rate of elderly home residence (18.9% vs. 11.3%, $p = 0.037$), RAPID high-risk category (23.1% vs. 14.6%, p = 0.034) and higher CCI (median 1 [0–3] vs. 1 [0–2], $p = 0.010$). Comorbidities were summarized in Table S1. Chronic renal diseases and neurological conditions were more common in the MPPI group. (Table S1)

Physiological, laboratory and radiological parameters

Physiological parameters were similar between the two groups (Table 2). Regarding laboratorial parameters, serum urea was significantly higher (6.2 mmol/l vs. 4.7 mmol/l, $p = 0.001$) while albumin was significantly lower (28 g/l vs. 31 g/l, $p < 0.001$) in the MPPI group, when compared to MNPI group (Table 3). Regarding pleural fluid parameters, pleural LDH was significantly higher (4276 units/l vs. 1567 units/l, $p < 0.001$), while pleural pH (7.34 vs. 7.68, $p < 0.001$), glucose (0.3 mmol/l vs. 1.6 mmol/l, $p = 0.006$) and protein (35.2 g/l vs. 46.6 g/l, $p < 0.001$) were significantly lower in MPPI group, when compared to MNPI group (Table 3). Documentations of septation on ultrasound and pleural enhancement on computed tomography were similar between the two groups. (Table 3)

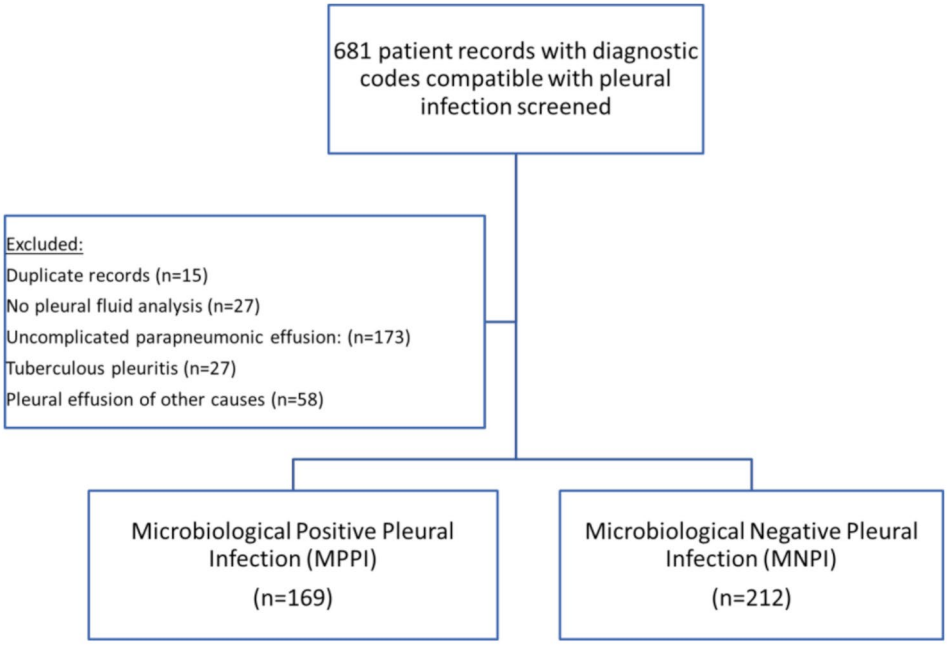

Fig. 1 Inclusion and exclusion of patients

Table 1 Baseline characteristics of study population

	Total (*n* = 381)	MPPI (*n* = 169)	MNPI (*n* = 212)	*p* value
PYNEH	280 (73.5%)	118 (69.8%)	162 (76.4%)	0.148
Male	288 (75.6%)	129 (76.3%)	159 (75.0%)	0.90
Age	65 (56–77)	65 (56–77)	65 (55–77)	0.508
Chinese	373 (97.9%)	166 (98.2%)	207 (97.6%)	0.693
Elderly home residence	56 (14.7%)	32 (18.9%)	24 (11.3%)	0.037
Antibiotic use before diagnosis	31 (8.1%)	9 (5.3%)	22 (10.4%)	0.073
Hospital-acquired	31 (8.1%)	15 (8.9%)	16 (7.5%)	0.637
CCI	1 (0–2)	1 (0–3)	1 (0–2)	0.010
CCI > = 2	134 (35.2%)	74 (43.8%)	60 (28.3%)	0.002
CCI > = 3	79 (20.7%)	46 (27.2%)	33 (15.6%)	0.005
>= 1 comorbidity	293 (76.9%)	143 (84.6%)	150/212 (70.8%)	0.001
RAPID score	3 (2–4)	3 (2–4)	3 (2–4)	0.017
RAPID high risk	70 (18.4%)	39 (23.1%)	31 (14.6%)	0.034
RAPID mod risk	147 (38.6%)	65 (38.5%)	82 (38.7%)	
RAPID low risk	164 (43.0%)	65 (38.5%)	99 (46.7%)	

MPPI: microbiological-positive pleural infection. MNPI: microbiological-negative pleural infection. PYNEH: Pamela Youde Nethersole Eastern Hospital. CCI: Charlson comorbidity index. RAPID: renal, age, purulence, infection source, dietary factor

Table 2 Physiological parameters at presentation

	Total (*n* = 381)	MPPI (*n* = 169)	MNPI (*n* = 212)	*p* value
Confusion	26 (6.8%)	16 (9.5%)	10 (4.7%)	0.068
MAP < 65	16 (4.2%)	8 (4.7%)	8 (3.8%)	0.643
Tachycardia *P* > 100	220 (57.7%)	93 (55.0%)	127 (59.9%)	0.338
Temp > 38 C or < 36 C	102 (26.8%)	44 (26%)	58 (27.4%)	0.772
Tachypnea RR > 20	112 (29.4%)	51 (30.2%)	61 (28.8%)	0.765
Hypoxemia	117 (30.7%)	58 (34.3%)	59 (27.8%)	0.173

MPPI: microbiological-positive pleural infection. MNPI: microbiological-negative pleural infection. MAP: Mean arterial pressure. Temp: Temperature

Table 3 Laboratorial and radiological parameters

	Total ($n=381$)	MPPI ($n=169$)	MNPI ($n=212$)	*p* value
Serum urea (mmol/l)	5.3 (3.8–8.1)	6.2 (4.1–10.2)	4.7 (3.5–6.9)	0.001
Serum albumin (g/l)	29 (25–33)	28 (24–32)	31 (27–34)	< 0.001
Pleural LDH (units/l) ($n=330$)	2162 (988–8425)	4276 (1082–14453)	1567 (919–4802)	< 0.001
Pleural pH ($n=282$)	7.59 (7.20–7.90)	7.34 (6.91–7.78)	7.68 (7.35–7.94)	< 0.001
Pleural glucose mmol/l ($n=297$)	0.7 (0.3–4.4)	0.3 (0.3–3.2)	1.6 (0.3–4.5)	0.006
Pleural protein g/l ($n=335$)	42.8 (32.5–50.5)	35.2 (22.4–45.9)	46.6 (39.4–51.8)	< 0.001
Septation on ultrasound ($n=371$)	160/371 (43.1%)	65/163 (39.9%)	95/208 (45.7%)	0.263
Pleural enhancement on computed tomography ($n=349$)	247/349 (70.8%)	99/148 (66.9%)	148/201 (73.6%)	0.171

MPPI: microbiological-positive pleural infection. MNPI: microbiological-negative pleural infection. LDH: Lactate dehydrogenase

Table 4 Treatments and length-of-stay

	Total ($n=381$)	MPPI ($n=169$)	MNPI ($n=212$)	*p* value
Large-bore (> = 20 F) chest tube ($n=361$)#	116/361 (32.1%)	66/161 (41.0%)	50/200 (25.0%)	0.001
Thrombolytic use ($n=361$)	117/361 (32.4%)	46/161 (28.6%)	71/200 (35.5%)	0.162
Surgery	10 (2.6%)	5 (3.0%)	5 (2.4%)	0.716
ICU	38 (10.0%)	16 (9.5%)	22 (10.4%)	0.768
LOS	31 (21– 43)	32 (23–45)	30 (21–41)	0.154

MPPI: microbiological-positive pleural infection. MNPI: microbiological-negative pleural infection. ICU: Intensive care unit. LOS: Length of stay

As opposed to smaller (< 20 F) chest tube

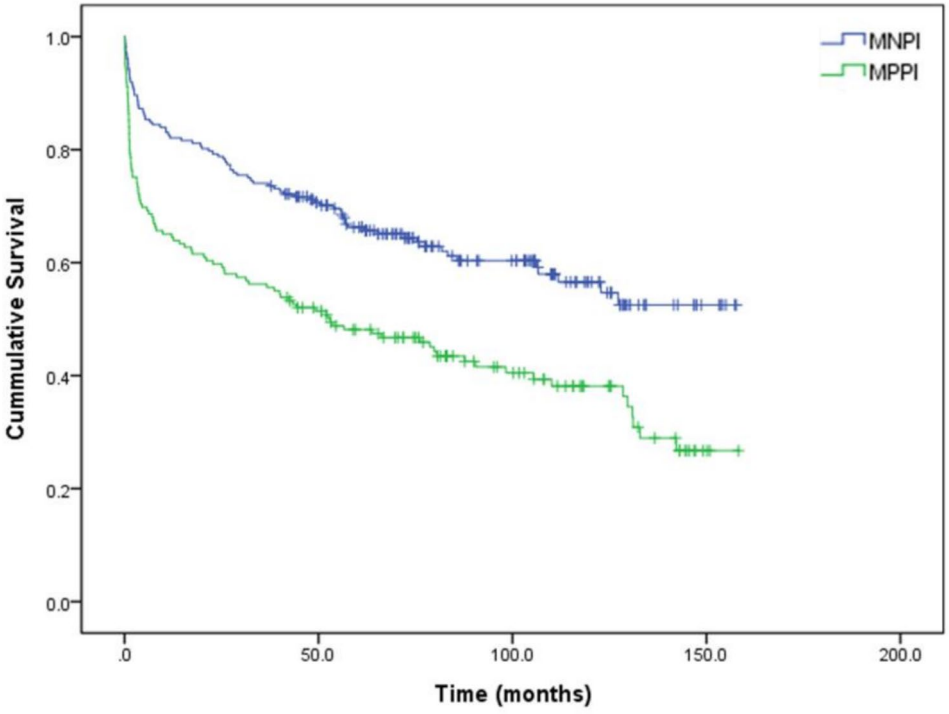

Fig. 2 Kaplan-Meier survival curves in the MPPI group and MNPI group
MPPI: microbiological-positive pleural infection. MNPI: microbiological-negative pleural infection

Treatments and length-of-stay

The majority (361/369) of patients were treated with chest tube insertion. In MPPI, the rate of large-bore chest tube (> = 20 F) use was higher (41% vs. 25%, $p=0.001$), compared to MNPI. The rates of surgery and intensive care unit admission, and length-of-stay were similar between MPPI group and MNPI group. (Table 4)

Primary outcome: survival analysis of MPPI vs. MNPI

Kaplan-Meier curves showed significant survival differences between MPPI and MNPI (log-rank $p<0.001$) (Fig. 2). Using multivariate Cox regression analysis, after adjusting for covariates, MPPI was associated with significantly increased risk of mortality (adjusted hazard ratio 1.46, 95% CI 1.08–1.98). (Table 5) Three-month mortality

Table 5 Cox regression analysis for survival analysis of MPPI vs. MNPI

	Hazard ratio (95% CI)	*P* value
Unadjusted analysis	1.86 (1.40–2.49)	< 0.001
Adjusted analysis*	1.46 (1.08–1.98)	0.015

Adjusted to components of RAPID score

MPPI: microbiological-positive pleural infection. MNPI: microbiological-negative pleural infection. CI: confidence interval

was significantly higher in MPPI compared to MNPI (24.9% vs. 10.4%, $p < 0.001$; adjusted odd ratio 2.05, 95% CI 1.11–3.80). The trend continued at 1, 3, 5 and 7 years. (Tables 6 and 7)

Sensitivity analysis

Sensitivity analysis was performed using multivariate analysis, taking additional potential covariates ($p < 0.05$) found during univariate analysis into consideration (model 1: elderly home residence, CCI and chest tube size; model 2: elderly home residence, chronic renal disease, chronic neurological disease and chest tube size). The sensitivity analysis showed consistent results to confirm the independent prognostic significance of microbiological positivity. (Table S2)

Table 7 Logistic regression analysis of mortality at various time points of MPPI vs. MNPI

Mortality	Unadjusted OR (95% CI)	*P* value	Adjusted OR* (95% CI)	*P* value
3 months	2.86 (1.63–5.01)	< 0.001	2.05 (1.11–3.80)	0.022
1 years	2.52 (1.57–4.04)	< 0.001	1.88 (1.10–3.21)	0.022
3 years	2.22 (1.44–3.43)	< 0.001	1.67 (1.00–2.79)	0.052
5 years	2.08 (1.35–3.20)	0.001	1.78 (1.05–2.99)	0.031
7 years	1.85 (1.16–2.96)	0.010	1.76 (1.00–3.08)	0.050

MPPI: microbiological-positive pleural infection. MNPI: microbiological-negative pleural infection. OR: odd ratio, CI: confidence interval

Adjusted to components in RAPID score

Secondary outcomes (I): prognostic significance of individual microorganism group

Altogether 229 microorganisms were isolated from 169 patients with MPPI (Fig. 3) (Table S3). In the MPPI group, isolation of *S aureus* (aHR 2.26 [1.43–3.57]) and *Gram-negative organisms other than Enterobacteriaceae* (aHR 2.00 [1.10–3.61]) were associated with worse survival, while isolation of *Streptococcus anginosus group*

Table 6 Mortality outcome at various time points in MPPI and MNPI

	Total ($n = 381$)	MPPI ($n = 169$)	MNPI ($n = 212$)	*p* value
3-month mortality	64 (16.8%)	42 (24.9%)	22 (10.4%)	< 0.001
1-year mortality	98 (25.7%)	60 (35.5%)	38 (17.9%)	< 0.001
3-year mortality	129 (33.9%)	74 (43.8%)	55 (25.9%)	< 0.001
5-year mortality ($n = 344$)	157 (45.6%)	87 (55.4%)	70 (37.4%)	0.001
7-year mortality ($n = 289$)	157 (54.3%)	87 (62.1%)	70 (47.0%)	0.010

MPPI: microbiological-positive pleural infection. MNPI: microbiological-negative pleural infection

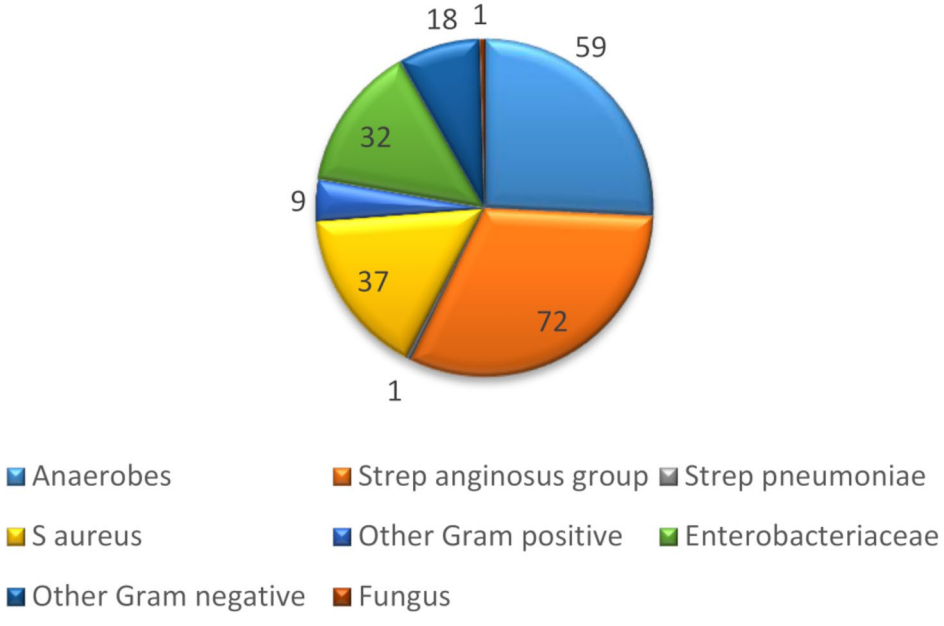

Fig. 3 Microorganisms ($n = 229$) isolated in 169 patients with microbiological-positive pleural infection

Table 8 3-month mortality stratified by microbiological positivity phenotype and RAPID score

	MPPI ($n=169$)		MNPI ($n=212$)	
3-month mortality	24.9%		10.4%	
	RAPID high risk ($n=39$)	**RAPID low - moderate risk ($n=130$)**	**RAPID high risk ($n=31$)**	**RAPID low–moderate risk ($n=181$)**
3-month mortality	48.7%	17.7%	35.5%	6.1%

MPPI: microbiological-positive pleural infection. MNPI: microbiological-negative pleural infection. RAPID: renal, age, purulence, infection source, dietary factor

was associated better survival (aHR 0.50 [0.32–0.78]). (Table S4)

Secondary outcomes (II): performance of RAPID score in MPPI and MNPI

RAPID score showed consistent discriminative performance in mortality prediction in both the MPPI and MNPI groups at various time points. (Table S5) C-statistics of RAPID score to predict 3-month and 1-year mortality were 0.71 [0.62–0.80] and 0.75 [0.67–0.82] in MPPI; and 0.84 [0.77–0.91] and 0.81 [0.74–0.88]) in MNPI. (Table S5) Mortality risks stratified by RAPID score and pleural fluid microbiological positivity were summarized in Table 8. Patients with MPPI and high-risk RAPID score had the highest 3-month mortality (48.7%), while those with MNPI and low-to-moderate RAPID score had better survival (3-month mortality 6.1%).

Discussion

We conducted a bicentric, retrospective observational study to evaluate the prognostic significance of microbiological positivity (MPPI) in pleural infection. The results showed that pleural infection is a heterogenous disease, and microbiological positivity in pleural fluid is associated with worse prognosis, with a two-fold increase in 3-month mortality, and the trend continued at 1, 3, 5 and 7 years. The long-term prognostic impact of microbiological positivity in pleural infection could be multifactorial including possible secondary effects on various organ systems, especially the cardiovascular system, by possible pathogenic mechanisms related to higher bacterial load and host response [20], in addition to higher prevalence of comorbidities.

The microbiological pattern of pleural infection observed in our study aligns with existing literature [21]. We observed that certain microorganisms are associated with worse prognosis, including *S aureus* and *Gram-negative organism other than Enterobacteriaceae*, while the *Strep anginosus group* is associated with better survival, which is consistent with recent study [16] and further support microbiological phenotyping in pleural infection. One possible explanation for the better survival observed in *Strep anginosus group* is its higher susceptibility to standard antibiotic treatments, resulting in earlier appropriate treatment and improved clinical outcomes. Other factors such as virulence factors, host immune response, and co-infections likely also contribute to these observations and should be investigated in future studies.

We also demonstrated that RAPID score has satisfactory performance in both MPPI and MNPI, supporting its clinical utility in these phenotypes, and in Asian-Chinese population. Thus, the microbiological phenotype should be considered together with RAPID score risk stratification in early phase of treatment to assist clinical decision making in patients with pleural infection. Although the role of RAPID score in routine clinical care is yet to be defined [22], our data support developing treatment paradigms by risk stratifying patients with pleural infection according to both microbiological phenotype and RAPID score in future prospective study. For instance, strategy focusing on early escalation of treatment in those with MPPI with a high RAPID score, should be considered in future clinical trials.

The rate of surgical treatment (2.6%) in the present study is lower than previous reports of pleural infection. This could be due to an elderly predominant cohort with high prevalence of comorbidities in this study, resulting in treatment decisions that favors non-surgical options due to concerns on high surgical risk. Previous large surgical case series also demonstrated a preference of intervening younger individuals with fewer co-morbidities [23, 24]. These results underscore the urgent need for randomized studies powered to evaluate the impact of more invasive treatments, including surgical intervention, on clinically important outcomes such as mortality. This will better inform the decision-making process regarding surgical intervention in patients with pleural infection.

Strengths of our study include a bicentric design across a 10-year period, which captures a reasonable number of subjects ($n=381$) with pleural infection in an Asian-Chinese predominant population. Follow-up data were available at 5-year in 90% ($n=344$) and at 7-year in 76% ($n=289$) of patients, respectively, which allowed analysis of long-term outcomes. We performed multivariate analysis using both planned model (RAPID score factors as covariates) and sensitivity analysis taking into account additional potential confounders found in univariate

analysis, which further strengthen the robustness of our results. Our study has several limitations. First, inherent to the nature of retrospective study, there was missing data for some variables, including sonographic and CT features. However, the key parameters responsible for the primary outcome were complete and therefore the primary results of our study remain valid. Second, the phenotypes in our study were dependent on gram staining and/or culture positivity. The microbial yield could have been affected by prior antibiotic use, timing and method of pleural fluid culture. The sensitivity of pleural fluid microbiology identification could be improved using genetic methods [16, 25], or by the use of blood culture bottles [26]. However, this was not a standard practice in our centers during the study period, thus the results may not be applicable to those using blood culture bottle's culture method to define pleural microbiological positivity. Future investigations into detection rate differences using blood culture bottles could offer valuable insights. Nonetheless, this study reflected real world practice and showed that mortality could be predicted by clinical phenotype defined by readily available parameter in routine practice.

Conclusions

Pleural fluid microbiological positivity indicates a high-risk phenotype in patients with pleural infection. The diagnosis of MPPI with a high RAPID score portends high mortality risk despite standard treatment by antibiotic and drainage. Future research focusing on treatment strategies based on both microbiological positivity and RAPID risk stratification is needed to inform the optimal management of adults presenting with pleural infection.

Abbreviations

aHR	Adjusted hazard ratio
aOR	Adjusted odd ratio
CCI	Charlson comorbidity index
C statistic	Concordance statistic
CT	Computed tomography
HR	Hazard ratio
ICU	Intensive care unit
IQR	Interquartile range
LDH	Lactate dehydrogenase
LOS	Length of stay
MNPI	Microbiological-negative pleural infection
MPPI	Microbiological-positive pleural infection
OR	Odd ratio
PYNEH	Pamela Youde Nethersole Eastern Hospital
RAPID	Renal, age, purulence, infection source, dietary factor
RH	Ruttonjee Hospital
S	Staphylococcus
SD	Standard deviation
Strep	Streptococcus

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12931-025-03129-5.

Supplementary Material 1

Author contributions

CW was involved with study concept and design; acquisition of data; analysis and interpretation of data; drafting of manuscript; critical revision of the manuscript for important intellectual content; and approval of the final version of the manuscript. HCF was involved with the study concept and design; acquisition of data; drafting of manuscript; and approval of the final version of the manuscript. NMR was involved with study concept and design; critical revision of the manuscript for important intellectual content; and approval of the final version of the manuscript. JCCW, HSC, PHC, CWT, FPLM, LYCY were involved with acquisition of data; analysis and interpretation of data; drafting of manuscript; and approval of the final version of the manuscript. All authors read and approved the final manuscript.

Funding

Nil.

Data availability

Nil.

Declarations

Ethical approval

The study was approved by the Institutional Review Board of the Hospital Authority Hong Kong East Cluster (HKECREC-2021-084).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Medicine, Pamela Youde Nethersole Eastern Hospital, 3 Lok Man Road, Chai Wan, Hong Kong
[2]Department of Medicine, Ruttonjee Hospital, Hong Kong, China
[3]University of Oxford, Oxford Respiratory Trials Unit, Oxford, UK
[4]Oxford NIHR Biomedical Research Centre, Oxford, UK
[5]Oxford Pleural Unit, Churchill Hospital, Oxford, UK

Received: 11 November 2024 / Accepted: 30 January 2025
Published online: 13 February 2025

References

1. Roberts ME, Rahman NM, Maskell NA, Bibby AC, Blyth KG, Corcoran JP, Edey A, Evison M, de Fonseka D, Hallifax R, Harden S, Lawrie I, Lim E, McCracken DJ, Mercer R, Mishra EK, Nicholson AG, Noorzad F, Opstad K, Parsonage M, BTS Pleural Guideline Development Group. British thoracic Society Guideline for pleural disease. Thorax. 2023;78(Suppl 3):s1–42. https://doi.org/10.1136/thorax-2022-219784
2. Bedawi EO, Ricciardi S, Hassan M, Gooseman MR, Asciak R, Castro-Añón O, Armbruster K, Bonifazi M, Poole S, Harris EK, Elia S, Krenke R, Mariani A, Maskell NA, Polverino E, Porcel JM, Yarmus L, Belcher EP, Opitz I, Rahman NM. ERS/ESTS statement on the management of pleural infection in adults. Eur Respir J. 2023;61(2):2201062. https://doi.org/10.1183/13993003.01062-2022
3. Falguera M, Carratalà J, Bielsa S, García-Vidal C, Ruiz-González A, Chica I, Gudiol F, Porcel JM. Predictive factors, microbiology and outcome of patients with parapneumonic effusion. Eur Respir J. 2011;38(5):1173–9. https://doi.org/10.1183/09031936.00000211
4. Sahn SA. Diagnosis and management of parapneumonic effusions and empyema. Clin Infect Diseases: Official Publication Infect Dis Soc Am. 2007;45(11):1480–6. https://doi.org/10.1086/522996
5. Brims F, Popowicz N, Rosenstengel A, Hart J, Yogendran A, Read CA, Lee F, Shrestha R, Franke A, Lewis JR, Kay I, Waterer G, Lee YCG. Bacteriology and clinical outcomes of patients with culture-positive pleural infection in

Western Australia: a 6-year analysis. Respirol (Carlton Vic). 2019;24(2):171–8. https://doi.org/10.1111/resp.13395
6. Chan KP, Ng SSS, Ling KC, Ng KC, Lo LP, Yip WH, Ngai JCL, To KW, Ko FWS, Lee YCG, Hui DSC. Phenotyping empyema by pleural fluid culture results and macroscopic appearance: an 8-year retrospective study. ERJ open Res. 2023;9(2):00534–2022. https://doi.org/10.1183/23120541.00534-2022
7. Meyer CN, Armbruster K, Kemp M, Thomsen TR, Dessau RB, Danish Pleural Empyema group. Pleural infection: a retrospective study of clinical outcome and the correlation to known etiology, co-morbidity and treatment factors. BMC Pulm Med. 2018;18(1):160. https://doi.org/10.1186/s12890-018-0726-1. Published 2018 Oct 12.
8. Rahman NM, Kahan BC, Miller RF, Gleeson FV, Nunn AJ, Maskell NA. A clinical score (RAPID) to identify those at risk for poor outcome at presentation in patients with pleural infection. Chest. 2014;145(4):848–55. https://doi.org/10.1378/chest.13-1558
9. Corcoran, J. P., Psallidas, I., Gerry, S., Piccolo, F., Koegelenberg, C. F., Saba,T., Daneshvar, C., Fairbairn, I., Heinink, R., West, A., Stanton, A. E., Holme, J.,Kastelik, J. A., Steer, H., Downer, N. J., Haris, M., Baker, E. H., Everett, C. F.,Pepperell, J., Bewick, T.,… Rahman, N. M. Prospective validation of the RAPID clinical risk prediction score in adult patients with pleural infection: the PILOT study. The European respiratory journal. 2020;56(5):2000130. https://doi.org/10.1183/13993003.00130-2020.
10. White HD, Henry C, Stock EM, Arroliga AC, Ghamande S. Predicting Long-Term outcomes in Pleural infections. RAPID score for risk stratification. Annals Am Thorac Soc. 2015;12(9):1310–6. https://doi.org/10.1513/AnnalsATS.201505-272OC
11. Touray S, Sood RN, Lindstrom D, Holdorf J, Ahmad S, Knox DB, Sosa AF. Risk stratification in patients with complicated parapneumonic effusions and Empyema using the RAPID score. Lung. 2018;196(5):623–9. https://doi.org/10.1007/s00408-018-0146-2
12. Wong D, Yap E. Pleural infection in a New Zealand centre: high incidence in Pacific people and RAPID score as a prognostic tool. Intern Med J. 2016;46(6):703–9. https://doi.org/10.1111/imj.13087
13. Yamazaki A, Ito A, Ishida T, Washio Y. Polymicrobial etiology as a prognostic factor for empyema in addition to the renal, age, purulence, infection source, and dietary factors score. Respiratory Invest. 2019;57(6):574–81. https://doi.org/10.1016/j.resinv.2019.06.008
14. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373–83. https://doi.org/10.1016/0021-9681(87)90171-8
15. Marks DJ, Fisk MD, Koo CY, et al. Thoracic empyema: a 12-year study from a UK tertiary cardiothoracic referral centre. PLoS ONE. 2012;7(1):e30074. https://doi.org/10.1371/journal.pone.0030074
16. Kanellakis NI, Wrightson JM, Gerry S, et al. The bacteriology of pleural infection (TORPIDS): an exploratory metagenomics analysis through next generation sequencing. Lancet Microbe. 2022;3(4):e294–302. https://doi.org/10.1016/S2666-5247(21)00327-X
17. Pencina MJ, D'Agostino RB, Sr. Evaluating discrimination of risk prediction models: the C statistic. JAMA. 2015;314(10):1063–4. https://doi.org/10.1001/jama.2015.11082
18. Park CK, Oh HJ, Choi HY, et al. Microbiological characteristics and predictive factors for mortality in pleural infection: a single-Center Cohort Study in Korea. PLoS ONE. 2016;11(8):e0161280. https://doi.org/10.1371/journal.pone.0161280. Published 2016 Aug 16.
19. (2021), O8-1: Microbiology and treatment outcomes of pleural infection in a tertiary hospital in Hong Kong: a 10-year review. Respirology, 26: 22–22. https://doi.org/10.1111/resp.14149_44
20. Restrepo MI, Faverio P, Anzueto A. Long-term prognosis in community-acquired pneumonia. Curr Opin Infect Dis. 2013;26(2):151–8. https://doi.org/10.1097/QCO.0b013e32835ebc6d. PMID: 23426328; PMCID: PMC4066634.
21. Hassan M, Cargill T, Harriss E, et al. The microbiology of pleural infection in adults: a systematic review. Eur Respir J. 2019;54(3):1900542. https://doi.org/10.1183/13993003.00542-2019. Published 2019 Oct 1.
22. Elsheikh A, Bhatnagar M, Rahman NM. Diagnosis and management of pleural infection. Breathe (Sheffield England). 2023;19(4):230146. https://doi.org/10.1183/20734735.0146-2023
23. Farjah F, Symons RG, Krishnadasan B, et al. Management of pleural space infections: a population-based analysis. J Thorac Cardiovasc Surg. 2007;133:346–51.
24. Marks DJ, Fisk MD, Koo CY, et al. Thoracic empyema: a 12-year study from a UK tertiary cardiothoracic referral centre. PLoS ONE. 2012;7:e30074.
25. 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. https://doi.org/10.1164/rccm.200601-074OC
26. Menzies SM, Rahman NM, Wrightson JM, Davies HE, Shorten R, Gillespie SH, Davies CW, Maskell NA, Jeffrey AA, Lee YC, Davies RJ. Blood culture bottle culture of pleural fluid in pleural infection. Thorax. 2011;66(8):658–62. https://doi.org/10.1136/thx.2010.157842

Publisher's note