Original research

Age-stratified patterns in clinical presentation, treatment and outcomes in acute pericarditis: a retrospective cohort study

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ABSTRACT

Background There are limited data on acute pericarditis according to different age groups. The aim of this study is to investigate the role of age-related features in clinical characteristics, management, and outcomes of acute pericarditis, with a focus on the geriatric population.

Methods Patients with a first episode of acute pericarditis were consecutively enrolled between January 2014 and June 2022, and divided into four groups according to age (G1: 18–35 years; G2: 35–55 years; G3: 55–75 years; G4: >75 years). Clinical characteristics and medical therapy were recorded at baseline, and during follow-up.

Results A total of 471 patients (median age 56.3 (IQR 33–73) years, 32.3% women) were included. Younger age (G1-G2-G3) was associated with a higher frequency of chest pain, pericardial rubs (p<0001), ECG changes (p=0.002) and were more commonly treated with colchicine (p<0.001), and non-steroidal anti-inflammatory drugs (p=0.006). Older patients (G4) depicted more commonly dyspnoea, pericardial/pleural effusion (p=0.007) and were more often treated with corticosteroids (p=0.037). A secondary cause of pericarditis was detected in 128/471 (27.2%) patients. Older patients were more commonly hospitalised and had a complicated course with new-onset atrial fibrillation (p<0.001) and cardiac tamponade (p=0.005), compared with younger patients, who presented more recurrences (respectively G1: 43.0%, G2: 34.7%, G3: 28.2% and G4: 16.2%; p<0.001). After multivariable analysis, younger age remained the strongest independent predictor for recurrences (HR 3.23, 95% CI 1.81 to 5.58, p<0.001).

Conclusion Older age is associated with less recurrences of pericarditis, but more severe complications with need for hospitalisation.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ There is limited evidence on age-related features of pericarditis.
⇒ Current European guidelines only provide expert opinions to guide the management of the elderly.

WHAT THIS STUDY ADDS

⇒ The study emphasises the crucial role of age in the clinical presentation, management and outcome of a first attack of pericarditis.
⇒ Young patients are more likely males, well diagnosed with the four classic diagnostic criteria and need to be treated aggressively, due to a high risk of recurrence.
⇒ In elderly patients, clinical suspicion is more challenging and pericarditis is often associated with pleuropulmonary involvement and other comorbidities, which often make pharmacological treatment difficult; however, the risk of pericarditis recurrence remain lower than in other age groups.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Knowing the differences in the diagnostic characteristics, management and outcomes of pericarditis between different age groups is of paramount importance for diagnosis and a patient-tailored approach.

INTRODUCTION

In recent decades, an increasing number of randomised controlled clinical trials[1–4] and cohort studies[5–8] on pericardial diseases have been published leading to a new evidence-based approach for the diagnosis and treatment of these conditions. However, several aspects of pericardial diseases remain poorly explored, and we still have limited published data on the different characteristics of acute pericarditis (AP) in different age groups.[9 10] In particular, there are no large specific studies conducted on the geriatric population, and the 2015 European guidelines on pericardial disease[11] provided only expert opinions on the management of this age group. Knowledge of specific characteristics of pericarditis in elderly is of utmost importance as the average age of population is increasing in high-income countries, and these patients are becoming increasingly common. The aim of this study is to assess the differences in diagnostic features, management and outcome among different age groups, wit a focus on the elderly.

METHODS

Population and study design

The flow diagram of the study population is summarised in figure 1. Consecutive patients (>18 years) referred for a first attack of AP to the

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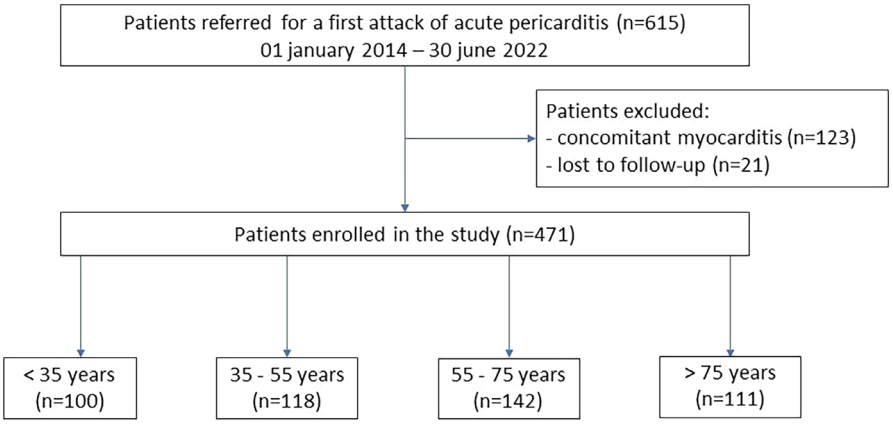

Figure 1 Flow diagram of the study population.

Cardiology Department of the University Hospital of Udine, between 1 January 2014 and 30 June 2022, were considered eligible for this study and retrospectively analysed.

According to the 2015 European Society of Cardiology guidelines for the diagnosis and treatment of pericardial diseases,[11] AP was diagnosed with the presence of two of the following criteria: chest pain, pericardial friction rub, ECG changes (such as new widespread ST-segment elevation or PR depression) and new or worsening pericardial effusion.

Patients with definite criteria for AP and concomitant elevated biomarkers of myocardial damage were excluded because they are known to have different features both clinically as well as in terms of management and outcome, and should be labelled as pericarditis with myocarditis.[12 13] Patients who did not complete the minimum follow-up of 18 months (which is considered the critical period for pericarditis recurrence[1]) were also excluded from the study.

Patients were then divided into four groups according to age at the time of the first AP attack. Age group 1 consisted of 'young adults' aged 18–35 years, age group 2 is formed by 'middle-aged adults' aged 35–55 years (which is considered the median age at the first attack of pericarditis), 'older adults' aged 55–75 years formed age group 3 and people aged >75 years constituted the 'geriatric group'. Historically, the elderly have been considered from the age of 65 years, however, as suggested by recent consensus, we formed the geriatric group by considering people older than 75 years.[14] Indeed, as life expectancy increases in high-income countries, this limit better selects the frailest population group. The study was conducted in accordance with the recommendations of the Strengthening the Reporting of Observational Studies in Epidemiology statement.

Study procedures

History and clinical examination, laboratory tests (including at least complete blood count, C reactive protein, troponin, liver and renal function tests), electrocardiography, echocardiographic evaluation were routinely performed in all patients at baseline and during follow-up. After the pericarditis attack, all patients were re-evaluated through structured follow-up scheduled at 14 days, 1-3-6-12-18 months and then once a year.

Treatment protocols

Patients were treated according to the treatment protocols provided by the European Society of Cardiology guidelines for the diagnosis and treatment of pericardial diseases.[11]

Baseline therapy

First-level treatments, including non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine, were administered to all patients unless contraindicated.

Colchicine was administered at a dose of 0.5 mg 'two times per day for 3 months, reduced to 0.5 mg daily in patients weighting <70 kg or with renal insufficiency.

NSAIDs were administered at the highest possible dose, and then gradually tapered when symptoms resolved and PCR normalised.

Corticosteroids were used as first-line therapy in specific circumstances: (1) patients already on maintenance therapy with these drugs for a systemic inflammatory disease, (2) postpericardiotomy syndromes, (3) concomitant use of therapies that interfere with NSAIDs, (4) renal failure (5) and pregnancy.

Cumulative therapy

In order to record all adverse drug effects, the cumulative therapy administered during the follow-up was recorded. For patients not responding to this first-level therapy, low-dose corticosteroids (eg, prednisone 0.2–0.5 mg/kg/day, tapered slowly) was administered in combination with colchicine (continued for at least 6 months). Patients not responding to therapy with colchicine, NSAIDs and corticosteroids were then treated with anakinra 100 mg/day subcutaneously, for at least 6 months and then gradually tapered.

Study end points

The main end point was the time to the first recurrence, diagnosed when chest pain recurred along with one or more of the following signs: fever, pericardial friction rub, ECG changes (new widespread concave ST-segment elevation or PR depression), or echocardiographic evidence of new or worsening pericardial effusion.[11] Other predefined objectives of the study are to evaluate the differences in clinical features, treatment and outcomes in the four subgroups.

STATISTICAL ANALYSIS

Continuous variables were expressed as mean±SD or median and IQR, according to the data distribution. The data were analysed using the Shapiro-Wilk test to verify the normal distribution. Categorical variables were presented as absolute numbers and percentages. The Student's t-test or the Mann-Whitney U test was used to compare continuous variables between groups, as appropriate.

Table 1 Baseline features of the studied population according to age subgroups

	All patients (n=471)	Age 18.0–35 years (n=100)	Age 35.0–55 years (n=118)	Age 55.0–75 years (n=142)	Age >75 years (n=111)	P value*
Age, mean (SD)	55.0 (20.1)	25.3 (5.1)	46.6 (5.4)	62.8 (5.3)	80.8 (3.8)	–
Gender, n (%)						
Female	152 (32.3%)	15 (15.0%)	37 (31.4%)	50 (35.2%)	50 (45.0%)	**<0.001**
Male	319 (67.7%)	85 (85.0%)	81 (68.6%)	92 (64.8%)	61 (55.0%)	
Fever, n (%)	206 (43.7%)	55 (55.0%)	55 (46.6%)	58 (40.8%)	45 (40.5%)	0.257
Chest pain, n (%)	412 (87.5%)	98 (98.0%)	108 (91.5%)	122 (85.9%)	84 (75.7%)	**<0.001**
Dyspnoea, n (%)	135 (28.7%)	10 (10.0%)	27 (22.9%)	45 (31.7%)	53 (47.7%)	**<0.001**
Pericardial rubs, n (%)	104 (22.1%)	33 (33.0%)	34 (28.8%)	29 (20.4%)	8 (7.2%)	**<0.001**
Widespread ST-segment elevation, n (%)	227 (48.2%)	69 (69.0%	62 (52.5%)	57 (40.1%)	39 (35.1%)	**0.002**
Low voltages, n (%)	35 (7.4%)	4 (4.0%)	11 (9.3%)	11 (7.8%)	9 (8.1%)	0.756
White blood cells (×10^3/µL), mean (SD)	10 453.6 (3572.2)	10 222.6 (3755.7)	10 598.0 (3411.3)	10 585.8 (3371.2)	10 339.4 (3798.0)	0.701
CRP (mg/dL), mean (SD)	104.7 (79.3)	101.5 (60.9)	101.7 (87.0)	107.9 (84.6)	106.7 (78.1)	0.590
CRP >10 mg/dL, n (%)	441 (93.6%)	97 (97.0%)	114 (96.6%)	129 (90.8%)	101 (91.0%)	0.193
eGFR (mL/min), mean (SD)	81.7 (19.4)	102.6 (18.4)	88.6 (30.1)	82.1 (25.9)	55.3 (20.2)	**<0.001**
EF, %, mean (SD)	60.6 (6.4)	60.5 (1.9)	60.9 (6.7)	61.3 (7.5)	59.5 (6.9)	0.860
PE, n (%)	284 (60.3%)	51 (51.0%)	66 (55.9%)	87 (61.3%)	79 (71.1%)	**0.007**
Moderate/Large, n (%)	116 (40.8%)	14 (27.5%)	27 (40.9%)	35 (40.2%)	40 (50.6%)	0.12
Mild, n (%)	168 (59.2%)	37 (72.5%)	39 (59.1%)	52 (59.8%)	39 (49.4%)	
Pleural effusion, n (%)	194 (41.2%)	35 (35.0%)	47 (39.8%)	54 (48.6%)	58 (40.8%)	**0.007**
Idiopathic/Postviral AP, n (%)	343 (72.8%)	89 (89.0%)	84 (71.2%)	91 (64.1%)	79 (71.8%)	0.654
Autoimmune disease, n (%)	34 (7.2%)	4 (4.0%)	10 (8.5%)	10 (7.0%)	10 (9.0%)	0.695
PCIS, n (%)	49 (10.8%)	1 (1.0%)	13 (11.0%)	26 (18.3%)	9 (8.1%)	0.365
Postvaccination, n (%)	17 (3.6%)	3 (3.0%)	6 (5.1%)	4 (2.8%)	4 (3.6%)	0.997
Neoplastic pericarditis, n (%)	13 (2.8%)	1 (1.0%)	2 (1.7%)	4 (2.8%)	6 (5.4%)	0.051
Purulent pericarditis, n (%)	2 (0.4%)	0	0	0	2 (1.8%)	–
Other causes, n (%)	13 (2.8%)	2 (2.0%)	3 (2.5%)	7 (5.9%)	1 (0.9%)	0.171
First line therapy						
Colchicine, n (%)	330 (70.0%)	91 (91.0%)	83 (70.3%)	92 (64.8%)	64 (57.7%)	**0.001**
Aspirin/NSAIDs, n (%)	393 (83.4%)	92 (92.0%)	106 (89.8%)	112 (78.9%)	63 (74.8%)	**0.004**
Corticosteroids, n (%)	83 (17.6%)	12 (12.0%)	18 (15.3%)	24 (16.9%)	29 (26.1%)	**0.007**

Values in bold indicate statistical significance at the p<0.05 level.
*The p value is calculated between group 4 and the other three groups.
CRP, C reactive protein; EF, ejection fraction; eGFR, estimated glomerular filtration rate; NSAIDs, non-steroidal anti-inflammatory drugs; PCIS, postcardiac injury syndrome; PE, pericardial effusion; WBC, white blood cells.

Comparison of categorical variables was performed by χ^2 analysis or the Fisher's exact test, as appropriate. Event-free survival was defined as freedom from recurrence and was determined using the Kaplan-Meier approach to match the different age groups. Comparisons between survival distributions were performed using the log-rank test, with estimation of the HR from a Cox regression model, after the proportional hazards assumption had been verified. Multivariable Cox regression analysis was also performed to assess risk factors for recurrences. Multivariable regression included all the significant variables with a p value <0.10 in the univariable analysis. Results are presented as HRs and 95% CIs. Analyses were performed using Stata V.18.0 (StataCorp, College Station, Texas, USA).

RESULTS

Baseline data

Baseline characteristics according to age groups are presented in table 1 and figure 2. The study includes 471 patients, and each age group comprised respectively 100, 118, 142 and 111 patients. Male/Female ratio was higher in the younger subgroup of patients and progressively decreases in the other groups (5.7, 2.2, 1.8, 1.2, respectively; p<0.001). In addition, younger patients presented more frequently with chest pain, pericardial rubs (p<0001), widespread ST-segment elevation (p=0.002) and were treated more often with colchicine (p<0.001) and NSAIDs (p=0.006). The geriatric group depicted more commonly dyspnoea, lower renal glomerular filtrate values (p<0.001), pericardial and pleural effusion (p=0.007) and were more often treated with corticosteroids (p=0.037).

Follow-up data

Follow-up data according to age subgroups are summarised in table 2 and figure 2. After a mean follow-up of 52±28 months, the geriatric group was characterised by higher rates of cardiac tamponade (p=0.005), hospitalisations, new-onset atrial fibrillation (AF) and experienced more therapy-related side effects (all p<0.001 with progressive decrease in younger age groups). On the other hand, pericarditis recurrences were lower in the geriatric group with a longer recurrence-free survival (log rank p<0.001, see figure 3). Pericarditis-related mortality was 0.4% (two elderly patients with comorbidities died due to cardiac tamponade).

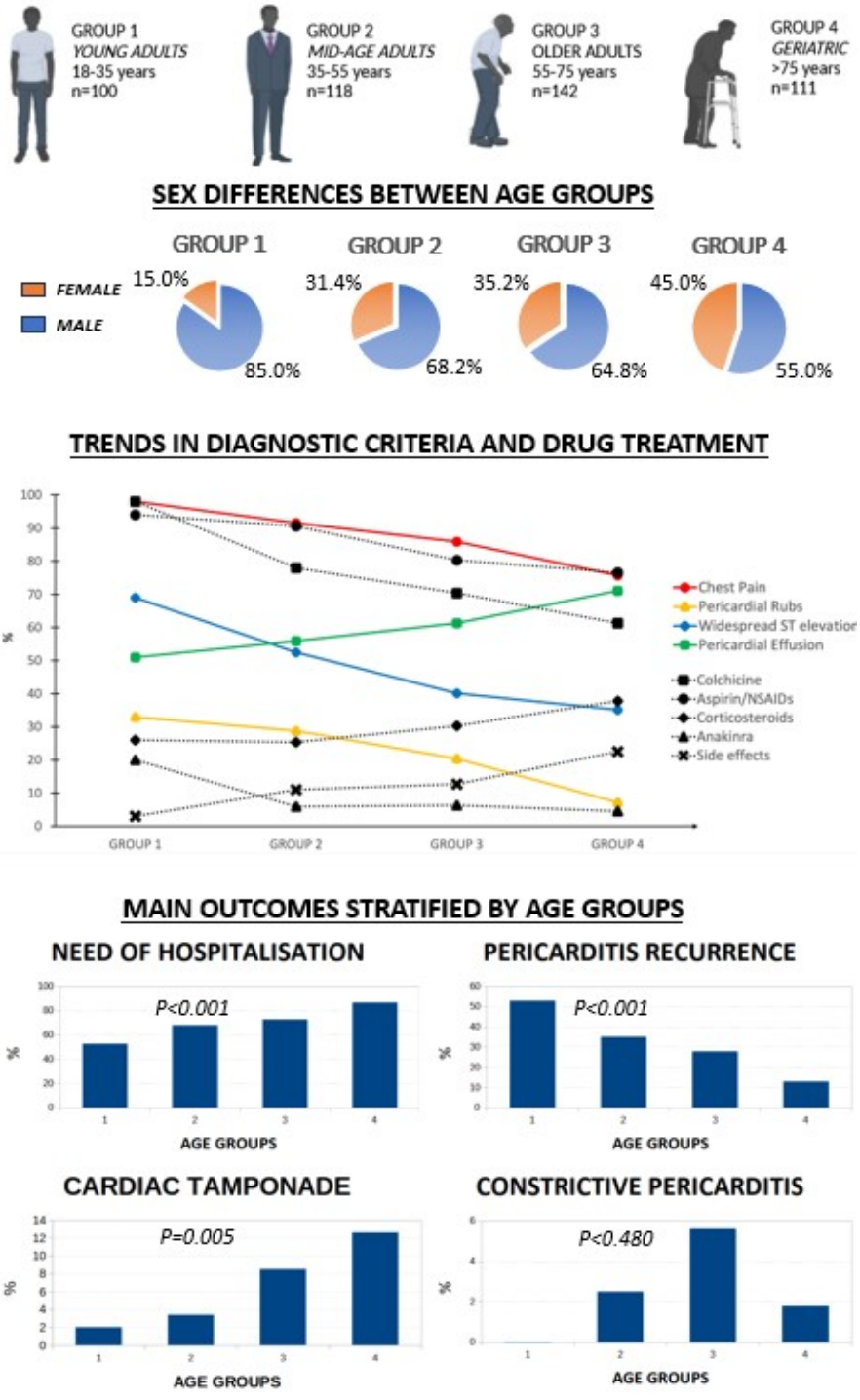

Figure 2 Trends in demographics and clinical outcomes of acute pericarditis. NSAID, non-steroidal anti-inflammatory drug.

In multivariable analysis, summarised in table 3, younger age was the stronger independent predictor of pericarditis recurrence (HR 3.23, 95% CI 1.81 to 5.58, p<0.001). Other independent predictors of pericarditis recurrence were pericardial effusion (HR 1.76, 95% CI 1.07 to 2.88, p=0.018) and pleural effusion (HR 2.05, 95% CI 1.30 to 3.24, p=0.002).

DISCUSSION

To the best of our knowledge, this is one of the largest studies evaluating the role of age in patients with first attack of AP, and it is the first study evaluating clinical features, diagnostic characteristics, treatment protocols and outcomes for the geriatric population over 75 years of age.

The largest study analysing differences in the first attack of pericarditis according to age was published by Lazaros *et al*.[9] The study enrolled 240 patients admitted for their first AP attack and divided them into two groups: 56% of the patients were older than 60 years. Interestingly, similar to our study, young patients were well diagnosed with the four classical diagnostic criteria and, after multivariate adjustment, older age remained an independent predictor of a lower risk of recurrent pericarditis. The main differences with our study are that we also

Table 2 Clinical outcomes of the studied population according to age subgroups

	All patients (n=471)	Age 18.0–35 years (n=100)	Age 35.0–55 years (n=118)	Age 55.0–75 years (n=142)	Age >75 years (n=111)	P value*
Mean follow-up, months (SD)	52 (28)	46 (24)	54 (29)	52 (26)	49 (26)	0.765
RP at 18 months, n (%)	142 (30.1%)	43 (43.0%)	41 (34.7%)	40 (28.2%)	18 (16.2%)	**<0.001**
Need of hospitalisation, n (%)	333 (70.7%)	53 (53.0%)	80 (67.8%)	103 (72.5%)	97 (87.4%)	**<0.001**
New-onset AF, n (%)	37 (7.9%)	0	2 (1.7%)	13 (9.2%)	22 (19.8%)	**<0.001**
Cardiac tamponade, n (%)	32 (6.8%)	2 (2.0%)	4 (3.4%)	12 (8.5%)	14 (12.6%)	**0.005**
Constrictive pericarditis, n (%)	13 (2.8%)	0	3 (2.5%)	8 (5.6%)	2 (1.8%)	0.480
Cumulative therapy						
Colchicine, n (%)	358 (76.0%)	98 (98.0%)	92 (78.0%)	100 (70.4%)	68 (61.3%)	**<0.001**
Aspirin/NSAIDs, n (%)	399 (84.9%)	94 (94.0%	106 (90.6%)	114 (80.3%)	85 (76.6%)	**0.006**
Corticosteroids, n (%)	141 (29.9%)	26 (26.0%)	30 (25.4%)	43 (30.3%)	42 (37.8%)	**0.037**
Anakinra, n (%)	41 (8.9%)	20 (20.0%)	7 (5.9%)	9 (6.3%)	5 (4.5%)	0.072
Adverse effects, n (%)	59 (12.5%)	3 (3.0%)	13 (11.0%)	18 (12.7%)	25 (22.5%)	**<0.001**
Death, n (%)†	36 (7.6%)	1 (1.0%)	6 (5.1%)	7 (4.9%)	22 (19.8%)	**<0.001**
Death related to AP, n (%)	2 (0.4%)	0	0	0	2 (1.8%)	–

Values in bold indicate statistical significance at the p<0.05 level.
*The p value is calculated between group 4 and the other three groups.
†Death from any cause during the entire follow-up.
AF, atrial fibrillation; NSAIDs, non-steroidal anti-inflammatory drugs; RP, recurrent pericarditis.

enrolled outpatients and that the elderly group was significantly older: 80.8 (3.8) vs 66 (48.9) years. This allowed a more homogeneous characterisation of patients >75 years, who are increasingly common in clinical practice.

Consistently with previous reports,[9 10] the male sex was predominant in our population, with a male/female ratio of 2.1. Interestingly, the ratio was much higher in group 1, and then gradually decreases with increasing age (figure 2). The reasons for these sex differences are still unknown, but could be explained by the pro-inflammatory role of testosterone in young male individuals, in contrast to the anti-inflammatory role of oestrogen in female individuals, as reported for myocarditis. From the menopausal age onward, oestrogen decreases and thus the rate of new diagnoses in women increases.[15]

Concerning diagnosis, it is crucial to know that young patients are well diagnosed with the four classic diagnostic criteria, presenting chest pain and typical ECG changes in almost all cases. On the other hand, in the elderly, clinical suspicion is more challenging, patients are often complaining dyspnoea and pericarditis is often associated with pleuropulmonary involvement, and other comorbidities.

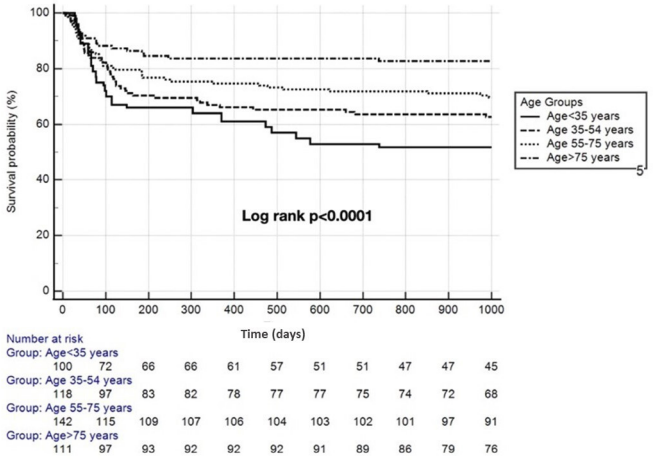

Figure 3 Recurrence-free survival according to age subgroups.

European guidelines on pericardial disease published in 2015[11] provide a stepwise algorithm for the treatment of AP. First-level treatments include NSAIDs and colchicine, while corticosteroids may have specific indication and could be first choices in patients already on maintenance therapy with these drugs, in postpericardiotomy syndromes, if concomitant use of therapies that interfere with NSAID (eg, anticoagulants) and in case of renal failure.[16] In our cohort, NSAIDs and colchicine were administered in >90% of cases in the young population, and then colchicine use gradually decreased in older age groups. In fact, when choosing drug therapy in elderly, it is important to consider comorbidities, contextual polypharmacy and cognitive impairment.[17] In these patients, NSAIDs are often not administered for concomitant renal disease, therefore corticosteroid therapy was used in more than a quarter of our geriatric patients.

Table 3 Multivariable Cox regression analysis to assess risk factors for time to pericarditis recurrence

	Multivariable analysis		
	HR	95% CI	P value
Age <75 years	3.23	1.81 to 5.58	**<0.001**
Gender (male)	1.09	0.62 to 1.75	0.741
Dyspnoea	0.84	0.58 to 1.46	0.877
Chest pain	1.43	0.80 to 2.54	0.456
Widespread ST-segment elevation	0.44	0.76 to 1.62	0.498
Fever	0.84	0.52 to 1.54	0.754
CRP	1.09	0.83 to 1.44	0.706
Idiopathic aetiology	1.63	0.97 to 2.49	0.059
Pericardial rubs	0.79	0.46 to 1.31	0.341
Pericardial effusion	1.76	1.07 to 2.88	**0.018**
Pleural effusion	2.05	1.30 to 3.24	**0.002**
NSAIDs	0.56	0.31 to 1.32	0.141
Colchicine	1.68	1.04 to 2.68	0.058
Corticosteroids	0.64	0.41 to 1.09	0.512

Values in bold indicate statistical significance at the p<0.05 level.
CRP, C reactive protein; NSAIDs, non-steroidal anti-inflammatory drugs.

Despite corticosteroids been associated with an increased risk of recurrence in younger populations in previous reports,[18] the elderly population still presented a significantly lower rate of recurrence than the other groups. The finding that the youngest age group is an independent predictor for pericarditis recurrence is biologically plausible, because inflammatory/immune response generally declines with age due to cellular senescence.[19] In this age group, other risk factors for recurrences could be the partial adherence to exercise restriction during the acute phase and, as mentioned above, a predisposing hormonal pattern (eg, high testosterone levels in young males).

In the elderly, there is higher risk of cardiac tamponade regardless of the aetiology of pericarditis and a higher risk of hospitalisation due to the frailty of these patients, comorbidities and frequent pleuropulmonary involvement. In contrast, the risk of developing constrictive pericarditis is higher in group 3 and group 2, due to a higher risk of postpericardiotomy syndromes in these age groups.[20] On the contrary, we did not record constrictive pericarditis in group 1, probably because the most common aetiology for these patients is idiopathic (which is known to lead to constriction in less than 1% of cases).[21] It is also possible that the risk of developing constriction was minimised due to the efficacy of anti-IL1 drugs, which are nowadays widely used and known to be very efficacious in preventing flare-ups of pericardial inflammation in recurrent or incessant pericarditis with corticosteroid dependence and colchicine resistance.[3] Moreover, new-onset AF was found in 7.9% of our patients, reaching almost 20% in the geriatric group, due to concomitant underlying heart disease and a higher frequency of pericardial effusion, a known trigger for AF.[22] Interestingly, AF relapsed in about 50% of our geriatric patients, confirming that these patients should be considered at high risk of AF recurrence. In these patients, we recommend starting permanent oral anticoagulation according to guideline recommendations.

STUDY LIMITATIONS

This study has potential limitations. First of all, this study was conducted in a single tertiary referral centre for pericarditis, thus patients' characteristics and outcomes might not be entirely representative of unselected populations. Second, it is an observational study, and thus results could be influenced by the confounding factors and biases typical of non-randomised studies.

CONCLUSIONS

Knowing the differences in diagnostic features, management and outcomes of pericarditis between different age groups is of paramount importance. In fact, young patients are more likely males, well diagnosed with the four classic diagnostic criteria and need to be treated aggressively, due to a high risk of recurrence. On the other hand, in the elderly, clinical suspicion is more challenging and pericarditis is often associated with pleuropulmonary involvement and other comorbidities, which often make pharmacological treatment difficult, however the risk of pericarditis recurrence remain lower than in other age groups. Further prospective studies with larger, multicentre patient cohorts are needed to provide a timely diagnosis and implement patient-tailored management.

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Contributors VC and MI contributed to the conception of the study. All authors contributed to the collection of data, writing, critical revision and final approval of the manuscript. VC is responsible for the overall content as guarantor.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study was approved by Institutional Review Board of Medical Department of Udine (IRB DAME 143/2024). The study was conducted in accordance with the Declaration of Helsinki. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

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