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Quantitative Pericardial Delayed Hyperenhancement Informs Clinical Course in Recurrent Pericarditis

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ABSTRACT

OBJECTIVES The aim of this study was to evaluate the prognostic value of quantitative assessment of pericardial delayed hyperenhancement (DHE) among patients with recurrent pericarditis (RP).

BACKGROUND Pericardial DHE on cardiac magnetic resonance may persist beyond the acute phase of pericarditis, suggesting continued pericardial inflammation.

METHODS This is a retrospective cohort study of 159 patients with RP who underwent DHE imaging and had a follow-up period of more than 6 months. Pericardial inflammation was quantified on short-axis DHE sequences by contouring the pericardium, selecting normal septal myocardium as a reference region, and then quantifying the pericardial signal that was >6 SD above the reference. Our primary outcome was clinical remission; secondary outcomes were time to recurrence and recurrence rate.

RESULTS The mean age of our patients was 46 ± 14 years, and 52% were women. During a median follow-up period of 23 months (interquartile range: 15 to 34 months), 32 (20%) patients achieved clinical remission. In the multivariable Cox proportional hazards model, lower quantitative pericardial DHE (hazard ratio: 0.77; 95% confidence interval: 0.64 to 0.93; $p = 0.008$) was independently associated with clinical remission. When added to background clinical and laboratory variables, quantitative pericardial DHE had incremental prognostic value over baseline clinical and laboratory variables (integrated discrimination improvement: 8%; net reclassification improvement: 36%). Furthermore, patients with a higher quantitative DHE had shorter time to subsequent recurrence ($p = 0.012$) and had a higher recurrence rate at 6 months ($p = 0.026$).

CONCLUSIONS Quantitative assessment of pericardial DHE was associated with clinical outcomes among patients with RP and provided incremental information regarding the clinical course of patients with RP.
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Recurrent pericarditis (RP) is a troublesome complication of acute pericarditis and occurs in 15% to 32% of cases (1). After a first recurrence, subsequent relapse is even more common (50%) (2). Occasionally, intractable recurrent pericarditis can lead to steroid dependence or even radical pericardiectomy (3,4). Recurrent episodes may be related to viral reactivation, autoinflammation, or inappropriate initial treatment (2,5,6). In pericardial disease, cardiac magnetic resonance (CMR) can be used to measure pericardial thickness, assess for constrictive physiology, and characterize pericardial edema and inflammation (7,8).

Among patients with RP, CMR-guided therapy may decrease recurrence and exposure to steroids (9). In patients with pericarditis, significant pericardial delayed hyperenhancement (DHE) likely represents organizing pericarditis with fibroblast proliferation and neovascularization, a process representing ongoing inflammation (10). The presence of significant DHE among patients with RP may therefore represent ongoing pericardial inflammation, despite treatment (11). Consequently, the aim of this study was to evaluate the value of a quantitative assessment of pericardial DHE in informing the clinical course among RP patients who had multiple recurrences by the time of presentation. We hypothesized that RP patients with higher pericardial DHE, despite treatment, likely had more ongoing pericardial inflammation and would therefore be less likely to achieve clinical remission.

METHODS

STUDY POPULATION AND STUDY DESIGN. We identified 217 consecutive patients with RP from January 1, 2007 through March 31, 2015 who underwent a CMR study, had echocardiographic assessment, and had inflammatory markers (either ultrasensitive C-reactive protein [us-CRP] or Westergren sedimentation rate [WSR]) drawn within a week. Patients were excluded if they had a history of pericardiectomy, lacked baseline DHE sequences, or had a follow-up period of <6 months. As outlined in current guidelines, RP was defined as recurrence of pericarditis after a documented first episode of pericarditis and a minimum symptom-free interval of 4 to 6 weeks (12). Clinical, laboratory, and demographic data were obtained via manual extraction from electronic medical records from a clinic visit within 1 week of the initial CMR.

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Patients were considered to have achieved clinical remission when they became symptom free, with disappearance of clinical, laboratory, echocardiographic, and electrocardiographic signs of pericarditis and were off all anti-inflammatory medications (2,13–15). Secondary outcomes were time to first recurrence and recurrence rate at 6 months from the baseline CMR. The study protocol was approved by the institutional review board with a waiver of the requirement for informed consent.

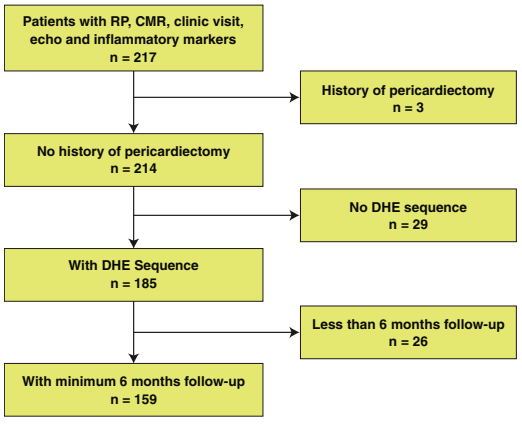
CMR. CMR studies were performed on a 1.5-T magnetic resonance imaging scanner (Achieva XR, Philips Medical Systems, Best, the Netherlands), and all imaging was performed using commercially available software, electrographic triggering, and dedicated phased-array receiver coils as previously described (10). DHE images were obtained in long- and short-axis orientations ≈10 min after the intravenous injection of gadolinium-diethylenetriamine penta-acetic acid (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 (16). The in-plane spatial resolution of DHE images was ≈2 mm. For quantitative analysis, a single observer blinded to clinical data and outcomes analyzed CMR studies using commercially available software (CMR42, Circle Cardiovascular Imaging Inc., Calgary, Canada). Qualitative assessment of pericardial DHE was graded as none, mild, moderate, or severe by level III expert readers (16). A quantitative analysis of pericardial inflammation was performed on short-axis DHE sequences by manually contouring the pericardium. Normal septal myocardium was then selected as a reference region, and the signal >6 SD above normal myocardium was quantified (16). Sequences with black blood preparation and breath holding were used to measure pericardial thickness. The intraobserver variability for quantitative DHE assessment was studied in a group of 20 randomly selected datasets by 1 observer on 2 different occasions. The interobserver variability was analyzed using a second observer who was unaware of the first observer's measurements on 2 different occasions. The intraobserver and interobserver absolute difference for the quantitative DHE was 6.8 ± 6.0 cm^3 and 10.1 ± 7.0 cm^3, respectively. The correlation coefficient for intraobserver variability was 0.96 ($p < 0.001$) and that for interobserver variability was 0.91 ($p < 0.001$), showing excellent agreement.

ECHOCARDIOGRAPHY. All patients had a comprehensive echocardiographic examination according to established guidelines (7,17). The peak early (E) and late diastolic velocities of mitral inflow, and respiratory change in mitral and tricuspid peak early diastolic velocity of mitral inflow wave (% from expiration) were obtained by pulsed Doppler echocardiography. The septal and lateral mitral annular peak early diastolic velocities were measured by tissue Doppler imaging in the apical 4-chamber view (7).

ABBREVIATIONS AND ACRONYMS

CI = confidence interval
CMR = cardiac magnetic resonance
DHE = delayed hyperenhancement
E = peak early diastolic velocity of mitral inflow
HR = hazard ratio
IQR = interquartile range
RP = recurrent pericarditis
us-CRP = ultrasensitive C-reactive protein
WSR = Westergren sedimentation rate

FIGURE 1 Flow Diagram Demonstrating Derivation of Study Cohort



CMR = cardiac magnetic resonance; DHE = delayed hyperenhancement; RP = recurrent pericarditis.

TABLE 1 Baseline Characteristics of the Study Cohort and Excluded Patients

	Study Cohort (n = 159)	Excluded Patients (n = 58)	p Value
Age, yrs	46 ± 14	48 ± 16	0.330
Female	83 (52)	31 (54)	0.777
NYHA functional class (II-IV)	88 (56)	23 (44)	0.127
Pericarditic chest pain	128 (83)	46 (82)	0.869
Fever	19 (13)	5 (9)	0.456
Duration since original diagnosis of pericarditis, months	9 (4–23)	10 (5–21)	0.190
Duration from last relapse, months	1 (0.5–2.0)	2 (1.0–3.5)	0.448
Number of recurrences before initial CMR	3 (2–6)	3 (2–5)	0.466
Etiology of pericarditis	82 (52)	34 (59)	0.357
Hypertension	39 (25)	20 (35)	0.131
Diabetes mellitus	14 (9)	5 (9)	0.984
Coronary artery disease	16 (10)	11 (19)	0.073
Anti-inflammatory medications before initial CMR			
NSAIDs	98 (62)	29 (51)	0.157
Colchicine	107 (67)	39 (68)	0.876
Prednisone	79 (50)	26 (46)	0.598

Values are mean ± SD, n (%), or median (interquartile range).

CMR = cardiac magnetic resonance; DHE = delayed hyperenhancement; NSAIDs = nonsteroidal anti-inflammatory drugs; NYHA = New York Heart Association.

STATISTICAL ANALYSIS. Normally distributed continuous data were expressed as mean ± SD and non-normally distributed continuous data were expressed as median (interquartile range [IQR]). Categorical data are presented as absolute numbers and percentages. Comparisons between groups were performed using the Student's *t* test, Wilcoxon rank sum test, chi-square test, and Fisher's exact test, as appropriate. Agreements between continuous variables were determined using Spearman's rank correlation coefficient.

To assess the primary outcome, Cox proportional hazards model analysis was used to determine the parameters associated with time to clinical remission, and multivariable hazard ratios (HRs) were calculated. The assumption of proportional hazards was graphically assessed based on the Schoenfeld residuals. In the multivariable model, we included relevant parameters based on previous reports and clinical experience including sex, etiology of pericarditis, number of anti-inflammatory medications before initial CMR, number of previous recurrences, duration of time since last relapse, chest pain, us-CRP, and quantitative DHE. Stepwise Cox proportional hazards model analysis was used to assess the independent and incremental value of chest pain, us-CRP, and DHE in the prediction of clinical remission over previously acquired information. The likelihood ratio test was performed to examine the significance of the addition of chest pain, us-CRP, and quantitative DHE to a baseline characteristics model that included sex, etiology, number of medications, number of previous recurrence, and duration since last recurrence. Incremental prognostic value was defined as the presence of both a statistically significant increase in global chi-square test and significant increase in continuous net reclassification improvement and integrated discrimination improvement (18,19). As a measure of discrimination, Harrell C-index was calculated from multivariable Cox regression models. Kaplan-Meier curves were created to assess cumulative incidence of clinical remission between groups and were compared by the log-rank test. A 2-sided p value <0.05 was considered statistically significant. All statistical analyses were performed with JMP 10.0 (SAS Institute Inc., Cary, North Carolina), SPSS 23.0 software (SPSS Inc., Chicago, Illinois), and R software version 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

PATIENT CHARACTERISTICS. Of the 217 consecutive patients with RP who underwent a CMR study at the Cleveland Clinic, 159 (73%) were included in the study (Figure 1). Included and excluded patients were similar (Table 1). In the 159 RP patients studied, 52% were women, and the mean age was 46 ± 14 years. The median number of recurrences at the time of initial CMR was 3 (IQR: 2 to 6), whereas the median duration from initial diagnosis of pericarditis to undergoing CMR was 9 months (IQR: 4 to 23 months). The majority of patients had a history of idiopathic pericarditis (52%), and 83% had pericarditic chest pain. Most patients (141 [89%]) were on anti-inflammatory therapy at the time of initial CMR and 44 (28%) were on triple therapy (nonsteroidal anti-inflammatory drugs, colchicine, prednisone). Further, 6 (4%) patients were on disease-modifying antirheumatic drugs such as azathioprine and biologics (e.g., anakinra) at the time of undergoing CMR.

At the time of initial CMR, 16 (10%) patients had pericarditic chest pain and electrocardiography changes, whereas 46 (29%) patients had pericarditic chest pain and new or worsening effusion by echocardiography. In comparison, only 8 (5%) patients had pericarditic chest pain and a pericardial friction rub. Additionally, 68 (45%) patients had pericarditic chest pain and elevated inflammatory markers (us-CRP/WSR).

Pericardial thickness was increased (>2 mm) on black blood sequences in 21 (13%) patients, and 24

(15%) patients demonstrated constrictive physiology on CMR (7). On qualitative DHE interpretation, 37 (23%) patients had none, 73 (46%) patients had mild, 32 (20%) had moderate, and 17 (11%) had severe pericardial inflammation. On quantitative analysis of pericardial DHE, patients with clinical remission and no recurrence at 6 months had lower values (Table 2, Figure 2). Based on quantitative DHE quartiles, the proportion of patients with clinical remission were as follows: quartile 1 (DHE ≤26 cm^3; 11 of 40 [27.5%]), quartile 2 (DHE between 26 cm^3 and 48 cm^3; 10 of 40 [25%]), quartile 3 (DHE between 48 cm^3 and 71 cm^3; 10 of 40 [25%]), and quartile 4 (DHE >71 cm^3; 1 of 39 [2.5%]).

CORRELATION OF QUANTITATIVE DHE WITH QUALITATIVE DHE ANALYSIS, PERICARDIAL THICKNESS, INFLAMMATORY MARKERS, AND PERICARDIAL EFFUSION. Overall, qualitative pericardial DHE interpretation showed a modest correlation with quantitative DHE (Spearman's rho = 0.66; $p < 0.001$). Figures 3A to 3C shows a representative patient with no significant pericardial DHE, compared with a patient with severe pericardial DHE (Figures 3D to 3F). Pericardial DHE quantification showed weak correlation with pericardial thickness on black blood imaging (rho = 0.24; p = 0.003). Moreover, quantitative DHE had a statistically significant but modest correlation with us-CRP (rho = 0.41; $p < 0.001$) and a weak correlation with WSR (rho = 0.22; p = 0.007).

Patients with pericardial effusion by CMR had significantly higher levels of us-CRP (p = 0.005) and DHE (p = 0.038) and a trend toward higher WSR (p = 0.083) when compared with those with no effusion on univariable analysis.

PERICARDIAL DHE AND CLINICAL OUTCOMES IN PATIENTS WITH RP. During a median follow-up period of 23 months (IQR: 15 to 34 months), 32 (20%) patients had clinical remission. The median time to clinical remission from the initial CMR was 20 months (IQR: 14 to 35 months).

To assess the primary outcome, pericarditic chest pain, us-CRP, and quantitative DHE were added to a baseline characteristic model containing age, sex, etiology of pericarditis, number of anti-inflammatory medications before initial CMR, and disease activity at baseline (number of previous recurrences, duration since last recurrence) using a series of Cox proportional hazards models in stepwise manner. In the final multivariable Cox proportional hazards model, lower quantitative DHE (HR: 0.77; 95% confidence interval [CI]: 0.64 to 0.93; p = 0.008) was independently associated with clinical remission (Table 3).

TABLE 2 Univariable Comparisons for Clinical Remission

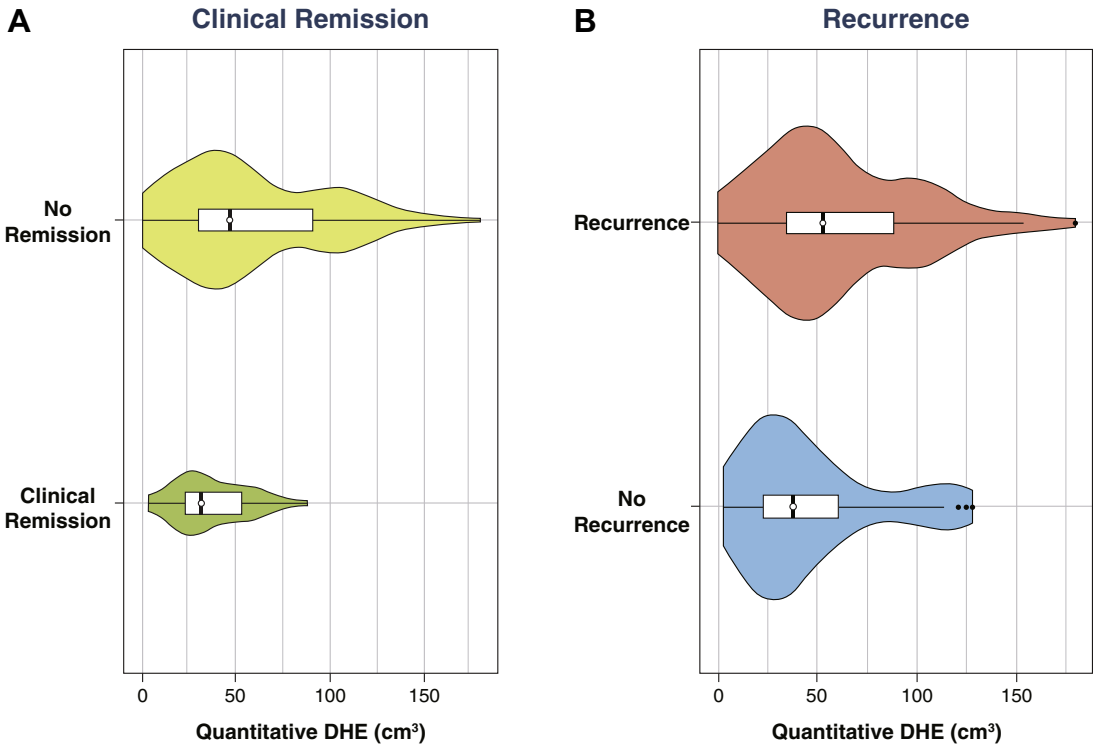
	Clinical Remission		
	Yes (n = 32)	No (n = 127)	p Value
Age, yrs	48 ± 16	45 ± 14	0.426
Female	16 (50)	67 (53)	0.780
Duration since original diagnosis of pericarditis, months	7 (4–21)	10 (4–24)	0.458
Duration from last relapse, months	1 (0.5–3.0)	1 (0.5–2.0)	0.081
Number of recurrences before initial CMR	3 (2–5)	3 (2–6)	0.937
Etiology of pericarditis	12 (38)	70 (55)	0.075
Anti-inflammatory medications before initial CMR			
Number of medications	1 (0–2)	2 (1–3)	0.002
NSAIDs	17 (53)	81 (64)	0.272
Colchicine	15 (47)	94 (74)	0.004
Prednisone	10 (31)	69 (54)	0.018
DMARDs/biologics	1 (3)	5 (4)	0.829
Anti-inflammatory medications after initial CMR			
Number of medications	2 (1–3)	3 (2–3)	<0.001
NSAIDs	28 (88)	115 (91)	0.617
Colchicine	26 (81)	121 (95)	0.016
Prednisone	12 (38)	88 (69)	0.001
DMARDs/biologics	1 (3)	13 (10)	0.205
Clinical features			
NYHA functional class (II–IV)	13 (41)	75 (59)	0.061
Pericarditic chest pain	23 (72)	105 (83)	0.168
Fever	2 (6)	16 (13)	0.311
Pericardial rub	3 (9)	5 (4)	0.257
ECG changes	3 (10)	15 (12)	0.730
Laboratory data			
us-CRP, mg/l	1.3 (0.6–4.9)	2.6 (0.9–17.8)	0.090
WSR, mm/h	5 (2–11)	8 (4–17)	0.270
Echocardiographic variables			
Ventricular septal shift	13 (41)	49 (39)	0.832
New or worsening pericardial effusion	6 (19)	45 (36)	0.060
Pericardial effusion ≥10 mm (moderate or large)	2 (6)	3 (2)	0.264
Mitral E respiratory variation, %	9.9 ± 14.7	8.0 ± 11.1	0.470
Tricuspid E respiratory variation, %	−16.1 ± 10.5	−12.2 ± 15.9	0.254
Septal e′, cm/s	8.5 ± 3.5	9.4 ± 2.8	0.154
Lateral e′, cm/s	11.3 ± 4.4	12.4 ± 3.3	0.118
IVC dilatation	1 (3)	5 (4)	0.854
CMR variables			
Qualitative DHE (none, mild/moderate, severe)	25 (78)/7 (22)	85 (67)/42 (33)	0.220
Quantitative DHE, cm^3	32 (22–54)	47 (30–91)	0.008
Pericardial thickness, DHE, mm	3 (2–3)	3 (2–3)	0.386
Pericardial thickness, black blood, mm	2 (1–2)	2 (2–2)	0.386
Constrictive physiology	5 (16)	19 (15)	0.925

Values are mean ± SD, n (%), or median (interquartile range).

DMARDs = disease-modifying antirheumatic drugs; E = peak early velocity of mitral inflow; e′ = peak early diastolic velocity; ECG = electrocardiography; IVC = inferior vena cava; NYHA = New York Heart Association; us-CRP = ultrasensitive C-reactive protein; WSR = Westergren sedimentation rate; other abbreviations as in Table 1.

Patients presenting with pericarditic chest pain (HR: 0.30; 95% CI: 0.12 to 0.75; p = 0.010) were also less likely to achieve clinical remission. Adding quantitative DHE to a model containing baseline characteristics, chest pain and us-CRP resulted in significant increase in the global chi square for the

FIGURE 2 Violin Plots for Patients With and Without Clinical Remission and With and Without Recurrence According to Quantitative Pericardial DHE



(A) Patients with and without clinical remission. **(B)** Patients with and without recurrence. Clinical remission was associated with lower baseline pericardial delayed hyperenhancement (DHE) values (median 32 cm^3 vs. 47 cm^3; p = 0.008). Similarly, recurrence was associated with higher baseline pericardial DHE values (median 53 cm^3 vs. 38 cm^3; p = 0.013).

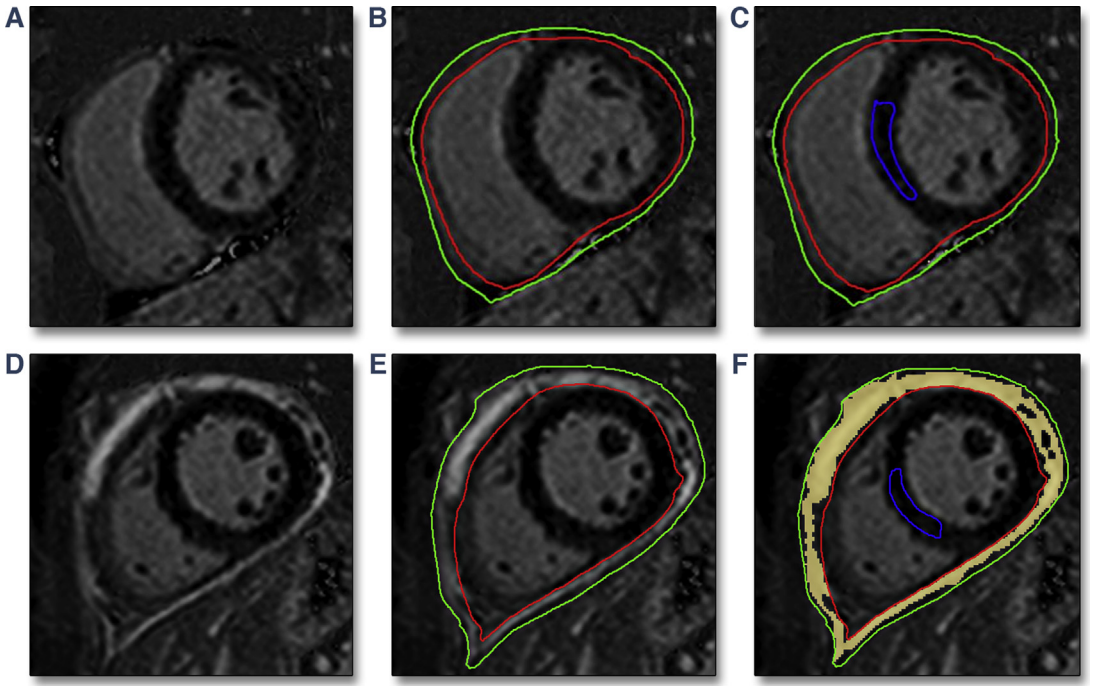
model predicting clinical remission (p = 0.004 for DHE) (Table 4, Figure 4). Similarly, adding quantitative DHE resulted in an improved prediction model with integrated discrimination improvement of 8% and net reclassification improvement of 36% (p < 0.001 for both).

In Kaplan-Meier analysis of RP patients stratified according to quartiles of DHE, the highest quartile was associated with significantly reduced clinical remission (p = 0.047) (Figure 5). Conversely, in the Cox proportional hazards model, clinical remission was not associated with pericardial DHE on qualitative reports (p = 0.065) on multivariable analysis.

Median time to recurrence from initial CMR was 124 days (IQR: 54 to 230 days) and 92 (58%) patients had recurrence at 6 months. Higher baseline quantitative DHE was associated with a shorter time to subsequent recurrence (HR: 1.01, 95% CI: 1.00 to 1.01; p = 0.012) (Online Table 1). Higher baseline quantitative DHE was also associated with a higher recurrence rate at 6 months from index CMR (odds ratio: 1.14; 95% CI: 1.02 to 1.29; p = 0.026) (Online Table 2). In comparison, DHE on qualitative reports was not associated with time to recurrence (p = 0.072) or higher recurrence rate at 6 months (p = 0.097) on multivariable analysis. In addition to the 32 patients who had been completely tapered off all anti-inflammatory medications (clinical remission), an additional 30 patients were on a single agent (nonsteroidal anti-inflammatory drug/colchicine) and had resolution of symptoms. A total of 100 (63%) patients were on prednisone after the initial CMR, of which 46 (46%) patients were successfully tapered off prednisone therapy.

Among 18 (11%) patients who were not on anti-inflammatory medications at the time of baseline CMR, all 3 patients in the highest quartile of pericardial DHE (>71 cm^3) did not show clinical remission at the end of the follow-up period.

FIGURE 3 Post-Gadolinium DHE Images From Patients With RP



(A to C) DHE images from a patient with no significant pericardial DHE. **(D to F)** Severe pericardial DHE in another patient with RP. On these short-axis images, the pericardium has been outlined (between **red** and **green tracings**), and normal septal myocardium has been outlined as a reference region **(blue tracing)**. DHE images show no significant enhancement **(A and B)**. Post-contouring, DHE images show very low quantitative DHE (quantitative DHE = 2 cm^3) **(C)**. The pericardium is bright from intense DHE **(D and E)**. Quantitative signal >6 SD above normal myocardium is shown (**F, yellow**; quantitative DHE = 146 cm^3). Abbreviations as in Figure 1.

DISCUSSION

The results of our study show: 1) lower pericardial quantitative DHE was associated with clinical remission among patients with RP who presented after multiple recurrences; 2) when compared with other clinical variables, quantitative pericardial DHE provided better discrimination for clinical remission; and 3) higher pericardial quantitative DHE was associated with a shorter time to recurrence and a higher recurrence rate.

TABLE 3 Multivariable Cox Proportional Hazards Model Analysis of Clinical Remission

	Multivariable HR (95% CI)	p Value
Female	0.42 (0.18–0.95)	0.038
Etiology of pericarditis	0.50 (0.23–1.08)	0.076
Number of anti-inflammatory medications before initial CMR	0.77 (0.52–1.13)	0.185
Number of previous recurrences	0.29 (0.12–0.68)	0.005
Duration since last recurrence	1.63 (0.64–4.16)	0.306
Pericarditic chest pain	0.30 (0.12–0.75)	0.010
us-CRP, per 1 mg/l increase	1.00 (0.98–1.01)	0.648
Quantitative DHE, per 10 cm^3 increase	0.77 (0.64–0.93)	0.008

CI = confidence interval; HR = hazard ratio; other abbreviations as in Tables 1 and 2.

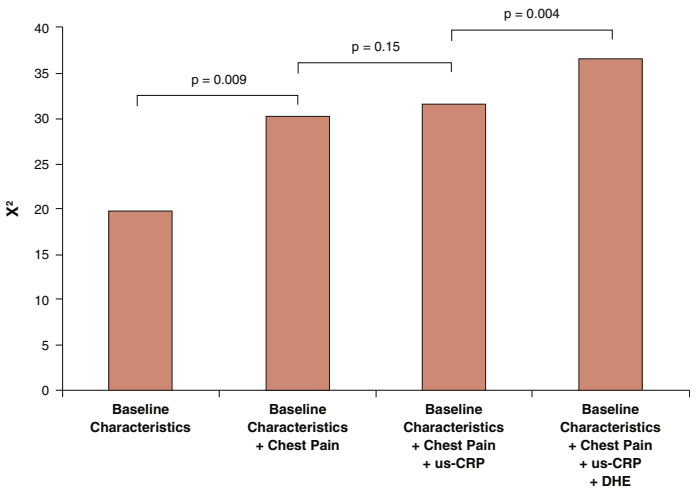
TABLE 4 Incremental Value of Adding Quantitative DHE to Clinical Variables to Predict Clinical Remission in Cox Proportional Hazards Model

	Chi-Square Test	p Value for Added Term	C-Index	IDI (95% CI)† p Value	NRI (95% CI)† p Value
Baseline characteristics*	19.8	–	0.743	–	–
+ Pericarditic chest pain	30.3	0.009	0.795	5% (-1 to 20) p = 0.098	27% (-12 to 59) p = 0.244
+ us-CRP per 1 mg/l increase	31.6	0.15	0.805	0.4% (-0.1 to 4.0) p = 0.244	-5% (-28 to 29) p = 0.829
+ Quantitative DHE, per 10 cm^3 increase	36.6	0.004	0.822	8% (2 to 18) p < 0.001	36% (4 to 55) p < 0.001

*Baseline characteristics were created with sex, etiology of pericarditis, number of anti-inflammatory medications before index CMR, disease activity at baseline (number of previous recurrences and duration since last recurrence). †Integrated discrimination improvement (IDI) and net reclassification improvement (NRI) were calculated between baseline characteristics vs. baseline characteristics + pericarditic chest pain, baseline characteristics + pericarditic chest pain model vs. baseline characteristics + pericarditic chest pain + us-CRP model, and baseline characteristics + pericarditic chest pain + us-CRP model vs. baseline characteristics + pericarditic chest pain + us-CRP + DHE model.

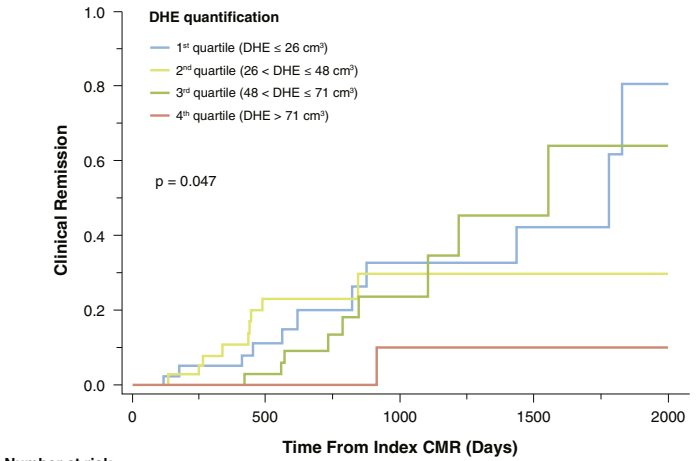
CI = confidence interval; other abbreviations as in Tables 1 and 2.

FIGURE 4 Incremental Prognostic Value of Pericardial DHE for Clinical Remission



Baseline characteristics included sex, etiology of pericarditis, number of anti-inflammatory medications before index cardiac magnetic resonance imaging, and disease activity at baseline (number of previous recurrences and duration since last recurrence).
DHE = delayed hyperenhancement; us-CRP = ultrasensitive C-reactive protein.

FIGURE 5 Kaplan-Meier Curves of Study Population, Separated on the Basis of Quantitative DHE Quartiles



Number at risk:

1st quartile	40	33	11	7	2
2nd quartile	40	23	11	6	3
3rd quartile	40	32	10	4	2
4th quartile	39	28	9	3	3

Patients with DHE >71 cm^3 (fourth quartile) had lower clinical remission than other groups ($p = 0.047$). Abbreviations as in Figure 1.

PROGNOSTIC VALUE OF DHE IN RELATION TO CLINICAL OUTCOMES. In addition to the main diagnostic criteria for RP specified by the European Society of Cardiology, in a recent consensus document of the American Society of Echocardiography on integrated cardiovascular imaging of pericardial diseases, elevated CRP or us-CRP and pericardial late gadolinium enhancement on CMR imaging were proposed as additional confirmatory criteria (7,12). Even though data are limited, in patients with RP CMR may confirm the diagnosis if the presentation is doubtful (20) and may inform subsequent therapy (9). Here we demonstrate that quantitative pericardial DHE may provide insight into the duration and expected response to treatment.

To our knowledge, our results are the first to demonstrate the incremental prognostic value of adding quantitative DHE to other clinical variables in patients with RP. In contrast, qualitative DHE reporting was not associated with clinical remission in a multivariable model, which suggests limitations of visual evaluation of pericardial DHE. Moreover, as shown in our study, the prognostic value of inflammatory markers (us-CRP) might be lower among patients with RP who are often on intense anti-inflammatory therapy at the time of evaluation. In such presentations, a baseline assessment of pericardial DHE may be of value. Traditional markers of prognostication for acute pericarditis such as fever and pericardial effusion (12) were also not associated with clinical outcomes in our cohort of RP patients with history of multiple recurrences.

PATHOPHYSIOLOGY OF DHE. Previous studies have shown that pericardial DHE correlates histologically with fibroplasia, organized fibrous pericarditis, neovascularization, and chronic inflammation (10,21). In patients without pericardial disease, the pericardium is nearly avascular and does not enhance. When the pericardium is inflamed, gadolinium-based contrast agents are retained in the pericardium, and with an inversion time to null the myocardium, the pericardium shows DHE (10,21). Of note, the distinction between the clinical implications of pericardial DHE in constrictive pericarditis versus RP is important. In 2 recent studies, the presence of intense pericardial DHE before initiation of anti-inflammatory therapy was associated with reversibility (16,22). In particular, constrictive pathophysiology may improve with anti-inflammatory therapy in patients with substantial pericardial DHE. However, the duration of anti-inflammatory therapy before clinical remission is

achieved was not assessed in these studies. Intense pericardial DHE on CMR among RP patients previously treated with anti-inflammatory therapy might help identify patients who require longer duration of therapy.

CLINICAL IMPLICATIONS. The diagnosis and management of RP, especially in patients with multiple recurrences, remain a challenge. Intense pericardial DHE seems to indicate a more prominent chronic inflammatory process. As noted in our study, the median time to clinical remission was 20 months. Given the duration of illness and associated morbidity, these patients could be the focus of future studies investigating more intensive and novel therapies.

STUDY LIMITATIONS. Our study was relatively small and retrospective from a single tertiary care referral center. To account for disease severity and potential confounders, we might have slightly overfit our final statistical model by conventional standards. The majority of patients had been on anti-inflammatory medications and had a history of multiple recurrences at the time of initial CMR. Consequently, our patients had advanced pericardial inflammation as evidenced by their high recurrence rate. Therefore, our results might be most applicable in selected group of RP patients who might have failed an initial trial of anti-inflammatory therapy. Furthermore, assessment of quantitative pericardial DHE is not well established and standardized. The process of gadolinium kinetics into and out of the pericardium at different stages of disease is unknown. In addition, quantitative values of pericardial DHE have not been compared across institutions, and although our work represents a first step, further validation is needed. Finally, even though we controlled for potential confounding factors, our analysis could have been affected by hidden confounders.

CONCLUSIONS

In patients with RP presenting after multiple recurrences, lower baseline pericardial quantitative assessment of DHE was associated with higher clinical remission and provides reasonable discrimination. Higher baseline DHE was also associated with shorter time to subsequent recurrence and a higher recurrence rate.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Intense pericardial DHE indicates chronic inflammation among RP patients. This study shows that, among patients with multiple recurrences of pericarditis, higher quantitative DHE on CMR indicates a longer clinical course.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Quantitative assessment of pericardial DHE has superior discriminatory power in predicting clinical outcomes among patients with RP. A higher baseline DHE is also associated with shorter time to recurrence and higher recurrent rate.

TRANSLATIONAL OUTLOOK: Whereas this investigation is hypothesis generating, in the future, clinical trials evaluating the interval change in pericardial DHE among patients with RP with correlation to clinical symptoms and inflammatory markers might better elucidate the precise timing of changes in medication dosing. Further, prospective, multicenter randomized controlled studies investigating the impact of new biological agents and disease-modifying agents on DHE and various clinical and cardiovascular outcomes among RP patients are needed.

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KEY WORDS cardiac magnetic resonance, clinical remission, delayed hyperenhancement, recurrent pericarditis

APPENDIX For supplemental tables, please see the online version of this article.

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