Influence of echocardiographic measurements and renal impairments on the prognosis of fulminant myocarditis

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Abstract
Fulminant myocarditis is a severe cardiac emergency that may lead to death if effective cardiopulmonary supports are not provided. This study aimed to evaluate the prognostic predictors in patients with fulminant myocarditis. We retrospectively analyzed the clinical characteristics, complications, laboratory findings, treatments, as well as electrocardiographic and echocardiographic data of 73 consecutive subjects diagnosed with fulminant myocarditis from June 2012 to June 2016. Logistic regression analysis was used to identify the independent predictive factors of nonsurvivor fulminant myocarditis.

Ten patients and 63 patients were assigned to the nonsurvivor and survivor fulminant myocarditis groups, respectively. Patients in the nonsurvivor fulminant myocarditis group had higher heart rates; were more likely to develop clinical complications and supraventricular tachycardia (SVT); and had higher serum creatinine (Scr) level, and had higher white blood cell (WBC) counts, and lower abbreviated estimated glomerular filtration rates (eGFR) than the patients in the survivor fulminant myocarditis group. Moreover, we observed larger left atrium dimension (LAd), larger left ventricular end systolic dimensions, and lower left ventricular ejection fraction in the patients from the nonsurvivor fulminant myocarditis group than in those from the other group. A logistic regression model was constructed and demonstrated that eGFR and LAd were 2 independent predictors of mortality in patients with fulminant myocarditis.

Higher heart rates, higher incidences of clinical complication, SVT, higher admission levels of Scr and eGFR, higher WBC counts, higher Scr and eGFR at stage of most severe renal damage, and abnormal echocardiographic findings were associated with high risk of mortality in patients with fulminant myocarditis. The major finding was that eGFR and LAd were independent predictors for in-hospital mortality in patients with fulminant myocarditis.

Abbreviations: AVB = atrioventricular blockade, CI = confidence interval, CK-MB = MB isoenzyme of creatine kinase, CRRT = continuous renal replacement therapy, cTnl = cardiac troponin I, eGFR = abbreviated estimated glomerular filtration rate, IABP = intra-aortic balloon pump, LAd = left atrium dimension, LVEDd = left ventricular end diastolic dimensions, LVEF = left ventricular ejection fraction, LVESd = left ventricular end systolic dimensions, OR = odds ratio, Scr = serum creatinine, SVT = supraventricular tachycardia, VT/VF = ventricular tachycardia/ventricular fibrillation, WBCs = white blood cells count.

Keywords: echocardiography, fulminant myocarditis, prognosis, renal function

1. Introduction
Viral myocarditis is an important cause of dilated cardiomyopathy, heart failure, and sudden death in young adults. It has been defined as direct virus-induced myocardial damage as well as an autoimmune disease against cardiac epitopes in experimental animal models and it has been identified using the clinical or histopathological criteria of apoptotic degeneration of the cardiomyocytes. Acute viral myocarditis may be identified on the basis of various asymptomatic or fulminant symptomatic changes based on the integration of the clinical manifestation, echocardiographic presentation, as well as hemodynamic and histological findings. Fulminant myocarditis is a rare and distinct clinical entity of viral myocarditis resulting in hemodynamic compromise and myocardial dysfunction with a normalized or dilated left ventricle.

Previous reports have identified the predictive risk factors of a fulminant course in acute myocarditis. Recently, Yang et al also reported that the presence of acute myocarditis associated with acute kidney injury resulted in a significant increase in the risk of mortality. However, limited information is available regarding the prognoses of adult patients with fulminant myocarditis, especially with respect to their kidney function. Thus, the present study aimed to identify the prognostic predictors in patients with fulminant myocarditis by conducting a retrospective analysis of their clinical, biological, and echocardiographic features and by determining whether renal dysfunction was associated with morality in these patients.
2. Material and methods

2.1. Study population

We performed a retrospective, single-center observational study in our hospital; 76 patients were included and admitted between June 2012 and June 2016 to the cardiac intensive care unit with a diagnosis of fulminant viral myocarditis. Our study was approved by local Ethics Committee (First Affiliated Hospital of Soochow University). All study procedures were as per the ethical principles of the Helsinki Declaration. Our study was registered at ClinicalTrials.gov with clinicalTrials.gov ID NCT03219996. In addition, all authors confirmed that all patients were identified by aliases, not by their real names. The definition of a fulminant course of acute myocarditis was the presence of rapid-onset aggressive life-threatening disease accompanied by cardiogenic shock with multiple organ dysfunction syndrome, acute severe heart failure, fatal arrhythmias, high-degree atrioventricular blockade (AVB), or sudden cardiac death following flu-like illness.[6,12] The patients require inotropic agents and mechanical circulatory support for survival.[13] Of the 76 patients in the present study, one patient was excluded because of incomplete data, one because of discharge against medical advice, and a third owing to the presence of chronic renal dysfunction that necessitated chronic peritoneal dialysis or hemodialysis. Therefore, the final study population included 73 subjects with fulminant myocarditis who were then divided into the non-survivor and survivor groups. All patients underwent standard transthoracic echocardiography at admission.

2.2. Data collection

Information regarding the patients’ baseline demographic characteristics (age and sex), previous medical and lifestyle history (hypertension, diabetes mellitus, myocardial infarction, stroke, smoking, and alcohol), clinical manifestations (pre-respiratory symptoms (cough, rhinorrhea, and dyspnea), pre-alimentary symptoms (nausea, vomiting, and abdominal pain), fever, chest tightness, or dyspnea, chest pain, and neurological symptoms, laboratory biomarker level, in-hospital complications [severe cardiac failure, cardiogenic shock, ventricular tachycardia/ventricular fibrillation (VT/VF), and multiple organ failure], treatments, as well as electrocardiographic and echocardiographic findings were collected from the hospital’s electronic medical records. The peak and admission levels of laboratory biomarkers, including white blood cells (WBCs, reference value 3.5–9.5 × 10^9/L), MB isoenzyme of creatine kinase (CK-MB, reference value 0–24 U/L), and cardiac troponin I (cTnI, reference value 0.01–0.08 μg/L) were measured. In addition, the levels of serum creatinine (Scr, normal range 0.7–1.5 mg/dL) and the abbreviated estimated glomerular filtration rate (eGFR) at admission and at the stage of most severe renal damage were measured as well. The adherence to therapeutic intravenous injections of intravenous immunoglobulin, methylprednisolone, diuretics, dopamine, dobutamine, norepinephrine, inotropic agent, and other medical assistance in the form of temporary pacemaker, ventilator support, intra-aortic balloon pump (IABP), and continuous renal replacement therapy (CRRT) were recorded. The associated electrocardiographic data, including heart rates, incident high-degree AVB, bundle branch block, and supraventricular tachycardia (SVT) as well as the echocardiographic measurements, including left atrium dimension (LAD), left ventricular end systolic dimension (LVESd), left ventricular end diastolic dimension (LVEDd), left ventricular ejection fraction (LVEF), pericardial effusion, weakening motion of the ventricular wall, valve regurgitation, and elevated pressure of the right atrium were evaluated in the current study. Finally, the variables related to incident death in patients with fulminant myocarditis were analyzed using multivariate logistic regression analyses to identify the independent predictors.

2.3. Statistical analyses

All data were summarized and analyzed. Continuous variables are presented as mean ± standard deviation or median (range) values, and categorical variables are presented as number (percentage) of patients. The statistical significance of the comparisons between the 2 groups (survivors and nonsurvivors) was analyzed using the independent-sample t test or Mann–Whitney U test. The Chi-square test was used for comparing the frequencies of the categorical variables. All statistical tests were 2-sided, and significance was defined as P < .05. Multivariate logistic regression analysis of various variables was performed to determine the outcome predictors in patients with fulminant myocarditis. All statistical analyses were performed using the SPSS version 17.0 (SPSS, Inc., Chicago, IL).

3. Results

3.1. Patients’ clinical characteristics, manifestations, laboratory findings, and treatments

The baseline characteristics, clinical manifestations, complications, and the initial and peak levels of laboratory parameters, and medical treatments were compared; the results have been summarized in Table 1. There were no significant differences in the age, gender, medical and lifestyle history, mean arterial blood pressure, the disease’s preceding presentation, and other clinical manifestations of between the 2 groups. Patients with fulminant myocarditis in the nonsurvivor group were more likely to develop cardiac shock, VT/VF, and multiple organ failure than those in the survivor group. They also had markedly higher levels of Scr [1.56 (0.82–2.05) vs 0.88 (0.72–1.33) mg/dL, P < .05] and eGFR [62.04 ± 38.10 vs 89.89 ± 37.85 mL/min/1.73 m^2, P < .05] at admission. Moreover, patients with fulminant myocarditis in the nonsurvivor group had higher peak WBC counts (19.55 ± 8.68 × 10^12/L vs 11.41 ± 6.62 × 10^12/L), Scr [3.01 (1.93–4.10) vs 0.89 (0.72–1.37) mg/dL], and eGFR [33.68 ± 36.02 vs 87.11 ± 42.96 mL/min/1.73 m^2] at the stage of most severe renal damage than survivors with fulminant myocarditis.

Although the admission and peak levels of cTnI and CK-MB (indicating severe myocardial damage) were not significantly different between the 2 groups, we observed a higher level of initial and peak cTnI and CK-MB in the nonsurvivor group. Patients with fulminant myocarditis were more likely to receive dopamine, noradrenaline, ventilator support, and CRRT treatments than those survivors. By contrast, no significant difference was observed with respect to the adherence to steroid, intravenous immunoglobulin, diuretics, dobutamine, inotropic agents, temporary pacemaker, and IABP between the 2 groups.

3.2. Evaluation of electrocardiographic and echocardiographic findings

The electrocardiographic and echocardiographic data regarding the electrocardiographic and echocardiographic measurements are summarized in Table 2. The patients with fulminant myocarditis in the nonsurvivor group had higher heart rates...
(113.80 ± 35.22 vs 76.95 ± 30.39 bpm, P < .05), and were more likely to have SVT on electrocardiograms (ECGs) than those in the survivor group. There was no statistically significant difference between the 2 groups in terms of high-degree AVB and bundle branch block on ECGs. With respect to the echocardiographic findings, patients with fulminant myocarditis who did not survive exhibited significant increases in the mean LAd (43.30 ± 6.58 vs 36.25 ± 6.07 mm, P < .05) and LVESd (44.40 ± 3.10 vs 37.76 ± 6.75 mm, P < .05), while there was a significant fall in their LVEF (0.32 ± 0.04 vs 0.47 ± 0.14, P < .05) compared with that in those who survived. The differences in the LVEDd, pericardial effusion, ventricular wall weakening, valve regurgitation, and elevated pressure of the right atrium of the 2 groups did not reach statistical significance.
Echocardiographic parameters independently correlated with the prognosis in patients with fulminant myocarditis, suggesting LAd increases and eGFR decreases were predictors for nonsurvivors with fulminant myocarditis of most severe renal damage remained as the 2 independent predictors of in-hospital mortality in patients with fulminant myocarditis. Furthermore, multivariate logistic regression analysis demonstrated that the LAd [odds ratio (OR): 1.226; 95% confidence interval (CI) 1.016–1.478; \( P =.034 \)] and level of eGFR (OR: 0.928; 95% CI 0.870–0.989; \( P =.022 \)) at the stage of most severe renal damage remained as the 2 independent predictors for nonsurvivors with fulminant myocarditis (Table 3), suggesting LAd increases and eGFR decreases were independently correlated with the prognosis in patients with fulminant myocarditis.

### Table 2

| Variables                                      | Nonsurvivor | Survivor |
|------------------------------------------------|-------------|----------|
| ECGs                                           |             |          |
| Heart rate, beats per minute                   | 113.80±35.22 | 76.95±3.09 |
| High-degree atrioventricular blockade [n (%)]  | 2 (20.0%)   | 23 (36.5%) |
| Bundle branch block [n (%)]                    | 3 (30.0%)   | 7 (11.1%)  |
| Supraventricular tachycardia [n (%)]           | 7 (70.0%)   | 18 (28.6%) |
| Echocardiographic parameters                   |             |          |
| Left atrium dimension, mm                      | 43.30±6.58* | 36.25±6.07 |
| Left ventricular end-diastolic dimension, mm   | 44.40±3.10* | 37.76±6.75 |
| Left ventricular end-systolic dimension, mm    | 53.10±3.60  | 49.98±5.25 |
| Left ventricular ejection fraction             | 0.32±0.04†  | 0.47±0.14  |
| Pericardial effusion [n (%)]                   | 6 (60.0%)   | 22 (34.9%) |
| Weakening motion of the ventricular wall [n (%)]| 10 (100.0%) | 49 (77.8%) |
| Valve regurgitation [n (%)]                    | 9 (90.0%)   | 57 (92.1%) |
| Elevated pressure of right atrium [n (%)]      | 4 (40.0%)   | 19 (29.8%) |

Data are presented as mean±standard deviation or n (%). 
* \( P < .05 \) (nonsurvivor group vs survivor group).
† \( P < .005 \) (nonsurvivor group vs survivor group).
‡ \( P < .001 \) (nonsurvivor group vs survivor group).

### 3.3. Clinical outcomes and predictors of prognosis in fulminant myocarditis

The mortality rate in the 73 patients with fulminant myocarditis was 13.7% (10 patients died); 8 patients died due to fatal VT/VF, and 2 owing to sudden cardiac arrest. Further, the average duration of hospital stay from the time of admission was 4.5 days (d) for the patients in the nonsurvivor group; 3 patients stayed in the hospital for 1 d, 4 stayed for 2 days, 1 stayed for 3 days, 1 stayed for a week, and 1 stayed for 24 days. In the survivor fulminant myocarditis group, 21 patients with severe AVB recovered fully and were discharged, and 2 patients were implanted with permanent pacemakers after 2 months for continued third-degree AVB. According to the echocardiographic results of these patients, 6 patients developed dilated cardiomyopathy, while the others recovered fully. Furthermore, multivariate logistic regression analysis demonstrated that the LAd [odds ratio (OR): 1.226; 95% confidence interval (CI) 1.016–1.478; \( P =.034 \)] and level of eGFR (OR: 0.928; 95% CI 0.870–0.989; \( P =.022 \)) at the stage of most severe renal damage remained as the 2 independent predictors for nonsurvivors with fulminant myocarditis (Table 3), suggesting LAd increases and eGFR decreases were independently correlated with the prognosis in patients with fulminant myocarditis.

### Table 3

Multivariate logistic regression analyses to identify the independent predictors of in-hospital mortality in patients with fulminant myocarditis.

| Variables                                      | Odds ratio (95% CI) | \( P \) |
|------------------------------------------------|---------------------|--------|
| Left atrium dimension, mm                      | 1.226 (1.016–1.478) | .034*  |
| Left ventricular ejection fraction             | 0.000 (0.000–5.013) | .071   |
| Serum creatinine, mg/dL                        | 2.894 (0.473–17.718) | .250   |
| Serum creatinine, mg/dL                        | 0.849 (0.408–1.766)  | .662   |
| eGFR\(^\text{c}\), mL/min/1.73 m\(^2\)          | 1.074 (0.980–1.176)  | .126   |
| eGFR\(^\text{c}\), mL/min/1.73 m\(^2\)          | 0.928 (0.870–0.989)  | .022*  |

\( e\text{GFR} = \text{estimated glomerular filtration rate; } Scr = \text{serum creatinine.} \)
* \( P < .05 \)
† Renal function at admission.
‡ Renal function at the most seriously damaged stage.

### 4. Discussion

Our study successfully analyzed the differences in the clinical data between the survivor and nonsurvivor groups and identified the risk factors that predicted mortality in patients with fulminant myocarditis. After observing 73 fulminant myocarditis patients, we determined that the propensity for in-hospital mortality could be raised in patients with fulminant myocarditis who had a rapid heart rate; life-threaten arrhythmias, such as VT/VF; cardiogenic shock; and multiple organ dysfunctions. Furthermore, Scr level at admission, peak WBC counts, and Scr level at the stage of most serious renal dysfunction were significantly higher in nonsurvivors with fulminant myocarditis than in survivors. Moreover, eGFR that reflects renal impairment was significantly lower at admission and at the stage of most severe renal damage stage in the nonsurvivor group than in the survivor group. In addition, we observed significant increases in the LVEsds and LAd and a decrease in the LVEF in the nonsurvivors compared with that in the survivors. On the basis of our logistic aggression analyses, eGFR and LAd were identified as 2 powerful predictors of mortality among patients with fulminant myocarditis.

Although the echocardiographic features of myocarditis are often nonspecific, their findings aid the diagnosis of myocarditis, evaluation of heart function, acute management, determination of prognosis, and ruling out of other causes of heart failure. Of the several echocardiographic parameters, decreased LVEF at admission was significantly associated with poor patient outcomes; this has also been previously reported.\(^{14}\) In addition, enlarged LA size previously reported to be associated with increased LA pressures and increased cardiovascular risk and disease burden.\(^{15}\) In this study, we found that patients with fulminant myocarditis who did not survive exhibited substantial enlargement in the LVEsds and LAd, with a decrease in the LVEF compared with those who survived. It is also noteworthy that LAd was an important predictor of in-hospital mortality in patients with fulminant myocarditis. These parameters indicated acute-onset systolic dysfunction of left ventricle and decompensated heart failure. The underlying mechanism might be that inflammation caused more severe atrium and ventricle edema in nonsurvivor patients than in the survivor fulminant myocarditis group.\(^{16}\) Cardiac and renal diseases have a complex interrelationship. Inflammatory factors, cellular immune-mediated injury, stress-mediated and...
neurohormonal responses, hemodynamic changes and acid–base or fluid imbalance might damage the heart, the kidneys, or both.\[17\] Therefore, cardiac injury in fulminant myocarditis might be closely related to renal injury from the pathophysiological perspective. Moreover, renal impairment is an important risk factor for mortality in patients with fulminant myocarditis.

Furthermore, the heart and the kidney are very closely interrelated; therefore, an enlarged LAd and decreased LVEF might affect kidney perfusion, worsening renal function.\[15,18\] Kidneys perform the vital function of maintaining balance in body volume, electrolytes, and acid–base as well as the crucial function of excreting nitrogen and other toxic molecules. Acute kidney injury has been strongly associated with unfavorable prognoses in critically ill patients with or without heart failure; it is also considered as an independent predictor of mortality.\[17,19–21\] Recently, Yang et al\[9\] retrospectively reviewed the medical records of 101 patients with acute myocarditis and proposed that patients with acute myocarditis together with acute kidney injury would result in a significant increase in mortality. It is noteworthy that in the current study, we found that acute renal insufficiency was closely associated with prognosis in patients with fulminant myocarditis. The exact underlying pathophysiological mechanism by which renal failure might worsen the prognosis has not yet been clearly identified. First, in the process of fulminant myocarditis, acute-onset cardiac dysfunction increased central vein pressure and induced hypoxia, which have been demonstrated to be closely related to renal vein congestion and kidney injury.\[22,23\] Increased renal vein congestion would lead to the renal interstitial pressure increases, renal parenchymal hypoxia, and tubule collapse damaged.\[24,25\] Eventually leading to a fall in the glomerular filtration rate reported to be directly associated with in-hospital mortality.\[24\] Second, impaired renal function leads to water and sodium retention and then further increases the preload (such as pulmonary edema and pleural effusion); impaired renal function increases vascular stiffness, activates the renin-angiotensin-aldosterone axis (RAAS), and then further increases afterload. These would deteriorate the process and prognosis in patients with fulminant myocarditis. Finally, patients with fulminant myocarditis together with renal dysfunction might induce metabolic acidosis and electrolytes disorders (hyperkalemia and hypocalcemia), which have connection with VTVF. There are certain limitations in our research. Our sample size was small; further studies should enroll more patients to reduce the latent bias. More detailed follow-ups studies are warranted to appropriately assess the effects of renal function on long-term prognosis in fulminant myocarditis patients. Moreover, more attention needs to be paid to renal vein congestion, renal function, and mortality in patients with fulminant myocarditis.

5. Conclusion

This study showed that a rapid heart rate, more severe clinical complications, higher peak WBC counts, elevated levels of Scr at admission and at the stage of most severe renal damage, decreased levels of eGFR at admission and at the stage of most severe renal damage, enlarged LAd and LVEFs, and decreased LVEF were potential risk factors for in-hospital mortality in patients with fulminant myocarditis. It was noteworthy that eGFR at the stage of most severe renal damage and LAd had an important prognostic value in patients with fulminant myocarditis.

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