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ORIGINAL RESEARCH

Differences in Prognosis and Cardiac Function According to Required Percutaneous Mechanical Circulatory Support and Histological Findings in Patients With Fulminant Myocarditis: Insights From the CHANGE PUMP 2 Study

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BACKGROUND: Prognoses and long-term cardiac function of patients with fulminant myocarditis have not been fully elucidated. Therefore, we clarified the prognoses and long-term cardiac function according to required percutaneous mechanical circulatory support and histological findings among patients with fulminant myocarditis.

METHODS AND RESULTS: We conducted a multicenter retrospective medical record review of 216 patients with fulminant myocarditis requiring percutaneous mechanical circulatory support. Sixty-one patients were treated with intra-aortic balloon pump or Impella alone, and 155 patients received veno-arterial extracorporeal membrane oxygenation and were treated with or without intra-aortic balloon pump or Impella. Histologically, 107 patients had lymphocytic myocarditis; 34, eosinophilic myocarditis; and 4, giant cell myocarditis. Freedom from composite end point (death, durable left ventricular assist device implantation, and heart transplantation) was 66% at 90 days, 62% at 1 year, and 57% at 6 years. Veno-arterial extracorporeal membrane oxygenation use was associated with poor prognosis in the multivariable analysis (hazard ratio [HR], 5.27; 95% CI, 1.60–17.36). The eosinophilic myocarditis subgroup showed better prognosis (HR, 0.28; 95% CI, 0.10–0.80) compared with the lymphocytic myocarditis subgroup but not in the multivariable analysis. Ventricular tachycardia/ventricular fibrillation rhythm at admission, high C-reactive protein level, and no endomyocardial biopsy were also associated with poor prognosis. The left ventricular ejection fraction at 1 year was ≤50% in 16% of patients and was lower in patients with eosinophilic myocarditis (median: 57.9% [48.8–65.0%]) than in those with lymphocytic myocarditis (65.0% [58.6–68.7%]) (P=0.036).

CONCLUSIONS: Patients with fulminant myocarditis who received veno-arterial extracorporeal membrane oxygenation had a poor prognosis. Long-term cardiac function was impaired in some patients, especially those with eosinophilic myocarditis.

Key Words: intra-aortic balloon pump ■ left ventricular ejection fraction ■ mechanical circulatory support ■ myocarditis ■ veno-arterial extracorporeal membrane oxygenation

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CLINICAL PERSPECTIVE

What Is New?

- In patients with fulminant myocarditis requiring mechanical circulatory support, patients with eosinophilic myocarditis had a better crude risk for death, durable left ventricular assist device implantation, or heart transplantation; required veno-arterial extracorporeal membrane oxygenation less frequently; and had a higher rate of steroid use than those with lymphocytic myocarditis.
- Long-term cardiac function remained impaired in some cases, especially those with eosinophilic myocarditis.
- The use of veno-arterial extracorporeal membrane oxygenation, ventricular tachycardia/ventricular fibrillation, C-reactive protein levels, and no biopsy were independent prognostic factors.

What Are the Clinical Implications?

- The following 2 therapeutic targets would constitute the cornerstone for improving the prognosis of patients with fulminant myocarditis: (1) suppressing myocardial inflammation and (2) preventing cardiac arrest and low output syndrome, which result in organ damage.
- A myocardial biopsy is suggested to be performed to provide an appropriate risk assessment and treatment including immunosuppressive therapy.
- Periodic evaluation for cardiac function and myocardial inflammation after discharge from a hospital would be recommended, especially in patients with eosinophilic myocarditis.

Nonstandard Abbreviations and Acronyms

EM	eosinophilic myocarditis
FM	fulminant myocarditis
GCM	giant cell myocarditis
LM	lymphocytic myocarditis

Acute myocarditis is caused by inflammation of the myocardium owing to infections, autoimmune diseases, and adverse drug reactions.[1] Fulminant myocarditis (FM) is a fatal disease that requires inotropes and/or mechanical circulatory support (MCS) owing to rapid deterioration of hemodynamic parameters. FM management includes inotrope and MCS use to prevent and improve multiple organ failure caused by impaired cardiac function and to maintain hemodynamics.[2–4] It also includes specific treatments that target the myocarditis cause or suppress myocardial inflammation.[2–4] Although these treatments are continued until cardiac dysfunction is alleviated, implantation of a durable left ventricular assist device (LVAD) or heart transplantation is sometimes required when the cardiac function does not improve sufficiently.[5–8] Different types of percutaneous MCS are used for the initial management of patients with FM to maintain stable hemodynamics, and changes in MCS strategies are necessary when cardiac dysfunction progresses or longer management is required.[9,10] Previously, patients with FM requiring MCS had poorer prognoses than patients treated with inotropes alone, especially when veno-arterial extracorporeal membrane oxygenation (VA-ECMO) was required.[11–13] However, the pathophysiological and prognostic differences between patients who can be treated with intra-aortic balloon pump (IABP) or Impella alone and those who require VA-ECMO remain elusive.

Myocarditis is histologically classified as lymphocytic myocarditis (LM), eosinophilic myocarditis (EM), and giant cell myocarditis (GCM).[1,14] LM usually results from a viral infection, whereas EM and GCM are often associated with adverse drug reactions and autoimmune diseases.[2–4,13–15] Immunosuppressive therapy has been recommended to suppress myocardial inflammation during EM and GCM; however, this treatment has not been clearly established via randomized control trials. Immunosuppressive therapy in patients with LM remains controversial.[2–4,13,14] The prognostic differences caused by the balance between beneficial and adverse effects of immunosuppressive therapy are unclear, especially in patients with FM requiring MCS. Therefore, the prognosis may differ depending on the histological subtypes owing to discrepancies in subtypes or treatments.

Additionally, although FM reportedly has a good long-term prognosis after acute phase, recurrence of myocarditis and long-term impairments of cardiac function have been described.[7,16–20] Most studies regarding FM are case reports or include a small number of patients; hence, prognoses and long-term cardiac function of patients remain uncertain.

Therefore, this study aimed to clarify the short- and long-term prognoses of patients with FM who undergo different types of percutaneous MCS and different histological subtypes. This study also determines whether these differences affect patients' long-term cardiac function. Furthermore, the prognostic factors of patients with FM who require MCS have been explored.

METHODS

This multicenter, retrospective study reviewed the medical records of patients with FM aged 15 years or

older who required percutaneous MCS. It has been termed the CHANGE PUMP 2 (Chart Review of in- and out-of-Prognosis in Patients with FM on Percutaneous Mechanical Circulatory Support 2) study. The study was conducted according to the 1975 Declaration of Helsinki and was approved by the Ethics Committee of Nagoya University Hospital (approval number: 2016-0002). The requirement of informed consent was waived by the committee because of the study aspect. Compared the CHANGE PUMP study, a previous study regarding patients with FM who underwent VA-ECMO,[21,22] the CHANGE PUMP 2 study included an extended patient enrolment period and enrolled patients treated with percutaneous MCS other than VA-ECMO. Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to the corresponding author.

Study Population and Diagnosis of Myocarditis

A total of 26 high-volume cardiovascular hospitals in the Tokai area in Japan were included in this study. Hospitals' databases were screened for disease names corresponding to the *International Classification of Diseases, Tenth Revision* (*ICD-10*) diagnostic codes (I400, I401, I408, I409, I514) from January 2000 to December 2020. Patients diagnosed with acute myocarditis who required percutaneous MCS, including IABP, VA-ECMO, and Impella 2.5/CP, were included. Patients who developed symptoms within 30 days before admission were enrolled. The diagnosis of acute myocarditis was made based on an endomyocardial biopsy, autopsy histology, or clinical findings according to the Japanese Circulation Society's Guidelines for Diagnosis and Treatment of Myocarditis.[23]

Data Collection, Study Outcomes, and Patient Classification

Laboratory, echocardiographic, and electrocardiographic data obtained at admission were used as baseline data. Death, implantation of a durable LVAD, and heart transplantation up to 90 days and 6 years after admission were evaluated as the composite end point. The left ventricular ejection fraction (LVEF) measured using echocardiography, 1 year after admission, was evaluated. Data regarding acute myocarditis history before admission for FM and recurrent acute myocarditis after discharge were also collected. Patients were divided into 2 groups based on their percutaneous MCS requirements: those treated only with IABP or Impella 2.5/CP (IABP/Impella group) and those who required VA-ECMO regardless of IABP or Impella 2.5/CP co-treatment (VA-ECMO group). Patients for whom myocardial biopsy or autopsy data were available were categorized using the histological subtypes LM, EM, and GCM. Patients whose subtypes were not definitely defined or were defined as bacterial myocarditis caused by *streptococcus pyogenes* were excluded from the histological subgroups. In addition, a subgroup analysis was conducted between patients who underwent a myocardial biopsy and those who did not.

Statistical Analysis

The patients' baseline characteristics were compared. As for histological groups, statistical comparisons were performed between the LM and EM subgroups owing to the small sample size of the GCM subgroup (n=4). Continuous variables are presented as medians and interquartile ranges, and categorical variables are presented as numbers and percentages. The Mann–Whitney *U* test was used to compare continuous variables as they had a skewed distribution. The chi-square or Fisher's exact test was used to compare categorical variables, as appropriate. The median duration of follow-up was calculated using reverse-Kaplan–Meier method. The composite end point was analyzed using the Kaplan–Meier method and log-rank test according to MCS category, histological subtype (LM and EM), and myocardial biopsy status. Cox proportional hazard analyses were used to calculate the hazard ratios (HRs) and 95% CIs of the composite end point up to 90 days. After univariable analysis of the original data set, missing covariables were imputed using multiple imputations with chained equations for the multivariable models. Histological subtypes were not imputed because many numbers were missing. We created 3 models for the multivariable Cox proportional hazard analysis using clinically relevant variables. When using EM subgroup in the model, the validity was evaluated by adding each variable in order for sensitivity analyses in addition to model 1 (VA-ECMO group, EM subgroup, and ventricular tachycardia [VT]/ventricular fibrillation [Vf] rhythm at admission). Multiple imputations using VT/Vf rhythm at admission and QRS ≥120 ms concomitantly could not be performed from the calculating aspects. Therefore, the 2 models without the variable of EM group were generated: model 2 (VA-ECMO group, systolic blood pressure, heart rate, VT/Vf rhythm at admission, C-reactive protein level, creatinine level, and no biopsy), and model 3 (VA-ECMO group, systolic blood pressure, heart rate, QRS ≥120 ms, C-reactive protein level, creatinine level, and no biopsy). In each model, 20 imputed data sets were generated, and the estimates of each analysis per data set were integrated using Rubin's rule. All statistical analyses were performed using Stata/MP 16.1 (Stata Corp., College Station, TX, USA). *P* values <0.05 were considered statistically significant.

RESULTS

Patient Characteristics

The data of 216 patients with FM requiring MCS were analyzed in this study. The patient flow for percutaneous MCS is depicted in Figure 1. The patient flow for percutaneous MCS is shown in Figure S1 according to the histological subtypes and in Figure S2 for the year based on when Impella became clinically available. The median duration from admission to first MCS initiation was 0 (0–1) day. Median duration from admission to steroid use and immunoglobulin use were 2 (1–5) days and 1 (0–2) days, respectively. The IABP/Impella group included 61 patients, and the VA-ECMO group included 155 patients. Patients' characteristics according to the IABP/Impella group and VA-ECMO group was shown in Table 1. The median patient age was 53 years, and 59.7% were men. In the IABP/Impella group, IABP was used for all patients except 1 who received only Impella. A total of 158 patients were evaluated histologically, including 155 via endomyocardial biopsy and 3 via autopsy. EM representation was higher in the IABP/Impella group than in the VA-ECMO group (P=0.002). The VA-ECMO group had significantly higher creatine (P=0.001), aspartate transaminase (P=0.023), alanine aminotransferase (P=0.042), lactate dehydrogenase (P=0.010), and creatine kinase–myocardial band (P=0.026) levels than the IABP/Impella group. Cardiac troponin I, which is a typical marker during cardiac failure, exhibited a trend of increase in the VA-ECMO group rather than in the IABP/Impella group (P=0.080). The VA-ECMO group had lower systolic (P=0.018) and diastolic (P<0.001) blood pressures than the IABP/Impella group. Of the patients who underwent endomyocardial biopsy or autopsy, 107 were classified as LM, 34 as EM, and 4 as GCM (Table 2). The EM subgroup included older patients (P=0.005), more men (P=0.004), and a lower percentage of patients treated with VA-ECMO (P=0.003) and included more patients who received steroids (P<0.001) than the LM subgroup. Patients in the LM subgroup tended to have lower systolic blood pressure (P=0.002) and higher levels of aspartate transaminase (P=0.022), lactate dehydrogenase (P=0.045), and creatine kinase (P<0.001) than those in the EM subgroup. The characteristics of patients who underwent myocardial biopsy have been compared with those of patients who did not undergo myocardial biopsy in Table S1. Steroid therapy was frequently used for patients who underwent myocardial biopsy (P=0.037).

Short- and Long-Term Prognoses

The median duration of follow-up was 607 days, and 81 composite events (76 deaths, 4 durable LVAD implantations, and 1 heart transplantation) occurred during the follow-up period. Within 90 days after admission, 70 composite events occurred, including 69 deaths and 1 durable LVAD implantation. Freedom from the composite end point was 73% at 30 days, 66% at 90 days, 62% at 1 year, and 57% at 6 years (Figure S3). In cases that survived up to 90 days, the median duration of IABP, Impella, VA-ECMO use were 7 (5–9) days, 9 (7–12) days, and 6 (5–8) days, respectively. Kaplan–Meier curves for freedom from the composite end point are depicted in Figure 2. The VA-ECMO group had a worse prognosis up to 90 days after admission than the IABP/Impella group (log-rank, P<0.001) (Figure 2A). The prognosis up to 6 years of the VA-ECMO group was also significantly worse (log-rank, P<0.001), but the difference was bridged between both groups 90 days after admission (Figure 2B; after the 90-day vertical line). Furthermore, the 90-day outcomes were significantly better in the EM subgroup than in the LM subgroup (log-rank, P=0.011) (Figure 2C). In addition, patients in the EM subgroup also had a better prognosis up to 6 years than those in the LM subgroup (log-rank, P=0.038) (Figure 2D). Kaplan–Meier curves for freedom from death are depicted in Figure S4. Patients who underwent myocardial biopsy had a better prognosis up to 90 days than those who did not (log-rank, P=0.009)

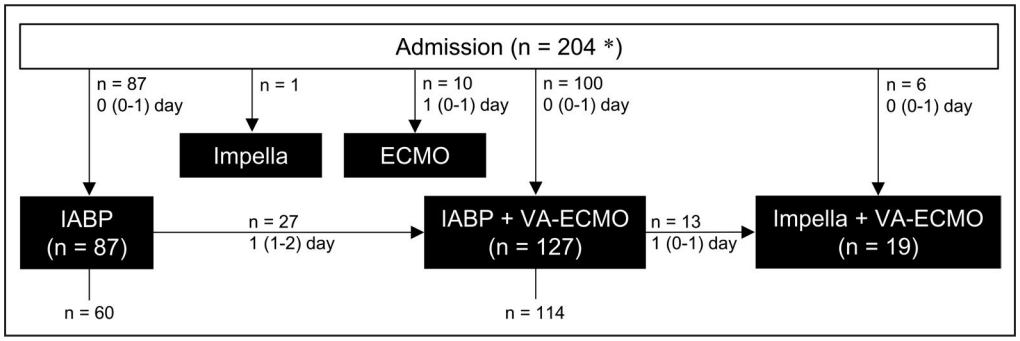

Figure 1. Patient flow for percutaneous mechanical circulatory support.
*Patients without date data were excluded (n=12). ECMO indicates extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; and VA-ECMO, veno-arterial extracorporeal membrane oxygenation.

Table 1. Patient Characteristics at Admission

	Available data	All (n=216)	IABP/Impella (n=61)	VA-ECMO (n=155)	*P* value
Age, y	216	53 (39–66)	53 (39–70)	52 (38–65)	0.306
Male sex, n (%)	216	129 (59.7)	41 (67.2)	88 (56.8)	0.159
Body mass index, kg/m^2	199	22.1 (20.1–24.6)	21.5 (19.9–23.7)	22.4 (20.3–25.0)	0.070
Mechanical circulatory support, n (%)					
VA-ECMO	216	155 (71.8)	0 (0.0)	155 (100.0)	<0.001
IABP	208	191 (91.8)	60 (98.4)	131 (89.1)	0.026
Impella	216	21 (9.7)	1 (1.6)	20 (12.9)	0.010
Biopsy, n (%)	216	155 (71.8)	45 (73.8)	110 (71.0)	0.680
Histological subtypes, n (%)	158				
Lymphocytic myocarditis		107 (67.7)	25 (55.6)	82 (72.6)	0.115
Eosinophilic myocarditis		34 (21.5)	17 (37.8)	17 (15.0)	0.002
Giant cell myocarditis		4 (2.5)	0 (0.0)	4 (3.5)	0.579
Others		1 (0.6)	0 (0.0)	1 (0.9)	>0.999
Unknown		12 (7.6)	3 (6.7)	9 (8.0)	>0.999
Systolic blood pressure, mm Hg	199	94 (83–108)	101 (88–111)	94 (80–107)	0.018
Diastolic blood pressure, mm Hg	190	61 (53–70)	67 (59–78)	60 (50–67)	<0.001
Heart rate, bpm	197	100 (86–119)	104 (90–119)	100 (80–120)	0.284
ECG findings at admission					
QRS ≥120 ms, n (%)	172	81 (47.1)	21 (38.9)	60 (50.8)	0.145
Ventricular tachycardia/ ventricular fibrillation, n (%)	203	12 (5.9)	1 (1.7)	11 (7.6)	0.186
Atrioventricular block, n (%)	203	20 (9.9)	4 (6.8)	16 (11.1)	0.443
Atrial fibrillation, n (%)	203	9 (4.4)	4 (6.8)	5 (3.5)	0.288
Left ventricular ejection fraction, %	176	30.0 (20.0–44.5)	34.3 (29.0–45.0)	30.0 (20.0–42.0)	0.054
Left ventricular diastolic dysfunction, mm	75	44.3 (40.0–47.6)	44.2 (40.0–48.0)	45.0 (41.0–47.0)	0.852
Laboratory data					
White blood cell count, μL	211	9500 (7100–13 180)	9100 (6500–13 000)	9550 (7250–13 190)	0.520
Eosinophil count, μL	150	250 (0–1080)	540 (150–2130)	200 (0–710)	0.009
C-reactive protein, mg/dL	204	4.2 (1.3–8.9)	4.1 (1.7–10.9)	4.3 (1.1–8.4)	0.275
Aspartate transaminase, IU/L	210	145 (77–349)	123 (70–191)	161 (79–429)	0.023
Alanine aminotransferase, IU/L	210	71 (40–166)	55 (36–112)	80 (43–238)	0.042
Lactate dehydrogenase, IU/L	207	553 (384–1030)	492 (353–651)	591 (430–1133)	0.010
Creatinine, mg/dL	209	1.1 (0.8–1.6)	0.9 (0.7–1.2)	1.1 (0.8–1.9)	0.001
CK, IU/L	204	713 (367–1284)	625 (298–1072)	734 (439–1452)	0.105
CK-myocardial band, ng/mL	130	63.2 (35.0–111.0)	52.8 (19.9–90.5)	68.0 (37.7–153.0)	0.026
cTnI, ng/mL	91	17.5 (5.3–49.3)	10.1 (2.7–28.7)	21.4 (6.6–57.8)	0.080
cTnI over the normal reference*, n (%)	91	89 (97.8)	30 (96.8)	59 (98.3)	>0.999
Treatment, n (%)					
Steroid	215	85 (39.5)	22 (36.1)	63 (40.9)	0.513
Immunoglobulin	215	93 (43.3)	18 (29.5)	75 (48.7)	0.010

Data excluding missing data are presented as median (interquartile range) or number (percentage).
CK indicates creatine kinase; cTnI, cardiac troponin I; IABP, intra-aortic balloon pump; and VA-ECMO, veno-arterial extracorporeal membrane oxygenation.
*Normal reference was 0.014 ng/mL.

(Figure 3). Finally, 5 patients had an acute myocarditis history before admission for FM, and 3 patients were hospitalized for recurrent acute myocarditis after FM. Patients characteristics of patients with history of acute myocarditis before FM or with recurrence of acute myocarditis after FM were shown in Table S2.

Table 2. Characteristics of Patients With Histological Subtypes

	LM (n=107)	EM (n=34)	Giant cell myocarditis (n=4)	*P* value (LM vs EM)
Age, y	52 (39–64)	61 (48–72)	40 (28–49)	0.005
Male sex, n (%)	58 (54.2)	28 (82.4)	2 (50.0)	0.004
Body mass index, kg/m^2	22.2 (19.7–24.5)	21.1 (19.4–23.0)	23.4 (18.8–29.0)	0.213
Mechanical circulatory support, n (%)				
Veno-arterial extracorporeal membrane oxygenation	82 (76.6)	17 (50.0)	4 (100.0)	0.003
Intra-aortic balloon pump	95 (92.2)	30 (96.8)	3 (75.0)	0.684
Impella	12 (11.2)	2 (5.9)	3 (75.0)	0.518
Systolic blood pressure, mm Hg	94 (80–106)	105 (96–113)	104 (91–123)	0.002
Diastolic blood pressure, mm Hg	61 (55–75)	64 (52–72)	68 (60–82)	0.626
Heart rate, bpm	103 (85–120)	96 (87–113)	100 (95–111)	0.327
ECG findings at admission				
QRS ≥120 ms, n (%)	42 (51.9)	12 (42.9)	1 (33.3)	0412
Ventricular tachycardia/ventricular fibrillation, n (%)	5 (5.1)	1 (3.1)	0 (0.0)	>0.999
Atrioventricular block, n (%)	10 (10.1)	3 (9.4)	0 (0.0)	>0.999
Atrial fibrillation, n (%)	6 (6.1)	1 (3.1)	0 (0.0)	>0.999
Left ventricular ejection fraction, %	30.0 (20.0–40.0)	30.0 (25.0–45.0)	39.5 (30.0–50.2)	0.299
Left ventricular diastolic dysfunction, mm	44.0 (41.0–47.6)	45.0 (43.0–47.0)	46.3 (38.0–61.0)	0.686
Laboratory data				
White blood cell count, μL	9000 (6800–13 200)	9950 (7400–13 600)	9250 (7250–12 200)	0.532
Eosinophil count, μL	160 (0–560)	2090 (714–10 800)	1460 (504–5410)	<0.001
C-reactive protein, mg/dL	3.6 (1.2–8.2)	5.9 (2.0–10.3)	7.4 (4.0–8.0)	0.213
Aspartate transaminase, IU/L	161 (81–354)	102 (52–185)	56 (37–71)	0.022
Alanine aminotransferase, IU/L	71 (40–182)	50 (32–121)	69 (33–99)	0.372
Lactate dehydrogenase, IU/L	602 (402–1048)	458 (353–844)	373 (271–460)	0.045
Creatinine, mg/dL	1.0 (0.8–1.6)	0.9 (0.8–1.5)	1.0 (0.8–1.5)	0.457
CK, IU/L	804 (464–1441)	369 (293–711)	150 (100–202)	<0.001
CK-myocardial band, ng/mL	63.3 (36.0–100.0)	40.8 (25.0–96.0)	101.8 (14.3–201.5)	0.442
cTnI, ng/mL	20.1 (3.7–49.6)	20.5 (6.7–24.7)	6.5 (4.3–7.6)	0.543
cTnI over the normal reference*, n (%)	42 (97.7)	17 (94.4)	4 (100)	0.507
Treatment, n (%)				
Steroid	31 (29.0)	27 (79.4)	4 (100.0)	<0.001
Immunoglobulin	51 (47.7)	10 (29.4)	2 (50.0)	0.075

Data excluding missing data are presented as median (interquartile range) or number (percentage).
CK indicates creatine kinase; cTnI, cardiac troponin I; EM, eosinophilic myocarditis; and LM, lymphocytic myocarditis.
*Normal reference was 0.014 ng/mL

Cox Proportional Hazard Analysis for Composite End Point up to 90 Days

In the univariable Cox proportional hazard analysis, VA-ECMO use; EM subgroup; systolic blood pressure; heart rate; QRS ≥120 ms; VT/Vf rhythm at admission; levels of C-reactive protein, creatinine, and creatine kinase; and no biopsy were significant factors associated with the composite end point up to 90 days (Table 3). The multivariable analyses showed that the VA-ECMO use (HR, 5.27, 95% CI, 1.60–17.36) and VT/Vf rhythm at admission (HR, 3.53; 95% CI, 1.15–10.85) were associated a worse prognosis in model 1. The EM subgroup showed with good prognosis (HR, 0.28; 95% CI, 0.10–0.80), but not in model 1 (HR, 0.41; 95% CI, 0.14–1.17). Similar results were observed in the sensitivity analyses (Table S3). In model 2 and model 3, high C-reactive protein level (model 2: HR, 1.04; 95% CI, 1.001–1.08; model 3: HR, 1.04; 95% CI, 1.001–1.08) and no biopsy (model 2: HR, 1.76; 95% CI, 1.02–3.04; model 3: HR, 1.83; 95% CI, 1.07–3.13) were significant factors for poor prognosis, in addition to VA-ECMO use (model 2:

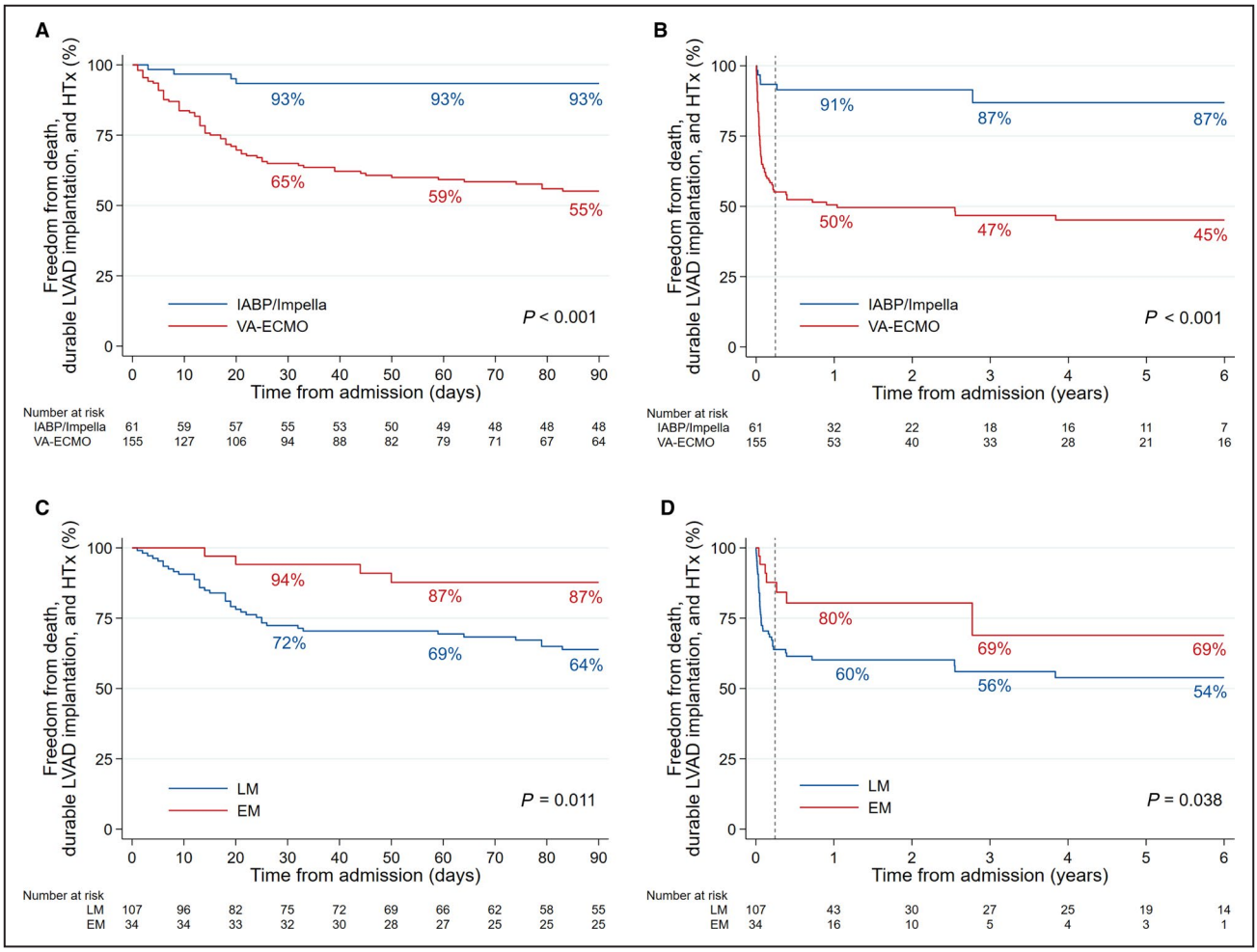

Figure 2. Kaplan–Meier curves for freedom from death, durable LVAD implantation, and HTx after admission to a hospital owing to FM.

A, The Kaplan–Meier curve for freedom from the composite end point up to 90 days after admission for each MCS group. **B**, The Kaplan–Meier curve for freedom from the composite end point up to 6 years after admission for each MCS group. The vertical dotted line represents up to 90 days. **C**, The Kaplan–Meier curve for freedom from the composite end point up to 90 days after admission for each histological subgroup. **D**, The Kaplan–Meier curve for freedom from the composite end point up to 6 years after admission for each histological subgroup. The vertical dotted line represents 90 days. Patients with GCM were removed from **C** and **D** owing to small sample size. ECMO indicates extracorporeal membrane oxygenation; EM, eosinophilic myocarditis; FM, fulminant myocarditis; GCM, giant cell myocarditis; HTx, heart transplantation; IABP, intra-aortic balloon pump; LM, lymphocytic myocarditis; LVAD, left ventricular assist device; MCS, mechanical circulatory support; and VA-ECMO, veno-arterial extracorporeal membrane oxygenation.

HR, 7.73; 95% CI, 2.77–21.58; model 3: HR, 7.98; 95% CI, 2.85–22.31) and VT/Vf rhythm (model 2: HR, 3.40; 95% CI, 1.43–8.12).

LVEF 1 Year After FM Admission

LVEF data were available at 1 year for 76 patients (median: 64.0% [57.2%–67.3%]) (Figure 4), including 8 patients (11%) with an LVEF ≤40%, 4 (5%) with an LVEF 41% to 50%, 14 (18%) with an LVEF 51% to 60%, and 50 (66%) with an LVEF >60%. There was no significant difference in LVEF at 1 year between the IABP/Impella and VA-ECMO groups (median: 64.0% [59.2%–68.8%] versus median: 63.0% [55.8%–66.3%]; *P*=0.348) and no significant difference by category (*P*=0.775). In contrast, LVEF of the EM subgroup (median: 57.9% [48.8%–65.0%]) was significantly lower than that of the LM subgroup (median: 65.0% [58.6%–68.7%]) (*P*=0.036), and a difference was found also by category (*P*=0.016).

DISCUSSION

This study indicates a dismal short-term prognosis for patients with FM requiring percutaneous MCS, especially in patients who required VA-ECMO, but the long-term prognosis after acute phase was relatively favorable. To the best of our knowledge, as for histological findings, the results of better prognosis

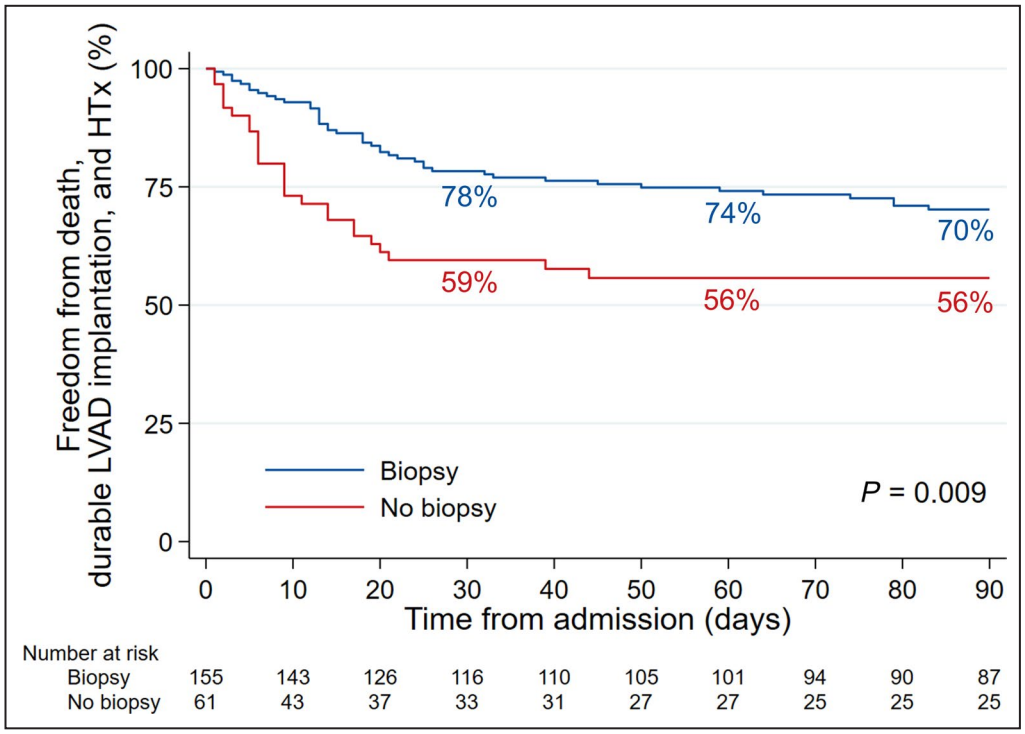

Figure 3. Kaplan–Meier curves for the freedom from death, durable LVAD implantation, and HTx after admission to a hospital owing to FM in patients who underwent and did not undergo a myocardial biopsy.
Patients who underwent myocardial biopsy had a better prognosis up to 90 days than patients who did not undergo a myocardial biopsy. FM indicates fulminant myocarditis; HTx, heart transplantation; and LVAD, left ventricular assist device.

in patients with EM than patients with LM and worse long-term cardiac function in patients with EM than in patients with LM are new findings. Furthermore, we also identified that the VT/Vf, C-reactive protein levels, and no biopsy were prognostic factors in patients with FM requiring percutaneous MCS.

This is the largest report evaluating the short- and long-term prognoses of patients with FM requiring percutaneous MCS to date. Although a large proportion of patients with FM requiring MCS died within 90 days of admission, the long-term prognosis after acute phase was relatively good, even in patients requiring VA-ECMO. These results are consistent with those of previous reports.[11,16,24] Creatine kinase–myocardial band levels were significantly higher in the VA-ECMO group than in the IABP/Impella group, suggesting that myocardial inflammation was more intense in the first group. Furthermore, high levels of hepatic enzymes and creatinine identified in patients requiring VA-ECMO imply multiple organ failure. Hypoxic encephalopathy and complications associated with VA-ECMO are also believed to be associated with poorer prognoses.

In our study, in addition to VA-ECMO use, VT/Vf rhythm, and C-reactive protein were identified as prognostic factors. C-reactive protein has been related to myocardial inflammation,[25] and it is not surprising that VT/Vf also originates from myocardial inflammation. Therefore, we believe that the following 2 therapeutic targets constitute the cornerstone for improving the prognosis of patients with FM: (1) suppressing myocardial inflammation and (2) preventing cardiac arrest and low output syndrome, which result in organ damage.

Our results indicate a more favorable prognosis of patients with EM than of patients with LM, which is a new insight as previous article on FM, including inotrope treatment, reported a similar prognoses but regardless of histological subtypes.[11] Because the EM was not an independent prognostic factor in the model when adjusted by VA-ECMO and VT/Vf rhythm at admission, EM may tend to be less severe than LM. The higher rate of steroid use among patients with EM may have helped prevent disease progression by reducing myocardial inflammation, especially in FM requiring MCS. The less favorable prognosis noted in patients who did not undergo myocardial biopsy may be owing to the inability to diagnose EM and administer steroids in time. These results suggest importance of early diagnosis by biopsy and the use of immunosuppressive therapy in appropriate cases. Further studies are required to evaluate the difference in prognosis

Table 3. Univariable and Multivariable Cox Proportional Hazard Analysis for Factors Associated With Death, Durable LVAD Implantation, and HTx Within 90 Days After Admission

	Univariate		Multivariate: model 1		Multivariate: model 2		Multivariate: model 3	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (for each increment of 10 y)	1.11 (0.96–1.27)	0.161						
Male sex	1.54 (0.94–2.54)	0.090						
Body mass index	1.05 (0.99–1.11)	0.137						
Veno-arterial extracorporeal membrane oxygenation group	8.28 (3.02–22.73)	<0.001	5.27 (1.60–17.36)	0.006	7.73 (2.77–21.58)	<0.001	7.98 (2.85–22.31)	<0.001
Eosinophilic myocarditis*	0.28 (0.10–0.80)	0.017	0.41 (0.14–1.17)	0.095				
Systolic blood pressure	0.99 (0.98–0.997)	0.008			1.00 (0.99–1.01)	0.854	1.00 (0.99–1.01)	0.457
Heart rate	0.99 (0.98–0.995)	0.002			0.99 (0.98–1.00)	0.055	0.99 (0.98–1.00)	0.077
QRS ≥120 ms	2.03 (1.17–3.50)	0.011					1.44 (0.82–2.53)	0.204
Ventricular tachycardia/ ventricular fibrillation	4.93 (2.34–10.39)	<0.001	3.53 (1.15–10.85)	0.028	3.40 (1.43–8.12)	0.006		
Atrioventricular block	1.23 (0.59–2.58)	0.579						
Atrial fibrillation	0.97 (0.30–3.08)	0.954						
Left ventricular ejection fraction	1.00 (0.98–1.02)	0.962						
White blood cell count (for each increment of 100/μL)	1.00 (1.00–1.01)	0.458						
C-reactive protein	1.04 (1.01–1.08)	0.016			1.04 (1.001–1.08)	0.047	1.04 (1.001–1.08)	0.043
Aspartate transaminase	1.00 (1.00–1.00)	0.242						
Alanine aminotransferase	1.00 (1.00–1.00)	0.786						
Lactate dehydrogenase	1.00 (1.00–1.00)	0.118						
Creatinine	1.54 (1.19–2.01)	0.001			1.07 (0.77–1.49)	0.693	0.99 (0.71–1.38)	0.943
Creatine kinase	1.00 (1.00–1.00)	0.028						
Steroid use	0.99 (0.61–1.59)	0.957						
Era (2011–2020)†	0.71 (0.43–1.17)	0.179						
No biopsy	1.89 (1.16–3.07)	0.010			1.76 (1.02–3.04)	0.042	1.83 (1.07–3.13)	0.028

HR indicates hazard ratio; HTx, heart transplantation; and LVAD, durable left ventricular assist device.
*Reference: lymphocytic myocarditis.
†Reference: 2000–2010.

according to histological findings as EM tended to be associated with good prognosis, although this was not significant in multivariate analysis.

The long-term LVEF after FM has been reported as relatively preserved; however, LVEF impairment remains in some patients.[11,26,27] Long-term cardiac function data of patients with FM were limited. Our results confirm impaired cardiac function in some patients with FM requiring MCS. This is the first report identifying the differences in impaired cardiac function based on histological subtypes of FM. The long-term impaired cardiac function noted in patients with EM may be owing to myocarditis relapse or may reflect an increased acute phase survival because of successful short-term steroid therapy. As the long-term effects on LVEF in patients with acute myocarditis with and without FM differ, the discrepancies in the long-term effects on LVEF according to histological subtypes in patients with acute myocarditis should be further studied.[27,28] Hence, we suggest long-term LVEF management in patients with FM, especially in those with EM. Periodic evaluations of myocardial inflammation after hospital,

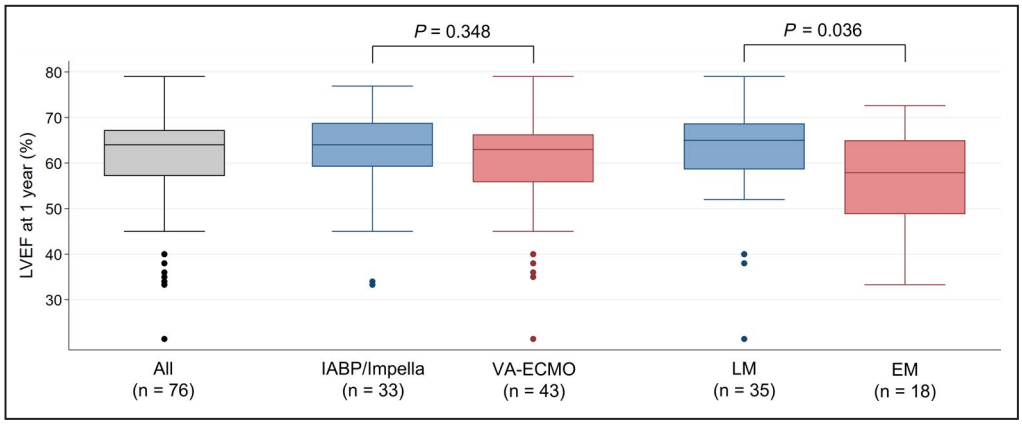

Figure 4. LVEF 1 year after admission for FM.
The LVEF categories of all patients, patients in each MCS category, and patients in each histological subgroup are shown. ECMO indicates extracorporeal membrane oxygenation; EM, eosinophilic myocarditis; FM, fulminant myocarditis; IABP, intra-aortic balloon pump; LM, lymphocytic myocarditis; LVEF, left ventricular assist device; and MCS, mechanical circulatory support.

including magnetic resonance imaging, discharge should be conducted as some patients had a history of myocarditis or experience recurrent myocarditis.

This study was not without limitations. First, this was a retrospective study in Japan, and the results may have been affected by data that could not be collected or patients who were lost to follow-up. The low number of heart transplantations in this study may also reflect the clinical situation in Japan, where the long waiting period for transplantation means that patients need to be bridged with a durable LVAD. Second, a myocardial biopsy was not performed for every patient enrolled. Although myocardial biopsies are helpful to diagnose myocarditis and guide treatment, patients are often treated for FM without having a myocardial biopsy, as some institutions do not routinely perform them. Finally, a polymerase chain reaction test for the detection of viruses in the myocardium was not performed for most patients of our study. Although polymerase chain reaction findings allow the determination of myocarditis-specific etiology, current recommendations support the use of immunosuppressive drugs based on histological findings.[2–4,14,15] How polymerase chain reaction findings will guide the treatment of patients with FM remains controversial and requires more research.[3,29–31]

CONCLUSIONS

In conclusion, patients with FM treated only with IABP or Impella had a better prognosis than those who required VA-ECMO. The prognosis of patients with EM was better than that of patients with LM in univariable analysis but was not significantly different compared with that of patients with LM in multivariable analysis. The LVEF at 1 year was lower in patients with EM than in patients with LM.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S3
Figures S1–S4

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SUPPLEMENTAL MATERIAL

Table S1. Characteristics of patients who underwent myocardial biopsy			
	Biopsy (n = 155)	No biopsy (n = 61)	p value
Age, years	52 (40–65)	55 (36–69)	0.566
Male, n (%)	94 (60.6)	35 (57.4)	0.659
Body mass index, kg/m^2	21.9 (19.8–24.3)	22.9 (20.6–25.6)	0.093
Mechanical circulatory support, n (%)			
VA-ECMO	110 (71.0)	45 (73.8)	0.680
IABP	139 (93.9)	52 (86.7)	0.097
Impella	20 (12.9)	1 (1.6)	0.010
Systolic blood pressure, mmHg	97 (86–108)	90 (80–106)	0.067
Diastolic blood pressure, mmHg	60 (53–72)	62 (44–68)	0.600
Heart rate, bpm	100 (86–120)	102 (81–119)	0.970
ECG findings at admission			
QRS ≥120 ms, n (%)	56 (46.3%)	25 (49.0%)	0.742
VT/Vf, n (%)	6 (4.1)	6 (10.3)	0.105
Atrioventricular block, n (%)	14 (9.7)	6 (10.3)	> 0.999
Atrial fibrillation, n (%)	7 (4.8)	2 (3.4)	> 0.999
LVEF, %	30.0 (20.0–45.0)	30.0 (20.0–42.3)	0.769
LVDd, mm	44.0 (41.0-47.0)	44.7 (40.0-50.0)	0.780
Laboratory data			
White blood cell count, μL	9,300 (6,830–13,200)	9,950 (7,700–12,800)	0.375
Eosinophil count, μL	200 (0–1,270)	220 (0–840)	0.499
C-reactive protein, mg/dL	3.8 (1.3–8.3)	5.8 (1.1–13.8)	0.136
AST, IU/L	135 (65–339)	170 (108–472)	0.033
ALT, IU/L	63 (35–156)	80 (46–249)	0.048
LDH, IU/L	527 (379–920)	621 (482–1245)	0.065
Creatinine, mg/dL	1.0 (0.8–1.5)	1.2 (0.9–2.2)	0.003
CK, IU/L	681 (306–1142)	821 (512–1622)	0.025
CK-MB, ng/mL	61.0 (28.3–105.2)	85.0 (44.0–155.7)	0.114
cTnI, ng/mL	16.4 (4.4–39.7)	25.4 (5.8–60.2)	0.461
cTnI over the normal reference *, n (%)	69 (97.2)	20 (100)	> 0.999
Treatment, n (%)			
Steroid	68 (43.9)	17 (28.3)	0.037
Immunoglobulin	67 (43.2)	26 (43.3)	0.989

Data excluding missing data are presented as median (interquartile range) or number (percentage).
ALT = alanine aminotransferase; AST = aspartate transaminase; CK = creatine kinase; CK-MB = creatine kinase-myocardial band; cTnI = cardiac troponin I; ECG = electrocardiogram; FM = fulminant myocarditis; IABP = intra-aortic balloon pump; LDH = lactate dehydrogenase; LVEF = left ventricular ejection fraction; LVDd = left ventricular end-diastolic diameter; VA-ECMO = veno-arterial extracorporeal membrane oxygenation; Vf = ventricular fibrillation; VT = ventricular tachycardia.
*normal reference was 0.014 ng/mL

Table S2. Patients characteristics of patients with history of acute myocarditis before FM or with recurrence of acute myocarditis after FM.					
Patient	History or recurrence	Age (years)	Sex	Histological subtype	Period between history of acute myocarditis and FM or between recurrence of acute myocarditis after FM admission (days)
1	History	37	Male		2314
2	Recurrence	40	Female	LM	54
3	History	30	Male	LM	2109
4	History	33	Female		2193
5	History	42	Male	Bacterial	943
6	History	40	Female	LM	585
7	Recurrence	36	Female		103
8	Recurrence	31	Female	LM	583
EM = eosinophilic myocarditis; FM = fulminant myocarditis; LM = lymphocytic myocarditis.					

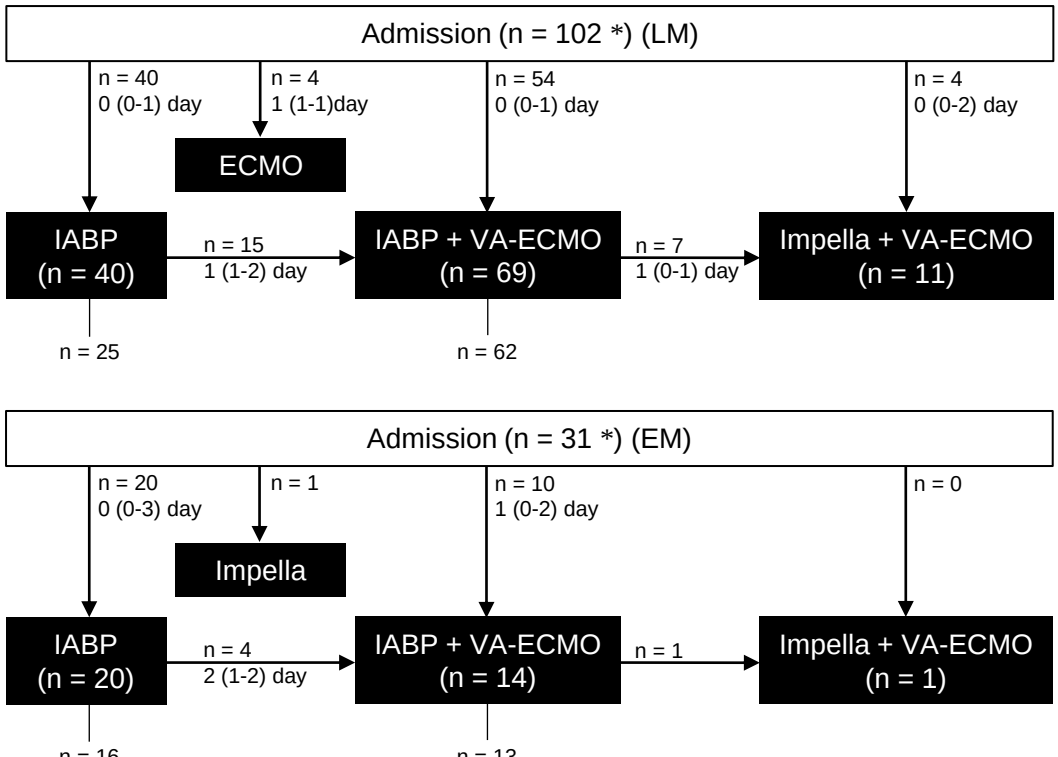
Table S3. Multivariable Cox proportional hazard analysis of factors associated with death, durable LVAD implantation, and HTx within 90 days after admission

	Extra model 1		Extra model 2		Extra model 3		Extra model 4	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
VA-ECMO group	5.26 (1.60–17.37)	0.006	5.01 (1.52–16.59)	0.008	5.64 (1.72–18.52)	0.004	4.30 (1.29–14.30)	0.017
EM *	0.41 (0.14–1.19)	0.101	0.39 (0.14–1.12)	0.080	0.36 (0.12–1.02)	0.054	0.36 (0.13–1.03)	0.056
VT/Vf	3.31 (1.01–10.82)	0.048	3.09 (1.02–9.39)	0.047	4.60 (1.45–14.58)	0.010	3.43 (1.132–10.41)	0.029
Systolic blood pressure	1.00 (0.98–1.01)	0.900						
Heart rate			0.99 (0.98–1.00)	0.309				
C-reactive protein					1.06 (1.02–1.12)	0.010		
Creatinine							1.71 (1.14–2.56)	0.009

CI = confidence interval; EM = eosinophilic myocarditis; HR = Hazard ratio; HTx = heart transplantation; Vf = ventricular fibrillation; VT = ventricular tachycardia.

*Reference: lymphocytic myocarditis.

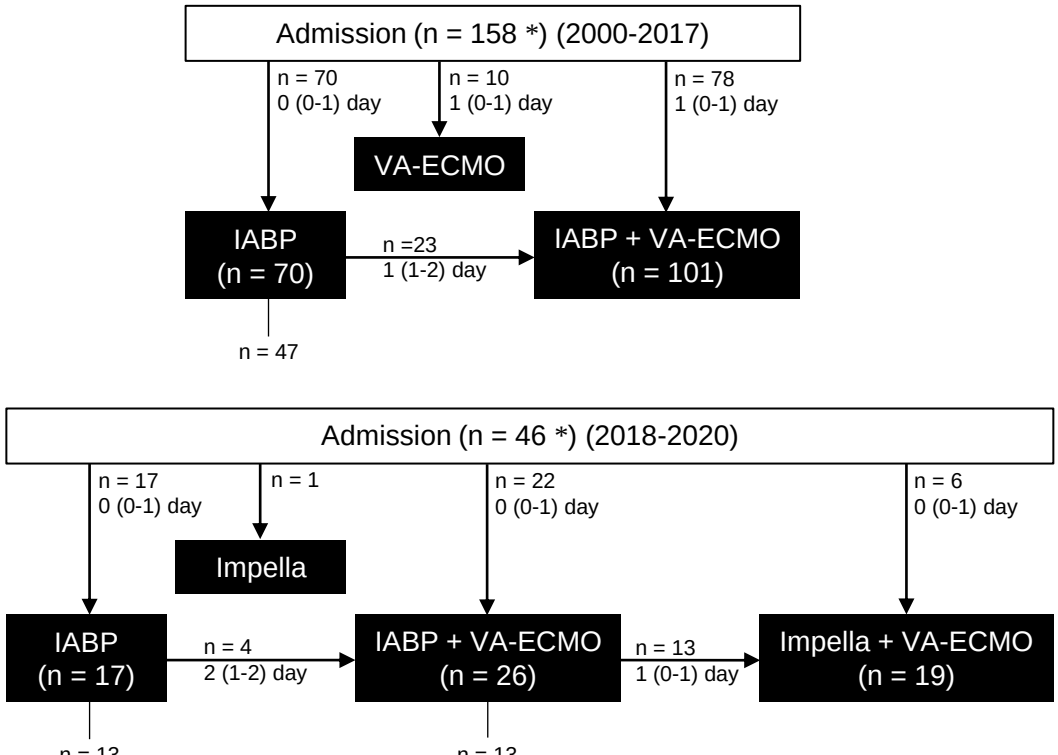
Figure S1. Treatment flow for percutaneous MCS in patients with LM and EM.



* Patients without date data were excluded (n = 8).

EM = eosinophilic myocarditis; IABP = intra-aortic balloon pump; LM = lymphocytic myocarditis;
MCS = mechanical circulatory support; VA-ECMO = veno-arterial extracorporeal membrane oxygenation

Figure S2. Treatment flow for percutaneous MCS in patients during 2000–2017 and 2018–2020

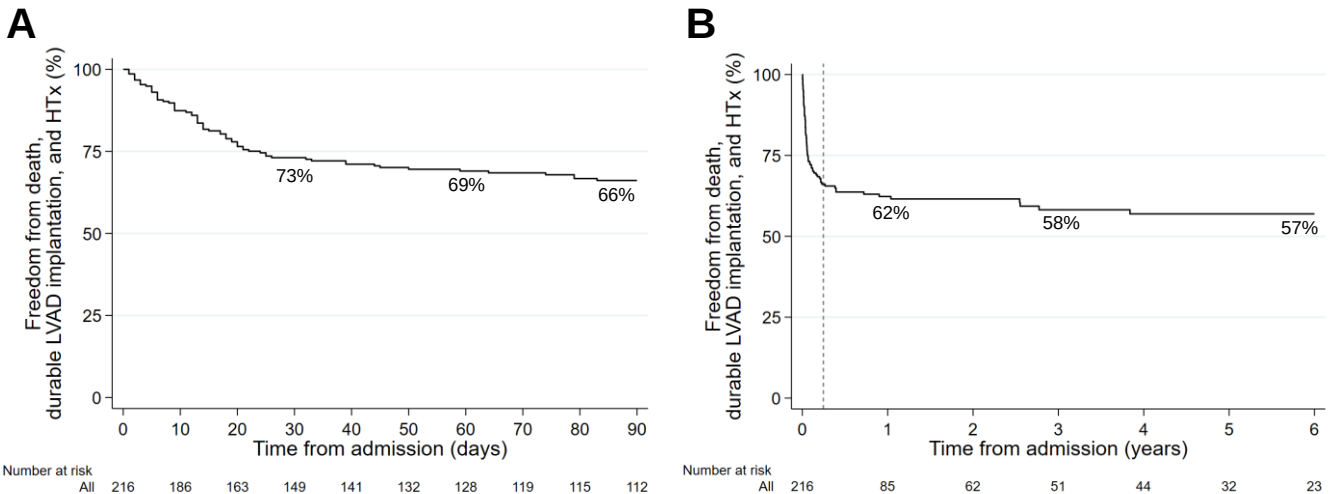


* Patients without date data were excluded (n = 12).

IABP = intra-aortic balloon pump; MCS = mechanical circulatory support;

VA-ECMO = veno-arterial extracorporeal membrane oxygenation

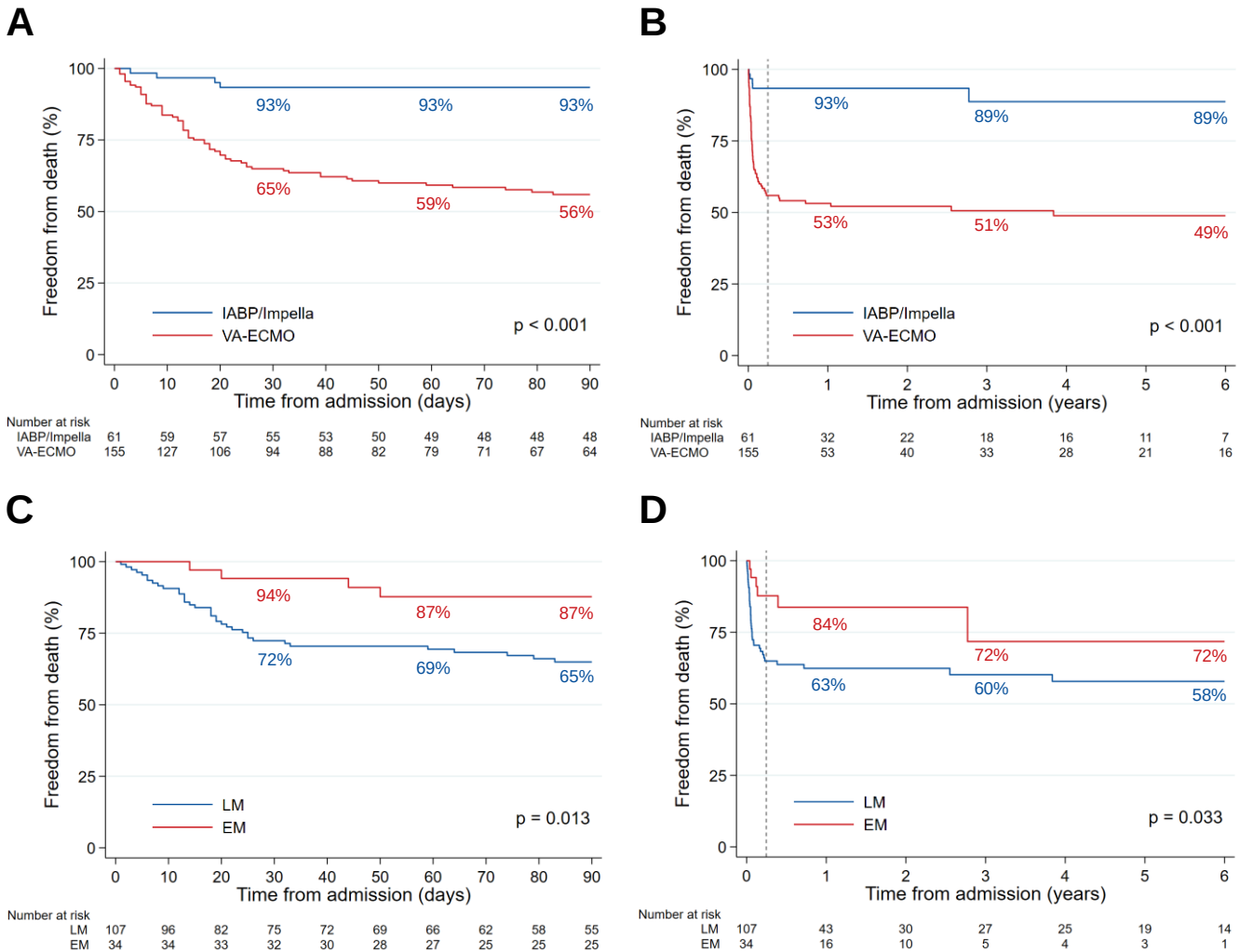
Figure S3. Kaplan–Meier curves for freedom from death, durable LVAD implantation, and HTx after admission to a hospital owing to FM in all patients.



A. Kaplan–Meier curve up to 90 days after admission. **B**. Kaplan–Meier curve up to 6 year after admission. The vertical dotted line represents 90 days.

FM = fulminant myocarditis; HTx = heart transplantation; LVAD = left ventricular assist device

Figure S4. Kaplan–Meier curves for freedom from death after admission to a hospital owing to FM.



A. The Kaplan–Meier curve for freedom from death up to 90 days after admission for each MCS group. **B**. The Kaplan–Meier curve for freedom from death endpoint up to 6 years after admission for each MCS group. The vertical dotted line represents 90 days. **C**. The Kaplan–Meier curve for freedom from death up to 90 days after admission for each histological subgroup. **D**. The Kaplan–Meier curve for freedom from death up to 6 years after admission for each histological subgroup. The vertical dotted line represents 90 days. Patients with GCM were removed from Supplemental Figure 4C and Supplemental Figure 4C due to small sample size.

EM = eosinophilic myocarditis; FM = fulminant myocarditis; GCM = giant cell myocarditis; IABP = intra-aortic balloon pump; LM = lymphocytic myocarditis; MCS = mechanical circulatory support; VA-ECMO = veno-arterial extracorporeal membrane oxygenation