Supplemental Material

SUPPLEMENTAL METHODS

Candidate red flags: justification for cutoff values

For left ventricular ejection fraction (LVEF), we used 60% to aid the discrimination between normality (LVEF ≥60%) and any degree of abnormality (LVEF <60%). In fact, in many genetic cardiomyopathies potentially overlapping with myocarditis, it is known that even a small LVEF decrement results in a negative prognostic value[12,26]. For premature ventricular complexes (PVC), the cutoff of 1000 PVC daily is supported by its diagnostic and prognostic relevance in arrhythmogenic cardiomyopathies[27]. For non-sustained ventricular tachycardia (NSVT), one single episode was deemed relevant in keeping with updated evidence[12].

SUPPLEMENTAL TABLES

Table S1. Selection of red flags

Domain	Red Flag		Rationale	References
Clinical	1	Family history of SCD <50 years, myocarditis, or cardiomyopathy	AM is generally an acquired disease (i.e., viral, autoimmune, or toxic); a remarkable family history, suggesting genetic etiology, should raise suspicion of HPC	[3,20]
	2	Recurrent (≥2) bursts of troponin release	AM with ACS-like presentation is usually characterized by a single rise-and-fall troponin release; recurrent bursts of troponin should raise suspicion of HPC	[3,16,20]
Imaging	3	LVEF <60% on echocardiogram at 12 months and/or LVEF <60% on CMR during follow-up	AM with uncomplicated presentation is usually associated with normal systolic function; heart failure with reduced LVEF should raise suspicion of HPC	[8,28]
	4	Ring-like pattern of LGE	AM usually shows inferolateral basal LV or, more rarely, septal LGE involvement; ring-like pattern, i.e., presence of LGE involving at least 3 contiguous segments within the same short-axis slice, should raise suspicion of HPC	[10,15,16]
	5	Stable or increased LGE extension during follow-up	AM usually shows reduction or resolution of LGE after the acute phase; stable or increased LGE extension at follow-up CMR should raise suspicion of HPC	[10,15,16]

	6	Any imaging sign of RV involvement (dilation, global or regional dysfunction, LGE, fatty infiltration)	AM usually involves only LV; RV only or biventricular involvement should raise suspicion of HPC	[15]
Electrical	7	Low QRS voltages in ECG peripheral leads	AM usually shows normal QRS voltages; low QRS voltages, pointing at extensive myocardial fibrosis, should raise suspicion of HPC	[29]
	8	Sustained VT or VF in age <45 years	Malignant VA, namely sustained VT or VF, in young age are an uncommon presentation of AM and should raise suspicion of HPC	[1,3,6,9]
	9	High burden of PVC persisting during follow-up (>1000/24 hours)	AM is usually associated with a reduction of PVC burden after the acute phase; a persistently high PVC burden during follow-up should raise suspicion of HPC; the cutoff of 1000/24 hours was defined based on existing literature about ARVC and *DSP*-related cardiomyopathy	[1,3,6,9]
	10	Recurrent NSVT (>1 episode)	Complex VA, such as recurrent NSVT episodes that persist also during follow-up, are uncommon in AM, and should raise suspicion of HPC	[1,3,6,9]

The list of each of the ten red flags is shown in the derivation and external multicenter cohorts with HPC, along with their rationale and references.

ACS=acute coronary syndrome; AM=acute myocarditis; ARVC=arrhythmogenic right ventricular cardiomyopathy; CMR=cardiac magnetic resonance; ECG=electrocardiogram; HPC="hot-phase" cardiomyopathy; LGE=late gadolinium enhancement; LV=left ventricle; LVEF=left ventricular ejection fraction; NSVT=non-sustained ventricular tachycardia; PVC=premature ventricular complexes; RV=right ventricle; VA=ventricular arrhythmias; VF=ventricular fibrillation; VT=ventricular tachycardia.

Table S2. Desmosomal gene variants and clinical features of study group

DGV carrier	Variant and ACMG class	Age (years)	Sex	Presentation	Family history
1	*DSP*, c.5428C>T, class 5	20	Male	Chest pain	Cardiomyopathy, AM
2	*DSP*, c.7903 G>T, class 5	54	Female	Chest pain	AM
3	*DSP*, c.5428C>T, class 5	22	Female	Chest pain	Cardiomyopathy, AM
4	*DSP*, c.5428C>T, class 5	57	Female	Chest pain	Cardiomyopathy
5	*DSP*, c.4198 C>T, class 4 *MYH6*, c.4192 C>T, class 3	29	Female	Chest pain	No
6	*DSP*, c.3155_3156del, class 5	23	Female	Major VA	Cardiomyopathy, SCD
7	*DSP*, c.5017G>T, class 4 *FLNC*, c.3511G>A, class 3 *LDB3*, c.1972G>A, class 3 *RYR2*, c.730T>A, class 3 *CDH2*, c.1781A>G, class 3	42	Female	VA	No

8	*DSP*, c.313C>T, class 5	34	Female	Major VA	No
9	*PKP2*, c.1440_1444del, class 4	23	Female	Major VA	No
10	*DSP*, c.7899dup, class 4	45	Female	Major VA	No
11	*DSP*, c.7903 G>T, class 5	20	Male	Chest pain	Cardiomyopathy, AM
12	*DSP*, c.3155_3156del, class 5	22	Male	Chest pain	Cardiomyopathy, AM
13	*PKP2*, c.368G>A, class 5 *LDB3*, c.158A>G, class 3	35	Male	Major VA	No
14	*DSP*, c.1416dup, class 4 *MYBPC3*, c.1003C>T, class 3	23	Female	Chest pain	No
15	*DSP*, c.6496C>T, class 5	52	Female	VA	No
16	*DSP*, c.3155_3156del, class 5	15	Female	Chest pain	Cardiomyopathy, AM
17	*DSP*, c.1408A>G and c.1696G>A (cis), class 4	16	Male	Chest pain	SCD
18	*DSP*, c.4198C>T, class 4 *SCN10A*, c.4304T>C, class 3	36	Female	Heart failure	No
19	*DSP*, c.5269C>T, class 4	44	Female	Heart failure	No
20	*DSP*, c.3155_3156del, class 5	10	Female	Chest pain	Cardiomyopathy, AM
21	*DSP*, c.5662_5663delAG, class 4	27	Female	Chest pain	No
22	*DSP*, c.2011delG, class 4	56	Male	VA	SCD, Cardiomyopathy

The list of DGV within the study cohort (n=22) is shown, along with clinical features at presentation. Patients n. 1, 3, and 4 were from the same family, as well as n. 6, 12, 16, and 60, while n. 5 and 18 were unrelated. *ACMG=American College of Medical Genetics; AM=acute myocarditis; DCM=dilated cardiomyopathy; DGV=desmosomal gene variant; DSP=desmoplakin gene; PKP2=plakophilin-2 gene; SCD=sudden cardiac death; VA=ventricular arrhythmias (major=sustained ventricular tachycardia, ventricular fibrillation, or cardiac arrest).*

Table S3. Comparison of baseline features, treatment, and outcomes between study and unmatched control groups

	HPC (*n*=22)	**AM (*n*=112)**	***p-value***
Clinical profile			
Age (y)	32±14	41±14	**0.007**
Female sex	16 (73)	27 (24)	**<0.001**
Caucasian	21 (95)	106 (95)	1.000
Family history of SCD, myocarditis, or cardiomyopathy	13 (59)	8 (7)	**<0.001**
Presentation			
Chest pain	12 (55)	70 (62)	0.485
Heart failure	2 (9)	12 (11)	1.000
Arrhythmias	8 (36)	30 (27)	0.299
Myocarditis diagnosis			
EMB-proven	14/17 (83)	76/102 (75)	0.761
CMR-proven	18/22 (82)	99/111 (89)	0.303
Both	10/22 (45)	47/112 (41)	0.816

Echocardiogram			
LVEDVi (mL/m^2)	60±15	57±14	0.366
LVEF (%)	53±9	55±7	0.246
TAPSE (mm)	21±4	22±3	0.742
Cardiac magnetic resonance			
Updated LLC+	18/22 (82)	94/111 (86)	0.751
T2-STIR +	14/22 (64)	80/111 (72)	0.449
LGE+	22/22 (100)	109/111 (98)	1.000
-Septal LGE	13/22 (59)	19/111 (17)	**0.001**
-RLP LGE	15/22 (68)	8/111 (7)	**<0.001**
Electrocardiogram			
First-degree AVB	3 (14)	7 (6)	0.212
QRS >120 ms	1 (5)	2 (2)	0.419
Therapy			
RAAS-inhibitors	20 (91)	85 (76)	0.160
Beta-blockers	20 (91)	80 (71)	0.063
Antiarrhythmics	12 (55)	43 (38)	0.235
ICD	5 (23)	15 (13)	0.774
ILR	10 (45)	37 (33)	**0.003**
Immunosuppressive therapy	12 (55)	50 (45)	0.485
Catheter ablation of VA	3 (14)	9 (8)	0.416
Outcomes			
Follow-up length (months)	84 (49-125)	82 (37-114)	0.845
Death	0 (0)	1 (1)	1.000
Heart transplant	0 (0)	1 (1)	1.000
Recurrent hot-phases	11 (50)	7 (6)	**<0.001**

Major VA (VT/VF/appropriate ICD therapy)	1 (5)	3 (3)	0.516
Last LVEF (%)	55±8	58±7	0.075

Clinical features and treatment are shown for the study vs. control groups. Unless otherwise specified, numbers are mean±standard deviation, median (quartiles 1-3), or count/fractions (percentages). Significant p-values are in bold font. As per the study design, the variables marked by * were matched between groups. **Genetic testing reports only pathogenic and likely pathogenic variants. Full details, including the list of variants of unknown significance, are shown in **Table S2**.

AM=acute myocarditis; AVB=atrioventricular block; CD=cluster of differentiation; CMR=cardiac magnetic resonance; CRP=C-reactive protein; ECV=extracellular volume; EMB=endomyocardial biopsy; ESR=erythrocyte sedimentation rate; FDG-PET=^{18}F-fluorodeoxyglucose positron emission tomography; HPC="hot-phase" cardiomyopathy; ICD=implantable cardioverter defibrillator; ILR=implantable loop recorder; LGE=late gadolinium enhancement; LLC=Lake Louise criteria; LVEDVi=left ventricular end-diastolic volume indexed; LVEF=left ventricular ejection fraction; NSVT=non-sustained ventricular tachycardia; PVC=premature ventricular complexes; RAAS=renin-angiotensin-aldosterone system; RV=right ventricular; RVEDVi=right ventricular end-diastolic volume indexed; RVEF=right ventricular ejection fraction; SCD=sudden cardiac death; STIR=short-tau inversion recovery; TAPSE=tricuspid annular plane systolic excursion; VA=ventricular arrhythmias; VF=ventricular fibrillation; VT=ventricular tachycardia.

Table S4. Clinical features of external cohort

	External multicenter HPC (*n*=30)
Clinical profile	

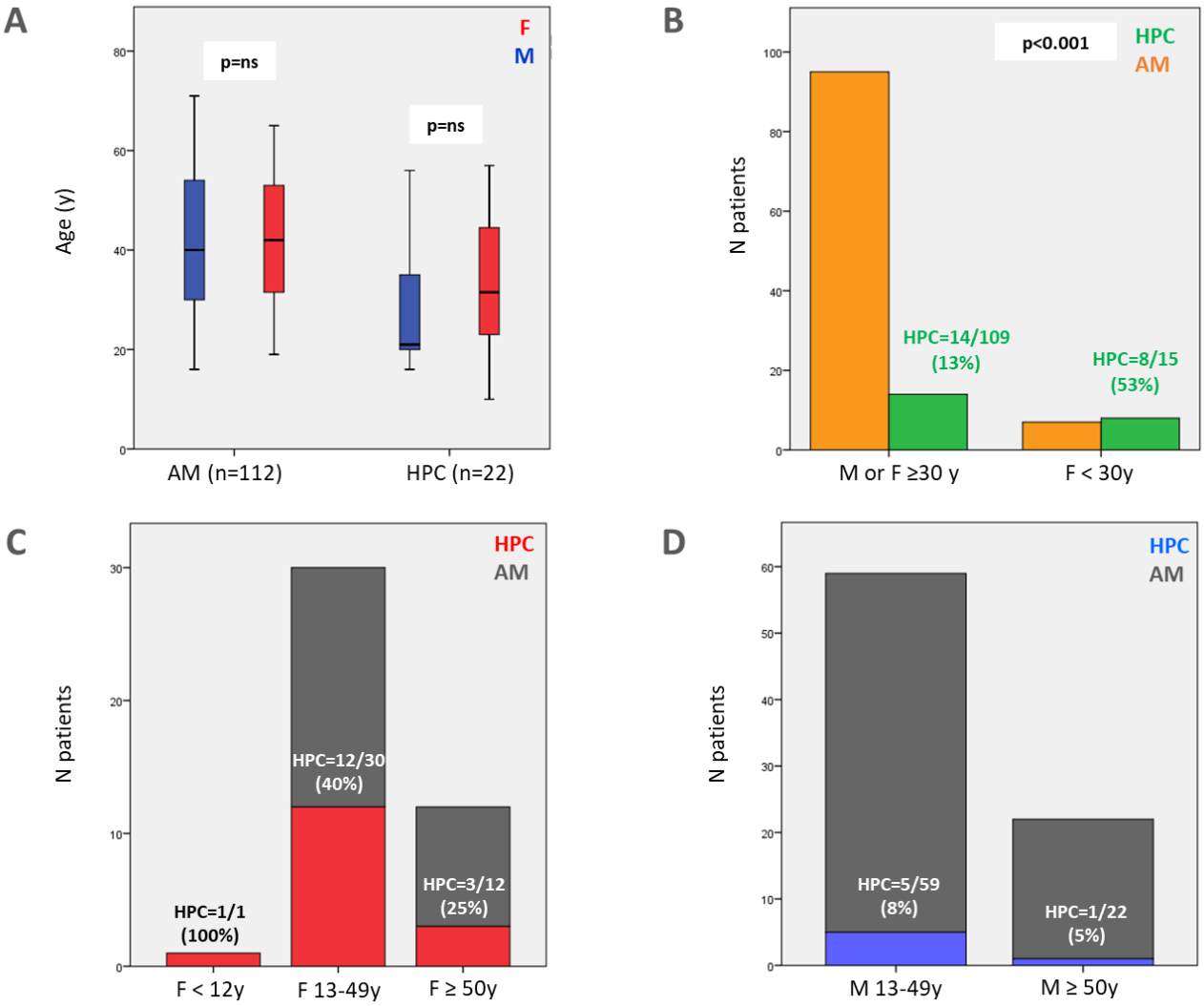
Age (years)	34±15
Female sex	11 (37)
Caucasian	29 (97)
Genotype	
DSP	24 (80)
PKP2	3 (10)
DSG2	3 (10)
Presentation	
Chest pain	18 (60)
Heart failure	6 (20)
Arrhythmias	6 (20)
Myocarditis diagnosis	
EMB-proven	2/3 (67)
CMR-proven	28/29 (97)
Both	1/2 (50)
Electrocardiogram	
First-degree AVB	4 (13)
QRS >120 ms	2 (7)
Fragmented QRS	13 (43)
Echocardiogram	
LVEDVi (mL/m^2)	63±17
LVEF (%)	47±11
LVEF <50%	14 (47)
Cardiac magnetic resonance	
LGE	26 (87)
Septal LGE	16 (53)

LGE, n segments of 17	5±4
Therapy	
RAAS-inhibitors Beta-blockers Antiarrhythmics	27 (90) 24 (80) 5 (17)
ICD	18 (60)
Outcomes	
Follow-up length	87 (68-140)
Death Heart transplant Major VA	1 (3) 2 (7) 10 (33)

The main clinical features other than "red flags" (Table 3), along with treatment and outcomes, are shown for the external multicenter cohort. Numbers are mean±standard deviation or count/fractions (percentages). *AVB=atrio-ventricular block; CMR=cardiac magnetic resonance; DSG2=desmoglein-2 gene; DSP=desmoplakin gene; EMB=endomyocardial biopsy; HPC="hot-phase" cardiomyopathy; ICD=implantable cardioverter defibrillator; LGE=late gadolinium enhancement; LVEDVi=left ventricular end-diastolic volume (indexed); LVEF=left ventricular ejection fraction; PKP2=plakophilin-2 gene; RAAS=renin-angiotensin-aldosterone system; VA=ventricular arrhythmias (major=sustained ventricular tachycardia, ventricular fibrillation, or appropriate ICD therapy).*

SUPPLEMENTAL FIGURES

Figure S1. Age and sex distribution in HPC and AM



Distribution of age and sex is shown for HPC and AM within the study cohort. Panel A. Age distribution in AM controls and HPC cases of both sexes. Panel B. Prevalence of HPC in females <30 years vs. males or females ≥30 years. Panel C. Prevalence of HPC in females pre-menarche, during fertile age, and after menopause. Panel D. Prevalence of HPC in males according to age groups, mirroring panel C clusters.

AM=acute myocarditis; F=female; HPC=hot-phase cardiomyopathy; M=male; N=number.