

Clinical features associated with risk category 4 in pleural infection: an application of the ACCP classification

Características clínicas asociadas a la categoría 4 de riesgo en infección pleural: una aplicación de la clasificación del ACCP

Renata Báez-Saldaña^{1,2,3*}, Jessica M. Contreras-Martínez^{1,2}, Héctor Molina-Corona^{1,2},
María E. Martínez-Rendón^{1,2} and Marco A. Íñiguez-García^{1,4}

¹Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas (INER); ²Faculty of Medicine, Universidad Nacional Autónoma de México; ³Department of Education, INER; ⁴Surgery Subdirector, INER. Mexico City, Mexico.

Abstract

Introduction: In pleural infection, including parapneumonic effusion and empyema, the risk category classification proposed by the American College of Chest Physicians (ACCP) is a useful tool to guide treatment. However, limited information is available on how different clinical characteristics of patients may influence this classification. **Objective:** To identify clinical, biochemical, and radiological factors associated with risk category 4 (poor prognosis) in patients with pleural infection, according to the ACCP classification. **Method:** Secondary analysis of a database from a cohort study of consecutive patients with confirmed pleural infection. Clinical, laboratory, and imaging variables were compared between patients classified as risk category 4 vs. categories 1, 2, and 3. Multivariate logistic regression was performed to identify factors independently associated with risk category 4. **Results:** A total of 208 patients were included, of whom 100 (48.1%) were classified as risk category 4. Independent factors associated with category 4 were: > 15 days between symptom onset and hospital admission (OR: 4.13; 95% CI: 2.01-8.48), glucose > 200 mg/dl (OR: 2.93; 95% CI: 1.21-7.11), presence of two or more loculations (OR: 2.42; 95% CI: 1.25-4.67), pleural thickening (OR: 4.82; 95% CI: 1.42-16.32) and positive microbiological identification (OR: 3.02; 95% CI: 1.55-5.86). **Conclusions:** Delayed medical care, hyperglycemia, extensive loculated involvement, pleural thickening, and positive microbiological identification were associated with a higher clinical risk. These findings may inform strategies for early evaluation and timely management of patients with parapneumonic effusion or empyema.

Keywords: Pleural infection. Risk categories. Risk factors. Hyperglycemia. Early diagnosis.

Resumen

Introducción: En la infección pleural, ya sea derrame pleural paraneumónico o empiema, la clasificación por categorías de riesgo propuesta por el American College of Chest Physicians (ACCP) es una herramienta útil para guiar el tratamiento. Sin embargo, se dispone de escasa información sobre cómo diversas características clínicas del paciente pueden influir en esta clasificación. **Objetivo:** Identificar los factores clínicos, bioquímicos y radiológicos asociados a la categoría 4 de riesgo para mal pronóstico en pacientes con infección pleural, según la clasificación del ACCP. **Método:** Análisis secundario de una base de datos de un estudio de cohorte de pacientes consecutivos con diagnóstico confirmado de infección pleural. Se compararon variables clínicas, de laboratorio e imagen entre pacientes clasificados en la categoría 4 de riesgo y en las categorías

*Correspondence:

Renata Báez-Saldaña
E-mail: baezrd@unam.mx

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1, 2 y 3. Se realizó un análisis multivariante mediante regresión logística para identificar los factores asociados de forma independiente con la categoría de riesgo 4. **Resultados:** Se incluyeron 208 pacientes, de los cuales 100 (48.1%) fueron clasificados como categoría 4 de riesgo. Se asociaron de forma independiente con la categoría 4: tiempo > 15 días entre el inicio de los síntomas y el ingreso hospitalario (OR: 4.13; IC 95%: 2.01-8.48), glucosa > 200 mg/dl (OR: 2.93; IC 95%: 1.21-7.11), presencia de dos o más lóculos (OR: 2.42; IC 95%: 1.25-4.67), paquipleuritis (OR: 4.82; IC 95%: 1.42-16.32) e identificación microbiológica positiva (OR: 3.02; IC 95%: 1.55-5.86). **Conclusiones:** El retardo en la atención médica, la presencia de hiperglucemia, la afectación loculada extensa, la paquipleuritis y la identificación microbiológica se asociaron con un mayor riesgo clínico. Estos hallazgos pueden orientar estrategias de evaluación temprana y de manejo oportuno en pacientes con derrame pleural paraneumónico o empiema.

Palabras clave: Infección pleural. Categorías de riesgo. Factores de riesgo. Hiperglucemia. Diagnóstico oportuno.

Introduction

Parapneumonic pleural effusion and thoracic empyema are dynamic inflammatory processes that develop in the space between the parietal and visceral pleura. This is a complex entity that encompasses clinical, imaging, and laboratory elements. Globally, its incidence has increased in recent years¹ and at our institution, it is one of the leading causes of hospitalization.

Patients with community-acquired pneumonia may develop pleural effusion, the frequency of which in the literature is described as ranging between 7 and 50%; of these cases, between 5 and 15% may present complicated parapneumonic effusion or pleural empyema, an entity associated with considerable morbidity and mortality, which can decrease substantially if the condition is recognized and treated early.²⁻⁴

Current treatment of empyema includes antibiotics and drainage of the pleural space, through the placement of an endopleural drain with or without the use of thrombolytics. This treatment fails in 30% of cases, in which a surgical approach is necessary, either video-assisted thoracoscopy or thoracotomy for cavity lavage and decortication, or open drainage of the cavity.⁵

In the year 2000, an expert panel from the American College of Chest Physicians (ACCP) developed a classification of parapneumonic pleural effusion into four risk categories, based on the anatomical characteristics of the fluid (A), the bacteriology of the pleural fluid (B), and the chemistry of the pleural fluid (C).⁶ Treatment of cases in categories 1 and 2 generally does not require cavity drainage, whereas for cases in categories 3 and 4 drainage is always recommended; however, in many instances it is insufficient for resolution of the problem, making another intervention necessary, such as the use of fibrinolytics and/or surgery, either video-assisted or via thoracotomy. According to the aforementioned classification, category 4 carries the highest risk of poor

prognosis. The individual characteristics of each of the three variables used to distinguish risk categories were based on relevant bibliographic sources; however, sufficient data were not available to reach a consensus on how various clinical characteristics of patients – such as age, concomitant diseases, and evidence of a persistent inflammatory response despite adequate antibiotic therapy – may affect these risk categories. The expert panel has noted that, in the initial evaluation of a patient with parapneumonic pleural effusion, it is fundamental to classify the prognosis according to risk categories in order to guide the selection of the most appropriate treatment.

The present study seeks to provide evidence supporting the validity of this approach and the risk classification proposed for pleural infection.⁶ Likewise, it aims to carry out a rigorous evaluation of clinical variables and risk factors associated with category 4 (corresponding to poor prognosis) in patients with pleural infection in the Mexican population, particularly in referral hospitals that manage cases of high clinical complexity. A more precise understanding of these determinants constitutes an essential step toward optimizing medical care and reducing the frequency of adverse outcomes in this disease.

The objective of the study was to identify the clinical, biochemical, and radiological factors associated with risk category 4 for poor prognosis in patients with pleural infection, according to the ACCP classification.

Method

Study design, patients, setting, and period

This was a secondary analysis of a database from a cohort study of consecutive patients diagnosed with parapneumonic pleural effusion and community-acquired empyema, conducted between August 2011

Table 1. Risk categories for poor prognosis in patients with parapneumonic pleural effusion

Pleural space anatomy		Pleural fluid bacteriology		Pleural fluid chemistry	Category	Risk of poor prognosis	Drainage
A0 Minimal, free, less than 10 mm	and	Culture and Gram stain unknown	and	Cx pH unknown	1	Very Low	No
A1 Small to moderate, free, more than 10 mm but less than half the hemithorax	and	Negative Gram stain and culture	and	C0 pH greater than 7.20	2	Low	No
A2 Large, free, more than half, or loculated, or thickening and effusion	or	B1 Positive Gram stain and culture	or	C1 pH less than 7.20	3	Moderate	Yes
	or	B2 pus			4	High	Yes

Modified from Colice et al.⁶

and 2017 at the Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas in Mexico City. The cohort study was approved by the institutional research ethics committee under number C11-11, and a waiver of informed consent was granted. For the purposes of this study, cases of secondary empyema, tuberculous empyema, and cases of nosocomial pleural infection were excluded.

All patients underwent helical chest tomography and thoracentesis for the study of pleural fluid within the first 24 hours after admission. Cases referred from another hospital who already had an endopleural drain in place did not undergo thoracentesis. The pleural fluid sample was obtained under aseptic conditions and processed according to a standardized protocol by the institution's laboratory. The macroscopic appearance of the pleural fluid was evaluated; the sample was then sent in sterile 20-ml syringes for culture of aerobic microorganisms, mycobacteria, and fungi. Likewise, the sample was systematically processed for cytological study and biochemical analysis, which included: cell differential, measurement of pH, lactate dehydrogenase (LDH), glucose, and proteins. In cases of empyema with viscous pleural fluid, the sample was sent only for microbiological study.

Parapneumonic pleural effusion was defined as one with exudate characteristics and cellularity with a predominance of polymorphonuclear neutrophils due to pneumonia.

The accepted criteria for the diagnosis of thoracic empyema, regardless of its origin, were:

- Frank pus at the time of thoracentesis, or the finding of microorganisms on Gram stain or culture, or all of the following positive tests in the pleural fluid: pH less than 7.2, glucose less than 60 mg/dl,

LDH greater than 1,000 IU/ml, more than 3 g/ml of protein, and total leukocytes of 15,000 cells/mm³.

- Physical signs such as fever, pleural effusion syndrome on physical examination of the thorax, pleural rub, tachypnea, antalgic positioning, or signs of local inflammation; radiological and laboratory findings compatible with a clinical picture suggestive of empyema.⁷

The outcome variable was risk category 4 for poor prognosis in parapneumonic pleural effusion. The independent variables were general and clinical characteristics (comorbidities, symptoms, exposures, time between symptom onset and diagnosis), characteristics on computed chest tomography such as effusion size (less than half the hemithorax or more than half the hemithorax), presence of pleural thickening (evidenced by diffuse pleural thickening, the split pleura sign, or ipsilateral volume loss), loculation and number of loculations, obesity (body mass index [BMI] > 30 kg/m²), and malnutrition (BMI < 18.5 kg/m² for women and < 20 kg/m² for men), time in days between the onset of symptoms and hospital admission, results of clinical and microbiological laboratory tests, referral from another hospital, and whether or not microorganisms were isolated from the pleural fluid. The results of selected clinical laboratory tests – such as leukocytes, neutrophils, lymphocytes, glucose, and albumin – were evaluated dichotomously according to different cutoff points shown in the results section.

Risk categories for poor prognosis in empyema were measured according to the ACCP criteria⁶ (Table 1). These consider the size of the pleural effusion and the bacteriological and chemical characteristics of the effusion fluid. According to the characteristics of each item, each patient's case was classified into one of four

categories. Category 1 referred to a small effusion (less than 10 mm thick on computed tomography in the decubitus position or measured by ultrasound), considered free. Risk category 2 corresponded to cases with a small-to-moderate effusion (> 10 mm thick but less than half the hemithorax), also considered free, with pH greater than 7.20 and a negative pleural fluid culture. Categories 1 and 2 carry a low risk of poor prognosis. Category 3 included effusions occupying more than half the hemithorax that were loculated, or that were associated with parietal pleural thickening, with positive Gram stain or pleural fluid cultures, pH less than 7.20, or glucose less than 60 mg/dl. When pus was obtained during thoracentesis, the case was classified as category 4. The risk of poor prognosis is considered high in categories 3 and 4, both of which indicated placement of thoracic drainage via an endopleural drain.⁶

Microbiological evaluation included pleural fluid samples for Gram stain and culture of aerobic microorganisms, sputum, and blood cultures. The indication for performing each of the above studies was individualized according to the case, except for the culture of pleural fluid samples, for which an attempt was made to obtain material in all cases. Detection of respiratory pathogens was performed according to standardized methods and microbiological guidelines in the institution's laboratory, which holds certification for its methods.

All patients were treated with intravenous antibiotics based on a double regimen that included, in most instances, a beta-lactam and another agent to cover anaerobes, such as clindamycin or metronidazole, or piperacillin/tazobactam, administered intravenously throughout the hospital stay and/or until completing four weeks of treatment. In all cases in which pus was obtained at the time of thoracentesis or in cases of parapneumonic effusion (PPE) with pH < 7.2, an endopleural drain was placed for cavity drainage. Intrapleural fibrinolytics were not used in any case, as this treatment was unavailable at the institution during the study period. If satisfactory drainage was not documented or if the patient failed to improve clinically or radiographically, the attending pulmonologist assessed, together with the thoracic surgeon, the decision to perform surgical treatment, the approach technique for which was defined by the surgeon.

Statistical analysis

The analysis was performed using the STATA statistical software package, version 17 (StataCorp LP, College Station, TX, USA).

Descriptive statistics were performed for the clinical characteristics of the studied sample. Continuous variables were expressed as median (interquartile range [IQR] 25-75) and discrete, dichotomous, and polytomous variables as frequencies and percentages. For the comparative analysis, patients were grouped according to their ACCP risk classification, contrasting those classified in categories 1, 2, and 3 with those in category 4. The decision to group categories 1 and 2 with category 3 was based on the small number of cases in the low-risk groups in order to contrast them with those classified in category 4.

Comparisons between two groups (category 3 vs. category 4) were performed using the chi-square test for dichotomous and polytomous discrete variables, and non-parametric statistics using the Mann-Whitney U test for continuous variables.

The measure of risk was evaluated by calculating the odds ratio (OR) using logistic regression models, in which the dependent variable was risk category 4, and the clinical variables were the independent variables. A multivariate model for risk category 4 was developed, evaluated through goodness-of-fit tests, specificity, and multicollinearity.

To measure the association between risk category 4 and surgical treatment and mortality, these latter two were treated as dependent variables.

ORs were reported as both crude and adjusted for each variable, with a 95% confidence interval (95% CI) and significance level (p) considered significant if < 0.05.

Results

A total of 208 patients were included, of whom 100 (48.1%) corresponded to category 4, and 108 (51.9%) to category 3, the latter group including five cases from category 2 and one from category 1 for poor prognosis.

The median age was 48 years (IQR: 37-60) for the total population, with no significant differences between groups (51 years in category 4 vs. 47 in category 3; $p = 0.2071$). The majority of patients were male (73.1%), with a similar distribution between groups (78 vs. 68.5%; $p = 0.123$).

Regarding exposure history, 64.4% reported current or past smoking, with a median smoking index of 5.5 (IQR: 2-17), with no significant differences between groups. The prevalence of alcoholism was 39.4%, and illicit drug use was uncommon (5.3%), with no statistically significant differences between categories. Exposure to wood smoke was reported in 38.5% of cases, with a similar exposure index in both groups ($p = 0.7209$).

Among comorbidities, *diabetes mellitus* was significantly more frequent in category 4 (46.0 vs. 31.5%; $p = 0.032$). Obesity showed a trend toward higher frequency in category 3 (29.6 vs. 18.0%; $p = 0.050$), though without reaching statistical significance. No relevant differences were observed in the prevalence of systemic arterial hypertension or cancer.

A total of 57.2% of patients were referred from another hospital, with no significant differences between groups ($p = 0.179$). However, the time between symptom onset and admission to the institute was significantly longer in category 4 (median: 30 days vs. 16 days; $p = 0.0046$), and a greater percentage of these patients had more than 15 days of symptomatic evolution at the time of admission (79.0 vs. 50.9%; $p < 0.001$).

Surgical treatment was more frequent in category 4 patients (64.0 vs. 46.3%; $p = 0.010$), and a significant difference was also observed in the length of hospital stay (median: 19 vs. 18 days; $p = 0.0428$). Overall mortality was 5.8%, with no significant differences between groups (7.0 vs. 4.6%; $p = 0.464$) (Table 2).

Regarding laboratory parameters, leukocytosis ($> 12,000/\text{mm}^3$) was observed in 47.1% of patients. This alteration was significantly more frequent in category 3 compared to category 4 (54.6 vs. 39.0%; $p = 0.024$). Neutrophilia ($> 7,500/\text{mm}^3$) was present in 69.7% of the population, with no statistically significant differences between groups (64.0% in category 4 vs. 75.0% in category 3; $p = 0.085$).

Lymphocytopenia ($< 1,000/\text{mm}^3$) was observed in 22.6% of cases, with similar frequency between both groups ($p = 0.893$). In contrast, anemia was present in 47.1% of the total, being significantly more common in the category 4 group (55.0 vs. 39.8%; $p = 0.028$).

Hyperglycemia ($> 200 \text{ mg/dl}$) was more frequent in category 4 patients (23.0 vs. 11.1%; $p = 0.022$). Hypoalbuminemia ($< 3 \text{ g/dl}$) was a nearly universal finding in the population (88.0%), with no differences between groups ($p = 0.993$).

Finally, microbiological identification was achieved in 37.0% of all patients, with a significantly higher frequency in category 4 than in category 3 (52.0 vs. 23.2%; $p < 0.001$) (Table 3).

In the imaging and clinical evaluation of pleural effusion, 81.7% of patients ($n = 170$) were found to have loculated effusion, while 18.3% ($n = 38$) had free effusion. The number of loculations was variable: 78 patients (37.5%) had a single loculation, 52 (25.0%) had two loculations, 29 (13.9%) had three, 10 (4.8%) had four, and one (0.5%) had five loculations. In total, 44.2% ($n = 92$) of patients had effusions with two or more loculations.

Pleural thickening was documented in 180 cases (86.5%), and macroscopic presence of pus in the pleural cavity was identified in 100 patients (48.1%).

Regarding the risk classification for poor prognosis, the majority of patients were distributed in categories 3 and 4, with 102 (49.0%) and 100 (48.1%) cases, respectively. Only 6 patients (2.9%) were classified in low-risk categories (categories 1 and 2) (Table 4).

Bivariate logistic regression was used to explore the association between various clinical variables and classification into risk category 4 for poor prognosis in patients with parapneumonic pleural effusion, and empyema was explored.

It was found that a time greater than 15 days between symptom onset and admission to the institute was significantly associated with a higher probability of belonging to category 4 (OR: 3.63; 95% CI: 1.97-6.68; $p < 0.001$). Likewise, having a diagnosis of diabetes (OR: 1.85; 95% CI: 1.05-3.26; $p = 0.032$), anemia (OR: 1.85; 95% CI: 1.06-3.21; $p = 0.029$), glucose $> 200 \text{ mg/dl}$ (OR: 2.39; 95% CI: 1.12-5.11; $p = 0.025$), presence of more than two loculations in the effusion (OR: 2.54; 95% CI: 1.45-4.47; $p = 0.001$), pleural thickening (OR: 6.86; 95% CI: 2.29-20.56), and positive microbiological identification (OR: 3.60; 95% CI: 1.98-6.52; $p < 0.001$) were also significantly associated with this higher-risk category.

On the other hand, a leukocyte count $> 12,000/\text{mm}^3$ was inversely associated with category 4 (OR: 0.53; 95% CI: 0.31-0.92; $p = 0.025$), suggesting a lower probability of belonging to this category in the presence of leukocytosis.

Variables such as age, male sex, smoking, wood smoke exposure, systemic arterial hypertension, obesity, hypoalbuminemia, lymphocytopenia, and neutrophilia did not show statistically significant associations with risk category 4 ($p > 0.05$) (Table 5).

A multivariate logistic regression analysis was performed to identify clinically significant variables associated with membership in risk category 4 for poor prognosis in patients with parapneumonic pleural effusion and empyema. The results showed that a time greater than 15 days between symptom onset and hospital admission remained a strong independent predictor, with an OR of 4.13 (95% CI: 2.01-8.48; $p < 0.001$). Likewise, hyperglycemia (glucose $> 200 \text{ mg/dl}$) was significantly associated with category 4 (OR: 2.93; 95% CI: 1.21-7.11; $p = 0.017$), as was the presence of more than two loculations in the effusion (OR: 2.42; 95% CI: 1.25-4.67; $p = 0.009$), pleural thickening (OR: 4.82; 95% CI: 1.42-16.32), and

Table 2. General characteristics and exposure history of the study population, by group, according to category 4 vs. category 3 risk for poor prognosis

Variable	Total population n = 208	Category 4 n = 100 (48.1%)	Category 3* n = 108 (51.9%)	p
Age, years [†]	48 (37-60)	51 (39-61)	47 (36-57)	0.2071
Male sex	152 (73.1%)	78 (78%)	74 (68.5%)	0.123
Current or past smoking	134 (64.4%)	66 (66%)	68 (63%)	0.648
Smoking index [†]	5.5 (2-17)	5.6 (2-20)	5 (2-14)	0.2266
Alcoholism	82 (39.4%)	43 (43.0%)	39 (36.1%)	0.310
Wood smoke exposure	80 (38.5%)	37 (37.0%)	43 (39.8%)	0.675
Exposure index, hours/year	38 (14-80)	38 (12-80)	36 (15-78)	0.7209
Illicit drug use	11 (5.3%)	6 (6.0%)	5 (4.6%)	0.659
Diabetes	80 (38.5%)	46 (46.0%)	34 (31.5%)	0.032
Systemic arterial hypertension	52 (25%)	26 (26.0%)	26 (24.07%)	0.749
Obesity	50 (24.04%)	18 (18.0%)	32 (29.6%)	0.050
Cancer	4 (1.9%)	1 (1.0%)	3 (2.8%)	0.351
Transfer from another hospital	119 (57.2%)	62 (62.0%)	57 (52.3%)	0.179
Antibiotic prior to hospital admission	154 (74%)	76 (76%)	78 (72.2%)	0.535
Time in days between symptom onset and admission to the institute [†]	25 (12-38)	30 (17-38)	16 (10-39)	0.0046
Time between symptom onset and admission to the institute > 15 days	134 (64.4%)	79 (79.0%)	55 (50.9%)	0.000
Surgical treatment	114 (54.1%)	64 (64.0%)	50 (46.3%)	0.010
Hospital stay, days [†]	18 (14-26)	19 (14-30)	18 (13-24)	0.0428
Death	12 (5.8%)	7 (7.0%)	5 (4.6%)	0.464

*Includes 1 case from category 1 and 5 cases from category 2.

[†]Median (interquartile range).**Table 3.** Selected clinical laboratory results for the study population and by group, according to category 4 vs. category 3 risk for poor prognosis

Variable	Total population n = 208	Category 4 n = 100 (48.1%)	Category 3* n = 108 (51.9%)	p
Leukocytes > 12,000/mm ³	98 (47.1%)	39 (39.0%)	59 (54.6%)	0.024
Neutrophils > 7,500/mm ³	145 (69.7%)	64 (64.0%)	81 (75.0%)	0.085
Lymphocytes < 1,000 mm ³	47 (22.6%)	23 (23.0%)	24 (22.2%)	0.893
Anemia [†]	98 (47.1%)	55 (55.0%)	43 (39.8%)	0.028
Glucose > 200 mg/dl	35 (16.8%)	23 (23.0%)	12 (11.1%)	0.022
Albumin < 3 g/dl	183 (88.0%)	88 (88.0%)	95 (88.0%)	0.993
Microbiological identification	77 (37.0%)	52 (52.0%)	25 (23.2%)	0.000

*Includes 1 case from category 1 and 5 cases from category 2.

[†]Anemia according to WHO cutoff points: women ≤ 11.9 g/dl, men ≤ 12.9 g/dl.

Table 4. Characterization of the type of pleural effusion/empyema

Variable	Total population n = 208
Free	38 (18.3%)
Loculated	170 (81.7%)
Number of loculations	
0	38 (18.3%)
1	78 (37.5%)
2	52 (25.0%)
3	29 (13.9%)
4	10 (4.8%)
5	1 (0.5%)
Two or more loculations	92 (44.2%)
Pleural thickening	180 (86.5%)
Pus	100 (48.1%)
Risk category	
1	1 (0.48%)
2	5 (2.4%)
3	102 (49.0%)
4	100 (48.1%)

positive microbiological identification (OR: 2.99; 95% CI: 1.57-5.71; $p = 0.001$).

In contrast, age and sex did not show a statistically significant association in the adjusted model (Table 6).

Of the total patients with parapneumonic pleural effusion or empyema, 114 of 208 (54.8%) required surgical intervention as part of their management. The most frequent procedure was lavage and decortication via thoracotomy, performed in 105 patients (92%), followed by open pleurotomy in 7 cases (6.3%) and video-assisted thoracoscopy in 2 patients (1.7%).

The median time between hospital admission and the performance of surgery was 9 days (IQR: 5-14.5). Subsequently, the time between surgery and hospital discharge had a median of 10 days (IQR: 7-20) (Table 7).

The association between death and category 4, as well as between surgery and category 4, was also evaluated, considering the latter as an independent variable in both analyses. An odds ratio (OR, 95% CI) of 1.55 (0.48-5.05) and 2.06 (1.18-3.60) was found, respectively. Similarly, surgery was associated with a lower probability of death, with an OR (95% CI) of 0.57 (0.17-1.86).

Discussion

Main findings

Our results revealed that a time greater than 15 days between symptom onset and hospital admission,

hyperglycemia at admission (glucose > 200 mg/dl), presence of more than two loculations in the effusion, pleural thickening, and positive microbiological identification in the pleural fluid were significantly associated with risk category 4 for poor prognosis.

In additional analyses, classification in ACCP category 4 was associated with a higher probability of requiring surgical intervention, which is consistent with its clinical definition as a more advanced stage of pleural infection. In contrast, while a trend toward higher mortality was observed in patients classified in category 4, this association did not reach statistical significance, which may be attributed to the sample size, the clinical heterogeneity of the patients, and the timely implementation of more aggressive therapeutic strategies in this group. Notably, surgery was associated with a lower probability of death, although without statistical significance – a finding that should be interpreted with caution due to the observational nature of the study and the possible indication bias. Taken together, these results suggest that, in our cohort, category 4 identifies patients with greater clinical complexity and the need for invasive management, without necessarily translating into a proportional increase in mortality, which may reflect the impact of timely and multidisciplinary therapeutic management.

Comparison with prior studies

Given that all cases in our cohort corresponded to advanced pleural infection, it is clinically relevant to identify associated factors that allow anticipating its course. Unlike previous studies that have proposed markers such as C-reactive protein > 100 mg/l, platelets > 400,000/ μ l, albumin < 3 g/dl, sodium < 130 mmol/l, and substance abuse as predictors of progression to pleural infection in the context of pneumonia,^{1,2} our analysis highlights other variables with significant associations, such as diabetes and hyperglycemia > 200 mg/dl. This finding reveals the possible value of hyperglycemia and diabetes as early risk indicators in patients with complicated pneumonia. The association between hyperglycemia (glucose > 200 mg/dl), to our knowledge, has not been reported in patients with pleural infection; however, scientific evidence exists that hyperglycemia produces immune dysfunction and, consequently, greater susceptibility to infections, which could explain its association with more severe forms of the disease.⁸ This is reflected in our sample, where diabetes was more frequent in high-risk patients, and hyperglycemia was an independent predictor of complications.

Table 5. Association between risk category 4 and selected clinical variables in patients with parapneumonic pleural effusion and empyema*

Variables	OR	95% CI	p
Age	1.01	0.99-1.03	0.185
Male sex	1.63	0.87-3.04	0.125
Transfer from another hospital	1.46	0.84-2.54	0.180
Current or past smoking	1.14	0.65-2.02	0.648
Wood smoke exposure	0.89	0.51-1.55	0.677
Arterial hypertension	1.11	0.59-2.08	0.749
Diabetes	1.85	1.05-3.26	0.032
Obesity	0.52	0.27-0.1.0	0.052
Time between symptom onset and the moment of admission to the institute > 15 days	3.63	1.97-6.68	0.000
Antibiotic prior to hospital admission	1.22	0.65-2.27	0.535
Leukocytes > 12,000/mm ³	0.53	0.31-0.92	0.025
Neutrophils > 7,500/mm ³	0.59	0.33-1.08	0.086
Lymphocytes < 1,000 mm ³	1.04	0.55-2.0	0.893
Anemia	1.85	1.06-3.21	0.029
Glucose > 200 mg/dl	2.39	1.12-5.11	0.025
Albumin < 3 g/dl	1.00	0.44-2.31	0.993
Loculations ≥ 2	2.54	1.45-4.47	0.001
Pleural thickening	6.86	2.29-20.56	0.001
Microbiological identification	3.60	1.98-6.52	0.000

*Bivariate logistic regression.

95% CI: 95% confidence interval; OR: odds ratio.

Table 6. Multivariate analysis of risk category 4 and selected clinical variables in patients with parapneumonic pleural effusion and empyema*

Variables	OR	95% CI	p
Age	1.00	0.98-1.03	0.646
Sex	1.34	0.64-2.79	0.441
Time between symptom onset and admission to the institute > 15 days	4.13	2.01-8.48	< 0.001
Glucose > 200 mg/dl	2.93	1.21-7.11	0.017
Loculations ≥ 2	2.42	1.25-4.67	0.009
Pleural thickening	4.82	1.42-16.32	0.012
Microbiological identification	3.02	1.55-5.86	0.001

*Multivariate logistic regression.

95% CI: 95% confidence interval; OR: odds ratio.

Table 7. Frequency and type of surgery performed in patients with parapneumonic pleural effusion

Variable	n (%)
Surgery	114/208 (54.8%)
Type of surgery	
Lavage and decortication via thoracotomy	105/114(92%)
Open pleurotomy	7/114 (6.3%)
Lavage and decortication via video-assisted thoracoscopy	2/114 (1.7%)
Time between patient admission and surgery, in days. Median (IQR)	9 (5-14.5)
Time between surgery and discharge, in days. Median (IQR)	10 (7-20)

IQR: interquartile range.

These results suggest that glycemic control may play an important role in the course of complicated pneumonia, and support the need to explore, in prospective studies, the impact of hyperglycemia as a prognostic marker in pleural infection.

With respect to smoking, although a higher frequency of this habit has been reported in patients with parapneumonic pleural effusion, a direct relationship with pleural infection has not been established.² In our study, the frequency of current or past smoking was high; however, no significant differences were observed between groups, nor was an association with risk category 4 found.

Positive microbiological identification, more frequent in patients classified in risk category 4, could reflect a higher bacterial load or the presence of particularly virulent pathogens, which would contribute to a more severe clinical course. Although in other contexts, identification of the etiological agent allows optimization of antibiotic treatment, in this study it may be acting as an indirect marker of advanced disease or more aggressive infection.

For its part, the presence of multiple loculations is associated with a more organized phase of the effusion and greater pleural compromise – conditions that hinder effective drainage, increase the need for invasive interventions, and justify the worse prognosis observed.⁵ The evidence of multiple loculations constitutes a marker of advanced disease. Its association with risk category 4 highlights the utility of computed chest tomography or thoracic ultrasound for risk stratification and planning of timely surgical interventions. More than 80% of our patients presented with loculated effusions, and nearly half had two or more loculations. At the time this study was conducted, the use of thoracic ultrasound was not as frequent at our institution as it is now, and we wish to emphasize that it is a highly sensitive method for identifying loculated pleural effusion.

Clinical implications

Despite advances in the diagnosis and treatment of pleural infection, a considerable proportion of patients progress to complicated forms, requiring surgical interventions, prolonged hospital stays, and, in some cases, presenting unfavorable outcomes, as was the case in the present study, in which we found that nearly half of the population was classified in risk category 4, corresponding to a clinical profile associated with poor prognosis according to the ACCP classification.⁶ This high proportion reflects the complexity of cases referred to

our referral center and the frequency with which patients are admitted in advanced stages of the disease and highlights the importance of early detection and timely management of empyema, as well as the relevance of metabolic and anatomical factors in the prognosis of the disease.

Delayed medical care is associated with greater complexity of pleural effusion and a worse prognosis in patients with empyema, as it allows progression of the inflammatory process and formation of multiple loculations, which complicates drainage and treatment, increasing morbidity and the need for more invasive surgical intervention, such as thoracotomy or video-assisted thoracoscopy,⁹ as occurred in more than half of our cases that required surgical intervention, with the thoracotomy-based pleural lavage and decortication technique predominating, and where the median time between admission and surgery was 9 days, indicating a window of opportunity that may be optimized in future care protocols.

These results reinforce the importance of establishing early diagnosis strategies and timely referral, as well as standardized radiological and laboratory evaluation protocols to guide early therapeutic interventions. They thus suggest that the use of clinical risk classification systems may prove useful in daily clinical practice for predicting clinical course and planning the management of this condition.

Strengths, limitations, and future directions

This study contributes relevant evidence, as it is one of the few series developed in Latin America that explores factors associated with poor prognosis in patients with empyema, using a representative sample from a national referral center. The inclusion of broad clinical, biochemical, and radiological characterization allowed for a comprehensive analysis of risk factors, which constitutes a methodological strength. Furthermore, the application of multivariate analysis facilitated the identification of independent associations, thereby strengthening the validity of the conclusions. One of the most relevant findings of this study was the association between a symptom duration of more than 15 days and a higher risk of belonging to the poor-prognosis category 4. Although the observational design of the study does not allow for a conclusive causal relationship to be established, this finding meets several of the criteria proposed by Bradford Hill¹⁰ to support a causal inference, such as temporality, strength of association,

biological plausibility, and coherence with existing knowledge. In this sense, the results suggest a probable causal relationship between delayed care and progression to severe forms of empyema. This evidence reinforces the need to strengthen referral and counter-referral networks, as well as to promote greater clinical suspicion and timely intervention at the primary and secondary levels of medical care.

This study has several limitations that should be considered when interpreting the results. Although the sample was relatively large, it was derived from a single center, which may limit the generalizability of findings to other populations or clinical settings. The lack of assessment of variables such as specific inflammatory markers or sequential imaging studies limits a deeper understanding of the dynamics of empyema. Finally, although significant associations were identified, causality cannot be established due to the observational design of the study. Future multicenter prospective studies could validate these findings and explore the impact of specific interventions targeting the identified risk factors. It would also be valuable to investigate the role of inflammatory biomarkers and sequential imaging follow-up to improve the prediction of complications and response to treatment.

Conclusions

The results of this study underscore the importance of early diagnosis and management of empyema to improve prognosis. The identification of factors such as delayed admission, hyperglycemia, and the anatomical complexity of the effusion (more than two loculations) can help stratify patient risk and guide more aggressive or earlier interventions, such as timely surgical management. Furthermore, the high frequency of microbiological identification among patients in risk category 4 suggests the need to optimize diagnostic techniques to rapidly identify causative agents and adjust antimicrobial treatment more precisely. Our findings contribute additional evidence regarding the clinical congruence and prognostic utility of the ACCP 2000 classification in a Latin American cohort, suggesting that its risk categories align with clinical, biochemical, and radiological factors associated with greater severity, without constituting a formal external validation of the classification.

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Conflicts of interest

The authors declare that there are no financial or personal interests that could have influenced the work presented in this article.

Ethical considerations

Protection of persons and animals. The authors declare that no experiments were performed on humans or animals for this research.

Confidentiality, informed consent, and ethical approval. The authors have obtained approval from the Ethics Committee for the analysis of routinely obtained and anonymized clinical data; therefore, informed consent was not required. The relevant recommendations have been followed.

Statement on the use of artificial intelligence. The authors declare that they did not use any type of generative artificial intelligence for the writing of this manuscript.

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