Received: 18 January 2022 | Revised: 8 June 2022 | Accepted: 23 June 2022

DOI: 10.1002/joa3.12751

Journal of Arrhythmia Open Access WILEY

ORIGINAL ARTICLE

Clinical and electrocardiographic characteristics in patients with fulminant myocarditis

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Funding information
No funding was received for this study.

Abstract

Background: The purpose of this study was to evaluate clinical and electrocardiographic characteristics in patients with fulminant myocarditis.

Methods: A total of 72 patients were divided into three groups: pericarditis (control: $n = 25$), acute myocarditis ($n = 27$), and fulminant myocarditis ($n = 20$). Patients' characteristics and electrocardiograms on admission were retrospectively analyzed in the three groups.

Results: BNP levels in the fulminant group were significantly higher than those in the other two groups. ST elevation was observed at lead aVR in the fulminant myocarditis group, whereas ST depression was observed at lead aVR in the other groups ($p = .001$). The maximum degree of ST elevation among the three groups was similar. However, the number of ST-elevation leads in the fulminant myocarditis group was significantly lower than that in the other groups ($p = .004$). The voltage of R wave in lead V5 in the fulminant myocarditis group was significantly lower than that in the other groups ($p = .005$). Moreover, in the Cabrera sequence, the prevalence of ST elevation in the inferior leads, aVR, and V3–V6 in the fulminant myocarditis group was significantly or nearly significantly lower than that in the other groups.

Conclusions: In fulminant myocarditis, ST-segment elevation was observed in lead aVR, and contrarily, the number and extent of ST-segment elevation and R wave voltage were smaller than those in the other groups. These results suggest that the number of myocytes with maintained action potential may be reduced following progressive myocardial damage and interstitial edema due to severe inflammation.

KEYWORDS
acute myocarditis, electrocardiography, fulminant myocarditis, pericarditis, prognosis, ST elevation

1 | INTRODUCTION

Acute myocarditis is mainly caused by inflammation of the myocardium due to viral infection. The main electrocardiogram (ECG) finding is widespread ST elevation. Some cases of acute myocarditis are known to be fulminant, and fulminant myocarditis has a poor prognosis.[1–3] It is extremely important to treat fulminant myocarditis as it has a high mortality rate. It has been well documented that in

addition to ST changes, a variety of arrhythmias, ranging from bradyarrhythmia to tachyarrhythmia, including fatal arrhythmias, occur as ECG changes in acute myocarditis.[4] In the field, when a first-touch ECG is encountered, it is clinically important to know whether it is suggestive of fulminant myocarditis or acute myocarditis.[5] However, only few ECG changes that are more characteristic of fulminant myocarditis have been studied so far.[6]

The purpose of this study was to clarify the differences in the changes in the 12-lead ECG that suggest the degree of myocardial damage to differentiate fulminant myocarditis from acute myocarditis and to examine the clinical significance of these changes.

2 | METHODS

2.1 | Study patients

A total of 72 patients were selected from 7235 consecutive patients admitted to the coronary care unit at our Memorial Heart Center based on medical records (T. K., Y. O., Y. A., J. A., and M. H.) between 1997 and 2014. The patients in this study were divided into three groups (Figure 1): pericarditis (control), acute myocarditis, and fulminant myocarditis.

Acute myocarditis was diagnosed according to the Japanese Circulation Society and European Society of Cardiology (ESC) position guidelines.[7,8] Fulminant myocarditis was defined as cases requiring extracorporeal membrane oxygenation (ECMO) or intra-aortic balloon pumping (IABP) during hospitalization in patients with acute myocarditis. Acute pericarditis was defined according to the ESC 2015 guidelines as follows: (i) chest pain, typically sharp and pleuritic, improved by sitting up and leaning forward; (ii) pericardial friction rub, a superficial scratchy or squeaking sound best heard with the diaphragm of the stethoscope over the left sternal border; (iii) electrocardiogram (ECG) changes with new widespread ST elevation or PR depression in the acute phase; and (iv) pericardial effusion.[9] The ECG system used was ECG-1460 (Nihon Kohden Tokyo, Japan). The system was not equipped with a band-pass filter. On the other hand, high-frequency filters were set up at 25, 35, 75, 100, and 150 Hz.

Patient characteristics, electrocardiograms on admission, and in-hospital events were retrospectively analyzed among the three groups. ECG analysis was performed in a blinded fashion by a skilled cardiologist (T.I.). The ST-amplitude and QRS-complex width on ECG were manually evaluated using a caliper device without magnification. The ST-amplitude was measured at the J80 point on the ECG.

2.2 | Definitions of electrocardiogram changes

The types of ST elevation (online Figures (A)–(C)) were classified into four groups: acute coronary syndrome-like pattern (a), pericarditis pattern without terminal QRS notching or slurring (b), pericarditis pattern with terminal QRS notching (c), and pericarditis pattern with terminal QRS slurring (d).[10] PR depression/elevation: PR deviation was defined according to a previous report, that is, a cut-off of ≥0.5 mm. Low voltage was defined according to the Minnesota code as follows: QRS voltage in every limb lead <0.5 mV or that in every chest lead <1.0 mV. The maximum degree of ST elevation or depression was determined among all leads. Degree of ST elevation was read as up to one decimal place based on 0.5 mm in each (not mV) by visual analysis. The data was shown as levels to two decimal places after converting from mm to mV.

2.3 | Prevalence of ST elevation according to the cabrera sequence

ST elevation in limb leads was converted to the Cabrera sequence,[11] which shows anatomical compatibility. The prevalence of ST

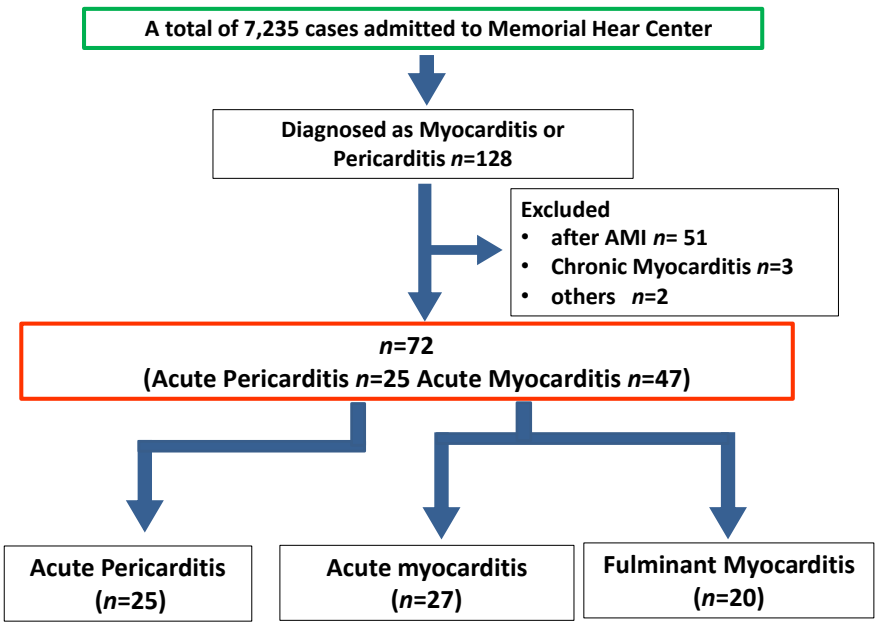

FIGURE 1 Study patients selection flow.

elevation according to the Cabrera sequence was compared among the three groups.

2.4 | Statistical analysis

Data are presented as mean ± standard deviation. Continuous values that were not normally distributed were compared among the three groups using a non-parametric test (Kruskal-Wallis test). Categorical data of the three groups were compared using the chi-square contingency test. After the non-parametric test, multiple comparisons were performed to assess the differences in each group comparison. The receiver operating characteristic (ROC) curve to predict fulminant myocarditis was evaluated using the area under the curve. Statistical significance was set at $p < .05$. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 21.0 (International Business Machines Corp., Chicago, IL, USA). The study was approved by the ethics committee of the Iwate Medical University. Informed consent was obtained from the study patients using the opt-out style. Correlation coefficients and Bland-Altman analysis were used to examine the degree of agreement of the analyzed data. Inter-observer variability was examined by comparing the T.I and Y.O data in a blind fashion. Inter- and intra-observer reproducibility were demonstrated in the supplemental online Figures (D)–(G).

3 | RESULTS

3.1 | Baseline patients and electrocardiographic characteristics

Patients in the fulminant group were significantly older than those in the acute myocarditis group. CK and BNP levels on admission were significantly higher in the fulminant group than in the other two groups. Moreover, systolic blood pressure and ejection fraction were the lowest in the fulminant myocarditis group. Coronary angiography demonstrated coronary stenosis in some cases, but there was no relationship with the patient's condition (Table 1). In the fulminant myocarditis group, the median time of starting ECMO or IABP was 1.7 h (range: 10 min to 240 h) after admission. Seventeen of the 20 patients (85%) received these assist devices within 24 h after admission. The patient who received ECMO at 240 h had repeated incessant VT/VF for 10 days and finally developed VF storm at 240 h.

The electrocardiogram on admission is shown in Table 2. The fulminant myocarditis group showed a lower prevalence of PR segment changes ($p = .027$). The prevalence of low-voltage QRS complexes in limb or chest leads was nearly significantly higher in the fulminant myocarditis group than in the other groups ($p = .056$). The voltage of SV1 + RV5 in the fulminant myocarditis group was significantly lower than that in the other groups ($p = .018$). The width of the QRS complex in the fulminant myocarditis group was significantly wider than that in the other two groups (Table 2). Although the maximum degrees of ST elevation among the three groups were similar, the degree of ST depression was the highest in the fulminant myocarditis group (Table 2). The all results of multiple comparisons are shown in the Tables S1 and S2 legends. ST elevation was observed at lead aVR in the fulminant myocarditis group, whereas ST depression was noted at lead aVR in the other groups (Figure 2). The number of ST-elevation leads in the fulminant myocarditis group was significantly lower than that in the other groups (Figure 3). Moreover, in the Cabrera sequence, the prevalence of ST elevation in the inferior leads, aVR, and V3–V6 in the fulminant myocarditis group was significantly lower than that in the other groups (Figure 4). Fatal arrhythmias, such as AV block or ventricular arrhythmia, were most frequent in the fulminant group. The in-hospital mortality in the fulminant myocarditis group was the worst at 40% (Table 3). Representative cases are shown in Figure 5 (standard 12-lead sequence) and the online supplementary Figures (H)–(J) (ECG of Cabrera sequence). Moreover, among the fulminant myocarditis group, a comparison of the deceased group and survival groups showed no patients and electrocardiographic features in the death group, except for a significantly higher frequency of complete AV block complications in the deceased group (Tables S1–S3).

3.2 | ROC analysis

First, BNP level was the strongest predictor of fulminant myocarditis in the study patients (AUC, 0.901; cut-off value, 347.5 pg/ml; sensitivity, 90.9%; specificity, 81.8%). Second, the AUCs of QRS-complex widths in V1 and V5 were 0.802 and 0.818, respectively (both cut-off values: 90 ms; sensitivity: 63.6%; specificity: 91.9%). Third, the AUC of ST change in lead aVR was 0.740 (cut-off value, −0.025 mV; sensitivity, 81.8%; specificity, 54.5%). Fourth, the AUC of the maximum degree of ST depression was 0.715 (cut-off value: 0.05 mV, sensitivity 90.9%, specificity: 36.4%), and AUC associated with the number of ST elevations (12-number of ST elevation) was 0.764 (cut-off value: < 4.5 leads, sensitivity 73.8%, and specificity 68.7%).

4 | DISCUSSION

This is the first report of a multidimensional examination of the 12-lead ECG in patients with acute pericarditis and acute and fulminant myocarditis, with a focus on the degree and extent of ST changes. This study can be summarized as follows: In fulminant myocarditis, compared with other conditions, (1) the QRS width was increased; (2) the degree of maximal ST elevation was similar but depression was more strongly observed; (3) ST elevation in aVR was observed; and (4) beyond expectations, the number of leads showing ST elevation was small and ventricular excitation evaluated by R wave of lead V5 voltage was low.

4.1 | Interpretation of ST changes in myocarditis

ST-segment elevation is the most basic finding indicating inflammatory damage to the myocardium. However, few studies

TABLE 1 Baseline clinical characteristics on admission

	Acute pericarditis ($n = 25$)	Acute myocarditis ($n = 27$)	Fulminant myocarditis ($n = 20$)	p value
Age (year-old)	60.9 ± 17.3	42.1 ± 17.1*	58.8 ± 17.3	<.001
Sex (male/female)	17/8	23/4	13/7	.220
BMI (kg/m^2)	22.2 ± 5.12	22.6 ± 4.0	20.7 ± 3.3	.309
Virus/bacterial/ eosinophilic/idiopathic	3/0/0/22#	17+/5/0/5	11++/2/1/6	<.001
SBP (mmHg)	145.8 ± 30.8	124.1 ± 22.9%	112.0 ± 26.5%	<.001
Heart rate (beats/min.)	90.0 ± 20.9	97.9 ± 23.3	103.4 ± 31.4	.395
CK(IU/l)	98.0 ± 61.9	525.2 ± 373.7&	1163.5 ± 971.6&	<.001
BNP (pg/ml)	104.3 ± 101.5	165.5 ± 150.5	1218.9 ± 814.5$	<.001
CRP (mg/dl)	5.7 ± 7.2	7.6 ± 7.4	6.3 ± 5.8	.59
Cr (mg/dl)	0.98 ± 0.69	1.48 ± 1.40	1.03 ± 0.71	.183
Coronary stenosis (present/absent)	4**/7	0**/19	3/16	.025
LVEF(%)	62.2 ± 8.9	51.3 ± 12.6##	33.9 ± 13.3##	<.001

Abbreviations: BMI, body mass index; BNP, brain natriuretic hormone; CK, creatine kinase; Cr, creatinine; CRP, C-reactive protein; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure.

Age: *: acute pericarditis vs. acute myocarditis, $p = .001$; acute myocarditis vs. fulminant myocarditis, $p = .005$, **etiology:** The number of viral infections was significantly smaller and the number of idiopathic cases was significantly larger in the acute pericarditis group than in the other groups (#). The number of viral infections was significantly larger (+, ++) and the number of idiopathic cases significantly smaller in the other groups. (Residual analysis), **SBP** (%): acute pericarditis vs. acute myocarditis, $p = .013$; acute pericarditis vs. fulminant myocarditis, $p < .001$. **CK**: acute pericarditis vs. acute myocarditis, $p < .001$; acute pericarditis vs. fulminant myocarditis, $p < .001$, **BNP** ($): Acute pericarditis vs. fulminant myocarditis, $p < .001$; acute myocarditis vs. fulminant myocarditis, $p < .001$ (Kruskal-Wallis test). **Coronary stenosis:** (**): Patients with acute myocarditis were significantly more likely to have no significant stenosis in the coronary arteries. Coronary artery stenosis was more common in patients with pericarditis. **LVEF** #: Acute pericarditis vs. acute myocarditis, $p = .019$; acute pericarditis vs. fulminant myocarditis, $p < .001$; acute myocarditis vs. fulminant myocarditis, $p = .003$ (Kruskal-Wallis test).

have examined their extent and degree in detail.[12] This study evaluated the degree of deviation in the lead of the maximum ST-segment elevation. As a result, the maximum degree of elevated ST-segment deviation was similar in the three disease conditions. Interestingly, beyond expectations, the number of ST-segment elevations in fulminant myocarditis was smaller than that in acute pericarditis and acute myocarditis. This may be due to further progression of a highly damaged myocardium to the extreme stage of inflammation, in addition to interstitial myocardial edema, resulting in a decrease in the number of ST-segment elevation inductions. In support of this, the myocardial potential shown by RV5 was lower in patients with fulminant myocarditis. In other words, although the myocardium begins to get damaged in acute myocarditis, many cardiomyocytes still have a well-maintained action potential, and ST elevation often reflects the extent of the inflamed myocardium. However, in fulminant myocarditis, the number of myocytes with maintained action potential may be reduced as a result of progressive myocardial damage with myocardial interstitial edema due to severe inflammation, which may be expressed in the form of a reduced number of ST-segment elevations despite the intensity of extensive damage. This may explain why the maximum ST deviation was similar in the three groups but the number of ST-segment elevation inductions was paradoxically smaller (cut-off value: <4.5 leads) in fulminant myocarditis, indicating the extent of damage and interstitial edema. In the evaluation of the Cabrera sequence, the number of ST-segment elevations, especially during thoracic induction, was significantly lower in patients with fulminant myocarditis. The anatomical spread of ST-segment elevation in fulminant myocarditis was also found to be lower, suggesting the above mechanism. Thus, in fulminant myocarditis, ST-segment elevation may be modified during the extreme phase of inflammation, despite the severity of the disease. On the other hand, the greater degree of ST depression in fulminant myocarditis may be a rather accurate representation of the degree of ST elevation observed from the contralateral side, as the ST-depressed side is not directly impaired by inflammation and is not modified during the inflammatory phase. Some studies evaluating myocardial damage due to myocarditis by MRI have reported that ST elevation in the ECG does not necessarily

TABLE 2 Electrocardiogram on admission

	Acute pericarditis ($n = 19$)	Acute myocarditis ($n = 25$)	Fulminant myocarditis ($n = 17$)	p value
PR elevation (aVR)	13[@]	12	4[@]	.027
PR depression	12	11	4	.057
Low voltage	0	2	4	.056
SV1 (mV)	0.47 ± 0.42	0.62 ± 0.52	0.26 ± 0.42	.064
RV5 (mV)	1.57 ± 0.64*	1.04 ± 0.49	0.92 ± 0.63*	.005
SV1 + RV5 (mV)	2.07 ± 0.89[%]	1.65 ± 0.75	1.18 ± 0.81[%]	.018
QRS (msec.)	64.2 ± 10.7[&]	80.0 ± 24.5[&]	92.9 ± 18.6[&]	.001
RBBB/LBBB	2/0	2/1	4/3	.096
ST elevation pattern** (a)/(b)/(c)/(d)	0/16[+]/1/0	7/13/2/1	9[#]/4/0/0/	.004
Degree of ST elevation (mV)	0.29 ± 0.24	0.32 ± 0.24	0.38 ± 0.24	.81
Degree of ST depression (mV)	−0.03 ± 0.10[$]	−0.05 ± 0.10	−0.14 ± 0.10[$]	.006

Notes: Patients with pacing rhythm on admission or discarding ECG were excluded from Table 1 in this analysis, **: Patients with LBBB or without ST elevation were excluded. Acute coronary syndrome-like pattern (a), pericarditis pattern without terminal QRS notching or slurring (b), pericarditis pattern with terminal QRS notching (c), and pericarditis pattern with terminal QRS slurring (d); RBBB: right bundle branch block; LBBB: left bundle branch block. QRS duration was measured in lead V5.

PR elevation (aVR) (@): The number of PR elevations (aVR) was significantly larger in the acute pericarditis group than in the other groups and significantly smaller than that in the fulminant myocarditis group (residual analysis), **RV5** (*): acute pericarditis vs. fulminant myocarditis, $p = .005$; acute pericarditis vs. acute myocarditis, $p = .011$. **SV1 + RV5** (%): acute pericarditis vs. fulminant myocarditis, $p = .014$. **QRS** (&): acute pericarditis vs. fulminant myocarditis, $p < .001$; acute pericarditis vs. acute myocarditis, $p = .035$, **ST elevation pattern (+):** The number of type-b cases in the acute pericarditis group was significantly larger than that in the other groups. #: The number of type-a cases in the fulminant myocarditis group was significantly larger than that in the other groups (residual analysis). **Degree of ST depression ($):** acute pericarditis vs. fulminant myocarditis, $p = .004$.

represent the assumed site of damage,[13] which may partially support the results of the present study.

4.2 | Significance of lead aVR

To date, lead aVR has been characterized in pericarditis or myocarditis by elevation of the PR portion. However, there is often a slight change. In coronary artery disease, ST elevation on aVR induction has been shown to be excellent in diagnosing acute coronary syndromes in the left main trunk and unstable angina with multivessel disease.[14–17] It has also been shown to be associated with prognosis. In the present study, we investigated ST elevation on aVR induction in myocarditis, focusing on the fact that ST changes in aVR induction in coronary artery disease indicate disease severity. We found that ST-segment changes during aVR induction were also elevated in fulminant myocarditis. The lead aVR from the upper right side is also called the intracardiac lead, and its ST elevation indicates ischemia in all layers and the entire ventricle. In the case of acute myocardial infarction, the entire left ventricle up to the base of the ventricular septum is exposed to ischemia due to occlusion of the left main trunk. The results of this study suggest that inflammation in fulminant myocarditis is also extensive, including up to the base.

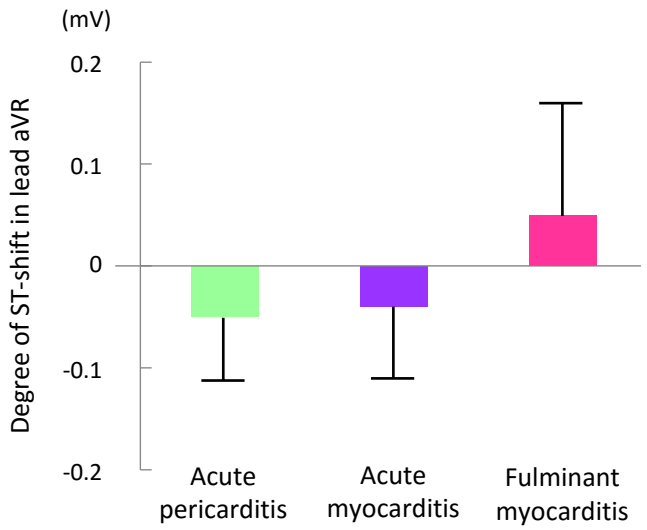

FIGURE 2 ST-segment shift in lead aVR. ST elevation was observed at lead aVR in the fulminant myocarditis group, whereas ST depression at lead aVR was observed in the other groups ($p = .001$). Degree of ST-shift were -0.053 ± 0.110 mV in Acute pericarditis group, -0.042 ± 0.110 mV in Acute myocarditis group, and 0.068 ± 0.110 mV in Fulminant myocarditis group.

4.3 | Fatal arrhythmias, QRS-complex width, and myocarditis

In cardiomyopathy and other diseases, an increase in the QRS-complex width in the chest leads has been reported to indicate ventricular conduction disturbances, suggesting myocardial damage. Similarly, an increase in the QRS width naturally indicates impairment of the stimulus conduction system, which may reflect the severity of myocarditis and its prognosis. Previous studies have shown similar results,[18–26] and the present study is consistent with these results. Because of disturbance of the stimulus conduction system, conduction block naturally occurs, and in this study, the frequency of dysregulation was higher in fulminant myocarditis. In particular, atrioventricular block was more frequent, and complications such as ventricular tachycardia, reflecting impaired cardiac function, were more frequent in fulminant myocarditis, which is consistent with previous reports.

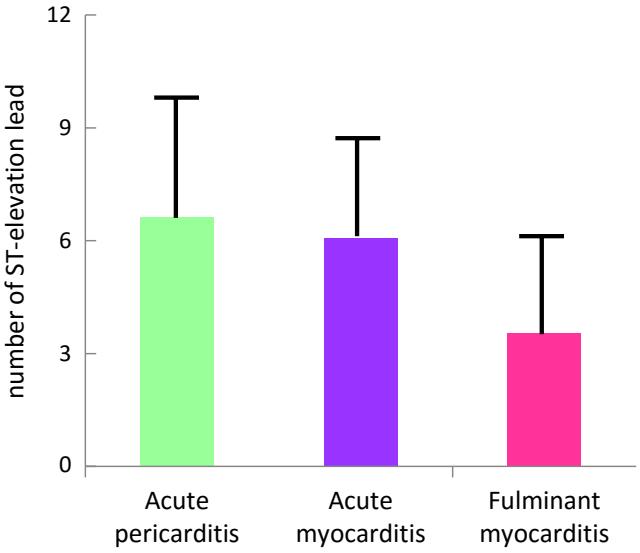

FIGURE 3 Number of ST-elevation lead: The number of ST-elevation lead in the fulminant myocarditis group was significantly lower than that in the other groups. Acute pericarditis: 6.63 ± 3.18, acute myocarditis: 6.08 ± 2.91, fulminant myocarditis: 3.53 ± 2.58 ($p = .004$).

4.4 | Clinical implications

A small number of ST elevation, ST-segment elevation at lead aVL, QRS-complex width, and low potential of R wave at V5 might be the electrocardiographic diagnostic factors in patients with fulminant myocarditis. These results may aid in early diagnosis in the clinical setting. Now, in the COVID-19 era,[27,28] in the future, these findings, combined with BNP levels, will contribute to establishing a clinical scoring system.

4.5 | Study limitations

This study has several limitations. First, it was a single-centre, retrospective study with a small number of cases. Second, it was not cross-checked with pathological findings. Multicentre prospective observational studies are necessary in the future. In addition, it is important to check whether the mechanism of ECG changes described

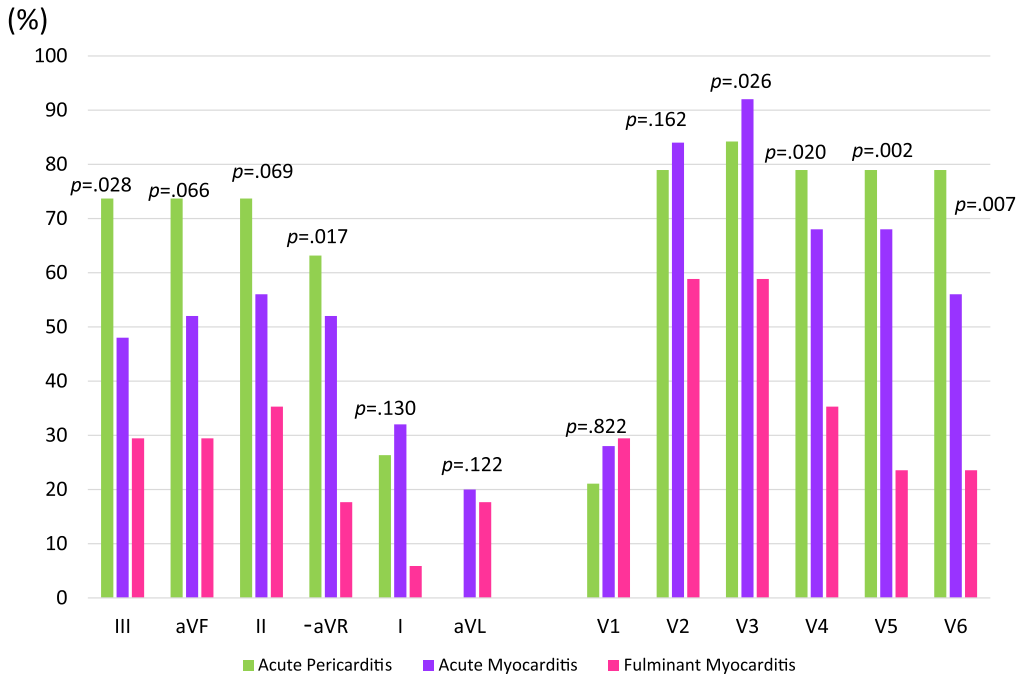

FIGURE 4 Prevalence of ST elevation according to the Cabrera sequence: The prevalence of ST elevation at inferior leads and anterior chest leads (V3 - V6) in the fulminant myocarditis group were almost significantly lower than that in the other groups.

TABLE 3 Arrhythmic event, assist device and mortality during hospitalization

	Acute pericarditis ($n = 25$)	Acute myocarditis ($n = 27$)	Fulminant myocarditis ($n = 20$)	p value
Atrial fibrillation	2	5	7	.074
AV block II	0	0	1	.274
AV block III	0	0	5	.01
Ventricular tachycardia	0	2	14*	<.001
Ventricular fibrillation	0	0	7	<.001
IABP	0	0	19	<.001
ECMO	0	0	13	<.001
respirator	1	1	15	<.001
Temporary pacing	0	1	9	<.001
In-hospital mortality (%)	0	0	40	<.001

Note: *, non-sustained; 3, sustained; 11, IABP: intra-aortic balloon pumping; AV, atrioventricular; ECMO, extracorporeal membrane oxygenation.

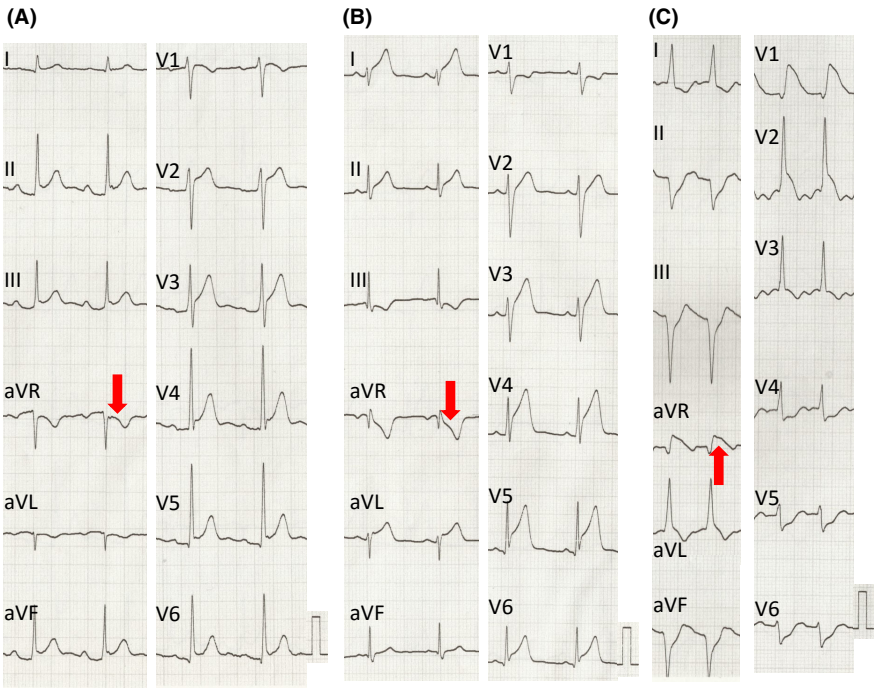

FIGURE 5 Representative cases: (A) Acute pericarditis, (B) Acute myocarditis, and (C) Fulminant myocarditis: Although ST-depressions of aVR lead were observed in cases of acute pericarditis and acute myocarditis, ST elevation was shown in a case of fulminant myocarditis (red arrows). ST-elevations like acute coronary syndrome combined with coved type ST-change were observed in V1-2 in a case of fulminant myocarditis (C). The number of ST-elevation leads in the fulminant myocarditis group was smaller (two leads) than that in the other groups (eight leads in each).

in this manuscript is correct and to compare it with the pathological findings. Third, the time from disease onset to hospitalisation was unknown. Unlike acute coronary syndrome, the time of onset of acute myocarditis is often unknown; therefore, the time from onset to ECG recording will be an issue to be examined in future prospective studies. Fourth, the diagnostic criteria for myocarditis were based on the existing diagnostic guidelines for myocarditis and not on the recent MRI-based Lake Louise Criteria. In addition, myocardial biopsy was not performed in all patients, which limited the diagnosis. In the future, it will be necessary to conduct a similar study using the Lake Louise criteria for inclusion criteria.

5 | CONCLUSIONS

In fulminant myocarditis, ST-segment elevation was observed in lead aVR compared to acute myocarditis and pericarditis, and both the number of ST-segment elevation inductions and R wave voltage (V5 induction) were smaller than the others. The number of myocytes with maintained action potential may be reduced following a progressive myocardial damage with interstitial edema due to severe inflammation, and it is thought that it may be expressed in the form of a reduced number of ST-segment elevations and less voltage with the extent of myocardial damage.

ACKNOWLEDGMENTS

The authors are grateful to the following members of the Iwate Medical University: Yumiko Okuyama (Research Nurse), Kayoko Fujiwara (Medical Secretary), Jun Anzai, MD, and Mizuka Hayashi, MD.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data are not available due to ethical restrictions.

- Approval of the research protocol: Date of IRB approval: March 22, 2021, No. MH2020-225 (Iwate Medical University).
- Informed Consent: Obtained by opt-out style.
- Clinical trial registration: None.
- Permission to reproduce material from other sources: NA.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Itoh T, Kobayashi T, Oshikiri Y, Arakawa Y, Satoh M, Morino Y. Clinical and electrocardiographic characteristics in patients with fulminant myocarditis. J Arrhythmia. 2022;38:763–771. https://doi.org/10.1002/joa3.12751