Original Article

Does Cardiac Remodeling in Pediatric Myocarditis Associated with Initial Cardiac Function?

Poomiporn Katanyuwong, MD[1,2], Siwat Srimuang, MD[1], Sakda Arj-Ong Vallibhakara, MD, PhD[3,4]

[1] Department of Pediatrics, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

[2] Division of Pediatric Cardiology, Department of Pediatrics, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

[3] Research & Innovation and Academic Affairs, ASEAN Institute for Health Development, Mahidol University, Nakhon Pathom, Thailand

[4] Child Safety Promotion and Injury Prevention Research Center (CSIP), Department of Pediatrics, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

Background: In pediatric myocarditis, the relationship between cardiac remodeling with initial cardiac function remains uncertain. The authors hypothesized that cardiac remodeling in viral myocarditis is not associated with initial cardiac function.

Objective: The primary objective is to determine an association between cardiac remodeling with initial cardiac function, and the secondary aim is to study the factors that influence cardiac remodeling.

Materials and Methods: A retrospective cohort study of children under 15 years old, clinically diagnosed as presumed acute viral myocarditis and treated at Ramathibodi Hospital between January 2002 and June 2017.

Results: Twenty-three patients were enrolled. Patients had a median age of two years (25 days-14.5 years), and 15 (65%) patients were female. The most common presenting symptoms were respiratory, cardiac, and gastrointestinal symptoms, respectively. The various supportive treatments included Dobutamine (80%), intravenous immunoglobulin (86%), and mechanical ventilator usage (80%). Fifteen patients (65%) survived at discharge, six (25%) expired, and two (9%) were referred to another institution for cardiac transplantation. Nineteen patients (83%) had an initial left ventricular ejection fraction (LVEF) of less than 55%. In this group, eight (40%) patients had completed cardiac remodeling during the follow-up period. The authors found that those with initial mild-to-moderate systolic dysfunction had a better chance for complete remodeling as compared with those who had an initial severe systolic dysfunction. Factor associated with incomplete cardiac remodeling was dopamine usage (OR 0.06, 95% CI 0.0049 to 0.7345, p=0.028).

Conclusion: Initial cardiac function is important and associated with complete cardiac remodeling. Those with initial mild-to-moderate systolic dysfunction have better remodeling and recovery than the one with initial severe systolic dysfunction.

Keywords: Myocarditis, Pediatric, Cardiac function, Cardiac remodeling

Received 25 August 2020 | Revised 15 September 2020 | Accepted 30 September 2020

J Med Assoc Thai 2020;103(10):977-86
Website: http://www.jmatonline.com

Myocarditis is an inflammatory process of cardiac myocyte caused by various etiologies. The current diagnosis of myocarditis proposed by the World Health Organization (WHO) is confirmed from histological, immunological, and immunohistochemical criteria[1,2]. Myocarditis can also be classified based on etiology, which is infectious, immunologic, and toxic[1,3]. Viral infection is the most common infectious etiology of acute myocarditis[2,4]. Compared with other acquired heart disease in children, myocarditis is rare and accounts for only 0.05% of all pediatric admissions to tertiary care hospital[5]. However, it carries significant cardiovascular morbidity and mortality from congestive heart failure, arrhythmias, cardiogenic shock, to sudden cardiac death[1,4]. The cardiac remodeling is a cellular change in myocyte and interstitium, which occurs after acute inflammation, resulting in adaptation of cardiac chambers shape,

Correspondence to:

Vallibhakara SA,

Research & Innonvation and Academic Affairs, ASEAN Institute for Health Development (AiHD), Mahidol University, Nakhon Pathom 73170, Thailand.

Phone: +66-82-5662211

Email: dr.sakda@gmail.com

ORCID: 0000-0001-5343-3297

How to cite this article:

Katanyuwong P, Srimuang S, Vallibhakara SA. Does Cardiac Remodeling in Pediatric Myocarditis Associated with Initial Cardiac Function? J Med Assoc Thai 2020;103:977-86.

doi.org/10.35755/jmedassocthai.2020.10.12128

size, and function of the heart after cardiac injury[6]. This process varies from patient-to-patient and can be accurately evaluated with non-invasive imaging such as echocardiogram or cardiac magnetic resonance imaging (MRI).

Based on the natural history of viral myocarditis, one-third of patients have a full recovery of cardiac function, one-third have a stable cardiac function, and one-third have deteriorated cardiac function, which ultimately needs cardiac transplantation[7]. Foerster et al demonstrated that cardiac remodeling occurred in 50% of patients with a biopsy-confirmed and probable myocarditis, with normalization of cardiac function detected by echocardiogram three years after diagnosis[8]. Because cardiac remodeling is the process that the heart has adapted after an inflammation, leading to ventricular dilation and hypertrophy, the factors associated with cardiac remodeling have been a major interest in the present study. There are many risk factors associated with high mortality in myocarditis[9-11]. The authors' investigator hypothesizes that cardiac remodeling in post-viral myocarditis has not been associated with initial cardiac function. Thus, the authors retrospectively evaluated initial cardiac function in patients with viral myocarditis and subsequently followed both clinical and imaging studies to the point of full recovery. The authors also investigated for the factor associated with normalization of cardiac function and survival of patients.

Materials and Methods

Study populations

The retrospective cohort was based on the Pediatric Cardiology Database. The investigators retrospectively reviewed the chart data of patients who were 15 years of age or younger and admitted to the Department of Pediatrics, Ramathibodi Hospital, Mahidol University, with a clinical diagnosis of acute myocarditis between January 2002 and December 2017. The medical records were searched for inpatient admissions with ICD-10 codes with myocarditis (I400: Infective myocarditis; I408: Other acute myocarditis; I409: Acute myocarditis, unspecified; I411: Myocarditis in viral disease classified elsewhere; I514: Myocarditis, unspecified; I012: Acute rheumatic myocarditis; I090: Rheumatic myocarditis). Based on the inclusion and exclusion criteria, the enrolled patients were reviewed for the clinical details, laboratories, echocardiographic data from the admission, and all subsequent follow-up until the most recent visit or when the patients had expired.

Inclusion criteria: Patients were diagnosed with acute myocarditis based on clinical presentations (acute heart failure, chest pain, syncope, and new-onset arrhythmias) and had at least two out of four of the following criteria. Based on the most recent proposed diagnostic classification of pediatric myocarditis, the authors' inclusion criteria have included all proposed standards (present of viral prodrome two to four weeks before presentation, presence of evidence of myocardial injury from electrocardiogram (EKG) or cardiac enzymes, presence of abnormal cardiac function from echocardiogram or cardiac MRI, and absence of a family history of cardiomyopathy), except myocardial biopsy[1]. The authors did not perform the routine cardiac biopsy at the authors' institution in suspected acute myocarditis due to a high risk of complications during the procedure.

Exclusion criteria: Patients with at least one or more of the following criteria were excluded from the present study such as the patient with presumed myocarditis with subsequent investigations identified the non-infectious causes such as acute rheumatic fever, Kawasaki disease, the patient with underlying systemic disorders with cardiac involvement or cardiac complication from treatment such as collagen vascular disease, cardiotoxicity from chemotherapy, or an endocrine disorder. Patient with underlying congenital heart disease or cardiomyopathy were also excluded.

Data collection

Data obtained from each patient medical record included demographic, presenting, and duration of symptoms, physical signs of heart failure, diagnostic tests, treatments, and outcomes. The clinical presentations were categorized according to the organ system listed as cardiovascular, respiratory, gastrointestinal (GI), and neurological systems. Initial blood tests included complete blood count (CBC), inflammatory markers (erythrocyte sedimentation rate [ESR] or C-reactive protein [CRP]), cardiac enzymes (creatine kinase myoglobin [CKMB] or troponin T), creatine kinase, NT-proBNP, lactate, arterial blood gas, blood urea nitrogen (BUN), creatinine, aspartate aminotransferase (AST), and alanine aminotransferase (ALT).

Viral studies, when available, were analyzed from polymerase chain reaction (PCR), serum antibody titer, ResPlex nasal swab, and stool enterovirus. Chest radiography were reviewed, including cardiothoracic ratio for cardiomegaly, presence, or absence of pulmonary venous congestion. Twelve-leads EKG

were reviewed for rate and rhythm, presence or absence of low voltage, abnormal ST-T changes, pathological Q wave, conduction abnormality, and ventricular hypertrophy.

All available recorded, digitalized echocardiographic data were reviewed by the primary investigator at the initial and subsequent study until the last study. If they were not available, data from echocardiographic records were used. Data measured, including left ventricular (LV) systolic function, LV end-diastolic dimension (LVEDD), LV posterior wall thickness during diastole (LVPWd), interventricular septum thickness during diastole (IVSd), and LV mass index were done in parasternal long and short-axis and apical views. LV systolic function was defined by ejection fraction (EF) or fraction shortening (FS) when EF was not available. LV systolic function was defined as normal when EF was 55% or greater. LV systolic dysfunction occurred when EF was less than 55% and was classified as mild systolic dysfunction (EF 41% to 54%), moderate systolic dysfunction (EF 31% to 40%) and severe systolic dysfunction (EF 30% or less)[12]. LVEDD was measured at the level of the posterior mitral leaflet and the end-diastole, defined by the peak of the R wave on the EKG and reported as Z score of LVEDD. LVPWd, IVSd, and LV mass index were reported as Z scores. Left atrium (LA) size, mitral and aortic valve regurgitation, and amount of pericardial effusion were assessed subjectively.

Patients were analyzed individually regarding the type of referral, length of hospital stay, and intensive care unit (ICU) stay. Each patient treatment was investigated, including medications used (inotropes, vasopressors, intravenous immunoglobulin [IVIG], methylprednisolone, diuretics, antiarrhythmic medications), mechanical ventilator support, pacemaker use (temporary or permanent), renal replacement therapy (continuous renal replacement therapy or peritoneal dialysis), intra-aortic balloon pump, and extracorporeal membrane oxygenation. The need for cardiopulmonary resuscitation was recorded.

Outcomes

Enrolled patients were longitudinally followed to determine the survival rate. The primary outcome for the study is to investigate the rate for complete remodeling in those with initial EF of less than 55%. The secondary outcome is to investigate the risk factors that predict complete or incomplete cardiac remodeling.

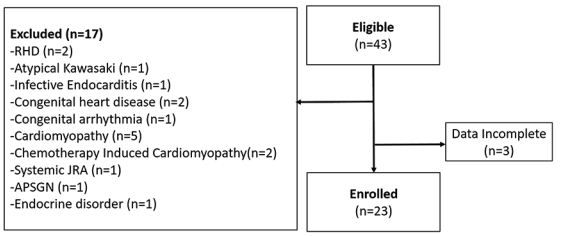

Figure 1. Flow of the study showed eligible subjects, excluded subjects, data incomplete, and enrolled subjects (n=23).

Statistical analysis

Statistical analysis was performed with Stata Statistical Software, version 16.0 (StataCorp LLC, College Station, TX, USA). The continuous variables are reported in mean and range, whereas the categorical variables are reported in count and percentage. The association between initial left ventricular ejection fraction (LVEF) and cardiac remodeling (LVEDD Z score and LVPWd Z score) was analyzed by logistic regression analysis to identify risk ratio. The factor associated with a complete remodeling of LV function was analyzed by logistic regression analysis to determine the odds ratio. All data with p-value less than 0.05 were considered as statistically significant. The survival of patients was analyzed and displayed with Kaplan-Meier curve analysis.

The authors asserted all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation of Mahidol University, Thailand, and with the Helsinki Declaration of 1975, as revised in 2008, and approved by the institutional committees (Committee on Human Rights Related to Research Involving Human Subjects, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Thailand, MURA2018/466).

Results

Of the 43 patients identified with acute myocarditis, 23 were enrolled, 20 were excluded, with three that had missing data (Figure 1). Patient demographic data are shown in Table 1. Of the 23 enrolled patients, 15 (65%) were female. The median age was two years (range 25 days to 14.5 years), and the median body weight was 10.6 kg (range 3.5 to 55 kg). Most patients (70%, n=16) lived in Bangkok and the central region and most, 18 (78%), were referred to the authors' hospital for definitive treatment.

Clinical presentations are shown in Table 2. Fever symptom was presented in 16 patients (69%). The

Table 1. Demographic data of enrolled patients (n=23)

Parameter	Values n (%)
Age; median (range)	2.08 (25 day to 14.5 year)
Sex: female	15 (65.22)
Weight (kg); median (range)	10.6 (3.5 to 55)
Height (cm); median (range)	85 (52 to 165)
Geographical region	
Bangkok	8 (34.78)
Central	8 (34.78)
East	4 (17.39)
Northeast	2 (8.70)
South	1 (4.35)

Table 2. Presenting symptoms and duration of enrolled patients (n=23)

Parameter	Values n (%)
Duration of all symptoms (hour); median (range)	24 (1 to 240)
Fever	16 (69.57)
Respiratory system	17 (73.91)
Dyspnea	13 (56.52)
Cough	10 (43.48)
Rhinorrhea	8 (34.78)
Cyanosis	6 (26.09)
Cardiovascular system	14 (60.87)
Shock	10 (43.48)
Chest pain	4 (17.39)
Edema	4 (17.39)
Palpitation	2 (8.70)
Presyncope/syncope	2 (8.70)
Cardiac arrest	2 (8.70)
Gastrointestinal system	12 (52.17)
Nausea/vomiting	10 (43.48)
Diarrhea	4 (17.39)
Abdominal pain	2 (8.70)
Central nervous system	9 (39.13)

involved organ system categorized symptoms found that the respiratory symptom was the most common presentation in acute myocarditis (74%, n=17) with dyspnea being the major presentation (56%, n=13). Cardiovascular symptoms presented in 14 (61%) with shock as the leading presentation (43%, n=10). GI symptoms were presented in 12 (52%) with nausea and vomiting as the most common presentation (43%, n=10). Central nervous system symptoms were the least common, presented in 9 (39%) patients. The median duration of all symptoms presented before admission was 24 hours (range, 1 to 240 hours).

Table 3. Initial laboratory tests, chest radiography, EKG of enrolled patients (n=23)

Parameter	Values Median (range)
WBC (/cumm)	11,000 (1,320 to 24,078)
Lactate	
Lactate (mmol/L)	1.75 (0.6 to 10.9)
Lactate (mg/dL)	24 (7 to 123)
Blood gas (pH)	7.38 (7.22 to 7.61)
BUN (mg/dL)	13 (1 to 49)
Cr (mg/dL)	0.54 (0.23 to 1.7)
AST (mg/dL)	146 (30 to 9396)
ALT (mg/dL)	86 (5 to 4215)
CK (U/L)	882 (103 to 4702)
CKMB	
CKMB fraction (U/L)	73.5 (46 to 449)
CKMB mass (ng/mL)	17.33 (1.87 to 84.99)
Troponin T (ng/mL)	0.38 (0.003 to 2.76)
Chest radiography	
CT ratio	0.60 (0.48 to 0.70)
Cardiomegaly; n (%)	21 (91.30)
Pulmonary venous congestion; n (%)	19 (82.61)
EKG; n (%)	
Rhythm	
• Normal sinus rhythm	8 (34.78)
• Sinus tachycardia	7 (30.43)
• Ventricular tachycardia	1 (4.35)
• Third degree AV block	4 (17.39)
• Atrial flutter with varying degree AV block	1 (4.35)
• First degree AV block	1 (4.35)
Interpretation	
• Low voltage	9 (39.13)
• Abnormal ST-T change	11 (47.83)
• Pathologic Q wave	1 (4.35)
• LVH	6 (26.09)
• RVH	4 (17.39)

WBC=white blood cell; BUN=blood urea nitrogen; Cr=creatinine; AST=aspatate aminotransferase; ALT=alanine aminotransferase; CK=creatine kinase; CKMB=creatine kinase myoglobin; CT=cardiothoracic ratio; EKG=electrocardiogram; AV=atrioventricular; LVH=left ventricular hypertrophy; RVH=right ventricular hypertrophy

The results of initial laboratory findings performed upon admission are shown in Table 3. The mean white

Table 4. Details of viral study

Parameter	Percentage tested	Percentage positive	Pathogen
Serum PCR (n=17)	73.91	23.59	Coxsakie B, EBV, CMV
Serum titer (n=12)	52.17	50.00	Coxsakie B, adenovirus, CMV, parvovirus B19, mycoplasma
Resplex nasal swab (n=17)	73.91	41.17	Rhino/enterovirus, adenovirus, parainfluenza virus, influenza virus

PCR=polymerase chain reaction; EBV=Epstein-Barr virus; CMV=cytomegalovirus

Table 5. Echocardiographic data of enrolled cases

Parameter	Values n (%)
Initial LVEF (%) (n=23); median (range)	20 (14 to 64)
Initial LVEF <55%	19 (83)
Initial LVEF ≥55%	4 (17)
Last LVEF (%) (n=14); median (range)	63.5 (41 to 76)
Last LVEF <55%	2 (14.3)
Last LVEF ≥55%	12 (85.7)
Last LVEDD Z score (n=11); median (range)	0.81 (–2.62 to 6.91)
Normal or Z score <2	8 (72.7)
Z score >2+	3 (27.3)
Last LVPWd Z score (n=9); median (range)	1.44 (–0.85 to 3.6)
Normal or Z score <2	7 (77.8)
Z score >2+	2 (22.2)

LVEF=left ventricular ejection fraction; LVEDD=left ventricular end-diastolic dimension during diastole; LVPWd=left ventricular posterior wall thickness during diastole

blood cell count of patients was 11,000/cumm (range 1,320 to 24,078). The cardiac enzyme was found to be a very sensitive test in myocarditis patients. For 14 patients who had CKMB mass analyzed, 12 (85%) had an elevated level. For 12 patients who had CKMB fraction analyzed, all 12 (100%) had elevated levels. Troponin T was analyzed in 22 patients, 21(95%) had an elevated level. Cardiomegaly (cardiothoracic ratio greater than 0.5) was detected on chest radiography in 21 patients (90%), pulmonary venous congestion in 19 patients (82%). The EKG revealed normal sinus rhythm only in eight patients (35%). Abnormal rhythms were sinus tachycardia in seven patients (30%), ventricular tachycardia (VT) in one patient (4%), and third-degree atrioventricular (AV) block in four patients (17%). The EKG findings revealed abnormal ST-T change (48%, n=11) and low voltage (39%, n=9).

Table 4 depicts the viral study on admission. Serum PCR was available in 17 patients and became positive in four (24%) in which cytomegalovirus (CMV) was the most common identified virus (75%, n=3). In serum, titer was tested in 12 patients and became positive in six (50%) with Coxsackie B as the commonly identified virus (33%, n=2). ResPlex nasal swab was available in 17 patients, which became positive in seven (41%) in which rhino or enterovirus (57%, n=4) was the commonly identified virus. The stool was sent to detect enterovirus by PCR (n=14) and the result was available in four patients, which all were negative.

Of 23 patients, 22 (96%) were admitted to pediatric ICU due to hemodynamic instability, one was admitted to the pediatric ward for observation. Most patients received dobutamine (82%, n=19), IVIG (87%, n=20), and diuretic (96%, n=22). Four patients (17%) received antiarrhythmic drugs due to arrhythmias. The mechanical ventilator was used in most patients (83%, n=19), with the median duration of using a mechanical ventilator for four days (range 1 to 26). A temporary pacemaker was used in three patients, with the median duration for seven days (range 6 to 12). Of the 23 enrolled patients, 15 (65%) survived to discharge, six (26%) died during the admission with the median hospital stays of six days (range 2 to 27) and two patients (9%) were transferred to another hospital for cardiac transplantation. The median length of hospital stays was 11 days (range 1 to 66). Of 15 survivors, three patients progressed to dilated cardiomyopathy. One dilated cardiomyopathy patient died from influenza type A pneumonia at 40 months after the initial diagnosis of myocarditis.

From the echocardiographic data of 23 enrolled patients, most patients (83%, n=19) had an initial LVEF of less than 55%, whereas a minority of patients (17%, n=4) had a normal LVEF of 55% or greater. All four patients with normal initial LVEF had been followed since the discharge until the last visit, and everyone still has had a normal LVEF. Whereas 19 patients with abnormal initial LVEF, eight (40%) have had a complete remodeling of cardiac function, but 11 (60%) have had incomplete cardiac remodeling, as shown in Table 5. During the most recent follow-up, which exclude seven death and two referral, the

Table 6. Association between an initial impaired cardiac function (LVEF <55%), cardiac size (last LVEDd Z score >2+) and wall thickness remodeling (last LVPWd Z score >2+)

Parameter	Risk ratio (95% CI)	p-value
Last LVEDD Z score >2+	1.64 (0.30 to 8.86)	0.568
Last LVPWd Z score >2+	1.36 (0.24 to 7.66)	0.725

LVEDD=left ventricular end-diastolic dimension during diastole; LVPWd=left ventricular posterior wall thickness during diastole; CI=confidence interval

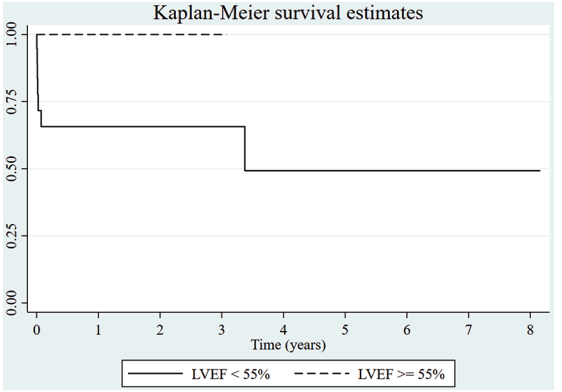

Figure 2. The survival rate between LVEF <55% vs. LVEF ≥55% was shown with the Kaplan-Meier curve.

authors found two patients (14%) with incomplete cardiac remodeling in LV function (assessed with last LVEF of less than 55%), three patients (27%) with incomplete cardiac remodeling in LV cavity size (assessed with last LVEDD Z score >2+), and two patients (22%) with incomplete cardiac remodeling in LV wall thickness (assessed with last LVPWd Z score >2+).

An association between initial impaired cardiac function (LVEF of less than 55%) and chance of cardiac remodeling was analyzed and reported in Table 6. Until the most recent follow-up, those patients who had abnormal initial LVEF, had a chance of having an incomplete cardiac remodeling, dilated LV (LVEDd Z score >2+), and hypertrophied LV (LVPWd Z score >2+) with a risk ratio of 1.64 and 1.36 respectively. The authors found that those patients with abnormal initial LVEF of less than 55% had a risk of having incomplete cardiac remodeling. But the risk has not been validated and showed in the present study.

Interesting factors were analyzed for the association with a complete remodeling of LV or normalization of LV function in patients with abnormal initial LVEF. The only statistically significant factor associated with incomplete remodeling was dopamine. Patients who received dopamine had a decreased probability of having normalization of LVEF (OR 0.06, 95% CI 0.0049 to 0.7345, p=0.028).

Twenty-three patients who were diagnosed with acute myocarditis in the present study had been followed. The survival rate was shown with the Kaplan-Meier curve (Figure 2). The authors found the patients with initial normal LVEF patients had a survival rate of 100% at three years after diagnosis. In contrast, the patients with an abnormal initial LVEF had a survival rate of 70% at three years, which declined to 50% at eight years after diagnosis.

Discussion

Acute myocarditis in children is a rare but essential health issue due to its high morbidity and mortality from the disease itself and delay diagnosis and transportation to a medical facility. The present study has demonstrated a retrospective cohort of 23 patients with acute myocarditis diagnosed between 2002 and 2017. The present study data has shown a high incidence of myocarditis at a young age with a median age of presentation at 2-year-old, which is similar to studies from Asian countries[13,14]. There is a difference in demographic data from the U.S. bimodal distribution study in the age of presentation[15]. Most patients usually present with respiratory and cardiovascular symptoms, which lead to early detection of acute myocarditis, whereas half of the patients present with GI symptoms from the present study data. Recognition of GI symptoms as a subtle manifestation of acute myocarditis is significant because delay in diagnosis can lead to death[9]. Neurological symptoms are detected in one-third of the patients, which is rarely described in other studies.

Soongswang et al[16] identified the cutoff point of troponin T for the diagnosis of acute myocarditis. During the study, the authors' institution used standard troponin T as a diagnostic test. The present study data has revealed a median troponin T of 0.38 ng/mL (range, 0.003 to 2.76). Using the cutoff point at 0.052 ng/mL, the authors found that 17 patients (77%) had a positive value for myocarditis, whereas 5 (23%) had a negative value. Moreover, troponin T could help identify those who have a complete cardiac remodeling. Patients with complete cardiac remodeling have a higher level of troponin T at 0.8 ng/mL (range 0.033 to 2.76) compare to those with incomplete cardiac remodeling at 0.144 ng/mL (range 0.046 to 2.25), respectively. The prognostic

value of troponin T is similar to a study by Kim et al[10]. EKG is one diagnostic tool for diagnosing acute myocarditis. The present study revealed an abnormal EKG for 65% in which sinus tachycardia is the most common identified rhythm. Hemodynamics significant arrhythmia, third-degree AV block, and VT presented in four (17%) and one (4%) patient, respectively. Three patients with third-degree AV block required a temporary pacemaker with a median duration of seven days (range 6 to 12 days), whereas one patient did not require a pacemaker. The four patients had a complete resolution of third-degree AV block and return to normal sinus rhythm. One patient with VT died from cardiac arrest. In general, third degree AV block has a better prognosis than VT in the present study.

The present study has introduced three essential findings. The first finding is the remodeling of initial cardiac function. Due to the high mortality of acute myocarditis, the initial cardiac function has been in the major interest of the present study. The authors found that 19 (83%) patients had an abnormal initial cardiac function (EF of less than 55%), while 4 (17%) had a normal initial cardiac function (EF of 55% or more). Most patients received appropriate care according to the hemodynamics status, including IVIG (87%). Those patients with normal initial cardiac function remain adequate hemodynamics throughout the hospital stay and continue to do well until the most recent follow-up with remaining normal cardiac function.

In contrast, those with abnormal initial cardiac function, eight (40%) patients have a complete cardiac function remodeling (EF of 55% or more). Eleven (60%) patients have incomplete cardiac function remodeling. Six patients died during hospitalization and two patients were referred to another institution for cardiac transplantation. The three patients left in this group has been followed and finally became to develop dilated cardiomyopathy. One of these patients died of influenza type A pneumonia. Therefore, the initial cardiac function is an important factor in predicting the survival of the patients. Even those with impaired cardiac function have a 40% chance of having a complete remodeling in long-term outcomes. The present study data is similar to the study by Foerster et al[8] that revealed a complete echocardiographic normalization of biopsy-confirmed acute myocarditis at the rate of 54% at 3-year after the initial diagnosis.

The second finding is the factors associated with complete cardiac remodeling (Table 7). By performing a subgroup analysis, the authors found two interesting factors that associated with a complete remodeling. First is using of inotropic drugs, especially dopamine, which is associated with an incomplete remodeling (OR 0.06, 95% CI 0.0049 to 0.7345, p=0.028). Norepinephrine had been used in the authors' patients and had shown a similar finding as dopamine but is not statistically significant. This may be related to the severity of initial cardiac function that the more severely depressed cardiac function leads to using of dopamine. When the authors performed a subgroup analysis of the initial cardiac function, the authors found those with mildly-to-moderately systolic dysfunction (EF 31% to 54%) had a complete remodeling compare with those who had a severely systolic dysfunction (EF of 30% or less). However, this finding is not statistically significant.

The third finding is the association between patients who had an initial abnormal cardiac function and the chance of developing dilated cardiomyopathy. Table 6 shows that those patients with initial impaired cardiac function had a risk of developing dilated LV in the long-term follow-up (RR 1.64, 95% CI 0.30 to 8.86, p=0.568). The present study data is not statistically significant and could be due to a small number of patients and the short time of follow-up. The present study demonstrated short-term mortality, defined by mortality within 30 days after admission, in six (26%) patients, and long-term mortality, defined by mortality beyond 30 days after admission, in one (4%) patient. Those patients with normal initial cardiac function have survival at 100% after a 3-year follow-up. In contrast, those with abnormal initial cardiac function has a survival of 70% at three years and 50% at eight years after initial diagnosis.

The present study has some limitations. First, data and clinical findings were studied retrospectively. Some echocardiography data was not in the digital system and was unable to analyze off-line. Second, the present study was a small sample size due to the rarity of the disease, limiting complex statistical analysis. The future suggestion is to do a multi-center, prospective cohort of acute myocarditis patients to validate the current era's cardiac remodeling, which included new treatment modalities such as extracorporeal membrane oxygenation (ECMO).

Conclusion

In conclusion, the authors found that initial cardiac function is important and has been associated with a complete cardiac remodeling in patients with initial mild-to-moderate systolic function.

Table 7. Factors associated with complete remodeling of LV function in patients with initial EF <55% (n=19)

Parameters	Complete remodeling Last EF ≥55% n (%)	Incomplete remodeling Last EF <55% n (%)	OR (95% CI)	p-value
Age (day); median (range)	1,811.37 (91.5 to 5,296.5)	761 (25 to 4,900.75)	1.00 (0.99 to 1.00)	0.37
Sex				
Female	5 (38.46)	8 (61.54)	1	
Male	3 (50.00)	3 (50.00)	1.60 (0.23 to 11.27)	0.64
Weight (kg); median (range)	21 (4.5 to 50)	10 (3.5 to 41)	1.04 (0.97 to 1.11)	0.25
Symptoms				
Fever	6 (42.11)	7 (53.85)	1.71 (0.23 to 12.89)	0.60
Respiratory system				
Dyspnea	3 (27.27)	8 (72.73)	0.25 (0.03 to 1.58)	0.13
Cough	5 (62.5)	3 (37.5)	4.44 (0.63 to 31.29)	0.13
Rhinorrhea	3 (50.00)	3 (50.00)	1.60 (0.23 to 11.27)	0.64
Cyanosis	3 (50.00)	3 (50.00)	1.60 (0.23 to 11.27)	0.64
Cardiovascular system				
Shock	4 (44.44)	5 (57.89)	1.2 (0.19 to 7.44)	0.84
Chest pain	2 (66.67)	1 (33.33)	3.33 (0.25 to 45.11)	0.36
Edema	1 (25.00)	3 (75.00)	0.38 (0.32 to 4.55)	0.45
Gastrointestinal system				
Nausea/vomiting	4 (40.00)	6 (60.00)	0.83 (0.13 to 5.17)	0.84
Central venous system				
Seizure	3 (60.00)	2 (40.00)	2.7 (0.33 to 21.98)	0.35
Headache	1 (50.00)	1 (50.00)	1.43 (0.08 to 26.89)	0.81
Alteration of consciousness	1 (50.00)	1 (50.00)	1.43 (0.08 to 26.89)	0.81
Initial laboratory; median (range)				
WBC (/cumm)	11,130 (6,590 to 18,400)	9,800 (1,320 to 24,078)	1.00 (0.99 to 1.00)	0.36
CKMB mass (ng/mL)	11.8 (4.15 to 34.87)	24.74 (1.87 to 56.55)	0.97 (0.89 to 1.05)	0.48
CKMB fraction (U/L)	86 (46 to 129)	74.5 (73 to 449)	0.99 (0.97 to 1.01)	0.45
Troponin T (ng/mL)	0.8 (0.033 to 2.76)	0.144 (0.046 to 2.25)	1.70 (0.49 to 5.83)	0.40
CK (U/L)	825.5 (248 to 1,808)	2,516.5 (227 to 4,702)	0.99 (0.99 to 1.00)	0.12
Lactate (mmol/L)	2 (0.6 to 10.9)	1.65 (0.9 to 4.9)	1.23 (0.74 to 2.06)	0.43
Lactate (mg/dL)	98 (7 to 123)	17 (8 to 50)	1.03 (0.99 to 1.07)	0.11
Blood gas (pH)	7.4 (7.259 to 7.53)	7.37 (7.22 to 7.61)	1.90 (0.00 to 17,906.03)	0.89
BUN (mg/dL)	19 (12 to 34)	12 (7 to 49)	1.00 (0.92 to 1.09)	0.94
Cr (mg/dL)	0.68 (0.5 to 1.7)	0.5 (0.3 to 1.7)	3.67 (0.36 to 37.83)	0.27
AST (mg/dL)	154.5 (30 to 9,396)	221 (42 to 2,720)	1.00 (0.99 to 1.00)	0.44
ALT (mg/dL)	97 (5 to 4,215)	116.5 (33 to 1,569)	1.00 (0.99 to 1.00)	0.43
Viral study				
Serum PCR positive	3 (75.00)	1 (25.00)	5.25 (0.40 to 68.95)	0.21
Serum titer positive	3 (60.00)	2 (40.00)	1 (0.08 to 12.56)	1
Resplex nasal swab +ve	3 (60.00)	2 (40.00)	4.50 (0.41 to 49.63)	0.22

WBC=white blood cell; BUN=blood urea nitrogen; Cr=creatinine; AST=aspatate aminotransferase; ALT=alanine aminotransferase; CK=creatine kinase; CKMB=creatine kinase myoglobin; CT=cardiothoracic ratio; EKG=electrocardiogram; LVH=left ventricular hypertrophy; RVH=right ventricular hypertrophy; PCR=polymerase chain reaction; CPR=cardiopulmonary resuscitation; LVEF=left ventricular ejection fraction; EF=ejection fraction; OR=odds ratio; CI=confidence interval

* Significant value when p<0.05

Table 7. (continued)

Parameters	Complete remodeling Last EF ≥55% n (%)	Incomplete remodeling Last EF <55% n (%)	OR (95% CI)	p-value
Chest Radiography				
CT ratio; median (range)	0.585 (0.55 to 0.67)	0.62 (0.48 to 0.7)	0.00 to 212,714.7	0.48
Pulmonary congestion	7 (41.18)	10 (58.82)	0.7 (0.04 to 13.18)	0.81
EKG				
Sinus rhythm	1 (16.67)	5 (83.33)	0.17 (0.01 to 1.90)	0.15
Sinus tachycardia	3 (50.00)	3 (50.00)	1.6 (0.23 to 11.27)	0.64
Low voltage	3 (42.86)	4 (57.14)	0.19 (0.01 to 2.66)	0.22
Abnormal ST-T change	5 (50.00)	5 (50.00)	1 (0.13 to 7.57)	1
LVH	1 (16.67)	5 (83.33)	0.1 (0.01 to 1.29)	0.08
RVH	1 (33.33)	2 (66.67)	0.33 (0.02 to 5.03)	0.43
Treatment				
Dopamine	3 (23.08)	10 (76.92)	0.06 (0.01 to 0.73)	0.03*
Norepinephrine	1 (14.29)	6 (85.71)	0.12 (0.01 to 1.32)	0.08
Adrenaline	5 (38.46)	8 (61.54)	0.62 (0.09 to 4.40)	0.64
Milrinone	5 (41.67)	7 (58.33)	0.95 (0.14 to 6.28)	0.96
Nitroglycerin	2 (40.00)	3 (60.00)	0.89 (0.11 to 7.11)	0.91
Anti-arrhythmic drug	2 (50.00)	2 (50.00)	1.5 (0.1636 to 13.7492)	0.72
Mechanical ventilator usage; median (range)	7 (41.18)	10 (58.82)	0.7 (0.04 to 13.18)	0.81
Mechanical ventilator duration (day); median (range)	7 (3 to 10)	3.5 (1 to 26)	1.01 (0.86 to 1.19)	0.88
Synchronize cardioversion	1 (50.00)	1 (50.00)	1.43 (0.08 to 26.89)	0.81
CPR	1 (20.00)	4 (80.00)	0.25 (0.02 to 2.84)	0.26
Length of hospital stay (day); median (range)	20.5 (7 to 66)	6 (1 to 46)	1.0554 (0.98 to 1.14)	0.16
Duration of all symptoms (hour); median (range)	24 (9 to 120)	48 (1 to 240)	0.99 (0.97 to 1.01)	0.23
Echo data; median (range)				
Initial LVEF (%)	40 (16 to 54)	25 (14 to 51)	1.06 (0.98 to 1.14)	0.14

WBC=white blood cell; BUN=blood urea nitrogen; Cr=creatinine; AST=aspatate aminotransferase; ALT=alanine aminotransferase; CK=creatine kinase; CKMB=creatine kinase myoglobin; CT=cardiothoracic ratio; EKG=electrocardiogram; LVH=left ventricular hypertrophy; RVH=right ventricular hypertrophy; PCR=polymerase chain reaction; CPR=cardiopulmonary resuscitation; LVEF=left ventricular ejection fraction; EF=ejection fraction; OR=odds ratio; CI=confidence interval

* Significant value when p<0.05

What is already known on this topic?

Viral myocarditis from the current report found that one-third of patients have deteriorated cardiac function, which ultimately needs cardiac transplantation. Previous studies found that the process of cardiac remodeling occurred in approximately about 50% of the patients with biopsy-confirmed myocarditis. Cardiac remodeling is the process that the heart has adapted after an inflammation, leading to ventricular dilation and hypertrophy, and finally affects the cardiac function in the long term. The factors associated with cardiac remodeling have been studied and the association between risk factors and the remodeling process have been questioned. Currently, researchers do not know much about how the remodeling process affects cardiac function in survival patients.

What this study adds?

This study showed the important factors affecting cardiac function after the inflammatory process. Those factors can predict the initial cardiac function and association with the complete cardiac remodeling in the long term if the patients with initial mild-to-moderate systolic dysfunction were found on first clinical presentation.

Acknowledgement

The authors would like to acknowledge Ms. Sukanya Siriyotha, who performed the statistical analysis, and Mr. Uthen Bunmee, who provided echocardiographic data records.

Funding disclosure

This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

Conflicts of interest

The authors declare no conflict of interest.

References

1. Canter CE, Simpson KE. Diagnosis and treatment of myocarditis in children in the current era. Circulation 2014;129:115-28.
2. Pollack A, Kontorovich AR, Fuster V, Dec GW. Viral myocarditis--diagnosis, treatment options, and current controversies. Nat Rev Cardiol 2015;12:670-80.
3. Singh R, Yeh J, Price J. Diagnosis and treatment strategies for children with myocarditis. Prog Pediatr Cardiol 2016;43:23-30.
4. Simspson KE, Anwar S, Canter CE. Myocarditis. In: Allen HD, editor. Moss & Adams' heart disease in infants, children, and adolescents, including the fetus and young adult. 9th ed. Philadelphia: Wolters Kluwer Health; 2016. p. 1313-30.
5. Klugman D, Berger JT, Sable CA, He J, Khandelwal SG, Slonim AD. Pediatric patients hospitalized with myocarditis: a multi-institutional analysis. Pediatr Cardiol 2010;31:222-8.
6. Cohn JN, Ferrari R, Sharpe N. Cardiac remodeling--concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. Behalf of an International Forum on Cardiac Remodeling. J Am Coll Cardiol 2000;35:569-82.
7. Magnani JW, Dec GW. Myocarditis: current trends in diagnosis and treatment. Circulation 2006;113:876-90.
8. Foerster SR, Canter CE, Cinar A, Sleeper LA, Webber SA, Pahl E, et al. Ventricular remodeling and survival are more favorable for myocarditis than for idiopathic dilated cardiomyopathy in childhood: an outcomes study from the Pediatric Cardiomyopathy Registry. Circ Heart Fail 2010;3:689-97.
9. Butts RJ, Boyle GJ, Deshpande SR, Gambetta K, Knecht KR, Prada-Ruiz CA, et al. Characteristics of clinically diagnosed pediatric myocarditis in a contemporary multi-center cohort. Pediatr Cardiol 2017;38:1175-82.
10. Kim G, Ban GH, Lee HD, Sung SC, Kim H, Choi KH. Left ventricular end-diastolic dimension as a predictive factor of outcomes in children with acute myocarditis. Cardiol Young 2017;27:443-51.
11. Abe T, Tsuda E, Miyazaki A, Ishibashi-Ueda H, Yamada O. Clinical characteristics and long-term outcome of acute myocarditis in children. Heart Vessels 2013;28:632-8.
12. Tissot C, Singh Y, Sekarski N. Echocardiographic evaluation of ventricular function-for the neonatologist and pediatric intensivist. Front Pediatr 2018;6:79.
13. Matsuura H, Ichida F, Saji T, Ogawa S, Waki K, Kaneko M, et al. Clinical features of acute and fulminant myocarditis in children - 2nd nationwide survey by Japanese Society of Pediatric Cardiology and Cardiac Surgery. Circ J 2016;80:2362-8.
14. Wu MH, Wu ET, Wang CC, Lu F, Chen HC, Kao FY, et al. Contemporary postnatal incidence of acquiring acute myocarditis by age 15 years and the outcomes from a nationwide birth cohort. Pediatr Crit Care Med 2017;18:1153-8.
15. Ghelani SJ, Spaeder MC, Pastor W, Spurney CF, Klugman D. Demographics, trends, and outcomes in pediatric acute myocarditis in the United States, 2006 to 2011. Circ Cardiovasc Qual Outcomes 2012;5:622-7.
16. Soongswang J, Durongpisitkul K, Nana A, Laohaprasittiporn D, Kangkagate C, Punlee K, et al. Cardiac troponin T: a marker in the diagnosis of acute myocarditis in children. Pediatr Cardiol 2005;26:45-9.