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ORIGINAL INVESTIGATIONS

Prognostic Relevance of Gene-Environment Interactions in Patients With Dilated Cardiomyopathy

Applying the MOGE(S) Classification

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ABSTRACT

BACKGROUND The multifactorial pathogenesis leading to dilated cardiomyopathy (DCM) makes stratification difficult. The recent MOGE(S) (morphofunctional, organ involvement, genetic or familial, etiology, stage) classification addresses this issue.

OBJECTIVES The purpose of this study was to investigate the applicability and prognostic relevance of the MOGE(S) classification in patients with DCM.

METHODS This study used patients from the Maastricht Cardiomyopathy Registry in the Netherlands and excluded patients with ischemic, valvular, hypertensive, and congenital heart disease. All other patients underwent a complete diagnostic work-up, including genetic evaluation and endomyocardial biopsy.

RESULTS A total of 213 consecutive patients with DCM were included: organ involvement was demonstrated in 35 (16%) and genetic or familial DCM in 70 (33%) patients, including 16 (8%) patients with a pathogenic mutation. At least 1 cause was found in 155 (73%) patients, of whom 48 (23%) had more than 1 possible cause. Left ventricular reverse remodeling was more common in patients with nongenetic or nonfamilial DCM than in patients with genetic or familial DCM (40% vs. 25%; $p = 0.04$). After a median follow-up of 47 months, organ involvement and higher New York Heart Association functional class were associated with adverse outcome ($p < 0.001$ and $p = 0.02$, respectively). Genetic or familial DCM per se was of no prognostic significance, but when it was accompanied by additional etiologic-environmental factors such as significant viral load, immune-mediated factors, rhythm disturbances, or toxic triggers, a worse outcome was revealed ($p = 0.03$). A higher presence of MOGE(S) attributes (≥2 vs. ≤1 attributes) showed an adverse outcome ($p = 0.007$).

CONCLUSIONS The MOGE(S) classification in DCM is applicable, and each attribute or the gene-environment interaction is associated with outcome. Importantly, the presence of multiple attributes was a strong predictor of adverse outcome. Finally, adaptation of the MOGE(S) involving multiple possible etiologies is recommended.
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ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

DCM = dilated cardiomyopathy

EMB = endomyocardial biopsy

HF = heart failure

HTx = heart transplantation

LV = left ventricular

LVEDDI = indexed left ventricular end-diastolic diameter

LVEF = left ventricular ejection fraction

LVRR = left ventricular reverse remodeling

MOGE(S) = morphofunctional, organ involvement, genetic or familial, etiology, stage

NYHA = New York Heart Association

PCR = polymerase chain reaction

Classification of cardiomyopathies has been subject to revisions for more than 60 years (1). To date, classification remains difficult because of incomplete knowledge about the mechanisms of the disease, its heterogeneous clinical presentation, and overlapping clinical and molecular findings (1,2). Dilated cardiomyopathy (DCM) is a myocardial disease characterized by left ventricular (LV) dilation and systolic dysfunction (2). DCM is assumed

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to be the end stage of multifactorial pathogenesis with common terminal pathophysiology. After exclusion of prevalent causes (e.g., coronary artery disease [CAD], valvular disease, congenital disease, hypertension) (2), DCM comprises poorly defined subgroups of cardiac inflammation with or without an infectious agent (3), cytotoxic medication or drugs (4,5), rhythm disturbances (6,7), and genetic mutations (8). Nevertheless, only some persons who are exposed to these triggers develop DCM. Additionally, in up to 50% of patients, the cause of DCM remains unknown (4,5).

The hypothesis is that gene-environment interactions (i.e., exposure to an environmental trigger in addition to an "underlying genetic background") may lead to DCM, but a family history of DCM is present in only 20% to 35% of patients with predominantly autosomal dominant inheritance (1,8). The genetic knowledge of cardiomyopathies has evolved exponentially (1,8), and in view of these developments, the World Heart Federation published a new classification scheme for cardiomyopathies, called MOGE(S) (morphofunctional, organ involvement, genetic or familial, etiology, stage) (1). In the MOGE(S) classification, a combination of phenotype, genetic variation, and etiologic annotation has been proposed, but studies investigating the applicability and prognostic value of this new classification are lacking. The routine use of endomyocardial biopsy (EMB), the referral of all patients with DCM to our specialized cardiogenetics unit, and long-term follow-up allowed us to evaluate gene-environment interactions in a large, well-characterized population with DCM.

METHODS

STUDY DESIGN. Between 2004 and 2014, 394 consecutive patients with unexplained heart failure (HF) caused by DCM were enrolled in the Maastricht Cardiomyopathy Registry. A complete diagnostic work-up was performed in 213 index patients by using medical history, 12-lead electrocardiogram, echocardiography, Holter monitoring, EMB, and genetic evaluation (Online Figure 1). Excluded patients with DCM (n = 181) had incomplete diagnostic work-ups and did not demonstrate significant differences in baseline characteristics (Online Table 1, Online Figure 2). The protocol was approved by the local ethics committee. All patients gave written informed consent.

Inclusion criteria were as follows: 1) left ventricular ejection fraction (LVEF) <50% and indexed left ventricular end-diastolic diameter (LVEDDI) >33 mm/m^2 (men) or >32 mm/m^2 (women) (9); 2) EMB performed; 3) genetic evaluation, including counseling, pedigree analysis, and genetic testing in index patients; and 4) age ≥18 years.

Exclusion criteria included the following: the presence of a previous history of myocardial infarction or significant CAD (stenosis >50%) determined by coronary angiography; primary valvular disease (mitral regurgitation grade ≥3, aortic regurgitation grade ≥2, or aortic stenosis <1 cm^2); hypertensive heart disease; congenital heart disease; (suspected) acute myocarditis; and (likely) diagnosis of arrhythmogenic right ventricular dysplasia.

Echocardiographic measurements were performed in the standard parasternal, apical, and subxiphoid views (10). Left ventricular reverse remodeling (LVRR) was defined as an absolute increase in LVEF of ≥10% or an LVEF ≥50% in addition to a decrease in LVEDDI of ≥10% or an LVEDDI ≤33 mm/m^2 (11).

Six EMB samples were taken from the right ventricle. Two to 3 specimens were used for immunohistological analysis and 3 for the detection of viral genomes by using polymerase chain reaction (PCR)

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and reverse transcriptase PCR analysis (12). Six primer pairs were used to detect cardiotropic deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) viruses, including adenovirus, enterovirus, cytomegalovirus, parvovirus B19, human herpes virus-6, and Epstein-Barr virus. Significant viral load was defined as ≥500 copies/μg DNA. Increased cardiac inflammation was defined as ≥14 infiltrating cells/mm^2 (2).

MOGE(S) CLASSIFICATION. All patients had, by definition, a morphofunctional diagnosis of DCM. Extracardiac organ involvement was considered positive if a specialist proved that the manifestation had a known or suspected relationship with DCM. Data considering extracardiac organ involvement were collected from patients' records and a standardized questionnaire, reviewed by 2 investigators. Disagreements were settled by consensus. Extracardiac organ involvement secondary to HF therapy was not included.

A minimum of 3 generations of family history of cardiomyopathy or sudden cardiac death was documented. Electrocardiography and echocardiography were performed in all first-degree relatives of patients who consented. Familial inheritance was based on the presence of 2 or more affected individuals in a single family or a first-degree relative with well-documented unexplained sudden cardiac death (13) at age <60 years. Genes were analyzed using Sanger sequencing (data not included). The selection of tested genes was based on the expertise of the clinical geneticist. In specific cases, noncardiac features or mixed phenotypes were initially considered based on clinical assessment, thus leading to evaluation of additional genes. Variants were classified in 5 different classes: pathogenic, likely pathogenic, variant of clinical unknown significance, likely benign, or benign. Pathogenic and likely pathogenic mutations were classified as pathogenic mutations, and others were classified as nonpathogenic. Genetic or familial DCM was classified as the presence of a familial inheritance pattern or the presence of a pathogenic mutation, or both.

DCM was divided into 7 causes, in line with the MOGE(S) classification and previous DCM recommendations (1,2,14): 1) genetic or familial; 2) virus-positive inflammatory (Vir+ Infl+); 3) virus-positive inflammatory-negative (Vir+ Infl−); 4) virus-negative inflammatory (Vir− Infl+); 5) virus-negative inflammatory negative with proven systemic disease (Vir− Infl− systemic+); 6) rhythmogenic (tachycardiomyopathy not improving, >20% premature ventricular beats) (6,7); and 7) toxic (alcohol abuse, hard drugs, chemotherapy) (4,5). Stage of HF was classified according to the New York Heart Association (NYHA) functional classification.

FOLLOW-UP. Patients were followed for at least 12 months after EMB, except for 1 patient, who died after 2 months. Follow-up data on death, heart transplantation (HTx), and life-threatening ventricular arrhythmias were collected using medical records, municipal population register, or telephone contact with general practitioners. End of follow-up was January 1, 2014. No patient was lost to follow-up. Echocardiography after 12 months (range, 6 to 18 months) was available in 93% of patients. The primary endpoint was the combination of HTx-free survival without life-threatening ventricular arrhythmias. Life-threatening ventricular arrhythmias were defined as nonfatal ventricular fibrillation (with or without implantable cardioverter-defibrillator shock), hemodynamic unstable ventricular tachycardia, or sustained ventricular tachycardia with implantable cardioverter-defibrillator shock.

The Online Appendix contains a more detailed description of the study methods.

STATISTICAL ANALYSIS. Variables are displayed as numbers (percentage), mean ± SD, or median (interquartile range), as appropriate. Categorical variables were compared using chi-square test or Fisher exact test. Continuous variables were compared using Student *t* test or Mann-Whitney *U* test. The Kaplan-Meier method was used to calculate survival curves (comparison between groups by log-rank test). Univariable Cox proportional hazards regression analysis was performed to assess clinical and demographic covariates associated with event-free survival. We tested for interactions between all covariates used in the univariable analysis. Etiology was consistently modeled as the presence or absence of 1 or more nongenetic causes unless indicated otherwise. Statistical significance was accepted at $p < 0.05$. Statistical analysis was performed using SPSS version 21.0 (IBM Corporation, Armonk, New York) software.

RESULTS

Baseline characteristics are summarized in **Table 1**. More than one-half of the patients were male. Genetic or familial DCM was diagnosed in approximately one-third of patients. The cardiac presence of 2 viruses was seen in 47 (23%) patients. Two patients had triple viral presence: parvovirus B19, human herpes virus-6, and Epstein-Barr virus. Viral presence was demonstrated in 47 (79%) patients with earlier viral prodromes. A significant viral load was demonstrated in only 36 (18%) patients, predominantly revealing parvovirus 19 infection. Dual infections

TABLE 1 Baseline Patient Characteristics

	All (N = 213)	Genetic or Familial DCM (n = 70)	Nongenetic or Familial DCM (n = 143)	p Value
Age at onset, yrs	51 ± 13	50 ± 13	51 ± 12	0.65
Sex, male/female	128/85	41/29	87/56	0.75
Heart rate, beats/min	74 ± 15	73 ± 16	75 ± 15	0.45
SBP, mm Hg	129 ± 20	126 ± 20	130 ± 20	0.22
DBP, mm Hg	79 ± 12	78 ± 10	79 ± 13	0.58
Body height, cm	175 ± 9.6	174 ± 9.7	175 ± 10	0.51
Body weight, kg	82 ± 18	80 ± 18	83 ± 18	0.33
BSA, m^2	1.6 ± 0.27	1.5 ± 0.27	1.6 ± 0.27	0.32
Symptoms				
Fatigue	75 (35)	25 (36)	50 (35)	0.91
Angina	35 (16)	13 (19)	22 (15)	0.56
Dyspnea	146 (69)	41 (59)	105 (73)	0.03
Peripheral edema	26 (12)	7 (10)	19 (13)	0.49
Palpitation	43 (20)	14 (20)	29 (20)	0.96
Dizziness	14 (7)	7 (10)	7 (5)	0.16
Syncope	9 (4)	5 (7)	4 (3)	0.14
Viral prodromes	64 (30)	18 (26)	46 (32)	0.47
OHCA	21 (10)	6 (9)	15 (10)	0.66
NYHA functional class				
I	62 (29)	29 (41)	33 (23)	0.006
II	73 (34)	21 (30)	52 (36)	0.36
III	46 (22)	10 (14)	36 (25)	0.07
IV	32 (15)	10 (14)	22 (15)	0.83
≥III	78 (37)	20 (29)	58 (41)	0.09
Symptom duration, months	9 (3-30)	9 (2-35)	9 (4-26)	0.84
Genetic/familial DCM	70 (33)	70 (100)	0 (0)	
Inheritance pattern +				
Autosomal dominant	64 (30)	64 (91)	0 (0)	<0.001
X-linked recessive	1 (1)	1 (1)	0 (0)	<0.001
Pathogenic mutation	11 (5)	11 (16)	0 (0)	<0.001
Inheritance pattern−				
Pathogenic mutation	5 (2)	5 (7)	0 (0)	<0.001
ECG				
LBBB	55 (26)	18 (26)	37 (26)	0.98
AV block	10 (5)	7 (10)	3 (2)	0.02
Atrial fibrillation	35 (17)	14 (20)	21 (15)	0.40

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with a significant viral load were not found. Patients with genetic or familial DCM had similar viral presence or significant viral load, as compared with patients with nongenetic or nonfamilial DCM (81% vs. 79%; p = 0.74 and 21% vs. 15%; p = 0.25, respectively).

MOGE(S) CLASSIFICATION. According to the MOGE(S) classification (Table 2), skeletal muscle involvement showed the highest prevalence (5%), followed by ocular involvement, including episcleritis (n = 3), uveitis anterior (n = 2), and uveitis posterior (n = 2). Cutaneous involvement was seen in 3%, including vascular purpura (n = 5) and alopecia (n = 2). We identified 2 patients with gene mutations associated with extracardiac organ involvement: 1 patient with autosomal dominant Emery-Dreifuss muscular dystrophy (*LMNA* mutation) and the other with previously unrecognized Becker dystrophy (*DMD* mutation) with a mild phenotype.

A total of 18 pathogenic mutations in 16 (8%) patients were found (Online Figure 3, Online Table 2). A significant lower yield of pathogenic mutations was demonstrated in patients with nonfamilial DCM as compared with patients with familial DCM (4% vs. 17%; p < 0.001).

Multiple possible causes were found in 48 (23%) patients, with the most prevalent combination of genetic predisposition and increased cardiac inflammation or viral infection in 15 (7%) and 9 (4%) patients, respectively. Three causes were demonstrated in 7 (3%) patients with the most prevalent combination of genetic or familial, Vir− Infl+, DCM, and rhythm in 4 (2%) patients. One patient demonstrated 4 causes, including increased cardiac inflammation without virus, genetic or familial, rhythm, and toxic exposure. Examples of patients using MOGE(S) annotations are given in Table 3.

SHORT-TERM AND LONG-TERM FOLLOW-UP WITH PREDICTION OF OUTCOME. Echocardiographic measurements after a mean of 1 year demonstrated LVRR in 70 (35%) patients (Table 2, Online Table 3). A significantly lower rate of LVRR was present in patients with genetic or familial compared with nongenetic or nonfamilial DCM (25% vs. 40%; p = 0.04). In contrast, the rate of LVRR was significantly higher in patients with toxic DCM versus not toxic DCM (75% vs. 33%; p = 0.003). The 3 toxic-triggered patients without LVRR after 12 months were persons who continued abusing alcohol. Whether patients had 1 cause or multiple possible causes, no significant differences in LVRR were seen after 12 months.

During a median follow-up of 47 months (interquartile range, 30 to 67 months), 26 (13%) patients reached the primary endpoints of death (n = 15; annual mortality 1.6%), HTx (n = 1), or life-threatening arrhythmias (n = 12). Regarding the MOGE(S) classification, the presence of extracardiac organ involvement or NYHA functional class ≥III showed a significantly worse outcome compared with those patients without extracardiac organ involvement or NYHA functional class <III (Table 4, Central Illustration) (p < 0.001 and p = 0.02, respectively). The incidence of the primary endpoint was similar in genetic or familial DCM and in nongenetic or nonfamilial DCM (Table 4, Central Illustration) (p = 0.36). Additionally, there was no difference in outcome between patients with 1 or more nongenetic, environmental causes (significant viral load, immune-mediated condition, rhythm disturbances,

or toxic triggers) versus those without an identifiable nongenetic, environmental cause (**Table 4**, **Central Illustration**) ($p = 0.54$). Moreover, no cumulative detrimental effect of the number of either nongenetic causes or all possible causes on outcome was found ($p = 0.28$ and $p = 0.29$, respectively; data not shown). In addition to the MOGE(S) attributes, a lower LVEF was also associated with worse outcome (**Table 4**). After testing for interactions among all covariates, only genetic or familial and nongenetic, environmental causes showed a significant interaction ($p = 0.03$). Interestingly, a worse outcome was demonstrated in patients with genetic or familial DCM combined with at least 1 additional nongenetic, environmental factor compared with patients with only a genetic predisposition (**Figure 1A**) ($p < 0.05$). Similar results were found comparing this gene-environment interaction group with all other patients without these combined triggers (**Figure 1B**) ($p = 0.03$). Excluding patients with proven systemic disease in the last 2 analyses demonstrated similar results ($p < 0.05$ and $p = 0.02$, respectively; data not shown).

Using a scoring system assigning 1 point to each attribute or the gene-environment interaction (organ involvement [O], gene-environmental etiology [G + E], and NYHA functional class [S]), significant worse outcome was evident in patients with MOGE(S) ≥2 points versus MOGE(S) ≤1 (**Figure 1C**) ($p < 0.007$).

TABLE 1 Continued

	All (N = 213)	Genetic or Familial DCM (n = 70)	Nongenetic or Familial DCM (n = 143)	p Value
Echocardiography				
LVEF, %	29 ± 11	31 ± 10	29 ± 11	0.72
LVEDD, mm	62 ± 8	61 ± 7	62 ± 9	0.81
LVEDDI, mm/m^2	40 ± 8	40 ± 7	41 ± 8	0.31
Comorbidities				
History of hypertension	83 (39)	25 (36)	58 (41)	0.50
Hyperlipidemia	36 (17)	13 (19)	23 (16)	0.60
OSAS	21 (10)	9 (13)	12 (8)	0.30
Diabetes mellitus	23 (11)	5 (7)	18 (13)	0.21
Hyperthyroidism	3 (1)	2 (3)	1 (1)	1.00
Hypothyroidism	6 (3)	2 (3)	4 (3)	1.00
Systemic disease*	17 (8)	1 (1)	16 (11)	0.01
EMB				
Cardiac inflammation	87 (41)	27 (39)	60 (42)	0.70
CD3+, cells/mm^2	4.7 (2-8)	3.7 (2-8)	5.2 (3-9)	0.05
CD45+, cells/mm^2	8.5 (6-13)	8.0 (5-13)	9 (6-14)	0.26
CD68+, cells/mm^2	3.0 (1-6)	2.6 (1-5)	3.3 (1-7)	0.50
Fibrosis, %	5.7 (3-10)	5.5 (2-12)	6.0 (3-10)	0.51
Viral presence	162 (76)	52 (74)	110 (77)	0.73
Parvovirus B19	152 (71)	48 (69)	104 (73)	0.99
HHV6	48 (23)	22 (31)	26 (18)	0.02
Epstein-Barr virus	11 (5)	2 (3)	9 (6)	0.29
Adenovirus	4 (2)	0 (0)	4 (3)	0.31
Enterovirus	0 (0)	0 (0)	0 (0)	-
Medication				
Beta-blocker	197 (92)	66 (94)	131 (92)	0.41
% opt	50 (25-75)	50 (25-56)	50 (25-75)	0.79
ACE inhibitor or ARB	203 (95)	64 (91)	139 (97)	0.08
% opt	50 (25-63)	50 (25-100)	50 (25-50)	0.10
MRA	69 (32)	18 (26)	51 (36)	0.15
Diuretics	131 (62)	43 (61)	88 (62)	0.90
Digoxin	29 (14)	10 (14)	19 (13)	0.85
Devices				
ICD	102 (48)	35 (50)	67 (47)	0.66
CRT	41 (19)	13 (19)	28 (20)	0.83
Pacemaker	5 (2)	1 (1)	4 (3)	1.00

Values are mean ± SD, n, n (%), or median (interquartile range). *Discovered after diagnosis of DCM.

% opt = percentage of optimal doses; ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; AV = atrioventricular; BSA = body surface area; CRT = cardiac resynchronization therapy; DBP = diastolic blood pressure; DCM = dilated cardiomyopathy; ECG = electrocardiogram; EMB = endomyocardial biopsy; HHV6 = human herpes virus-6; ICD = implantable cardioverter-defibrillator; LBBB = left bundle branch block; LVEDD = left ventricular end-diastolic diameter; LVEDDI = indexed LVEDD; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association; OHCA = out-of-hospital cardiac arrest; OSAS = obstructive sleep apnea syndrome; SBP = systolic blood pressure.

DISCUSSION

The newly proposed MOGE(S) classification is applicable, with prognostic value in patients diagnosed with DCM (**Central Illustration**). All tested attributes of the MOGE(S) classification proved to be associated with worse outcome. Nonetheless, prognosis overall was favorable in this cohort of patients with well-defined DCM, independent of prognostic risk factors. Furthermore, our results demonstrate that a cause can be found in more than 70% of patients with DCM, and more than 1 possible cause is present in approximately one-fourth of patients.

MULTIFACTORIAL PATHOGENESIS OF DCM. During the past decade, several environmental causes of DCM development have been discovered. In parallel, more than 40 genes causing DCM have been identified, many of which are also associated with phenotypes besides DCM. This situation illustrates the complexity of this multifactorial disease and has led to continuous revision of the classification system proposed by the American Heart Association (9), the European Society of Cardiology (15), and the World Health Organization (16). In view of the last-mentioned system, the World Heart Federation proposed a new classification system for myocardial disorders that is called MOGE(S) (1). This system extends previous classifications by including the extent of organ involvement and the severity of HF.

Although only 1 etiologic annotation is applicable in the current MOGE(S) classification system, our results indicate that more than 1 possible cause can be found in one-fourth of patients DCM who undergo

TABLE 2 MOGE(S) Classification*

	Attribute Present (Rate of LVRR)	Attribute Not Present (Rate of LVRR)	p Value
(M)orphofunctional			
DCM	35 (70/198)	–	–
(O)rgan involvement	30 (9/30)	36 (61/168)	0.38
Skeletal muscle	29 (2/7)	36 (68/191)	0.70
Auditory system	60 (3/5)	35 (67/193)	0.35
Kidney	25 (1/4)	36 (69/194)	1.00
Nervous system	50 (1/2)	35 (69/196)	1.00
Liver	0 (0/2)	36 (70/196)	0.54
Gastrointestinal system	50 (1/2)	35 (69/196)	0.54
Cutaneous	40 (2/5)	35 (68/193)	1.00
Ocular system	40 (2/5)	35 (68/193)	1.00
Mental retardation	0 (0/1)	36 (70/197)	1.00
(G)enetic or familial	25 (15/61)	40 (55/137)	0.04
pathogenic mutation	13 (2/16)	37 (68/182)	0.05
(E)tiology (nongenetic)	36 (43/120)	35 (27/78)	0.86
Idiopathic	41 (22/54)	33 (48/144)	0.33
Viral infection	38 (14/37)	35 (56/161)	0.73
Vir+ Infl−	35 (8/23)	35 (62/175)	0.95
Vir+ Infl+	43 (6/14)	35 (64/184)	0.57
Immune-mediated	35 (27/78)	36 (43/120)	0.86
Vir− Infl+	38 (26/69)	34 (44/129)	0.62
Vir− Infl− Syst+	11 (1/9)	37 (69/189)	0.16
Rhythm disturbances	24 (4/17)	37 (66/181)	0.43
Toxic exposure	75 (9/12)	33 (61/186)	0.003
(S)tage of heart failure			
NYHA functional class ≥III	42 (31/74)	32 (39/124)	0.14
Number of possible etiologies†			0.70‡
0	41 (22/54)	35 (68/190)	0.72
1	33 (30/92)		
2	39 (17/44)		
≥3	25 (2/8)		

Values are % (n/N). *Patients (n = 198) with echocardiographic follow-up showing the rates of LVRR after 12 months as a function of each attribute. †Includes genetic and nongenetic etiologies. ‡Overall p value.

LVRR = left ventricular reverse remodeling; Vir+ Infl− = virus-positive inflammatory-negative DCM; Vir− Infl+ = virus-negative inflammatory DCM; Vir+ Infl+ = virus-positive inflammatory DCM; Vir− Infl− Syst+ = virus-negative, inflammatory-negative DCM with proven systemic disease; other abbreviations as in Table 1.

TABLE 3 Examples of MOGE(S) Annotations in Patients With DCM

Example	MOGE(S)
Genetic mutation	$M_D\ O_{H+M}\ G_{AD}\ E_{G\text{-}LMNA[p.Lys270Lys,\ predicting\ aberrant\ splicing]}\ S_{NYHA\text{-}2}$
Multiple genetic mutations	$M_D\ O_H\ G_{AD}\ E_{G\text{-}MYBPC3[p.Arg1022Pro]\ +\ PLN[p.Arg14Del]}\ S_{NYHA\text{-}4}$
Genetic mutation and viral myocarditis	$M_D\ O_{H+M}\ G_{XLR}\ E_{G\text{-}DMD[Del\ exons\ 45\text{-}48]\ +\ M:PVB19\ (1147\ copies/mcg\ DNA)}\ S_{NYHA\text{-}3}$
Immune-related conditions	$M_D\ O_{H+LU+E}\ G_N\ E_{AI\text{-}P\ [sarcoidosis]}\ S_{NYHA\text{-}2}$
Toxic exposure	$M_D\ O_H\ G_N\ E_{T\ [anthracyclines]}\ S_{NYHA\text{-}2}$
Rhythm disturbances	$M_D\ O_H\ G_N\ E_{R\ [34\%\ PVC]}\ S_{NYHA\text{-}3}$

M = morphofunctional: $_D$ = dilated cardiomyopathy; O = organ involvement: $_H$ = heart, $_M$ = muscle-skeletal, $_{LU}$ = lungs, $_E$ = eye; G= genetic or familial: $_{AD}$ = autosomal dominant, $_{XLR}$ = X-linked recessive, $_N$ = negative; E= etiology: $_G$ = genetic followed by specific mutation(s), $_M$ = myocarditis followed by specific cause, $_{PVB19}$ = parvovirus B19, $_{mcg}$ = micrograms, $_{AI\text{-}P}$ = proven auto-immune disease followed by specific disease, $_T$ = toxic followed by specific exposure, $_R$ = rhythm disturbances followed by specific arrhythmia, $_{PVC}$ = premature ventricular complex, $_{34\%\ PVC}$ = 34% premature ventricular complexes of total QRS complexes; S = stage of disease: $_{NYHA}$ = New York Heart Association.

TABLE 4 Association of Variables With Combined Endpoint*

	Univariable Analysis			
	HR	95% CI	Wald Test	p Value
Demographics				
Age, per 1 yr	1.01	0.98–1.05	0.39	0.53
Male	0.74	0.33–1.66	0.53	0.46
Medical history				
Duration of symptoms, per 1 yr	0.90	0.75–1.06	1.55	0.21
History of hypertension	0.41	0.15–1.09	3.20	0.059
Atrial fibrillation	1.54	0.64–6.78	1.84	0.31
Complete LBBB	1.07	0.45–2.54	0.02	0.89
Hyperlipidemia	0.22	0.03–1.63	2.19	0.14
Diabetes mellitus	0.04	0.00–7.20	1.47	0.23
OSAS	1.77	0.61–5.16	1.11	0.29
Hyperthyroidism	2.30	0.31–17.0	0.66	0.42
Hyperthyroidism	2.75	0.65–12.0	1.88	0.17
Systemic disease	0.94	0.22–3.97	0.007	0.93
Echocardiography				
LVEF, per 1-U	0.96	0.93–1.00	4.08	0.043†
LVEDD, per 1-U	1.04	1.00–1.08	2.74	0.098
MOGE(S)				
(O)rgan involvement	3.34	1.50–7.45	8.68	0.003†
(G)enetic or familial inheritance	1.43	0.66–3.09	0.82	0.37‡
(E)tiology known	0.75	0.34–1.64	0.53	0.47‡
Number of nongenetic etiologies	1.17	0.74–1.85	0.44	0.51
(G)+(E)	2.38	1.06–5.35	4.41	0.036†‡
(S)tage of disease: NYHA≥3	2.43	1.13–5.23	5.12	0.024†

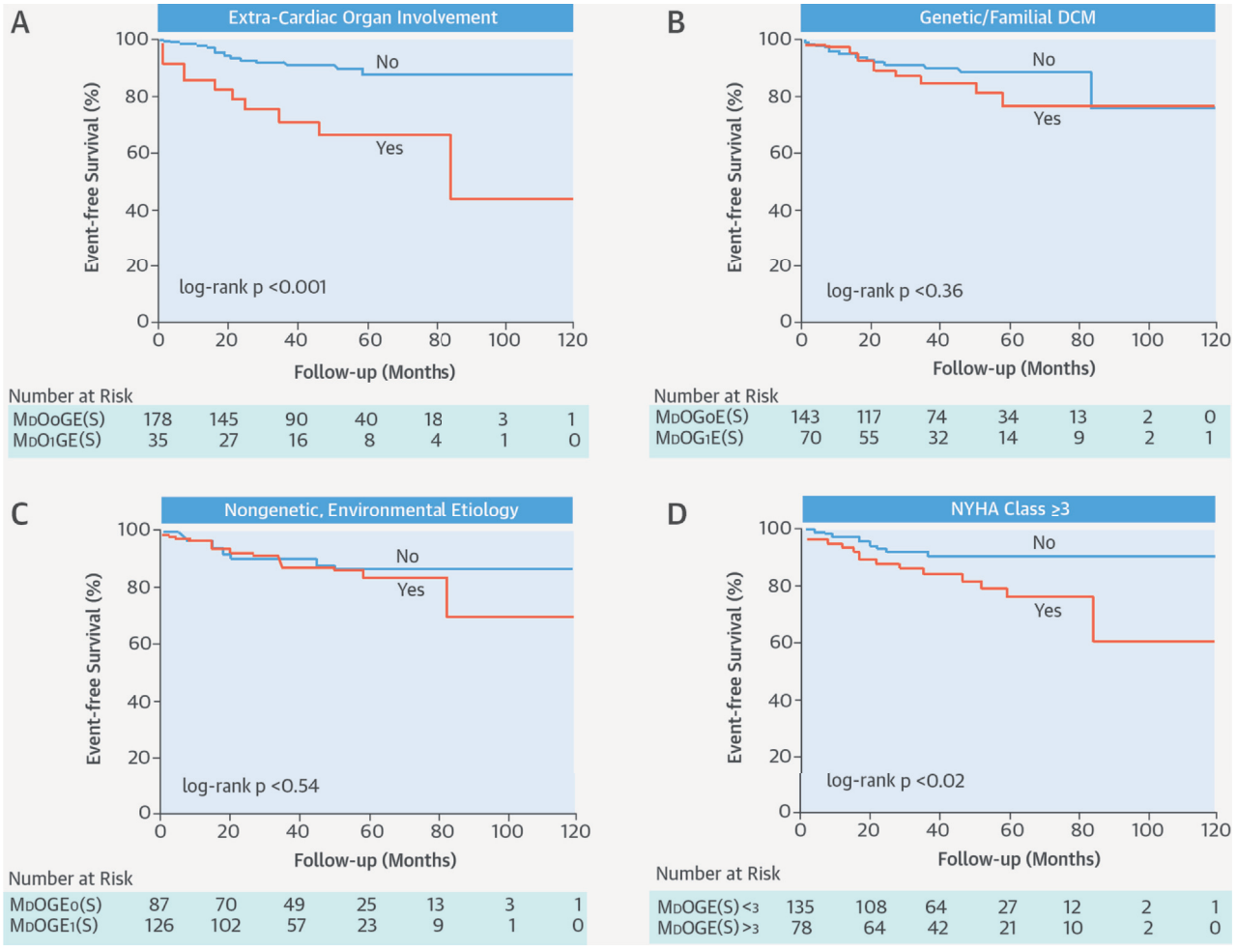
*Death, heart transplantation, life-threatening arrhythmia. †Variables were considered significant at the 95% confidence interval ($p < 0.05$). ‡Significant interaction between covariates ($p < 0.05$).

CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

a comprehensive diagnostic work-up. Importantly, the combination of multiple causes (genetic predisposition combined with an additional etiologic-environmental factor) revealed significant prognostic relevance. This finding is in line with current consensus that DCM is an end stage of a multifactorial pathogenesis leading to a single, final phenotype (8,17). In view of this, adaptation of the etiologic annotation in the MOGE(S) classification system is required. Moreover, excluding patients with DCM who also have CAD or hypertension, all possible evolving comorbidities during a patient's aging process, remains a limitation of all DCM classification systems. As for any other disease, comorbidities can be present, but they may not have a clinical influence on the DCM phenotype. In the future, the concept of excluding common causes of DCM (e.g., hypertension or CAD) may change with expanding knowledge of disease modifiers.

Finally, our results demonstrate that after a comprehensive diagnostic work-up, including genetic

CENTRAL ILLUSTRATION **Event-Free Survival Curves for Patients With DCM for All Different Attributes of the MOGE(S) Classification**



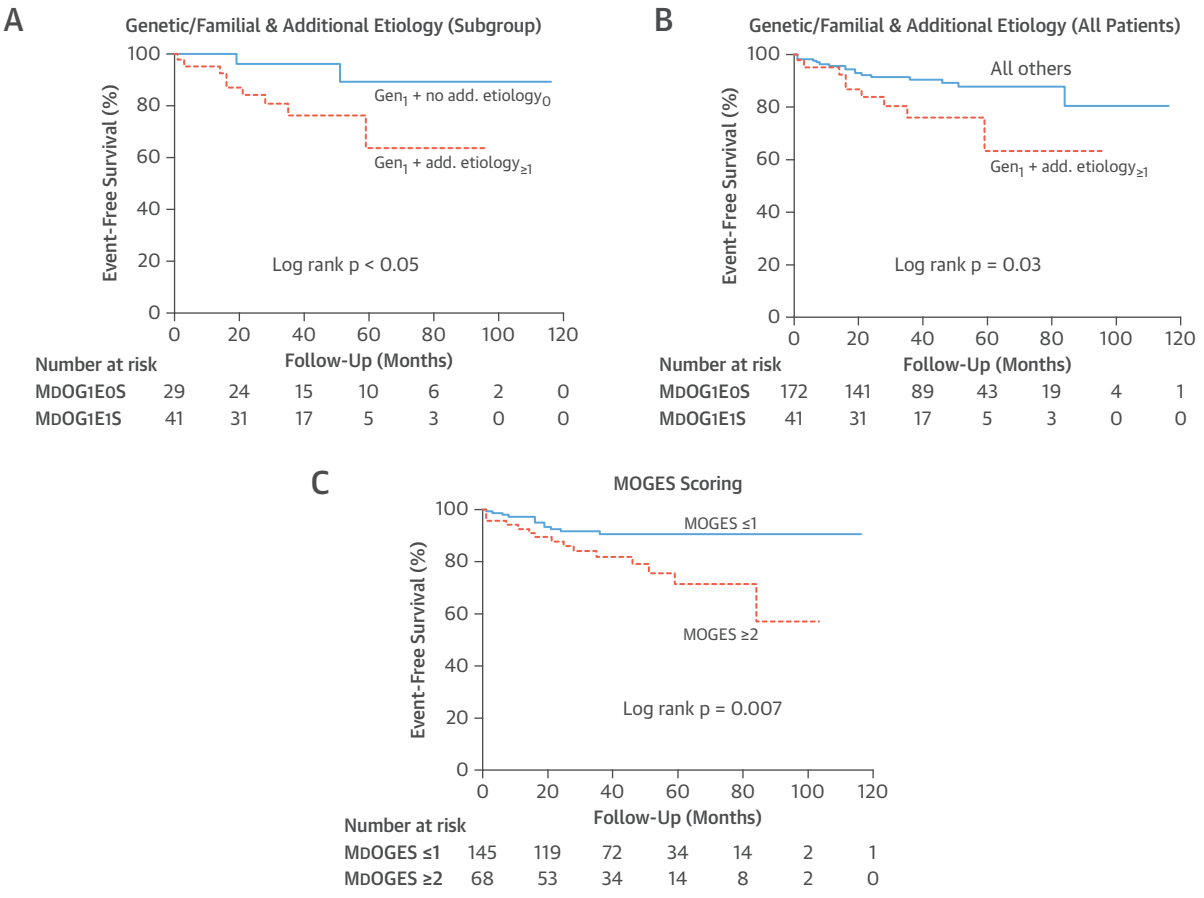
Hazebroek, M.R. et al. J Am Coll Cardiol. 2015; 66(12):1313–23.

Event-free survival curves of patients with dilated cardiomyopathy (DCM) compare the following: **(A)** the presence or absence of organ involvement; **(B)** patients with genetic or familial versus nongenetic or nonfamilial DCM; **(C)** patients with DCM versus without a nongenetic, environmental cause (significant viral load, increased cardiac inflammation, rhythm disturbances, or toxic triggers); and **(D)** patients with DCM with New York Heart Association (NYHA) functional class <III versus NYHA ≥III.

evaluation and EMB, a possible cause for DCM can be found in 73% of patients. This finding differs from previous reports of large populations of patients with DCM that described a cause of DCM in 50% of patients (4,5). The most likely explanations for this difference are the use of immunohistochemistry testing for detection of (low-grade) cardiac inflammation, DNA/RNA extraction for viral presence detection, and genetic testing, methods that were largely not available at the time of the previous reports.

Although our clinical genetics department performs routine assessment of organ involvement, with referral to a designated specialist if needed, it proved to be difficult in some cases to apply the MOGE(S) classification in this study because organ involvement is not fully specified in the proposal. We recognize the importance of extracardiac organ involvement, which can offer preliminary diagnostic clues and identify "red flags." In view of the latter, several immune-mediated diseases can have distinct extracardiac involvement (e.g., sarcoidosis), although other disorders may have indistinct involvement. For instance, in patients with increased cardiac inflammation without an identifiable cause, classifying

FIGURE 1 Event-Free Survival Curves for DCM Subgroups



Event-free survival curves demonstrate the cumulative impact of genetic and other factors on patients with dilated cardiomyopathy (DCM). Subgroups compared included **(A)** patients with familial or genetic DCM and at least 1 additional etiologic-environmental factor (significant viral load, immune-mediated condition, rhythm disturbances, or toxic triggers: Gen_1+ add. $etiology_{\geq 1}$) versus patients with DCM who had only familial or genetic DCM (Gen_1+ no add. $etiology_0$); **(B)** patients with familial or genetic DCM and at least 1 additional etiologic-environmental factor versus all patients with DCM without this combination (only familial or genetic, only nongenetic cause, or neither); and **(C)** patients with DCM with ≥2 positive MOGE(S) attributes versus those with ≤1 positive attribute.

extracardiac involvement remains difficult when associations are unknown. Therefore, extracardiac organ involvement was considered positive only if the condition was proved by a specialist and had a known or suspected relationship with the cause of DCM. Interestingly, organ involvement was a strong independent predictor of outcome. This association may reflect disease severity, in which extracardiac organ involvement may represent an advanced stage of the underlying systemic or genetic disease. In contrast, hitherto unknown or unidentified syndromes may underlie the DCM phenotype in these patients.

A familial inheritance pattern was found in one-third of patients, similar to previous reports (18,19). A pathogenic mutation was identified in 16 (8%) patients with DCM: 11 had a positive family history, and 5 had phenotypically sporadic DCM. This finding extends the current knowledge that genetic testing should not be restricted to familial cases because variable expression or incomplete family history may influence the inheritance pattern. Moreover, genetic defects can be de novo, have an age-dependent penetrance, or be present in unique survivors or small families, again masking a familial inheritance.

Several relatively large studies have evaluated a genetic cause for DCM. Hershberger et al. identified a putative genetic cause in 20% to 30% of >300 index patients with DCM (20–23). Two studies using a setup similar to ours identified a pathogenic mutation in

17% to 20% of their patients with DCM (24,25). However, 52% to 58% of patients in the latter studies had a positive family history of DCM versus 31% in our cohort. Therefore, the higher yields of pathogenic mutations in the previous studies could be explained by the following: our routine referral of all patients with DCM, irrespective of an already known nongenetic cause or a positive family history; regional differences in incidence or prevalence of gene mutations, whereas founder mutations can strongly determine the yield of pathogenic mutations (25); or number of genes tested per patient.

Genetics in DCM remains challenging because of the high number of disease-specific and candidate genes and the presence of many rare or novel mutations, usually specific for a single individual or family ("private" mutations), as well as difficulties in determining whether DNA variants are clinically relevant, particular in the era of next-generation sequencing (8). Thus, irrespective of the number of genes tested, it is likely that the number of genes influencing the phenotype of DCM is significantly higher than currently known. Although more than 40 causative genes for DCM development are described, few studies exist on genotype-phenotype correlations and their impact on outcome. Several mutations are associated with prominent conduction disease and arrhythmia *(DES, LMNA, SCN5A, PLN),* whereas *LMNA* and *PLN* carriers in particular have a high prevalence of both life-threatening ventricular arrhythmias and end-stage HF (26,27). Although a recent paper demonstrated a significantly worse outcome in patients with DCM who had a pathogenic mutation compared with no pathogenic mutation (25), the result was highly dependent on the high prevalence of the *PLN* founder and *LMNA* mutations (74% of patients with pathogenic mutations). The relatively low prevalence of the latter mutations in our cohort may explain why we did not observe a worse long-term outcome in patients with familial or genetic DCM.

Furthermore, the lower rate of LVRR in familial or genetic DCM may be explained by the predominance of sarcomeric mutations that influence cardiac structure and function without a strong effect on long-term outcome. In contrast to other nongenetic environmental factors that may reverse spontaneously or after therapy, the genetic or familial cause is irreversible. Moreover, the fact that we performed genetic analysis in all consenting patients, independent of DCM severity or the presence of a nongenetic cause, may have led to a broad spectrum of phenotypic expression of specific gene mutations that could account for a less severe phenotype in our study. It is likely that not all mutations associated with DCM are equally malignant; that seems to be the case in our population. Finally, the paradoxical finding that familial or genetic DCM negatively predicts LVRR but not long-term outcome may also reflect the fact that clinical outcome (death, HTx, life-threatening arrhythmias) and LVRR (morphofunctional improvement) are in part independent of each other and therefore may be determined by different etiologic factors.

Routine use of EMB allowed us to evaluate both viral presence and cardiac inflammation and their relationship with genetic background. Our results demonstrating viral presence in 76% of patients with DCM and increased cardiac inflammation in 41% of patients with DCM are in line with previous reports (28,29). As previously shown, viral infection may cause cardiac inflammation, and viral persistence may play a contributory role in developing DCM (30). Although almost 90% of adults will encounter one of these viruses during their life, as demonstrated by the presence of serologic anti-immunoglobulin G in a large population study, few will develop cardiac sequelae (31). This finding suggests that viral susceptibility, possibly genetically predisposed, plays an important role in the development of DCM, as reflected in our results demonstrating that no single cause determines outcome, which instead stems from the combination of genetic predisposition and an additional etiologic-environmental factor. Therefore, susceptibility to DCM development should not be restricted to viruses and cardiac inflammation, but to all triggers that can either cause or contribute to DCM after excluding other, more prevalent causes.

Implementation of the MOGE(S) classification may play a significant role in stratifying patients who will benefit most from etiologically based treatments, in addition to a standard HF regimen. However, whether the latter approach improves outcome in terms of LVRR or event-free survival remains to be tested prospectively. Given that the outcome largely depends on the gene-environment interaction, we recommend genetic evaluation of all patients with DCM irrespective of the suspicion of another nongenetic cause of the disease and, similarly, would recommend further etiologic examinations including consideration of cardiac biopsies in patients with DCM and a proven gene mutation.

A significant percentage of our patients (27%) received etiologically based treatment strategies, such as intravenous immunoglobulins or immunosuppressive therapy in those patients demonstrating (viral) inflammatory DCM. Although the nonrandomized nature of this study is unable to prove a

beneficial effect of our treatment strategies, we do show excellent survival rates after a mean of more than 4 years.

STUDY LIMITATIONS. This study represents an unbiased analysis of the clinical, biological, and morphometric data derived from using predefined definitions to predict outcome and functional improvement. Patients with DCM comprise a heterogenic patient population, predominantly because of the still exploratory nature of this field, in which many entities remain unknown. With respect to LVRR after 12 months, classifying patients into these predefined subgroups sometimes resulted in a relatively small number of patients. Therefore, these results should be interpreted with caution. Although we routinely perform EMB and refer all patients with DCM for genetic screening, a potential selection bias may have occurred because not all patients consented to these investigations. Nevertheless, comparison of baseline characteristics between selected and excluded patients did not show any significant difference. Although the most evidence-based or severe (early-onset, worse prognosis) pathogenic mutations *(MYH7, TPM1, LMNA, DES)* were tested in 92% of patients, the number of index patients screened for each gene differed as a result of ongoing recruitment of patients over a period of 10 years and improved insight into different genes that could cause DCM. Because of the relative low event rate in our cohort, the current study had insufficient power to perform multivariable modeling to test for independent predictors of outcome.

CONCLUSIONS

Our results revealed that improved stratification of patients with DCM is possible by using the attributes of the MOGE(S) classification by combining genetic evaluation and nongenetic, environmental factors, including EMB. The paradoxical finding that genetic or familial DCM was a negative predictor of short-term LVRR, whereas only the gene-environment interaction was a negative predictor of long-term outcome, raises interest. In the future, knowing one's genetic predisposition may have clinical implications because preventive measures would be more important in such patients and their relatives. Finally, our study demonstrated that a complete diagnostic work-up increased diagnostic yield and is associated with excellent survival rates, if the underlying cause of DCM is recognized and treated accordingly.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Each component of the MOGE(S) classification scheme for patients with DCM is associated with prognosis. The strongest predictors of adverse outcome are involvement of organs other than the heart, higher New York Heart Association functional class, and the product of gene-environment interaction.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Genetic evaluation of patients with DCM may have prognostic implications even when nongenetic causes are identified and vice versa.

TRANSLATIONAL OUTLOOK: More research in larger cohorts of patients with DCM of various causes (genetic and nongenetic) is needed to identify variables other than those captured by the MOGE(S) classification that are associated with clinical outcomes and have therapeutic implications.

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KEY WORDS autoimmune, etiology, toxic, virus

APPENDIX For an expanded Methods section as well as supplemental tables and figures, please see the online version of this article.