A predictive model for dilated cardiomyopathy with pulmonary hypertension

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Abstract

Aims Dilated cardiomyopathy (DCM) is defined as a serious cardiac disorder caused by the presence of left ventricular dilatation and contractile dysfunction in the absence of severe coronary artery disease and abnormal loading conditions. The incidence of cardiac death is markedly higher in patients with DCM with pulmonary hypertension (PH) than in DCM patients without PH. No previous studies have constructed a predictive model to predict PH in patients with DCM.

Methods Data from 218 DCM patients (68.3% man; mean age 57.33) were collected. Patients were divided into low, intermediate and high PH-risk groups based on the echocardiographic assessment at the tricuspid regurgitation peak velocity (TRV) in conjunction with the presence of echocardiographic signs from at least two different categories. Basic information, vital signs, comorbidities and biochemical data of each patient were determined. The impact of each parameter on PH probability was analysed by univariable and multivariable analyses, the data from which were employed to establish a predictive model. Finally, the discriminability, calibration ability and clinical efficacy of the model were verified for both the modelling group and the external validation group.

Results We successfully applied a history of chronic obstructive pulmonary disease (COPD) or chronic bronchitis, systolic murmur (SM) at the tricuspid area, SM at the apex and brain natriuretic peptide (BNP) level to establish a model for predicting PH probability in DCM. The model was proven to have high accuracy and good discriminability (area under the receiver operating characteristic curve 0.889), calibration ability and clinical application value.

Conclusions A model for predicting PH probability in patients with DCM was successfully established. The new model is reliable for predicting PH probability in DCM and has good clinical applicability.

Keywords Dilated cardiomyopathy; Pulmonary hypertension; Predictive model; Echocardiographic

Introduction

Dilated cardiomyopathy (DCM) is defined as a serious cardiac disorder caused by the presence of left ventricular dilatation and contractile dysfunction in the absence of severe coronary artery disease and abnormal loading conditions.¹ ² It has been reported that DCM is one of the most common causes of heart failure, with an annual morbidity of 7 per 100 000 individuals owing to its complications.³

At present, related studies have shown that over one in five DCM patients has a high pulmonary hypertension (PH) risk, and the longer DCM lasts, the higher the likelihood of developing PH because of the resulting chronic increase in pressure in the left atrium.⁴ PH was defined by the 2015 European Society of Cardiology and the European Respiratory Society (ESC/ERS) Guidelines as an increase in mean pulmonary arterial pressure (PAPm) ≥ 25 mmHg at rest as measured haemodynamically via right heart catheterization (RHC).⁵ Marked by a combination of constriction and remodelling within the pulmonary vasculature, PH is a complex and progressive condition that can be divided into five major categories based on the underlying cause and haemodynamic parameters: (1) pulmonary arterial hypertension (PAH), (2) PH due to left heart disease (LHD), (3) PH due to interstitial lung
diseases and/or hypoxia, (4) chronic thromboembolic PH (CTEPH) and (5) PH with unclear and/or multifactorial origin.\textsuperscript{5,6} PH-DCM easily falls into the second category, which is the most common in contemporary clinical settings among the five categories.\textsuperscript{5} In a recent study, among patients with PH, 69% had LHD, and the 1-year mortality for PH-LHD patients was 26.6%.\textsuperscript{7} Additionally, according to previous studies, the incidence of cardiac death is markedly higher in patients with DCM and PH than in DCM patients without PH, with a hazard incidence of cardiac death is markedly higher in patients with a predictor of morbidity or mortality in patients with DCM.

Although RHC is the gold standard for PH diagnosis, it is relatively complicated, expensive and invasive and is associated with a number of complications.\textsuperscript{10} Consequently, Doppler echocardiography is recommended by the ESC/ERS Guidelines as a tool for the detailed assessment of right heart hemodynamics, as it is considered a non-invasive and widely available diagnostic instrument for PH-DCM patients.\textsuperscript{11} However, Doppler echocardiography could be technically demanding and often involves a significant cost; thus, the prediction of PH appears to be an impossible mission in some community hospitals with poorer methods of examination.\textsuperscript{11} Moreover, PH-DCM can not only result in more severe symptoms, worse exercise tolerance and higher hospitalization rates but also cause patients to suffer from major implications associated with quality of life and healthcare costs.\textsuperscript{12} To address these problems, it is important to focus on finding a non-invasive and easily obtainable method to detect PH in DCM patients.

Therefore, we aimed to construct a non-invasive model that may be used to predict PH for patients with DCM, which has not been reported in previous studies to the best of our knowledge.

Materials and methods

Patients

The data were collected from all patients with DCM who were admitted to the First Affiliated Hospital of Guangzhou University of Chinese Medicine (Guangzhou, Guangdong Province of China) from October 2008 to January 2021. The inclusion criteria were as follows: (1) age \textgreater{} 18 years; (2) a clinical diagnosis of DCM; and (3) a detailed diagnostic work-up, including clinical evaluations, laboratory tests, electrocardiography (ECG) and echocardiography. Patients with significant coronary artery disease, primary heart valve disease, restrictive or obstructive cardiomyopathy, congenital heart disease and severe arterial hypertension were excluded from participating in the study. No patients had histories of acute viral myocarditis or familial DCM or evidence of immune triggers. Echocardiographic assessments were carried out at index hospital admission or during outpatient visits in stable patients or after stabilization in the case of an urgent admission.

A total of 218 patients, including 83 patients with high PH probability, 59 patients with intermediate PH probability and 76 patients with Low PH probability, who met the inclusion criteria were enrolled in this study as the modelling group. One hundred other patients who met the inclusion criteria were enrolled in the study as the external validation group. Data collection for patients in the external validation group was performed after the predictive model was established. The application of the predictive model and the collection of clinical data from the external validation group were independent processes. Patients were allocated to two groups on the basis of the probability of PH (intermediate or high-PH probability group and low-PH probability group). Basic information and vital signs for each patient, such as sex, age, systolic blood pressure (BP), diastolic BP and heart rate, were recorded. The presence of comorbidities, such as hypertension, diabetes mellitus, prior stroke, chronic obstructive pulmonary disease, pulmonary infection, atrial fibrillation and left bundle branch block (LBBB), was established by medical documentation or in-hospital diagnosis. Among them, the patient who developed a cough, moist rales in the lungs and one of the following conditions was diagnosed as a pulmonary infection: (1) fever, (2) increased leukocyte or the proportion of neutrophil and (3) X-ray showing inflammatory infiltrating lesions in the lungs. The study protocol complied with the Declaration of Helsinki. Prior to the study, the relevant institutional committees and the First Affiliated Hospital of Guangzhou University of Chinese Medicine Ethical Committee approved the study (chairperson: Chuanjin Luo; protocol number: K[2020]135; date of approval: 15 December 2020). This was a retrospective study; thus, the Ethical Committee waived the requirement to obtain informed consent from the patients.

PH probability

The probability of PH was diagnosed in accordance with the 2015 ESC/ERS Guidelines.\textsuperscript{5} Briefly, patients were divided into low, intermediate and high PH-risk groups based on the echocardiographic assessment at the tricuspid regurgitation peak velocity (TRV) in conjunction with the presence of echocardiographic signs from at least two different categories: (1) pulmonary artery (PA) signs, such as PA diameter or acceleration time; (2) inferior vena cava (IVC) and right atrium (RA) signs, such as diameter and the inspiratory collapse of IVC and RA end-systolic area; and (3) ventricular signs.

Evaluation of the predictive model

To evaluate the predictive model in its ability to identify the probability of PH, the results from echocardiography were
used as the standard, the receiver operating characteristic (ROC) curve of the predictive model was plotted, and the area under the ROC curve (AUC), sensitivity, specificity and Youden’s index were calculated. The point at which the sum of sensitivity and specificity was largest was selected as the optimal cut-off value. The validity of the predictive model was evaluated by the consistency statistic (corresponding to AUC), and AUC > 0.7 was considered effective. The discriminability of the model was determined by the ROC curve of the model for both the modelling group and external validation group.

The calibration ability of the predictive model was evaluated by the Hosmer–Lemeshow test and a calibration scatter plot of the two groups. Decision curve analysis (DCA) of the two groups was carried out to evaluate the clinical efficacy of the model.

Statistical analysis

Statistical analysis was performed by Stata 14.0 software. Data are expressed as the mean ± SD and medians (interquartile range or n [%]). All continuous variables were tested for the normal distribution of data with the Shapiro-Wilk test. Comparisons of continuous variables between two groups were conducted with the independent samples t-test or the Mann–Whitney U test. The chi-square test was performed to compare qualitative parameters between two groups. Multivariable analysis was performed by backward WALD regression analysis. The calibration plot figures were obtained using Excel. The ROC curve, Hosmer-Lemeshow test results, DCA and nomogram were obtained using Stata 14.0 software. A model will be considered to have good discriminability if the AUC is higher than 0.7. The higher the AUC, the better the discriminating ability of the model. All statistical analyses were two-tailed, and P < 0.05 was considered statistically significant.

Results

Patient characteristics

Based on the echocardiography results as the standard, we divided the patients into two groups: the intermediate or high-PH probability group and the low-PH probability group. The age and sex of the patients and duration of the disease in the two groups were not significantly different (P > 0.05), and thus, the two groups could be compared. Importantly, there were no patients with any ventricular signs; all of the patients had a smaller right ventricle than left ventricle basal diameter, and there was no flattening of the intraventricular septum. The general characteristics of the modelling group and external validation group are shown in Tables 1 and 2.

Univariable analysis of clinical parameters

The t-test, Mann–Whitney U test, chi-square test and univariable logistic regression analysis were used in the

| Table 1 | Comparison of general characteristics in the modelling group, n = 142 |
|---------|---------------------------------------------------------------|
| Parameter                          | Intermediate or high-PH probability, n = 142 | Low PH probability, n = 76 | All patients, n = 218 | P-value |
| Age (years)                        | 57.44 ± 13.41 | 57.12 ± 14.88 | 57.33 ± 13.90 | 0.870 |
| Male (n, %)                         | 99 (69.7%) | 50 (65.8%) | 149 (68.3%) | 0.552 |
| Duration of the disease (years)    | <1 | 83 (58.5%) | 51 (67.1%) | 134 (61.5%) | 0.242 |
|                                     | >1 | 44 (31.0%) | 18 (23.7%) | 62 (28.4%) | 0.194 |
|                                     | >5 | 15 (10.6%) | 7 (9.2%) | 22 (10.1%) | 0.590 |
| Implemented heart failure therapy (n, %) | 33 (23.2%) | 22 (28.9%) | 55 (25.2%) | 0.355 |
| Systolic BP (mmHg)                 | 131.75 ± 25.68 | 131.29 ± 24.59 | 131.59 ± 25.25 | 0.897 |
| Diastolic BP (mmHg)                | 88.82 ± 21.39 | 85.14 ± 16.56 | 87.54 ± 19.88 | 0.194 |
| Heart rate (beats/min)             | 93.82 ± 22.08 | 95.41 ± 18.02 | 94.37 ± 20.73 | 0.590 |
| TRV (n, %)                         | <2.9 m/s | 31 (21.8%) | 76 (100%) | 107 (49.1%) | <0.001 |
|                                     | 2.9–3.4 m/s | 44 (31.0%) | 0 | 44 (20.2%) | 0.207 |
|                                     | >3.4 m/s | 67 (47.2%) | 0 | 67 (30.7%) | 0.706 |
| Left ventricle diameter (mm)       | 65.82 ± 9.46 | 64.32 ± 7.86 | 65.29 ± 8.94 | 0.238 |
| Right ventricle diameter (mm)      | 25.35 ± 7.46 | 20.58 ± 5.56 | 23.69 ± 7.21 | <0.001 |
| Additional PH signs: (+)PA (n, %)  | 99 (69.7%) | 19 (25.0%) | 118 (54.1%) | <0.001 |
| Additional PH signs: (+)IVC and RA (n, %) | 107 (75.4%) | 20 (26.3%) | 127 (58.3%) | <0.001 |
| Tricuspid regurgitation (n, %)     | 127 (89.4%) | 52 (68.4%) | 179 (82.1%) | <0.001 |
| Mitral regurgitation (n, %)        | 129 (90.8%) | 60 (78.9%) | 189 (86.7%) | 0.014 |

Data are presented as mean ± SD and medians (interquartile range or n [%]). P < 0.05 is considered statistically significant. (+), a positive sign of either PA or RA; BP, blood pressure; IVC, inferior vena cava; PA, pulmonary artery; PH, pulmonary hypertension; RA, right atrium; TRV, tricuspid regurgitation peak velocity.
univariable analysis. The results summarized in Table 3 show that the incidences of COPD or chronic bronchitis, SM at the tricuspid area and SM at the apex and the levels of HDL-C and BNP of the two groups were significantly different ($P < 0.05$). In contrast, the incidences of ankle oedema, smoking, drinking, hypertension classification, diabetes mellitus, prior stroke, NYHA class, pulmonary infection, atrial flutter/atrial flutter, LBBB and the levels of Hb, PLT, leukocytes, NEU%, TC, TG, LDL-C and fasting glucose of the two groups were not significantly different ($P > 0.05$).

**Table 2** Comparison of general characteristics in the external validation group, $n$

| Parameter | Intermediate or high-PH probability, $n = 61$ | Low-PH probability, $n = 39$ | All patients, $n = 100$ | $P$-value |
|-----------|---------------------------------------------|-------------------------------|--------------------------|-----------|
| Age (years) | 55.20 ± 12.19 | 57.46 ± 12.95 | 56.08 ± 12.47 | 0.379  |
| Male ($n, \%)$ | 47 (77.0%) | 27 (69.2%) | 74 (74.0%) | 0.385  |
| Duration of the disease (years) | <1 | 39 (63.9%) | 26 (66.7%) | 65 (65.0%) | 0.993 |
| 1–5 | 15 (24.6%) | 6 (15.4%) | 21 (21.0%) |  |
| >5 | 7 (11.5%) | 7 (17.9%) | 14 (14.0%) |  |
| Implemented heart failure therapy ($n, \%)$ | <2.9 m/s | 17 (27.9%) | 39 (100%) | 56 (56.0%) | <0.001 |
| 2.9–3.4 m/s | 25 (41.0%) | 0 | 25 (25.0%) |  |
| >3.4 m/s | 19 (31.1%) | 0 | 19 (19.0%) |  |
| Left ventricle diameter (mm) | 69.48 ± 8.50 | 61.97 ± 8.94 | 66.55 ± 9.38 | <0.001 |
| Right ventricle diameter (mm) | 24.66 ± 5.92 | 19.57 ± 5.06 | 22.73 ± 6.11 | <0.001 |
| Additional PH signs: ($+$)PA ($n, \%) | 46 (75.4%) | 7 (17.9%) | 53 (53.0%) | <0.001 |
| Additional PH signs: ($+$)IVC and RA ($n, \%) | 51 (83.6%) | 11 (28.2%) | 62 (62.0%) | <0.001 |
| Tricuspid regurgitation ($n, \%)$ | 55 (90.2%) | 24 (61.5%) | 79 (79.0%) | 0.001 |
| Mitral regurgitation ($n, \%)$ | 56 (91.8%) | 27 (69.2%) | 83 (83.0%) | 0.003 |

Data are presented as mean ± SD and medians (interquartile range or $n, \%)$. $P < 0.05$ is considered statistically significant. (+), a positive sign of either PA or RA; BP, blood pressure; IVC, inferior vena cava; PA, pulmonary artery; PH, pulmonary hypertension; RA, right atrium; TRV, tricuspid regurgitation peak velocity.

**Table 3** Univariable analysis of clinical parameters

| Parameter | Intermediate or high-PH probability, $n = 142$ | Low-PH probability, $n = 76$ | Exp (B) (95% CI) | $P$-value |
|-----------|---------------------------------------------|-------------------------------|------------------|-----------|
| Ankle oedema ($n, \%)$ | 82 (57.7%) | 35 (46.1%) | 1.601 (0.914–2.805) | 0.099 |
| Smoker ($n, \%)$ | 53 (37.3%) | 24 (31.6%) | 1.290 (0.714–2.331) | 0.398 |
| Drinker ($n, \%)$ | 36 (25.4%) | 16 (21.1%) | 1.274 (0.653–2.485) | 0.478 |
| Hypertension classification 1/2/3 ($n$) | 9/24/45 | 4/17/22 | 0.991 (0.802–1.224) | 0.985 |
| Diabetes mellitus ($n, \%)$ | 32 (22.3%) | 17 (22.4%) | 1.010 (0.518–1.969) | 0.978 |
| Prior stroke ($n, \%)$ | 12 (8.5%) | 3 (3.9%) | 2.246 (0.614–8.219) | 0.211 |
| NYHA Class 1/2/3/4 ($n$) | 1/4/63/50 | 1/27/37/11 | 1.231 (0.857–1.769) | 0.239 |
| COPD or chronic bronchitis ($n, \%)$ | 29 (20.4%) | 7 (9.2%) | 2.530 (1.051–6.087) | 0.034 |
| Pulmonary infection ($n, \%)$ | 50 (35.2%) | 31 (40.8%) | 0.789 (0.445–1.499) | 0.417 |
| Atrial fibrillation/atrial flutter ($n, \%)$ | 41 (28.9%) | 16 (21.1%) | 1.522 (0.787–2.946) | 0.211 |
| LBBB ($n, \%)$ | 16 (11.3%) | 8 (10.5%) | 1.079 (0.440–2.651) | 0.868 |
| SM at the tricuspid area ($n, \%)$ | 107 (75.4%) | 11 (14.5%) | 18.065 (8.582–38.026) | <0.001 |
| SM at the apex ($n, \%)$ | 120 (84.5%) | 28 (36.8%) | 9.351 (4.876–17.930) | <0.001 |
| Hb (g/L) | 132.99 ± 21.88 | 135.93 ± 22.19 | 0.994 (0.981–1.007) | 0.348 |
| PLT ($10^{12}$/L) | 211.72 ± 68.85 | 202.18 ± 52.74 | 1.002 (0.998–1.007) | 0.256 |
| Leukocyte ($10^{9}$/L) | 7.63 ± 2.61 | 7.31 ± 2.41 | 1.053 (0.940–1.179) | 0.376 |
| NEU% | 66.30 ± 10.59 | 64.26 ± 11.18 | 1.018 (0.992–1.045) | 0.186 |
| TC (mmol/L) | 4.22 ± 1.07 | 4.27 ± 0.92 | 0.960 (0.731–1.261) | 0.771 |
| TG (mmol/L) | 1.15 ± 0.56 | 1.36 ± 1.03 | 0.699 (0.479–1.021) | 0.099 |
| LDL-C (mmol/L) | 2.81 ± 0.87 | 2.73 ± 0.77 | 1.125 (0.802–1.578) | 0.498 |
| HDL-C (mmol/L) | 0.94 ± 0.34 | 1.04 ± 0.31 | 0.404 (0.173–0.947) | 0.034 |
| Fasting glucose (mg/dL) | 5.23 ± 1.35 | 5.55 ± 2.15 | 0.895 (0.757–1.059) | 0.179 |
| BNP (pg/mL) | 1792.5 (870.5–2389.6) | 973.7 (388.5–1899.1) | 1.000 (1.000–1.001) | <0.001 |

Data are presented as mean ± SD and medians (interquartile range or $n, \%)$. $P < 0.05$ is considered statistically significant.

BNP, brain natriuretic peptide; CI, confidence interval; COPD, chronic obstructive pulmonary disease; Hb, haemoglobin; HDL-C, high-density lipoprotein cholesterol; LBBB, left bundle branch block; LDL-C, low-density lipoprotein cholesterol; NEU, neutrophil; NYHA, New York Heart Association; PLT, platelets; SM, systolic murmur; TC, total cholesterol; TG, triglyceride.
Multivariable analysis of clinical parameters

The parameters shown in Table 3 for which \( P \leq 0.200 \) were subjected to multivariable analysis, which was carried out using backward WALD regression analysis. As illustrated in Tables 4 and 5, four factors, including COPD or chronic bronchitis, SM at the tricuspid area, SM at the apex and BNP/100, in DCM patients with intermediate or high-PH probability were significantly different \( (P < 0.05) \) from those in DCM patients with low-PH probability.

Establishment of the predictive model

Based on the backward WALD regression analysis results, COPD or chronic bronchitis, SM at the tricuspid area, SM at the apex and BNP/100 were employed to establish the DCM with intermediate or high-PH probability predictive model. As shown in Table 5, the predictive model was obtained as follows: \[ \ln \left[ \frac{P}{1-P} \right] = 1.263 \times (\text{COPD or chronic bronchitis}) + 2.575 \times (\text{SM at the tricuspid area}) + 1.673 \times (\text{SM at the apex}) + 0.029 \times (\text{BNP/100}) - 2.267. \]

Accuracy of the predictive model

The accuracy, positive predictive value and negative predictive value of the predictive model were calculated for all 218 patients enrolled in the modelling group. As shown in Table 6, the predictive model had a high accuracy of 83.5% and a high positive predictive value of 88.0%. The accuracy and the positive predictive value indicate the possibility of correctly identifying the probability of PH: The higher these values, the more likely the diagnosis is correct.

Table 4 Multivariable analysis of clinical parameters

| Parameter | Intermediate or high-PH probability, \( n = 142 \) | Low-PH probability, \( n = 76 \) | \( P \)-value |
|-----------|-----------------------------|-----------------------------|-------------|
| Ankle oedema (\( n, \% \)) | 82 (57.7%) | 35 (46.1%) | 0.379 |
| COPD or chronic bronchitis (\( n, \% \)) | 29 (20.4%) | 7 (9.2%) | 0.023 |
| SM at the tricuspid area (\( n, \% \)) | 107 (75.4%) | 11 (14.5%) | <0.001 |
| SM at the apex (\( n, \% \)) | 120 (84.5%) | 28 (36.8%) | <0.001 |
| NEU\% | 66.30 ± 10.59 | 64.26 ± 11.18 | 0.416 |
| TG (mmol/L) | 1.15 ± 0.56 | 1.36 ± 1.03 | 0.421 |
| HDL-C (mmol/L) | 0.94 ± 0.34 | 1.04 ± 0.31 | 0.410 |
| Fasting glucose (mg/dL) | 5.23 ± 1.35 | 5.55 ± 2.15 | 0.353 |
| BNP (pg/mL) | 1792.5 (870.5–2839.6) | 973.7 (388.5–1899.1) | 0.048 |

Data are presented as mean ± SD and medians (interquartile range or \( n, \% \)). \( P \leq 0.05 \) is considered statistically significant.

BNP, brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; HDL-C, high-density lipoprotein cholesterol; NEU, neutrophil; SM, systolic murmur; TG, triglyceride.

Table 5 Parameters used to establish the DCM with intermediate or high PH probability prediction model

| Parameter | B | SE | Wals | df | Sig | Exp (B) | 95%CI of exp (B) |
|-----------|---|----|------|----|-----|---------|-----------------|
| COPD or chronic bronchitis | 1.263 | 0.580 | 4.740 | 1 | 0.029 | 3.535 | 1.134–11.016 |
| SM at the tricuspid area | 2.575 | 0.409 | 39.556 | 1 | 0.000 | 13.135 | 5.887–29.308 |
| SM at the apex | 1.673 | 0.406 | 16.972 | 1 | 0.000 | 5.328 | 2.404–11.808 |
| BNP/100 | 0.029 | 0.014 | 4.199 | 1 | 0.040 | 1.030 | 1.001–1.059 |
| Constant | −2.267 | 0.440 | 26.517 | 1 | 0.000 | 0.104 | 0.010–1.000 |

BNP, brain natriuretic peptide; CI, confidence interval; COPD, chronic obstructive pulmonary disease; df, degree of freedom; SM, systolic murmur.
Evaluation of the calibration ability of the predictive model

To evaluate the calibration ability of the predictive model, we used the Hosmer–Lemeshow test to calculate the $\chi^2$ for the modelling group. The results showed that the $\chi^2$ of the modelling group was 8.24 and the $P$-value was 0.411. The $P$-values were higher than 0.05, indicating that the model accurately predicted DCM with intermediate or high-PH probability. The calibration scatter plots are shown in Figure 3. According to the plots, all scattered points fluctuated around the reference line without significant deviation. This result
suggests that using the predictive model, the prediction of intermediate or high-PH probability patients was in good agreement with the actual intermediate or high-PH probability patients.

**Evaluation of the clinical efficacy of the predictive model**

We used DCA to evaluate the clinical efficacy of the predictive model. The DCA curves were drawn using the predicted probability of PH for the model group and the external validation group and the actual occurrence of PH probability. The DCA curves of the two groups are shown in Figure 4. In the figure, the grey line indicates that for extreme cases, the model predicted that all patients with DCM had low-PH probability and the clinical net benefit was 0. The orange line, which has a negative slope and indicates the clinical net benefit, suggests that in extreme cases, the model predicted that all patients with DCM had intermediate or high-PH probability. The black line is the DCA curve of the predictive model. As shown in the figure, the black line is higher than the grey and orange lines, suggesting that both groups of patients could benefit from the predictive model when it is applied to the two cohorts. It also suggests that the predictive model is clinically efficacious.

**Discussion**

Nomograms are a relatively recent development and are widely used by clinicians, as they are more intuitive and individualized than models established based on risk factors. In our study, we built and validated a nomogram that estimates the individual risk of PH in DCM patients based on four variables determined by a regression model, including a history of COPD or chronic bronchitis, SM at the tricuspid area, SM at the apex and the BNP level of the patient. The four variables were firmly associated with PH-DCM patients, and it would be easy to obtain these indicators in clinical practice, even in community hospitals lacking the ability to perform echocardiography. In validating new model, we found that the model had good discriminability, calibration ability and clinical application value. Thus, we conclude that the new model could accurately predict DCM-PH and help promote early prevention, intervention and treatment.

The development of PH during the course of DCM is a multistage process. Patients with DCM suffer from left ventricular dilation, which leads to left ventricular systolic or diastolic dysfunction and results in mitral regurgitation (MR), presenting as SM at the apex on auscultation. Afterwards, given the passive backward transmission of elevated
left-sided filling pressures, the pressure in the left atrium chronically increases, which in turn increases the pressure in the pulmonary veins and pulmonary arteries. At this point before the irreversible remodelling of pulmonary vessels, the phase is likely to be reversible if the left heart haemodynamics are improved. Therefore, if PH-DCM can be detected before this phase and treatment can be obtained in time, the patients’ prognosis may be improved to a large extent. However, should the PH-DCM continue, unfortunately, pulmonary endothelial dysfunction will occur, resulting in significant vasoconstriction and irreversible remodelling of the pulmonary vessels, which will lead to right ventricular stasis and hypertrophy, eventually resulting in tricuspid regurgitation (TR) and SM at the tricuspid area on auscultation. As the right ventricle is much more sensitive to prolonged pressure overload, over time, the right heart can be irreversibly damaged, eventually resulting in heart failure.

Based on the pathological process of the development of DCM described above, it is suggested that SM at the apex and tricuspid area, which, respectively indicate the presence of MR and TR, are feasible factors for predicting PH probability in DCM patients. Weitsman et al. identified significant valve malfunction in 51% of PH-LHD patients, the most common of which was MR, which is considered a direct cause of increased PH due to the transfer of hydrostatic pressure to the atria during ventricular contraction. In PH-DCM, a vicious cycle of worsening MR, pulmonary venous congestion and pulmonary hypertension are the result of the expansion of intravascular veins. Additionally, the prevalence of TR is higher in patients with PH. TR can be caused by organic valve diseases but is also often present in structurally normal tricuspid valves, where it is called functional TR (FTR). Valvular tethering is the main mechanism underlying PH-FTR, in which RV remodelling occurs with RV dilatation related to volume overload. The study by Abramson et al. first assessed systolic PA pressure using the peak velocity of TR to non-invasively assess PH in the prognosis of DCM patients. Their logistic regression models showed the importance of the peak velocity of TR as a predictive factor.

Chronic bronchitis is a syndrome defined epidemiologically by chronic cough and sputum production for at least 3 months in each of at least two consecutive years. In the case of chronic bronchitis, exposure to noxious particles or gases can lead to mucosal and glandular inflammation, with increased mucus discharge, epithelial cell hyperplasia and altered tissue repair in small conducting airways. Moreover, chronic bronchitis is considered a component of COPD when associated with a progressive, incompletely reversible limitation of airflow caused by a mixture of small airway disease and gas exchange impediment through parenchymal destruction. COPD is a common, preventable and treatable disease characterized by persistent respiratory symptoms and progressive airflow obstruction as recorded by spirometry. It was estimated by the World Health Organization (WHO) that approximately 5% of all deaths worldwide can be attributed to COPD, which is likely to become the third major cause of death by 2030. The pathological changes in COPD include permanent bronchoconstriction, small airway remodelling, alveolar destruction and pulmonary vascular remodelling. Therefore, there is no doubt that PH can be triggered due to hyperinflation, airflow obstruction and airway collapse in advanced COPD. In summary, DCM patients with chronic bronchitis or COPD have a higher likelihood of developing PH.

As an important natriuretic peptide, BNP is a fast, sensitive and non-invasive biomarker for diagnosing heart failure and an indicator of increased ventricular mass. In response to the stretching of the ventricular wall with increased pressure or volume overload, N-terminal pro-brain natriuretic peptide (NT-proBNP) is secreted by cardiomyocytes, and accordingly, circulating BNP is elevated in patients with right ventricular diastolic dysfunction as well as PH, in which it demonstrates vasodilation, anti-hypertrophy and anti-fibrosis effects and counteracts the effects of HF. Right cardiac pressure variations account for up to 30% of plasma BNP level changes, and therefore, the degree of BNP level changes could be relevant to the severity of PH-DCM. Moreover, the ESC/ERS Guidelines recommend the measurement of NT-proBNP and BNP as part of a multi-parametric assessment for prognosis and as a goal to evaluate treatment outcomes for patients with PAH, simultaneously providing thresholds to define low-risk (NT-proBNP < 300 ng/L, BNP < 50 ng/L), intermediate-risk (NT-proBNP 300–1400 ng/L, BNP 50–300 ng/L) and high-risk patients (NT-proBNP > 1400 ng/L, BNP > 300 ng/L). Although both compounds can be elevated in almost any LHD, compared with NT-proBNP, BNP appears to have a slightly better correlation with PH and is less affected by kidney function. Thus, we chose BNP as one of the predictive factors of PH probability in DCM patients.

There are some limitations to this study. Above all, we were not performing the RHC for the PH diagnosis. Even though RHC is an invasive and expensive examination, there is no doubt that as the gold standard for the diagnosis of PH, it is more accurate for the determination of parameters related to PH. In addition, although our predictive model was proven to be simple, feasible and highly accurate, the sample size in our study was small, and the data were obtained from only one screening practice in China; thus, the model may only be applicable to the Chinese population and not to other ethnicities. Therefore, if we want to expand the applicable population for the predictive model,
Conclusion

Our study identified four clinical prognostic factors, which were incorporated to develop a non-invasive model to predict PH probability in DCM patients. The four clinical prognostic factors, including a history of COPD or chronic bronchitis, SM at the tricuspid area, SM at the apex and BNP level, were closely associated with the progression of PH-DCM and are easy to obtain in clinical practice. Additionally, a nomogram was developed and proven to have high accuracy and good discriminability, calibration ability and clinical application value.

Conflict of interest

Jiahua Liang, Ruochen Zhu, Yi Yang, Rong Li, Chuangxiong Hong and Chuanjin Luo declare that they have no conflict of interest.

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