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Cardiac magnetic resonance (CMR) offers the capability to objectively detect pericarditis by identifying pericardial thickening, edema/inflammation by Short-TI Inversion Recovery-T2 weighted (STIR-T2w) imaging, edema/inflammation or fibrosis by late gadolinium enhancement (LGE), and presence of pericardial effusion. This is especially helpful for the diagnosis of recurrent pericarditis. Aim of the present paper is to assess the diagnostic accuracy of CMR findings as well as their potential prognostic value for the diagnosis of recurrent pericarditis. Multicenter cohort study of consecutive patients with recurrent pericarditis evaluated by CMR. We included 128 consecutive cases (60 males, 47%; mean age 48 ± 14 years). CMR was performed at a mean time of 12 days (95% confidence interval 15 to 21) after the clinical diagnosis. We evaluated the diagnostic accuracy and areas under the receiver operating characteristic (ROC) curve for CMR diagnostic criteria and complications (additional recurrences, cardiac tamponade, and constrictive pericarditis). Areas under the ROC curve were respectively 64% for pericardial thickening, 84% for pericardial edema, 82% for pericardial LGE, and 71% for pericardial effusion. After a mean follow-up of 34 months, recurrences occurred in 52% of patients, tamponade in 6%, and constrictive pericarditis in 11%. Using a multivariable Cox model, elevation of CRP and presence of CMR pericardial thickening were predictors of adverse events, whereas the presence of CMR LGE was associated with a lower risk. The prognostic model for adverse events using gender, age, CRP level, and all CMR variables showed a C-index of 0.84. In conclusion, CMR findings show high diagnostic accuracy and may help identifying patients at higher risk of complications.

The diagnosis of pericarditis is usually based on clinical criteria (e.g., pericarditic chest pain, pericardial rubs, ECG changes, and new or worsening pericardial effusion).[1] European guidelines acknowledge the possible diagnostic role of elevated C-reactive protein[2,3] and imaging, especially cardiac magnetic resonance (CMR), when the diagnosis cannot be reached by conventional clinical criteria, especially for recurrent pericarditis.[1-5] CMR offers the capability to detect pericarditis by assessment of pericardial thickening, edema/inflammation by Short-TI Inversion Recovery-T2 weighted (STIR-T2w) imaging, edema/inflammation/fibrosis by late gadolinium enhancement (LGE), and pericardial effusion.[4-9] Nevertheless, there are limited data on the prevalence and potential incremental value of these findings in pericarditis. The present study assesses the diagnostic accuracy of CMR findings in patients with recurrent pericarditis over clinical criteria and C-reactive protein elevation as well as their potential prognostic value in the same patients.

Methods
Multicenter observational cohort study of consecutive patients with recurrent pericarditis evaluated by CMR for this indication from January 2013 to December 2015 in 3 Italian referral centers for pericardial diseases (Torino, Milano, Bergamo). Informed consent was obtained from patients and the study protocol was approved by the Institutional Ethical Committee.
A clinical diagnosis of pericarditis according to 2015 ESC criteria was reached when at least 2 of 4 clinical criteria were satisfied.[2] C-reactive protein was assessed in each patient as additional diagnostic criterion for pericarditis if elevated beyond upper limit of normal range. A clinical and echocardiographic follow-up was performed at 1 week, 1 month and then at additional times as indicated by clinical conditions. A minimal follow-up of 18 months was obtained for each patient. Patients were considered to have clinical remission when symptoms free, with disappearance of clinical, laboratory, echocardiographic, and electrocardiographic signs of pericarditis and were off all anti-inflammatory medications. The following adverse events were considered during follow-up: Recurrences, cardiac tamponade, and constrictive pericarditis.
All patients had a comprehensive echocardiographic examination at presentation, after 1 week and during follow-up. CMR evaluations were performed on a 1.5-T magnetic resonance imaging scanner (multivendor scanners were included in different institutions) as soon as possible after the onset of symptoms. All imaging was performed using commercially available software, electrographic triggering, and dedicated phased-array receiver coils. The CMR protocol included the detection of pericardial thickness on T1-weighted morphological imaging, pericardial edema/inflammation by STIR T2-weighted imaging and myocardial and pericardial LGE. STIR T2-weighted and LGE images were obtained in the long- and short-axis orientations as the cine images. The LGE images were acquired 10 minutes after the intravenous injection of gadolinium contrast agent (0.1 to 0.2 mmol/kg

body weight) using a phase-sensitive inversion recovery technique, and inversion time was selected for optimal nulling of the myocardium. The following CMR findings for pericarditis were considered: (1) pericardial thickening, (2) pericardial edema by STIR-T2w imaging, (3) pericardial LGE, and (4) pericardial effusion. A diagnosis of pericarditis according to CMR was performed with at least 2 CMR criteria. Pericardial thickness was considered normal with values <3 mm on CMR. The presence of pericardial edema on T2-weighted imaging or pericardial LGE was considered abnormal. For CMR studies 2 expert observers, blinded to clinical data and outcomes, analyzed CMR studies offline. Interobserver and intraobserver reproducibility of assessment of pericardial edema and LGE were excellent.

Continuous data were expressed as mean ± SD or median and interquartile range (IQR) based on their distribution. Categorical data are presented as numbers and percentages. Comparisons between groups were performed using the t test, Chi-square and Fisher's exact test, as appropriate. Diagnostic accuracy was expressed as sensitivity, specificity, predictive values, likelihood ratios, and area under the receiver operating characteristic (ROC) curve for each MR diagnostic criterion, as well as the 2015 ESC clinical criteria only, 2015 ESC clinical criteria plus C-reactive protein elevation, and CMR diagnostic criteria for pericarditis.

For the assessment of the diagnostic accuracy of CMR all cases were matched for age and gender with patients without pericarditis who were evaluated for other cardiac diseases different than pericarditis using CMR during the same days as the index cases.

A survival analysis was performed in order to evaluate the effect of CMR findings on the risk of event during the follow up after a pericarditis event by using a stepwise procedure for variables selection (Cox model included gender, age, CRP elevation at presentation, and the 4 CMR findings). The Kaplan-Meier event-free survival curves for combined adverse events were compared using the log-rank test. Data were censored at the time of the first event or last visit. The square of Spearman's rho rank correlation was used to evaluate the prognostic weight of CMR variables. The predictive capacity of the prognostic model was assessed using the C-index. Calibration was performed by bootstrap analysis (1,000 repetitions) and a nomogram for the risk of adverse events during the follow up was evaluated based on this model. A probability value <0.05 was considered to show statistical significance. Analyses were performed by MedCalc Statistical Software version 18 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2018), STATA 13.1 (StataCorp, College Station, Texas), and R 3.5.0.

Results

We included 128 consecutive cases of patients with idiopathic recurrent pericarditis (60 males, 47%; mean age 48 ± 14 years) who performed a CMR. CMR was performed at a mean time of 12 days (95% confidence interval [CI] 15 to 21) after the clinical diagnosis. Baseline characteristics and main CMR findings of the studied population are reported in Table 1. At least 2 of 4 CMR findings were found in 92 of 128 patients (72%). An illustrative case is reported in Figure 1. Considering the time delay of CMR from symptoms onset and diagnosis, it is evident that most findings were especially evident within 2 weeks and that CMR findings such as pericardial edema and pericardial LGE cannot be recorded when CMR is performed >4 weeks from the diagnosis (Table 2). In a univariate logistic model, LGE was associated with elevation of CRP (odds ratio [OR] 15.89 95%CI 8.02 to 31.47, p <0.01) but this association was lost in a multivariate model including time to CMR (OR 1.3 95%CI 0.48 to 3.52, p = 0.59), that reflects treatment effect. Indeed, a prompt therapy affects CRP values, and, stratifying by the time course of CMR (OR 0.75 95%CI 0.08 to 7.18, p = 0.80 if the logistic model is restricted to CMR performed by 14 days after the diagnosis of pericarditis), there is no association between CRP and pericardial LGE in this cohort study. Pericardial edema and pericardial LGE on CMR had an overall AUC of 0.8 (95% CI 0.73 to 0.83) and of 0.76 (95% CI 0.71 to 0.81) to identify pericarditis, respectively (Figure 2). Overall diagnostic accuracy of CMR criteria for pericarditis is summarized in Table 3. Pericardial edema and LGE have high specificity and moderate sensitivity compared with pericardial thickening and pericardial effusion, both with low sensitivities. A combination of pericardial edema and LGE has a sensitivity of 73% and specificity of 99% for the diagnosis of pericarditis.

After a mean follow-up of 34 months additional recurrences occurred in 67 of 128 cases (52%), cardiac tamponade in 7 of 128 (6%), and constrictive pericarditis in 14 of 128 (11%). Using a

multivariable Cox model, elevation of CRP (hazard ratio [HR] 11.7 95%CI 5 to 27.2), and presence of CMR pericardial thickening (HR 2.6 95%CI 1.6 to 4.4) were predictors of adverse events during follow-up, whereas the presence of LGE was associated with a lower risk (HR 0.3 95%CI 0.1 to 0.7). We also evaluated a prognostic model for adverse events using gender, age, CRP level, and all CMR variables. The C-index of the model was 0.84. The prognostic nomogram is shown in Figure 3.

Discussion

This is the first multicenter study exploring the potential usefulness of CMR findings for diagnosis of recurrent pericarditis. All CMR findings showed a high diagnostic accuracy and, a high specificity (higher than 88%) in identifying recurrent pericarditis. The presence of both pericardial edema and LGE has a sensitivity of 73% and a specificity of 99% for the diagnosis of pericarditis and has the best diagnostic accuracy over other criteria.

At present, the clinical diagnosis is essentially based on the following clinical criteria.[1,3-5] However, the predictive value of some of these criteria is rather low, and although pericarditic chest pain is reported >90% of cases, other criteria are less common especially for recurrences (e.g., pericardial rubs are detected in one-third of cases, ECG changes are especially reported with concomitant myocarditis, and pericardial effusion is found in <60% of cases).[4] Imaging of pericardial inflammation may be a more reliable marker for diagnosis and CMR has the potential to detect pericardial inflammation by increased pericardial thickness, edema and LGE.[6-9]

In a previous pilot study on 63 patients with atypical presentation of pericarditis, CMR was performed within the first week from symptom onset. The main CMR findings were: Pericardial thickening in 59% of cases, pericardial effusion in 32% of cases, pericardial edema in 70% of cases, and pericardial LGE in 87% of cases. Higher values of CRP were detected in patients with pericardial effusion and pericardial LGE.[7] These findings are confirmed by our study in a larger number of cases. In addition, we showed that the time delay in performing CMR from symptoms onset might attenuate the findings, especially pericardial edema and LGE tends to resolve by the 4th week from symptoms onset. A similar observation has been made in acute myocarditis where the diagnostic pick-up rate of CMR was higher when performed within 2 weeks from symptoms onset.[10]

We also suggested a possible nomogram for the evaluation of risk of adverse events during the follow-up. The presence of pericardial thickening and an elevated level of CPR at the first evaluation were the strongest negative predictors. This finding can be explained by an increased risk of developing constrictive pericarditis, which is characterized in most cases (about 80%) by pericardial thickening.[11-13] Additional contributions of CMR in this setting are represented by the capability to detect concomitant myocarditis, unknown myocardial infarction, pericardial thickening, and constrictive physiology (e.g., ventricular interdependence on cine real-time CMR).[8,9,14] On the other hand, an older age and pericardial LGE were found to be protective against complications during follow-up. Younger age may be associated with a more intense inflammatory process, whereas pericardial LGE may confirm the presence of inflammation that could be potentially reversible with anti-inflammatory therapy. The nomogram, we presented, underlines potential use of CMR for managing pericarditis and, in particular, its role in early detection of patients who need a close follow up for a higher risk of adverse events. We acknowledge possible study limitations related to the time course of CMR studies. Patients were treated according to available guidelines and it is possible that initiation of treatment before CMR may have mitigated some CMR findings. However, this study reflects the contribution of CMR in real practice and this limitation cannot be overcome since not all CMR studies can be performed at the onset of symptoms. On the contrary, the study strength is that it reflects the diagnostic contribution in real clinical practice, and may also stimulate additional research on the topic. In conclusion, CMR criteria for pericarditis may be helpful for diagnosis, especially if CMR is performed within 2 weeks from symptoms onset, and for identifying patients at higher risk of complications.

Disclosures

the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health and Social Care.

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Table 1. Baseline characteristics of patients with recurrent pericarditis

Variable	Patient with recurrent pericarditis (n = 128)
Age (years; mean, sd)	48,5 (±14.1)
Male	60 (47%)
Pericarditic chest pain	125 (98%)
Pericardial rubs	39 (31%)
Electrocardiographic changes	56 (44%)
Pericardial effusion (echo)	89 (70%)
Elevation of C-reactive protein	103 (81%)
CMR findings for pericarditis:	
(1) Pericardial thickening ≥3 mm	37 (29%)
(2) Pericardial Edema (STIR-T2w imaging)	87 (68%)
(3) Pericardial late gadolinium enhancement	83 (65%)
(4) Pericardial Effusion	67 (52%)

Table 2. CMR findings according to CMR delay from symptoms onset

CMR criterion	All	<2 weeks	2-4 weeks	>4 weeks
Empty Cell	(n = 128)	(n = 73)	(n = 42)	(n = 13)
Pericardial thickening	37 (28.9%)	17 (23.3%)	18 (42.9%)	2 (15.4%)
Pericardial edema	87 (68.0%)	58 (79.5%)	29 (69.0%)	0
Pericardial LGE	83 (64.8%)	55 (75.3%)	28 (66.7%)	0
Pericardial effusion	67 (52.3%)	39 (53.4%)	26 (61.9%)	2 (15.4%)
0 of 4 RM criteria	16 (12.5%)	5 (6.8%)	3 (7.1%)	8 (61.5%)
1 of 4 RM criteria	19 (14.8%)	7 (9.6%)	8 (19.0%)	3 (30.8%)
At least 2 of 4 RM criteria	93 (83.6%)	61 (73.8%)	31 (73.8%)	1 (7.7%)

Table 3. Diagnostic accuracy of CMR criteria for the diagnosis of recurrent pericarditis (as percentage and 95% confidence interval)

CMR criteria	Se	Spe	PPV	NPV	LR+	LR-
(1) Pericardial thickening	28.9 (21.1-37.6)	98.4 (94.5-99.8)	94.9 (82.799.4)	58.1 (51.2-64.7)	18.5 (4.6-75.1)	0.7 (0.6-0.8)
(2) Pericardial edema (T2w)	68 (59.1-75.9)	100 (97.2-100)	100 (95.8-100)	75.7 (68.6-82)	N.A.[*]	0.3 (0.2-0.4)
(3) Pericardial LGE	64.8 (55.9-73.1)	99.2 (95.7-100)	98.8 (93.5-100)	73.8 (66.6-80.2)	83 (11.7-587)	0.4 (0.3-0.5)
(4) Pericardial effusion	52.3 (43.3-61.2)	89.8 (83.3-94.5)	83.8 (73.8-91.1)	65.3 (57.8-72.3)	5.2 (3-8.9)	0.5 (0.4-0.6)
Pericardial edema and LGE	72.7 (64.1-80.2)	99.2 (95.7-100)	98.9 (94.2-100)	78.4 (71.3-84.5)	93 (13.2-657)	0.3 (0.2-0.4)

Using presence of pericardial edema at CMR as diagnostic test, 0 false positive results were obtained; LR, likelihood ratio; NPV, negative predictive value; PPV, positive predictive values; Se, sensitivity; Spe, specificity.

Figure 1. An illustrative case of CMR findings in pericarditis: Panel A shows pericardial thickening on T1w imaging, panel B shows pericardial edema on T2w imaging, and panel C shows pericardial LGE. Additional finding is the presence of bilateral basal pleural effusion (red arrows).
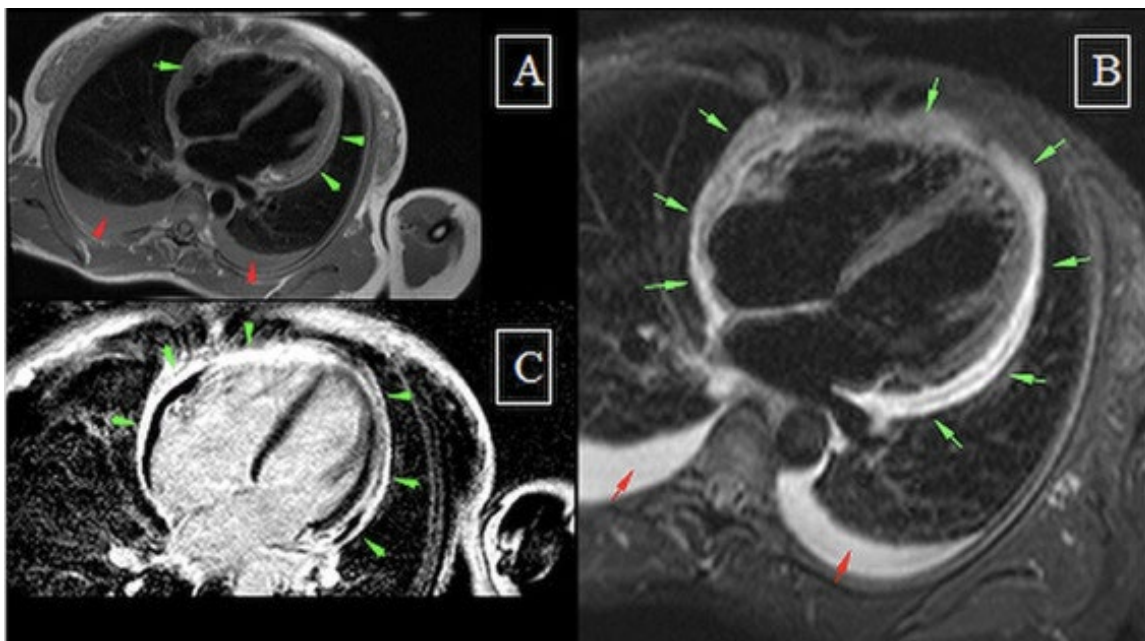
Figure 2. Comparison of AUC between different CMR criteria for the diagnosis of pericarditis: (1) Pericardial thickness, (2) pericardial edema, (3) pericardial LGE, (4) pericardial effusion, and both pericardial edema and LGE.

Delta AUC of pericardial edema and LGE vs pericardial thickness, p <0.01; pericardial edema and LGE vs pericardial edema, p >0.05; pericardial edema and LGE vs pericardial LGE, p <0.01; pericardial edema and LGE vs pericardial effusion, p <0.01.
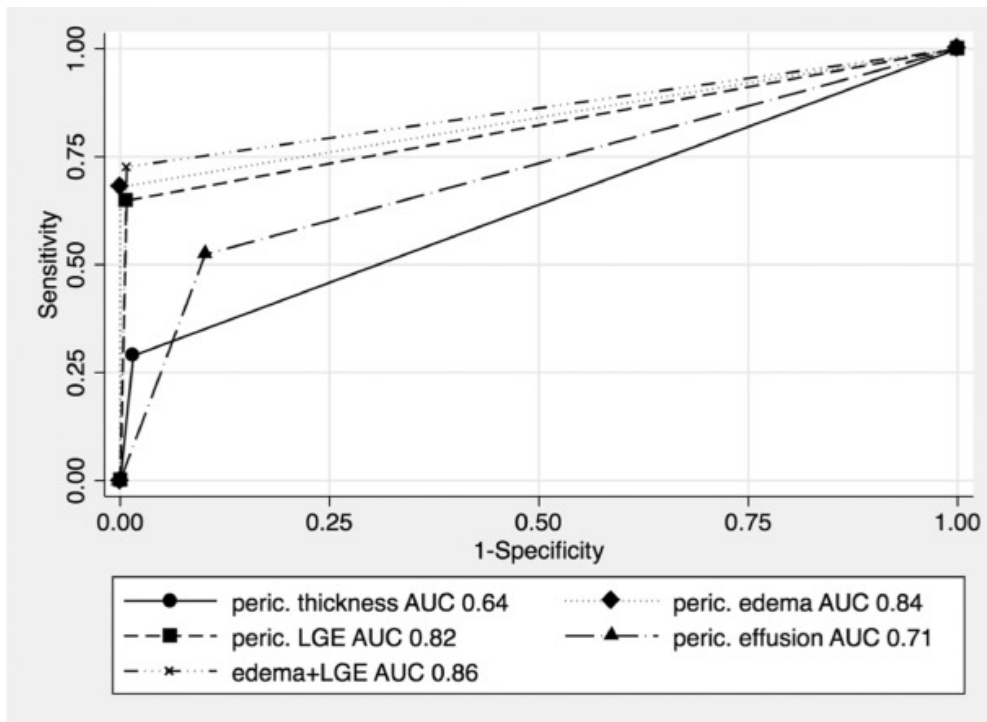
Figure 3. The prognostic model and the nomogram based on the prognostic model of adverse event during follow-up.