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ORIGINAL ARTICLE

INFLA-score: A new diagnostic paradigm to identify pericarditis

Alessandro Andreis,[1,2] Andrea Solano,[1] Marco Balducci,[1] Cristina Picollo,[1] Margherita Ghigliotti,[1] Mario Giordano,[1] Alessandra Agosti,[1] Valentino Collini,[4] Matteo Anselmino,[1] Gaetano Maria De Ferrari,[1] Mauro Rinaldi,[3] Gianluca Alunni,[2,*] Massimo Imazio[4,*]

ABSTRACT

BACKGROUND Diagnosis of pericarditis may be challenging because not all patients meet the conventional criteria. An overlooked diagnosis implies a longer course of symptoms and an increased risk of recurrences. C-reactive protein (CRP), widely used as an inflammation marker, has some limitations. This study aimed to assess the usefulness and prognostic value of INFLA-score, a validated index assessing low-grade inflammation, in the definite diagnosis of pericarditis.

METHODS Patients with suspected pericarditis were included. The INFLA-score was computed based on white blood cells and platelet count, neutrophil-to-lymphocyte ratio, and CRP, ranging from −16 to +16. An INFLA-score > 0 was considered positive for the presence of pericardial inflammation. The primary end point was the association of INFLA-score with diagnosis of pericarditis according to conventional criteria. The recurrence of pericarditis at 6 months was the secondary end point.

RESULTS A total of 202 patients were included, aged 47 ± 17 years, and 57% were females. Among 72 (36%) patients with a diagnosis of pericarditis, an INFLA-score > 0 was observed in 86% (vs. 36%, $p < 0.001$), abnormal CRP in 42% (vs. 10%, $p < 0.001$), pericardial effusion in 44% (vs. 19%, $p < 0.001$), abnormal electrocardiogram in 56% (vs. 24%, $p < 0.001$), and rubs in 5% (vs. 0.1%, $p = 0.072$). INFLA-score > 0 had the strongest predictive value for the diagnosis of pericarditis (hazard ratio 8.48, 95% confidence interval [CI] 3.39–21.21), with 86% sensitivity and 64% specificity, as opposed to CRP (hazard ratio 1.72, non-significant 95% CI 0.69–4.29). Recurrent pericarditis at 6 months was more frequent in patients with a positive INFLA-score (37% vs. 8%, $p < 0.001$, rate ratio 4.15, 95% CI 2.81–6.12). In patients with normal CRP, INFLA-score–confirmed ongoing inflammation in 78% of the cases. Compared with the conventional criteria, the INFLA-score had the highest accuracy (area under the curve = 0.82). Different cutoffs were valuable to rule out (INFLA-score > 0, sensitivity 86%, and negative likelihood ratio 0.22) or rule in (INFLA-score ≥ 10, specificity 97%, and positive likelihood ratio 13) the diagnosis.

CONCLUSIONS The INFLA-score is a useful diagnostic tool to assess the probability of pericarditis, with a strong prognostic value for further recurrences, outperforming CRP. (Hellenic Journal of Cardiology 2024;■:■-■) © 2024 Hellenic Society of Cardiology. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

[1]Division of Cardiology, Città della Salute e della Scienza di Torino University Hospital, Department of Medical Sciences, University of Torino, Turin, Italy
[2]Advanced Cardiovascular Echocardiography Unit, Cardiovascular and Thoracic Department, Città della Salute e della Scienza di Torino University Hospital, Turin, Italy
[3]Department of Surgical Sciences, University of Turin, Turin, Italy
[4]Department of Medicine (DMED), University of Udine, and Cardiothoracic Department, University Hospital Santa Maria della Misericordia, Udine, Italy
*These authors equally contributed as co-senior authors.
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1. INTRODUCTION

Pericarditis is the most common pericardial syndrome, accounting for 5% of emergency department admissions for acute chest pain.[1,2] According to the guidelines, clinical diagnosis is confirmed based on conventional criteria, requiring at least two features among the following: pericardial chest pain, pericardial friction rubs, electrocardiogram (ECG) abnormalities, new or worsening pericardial effusion. The elevation of inflammatory markers, such as C-reactive protein (CRP) or erythrocyte sedimentation rate, or the detection of inflammation by imaging techniques, such as cardiac magnetic resonance or computed tomography, are considered as additional supporting findings.[3]

However, in clinical practice, many patients with pericarditis do not meet the conventional criteria and the only consistent feature is typical pericardial chest pain, making it challenging for clinicians to reach a definite diagnosis. Indeed, it has been reported that a substantial number of pericarditis cases are overlooked and incorrectly labeled as different diagnoses.[4–8] A missed diagnosis of pericarditis may imply a longer course of disease and an increased risk of recurrent (up to 50% of cases) or incessant type, and the latter is associated with a higher risk of pericardial constriction.[9,10]

Despite the extensive use as a diagnostic clue in clinical practice, CRP may be normal in up to $^{1}/_{4}$ of patients at the first episode of pericarditis and even more in patients with recurrent pericarditis.[10–12]

Considering the limitations of CRP in the identification of active inflammation underlying acute and recurrent pericarditis, we hypothesized that a simple and validated index assessing the multiple inflammatory biomarkers of low-grade inflammation (INFLA-score) could be used with increased accuracy and prognostic value for this purpose.

This study aimed to assess the usefulness and prognostic value of the INFLA-score in the diagnosis of pericarditis.

2. METHODS

2.1. STUDY DESIGN AND POPULATION. The present prospective study included consecutive patients with signs or symptoms suggestive of pericarditis, who were referred for evaluation at an outpatient center for pericardial disease of tertiary care university hospital. This multicenter study was conducted at two referral centers for pericardial diseases in northwest Italy (Division of Cardiology, Città della Salute e della Scienza di Torino Hospital, University of Turin, Turin) and in the northeast (Cardiology and Cardiothoracic Department, University Hospital Santa Maria della Misericordia, University of Udine, Udine). All patients provided oral and written informed consent for study participation. Patients with hematologic disease or other known causes of acute inflammation (i.e. sepsis) were excluded.

Clinical and laboratory testing (including complete blood count and CRP) and electrocardiographic and echocardiographic assessments were performed in all patients at the time of enrollment, according to local practice, in keeping with guideline recommendations.[3] According to study protocol, patients were followed up with clinical visits (including laboratory testing and electrocardiographic and echocardiographic assessments) at 3 and 6 months. Protocol data were collected in accordance with the institutional review board and adhered to the Declaration of Helsinki.

The INFLA-score, previously reported as a useful tool to assess low-grade inflammation, was computed based on laboratory tests (CRP, white blood cell and platelet counts, and neutrophil-to-lymphocyte ratio).[13] The INFLA-score ranged from −16 to +16. An INFLA-score $>$ 0 was considered positive for the presence of low-grade inflammation. The upper normal value of CRP was 5 mg/dl. Patients who received a diagnosis of pericarditis were treated according to guideline recommendations.[3] All patients were subsequently followed up for 6 months. This cohort study followed the recommendations of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

2.2. END POINTS. The primary end point was the association of the INFLA-score with the clinical diagnosis of pericarditis, defined according to established guidelines.[3] The recurrence of pericarditis at 6 months, defined according to the guidelines,[3] was assessed as a secondary end point.

2.3. STATISTICAL ANALYSIS. Continuous variables were presented as means and standard deviations and compared using non-parametric tests: the Mann-Whitney test was used for independent data. Categorical variables, presented as counts and percentages, were compared using the chi-square test with Yates correction or Fisher's exact test, as appropriate. Univariate logistic analysis was used to determine the association between baseline factors and the clinical diagnosis of pericarditis. Multivariate logistic regression was performed to examine the effects of different possible confounding variables.

TABLE 1 Demographics at the time of enrollment

Variable	Population (n = 202)	Pericarditis− (n = 130)	Pericarditis+ (n = 72)	p-value
Age	47 ± 17	47 ± 16	46 ± 18	0.694
Female gender	116 (57%)	72 (55%)	44 (61%)	0.460
Recurrent pericarditis	129 (64%)	84 (65%)	45 (63%)	0.762
Incessant symptoms	12 (6%)	4 (3%)	8 (10%)	0.030
Fever	12 (6%)	2 (2%)	10 (13%)	0.001
Myo-pericarditis	24 (12%)	17 (13%)	7 (10%)	0.506
Pleuritic chest pain	111 (54%)	39 (30%)	72 (100%)	<0.001
Pericardial effusion	57 (28%)	25 (19%)	32 (44%)	<0.001
ECG abnormalities	71 (35%)	31 (24%)	40 (56%)	<0.001
Pericardial rubs	5 (2%)	1 (0.1%)	4 (5%)	0.072
Heart rate	72 ± 13	68 ± 11	78 ± 15	<0.001
Laboratory tests:				
WBC count ($\times 10^9$/L)	7.78 ± 3.02	6.79 ± 1.67	9.54 ± 3.98	<0.001
Neutrophils, %	57 ± 12	53 ± 9	64 ± 13	<0.001
Lymphocytes, %	31 ± 11	35 ± 8	26 ± 12	<0.001
Platelet count ($\times 10^3$/L)	257 ± 74	243 ± 61	282 ± 89	0.001
Neutrophil-to-lymphocyte ratio	2.42 ± 2.16	1.71 ± 0.75	3.70 ± 3.10	<0.001
CRP, mg/dL	13.1 ± 44.6	2.7 ± 5.9	31.7 ± 70	<0.001
CRP elevation	43 (21%)	13 (10%)	30 (42%)	<0.001
INFLA-score	1.60 ± 7.25	−1.23 ± 5.92	6.71 ± 6.62	<0.001

CRP = C-reactive protein, ECG = electrocardiogram, WBC = white blood cells.

The survival probability and the freedom from events were evaluated with Kaplan-Meier curves and compared using the log-rank test. The discriminant ability of a test was evaluated by receiver operating characteristic curve analysis, a plot of true-positive rates (sensitivity) vs. false-positive rates (1− specificity). The area under the curve measured the quality of discrimination, ranging from 0.5 (poor) to 1 (excellent). The cut-off value to determine the presence/absence of a disease was obtained through the simultaneous maximization of sensitivity and specificity via their harmonic mean. All analyses were performed using STATA version 17 (StataCorp, College Station, Texas, United States), and a two-sided significance level of <0.05 was considered as statistically significant.

3. RESULTS

A total of 202 patients were enrolled in the present study, aged 47 ± 17 years, 57% were of the female gender, and 64% had recurrent pericarditis. Pleuritic chest pain was reported by 54% of patients, pericardial effusion observed in 28%, ECG abnormalities consistent with pericarditis in 35%, and pericardial rubs in 2%. The average CRP was 13.1 ± 44.6 mg/dl and was elevated in 21% of patients. The average INFLA-score was 1.60 ± 7.25 and positive in 54% of patients.

A diagnosis of pericarditis was made in 36% of the patients, as described in **Table 1**. Further details on diagnostic criteria are reported in Supplementary Table 1a in the Appendix. Among 72 patients with a definite diagnosis of pericarditis, the INFLA-score was positive in 86% vs. 36% of other patients ($p < 0.001$), and CRP was elevated in 42% vs. 10% ($p < 0.001$). Pericardial effusion was observed in 44% vs. 19% ($p < 0.001$), ECG was consistent with pericarditis in 56% patients vs. 24% ($p < 0.001$), and pericardial rubs were evident in 5% vs. 0.1% ($p = 0.072$).

The logistic regression model for the clinical diagnosis of pericarditis showed that an INFLA-score > 0 was the strongest single baseline factor associated with the diagnosis of pericarditis (hazard ratio [HR] 8.48, 95% confidence interval [CI] 3.39-21.21), as described in **Table 2** and Supplementary Table 2a.

A receiver operating characteristic curve comparison of the INFLA-score with the conventional diagnostic criteria for the clinical diagnosis of pericarditis showed a good predictive ability of the INFLA-score, yielding an area under the curve of 0.82 (95% CI 0.75-0.89), as shown in **Fig. 1**. The sensitivity analysis of the INFLA-score showed a good performance when using a cutoff of 0 (sensitivity 86%, specificity 64%, positive likelihood ratio [LR] 2.38, and negative LR 0.22) and a very high

TABLE 2 Logistic regression model for diagnosis of pericarditis

	Univariable		Multivariable	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	0.99 (0.98-1.01)	0.719	-	
Female gender	1.26 (0.70-2.28)	0.431	-	
Recurrent pericarditis	0.91 (0.50-1.65)	0.764	-	
Incessant symptoms	3.94 (1.14-13.57)	0.030	1.60 (0.33-7.89)	0.564
Fever	10.32 (2.19-48.54)	0.003	4.10 (0.70-23.97)	0.117
Myo-pericarditis	0.70 (0.28-1.79)	0.459	-	
Pleuritic chest pain	-	-	-	
Pericardial effusion	3.36 (1.77-6.35)	<0.001	3.36 (1.46-7.73)	0.004
ECG abnormalities	3.99 (2.16-7.39)	<0.001	5.23 (2.31-11.85)	<0.001
Pericardial rubs	7.58 (0.83-69.23)	0.072	-	
Heart rate	1.06 (1.03-1.08)	<0.001	1.03 (1-1.07)	0.034
Laboratory tests:				
WBC count ($\times 10^9$/L)	1.65 (1.38-1.97)	<0.001	-	
Neutrophils, %	1.09 (1.06-1.12)	<0.001	-	
Lymphocytes, %	0.91 (0.89-0.95)	<0.001	-	
Platelet count ($\times 10^3$/L)	1.01 (1-1.01)	0.001	-	
Neutrophil-to-lymphocyte ratio	2.22 (1.62-3.05)	<0.001	-	
CRP, mg/dL	1.07 (1.02-1.12)	0.006	-	
CRP elevation	6.42 (3.06-13.47)	<0.001	1.72 (0.69-4.29)	0.247
INFLA-score	1.22 (1.15-1.30)	<0.001	-	
INFLA-score >0	10.77 (5.24-22.09)	<0.001	8.48 (3.39-21.21)	<0.001
High INFLA-score (≥8)	20.17 (8.58-47.38)	<0.001	-	
Very high INFLA-score (≥10)	20.05 (6.65-60.37)	<0.001	-	

CI = confidence interval, CRP = C-reactive protein, ECG = electrocardiogram, HR = hazard ratio, WBC = white blood cell.

specificity using a higher cutoff of 8 (sensitivity 57%, specificity 93%, positive LR 9.25, and negative LR 0.46) or 10 (39% and 97%, respectively, positive LR 13, negative LR 0.63), as reported in Table 3.

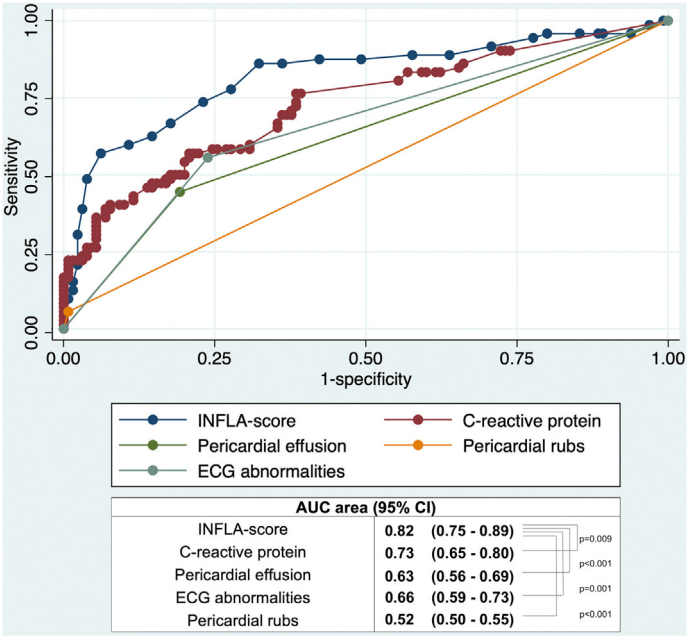
Over a 6-month follow-up, a total of 38 recurrent pericarditis events were observed. These occurred at 6 months in 8% of patients with a negative (≤0) INFLA-score vs. 37% of patients with a positive INFLA-score (log-rank $p < 0.001$, rate ratio 4.15, 95% CI 2.81-6.12). A subgroup analysis (Table 4, Fig. 2) showed that in patients with a negative INFLA-score, there was no prognostic difference between those with a diagnosis of pericarditis according to conventional criteria and those without (recurrence rate 0% vs. 9%, log-rank $p = 0.349$). On the other hand, in patients with a diagnosis of pericarditis, only those with a positive INFLA-score had a significantly increased risk of subsequent 6-month pericarditis recurrence (recurrence rate 50% vs. 0%, log-rank $p = 0.019$).

The cohort of the study was further assessed comparing the diagnostic usefulness of CRP with the INFLA-score. In 159 patients with a negative CRP, the INFLA-score was positive in 77% of patients with pericarditis vs. 23% of other patients ($p < 0.001$). The high diagnostic accuracy of the INFLA-score was indeed confirmed in patients with abnormal and normal CRP, as shown in Fig. 3. In addition, a definite diagnosis of pericarditis was supported by abnormal CRP in 30 (42%) cases and by positive INFLA-score in 62 (86%) cases, as shown in Fig. 4. Of the 42 (58%) patients with pericarditis and a negative CRP, a positive INFLA-score confirmed the diagnosis in 33 of 42 (78%) cases. Indeed, a positive INFLA-score at the time of diagnosis was associated with an increased risk of recurrent pericarditis at 6 months (log-rank $p = 0.019$), as opposed to abnormal CRP (log-rank $p = 0.119$).

4. DISCUSSION

To the best of our knowledge, the present research reports, for the first time, the usefulness of a new diagnostic paradigm based on the INFLA-score algorithm, with the ability to detect the presence of active, low-grade inflammation in patients with suspected pericarditis. The use of this diagnostic tool in the setting of pericardial diseases has a strong pathophysiological rationale, outperforming the currently widely used CRP.

FIG. 1 ROC curve comparison of conventional diagnostic criteria of pericarditis, C-reactive protein and INFLA-score



CRP is an acute phase protein that is used as a marker of active inflammation during the diagnostic workup of suspected pericarditis. However, it should be recognized that the use of CRP has some limitations. It is released by hepatocytes, mainly under transcriptional control by interleukin-6 cytokine. The plasma half-life is 19 h, and its concentration strictly depends on synthesis rate, reflecting the intensity of the pathological stimuli causing inflammation. As a consequence, when the stimulus is cleared, the CRP plasma concentration falls rapidly, although, in many cases, the pericardial inflammation persists, along with symptoms.[12,14,15] Pericardial inflammation is caused by a complex interaction between environmental (microbial or sterile stimuli) and immune (adaptive and innate) factors in predisposed subjects. It is known from previous studies that after the first episode of inflammation, after the hyper-acute phase (when the CRP is usually elevated), autoreactive inflammatory pathways (mainly involving nucleotide oligomerization domain-like receptor protein 3—NOD-like receptor protein 3 inflammasome with downstream production of interleukin-1 cytokine) are started and then auto-sustained over time, establishing a state of low-grade inflammation,[16–21] as shown in Fig. 4 (upper panel).

Low-grade inflammation has been recognized as a risk factor for multiple chronic diseases, although it is difficult to quantify directly. In an effort to assess low-grade inflammation, a group of Italian researchers in 2015 proposed and validated the INFLA-score, an index summarizing the effect of multiple inflammatory biomarkers.[13,22,23]

In the present study, in keeping with the pathophysiology of pericardial inflammation, the INFLA-score performed well in the assessment of low-

TABLE 3 Diagnostic accuracy of INFLA-score

INFLA-score cutoff	Sensitivity	Specificity	LR+	LR−	PPV (%)	NPV (%)	Accuracy (%)
≥10	39%	97%	13	0.63	88%	74%	76%
≥8	57%	93%	9.25	0.46	84%	80%	81%
>0	86%	64%	2.38	0.22	54%	90%	68%

LR = likelihood ratio, NPV = negative predictive value, PPV = positive predictive value.

TABLE 4 Recurrent pericarditis at 6 months according to the INFLA-score and clinical diagnosis of pericarditis

INFLA-score >0	Clinical diagnosis of pericarditis	Pericarditis at 6 months	Log-rank p	Log-rank p	Pericarditis at 6 months	Log-rank p
+	+	50%	$p < 0.001$		37%	
+	−	18%		0.980		$p < 0.001$
−	−	9%	$p = 0.349$		8%	
−	+	0%				

grade inflammation underlying ongoing pericarditis, outperforming CRP evaluation. A positive INFLA-score held an HR of 8.48 (95% CI 3.39-21.21) for the diagnosis of pericarditis on the multivariable analysis, contrary to positive CRP, with a non-significant HR of 1.72 (3.39-21.20). Indeed, in the present cohort, the INFLA-score was able to detect low-grade inflammation, especially in patients with normal CRP ($p < 0.001$). In patients with normal CRP, the adoption of the INFLA-score confirmed the presence of ongoing inflammation in 78% of cases, which would have been alternatively missed.

Furthermore, the INFLA-score could be helpful in clinical practice compared with conventional criteria, considering its very high specificity and positive LR when a cutoff of 10 is used, allowing an accurate diagnosis rule in (specificity 97%, positive LR 13) and a high sensitivity and low negative LR when a cutoff of 0 is used, allowing accurate diagnosis rule out (sensitivity 86%, negative LR 0.22).

Beyond diagnostic usefulness, the INFLA-score yielded a strong prognostic significance for the prediction of pericarditis events at 6 months. Indeed, a positive INFLA-score had a rate ratio of 4.15 (95% CI 2.81-6.12) for subsequent pericarditis events. Furthermore, it was interesting to observe that in patients with a clinical diagnosis of pericarditis, only those with a positive INFLA-score had a significantly increased risk of 6-month pericarditis flares (recurrence rate 50% vs. 0%). This supports the value of this new paradigm in the assessment of low-grade pericardial inflammation and may favor the hypothesis that, in most cases, the acute inflammatory response of pericardium progressively extinguish over time.[24,25]

A limitation of this study is its observational design, the inclusion of patients with a working diagnosis of pericarditis, and the lack of a healthy control group. However, previous studies have tested the validity of the INFLA-score algorithm in large cohorts of healthy patients. Indeed, external validation is missing in the

FIG. 2 Recurrent pericarditis at 6 months, according to INFLA-score (panel A); Recurrent pericarditis at 6 months, according to INFLA-score and pericarditis diagnosis (panel B)

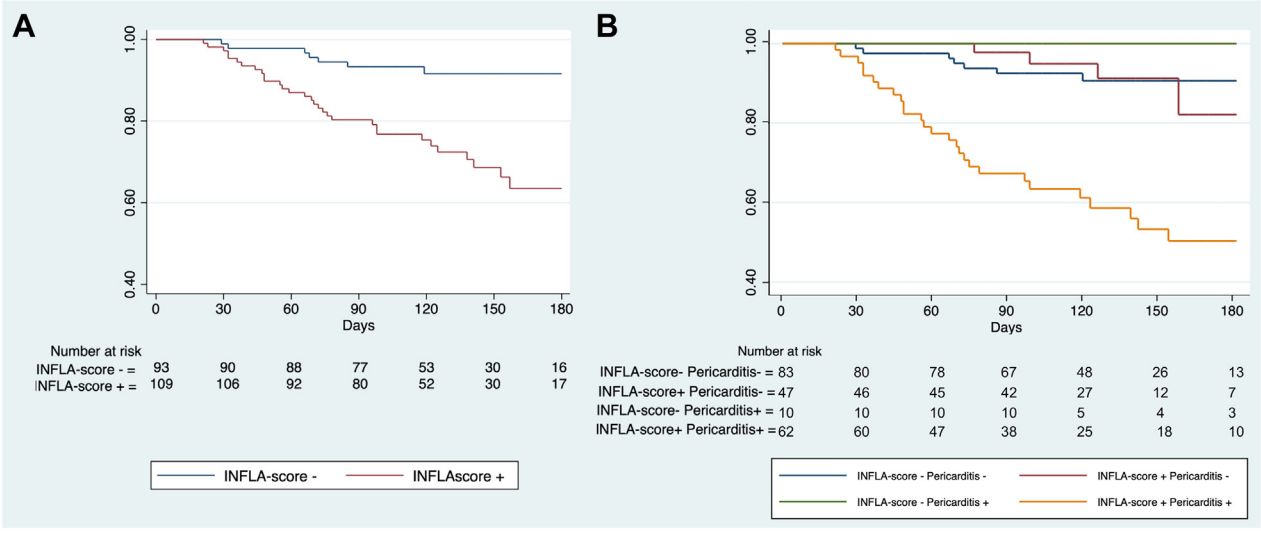


FIG. 3 **ROC curve comparison of diagnostic criteria of pericarditis and INFLA-score, among patients with abnormal (panel A) and normal (panel B) C-reactive protein**

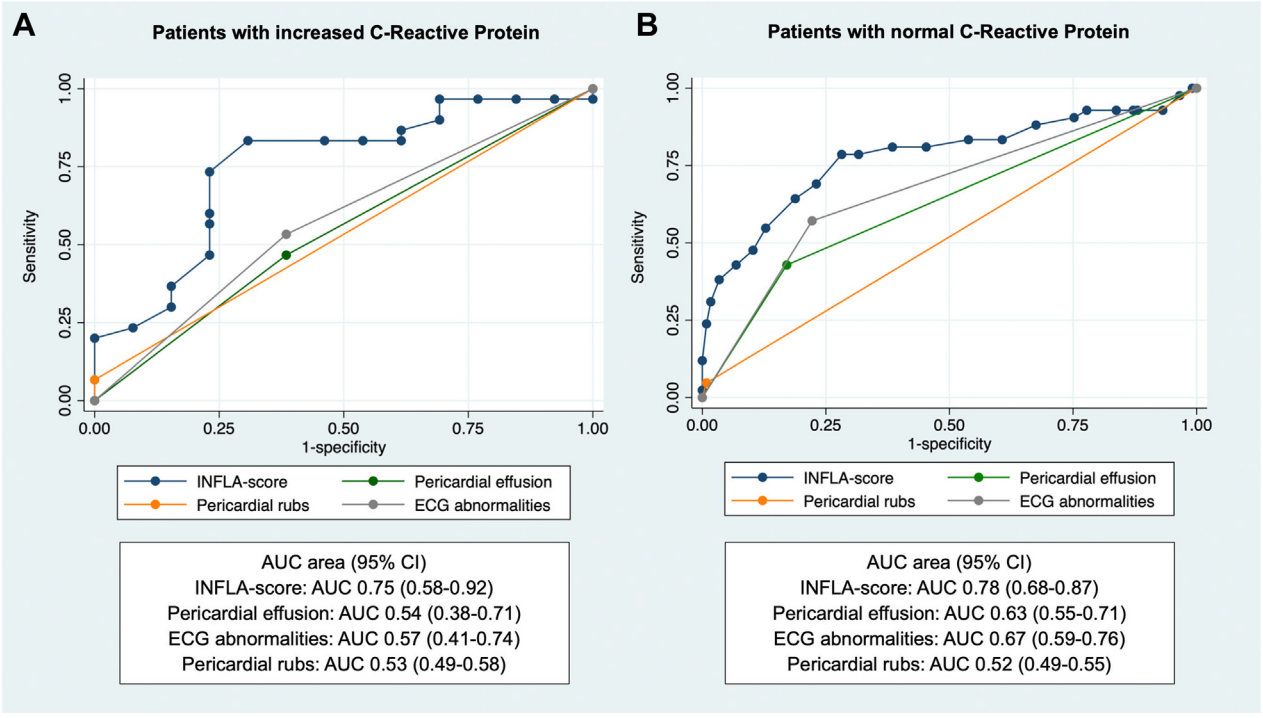
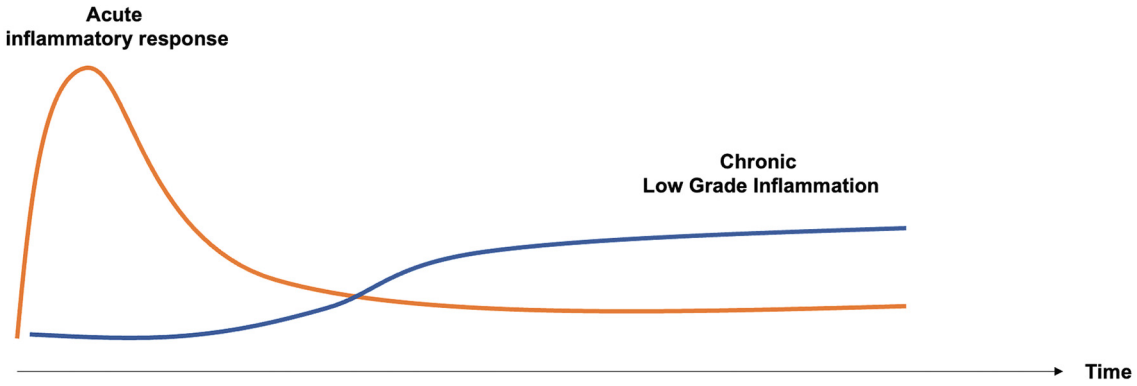


FIG. 4 **Acute inflammatory response and Chronic Low-Grade Inflammation (upper panel). Comparison of INFLA-score and C-reactive protein among patients with diagnosis of pericarditis (lower panel)**



	Abnormal CRP (+) INFLA-score < 0 (-)	Abnormal CRP (+) INFLA-score > 0 (+)	Normal CRP (-) INFLA-score > 0 (+)	Normal CRP (-) INFLA-score < 0 (-)
Patients with pericarditis	**1**/72 (1%)	**29**/72 (40%)	**33**/72 (46%)	**9**/72 (13%)
Pericarditis at 6 months	0%	58%	39%	0%
Pericarditis at 6 months	**56%**		**31%**	
Log-rank p	*0.119*			
Pericarditis at 6 months	**0%**	**50%**		**0%**
Log-rank p	*0.019*			

current study and this should be further assessed in future studies.

In conclusion, the INFLA-score is a useful diagnostic tool, which is based on complete blood count and CRP, enabling the clinician to corroborate a diagnostic suspicion of pericarditis, especially in patients with negative CRP. Furthermore, it carries a meaningful prognostic value for the prediction of further pericarditis episodes.

DECLARATIONS OF INTEREST

None.

CORRESPONDING AUTHOR. Department of Medicine (DMED), University of Udine, and Cardiothoracic Department, University Hospital Santa Maria della Misericordia, Udine, Italy. E-mail: massimo.imazio@uniud.it.

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KEYWORDS Pericarditis, Low-grade inflammation, Diagnosis, C-reactive protein

APPENDIX B. SUPPLEMENTARY DATA Supplementary data related to this article can be found at https://doi.org/10.1016/j.hjc.2024.03.010.