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Clinical characteristics and treatment effects of astragalus injection in non-pediatric patients with acute fulminant myocarditis

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Abstract

To explore the clinical characteristics of non-pediatric patients with acute fulminant myocarditis (AFM) and evaluate the treatment effects of astragalus injection on this disease.

A total of 54 AFM patients were screened out from 586 patients with acute myocarditis, admitted to the department of cardiology between January 2011 to June 2018. The demographic and clinical data, investigations, treatments, and short-term outcomes were collected and retrospectively analyzed.

The mean age of the 54 AFM patients was 34 ± 16.5 years old (range: 13–70 years), including 24 (44.5%) men and 30 (55.5%) women, with a high incidence in 2 age groups: 13–19 and 40–49 years old, despite an inverse trend to the increase of age. All these cases were admitted in emergency conditions: 26 (48.1%) cardiogenic shock, 18 (33.4%) malignant arrhythmias, 8 (14.8%) severe heart failure, and 2 (3.7%) acute pericardial tamponade. Apart from first-aid measures, 37 (68.5%) patients received astragalus injection. During hospitalization, 11 (20.4%) patients died, and 4 (36.3%) of them were from astragalus group while 7 (63.7%) of them from without-astragalus group (P=0.03). Furthermore, the levels of cardiac injury biomarkers, renal function and left ventricular ejection fraction of astragalus group were significantly improved compared with those of without-astragalus group at discharge (all $P < .05$).

Middle-aged people were also prone to AFM. And cardiac shock was the most common, while acute pericardial tamponade was a rare presentation in non-pediatric AFM patients. Astragalus was a potential adjuvant medicine for the treatment of AFM.

Abbreviations: AFM = acute fulminant myocarditis, ALT = alanine aminotransferase, AMC = acute myocarditis, AST = aspartate transaminase, CAG = coronary artery angiography, CK-MB = creatine kinase-myoglobin, CPR = cardiorespiratory resuscitation, CTA = computed tomography angiography, cTnI = cardiac troponin I, CVB3 = coxsackievirus B3, ECMO = extracorporeal membrane oxygenator, EMB = endomyocardial biopsy, ER = endoplasmic reticulum, HF = heart failure, IgM = immunoglobulin M, LGE-cMRI = late gadolinium-enhanced cardiac MRI, LVEF = left ventricular ejection fraction, TCM = traditional Chinese medicine, UCG = echocardiogram, WBC = white blood cell.

Keywords: acute fulminant myocarditis, astragalus injection, clinical characteristics, mortality, non-pediatric patients

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JY conceived and designed the study, and also guided the completion of the manuscript; H-M Y analyzed the data and wrote the manuscript; All the authors undertook data collection and quality assessments.

The data used to support the findings of this study are included within the article.

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The data that support the findings of this study are available from a third party, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are available from the authors upon reasonable request and with permission of the third party.

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1. Introduction

Acute fulminant myocarditis (AFM), the most severe type of acute myocarditis (AMC), is a sudden onset and quickly developed life-threating heart disease, which commonly occurs in children and young adults.[1] Due to the diversity of its etiology and clinical manifestations, the incidence of AFM is difficult to identify. Nevertheless, the data from pediatric patients has shown that AFM constitutes approximately 10% to 38% of AMC,[2–5] and only about 51.6% child patients could survive from AFM.[6] By contrast, the clinical studies about adult AFM patients are relatively less,[7] and more studies are needed to enrich them and improve patient outcomes.

Of all reasons, viral infection has been considered as an important cause of AFM. However, besides emergency salvages, now there is no specific treatment for AFM, even though some pathogenic viruses have been identified.[8,9] Astragalus is a traditional Chinese medicine (TCM), consisting of several ingredients such as astragaloside IV, flavonoids, polysaccharides and saponin.[10] In recent years, a series of clinical and experimental studies revealed that astragalus plays a protective role in AMC by presenting anti-inflammatory, antiviral, antifibrotic, and immunoregulatory effects on myocardial injuries.[11–14] Unavoidably, it might be used in some AFM patients. But so far, we did not find the relevant reports yet.

Therefore, the aim of this study was firstly to retrospectively collect and analyze the clinical features of AFM in non-pediatric patients, and secondly to explore the effects of astragalus on AFM, based on the regular treatment.

2. Methods

2.1. Patients

We began this study with retrospectively assessing AMC patients, aged over 12 years old, who were admitted to our department of Cardiology between January 2011 and June 2018. And finally, a total of 54 AFM patients were screened out from 586 AMC patients for this study. The diagnosis of AMC was established mainly according to *2013 ESC statement on myocardial and pericardial diseases*.[9] On the basis of this statement and the Japanese criteria for pediatric AFM,[6] AFM was diagnosed with the following conditions:

(1) a recent history of prodromal infection, especially respiratory or gastrointestinal infection;
(2) sudden onset of severe cardiac dysfunctions, such as cardiogenic shock, aggravation of heart failure (HF), and malignant arrhythmias;
(3) evidence of severe myocardial damages, including significant elevation in levels of myocardial injury biomarkers [creatine kinase-myoglobin (CK-MB) / troponin I (TnI)], changes in electrocardiogram (ST-T segment elevation, high degree of atrioventricular block, and /or ventricular arrhythmias) and echocardiogram (UCG: an obvious decrease in systolic and/or diastolic function, while an increase in cardiac chambers);
(4) requirements of vasoactive drugs, life-support machines [ventilator, extracorporeal membrane oxygenator (ECMO), or intra-aortic balloon pump], and/or cardiorespiratory resuscitation (CPR);
(5) exclusions of coronary artery disease and other diseases.

2.2. Treatments

All of AFM patients were treated urgently at admission. The life-support treatment included vasoactive drugs, CPR, intra-aortic balloon pump, ECMO, respirator, and implantable cardioverter defibrillator. Besides this, we divided them into 2 groups, according to whether they had received astragalus injection. Astragalus injection was approved for the treatment of viral myocarditis by China Food and Drug Administration in 2002.[12] It contains astragalus, at a concentration equivalent to 2 g of raw drugs per milliliter. Generally, it was injected via an intravenous drip per day, with 20 mL solution containing 40 g astragalus added in 5% glucose solution. A therapeutic duration of this TCM was 7 to 14 days.

2.3. Data collection

The information of each patient was obtained from hospital electronic medical records, including demographics and clinical symptoms, laboratory investigations, electrocardiogram, chest X ray, UCG, late gadolinium-enhanced cardiac MRI (LGE-cMRI), coronary artery angiography (CAG) or computed tomography angiography (CTA). And the clinical data comprised values at admission and discharge, as well as the peak values of cardiac troponin I (cTnI). The short-term outcomes of AFM patients were also collected for retrospectively evaluation. This study was performed in accordance with the ethical guidelines of the 1975 Declaration of Helsinki, as revised in 2008 and approved by the ethics committee of Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China.

The viral pathogen, mainly referring to enterovirus, was detected by the method of polymerase chain reaction from blood samples. The serum immunoglobulin M (IgM) antibodies against viruses, including coxsackievirus B3 (CVB3) /B5 and giant cell virus, were measured by enzyme linked immunosorbent assay.

2.4. Statistical analysis

Data were analyzed using SPSS ver. 24.0 (SPSS Inc., Chicago, IL). Continuous variables were expressed as mean ± standard deviation (SD) or median [interquartile range (IQR)] according to normal or nonnormal distribution and categorical data are reported as proportions. The data was compared between the 2 groups by use of the unpaired Student t-test or Mann–Whitney U test, whereas categorical variables were compared via the Pearson chi-squared tests. The relationship between the short outcome of AFM patients and clinical risk factors was analyzed by stepwise multiple regression. All statistical tests were two-sided, and significance was defined as $P < .05$.

3. Results

3.1. Demographics and initial symptoms

The mean age of 54 non-pediatric AFM patients, accounted for 9.2% of AMC patients admitted for hospitalization, was 34.0 ± 16.5 years old (range, 13–70 years). As shown in Figure 1, non-pediatric AFM had a high incidence in two age groups: 13 to 19 and 40 to 49 years old, although it indicated an inverse trend to the increase of age. Among all patients, 24 (44.5%) were men and 30 (55.5%) were women, and over 60% had a recent history of prodromal infection. Most patients presented with cardiac shock

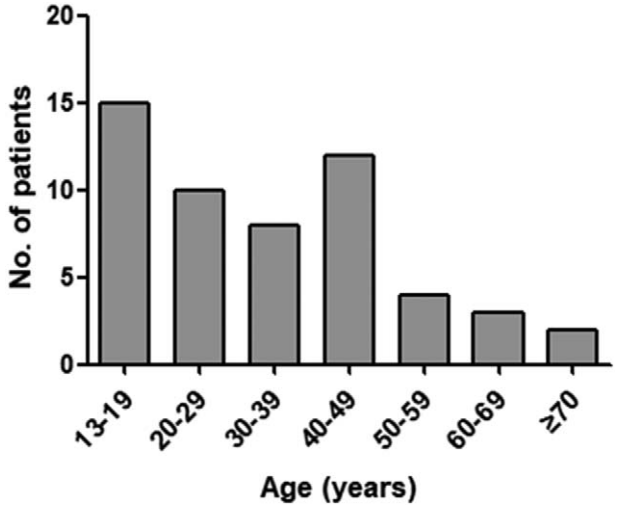

Figure 1. Age distribution of 54 non-pediatric AFM patients (range 13–70 years old). Bars stand for numbers of patients in each age group.

(48.1%) at onset, followed by fatal arrhythmias (33.4%) and severe HF (14.8%), while 2 patients developed acute pericardial tamponade, which was rarely happened in AFM (Table 1).

Out of 54 AFM patients, 37 (68.5%) received astragalus injection, who were younger than those without astragalus treatment (29.8 ± 15.1 vs 43.1 ± 16.0 years, $P = .01$). Moreover, there was a significant difference in clinical manifestations between these 2 groups ($P = .01$), with no pericardial tamponade in astragalus treated group and more fatal arrhythmias (71.4%) in without-astragalus patients. The sex, previous history, disease course, incidence of prodromal infection, heart rate and low blood pressure were similar in both groups (Table 1).

3.2. Clinical investigations at admission

The values of clinical investigations conducted at admission were shown in Table 2. The levels of cTnI and white blood cell (WBC) were all obviously elevated in both groups, especially those in without-astragalus treated group, but there was only a difference in WBC counts between these two groups (8.9 [6.6–12.1] vs 11.0 [7.6–21.8] G/L, $P = .03$). The similar changes as cTnI were also found in the levels of creatine kinase, CK-MB, lactate dehydrogenase, alanine aminotransferase (ALT), and aspartate transaminase (AST), although each of them presented a mild or moderate increase. However, the median levels of blood creatinine in without-astragalus treated patients were higher than those in astragalus treated patients, even though both of them remained in normal range. Meanwhile, a mild-to-morderate and equivalent reduction of left ventricular ejection fraction (LVEF) was observed in two groups [(43.0 ± 16.4) % vs (44.8 ± 12.5) %, $P = .68$].

Viral investigation was completed in 35 (64.8%) patients. Of these patients, 15 (42.9%) were tested positive for enterovirus, with 12 in astragalus treated group [7 enterovirus-RNA (+), 3 CVB3-IgM (+), 2 enterovirus-RNA + coxsackievirus B5-IgM (+)] and 3 [enterovirus-RNA (+)] in without-astragalus group respectively. Giant cell virus-IgM antibodies were not found in both groups. And there was no difference in viral infection between patients with or without astragalus treatment ($P = .42$).

3.3. Astragalus treatment and mortality

During hospitalization, 11 (20.4%) patients died in 5 days, including 6 (54.5%) cardiac shock, 4 (36.4%) fatal arrhythmias, and 1 (9.1%) severe HF. As the illness was too serious, all of them did not undergo the tests of LGE-cMRI and CAG/CTA. Except that, all survivors completed the LGE-cMRI examination to confirm the diagnosis of AFM, and 30 (69.8%) of them, aged over 25 years, underwent CAG/CTA test to exclude the diagnosis

Table 1

The demographics and clinical presentations of non-pediatric AFM patients.

Characteristics	Total	Astragalus group	Without-astragalus group	*P* values
Number	54	37 (68.5%)	17 (31.5%)	/
Age (yr)	34.0 ± 16.5	29.8 ± 15.1	43.1 ± 16.0	.01
Sex (male)	24 (44.5%)	16 (43.2%)	8 (47.1%)	.79
Previous history				
Hypertension	1 (1.9%)	0	1 (5.8%)	.69
Smoking	0	0	0	1.00
Drug addiction	0	0	0	1.00
Disease course (days)	7 (5–7)	7 (4.5–7)	7 (5–14)	.98
Recent prodromal infection				
Digestive infection	8 (14.8%)	5 (13.5%)	3 (17.6%)	.70
Respiratory infection	29 (53.7%)	19 (51.4%)	10 (58.8%)	.61
Fever	21 (38.9%)	16 (43.2%)	5 (29.4%)	.33
Vital signs at admission				
Heart rate (bpm)	98.5 ± 35.0	94.3 ± 33.8	107.4 ± 36.7	.21
SBp (mmHg)	101.2 ± 18.3	98.9 ± 17.4	105.8 ± 19.7	.21
DBp (mmHg)	63.8 ± 11.9	63.5 ± 12.0	64.3 ± 12.1	.82
Clinical presentations at onset				.01
Cardiac shock	26 (48.1%)	16 (43.3%)	8 (47.1%)	/
Severe heart failure	8 (14.8%)	8 (21.6%)	0	/
Maligant arrhythmias	18 (33.4%)	13 (35.1%)	5 (71.4%)	/
Pericardial tamponade	2 (3.7%)	0	2 (28.6%)	/

Values are mean ± SD, n (%) or median (interquartile range (IQR)). *P*-value refers to the difference between astragalus and without-astragalus groups, and *P* value < .05 was considered statistically significant. AFM = acute fulminant myocarditis, bpm = beats per minute, DBp = diastolic blood pressure, mmHg = millimeters of mercury, SBp = systolic blood pressure.

Table 2

Clinical investigations at admission in non-pediatric AFM patients.

Variables	Total (n = 54)	Astragalus group (n = 37)	Without-astragalus group (n = 17)	*P* values
WBC (G/L)	9.6 (7.1–14.1)	8.9 (6.6–12.1)	11.0 (7.6–21.8)	.03
ALT (U/L)	127.5 (70.5–525.0)	119.0 (66.5–524.3)	314.5 (83.3–1462)	.34
AST (U/L)	161.0 (68.8–679.5)	128.5 (55.5–657.3)	343.0 (130.8–944.3)	.11
BUN (mmol/L)	6.8 (5.1–11.6)	6.8 (4.9–10.6)	8.3 (6.0–14.6)	.18
Cr (μmol/L)	72.2 (58.2–120.6)	63.7 (54.9–105.2)	88.5 (72.8–159.1)	.02
CK (U/L)	290.0 (75.5–1184.0)	231.5 (74.3–1174.8)	728.0 (95.0–1527.0)	.28
CK-MB (ng/ml)	13.3 (4.6–62.0)	11.5 (3.1–45.7)	36.3 (5.9–69.1)	.46
LDH (U/L)	650.0 (328.5–1204.0)	564.0 (299.8–1095.8)	666.0 (50.0–1385.0)	.28
cTnI (pg/ml)	8799.8 (1091.6–28307.2)	7544.8 (1088.5–18043.0)	12162.8 (1091.6–46216.1)	.47
Viral investigation	35 (64.8%)	24 (64.9%)	11 (64.7%)	.44
Positive (+)	15 (42.9%)	12 (50%)	3 (27.2%)	.42
Enterovirus-RNA (+)	10 (66.7%)	7 (58.3%)	3 (100%)	/
CVB3-IgM (+)	3 (20%)	3 (25%)	0 (0%)	/
Enterovirus+CVB5-IgM (+)	2 (13.3%)	2 (16.7%)	0 (0%)	/
Giant cell virus-IgM (+)	0 (0%)	0 (0%)	0 (0%)	/
LVEF (%)	43.6 ± 15.2	43.0 ± 16.4	44.8 ± 12.5	.68

Values are mean ± SD, n (%) or median (interquartile range (IQR)). *P*-value refers to the difference between astragalus and without-astragalus groups, and *P* value < .05 was considered statistically significant. ALT = alanine aminotransferase, AST = aspartate transaminase, BUN = blood urine nitrogen, CK = creatine kinase, CK-MB = creatine kinase-myoglobin, Cr = creatinine, cTnI = cardiac troponin I, CVB3 = Coxsackievirus B3, CVB5 = Coxsackievirus B5, IgM = immunoglobulin M, LDH = lactate dehydrogenase, LVEF = left ventricular ejection fraction, WBC = white blood cell count.

of coronary artery disease. Although 2 patients with acute pericardial tamponade were survived from the disease, there were no significant differences in clinical types and life-support treatments between survivors and the death except for CPR. However, of 43 survivors, 33 (76.7%) received astragalus treatment at admission, differed from the death with only 4 (36.4%) astragalus treated patients (P = .03) (Table 3).

Beyond that, a comparison of the clinical data showed that, the death had more higher level of cTnI and CK-MB than survivors, whether those at admission [41220.3 (18469.0–125637.1) vs 3547.0 (809.0–16591.9) pg/ml, *P* = .004 and 55.2 (35.5–90.1) vs 10.4 (2.7–36.3) ng/mL, P = .02, respectively] or their peak levels in hospitalization [51867.2 (25573.3–134976.5) vs. 8504.6 (809.0–19085.0) pg/mL, *P* = .005 and 56.0 (38.5–115.7) vs 13.1 (2.7–46.1) ng/mL, *P* = .004, respectively]. And no differences were found in sex, age, heart rate, incubation period, blood pressure, and levels of WBC, AST, ALT, blood urea nitrogen, creatinine, CK or lactate dehydrogenase between these 2 groups (Table 4).

After entering all significant variables including astragalus treatment, CPR, cTnI and CK-MB levels at admission, peak levels of cTnI and CK-MB into the stepwise multiple regression analysis, it showed that only astragalus treatment [standard partial regression coefficient (β) = −1.758, *P* = .027] was the predictor to the outcome of non-pediatric AFM patients during hospitalization, and the adjusted R^2 of the final model was 0.6 [Supplemental Digital Content (Suppl Table 1, http://links.lww.com/MD/F209)]. However, considering the limitation of sample size, the reliability of this result might not be sufficiently strong.

Table 3

The motality and treatments of non-pediatric AFM patients during hospitalization.

Characteristics	Total	Survivor	Death	*P* values
Number	54	43 (79.6%)	11 (20.4%)	/
Astragalus treatement group	37 (68.5%)	33 (76.7%)	4 (36.4%)	.03
Clinical presentations				.81
Cardiac shock	26 (48.1%)	20 (46.5%)	6 (54.5%)	/
Sever heart failure	8 (14.8%)	7 (16.2%)	1 (9.1%)	/
Fatal arrhythmias	18 (33.4%)	14 (32.6%)	4 (36.4%)	/
Pericardial tamponade	2 (3.7%)	2 (4.7%)	0 (0%)	/
Life-support treatments				
Vasoactive drugs	39 (72.2%)	28 (65.1%)	11 (100%)	.61
CPR	19 (35.2%)	8 (18.6%)	11 (100%)	<.001
IABP	8 (14.8%)	7 (16.3%)	1 (9.1%)	.40
ECMO	2 (3.7%)	2 (4.7%)	0 (0%)	.84
Respirator	14 (25.9%)	9 (20.9%)	5 (45.5%)	.20
ICD	9 (16.7%)	7 (16.3%)	2 (18.2%)	.79
LGE-cMRI	43 (79.6%)	43 (100%)	0 (0%)	<.001
CAG/CTA	30 (55.6%)	30 (69.8%)	0 (0%)	<.001

Values are expressed as the number of patients (%). *P*-value refers to the difference between the survivors and the death, and *P* value <.05 was considered statistically significant.
CAG/CTA = coronary artery angiography/computed tomography angiography, CPR = cardiopulmonary resuscitation, ECMO = extracorporeal membrane oxygenation, IABP = intra-aortic balloon pump, ICD = implantable cardioverter defibrillator, LGE-cMRI = late gadolinium-enhanced cardiac MRI.

Table 4

Clinical risk factors associated with AFM in-hospital mortaliy.

Characteristics	Survivor (n = 43)	Death (n = 11)	*P* values
Sex (male)	19 (44.2%)	5 (45.5%)	1.00
Age (yr)	32.3 ± 16.5	42.4 ± 20.3	.76
Heart rate (bpm)	94.3 ± 36.0	114.7 ± 26.1	.08
Incubation period (days)	7 (5–7)	7 (4–14)	.98
SBp (mmHg)	99.5 (90.0–108.0)	98.0 (92.0–105.0)	.84
DBp (mmHg)	63.6 ± 12.0	64.8 ± 12.3	.76
Levels at admission			
WBC (G/L)	9.5 (6.7–14.1)	9.7 (7.7–13.5)	.61
ALT (U/L)	173.5 (82.5–525.0)	88.0 (40.8–373.3)	.11
AST (U/L)	161.0 (74.3–712.8)	186.5 (45.3–642.0)	.72
BUN (mmol/L)	6.8 (5.3–11.7)	8.3 (4.8–10.9)	.68
Cr (μmol/L)	70.7 (56.7–109.6)	104.3 (65.2–162.8)	.12
CK (U/L)	241.0 (65.0–1184.0)	905.5 (415.0–1335.3)	.09
CK-MB (ng/ml)	10.4 (2.7–36.3)	55.2 (35.5–90.1)	.02
LDH (U/L)	592.0 (294.0–1121.0)	715.5 (493.8–1363.0)	.30
cTnI (pg/ml)	3547.0 (809.0–16591.9)	41220.3 (18469.0–125637.1)	.004
Peak levels			
WBC (G/L)	14.4 ± 7.0	12.8 ± 4.9	.52
ALT (U/L)	313.0 (91.3–703.0)	99.5 (62.0–1611.8)	.32
AST (U/L)	296.0 (80.0–757.0)	241.5 (120.0–1908.5)	.83
BUN (mmol/L)	8.9 (6.8–13.3)	9.4 (6.5–18.1)	.77
Cr (μmol/L)	81.9 (62.5–152.6)	155.3 (71.4–209.4)	.14
CK (U/L)	359.0 (65.0–1184.0)	1049.5 (581.5–1889.0)	.11
CK-MB (ng/mL)	13.1 (2.7–46.1)	56.0 (38.5–115.7)	.004
LDH (U/L)	674.0 (355.0–1287.0)	1208.5 (731.5–2344.8)	.10
cTnI (pg/mL)	8504.6 (809.0–19085.0)	51867.2 (25573.3–134976.5)	.005

Values are mean ± SD, n (%) or median (interquartile range (IQR)). *P* value refers to the difference between the survivors and the death, and *P* value <.05 was considered statistically significant. ALT = alanine aminotransferase, AST = aspartate aminotransferase, BUN = blood urine nitrogen, CK = creatine kinase, CK-MB = creatine kinase-myoglobin, Cr = creatinine, cTnI = cardiac troponin I, LDH = lactate dehydrogenase, WBC = white blood cell.

3.4. Astragalus treatment for survivors

Compared the clinical data from peak levels to those at discharge, astragalus group presented apparent improvements in cardiac injury biomarkers, LVEF, WBC counts, liver function, renal function and atrioventricular block (all $P \leq .05$). In without-astragalus group, most of these parameters were also ameliorated, but the differences were just found in WBC, ALT, and AST levels (all $P < .05$) (Table 5).

4. Discussion

In this study, the proportion of non-pediatric AFM in AMC inpatients was 54/586 (9.2%), less than that of pediatric patients. A relative imperfect immune system in children might be a plausible explanation for this discrepancy. However, besides young persons, patients aged 40 to 49 years were also found displaying a high incidence of AFM in present study. But in 2017, an Italian study, enrolled 55 AFM patients with the similar age

Table 5

Effects of astragalus treatment on survivors of in-hospital non-pediatric AFM patients.

	Astragalus group (n = 37)			Without-astragalus group (n = 17)		
Variables	Peak levels	At discharge	*P* values	Peak levels	At discharge	*P* values
WBC (G/L)	12.2 ± 4.8	8.4 ± 4.4	.001	18.5 ± 8.3	9.1 ± 3.8	.001
ALT (U/L)	177.5 (82.5–534.0)	81.5 (40.3–127.0)	.001	423.5 (89.3–1768.5)	80.5 (59.8–194.3)	.04
AST (U/L)	210.0 (59.0–786.3)	34.5 (28.0–58.8)	<.001	343.0 (137.0–998.3)	66.0 (48.3–257.5)	.01
BUN (mmol/L)	8.8 (6.4–12.4)	6.3 (4.3–8.5)	.004	11.0 (7.6–20.9)	8.9 (5.7–18.0)	.36
Cr (μmol/L)	76.7 (63.8–128.8)	60.8 (49.8–74.1)	.003	162.8 (76.1–216.8)	120.1 (59.4–205.2)	.41
CK (U/L)	409.5 (110.5–1175.3)	51.5 (33.5–209.8)	<.001	756.0 (95.0–2330.5)	94.0 (42.0–897.0)	.67
CK-MB (ng/ml)	15.9 (3.1–66.5)	2.3 (0.9–5.8)	<.001	36.3 (8.0–82.5)	5.0 (2.0–56.0)	.13
LDH (U/L)	811.0 (371.8–1287.0)	345.0 (253.0–771)	.01	758.0 (556.0–1964.5)	627.0 (421.5–779.0)	.11
cTnI (pg/ml)	11803.5 (1088.5–26852.8)	272.0 (109.1–8317.1)	.001	12162.8 (1091.6–70192.0)	1229.2 (165.2–32955.4)	.08
ST- elevation	26 (70.3%)	27 (73.0%)	.76	11 (64.7%)	8 (47.1%)	.30
Q-wave	15 (40.5%)	10 (27.0%)	.21	1 (5.9%)	1 (5.9%)	1.00
AVB-III	6 (16.2%)	1 (2.7%)	.04	1 (5.9%)	0 (0%)	.23
LVEF (%)	41.7 ± 16.5	54.2 ± 16.7	.003	44.5 ± 12.2	50.5 ± 12.6	.19

Values are mean ± SD, n (%) or median (interquartile range (IQR)). *P* value refers to the difference between the peak levels and the discharge in astragalus group or without-astragalus group, and *P* value <.05 was considered statistically significant. ALT = alanine aminotransferase, AST = aspartate aminotransferase, AVB = atrioventricular block, BUN = blood urine nitrogen, CK = creatine kinase, CK-MB = creatine kinase-myoglobin, Cr = creatinine, cTnI = cardiac troponin I, LDH = lactate dehydrogenase, LVEF = left ventricular ejection fraction, WBC = white blood cell.

composition, showed that AFM accounted for up to 29.4% AMC patients.[15] The diversity might be associated with genetic and environmental factors. And the high risk in the middle-aged group was probably from their sub-healthy condition under too much stress. Moreover, lack of a definitive and uniform diagnostic criteria was a tricky problem in AFM epidemiology because of the subjective assessment of the disease severity.[1,9]

The clinical manifestations are of great value in the diagnosis of AFM. Generally, cardiac shock, fatal arrhythmias, and severe HF are indicated to be the common presentations.[16] In this study, we found that acute pericardial tamponade could be a new clinical type of AFM. Certainly, it should be emphasized that only patients simultaneously combined with great elevation of cTnI and hemodynamic instability were considered as AFM. Although the prompt pericardiocentesis partly alleviated the emergency, the two patients with pericardial tamponade in this study recovered after undergoing CPR and treatment of myocardial protective medicines. Besides this, it should be noted that, along with the serious condition, the LVEF at admission was not reduced as much as expected in AFM patients. The reason might be associated with the time for UCG examination, some of which followed the rescue of cardiac shock on the admission day. Additionally, not all AFM patients had a history of prodromal infection or the evidence of viral infection. But the increase of blood WBC suggested the existence of inflammation caused by bacteria or other pathogens. Considering that both AFM and severe sepsis could lead to multiple organ dysfunctions and even shock, accompanied by elevation of cTnI, AFM was diagnosed on condition that myocardial damages were the primary and the most severe presentations.

As we known, endomyocardial biopsy (EMB) and histopathology are actually the gold standard for AMC diagnosis, [17,18] and the blood measurements of antiviral IgM antibodies and WBC are unspecific indicators for inflammation.[9] Nevertheless, EMB is not a routine test and unsuitable for emergency patients. And up to now there is still no definite time for it to be carried out during the course of AFM.[19] Most importantly, the endomyocardial bioptome was not used in China until recent years. Thus, LGE-cMRI and Lake-Louise criteria are a valuable method for the diagnosis of AMC in this study.[9,20,21] So with the exception of the death, all survivors out of danger were investigated by CMR-LGE, and the evidence of myocardial inflammation and fibrosis supported the final diagnosis of AFM integrating with all clinical data, based on exclusion of other heart diseases. In addition, the detection of blood enterovirus-RNA and coxsackievirus IgM antibodies suggested enterovirus was the most common pathogen for non-pediatric AFM in this study, despite that giant cell virus was usually as an important causative virus.

The outcome of AFM is mainly determined by the severity of myocardial damages. To some extent, it could be predicted by serological biomarkers, viral examination, decreased LVEF, prolonged QRS duration, systolic hypotension, etc.[22–25] In the present study, the in-hospital mortality of non-pediatric AFM was 20.4%, far below pediatric patients'.[6] And the higher cTnI levels means the worse outcomes. In addition, unexpectedly, there was a difference in astragalus treatment between the death and survivors. Of note, the insufficient treatment time for the dead patients and the younger age in treatment group might not enough to support the significance of astragalus injection, but the improvements of astragalus treatment in survivors at discharge further presented its potential benefits to AFM patients. The protective mechanism of this TCM on myocarditis was related to its ingredients, which has been proved as follows: (1) Calycosin-7-O-beta-D-glucopyranoside, derived from astragalus membranaceus, exerted significant anti-CVB3 activities by inhibiting CVB3-mediated cytopathic effects and reducing the myocardial virus titers.[26] (2) astragaloside IV inhibited CVB3 proliferation by upregulating interferon-gamma,[27] and reduced cardiomyocyte apoptosis through suppressing FAS/FASL signaling pathway and myocardial expression of inflammatory cytokines.[28] (3) astragalus polysaccharide ameliorated CVB3-induced myocardial damages and inflammation by blocking TLR-4/NF-κB p65 signaling pathway,[29] and enhanced the immunity to viruses.[30] (4) astragalus flavonoids prevented arrhythmias by alleviating endoplasmic reticulum stress, increasing connexcin 43 (Cx43) expression,[31] and improving CVB3-induced dysfunction of endoplasmic reticulum -mediated Ca^{2+} homeostasis.[11] Currently, although the mechanical circulatory support, especially ECMO), is strongly recommended for AFM treatment,[32–34] it is not fully used in a majority of hospitals yet. And without EMB results and definite clinical evidence, there is still ambiguous in adding immunosuppressant,[1,9,35] immunoglobulin (IgA)[1,36,37] or interferon antiviral therapies.[38,39] In this event, astragalus injection might be an option to be considered, based on the conventional treatments.

5. Conclusions

Middle-aged people were also prone to AFM. And cardiac shock was the most common, while acute pericardial tamponade was a rare presentation in non-pediatric AFM patients. Astragalus was a potential adjuvant medicine for the treatment of AFM.

6. Limitations

There are some limitations should be pointed out in this study. First, EMB was not performed to confirm the AFM diagnosis. Second, the long-term outcomes need to be followed up in non-pediatric AFM patients. Third, the efficacy of astragalus treatment for AFM needs further studies. And finally, the sample size is relatively small, and we hope to carry out a multi-center investigation or prospective study to support the conclusions in the future.

Author contributions

Jing Yuan conceived and designed the study, and also guided the completion of the manuscript; Hongmin Yang analyzed the data and wrote the manuscript; All the authors undertook data collection and quality assessments.

References

[1] Veronese G, Ammirati E, Cipriani M, et al. Fulminant myocarditis: characteristics, treatment, and outcomes. Anatol J Cardiol 2018;19:279–86.
[2] Amabile N, Fraisse A, Bouvenot J, et al. Outcome of acute fulminant myocarditis in children. Heart 2006;92:1269–73.
[3] Saji T, Matsuura H, Hasegawa K, et al. Comparison of the clinical presentation, treatment, and outcome of fulminant and acute myocarditis in children. Jpn Circ J 2012;76:1222–8.
[4] Sankar J, Khalil S, Jeeva SM, et al. Short-term outcomes of acute fulminant myocarditis in children. Pediatr Cardiol 2011;32:885–90.
[5] Lee EY, Lee HL, Kim HT, et al. Clinical features and short-term outcomes of pediatric acute fulminant myocarditis in a single center. Korean J Pediatr 2014;57:489–95.

[6] Matsuura H, Ichida F, Saji TM, 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.
[7] Mccarthy RE, Boehmer JP, Hruban RH, et al. Long-term outcome of fulminant myocarditis as compared with acute (nonfulminant) myocarditis. N Engl J Med 2000;342:690–5.
[8] Ginsberg F, Parrillo JE. Fulminant myocarditis. Crit Care Clin 2013;29:465–83.
[9] Caforio AL, Pankuweit S, Arbustini E, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J 2013;34:2636–48.
[10] Li X, Qu L, Dong Y, et al. A review of recent research progress on the astragalus genus. Molecules 2014;19:18850–80.
[11] Zhou X, Xin Q, Wang Y, et al. Total flavonoids of astragalus plays a cardioprotective role in viral myocarditis. Acta Cardiol Sin 2016;32:81–8.
[12] Piao YL, Liang XC. Astragalus membranaceus injection combined with conventional treatment for viral myocarditis: a systematic review of randomized controlled trials. Chin J Integr Med 2014;20:787–91.
[13] Zhang Z, Dai X, Qi J, et al. Astragalus mongholicus (Fisch.) Bge improves peripheral Treg cell immunity imbalance in the children with viral myocarditis by reducing the levels of miR-146b and miR-155. Front Pediatr 2018;6:139.
[14] Shahzad M, Shabbir A, Wojcikowski K, et al. The antioxidant effects of radix astragali (astragalus membranaceus and related species) in protecting tissues from injury and disease. Curr Drug Targets 2016;17:1331–40.
[15] Ammirati E, Cipriani M, Lilliu M, et al. Survival and left ventricular function changes in fulminant versus nonfulminant acute myocarditis. Circulation 2017;136:529–45.
[16] Robb D Kociol, Leslie T Cooper, James C Fang, et al. American Heart Association Heart Failure and Transplantation Committee of the Council on Clinical Cardiology. Recognition and Initial Management of Fulminant Myocarditis: a scientific statement from the American Heart Association. Circulation 2020;141:e69–92.
[17] Yilmaz A, Kindermann I, Kindermann M, et al. Comparative evaluation of left and right ventricular endomyocardial biopsy: differences in complication rate and diagnostic performance. Circulation 2010; 122:900–9.
[18] Leone O, Veinot JP, Angelini A, et al. 2011 consensus statement on endomyocardial biopsy from the Association for European Cardiovascular Pathology and the Society for Cardiovascular Pathology. Cardiovasc Pathol 2012;21:245–74.
[19] Pollack A, Kontorovich AR, Fuster V, et al. Viral myocarditis–diagnosis, treatment options, and current controversies. Nat Rev Cardiol 2015;12:670–80.
[20] Gannon MP, Schaub E, Grines CL, et al. State of the art: evaluation and prognostication of myocarditis using cardiac MRI. J Magn Reson Imaging 2019;49:e122–31.
[21] Friedrich MG, Sechtem U, Schulz-Menger J, et al. Cardiovascular magnetic resonance in myocarditis: a JACC White Paper. J Am Coll Cardiol 2009;53:1475–87.
[22] Inaba O, Satoh Y, Isobe M, et al. Factors and values at admission that predict a fulminant course of acute myocarditis: data from Tokyo CCU network database. Heart Vessels 2017;32:952–9.
[23] Albiltagi M, Issa M, Hagar HA, et al. Circulating cardiac troponins levels and cardiac dysfunction in children with acute and fulminant viral myocarditis. Acta Paediatr 2010;99:1510–6.
[24] Lee CH, Tsai WC, Hsu CH, et al. Predictive factors of a fulminant course in acute myocarditis. Int J Cardiol 2006;109:142–5.
[25] Kato S, Morimoto S, Hiramitsu S, et al. Risk factors for patients developing a fulminant course with acute myocarditis. Circ J 2004;68:734–9.
[26] Zhu H, Zhang Y, Ye G, et al. In vivo and in vitro antiviral activities of calycosin-7-O-beta-D-glucopyranoside against coxsackie virus B3. Biol Pharm Bull 2009;32:68–73.
[27] Zhang Y, Zhu H, Huang C, et al. Astragaloside IV exerts antiviral effects against coxsackievirus B3 by upregulating interferon-gamma. J Cardiovasc Pharmacol 2006;47:190–5.
[28] Liu T, Yang F, Liu J, et al. Astragaloside IV reduces cardiomyocyte apoptosis in a murine model of coxsackievirus B3-induced viral myocarditis. Exp Anim 2019;68:549–58.
[29] Liu T, Zhang M, Niu H, et al. Astragalus polysaccharide from astragalus melittin ameliorates inflammation via suppressing the activation of TLR-4/NF-(B p65 signal pathway and protects mice from CVB3-induced virus myocarditis. Int J Biol Macromol 2019;126:179–86.
[30] Kallon S, Li X, Ji J, et al. Astragalus polysaccharide enhances immunity and inhibits H9N2 avian influenza virus in vitro and in vivo. J Anim Sci Biotechnol 2013;4:22.
[31] Liu H, Hurile B, Xiong Y, et al. Effects of total flavonids of astragalus on arrhythmia, endoplasmic reticulum stress in mice with viral myocarditis. Zhongguo Ying Yong Sheng Li Xue Za Zhi 2018;34:16–8.
[32] Saito S, Toda K, Miyagawa S, et al. Diagnosis, medical treatment, and stepwise mechanical circulatory support for fulminat myocarditis. J Artif Organs 2018;21:172–9.
[33] Wilmot I, Morales DL, Price JF, et al. Effectiveness of mechanical circulatory support in children with acute fulminant and persistent myocarditis. J Card Fail 2011;17:487–94.
[34] Okada N, Murayama H, Hasegawa H, et al. Peripheral veno-arterial extracorporeal membrane oxygenation as a bridge to decision for pediatric fulminant myocarditis. artif organs 2016;40:793–8.
[35] Frustaci A, Chimenti C. Immunosuppressive therapy in myocarditis. Circ J 2015;79:4–7.
[36] Yen CY, Hung MC, Wong YC, et al. Role of intravenous immunoglobulin therapy in the survival rate of pediatric patients with acute myocarditis: a systematic review and meta-analysis. Sci Rep 2019;9:10459.
[37] Isogai T, Yasunaga H, Matsui H, et al. Effect of intravenous immunoglobulin for fulminant myocarditis on in-hospital mortality: propensity score analyses. J Card Fail 2015;21:391–7.
[38] Kühl U, Pauschinger M, Schwimmbeck PL, et al. Interferon-beta treatment eliminates cardiotropic viruses and improves left ventricular function in patients with myocardial persistence of viral genomes and left ventricular dysfunction. Circulation 2003;107:2793–8.
[39] Fechner H, Pinkert S, Geisler A, et al. Pharmacological and biological antiviral therapeutics for cardiac coxsackievirus infections. Molecules 2011;16:8475–503.