Acute Myocarditis Associated With Desmosomal Gene Variants

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ABSTRACT

BACKGROUND The risk of adverse cardiovascular events in patients with acute myocarditis (AM) and desmosomal gene variants (DGV) remains unknown.

OBJECTIVES The purpose of this study was to ascertain the risk of death, ventricular arrhythmias, recurrent myocarditis, and heart failure (main endpoint) in patients with AM and pathogenic or likely pathogenetic DGV.

METHODS In a retrospective international study from 23 hospitals, 97 patients were included: 36 with AM and DGV (DGV[+]), 25 with AM and negative gene testing (DGV[−]), and 36 with AM without genetics testing. All patients had troponin elevation plus findings consistent with AM on histology or at cardiac magnetic resonance (CMR). In 86 patients, CMR changes in function and structure were re-assessed at follow-up.

RESULTS In the DGV(+) AM group (88.9% *DSP* variants), median age was 24 years, 91.7% presented with chest pain, and median left ventricular ejection fraction (LVEF) was 56% on CMR (P = NS vs the other 2 groups). Kaplan-Meier curves demonstrated a higher risk of the main endpoint in DGV(+) AM compared with DGV(−) and without genetics testing patients (62.3% vs 17.5% vs 5.3% at 5 years, respectively; $P < 0.0001$), driven by myocarditis recurrence and ventricular arrhythmias. At follow-up CMR, a higher number of late gadolinium enhanced segments was found in DGV(+) AM.

CONCLUSIONS Patients with AM and evidence of DGV have a higher incidence of adverse cardiovascular events compared with patients with AM without DGV. Further prospective studies are needed to ascertain if genetic testing might improve risk stratification of patients with AM who are considered at low risk.
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Most cases of acute myocarditis (AM) have a viral trigger or an autoimmune etiology,[1-3] and a genetic predisposition has been sporadically reported.[4-10] Occasionally, patients with AM may have a positive family history for AM, arrhythmogenic right ventricular (RV) cardiomyopathy, or sudden cardiac death that can lead to genetic testing for desmosomal gene variants (DGVs).[5,6,8-12] Furthermore, patients with arrhythmogenic RV cardiomyopathy may have a previous history of AM.[12,13] Small case series and case reports of patients presenting with AM associated with pathogenic or likely pathogenic DGVs have been recently described,[5-7,9-12,14-17] particularly in pediatric patients presenting with AM with a dilated cardiomyopathy phenotype,[16] or with sudden cardiac death.[15]

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Patients with AM and normal or near-normal left ventricular ejection fraction (LVEF) generally have a low risk of adverse cardiac events at follow-up.[18-20] Recent studies reported myocarditis recurrence or ventricular arrhythmias in 3.1% to 9.3%, respectively, in patients with AM and preserved LVEF or uncomplicated presentation, with a median follow-up that spanned from 19 to 35 months.[19,20] The septal distribution of late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR) allowed the identification of a subgroup of patients at higher risk within those with AM and preserved LVEF.[18] The recent description of cases of AM associated with DGVs led us to ascertain if the subgroup of AM with pathogenic or likely pathogenic DGVs (DGV[+]) is at increased risk of adverse cardiovascular events. Here, we present the clinical characteristics, diagnostic findings, and outcome of an international cohort of patients presenting with AM and DGV(+) in comparison with a group of AM and negative DGV (DGV[−]) and AM without genetic tests (AM without genetics).

ABBREVIATIONS AND ACRONYMS

AM = acute myocarditis

CMR = cardiac magnetic resonance

DGV = desmosomal gene variant

EF = ejection fraction

LGE = late gadolinium enhancement

LV = left ventricle/ventricular

LVEF = left ventricular ejection fraction

RV = right ventricle/ventricular

RVEF = right ventricular ejection fraction

VF = ventricular fibrillation

VT = ventricular tachycardia

METHODS

STUDY POPULATION. DGV(+) patients. This is a retrospective, international, multicenter cohort study that enrolled a series of genotyped probands who were admitted with suspected AM. Diagnosis of AM was based on symptoms in combination with increased troponin levels and CMR findings consistent with the diagnosis of AM,[21] or based on histology.[1] Twenty-three hospitals from Europe (n = 15), the United States (n = 6), Canada (n = 1), and Israel (n = 1) contributed to the "Desmosomal-associated Acute Myocarditis Registry" (the list of centers is available in the Supplemental Methods). The Niguarda Hospital in Milano, Italy, acted as coordinating center. The Institutional

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TABLE 1 Clinical Presentation and Diagnostic Findings in Patients With AM With DGV(+) vs Patients Without DGV(−) or Without Genetic Tests

	No. of Patients With Available Data	DGV(+) AM (n = 36)	DGV(−) AM (n = 25)	AM Without Genetic Tests (n = 36)	*P* Value
Demographics					
Age, y	36/25/36	24 (17-38)	30 (24-33)	31 (20-37)	0.28
Age <30 y	36/25/36	25 (69.4)	11 (44.0)	15 (41.6)	**0.038**
Female	36/25/36	12 (33.3)	5 (20.0)	**2 (5.6)**	**0.012**
Family/personal history					
Previous episode of myocarditis	36/25/36	9 (25.0)	6 (24.0)[a]	**1 (2.8)**	**0.020**
Known family history of myocarditis at the time of admission	36/25/36	8 (22.2)	**0 (0)**	**0 (0)**	**0.0006**
Known family history of ARVC at time of admission	36/25/36	4 (11.1)	0 (0)	0 (0)	**0.029**
First-degree relative with history of SCD or aborted SCD <65 y of age	36/25/36	6 (16.7)	0 (0)	1 (2.8)	**0.020**
History/current competitive sport	34/24/34	5 (14.7)	4 (16.7)	2 (5.9)	0.38
Use of recreational drugs	34/25/36	4 (11.8)	1 (4.0)	1 (2.8)	0.26
Prodromal symptoms	36/25/36	13 (39.4)	12 (48.0)[a]	**32 (88.9)**	**<0.0001**
Presenting symptoms					
Dyspnea	36/25/36	3 (8.3)	3 (12.0)	6 (16.7)	0.56
Chest pain	36/25/36	33 (91.7)	23 (92.0)	35 (97.2)	0.56
Syncope	36/25/36	4 (11.1)	0 (0)	1 (2.8)	0.11
Palpitations	36/25/36	6 (16.7)	2 (8.0)	1 (2.8)	0.12
Out-of-hospital cardiac arrest	36/25/36	2 (5.6)	0 (0)	0 (0)	0.18
Laboratory findings					
Increased troponin	36/25/36	36 (100)	25 (100)	36 (100)	–
Fold increase of troponin above the URL	31/20/35	230 (34-598)	96 (34-361)	114 (59-178)	0.08
ECG on admission[b]					
Sinus rhythm	34/24/35	33 (97.1)	24 (100)	35 (100)	0.42
I-degree AV block	31/24/34	1 (3.2)	1 (4.2)	0 (0)	0.52
II- or III-degree AV block	31/24/34	0 (0)	2 (8.3)	0 (0)	0.06
Left bundle branch block	31/23/32	0 (0)	0 (0)	0 (0)	–
Right bundle branch block	31/23/32	1 (3.2)	1 (4.3)	0 (0)	0.53
ST-segment elevation	31/24/34	17 (54.8)	13 (54.2)	27 (79.4)	0.06
Negative/flat T-wave on anterior leads	31/23/28	3 (9.7)	4 (17.4)	1 (3.6)	0.25
Negative/flat T-wave on V_5-V_6 leads	31/23/28	5 (16.1)	1 (4.3)	6 (21.4)	0.22
Negative/flat T-wave on inferior leads	31/23/28	6 (19.4)	4 (17.4)	5 (17.9)	0.98

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Review Board in Milano (Ethics Committee Milano Area 3) approved this retrospective study during the session of May 27, 2020. The participating centers obtained local institutional review board approval for the collection of retrospective anonymous data as needed.

Inclusion criteria were as follows: 1) demonstration of symptomatic clinically suspected AM; 2) increased levels of troponin during the index hospitalization; 3) histologic or CMR criteria consistent with AM (classic or updated Lake Louis criteria or presence of epicardial LGE pattern);[21] and 4) evidence of DGVs, including desmoplakin (*DSP gene*), desmocollin-2 (*DSC2*), desmoglein-2 (*DSG2*), plakophilin-2 (*PKP2*), and plakoglobin (*JUP*). Genetic testing was carried out using the next generation sequencing when available, or by direct gene sequencing with di-deoxy Sanger technique, which was also used to confirm variants. Exclusion criteria were as follows: 1) benign, likely benign gene variants or variants of uncertain significance;[22] and 2) evidence of major or minor imaging criteria for arrhythmogenic RV cardiomyopathy in agreement with the 2010 revised Task Force criteria at initial presentation.[23]

Between August 2010 and April 2020, 66 potentially suitable patients with DGV(+) were identified. After careful review of the data, 30 (45.5%) cases were excluded (see Supplemental Methods). Thus, 36 DGV(+) patients with AM were included in the final analysis, of whom 13 (36.1%) have been previously published as case reports or as part of a small case series.[5,6,8-11]

Control groups. To assess whether the frequency of events in the DGV(+) AM group was higher than expected in patients admitted with AM, we identified 2 different control groups: DGV(−) AM and AM without genetics. Criteria for the diagnosis of AM were the

TABLE 1 Continued

	No. of Patients With Available Data	DGV(+) AM (n = 36)	DGV(−) AM (n = 25)	AM Without Genetic Tests (n = 36)	*P* Value
Echocardiography on admission					
LVEF, %	28/23/34	59 (50-65)	55 (45-60)	56 (44-61)	0.29
RV dilation	28/24/33	0 (0)	3 (12.5)	2 (6.1)	0.16
RV dysfunction	28/24/33	0 (0)	4 (16.7)	2 (6.1)	0.06
Coronary angiogram[c]	36/25/36	21 (58.3)	20 (80.0)[a]	17 (47.2)	**0.04**
Available histology from EMB or postmortem examination	36/25/36	13 (36.1)	7 (28.0)	10 (27.8)	0.70
Histology diagnostic for myocarditis based on ESC criteria	13/7/10	9 (69.2)	5 (71.4)	5 (50.0)	0.56
In-hospital telemetry monitoring					
NSVT	36/25/36	14 (38.9)	**2 (8.0)**	**5 (13.9)**	**0.006**
SVT/VF	36/25/36	2 (5.6)	0 (0)	0 (0)	0.18
Treatment					
Need for inotropic support	36/25/36	1 (2.8)	1 (4.0)	2 (5.6)	0.46
Need for temporary MCS	36/25/36	1 (2.8)	0 (0)	0 (0)	0.42
Use of NSAIDs	36/25/36	11 (30.6)	7 (28.0)	16 (44.4)	0.32
Use of corticosteroids	36/25/36	6 (16.7)	8 (32.0)	3 (8.3)	0.06
Use of IVIG	36/25/36	2 (5.6)	0 (0)	0 (0)	0.18
Use of colchicine	36/25/36	2 (5.6)	3 (12.0)	0 (0)	0.11
Use of azathioprine	36/25/36	1 (2.0)	0 (0)	0 (0)	0.42
Use of beta-blockers at discharge	36/25/36	26 (72.2)	14 (56.0)	22 (61.1)	0.39
Use of ACEI/ARBs at discharge	36/25/36	18 (50.0)	13 (52.0)	22 (61.1)	0.61
Follow-up duration, d	36/25/36	1,256 (499-2,251)	820 (517-1,364)	1,220 (563-1,826)	0.40

Values are n (%) or median (Q1-Q3), unless otherwise indicated. The *P* value reported in the last column refers to the comparison among the 3 groups. In **bold** are reported significant differences after multiple comparison-adjustment ($P < 0.0166$) with DGV(+). [a]Indicates a significant difference after multiple comparison-adjustment ($P < 0.0166$) between DGV(−) and AM without genetic tests group. [b]1 patient (case 24) presented with sustained ventricular tachycardia. ECG was available after cardioversion. [c]The median age of patients without coronary angiogram was 18 years (Q1-Q3: 16-20 years).

ACEI = angiotensin converting enzyme inhibitor; AM = acute myocarditis; ARB = angiotensin receptor blocker; ARVC = arrhythmogenic right ventricular cardiomyopathy; AV = atrioventricular; DGV(+) = positive desmosomal gene variants; DGV(−) = negative desmosomal gene variants; ECG = electrocardiogram; EMB = endomyocardial biopsy; ESC = European Society of Cardiology; IVIG = intravenous immunoglobulins; LVEF = left ventricular ejection fraction; MCS = mechanical circulatory support; NSAID = nonsteroidal anti-inflammatory drug; NSVT = nonsustained ventricular tachycardia; Q1-Q3 = first to third quartile; RV = right ventricular; SCD = sudden cardiac death; SVT = sustained ventricular tachycardia; URL = upper reference limit; VF = ventricular fibrillation.

same used for the DGV(+) patients. The reason for including a group without genetic tests was based on the retrospective nature of the study. In fact, the request for genetic testing by the physician could have introduced a bias that might lead to the selection of patients with AM at increased risk of events. The main reason to carry out the genetic test in the DGV(+) and DGV(−) AM groups is reported in the Supplemental Table 1. The criteria to identify patients in the AM without genetics control group are described in the Supplemental Methods.

CMR. Baseline CMR was obtained in 35 (97.2%), 24 (96.0%), and 36 (100%) in DGV(+), DGV(−) AM, and AM without genetics patients, respectively. One DGV(+) patient died before CMR scanning and postmortem examination confirmed the diagnosis of AM, and 1 patient with DGV(−) AM had a histologic diagnosis of myocarditis on endomyocardial biopsy. CMR was performed at 1.5-T in all but 1 patient in whom a 3.0-T scanner was used. Global ventricular volumes indexed by body surface area and systolic function were measured. The presence and regional distribution of abnormal signals at T2-weighted short-Tau inversion recovery with fat suppression technique and T1-weighted LGE sequences were allocated to the American Heart Association 17-segments model for the LV. The presence of LGE with circumferential pattern in accordance with the definition proposed by previous studies (at least 3 contiguous segments in the same short-axis slice),[24] and septal nonischemic pattern on CMR was specifically requested to be reported by the centers. The presence of major or minor CMR criteria for the diagnosis of arrhythmogenic RV cardiomyopathy were evaluated, and patients were excluded if present at initial CMR (see the Supplemental Methods for further details).[23,25] Eighty-six patients (86 of 97; 88.7%) had both a baseline and a follow-up CMR scans after a median time of 419 days (Q1-Q3, 167-858; based on 83 cases with known time between CMR). In these patients, we assessed changes in LVEF, LV-indexed end-diastolic volume, right ventricular ejection fraction (RVEF), and RV-indexed end-diastolic volume, numbers of LGE

segments, and occurrence of major or minor CMR criteria for arrhythmogenic RV cardiomyopathy.[23]

HISTOLOGY AND IMMUNOHISTOCHEMISTRY. Histology was available in 13 (36.1%) (**Table 1**) cases (12 endomyocardial biopsies and 1 postmortem examination) among patients with DGV(+) AM and in 9 of them (69.2%) an increased number of inflammatory cells (>14 inflammatory cells/mm^2 of which T-cell count >7/mm^2) compatible with AM based on European Society of Cardiology criteria was observed.[1] The proportion of patients who underwent endomyocardial biopsy in DGV(−) and without genetics AM were 28.0% and 27.8%, and the histologic diagnosis of myocarditis was reached in 71.4% and 50.0%, respectively (**Table 1**). See the Supplemental Methods for further details on genome search for viruses in heart tissue and immunohistochemical staining of myocardial tissue for desmoplakin. No sample showed major or minor (ie, presence of fatty replacement) evidence for arrhythmogenic RV cardiomyopathy.[23,25]

GENETIC ANALYSIS AND INTERPRETATION. Genetic analysis of the DGVs was performed and results were reported to the coordinating center. The genetic variants identified were independently evaluated (A.M. and D.K., Pavia, Italy) according to the American College of Medical Genetics and Genomics and the Association for Molecular Pathology criteria.[22] Only carriers of variants adjudicated as pathogenic or likely pathogenic were included in the study. See the Supplemental Methods for details on the time between index AM and genetic test.

STATISTICAL ANALYSIS. As data for the study were taken from a retrospective registry, aiming to describe the clinical characteristics and outcome of this population with DGV(+) AM, no sample size calculation was performed and we included all patients meeting the inclusion criteria. The main endpoint of the study was composite and defined as the time from diagnosis of AM to the first event among death, sustained ventricular tachycardia (VT) or ventricular fibrillation (VF; including in-hospital and post-discharge events), hospitalization for heart failure, or myocarditis recurrence. We also specifically assessed separately: 1) myocarditis recurrence; and 2) death plus sustained ventricular arrhythmias (in-hospital and post-discharge events). We analyzed the incidence of each single type of event, also considering events that occurred more than once in a subject. We also assessed the associations between the DGV(+) vs DGV(−) and other potentially relevant variables, with the main endpoint using univariate and multivariate Cox regression, in the 2 groups with available genetic results (n = 61). Details of the statistical tests used are in the Supplemental Methods.

RESULTS

BASELINE CHARACTERISTICS. Although median age at hospitalization did not differ among the 3 groups, female prevalence was significantly different, with a higher prevalence in the DGV(+) AM group (**Table 1**). A known family history of myocarditis was significantly more frequently reported in the DGV(+) group (22.2%) compared with the DGV(−) AM and AM without genetics groups, with zero cases in both. Previous myocarditis and lower incidence of prodromal symptoms were significantly more frequently observed among AM patients who underwent genetics tests (both DGV[+] and DGV[−] AM) compared with AM without genetics. Chest pain was the most common symptom on admission in all 3 groups. Echocardiography on admission revealed a median LVEF of 59% (Q1-Q3: 50%-65%) in DGV(+) AM with no evidence of RV dilation or dysfunction. Similar findings were observed in the other 2 groups. Nonsustained VT was detected by telemetry monitoring during hospital stay in 38.9% of the DGV(+) AM patients, a figure significantly higher compared with both DGV(−) AM and AM without genetics (8.0% and 13.9%, respectively). Individual features of the 36 patients with DGV(+) AM are reported in Supplemental Table 2.

On baseline CMR, median LVEF was 56% and RVEF 57% in DGV(+) AM, and they did not differ from AM without genetics and DGV(−) AM (**Table 2**). No patients had RV aneurysm and only 2 patients in the DGV(+) AM group presented regional akinesia (patient 12: RVEF of 62% and RV- indexed end-diastolic volume of 92 mL/m^2, and patient 33: RVEF of 50% and RV-indexed end-diastolic volume of 75 mL/m^2). Edema on T2-weighted short-Tau inversion recovery sequence significantly differed among groups, with AM without genetics having the highest proportion of patients with positive findings (97.5%). All patients had nonischemic pattern of LGE. Median number of LGE segments varied among groups, with the largest number observed in the DGV(+) AM (n = 9). DGV(+) AM cases revealed septal LGE pattern in 85.3% and ring-like LGE pattern in 67.6%, which were figures significantly higher compared with both DGV(−) AM and AM without genetics groups.

OUTCOMES. The median length of follow-up did not significantly differ ($P = 0.40$) among DGV(+), DGV(−) AM, and AM without genetics (**Table 1**). In the DGV(+) AM group, 20 of 36 (55.6%) patients suffered an

TABLE 2 CMR Findings in Patients Admitted With AM and DGV(+) vs Patients Without DGV(−) or Without Genetic Tests

Baseline CMR	No. of Patients With Available Data	DGV(+) AM (n = 35)	DGV(−) AM (n = 24)	AM Without Genetic Tests (n = 36)	*P* Value
Time to CMR, d	35/22/36	4 (1-21)	4 (2-14)	4 (1-8)	0.67
LVEF, %	35/22/36	56 (52-61)	53 (48-57)[a]	61 (52-66)	**0.03**
LV-EDV-i, mL/m^2	34/19/34	87 (74-103)	85 (76-98)	80 (67-87)	0.09
RVEF, %	32/21/34	57 (50-62)	54 (49-60)	58 (54-61)	0.11
RV-EDV-i, mL/m^2	31/20/34	77 (63-92)	84 (76-96)	79 (65-87)	0.16
Presence of RV aneurysm	35/23/36	0 (0)	0 (0)	0 (0)	–
Presence of RV regional akinesia	35/23/36	2 (5.7)	0 (0)	0 (0)	0.18
Edema on STIR T2-weighted images	35/24/36	25 (71.4)	21 (87.5)	**35 (97.2)**	**0.009**
Edema of the septum on STIR T2-weighted images	35/23/36	16 (45.7)	7 (30.4)	9 (25.0)	0.17
No. of segments with edema on STIR T2-weighted images	35/23/36	3 (0-6)	5 (2-8)	**6 (3-8)**	**0.009**
Edema of the RV on STIR T2-weighted images	34/23/36	2 (5.9)	1 (4.3)	7 (19.4)	0.10
Presence of LGE[b]	34/24/35	34 (100)	24 (100)	35 (100)	–
Septal LGE	34/24/35	29 (85.3)	**8 (33.3)**	**9 (25.7)**	**<0.0001**
Ring-like LGE pattern	34/24/35	23 (67.6)	**7 (29.1)**	**5 (14.3)**	**<0.0001**
No. of segments with LGE	34/24/35	9 (4-12)	6 (3-8)	5 (3-8)	**0.03**
Presence of LGE of the RV	34/24/35	2 (5.9)	2 (8.3)	4 (11.4)	0.71
Pericardial effusion	35/23/36	9 (25.7)	8 (34.8)	12 (33.3)	0.70
Edema on STIR T2-weighted images of the pericardium	34/23/36	2 (5.9)	1 (4.3)	1 (2.8)	0.81
LGE of the pericardium	34/24/35	1 (2.9)	2 (8.3)	0 (0)	0.20

Values are median (Q1-Q3) or n (%), unless otherwise indicated. The *P* value reported in the last column refers to the comparison among the 3 groups. In **bold** are reported significant difference after multiple comparison-adjustment ($P < 0.0166$) with DGV(+). [a]Indicates a significant difference after multiple comparison-adjustment ($P < 0.0166$) between DGV(−) and AM without genetics groups. [b]In 2 cases CMR was not performed, and diagnosis of myocarditis was based on postmortem examination or endomyocardial biopsy, and in 1 case contrast was not administered.

CMR = cardiac magnetic resonance; LGE = late gadolinium enhancement; LV-EDV-i = indexed left ventricular end-diastolic volume; RV-EDV-i = indexed right ventricle end-diastolic volume; RVEF = right ventricular ejection fraction; STIR = short-tau inversion recovery; other abbreviations as in Table 1.

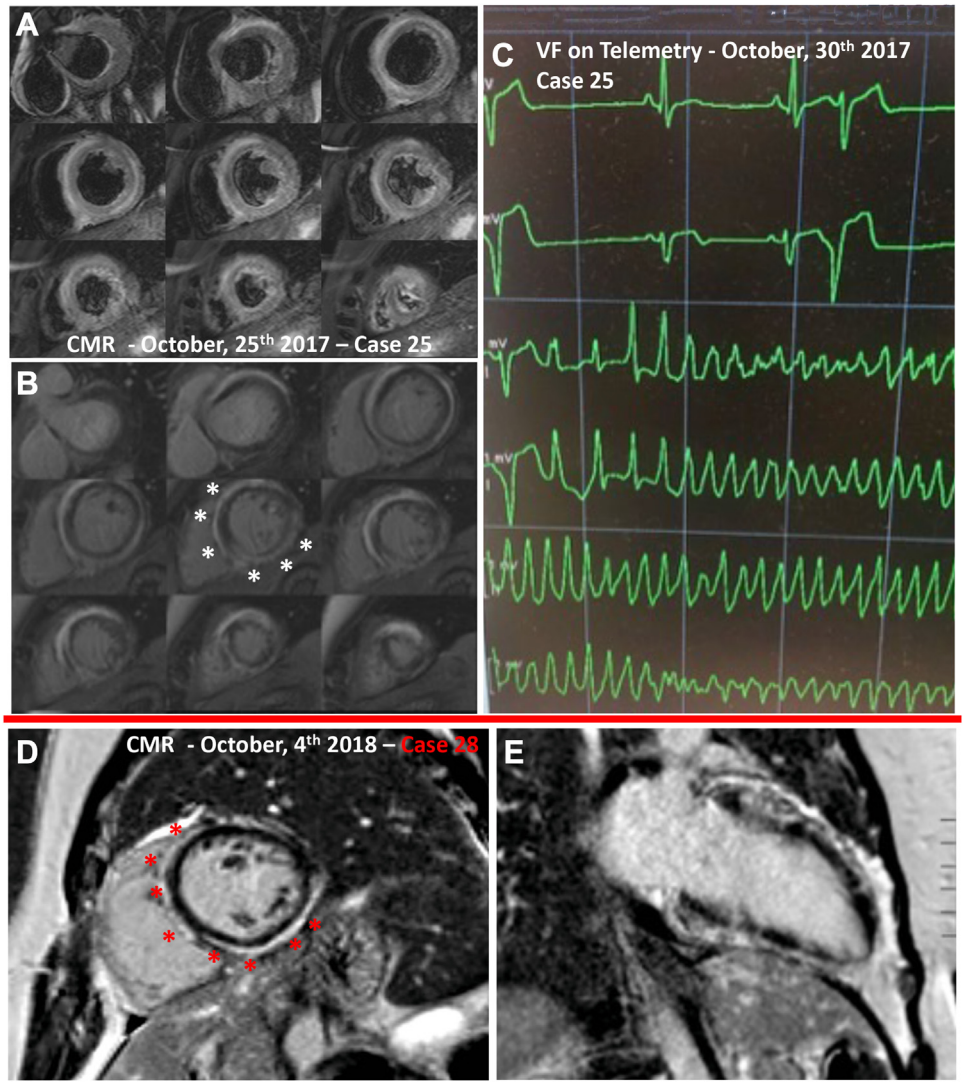
adverse cardiovascular event (death, sustained VT/VF, or myocarditis recurrence) during hospitalization or follow-up. One patient (Patient #24) had a sustained VT on admission (a second episode occurred after 1025 days), a second patient (#25) had a resuscitated cardiac arrest caused by a VF 21 days since myocarditis onset (Figure 1). Two more patients (#28 and #8) had sustained VTs after 489 and 714 days from the index AM. A 5th patient had irreversible brain damage and died 3 days after admission caused by a prolonged out-of-hospital cardiac arrest (#2) (Supplemental Figure 1). Including all adverse cardiovascular events, in the DGV(+) AM group there was a significantly higher number of events per 100-patient-years: 25.2 vs 6.9 in the DGV(−) AM and 2.2 in the AM without genetics, both with a value of $P < 0.001$ (Table 3).

Kaplan-Meier curves estimated a risk of composite endpoint (death, VT/VF, episode of acute heart failure, and myocarditis recurrence) of 62.3% at 5 years in the DGV(+) AM group, a figure significantly higher compared with both DGV(−) AM (17.5%) and AM without genetics (5.3%) (Figure 2A), mainly driven by a higher myocarditis recurrence in the DGV(+) AM group (Figure 2B). Kaplan-Meier curves estimated a composite risk of death or VT/VF of 16.1% at 5 years in the DGV(+) AM group, vs 0 events in both DGV(−) AM and AM without genetics (log-rank $P = 0.01$, figure not shown). Further results about implantable cardiac defibrillator use are reported in the Supplemental Results.

FACTORS ASSOCIATED WITH THE MAIN OUTCOME AMONG PATIENTS WITH GENETIC TESTS. In 61 patients with available genetic results, we tested factors associated with the main endpoint by univariate analysis. The only 2 variables significantly associated with outcome were DGV(+) and septal LGE (Table 4). In a multivariate analysis including variables with a $P < 0.05$ (model 1) DGV(+) had a HR of 2.62 (95% CI: 0.83-8.29), whereas the septal LGE pattern had a HR of 2.21 (95% CI: 0.70-6.98). Although the septal LGE pattern was significantly associated with the endpoint by univariate analysis, it was not included in the model 2 multivariate analysis because it was strongly associated (almost overlaid) with DGV(+) (Fisher test $P < 0.001$). In model 2 multivariate analysis including variables with $P < 0.10$ (age <30 years and known family history of myocarditis), DGV(+) remained significantly associated with the outcome (Table 4).

CMR FINDINGS AT FOLLOW-UP IN PATIENTS WITH DGV(+) AM VS OTHER GROUPS. In DGV(+) AM patients, LVEF, RVEF and LV- and RV-indexed end-

FIGURE 1 Representative Cases of 2 Siblings Who Experience an AM in the Same Year With Evidence of *DSP* Pathogenic Variant



(A, B) Cardiac magnetic resonance (CMR) revealed a circumferential extension of edema on T2-weighted short-Tau inversion recovery images **(A)** and a ring-like late gadolinium enhancement (LGE) pattern with septal involvement **(white asterisks, B)** in a 33-year-old man complaining chest pain (Supplemental Table 2) (case 25). **(C)** In-hospital telemetry monitoring revealed ventricular fibrillation (VF) at 21 days from the onset of acute myocarditis (AM) that was treated with external shock. **(D, E)** After approximately 1 year, his 40-year-old sister was admitted due to AM (case 28). CMR was performed 15 days after initial admission showing a ring-like LGE pattern **(red asterisks)** that was similar to the one observed in her brother.

diastolic volumes were substantially unchanged at follow-up (Supplemental Figure 2, **Table 5**) whereas both DGV(−) AM, and AM without genetics patients had a significant increase in LVEF, whereas other CMR parameters remained stable (Supplemental Figures 3 and 4, **Table 5**).

When CMR findings were compared, the presence of LGE septal pattern was still more frequently observed in DGV(+) AM patients, and the number of LGE segments was significantly higher in DGV(+) AM patients compared with the other 2 groups (**Figures 3A to 3B, Table 5**). Specifically, the number of LGE segments did not change at follow-up in DGV(+) AM patients, whereas there was a significant decrease in the number of LGE segments in the other 2 groups (**Figures 3C to 3E**).

Finally, among the 26 patients with an available follow-up CMR, 6 patients (23.1%) reached a major

(n = 2) or minor (n = 4) CMR-based criterion for arrhythmogenic RV cardiomyopathy in the DGV(+) AM group compared with 1 (4.3%) in the DGV(−) AM group and zero in the without genetics group (Table 5).

DESMOPLAKIN STAINING ON MYOCARDIAL TISSUE. We centrally stained available myocardial tissue from 4 DGV(+) AM patients (cases 2, 25, 30, and 31, all with truncation of *DSP*), for desmoplakin by immunohistochemistry, which showed that *DSP* expression was partially reduced but correctly localized in intercalated discs. The 2 control cases revealed regular desmoplakin expression in intercalated discs. Three representative cases are reported in Supplemental Figure 5.

GENETIC TEST RESULTS. Genetic screening identified 30 distinct desmosomal allelic variants in 36 patients (Supplemental Table 2). Most variants (26 of 30, 87%) identified were variants on *DSP* gene, whereas the remaining 4 were variants on *DSG2* gene (2 of 30, 6.5%) and *PKP2* gene (2 of 30, 6.5%). Overall, the most common types of DSP variants were truncating variants (23 of 26, 88%) followed by 2 missense variants and 1 intronic variant likely to affect splicing. On the other hand, 1 of 2 (50%) *PKP2* variants were missense variants, whereas all *DSG2* variants were missense variants. Interestingly, myocarditis exhibited a familial pattern in 10 cases, with 3 couples of siblings (cases 18 and 21, cases 25 and 28, and cases 30 and 31) and 2 pairs of parents and children (cases 3 and 13, and cases 11 and 19) being affected.

TABLE 3 Incidence Rates (per 100 Patient-Years) With 95% CIs in Patients With DGV(+) vs DGV(−) AM vs AM Without Genetic Tests

	DGV(+) AM	DGV(−) AM	AM Without Genetics Test
Patient-y at follow-up	139.2	86.9	134.1
Event: death			
No. of events	1	0	0
Incidence rate (95% CI)	0.72 (0.02-4.00)	0 (0-4.24)	0 (0-2.75)
Event: VT/VF			
No. of events	5	0	0
Incidence rate (95% CI)	3.59 (1.17-8.38)	0 (0-4.24)	0 (0-2.75)
Event: VT/VF or death			
No. of events	6	**0**[a]	**0**[a]
Incidence rate (95% CI)	4.31 (1.58-9.38)	**0 (0-4.24)**	**0 (0-2.75)**
Event: recurrent myocarditis			
No. of events	29	**5**[a]	**2**[a]
Incidence rate (95% CI)	20.84 (13.95-29.92)	**5.75 (1.87-13.43)**	**1.49 (0.18-5.39)**
Event: episode of acute HF			
No. of events	0	1	1
Incidence rate (95% CI)	0 (0-2.65)	1.15 (0.03-6.41)	0.75 (0.02-4.15)
All events			
No. of events	35	**6**[a]	**3**[a]
Incidence rate (95% CI)	25.15 (17.52-34.97)	**6.90 (2.53-15.03)**	**2.24 0.46-6.54)**

[a]Indicates significant differences with respect to group DGV(+) AM using Bonferroni adjusted alpha = 0.0167. Pairwise comparisons (original *P* values are reported to be compared with Bonferroni adjusted alpha = 0.0167): 1) no significant differences between groups for death and heart failure (HF); 2) ventricular tachycardia (VT) or VF: DGV(+) AM vs DGV(−) AM vs $P = 0.025$; DGV(+) vs AM without genetic tests $P = 0.025$; 3) VT or VF or death: DGV(+) AM vs DGV(−) AM vs $P = 0.014$; DGV(+) vs AM without genetic tests $P = 0.014$; 4) myocarditis recurrence: DGV(+) AM vs DGV(−) AM $P = 0.001$; DGV(+) AM vs AM without genetic tests $P < 0.001$; and 5) all events: DGV(+) AM vs DGV(−) AM $P < 0.001$; DGV(+) AM vs AM without genetic tests $P < 0.001$.

Abbreviations as in Table 1.

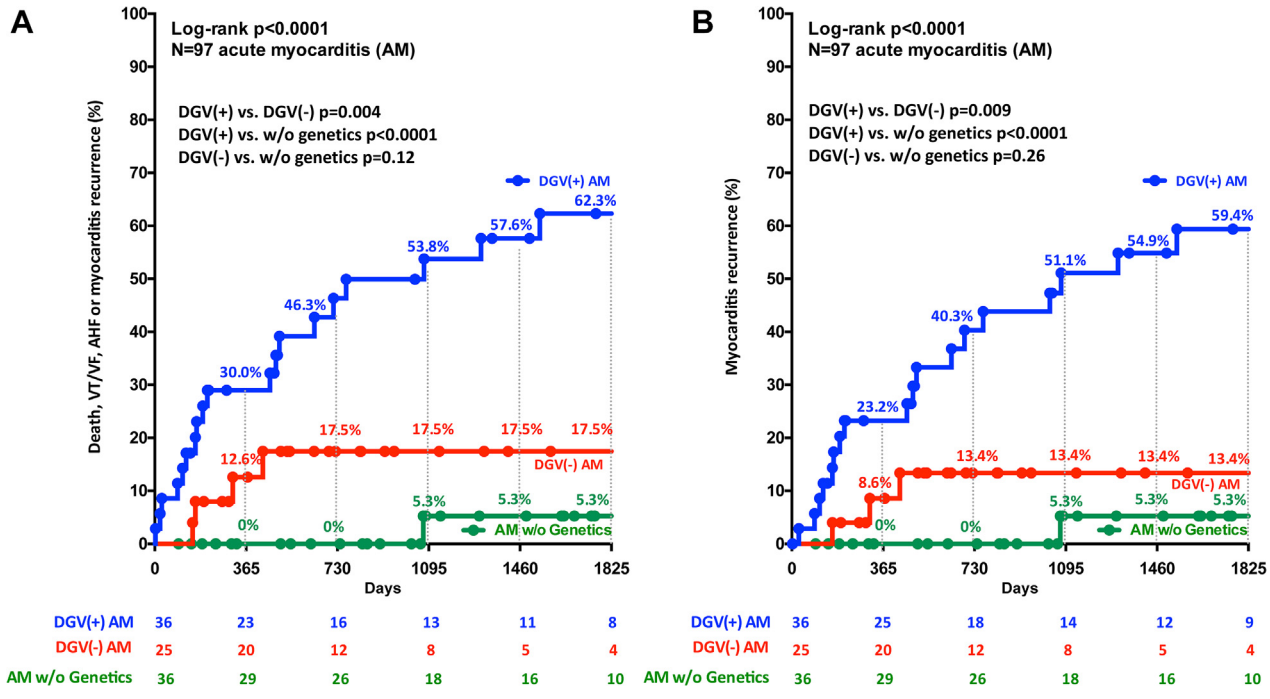
DISCUSSION

We describe the characteristics and outcome of a subpopulation of patients with AM and evidence of DGVs. DGV(+) AM patients most commonly presented with chest pain as the main symptom and had preserved or mildly reduced biventricular systolic function. Generally, these features should suggest a benign long-term prognosis.[19] Nonetheless, patients with DGV(+) had an estimated risk of death, ventricular arrhythmias, and recurrent episodes of myocarditis as high as 62.3% at 5 years of follow-up, a figure significantly higher compared with DGV(−) AM and AM without genetics. Including all events, the incidence rate of ventricular arrhythmias plus death was 4.3 per 100 patient-years and the incidence rate of recurrent myocarditis was 20.8 per 100 patient-years among DGV(+) AM patients: these were significantly higher than in DGV(−) AM and AM without genetics.

In accordance with our results, the incidence of adverse events at follow-up in the DGV(+) AM population appears higher compared with that of patients with AM and similar characteristics reported in the published reports. Sanguineti et al[20] reported an incidence of myocarditis recurrence and ventricular arrhythmias of 9.3% at a median follow-up of 19 months in a series of 203 AM patients with a median LVEF of 57% and LGE in all cases on CMR. We previously reported an incidence of myocarditis recurrence and ventricular arrhythmias of 3.1% at a median follow-up of 35 months among the 325 patients with uncomplicated AM in the Lombardy registry (median LVEF of 61% and all with LGE on CMR).[19]

Finally, in the subset of patients with available CMR data at follow-up, the distinctive traits of DGV(+) AM patients were a larger extent of LGE (median of 8 segments) and more frequent involvement of the septum (in up to 76.9%). The higher burden of LGE correlates with higher risk of ventricular arrhythmias in previous studies.[26,27] It is uncertain if the larger extent of LGE is caused by recurrent symptomatic or asymptomatic episodes of inflammatory myocardial injury. The mechanisms in which DGV are associated with more inflammation remain uncertain.

FIGURE 2 Outcome in DGV(+) AM vs DGV(−) AM vs Without Genetics AM



Kaplan-Meier estimated cumulative incidence of **(A)** composite endpoint (first event of death, ventricular tachycardia [VT]/VF, acute heart failure [AHF], or myocarditis recurrence); **(B)** myocarditis recurrence. **Numbers reported below plots** indicate patients at risk. The log-rank test *P* value of the comparison among the 3 groups is reported as well as *P* values of pairwise comparisons (to be compared with Bonferroni adjusted alpha = 0.0167). DGV(+) = positive desmosomal gene variants; DGV(−) = negative desmosomal gene variants; w/o = without; other abbreviations as in Figure 1.

Recent consensus for genetic testing in patients with inherited cardiovascular disease does not include myocarditis among the recommendations,[28] and thus, genetic analysis is usually not available in patients with AM. Nevertheless, in a pediatric population of 20 patients with histologically proven lymphocytic myocarditis with a dilated cardiomyopathy phenotype, 35% of children had a pathogenic or likely pathogenic variant, mostly on sarcomeric genes.[16] Furthermore, other non-DGVs have been described in a cohort of 36 adult patients with lymphocytic myocarditis that underwent genetic testing.[29] Of these, 11 (30.6%) had a pathogenic or likely pathogenic variant in structural cardiomyopathy-related genes (*TTN* in 73% of cases), whereas only 1 case had a *DSP* variant. It must be noted that in the study by Artico et al,[29] the main indications for endomyocardial biopsy was refractory unexplained heart failure (in 75% of cases), whereas in our study most patients presented with chest pain (in 91.7% of cases) with preserved or mildly reduced LV function. The different disease phenotypes (refractory heart failure vs preserved/mildly reduced LVEF) could explain the different genetic background of the patients in the 2 studies, even if in both studies patients had a diagnosis of myocarditis. Another study identified putative deleterious variants in 19 of 117 (16.2%) patients with AM, and again *TTN* was the most commonly found gene variant in 8 cases, whereas *DSP* variants were observed only in 3 cases.[14] In this study by Kontorovich et al,[14] phenotypes of subjects who had AM with or without deleterious variants were similar, indicating that genetic testing is necessary to differentiate them.

Our study also suggests features that identify patients with AM at a higher likelihood of a positive genetic test for DGV. Specifically, family history of myocarditis (in 22.2%), occurrence of nonsustained VT on in-hospital telemetry monitoring (in 38.9%), and the presence of ring-like or septal LGE patterns on CMR (in 67.6% and 85.3%, respectively) have been observed significantly more frequently in DGV(+) AM patients compared with DGV(−) AM or AM without genetics groups, thus these features could be considered red flags to prompt genetic tests (**Central Illustration**). Other clinical characteristics that might

help to identify cases with a genetic background are female sex and absence of prodromal symptoms. The sex prevalence of DGV(+) AM can be indirectly surmised based on a retrospective analysis involving 236 patients with arrhythmogenic RV cardiomyopathy from the Johns Hopkins arrhythmogenic RV cardiomyopathy registry, where the authors identified 12 patients, all women, with previous myocarditis before the diagnosis of arrhythmogenic RV cardiomyopathy and *DSP* variants in 10 of 12.[12] Absence of typical prodromal symptoms before the myocarditis can also suggest the possibility of an AM with a genetic background. In fact only 39.4% DGV(+) AM had viral prodromal symptoms, a figure significantly lower than that observed in AM registries reporting prodromal symptoms in up to 80.5% of cases,[19] in line with our control groups of AM without genetics. However, it is speculated that on a genetic background that can favor myocarditis, a second hit such as a transitory viral infection can precipitate an acute episode. As desmoplakin is a force transducer between desmosomes and intermediate filaments, it has been hypothesized that mechanical stress could have deleterious effect on patients with truncating *DSP* variants, leading to troponin release and AM.[9] Nevertheless, in our series, the proportion of patients that practiced sport at competitive level was relatively low (14.7%), and not different from the control groups. Thus, potential triggers of myocarditis in DGV(+) patients remain to be elucidated. Practically, in managing a patient with recurrent myocarditis, but preserved or mildly reduced LVEF and septal or ring-like LGE pattern on CMR, genetic testing could be considered, especially when a family history of myocarditis is reported, or nonsustained VTs are registered. Potential differential diagnoses that can be identified by endomyocardial biopsy include cardiac sarcoidosis. Sarcoid can share similar features with DGV(+) AM, such as subepicardial and septal inflammatory scars of the LV on CMR.[30] Interestingly, sarcoidosis, a highly arrhythmogenic granulomatous myocarditis, also shares with DGV(+) AM the involvement of desmosomal proteins. In fact, a reduced expression of plakoglobin, encoded by the *JUP* gene, has been observed in patients with cardiac sarcoidosis.[31] In 4 DGV(+) AM patients in whom desmoplakin staining has been performed, we observed a correct localization but partially reduced expression of desmoplakin in intercalated discs. We cannot provide mechanistic explanations that put in relation this pattern of expression of desmoplakin, and the increased risk of inflammatory injury, even if it is possible that other genetic, epigenetic, or exogenous modifiers are responsible for the pathobiology.

TABLE 4 Univariate and Multivariate Analysis of Factors Associated With the Occurrence of the Main Endpoint in the DGV(+) AM Population and in Patients With AM and DGV(−)

	HR (95% CI) for the Main Endpoint		
	Univariate	Multivariate (Model 1)	Multivariate (Model 2)
Genetic test			
Pathogenic or likely pathogenic DGV	**4.16 (1.43-12.09)**	2.62 (0.83-8.29)	**3.33 (1.08-10.26)**
Demographics			
Age, y	0.97 (0.94-1.01)	–	–
Age <30 y	2.23 (0.93-5.35)		1.61 (0.66-3.93)
Female	1.05 (0.42-2.63)	–	–
Family/personal history			
Previous episode of myocarditis	1.82 (0.77-4.30)	–	–
Known family history of myocarditis at the time of admission	2.32 (0.92-5.87)		1.43 (0.55-3.73)
Known family history of ARVC at time of admission	2.48 (0.84-7.32)	–	–
First-degree relative with history of SCD or aborted SCD <65 y of age	1.88 (0.56-6.36)	–	–
Presenting symptoms			
Dyspnea	0.46 (0.14-1.56)	–	–
Chest pain	0.22 (0.03-1.64)	–	–
Syncope	1.65 (0.38-7.08)	–	–
Laboratory findings			
>159-fold increase of troponin above the URL[a]	1.20 (0.51-2.79)	–	–
In-hospital telemetry monitoring			
NSVT, SVT/VF	1.83 (0.84-3.99)	–	–
Baseline CMR			
LVEF <50%[a]	1.57 (0.54-4.60)	–	–
RVEF <50%[a]	0.71 (0.28-1.85)	–	–
Edema on STIR T2-weighted images[a]	1.16 (0.39-1.32)	–	–
Septal LGE[a]	**3.28 (1.13-9.59)**	2.21 (0.70-6.98)	–
Ring-like LGE pattern[a]	1.75 (0.76-4.05)	–	–
LGE segments >7[a]	1.81 (0.80-4.08)	–	–

Dashes indicate that variables were not included in the multivariate model. In **bold** significant results at univariate and multivariate analysis. Threshold of 159-fold increase of troponin and 7 LGE segments were identified based on the median value among the DGV(+) and DGV(−) patients with available data. [a]Data were not available for all 61 patients with available genetic tests. Specifically, available data for troponin levels were 51, for LVEF 57, RVEF 53, Edema on STIR T2-weighted images 59, septal LGE 58, ring-like LGE pattern 58, LGE segments <7 on CMR 58.

Abbreviations as in Tables 1 and 2.

Previous studies have also shown that septal LGE on CMR can be associated with adverse events in patients with AM,[32] including those with preserved LVEF.[18] Hypothetically, unrecognized DGV(+) cases might explain why patients with AM with preserved LVEF and septal LGE involvement may have more events.[18] The multivariate analyses did not show DGV(+) to be a significant prognosticator when septal LGE is included as a predictor, which also lost significance (**Table 4**). This may be caused by the collinearity of the 2 variables (in DGV[+] patients with AM, 85.3% had septal LGE) and/or due to the small sample size. Future research should investigate whether a DGV(+) background could specifically favor the septal injury, or if the involvement of the

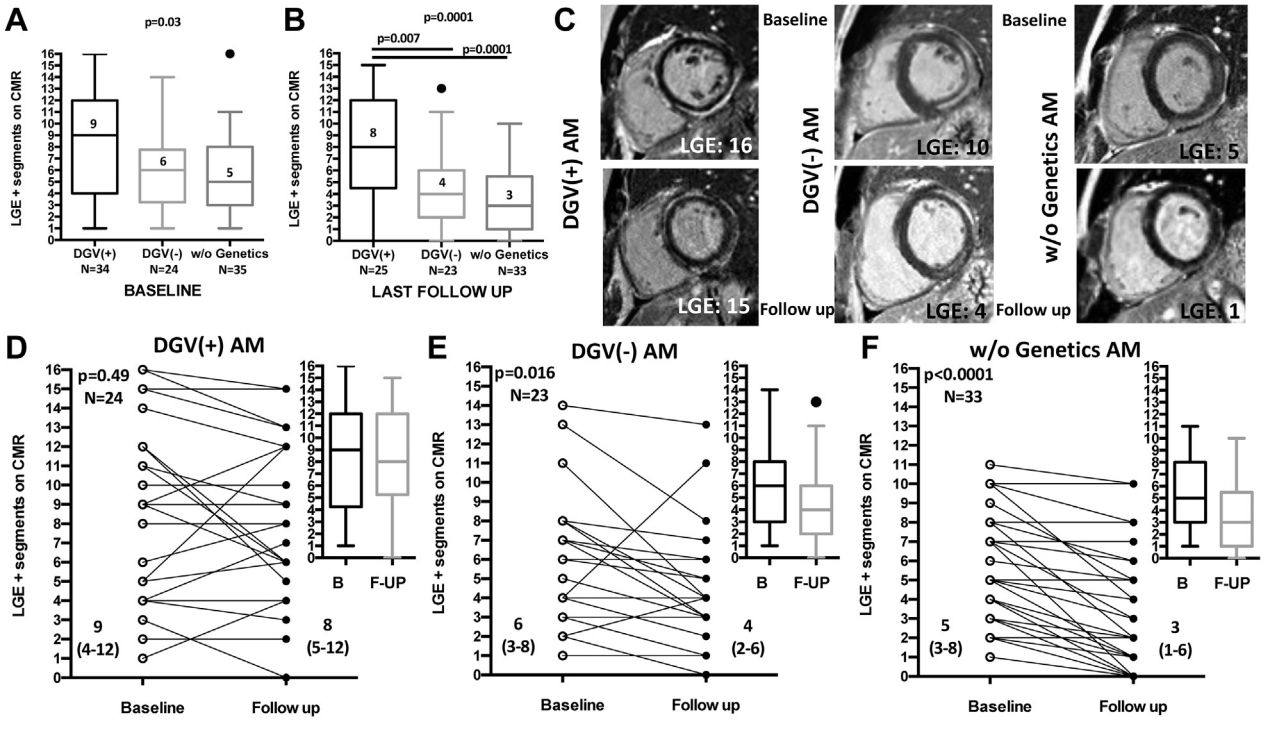
TABLE 5 Follow-Up CMR Findings

	No. of Patients With Available Data	DGV(+) AM (n = 28)	DGV(−) AM (n = 24)	AM Without Genetic Tests (n = 34)	*P* Value
Time between CMR, d	28/21/34	867 (199-1,658)	380 (171-520)	289 (152-645)	0.03
LVEF, %	28/24/34	56 (51-62)	58 (54-65)	**65 (57-67)**	**0.0004**
LV-EDV-i, mL/m^2	26/23/30	89 (70-95)	81 (72-101)	74 (63-85)	0.09
RVEF, %	26/23/30	56 (50-61)	55 (52-59)[a]	**61 (55-65)**	**0.009**
RV-EDV-i, mL/m^2, median (Q1-Q3)	25/23/29	78 (67-101)	86 (80-93)	77 (69-89)	0.16
Presence of RV aneurysm	28/23/33	2 (7.1)	0 (0)	0 (0)	0.13
Presence of RV regional akinesia	28/23/33	8 (28.6)	2 (8.7)	**0 (0)**	**0.002**
Major/minor ARVC criteria by CMR	26/23/33	6 (23.1)	1 (4.3)	**0 (0)**	**0.005**
Major ARVC criteria by CMR	26/23/33	2 (7.7)	0 (0)	0 (0)	0.11
Minor ARVC criteria by CMR	26/23/33	4 (15.4)	1 (4.3)	0 (0)	**0.045**
Edema on STIR T2-weighted images	28/24/33	7 (25.0)	3 (12.5)	**0 (0)**	**0.01**
Presence of LGE[b]	26/23/33	25 (96.2)	22 (95.7)	27 (81.8)	0.11
Septal LGE	26/23/33	20 (76.9)	**9 (39.1)**	**5 (15.2)**	**<0.0001**
No. of segments with LGE	25/23/33	8 (4-12)	**4 (2-6)**	**3 (1-6)**	**0.0001**
Presence of LGE of the RV	25/24/33	1 (4.0)	2 (8.3)	2 (6.1)	0.82

Values are median (Q1-Q3) or n (%), unless otherwise noted. The *P* value reported in the last column refers to the comparison among the 3 groups. In **bold** are reported significant difference after multiple comparison-adjustment ($P < 0.0167$) between DGV(+) and/or AM without genetic tests groups. [a]Indicates a significant difference after multiple comparison-adjustment ($P < 0.0167$) between DGV(−) and AM without genetic tests groups. [b]1 patient had LGE, but it has not been specified the localization of positive LGE segments.

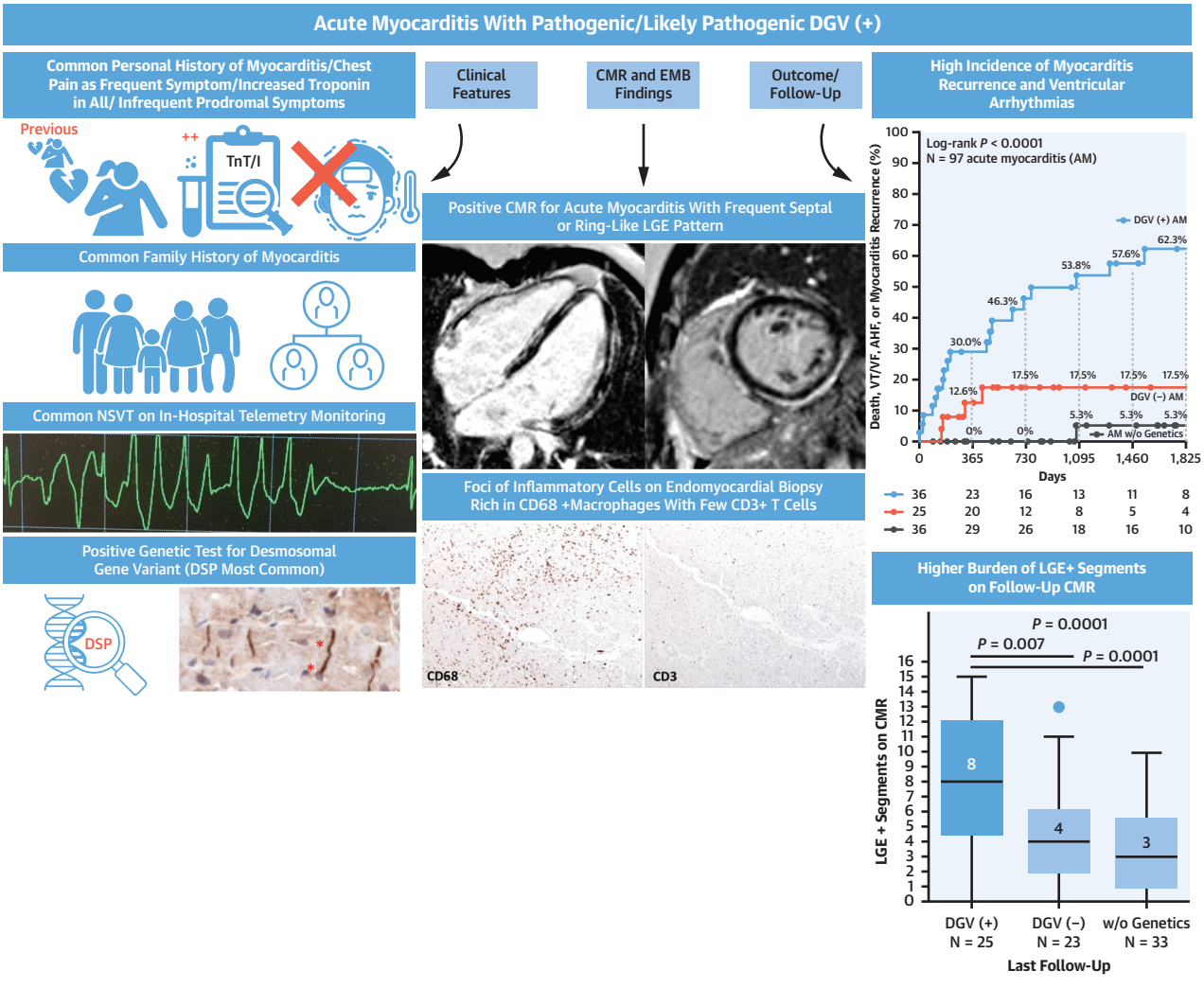
Abbreviations as in Tables 1 and 2.

FIGURE 3 Changes in LGE Extent Between Baseline and Follow-Up CMR Among the 3 Groups of Patients With AM



(A, B) Number of LGE segments in the 3 groups on baseline and follow-up CMR. **(C)** Representative cases from each group showing changes in LGE burden on CMR (the number indicates the number of LGE-positive segments). **(D)** No significant reduction in LGE-positive segments was observed in DGV(+) AM patients, whereas **(E, F)** a significant reduction in the number of LGE-positive segments was observed both in the DGV(−) AM and AM without genetics groups on follow-up CMR. Wilcoxon matched-pairs signed-rank test was used. Median and first to third quartile are reported. **Solid black dots** indicate values beyond the Tukey whiskers of the dot plot. F-UP = follow-up; other abbreviations as in Figures 1 and 2.

CENTRAL ILLUSTRATION **Myocarditis Recurrence and Ventricular Arrhythmias in Patients With Acute Myocarditis Associated With Desmosomal Gene Variants**



Ammirati E, et al. J Am Coll Cardiol HF. 2022;10(10):714-727.

Resume of the clinical features, cardiac magnetic resonance (CMR) and endomyocardial biopsy findings and outcome in the follow-up of patients with positive desmosomal gene variants (DGV[+]). We refer to a *common* feature when it occurs between 15% and 50%; and *frequent* feature when it occurs in more than 50% of cases. Even though prodromal symptoms occurred in 39.4%, they were reported as an *infrequent* feature because the frequency is by far lower compared with data from recent registries on acute myocarditis (AM) that reported a frequency of up to 80.5% and the AM without genetics control group. **Solid blue dot** indicates a value beyond the Tukey whiskers of the dot plot. ++ = highly increased troponin; AHF = acute heart failure; DGV(+) = positive desmosomal gene variants; DGV(−) = negative desmosomal gene variants; EMB = endomyocardial biopsy; LGE = late gadolinium enhancement; NSVT = nonsustained ventricular tachycardia; TnT/I = troponin T/I; VF = ventricular fibrillation; VT = ventricular tachycardia; w/o = without.

septum is the consequence of a larger extent of post-inflammatory scars.

In addition, our findings are potentially complementary to the recent description of a distinct DSP cardiomyopathy.[33] In the study by Smith et al,[33] it was observed that 10 of 107 patients with DSP cardiomyopathy had episodes of acute myocardial injury and documented LGE in the LV on CMR. It is possible that our observations are snapshots of early stages of a specific inherited cardiomyopathy that is characterized by an inflammatory phenotype. Nevertheless, our findings suggest that early inflammatory phenotype is frequently, but not exclusively, associated with *DSP* variants, as it has been also seen with other DGVs (*PKP2* and *DSG2*). The main significant difference compared with DGV(−) AM and AM without

genetics was the higher burden of LGE on the follow-up CMR, thus resembling the phenotype of left dominant arrhythmogenic cardiomyopathy. The identification of an early phase of inherited cardiomyopathy can be relevant for the long-term surveillance, lifestyle considerations (for instance, resuming sport after 6 months in AM vs suggesting stopping intense sports in arrhythmogenic RV cardiomyopathy or DSP cardiomyopathy), and family screening.

From a genetic point of view, most variants identified were *DSP*, whereas previous studies of arrhythmogenic RV cardiomyopathy suggest *DSP* is only responsible for 5% of cases.[34] Truncating variants of DSP were the most frequent variants reported in the present work, in line with the other case reports.[12,14] Interestingly, in a previous study that evaluated the role of DGVs in patients with idiopathic cardiomyopathy who underwent heart transplantation, it has been found that 12 of 89 (13%) patients had pathogenic DGVs.[35] In that population, there was no history of sustained VT, and no nonsustained VT was noted on telemetry monitoring. If one compares the DGVs reported in the 2 studies, there was only 1 common allelic variant between them (DSG2: c.1003A>G).[35]

STUDY LIMITATIONS. The DGV(+) AM population is relatively small and data were collected retrospectively. However, the event rates at follow-up were higher than those previously reported in patients with similar clinical characteristics,[19,20] and compared with 2 control groups of patients with AM. DGV(+) patients with AM received disparate therapies reflecting their origin from multiple centers and the absence of evidence-based treatments for myocarditis, but not different compared with DGV(−) AM and AM without genetics. Currently, there is no evidence that specific immunomodulatory drugs prevent recurrent events after an episode of AM.[1] Finally, in line with current recommendations, we did not perform endomyocardial biopsies in all cases. Endomyocardial biopsy is generally performed for patients with AM with high-risk features, whereas most DGV(+) patients presented with chest pain and preserved or mildly reduced LVEF.

CONCLUSIONS

Patients with AM with DGVs are at high risk for recurrent myocarditis and ventricular arrhythmias. Our study adds to a growing body of work[6,9] that supports broadening indication for genetic testing in patients with AM. DGVs were strongly associated with patients with a family history of myocarditis, nonsustained VT on telemetry, or a septal or ring-like LGE pattern on CMR. Further prospective studies are needed to determine the frequency of DGV in AM and confirm these preliminary observations that might help to better stratify patients with AM who at present are considered at low risk of future adverse events.

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Dr Ammirati has received a grant from the Italian Ministry of Health (GR-2019-12368506) and is a consultant for Kiniksa and Cytokinetics. Dr Adler is a consultant for Abbott, Abiomed, AstraZeneca, Endotronix, Ionis, Medtronic, and Novartis; is on the board of directors of Genstem Therapeutics; and is a shareholder of Rocket Pharmaceuticals. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: A genetic background characterized by DGVs can be identified in selected patients presenting with AM. Patients with DGVs and myocarditis have a risk of death, ventricular arrhythmias, and myocarditis up to 25.2 events per 100 patient-years.

TRANSLATIONAL OUTLOOK: Awareness of this novel inflammatory phenotype could lead to better stratification of patients with AM and preserved or only mildly reduced LVEF. Myocarditis associated with DGVs could support indication for genetic testing in selected patients with AM.

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KEY WORDS acute myocarditis, cardiac magnetic resonance, desmoplakin, desmosomal gene variants, prognosis

APPENDIX For expanded Methods and Results sections as well as supplemental figures and tables, please see the online version of this paper.