

Lactate Dehydrogenase Indicates Development From Fulminant Myocarditis to Chronic Persistent Myocarditis: A Multicenter Retrospective Cohort Study in China

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Background: Fulminant myocarditis (FM) is a critical manifestation of myocarditis. However, the clinical features and risk factors associated with its adverse outcomes are not fully understood. Given the high mortality and potential for long-term complications, it is crucial to identify factors that could predict the progression of FM to chronic persistent myocarditis. We hypothesize some clinical or laboratory markers may be predictive of this progression. This study aims to identify clinical factors that may help predict the progress of FM to chronic persistent myocarditis.

Methods: A total of 82 patients with FM treated based on Chinese protocol were included. Kaplan–Meier curve and regression analysis were used to determine the clinical features and prognostic predictors of chronic persistent myocarditis in patients with 24 months of follow-up.

Results: Chronic persistent myocarditis was observed in 20 patients during the follow-up. ROC curve showed that the critical value for chronic persistent myocarditis caused by lactate dehydrogenase (LDH) was 577.00U/L (sensitivity 75.0%, specificity 74.2%). Time from onset to admission over 6 days and LDH > 577.00U/L were identified as risk factors for chronic persistent myocarditis in patients with FM in both univariate and multivariate cox analysis. The hazard ratio and 95% Confidence intervals were 3.35 (1.32–8.50) ($p = 0.011$) and 6.11 (2.02–18.48) ($p < 0.001$), respectively. The per standard deviation of increment in LDH was associated with the 55% (1.55, 1.11–2.18) in HR and 95% CI of the occurrence of chronic persistent myocarditis.

Conclusion: About 24.4% of the patients with FM treated based on the life support measures proposed in the consensus of Chinese Society of Cardiology have been observed chronic persistent myocarditis. Time from onset to admission over 6 days and LDH levels >577.00 U/L at admission may serve as risk factors for the progression from FM to chronic persistent myocarditis.

Keywords: fulminant myocarditis, chronic persistent myocarditis, prognosis

Introduction

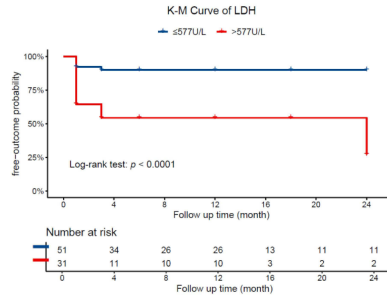
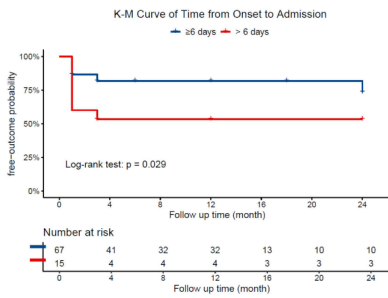
Fulminant myocarditis (FM) is the most dangerous form of acute myocarditis with low morbidity and high mortality and can progress suddenly and rapidly to severe heart failure, refractory arrhythmias, cardiogenic shock and even death in as little as several days.^{1,2} Acute lymphocytic myocarditis represents the predominant pathological subtype of fulminant myocarditis.^{3,4} The swift advancement of the disease poses challenges for patients to receive a prompt and accurate diagnosis, leading to delayed diagnosis, misdiagnosis, or even fatality. Nevertheless, timely mechanical support and immunoregulatory therapy are believed to considerably decrease in-hospital mortality rates in patients with fulminant myocarditis.⁵

Graphical Abstract

Which clinical factors can help predict the progress of fulminant myocarditis to chronic persistent myocarditis?

fulminant myocarditis treated based on Chinese protocol (n=82)

Kaplan-Meier curve



Multivariate cox analysis

	95.0% CI	p
Time from onset to admission >6d	3.35 (1.32 - 8.50)	0.011
LDH > 577.00U/L	6.11 (2.02-18.48)	<0.001

Time from onset to admission over 6 days and LDH levels >577.00 U/L may be risk factors from FM to chronic persistent myocarditis in adult patients

The prognosis of FM is a topic of debate. A single-center retrospective cohort study with average period of follow-up was 5.6 years in 2000⁶ reported that FM has a better prognosis than non-fulminant myocarditis (NFM). However, the results of this study are now thought to be affected by the low incidence of endomyocardial biopsy (EMB) and limited choice of mechanical circulatory support (MCS) devices.⁷ This can lead to differential diagnosis and misleading pathological diagnosis, which may result in an incorrect conclusion. Recently, a retrospective, international, multicenter cohort study⁸ have shown that impaired haemodynamics at presentation is a major determinant of both short and long-term prognosis in FM patients, with the incidence of cardiac death or heart transplantation (HTx) being 28% at day 60 and 47.7% at 7 years. Histological subtype^{4,9} and QRS width on electrocardiogram (ECG)⁸ of FM patients may also had independent prognostic value. However, the factors that contribute to chronic persistent myocarditis in FM patients require further investigation.

This study aims to identify clinical factors that may influence the progression of fulminant myocarditis to chronic persistent myocarditis after treatment. The findings will provide valuable information for predicting the risk of chronic persistent myocarditis for FM patients after hospitalization.

Methods

Study Population

This multicenter retrospective cohort study included acute myocarditis patients admitted to Tongji Hospital Tongji Medical College of Huazhong University of Science and Technology and Minda Hospital of Hubei Minzu University from February 2017 to June 2023. The diagnosis of acute myocarditis was made by an experienced clinician and requires at least one clinical manifestation and one diagnostic criteria, or at least two diagnostic criteria, and the exclusion of other

diseases with similar manifestations.¹⁰ The clinical manifestation¹⁰ goes to: (1) acute chest pain, pericarditic, or pseudo-ischaemic; (2) new-onset or worsening of dyspnoea at rest or exercise, and/or fatigue, with or without left and/or right heart failure signs; (3) subacute/chronic or worsening of fatigue, with or without left and/or right heart failure signs and/or dyspnoea at rest or exercise; (4) aborted sudden cardiac death, and/or palpitation, and/or unexplained arrhythmia symptoms and/or syncope; (5) unexplained cardiogenic shock. The diagnostic criteria¹⁰ go to: (1) newly abnormal 12 lead ECG and/or Holter and/or stress testing; (2) elevated TnT/TnI; (3) functional and structural abnormalities on cardiac imaging; (4) tissue characterization by cardiac magnetic resonance (CMR). Fulminant myocarditis, as previous studies have reported,⁸ was defined as acute presentation with hemodynamic compromise requiring inotropes and/or MCS, such as intra-aortic balloon pump (IABP) and extracorporeal membrane oxygenation (ECMO).^{8,11} The inclusion criteria for this study were as follows: (1) clinical diagnosis of FM; (2) hospitalization of more than 48 hours. Exclusion criteria for this study were as follows: (1) not confirmed by EMB or CMR; (2) death or HTx during hospitalization; (3) refusal of follow-up; (4) history of ischaemic cardiomyopathy, myocarditis, cardiomyopathy, malignant tumor/cancer and other diseases affecting cardiac function and prognosis; (5) time from onset to hospitalization longer than 30 days; (6) children (<15 years old).

End Points

The end point of this study was chronic persistent myocarditis. According to the guideline from Japanese Circulation Society (JCS)³ and the expert consensus document of acute myocarditis and chronic inflammatory cardiomyopathy in 2020,¹ chronic persistent myocarditis was defined as highly sensitive cardiac troponin levels in the blood of FM patients continuously elevated for more than 30 days after discharge. In this study, we defined highly sensitive cardiac troponin level as high-sensitivity cardiac troponin I (hs-cTnI) >15.6 pg/mL according to the test standard of the clinical lab of the hospital. Outpatient follow-up was scheduled at 1, 3, and 6 months post-discharge, with subsequent visits every 6 months for patients in stable condition. These follow-up appointments included adjustments to medications, hs-cTnI testing and echocardiographic evaluations. In the event of acute episodes or special conditions, patients have access to dedicated communication channels for the timely identification and management of emergencies. Two or more times of increased hs-cTnI detected within the 6-month follow-up was considered as the occurrence of the endpoint. The time when hs-cTnI elevation was first detected was taken as the time the end point occurred.

Laboratory methods

Laboratory tests for blood samples were collected and tested within two hours of admission. Laboratory tests included routine blood tests, aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine, high-sensitive cardiac troponin I (hs-cTnI), N-terminal pro-B-type natriuretic peptide (NT-proBNP), lactate dehydrogenase (LDH), Creatine Kinase MB isoenzyme (CK-MB) or Creatine Kinase (CK), high-sensitive C-reactive protein (hs-CRP), erythrocyte sedimentation rate (ESR), procalcitonin (PCT), Interleukin-1 β (IL-1 β), Interleukin-2 receptor (IL-2R), Interleukin-6 (IL-6), Interleukin-8 (IL-8), Interleukin-10 (IL-10), tumor necrosis factor α (TNF- α), Procalcitonin (PCT), Lactic Acid (LA), D-D Dimer, activated partial thromboplastin time (APTT) and prothrombin time (PT).

Endomyocardial Biopsy

EMB was done as previous described.¹² The bioptome was accurately positioned on the apical left ventricular septum. Ideally, the specimens should measure between 2 and 3 mm³ in size. A minimum of 3 to 5 biopsy samples should be obtained to ensure adequate sampling. The specimens are routinely processed for staining and subsequent histological examination. The diagnosis of pathological classification was based on the Dallas criteria.¹³

Cardiac Magnetic Resonance Imaging

CMR was conducted during the hospital stay using a 1.5-T system equipped with a 32-channel cardiac coil. The CMR protocol included cine imaging, T2-weighted sequences, first-pass perfusion, and breath-held late gadolinium enhancement (LGE), consistent with previously reported.¹⁴

Treatment of Patients

We implemented a comprehensive treatment plan based on the life support measures proposed in the consensus of the Chinese Society of Cardiology^{5,15} in both hospitals. The treatment plan was mainly based on the following 4 principles: (1) mechanical life support, including the utilization of mechanical ventilators and circulatory support systems such as ECMO, IABP, continuous renal replacement therapy (CRRT), temporary pacemakers, etc.; (2) immunomodulation through appropriate administration of corticosteroids and intravenous immunoglobulin (IVIG); (3) antiviral therapy. Patients were given oral glucocorticoids tablets after discharge for months. The complications of the patient at discharge and other drug use during follow-up were shown in [Table S1](#).

Statistical Analysis

The baseline characteristics of the analyzed samples were summarized based on the occurrence of chronic persistent myocarditis. Categorical variables were presented as frequencies and percentages, while continuous variables were reported as medians with interquartile ranges (IQR). The chi-square test was employed for categorical variables, and the Student's *t*-test was used to compare baseline characteristics in terms of continuous variables. Differences in categorical data were analyzed using the Fisher exact test. Predictive mean matching was used to interpolate for variables with missing values of 5–20%. To identify clinically relevant prognostic factors, logistic and cox regression analysis was used to identify predictors associated with outcome. In the regression analysis, variables with $p < 0.05$ were included in the regression model.

The *p*-value of the interaction was calculated to assess the consistency of the patterns observed in the main results. Analyses and plotting were conducted using GraphPad Prism version 10.0.0 for Windows (GraphPad Software, Boston, MA, www.graphpad.com, USA) and R software (the R Foundation, <http://www.r-project.org>, version 4.0.2) with a two-sided significance threshold of $p < 0.05$.

Results

The Population of FM Patients

A total of 82 FM patients were selected from a group of 304 patients who had received clinical diagnosis for acute myocarditis from February 2017 to June 2023 in Tongji Hospital affiliated to Huazhong University of Science and Technology and Minda Hospital of Hubei Minzu University from China. The flow chart is presented in [Figure S1](#). The mean age of patients enrolled was 34 years old (IQR 24–47 years old) and 41.5% were male, with a median hospitalization of 12 days (IQR 9–17 days) and a median time from onset to hospital admission of 3 days (IQR 2–5 days). A total of 45 patients (54.9%) underwent EMB, all of whom were diagnosed with lymphocytic myocarditis. Additionally, 75 patients (91.5%) underwent CMR. Notably, 38 patients (46.3%) received both EMB and CMR examinations. Chronic persistent myocarditis was observed in 20 patients (24.4%) during follow-up. The main characteristics of the patients did not develop chronic persistent myocarditis ($n = 62$) and those developed chronic persistent myocarditis ($n = 20$) are shown in [Tables 1](#) and [S2](#). At baseline, the patients did not develop chronic persistent myocarditis were found lower levels of hs-cTnI, AST and LDH compared with those developed chronic persistent myocarditis. There were no significant differences in age, sex, clinical manifestation, medical history, blood pressure, left ventricular ejection fraction (LVEF), NT-proBNP, leukocytosis, neutrophil count, lymphopenia, hs-CRP, ESR, PCT and serum inflammatory parameters (IL-1 β , IL-2R, IL-6, IL-8, IL-10 and TNF- α) between the two groups.

Outcome of Patients With FM

In-hospital management of the patients is detailed in the [Table S3](#). All patients received immunosuppressive therapy. Glucocorticoids were used in all patients and IVIG in 79 patients, with no difference in dose between the two groups. Regarding mechanical circulatory support, IABP was the most common MCS used in 93.9% of patients developed chronic persistent myocarditis (median time 4 days, IQR: 3–6 days) and 81.5% of those did not (median time 4 days, IQR: 2–7 days), showing no difference between the two groups. The use of temporary external pacing, CRRT and ECMO also showed no difference.

Table 1 Baseline Characteristics of Patients in the Study

Variables	Patients with Available Data, n	No Chronic Myocardial (n=62)	Chronic Myocardial (n=20)	P-value
Demographics				
Sex (male)	82	25 (40.3)	9 (45.0)	0.712
Age, y	82	34.92 (13.66)	38.90 (17.97)	0.299
Time from onset to admission, d	82	3.00 (2.00, 5.00)	4.00 (2.00, 7.00)	0.117
Hospitalization Time, d	82	12.00 (9.25, 17.00)	11.50 (8.75, 15.25)	0.585
Blood Pressure				
Systolic Blood Pressure (SBP)	78	95.00 (90.00, 106.50)	102.00 (91.00, 112.00)	0.518
Diastolic Blood Pressure (DBP)	78	63.00 (55.00, 72.50)	64.00 (58.50, 69.00)	0.93
Electrocardiogram				
ST-T Changes	82	39 (62.9)	15 (75.0)	0.321
Arrhythmology	82	30 (48.4)	8 (40.0)	0.513
Echocardiography				
LVEF at admission	82	41.24 (12.99)	35.80 (13.91)	0.113
Lowest LVEF	82	35.69 (14.68)	33.89 (14.14)	0.639
Laboratory Examination				
hs-cTnI, pg/mL	82	18,829.50 (3423.50, 36,280.50)	42,613.00 (19,673.50, 50,000.00)	0.012
Elevated CK/CK-MB	69	44 (84.6)	15 (88.2)	>0.999
NT-proBNP, pg/mL	82	4136.00 (1500.50, 7475.50)	5712.50 (1616.50, 20,593.50)	0.154
LDH, U/L	77	423.50 (310.75, 594.75)	680.50 (565.75, 817.00)	0.001
Leukocyte, *10 ⁹ /L	82	9.18 (6.95, 12.18)	9.45 (6.86, 11.52)	0.825
Neutrophil, *10 ⁹ /L	82	7.28 (5.47, 9.70)	7.53 (5.19, 10.13)	0.804
Lymphocyte, *10 ⁹ /L	82	1.04 (0.76, 1.64)	1.10 (0.66, 1.63)	0.927
hs-CRP, mg/L	82	19.70 (8.00, 68.00)	27.30 (7.95, 69.70)	0.964
ESR, mm/H	80	7.00 (4.00, 16.00)	12.00 (3.50, 18.50)	0.518
IL-1 β , pg/mL	57	5.00 (5.00, 6.70)	5.00 (5.00, 19.70)	0.532
IL-2R, U/mL	51	509.00 (358.00, 770.00)	640.50 (526.50, 784.75)	0.367
IL-6, pg/mL	57	10.53 (4.21, 27.82)	24.21 (5.50, 89.38)	0.183
IL-8, pg/mL	57	34.10 (11.70, 64.40)	46.45 (22.00, 96.50)	0.499
IL-10, pg/mL	57	5.00 (5.00, 10.90)	7.30 (5.00, 9.03)	0.56
TNF- α , pg/mL	57	9.70 (7.00, 12.80)	11.45 (8.47, 22.17)	0.147
PCT, ng/mL	57	0.16 (0.05, 0.40)	0.29 (0.05, 0.49)	0.775
EMB				
Lymphocytic	45	37(59.68)	8(40.0)	0.124

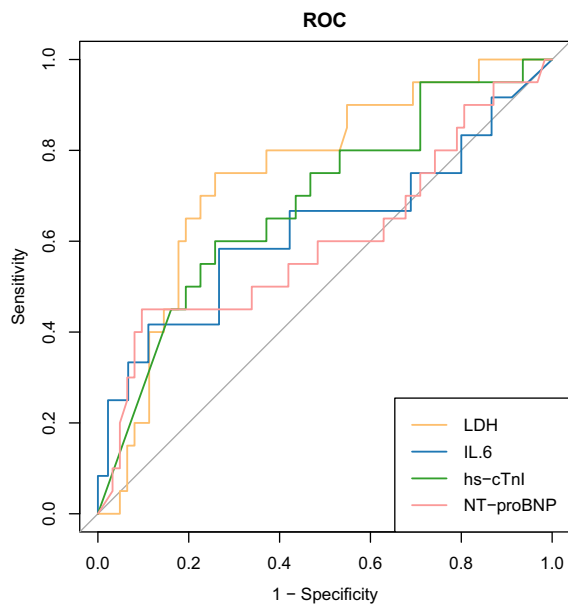
Notes: n, Patients with available data; Values are median [IQR] or n (%).

Abbreviations: SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; LVEF, left ventricular ejection fraction; hs-cTnI, high-sensitive cardiac troponin I; NT-proBNP, N-terminal pro-B-type natriuretic peptide; LDH, lactate dehydrogenase; CK-MB, Creatine Kinase MB isoenzyme; CK, Creatine Kinase; hs-CRP, high-sensitive C-reactive protein; ESR, erythrocyte sedimentation rate; IL-1 β , Interleukin-1 β ; IL-2R, Interleukin-2 receptor; IL-6, Interleukin-6; IL-8, Interleukin-8; IL-10, Interleukin-10; TNF- α , tumor necrosis factor α ; PCT, Procalcitonin; EMB, endomyocardial biopsy.

We did not find a strong association between hs-cTnI and cardiac function (presented as LVEF) during the follow-up ([Table S4](#)). The changes in hs-cTnI and LVEF of two typical patients were depicted in [Figure S2](#), one with chronic persistent myocarditis ([Figure S2a](#)) and one with complete recovery ([Figure S2b](#)), showing LVEF to improve as hs-cTnI decreased.

Analysis of Factors Associated With Chronic Persistent Myocarditis

To identify clinically relevant prognostic factors for the occurrence of chronic persistent myocarditis in patients with FM, we performed both univariate logistic and univariate cox regression analysis of baseline data and hospital admissions factors in the two groups to get a more stable and reliable results ([Table S5](#)). Time from onset to admission over 6 days, hs-cTnI, NT-proBNP, LDH and IL-6 were significantly associated with the occurrence of chronic persistent myocarditis in both univariate logistic and univariate cox analysis. The ROC curve ([Figure 1](#)) showed that the LDH and hs-cTnI were



	LDH	IL-6	hs-cTnI	NT-proBNP
Cutoff value	577.00	20.46	34991.50	12372.00
Sensitivity	75.0%	58.3%	60.0%	45.0%
Specificity	74.2%	73.3%	74.2%	90.3%
AUC	0.747	0.626	0.686	0.602
CI	(0.63-0.87)	(0.41-0.84)	(0.55-0.82)	(0.44-0.76)
p value	0.0005	0.60	0.006	0.087

Figure 1 ROC curve for chronic persistent myocarditis.

Abbreviations: AUC, area under the curve; CI, confidence interval; LDH, lactate dehydrogenase; IL-6, Interleukin-6; hs-cTnI, high-sensitive cardiac troponin I; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

predictive values for chronic persistent myocarditis compared with other laboratory results statistically significant in univariate analysis. The cutoff value of LDH was 577.00U/L (sensitivity 75.0%, specificity 74.2%). The cutoff value of hs-cTnI was 34991.50pg/mL (sensitivity 74.2%, specificity 60.0%).

The results of stepwise multivariable cox regression analysis (Table 2) showed that time from onset to admission over 6 days and LDH > 577.00U/L were identified as risk factors for chronic persistent myocarditis in patients with FM after discharge in multivariate cox analysis. We adjusted these two factors with sex and age as demographic confounding factors in Model 2 and used EMB¹⁶ and LVEF at admission⁴ as clinically relevant confounding factors according to previous research in Model 3. Time from onset to admission over 6 days and LDH > 577.00U/L still showed statistical significance in these two models. The HR and 95% Confidence intervals were 3.35 (1.32–8.50) ($p = 0.011$) and 6.11 (2.02–18.48) ($p < 0.001$), respectively in model 1. The per standard deviation (SD) of increment in LDH was associated with the 55% (1.55, 1.11–2.18) in HR and 95% confidence interval (CI) of the occurrence of chronic persistent myocarditis. The unadjusted Kaplan–Meier survival curve showed a significant difference between the groups of patients with different levels of time from onset to admission and LDH (Figure 2a and b). Compared to patients admitted within 6 days after onset, those who admitted over than 6 days were more likely to develop chronic

Table 2 Multivariate Cox Analysis of Factors Associated With the Occurrence of Chronic Persistent Myocarditis

	Model 1		Model 2		Model 3	
	95.0% CI	p	95.0% CI	p	95.0% CI	p
Age			0.99 (0.96–1.02)	0.687		
Sex			1.26 (0.49–3.21)	0.632		
EMB					0.77 (0.29–2.00)	0.586
LVEF at admission					1.01 (0.96–1.05)	0.827
Time from onset to admission >6d	3.35 (1.32–8.50)	0.011	3.91 (1.38–11.13)	0.011	3.47 (1.28–9.37)	0.014
LDH > 577.00U/L	6.11 (2.02–18.48)	< 0.001	7.38 (2.56–21.23)	< 0.001	7.32 (2.33–23.00)	< 0.001
hs-cTnI >34991.5 pg/mL	1.52 (0.58–3.92)	0.396				

Abbreviations: LVEF, left ventricular ejection fraction; EMB, endomyocardial biopsy; LDH, lactate dehydrogenase; hs-cTnI, high-sensitive cardiac troponin I.

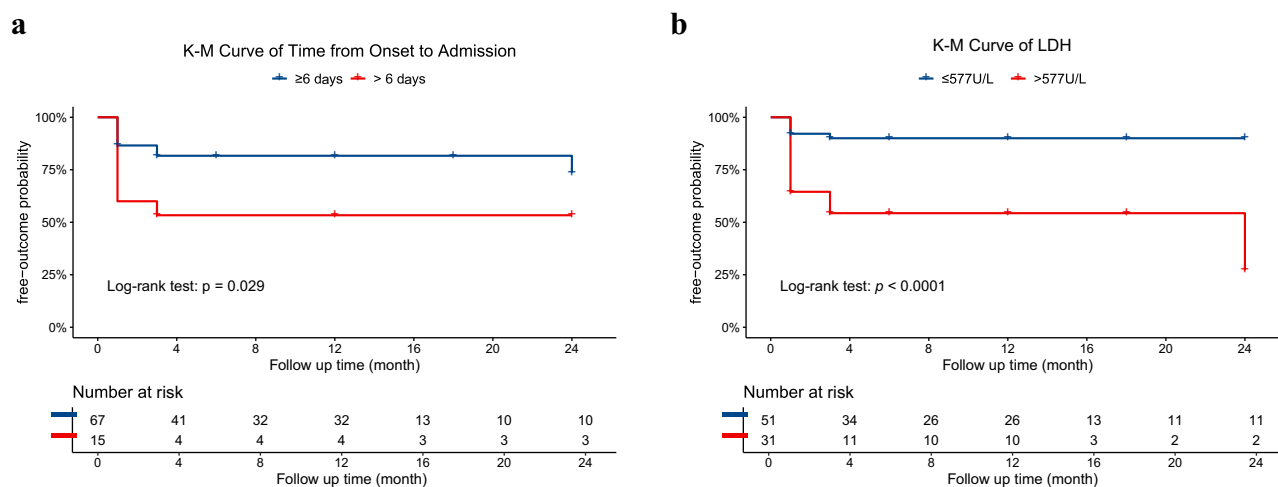


Figure 2 Unadjusted K-M curve of chronic persistent myocarditis in sub group of time from onset to admission (a) and LDH (b).
Abbreviation: LDH, lactate dehydrogenase.

persistent myocarditis ($p = 0.029$), with post-hoc power 58.6%. Patients with LDH $> 577.00\text{U/L}$ (divided according to the cutoff value of ROC curve) were more likely to develop chronic persistent myocarditis than those with LDH $\leq 577.00\text{U/L}$ ($p < 0.001$), with post-hoc power 98.7%.

Discussion

Acute myocarditis can be caused by infection with viruses, parasites, mycoplasmas and fungi. Viruses are the most common cause of infection, including Coxsackievirus B3, parvovirus B19, human herpesvirus 6¹⁷ and upper respiratory viruses such as SARS-CoV-2.¹⁸ HIV, toxins, drugs and autoimmune phenomena can also cause acute myocarditis. The pathophysiological process of acute myocarditis caused by coxsackie virus infection in humans can be divided into three stages:¹⁷ (1) Coxsackie virus binds to corresponding receptors on the cell surface, and the resultant complex is internalized by the cell, leading to the activation of the host innate immunity. Then, virus replication in cardiomyocytes leads to cell lysis, which triggers a cascade of reactions resulting in cytokine release. (2) Specific immunity is activated, and natural killer cells, macrophages, and virus-specific T cells converge at the site of infection. High levels of cytokines, including TNF α , IL-1 α , IL-1 β , IL-2, and interferon-gamma (IFN- γ), can even cause inflammatory storms,⁷ leading to autoimmune-mediated damage. (3) Inflammation generally resolves after a few weeks, and in most patients, the myocardial damage completely resolves with the elimination of the virus. Early and timely use of MCS and corticosteroids and IVIG can effectively control the inflammatory storm caused by immune overactivation in FM patients.^{7,15} However, there are still a small number of patients develop chronic inflammation and dilated cardiomyopathy (DCM).

The pathophysiological mechanism leading to the transformation of acute myocarditis into chronic inflammatory is not yet clear, and chronic persistent myocarditis can be regarded as a transitional stage between acute myocarditis and chronic inflammatory cardiomyopathy.¹ One possible reason is the persistence of the viral genome.¹⁷ Clinical studies have demonstrated that clearance of the viral genome can substantially enhance both the left ventricular end diastolic and end systolic diameters, as well as LVEF in myocarditis patients.^{19,20} Host genetics also plays a significant role in the progression of myocardial inflammation into chronic inflammation. In human, the polymorphism of MHC,^{21,22} CD45²³ are associated with an increased risk of acute myocarditis developing into chronic inflammation. In animal models, studies have shown that deletion of certain key genes, such as TLR3,²⁴ ISG15,²⁵ TRIM18,²⁶ may lead to a weakened innate immune response to enterovirus infection in individuals, resulting in reduced viral clearance and an increased risk of chronic inflammation. Genetic predispositions and environmental factors can work together to drive chronic inflammation. In addition to viral genomes, cardiotoxic agents and hemodynamic changes are also contributors to this process.²⁷ However, eliminating the virus, even with favorable genetic and environmental factors, does not guarantee the resolution of chronic inflammation. Studies show that myocardial inflammation can persist in mice after virus

clearance,²⁸ possibly due to over-activation of autoimmune reactivity. Pro-inflammatory Th17 cells and regulatory T (Treg) cells, which suppress inflammation, play pivotal roles in the chronic progression of myocarditis.²⁹ Th17 cells contribute to the overactivation of autoimmune responses by secreting pro-inflammatory cytokines such as IL-17, TNF- α , and IL-1 β . An increased presence of Th17 cells has been associated with myocardial fibrosis and a worsening of functional status, as indicated by the New York Heart Association (NYHA) classification.³⁰ In contrast, Treg cells exhibit protective effects by suppressing excessive inflammation and were shown to inhibit the development of cardiomyopathy in murine models of myocarditis induced by CVB3 infection.³¹ Beyond the Th17/Treg balance, targeting other immune components, including NLRP3 inflammasome,³² complement pathways, NK cells,³³ and mast cells³⁴ may also help reduce inflammation and prevent chronic inflammation progression. The role of TGF- β in viral myocarditis is particularly complex. While it supports Treg function to suppress immune responses against heart tissue and maintain antiviral immunity,³⁵ it also promotes myofibroblast formation and myocardial fibrosis progression through the Wnt/ β -catenin pathway.³⁶

The innovation of this study is that we examine the end point of chronic persistent myocarditis, which has never been used as a prognostic outcome for FM patients, with most studies of acute myocarditis have focused on death, HTx or DCM. Our study identified that prolonged time from onset to admission and high LDH as risk factor for FM patients to develop chronic persistent myocarditis. It is easy to understand that a short time from onset to admission, which is nearly equivalent to early treatment, may reduce the risk of chronic persistent myocarditis in FM patients – it allows early intervention in this rapidly progressing disease. A number of studies have also provided evidence for early treatment in the acute stage of FM, and early treatment was strongly recommended in the Chinese guidelines for the diagnosis and treatment of adult fulminant myocarditis.¹⁵ This finding also indicates that clinicians should devote greater attention to patients with prolonged time from onset to admission, thereby facilitating the earlier detection of potential chronic progression.

Imaging techniques differ in sensitivity and applicability for effective myocarditis monitoring, depending on their specific function. Traditional echocardiography, while accessible and useful for assessing cardiac structure and function, lacks the sensitivity needed to detect inflammation. Two- and three-dimensional speckle-tracking echocardiography is a valuable tool for predicting adverse prognosis in acute myocarditis patients,³⁷ though its use may be restricted to non-critical cases.³⁸ Advanced methods like FDG-PET and CMR are effective in identifying early myocardial damage, edema, and fibrosis¹ and they offer predictive value for adverse outcomes in acute myocarditis.³⁹ However, their high costs and the need for specialized expertise limit their use in resource-constrained settings, making them not ideal for routine follow-up. CT is primarily employed to evaluate structural changes or exclude other conditions but is not routinely used for myocarditis. Additionally, certain patient factors, such as physical limitations or contraindications like metal implants, may restrict the use of these imaging modalities. Therefore, there is a need to identify reliable biological markers to monitor the prognosis of myocarditis patients.

Biomarkers that indicate myocardial injury were not only used in the clinical diagnosis of myocarditis,^{2,40} but also were frequently mentioned in the prognosis of myocarditis. Study from Ekstrom et al⁴¹ and Okura et al⁴² found that elevated NT-proBNP and cardiac troponin, and reduced LVEF were predictors of a poor prognosis in patients with giant cell myocarditis. Decrease in hs-cTnI within 24h was also found to be associated with in-hospital mortality of FM patients.⁴³ Hs-cTnI is widely recognized as a biomarker for myocardial injury in clinical practice. Although, in our study, there was significant difference in hs-cTnI between patients who developed chronic persistent myocarditis and those who did not, it remains insignificant in multivariate cox analysis. Instead, another biomarker suggesting myocardial injury, LDH, was found significant in both univariate and multivariate analysis, indicating that LDH may be a more sensitive prognostic biomarker than troponin in FM. LDH is an enzyme that catalyzes the conversion between lactic acid and pyruvate and may have proinflammatory or anti-inflammatory effects in different pathophysiological environments.⁴⁴ It was widely detected high level in acute myocarditis patients⁴⁵ and animals.^{46,47} Lei et al⁴⁸ and Xu et al⁴⁹ reported that LDH as the risk factor for severe immune checkpoint inhibitor-induced myocarditis compared with the mild one. In the study of Stasa et al,⁵⁰ LDH > 1780 mmol/l was regarded as the cutoff value for pediatric acute myocarditis to develop DCM, with larger specificity than CK, CK-MB and AST. However, they found no statistically significant difference in LDH levels observed in the univariate cox analysis between the patients who developed DCM and those who did not.

Our results found LDH > 577.0 U/L a potential risk factor for occurrence of chronic persistent myocarditis in adult patients with FM. Elevated LDH levels at admission may indicate the need for enhanced post-discharge monitoring and care for patients with FM. Continuous monitoring of LDH during follow-up may provide clinicians with reliable reference information regarding disease progression and recovery, thereby facilitating more informed clinical decision-making.

Limitation

This study has several limitations. First, as a retrospective study, it inherently lacks the ability to establish a definitive causal relationship between the potential impact factors and the observed outcomes. Our findings suggest that time from onset to admission and LDH may serve as potential predictors of chronic persistent myocarditis in patients with FM. However, causal inferences cannot be drawn, and these findings require validation in prospective studies. Secondly, the small sample size limits the statistical power of the analysis, making it challenging to detect subtle differences or small effects within the population. This increases the risk of Type II errors and may lead to biased results, ultimately undermining the study's overall robustness and reliability. Furthermore, the study's follow-up period of only 24 months may be insufficient to fully capture the long-term progression of myocarditis, potentially resulting in an incomplete assessment of its long-term prognosis. Large scale studies were needed. Thirdly, only 54.9% of the participants were diagnosed with myocarditis through EMB, which is the gold standard for confirming myocarditis. The remaining participants were diagnosed using CMR, which may introduce misclassification bias. Last, we determined the time from onset to admission based on the initial occurrence of clinical symptoms as described in the patient's chief complaint. However, individual differences in symptom perception, such as variations in pain sensitivity, and variations in pathogen incubation periods may introduce unavoidable random errors into our measurements of the time from onset to admission.

Conclusion

About 24.4% of the patients with fulminant myocarditis treated based on the life support measures proposed in the consensus of the Chinese Society of Cardiology have been observed the occurrence chronic persistent myocarditis. Time from onset to admission over 6 days and LDH >577.0 U/L at admission may be risk factors from FM to chronic persistent myocarditis in adult patients.

Abbreviations

FM, Fulminant myocarditis; K-M, Kaplan-Meier; EMB, Endomyocardial biopsy; MCS, Mechanical circulatory support; HTx, heart transplantation; CMR, Cardiac magnetic resonance; IABP, Intra-aortic balloon pump; ECMO, Extracorporeal membrane oxygenation; CRRT, Continuous renal replacement therapy; IVIG, intravenous immunoglobulin; DCM, Dilated cardiomyopathy.

Data Sharing Statement

The datasets generated and/or analyzed during the current study are not publicly available due reason why data are not public but are available from the corresponding author on reasonable request.

Ethics Approval and Informed Consent

This study has received approval from the Research Ethics Commissions of Tongji Hospital Tongji Medical College of Huazhong University of Science and Technology (TJ-C20160202). The Executive Committee planned and oversaw the study's execution as well as its data analysis. Following the guidelines set out by the International Conference on Harmonization of Guidelines for Good Clinical Practice⁵¹ and the Declaration of Helsinki,⁵² all procedures and methodologies underwent ethical review and approval by local ethics committees.

Consent for Publication

As this is a retrospective study using de-identified data, the Institutional Review Board did not require patient consent.

Acknowledgments

The authors thank to the participating subjects and follow-up staff for their valuable assistance in this study. Additionally, the authors acknowledge Minda Hospital of Hubei Minzu University for providing the subjects.

Author Contributions

All authors made substantial contributions to the work, including the conception, study design, execution, data acquisition, analysis, or interpretation. They were involved in drafting, revising, or critically reviewing the manuscript, approved the final version for publication, agreed on the journal for submission, and take full responsibility for all aspects of the work.

Funding

Open access publication fees were funded by the Tongji Hospital affiliated to Huazhong University of Science and Technology, and there were no other sources of funding.

Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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