A retrospective study: Cardiac MRI of fulminant myocarditis in children - Can we evaluate the short-term outcomes?

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Background: Fulminant myocarditis (FM) is an inflammatory disease of the myocardium that results in ventricular systolic dysfunction and causes acute-onset heart failure. Cardiac magnetic resonance (CMR) has become the primary noninvasive tool for the diagnosis and evaluation of myocarditis. The aim of our study was to assess the CMR findings at different course of FM and the short-term outcomes of fulminant myocarditis (FM) in children.

Methods: 8 FM children with CMR examinations were included in our study. Initial baseline CMR was performed 10 days (range, 7 to 20 days) after onset of FM and follow-up CMR after 55 days (range, 33 to 75 days). Cardiac morphology and function and myocardial tissue characterization at baseline and follow-up CMR were compared using paired T-test and Mann-Whitney U test. The clinical data and initial CMR findings were also compared to predict short-term outcomes.

Results: The median age of eight FM children was 8.5 years old(range, 3 to 14).The initial CMR findings were most common with early gadolinium enhancement (EGE, 100 %), followed by signal increasing on T2WI and late gadolinium enhancement (LGE, 87.5%), increased septal thickness (75.0%) and increased left ventricle ejection fraction (LVEF, 50.0%). Only three LGE (37.5%), one signal increasing on T2WI (12.5%) and one increased LVEF (12.5%) were found at follow-up. Statistically significant differences were found between initial and follow-up CMR abnormalities in the septal thickness, left ventricular end-diastolic diameter (LVEDD), end-systolic volume (ESV), LVEF, left ventricular mass, T2 ratio and LGE area (P=0.011, P=0.042, P=0.016, P=0.001, P=0.003, P=0.011, P=0.020).The children with full recovery performed higher incidence of III° atrioventricular block (AVB, 5 cases VS 0 case) and smaller LGE area (104.0±14.5 mm2 VS 138.0±25.2 mm2) at baseline CMR.

Discussion: The CMR findings of FM in children were characteristic and useful for early diagnosis. Full recovery of clinical manifestations, immunological features and CMR findings could be found in most FM children. The presence of III° AVB and smaller LGE area at baseline CMR might indicate better short-term outcomes.

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15   **Abstract**

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17   that results in ventricular systolic dysfunction and causes acute-onset heart failure.

18   Cardiac magnetic resonance (CMR) has become the primary noninvasive tool for the

19   diagnosis and evaluation of myocarditis. The aim of our study was to assess the CMR

20   findings at different course of FM and the short-term outcomes of fulminant myocarditis

21   (FM) in children.

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23   baseline CMR was performed 10 days (range, 7 to 20 days) after onset of FM and follow-

24   up CMR after 55 days (range, 33 to 75 days). Cardiac morphology and function and

25   myocardial tissue characterization at baseline and follow-up CMR were compared using

26   paired T-test and Mann-Whitney U test. The clinical data and initial CMR findings were

27   also compared to predict short-term outcomes.

28   **Results:** The median age of eight FM children was 8.5 years old(range, 3 to 14).The

29   initial CMR findings were most common with early gadolinium enhancement (EGE, 100

30   %), followed by signal increasing on T2WI and late gadolinium enhancement (LGE,

31   87.5%), increased septal thickness (75.0%) and increased left ventricle ejection fraction

32   (LVEF, 50.0%). Only three LGE (37.5%), one signal increasing on T2WI (12.5%) and

33   one increased LVEF (12.5%) were found at follow-up. Statistically significant differences

34   were found between initial and follow-up CMR abnormalities in the septal thickness, left

35   ventricular end-diastolic diameter (LVEDD), end-systolic volume (ESV), LVEF, left

36   ventricular mass, T2 ratio and LGE area (P=0.011, P=0.042, P=0.016, P=0.001,

37   P=0.003, P=0.011, P=0.020).The children with full recovery performed higher incidence

38   of III° atrioventricular block (AVB, 5 cases VS 0 case) and smaller LGE area (104.0±14.5

39   mm^2 VS 138.0±25.2 mm^2) at baseline CMR.

40   **Discussion:** The CMR findings of FM in children were characteristic and useful for early

41   diagnosis. Full recovery of clinical manifestations, immunological features and CMR

42   findings could be found in most FM children. The presence of III° AVB and smaller LGE

43   area at baseline CMR might indicate better short-term outcomes.

44

Introduction

46 Fulminant myocarditis (FM) is an inflammatory disease of the myocardium that results in

47 ventricular systolic dysfunction and causes acute-onset heart failure (Gupta S, et al.,

48 2008; Felker et al., 2000; Ginsberg&Parrillo, 2013).Despite the initial severe presentation,

49 excellent short-term and long-term outcomes of FM with complete recovery of clinical

50 manifestations and cardiac function have been found in the adult population (Felker et al.,

51 2000; Ginsberg&Parrillo, 2013; McCarthy et al., 2000). While in the pediatric population,

52 the outcomes of FM are controversial, with the mortality varied from 9.1% to 48.4%

53 (Amabile N et al., 2006; Saji et al., 2012; Lee et al., 2014).

54 Dallas Criteria, the standardized histologic criteria, have been identified as the gold

55 standard in the diagnosis of myocarditis (Cooper et al., 2007). Because of the

56 disadvantages of invasive procedure, sampling error, severe complications and poor

57 inter-observer agreement (Chow et al., 1989; Hauck, Kearney&Edwards, 1989; Shirani,

58 Freant&Roberts, 1993), its application was limited only if it might alter management or

59 offer a meaningful prognosis (Cooper et al., 2007).

60 Nowadays, cardiac magnetic resonance (CMR) has become the primary noninvasive

61 tool for the diagnosis and evaluation of myocarditis (Bruder et al., 2009). The diagnostic

62 CMR criteria for myocarditis, Lake Louise Criteria, have been proposed with a diagnostic

63 accuracy of 78% (Friedrich et al., 2009). However, to our knowledge, few studies have

64 reported the CMR findings of FM in adults, and scarce in children. Besides, the recovery

65 of myocardial tissue characterization was seldom considered in the outcomes of FM.

66 The aim of our study was to assess the CMR findings at different course of FM in

67 children, to evaluate the short-term outcomes of FM from the aspect of clinical

68 manifestations, immunological features and initial CMR findings, to find out the

69 predictors of the short-term outcomes of FM.

70

71 **Materials & Methods**

72 In this retrospective study, all FM children with CMR examinations in Shandong

73 Provincial Hospital from January 2010 to December 2015 were assessed and eight

74 children with initial and follow-up CMR examinations were enrolled in our study. Written

75 informed consent was obtained from the parents of FM children. The median age of eight

76 children was 8.5 years old (range, 3 to 14). All eight FM children were clinically

77 diagnosed by an experienced pediatrician who had more than 30 years working

78 experience and satisfied following criteria:(1) Recent history of viral prodromata with

79 fever lasting<2 weeks;(2)Acute onset (time interval between onset and hospital

80 admission <7 days); (3) Severe heart failure (at minimum requiring intravenous inotropic

81 support), cardiac shock or severe arrhythmia; (4) Left ventricular dysfunction assessed

82 by echocardiography; (5) Exclusion criteria: acute or chronic myocarditis, other non-

83 ischemic cardiomyopathy,   congenital heart disease, myocardial infarctions, cardiac

84 tumors, autoimmune disease or extra-cardiac diseases that could explain the clinical

85 manifestations (Lieberman et al., 1991; Ramachandra et al., 2010). Clinical

86 manifestations, immunological features, viral serology, electrocardiography and initial

87 and follow-up CMR findings and treatment of eight children were recorded. The study

88 protocol was approved by the institutional ethics committee of Shandong Medical

89 Imaging Research Institute (NO.2016-001)

90 CMR imaging protocol

91 CMR imaging was performed with a clinical3.0-T MR scanner (Achieva 3.0T TX; Philips

92 Healthcare, Best, The Netherlands) equipped with dual-source parallel radiofrequency

93 transmission. A 16-channel torso phased-array receiver coil was used for signal

94 reception. All data acquisition was retrospective ECG gated. Children (>7 years) who

95 could control breathing would acquire data with respiratory gating. Small children (<7

96 years) would be sedated with 10% chloral hydrate and examined under free-breathing

97 condition. Multiple signal averaging were applied in children with free-breathing scanning

98 to "average out" the respiratory motion and the through plane motion artifacts.

99 (Krishnamurthy R, et al., 2015; Abd-Elmoniem KZ, et al., 2011)

100 The CMR imaging protocols included cine imaging, T2-weighted imaging, early

101 gadolinium enhancement (EGE) and late gadolinium enhancement (LGE). Cine images

102 in three long axis (4-chamber, 2-chamber and 3-chamber) and sequential short axis (SA)

103 from ventricular base to apex were acquired with balanced steady state free precession

104 (b-SSFP) sequences. Imaging parameters were: repetition time (TR), 3.0 ms; echo time

105 (TE), 1.5 ms; flip angle (FA), 45°;field of view (FOV),220×280 mm^2; matrix,200×256;slice

106 thickness: 8 mm without slice gap; number of signal averages (NSAs), 1 (breath-hold

107 children) or 3 (free-breathing children).T2-weighted images were acquired in4-chamber

108 and SA with a triple inversion recovery fast spin echo sequence to evaluate myocardial

109 edema. Imaging parameters were: TR, 2 × beats ms; TE, 60 ms; FA, 90°;FOV, 220×280

110 mm²; matrix, 208×167;slice thickness: 8 mm. Pre and post T1fast spin echo (FSE)

111 imaging were acquired in 4-chamber before and after an intravenous bolus of 0.1

112 mmol/kg Gd-DTPA (Magnevist, Bayer, Germany)within 3 minutes. T1 FSE imaging

113 parameters were: TR, 1 × beats ms; TE, 10 ms; FA, 90°; FOV, 220×280 mm²; matrix,

114 228×171; slice thickness: 8 mm.After EGE, another 0.1 mmol/kg Gd-DTPA was injected

115 and LGE were performed in three long axis and sequential SA7-10 minutes later, using

116 an a 3D phase-sensitive inversion recovery (3D-PSIR) sequence. Imaging parameters

117 were: TR, 5.3 ms; TE, 2.5 ms; FA, 25°; FOV, 220×280 mm²; matrix, 156×150; slice

118 thickness: 8 mm; NSAs, 1 (breath-hold children) or 3 (free-breathing children) .

119 CMR imaging analysis

120 The left ventricle (LV) morphology and cardiac function were quantitatively evaluated on

121 the cine images with the work station (EWS, Philips Healthcare). Two experienced CMR

122 radiologists assessed the CMR findings independently and consensus was reached. The

123 endocardial and epicardial contours of LV in the sequential SA of cine images were

124 adjusted manually and the following LV cardiac functional parameters were

125 automatically acquired: the end-diastolic volume (EDV), end-systolic volume (ESV),

126 ejection fraction (EF), and LV mass. The papillary muscles and trabeculations were

127 included as part of LV mass (Buechel et al., 2009). Impaired LV systolic function were

128 considered if EF<50% and enhanced LV systolic function if EF>70%. Left ventricular

129 end-diastolic diameter (LVEDD) was measured in 4-chamber. The end-diastolic mid-

130 septal thickness was measured and averaged in 4-chamberand SA of cine images.

131 Increased septal thickness was considered by visual comparison at different stages of

132 FM.

133 In 4-chamber and SA of T2 weighted images, regional or global signal intensity of LV

134 myocardium was measured as well as the signal intensity of subscapularis muscle in the

135 same slice, excluding high signal of inadequately suppressed slowly flowing cavitary

136 blood. The global signal intensity of LV myocardium as well as subscapularis muscle in

137 4-chamber of pre- and post-T1 weighted images were also measured. Then the T2 ratio

138 and EGE ratio were calculated according to Lake Louise criteria (Friedrich et al., 2009).

139 Myocardial edema and hyperemia were considered if T2 ratio>1.9 and EGE

140 ratio>4.0.The segments, patterns and areas of myocardial necrosis/fibrosis on the LGE

141 images were assessed and recorded using the 17-segment American Heart Association

142 (AHA) model (Cerqueira et al., 2002).

143 Short-term outcomes

144 The short-term outcomes of FM in children were evaluated according to clinical

145 manifestations, immunological features and CMR findings at follow-up CMR. Poor short-

146 term outcomes were defined as persistent clinical manifestations, abnormal levels of

147 myocardial enzymes and CMR abnormalities within 3 months. Then the clinical data and

148 imaging findings at baseline CMR of FM were evaluated to find out the predictors of

149 short-term outcomes of FM.

150 Statistical analysis

151 Categorical data were reported as percentage, and continuous data as the mean ±

152 standard deviation (SD) or median (range). The normality of the variables was assessed

153 by the Shapiro–Wilk test. Paired T-test and Mann-Whitney U test were used to compare

154 the intervals from onset to CMR examinations, the levels of cardiac troponin T (cTnT)

155 and brain natriuretic peptide (BNP), cardiac morphology and function parameters and

156 myocardial tissue characterization (T2 ratio, EGE ratio and LGE) at baseline and follow-

157 up CMR of FM. All statistical tests were two-sided, and *P*-values less than 0.05 were

158 considered as statistical significant. The clinical data and initial CMR findings between

159 FM children with different short-term outcomes were directly compared because of small

160 sample size.

161 The statistical analysis was carried out using SPSS version 19.0 (SPSS INC, Chicago,

162 Illinois)

163

164 **Results**

165 Patient characteristics

166 Patient characteristics and clinical data of FM at presentation were showed in Table 1.

167 Viral serology was showed in Table S1. Echocardiography was performed within 72

168 hours of the onset and the LVEF of FM children were 36.5±8.2 %. The clinical

169 manifestations of FM were varied, including heart failure (8 cases, 100.0%), cardiac

170 shock (4 cases, 50.0%) and Adams-Stokes syndrome (4 cases, 50.0%).   ST-T changes

171   in the electrocardiographic (ECG) examinations were observed in all FM children (100%),

172   followed by III° atrioventricular block (AVB, 62.5%). All children showed abnormal levels

173   of cTnT (1711.5 pg/ml, 129.4 to 6457.0 pg/ml; reference limit: 3.0-14.0 pg/ml) and

174   BNP(11426.5 pg/ml, 546.1 to 31648.0 pg/ml; reference limit: 0-125.0 pg/ml) in the

175   course of FM. All eight children received intravenous immunoglobulin and

176   methylprednisolone after admission. Inotropic support was required in children for

177   severe haemodynamic compromise: isoprenaline in five children and dobutamine in

178   three children. Ventricle-assist devices also were implanted in two children.

179   The median intervals from onset to initial and follow-up CMR examinations were 10 days

180   (range, 7 to 20) and 55 days (range, 33 to 75). At initial CMR, the clinical manifestations

181   of FM had been markedly improved. Abnormal levels of cTnT (79.7±71.1pg/ml) were

182   observed in six children (75%) and BNP (443.6pg/ml, 75.5 to 4498.0) in seven children

183   (87.5%). ST-T abnormalities were also observed in seven FM children (87.5%). At

184   follow-up CMR, the symptoms of all FM children recovered completely. Only one

185   children showed abnormal level of BNP (340.0 pg/ml).

186   CMR findings

187   The CMR findings of FM at baseline and follow-up CMR were shown in Table 2. Two

188   children (age, 3 and 6 years old) were sedated and examined under free-breathing

189   condition and the others with respiratory gating.

190   At baseline CMR, the characteristic CMR findings were the increased myocardial

191   thickness in six children (11.8±2.9mm). Four children (50.0%) performed increased

192   LVEF (77.2±4.5%) and others with normal LVEF. No obviously abnormal myocardial

193   motion was found. Pericardial effusion was found in three children (37.5%). At follow-up

194   CMR, myocardial thickness returned to normal and 1children (12.5%) showed increased

195   LVEF (79.0%). Pericardial effusion in three children disappeared. Compared with follow-

196   up CMR, FM children at baseline CMR showed increased septal thickness (*P*=0.011),

197   increased LV mass (*P*=0.003), higher EF (*P*=0.001), smaller LVEDD (*P*=0.042) and

198   lower ESV (*P*=0.016). (Figure 1)

199   The myocardial tissue characterization of FM at baseline CMR were most common with

200   increased EGE ratio (8.9±3.5) in five FM children (100%). Regional or global increased

201   T2WI signal was found in seven FM children (87.5%), with mean T2 ratio of 2.03±0.15. In

202   the LGE images, regional mid-wall enhancement were found in six cases (75.0%),

203   followed by one subepicardial enhancement (12.5%). No predilections of myocardial

204   segments were found for LGE. Diagnostic sensitivity of CMR abnormalities at baseline

205   CMR for FM was 100% according to Lake Louise criteria. At follow-up CMR, only three

206   children with decreased area of LGE (37.5%) and one child with increased T2WI signal

207   (12.5%) were found. Statistically significant differences were found between initial and

208   follow-up CMR in T2 ratio (*P*=0.011) and LGE area (*P*=0.020). (Figure 1)

209   Short-term outcomes

210   In our study, all children with FM survived. The short-term outcomes of FM in children

211   were excellent. Full recovery of clinical manifestations, immunological features and CMR

212   findings could be found in five FM children (62.5%) at follow-up CMR. (Figure 2)

213 Abnormal levels of BNP and myocardial tissue characterization were also found in three

214 children (37.5%). There were no significant differences of age, heart rate or intervals

215 from onset to CMR examinations between FM children with and without full recovery.

216 Compared with three children without full recovery, the other five children showed higher

217 incidence of III° AVB (5 cases VS 0 case), smaller LGE area (104.0±14.5 mm^2 VS

218 138.0±25.2 mm^2) at baseline CMR of FM, which might indicate better short-term

219 outcomes.

220

221 **Discussion**

222 In this study, we assessed the CMR findings at different course of FM in children. The

223 CMR findings of FM in children were characteristic and useful for early diagnosis. Full

224 recovery of clinical manifestations, immunological features and CMR findings could be

225 found in most FM children. The presence of III° AVB and smaller LGE areaat baseline

226 CMR might indicate better short-term outcomes.

227 In our study, positive viral antibodies were observed in children, while the viral serology

228 was not applied in the diagnosis of FM. Positive viral serology does not imply myocardial

229 infection but rather indicates the interaction of the peripheral immune system with an

230 infectious agent. (Caforio AL et al., 2013) The prevalence of circulatory viral antibodies

231 (IgG) was also found in health children. Besides, no correlation between virus serology

232 and EMB findings was found. (Mahfoud F, et al., 2011)

233 In our study, myocardial thickness increased in 75% FM children at baseline CMR and

234   returned to normal at follow-up. Similar findings were also found in several previous

235   studies. Felker GM and his coworkers found increased septal thickness in 11 FM

236   patients at presentation by echocardiography and normal septal thickness six months

237   later, compared with normal septal thickness in acute myocarditis (AM) (Felker et al.,

238   2000). Felker GM attributed the increased myocardial thickness to inflammatory

239   response seen on EMB. Severe LV wall thickening was also reported in a 22-year-old

240   FM woman with cardiogenic shock (Shillcutt et al., 2015). In our study, we also found the

241   correlation between increased myocardial thickness and myocardial edema. At baseline

242   CMR, all FM children with increased myocardial thickness performed myocardial edema.

243   At follow-up CMR, the myocardial thickness returned to normal, with only one myocardial

244   edema left.   Increased myocardial thickness might be the response of myocardial

245   inflammation and could be a characteristic radiological finding to distinguish FM from AM.

246   In our study, increased or normal LVEF (71.8±6.9%) was found in all children at baseline

247   CMR of FM, compared with impaired LVEF (36.5± 8.2%) within 72 hours of onset. The

248   LV cardiac function returned to normal (64.9±7.1%) at follow-up. Clinical interventions

249   and treatment undoubtedly played a primary role in the recovery of LV systolic function

250   (Ginsberg&Parrillo, 2013; McCarthy et al., 2000). While we thought that increased LVEF

251   might also be associated with increased myocardial thickness. At baseline CMR,

252   increased myocardial thickness could be found in 75% children, leading to significantly

253   decreased ESV (12.9±5.0 VS 18.2±7.4 ml, *P*=0.016) and little change of EDV (44.6±12.6

254   VS 50.6±16.5 ml, *P*=0.161), compared with those at follow-up. Then LVEF increased

255 according to the formula:

256   LVEF= (EDV-ESV)/EDV

257 The ESV in children was more vulnerable to be affected by myocardial thickness

258 because of their small LV volume.

259 One of the advantages of CMR was the noninvasive evaluation of myocardial tissue

260 characterization. In our study, myocardial hyperemia was shown in 100% children,

261 followed by myocardial edema and necrosis/fibrosis (87.5%), which indicated more

262 severe inflammatory response. The CMR diagnostic sensitivity for FM at baseline CMR

263 was considerably high (100%). Endomyocardial biopsy(EMB) had confirmed that "active

264 myocarditis" was more common in FM than that in AM, which indicated higher degree of

265 myocardial inflammation in FM.(Felker et al., 2000).In AM with "borderline myocarditis",

266 myocardial tissue characterization might not be observed because of less severe

267 inflammation (Friedrich et al., 2009; De Cobelli et al., 2006). While in FM with more

268 common "active myocarditis", CMR tissue characterization could be a useful tool for FM

269 diagnosis.

270 The exact pathophysiology of LGE in myocarditis is still under investigation. Myocardial

271 inflammation and/or necrosis in the acute phase seemed to play a major role.

272 (Mavrogeni S et al., 2012) High specificity of LGE for the detection of myocardial injury in

273 myocarditis had been demonstrated in several studies (Cooper et al., 2007; Abdel-Aty H

274 et al., 2005; Mahrholdt H et al., 2004).In our study, patchy mid-wall or subepicardial LGE

275 in the LV walls were found in seven FM children (87.5%), which were similar to those in

276 AM children (Banka et al., 2015; Sachdeva et al., 2015). Similar mid-wall LGE were also

277 found in a 33-year-old female FM patient (Ryu et al., 2013). While Takeuchi and

278 Mavrogeni found normal LGE in their reports (Takeuchi et al., 2010; Mavrogeni et al.,

279 2012). One of the possible reasons for this might be the longer intervals from onset to

280 CMR examinations (10 days, 7 to 20) in our study. Besides, the differences of FM

281 between adult and children need further study.

282 The outcomes of FM in the pediatric population were controversial. Amabile N and his

283 coworkers found that 90.9%FM children performed favorable outcomes, with no

284 symptoms and normalized LVEF (Amabile et al., 2006).While in a nationwide survey of

285 Japanese children and adolescents reported by Saji T showed that the survival rate for

286 children with fulminant MC was disappointing (51.6%)(Saji et al., 2012).In our study, full

287 recovery of clinical manifestations and cardiac function could be found in all FM children

288 at follow-up. Myocardial inflammation disappeared completely in 62.5% FM children.

289 Ryu DR et al. reported a 33-year-old female FM patient with increased T2WI signal and

290 LGE and these findings disappeared 3 months later (Ryu et al., 2013). While for three

291 children with potential myocardial inflammation, myocardial edema had lightened (T2

292 ratio, 1.96±0.22 VS 1.90±0.08) and LGE areas were smaller (138.0±25.2 mm^2 VS

293 95.0±26.0 mm^2). We thought the still presences of myocardial inflammation were due to

294 short intervals of follow-up CMR (median, 54 days).

295 In our study, we found the presence of III° AVB at baseline CMR of FM might indicate

296 better short-term outcomes. The favorable outcomes associated with complete AVB in

297 FM and AM were also reported. Lee EY, et al. reported the short-term outcomes of FM

298 children in a single center and found that all 7 FM children with complete AVB on the

299 initial EKG survived. (Lee EY, et al., 2014) The AM patients with complete AVB perform

300 excellent survival rates (89%-100%) and long-term outcomes (100%). 11-28% AM

301 patients had persistent complete AVB at hospital discharge and became normal at

302 follow-up. (Chien SJ, et al., 2008; Wang JN, et al., 2002; Batra AS, et al., 2003) The

303 reason why FM children with complete AVB had good outcomes was unclear. We

304 presumed that because of the more specific manifestations of myocarditis with CAVB,

305 such as hypotension and Stokes-Adams seizures (Chien SJ, et al., 2008), patients could

306 receive earlier treatment before the development of obvious congestive heart failure.

307 (Wang JN, et al., 2002)

308 Smaller LGE area at baseline CMR of FM also indicated better short-term outcomes.

309 The value of CMR in the assessment of FM outcomes had not been reported. CMR has

310 been applied to predict the outcomes of AM. Sachdeva S et al. reported that LGE could

311 be found in half of AM children and it could be identified as predictors of poor outcomes

312 (Sachdeva et al., 2015). Barone-Rochette G et al. also applied a simplified visual

313 quantitative score of LGE to identify the outcomes of AM patients, with LGE identified as

314 an independent predictor of all cause and cardiac mortality in these AM patients.(

315 Barone-Rochette G, et al., 2014) In patients with AM, significantly continuous decrease

316 of LGE volume percentage had been observed over several follow-up CMR

317 examinations, which demonstrated a rapid and continuous decrease of myocardial

318 inflammation (Luetkens JA et al., 2016). The myocardial inflammation was easier to

319 subside in a small area of LGE, which indicated better outcomes.

320 Nowadays, T1 and T2 myocardial mapping techniques have been applied in the

321 assessment of myocarditis as novel quantitative tissue markers. (Moon JC et al., 2013;

322 Hamlin SA et al., 2014; Radunski UK et al., 2014; Lurz P et al., 2016) The extracellular

323 volume (ECV), as calculated by the pre-and post-contrast T1 values and HCT, could

324 directly and non-invasively measure the proportion of extracellular space within the

325 myocardium. Compared with Lake louise criteria, significantly improved diagnostic

326 accuracy had been reported in patients with myocarditis using mapping techniques

327 (Radunski UK et al., 2014; Lurz P et al., 2016). Lurz et al. reported that mapping

328 techniques could provide a useful tool for the diagnosis of acute myocarditis and were

329 superior to the LLC (Lurz P et al., 2016). Radunski UK et al. found that ECV combined

330 with LGE imaging could significantly improve the diagnostic accuracy of CMR compared

331 with standard Lake-Louise criteria in patients with severe myocarditis (Radunski UK et

332 al., 2014). In our study, Lake louise criteria was applied in the CMR diagnosis of FM. The

333 diagnostic accuracy of mapping techniques would be discussed in the future.

334 This study has several potential limitations. First of all, the number of patients included in

335 the study was small. While all children performed CMR examinations twice at different

336 course of FM, the CMR findings were convictive by comparing at baseline and follow-up

337 CMR. Second, we have utilized clinical rather than histologic criteria in making the

338 diagnosis of FM. Since the clinical manifestations and CMR findings of our patients were

339 consistent with FM and full recovery of cardiac function was found with supportive care,

340 the diagnosis of FM was definite. Third, the EGE examinations were performed in 62.5%

341 FM children at baseline CMR and only 1 child at follow-up. As a result, we could not

342 evaluate the recovery of myocardial hyperemia. Fourth, the intervals from onset to CMR

343 examinations were varied based on patient's conditions, which might had an influence

344 on the CMR findings. Fifth, the CMR protocol in 8 children was different because multiple

345 signal averaging were applied in the cine imaging and LGE imaging of two small children

346 under free-breathing condition. In our study we focused on the CMR differences at

347 baseline and follow-up. The CMR protocol at baseline and follow-up in each child was

348 same and paired T-test was used. We didn't compare the CMR findings between free-

349 breathing and breath-hold children. So the protocol difference had no influence on our

350 results. Sixth, because of the small sample size, the clinical data and initial CMR findings

351 between FM children with different short-term outcomes were directly compared. The

352 predictors of FM outcomes were not demonstrated by the statistical analysis but by the

353 differences between the two groups that are only described.

354 **Conclusions**

355 The CMR findings of FM in children were characteristic and useful for early diagnosis.

356 Full recovery of clinical manifestations, immunological features and CMR findings could

357 be found in most FM children. The presence of III° AVB and smaller LGE areaat baseline

358 CMR might indicate better short-term outcomes.

359

360

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364

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528

529   Table 1. Characteristics and clinical data of eight FM children at presentation

Characteristics	N(%)/median(range)
Sex (M)	5 (62.5%)
Median age (years)	8.5 (3,14)
LVEF (%)	36.5±8.2
Clinical manifestations	
General symptoms	5 (62.5%)
Fatigue	5 (62.5%)
Fever	1 (12.5%)
Gastrointestinal symptoms	8 (100%)
Nausea and vomiting	6 (75.0%)
Abdominal pain	5 (62.5%)
Cardiovascular sysptoms	8 (100%)
Heart failure	8 (100%)
Cardiac shock	4 (50.0%)
Chest pain/distress	3 (37.5%)
Neurological symptoms	5 (62.5%)
headache/dizziness	4 (50.0%)
seizure	4 (50.0%)
Abnormal electrocardiogram	
ST-T changes	8 (100%)
III°AVB	5 (62.5%)

The highest levels of myocardial enzymes	
cTnT(pg/ml)	1711.5 (129.4, 6457.0)
BNP(pg/ml)	11426.5 (546.1, 31648.0)
Treatment	
Intravenous immunoglobulin	8 (100%)
Steroids	8 (100%)
isoprenaline	5 (62.5%)
dopamine	3 (37.5%)
ventricle-assist device	2 (25.0%)

530

531 Values are presented as N (%) or median (range). AVB, atrioventricular block; LVEF, left

532 ventricle ejection fraction; cTnT, cardiac troponin T, reference limit: 3.0-14.0 pg/ml; BNP,

533 brain natriuretic peptide, reference limit: 0-125.0 pg/ml.

534

535   Table 2. Comparison between clinical data and CMR findings at baseline and follow-up

536   CMR

	Baseline(N=8)	Follow-up(N=8)	*P* values
Heart rate(/min)	78.9±14.0	86.9±13.3	0.162
Interval(days)	10(7,20)	55(33,75)	<0.001*
cTNT(pg/ml)	79.7±71.1	12.5±5.5	0.061
BNP(pg/ml)	443.6(75.5,4498.0)	55.2(1.0,340.2)	0.011*
Cardiac morphology and function			
IVST(mm)	10.9±3.1	8.1±1.2	0.011*
EDV(ml)	44.6±12.6	50.6±16.5	0.161
ESV(ml)	12.9±5.0	18.2±7.4	0.016*
LVEF(%)	71.8±6.9	64.9±7.1	0.001*
LVM(g)	48.9±15.6	36.9±12.6	0.003*
LVEDD(mm)	36.8±4.4	38.4±4.5	0.042*
Myocardial tissue characterization			
T2 ratio	2.03±0.15	1.80±0.11	0.011*
EGEr	8.9±3.5	3.5	-
LGEsegments	21(15.4%)	11(8.1%)	0.060
LGE areas(mm^2)	113.5(0,165.0)	0(0,125.0)	0.020*

537

538 Values are presented as a mean ± SD, median (range) or n (%).*P values < 0.05. cTnT,

539 cardiac troponin T; BNP, brain natriuretic peptide; IVST, inter-ventricular septal thickness;

540 EDV, end-diastolic volume, ESV, end-systolic volume, LVEF, left ventricle ejection

541 fraction; LVM, LV mass; LVEDD, Left ventricular end-diastolic diameter; EGE, early

542 gadolinium enhancement; LGE, late gadolinium enhancement.

543

544   Figure 1.Comparison of CMR findings in patients with FM at baseline and follow-up

545   CMR.(A) EDV, end-diastolic volume; (B) ESV, end-systolic volume; (C) EF, ejection

546   fraction; (D) LVEDD, left ventricular end-diastolic diameter; (E) IVS, inter-ventricular

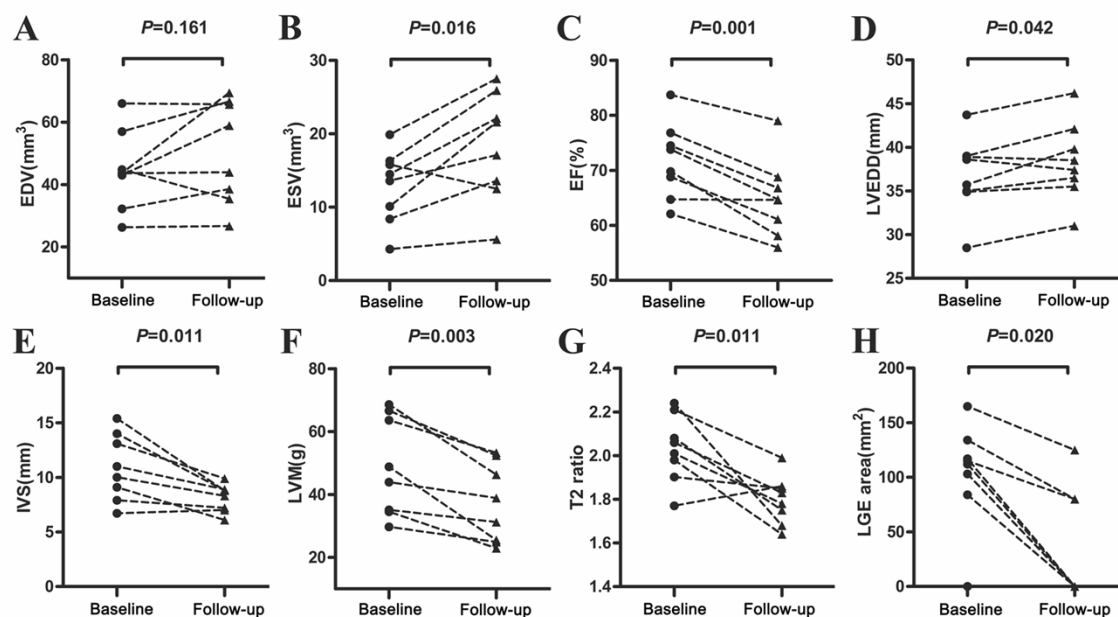
547   septal thickness;(F) LVM, LV mass; (G) T2 ratio; (H) LGE area. Compared with the CMR

548   findings of FM at follow-up, FM children at baseline CMR performed increased septal

549   thickness (*P*=0.011), LV mass (*P*=0.003), EF (*P*=0.001), T2 ratio (*P*=0.011), LGE area

550   (*P*=0.020) and smaller LVEDD (*P*=0.042) and ESV (*P*=0.016).

551

552

553 Figure 2 showed the CMR findings of a 13 year-old child 10 days (A,B,E,F,I,J,L,M) and

554 56 days (C,D,G,H,K,N,O) after the onset of FM. He was hospitalized after four days of a

555 viral syndrome followed by acute hemodynamic collapse with 38% of LVEF. Increased

556 myocardial thickness and normal LVEDD was found in the end-diastolic (A,E) and end-

557 systolic cine images (B,F) at baseline CMR. At follow-up CMR, myocardial thickness

558 returned to normal (C,D,G,H). Diffuse myocardial edema was shown in the T2-weighted

559 images with the T2 ratio of 1.98 at baseline CMR (I,J) and disappeared at follow-up (K,

560 T2 ratio:1.64). Regional mid-wall LGE within the anteroseptal and inferoseptal walls were

561 found at baseline CMR (L,M) and disappeared at follow-up(N,O).

562 CMR, cardiac magnetic resonance; FM, fulminant myocarditis; LVEF, left ventricle

563 ejection fraction; LVEDD, Left ventricular end-diastolic diameter; LGE, late gadolinium

564 enhancement.

565