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ORIGINAL ARTICLE

Clinical characteristics, diagnosis and short-term outcomes of COVID-19–associated acute myocarditis in China

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Abstract

Aims Acute myocarditis (AM) has been recognized as a rare complication of coronavirus disease 2019 (COVID-19) infection. This study was conducted to present the clinical characteristics, disease courses and short-term prognoses of Omicron variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) induced AM in China, which has been unavailable so far.

Methods and results Data from 28 patients diagnosed with definite COVID-19–associated AM from 6 hospitals in China between 1 December 2022 and 30 June 2023 were collected and analysed. The diagnosis of AM was based on increased troponin level plus typical findings of AM on cardiac magnetic resonance (CMR) imaging and/or endomyocardial biopsy. Among 28 patients with definite COVID-19–related AM, median age was 37 years (Q1–Q3: 22–52) and 53.6% were men. Twenty-three patients occurred within 2 weeks of the onset of COVID-19 infection, 10 patients underwent endomyocardial biopsy and CMR was performed in all patients. Seven (25.0%) patients developed fulminant myocarditis that required inotropic agents or temporary mechanical circulatory support. Of the nine patients (32.1%) with left ventricular ejection fraction (LVEF) below 50% on admission, five had fully recovered LVEF and two demonstrated improvement but to levels below normal at discharge. The comparison of CMR parameters between the baseline and first follow-up showed that ECV was decreased at the first follow-up [28.95 (25.38, 32.55)% vs. 33.65 (31.58, 37.55)%, P = 0.028), while other CMR parameters had no significant changes. Eighteen patients (64.3%) were prescribed with corticosteroids, and seven patients (25.0%) underwent temporary mechanical circulatory support. Only two patients died during hospitalization.

Conclusions The majority of COVID-19–associated AM occurred within 2 weeks of Omicron variant infection. Fulminant myocarditis complicated by hemodynamic instability requiring temporary mechanical circulatory support was not uncommon. However, short-term outcome was generally good and most AM patients fully recovered.

Keywords COVID-19; Myocarditis; Outcome; SARS-CoV-2

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Introduction

Coronavirus disease 2019 (COVID-19) is a disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, which predominately attack respiratory system.[1] Notably, it can also damage other systems and organs including the cardiovascular system. Cardiac manifestations of COVID-19 infection include myocardial injury, acute heart failure (HF), arrhythmia, acute coronary syndrome and stress cardiomyopathy.[1] Acute myocarditis (AM) has also been recognized as a relatively rare clinical manifestation associated with COVID-19 infection.[2] Although viral myocarditis usually has benign clinical course, it can present with 'infarct-like' symptoms and/or signs of acute HF. Previous reports regarding COVID-19–associated AM consist mainly of case reports. The largest clinical study of COVID-19–associated AM was a multicentre, multinational, retrospective study that included 54 patients with definite or probable COVID-19–associated AM. Patients in this report were diagnosed by either endomyocardial biopsy in 17 (31.5%) of the cases or cardiac magnetic resonance (CMR) in 50 (92.6%) cases.[1] Another review of published cases of suspected COVID-19–associated AM worldwide included 38 patients, but only 12 of whom had histological data (eight endomyocardial biopsies and four autopsies) and the diagnosis of AM was mainly confirmed by CMR (25 cases).[3] However, at present, there is no data available regarding the clinical presentation, disease course and short-term outcome of COVID-19–associated AM in China.

During the winter of 2022, China experienced an epidemic of COVID-19 in which the dominant strains causing infection were Omicron variants BA.5.2.48 (61.1%) and BF.7.14 (27.8%). During this phase of the epidemic, there was information that myocardial injury occurred in several patients around the country. However, there were only isolated case reports of one or two patients with COVID-19 Omicron variant infection–related AM from around the world at the time. Thus, to better understand the clinical characteristics, treatment that was being used and short-term outcomes of AM associated with Omicron variant of SARS-CoV-2 infection in China, we conducted a prospective study in which data were collected from patients diagnosed with AM associated with COVID-19 in China at that time of their hospitalization.

Methods

Study population

This is a multicentre, prospective cohort study in China involving six cardiology centres from four provinces, including Beijing (n = 1), Hunan (n = 2), Jiangsu (n = 2) and Henan (n = 1). Patients admitted between 1 December 2022 and 28 February 2023, with a history of SARS-CoV-2 infection, who were diagnosed with definite COVID-19–associated AM according to the 2022 ACC Expert Consensus[2] were enrolled (n = 28). All patients had CMR evidence of AM and 10 (35.7%) of them had AM confirmed by endomyocardial biopsy. Ethics committees from all six hospitals approved this study at each site. Informed consent was obtained from all patients before enrollment in the study.

Data collection and clinical definitions

Data on demographic, clinical, laboratory, electrocardiograph, echocardiography, CMR, chest computed tomography and computed tomography coronary angiography (CTCA) were collected from each patient through in-hospital electronic medical records. Follow-up information was collected by manual extraction from electronic medical records and telephone calls. Left ventricular systolic function was categorized as normal using transthoracic echocardiography if left ventricular ejection fraction (LVEF) was $\geq$50%, mildly reduced if LVEF was between 41% and 49%, reduced if it was $\leq$40%. The decision and timing to perform CMR examination and/or endomyocardial biopsy were at the discretion of the local clinical teams.

Statistical analysis

Continuous variables were expressed as means and standard deviations (normal distribution) or medians and interquartile ranges (skewed distribution), categorical variables were presented as frequencies and percentages. The differences of baseline characteristics were analysed based on onset time of AM (early-onset vs. delayed-onset). Student's t test, Wilcoxon rank-sum test or paired tests were used for comparing continuous variables where appropriate. Chi-square test or Fisher's exact test was used to compare categorical variables. Subject-specific longitudinal trajectories (on admission and before discharge) of markers of myocardial injury, cardiac structure, cardiac function and other major laboratory parameters were also depicted to characterize in-hospital dynamic disease progression. In all statistical analyses, two-tailed P values <0.05 were considered to be statistically significant. All analyses were performed using R 4.2.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline clinical characteristics

Clinical characteristics of the 28 patients with confirmed COVID-19–associated AM are presented in *Tables* 1 and 2.

Table 1 Demographic, biochemical, and imaging data for patients diagnosed with COVID-19–associated acute myocarditis

Patients	Age (y) and sex	Cardiac symptoms	Time from COVID-19 diagnosis (days)[a]	Peak of troponin, ng/mL, NT-proBNP/BNP, pg/mL	ECG findings	ECHO findings
1	17M	Dyspnoea, chest pain, chest tightness	2	cTnI: 2.6, NT-proBNP: 30 000	Sinus tachycardia, abnormal Q wave, ST segment elevation in V1-V3 and T wave inversion	LV 53 mm, EF 30%, E/e' 13, PCE
2	16F	Palpitation, chest tightness	21	cTnI: 5.51, NT-proBNP: 639	Sinus tachycardia, ST segment elevation	LV 45 mm, EF 53%, E/e' 7.2
3	16M	Chest tightness	6	cTnI: 0.275, NT-proBNP: 1302	Sinus rhythm, right axis deviation; Small R waves in V2 and V3	LV 39 mm, EF 49%, E/e' 11, PCE
4	71M	Dyspnoea, chest tightness	5	cTnI: 0.559, NT-proBNP: 295	Sinus rhythm, ventricular premature contractions, T wave inversion	LV 38 mm, EF 60%, E/e' 6.5, PCE
5	73M	Dyspnoea, chest tightness	11	cTnI: 1.27, NT-proBNP: 21 189	Atrial fibrillation, right axis deviation, right bundle branch block, ST segment elevation and T wave inversion	LV 43 mm, EF 60%,
6	53F	Dyspnoea, chest tightness, palpitation, syncope	0	cTnI: 0.217, NT-proBNP: 13 542	Sinus rhythm, abnormal Q wave, poor chest lead R wave progression, and T wave inversion.	LV 35 mm, EF 62%, E/e' 18, PCE
7	63M	Chest pain	5	cTnI: 0.292, NT-proBNP: 930	Sinus rhythm, abnormal Q wave, poor chest lead R wave progression, V5 R/S<1	LV 50 mm, EF 55%, E/e' 13
8	34F	Chest tightness	24	cTnI: 0.053, NT-proBNP: 6418	Sinus tachycardia, first-degree atrioventricular block, incomplete right bundle branch block	LV 50 mm, EF 53%, E/e' 9, PCE
9	34M	Dyspnoea, chest pain, chest tightness	1	cTnI: 28.3, NT-proBNP: 27 431	Sinus tachycardia, ectopic atrioventricular dissociation, accelerated junctional rhythm	LV 41 mm, EF 55%, E/e' 10, PCE
10	39M	Chest pain, chest tightness	20	cTnI: 0.197, NT-proBNP: 1330	Sinus rhythm (ventricular rate of 113 bpm), ST segment elevation in leads II, III, and aVF	LV 50 mm, EF 60%, E/e' 8, PCE
11	34M	Chest tightness	11	cTnI: 0.112, NT-proBNP: 1950	Sinus bradycardia, abnormal Q wave, poor chest lead R wave progression, ST-T segment depression, T wave inversion, long QT interval	LV 69 mm, EF 33%, E/e' 8.1
12	40M	Dyspnoea, chest tightness	10	cTnI: 2.99, NT-proBNP: 14 174	Sinus tachycardia, shortened PR interval, low voltage of QRS wave in limb leads, T wave inversion	LV 50 mm, EF 22%, PCE
13	55F	Chest pain, chest tightness	3	cTnI: 88, NT-proBNP: 35 000	Sinus rhythm, biphasic T waves in V4-V6, poor progression of R waves in the anterior wall	LV 38 mm, EF 24%,
14	51F	Dyspnoea	3	cTnI: 0.65, NT-proBNP: 35 000	Sinus tachycardia, QRS low voltage	LV 50 mm, EF 27%,
15	37F	Dyspnoea, chest tightness	6	cTnI: 0.01, NT-proBNP: 80	Sinus rhythm, T wave inversion in V1	LV 46 mm, EF 67%,
16	40F	Chest pain, chest tightness	1	hs-TnT: 0.248, NT-proBNP: 35 000	Sinus rhythm, T wave inversion, long QT interval	LV 49 mm, EF 54.9%, E/e' 13.2, PCE
17	18M	Chest pain, chest tightness	10	hs-TnT: 0.009, NT-proBNP: 60	Sinus rhythm, second degree type I atrioventricular block, left ventricular high voltage	LV 51 mm, EF 66.9%, E/e' 6.5

Table 1 (continued)

Patients	Age (y) and sex	Cardiac symptoms	Time from COVID-19 diagnosis (days)[a]	Peak of troponin, ng/mL, NT-proBNP/BNP, pg/mL	ECG findings	ECHO findings
18	35F	Dyspnoea, chest tightness	4	hs-TnT: 0.066, NT-proBNP: 4420	Sinus tachycardia, right axis deviation, ST segment upsloping elevation in leads I, avL, avF, and V2-V6, low voltage	LV 38 mm, EF 60.3%, E/e' 7.9, PCE
19	51F	Chest tightness	3	cTnI: 0.531, NT-proBNP: 5230	Sinus tachycardia, ST elevation in the inferior and lateral wall leads, T wave inversion and low voltage of limb leads	LV 46 mm, EF 57.9%, E/e' 10.6
20	15M	Chest pain	1	cTnI: 0.05, BNP: 1080	Sinus rhythm, right axis deviation, complete right bundle branch block, ST segment elevation and T wave inversion	LV 41 mm, EF 39%, PCE
21	35F	Dyspnoea, chest tightness	1	cTnI: 6.27, NT-proBNP: 1170	Sinus rhythm, atrial premature contractions, ST segment elevation	LV 42 mm, EF 16%, PCE
22	55F	Chest pain, palpitation,	0	cTnI: 0.05, NT-proBNP: 102	Sinus rhythm, premature atrial or ventricular contractions	LV 55 mm, EF 56%, PCE
23	53F	Chest tightness, palpitation	50	hs-TnT: 1.5, NT-proBNP: 1958	Sinus tachycardia, low voltage of QRS wave in limb leads, abnormal Q wave, mild elevation of ST segment in inferior and lateral wall leads, T wave inversion, prolonged QTc interval	LV 42 mm, EF 59%, PCE
24	23M	Chest pain	14	cTnI: 1.16, NT-proBNP: 529	Sinus rhythm, ST segment elevation	LV 48 mm, EF 57%
25	25M	Chest pain	11	hs-TnT: 2.293, NT-proBNP: 1930	Sinus rhythm, ST segment elevation	LV 42 mm, EF 64%
26	38M	Chest tightness	9	hs-TnT: 5.29, BNP: 155	Sinus rhythm, low voltage of QRS wave in limb leads, ST segment elevation in V2-V6, T wave inversion	LV 53 mm, EF 47%, E/e' 11
27	21M	Palpitation	1	hs-TnT: 4.78, BNP: 545	Sinus rhythm, right bundle branch block, wide QRS tachycardia, prolonged QT interval	LV 53 mm, EF 57%, E/e' 6.52
28	17F	Chest pain, chest tightness	0	hs-TnT: 0.231, NT-proBNP: 128	Sinus rhythm, shortened PR interval	LV 45 mm, EF 60.5%, E/e' 7.69

BNP, B-type natriuretic peptide;cTnI, cardiac troponin I; CMR, cardiac magnetic resonance; COVID-19, Coronavirus disease 2019; CT, computerized tomography; CTCA/CAG, computed tomography coronary angiography/coronary angiography; ECHO, echocardiography; ECMO, extracorporeal membrane oxygenation; ECV, extracellular volume; EF, ejection fraction; EMB, endomyocardial biopsy; GDMT, guideline-directed medical treatment; hs-TnT, hypersensitive troponin T; IABP, intra-aortic balloon pump; LAD, left anterior descending artery; LCX, left circumflex artery; LGE, late gadolinium enhanced; LMWH, low molecular weight heparin; LV, left ventricular; NCM, not consistent with myocarditis; NOAC, novel oral anticoagulants; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PCE, pericardial effusion; RCA, right coronary artery; rhBNP, recombinant human brain natriuretic peptide.
[a]Time from COVID-19 diagnosis to the onset of myocarditis symptoms.
[1b]Time from the onset of myocarditis symptoms to the CMR examination.

Table 1 (continued)

Patients	Time to first CMR (days)[b]	CMR findings	EMB findings	Chest X-ray/CT	CTCA/CAG	Treatment	Follow-up ECHO (time and findings)	Follow-up CMR (time and findings)
1	7	↑T1, ↑T2, ↑ECV (mean 31.8%), PCE	Inflammatory cells>14 cells/mm^2, CD3+, CD68+, CD4+, CD8+, CD20+	+	CTCA Normal	Methylprednisolone ivgtt 7d, prednisone po 112d, immune globulin 6d, Paxlovid 6d, LMWH 6d, dopamine 10d, noradrenaline 3d, non-invasive ventilator 7d, IABP 6d, GDMT	8 weeks: LV 41 mm, EF 63%, E/e' 4.7; 12 weeks: LV 43 mm, EF 60%, E/e ' 9	8 weeks: Reduced oedema and PCE disappeared; 24 weeks, Normal
2	7	↑T1,↑T2, LGE (2.3%), ↑ECV (mean 30.9%)	Cardiomyocyte hypertrophy, NCM	N/A	CTCA Normal	GDMT	32 weeks: Normal	4 weeks; Residual LGE and reduced oedema; 16 weeks: Normal; 32 weeks: Normal
3	8	↑T1, ↑T2, LGE (1.6%), PCE, ↑ECV (mean 37.4%)	Cardiomyocyte hypertrophy, inflammatory cells>14 cells/mm^2, CD3+, CD68+, CD4+, CD8+	Normal	N/A	Prednisone po 107d, immune globulin 1d, GDMT	4 weeks: LV 48 mm, EF 62%, E/e' 8 12 weeks: LV 45 mm, EF 67%, E/e ' 7	4 weeks: Reduced oedema and PCE; 12 weeks: Normal
4	8	↑T1, ↑T2, LGE (27.2%), ↑ECV (mean 34.9%), PCE	Cardiomyocyte hypertrophy, CD68+, NCM	+	CTCA Normal	LMWH 2d, sodium nitroprusside 1d, non-invasive ventilator 3d	4 weeks: LV 48 mm, EF 61%, E/e' 10 12 weeks: LV 43 mm, EF 60%, E/e ' 13	N/A
5	5	↑T1, ↑T2, ↑ECV (mean 31.3%)	N/A	Normal	CAG -LAD 60% stenosis, RCA 70% stenosis	methylprednisolone ivgtt 7d, immune globulin 5d, azvudine 6d, LMWH 7d, dopamine 1d, noradrenaline 1d, ventilator 1d, GDMT	N/A	N/A
6	3	↑T1, ↑T2, LGE (2.4%), ↑ECV (mean 34.1%), PCE	Cardiomyocyte hypertrophy, Inflammatory cells<14cells/mm^2, fatty degeneration, CD3+, CD68+	+	CTCA Normal	methylprednisolone ivgtt 6d, prednisone po 118d, immune globulin 6d, Paxlovid 6d, LMWH 12d, GDMT	4 weeks: LV 44 mm, EF 68%, E/e' 9.78; 24 weeks: LV 42 mm, EF 66%	4 weeks: Residual LGE and Reduced oedema; 24 weeks: Normal
7	7	↑T1, ↑T2, ↑ECV (mean 31.5%)	Cardiomyocyte hypertrophy, inflammatory cells >14 cells/mm^2, CD3+, CD68+	Normal	CAG Normal	prednisone po 89d, GDMT	4 weeks: LV 53 mm, EF 69%, E/e' 9	10 weeks: Normal
8	1	↑T1,↑T2, ↑ECV (mean 37.6%), PCE	Cardiomyocyte hypertrophy, inflammatory cells >14 cells/mm^2, CD3+, CD68 + , CD8+	Normal	CTCA Normal	methylprednisolone ivgtt 8d, prednisone po 94d, immune globulin 3d, LMWH 11d, GDMT	4 weeks: LV 47 mm, EF 67%, E/e' 7	8 weeks: Normal

Table 1 (continued)

Patients	Time to first CMR (days)[b]	CMR findings	EMB findings	Chest X-ray/CT	CTCA/CAG	Treatment	Follow-up ECHO (time and findings)	Follow-up CMR (time and findings)
9	3	↑T1,↑T2, LGE (32.7%), ↑ECV (mean 40.7%), PCE	Cardiomyocyte hypertrophy, inflammatory cells >14 cells/mm^2, CD3+, CD68+, CD4+, CD8+, CD20+	Normal	CTCA Normal	methylprednisolone ivgtt 3d, immune globulin 4d, LMWH 4d, rhBNP 2d, dopamine 1d, noradrenaline 1d, non-invasive ventilator 1d, ventilator 1d, IABP 1d, ECMO 1d	N/A	N/A
10	5	T2WI (+), LGE (1.6%), PCE	N/A	+	CTCA Normal	prednisone po 1d	12 weeks: LV 47 mm, EF 63%, E/e ' 4.1	12 weeks: Residual LGE and PCE disappeared
11	13	LGE (23.9%), ↑T1, ↑ECV (mean 59.1%)	Cardiomyocyte hypertrophy, inflammatory cells >14 cells/mm^2, CD3+, CD68+	Normal	CTCA-LAD 70% stenosis LCX 50% stenosis	methylprednisolone ivgtt 3d, prednisone po 90d, immune globulin 7d, Paxlovid 5d, NOAC persistent, dopamine 7d, noradrenaline 3d	4 weeks: LV 68 mm, EF 39%, E/e' 6.6; 24 weeks: LV 64 mm, EF 44%, E/e ' 10	4 weeks: Residual LGE; 24 weeks: Improved LV systolic function
12	8	↑T1, ↑T2, ↑ECV (mean 33.2%), LGE (21.2%), PCE	inflammatory cells>14 cells/mm^2, CD3+, CD68+, CD8+	Normal	CTCA Normal	methylprednisolone ivgtt 3d, prednisone po 82d, immune globulin 5d, rhBNP 7d, Paxlovid 5d, non-invasive ventilator 1d, IABP 7d, GDMT	4 weeks: LV 41 mm, EF 57%, E/e' 7	4 weeks: Reduced oedema and PCE
13	10	T2 STIR (+), LGE, ↑ECV	N/A	+	CAG Normal	methylprednisolone ivgtt 6d, immune globulin 4d, LMWH 4d, IABP 4d, GDMT	N/A	N/A
14	8	T2WI (+), ↑ECV	N/A	N/A	N/A	methylprednisolone ivgtt 6d, immune globulin 4d, LMWH 6d, dopamine 1d, noradrenaline 7d, IABP 5d	N/A	N/A
15	5	T2WI (+), ↑ECV	N/A	N/A	N/A	N/A	N/A	N/A
16	13	↑T1, ↑T2, LGE, ↑ECV, PCE	N/A	+	CAG Normal	methylprednisolone ivgtt 20d, methylprednisolone po 2d, heparin 11d, LMWH 2d, dopamine 1d, noradrenaline 4d	N/A	N/A

Table 1 (continued)

Patients	Time to first CMR (days)[b]	CMR findings	EMB findings	Chest X-ray/CT	CTCA/CAG	Treatment	Follow-up ECHO (time and findings)	Follow-up CMR (time and findings)
17	3	↑T1, ↑T2, LGE, ↑ECV	N/A	N/A	N/A	methylprednisolone ivgtt 2d	N/A	N/A
18	14	↑T1, ↑T2, LGE, ↑ECV, PCE	N/A	Normal	N/A	methylprednisolone ivgtt 7d, immune globulin 3d, rhBNP 2d, GDMT	N/A	N/A
19	11	↑T1, T2WI (+), LGE, ↑ECV	N/A	Normal	N/A	methylprednisolone ivgtt 13d, LMWH 9d, noradrenaline 4d, GDMT	N/A	N/A
20	9	T2WI (+), LGE, ↑ECV, PCE	N/A	+	N/A	hydrocortisone ivgtt 6d, immune globulin 6d, heparin 8d, ECMO 3d, GDMT	N/A	N/A
21	12	T2-STIR (+), LGE, ↑ECV, PCE	N/A	+	CAG Normal	methylprednisolone ivgtt 13d, immune globulin 9d, azvudine 8d, argatroban 10d, dopamine 2d, IABP 9d, ECMO 9d	N/A	N/A
22	5	T2WI (+), LGE, PCE	N/A	+	N/A	N/A	N/A	N/A
23	8	↑T2, LGE, ↑ECV, PCE	N/A	Normal	CAG Normal	LMWH 4d, GDMT	N/A	N/A
24	3	T2WI (+), LGE, ↑ECV	N/A	Normal	CAG Normal	GDMT	N/A	N/A
25	4	T2WI (+), LGE, ↑ECV	N/A	Normal	N/A	GDMT	N/A	N/A
26	3	T2-STIR (+), LGE, ↑ECV	N/A	Normal	N/A	N/A	N/A	N/A
27	8	T2WI (+), LGE, ↑ECV	N/A	N/A	CTCA Normal	N/A	N/A	N/A
28	1	T2WI (+), LGE, ↑ECV	N/A	N/A	N/A	N/A	N/A	N/A

BNP, B-type natriuretic peptide;cTnI, cardiac troponin I; CMR, cardiac magnetic resonance; COVID-19, Coronavirus disease 2019; CT, computerized tomography; CTCA/CAG, computed tomography coronary angiography/coronary angiography; ECHO, echocardiography; ECMO, extracorporeal membrane oxygenation; ECV, extracellular volume; EF, ejection fraction; EMB, endomyocardial biopsy; GDMT, guideline-directed medical treatment; hs-TnT, hypersensitive troponin T; IABP, intra-aortic balloon pump; LAD, left anterior descending artery; LCX, left circumflex artery; LGE, late gadolinium enhanced; LMWH, low molecular weight heparin; LV, left ventricular; NCM, not consistent with myocarditis; NOAC, novel oral anticoagulants; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PCE, pericardial effusion; RCA, right coronary artery; rhBNP, recombinant human brain natriuretic peptide.

[a]Time from COVID-19 diagnosis to the onset of myocarditis symptoms.

[b]Time from the onset of myocarditis symptoms to the CMR examination.

Table 2 Baseline characteristics of patients admitted with COVID-19–associated AM according to the onset time

Variables	No. of patients with available data	Overall (*N* = 28)	The onset time		*P* value
			Early onset (*N* = 23)	Delayed onset (*N* = 5)	
Demographics					
Male, *n* (%)	28	15 (53.6%)	13 (56.5%)	2 (40.0%)	0.639
Age, years	28	37.0 (22.0, 52.0)	37.5 (22.0, 52.5)	34.0 (23.0, 39.0)	0.472
BMI, kg/m^2	28	23.8 (21.6, 28.4)	23.8 (21.5, 25.8)	23.8 (23.6, 28.4)	0.455
Co-morbidity					
Hypertension, *n* (%)	28	3 (10.7%)	3 (13.0%)	0 (0.0%)	1.000
Diabetes, *n* (%)	28	3 (10.7%)	2 (9.1%)	1 (20.0%)	1.000
Coronary heart disease, *n* (%)	28	2 (7.1%)	2 (8.7%)	0 (0.0%)	1.000
Heart failure, *n* (%)	28	2 (7.1%)	2 (8.7%)	0 (0.0%)	1.000
Thyroid disease, *n* (%)	28	2 (7.1%)	2 (8.7%)	0 (0.0%)	1.000
Previous myocarditis/pericarditis, *n* (%)	28	2 (7.1%)	2 (8.7%)	0 (0.0%)	1.000
Previous/current smoking, *n* (%)	28	5 (17.9%)	4 (17.4%)	1 (20.0%)	1.000
Autoimmune disorder, *n* (%)	28	1 (3.6%)	1 (4.3%)	0 (0.0%)	1.000
Current/previous cancer, *n* (%)	28	1 (3.6%)	0 (0%)	1 (20.0%)	0.179
SARS-CoV2 vaccination, *n* (%)	24	18 (75.0%)	14 (73.7%)	4 (80.0%)	1.000
Symptoms of myocarditis					
Palpitation, *n* (%)	28	5 (17.9%)	3 (13.0%)	2 (40.0%)	0.207
Dyspnoea, *n* (%)	28	10 (35.7%)	10 (43.5%)	0 (0.0%)	0.128
Chest pain, *n* (%)	28	12 (42.9%)	10 (45.5%)	2 (40.0%)	1.000
Chest tightness, *n* (%)	28	21 (75.0%)	18 (78.3%)	3 (60.0%)	0.574
Clinical presentation					
Systolic blood pressure, mmHg	28	112 (95, 119)	105 (95, 121)	112 (112, 112)	0.509
Diastolic blood pressure, mmHg	28	71 (67, 80)	69 (66, 80)	78 (70, 80)	0.674
Heart rate, b.p.m.	28	90 (82, 104)	90 (81, 104)	90 (84, 104)	0.674
Body temperature, °C	28	36.5 (36.2, 36.7)	36.3 (36.2, 36.6)	36.8 (36.7, 37.2)	0.017
Respiratory rate, b.p.m.	28	20.0 (19.0, 22.0)	20.0 (18.5, 20.0)	22.0 (20.0, 22.0)	0.069
Cardiogenic shock, *n* (%)	28	5 (17.9%)	5 (21.7%)	0 (0.0%)	0.550
Fulminant myocarditis, *n* (%)	28	7 (25.0%)	7 (30.4%)	0 (0.0%)	0.290
Pneumonia, *n* (%)	28	10 (35.7%)	9 (39.1%)	1 (25.0%)	1.000
Need for supplemental oxygen, *n* (%)	28	18 (64.3%)	15 (65.2%)	3 (60.0%)	1.000
Liver function injury, *n* (%)	28	14 (50.0%)	13 (56.5%)	1 (20.0%)	0.326
Renal function injury, *n* (%)	28	8 (28.6%)	7 (30.4%)	1 (20.0%)	1.000
Markers of myocardial injury					
Baseline NT-proBNP, pg/mL	25	1958.0 (440.1, 14 174.7)	4630.5 (550.6, 19 435.4)	529.0 (440.1, 1958.0)	0.297
Peak NT-proBNP, pg/mL	25	1950.0 (639.0, 14 174.0)	3185.0 (771.25, 22 749.5)	1330.0 (639.0, 1958.0)	0.233
Baseline cTnI, ng/mL	20	0.560 (0.156, 2.993)	0.560 (0.156, 2.993)	0.679 (0.089, 4.423)	0.915
Peak cTnI, ng/mL	20	0.531 (0.155, 1.935)	0.531 (0.165, 1.935)	0.679 (0.161, 2.248)	0.671
Baseline hs-TnT, ng/mL	20	0.374 (0.090, 2.052)	0.286 (0.081, 2.035)	1.138 (0.300, 7.975)	0.299
Peak hs-TnT, ng/mL	20	0.374 (0.115, 2.280)	0.286 (0.115, 2.280)	1.415 (0.396, 8.018)	0.395
Inflammatory markers					
WBC count, $\times 10^9$/L	28	9.34 (6.35, 15.01)	8.90 (6.21, 15.39)	12.8 (12.7, 13.9)	0.418
Lymphocyte count, $\times 10^9$/L	28	1.23 (0.90, 1.90)	1.22 (0.80, 1.86)	1.42 (0.95, 1.88)	0.574
CRP, mg/L	19	35.5 (3.7, 88.7)	19.2 (3.2, 88.6)	211.4 (134.6, 288.2)	0.184
ESR, mm/h	17	20 (9, 47)	60 (33, 80)	17 (10, 37)	0.281
Ferritin, ng/mL	16	574.7 (171.1, 974.7)	858.3 (522.5, 974.7)	564.32 (148.2, 890.8)	0.564
IL-6, pg/mL	12	13.17 (9.39, 71.92)	10.10 (6.42, 74.58)	15.05 (9.55, 48.42)	0.814

(*Continues*)

Table 2 (continued)

Variables	No. of patients with available data	Overall (N = 28)	The onset time		P value
			Early onset (N = 23)	Delayed onset (N = 5)	
Other laboratory results					
ALB, g/L	28	37.62 (34.60, 40.53)	40.80 (37.12, 41.65)	37.26 (34.60, 39.48)	0.355
ALT, IU/L	28	43.00 (19.75, 80.50)	34.60 (18.62, 80.50)	55.00 (45.50, 81.00)	0.434
Creatinine, μmol/L	28	66.60 (49.50, 86.40)	63.26 (49.38, 98.36)	69.20 (46.55, 86.27)	0.950
eGFR, mL/min	28	103.30 (91.50,123.64)	104.00 (90.00, 121.00)	98.00 (86.76, 138.20)	1.000
D-Dimer, mg/L	24	1.16 (0.33, 2.65)	1.45 (0.30, 2.67)	1.05 (0.45, 3.49)	0.859

ALB, albumin; ALT, alanine transaminase; AM, acute myocarditis; BMI, body mass index; COVID-19, Coronavirus disease 2019; CRP, C-reactive protein; cTnI, cardiac troponin I; eGFR, estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate; hs-TnT, hypersensitive troponin T; IL-6, interleukin-6; N-terminal pro-B-type natriuretic peptide; SARS-CoV2, severe acute respiratory syndrome coronavirus 2; WBC, white blood cell.

Their median age was 37 years (Q1–Q3: 22–52) and 53.6% were men. Two patients (7.1%) had a history of previous myocarditis/pericarditis, and one patient (3.6%) had previously been diagnosed with an autoimmune disorder. Among the 28 patients, 18 (64.3%) had been vaccinated (CoronaVac, Sinovac, China) against SARS-CoV-2 and time from the last vaccination to the symptom of myocarditis was longer than 3 months. All patients were diagnosed with COVID-19 by positive real-time polymerase chain reaction or SARS-CoV-2–specific antibodies or antigens.

The most frequent cardiac symptoms were chest tightness in 21 (75.0%), chest pain in 12 (42.9%) and dyspnoea in 10 (35.7%). Out of 28 AM patients, 7 (25.0%) presented with fulminant myocarditis, 5 (17.9%) with cardiogenic shock, 10 (35.7%) with pneumonia, 8 (28.6%) with renal impairment and 14 (50.0%) with liver dysfunction.

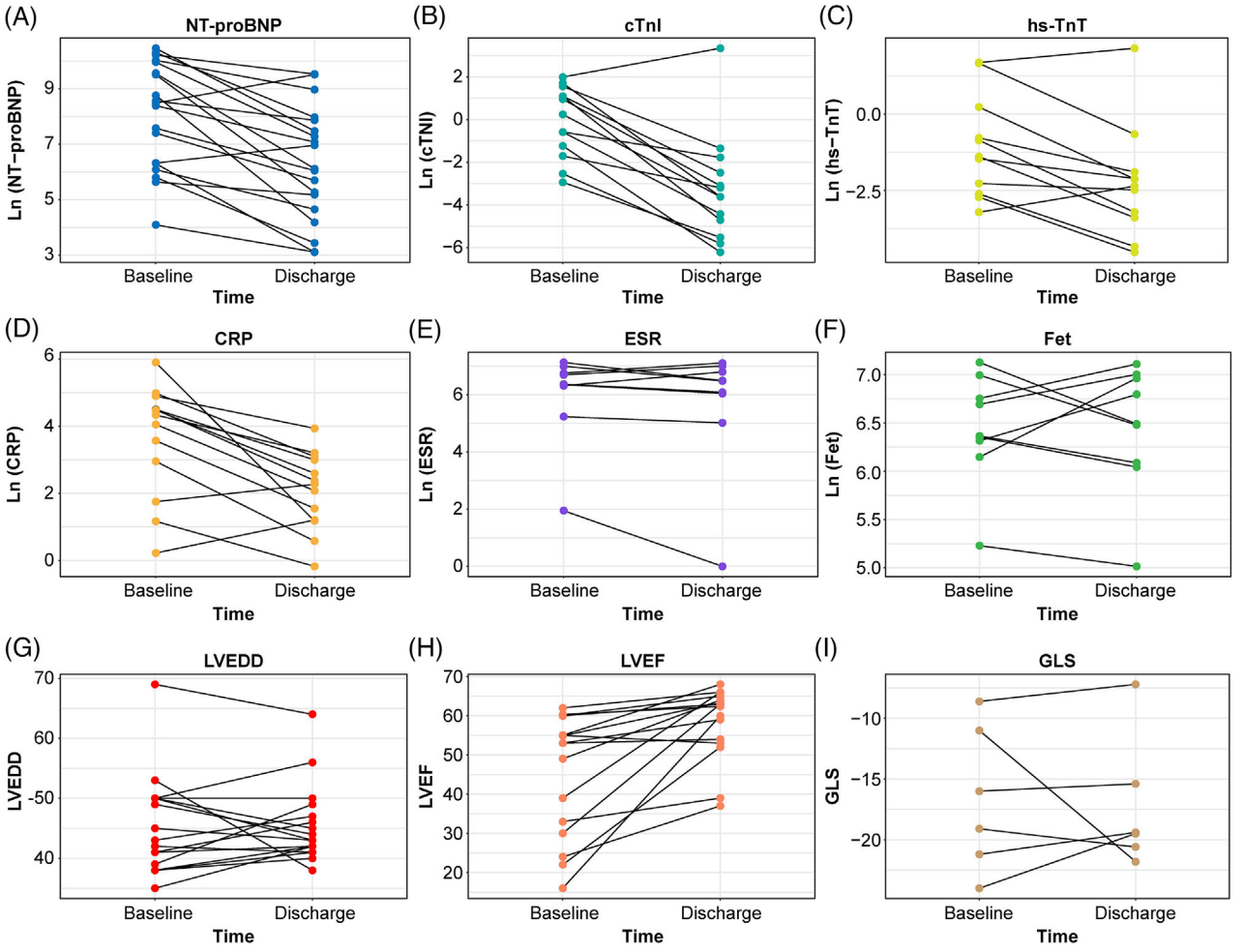
The interval from SARS-CoV-2 infection to the onset of AM was considered to be early-onset in that it occurred less than 2 weeks from the onset of COVID-19 symptoms and 23 cases (82.1%) met this criterion. The remaining five cases (17.9%) developed evidence of AM later than 2 weeks after COVID-19 diagnosis, and they were considered as having delayed-onset. There were no significant differences in demographic characteristics, comorbidities, cardiac symptoms and other significant clinical manifestations between the early- and delayed-onset AM.

Markers of heart failure and myocardial injury

Twenty-five patients were tested for markers of HF at the time of AM diagnosis. As shown in *Table* 2, the median value of baseline N-terminal pro-B-type natriuretic peptide (NT-proBNP) was 1958.0 pg/mL (Q1–Q3: 440.1–14 174.7, n = 25), which was similar to the median of peak level of NT-proBNP [1950.0 pg/mL (Q1–Q3: 639.0–14 174.0), n = 25)]. There were no significant differences regarding NT-proBNP levels either at baseline or in peak values between early- and delayed-onset AM. As depicted in *Figure* 1A, NT-proBNP levels decreased significantly from baseline to discharge (n = 19, $P < 0.001$) and were then maintained at a steady level at 1-month follow-up (*Figure* 2B).

Markers of myocardial injury (cardiac troponin I and/or hypersensitive troponin T) were elevated in all patients. The median value of baseline cardiac troponin I was 0.560 ng/mL (Q1–Q3: 0.156–2.993, n = 20), and the peak value of cardiac troponin I was close to the baseline (*Figure* 2C). The median value of baseline hypersensitive troponin T was 0.374 ng/mL (Q1–Q3: 0.090–2.052, n = 20), and its peak level was similar (0.374 ng/mL, Q1–Q3: 0.115–2.280, n = 20). There were no significant differences in these markers of myocardial injury between early- and delayed-onset AM. As shown in *Figure* 1B, the levels of cardiac troponin I decreased significantly during hospitalization

Figure 1 The changes of biochemical and echocardiological parameters from admission to discharge. CRP, C-reactive protein; cTnI, cardiac troponin I; ESR, erythrocyte sedimentation rate; Fet, ferritin; GLS, global longitudinal strain; hs-TnT, hypersensitive troponin T; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide.



(n = 13, P = 0.021), but there was no significant decrease in the level of hypersensitive troponin T (n = 11, P = 0.067, *Figure* 1C).

Inflammatory and autoimmune-related markers

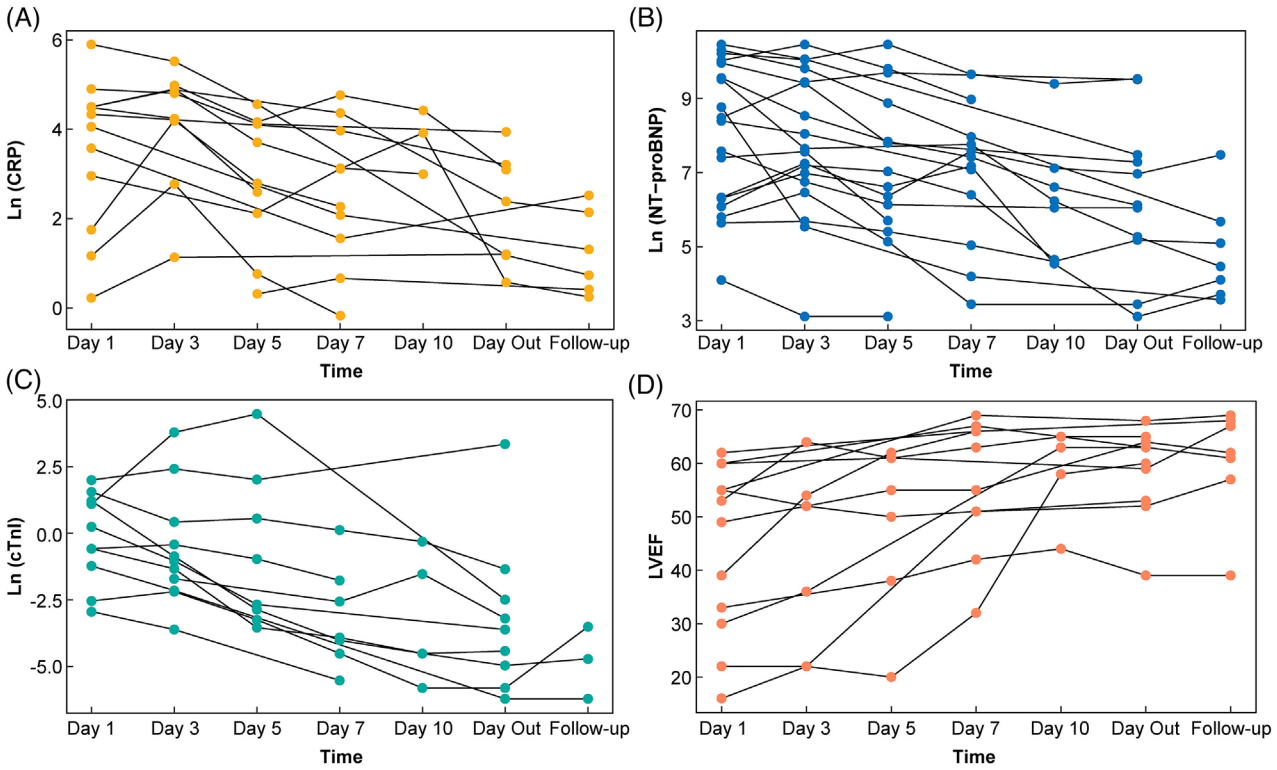
Elevated white blood cell was noted in 13 patients, while lymphopenia was present in 9 patients on admission. Elevations in inflammatory markers were also noted. Elevation in C-reactive protein was observed in 11 of 19 patients (57.9%) for whom baseline levels were available, 11 of 16 patients (68.8%) with baseline ferritin levels, 9 of 17 patients (52.9%) with baseline erythrocyte sedimentation rate, and 9 of 12 patients (75.0%) who had IL-6 levels drawn. In general, the inflammatory markers of AM patients showed a downward trend from admission to discharge (*Figure* 1D–F). At 1-month follow-up, five of the six patients who had C-reactive protein measured had lower levels than at the time of hospital discharge (*Figure* 2A).

Regarding autoimmune-related examinations, it is worth noting that 6 out of 14 patients were tested positive for antinuclear antibodies, 3 out of 14 patients had decreased complement levels, 3 out of 12 patients had elevated rheumatoid factor levels, 1 out of 9 patient was positive for lupus anticoagulant, and 1 out of 9 patients was positive for anti-β2 glycoprotein antibody. In terms of thromboembolism-related parameters, elevated D-dimer levels were noted in 16 of 24 patients.

Electrocardiograph and imaging tests

As shown in *Table* 1, electrocardiographic findings in 28 patients differed quite broadly. One patient exhibited atrial fibrillation and 27 patients were with sinus rhythm. Nine pa-

Figure 2 The dynamic changes in CRP, NT-proBNP, cTnI, and LVEF during hospitalization and at follow-up. CRP, C-reactive protein; cTnI, cardiac troponin I; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide.



tients showed sinus tachycardia and one patient showed sinus bradycardia. Additionally, four patients showed right bundle branch block, one patient showed first-degree atrioventricular block and one patients showed second degree type I atrioventricular block. Furthermore, 12 patients had ST-segment elevation, 1 patient had ST-segment depression, and 12 patients had T-wave inversion. During hospitalization, two patients experienced ventricular tachycardia and received electrical cardioversion.

Echocardiography was performed in all 28 patients. The median LVEF of this cohort was 55.5% (45%, 60%), and median left ventricular end-diastolic dimension was 46 (41.75, 50) mm. More than half of the patient (n = 19, 67.9%) had normal systolic function, whereas 2 (7.1%) had mild reduced and 7 (25.0%) had reduced systolic dysfunction. Among patients with LVEF $<$50% at baseline, five patients recovered to normal LVEF at discharge, and two patients had an improvement but remained lower than normal LVEF (*Figure* 1H). The seven patients who underwent echocardiography examination at 1-month follow-up demonstrated only minimal change in their LVEF over this period of time (*Figure* 2D). Although pericardial effusion was observed in 14 patients (50.0%) on admission, it was considered to be large in only 1 patient. Pericardial effusion had spontaneously reduced or resolved during the follow-up.

All 28 patients underwent CMR examinations. The CMR imaging showed myocardial oedema (96.4%, *Figure* 3A), late gadolinium enhancement (LGE, 78.6%) or both (75.0%). Nine patients (32.1%) underwent CMR examinations for at least one time during follow-up. Among them, six patients showed reduced myocardial oedema at 1-month post-discharge, six patients were completely normal at 2 to 8 months after discharge, one patient had residual LGE and disappearance of pericardial effusion at 3 months, and one patient showed a significant improvement in LVEF 6 months after discharge. The comparison of CMR parameters between the baseline and first follow-up (median: 4 weeks; available in nine patients) were shown in *Table* 3. Compared with the baseline indicators, ECV was decreased at the first follow-up [28.95 (25.38, 32.55)% vs. 33.65 (31.58, 37.55)%, P = 0.028), while other CMR parameters had no significant changes.

Of the 17 patients who underwent CTCA or coronary angiography after admission, 15 had normal coronary arteries while 2 had significant coronary lesions.

Endomyocardial biopsy and histological findings

During hospitalization, endomyocardial biopsy was performed in 10 patients. Cardiomyocyte hypertrophy was com-

Figure 3 Cardiac magnetic resonance (CMR) imaging and histological findings of 1 patient with COVID-19–associated fulminant myocarditis. (A) CMR images at 3.0 Tesla of a 17-year-old patient (case 1 in *Table* 1). CMR imaging presented myocardial oedema and pericardial effusion. Short-tau inversion recovery (STIR) T2-weighted imaging showed a slightly increased signal intensity in the left ventricular myocardium, especially in the ventricular septum. T1 mapping value ranged from 1250 to 1450 ms (reference range: 1200–1250 ms) and T2 mapping values ranged from 44 to 48 ms (reference range: 40–45 ms). However, post-contrast images did not show apparent late gadolinium enhancement (LGE). (B) Endomyocardial biopsy (EMB) findings from this patient showed inflammatory infiltration in the myocardium (left images, haematoxylin and eosin images at 10× and 20× magnification) and positive CD3 and CD68 immunohistochemical stains (right images, images at 20 × magnification). COVID-19, coronavirus disease 2019.

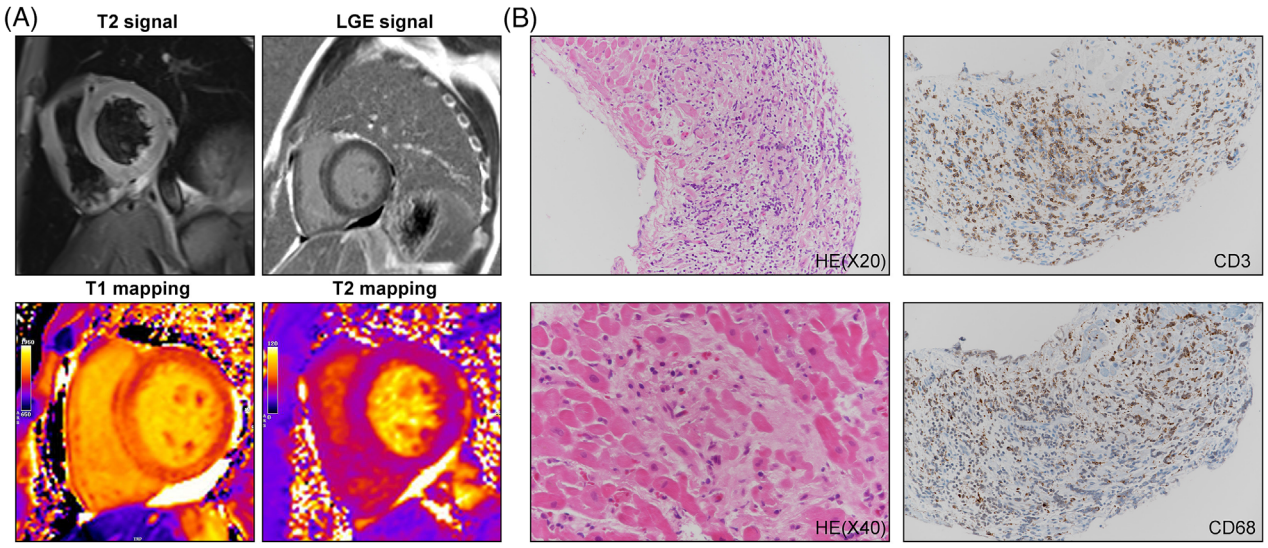


Table 3 The parameters of cardiac magnetic resonance (CMR) at baseline and first follow-up of nine patients from the same center

	Baseline	First follow-up	*P* value
LGE mass (g)	1.55 (0, 11.8)	8.45 (5.03, 18.63)	0.463
LGE extent (%)	1.95 (0, 23.23)	25.0 (13.35, 29.48)	0.116
T1 mean (ms)	1335.85 (1282.75, 1374.90)	1268.40 (1238.95, 1334.78)	0.327
T2 mean (ms)	46.10 (42.40,51.40)	48.50 (40.20, 53.10)	0.249
ECV mean (%)	33.65 (31.58, 37.55)	28.95 (25.38, 32.55)	0.028

ECV, extracellular volume; LGE, late gadolinium enhanced.

mon, but no vacuolar degeneration was observed. In eight patients (80.0%), myocardial tissue showed interstitial mononuclear lymphocytes and neutrophils infiltration, with ≥14 cells/mm^2 in seven cases (meeting lymphocytic myocarditis criteria; *Figure* 3B) and <14 cells/mm^2 in one case. Immunohistochemical staining showed CD3$^+$ and CD68$^+$ in all eight patients, of which two cases with fulminant myocarditis showed CD3$^+$, CD20$^+$, CD4$^+$, CD8$^+$ and CD68$^+$. No myocardial inflammation changes were observed in the other two cases (20.0%). The electronic microscopy did not detect SARS-CoV-2 in the myocardial tissue of all 10 patients.

Treatment and short-term prognosis

A total of 18 of the 28 patients (64.3%) were treated with corticosteroids. Fifteen were treated with intravenous agents during hospitalization with an average duration of 7.3 days, and three patients were given oral prednisone. Nine of the 18 patients continued to take oral corticosteroids post-discharge. The mean initial dose was 42 mg (in terms of prednisone), and therapy was continued over a mean duration of 77.2 days. Immunoglobulin was given to 13 patients (46.4%), with an average duration of 4.8 days and a mean cumulative dose of 90 g. No patients received tocilizumab or baricitinib. Antiviral treatment was administered to six patients (21.4%), four patients of whom received Paxlovid for an average of 5.5 days and two patients (7.1%) who received azvudine for a mean of 7.0 days. Vasoactive drugs including dopamine and norepinephrine were used in seven patients (25.0%). Five patients (17.9%) required mechanical ventilation, with an average duration of 3.6 days; in six patients (21.4%), an intra-aortic balloon pump was used with an average duration of 5.0 days. The three patients (10.7%) with fulminant myocarditis required extracorporeal membrane oxygenation support, with an average duration of 4.3 days.

Overall, 2 of 28 patients (7.1%) with COVID-19–associated AM died due to heart and other organ failure during hospitalization while all the others survived and recovered well at 1 month follow-up.

Discussion

This study provides a description of the clinical course, management and outcomes of a large cohort of patients in China who developed AM in association with COVID-19 infection. The main findings are that most patients developed myocarditis within 2 weeks after the onset of COVID-19 infection and that fulminant myocarditis occurred in about one-quarter of the cases. Biomarkers reflecting increased myocardial wall stress and myocardial injury were elevated in most patients, and biomarkers of inflammation were elevated in many of the patients in whom they were obtained. We feel that the outcome in this cohort was generally favourable with only 2 of 28 patients died. The vast majority of the patients with COVID-19–associated AM recovered fully by 1 month after hospital discharge.

The SARS-CoV-2 has demonstrated frequent genetic mutations during transmission among humans. To date, the World Health Organization has proposed five variants of concern. The Omicron variant emerged in the fall of 2021 and replaced the Delta variant as the dominant strain by early 2022.[4] Evidence suggests that the pulmonary pathogenicity of the Omicron variant is reduced from earlier variants, and its clinical presentations have changed from pneumonia to upper respiratory infection.[4] Because angiotensin converting enzyme 2 receptors that mediate the uptake of virus into cells are widely distributed throughout the body including the myocardium, it has been suggested that SARS-CoV-2 might invade myocardium and cause myocarditis.[5] A recent study by Ammirati et al.[1] reported that of patients hospitalized with COVID-19 infection, 2.4 per 1000 patients had definite/probable evidence of AM and an additional 1.7 per 1000 had possible AM. In their study, patients with definite/probable AM supported by CMR in 92.6% patients or endomyocardial biopsy in 31.5%. Nearly half (42.6%) of the patients had COVID-19 related pneumonia and 38.9% were diagnosed with fulminant myocarditis. Similarly, in the present study, COVID-19–associated AM was definitely identified by CMR (100%) and/or endomyocardial biopsy (35.7%). Of these, 25.0% presented with fulminant myocarditis and 35.7% occurred in the presence of COVID-19 associated pneumonia.

Laboratory data plays an important role in making the diagnosis of COVID-19–associated AM. Abnormal white blood cell, elevations in cardiac biomarkers and inflammatory markers in the appropriate clinical setting should raise suspicion of the diagnosis of both early-onset and delayed-onset myocarditis. Overall, our findings regarding inflammatory biomarkers are consistent with previous literature.[6] We also noted abnormalities in autoimmune-related indicators in some patients. These results support the possibility that inflammatory and autoimmune mechanisms may play an important role in the pathogenesis of COVID-19–associated AM. Notably, changes in inflammatory markers, such as C-reactive protein, during hospitalization was roughly paralleled changes in markers related to myocardial injury.

CMR is one of the most important non-invasive diagnostic examinations for AM. Common findings include subepicardial oedema and necrosis, mainly affecting the lateral and inferolateral walls of the left ventricle. Myocardial lesions in non-ischaemic myocardial inflammation tend to be patchy occurring in subepicardial and midwall regions (as opposed to ischaemic lesions that are more common in the subendocardial regions).[7] CMR cannot, however, distinguish AM caused by acute viral infection from that due to secondary immune response. COVID-19–associated AM has been reported to show prolonged myocardial T1 and especially T2 relaxation time on CMR. Oedema is manifested by regional or global signal intensity increase on T2-weighted images, while T2 mapping allows direct measurement of water-induced prolonged myocardial T2 relaxation.[8] Although the presence of both positive T1 and T2 markers increases the specificity in detecting AM, satisfying only one of them still supports the diagnosis of AM in appropriate clinical scenarios. Ferreira et al.[9] reported that T1 localization alone had an 89% diagnostic accuracy within 14 days of symptom onset in patients hospitalized for AM.

In this study, nearly one-third of the patients had a reduced LVEF on echocardiography. During hospitalization, LVEF had largely improved to the baseline level at discharge, which was significantly higher than on admission. In addition to reduced LVEF, echocardiography can show abnormal ventricular dimensions and less frequently increased wall thickness due to secondary oedema in patients with COVID-19–associated AM.[10] AM patients usually showed recovery of left ventricular systolic function and complete resolution of myocardial hypertrophy after treatment.[11,12]

Current guidelines recommend that for men over 50 years and women over 55 years diagnosed with COVID-19–associated AM, acute coronary syndrome should be ruled out.[1] In this study, all three patients in this age group underwent CTCA or coronary angiography examination, of which one patient had a 60% stenosis of left anterior descending artery and 70% stenosis of right coronary artery but acute coronary syndrome was ruled out according to clinical symptoms, electrocardiographic findings, trending in cardiac troponin I and CMR findings. In addition, another patient aged 35 years with CTCA-confirmed coronary artery disease (70% stenosis of left anterior descending artery and 50% stenosis of left circumflex artery) underwent endomyocardial biopsy and fulfilled the histological criteria of AM.

The pathogenesis of acute myocardial damage in SARS-CoV-2 infection is uncertain. It is suggested that this virus may attack myocardium through both direct and indirect pathways. Studies have found that the spike protein, which is distributed on the surface of SARS-CoV-2, could enter various cells by coupling with its receptor, angiotensin converting enzyme 2, causing direct damage. Moreover, angiotensin converting enzyme 2 is highly expressed in cardiomyocytes, making them more susceptible to the virus. Viral particles have been directly observed in myocardial tissue from endomyocardial biopsy using electron microscopy.[13,14] Furthermore, the SARS-CoV-2 RNA has been found in interstitial cells of the myocardium by autopsies.[15] In addition, the COVID-19 could induce excessive inflammatory reactions and cytokine storms through immune mediation, and lead to microvascular damage and thrombosis formation. Autopsies showed that 14%–40% of patients with COVID-19 had lymphocytic myocarditis.[16–18] In the present study, viral particles were not detected in any of the 10 myocardial biopsies, which may be attributed to the limited biopsy sites on the right ventricular free wall and the right ventricular side of the interventricular septum. Another reason may be that the pathogenesis of COVID-19–associated AM is more closely related to indirect pathways. We also observed that 77.8% of the patients showed widespread infiltration of inflammatory cells, including $CD3^+$ and $CD68^+$, in myocardial biopsies, suggesting that cell immune response involving mature T cells and macrophages contributed to the occurrence and development of AM. In regard to the two cases of fulminant myocarditis undergoing endomyocardial biopsy, lymphocyte surface antigens were universally expressed, illustrating that both cellular and humoral immunity were involved in this active abnormal immune response.

The treatment of COVID-19–associated AM remains largely empiric as definite evidence of efficacy of any of the currently available treatment approaches is lacking. Regardless, the prevailing treatment strategy for COVID-19–associated myocarditis is similar to that used for other viral related myocarditis. Supportive care, corticosteroids, antiviral drugs, and immunoglobulins may be used when needed. Given the complex aetiology of COVID-19–associated AM involving multiple immune mechanisms, corticosteroids may be somewhat beneficial. Previous studies have shown that corticosteroids improved left ventricular systolic function in patients with severe myocarditis, but did not reduce mortality.[19,20] Similar to previous studies, we observed no significant correlations between corticosteroid use and mortality of patients. The EPIC-HR study showed that Paxlovid significantly reduced the risk of severe illness,[21] but whether this drug improves the long-term prognosis of COVID-19–associated AM is still unknown. In this study, Paxlovid use was relatively low, and there were no significant associations with patient outcomes. In the future, randomized trials of these and other therapies are needed to determine whether their use is beneficial in patients with COVID-19–associated AM.

Limitations

This study has several limitations that should be noted. First, it lacks data regarding the prevalence of AM caused by Omicron variants of SARS-CoV-2 in China and in the populations served by the centres that contributed data to the study. Also, not all patients with AM were tested for other potential viruses besides SARS-CoV-2 that can cause myocarditis. Among nine patients tested for other virus, only two had evidence of EB virus infection and one patient tested positive for Enterovirus 71. Additionally, not all patients had testing done to rule out autoimmune disease that might cause AM. Finally, not all patients suspected for AM would receive CMR examination or endomyocardial biopsy in clinical practice, so there may have some selection bias in the patients that did undergo these procedures, which may influence the results reported in this study.

Conclusions

Although AM is an uncommon manifestation of COVID-19 infection, it may be overlooked when it occurs. Our results indicated that patients who develop Omicron variant of SARS-CoV-2–associated AM usually manifest this condition within 2 weeks of infection. More definitive evidence comes from cardiac imaging, particularly CMR examination. Although steroids appear helpful in alleviating symptoms, there is uncertainty about the impact on long-term outcome. Fulminant myocarditis that was often complicated with hemodynamic instability and needed temporary mechanical circulatory support was not unusual. However, most COVID-19–associated AM patients recovered well and had a favourable prognosis. In short, this study presents the characteristics of a type of coronavirus-mediated myocarditis in detail, which may be of a certain significance for understanding the pathophysiological mechanisms and prognosis of virus-mediated myocarditis and providing novel data to support future research on the treatment of this disease. As the COVID-19 pandemic appears to be evolving into a chronic situation, better understanding of factors predisposing to AM with COVID-19 infection, optimal means of diagnosis, risk of deterioration, long-term consequence and, in particular, identifying effective treatment is needed. Prospective registries which collect data over an extended period are encouraged.

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Conflict of interest

The authors report no conflicts of interest in this work.

References

1. Ammirati E, Lupi L, Palazzini M, Hendren NS, Grodin JL, Cannistraci CV, *et al*. Prevalence, characteristics, and outcomes of COVID-19-associated acute myocarditis. *Circulation* 2022;**145**:1123-1139. doi:10.1161/CIRCULATIONAHA.121.056817
2. Writing Committee, Gluckman TJ, Bhave NM, Allen LA, Chung EH, Spatz ES, *et al*. 2022 ACC Expert Consensus Decision Pathway on cardiovascular sequelae of COVID-19 in adults: myocarditis and other myocardial involvement, post-acute sequelae of SARS-CoV-2 infection, and return to play: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol* 2022;**79**:1717-1756. doi:10.1016/j.jacc.2022.02.003
3. Castiello T, Georgiopoulos G, Finocchiaro G, Claudia M, Gianatti A, Delialis D, *et al*. COVID-19 and myocarditis: a systematic review and overview of current challenges. *Heart Fail Rev* 2022;**27**:251-261. doi:10.1007/s10741-021-10087-9
4. Hui KPY, Ho JCW, Cheung MC, Ng KC, Ching RHH, Lai KL, *et al*. SARS-CoV-2 omicron variant replication in human bronchus and lung ex vivo. *Nature* 2022;**603**:715-720. doi:10.1038/s41586-022-04479-6
5. Fan Y, Li X, Zhang L, Wan S, Zhang L, Zhou F. SARS-CoV-2 omicron variant: recent progress and future perspectives. *Signal Transduct Target Ther* 2022;**7**:141. doi:10.1038/s41392-022-00997-x
6. Bajaj R, Sinclair HC, Patel K, Low B, Pericao A, Manisty C, *et al*. Delayed-onset myocarditis following COVID-19. *Lancet Respir Med* 2021;**9**:e32-e34. doi:10.1016/S2213-2600(21)00085-0
7. Brambatti M, Matassini MV, Adler ED, Klingel K, Camici PG, Ammirati E. Eosinophilic myocarditis: characteristics, treatment, and outcomes. *J Am Coll Cardiol* 2017;**70**:2363-2375. doi:10.1016/j.jacc.2017.09.023
8. Fernández-Jiménez R, Sánchez-González J, Aguero J, Trigo MD, Galán-Arriola C, Fuster V, *et al*. Fast T2 gradient-spin-echo (T2-GraSE) mapping for myocardial edema quantification: first in vivo validation in a porcine model of ischemia/reperfusion. *J Cardiovasc Magn Reson* 2015;**17**:92. doi:10.1186/s12968-015-0199-9
9. Ferreira VM, Piechnik SK, Dall'Armellina E, Karamitsos TD, Francis JM, Ntusi N, *et al*. Native T1-mapping detects the location, extent and patterns of acute myocarditis without the need for gadolinium contrast agents. *J Cardiovasc Magn Reson* 2014;**16**:36. doi:10.1186/1532-429X-16-36
10. Ferreira VM, Schulz-Menger J, Holmvang G, Kramer CM, Carbone I, Sechtem U, *et al*. Cardiovascular magnetic resonance in nonischemic myocardial inflammation: expert recommendations. *J Am Coll Cardiol* 2018;**72**:3158-3176. doi:10.1016/j.jacc.2018.09.072
11. Naneishvili T, Khalil A, O'Leary R, Prasad N. Fulminant myocarditis as an early presentation of SARS-CoV-2. *BMJ Case Rep* 2020;**13**:e237553. doi:10.1136/bcr-2020-237553
12. Bernal-Torres W, Herrera-Escandón Á, Hurtado-Rivera M, Plata-Mosquera CA. COVID-19 fulminant myocarditis: a case report. *Eur Heart J Case Rep* 2020;**4**:1-6. doi:10.1093/ehjcr/ytaa212
13. Bailey AL, Dmytrenko O, Greenberg L, Bredemeyer AL, Ma P, Liu J, *et al*. SARS-CoV-2 infects human engineered heart tissues and models COVID-19 myocarditis. *JACC Basic Transl Sci* 2021;**6**:331-345. doi:10.1016/j.jacbts.2021.01.002
14. Bojkova D, Wagner JUG, Shumliakivska M, Aslan GS, Saleem U, Hansen A, *et al*. SARS-CoV-2 infects and induces cytotoxic effects in human cardiomyocytes. *Cardiovasc Res* 2020;**116**:2207-2215. doi:10.1093/cvr/cvaa267
15. Lindner D, Fitzek A, Brauninger H, Aleshcheva G, Edler C, Meissner K, *et al*. Association of cardiac infection with SARS-CoV-2 in confirmed COVID-19 autopsy cases. *JAMA Cardiol* 2020;**5**:1281-1285. doi:10.1001/jamacardio.2020.3551
16. Fox SE, Li G, Akmatbekov A, Harbert JL, Lameira FS, Brown JQ, *et al*. Unexpected features of cardiac pathology in COVID-19 infection. *Circulation* 2020;**142**:1123-1125. doi:10.1161/CIRCULATIONAHA.120.049465
17. Fox SE, Lameira FS, Rinker EB, Heide RSV. Cardiac endotheliitis and multisystem inflammatory syndrome after COVID-19. *Ann Intern Med* 2020;**173**:1025-1027. doi:10.7326/L20-0882
18. Schaller T, Hirschbuhl K, Burkhardt K, Braun G, Trepel M, Märkl B, *et al*. Postmortem examination of patients with COVID-19. *JAMA* 2020;**323**:2518-2520. doi:10.1001/jama.2020.8907
19. Chen HS, Wang W, Wu SN, Liu JP. Corticosteroids for viral myocarditis. *Cochrane Database Syst Rev* 2013;**2013**:CD004471. doi:10.1002/14651858.CD009481.pub2
20. Sawalha K, Abozenah M, Kadado AJ, Battisha A, Al-Akchar M, Salerno C, *et al*. Systematic review of COVID-19 related myocarditis: insights on management and outcome. *Cardiovasc Revasc Med* 2021;**23**:107-113. doi:10.1016/j.carrev.2020.08.028
21. Hammond J, Leister-Tebbe H, Gardner A, Abreu P, Bao W, Wisemandle W, *et al*. Oral nirmatrelvir for high-risk, nonhospitalized adults with Covid-19. *N Engl J Med* 2022;**386**:1397-1408. doi:10.1056/NEJMoa2118542