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Long-Term Follow-Up of Biopsy-Proven Viral Myocarditis

Predictors of Mortality and Incomplete Recovery

Stefan Grün, MD,* Julia Schumm, MD,* Simon Greulich, MD,* Anja Wagner, MD,† Steffen Schneider, PHD,‡ Oliver Bruder, MD,‡ Eva-Maria Kispert, RN,* Stephan Hill, MD,* Peter Ong, MD,* Karin Klingel, MD,§ Reinhardt Kandolf, MD,§ Udo Sechtem, MD,* Heiko Mahrholdt, MD*

Stuttgart, Essen, and Tübingen, Germany; and Stamford, Connecticut

Objectives This study sought to evaluate the long-term mortality in patients with viral myocarditis, and to establish the prognostic value of various clinical, functional, and cardiovascular magnetic resonance (CMR) parameters.

Background Long-term mortality of viral myocarditis, as well as potential risk factors for poor clinical outcome, are widely unknown.

Methods A total of 222 consecutive patients with biopsy-proven viral myocarditis and CMR were enrolled. A total of 203 patients were available for clinical follow-up, and 77 patients underwent additional follow-up CMR. The median follow-up was 4.7 years. Primary endpoints were all-cause mortality and cardiac mortality.

Results We found a relevant long-term mortality in myocarditis patients (19.2% all cause, 15% cardiac, and 9.9% sudden cardiac death [SCD]). The presence of late gadolinium enhancement (LGE) yields a hazard ratio of 8.4 for all-cause mortality and 12.8 for cardiac mortality, independent of clinical symptoms. This is superior to parameters like left ventricular (LV) ejection fraction, LV end-diastolic volume, or New York Heart Association (NYHA) functional class, yielding hazard ratios between 1.0 and 3.2 for all-cause mortality and between 1.0 and 2.2 for cardiac mortality. No patient without LGE experienced SCD, even if the LV was enlarged and impaired. When focusing on the subgroup undergoing follow-up CMR, we found an initial NYHA functional class >I as the best independent predictor for incomplete recovery ($p = 0.03$).

Conclusions Among our population with a wide range of clinical symptoms, biopsy-proven viral myocarditis is associated with a long-term mortality of up to 19.2% in 4.7 years. In addition, the presence of LGE is the best independent predictor of all-cause mortality and of cardiac mortality. Furthermore, initial presentation with heart failure may be a good predictor of incomplete long-term recovery. (J Am Coll Cardiol 2012;59:1604–15) © 2012 by the American College of Cardiology Foundation

Viral myocarditis is a common cardiac disease that is identified in up to 9% of post-mortem examinations (1,2). It appears to be a major cause of sudden, unexpected death (3), and may progress to dilated cardiomyopathy (4,5).

Advanced diagnostic procedures such as cardiovascular magnetic resonance (CMR) or immunohistologic and molecular pathologic workup of endomyocardial biopsies provided new insights into this common, but not well characterized, disease (6,7). However, the clinical management remains difficult, and the long-term mortality of viral myocarditis, as well as potential risk factors for poor clinical outcome, are widely unknown.

Recent publications suggested several parameters that may be associated with poor outcome (8–10), including clinical symptoms, type of viruses, left ventricle (LV) size and LV function, and late gadolinium enhancement (LGE), which has been identified as a predictor of long-term mortality in other nonischemic heart diseases (11,12).

Consequently, the primary objective was to evaluate the long-term mortality in patients with viral myocarditis, as well as to establish the long-term prognostic value of various clinical, functional, and CMR parameters in this patient group.

From the *Department of Cardiology, Robert-Bosch-Medical Center, Stuttgart, Germany; †Comprehensive Cardiology of Stamford and Greenwich, Stamford, Connecticut; ‡Institut für Herzinfarktforschung Ruhr, Essen, Germany; and the §Department of Molecular Pathology, University of Tübingen, Tübingen, Germany.
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Specifically, we sought to demonstrate that the presence of LGE predicts future cardiac death. In addition, we aimed at describing predictors for incomplete recovery during long-term follow-up.

Methods

Patient population. Two hundred twenty-two consecutive patients presenting at our institution in Stuttgart for workup of myocarditis (all comers; referrals [62.9%] and self-presenting [37.1%]) were enrolled in the long-term follow-up between January 2002 and January 2008 if they fulfilled all of the following criteria: 1) biopsy-proven viral myocarditis defined as presence of myocardial inflammation and viral genome; 2) ruling out of relevant coronary artery disease (stenosis >50%) by angiography; and 3) CMR performed within 5 days of initial presentation. Patients with valvular or congenital heart disease demonstrated by CMR were not included. All patients gave informed consent. Some patients were also part of previous reports (6,9).

CMR protocol. Electrocardiography-gated CMR imaging was performed in breath-hold using a 1.5T Magnetom Sonata (Siemens Healthcare, Erlangen, Germany) in line with the Society of Cardiovascular Magnetic Resonance/European Cardiovascular Magnetic Resonance recommendations (13). Both cine and LGE short-axis CMR images were prescribed every 10 mm (slice thickness 6 mm) from base to apex. In-plane resolution was typically 1.2 × 1.8 mm. Cine CMR was performed using a steady-state free precession sequence. LGE images were acquired on average 5 to 10 min after contrast administration using segmented inversion recovery gradient echo sequence (14) constantly adjusting inversion time (15). The contrast dose (gadodiamide or gadopentetate-dimeglumine) was 0.15 mmol/kg. In addition, fat-saturated and T2-weighted images were obtained to allow differentiation between subepicardial LGE, epicardial fat, and pericardial effusion.

CMR analysis. Cine and contrast images were evaluated by two experienced observers as described elsewhere (6,9). In brief, endocardial and epicardial borders were outlined on the short-axis cine images. Volumes and ejection fraction (EF) were derived by summation of epicardial and endocardial contours. The LV mass was calculated by subtracting endocardial from epicardial volume at end-diastole and multiplying by 1.05 g/cm^3 (16). Extent of LGE was assessed using the Siemens Healthcare Argus analysis software package and the results were expressed as percentage of myocardial mass.

Endomyocardial biopsy protocol. Endomyocardial biopsies were performed in all patients. At least five biopsies were preferentially taken from the ventricle demonstrating LGE. Patients demonstrating LGE exclusively in the LV lateral wall underwent selective LV biopsies (30.9%), while those demonstrating LGE in the septum or having no LGE at all underwent either biventricular (54.1%) or selective right ventricular biopsies (15%).

Histopathological analysis. Endomyocardial biopsies were stained with Masson's trichrome as well as Giemsa and examined by light microscopy. For immunohistology, tissue sections were treated with an avidin-biotin-immunoperoxidase method (Vectastain Elite Kit, Vector, Burlingame, California), applying the following monoclonal antibodies: CD3 (T-cells, Novocastra Laboratories, Newcastle, United Kingdom), CD68 (macrophages, DAKO, HAMBURG, GERMANY), and human leukocyte antigen-DR (DAKO) as described previously. The detection of >14 infiltrating leukocytes/mm^2 (CD3+ T-lymphocytes and/or CD68+ macrophages) in the presence of myocyte damage and/or fibrosis in addition to enhanced human leukocyte antigen class II expression in professional antigen-presenting immune cells and endothelium was used for the diagnosis of myocarditis (6,9).

Abbreviations and Acronyms

CMR = cardiovascular magnetic resonance
EDV = end-diastolic volume
EF = ejection fraction
HHV = human herpes virus
HR = hazard ratio
ICD = implantable cardioverter-defibrillator
LGE = late gadolinium enhancement
LV = left ventricle/left ventricular
NYHA = New York Heart Association
PVB19 = parvovirus B19
SCD = sudden cardiac death

Detection of viral genomes. Deoxyribonucleic acid and ribonucleic acid were extracted with the use of proteinase-K digestion followed by extraction with phenol/chloroform. Nested polymerase chain reaction/reverse transcriptase–polymerase chain reaction was performed for the detection of enteroviruses (including coxsackieviruses group A & B and echoviruses), parvovirus B19 (PVB19), adenoviruses, human cytomegalovirus, Epstein-Barr virus, and human herpes virus type 6 (HHV6). As control for successful extraction of deoxyribonucleic acid and ribonucleic acid, oligonucleotide sequences were chosen from the glyceraldehyde-3-phosphate-dehydrogenase gene. Specificity of all viral amplification products was confirmed by automatic deoxyribonucleic acid sequencing (6,9).

Clinical and CMR follow-up. Clinical follow-up was performed using a standardized questionnaire at least 3 years after initial presentation. CMR follow-up using an imaging protocol identical to that used initially was offered to all surviving patients without contraindications to CMR.

In case of a suspected event, all necessary medical records were obtained and reviewed by the authors acting as endpoint committee.

Variables, endpoints, and definitions. All variables were collected directly from patients, and/or medical records except CMR parameters, which were evaluated as described previously. Variables include general characteristics and follow-up results. Most variables are self-explanatory; all others are defined below.

There were three primary endpoints: 1) all-cause death, defined as death from any cause, including aborted sudden cardiac death (SCD); 2) cardiac death, defined as death

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from all cardiac causes, including SCD, heart failure, and aborted SCD; and 3) SCD, defined as unexpected arrest of presumed cardiac origin within 1 h after onset of any symptoms that could be interpreted as being cardiac in origin. Aborted SCD was considered as resuscitation after cardiac arrest defined as performance of the physical act of cardioversion, appropriate implantable cardioverter-defibrillator (ICD) shocks, or cardiopulmonary resuscitation in a patient who remained alive 28 days later. For appropriate ICD shocks, defibrillator discharges were considered appropriate and included automatic defibrillation shocks triggered by ventricular tachycardia or fibrillation and documented by stored intracardiac electrocardiographic data.

Incomplete recovery was used as a secondary endpoint in the group of patients with CMR follow-up. Incomplete recovery was defined as EF <60% or end-diastolic volume (EDV) >180 ml, or clinical signs of heart failure (New York Heart Association [NYHA] functional class >I).

Statistical analysis. Absolute numbers and percentages were computed to describe the patient population. Medians (with interquartile range) or mean ± SD were computed as appropriate. Categorical values were compared by chi-square test or Fisher exact test as appropriate. Kaplan-Meier curves were calculated for visualizing the cumulative survival of patients with and without LGE. A log-rank test was performed to compare both survival curves. A multivariable Cox proportional hazards model was used for analyzing independent associations with all-cause and cardiac mortality. All p values <0.05 were considered significant. All p values are results of 2-tailed tests. All statistical analyses were performed using the SAS statistical package, version 9.2 (SAS Institute, Cary, North Carolina).

Results

Patient characteristics. Two hundred three of all 222 patients were available for clinical follow-up, yielding a follow-up rate of 91.5%. The remaining 19 patients were lost due to no contact. The following paragraphs describe the characteristics of the 203 patients who underwent clinical follow-up.

At inclusion, patients were 52 years old (interquartile range: 40 to 54). Chest pain was the primary reason to seek medical attention (n = 74), followed by new onset of heart failure (n = 62), and various combinations of malaise and palpitations (n = 49) (Table 1). Most patients had an abnormal electrocardiogram upon admission (n = 188 of 203, 92.6%), with ST-segment abnormalities as the most common finding (n = 111 of 188, 59%), followed by bundle branch block (n = 20 of 188, 10.6%).

Endomyocardial biopsy revealed PVB19 as most frequent virus (n = 113), followed by HHV6 (n = 49), and the combination of PVB19 and HHV6 (n = 35). Epstein-Barr virus was also present, whereas other viruses were not found (Table 1).

Table 1 Baseline Patient Characteristics (All Patients With Clinical Follow-Up)

All patients with follow-up	203 (91.5)
Time to follow-up, days	1,685 (1,267–2,102)
Female	63 (31.0)
Age, yrs	52 (40–54)
BMI, kg/m^2	26.3 (24.0–29.1)
BSA, m^2	2.0 (1.8–2.1)
Primary clinical presentation	
Symptoms of ACS	74 (36.5)
Subacute new-onset HF	62 (30.5)
Reoccurring episodes of overt HF	18 (8.9)
Combination of palpitations, fatigue, dyspnea on exertion	49 (24.1)
Aborted SCD	0
Initial NYHA functional class	
I	48 (23.6)
II	64 (31.5)
III	71 (35.0)
IV	20 (9.9)
Virus type by endomyocardial biopsy	
PVB19	113 (55.7)
HHV6	49 (24.1)
PVB19/HHV6	35 (17.2)
EBV	2 (1.0)
PVB19/HHV6/EBV	1 (0.5)
PVB19/EBV	2 (1.0)
HHV6/EBV	1 (0.5)
Blood testing	
Troponin positive	46 (22.7)
BNP, pg/ml	190 (39–652)
NT-proBNP, pg/ml	1,938 (220–8822)
CMR imaging parameter	
LVEF, %	45 (31–60)
EF indexed, %/m^2	23.7 (15.9–31.2)
LVEDV, ml	167 (129–210)
LVESV, ml	90 (47–144)
LGE present	108 (53.2)
LGE mass, g	5.3 (3.2–18.6)
LGE, % of LV mass	4.2 (2.3–9.3)
Event	
All-cause death	39 (19.2)
Cardiac death	29 (15.0)
SCD	18 (9.9)

Values are n (%) or median (interquartile range).

ACS = acute coronary syndrome; BMI = body mass index; BNP = B-type natriuretic peptide; BSA = body surface area; CMR = cardiovascular magnetic resonance; EBV = Epstein-Barr virus; HF = heart failure; HHV6 = human herpes virus type 6; LGE = late gadolinium enhancement; LV = left ventricle/left ventricular; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; NT-proBNP = N-terminal pro–B-type natriuretic peptide; NYHA = New York Heart Association; PVB19 = parvovirus B19; SCD = sudden cardiac death.

All patients presenting with heart failure were treated with state-of-the-art heart failure medication according to guidelines. If indicated, an ICD was offered, which was accepted by 23 patients. No patient in this cohort received additional immunosuppressive, immunomodulatory, or antiviral therapy.

CMR findings. The mean LVEF was 45% and the mean LVEDV was 167 ml (Table 1). LGE was present in 108 of

Table 2 Characteristics of Patients With and Without LGE

	LGE Present (n = 108)	No LGE (n = 95)	p Value	OR (95% CI)
Age, yrs	55.0 (40.5–67.5)	50.0 (38.0–59.0)	0.08	
Female	26 (24.1)	37 (38.9)	<0.05	0.50 (0.27–0.91)
BMI, kg/m^2	26.8 (24.5–29.4)	25.8 (23.5–28.4)	0.16	
BSA, m^2	2.0 (1.8–2.2)	1.9 (1.8–2.1)	<0.05	
Primary clinical presentation				
Symptoms of ACS	37 (34.3)	37 (38.9)	0.49	0.82 (0.46–1.45)
Subacute new-onset heart failure	37 (34.3)	25 (26.3)	0.22	1.46 (0.80–2.67)
Reoccurring episodes of overt HF	11 (10.2)	7 (7.4)	0.48	1.43 (0.53–3.84)
Combination of palpitations, fatigue, dyspnea on exertion	23 (21.3)	26 (27.4)	0.31	0.72 (0.38–1.37)
Aborted SCD	0 (0)	0 (0)	1.00	
Initial NYHA functional class				
I	25 (23.1)	23 (24.2)	0.86	0.94 (0.49–1.80)
II	32 (29.6)	32 (33.7)	0.53	0.83 (0.46–1.50)
III	40 (37)	31 (32.6)	0.51	1.21 (0.68–2.17)
IV	11 (10.2)	9 (9.5)	0.87	1.08 (0.43–2.74)
Virus type by endomyocardial biopsy				
PVB19	61 (56.5)	52 (54.7)	0.80	1.07 (0.62–1.87)
HHV6	23 (21.3)	26 (27.4)	0.31	0.72 (0.38–1.37)
PVB19/HHV 6	20 (18.5)	15 (15.8)	0.61	1.21 (0.58–2.53)
EBV	1 (0.9)	1 (1.1)	0.93	0.88 (0.05–14.24)
PVB19/HHV6/EBV	1 (0.9)	0 (0)	0.35	
PVB 19/EBV	2 (1.9)	0 (0)	0.18	
HHV6/EBV	0 (0)	1 (1.1)	0.29	
Blood testing				
Troponin positive	30 (27.8)	16 (16.8)	0.06	1.90 (0.96–3.76)
BNP, pg/ml	336 (82–983)	67 (27–457)	<0.001	
NT-proBNP, pg/ml	2,359 (547–18,092)	1,938 (38–4,391)	0.55	
CMR imaging parameter				
LVEF, %	37.5 (24.5–57.0)	53.0 (39.0–64.0)	<0.0001	
EF indexed, %/m^2	19.9 (12.7–28.4)	26.8 (19.6–33.8)	<0.0001	
LV-EDV, ml	187.5 (140–263)	155.0 (120–193)	<0.001	
LV-ESV, ml	119.5 (57.5–179.0)	73.0 (43.0–113.0)	<0.0001	
LGE mass, g	5.3 (3.2–18.6)	—		
LGE, % of LV mass	4.2 (2.3–9.3)	—		

Values are median (25th–75th percentile) or n (%).
CI = confidence interval; OR = odds ratio; other abbreviations as in Table 1.

203 patients. LGE was usually located in the subepicardial or intramural areas of the LV.

Using the presence of LGE as only diagnostic criterion, the sensitivity of LGE to detect myocarditis was 53.2%. However, when also taking morphological and functional information into account, we found that 170 of 203 patients had an abnormal CMR (LVEF <60% and/or LVEDV >180 ml and/or presence of LGE). Thus, the overall diagnostic performance of CMR to detect myocarditis was 83.7% using morphology, function, and LGE according to 2008 Society of Cardiovascular Magnetic Resonance/European Cardiovascular Magnetic Resonance recommendations (13).

Dividing our patient population in groups with and without LGE reveals that patients with LGE had larger ventricles, poorer LVEF, and were more likely to have elevated levels of B-type natriuretic peptide (Table 2). However, we did not find significant differences in clinical symptoms or type of viruses between the 2 groups with and without LGE (Table 2). Typical CMR results are displayed in Figure 1.

Follow-up results. During follow-up 28 of 203 patients died, and 11 patients survived SCD due to adequate ICD discharge. Those 11 patients were also counted as events as described previously (Table 1). The majority of events (n = 29) occurred for cardiac reasons, and the remaining 10 events were related to cancer, fatal infections, or accidents. Note that no patient with normal CMR at initial presentation (n = 33) died.

Seventy-seven of the surviving patients without ICD (n = 141) agreed to undergo follow-up CMR in addition to clinical follow-up (54.6%). The mean time between initial and follow-up CMR was 4.7 years. During this time 24 of the 77 patients recovered fully (LVEF ≥60% and LVEDV ≤180 ml and no clinical signs of heart failure).

Predictors of events. For evaluation of predictors for events we looked at: 1) all patients who experienced any

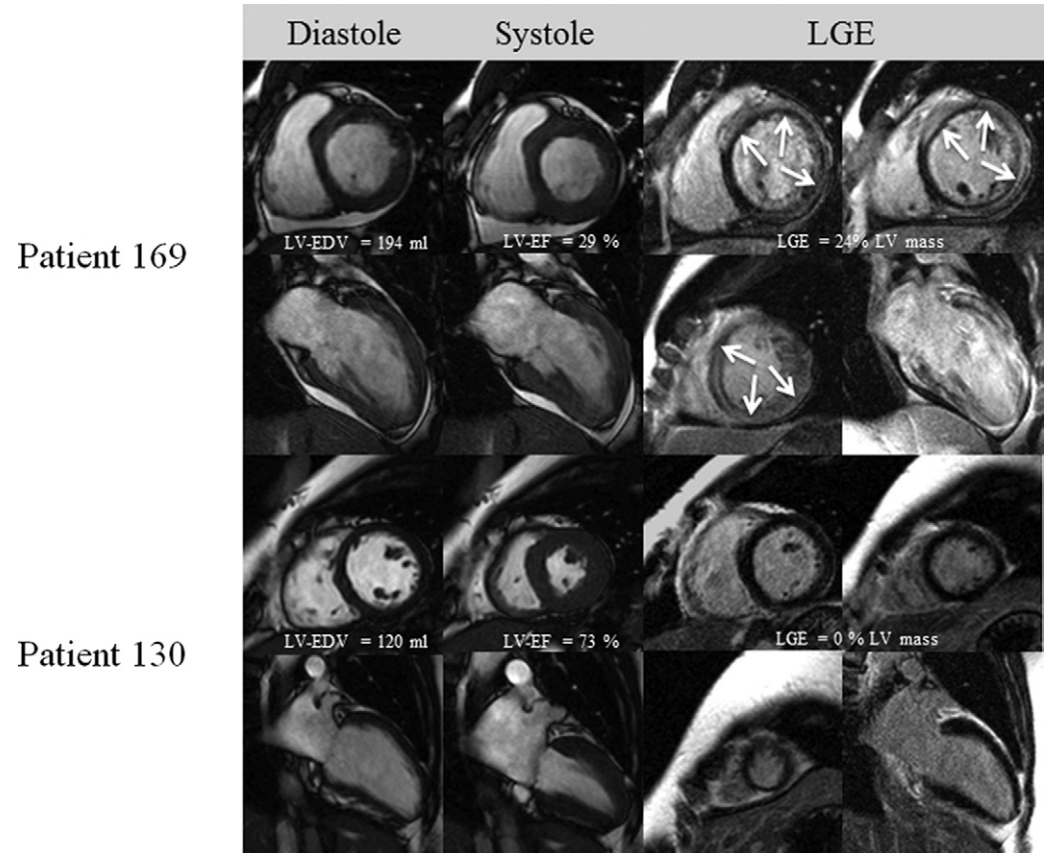

Figure 1 **Typical Cardiac Magnetic Resonance Results**

Cardiovascular magnetic resonance of a 25-year-old male patient presenting for workup of new heart failure (**top row**, Patient #169). Cine images show an enlarged left ventricle (LV) with severely impaired left ventricular ejection fraction (LVEF). Late gadolinium enhancement (LGE) is present in many areas **(white arrows)** adding up to 24% of LV mass. Endomyocardial biopsy revealed human herpes virus type 6 myocarditis. The **bottom row** (Patient #130) displays cardiovascular magnetic resonance findings in a 52-year-old female presenting for workup of chest pain. LVEF and LV size is normal (cine) and no LGE can be found. This patient was diagnosed with parvovirus B19 myocarditis. LVEDV = left ventricular end-diastolic volume.

death (all-cause mortality); 2) the subgroup of patients who experienced cardiac death (cardiac mortality); and 3) the subgroup of patients experiencing SCD. Univariate analysis (all-cause mortality, cardiac mortality, SCD) is displayed in Table 3, 4, and 5. There is no significant correlation between events and clinical presentation (except reoccurring episodes of overt heart failure), type of virus, or positive troponin at initial presentation. However, there is a trend to poorer outcome in combined PVB19/HHV6 infection.

Besides age, which is obviously related to mortality and morbidity, functional parameters such as LVEF, LVEDV, and the presence of LGE reached statistical significance. In fact, the presence of LGE yields an odds ratio for death of 24.2 in the all-cause mortality group and 36.7 in the cardiac mortality group. The odds ratio for SCD could not be calculated because no patient without LGE experienced SCD. Typical examples are displayed in Figure 2.

Kaplan-Meier survival curves for all-cause mortality, cardiac mortality, and SCD comparing patients with LGE with patients without LGE are displayed in Figures 3A to 3C. Note that only 1 patient without LGE experienced cardiac death during follow-up (Fig. 3B) and that no patient without LGE experienced SCD (Fig. 3C).

Multivariable Cox proportional hazards regression analysis including the initial presence of LGE, the initial LVEF, the initial LVEDV, and the initial NYHA functional class also revealed LGE as the best independent predictor of all-cause mortality (hazard ratio [HR]: 8.4, $p = 0.004$). In this model neither initial LVEDV (HR per milliliter increase in LVEDV: 1.003, $p = 0.08$), nor initial NYHA functional class (HR: 3.2, $p = 0.11$), nor initial LVEF (HR per percent increase in LVEF: 0.98, $p = 0.13$) reached significance. Looking at patients experiencing cardiac death only, LGE was also the best independent predictor of cardiac death (HR: 12.8, $p < 0.01$). Also in this model neither initial LVEDV (HR per milliliter increase in LVEDV: 1.004, $p = 0.09$), nor initial LVEF (HR per percent increase in LVEF: 0.98, $p = 0.16$), nor initial NYHA functional class (HR: 2.2, $p = 0.30$) reached significance. Those results do not change if the variable

Table 3 Univariate Analysis: All-Cause Mortality

	No Event (n = 164)	All-Cause Death (n = 39)	p Value	OR (95% CI)
Age, yrs	50.0 (38.5–63.0)	61.0 (44.0–69.0)	<0.05	
Female	51 (31.1)	12 (30.8)	0.97	0.98 (0.46–2.10)
BMI, kg/m^2	26.3 (24.1–29.1)	26.0 (23.6–28.7)	0.86	
BSA, m^2	2.0 (1.8–2.1)	2.0 (1.8–2.2)	0.26	
Primary clinical presentation				
Symptoms of ACS	62 (37.8)	12 (30.8)	0.41	0.73 (0.35–1.55)
Subacute new-onset HF	49 (29.9)	13 (33.3)	0.67	1.17 (0.56–2.47)
Reoccurring episodes of overt HF	10 (6.1)	8 (20.5)	<0.01	3.97 (1.45–10.87)
Combination of palpitations, fatigue, dyspnea on exertion	43 (26.2)	6 (15.4)	0.16	0.51 (0.20–1.31)
Aborted SCD	0 (0)	0 (0)		
Initial NYHA functional class				
I	46 (28.0)	2 (5.1)	<0.01	0.14 (0.03–0.60)
II	52 (31.7)	12 (30.8)	0.91	0.96 (0.45–2.04)
III	51 (31.1)	20 (51.3)	<0.05	2.33 (1.15–4.74)
IV	15 (9.1)	5 (12.8)	0.49	1.46 (0.50–4–30)
Virus type by endomyocardial biopsy				
PVB19	95 (57.9)	18 (48.2)	0.18	0.62 (0.31–1.26)
HHV6	41 (25.0)	8 (20.5)	0.56	0.77 (0.33–1.82)
PVB19/HHV6	26 (15.9)	9 (23.1)	0.28	1.59 (0.68–3.74)
EBV	1 (0.6)	1 (2.6)	0.27	4.29 (0.26–70.13)
PVB19/HHV6/EBV	0 (0)	1 (2.6)	<0.05	
PVB19/EBV	0 (0)	2 (5.1)	<0.01	
HHV6/EBV	1 (0.6)	0 (0)	0.62	
Blood testing				
Troponin positive	34 (20.7)	12 (30.8)	0.18	1.70 (0.78–3.70)
BNP, pg/ml	152 (35–511)	674 (140–1,432)	<0.01	
NT-proBNP, pg/ml	1,132 (69–3,055)	3,697 (1,444–18,092)	0.12	
CMR imaging parameter				
LVEF, %	52.5 (34.0–63.5)	34.0 (20.0–42.0)	<0.0001	
EF indexed, %/m^2	26.0 (17.8–32.9)	16.3 (9.6–21.0)	<0.0001	
LVEDV, ml	160.0 (123.5–198.0)	207.0 (181.0–312.0)	<0.0001	
LVESV, ml	77.5 (44.0–125.5)	149.0 (119.0–214.0)	<0.0001	
LGE present	71 (43.3)	37 (94.8)	<0.0001	24.23 (5.65–103.9)
LGE mass, g	4.5 (2.2–7.8)	18.9 (5.2–30.9)	<0.0001	
LGE, % of LV mass	3.2 (1.9–5.5)	9.7 (4.6–20.4)	<0.0001	

Values are median (25th–75th percentile) or n (%).
Abbreviations as in Tables 1 and 2.

"initial presentation as heart failure" is introduced in the regression models (HR: 0.77, p = 0.45). For SCD the analysis could not be performed because no patient without LGE experienced SCD.

When focusing on the 77 patients that underwent CMR follow-up, univariate analysis revealed an initial NYHA functional class >I as the best predictor of incomplete recovery, followed by initial LVEF (Table 6). This finding was also confirmed by multivariable regression revealing initial NYHA functional class >I as the best independent predictor of incomplete recovery (p = 0.03). In this model neither initial LVEF (p = 0.16), nor initial LVEDV (p = 0.61), nor LGE (p = 0.70) reached significance. Figure 4 compares typical initial to follow-up CMR results.

Discussion

This study is unique in that we could demonstrate that the presence of LGE is the best independent predictor of death in patients with viral myocarditis. In comparison with previous studies (8,10,17,18), we only included patients with biopsy-proven viral myocarditis, who all underwent CMR imaging within 5 days after initial presentation. Our data indicate that there is a relevant long-term mortality in myocarditis patients (Table 1). In addition the presence of LGE may be useful for noninvasive risk stratification of myocarditis patients, yielding a Cox proportional hazards HR of 8.4 for all-cause mortality and 12.8 for cardiac mortality, independent of clinical symptoms. This is supe-

Table 4 Univariate Analysis: Cardiac Mortality

	No Event (n = 164)	Cardiac Death (n = 29)	p Value	OR (95% CI)
Age, yrs	50.0 (38.5–63.0)	61.0 (47.0–67.0)	<0.05	
Female	51 (31.1)	6 (20.7)	0.26	0.58 (0.22–1.51)
BMI, kg/m^2	26.3 (24.1–29.1)	26.9 (24.1–29.6)	0.59	
BSA, m^2	2.0 (1.8–2.1)	2.1 (1.9–2.2)	<0.05	
Primary clinical presentation				
Symptoms of ACS	62 (37.8)	11 (37.9)	0.99	1.01 (0.45–2.27)
Subacute new-onset HF	49 (29.9)	9 (31)	0.90	1.06 (0.45–2.48)
Reoccurring episodes of overt HF	10 (6.1)	5 (17.2)	<0.05	3.21 (1.01–10.20)
Combination of palpitations, fatigue, dyspnea on exertion	43 (26.2)	4 (13.8)	0.15	0.45 (0.15–1.37)
Aborted SCD	0 (0)	0 (0)		
Initial NYHA functional class				
I	46 (28.0)	2 (6.9)	<0.05	0.19 (0.04–0.83)
II	52 (31.7)	9 (31.0)	0.94	0.97 (0.41–2.27)
III	51 (31.1)	13 (44.8)	0.15	1.80 (0.81–4.02)
IV	15 (9.1)	5 (17.2)	0.19	2.07 (0.69–6.22)
Virus type by endomyocardial biopsy				
PVB19	95 (57.9)	14 (48.3)	0.33	0.68 (0.31–1.50)
HHV6	41 (25.0)	5 (17.2)	0.37	0.63 (0.22–1.74)
PVB19/HHV6	26 (15.9)	7 (24.1)	0.27	1.69 (0.65–4.36)
EBV	1 (0.6)	1 (3.4)	0.16	5.82 (0.35–95.8)
PVB19/HHV6/EBV	0 (0)	1 (3.4)	<0.05	
PVB19/EBV	0 (0)	1 (3.4)	<0.05	
HHV6/EBV	1 (0.6)	0 (0.0)	0.67	
Blood testing				
Troponin positive	34 (20.7)	10 (34.5)	0.10	2.01 (0.86–4–73)
BNP, pg/ml	152 (35–511)	674 (107–1,432)	<0.01	
NT-proBNP, pg/ml	1,132 (69–3,055)	3,003 (1,146–15,563)	0.18	
CMR imaging parameter				
LVEF, %	52.5 (34.0–63.5)	31.0 (19.0–42.0)	<0.0001	
EF indexed, %/m^2	26.0 (17.8–32.9)	14.5 (8.4–21.0)	<0.0001	
LVEDV, ml	160 (123.5–198.0)	207.0 (190.0–312.0)	<0.0001	
LVESV, ml	77.5 (44.0–125.5)	162.0 (125.0–224.0)	<0.0001	
LGE present	71 (43.3)	28 (96.6)	<0.0001	36.68 (4.87–276.1)
LGE mass, g	4.5 (2.2–7.8)	20.7 (5.2–35.4)	<0.0001	
LGE, % of LV mass	3.2 (1.9–5.5)	15.0 (5.1–22.0)	<0.0001	

Values are median (25th–75th percentile) or n (%).
Abbreviations as in Tables 1 and 2.

rior to functional or clinical parameters such as LVEF, LVEDV, or NYHA functional class, yielding HRs between 1.0 and 3.2 for all-cause mortality and between 1.0 and 2.2 for cardiac mortality. Importantly, in our population no patient without LGE experienced SCD, even if the LV was enlarged and the LVEF was severely impaired (LVEDV >180 ml and LVEF <35% and no LGE; n = 14) (Fig. 3C).

Patient characteristics. Most patients presented for workup of chest pain or heart failure, which is in line with previous results (6,9,19). Also types of viruses found are similar to our (6,9,19) and other previous reports (10,20). In addition to chest pain and heart failure patients presented with a broad variety of symptoms, ranging from mild to severe. Nevertheless, in comparison with previous studies (6,9) the current patients are less symptomatic on average. This is also reflected by the fact that in the current population just 22.7% of patients had elevated troponin at presentation.

CMR findings. We found a broad range of normal or dilated ventricles with either normal or impaired function. LGE was present in 108 of 203 patients, and was usually located in the subepicardial or intramural areas of the LV, which is in line with previous findings (6,9,21).

The sensitivity for LGE to detect myocarditis was 53.2% in the current study, which is lower than that in our previous reports (6,9), but well in line with the mean sensitivity of LGE of 59% described in a recent meta-analysis (22). The most likely explanation for different sensitivities reported is

Table 5 Univariate Analysis: SCD

	No Event (n = 164)	SCD (n = 18)	p Value	OR (95% CI)
Age, yrs	50.0 (38.5–63.0)	60.5 (47.0–65.0)	0.11	
Female	51 (31.1)	3 (16.7)	0.20	0.44 (0.12–1.60)
BMI, kg/m^2	26.3 (24.1–29.1)	27.3 (25.4–33.1)	0.25	
BSA, m^2	2.0 (1.8–2.1)	2.1 (1.9–2.2)	<0.05	
Primary clinical presentation				
Symptoms of ACS	62 (37.8)	6 (33.3)	0.71	0.82 (0.29–2.30)
Subacute new-onset HF	49 (29.9)	6 (33.3)	0.76	1.17 (0.42–3.31)
Reoccurring episodes of overt HF	10 (6.1)	3 (16.7)	0.10	3.08 (0.76–12.43)
Combination of palpitations, fatigue, dyspnea on exertion	43 (26.2)	3 (16.7)	0.38	0.56 (0.16–2.04)
Aborted SCD	0 (0)	0 (0)		
Initial NYHA functional class				
I	46 (28.0)	1 (5.6)	<0.05	0.15 (0.02–1.17)
II	52 (31.7)	3 (16.7)	0.19	0.43 (0.12–1.55)
III	51 (31.1)	11 (61.1)	<0.05	3.48 (1.28–9.50)
IV	15 (9.1)	3 (16.7)	0.31	1.99 (0.52–7.65)
Virus type by endomyocardial biopsy				
PVB19	95 (57.9)	9 (50.0)	0.52	0.73 (0.27–1.92)
HHV6	41 (25.0)	3 (16.7)	0.43	0.60 (0.17–2.18)
PVB19/HHV6	26 (15.9)	4 (22.2)	0.49	1.52 (0.46–4.97)
EBV	1 (0.6)	1 (5.6)	0.06	9.59 (0.57–160.3)
PVB19/HHV6/EBV	0 (0)	0 (0)		
PVB19/EBV	0 (0)	1 (5.6)	<0.01	
HHV6/EBV	1 (0.6)	0 (0)	0.74	
Blood testing				
Troponin positive	34 (20.7)	6 (33.3)	0.22	1.91 (0.67–5.46)
BNP, pg/ml	152 (35–511)	890 (165–1,432)	<0.01	
NT-proBNP, pg/ml	1,132 (69–3,055)	1,742 (1,146–3,003)	0.49	
CMR imaging parameter				
LVEF, %	52.5 (34–63.5)	30.0 (19.0–42.0)	<0.0001	
EF indexed, %/m^2	26.0 (17.8–32.9)	13.7 (8.4–19.7)	<0.0001	
LVEDV, ml	160.0 (123.5–198.0)	232.0 (196.0–331.0)	<0.001	
LVESV, ml	77.5 (44.0–125.5)	166.5 (119.0–266.0)	<0.001	
LGE present	71 (43.3)	18 (100.0)	<0.0001	
LGE mass, g	4.5 (2.2–7.8)	7.7 (3.8–24.9)	<0.05	
LGE, % of LV mass	3.2 (1.9–5.5)	6.2 (2.8–19.9)	<0.05	

Values are median (25th–75th percentile) or n (%).
Abbreviations as in Tables 1 and 2.

different patient populations with a broad range of disease severity. The overall sensitivity of CMR to detect myocarditis using morphology, function, and LGE as described previously was 83.7%.

Furthermore, our data demonstrate that patients with scar indicated by LGE have larger ventricles and poorer LVEF compared with those without scar (Table 2). This finding is illustrated in Figure 1, and nicely matches the results from Assomull et al. (11), who reported the same relationship in dilated cardiomyopathy. As scarring may lead to LV dilatation and impaired LVEF, this finding conceptually makes sense.

Follow-up results and predictors of events. In our population with symptoms ranging from mild to severe all-cause mortality was 19.2%, cardiac mortality was 15%, and SCD occurred in 9.9% of patients during follow-up. Thus, our event rate is lower than in the Mason et al. myocarditis trial (23), most likely due to different inclusion criteria and disease severity, but is almost as high as in the nonischemic cardiomyopathy group of the SCD-HeFT (Sudden Cardiac Death in Heart Failure) trial (24), although LV function was much better in our patients, underscoring the importance of risk stratification and optimal clinical management in myocarditis.

In the group of 39 patients experiencing death during follow-up, most individuals died from cardiac events (n = 29), emphasizing that cardiac events are the main cause of mortality among various symptomatic myocarditis patients. In the clinical routine, however, risk stratification based on clinical and

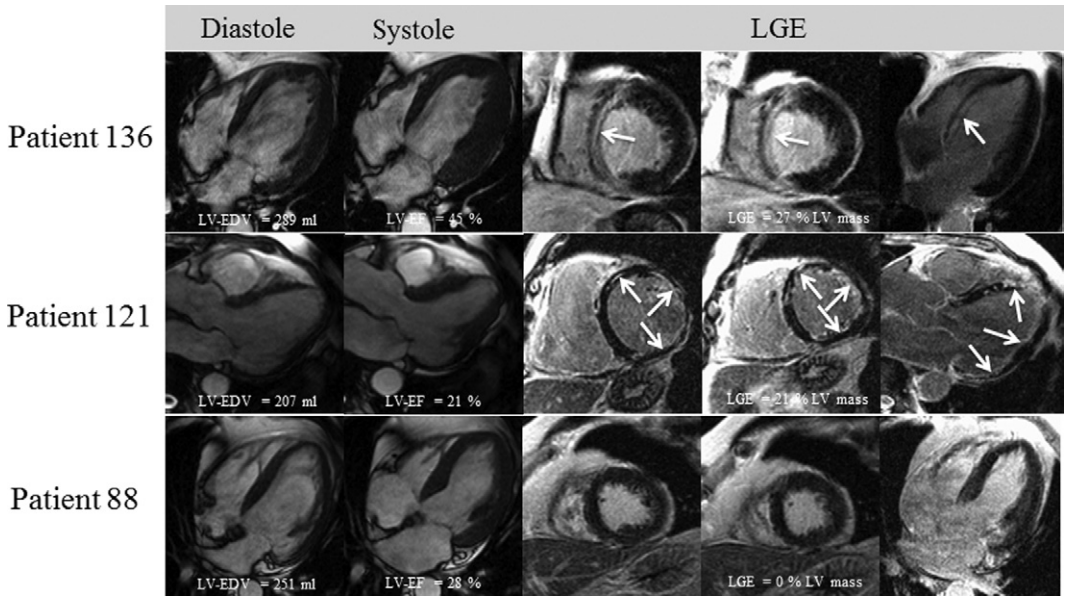

Figure 2 **LV Function, Presence of LGE, and Sudden Cardiac Death**

The **top row** demonstrates cardiovascular magnetic resonance findings of a 73-year-old male with parvovirus B19 myocarditis (Patient #136). This patient has a dilated, mildly impaired LV with mostly septal LGE (27% of LV mass, **white arrows**). He clinically recovered from myocarditis, but experienced sudden cardiac death about 3.5 years after initial presentation, despite only mildly impaired LVEF. The **middle row** shows cardiovascular magnetic resonance images of a 65-year-old male patient with combined parvovirus B19/human herpes virus type 6 myocarditis (Patient #121). The LV is enlarged and LVEF is severely impaired, and LGE is present at multiple locations (**white arrows**, 21% of LV mass). This patient never completely recovered and experienced cardiac death from heart failure about 2 years after initial presentation. Cardiovascular magnetic resonance results of a 54-year-old male diagnosed with human herpes virus type 6 myocarditis (Patient #88) can be viewed in the **bottom row**. The LV is also dilated and LVEF is severely impaired, but no LGE is present. This patient was still alive at follow-up. Abbreviations as in Figure 1.

functional parameters remains difficult despite the value of LVEF, LVEDV, and NYHA functional class (8,10,17). For example, in the current study 11 patients in NYHA functional classes I and II experienced cardiac death, 4 of them SCD (Table 5). In addition, several patients died despite only mildly impaired LV function (n = 5, LVEF ≥45%) or a normal-sized LV (n = 13, LVEDV ≤180 ml). Other factors, such as the type of virus detected in the myocardium, suggested to be of prognostic value in previous studies (8,9) could not yet be confirmed, despite a trend toward a poorer outcome in patients with combined PVB19/HHV6 myocarditis, which is in line with previous findings (9,20).

Our findings fit to the fact that LGE has also been shown to be a good predictor of adverse events in other nonischemic heart diseases, such as dilated (11) or hypertrophic cardiomyopathy (12). These results may help to explain why no patient without LGE experienced SCD (0 of 18) (Table 2), and only 1 patient without LGE experienced cardiac death (1 of 29) (Table 2), even when the LVEF was severely impaired and/or the LV was severely dilated. This concept is highlighted by Figure 2.

Even with our encouraging data, however, it is important to keep in mind that there is not a 1-to-1 relationship between the presence of LGE and cardiac death. Thus, to further improve possible CMR risk stratification, we also thought about a possible incremental value of additional CMR-related parameters, such as the pattern of LGE (9), scar volume and surface area (12), or decrease of LGE over time (6). However, we were not able to discriminate their individual predictive potential due to the limited number of cases and events available in the present study. This topic shall be revisited when the data of the European Cardiovascular Magnetic Resonance Registry or the Magnetic Resonance in Myocarditis Registry becomes available.

When focusing on the subgroup of patients who also underwent follow-up CMR (n = 77), analysis revealed an initial NYHA functional class >I as the best independent predictor for incomplete recovery (p = 0.03), matching results from other studies (8,10,17), whereas surprisingly LGE does not seem to play a relevant role in this setting. This concept is highlighted by Figure 4. However, one needs to keep in mind that this subgroup of patients undergoing follow-up CMR obviously lacks all patients that died during follow-up (n = 39) and all patients who received an ICD (n = 23), causing a selection bias possibly affecting reliability and resulting in an underestimation of the role of LGE.

Clinical implications. Although our data demonstrate an association between LGE and death in myocarditis patients, prospectively designed international trials are required to definitively establish LGE as causally related to death risk, especially because myocarditis populations in other countries may show lower incidences of PVB19. However, with

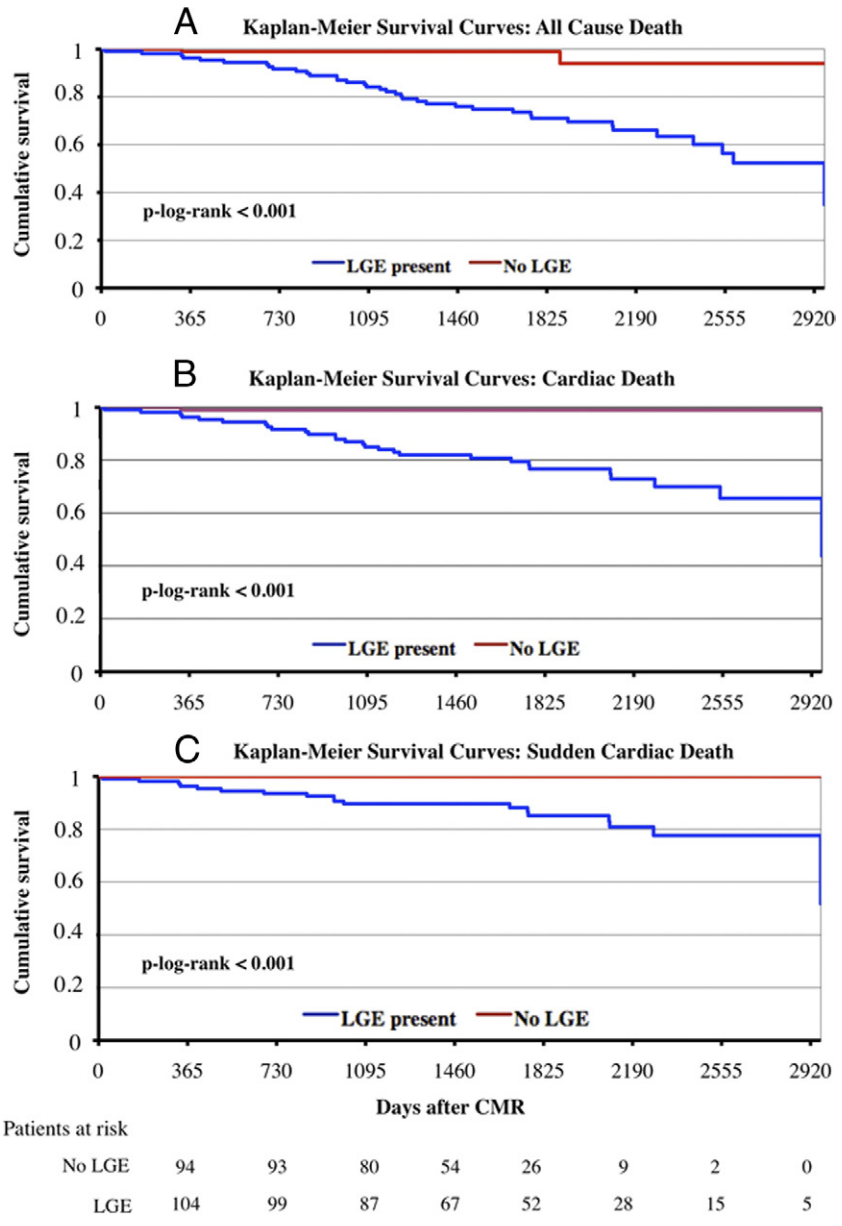

Figure 3 Kaplan-Meier Survival Curves for All-Cause, Cardiac, and Sudden Cardiac Death

Kaplan-Meier survival curves with regard to all-cause mortality **(A)**, cardiac mortality **(B)**, and sudden cardiac death **(C)**. The number of patients at risk is shown at the bottom of the figure. Note that in the group without any scar not a single patient experienced sudden cardiac death during follow-up. CMR = cardiovascular magnetic resonance; other abbreviation as in Figure 1.

regard to our data and the results from other groups some speculations could be made that may influence clinical management. 1) Myocarditis patients with normal CMR (LVEF ≥60% and LVEDV ≤180 ml and no LGE) seem to have a good prognosis. Thus, patients with clinically suspected myocarditis and normal CMR are also likely to have a good prognosis, which may give afflicted patients and worrying physicians some peace of mind. 2) Myocarditis patients without LGE did not experience SCD in our study, even if the LV was dilated and the LVEF severely impaired. Consequently, if LGE and not LV function or size is closer to the substrate for SCD, we may speculate about treating all myocarditis patients demonstrating LGE with beta-blockers, independent of LV function and size, to prevent potentially lethal arrhythmias. This speculation satisfactorily fits to the results of Kindermann et al. (10), describing the lack of beta-blocker therapy as a predictor for poor clinical outcome. 3) We found initial heart failure (NYHA functional class >I) as the best predictor for

Table 6 Univariate Analysis: Predictors for Incomplete Recovery

	Full Recovery* (n = 24)	Incomplete Recovery† (n = 53)	p Value	OR (95% CI)
Age, yrs	40.0 (33.0–50.5.0)	52.0 (43.0–64.0)	<0.01	
Female	6 (25)	20 (37.7)	0.27	0.55 (0.19–1.62)
BMI, kg/m^2	26.0 (24.0–28.4)	26.8 (24.0–30.6)	0.57	
BSA, m^2	2.1 (2.0–2.1)	1.9 (1.8–2.1)	0.08	
Primary clinical presentation				
Symptoms of ACS	10 (41.7)	23 (43.4)	0.89	0.93 (0.35–2.47)
Subacute new-onset HF	3 (12.5)	16 (30.2)	0.10	0.33 (0.09–1.27)
Reoccurring episodes of overt HF	2 (8.3)	2 (3.8)	0.40	2.32 (0.31–17.52)
Combination of palpitations, fatigue, dyspnea on exertion	9 (37.5)	12 (22.6)	0.18	2.05 (0.72–5.84)
Aborted SCD	0 (0)	0 (0)		
Initial NYHA functional class				
I	15 (62.5)	15 (28.3)	0.58	4.22 (1.52–11.71)
II	7 (29.2)	13 (24.5)	0.67	1.27 (0.43–3.73)
III	1 (4.2)	21 (39.6)	<0.01	0.07 (0.01–0.53)
IV	1 (4.2)	4 (7.5)	<0.01	0.53 (0.06–5.04)
Virus type by endomyocardial biopsy				
PVB19	12 (50)	29 (54.7)	0.70	0.83 (0.32–2.17)
HHV6	6 (25)	16 (30.2)	0.64	0.77 (0.26–2.30)
PVB19/HHV6	6 (25)	7 (13.2)	0.20	2.19 (0.65–7.41)
EBV	0 (0)	0 (0)		
PVB19/HHV6/EBV	0 (0)	0 (0)		
PVB19/EBV	0 (0)	0 (0)		
HHV6/EBV	0 (0)	1 (1.9)	0.50	
Blood testing				
Troponin positive	6 (25.0)	11 (20.8)	0.68	1.27 (0.41–3.97)
BNP, pg/ml	62 (23–139)	225 (59–487)	<0.01	
NT-proBNP, pg/ml	86.5 (37–1,037)	874 (220–1,132)	0.38	
CMR imaging parameter (baseline)				
LVEF, %	62.5 (52–68.5)	53 (33–60)	<0.05	
EF indexed, %/m^2	31.6 (24.3–34.0)	25.7 (17.9–33.7)	0.12	
LVEDV, ml	147.5 (125.5–169.0)	147.0 (117–194.0)	0.79	
LVESV, ml	49.0 (42.5–84.5)	69.0 (41.0–125.0)	0.20	
LGE present	10 (41.7)	28 (52.8)	0.36	0.64 (0.24–1.69)
LGE mass, g	4.3 (1.2–8.8)	3.7 (2.3–7.0)	0.91	
LGE, % of LV mass	3.2 (1.4–7.4)	2.8 (1.9–5.3)	0.75	

Values are median (25th–75th percentile) or n (%). Only patients with follow-up CMR (n = 77) included. *Full recovery is defined as LVEF ≥60% and LVEDV ≤180 ml and no signs of heart failure. †Incomplete recovery is defined as LVEF <60% or LVEDV >180 ml or NYHA functional class >I at follow-up. Abbreviations as in Tables 1 and 2.

incomplete recovery. Despite the limitations discussed previously, one should carefully optimize heart failure therapy in all myocarditis patients presenting with even the mildest signs of heart failure to improve the chance of complete recovery.

Conclusions

Among our population with a wide range of clinical symptoms, biopsy-proven viral myocarditis is associated with a long-term mortality of up to 19.2% in 4.7 years. In addition, the presence of scar indicated by LGE is the best independent predictor of all-cause mortality and cardiac mortality. Furthermore, initial presentation with heart failure (NYHA functional class >I) may be a good predictor of incomplete long-term recovery. These data support the necessity for future large longitudinal follow-up studies to definitely establish LGE as an independent predictor of cardiac death in viral myocarditis, as well as to evaluate the incremental prognostic value of additional parameters.

Reprint requests and correspondence: Dr. Heiko Mahrholdt, Robert-Bosch-Medical Center, Auerbachstrasse 110, 70376 Stuttgart, Germany. E-mail: Heiko.Mahrholdt@rbk.de.

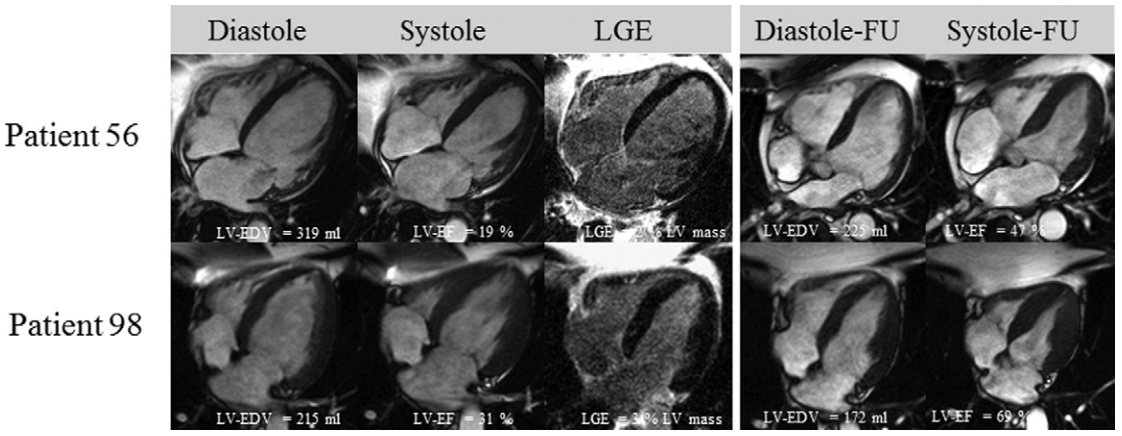

Figure 4 **Initial Heart Failure Is Related to Incomplete Recovery**

The **top row** displays typical cardiovascular magnetic resonance results of a 64-year-old female at initial presentation and at follow-up 4 years later. The patient presented for workup of New York Heart Association functional class IV heart failure and was diagnosed with parvovirus B19–related myocarditis (Patient #56). The patient improved over time (compare left vs. right cine images) but never recovered fully. The **bottom row** shows cardiovascular magnetic resonance images of another patient diagnosed with parvovirus B19–related myocarditis (Patient #98, male, 49 years old). This patient presented for workup of chest pain and was clinically New York Heart Association functional class I despite the initially dilated LV with severely impaired LVEF **(left columns)**. This patient recovered fully during follow-up (**right columns**, 5 years later). FU = follow-up; other abbreviations as in Figure 1.

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Key Words: cardiovascular magnetic resonance ■ mortality ■ myocarditis ■ prognosis.