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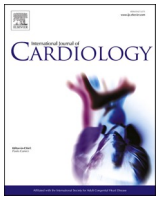

Prognostic role of genetic variants in recurrent pericarditis

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ABSTRACT

Background: Recent interest in the genetic basis of pericarditis has prompted investigation into the prognostic relevance of disease-associated genetic variants (DAVs), particularly in recurrent pericarditis (RP). Auto-inflammatory mechanisms have been implicated in RP, suggesting that genetic predisposition may influence disease severity, treatment response, and long-term outcomes. This study aimed to evaluate the prognostic impact of DAVs in adults with RP.

Methods: A prospective observational cohort study was conducted at a tertiary referral centre for pericardial diseases, enrolling all consecutive adult patients with at least three RP episodes between October 2017 and December 2021. Whole exome sequencing was used to identify DAVs.

Results: Of the 131 patients included, 30 (22.9 %) were found to carry a DAV. Compared with those without DAVs, these patients more frequently exhibited systemic inflammatory features, including elevated C-reactive protein (>10 mg/L in 93.3 % vs 77.7 %, $p = 0.049$) and fever (76.7 % vs 49.5 %, $p = 0.008$). After a median follow-up of 47 months (IQR 34–75), long-term remission was achieved in only 33.3 % of DAV carriers, compared to 67.3 % in the control group (log-rank $p = 0.03$). In multivariable Cox regression analysis, the presence of a DAV remained independently associated with a reduced likelihood of achieving sustained remission (HR 0.468, 95 % CI 0.240–0.984; $p = 0.045$).

Conclusions: This is the first study to assess outcomes in RP patients with DAVs. Approximately one in four patients showed a genetic predisposition, which was linked to a larger inflammatory burden and a significantly lower probability of long-term remission, highlighting the prognostic value of genetic testing in RP.

1. Introduction

Recurrent pericarditis (RP) is the most frequent and troublesome complication of pericarditis [1]. Approximately 6 % of patients after a first episode of acute pericarditis (AP) will develop three or more recurrences and a long course of the disease, lasting years.

The pathogenesis is not yet fully elucidated, however, also in consideration of the excellent efficacy of interleukin-1 (IL-1) inhibitors [2–4], the leading hypothesis is that RP is mediated by auto-inflammatory mechanisms [5,6]. In recent years, targeted genetic analytical approaches has therefore been initiated focusing on specific gene panels to evaluate the presence of monogenic autoinflammatory conditions, such as Familial Mediterranean Fever (FMF), and Tumor Necrosis Factor Receptor-Associated Periodic Syndrome (TRAPS), finding them in only 5–10 % of cases [7,8]. In this scenario, our group recently published the first observational study using whole exome sequency (WES) to assess disease associated variants (DAV) in these patients, finding that 15 % of patients carry at least one variant that could be related to the disease [9]. However, it was never shown if patients with DAV have more severe disease than other patients. This study therefore aims to define the differences in outcomes when classifying these patients according to the genotype.

2. Methods

2.1. Study population

This is an observational cohort study including 131 consecutive adult

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patients (>18 years) with at least three episodes of RP, in order to identify a high-risk group for possible genetic variants. All patients were enrolled at the Cardiothoracic Department, University Hospital Santa Maria della Misericordia (Udine, Italy) from October 2017 to December 2021 and sent for genetic testing at the Institute of Medical Genetics, University Hospital Santa Maria della Misericordia (Udine, Italy). According to the 2015 European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of pericardial diseases, RP was diagnosed with a documented first episode of AP, a symptom-free interval of 4–6 weeks or longer and evidence of subsequent recurrence despite guideline-based medical treatment. Recurrence of pericarditis was defined as an episode of pericardial chest pain associated with at least one of the following: new or worsening pericardial effusion (PE), electrocardiographic changes suggestive of pericarditis, new onset pericardial rubs. The study was approved by the Institutional Review Board of the Department of Medicine at the University of Udine (Prot. IRB 200/2023).

2.2. Study procedures

Detailed clinical data, laboratory tests, electrocardiographic and echocardiographic assessment were routinely performed for all patients. All events during the disease course were registered, including recurrences, cardiac tamponade requiring pericardiocentesis, pericardial constriction (transient or requiring pericardiectomy). The cumulative therapy was also registered. All patients underwent genetic testing by WES. The test was performed with a three-layer analytical strategy involving evaluation of variants in: genes already associated with RP, a subset of genes related to inflammation and autoimmunity, and WES. After WES we divided the study population in two groups: the group with positive genetics for variants related to inflammation and the control group.

2.3. DNA extraction and next-generation sequencing genomic

DNA was extracted from peripheral blood samples collected into 10 ml K2 Ethylenediaminetetraacetic acid collection tubes using the QIAsymphony SP/AS instrument (Qiagen, Hilden, Germany) according to the manufacturer's instruction. DNA concentration was estimated using the Qubit dsDNA HS Assay Kit on a Qubit 4.0 Fluorometer (Thermo Fisher Scientific, Waltham, MA, USA). WES was performed in all cases. A detailed description of the methodology of genetic analysis is reported as supplementary web addenda. All samples underwent WES. Variants were confirmed with orthogonal methods (Sanger sequencing and qPCR).

2.4. Endpoints

The primary endpoint was the remission rate calculated as the proportion of patients who discontinued all pericarditis-related therapies for at least six consecutive months due to clinical improvement. Secondary analyses included the comparison of clinical characteristics between patients with DAV and those without. Finally, we investigated potential predictors for a longer disease duration.

2.5. Statistical analysis

Continuous variables were expressed as mean ± SD or median and IQR, according to the data distribution. The data were analyzed using the Shapiro-Wilk test to verify the normal distribution. Categorical variables were presented as absolute numbers and percentages. The Student *t*-test or the Mann-Whitney *U* test was used to compare continuous variables between groups, as appropriate. Comparison of categorical variables was performed by $\chi 2$ analysis or the Fisher exact test, as appropriate. Event-free survival was determined using the Kaplan Meier approach. 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. Univariable and multivariable Cox regression analyses were also performed to determine the effect of each variable on survival. 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. The proportional hazard assumption was tested using the Schoenfeld residual test. Analyses were performed using R version 4.5.0 (April 2025).

3. Results

3.1. Genetic studies

To identify patients with genetically determined RP, WES was performed. We found 30 (22.9 %) patients that had variants in genes related to the inflammatory response. 15 (50 %) variants were located in genes already associated with recurrent pericarditis (*NLRP3*, *TNFRSF1A* and *MEFV*) and 15 (50 %) variants in inflammation/immunodeficiency-related genes (*IFIH1, NFKBIA, JAK1, NOD2, ALPK1, AIRE, MPO, NFKB2, BACH2, C5, RNASEH2B, MAP4K1, DNASE1L3 and PSMB9*). A detailed classifications of all gene variants is reported in the supplementary web addenda.

3.2. Baseline characteristics

Overall, 130 patients diagnosed with at least three episodes of RP were included in this study and among them, a DAV was found in 30 (22.9 %) patients. The baseline clinical features of the studied population are reported in Table 1. The median age at enrolment was 35 years (±13), and 66.4 % of patients were female. The reported etiology of pericarditis was idiopathic in 89 patients (67.9 %), a pericardial effusion was documented in 93 (71.0 %) patients. As reported in Table 1 baseline characteristics were similar between the two groups, except for a higher frequency of elevated C-reactive protein (CRP) (> 10 mg/l in 93.3 % vs 77.2 %, $p = 0.049$), and fever (76.7 vs 49.5 %, $p = 0.008$) in the genetic group.

3.3. Clinical remission

During a median follow-up of 47 [34–75] months, 78 patients (59.5 %) achieved clinical remission. Patients with genetically determined pericarditis exhibited a significantly lower remission rate (Fig. 1, log-rank $p = 0.03$). In consistency with complicated cases of pericarditis, the median number of recurrences was 5 (4–6), with 109 patients (83.2 %) receiving corticosteroids and 76 (58.0 %) patients treated with anakinra. After multivariable Cox regression analysis (Table 2), the presence of a DAV (HR 0.468, 95 % CI 0.240–0.984, $p = 0.045$) and treatment with anakinra (HR 0.513, 95 % CI 0.321–0.822, $p = 0.005$) emerged as independent predictors of longer disease duration.

4. Discussion

To the best of our knowledge, this is the first study specifically evaluating outcomes in patients with RP and disease associated variants.

The main result is that among 131 patients followed for a median of about four years (34–75 months), only 33.3 % of individuals with a DAV achieved sustained remission, compared to 67.3 % in the control group (log-rank $p = 0.03$).

To date, genetic variants in RP have been evaluated in a limited subset of genes, clustered in autoinflammatory disease-related genes such as TNFRSF1A, MVK, NLRP3 and the IL-1 gene locus [7–10]. However these variants are only able to explain 5–10 % of cases and the putative genetic basis of this disease is far from being clarified. In this scenario, we employed WES to expand the search to genes implicated in inflammation and immunodeficiency. We identified DAV in 22.9 % of

Table 1
Baseline characteristics and outcomes of the studied population according to the genetics.

Baseline characteristics	Total ($n = 131$)	Control group ($n = 101$)	Genetic group ($n = 30$)	P value
Age at onset, mean (SD)	35 ± 13	36 ± 12	34 ± 15	0.652
Female gender, n (%)	87 (66.4 %)	65 (64.4 %)	22 (73.3 %)	0.361
Caucasian, n (%)	131 (100 %)	101 (100 %)	30 (100 %)	1.000
Family history of pericarditis,[1] *n* (%)	7 (5.3 %)	4 (4.0 %)	3 (10.0 %)	0.197
Idiopathic etiology, n (%)	89 (67.9 %)	69 (68.3 %)	20 (66.6 %)	0.865
PCIS, n (%)	12 (9.2 %)	8 (7.9 %)	4 (13.3 %)	0.367
Post vaccination, n (%)	12 (9.2 %)	9 (8.9 %)	3 (10.0 %)	0.843
Autoimmune, n (%)	8 (6.1 %)	7 (6.9 %)	1 (3.3 %)	0.469
Other, n (%)	10 (7.6 %)	8 (7.9 %)	2 (6.7 %)	0.820
Chest pain, n (%)	131 (100 %)	101 (100 %)	30 (100 %)	1.000
Fever, n (%)	**72 (55.0 %)**	**50 (49.5 %)**	**23 (76.7 %)**	**0.008**
ST-segment elevation, n (%)	65 (49.6 %)	46 (45.5 %)	19 (63.3 %)	0.087
PR depression, n (%)	62 (47.3 %)	45 (42.6 %)	17 (63.3 %)	0.243
Pericardial effusion, n (%)	93 (71.0 %)	74 (73.3 %)	19 (63.3 %)	0.292
CRP > 10 mg/l, n (%)	**106 (80.9 %)**	**78 (77.2 %)**	**28 (93.3 %)**	**0.049**
Pleural effusion, n (%)	40 (30.5 %)	27 (26.7 %)	12 (40.0 %)	0.163
Cumulative medical therapy				
Colchicine, n (%)	122 (93.1 %)	95 (94.1 %)	27 (90.0 %)	0.490
NSAIDs, n (%)	121 (92.4 %)	94 (93.1 %)	27 (90.0 %)	0.578
Corticosteroids, n (%)	109 (83.2 %)	85 (84.6 %)	24 (80.0 %)	0.593
IVIG, n (%)	12 (9.2 %)	8 (7.9 %)	4 (13.3 %)	0.367
Anakinra, n (%)	76 (58.0 %)	56 (55.4 %)	20 (66.6 %)	0.273
Outcomes				
Mean follow-up, median (IQR)	47 [34–75]	49 [34–77]	43 [30–75]	0.349
Remission, n (%)	**78 (59.5 %)**	**68 (67.3 %)**	**10 (33.3 %)**	**0.001**
Number of recurrences, median (IQR)	5 [4–6]	5 [4–6]	5 [5–7]	0.893
Cardiac tamponade, n (%)	6 (4.6 %)	4 (4.0 %)	2 (6.7 %)	0.534
Constrictive pericarditis, n (%)	5 (3.8 %)	4 (4.0 %)	1 (3.3 %)	0.875

SD = standard deviation, PCIS = post cardiac injury syndrome, CRP = C-reactive protein, IQR = interquartile range, NSAIDs = non-steroidal anti-inflammatory drugs, IVIG = intravenous immunoglobulins.
[1] First-degree relative with a confirmed episode of acute pericarditis.

patients, suggesting a high prevalence of genetic susceptibility in this group of patients.

Patients with DAV depicted a distinct clinical profile, with a significantly higher frequency of fever (76.7 % vs. 49.5 %), and elevated CRP (93.3 % vs. 77.2 %) compared to the control group. In these patients, therefore, there seems to be a greater predisposition to develop a systemic autoinflammatory disease with clinical similarities to the autoinflammatory syndromes. The resulting hyperactivation of innate immune system stimulates the inflammasome, leading to a significant release of proinflammatory cytokines, in which IL-1 plays a central role in initiating and in perpetuating the inflammatory process [11]. This seems also to be confirmed by the excellent response of these patients to therapy with IL-1 inhibitors resulting in rapid reduction of fever, CRP and chest pain within a few days [12]. Two previous studies had analyzed the duration of disease in patients with RP. In the first study [13], during a median follow up of 21 months (IQR: 12–38 months), 30 (24 %) achieved clinical remission (approximately 14 %/year). In the second [14], after a median follow-up of 4.9 (IQR 2.8–8.4) years, 34.1 % of patients (95 % CI 28.7 %–40.4 %) were in remission (~ 7 %/year). Our findings are consistent with these reports: the overall cohort showed a remission rate of approximately 12 % per year, whereas the genetically positive subgroup had a markedly lower rate (~8 % per year). Multivariable Cox regression confirmed the independent association between DAV ($p = 0.02$) and IL-1 inhibitors ($p < 0.001$) [15] and longer disease duration. In contrast, the incidence of the most serious complications of pericarditis was comparable between groups. Cardiac tamponade occurred in less than 5 % of patients, in each case within the first year of the disease. Transient or persistent pericardial constriction also occurred in less than 5 % of patients, necessitating pericardiectomy in only one case. Constriction did not correlate with either the duration of disease or the number of recurrences.

4.1. Clinical implications and future perspective

The identification of DAV associated with RP might have significant clinical implications. This is a high-risk population with a high recurrence rate. Identifying a DAV in a patient with recurrent pericarditis is important because it can justify the need for a prolonged continued therapy for pericarditis and it can represent a rare disease with possible exemption code for healthcare expenses in National Healthcare systems, such as the Italian one. Carriers of such variants, often exhibit a systemic inflammatory phenotype. Incorporating genetic testing into the diagnostic workup of patients with RP, especially those presenting with systemic inflammatory features, could enhance risk stratification and guide therapeutic decisions. Early identification of genetic predisposition may prompt clinicians to consider early more aggressive or targeted therapies, such as IL-1 inhibitors, which have shown efficacy in managing autoinflammatory conditions. Looking ahead, prospective multicenter studies are warranted to validate these findings and to establish standardized protocols for genetic screening in RP. Such research could elucidate the full spectrum of genetic variants contributing to RP and refine therapeutic strategies.

4.2. Study limitations

This is an observational study with a relatively small sample, including difficult-to-treat patients observed in a tertiary center. We included more complicated and severe cases, and these data may not be generalizable to community practice. However, the high proportion of patients with DAV in this study highlights that rigorous selection of these cases could improve the detection of rare, potentially causative variants.

5. Conclusions

In conclusion, this is the first study aimed to evaluate clinical outcomes in patients with recurrent pericarditis and disease associated genetic variants. Such patients have a systemic inflammatory phenotype, characterized by fever, and elevated CRP and a longer-lasting disease. These results underscore the potential clinical relevance of genetic screening in patients with recurrent pericarditis.

CRediT authorship contribution statement

Valentino Collini: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Formal analysis, Data curation. **Flavio Faletra:** Writing – review & editing, Validation, Supervision, Formal analysis, Data curation. **Francesco Venturelli:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Formal analysis, Data curation.

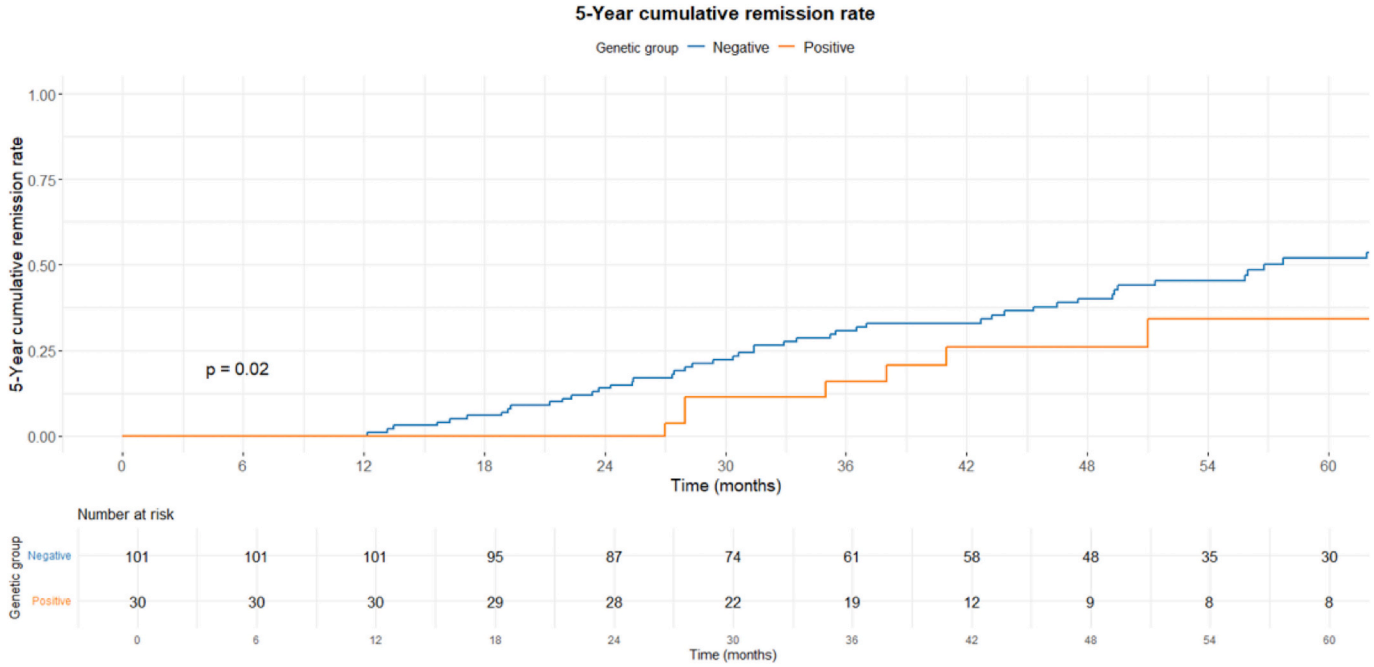

Fig. 1. Remission rates in patients with or without disease associated genetic variants.

Table 2
Univariable and multivariable Cox regression analysis to assess predictors for achieving sustained remission.

Univariable analysis			
	HR	95 % CI	*P* value
Genetics	**0.447**	**0.221–0.905**	**0.025**
Female gender	1.501	0.920–2.449	0.104
Age (> 35 years)	0.993	0.629–1.566	0.975
Idiopathic etiology	1.297	0.778–2.161	0.319
Fever	0.641	0.408–1.006	0.053
ST segment elevation	0.652	0.413–1.029	0.066
Pericardial effusion	1.289	0.755–2.201	0.352
Pleural effusion	0.700	0.422–1.161	0.167
PCR > 10 mg/dl	0.613	0.354–1.060	0.080
Cardiac tamponade	0.668	0.207–2.160	0.500
Pericardial constriction	0.977	0.355–2.689	0.964
Corticosteroids	0.685	0.398–1.181	0.174
Anakinra	**0.488**	**0.306–0.778**	**0.003**
Multivariable analysis			
Genetics	**0.468**	**0.240–0.984**	**0.045**
Anakinra	**0.513**	**0.321–0.822**	**0.005**

HR = hazard ratio, CI = confidence interval, CRP = C-reactive protein.

Alberto Maria Gava: Writing – review & editing, Validation, Methodology, Investigation, Data curation. **Catia Mio:** Writing – review & editing, Validation, Methodology, Investigation, Formal analysis, Data curation. **Giuseppe Damante:** Writing – review & editing, Validation, Supervision, Investigation, Funding acquisition. **Massimo Imazio:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2025.133621.

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