Establishment and assessment of a nomogram model for predicting the risk of fulminant myocarditis

A STROBE compliant cross-sectional study

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Abstract

We aimed to identify potential clinical predictors associated with the risk of fulminant myocarditis, and further to establish and assess a nomogram model based on significant attributes for clinical practicability.

This is a retrospective, cross-sectional study, involving 28 patients with fulminant myocarditis and 35 age-, and sex-matched patients with non-fulminant myocarditis. Effect-size estimates are expressed as odds ratio (OR) and 95% confidence interval (CI).

Fifteen factors were primarily identified to be associated with the significant risk of fulminant myocarditis after adjusting for confounders. Due to strong correlation, 6 factors were retained, including mean arterial pressure (OR, 95% CI, \(P\): .82-.72-.94, .005), creatinine (2.15, 1.13-4.10, 0.020), blood urea nitrogen (1.45, 1.04-2.02, 0.028), aspartate aminotransferase (2.62, 1.16-5.91, 0.021), troponin I (1.43, 1.07-1.90, 0.015), and ventricular wall motion abnormality (25.81, 2.52-264.69, 0.006). The contribution of the 6 significant factors to predicting fulminant myocarditis risk was significant from multi-angle analyses, and regressing these factors in a nomogram model exhibited good predictive accuracy, as reflected by both C-index (>90%, \(P < .001\)).

We have identified 6 clinical factors in significant association with fulminant myocarditis, and their prediction capability was more obvious in a nomogram model. Further investigations with larger sample sizes and longer follow-up intervals are warranted.

Abbreviations: AIC = Akaike information criterion, ALT = alanine aminotransferase, AST = aspartate aminotransferase, AUROC = area under the receiver operating characteristic, BIC = Bayesian information criterion, BNP = brain natriuretic peptide, BUN = blood urea nitrogen, CKMB = MB isoenzyme of creatine kinase, CRP = C-reactive protein, FM = fulminant myocarditis, HDL = high-density lipoprotein, HL test = Hosmer–Lemeshow test, IDI = integrated discrimination improvement, IVPWT = interventricular posterior wall thickness, IVST = interventricular septal thickness, LAD = left atrium dimension, LDH = lactate dehydrogenase, LVEDD = left ventricular end diastolic diameter, LVEF = left ventricular ejection fraction, MAP = mean arterial pressure, NFM = non-fulminant myocarditis, NRI = net reclassification improvement, SV = stroke volume, TNI = troponin I, VWMA = ventricular wall motion abnormality, WBC = white blood cell.

Keywords: fulminant myocarditis, nomogram model, prediction, risk factor

1. Introduction

Fulminant myocarditis is a relatively rare syndrome clinically characterized by sudden and severe diffuse cardiac inflammation, and it frequently leads to fatal outcomes, such as ventricular arrhythmias, cardiogenic shock, and multiple organ failure.\cite{1-3} These fatal outcomes often occur in the acute stage, and if treated promptly, the survival rate for patients with fulminant myocarditis can reach over 50%.\cite{4-6} Hence, the early identification of individuals at high risk for fulminant myocarditis is crucial to implement measures that may prevent the progression to overt...
fulminant myocarditis and reduce the occurrence of resultant fatal outcomes.\textsuperscript{[7]}

In medical literature, some clinical manifestations or laboratory biomarkers have been identified as promising predictors for the development of fulminant myocarditis.\textsuperscript{[8–11]} For example, low systolic blood pressure and high creatine kinase were reported to be associated with an increased risk of fulminant myocarditis.\textsuperscript{[11]} Besides, echocardiography, as a noninvasive and easily performed technique to examine heart structures and function, is widely used in assessing fulminant myocarditis.\textsuperscript{[12,13]} Current evidences have showed that fulminant myocarditis is distinguishable from non-fulminant myocarditis by echocardiography.\textsuperscript{[14]} and echocardiography can further provide prognostic insights.\textsuperscript{[13]} Thus, early appraisal based on the integration of clinical, biological, and echocardiographic characteristics is important and imperative.

To yield more information for further investigations, we undertook a retrospective, cross-sectional study based on 28 patients with fulminant myocarditis and 35 age-, and sex-matched patients with non-fulminant myocarditis to identify potential predictors associated with the risk of fulminant myocarditis. Meanwhile, to enhance clinical practicability, we next attempted to establish and assess a nomogram prediction model for fulminant myocarditis based on significant attributes.

2. Methods

2.1. Ethical approval and informed consent

The conduct of this present study was reviewed and approved by the Ethics Committee of The First Affiliated Hospital of Fujian Medical University. Written informed consent was obtained from all study subjects if they had the capacity to provide it, and if subjects cannot give consent, a relative or representative gave proxy consent.

2.2. Study design and subjects

This is a retrospective, cross-sectional study conducted during the period from January 2016 to December 2018 at the Department of Cardiology, The First Affiliated Hospital of Fujian Medical University. A total of 63 adult subjects were enrolled in this study, involving 28 patients with fulminant myocarditis and 35 age-, and sex-matched patients with non-fulminant myocarditis.

2.3. Definitions of fulminant myocarditis

Fulminant myocarditis is defined as the sudden and severe diffuse cardiac inflammation, accompanied by hemodynamic dysfunction (such as ventricular arrhythmias, cardiogenic shock), or multiple organ failure.\textsuperscript{[11,16]}

2.4. Baseline characteristics

At the time of admission, data on demographic and lifestyle factors, clinical characteristics, laboratory biomarkers, and echocardiographic indexes were recorded and double checked for the sake of accuracy.

Demographic factors included age at the time of admission and sex. Lifestyle factors included cigarette smoking and alcohol drinking status. Smoking was classified into never smoking and ever (current or former) smoking. Drinking was classified into never drinking and ever (current or former) drinking. Clinical characteristics included mean arterial pressure (MAP) and pulse. Laboratory biomarkers (units) included white blood cells (\(\times 10^9/L\)), neutrophil percentage (\%), neutrophil count (\(\times 10^9/L\)), lymphocyte count (\(\times 10^9/L\)), hemoglobin (g/L), platelet (\(\times 10^9/L\)), C-reactive protein (mg/L), procalcitonin (ng/L), blood glucose (mmol/L), Kalium (mmol/L), magnesium (mmol/L), uric acid (\(\mu\)mol/L), creatinine (\(\mu\)mol/L), blood urea nitrogen (BUN) (mmol/L), D-dimer (mg/L), fibrinogen (g/L), NT-proBNP (brain natriuretic peptide) (pg/mL), troponin I (TNI) (ng/mL), lactate dehydrogenase (U/L), creatine kinase (U/L), MB isoenzyme of creatine kinase (U/L), total bilirubin (\(\mu\)mol/L), direct bilirubin (\(\mu\)mol/L), albumin (g/L), alanine aminotransferase (U/L), aspartate aminotransferase (U/L), total cholesterol (mmol/L), triglyceride (mmol/L), high-density lipoprotein (HDL) (mmol/L), and low-density lipoprotein (LDL) (mmol/L).

At the time of admission, echocardiographic indexes were measured, including left atrium dimension (LAD), left ventricular end diastolic diameter (LVEDD), interventricular septal thickness (IVST), left ventricular posterior wall thickness (IVPWT), stroke volume (SV), left ventricular ejection fraction (LVEF), and ventricular wall motion abnormality (VWMA). In addition, the same echocardiography was done after 3 months after discharge from The First Affiliated Hospital of Fujian Medical University, and these indexes were recorded and compared with the initial records.

2.5. Statistical analyses

Statistical analyses were performed using the STATA software (version 14.0, Stata Corp., TX) and R programming environment (version 4.0.2). Two-sided \(P\) values <0.05 were considered statistically significant. Continuous variables were assessed for normality by use of the skewness and kurtosis test, and they are presented as median (interquartile range) for skewed variables. Categorical variables are presented as count (percentage). Rank-sum test or Chi-squared test was used to compare baseline characteristics between groups.

Logistic regression analyses were done to identify statistically significant factors attributable to fulminant myocarditis before and after adjusting for confounders, including age, sex, cigarette smoking, and alcohol drinking. Effect-size estimates are expressed as odds ratio (OR) and 95\% confidence interval (CI). Spearman correlation analyses were used to illustrate the relationship of significant factors, and those with pairwise correlation coefficient <0.5 were selected as potential independent predictors for fulminant myocarditis.

Predictive accuracy was appraised by adding significant characteristics to the basic model, which included age, sex, cigarette smoking, alcohol drinking, and C-reactive protein (CRP). Akaike information criterion (AIC), Bayesian information criterion (BIC), the -2-log likelihood ratio test, and Hosmer–Lemeshow goodness-of-fit test were used to evaluate how closely the prediction probability by adding significant characteristics was. Integrated discrimination improvement (IDI) and area under the receiver operating characteristic (AUROC) were used to see whether the addition of significant factors can differentiate patients with fulminant myocarditis from non-fulminant myocarditis. The receiver operating characteristic (ROC) curves were plotted for models with and without significant factors.

Finally, a prediction nomogram model for fulminant myocarditis was established by implementing “rms” package in the R programming environment. The area under the receiver

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operating characteristics curve (concordance index or C-index) was used to justify the predictive accuracy.

3. Results

3.1. Baseline characteristics

The baseline characteristics of study subjects are summarized in Table 1. Five deaths in patients with fulminant myocarditis occurred. Compared with patients with non-fulminant myocarditis, patients with fulminant myocarditis tended to have lower MAP, worse biological, and echocardiographic performance.

3.2. Identification of statistically significant characteristics

Table 2 displays the identification of statistically significant factors for fulminant myocarditis. Fifteen factors, including MAP, blood glucose, D-dimer, creatinine, BUN, aspartate

### Table 1: The baseline characteristics of study subjects.

| Characteristics | Patients with FM (n=28) | Patients with NFM (n=35) | P  |
|-----------------|-------------------------|--------------------------|----|
| Age, y          | 47.5 (37, 63)           | 48 (38, 69)              | .63|
| Males           | 14 (50%)                | 17 (49%)                 | .74|
| Cigarette smoking | 9 (32.1%)              | 11 (31.4%)               | .93|
| Alcohol drinking | 6 (21.4%)               | 10 (28.6%)               | .67|
| MAP, mm Hg      | 96.33 (82.67, 107)      | 134 (122.67, 148)        | <.01|
| Pulse (per minute) | 82 (60, 96)           | 80 (70, 90)              | .78|
| Laboratory biomarkers |                     |                          |    |
| WBC (×10⁹/L)    | 8.19 (7.37, 9.14)       | 6.43 (5.27, 8.01)        | .01|
| Neutrophil percentage (%) | 82.35 (73.2, 85.8) | 66.6 (52.9, 73.1)        | <.01|
| Neutrophil count (×10⁹/L) | 6.06 (5.43, 7.38) | 4.29 (3.05, 5.72)        | <.01|
| Hemoglobin, g/L | 141.5 (127, 145)        | 141 (131, 151)           | .89|
| Platelet (×10⁹/L) | 213.5 (133, 222)      | 214 (182, 231)           | .26|
| CRP, mg/L       | 26.99 (11.23, 49.95)    | 20.62 (5.46, 49.95)      | .55|
| Procalcitonin, ng/L | 0.19 (0.08, 0.8)      | 0.07 (0.05, 0.18)        | .04|
| Blood glucose, mmol/L | 10.63 (7.02, 13.71)  | 5.33 (4.48, 6.56)        | <.01|
| Kalium, mmol/L | 3.96 (3.76, 4.19)       | 4.2 (3.87, 4.36)         | .15|
| Magnesium, mmol/L | 0.95 (0.88, 1.02)     | 0.87 (0.82, 0.93)        | .07|
| Uric acid, μmol/L | 375.95 (261, 461)    | 326.8 (249, 364.6)       | .18|
| Creatinine, μmol/L | 74 (56.9, 98.7)       | 64 (61, 70.5)            | .25|
| BUN, mmol/L | 8.43 (4.92, 10.08)      | 4.5 (3.9, 6.42)          | <.01|
| D-dimer, mg/L | 2.12 (0.8, 3.57)        | 0.33 (0.21, 0.51)        | <.01|
| Fibrinogen, g/L | 3.56 (2.57, 4.15)       | 3 (2.36, 3.84)           | .36|
| NT-proBNP, pg/mL | 8965 (5700, 21500)    | 291 (82, 675.8)          | <.01|
| TNI, ng/mL | 4.35 (0.67, 8)          | 0.77 (0.28, 1.6)         | .01|
| LDH, U/L       | 556.5 (414, 863)        | 245 (207, 288)           | <.01|
| Creatine kinase, U/L | 443.5 (114, 943)     | 209 (83, 350)            | .06|
| CRKMB, U/L | 59.5 (19, 77)           | 21 (12, 31)              | .02|
| Total bilirubin, μmol/L | 12.3 (8, 18.7)       | 10.3 (6.9, 13.8)         | .21|
| Direct bilirubin, μmol/L | 5.55 (3.4, 7)         | 3.9 (2.9, 5.6)           | .06|
| Albumin, g/L | 38.5 (35.5, 40.6)       | 38.2 (36.6, 41.7)        | .48|
| ALT, U/L | 101.0 (51, 140)         | 23 (16, 43)              | <.01|
| AST, U/L | 138.5 (38, 254)         | 34 (23, 48)              | <.01|
| Total cholesterol, mmol/L | 3.6 (3.32, 4.68)    | 3.61 (3.16, 4.24)        | .84|
| Triglyceride, mmol/L | 0.89 (0.68, 1.33)    | 1.06 (0.53, 1.39)        | .81|
| HDL, mmol/L | 0.95 (0.7, 1.27)        | 1.05 (0.83, 1.22)        | .47|
| LDL, mmol/L | 2.52 (1.75, 3.13)       | 2.1 (1.96, 2.63)         | .30|
| Echocardiographic indexes |                  |                          |    |
| LAD, cm | 3.52 (3.3, 3.98)        | 3.58 (3.24, 3.90)        | .99|
| LVEDD, cm | 4.9 (4.32, 5.17)       | 4.87 (4.61, 5.01)        | .84|
| IVST, cm | 1.13 (1.02, 1.29)       | 0.89 (0.82, 0.94)        | <.01|
| IVRT, cm | 0.98 (0.91, 1.13)       | 0.79 (0.72, 0.84)        | <.01|
| SV, mL | 51.63 (45.66, 63.36)    | 72.09 (66.81, 79.73)     | <.01|
| LVEF (%) | 50.13 (38.1, 58.43)     | 67.16 (62.7, 70.06)      | <.01|
| VWMA | 16 (57.1%)              | 2 (5.7%)                 | <.01|

Data are expressed as median (interquartile range) or count (percent). 
ALT = alanine aminotransferase, AST = aspartate aminotransferase, BNP = brain natriuretic peptide, BUN = blood urea nitrogen, CKMB = MB isoenzyme of creatine kinase, CRP = C-reactive protein, FM = fulminant myocarditis, HDL = high-density lipoprotein, LPV = left ventricular posterior wall thickness, IVST = interventricular septal thickness, LAD = left atrium dimension, LDH = lactate dehydrogenase, LDL = low-density lipoprotein, LVEDD = left ventricular end diastolic diameter, LVEF = left ventricular ejection fraction, MAP = mean arterial pressure, NFM = non-fulminant myocarditis, SV = stroke volume, TNI = Troponin I, VWMA = ventricular wall motion abnormality, WBC = white blood cell.
P-value was calculated by using the rank-sum test or the Chi-squared test where appropriate.
amino transferase (AST), TNI, lactate dehydrogenase (LDH), creatine kinase (CK), MB isoenzyme of creatine kinase (CKMB), IVST, IVPWT, SV, LVEF, and VWMA, were observed to be significantly associated with the risk of fulminant myocarditis after adjusting for age, sex, cigarette smoking, and alcohol drinking (all P < .05). Three factors were predictive for fulminant myocarditis, including MAP (OR, 95% CI, P. .84, .72–.94, .005), SV (0.85, 0.76–0.95, 0.003), and LVEF (0.81, 0.70–0.93, 0.003). By contrast, the other factors were risky for fulminant myocarditis, including D-dimer (5.90, 1.65–21.34, 0.006), creatinine (2.15, 1.13–4.10, 0.020), BUN (1.45, 1.04–2.02, 0.028), TNI (1.43, 1.07–1.90, 0.015), and IVPWT (5.53, 1.82–16.86, 0.003).

### 3.3. Correlation analyses

Spearman correlation analyses revealed that there were close correlations of blood glucose, D-dimer, LDH, CK, CKMB, IVST, SV, LVEF, and IVPWT with the other significant factors (pairwise correlation coefficients > 0.8) (Supplementary Figure I, http://links.lww.com/MD2/A94). Finally, MAP, creatinine, BUN, AST, TNI, and VWMA were selected as potential predictors for fulminant myocarditis.

### 3.4. Prediction accuracy assessment

Two models were constructed to assess the prediction accuracy of identified predictors, viz., the basic model and the full model. The basic model included age, sex, cigarette smoking, alcohol drinking, and pulse, and the full model additionally included MAP, creatinine, BUN, AST, TNI, and VWMA. As presented in Table 3, both calibration and discrimination statistics were assessed by adding identified predictors to the basic model. Compared with the basic model, prediction accuracy was significantly improved in the full model (all P < .05). The benefits gained by adding significant predictors to the basic model were higher than that of the basic model (Fig. 1).

### 3.5. Prediction nomogram model

A prediction nomogram model was established for fulminant myocarditis on the basis of identified significant predictors, including MAP, creatinine, BUN, AST, TNI, and VWMA (Fig. 2). The predictive accuracy was good, as reflected by both C-index of over 90% (P < .001) and calibration curve (Supplementary Figure 2, http://links.lww.com/MD2/A94).

### 3.6. Changes of predictive echocardiographic performance during follow-ups

As illustrated in Fig. 3, in patients with fulminant myocarditis, IVPWT was significantly decreased at 3rd month after discharge from hospital, whereas SV and LVEF were significantly increased.

### 4. Discussion

In this retrospective, cross-sectional study, we aimed to identify potential predictors associated with the risk of fulminant...
myocarditis in a Chinese population. The key finding of this study is that 6 unrelated clinical factors were identified to be significantly associated with fulminant myocarditis, including MAP, creatinine, BUN, D-dimer, AST, TNI, and VWMA, and importantly their prediction capability was more obvious in a nomogram model. To the best of our knowledge, this is the first study that has established and assessed a prediction nomogram model for fulminant myocarditis in current literature.

Some studies have attempted to unravel the risk profiling of fulminant myocarditis by focusing on individual factors, whereas disregarding the establishment of risk scores or prediction models.\cite{10,17,18} Considering the fact that fulminant myocarditis is a complex fatal disease, the role of any single factors in the pathogenesis of fulminant myocarditis is likely to be small when assessed individually, but may be more pronounced in the presence of other risk factors. To shed some light on this issue, we employed the logistic regression analyses before and after adjusting for confounding factors, as well as the Spearman correlation analyses to identify potential unrelated factors that are independently and significantly associated with the risk of

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**Figure 1.** Decision curve analysis on the net benefits of adding significant uncorrelated factors to the basic model.

**Figure 2.** The prediction nomogram model for fulminant myocarditis. AST=aspartate aminotransferase, BUN=blood urea nitrogen, MAP=mean arterial pressure, TNI=Troponin I, VWMA=ventricular wall motion abnormality.
fulminant myocarditis, and finally 6 such factors were teased out. To appraise prediction performance, we conducted both Hosmer–Lemeshow and likelihood ratio tests, as well as AIC, BIC, net reclassification improvement (NRI), IDI, and AUROC statistics and visual inspection of decision curve analysis curves. These multi-angle analyses revealed that the addition of 6 identified factors can significantly improve the prediction capability of the basic model. To enhance clinical practicability, we here established a nomogram model by regressing these 6 factors, with a decent prediction accuracy. For practical reasons, we agree that external validation of our findings is of added interest.

Consistent with the results of previous studies,[18–20] our findings indicated that both cardiac and renal dysfunction made a critical difference in the progress of fulminant myocarditis. It is widely recognized that cardiac and renal diseases interplay bilaterally and interdependently due to shared pathways,[21] which may be explained by over-activation of the neurohormonal systems (such as renin-angiotensin-aldosterone system) and elevated venous pressure.[22] Consequently, monitoring renal function and providing timely intervention are of vital importance at the early onset of fulminant myocarditis.

Additionally, we found that increased D-dimer level was associated with a high risk of fulminant myocarditis. D-dimer is regarded as a valuable biomarker of coagulation and fibrinolysis,[23] which can be induced by inflammation and further interact with each other.[24] Moreover, there is a large population study suggesting that D-dimer can independently lead to functional decline and mortality.[25] Both dependent and independent impacts of D-dimer play essential roles in the development of fulminant myocarditis, and so it is necessary to give more concerns to patients with increased D-dimer level, especially those with sharp D-dimer increment.[26]

In terms of echocardiographic characteristics, our findings highlight the important roles of IVPWT, SV, and LVEF in predicting fulminant myocarditis. Thicker IVPWT reflects structural changes in heart at early onset, whereas decreased SV and LVEF reflect functional changes. Those changes are mainly caused by inflammatory response and edema,[6] and can remarkably recover within a short period in our study. However, there is a paucity of data regarding the adverse outcomes of fulminant myocarditis.[27] This discrepancy may be determined by histologic subtype, with giant cell myocarditis portending the worst prognosis.[28] Yet, detection of histologic changes, depending on results of endomyocardial biopsy, is restricted due to hemodynamic dysfunction of fulminant myocarditis.

4.1. Limitations

Some limitations should be acknowledged when interpreting our findings. Firstly, this study is cross-sectional in design, which precludes further comments on causality, and more prospective investigations with longer follow-up intervals are warranted. Secondly, given the fact that the prevalence of fulminant myocarditis is extremely low, the sample size of our study was relatively small. Further large-scale studies are needed to confirm or refute our conclusions. Thirdly, all study subjects were enrolled from a single hospital in Fuzhou, China, which restricts the generalizability of our findings to other groups.

5. Conclusions

Taken together, we have identified 6 clinical factors in significant association with fulminant myocarditis, and their prediction capability was more obvious in a nomogram model. For practical reasons, we hope that this study will not be just an end point of explorations instead of a start to establish underpinning data to further identify and characterize risk profiling of fulminant myocarditis, as well as the potential biological mechanisms.

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