A Risk Prediction Model for In-hospital Mortality in Patients with Suspected Myocarditis

Duo Xu1,2, Ruo-Chi Zhao1, Wen-Hui Gao2, Han-Bin Cui1

1Department of Cardiology, Ningbo First Hospital, Ningbo, Zhejiang 315010, China
2Department of Cardiology, CHC International Hospital, Cixi, Zhejiang 315310, China

Abstract

Background: Myocarditis is an inflammatory disease of the myocardium that may lead to cardiac death in some patients. However, little is known about the predictors of in-hospital mortality in patients with suspected myocarditis. Thus, the aim of this study was to identify the independent risk factors for in-hospital mortality in patients with suspected myocarditis by establishing a risk prediction model.

Methods: A retrospective study was performed to analyze the clinical medical records of 403 consecutive patients with suspected myocarditis who were admitted to Ningbo First Hospital between January 2003 and December 2013. A total of 238 males (59%) and 165 females (41%) were enrolled in this study. We divided the above patients into two subgroups (survival and nonsurvival), according to their clinical in-hospital outcomes. To maximize the effectiveness of the prediction model, we first identified the potential risk factors for in-hospital mortality among patients with suspected myocarditis, based on data pertaining to previously established risk factors and basic patient characteristics. We subsequently established a regression model for predicting in-hospital mortality using univariate and multivariate logistic regression analyses. Finally, we identified the independent risk factors for in-hospital mortality using our risk prediction model.

Results: The following prediction model for in-hospital mortality in patients with suspected myocarditis, including creatinine clearance rate (Ccr), age, ventricular tachycardia (VT), New York Heart Association (NYHA) classification, gender and cardiac troponin T (cTnT), was established in the study: 

\[ P = 3.10 \times \text{Ccr} + 2.99 \times \text{age} - 7.34 \times \text{VT} - 1.39 \times \text{NYHA} - 3 \times \text{male} - 1.25 \times \text{cTnT} - 1.13 \times \text{Ccr} - 60 \times \text{age} - 50 \times \text{VT} - 1 \times \text{male} + 1.00 \times \text{cTnT} - 50 \times \text{L} - 0.00 \]

The area under the receiver operating characteristic curve was 0.96 (standard error = 0.015, 95% confidence interval [CI]: 0.93–0.99). The model demonstrated that a Ccr <60 ml/min (odds ratio [OR] = 19.94, 95% CI: 5.66–70.26), an age ≥50 years (OR = 7.43, 95% CI: 2.18–25.34), VT (OR = 6.89, 95% CI: 1.86–25.44), a NYHA classification ≥3 (OR = 4.03, 95% CI: 1.13–14.32), male gender (OR = 3.48, 95% CI: 0.99–12.20), and a cTnT level ≥50 µg/L (OR = 3.10, 95% CI: 0.91–10.62) were the independent risk factors for in-hospital mortality.

Conclusions: A Ccr <60 ml/min, an age ≥50 years, VT, an NYHA classification ≥3, male gender, and a cTnT level ≥50 µg/L were the independent risk factors resulting from the prediction model for in-hospital mortality in patients with suspected myocarditis. In addition, sufficient life support during the early stage of the disease might improve the prognoses of patients with suspected myocarditis with multiple risk factors for in-hospital mortality.

Key words: In-hospital Mortality; Logistic Model; Myocarditis; Risk Factors

INTRODUCTION

Myocarditis is an inflammatory disease of the myocardium. The majority of cases of the disease result from viral infection.1,2 The clinical presentations of patients with myocarditis can be extremely variable as affected patients may present with symptoms ranging from slight palpitations to cardiac death.3 In Finland, the morbidity rate associated with sudden cardiac death in young persons aged 15–39 years was 100,000 person-years from 2001 to 2008.4 In a postmortem study, 12% of cases of sudden cardiac death in young persons aged 15–39 years were due to myocarditis.5

Address for correspondence: Dr. Han-Bin Cui, Department of Cardiology, Ningbo First Hospital, Ningbo, Zhejiang 315010, China
E-Mail: hanbincui@hotmail.com

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adults were attributable to myocarditis. Most patients with myocarditis have a favorable prognosis. However, a small proportion of patients with certain clinical risk factors have undesirable outcomes, including heart failure, cardiac shock, severe arrhythmia, or even death. The majority of myocarditis-related deaths occur during hospitalizations caused by severe heart muscle damage. However, to date, little is known about the predictors of in-hospital mortality in patients with myocarditis.

Currently, the gold standard criteria for the diagnosis of myocarditis are the Dallas criteria for the classification of viral myocarditis. However, these criteria are sometimes too restrictive for physicians to make a diagnosis of myocarditis by myocardial biopsy. In medical practice, physicians frequently encounter patients with suspected myocarditis. It is necessary for clinicians to be able to distinguish between patients with favorable prognoses and patients who are in danger of dying. Thus, it is also necessary to establish a risk prediction model for evaluating the conditions of patients with suspected myocarditis.

**Methods**

We retrospectively studied inpatients with a diagnosis of myocarditis who were treated between January 2003 and December 2013 in Ningbo First Hospital (a regional medical center) of China. The diagnosis of myocarditis was made based on patient clinical presentations and auxiliary examination findings. We reconfirmed the diagnosis of myocarditis using objective patient medical records, in accordance with the diagnostic criteria for clinically suspected myocarditis developed by the European Society of Cardiology. These diagnostic criteria, which included criteria pertaining to patient clinical presentations and diagnostic testing, are not listed successively herein due to restrictions regarding the length of this paper. Patients with a primary discharge diagnosis of myocarditis, according to the diagnostic criteria of the European Society of Cardiology, and intact medical records were included in the study. Patients in whom the diagnosis of myocarditis was uncertain or in whom myocarditis was a minor diagnosis were excluded from the study. According to the previously established risk factors and basic patient characteristics, we investigated the potential risk factors for in-hospital mortality to maximize the effectiveness of the prediction model and minimize bias as much as possible. The two endpoints of the study were in-hospital survival and nonsurvival. Patients’ deaths must have resulted from myocarditis, either directly or indirectly.

SPSS Statistics version 21.0 (International Business Machines Corp., Armonk, New York, USA) was used to perform the data analysis. Classified variables were expressed as percentages, while continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range [IQR]). First, differences in the potential risk factors for in-hospital mortality between the survival and nonsurvival groups were compared using Chi-square test, continuity correction Chi-square test, or Fisher’s exact test for categorical variables and Student’s t-test, separate variance estimation t-test, or Mann-Whitney U test for continuous variables, as appropriate. Homogeneity of variance was examined using the F-test. We did all statistical tests at a two-tailed significance level of 0.05. Statistical significance was a requirement for variables to enter the next analysis. Second, multicollinearity, which can result in misleading interpretations of results, must have been diagnosed in the regression analysis. If the potential risk factors for myocarditis were found to be linearly correlated, the risk factors included in the final regression model could not be independent from the other risk factors. Currently, several methods may be used to diagnose multicollinearity, and calculating tolerance (TOL) and variance inflation factor (VIP) are the most popular methods of diagnosing multicollinearity as proposed in literature. VIP is calculated as follows: $VIP = 1 / (1 - R_i^2)$, and TOL is calculated as follows: $TOL = 1 - R_i^2$, where $R_i^2$ is the coefficient of association of each variable regressed on the remaining predictor variables.

In general, a $TOL \leq 0.2$ or $VIP \geq 5$ is indicative of the potential existence of multicollinearity between a particular variable and the remaining variables. Finally, we used univariate and multivariate logistic regression analyses to form the risk prediction model, which was tested using Hosmer–Lemeshow statistics and receiver operating characteristic (ROC) curves. $\alpha_{in} = 0.05$ and $\alpha_{out} = 0.1$ were the standards for the prediction model.

**Results**

According to the above-mentioned inclusion and exclusion criteria, a total of 403 consecutive patients, including 238 males (59%) and 165 females (41%), were investigated in this study. Regarding the age distributions of the patients enrolled in the study, patients between 30 and 39 years of age constituted the largest proportion of the population as this group accounted for 25.8% (n = 104) of patients, while patients exceeding 60 years old constituted the smallest proportion of the population as this group accounted for 4% (n = 16) of patients. Our comparison of lengths of stay between the survival and nonsurvival groups [Figure 1] showed that 6.6% (24/364) of patients in the survival group were discharged from the hospital within 3 days, while 69.2% (27/39) of patients in the nonsurvival group were discharged within 3 days.

The baseline characteristics of the patients enrolled in the study are shown in Table 1. The potential risk factors for myocarditis that were noted among the survivors and nonsurvivors are shown in Table 2. Twenty-eight risk factors met the above-mentioned requirement of statistical significance ($P < 0.05$) and were entered into the next analysis (age; male gender; smoking habits; hypertension; syncope; digestive symptoms; blood glucose; systolic blood pressure; hematocrit; platelets; C-reactive protein; alanine aminotransferase; aspartate aminotransferase [AST]; creatine kinase [CK]; CK-MB; lactate dehydrogenase [LDH]).
N-terminal pro-brain natriuretic peptide; D-dimer; ventricular tachycardia [VT]; ST-segment elevation; Q-waves; QTc interval, delayed; left ventricular ejection fraction [LVEF]; left ventricular fractional shortening; pulmonary edema; a creatinine clearance rate [Ccr] <60 ml/min; a cardiac troponin T [cTnT] level ≥50 μg/L; and a New York Heart Association [NYHA] classification ≥3). Before performing logistic regression analysis, we performed multiple linear analyses to investigate the collinearity of the above risk factors. Variables with a TOL ≤0.2 or variance inflation factor ≥5 were considered to have significant collinearity and were rejected. The results of the analysis [Table 3] showed that AST, LDH, and D-dimer should be excluded from subsequent analyses.

The remaining 25 variables screened in the previous analysis were entered into the logistic regression analysis. The step-wise regression analysis, the final results of which are shown in Table 4, demonstrated that the following variables — whose beta coefficients are presented in descending order — were independent risk factors for in-hospital mortality in patients with suspected myocarditis: a Ccr <60 ml/min, an age ≥50 years, VT, an NYHA classification ≥3, male gender, and a cTnT level ≥50 μg/L. The following risk prediction model was used in this study: 

\[
P = e^a/(1 + e^a)\]

where e is the exponential function, P is the probability of in-hospital death, and 

\[
a = -7.34 + 2.99 \times [\text{Ccr} < 60 \text{ ml/min} = 1, \text{Ccr} \geq 60 \text{ ml/min} = 0] + 2.01 \times [\text{age} \geq 50 \text{ years} = 1, \text{age} < 50 \text{ years} = 0] + 1.93 \times [\text{VT} = 1, \text{no VT} = 0] + 1.39 \times [\text{NYHA} \geq 3 = 1, \text{NYHA} < 3 = 0] + 1.25 \times [\text{male} = 1, \text{female} = 0] + 1.13 \times [\text{cTnT} \geq 50 \mu g/L = 1, \text{cTnT} < 50 \mu g/L = 0)].

Moreover, Hosmer–Lemeshow statistics showed that the goodness of fit was adequate (χ² = 14.139, df = 7, P = 0.053). We generated an ROC curve to test the sensitivity and specificity of the prediction model [Figure 2]. The area under the ROC curve was 0.96 (standard error = 0.015, 95% CI: 0.93–0.99).

**Table 1: Baseline characteristics of patients with suspected myocarditis (n = 403)**

| Variables                          | Values |
|-----------------------------------|--------|
| Age (years), mean ± SD            | 33.0 ± 13.7 |
| Sex (male), n (%)                 | 238 (59.1) |
| Smoking habit*, n (%)             | 96 (23.8) |
| Underlying diseases, n (%)        |        |
| Hypertension                      | 44 (10.9) |
| Diabetes                          | 5 (1.2) |
| Stroke                            | 0       |
| Coronary artery disease           | 17 (4.2) |
| Congenital heart disease          | 4 (1.0) |
| Chronic pulmonary disease         | 8 (2.0) |
| Symptom†, n (%)                   |        |
| Syncope                           | 65 (16.1) |
| Chest pain                        | 92 (22.8) |
| Chest distress                    | 245 (60.8) |
| Palpitation                       | 76 (18.9) |
| The NYHA classification, n (%)    |        |
| Grade 1                           | 167 (41.4) |
| Grade 2                           | 121 (30.0) |
| Grade 3                           | 28 (6.9) |
| Grade 4                           | 87 (21.7) |
| Used medicine, n (%)              |        |
| Glucocorticoid†                   | 182 (45.2) |
| β-blocker§                        | 134 (33.3) |

*Smoking in the past year; †The presentation on admission; ‡Methylprednisolone or dexamethasone; §Metoprolol or bisoprolol. SD: Standard deviation; NYHA: New York Heart Association classification.

**Figure 1:** The comparison of in-hospital days between survival and nonsurvival groups. It showed that 69.2% of patients in the nonsurvival group were discharged from the hospital within 3 days due to death whereas 6.6% of patients in the survival group were discharged from the hospital within 3 days due to recovery.

**Figure 2:** Receiver operating characteristic curve of the prediction model for in-hospital mortality in patients with suspected myocarditis. The area under the receiver operating characteristic curve (AUC) was 0.96 (standard error = 0.015, 95% confidence interval: 0.93–0.99). It shows that the sensitivity and specificity of the prediction model are adequate in statistics.
### Table 2: Potential risk factors in survivors and nonsurvivors with suspected myocarditis

| Variables                              | Survivors (n = 364) | Nonsurvivors (n = 39) | Statistics   | P     |
|----------------------------------------|---------------------|-----------------------|--------------|-------|
| Age (≥50 years), n (%)                 | 90 (24.7)           | 30 (76.9)             | 45.90*       | <0.001|
| Male, n (%)                            | 207 (56.9)          | 31 (79.5)             | 7.45*        | 0.006 |
| BMI (kg/m²), mean ± SD                 | 22.3 ± 3.2          | 22.7 ± 2.4            | 0.68*        | 0.495 |
| Smoking habit, n (%)                   | 80 (22)             | 16 (41)               | 7.04*        | 0.008 |
| Underlying diseases, n (%)             |                     |                       |              |       |
| Hypertension                           | 36 (9.9)            | 8 (20.5)              | 3.07*        | 0.080 |
| Diabetes                               | 4 (1.1)             | 1 (2.6)               | 0.62*        | 0.433 |
| Stroke                                 | 0                   | 0                     | –            | –     |
| Coronary artery disease, n (%)         | 13 (3.6)            | 4 (10.3)              | 2.42*        | 0.120 |
| Congenital heart disease, n (%)        | 4 (1.1)             | 0                     | –            | –     |
| Chronic pulmonary disease, n (%)       | 8 (2.2)             | 0                     | –            | –     |
| Symptom on admission, n (%)            |                     |                       |              |       |
| Syncope                                | 53 (14.6)           | 12 (30.8)             | 6.41*        | 0.011 |
| Chest pain                             | 80 (22)             | 12 (30.8)             | 0.79*        | 0.373 |
| Chest distress                         | 217 (59.6)          | 28 (71.8)             | 2.192*       | 0.139 |
| Palpitation                            | 65 (17.9)           | 11 (28.2)             | 2.47*        | 0.116 |
| Digestive symptom, n (%)               | 56 (15.4)           | 15 (38.5)             | 12.93*       | <0.001|
| Abnormal heart rate, n (%)             | 152 (41.8)          | 19 (48.7)             | 0.61*        | 0.404 |
| Fever, n (%)                           | 82 (22.5)           | 12 (30.8)             | 1.34*        | 0.247 |
| Blood glucose (mmol/L), mean ± SD     | 9.5 ± 4.5           | 10.2 ± 6.4            | 0.68*        | 0.498 |
| Neutrophil (×10⁹/L), mean ± SD        | 7.1 ± 4.6           | 8.3 ± 5.8             | 1.44*        | 0.150 |
| Red blood cell (×10⁹/L), mean ± SD    | 4.3 ± 0.5           | 4.5 ± 0.3             | 2.58*        | 0.012 |
| Hematocrit (%), mean ± SD             | 38.2 ± 5.1          | 40.4 ± 3.9            | 2.63*        | 0.009 |
| MCV (fl), mean ± SD                   | 89.9 ± 5.5          | 90.4 ± 4.4            | 0.56*        | 0.574 |
| Platelet count (×10⁹/L), mean ± SD    | 199.7 ± 51.3        | 154.3 ± 78.0          | –3.56*       | 0.001 |
| C-reactive protein (mg/L), median (IQR)| 17.4 (2.8–31.9)    | 55.3 (30.9–99.9)      | –5.11*       | <0.001|
| ALT (U/L), median (IQR)                | 37.5 (19.0–67.0)    | 1235.0 (93.0–1412.7)  | –6.29*       | <0.001|
| AST (U/L), median (IQR)                | 37.0 (22.0–92.8)    | 609.5 (150.3–1981.5)  | –6.44*       | <0.001|
| CK (U/L), median (IQR)                 | 166.0 (60.0–495.0)  | 2659.7 (1309.0–4516.0)| –6.94*       | <0.001|
| CKMB (U/L), median (IQR)               | 24.0 (12.0–40.5)    | 164.2 (83.0–391.0)    | –6.93*       | <0.001|
| LDH (U/L), median (IQR)                | 240.0 (171.0–405.0) | 1967.2 (1415.0–3045.0)| –7.35*       | <0.001|
| NT-proBNP (pg/ml), median (IQR)        | 2945.7 (234.0–5771.5)| 9850.4 (7060.0–21,665.0)| –7.00*       | <0.001|
| D-dime (mg/L), median (IQR)            | 848.2 (198.0–1118.0)| 1092.0 (791.0–2173.9)| –6.72*       | <0.001|
| Coxsackie virus B (+), n (%)           | 5 (1.4)             | 0                     | –            | –     |
| Arhythmia, n (%)                       |                     |                       |              |       |
| AVB III                                | 38 (10.4)           | 7 (17.9)              | 0.34*        | 0.561 |
| VT                                     | 35 (9.6)            | 22 (56.4)             | 63.52*       | <0.001|
| SVT                                    | 16 (4.4)            | 0                     | –            | –     |
| Electrocardiogram                      |                     |                       |              |       |
| ST-segment elevation, n (%)            | 49 (13.5)           | 23 (59)               | 49.73*       | <0.001|
| Q-wave, n (%)                          | 49 (13.5)           | 11 (28.2)             | 6.04*        | 0.014 |
| QTc interval delayed, n (%)            | 65 (17.9)           | 19 (48.7)             | 20.33*       | <0.001|
| QRS duration (ms), mean ± SD          | 96.9 ± 25.0         | 102.6 ± 40.5          | 0.86*        | 0.393 |
| Cardiac ultrasound                    |                     |                       |              |       |
| LVEF (%), mean ± SD                   | 63.9 ± 9.7          | 50.5 ± 7.6            | –6.08*       | <0.001|
| Atrium enlargement, n (%)              | 28 (7.7)            | 0                     | –            | –     |
| LVFS <0.25, n (%)                      | 72 (19.8)           | 19 (48.7)             | 16.87*       | <0.001|
| Chest CT, n (%)                        |                     |                       |              |       |
| Podoid enlargement                     | 74 (20.3)           | 8 (20.5)              | 0.001*       | 0.978 |
| Pulmonary edema                        | 64 (17.6)           | 16 (41)               | 12.17*       | <0.001|
| Ccr <60 ml/min, n (%)                  | 49 (13.5)           | 32 (82.1)             | 103.19*      | <0.001|

*Contd...*
**Table 2: Contd...**

| Variables                      | Survivors (n = 364) | Nonsurvivors (n = 39) | Statistics   | P     |
|-------------------------------|---------------------|-----------------------|--------------|-------|
| Thyroid dysfunction, n (%)    | 78 (21.4)           | 8 (20.5)              | 0.018*       | 0.894 |
| cTnT ≥50 µg/L, n (%)          | 28 (7.7)            | 20 (51.3)             | 63.79*       | <0.001|
| Used medicine, n (%)          |                     |                       |              |       |
| Glucocorticoid                | 159 (43.7)          | 23 (59.0)             | 3.33*        | 0.068 |
| β-blocker                     | 126 (34.6)          | 8 (20.5)              | 3.16*        | 0.076 |
| NYHA ≥3, n (%)                | 85 (23.4)           | 30 (76.9)             | 49.57*       | <0.001|

*The statistics were calculated using Chi-square test, continuity correction Chi-square test, or Fisher’s exact test, as appropriate; †The statistics were calculated using Student’s t-test or separate variance estimation t-test, as appropriate; ‡The statistics were calculated using Mann-Whitney U test. All the data were from the results of the first tests after admission. –: No data. SD: Standard deviation; IQR: interquartile range; WBC: White blood cell; MCV: Mean corpuscular volume; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CK: Creatine kinase; CKMB: Creatine kinase MB; LDH: Lactate dehydrogenase; AVB: Auriculo-ventricular block; SVT: Supraventricular tachycardia; LVEF: Left ventricular ejection fraction; LVFS: Left ventricular fractional shortening; NYHA: New York Heart Association classification; BMI: Body mass index; NT-proBNP: N-terminal pro-brain natriuretic peptide; cTnT: Cardiac troponin T; Ccr: Creatinine clearance rate; VT: Ventricular tachycardia; CT: Computed tomography.

**Table 3: Results of test to multicollinearity in screened risk factors**

| Variables                      | TOL     | VIP     |
|-------------------------------|---------|---------|
| Age (≥50 years)               | 0.604   | 1.656   |
| Male                          | 0.526   | 1.902   |
| Smoking habit                 | 0.503   | 1.988   |
| Hypertension                  | 0.500   | 1.999   |
| Syncope                       | 0.584   | 1.713   |
| Digestive symptom             | 0.670   | 1.492   |
| VT                            | 0.468   | 2.138   |
| ST-segment elevation          | 0.400   | 2.501   |
| Q-wave                        | 0.512   | 1.952   |
| QTc interval delayed          | 0.407   | 2.459   |
| LVFS ≤0.25                    | 0.747   | 1.338   |
| Pulmonary edema               | 0.621   | 1.610   |
| Ccr <60 ml/min                | 0.553   | 1.808   |
| cTnT ≥50 µg/L                 | 0.375   | 2.666   |
| NYHA ≥3                       | 0.377   | 2.651   |
| Blood glucose                 | 0.382   | 2.617   |
| Systolic pressure             | 0.594   | 1.684   |
| LVEF                          | 0.590   | 1.695   |
| Hematocrit                    | 0.734   | 1.362   |
| Platelet count                | 0.487   | 2.055   |
| C-reactive protein            | 0.554   | 1.805   |
| AST*                          | 0.189   | 5.289   |
| ALT                           | 0.211   | 4.738   |
| CK                            | 0.240   | 4.172   |
| CKMB                          | 0.222   | 4.510   |
| LDH*                          | 0.156   | 6.402   |
| NT-proBNP                     | 0.299   | 3.342   |
| D-dimer*                      | 0.160   | 6.231   |

TOL and VIP were the two parameters for diagnosing multicollinearity (VIP is calculated as follows: \( \text{VIP} = \frac{1}{\left[1 - R^2_i\right]} \)), and TOL is calculated as follows: \( \text{TOL} = 1 - R^2_i \), where \( R^2_i \) is the coefficient of association of each variable regressed on the remaining predictor variables. A TOL ≤0.2 or VIP ≥5 was indicative of the potential existence of multicollinearity between a particular variable and the remaining variables. *According to the rule, AST, LDH, and D-dimer should be excluded from subsequent analyses. TOL: Tolerance; VIP: Variance inflation factor; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CK: Creatine kinase; CKMB: Creatine kinase MB; LDH: Lactate dehydrogenase; LVEF: Left ventricular ejection fraction; LVFS: Left ventricular fractional shortening; NYHA: New York Heart Association classification; VT: Ventricular tachycardia; cTnT: Cardiac troponin T; Ccr: Creatinine clearance rate; NT-proBNP: N-terminal pro-brain natriuretic peptide.

**DISCUSSION**

We established a model for predicting in-hospital mortality in patients with suspected myocarditis. This model demonstrated that a Ccr <60 ml/min (odds ratio \( OR = 19.94, 95\% CI: 5.66–70.26 \)), an age ≥50 years (\( OR = 7.43, 95\% CI: 2.18–25.34 \)), VT (\( OR = 6.89, 95\% CI: 1.86–25.44 \)), an NYHA classification ≥3 (\( OR = 4.03, 95\% CI: 1.13–14.32 \)), male gender (\( OR = 3.48, 95\% CI: 0.99–12.20 \)), and a cTnT level ≥50 µg/L (\( OR = 3.10, 95\% CI: 0.91–10.62 \)) were independent risk factors for in-hospital mortality. Moreover, our results demonstrated that the Ccr (\( β = 2.99 \)) was associated with the highest risk of in-hospital mortality among these factors. In addition, we also found that the majority of deaths of patients with suspected myocarditis happened within 3 days after the patients were admitted to the hospital. As shown in Figure 2, 69.2% of patients in the nonsurvivor group were discharged from the hospital within 3 days due to death whereas 6.6% of patients in the survival group were discharged from the hospital within 3 days due to recovery. These results demonstrate that diagnosing and treating myocarditis within the first 3 days after admission is crucial with respect to the prognoses of patients with suspected myocarditis.

The Ccr is a laboratory parameter that is frequently used to evaluate kidney damage severity. Renal functional deterioration in patients with myocarditis may be associated with acute heart failure.[12-13] Chronic kidney disease is divided into five stages, according to the glomerular filtration rate, in the National Kidney Foundation guide.[14] The Ccr may be used instead of the glomerular filtration rate in clinical practice. We performed classified analysis based on the above staging system and noted a significant difference in in-hospital mortality between patients with a Ccr >60 ml/min and patients with a Ccr <60 ml/min. In their study, before adjusting for multiple relevant factors, Miyake et al. discovered that increases in the Ccr are related to poor outcomes (\( P = 0.01, OR = 4.5, 95\% CI: 1.40–14.30 \)) in young patients with acute myocarditis.[15] However, the Ccr was not significantly associated with poor outcomes in young patients with myocarditis after Bonferroni correction. In another retrospective study, acute kidney injuries (AKIs)
defined as AKI Network Stage 3 ($P = 0.007$) and Sequential Organ Failure Assessment scores ($P = 0.03$) were identified as predictors of in-hospital mortality in multivariate analysis.$^{[16]}$

Myocarditis is an inflammatory reaction in myocardial cells that frequently leads to the occurrence of myocardial ischemia-anoxia.$^{[17]}$ It is conceivable that myocarditis promotes electrophysiological dysfunction in myocardial cells. VT, a type of severe arrhythmia, often causes hemodynamic changes or ventricular fibrillation, thereby triggering sudden death.$^{[18]}$ Miyake et al. found that in-hospital arrhythmias were associated with worse outcomes in patients with myocarditis ($P = 0.01$, $OR = 7.59$, 95% CI: 2.61–22.07), these outcomes included mechanical-assist device use, heart transplantation, or death.$^{[15]}$ In a study on children with acute fulminant myocarditis, the overall patient survival rate was 78% (14/18), and three of the four nonsurviving patients died of VT and heart failure refractory to medical treatment.$^{[19]}$

The prognoses of hospitalized patients with myocarditis were significantly different between men and women. Our study population comprised 403 patients, including 238 men (59%) and 165 women (41%). The survival group comprised 364 patients, including 207 men (56.9%) and 157 women (43.1%), while the nonsurvival group comprised 39 patients, including 31 men (79.5%) and 8 women (20.5%). Unadjusted comparisons between the survival and nonsurvival groups showed that men had worse outcomes than women ($P = 0.009$, $OR = 7.59$, 95% CI: 2.61–22.07). This result remained significant after adjustment for age and smoking status ($P = 0.019$, $OR = 3.14$, 95% CI: 1.20–8.18). Kytö et al. discovered that myocarditis was more common in men (76.61%; 95% CI 75.11–78.05%) than in women (23.39%; 95% CI: 21.95–24.89%, $P < 0.0001$) and that men are significantly more susceptible to myocarditis than women.$^{[20]}$ In addition, the authors of another study found that women with myocarditis were more likely to develop ventricular arrhythmias than men with myocarditis ($OR = 2.43$, 95% CI: 1.12–5.27) and that women possessed longer QT intervals, as demonstrated by electrocardiography, due to decreases in the expression levels of some pivotal proteins.$^{[21]}$ Moreover, myocarditis prolongs ventricular repolarization times in approximately 70% of patients. The combination of these changes, the QT interval fluctuations caused by the menstrual cycle in women,$^{[22]}$ and the decreases in action potential durations induced by testosterone production in men$^{[23]}$ are responsible

### Table 4: Logistic regression analysis for independent risk factors of in-hospital mortality

| Variables | Univariate analysis | | | Multivariate analysis | | |
| --- | --- | --- | --- | --- | --- | --- |
| Age ($\geq 50$ years)* | $20.71$ (7.86–54.53) | $<0.001$ | $7.43$ (2.18–25.34) | $0.001$ |
| Male* | $5.94$ (3.32–8.57) | $<0.001$ | $3.48$ (0.99–12.20) | $0.052$ |
| Smoking habit | $2.47$ (1.25–4.90) | 0.010 | – | – |
| Hypertension | $2.35$ (1.01–5.50) | 0.049 | – | – |
| Syncope | $2.61$ (1.25–5.47) | 0.011 | – | – |
| Digestive symptom | $3.44$ (1.70–6.96) | 0.001 | – | – |
| VT* | $12.17$ (5.91–25.05) | $<0.001$ | $6.89$ (1.86–25.44) | $0.004$ |
| ST-segment elevation | $9.24$ (4.56–18.71) | $<0.001$ | – | – |
| Q-wave | $2.53$ (1.18–5.40) | 0.017 | – | – |
| QTC interval delayed | $4.38$ (2.21–8.65) | $<0.001$ | – | – |
| LVFS <0.25 | $3.85$ (1.95–7.60) | $<0.001$ | – | – |
| Pulmonary edema | $3.26$ (1.63–6.52) | 0.001 | – | – |
| Ccr <60 ml/min* | $29.39$ (12.30–70.25) | $<0.001$ | $19.94$ (5.66–70.26) | $<0.001$ |
| cTnT ≥50 µg/L* | $19.56$ (8.96–42.73) | $<0.001$ | $3.10$ (0.91–10.62) | 0.072 |
| NYHA ≥3* | $10.94$ (5.00–24.00) | $<0.001$ | $4.03$ (1.13–14.32) | 0.031 |
| Blood glucose | $1.18$ (1.07–1.30) | 0.001 | – | – |
| Systolic pressure | $0.51$ (0.28–0.94) | 0.031 | – | – |
| LVEF | $0.90$ (0.87–0.93) | $<0.001$ | – | – |
| Hematocrit | $1.74$ (0.94–3.20) | 0.077 | – | – |
| Platelet count | $0.99$ (0.98–0.99) | $<0.001$ | – | – |
| C-reactive protein | $1.01$ (1.00–1.01) | $<0.001$ | – | – |
| ALT | $1.00$ (1.00–1.00) | $<0.001$ | – | – |
| CK | $1.00$ (1.00–1.00) | $<0.001$ | – | – |
| CKMB | $1.01$ (1.01–1.01) | $<0.001$ | – | – |
| NT-proBNP | $1.00$ (1.00–1.00) | $<0.001$ | – | – |

*After univariate and multivariate logistic regression analyses, the final prediction model including six variables was established including a Ccr <60 ml/min, an age ≥50 years, VT, an NYHA classification ≥3, male gender, and a cTnT level ≥50 µg/L. OR: Odds ratio; CI: Confidence interval; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CK: Creatine kinase; CKMB: Creatine kinase MB; LDH: Lactate dehydrogenase; LVFS: Left ventricular ejection fraction; LVFS: Left ventricular fractional shortening; NYHA: New York Heart Association classification; VT: Ventricular tachycardia; cTnT: Cardiac troponin T; Ccr: Creatinine clearance rate; NT-proBNP: N-terminal pro-brain natriuretic peptide. –: Not applicable.
for the more frequent occurrences of ventricular arrhythmias in women than in men. Fairweather et al. obtained similar results in their study as they found that women with myocarditis and dilated cardiomyopathy had better outcomes than men with myocarditis and dilated cardiomyopathy, possibly because the incidences of ischemic heart disease and heart failure with a higher LVEF are lower in women than in men.[24] Furthermore, in a cardiovascular magnetic resonance imaging study, Cocker et al. found that women were twice as likely as women to develop myocardial fibrosis (73.2 vs. 37.5%, P < 0.01).[25]

The NYHA classification is commonly used to evaluate heart function in clinical practice. In an investigation of 181 patients with suspected myocarditis, Kindermann et al. discovered that an NYHA Grade III or IV classification was an independent predictive factor for cardiac death or heart transplantation (hazard ratio 3.20; 95% CI: 1.36–7.75, P < 0.01).[26] Grün et al. demonstrated that the presence of late gadolinium enhancement was the best independent predictor of all-cause mortality and cardiac mortality. The authors of another study found that an initial presentation of heart failure may be a good predictor of an incomplete long-term recovery.[27] In addition, Arbustini et al. determined that survival rates were negatively correlated with the NYHA grades in their study, in which they followed up to 26 patients with myocarditis for 10 years.[28]

Age is usually associated with the occurrence of cardiovascular diseases, such as hypertension, coronary heart disease, or atrial fibrillation. In our study, an age exceeding 50 years was an independent risk factor for in-hospital mortality in patients with suspected myocarditis (OR = 8.29; 95% CI: 4.09–16.82, P < 0.001). Moreover, our analysis for cutoff value showed that a significant difference in in-hospital mortality existed between patients older and younger than 50 years of age. In a study of 65 patients with acute myocarditis, Cocker et al. discovered that patients younger than 40 years of age were more likely to present with myocardial edema on magnetic resonance imaging than patients older than 40 years of age. However, early enhancement was noted more frequently in patients older than 40 years than in patients younger than 40 years (84.2% vs. 61.5%, P < 0.05).[29] In a study evaluating 222 patients with biopsy-proven myocarditis over a median follow-up period of 4.7 years, age was demonstrated to be associated with all-cause mortality, cardiac mortality, and incomplete recovery by univariate analysis.[27] The investigators did not perform cutoff analysis; thus, the value was not determined. In contrast, Kindermann et al. found that age was not a predictor of a poor prognosis in their study of 181 patients with suspected myocarditis.[26]

Serum cardiac biomarker levels are routinely measured in patients with suspected myocarditis. Troponin, which comprises troponin T, troponin I, and troponin C, is a type of regulatory protein that controls muscle contraction and is released into the circulation from damaged myocardium; thus, its serum level can serve as a parameter of the degree of tissue damage. In our study, troponin T was converted into categorical data to be explained concisely. Subsequently, our analysis for cutoff value showed that a significant difference in in-hospital mortality existed between patients with a cTnT concentration ≥50 µg/L and patients with a cTnT concentration <50 µg/L. In their study on the diagnosis of acute myocarditis in children, Soongswang et al. found that a cardiac cTnT level of 0.052 ng/ml was an appropriate cutoff value for the diagnosis of acute myocarditis.[29] Ammann et al. found that the degree of troponin elevation in early acute myocarditis was an indicator of the degree of myocardial injury, but this parameter was not related to the LVEF in the early or later stage of the disease. This result illustrated that cTnT level was not associated with the prognosis of acute myocarditis.[30]

In the nonsurvival group, nearly 70% of patients died within 3 days after admission, a phenomenon for which no explanation exists. Regarding the possible pathophysiological mechanism underlying the phenomenon, a previous study showed that typical viral infections led to viremia within an average time period of 3 days. Tissue inflammation subsequently developed within 5–10 days due to macrophage and IgM antibody production. Approximately 14 days later, specific IgG antibody levels reached their summit, resulting in myocardial injury and fibrosis.[31] However, patients with myocarditis are not commonly admitted to regional hospitals during early stage of the disease in the absence of severe complications. When patients with risk factors for myocarditis are admitted to the hospital, the majority of their cardiac symptoms have usually appeared, and the opportunity for sufficient treatment of their disease has passed, possibly because severe cardiac injury has occurred.

Several limitations of this study should be noted. First, the small sample size of the study may have resulted in bias. Adabag et al. used a model to predict sudden cardiac death in 4128 patients with heart failure and preserved ejection fractions.[32] Second, all the data analyzed herein were obtained from a regional hospital in China. Our results must be verified in studies involving different medical institutions. Third, none of the patients underwent a myocardial biopsy to verify their diagnoses of myocarditis; thus, it is possible that nonmyocarditis patients were included in the study. Fourth, we did not utilize cardiovascular magnetic resonance imaging because it is used infrequently in our hospital; however, several studies have shown that cardiovascular magnetic resonance imaging can predict clinical outcomes in patients with myocarditis.[33-35] Fifth, in-hospital mortality was also associated with the use of life support-related medical equipment. A study on acute fulminant myocarditis in children revealed that timely use of extracorporeal membrane oxygenation (ECMO) can improve survival rates.[39] Our hospital does not have ECMO equipment.
Finally, the validity of a prediction model should be verified by external data. However, such a work was not performed due to the small number of patients with the disease.

In conclusion, a model for predicting in-hospital mortality in patients with suspected myocarditis was established in the study. The model demonstrated that a Ccr <60 ml/min, an age ≥50 years, VT, an NYHA classification ≥3, male gender, and a cTnT level ≥50 µg/L were independent risk factors for in-hospital mortality in patients with suspected myocarditis. In addition, nearly 70% of patients in the non-survival group died within 3 days after admission. This finding indicated that providing sufficient life support during the early stage of the disease may improve the prognoses of patients with suspected myocarditis with multiple risk factors for in-hospital mortality. Due to the limitations in our study, the clinical implications in terms of prediction of in-hospital mortality needed to be further determined by multi-center studies with large sample size.

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Conflicts of interest
There are no conflicts of interest.

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