# A nomogram predicting atrial fibrillation in patients with dilated cardiomyopathy

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*To the Editor:* Dilated cardiomyopathy (DCM) is a type of primary myocardial disease with unknown etiology.[1] It is a disorder of the heart muscle mainly characterized by left ventricular dilation and systolic dysfunction, resulting from the response of the myocardium to genetic and environmental insults. The clinical manifestations are progressive heart failure, arrhythmia, thromboembolism, and even sudden death. The morbidity and mortality of DCM have been steadily increasing, which has become one of the main causes of death in cardiomyopathy. DCM may involve the conduction system and is often associated with various types of arrhythmias, such as atrial fibrillation (AF).[2] AF can increase the risk of vascular embolism. Studies have shown that patients with AF have a five-fold increased incidence of stroke and a two-fold increased mortality. About 15%–20% of ischemic strokes are caused by AF. The hemodynamic changes and increased risk of thromboembolic events caused by AF in patients with DCM increase their disability rate and mortality. Therefore, early prediction and intervention of AF in patients with DCM can effectively improve the prognosis and quality of life. An accurate risk classification of AF in patients with DCM is very important to guide intervention. The nomogram is based on the results of multivariate logistic regression analysis. It integrates multiple prediction indexes and visualizes the correlation among various variables for the outcome prediction in the form of a graph.[3] In this study, we aimed to identify patients with DCM who are likely to develop AF by developing a nomogram.

Data of consecutive DCM patients were collected in this study at the First Affiliated Hospital of Nanjing Medical University from September 2009 to November 2015. Inclusion criteria were (1) left ventricular end-diastolic dimension (LVEDd) >5.5 cm in male and LVEDd >5.0 cm in female, or LVEDd >117% (>2 standard deviation [SD] of the predicted value of 112% corrected for age and body surface area); (2) left ventricular fractional shortening <25% (>2 SD) and/or left ventricular ejection fraction (LVEF) <45% (>2 SD); (3) no AF was found in the previous medical records and electrocardiogram (ECG) data. Exclusion criteria were (1) patients with hypertensive heart disease, valvular heart disease, congenital heart disease, or ischemic heart disease; (2) children <18 years of age and alcoholics; (3) severe hepatic and renal insufficiency. Basic clinical characteristics were collected by reviewing the electronic medical records of the enrolled patients. Patients were followed up at the clinical department or hospital every 3 months in this study. Follow-up information and death events were recorded. The primary endpoint was AF. AF is shown by ECG or a 24-hours dynamic ECG.

Data were presented as mean ± SD or median (interquartile range). Categorical variables were presented as numbers with percentages. To generate the nomogram for the training set, multivariable logistic regression analysis was performed to predict the probability of AF using a forward stepwise method that included all variables with a probability ($P$) value <0.20 in the univariable analysis. Variables with $P$ values that were <0.05 in the multivariable logistic regression were entered into the prediction model. The main outcome of this study was the risk of AF based on the baseline characteristics. The multivariate logistic regression model was used to estimate the odds ratio (OR) and 95% confidence intervals (CIs) of the risk of AF in the model.

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The area under the ROC curve (AUC) can be considered as a generalization of the area under the receiver operating characteristic (ROC) curve and is calculated by analyzing all possible patients. The calibration of the model was validated by Hosmer-Lemeshow goodness-of-fit test ($P > 0.05$) and calibration plots. The clinical value of the predictive model was tested using a decision curve analysis (DCA).

Nomogram was developed according to the logistic regression by the software R 3.6.3. (The R Foundation; http://www.r-project.org;version3.6.3). All $P$ value $< 0.05$ (two tail) was considered statistically significant.

Between September 2009 and December 2015, a total of 243 consecutive patients with DCM were admitted to the First Affiliated Hospital of Nanjing Medical University. Thirty patients with missing data and 16 patients lost to follow-up were excluded from this study. The remaining 197 patients were eligible for analysis. The demographics and clinical characteristics for the training set ($n = 138$, mean age $= 56.4 \pm 14.9$ years, 80.4% male) and the test set ($n = 59$, mean age $= 58.1 \pm 14.7$ years, 74.6% male) are listed in Supplementary Table 1, http://links.lww.com/CM9/A872. In the training set, 30 patients (21.7%) developed AF, whereas in the test set, 13 patients (22%) developed AF. The median follow-up was 92.9 (66.5-172.6) months.

Multivariate analyses demonstrated that age (OR: 3.91, 95% CI: 1.71–8.93, $P < 0.01$), weight (OR: 5.11, 95% CI: 2.23–11.70, $P < 0.01$), thyroid stimulating hormone (TSH) (OR: 1.55, 95% CI: 1.11–2.16, $P = 0.01$), d-dimer (D-D) (OR: 1.47, 95% CI: 1.06–2.03, $P = 0.02$), left atrial diameter (LAD) (OR: 2.34, 95% CI: 1.04–5.25, $P = 0.04$), and LVEF (OR: 0.33, 95% CI: 0.15–0.75, $P < 0.01$) were independent risk factors for AF in patients with DCM [Supplementary Table 2, http://links.lww.com/CM9/A872]. The nomogram was developed by assigning a graphic initial score to each of the six independent prognostic factors (age, weight, TSH, D-D, LAD, and LVEF), with a point range from 0 to 100. The scores for all variables were then added to obtain the total score, and a vertical line was drawn from the total points row to indicate the estimated probability of AF being present [Figure 1]. It was predicted that a higher total score in the nomogram was associated with a higher likelihood of AF, whereas a lower total score was associated with a lower likelihood of AF.

The AUC-ROC was 0.931 (95% CI: 0.86–0.99) in the training set and 0.90 (95% CI: 0.80–0.95) in the test set [Supplementary Figure 1, http://links.lww.com/CM9/A872].

The nomogram model was calibrated using the Hosmer-Lemeshow goodness-of-fit test and a calibration plot. The Hosmer-Lemeshow test revealed high concordance between the predicted and observed probabilities for both the training set ($\chi^2 = 7.83$, df $= 8$, $P = 0.45$) and the test set ($\chi^2 = 8.51$, df $= 8$, $P = 0.49$). The calibration plot also showed good agreement between the predicted and observed outcomes for the training and test sets [Supplementary Figure 2, http://links.lww.com/CM9/A872].

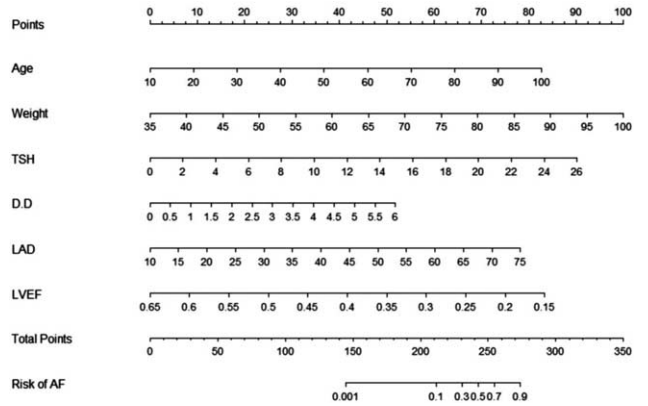


**Figure 1:** Nomogram used for predicting AF in patients with DCM. The final score (ie, total points) is calculated as the sum of the individual score of each of the six variables included in the nomogram. AF: Atrial fibrillation; DCM: Dilated cardiomyopathy; D-D: D-dimer; LAD: Left atrial diameter; LVEF: Left ventricular ejection fraction; TSH: Thyroid stimulating hormone.

DCA was applied to assess the clinical validity of the nomogram [Supplementary Figure 3, http://links.lww.com/CM9/A872], which corroborated good clinical applicability of the nomogram in predicting AF because the ranges of threshold probabilities were wide and practical for the training and test sets.

The main findings of this study were as follows: (1) DCM patients were susceptible to AF (21.8%). (2) Age, weight, TSH, D-D, LAD, and LVEF were independent predictors for AF occurrence in DCM patients. (3) The nomogram was feasible for predicting AF in DCM patients at our hospital and showed good predictive performance.

Studies have shown that patients with DCM are susceptible to AF. This may be related to cardiac degenerative diseases, such as enlargement of cardiomyocytes, reduced atrioventricular compliance, and degeneration of fibrous tissue in patients with DCM.[4] Due to the non-regeneration of myocardial cells, atrial enlargement is often accompanied by the occurrence of cardiac chamber fibrosis, forming focal or patch-like scar, leading to slowing of local conduction speed, resulting in heterogeneity of electrical impulse conduction, and irregular impulse conduction of ectopic lesions with rapid discharge, which contributes to the occurrence of AF. AF leads to uncoordinated atrioventricular contraction. The atria cannot contract effectively and blood cannot be pumped out by the heart in a timely manner. Ventricular diastolic blood flow cannot be completely filled and ventricular filling volume decreases.[5] The above adverse effects on hemodynamics eventually lead to reduced perfusion of the heart, brain, kidney, and other important organs, which can progress to multi-organ damage and failure in the long-term.

We developed and validated a new AF risk model primarily based on clinical baseline data and biomarkers and demonstrated that the model provides an acceptable level of performance for predicting AF in patients with DCM. The nomogram used these six independent

variables to predict AF, which are easily and readily obtainable during the patients' admission to the hospital. This nomogram for the individualized prediction of the probability of AF in patients with DCM. Nomogram has emerged as a simpler and more advanced tool for prediction. It is a pictorial representation of a statistical predictive model that generates a numerical probability of a clinical event, so it is more accurate.[6] The nomogram developed in this study assigns an accurate probability (from 0.1% to 90%) of AF outcome. The nomogram can provide individualized and highly estimated AF risk by combining six independent variables and assigning an appropriate weight to each variable based on its prognostic value, making it easy to use and facilitates management-related decision-making for doctors.

Our prediction model showed that older patients and those with severe or critical DCM had more frequent AF, which was associated with cardiac degenerative changes, such as cardiac enlargement, cardiomyocyte degeneration, and increased fibrous tissue resulting in electrical remodeling. Multivariate logistic regression analysis showed that LAD, left atrial enlargement, was one of the risk factors for DCM with AF, which was consistent with the previous reports. All the animal models with atrial fibrosis showed left atrium enlargement. Hence, we hypothesized that atrial enlargement and atrial fibrosis coexist and influence each other. Left atrial enlargement and fibrosis are concomitant in DCM patients, which can lead to atrial structural remodeling and AF.[7] Meanwhile, this prediction model also found that the lower the LVEF, the more frequent the AF. This may be associated with the occurrence of heart failure in patients with DCM, resulting in the reduced effective circulation of blood volume, reduced renal blood flow, and activation of the renin-angiotensin system. Elevated angiotensin II directly causes myocardial cell apoptosis and interstitial fibrosis, and further accelerates atrial structural remodeling. In patients with DCM, abnormal hemorheology is caused by the enlargement of the heart and weakened ventricular pulse, which makes the blood hypercoagulable and increases the D-2 polymer level.[8] This study found that elevated D-2 levels were associated with an increased risk of AF in patients with DCM. Previous studies showed that DCM patients typically have concomitant hyperthyroidism and heart disease; wherein TSH is decreased and thyroid hormone is increased, which can directly affect the cardiac muscle, decrease the sinoatrial node action potential time, increase atrial muscle excitability, and decrease refractory period. This is likely to lead to AF. In contrast, our study found that if TSH is higher in patients with DCM, they are more susceptible to AF, which may be due to the small sample size. Hence, we need to expand the sample size in future studies.

This study had some limitations. First, this was a singlecenter retrospective study with a small sample size, which might have limited the statistical power of the results. Second, our model has not been validated in external cohorts. Third, our model cannot distinguish various subtypes of AF, such as persistent and paroxysmal AF. Further studies addressing these limitations are necessary so that this nomogram could be improved and has a better predictive performance.

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## Conflicts of interest

None.

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