



# Clinical significance of pleural effusions and association with outcome in patients hospitalized with a first episode of acute pericarditis

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## Abstract

The clinical significance of pleural effusions (PLEs) in the setting of acute pericarditis remains poorly investigated. We sought to identify predictive factors for PLEs and their association with the short- and long-term prognosis of patients with acute pericarditis. We enrolled 177 patients hospitalized with a first episode of acute pericarditis. In all cases an extensive clinical, biochemical, and diagnostic work-up to detect PLEs and establish etiological diagnosis was performed. All patients included were prospectively followed for a maximum of 18 months (median 12, range 1–18) and complications were recorded. PLEs were detected in  $n = 94$  cases (53.1% of the cohort; bilateral 53.2%, left-sided 28.7%, right-sided 18.1%) and were strongly associated with c-reactive protein (CRP) levels at admission ( $\rho = 0.328$ ,  $p < 0.001$ ). In multivariate logistic regression, independent predictors for PLEs were female gender (OR = 2.46, 95% CI 1.03–5.83), age (per 1-year increment OR = 1.030, 95% CI 1.005–1.056), CRP levels (per 1 mg/L increment OR = 1.012, 95% CI 1.006–1.019) and size of pericardial effusion (per 1 cm increment, OR = 1.899, 95% CI 1.228–2.935). Bilateral PLEs were associated with increased risk for in-hospital cardiac tamponade (OR = 7.52, 95% CI 2.16–26.21). There was no association of PLEs with new onset atrial fibrillation or pericarditis recurrence during long-term follow-up ( $\chi^2 = 0.003$ ,  $p = 0.958$ ). We conclude that PLEs are common in patients hospitalized with a first episode of acute pericarditis. They are related to the intensity of inflammatory reaction, and they should not be considered necessarily as a marker of secondary etiology. Bilateral PLEs are associated with increased risk of in-hospital cardiac tamponade, but do not affect the long-term risk of pericarditis recurrence.

**Keywords** Acute pericarditis · Pleural effusions · Prognosis · Secondary pericarditis · Imaging modalities · Cardiac tamponade

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## Introduction

The most common pericardial syndromes include acute pericarditis, either a first episode or subsequent recurrences, chronic pericardial effusion and constrictive pericarditis [1, 2]. The reported incidence of AP in North Italy is estimated at 27.7 cases/100.000 subjects per year, and according to our institutional experience it accounts for ~3% of overall admissions to the cardiology department [3–5]. In the most recent guidelines on the diagnosis and management of pericardial diseases, well-defined criteria for the diagnosis of acute pericarditis have been proposed for the first time, which is of paramount importance for both clinical and research purposes [3].

Despite this important step forward, several issues in the context of acute pericarditis remain still controversial or less well-explored. Among others, the clinical significance and prognostic importance of pleural effusions (PLEs) in acute pericarditis has been poorly investigated. There are scant (if any) data available on PLEs' incidence in this setting, or their etiology, associations with patients' clinical profile and prognostic impact [6, 7]. Notably, the presence of PLEs typically shifts diagnostic orientation towards secondary causes of pericarditis (such as autoimmune or neoplastic conditions), and often triggers unnecessary investigations and treatments.

In this work we have for the first time systematically recorded the presence of PLEs in patients hospitalized with a first episode of acute pericarditis, and investigated their relationships with clinical characteristics, with emphasis on the association with secondary (non-idiopathic) forms of acute pericarditis and overall impact on the short-term and long-term clinical outcome in this setting.

## Methods

### Study population

This was a prospective clinical study enrolling 177 treatment-naïve, consecutive patients hospitalized with a first episode of acute pericarditis between January 2010 and March 2017 at the 1st Cardiology Department, Hippokratia General Hospital, Athens Greece, which is a Referral Center for the Diagnosis and Treatment of Pericardial Diseases. The diagnosis of acute pericarditis was established according to the current recommendations [3, 8]. Exclusion criteria included history of recurrent pericarditis, concurrent myocardial involvement, pregnancy and lactation and history of chronic PLEs due to respiratory or other diseases. Patients with tuberculous pericarditis were

not included since these patients are referred to centers specialized in this disease upon diagnosis.

### Diagnostic work-up

Clinical and demographic data were recorded at baseline in all patients enrolled. According to the current guidelines' recommendations, diagnostic work-up included past medical history, thorough clinical examination, chest X-ray (standard posteroanterior and lateral projections), electrocardiogram, comprehensive echocardiography (including posterior views obtained bilaterally from the patients back to unveil PLEs) and routine blood tests including complete blood count, blood chemistry tests, hs troponin I and admission high-sensitivity C-reactive protein (CRP) as well as peak CRP levels determined by serial measurements every 48 h for the length of hospital stay. Moreover, serological screening for systemic autoimmune disorders and thyroid function tests was performed. In patients with elevated antinuclear antibody (ANA titers  $\geq 1:160$ ) or when the diagnosis of an autoimmune disease was suspected, a rheumatology consultation was performed.

For the requirements of the current study, chest computed tomography (CT) imaging was performed in all patients. In patients with PLEs, the amount of fluid was qualitatively assessed employing the method of Moy et al. [9]. Briefly, the amount of PLEs is estimated by CT imaging by dividing each hemithorax in four quartiles in its anteroposterior diameter at the midclavicular line. Effusions limited to the first quartile (0–25% of the anteroposterior diameter) were classified as small, those occupying 25–50% of the hemithorax were classified as moderate and finally those exceeding the second quartile (>50% of the hemithorax) as large. Separate measurements were performed for the right and left hemithorax and the atelectatic lung was excluded from the measurement.

### Treatment and follow-up protocol

The treatment protocol used in our clinic is elsewhere described [4]. In brief, according to the contemporary guidelines, non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine were administered as first-line treatment [3, 10, 11], whereas steroids were administered in the presence of a specific indication (e.g., autoimmune disease) and in cases of failure, intolerance or contraindication to NSAIDs. All patients included were prospectively followed up until the appearance of a first recurrence, for a maximum of 18 months (median 12, range 1–18), which is considered a critical period for pericarditis recurrences [3, 12]. Follow-up visits were scheduled at 1 and 3 months from the index episode and every 3 months thereafter. Patients were advised

to seek medical attention at any time, if symptoms compatible with recurrence appeared.

### Statistical analysis

Normally distributed continuous variables are presented as mean  $\pm$  standard deviation, while non-normally distributed as median [interquartile range]. Comparisons of characteristics between different groups of patients were performed using unpaired *t* test for 2 groups or ANOVA for 3 or more groups as appropriate. Categorical variables were compared using  $\chi^2$  test as appropriate. Correlations between continuous variables were assessed using bivariate analysis, and Pearson's *r* or Spearman's rho coefficient was estimated as appropriate. To test for independent predictors of PLEs a binary backwards logistic regression was used. The association between PLEs and in-hospital tamponade or new onset atrial fibrillation was explored in logistic regression models, while Cox regression analysis was used to evaluate the association of PLEs with pericarditis recurrence. A two-tailed *p* value  $< 0.05$  was considered statistically significant for all comparisons. Statistical package SPSS version 25.0 was used for statistical analysis.

### Results

Overall 177 patients are included in the study; their demographic and clinical characteristics are summarized in Table 1. A secondary cause of pericarditis was detected in 41 patients (23.2% of the entire cohort). The most common secondary etiology was malignancy (17 cases, 9.6% of the study population), with lung cancer being the most common etiology (7 patients). Other secondary causes included post cardiac injury syndrome in 14 cases (7.9% of the study population) and connective tissue diseases in 10 cases (5.6% of the study population, 8 cases of rheumatoid arthritis, 1 of systemic lupus erythematosus and 1 case of Sjögren's syndrome).

Among patients with acute pericarditis, more than half ( $n = 94$ , 53.1% of the overall cohort) had evidence of PLEs. Patients with PLEs were older and more frequently women (Table 1). PLEs were small in the majority of cases ( $n = 83$ , 88%), bilateral in 53.2%, left-sided only in 28.7%, and right-sided only in 18.1% of patients with PLEs. In cases without recurrences, 97% of PLEs regressed at 1 month during follow-up, and in all cases at 3 months. PLEs regressed at a later time as compared with pericardial effusion. Pleural fluid aspiration (thoracentesis) was performed in 8 patients for diagnostic purposes, and the aspirated fluid was exudate in all cases according to the current recommendations [13, 14]. Interestingly, PLEs were detected in nine patients in the absence of pericardial effusion. Echocardiography had

an excellent diagnostic accuracy independent of the effusion size (overall accuracy of 97.3%, and 97.0% for small PLEs). The diagnostic accuracy of chest X-ray was overall fair (72.3%), but poor for small PLEs (65.1%).

In the subgroup of patients with idiopathic acute pericarditis (77%,  $n = 136$ ), PLEs were detected in 71 (52.2%) patients:  $n = 36$  (26.5%) bilateral,  $n = 24$  (17.6%) left-sided only, and  $n = 11$  (8.1%) right-sided only. No association was found between PLEs and connective tissue disease ( $n = 10$ ,  $\rho = -0.171$ ,  $p = 0.346$ ), malignant tumors ( $n = 17$ ,  $\rho = 0.067$ ,  $p = 0.379$ ) or with the overall secondary etiology of acute pericarditis ( $n = 41$ ,  $\rho = -0.10$ ,  $p = 0.897$ ).

Overall, there was no difference in the proportion of patients with PLEs among those with the idiopathic (52.2%,  $n = 71$ ) or secondary (56.1%,  $n = 23$ ) forms of acute pericarditis ( $p = 0.722$ , by Fisher's exact test).

In bivariate analysis, presence of PLEs positively correlated with presence of PE ( $\rho = 0.150$ ,  $p = 0.046$ ), PE diameter ( $\rho = 0.239$ ,  $p = 0.003$ ) and admission CRP levels ( $\rho = 0.328$ ,  $p < 0.001$ ). Interestingly, bilateral and left-sided only PLEs are associated with significantly higher admission CRP levels compared to patients without PLEs (Fig. 1). There is a trend, albeit non-significant, for increased use of corticosteroids in the presence of PLEs ( $\rho = 0.125$ ,  $p = 0.098$ ).

### Multivariate analysis for predictors of pleural effusions

To search for predictors of PLEs in patients with a first episode of acute pericarditis, we performed a multivariate logistic regression with backwards elimination including age, gender, chest pain, pericardial rub, dyspnea, ST elevation, pericardial effusion size, ANA positivity (titer  $\geq 1:160$ ), secondary cause of acute pericarditis and corticosteroid treatment as independent variables in the model (*p* value for entry 0.05 and *p* value for removal 0.10). After adjustment for confounders, female gender, age, CRP admission levels, and pericardial effusion size are independently associated with the presence of PLEs (Table 2).

### Association of pleural effusion with in-hospital complications and recurrences

Next, we searched whether the presence of PLEs at admission predicts an adverse clinical outcome in patients with a first episode of acute pericarditis. Regarding in-hospital complications, bilateral PLEs were associated with increased incidence of cardiac tamponade in the study population (OR = 7.52, 95% CI 2.16–26.21,  $p = 0.002$ , Fig. 2A–B), which remains significant after adjustment for age, gender, and secondary causes of acute pericarditis (OR = 9.19, 95% CI 2.58–32.79,  $p = 0.001$ ). Interestingly only bilateral

**Table 1** Clinical characteristics of the study population

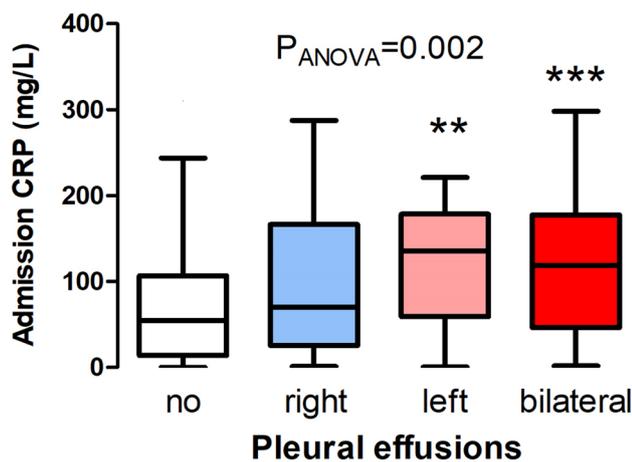
	All	With PLEs	Without PLEs	<i>p</i> value
<i>Participants, n (%)</i>	177	94 (53.1)	83 (46.9)	
Age (years)	58.5 ± 18.9	62.3 ± 18.5	53.8 ± 18.5	<b>0.006</b>
Male gender, <i>n (%)</i>	105 (59.3)	47 (50.0)	58 (69.9)	<b>0.009</b>
Smoking, <i>n (%)</i>	49 (27.7)	24 (25.5)	25 (30.1)	0.506
SBP (mmHg)	123.4 ± 16.5	121.5 ± 17.4	126.0 ± 15.0	0.099
DBP (mmHg)	77.8 ± 10.1	76.7 ± 10.7	78.9 ± 9.12	0.233
<i>Clinical presentation</i>				
Chest pain, <i>n (%)</i>	138 (77.9)	72 (76.5)	66 (79.5)	0.712
Fever, <i>n (%)</i>	79 (44.6)	48 (51.1)	31 (37.3)	0.071
Pericardial rub, <i>n (%)</i>	34 (19.2)	19 (20.2)	15 (18.1)	0.718
Dyspnoea, <i>n (%)</i>	92 (52.0)	60 (63.8)	32 (38.6)	<b>0.001</b>
<i>ECG findings</i>				
ST elevation, <i>n (%)</i>	36 (20.3)	12 (12.8)	24 (28.9)	<b>0.007</b>
Heart rate (bpm)	90.2 ± 16.1	91.1 ± 16.3	89.3 ± 15.8	0.462
<i>Imaging findings</i>				
Pericardial effusion, <i>n (%)</i>	148 (83.6)	84 (89.4)	64 (77.1)	<b>0.041</b>
Size* (cm)	1.7 [1.0–2.4]	1.9 [1.3–2.5]	1.4 [0.7–2.2]	<b>0.002</b>
Pleural effusion, <i>n (%)</i>	94 (53.1)	94 (100)	0 (0)	
<i>Localization, n (%)</i>				
No	83 (46.9)	0 (0)	0 (0.0)	
Right	17 (9.6)	17 (18.1)	0 (0.0)	
Left	27 (15.3)	27 (28.7)	0 (0.0)	
Bilateral	50 (28.2)	50 (53.2)	0 (0.0)	
<i>Size, n (%)</i>				
Small	83 (46.9)	83 (88.3)	0 (0.0)	
Moderate	10 (5.6)	10 (10.6)	0 (0.0)	
Large	1 (0.6)	1 (1.1)	0 (0.0)	
<i>Diagnostic modality</i>				
Computed tomography, <i>n (%)</i>	94 (53.1)	94 (100.0)	0 (0.0)	
Echocardiography, <i>n (%)</i>	89 (50.3)	89 (94.7)	0 (0.0)	
Chest X-ray, <i>n (%)</i>	42 (23.7)	42 (44.7)	0 (0.0)	
<i>Biochemical data</i>				
CRP admission* (mg/L)	73.8 [28.6–152.3]	116 [46.7–177.0]	52.7 [3.8–104.4]	<b>0.001</b>
CRP peak (mg/L)*	89.9 [35.2–161.9]	125.0 [60.6–185.4]	57.2 [16.6–125.2]	<b>0.001</b>
ESR (mm/h)	71.1 ± 36.2	77.7 ± 34.5	61.8 ± 37.4	0.103
Creatinine (mg/dL)	1.13 ± 0.87	1.20 ± 1.05	1.06 ± 0.57	0.301
Positive ANA, <i>n (%)</i>	27 (15.2)	15 (15.9)	12 (14.5)	0.980
<i>Secondary cause, n (%)</i>	41 (23.2)	23 (24.5)	18 (21.7)	0.723
Malignancy, <i>n (%)</i>	17 (9.6)	12 (12.8)	5 (6.0)	0.200
PCIS, <i>n (%)</i>	14 (7.9)	7 (7.4)	7 (8.4)	0.999
Autoimmune disease, <i>n (%)</i>	10 (5.6)	4 (4.3)	6 (7.2)	0.519

PLEs pleural effusions, SBP systolic blood pressure, DBP diastolic blood pressure, ECG electrocardiogram, CRP c-reactive protein, ESR erythrocyte sedimentation rate, ANA antinuclear antibodies, PCIS post cardiac injury syndrome

\*Non-normally distributed variables are expressed as median [interquartile range]

PLEs are associated with the risk of tamponade but not left- or right-sided only PLEs (Fig. 2B). Finally, there was no association between PLEs and new onset atrial fibrillation (Fig. 2C).

With respect to the long-term outcome, recurrent pericarditis developed in 70 out of 177 patients (39.5%) during the follow-up period. In survival analysis presence of PLEs is not associated with the risk of pericarditis recurrence



**Fig. 1** Association between admission c-reactive protein (CRP) levels and pleural effusions subtypes. \*\* $p < 0.01$ ; \*\*\* $p < 0.001$  vs no pleural effusions group

during the clinical follow-up (log-rank  $\chi^2 = 0.003$ ,  $p = 0.958$ , Fig. 2D).

## Discussion

To the best of our knowledge this is the first prospective study assessing the clinical and prognostic significance of PLEs in patients hospitalized with a first episode of acute pericarditis. We report the incidence of PLEs, associations with the patient profile, and their impact on clinical outcomes. PLEs are detected in more than half (53.1%) of acute pericarditis patients. Age, female gender, PE size and admission CRP levels are independently associated with PLEs in this cohort. PLEs' prevalence did not differ between idiopathic and secondary acute pericarditis forms, and therefore there is no rationale to prompt unnecessary diagnostic tests in these patients, unless there are other clinical, laboratory or imaging findings suggesting a secondary cause. Importantly bilateral PLEs are associated with increased risk of in-hospital cardiac tamponade, but they did not affect the long-term risk for pericarditis recurrence.

Our study reports some unique information on PLEs in the context of acute pericarditis, since this is an issue

that has not been systematically studied. In the most recent guidelines, reference to PLEs has been made only in the specific context of acute pericarditis due to post cardiac injury syndrome, where PLEs are included among the diagnostic criteria and observed in 12–25% of cases [7, 15]. Nevertheless, no information is provided on the significance of PLEs in the whole spectrum of patients with acute pericarditis [3]. Data in the published literature on PLEs in acute pericarditis are limited, and found mainly in older clinical reports, which employed chest X-ray for their diagnosis [7]. In one study radiologic evidence of PLEs appears in 4 out of 23 idiopathic acute pericarditis cases (17%) [16]. In two other reports including acute pericarditis patients with both idiopathic and secondary underlying etiologies, PLEs are found to be small (83%) and left-sided or bilateral in the great majority of cases [17, 18]. Finally, Brucato et al. in 61 patients with difficult-to-treat recurrent pericarditis (70.5% with idiopathic forms), report PLEs in 22 cases (36%) during the first attack [6]. Interestingly, only half of patients had PLE recurrence in the next attack of acute pericarditis, and no patient had PLE at the end of the follow-up (average 8.3 years).

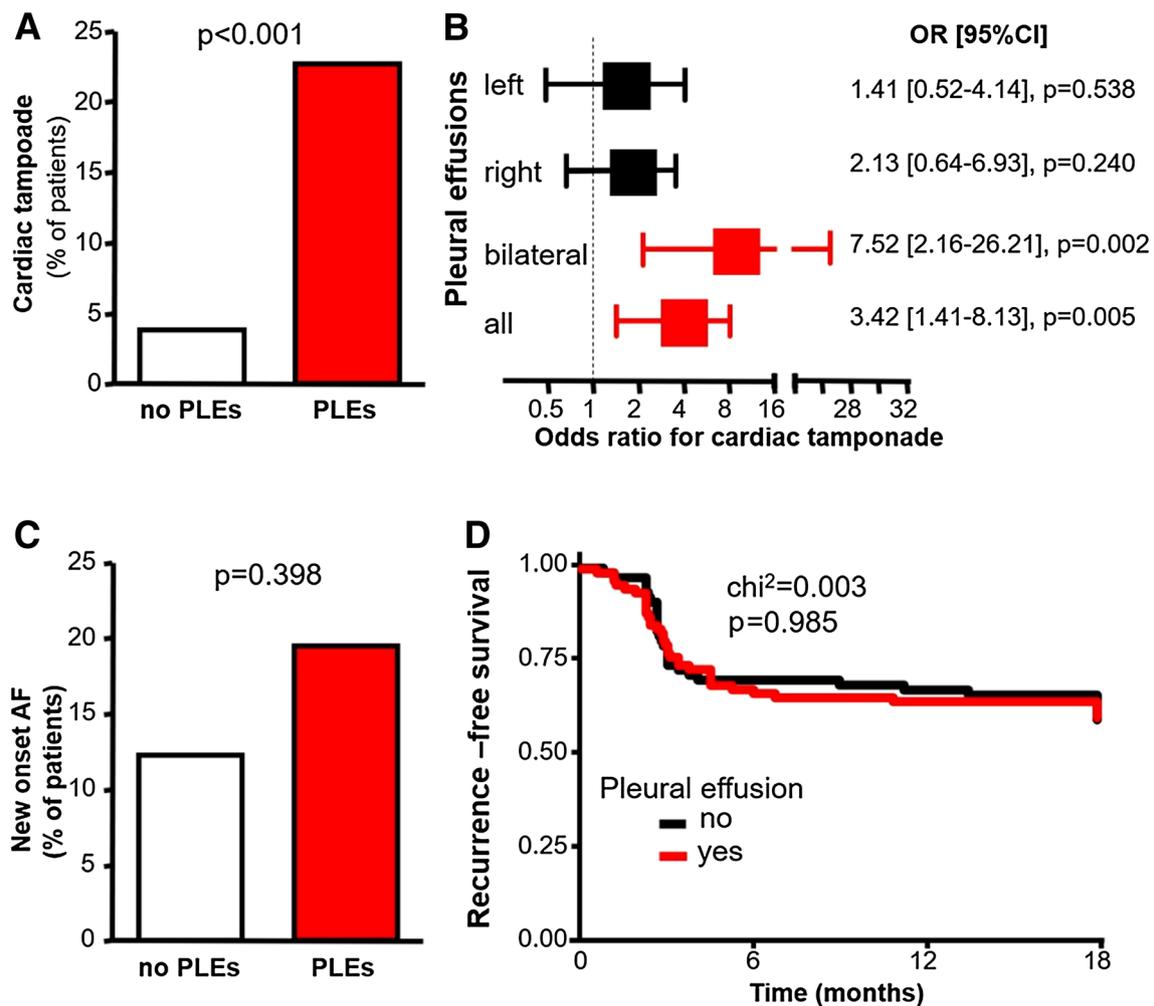
The present work has been conducted in a tertiary referral centre for pericardial diseases, and therefore the population includes more severe cases of acute pericarditis that require hospitalization. This may explain the higher prevalence of secondary acute pericarditis cases, as well as the higher rate of pericardial effusions and pericarditis recurrences in our population compared with previous reports [19–24]. By systematically investigating PLEs in the context of acute pericarditis, we report an incidence of 53.1% in this setting, which is in line with previous reports [25]. PLEs are mostly bilateral (53.2%), and small in size (88%) and usually regress within a month of treatment. In our experience integrative cardiopulmonary ultrasound approach had an excellent overall diagnostic performance (AUC = 97.3%) for PLEs (5 out of 94 non-detected PLEs compared to chest CT), but the diagnostic performance of chest X-ray is poor for small PLEs (AUC = 65.1%, overall 52 non-detected PLEs compared to chest CT), which highlights the need to not rely solely on chest X-ray for PLEs diagnosis.

Female gender, older age, larger pericardial effusion size and higher admission CRP levels are all independently

**Table 2** Multivariate logistic regression for predictors of pleural effusions in patients with a first episode of acute pericarditis

Variable	Beta	OR	95% CI	$p$ value
Female sex	0.900	2.460	1.031 5.828	<b>0.042</b>
Age (years) (per 1-year increment)	0.030	1.030	1.005 1.056	<b>0.019</b>
Admission CRP (mg/L) (per 1 mg/L increment)	0.012	1.012	1.006 1.019	<b>0.0001</b>
Max. diameter pericardial effusion (per 1 cm increment)	0.641	1.899	1.228 2.935	<b>0.004</b>
Pericardial rub	− 1.002	0.367	0.119 1.129	0.081

CI confidence interval, CRP c-reactive protein, Max maximum, OR odds ratio



**Fig. 2** **a** Relationship between pleural effusions (PLEs) and the incidence of cardiac tamponade in the study population. **b** Forest plot for the association between PLEs subtypes and the odds ratio (OR) with 95% confidence interval (95% CI) for in-hospital cardiac tamponade,

**c** Association between PLEs and the incidence of new onset atrial fibrillation (AF). **d** Kaplan–Meier curves for pericarditis recurrence according to the presence/absence of PLEs at initial hospital admission.  $P$  values from  $\chi^2$  in **a** and **c**

associated with the presence of PLEs in this cohort. In contrast, secondary etiologies including malignancies and autoimmune disorders are not related with PLEs. This finding is important because in everyday clinical practice there is a trend to attributing PLEs to the presence of an underlying secondary disease, which triggers an extensive and often unnecessary diagnostic work-up [3, 26].

From a mechanistic point of view, the intensity of the inflammatory response is presumably related with the extension of pericardial inflammation to the surrounding pleura. This could justify the relationship between higher CRP levels and bilateral or left-sided PLEs. Another possible explanation is that the inflammatory process leading to pericarditis simultaneously injures the pleura. Our finding that bilateral PLEs are associated with increased risk of in-hospital cardiac tamponade, suggests that these

patients warrant close clinical monitoring. In contrast, PLEs are not associated with pericarditis recurrence in the long-term, which is considered the most problematic complication of pericarditis [1]. Finally, a relationship of PLEs and the development of constrictive pericarditis cannot be excluded since the follow-up period was limited to 18 months.

Certain limitations relevant to this study should be acknowledged. This is a prospective, single-centre observational study reporting on local institutional clinical practice, and therefore the usual limitations of cohort studies related to confounding and selection bias may apply. Moreover, since our hospital is a referral centre for pericardial diseases for a large urban area, the population studied reflects more severe cases of acute pericarditis requiring hospitalization. As a result, our findings may not be directly applicable to

the whole spectrum of patients with a first attack of acute pericarditis.

In conclusion, with the adoption of sensitive imaging techniques such as chest CT and comprehensive echocardiography, PLEs are reported in ~53% of acute pericarditis patients. Presence of PLEs is related to the intensity of inflammatory response, and is not associated with a secondary etiology of acute pericarditis. Importantly, we report an association of bilateral PLEs and the short-term in-hospital risk of cardiac tamponade, but not with pericarditis recurrence at long-term; conclusively, the presence of PLEs should be interpreted as a marker of intense local inflammation, and although extensive diagnostic work-up is not always justifiable, patients should be closely monitored for signs of cardiac tamponade.

### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Human and animal rights** All procedures performed in this study were in accordance with the ethical standards of the institutional or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

**Informed consent** All patients enrolled gave their informed consent for participating in the study.

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