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ORIGINAL RESEARCH

Red Flags for Differentiating Desmosomal "Hot-Phase" Cardiomyopathy From Acute Myocarditis

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BACKGROUND: Desmosomal "hot-phase" cardiomyopathy (HPC), characterized by bursts of myocardial inflammation mimicking acute myocarditis (AM), carries relevant risks of adverse outcomes. This study aimed to identify diagnostic "red flags" favoring HPC over AM.

METHODS: Patients (n=134) receiving a first diagnosis of AM, proven by endomyocardial biopsy or cardiac magnetic resonance plus troponin elevation, were retrospectively identified at a referral center. HPC was defined by presence of pathogenic desmosomal gene variants (DGVs). Clinical, imaging, and electrical features were compared between HPC cases and controls with gene-negative AM to identify red flags. Diagnostic algorithms were derived and tested in an external multicenter cohort of DGV carriers (n=30).

RESULTS: Patients with HPC (n=22; 91% *DSP*+) were more frequently female (73% versus 24%, $P<0.001$) and younger than unmatched controls with AM (32±14 versus 41±14 years, $P=0.007$). When matched 1:1 by age, sex, and presentation, DGV carriers showed distinctive red flags: family history of cardiomyopathy/AM/sudden death; recurrent troponin peaks; persistent left ventricular systolic dysfunction; right ventricular involvement; ring-like late gadolinium enhancement; late gadolinium enhancement persistence or extension; low QRS voltages; life-threatening ventricular arrhythmias at <45 years; persistent >1000/24 hours ventricular ectopy; and recurrent nonsustained ventricular tachycardia. A "first-contact" algorithm based on female sex and age <30 years achieved 77% accuracy, identifying 63% of DGV carriers in the external cohort. An alternative algorithm incorporating ring-like late gadolinium enhancement, right ventricular involvement, and family history showed higher accuracy (93%) and yield (93%).

CONCLUSIONS: Myocarditis in DGV carriers predominantly affects young women. A red flag-based approach improves recognition of desmosomal HPC over classic AM.

Key Words: arrhythmias ■ cardiomyopathy ■ desmoplakin ■ desmosomal ■ hot-phase ■ myocarditis

Over the past decade, an increasing amount of evidence supported the existence of an overlap between inflammatory and genetic cardiomyopathies.[1] In particular, bursts of myocardial inflammation mimicking myocarditis have been reported in several patients carrying pathogenic desmosomal gene variants

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CLINICAL PERSPECTIVE

What is New?

- This study identifies clues that distinguish desmosomal "hot-phase" cardiomyopathy from classic acute myocarditis. Although female sex and young age may point to "hot-phase" cardiomyopathy, 3 red flags, namely ring-like late gadolinium enhancement, right ventricular involvement, and positive family history, achieve 93% diagnostic sensitivity.

What Are the Clinical Implications?

- Using this red flag-based approach can enhance early recognition of "hot-phase" cardiomyopathy, guiding timely genetic testing and personalized management strategies to mitigate risks of arrhythmias, heart failure, and sudden cardiac death.

Nonstandard Abbreviations and Acronyms

AM	acute myocarditis
DGV	desmosomal gene variant
EMB	endomyocardial biopsy
FDG-PET	^{18}F-fluorodeoxyglucose positron emission tomography
HPC	"hot-phase" cardiomyopathy
LGE	late gadolinium enhancement
PVC	premature ventricular complexes
VA	ventricular arrhythmias

(DGVs), a condition known as "hot-phase" cardiomyopathy (HPC).[2] Although myocardial inflammation has been documented in association with cardiomyopathy-associated genes,[1] recent studies suggested that DGVs account for the vast majority of HPC, which is frequently misdiagnosed as idiopathic acute myocarditis (AM) at clinical presentation.[2,3]

Although preliminary data indicate that a number of clinical and imaging clues may favor the suspicion of HPC over classic AM, no studies so far attempted to systematically track the profile of desmosomal HPC through a multimodal and multidisciplinary approach.

The issue is clinically relevant as, at variance from classic AM, desmosomal HPC is frequently burdened by adverse outcomes, including relapse of myocardial inflammatory bursts and life-threatening arrhythmias.[3]

In other clinical settings, the red flag-based approach has been previously proposed to differentiate true genetic cardiomyopathies from their phenocopies.[4] Similarly, we hereby present a study aimed to define the diagnostic classifiers ("red flags") that favor the recognition of DGV-associated HPC over classic AM, in a uniform setting of patients presenting with their first episode of myocarditis.

METHODS

Study Design

This is a retrospective, multicenter study aimed to provide a comprehensive comparison between HPC and true AM in patients presenting with their first episode of myocarditis. The study cohort was identified between January 2013 and March 2024 at a single center (San Raffaele Hospital, Milan, Italy), based on the following inclusion criteria: (1) hospital admission for clinically suspected myocarditis (first episode) with any clinical presentation (chest pain, heart failure, arrhythmias); (2) proven diagnosis of myocarditis according to gold standard techniques, namely (a) endomyocardial biopsy (EMB), based on the histological, immunohistochemical and molecular criteria proposed by the European Society of Cardiology in 2013[5]; or (b) cardiac magnetic resonance (CMR) according to the 2018 updated Lake Louise criteria.[6] In the event of lack of necrosis on EMB ("borderline myocarditis"), as well as in CMR-only proven cases, elevated troponin was an additional requirement for enrolment; (3) genetic testing for the screening of cardiomyopathy-associated variants, including DGV (*DSC2*, *DSG2*, *DSP*, *JUP*, and *PKP2*) as the minimum panel.

The exclusion criteria were (1) known systemic autoimmune disease, including extracardiac sarcoidosis; (2) histotypes other than lymphocytic (ie, sarcoidosis, giant cell, eosinophilic myocarditis); (3) known exposure to exogenous pathogenic noxae (vaccines, alcohol, drugs, toxic agents, or prior chemo/radio/immunotherapy); (4) DGV of classes other than 4/5 according to the American College of Medical Genetics classification[7]; (5) class 4/5 DGV identified in a context other than acute myocarditis (ie, cardiomyopathy in outpatient setting; asymptomatic relatives undergoing family screening); (6) coexistent class 4/5 variants in other cardiomyopathy-associated genes; and (7) obstructive coronary artery disease or abnormal loading conditions (valvular heart diseases of degree moderate to severe, congenital heart diseases, uncontrolled hypertension).

The study flow chart is shown in Figure 1. In compliance with the Declaration of Helsinki, all participants signed written informed consent for enrolment in a research registry, approved by the local institutional review board. In patients with uncomplicated myocarditis (control group), genetic testing for DGV was performed as a part of an approved clinical research

protocol (GEAM [Yield of Genetic Testing in Arrhythmic Myocarditis] study). The data supporting the study findings will be made available upon reasonable request.

Diagnostic Techniques

The standard in-hospital diagnostic workup included 12-lead ECG telemonitoring, transthoracic echocardiogram, and assessment of cardiac biomarkers (troponin, brain natriuretic peptide). ECG-defined low voltages were diagnosed in the presence of a QRS amplitude <0.5 mV in all peripheral leads. Whenever clinically indicated, EMB was performed by percutaneous approach and fluoroscopy-guided right ventricular (RV) sampling. Cardiac tissue (3–5 samples per patient) was analyzed by experienced cardiac pathologists, according to histological (Dallas), immunohistochemical (≥14 leucocytes/mm^2, including up to 4 CD68+ monocytes/mm^2 and ≥7 CD3+ T lymphocytes/mm^2), and molecular criteria (polymerase chain reaction for viral genomes). CMR was analyzed according to the recommended standards.[8] In detail, T2-weighted images included black blood T2-short tau inversion recovery sequences on 2 orthogonal planes and parametric T2 mapping. Late gadolinium enhancement (LGE) images were acquired 10 minutes after gadolinium injection using 2-dimensional T1-weighted segmented inversion-recovery gradient-echo sequences, and analyzed on 2 orthogonal planes. The ring-like pattern was defined in the presence of LGE involving at least 3 contiguous segments within the same short-axis slice.[9,10] CMR data were reviewed by expert personnel blinded to the study design and outcomes. In the event of discordant findings, EMB results were prioritized over CMR. Reflecting the local practice, next-generation sequencing genetic testing was performed by the Illumina TruSight One-Sequence panel (Illumina, Redwood City, CA). Variants were filtered and prioritized based on information available in public databases and classified according to American College of Medical Genetics guidelines.[7] Additional patient-tailored diagnostic tests included ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET), and electroanatomical map (EAM) in patients undergoing catheter ablation of arrhythmias.

Treatment and Follow-Up

Treatment choices, including cardiological medical therapy, device implant, immunosuppressive therapy,

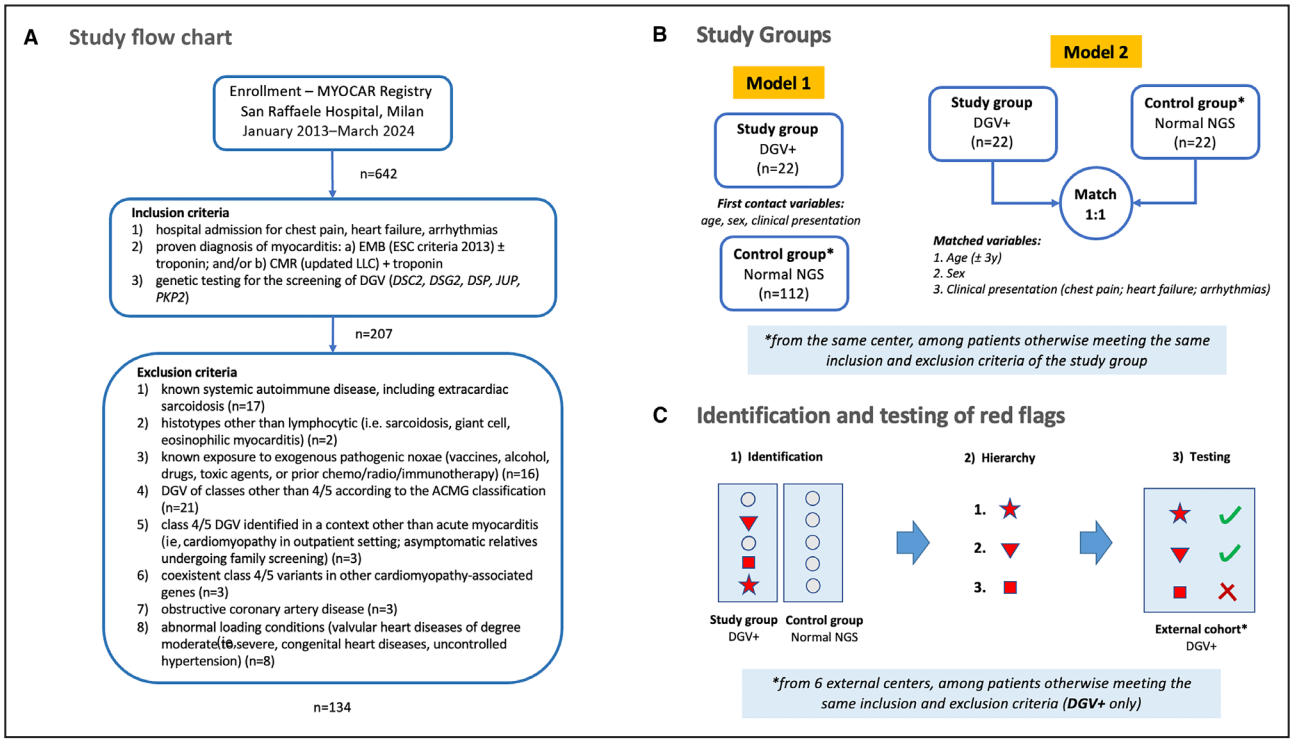

Figure 1. Study design.
The overview of the study design is presented, including a flow chart (**A**), definition of groups based on 2 models (**B**), and steps for red flag identification and sensitivity testing (**C**). ACMG indicates American College of Medical Genetics; CMR, cardiac magnetic resonance; DGV, desmosomal gene variants; *DSC2*, desmocollin-2 gene; *DSG2*, desmoglein-2; *DSP*, desmoplakin gene; EMB, endomyocardial biopsy; ESC, European Society of Cardiology; *JUP*, plakoglobin gene; LLC, Lake Louise criteria; NGS, next generation sequencing; and *PKP2*, plakophilin-2 gene.

and catheter ablation, complied with international guideline recommendations[5,11,12] and were personalized by the local multidisciplinary Disease Unit for myocarditis and arrhythmogenic cardiomyopathies. Laboratory exams, ECG, and echocardiogram were reassessed every 6 (range 3–12) months during prospective follow-up. Arrhythmias were recorded by 12-lead 24h-Holter ECGs, and cardiac device telemonitoring whenever applicable.

Events

Ventricular arrhythmias (VA) were defined based on accepted definitions[13] and further classified into monomorphic/polymorphic or regular/irregular as previously described.[14] Major VA included either sustained ventricular tachycardia (VT), ventricular fibrillation, or appropriate implantable cardioverter-defibrillator therapy, namely antitachycardia pacing or shock. HP bursts were defined as new symptomatic episodes of troponin release occurring after the proven resolution of a prior episode (full remission of chest pain and normal troponin).

Patient Groups

Cases and controls were selected among the 38% genotyped patients with AM within the MYOCAR registry. The GEAM study, aimed to explore the prevalence of cardiomyopathy-associated variants in myocarditis, provided genotype for uncomplicated cases (control group). The study groups were defined based on the results of the genetic test. In detail, patients carrying class 4/5 (likely pathogenic/pathogenic) DGVs were labeled as HPC and compared with controls. In a first model (Model 1), the comparison was made according to "first-contact" variables, namely age, sex, and type of clinical presentation (infarct-like chest pain, dyspnea/heart failure, or arrhythmias causing syncope/palpitation). In a second model (Model 2), aimed to identify the red flags of HPC based on an accurate multimodality diagnostic workup, the comparison was made between DGV carriers with controls with gene-negative AM matched 1:1 according to age (same ± 3 years), sex, and type of clinical presentation. In the presence of a match greater than 1:1, subselection was made according to the following order of priority: (1) comparable diagnostic workup on top of CMR/EMB (ie, FDG-PET, EAM), and (2) closest length of follow-up. Details about the rationale for selection of red flags in Table S1.

External Multicenter Cohort

To test the sensitivity of Models 1 and 2, the identified predictors were assessed in an external multicenter cohort of desmosomal HPC (n=30 patients) meeting the same inclusion and exclusion criteria. As a part of research registries approved by the local institutional review boards, patients were recruited retrospectively from the following participating centers: Nantes Hospital (n=10), Trieste Hospital (n=6), Padua University Hospital (n=5), Michigan Hospital (n=3), Florence Careggi (n=3), and Rome Policlinico Casilino (n=3).

Statistical Analysis

SPSS Version 20 (IBM Corp., Armonk, NY) was used for analysis. Continuous variables are expressed as mean or median with SD or range, and compared by a permutation version of the *t* test (https://kenrice.shinyapps.io/PermutationOneWayTests). Categorical variables are reported as counts and percentages and were compared by Fisher's exact test. The candidate predictors ("red flags") were defined based on the wide-scope comparison between groups, including but not limited to the variables suggested by the published literature. Clinically relevant cutoff values were defined for continuous variables (left ventricular ejection fraction [LVEF], premature ventricular complexes [PVC], nonsustained VT), as detailed in Supplemental Material. Classification and regression trees (chi-square automatic interaction detection algorithm) with custom node size 8 (primary) and 4 (secondary) were used to hierarchize the candidate predictors within the derivation cohort. Analysis was performed independently for first-contact variables (Model 1) and red flags (Model 2). The sensitivity of the resulting algorithms was subsequently evaluated in the external HPC cohort (a full validation was prevented by the absence of available genotyped controls with AM). Two-sided P values <0.05 were set as statistically significant. The Bonferroni method was applied to correct for multiple comparisons in patients undergoing repeated measurement of continuous variables (LVEF, PVC) during follow-up.

RESULTS

General Features of the Study Population

The study cohort includes 22 patients with desmosomal HPC (from n=16 families; mean age 32±14 years; 73% female) and 112 controls with AM (Figure 1). All DGV carriers were admitted to the hospital following presentation with either chest pain (n=12), heart failure (n=2), or arrhythmias (n=8). Within the HPC group, the mean LVEF on admission was 53±9%. Myocarditis was proven by EMB in 14/17 cases (83%) and by CMR plus troponin release in 18/22 (82%). Most patients (19/22; 86%) underwent genetic testing during follow-up, late after clinical presentation, and most of the identified DGVs (20/22; 91%) involved the *DSP* gene (list in

Table S2). Full comparison between DGV carriers and unmatched controls is shown in Table S3. Table 1 shows the full comparison between HPC and n=22 matched AM groups, which enabled the selection of red flags.

Treatment within the DGV group included antiremodeling agents (91%), beta blockers (91%), immunosuppressive therapy (55%), and catheter ablation of VA (14%). Arrhythmias were monitored by implantable cardioverter-defibrillator (23%) and loop recorders (45%) on top of Holter ECG (median per patient: 10 exams). FDG-PET and EAM were available in 7 (31%) and 6 patients (27%), respectively. The median follow-up was 84 (interquartile range, 49–125) months. Outcomes in matched groups are shown in Table 2. No patients died, and no one underwent a heart transplant.

All red flags identified for differentiating desmosomal HPC from AM are summarized in Central Figure/Graphical Abstract.

First-Contact Variables

As compared with unmatched controls with AM (Model 1), cases with HPC were more commonly women (respectively: 16/22 [73%] versus 27/112 [24%], $P<0.001$) and younger at presentation (respectively: 32±14 versus 41±14 years, $P=0.007$; age <30 years: 12/22 versus 26/112, $P=0.008$). Age and sex distribution in cases and controls is shown in Figure S1. Racial groups were comparable (White 95% in both groups, $P=1.00$), as well as the type of clinical presentation (respectively: chest pain 55% versus 62%, $P=0.485$; heart failure 9% versus 11%, $P=1.00$; arrhythmias 36% versus 27%, $P=0.299$).

Clinical Red Flags

As compared with the matched controls with genetically negative AM (Model 2), cases with HPC more commonly reported family history of sudden cardiac death <50 years, myocarditis, or cardiomyopathy (13/22 versus 2/22, $P=0.001$; details in Table S2). In addition, cases with HPC were more likely to experience recurrent, symptomatic bursts of troponin release (11/22 versus 1/22, $P=0.002$), with a median of 2 (range 1–10) versus 1 (range 1–2) episodes from clinical onset to the end of follow-up. Following HP bursts, reactivation of myocarditis was proven by CMR or EMB in all tested cases (n=8 HPC and n=1 AM) but not in the whole cohort. No other major differences were found in medical history and baseline clinical features, including blood exams.

Selected clinical "red flags" for desmosomal HPC were (1) family history of sudden cardiac death <50 years, myocarditis, or cardiomyopathy; and (2) recurrent symptomatic bursts of myocardial injury (ie, acute chest pain plus troponin release), with or without proven reactivation of myocarditis.

Imaging Red Flags

At baseline, the echocardiogram was comparable between groups with HPC and AM (Table 1). However, cases with HPC more commonly failed to fully normalize the systolic function by 12 months (LVEF <60%: 17/22 versus 4/22, $P<0.001$) and had lower LVEF even at the last follow-up (55±8 versus 59±6, $P=0.069$). Findings were confirmed on the last CMR at a median follow-up of 40 months, where LVEF was <60% in 15/18 patients with HPC versus 2/18 patients with AM, $P<0.001$. In addition, although both the presence of LGE and involved LV wall layers were similar between groups, patients with HPC more frequently exhibited a ring-like pattern of LGE (15/22 versus 1/22, $P<0.001$), septal localization (13/22 versus 4/22, $P=0.012$), greater extension (on average 5±3 versus 3±1 segments, $P=0.005$), and lack of LGE reduction during follow-up (either stable or increased number of segments: 17/18 versus 9/18 patients, $P=0.007$). An example of a ring-like pattern is shown in Figure 2. Lastly, imaging signs of RV involvement (ie, dilation, global or regional systolic dysfunction, LGE, or fatty replacement) were documented in 10/22 patients with HPC (including all the *PKP2* mutation carriers) versus 1/22 controls with AM ($P=0.004$).

Selected imaging "red flags" for desmosomal HPC were (3) failure to fully normalize LVEF by 12-month follow-up; (4) ring-like pattern of LGE; (5) either stable or increased extension of LGE during follow-up; and (6) imaging signs of RV involvement (dilation, global or regional systolic dysfunction, LGE, or fatty replacement).

Electrical Red Flags

The groups with HPC and AM showed no differences in baseline ECG, except for a higher prevalence of low QRS voltages in peripheral leads (14/22 versus 3/22, $P=0.002$) and a trend toward QRS widening and fragmentation, in the absence of significant incidence of atrioventricular blocks (Table 1). Instead, the incidence of VA was higher among cases with HPC: in particular, presentation with sustained VT or ventricular fibrillation by the age of 45 years was observed only in DGV carriers (5/22 versus 0/22, $P=0.009$). In addition, HPC was associated with persistence of relevant VA during follow-up, namely: frequent PVC (median daily burden 1133 versus 34, $P<0.001$; <100 per day: 3/22 versus 16/22, $P<0.001$; >1000 per day: 13/22 versus 1/22, $P<0.001$), and recurrent nonsustained VT (at least 2 episodes: 12/22 versus 2/22, $P=0.003$). During the HP bursts, a relative increase in VA burden was observed,

Table 1. Comparison of Baseline Features Between Study and Control Groups

	Total cohort (n=44)	HPC (n=22)	AM (n=22)	*P* value
Clinical profile				
Age, y*	32±14	32±14	33±14	0.824
Female sex*	32 (73)	16 (73)	16 (73)	1.000
White	42 (95)	21 (95)	21 (95)	1.000
Family history of sudden cardiac death, myocarditis, or cardiomyopathy	15 (34)	13 (59)	2 (9)	0.001†
Cardiovascular risk factors	10 (23)	4 (18)	6 (27)	0.721
Competitive sport	6 (14)	2 (9)	4 (18)	0.664
Presentation				
Chest pain*	24 (55)	12 (55)	12 (55)	1.000
Heart failure*	4 (9)	2 (9)	2 (9)	1.000
Arrhythmias*	16 (36)	8 (36)	8 (36)	1.000
Fever in past 30 d	10 (23)	3 (14)	7 (32)	0.281
Myocarditis diagnosis				
Endomyocardial biopsy proven	26/33 (79)	14/17 (83)	12/16 (75)	0.688
Cardiac magnetic resonance proven	37/44 (84)	18/22 (82)	19/22 (86)	1.000
Both	19/44 (43)	10/22 (45)	9/22 (41)	1.000
Genetic testing‡				
DSP	20 (45)	20 (91)	0 (0)	…
PKP2	2 (4)	2 (9)	0 (0)	…
Blood exams				
Troponin T (ng/L) (n.v. <14)	45 (11–279)	89 (21–1056)	41 (16–288)	0.156
N-terminal pro-B-type natriuretic peptide (pg/mL) (n.v. <125)	456 (118–1590)	235 (109–712)	198 (96–590)	0.369
C-reactive protein (mg/L) (n.v. <6.0)	6 (2–18)	5 (2–16)	7 (3–20)	0.491
Erythrocyte sedimentation rate (mm/h) (n.v. <15)	11 (6–23)	11 (5–24)	12 (4–22)	0.696
Echocardiogram				
LVEDVi (mL/m^2)	59±16	60±15	58±16	0.678
LVEF (%)	54±9	53±9	55±8	0.456
LVEF <50%	13 (30)	7 (32)	6 (27)	1.000
Tricuspid annular plane systolic excursion (mm)	21±3	21±4	22±3	0.361
Pericardial effusion	11 (25)	4 (18)	7 (32)	0.488
Cardiac magnetic resonance				
LVEDVi (mL/m^2)	76±16	77±16	76±17	0.848
LVEF (%)	55±9	55±9	55±9	1.000
RV end-diastolic volume index (mL/m^2)	68±18	69±17	66±18	0.613
RV ejection fraction (%)	60±10	59±10	62±9	0.327
Updated Lake Louise criteria+	37 (84)	18 (82)	19 (86)	1.000
T2-short-tau inversion recovery+	29 (66)	14 (64)	15 (68)	1.000
LGE+	44 (100)	22 (100)	22 (100)	1.000
T2 >50 ms	19/23 (83)	10/12 (83)	9/11 (81)	1.000
Native T1 >1045 ms	22/23 (96)	12/12 (100)	10/11 (91)	1.000
Extracellular volume >27%	19/23 (83)	10/12 (83)	9/11 (81)	1.000
Subepicardial LGE	34 (77)	18 (82)	16 (73)	0.721
Midwall LGE	20 (45)	12 (55)	8 (36)	0.364
Septal LGE	17 (38)	13 (59)	4 (18)	0.012†
Inferolateral LGE	41 (93)	21 (95)	20 (91)	1.000

(*Continued*)

Table 1. Continued

	Total cohort (n=44)	HPC (n=22)	AM (n=22)	*P* value
Ring-like LGE	16 (63)	15 (68)	1 (5)	<0.001†
LGE, n segments of 17	4±3	5±3	3±1	0.005†
RV fatty replacement	4 (9)	4 (18)	0 (0)	0.108
RV LGE	5 (11)	5 (23)	0 (0)	0.049†
Any RV involvement	11 (25)	10 (45)	1 (5)	0.004†
Electrocardiogram				
First-degree AVB	4 (9)	3 (14)	1 (5)	0.607
QRS >120 ms	1 (2)	1 (5)	0 (0)	1.000
Fragmented QRS	17 (39)	12 (55)	5 (23)	0.062
Low QRS voltage	17 (39)	14 (64)	3 (14)	0.002†
ST-segment abnormalities	16 (36)	7 (32)	9 (41)	0.755
Negative inferolateral T waves	27 (61)	16 (73)	11 (50)	0.215
Baseline arrhythmias				
Major VA (VT/VF)	6 (14)	5 (23)	1 (5)	0.185
Major VA (VT/VF) by age 45	5 (11)	5 (23)	0 (0)	0.009†
Nonsustained VT	9 (20)	7 (32)	3 (14)	0.281
Lown's grade ≥2 premature ventricular complexes	23 (52)	15 (68)	8 (36)	0.069
Atrial fibrillation	0 (0)	0 (0)	0 (0)	1.000
Second-/third-degree AVB	1 (2)	1 (5)	0 (0)	1.000
Endomyocardial biopsy				
CD3+ T lymphocytes >7/mm^2	26/33 (79)	14/17 (83)	12/16 (75)	0.688
Necrosis	9/33 (27)	4/17 (24)	5/16 (31)	0.708
Fibrosis	15/33 (45)	11/17 (65)	4/16 (25)	0.037†
Samples with fibrosis, n	1.0±0.7	1.3±0.7	0.7±0.4	0.005†
Myocyte hypertrophy	12/33 (36)	8/17 (47)	4/16 (25)	0.281
Viral genomes	5/33 (15)	2/17 (12)	3/16 (19)	0.656
Low-load parvovirus B19	3/33 (9)	2/17 (12)	1/16 (6)	1.000
FDG positron emission tomography				
Abnormal ^{18}F-fluorodeoxyglucose uptake	5/11 (45)	4/7 (57)	1/4 (25)	0.545
Electroanatomical mapping				
Epicardial approach	6/6 (100)	6/6 (100)	6/6 (100)	1.000
Low-voltage areas	6/6 (100)	3/3 (100)	3/3 (100)	1.000
Segments involved, n	5±2	7±2	3±1	0.034†
Inferolateral substrate	6/6 (100)	3/3 (100)	3/3 (100)	1.000
Therapy				
Renin-angiotensin-aldosterone system -inhibitors	37 (84)	20 (91)	17 (77)	0.412
Beta blockers	36 (82)	20 (91)	16 (73)	0.240
Antiarrhythmics	21 (48)	12 (55)	9 (41)	0.547
Amiodarone	7 (16)	4 (18)	3 (14)	1.000
Sotalol	8 (18)	5 (23)	3 (14)	0.698
Implanted devices	26 (59)	15 (68)	11 (50)	0.358
Implantable cardioverter defibrillator	9 (20)	5 (23)	4 (18)	1.000
Implantable loop recorder	17 (39)	10 (45)	7 (32)	0.537
Immunosuppressive therapy	23 (52)	12 (55)	11 (50)	1.000
Steroids	23 (52)	12 (55)	11 (50)	1.000
Oral immunosuppressants	19 (43)	10 (45)	9 (41)	1.000

(*Continued*)

Table 1. Continued

	Total cohort (n=44)	HPC (n=22)	AM (n=22)	*P* value
Biological agents	5 (11)	4 (18)	1 (5)	0.345
Treatment duration, mo	16±3	18±3	12±2	<0.001†
Catheter ablation of VA	6 (14)	3 (14)	3 (14)	1.000

Clinical features and treatment are shown for the study vs control groups. Unless otherwise specified, numbers are mean±SD, median (quartiles 1–3), or count/fractions (percentages). AM indicates acute myocarditis; AVB, atrioventricular block; FDG, ^{18}F-fluorodeoxyglucose;HPC, "hot-phase" cardiomyopathy; LGE, late gadolinium enhancement; LVEDVi, left ventricular end-diastolic volume indexed; LVEF, left ventricular ejection fraction; n.v., normal values; RV, right ventricular; VA, ventricular arrhythmias; VF, ventricular fibrillation; and VT, ventricular tachycardia.

*Indicates variables matched between groups.

†Indicates significant *P* values.

‡Genetic testing reports only pathogenic and likely pathogenic variants. Full details, including the list of variants of unknown significance, are shown in Table S2.

as well as in the prevalence of polymorphic/irregular arrhythmias. A representative example is shown in Figure 3.

Selected electrical "red flags" for desmosomal HPC were (7) low QRS voltages in peripheral leads; (8) presentation with sustained VT or ventricular fibrillation by the age of 45 years; (9) high PVC burden persisting during follow-up (as a practical rule, >1000/24 hours to rule in, and <100 to rule out); and (10) recurrent (ie, at least 2 distinct) nonsustained VT episodes.

Table 2. Comparison of Outcomes Between Study and Matched Control Groups

	Total study cohort (*n*=44)	HPC (*n*=22)	AM (*n*=22)	*P* value
Outcomes				
Follow-up length, mo	87 (46–124)	84 (49–125)	87 (41–113)	0.832
Death or heart transplant	0 (0)	0 (0)	0 (0)	1.000
Recurrent hot-phases	12 (27)	11 (50)	1 (5)	0.002*
Troponin peaks, n (range)	1 (1–10)	2 (1–10)	1 (1–2)	0.028*
Time last echo, mo	76 (39–118)	79 (44–120)	82 (37–106)	0.792
Last LVEF, %	57±7	55±8	59±6	0.068
LVEF <60% by 12 mo	21 (48)	17 (77)	4 (18)	<0.001*
LVEF <50% by 12 mo	6 (14)	4 (18)	2 (9)	0.664
Time last cardiac magnetic resonance, mo	40 (15–57)	42 (17–61)	36 (12–51)	0.356
Last LVEF <60%	17/36 (47)	15/18 (83)	2/18 (11)	<0.001*
Last right ventricular ejection fraction <60%	10/36 (28)	8/18 (44)	2/18 (11)	0.060
Late gadolinium enhancement segments = or ↑	26/36 (72)	17/18 (94)	9/18 (50)	0.007*
Time last telemonitoring (mo)	80 (41–117)	79 (44–116)	81 (39–117)	0.963
Continuous monitoring	26 (59)	15 (68)	11 (50)	0.358
Number Holter	10 (6–14)	11 (8–17)	10 (5–13)	0.789
Daily PVC count, average	214 (3–1100)	1133 (265–1816)	3 (0–89)	<0.001*
>100 PVC/d, n	25 (57)	19 (86)	6 (27)	<0.001*
>1000 PVC/d, n	14 (32)	13 (59)	1 (5)	<0.001*
NSVT (≥1 episode)	21 (48)	15 (68)	6 (27)	0.015*
Recurrent NSVT (≥2 episodes)	14 (32)	12 (55)	2 (9)	0.003*
Number of NSVT episodes	0 (0–2)	2 (0–5)	0 (0–1)	0.003*
Major ventricular arrhythmia (ventricular tachycardia/ventricular fibrillation/appropriate ICD therapy)	1 (2)	1 (5)	0 (0)	1.000
New ICD implant	3 (7)	3 (14)	0 (0)	0.233

Outcomes are shown for the study vs control groups. Unless otherwise specified, numbers are mean±SD, median (quartiles 1–3), or count/fractions (percentages). AM indicates acute myocarditis; HPC, "hot-phase" cardiomyopathy; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; NSVT, nonsustained ventricular tachycardia; and PVC, premature ventricular complexes.

*Indicates significant *P* values.

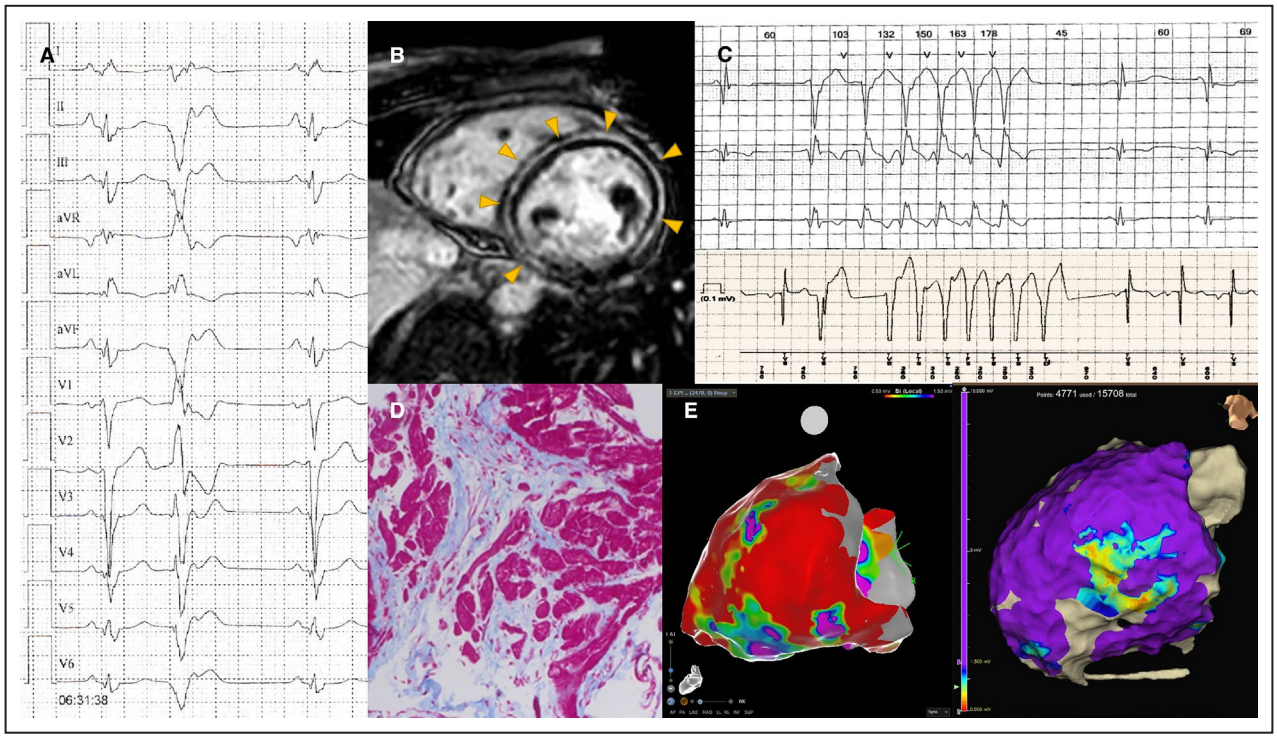

Figure 2. Diagnostic workup.
Representative examples of the diagnostic workup are shown. **A**, 12-lead ECG in a patient with desmosomal HPC: widened and fragmented QRS, low voltages in peripheral leads, and a premature ventricular complex with right bundle-branch block and superior axis morphology are visible. **B**, Cardiac magnetic resonance image, midventricular short-axis view, in a patient with HPC: a ring-like pattern of late gadolinium enhancement is shown (arrows), associated with signs of right ventricular involvement including mild dilation. **C**, Examples of nonsustained ventricular tachycardia episodes recorded by Holter ECG (**upper**) or by implanted loop recorder (**lower**) in patients with HPC: both traces were recorded during a "hot-phase," and both show variability in beat-to-beat cycle length. **D**, Endomyocardial biopsy sample, trichrome assay, showing areas of fibrosis (blue), suggesting a chronic cardiomyopathic substrate in a patient presenting with HPC. **E**, Examples of epicardial electroanatomical voltage maps, obtained in a patient with HPC (**left**; CARTO3 system) and another one with classic AM (**right**; ENSITE-X system): the patient with HPC shows extensive areas of low-voltage (red) involving the inferior-posterior-lateral wall of the left ventricle from the basis to the apex, mimicking the ring-like substrate detected by cardiac magnetic resonance; the patient with classic AM shows a focal area of low voltages involving the midsegment of the posterior left ventricular wall, surrounded by healthy myocardium (purple). AM indicates acute myocarditis; and HPC, "hot-phase" cardiomyopathy.

Histological, Metabolic, and Electroanatomical Red Flags

Overall, histology was available in 17 patients with HPC and 16 patients with AM and was concordant with CMR in most cases (76%). Inflammatory infiltrates uniformly included CD3+ T lymphocytes (Table 1). Within the group with HPC, EMB-proven fibrosis was both more common (11/17 versus 4/16, P=0.037) and more extensive in terms of the number of samples involved (1.3±0.7 versus 0.7±0.4, P=0.005). A total of 11 patients (7 with HPC and 4 with AM) underwent FDG-PET, which showed increased FDG uptake, especially among cases with HPC (4/7 versus 1/4, P=0.545). To ablate VA, 6 patients underwent EAM, which revealed more extensive low-voltage areas within the group with HPC (7±2 versus 3±1, P=0.041). Representative examples of histology and EAM are shown in Figure 2. Immunosuppressive therapy to target myocarditis was longer for n=12 cases with HPC as compared with n=11 controls with AM (18±3 versus 12±2 months, respectively, P<0.001).

There were no additional candidate "red flags" for desmosomal HPC, for insufficient amount of data. However, histology and EAM were concordant with CMR in showing more extensive areas of fibrosis, overall suggesting a chronic inflammatory process, requiring immunosuppression at a longer term.

Hierarchy and Sensitivity of Models 1 and 2

As defined by the regression trees shown in Figure 4, the biological variables "female sex" and "age <30 years" allowed identification of 20/22 (91%) of DGV carriers and correctly classified 77% of cases and controls overall (Model 1).

In the analysis on matched groups (Model 2), 3 red flags were hierarchically allocated to maximize the

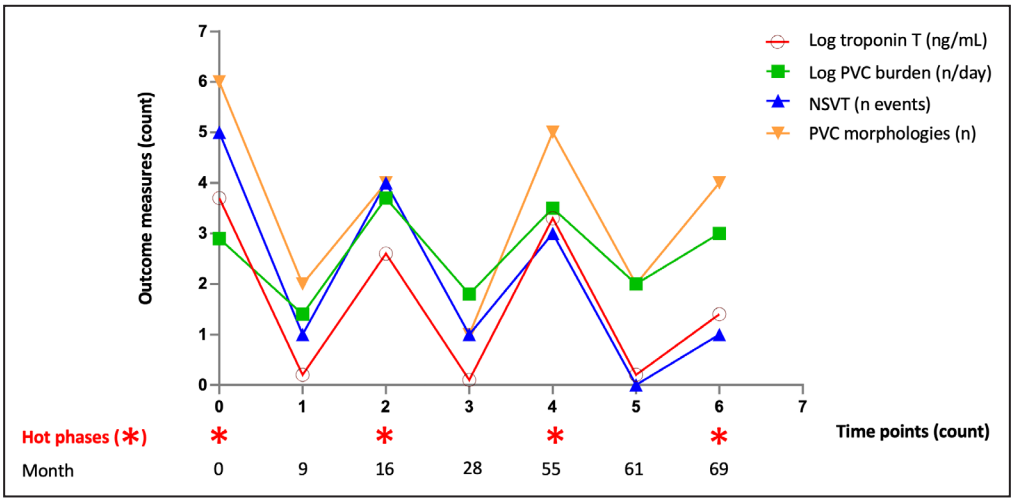

Figure 3. Arrhythmia pattern changes during the "hot phases."
Modification of ventricular arrhythmia pattern during "hot" vs "cold" phases is shown, as recorded in a patient undergoing monitoring by both 12-lead 24-h Holter ECGs and implantable loop recorder. Each "hot phase" (n=4) is labeled by a red asterisk. Troponin T values and daily PVC burden are expressed in logarithmic scale (Log). For NSVT and PVC morphologies, raw numbers are shown. The *x* axis shows follow-up time in months (nonlinear scale). The graph shows an increase in arrhythmia incidence, burden, and polymorphism, in association with symptomatic bursts of troponin release. NSVT indicates nonsustained ventricular tachycardia; and PVC, premature ventricular complexes.

discrimination of HPC over matched controls with AM, namely: (1) ring-like pattern of LGE; (2) any evidence of RV involvement at cardiac imaging; and (3) family history of sudden death, myocarditis, or cardiomyopathy. Model 2 allowed identification of 22/22 (100%) of DGV carriers and resulted in a higher overall rate of correct disease classification (93%, Figure 4).

Even applied to the external multicenter cohort, the accuracy of Model 2 was higher, because it allowed the identification of 28 of the 30 DGV carriers (93%) with AM-like presentation; in contrast, Model 1 identified only 19 of 30 cases with HPC (63%) in external cohort, where the prevalence of female DGV carriers was remarkably lower (36%). Table 3 shows the distribution of biological variables plus 10 red flags within the derivation and external cohorts with HPC. The other clinical features of the external multicenter cohort, including treatment and outcomes, are reported in Table S3. In Figure 5, we also presented practical nomograms to guide clinicians in recognizing DGV-related HPC in daily clinical practice.

DISCUSSION

Main Study Findings

We showed that, in patients presenting with their first episode of myocarditis, several red flags suggest underlying desmosomal HPC over classic AM. At first contact, female sex and young age are the main variables pointing to DGV (Model 1). Following baseline diagnostic workup, 3 red flags, namely a ring-like pattern of LGE, any evidence of RV disease, and a remarkable family history (Model 2), were found to be more sensitive in identifying DGV-related HPC. Enhanced arrhythmic patterns, recurrent symptomatic bursts of troponin release, and failure to improve LGE or normalize LVEF serve as additional supporting clues during follow-up.

These red flags could help cardiologists, radiologists, electrophysiologists, and any other specialists involved in clinical decision-making, to identify patients requiring distinct management strategies as compared with classic AM.

Comparison With Existing Literature

DGVs have been recently reported as the main cause of nonischemic cardiomyopathy overlapping with AM.[2,3] Actually, most of our findings were consistent with prior reports on DGV-related HPC, including: high prevalence in the female sex[15]; unexpectedly high prevalence of family history of myocarditis/cardiomyopathy/sudden death[1]; recurrent bursts of chest pain with troponin release[3,16]; enhanced arrhythmic pattern, including high-burden PVC,[15] nonsustained VT, and VT/ventricular fibrillation in young age[15,16]; relative increase in both arrhythmic burden and polymorphic/irregular VA during the hot phases (Figure 3), as previously described in patients with EMB-proven active myocarditis[14]; extensive LGE suggesting myocardial scarring[17] that, in light of the dominant subepicardial distribution, frequently exceeds the degree of systolic dysfunction[18]; distinct ECG signs, such as low QRS voltages

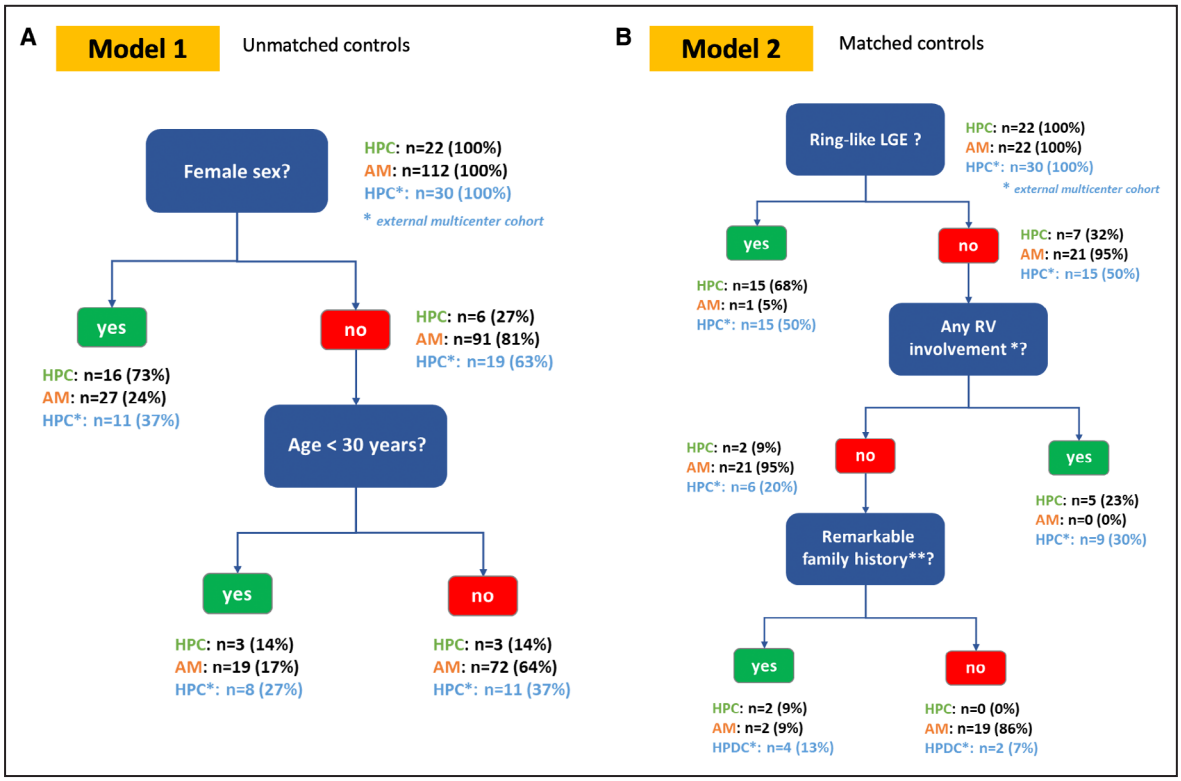

Figure 4. Identification of HPC by first-contact variables (Model 1) and red flags (Model 2).
The algorithms summarizing the main study results and enabling optimal identification of desmosomal HPC over classic AM are shown, based on both first-contact variables (Model 1 with n=22 cases and n=112 unmatched controls, **A**) and red flags (Model 2 with n=22 cases and n=22 matched controls, **B**). Classification and regression tree showing the 3 red flags resulting in the maximal sensitivity in identifying HPC over classic AM. For each step, the number and percentage of patients from the derivation HPC study (green), derivation AM control (orange), and external multicenter HPC cohorts (blue) are shown. AM indicates acute myocarditis; HPC, "hot-phase" cardiomyopathy; LGE, late gadolinium enhancement; and RV, right ventricular. *RV involvement = dilation, systolic dysfunction, late gadolinium enhancement, or fatty replacement. **Family history refers to either sudden cardiac death, AM, or cardiomyopathy.

in peripheral leads, fragmented QRS, and negative T waves in inferolateral leads, which frequently mirror the distribution of LGE[18,19]; ring-like pattern of LGE and septal involvement on CMR,[16,20] although this feature is nonpathognomonic of DGV and shared with other genetic cardiomyopathies of the dilated/nondilated spectrum[12,21]; extensive areas of substrate abnormalities (ie, low-voltage areas, late potentials) on EAM (Figure 2), which may be considered as an equivalent of the ring-like LGE[16,22]; hypermetabolic status, as already detected by FDG-PET in arrhythmogenic cardiomyopathy[23]; and greater occurrence of adverse outcomes as compared with myocarditis.[3]

Clinical Implications

The "red flags" method has already proven useful and effective to identify distinct genetic cardiomyopathies among patients presenting with a uniform phenotype.[4,12] Importantly, we identified both first-contact variables (female sex, age <30 years) suggesting HPC and a number of red flags that added accuracy in guiding the clinician to recognize HPC. The latter approach is in line with the "cardiomyopathy mindset" endorsed by the recent guidelines[12] and enabled better discrimination of HPC from classic AM (Figure 4). As compared with the existing literature, our study also represents the first attempt to hierarchically sort those features indicating HPC diagnosis over classic AM.

Indeed, identifying HPC has relevant clinical implications: (1) genetic testing could be recommended as early as a critical number of red flags are found; to be noted, genetic testing is not part of the current diagnostic standard for AM, particularly with uncomplicated chest pain presentation[24]; (2) subsequent family screening would be recommended, as for other genetic cardiomyopathies[12]; (3) early implantable cardioverter-defibrillator implant should be considered in light of increased arrhythmic risk—in fact, a risk stratification score has been recently developed for *DSP* mutation carriers,[15] representing the main subgroup with HPC also in our cohort; and (4) medical treatment, including antiremodeling drugs, beta blockers, antiarrhythmics, and even immunomodulatory drugs

Table 3. Red Flags in Derivation and External Multicenter Cohorts

Domain	Red flag		Derivation HPC (n=22)	External HPC (n=30)	*P* value
First-contact (unmatched)	Female sex		16 (73)	11 (36)	0.013*
	Age <30 y		12 (55)	12 (40)	0.400
Clinical	1	Family history of sudden cardiac death <50 y, myocarditis, or cardiomyopathy	13 (59)	17 (57)	1.000
	2	Recurrent (≥2) bursts of troponin release	11 (50)	16 (53)	1.000
Imaging	3	LVEF <60% on echocardiogram at 12 mo or LVEF <60% on cardiac magnetic resonance during follow-up	17 (77)	25 (83)	0.725
	4	Ring-like pattern of LGE	15 (68)	15 (50)	0.259
	5	Stable or increased LGE extension during follow-up	17/18 (94)	18/18 (100)	1.000
	6	Any imaging sign of right ventricular involvement (dilation, global or regional dysfunction, LGE, fatty infiltration)	10 (45)	13 (43)	1.000
Electrical	7	Low QRS voltages in ECG peripheral leads	14 (64)	18 (60)	1.000
	8	Sustained VT or ventricular fibrillation in age <45 y	5 (23)	7 (23)	1.000
	9	High burden of premature ventricular complexes persisting during follow-up (>1000/24 h)	13 (59)	14/27 (52)	0.773
	10	Recurrent nonsustained VT (>1 episode)	12 (55)	10/21 (48)	0.764

The prevalence of first-contact variables (n=2) and red flags (n=10) is shown in the derivation and external cohorts with HPC. HPC indicates "hot-phase" cardiomyopathy; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; and VT, ventricular tachycardia.
*Indicates significant *P* value.

may be considered for a longer term, in light of the chronic/recurrent nature of the disease.[16] In particular, it is worth noting that the finding of EMB-proven virus-negative lymphocytic myocarditis enabled the use of immunosuppressive therapy in a consistent proportion of patients within the derivation cohort, including both the groups with HPC and AM (Table 1). At the leading center, EMB was performed in clinically demanding scenarios, including persistent systolic dysfunction, arrhythmias, or symptomatic troponin release.

The algorithms to identify desmosomal HPC (Figure 4) were notable for including only variables readily measurable at the time of baseline workup, including family history, echocardiogram, and CMR. However, many other relevant features (ie, recurrent troponin release, active arrhythmic patterns, or failure to normalize LVEF/LGE) may become manifest late after the first medical contact. To support the clinicians in their daily clinical practice, we also presented practical flow charts (Figure 5) to enable the prompt recognition of red flags at any time during follow-up. Confirmatory data are awaited by future studies.

Limitations

This study is mainly limited by the small sample size, which is in part justified by the rarity of the disease, and extensive availability of diagnostic exams at a referral center for the multidisciplinary management of myocarditis.[16] However, we attempted to improve the consistency of the study findings by validating the red flags in a multicenter cohort of HPC displaying a distinct clinical profile (Table S4) but a uniform AM-like presentation. An important limitation of our study was the lack of genetic testing in controls with AM within the external multicenter cohort. Subsequently, the validation of the study results was incomplete and limited to the sensitivity (but not the specificity) of algorithms. We also acknowledge that the chi-square automatic interaction detection method may be limited by overfitting because it was applied to very small groups. Coherently with HPC epidemiology and in contrast with classic AM,[15] HPC was more common in women; however, larger studies are needed to confirm the role of female sex as a red flag for DGV. Importantly, our study did not include sarcoidosis and giant cell myocarditis as an alternative source of life-threatening VA in myocarditis.[25] Although a selection bias is expected by including a few individuals from the same family (Table S2), all members presented independently with symptomatic AM and displayed hugely variable clinical courses. Because we focused only on the "first myocarditis" clinical presentation, our study has no claims to generalize findings to outpatients with desmosomal HPC or asymptomatic relatives. Finally, our analysis mainly included *DSP* and did not include genetic HPC related to nondesmosomal gene variants; future studies will be needed to explore them.

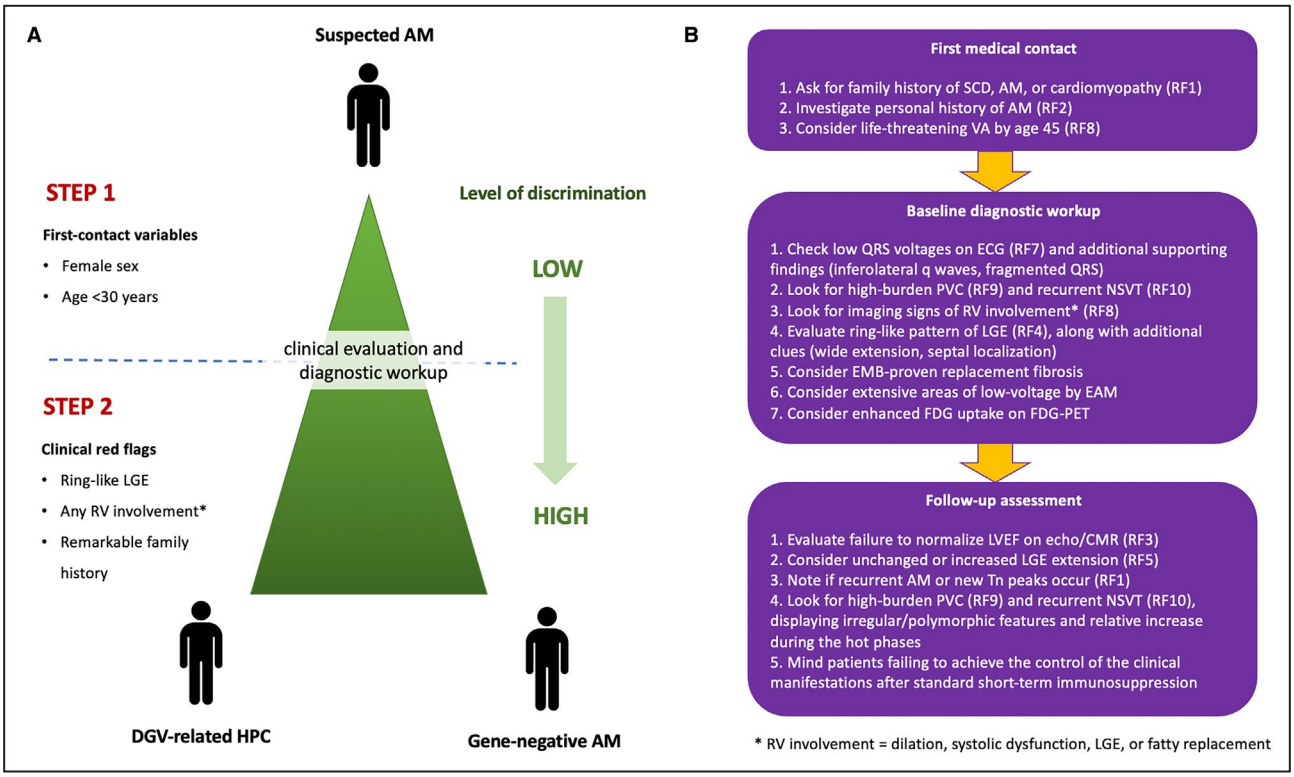

Figure 5. Clinical nomograms.
A, Sequential assessment of first-contact variables (Model 1) and main red flags (Model 2), allowing to progressively discriminate DGV-related HPC from gene-negative AM at clinical presentation. **B**, Chronological nomogram constructed based on the 10 red flags, to help clinicians to identify HPC over classic AM both at clinical presentation and during follow-up. AM indicates acute myocarditis; CMR, cardiac magnetic resonance; DGV, desmosomal gene variants; EAM, electroanatomical map; EMB, endomyocardial biopsy; f-QRS, fragmented QRS; FDG-PET, ^{18}F-fluorodeoxyglucose positron emission tomography scan; HPC, "hot-phase" cardiomyopathy; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; NSVT, nonsustained ventricular tachycardia; PVC, premature ventricular complexes; RF, red flag; RV, right ventricular; SCD, sudden cardiac death; and VA, ventricular arrhythmias.

CONCLUSIONS

This study identified a series of red flags that can support clinicians in the differential diagnosis between desmosomal HPC and AM. AM presentation in young women very likely represents a DGV-related myocardial disorder. Beyond biological variables available at first contact, the most relevant diagnostic clues include the ring-like pattern of LGE, RV involvement, and a significant family history of sudden death or cardiomyopathy. These findings not only enhance the understanding of HPC's clinical characteristics but also provide a practical tool for personalized clinical management. Early adoption of these criteria could guide critical decisions, such as indications for genetic testing, family screening, and arrhythmia prevention strategies. Despite the limitations related to sample size, our work lays the foundation for further prospective studies that could strengthen the use of these criteria in clinical practice. We encourage other institutions to test and implement this approach to improve care for patients with suspected DGV-related HPC.

ARTICLE INFORMATION

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Disclosures

The authors report no conflicts of interest regarding the content of this article.

Supplemental Material

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Tables S1–S4
Figure S1
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