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Research article

Using machine learning to predict one-year cardiovascular events in patients with severe dilated cardiomyopathy

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ABSTRACT

Purpose: Dilated cardiomyopathy (DCM) is a common form of cardiomyopathy and it is associated with poor outcomes. A poor prognosis of DCM patients with low ejection fraction has been noted in the short-term follow-up. Machine learning (ML) could aid clinicians in risk stratification and patient management after considering the correlation between numerous features and the outcomes. The present study aimed to predict the 1-year cardiovascular events in patients with severe DCM using ML, and aid clinicians in risk stratification and patient management.

Materials and Methods: The dataset used to establish the ML model was obtained from 98 patients with severe DCM (LVEF $<$ 35%) from two centres. Totally 32 features from clinical data were input to the ML algorithm, and the significant features highly relevant to the cardiovascular events were selected by Information gain (IG). A naive Bayes classifier was built, and its predictive performance was evaluated using the area under the curve (AUC) of the receiver operating characteristics by 10-fold cross-validation.

Results: During the 1-year follow-up, a total of 22 patients met the criterion of the study end-point. The top features with IG $>$ 0.01 were selected for ML model, including left atrial size (IG = 0.240), QRS duration (IG = 0.200), and systolic blood pressure (IG = 0.151). ML performed well in predicting cardiovascular events in patients with severe DCM (AUC, 0.887 [95% confidence interval, 0.813–0.961]).

Conclusions: ML effectively predicted risk in patients with severe DCM in 1-year follow-up, and this may direct risk stratification and patient management in the future.

1. Introduction

Dilated cardiomyopathy (DCM) is a common form of cardiomyopathy characterized by left ventricular (LV) cavity enlargement and impaired contractility [1]. Despite therapeutic advances, the 5-year mortality of DCM still remains as high as 20% [2].

A certain proportion of patients with severe DCM (left ventricular ejection fraction, [LVEF] < 35%) are recommended defibrillator implantation, resynchronization therapy, or heart transplantation, according to current guidelines [3]. However, such clinical managements may not significantly increase longevity in these patients [4], and the predictive performance of LVEF in patients with severe systolic dysfunction seems inadequate [5,6]. The Meta-analysis Global Group in Chronic Heart Failure (MAGGIC) score was recently recognised as a convenient predictor of mortality in patients with heart failure, it can be obtained via an easy-to-use website (www.heartfailurerisk.org) [7]; The MAGGIC Score can also be used to predict mortality in patients with DCM [8], although it originally aimed to identify patients who were at high-risk of heart failure, rather than those with severe DCM.

Machine learning (ML) uses computational algorithms to fit a model

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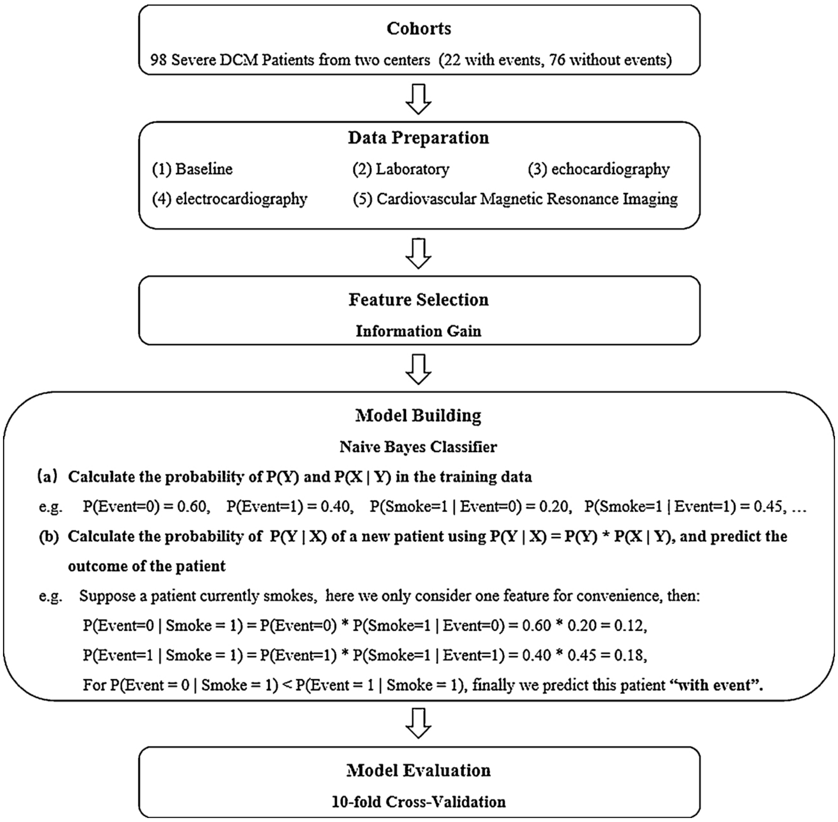

Fig. 1. Workflow for the Classification of Patients with Severe Dilated Cardiomyopathy with and Without Cardiovascular Events using Machine Learning. Y represents the label (with or without event), X represents the features (e.g. age, gender, smoke, etc), P(Y) denotes the probability of Y, P (Y|X) denotes the conditional probability of Y given X, and P (X|Y) denotes the conditional probability of X given Y.
Abbreviations: DCM, dilated cardiomyopathy; LVEF, left ventricular ejection fraction; MAGGIC, Meta-analysis Global Group in Chronic Heart Failure; ROC, receiver operating characteristic.

to relate a set of features with the outcome based on the given datasets. It could be used to establish a comprehensive risk stratification system involving numerous features. In addition, ML could aid the risk stratification decision-making process in each patient. Previous studies have used ML to effectively predict the events in patients with coronary artery disease, acute myocardial infarction, and pulmonary hypertension [9–11]. Therefore, a risk model using ML to predict cardiovascular events would likely show high performance in clinical research.

The aim of the present study was to establish and test an ML-based risk model using the features derived from baseline, laboratory, electrocardiography (ECG), echocardiography, and cardiovascular magnetic resonance (CMR) imaging to predict 1-year cardiovascular events in patients with severe DCM.

2. Materials and methods

2.1. Study population

All patients in the present study were aged ≥18 years and had been diagnosed with severe DCM at one of two different hospitals in different cities between October 2014 and March 2017.

The inclusion criteria were as follows: (a) increased left ventricular end-diastolic volume index, compared with the reference range [12]; and (b) LVEF < 35% on CMR. The exclusion criteria were as follows: (a) significant coronary artery disease (defined as ≥50% luminal stenosis) or previous coronary revascularization or myocardial infarction; (b) valvular disease; (c) congenital heart disease; and (d) estimated glomerular filtration rate < 30 mL/min/1.73 m^2 or an implanted device.

2.2. Follow-up

The study end-point was defined as any cardiovascular events, including cardiac death, heart transplantation, and hospitalisation due to heart failure (details were given in the supplementary materials). Follow-up information was obtained from in-person or telephone interviews at 3-month intervals. The event-free rate was tracked for more than 1 year. Time to event was defined as the duration from the CMR scan to the event.

2.3. Image analysis

CMR was performed using a 3 T Philips scanner (Ingenia, Philips Medical Systems, Best, The Netherlands) or 3 T Siemens scanner (Verio, Siemens, Erlangen, Germany). The body coil was used for radiofrequency transmission with 32 elements for reception. Along with the long-axis planes (two-, three-, and four-chamber views), a stack of short-axis single-shot balanced standard steady-state in free-precession sequence images from apex to base were collected. The imaging parameters were as follows: field of view, (230–280) mm × (230–280) mm; voxel, 2 mm × 2 mm × 8 mm; repetition time, shortest; echo time, shortest; sense factor, 2; minimum inversion times, 105 ms; flip angle, 45°.

Late gadolinium enhancement (LGE) images were obtained along the long-axis and short-axis using phase sensitive inversion recovery 15 min after a total dose of 0.2 mmol/kg Gd-DTPA (gadopentetate dimeglumine injection; Consun Pharmaceutical Co., Ltd.) was injected. The imaging parameters were as follow: field of view, (230–280) mm × (230–280) mm; voxel, 2 mm × 2 mm × 8 mm; repetition time, shortest; echo time, shortest; inversion time, measured at the time.

LGE extent was quantified by a semiautomatic detection method using full width at half-maximum and reported as a percentage of total LV mass in QMass 8.1 (Medis, Leiden, The Netherlands).

Transthoracic two-dimensional and Doppler echocardiographic examinations were performed in patients with severe DCM, using a Vivid E9 system (GE Vingmed Ultrasound AS, Horten, Norway) equipped with a 2.5-MHz transducer. Standard views were acquired from three consecutive beats (frame rate, 50–70 frames/sec). The severity of regurgitation was determined using an integrative method that included both quantitative and qualitative criteria [13].

2.4. Machine learning

The ML system consisted of three parts: feature selection, model building, and model evaluation. It was mainly implemented in WEKA 3.8. All features were pre-processed according to the clinical criterion or reference values (Supplementary Table 1) before the ML procedures Fig. 1.

Information gain (IG) is used for feature selection [14], which measures how much "information" a feature provides for classification and the reduction in entropy. The features with an IG > 0.01 were recognized as significant features and used in model building in the present study.

To explore the suitable classifiers, we have conducted the experiments to ascertain the performance of different classifiers (e.g. naive Bayes, Random Forest, Bagged Trees and Boosted Trees). The full details of model selection were shown in Table 3 of the supplementary material. After the experiments, the naive Bayes classifier, a simple, transparent, and powerful classifier, was selected as the ML model [15]. To simplify the model, a naive Bayes classifier assumes the independence of the features. Hence, given the dataset of patients with severe DCM, we described the feature vectors as X ($x_1, x_2, ...x_n$), and estimated its class label Y by maximising the likelihood $P(XY) = P(x_1, x_2, ..., x_n|Y)$. Here we denoted the patients without cardiovascular events as "Y = 0″ and the patients with events as "Y = 1″. Based on the assumption of the naive Bayes classifier, the model was simplified as $P(XY) = \prod_{i=1}^{n} P(x_i|Y)$ (the details of the algorithm could be found in the supplementary materials).

The performance of this ML model was assessed using 10-fold cross-validation. The dataset was randomly divided into 10 folds with approximately the same number of patients. Nine folds were used as the training set, while the remaining fold was used as the validation set. Every fold was used as a training set nine times and a validation set once. Therefore, the outcome of every DCM patient was predicted once.

2.5. Statistics

Continuous features are described as mean ± standard deviation. Binary features were recorded as "0" or "1" and expressed as numbers (percentage). The area under the ROC curve (AUC) in 10-fold cross-validation was the main metric of overall predictive performance in the validation for ML. To further confirm and test the effectiveness of ML, the confidence interval of AUC of ML was compared with the clinical indicator (LVEF in CMR) and the useful risk score (MAGGIC Score) using DeLong's test [16]. P-values < 0.05 were considered statistically significant. All statistical analyses were performed using statistical software R version 3.4.1 (R Foundation, Vienna, Austria). The pROC R package was used to plot and compare the ROC curves.

3. Results

In total, 249 patients with suspected severe DCM were initially screened; 93 were excluded because of significant coronary artery disease, 27 because they had an LVEF > 35%, and another 31 because they were lost to follow-up. Finally, 98 patients were left.

All baseline characteristics were depicted in Table 1. During a median follow-up of 18 months (interquartile range, 12–30 months), totally 98 patients were enrolled in the study, while 22 of them met the criterion of the study end-point. The MAGGIC Score was similar between patients with and without cardiovascular events (21.3 ± 4.5 vs. 19.7 ± 4.9, P = 0.141).

Fig. 2 shows the IG of all 32 features in the dataset. The top features with IG > 0.01 were selected for the training of naive Bayes classifiers. In total, 18 features were recognized as the significant features; some of the top features were summarised as follows: left atrial size (IG = 0.240) from CMR, QRS duration (IG = 0.200) from ECG, systolic blood pressure (IG = 0.151) and diastolic blood pressure (IG = 0.076)

Table 1
Characteristics of the patients with severe DCM.

Features	All Patients (n = 98)	Patients with Events (n = 22)	Patients without Events (n = 76)
Baseline			
Age, years (mean ± SD)	47 ± 14	44 ± 14	48 ± 14
Sex, n (%)			
Male	77 (79%)	18 (82%)	59 (78%)
Female	21 (21%)	4 (18%)	17 (22%)
Body mass index (kg/m^2)	25 ± 4.3	25 ± 4.9	25 ± 4.2
Systolic blood pressure (mmHg)	111 ± 13	107 ± 17	112 ± 12
Diastolic blood pressure (mmHg)	72 ± 9.3	70 ± 12.7	72 ± 8.2
Heart rate (bpm)	81 ± 15	79 ± 14	81 ± 15
NYHA functional class, n (%)			
≤ II	40 (41%)	5 (23%)	35 (46%)
≥III	58 (59%)	17 (77%)	41 (54%)
Creatine (μmol/L)	87 ± 24	94 ± 32	85 ± 21
Risk Factors, n (%)			
Diabetes	15 (15%)	5 (23%)	10 (13%)
Hypertension	23 (23%)	5 (23%)	18 (24%)
Atrial fibrillation	20 (20%)	4 (18%)	16 (21%)
Hyperlipidaemia	22 (22%)	6 (27%)	16 (21%)
Left bundle branch block	22 (22%)	7 (32%)	15 (20%)
History of smoking	41 (42%)	10 (45%)	31 (41%)
Alcohol	21 (21%)	3 (14%)	18 (24%)
MAGGIC Score	20 ± 4.8	21 ± 4.5	20 ± 4.9
Medicine, n (%)			
Beta-blocker	96 (98%)	22 (100%)	74 (98%)
Angiotensin-converting inhibitors	72 (73%)	16 (73%)	56 (74%)
Angiotensin II receptor blockers	16 (16%)	2 (9%)	14 (18%)
Spironolactone	91 (93%)	21 (95%)	70 (92%)
Diuretics	97 (99%)	22 (100%)	75 (99%)
Function, Structure, and Tissue			
LVEF (%)	19 ± 7.9	19 ± 8.9	19 ± 7.6
LVEDVI (mL/m^2)	195 ± 74	238 ± 81	182 ± 67
LVESVI (mL/m^2)	159 ± 66	193 ± 74	150 ± 60
RVEF (%)	27 ± 15	22 ± 14	29 ± 14
RVEDVI (mL/m^2)	99 ± 40	118 ± 45	94 ± 37
RVESVI (mL/m^2)	74 ± 38	93 ± 40	69 ± 36
Anteroposterior (mm)	45 ± 9.7	55 ± 9.6	43 ± 7.8
LGE present (n, %)	82 (84%)	19 (86%)	63 (83%)
LGE mass (g)	7.2 ± 8.8	10 ± 10	6.3 ± 8.2
LGE extent (%)	7.4 ± 9.0	10 ± 11	6.5 ± 8.3
Hydropericardium (n, %)	46 (47%)	10 (45%)	36 (47%)
Mitral regurgitation (n, %)			
Normal, mild or moderate (0–2 degree)	59 (60%)	7 (32%)	52 (68%)
Severe (3 degree)	39 (40%)	15 (68%)	24 (32%)
Tricuspid regurgitation (n, %)			
Normal, mild or moderate (0–2 degree)	88 (90%)	17 (78%)	71 (93%)
Severe (3 degree)	10 (10%)	5 (22%)	5 (7%)
Pulmonary Artery hypertension (n, %)			
Normal	56 (57%)	7 (32%)	49 (64%)
Mild	26 (27%)	7 (32%)	19 (25%)
Moderate	16 (16%)	8 (36%)	8 (11%)

ACE, angiotensin-converting enzyme; BNP, blood natriuretic protein; DCM, dilated cardiomyopathy; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; LVEDVI, left ventricular end-diastolic volume index; MAGGIC, Meta-analysis Global Group in Chronic Heart Failure; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association; RVEDVI, right ventricular end-diastolic volume index; RVEF, right ventricular ejection fraction; RVESVI, right ventricular end-systolic volume index.

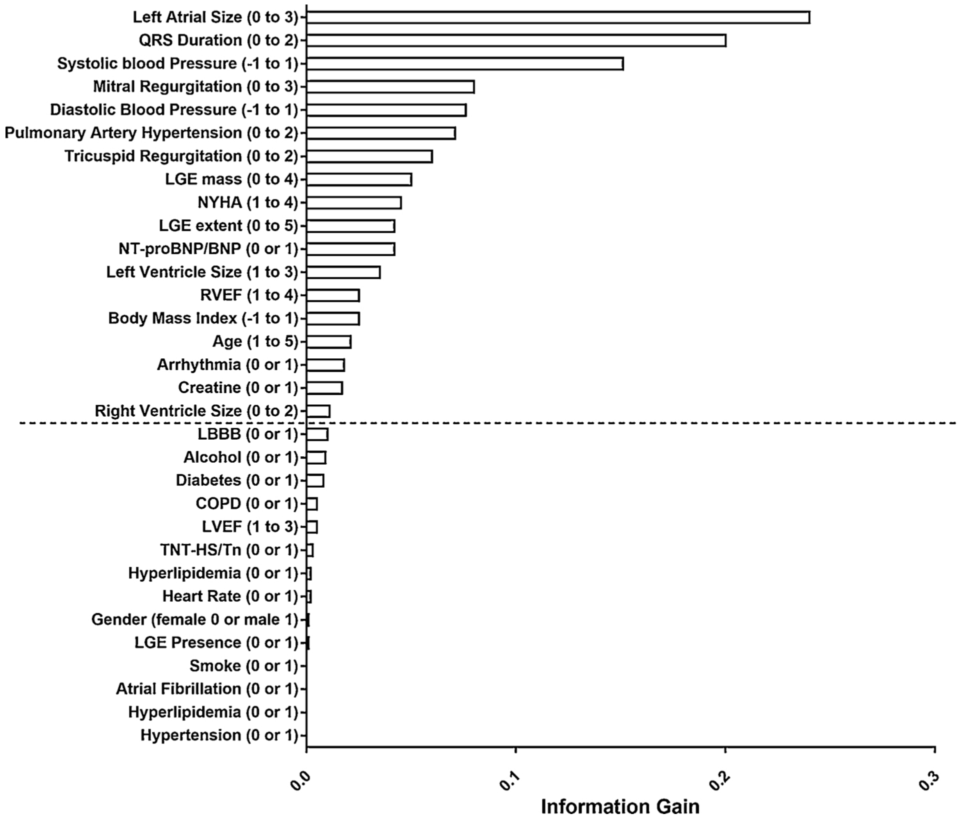

Fig. 2. Feature selection. Information gain was used to estimate the significance of each feature through the entropy gain with respect to outcome. The features were ranked in the descending order by IG. The features with an information gain > 0.01 were used for model building. Indications: baseline features (Systolic blood Pressure*, Diastolic Blood Pressure*, NYHA*, Body Mass Index*, Age*, Alcohol, Diabetes, COPD, Heart Rate, Gender, Smoke, Hyperlipidaemia, Hypertension); laboratory features (NT-proBNP/BNP*, Creatine*, TNT-HS/Tn); electrocardiography features (QRS Duration*, Arrhythmia*, LBBB, Atrial Fibrillation); echocardiography features (Mitral Regurgitation*, Pulmonary Artery Hypertension*, Tricuspid Regurgitation*); cardiovascular magnetic resonance features (Left Atrial Size*, LGE mass*, LGE extent*, Left Ventricle Size*, RVEF*, Right Ventricle Size*, LVEF, LGE Presence); The features above were ranked the descending order by information gain, and the features with * were recognized significant. LGE, late gadolinium enhancement; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; RVEF, right ventricular ejection fraction.

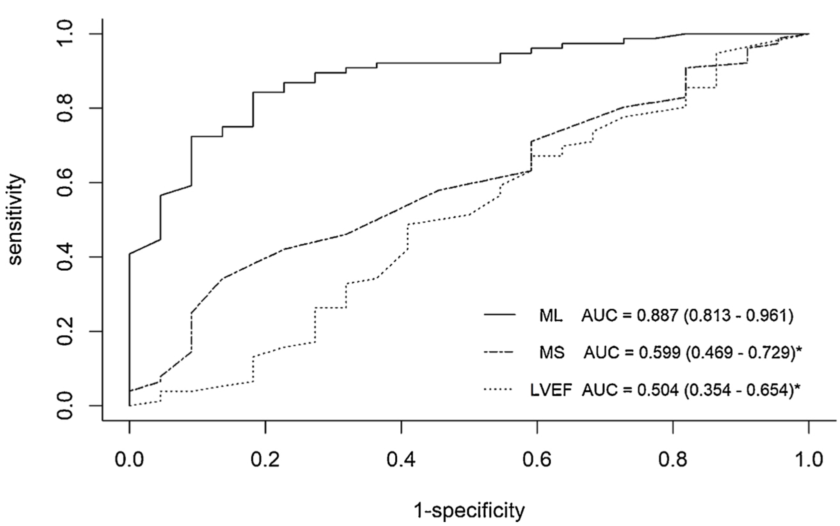

Fig. 3. Receiver operating characteristic curves for the predictive performance during 1-year follow-up. Machine learning using the naive Bayes classifier in 10-fold cross-validation showed a significantly higher area under the curve for cardiovascular event prediction than LVEF and MAGGIC score using DeLong's test ($P < 0.01$ in all cases, denoted by * in the figure). AUC, area under the curve; LVEF, left ventricular ejection fraction; ML, machine learning; MS, MAGGIC score; ROC, receiver operating characteristic; MAGGIC, Meta-analysis Global Group in Chronic Heart Failure.

from baseline characteristics, mitral regurgitation (IG = 0.080) and pulmonary artery hypertension (IG = 0.071) from echocardiography.

Fig. 3 compares the ROC curves among ML, MAGGIC score, and LVEF. ML exhibited a significantly higher AUC than MAGGIC score (0.887 vs 0.599, $P < 0.01$) and LVEF (0.887 vs 0.504, $P < 0.01$). The specificity and sensitivity of ML were 0.842 and 0.818, respectively, higher than those of the MAGGIC score (0.342 and 0.864, respectively) and LVEF (0.947 and 0.136, respectively).

4. Discussion

The results of the present study indicated that ML using naive Bayes classifier was well-suited for risk prediction in patients with severe DCM confirmed by 10-fold cross-validation (AUC, 0.887 [95% confidence interval, 0.813–0.961]). Although the traditional risk factor (LVEF) and useful risk score (MAGGIC Score) could provide effective information to stratify risk in patients with DCM, it still remains a major challenge, despite therapeutic advances, especially in patients with severe DCM. Previous studies have found that the association between the decrease of LVEF and the increase of mortality became weaker when LVEF was < 25% [6], probably because most patients with lower LVEF responded favourably to medical therapy with improvements in LV functional indices [17]. Therefore, it was difficult to determine whether the patients with severe DCM were at higher risk relied on LVEF, and the similar result about risk stratification in LVEF (AUC, 0.504) was found in the present study. To increase predictive performance, MAGGIC score was recently induced. It provides a prognostic model in patients with heart failure, and has been subsequently recognised as a user-friendly and successful risk scoring system [7]. In the research of DCM, Puntmann et al showed that the cardiovascular events in patients with relatively mild DCM (LVEF, 47 (29–50)%) could be effectively predicted using MAGGIC Score [8], whereas, Kuschyk et al implied that MAGGIC score may over-estimate the 1-year mortality (actual vs predicted by MAGGIC score: 5.2% vs 18.4%, $p < 0.001$) in patients with severe DCM (LVEF, 23.1 ± 7.9%) [18]. It is shown that MAGGIC Score performed well in patients with relatively mild DCM, rather than in those with severe DCM. Furthermore, MAGGIC Score only relies on a few fixed features (e.g. LVEF, NYHA, creatine, etc), while ignoring many other features that may contribute to cardiovascular events (e.g. the presence and extent of LGE, ventricular size, atrial size, etc). It was probably for these reasons that, MAGGIC Score (AUC, 0.599) was still unsatisfactory in the present study. Therefore, a new risk-predicting system with better predictive performance is still needed. To build such a system, ML is a useful tool, because it can handle a large number of features and better focus on predicting events in each individual [10]. Indeed, it achieved better performance than LVEF and MAGGIC Score in the present study.

ML model usually requires more features than the previous method, and it is important that the input features are always available in patients with severe DCM. To solve this problem, only features derived from routine modalities were input to the ML model. As a result, the ML model will be easy to apply, and the medical expenses may not increase in the future. In the present study, many features were considered in the ML model that may have contributed to cardiovascular events in patients with DCM, including those derived from baseline, laboratory, routine ECG, echocardiography, and CMR. Recognition and diff ;erentiation of the underlying pathological substrate leading to ventricular dilatation may be crucial for better individual risk stratification and therapy, because different prognostic implications are associated with diff ;erent forms of disease. Therefore, the examinations mentioned above are usually needed in patients with DCM. Generally, laboratory test, ECG, and echocardiography are always carried out as routine assessments in all patients with DCM. In addition, CMR allows clinicians to further identify the cause of DCM, characterize the presence and location of myocardial damage, and assess biventricular regional and global function. Thus, in the last few years, the routine diagnostic imaging workup of patients with DCM has been integrated using CMR [19].

Before predicting the 1-year risk in each patient, the ML system we proposed could evaluate the worth of each feature during feature selection, and it may help clinicians to quickly identify the significant features for risk stratification. In the present study, the features were ranked by IG, which measured how much "information" a feature provided for classification. Features with larger IG values are better able to identify patients with or without events, while the those with IG values larger than 0.01 were recognized as the significant ones in the present study, including systolic blood pressure (IG = 0.151), QRS duration (IG = 0.200), left atrial size (IG = 0.240), LGE extent (IG = 0.042), mitral regurgitation degree (IG = 0.080), and tricuspid regurgitation degree (IG = 0.060). To some extent, these findings were in accordance with the evolution of DCM. Reportedly, the presence and severity of mitral or tricuspid regurgitation in patients with DCM are the effective predictors of adverse outcomes, and they perpetuate ventricular remodelling and increase the risk of cardiovascular events in patients with DCM [1]. Rossi et al reported that, the event-free rate in patients with severe mitral regurgitation was 7%, while in patients without mitral regurgitation was 40% [20]. Regarding ECG, the prolongation of QRS duration is a significant indicator of mechanical desynchrony, which is also recognised as a significant risk factor [21]. Specifically, patients with a QRS duration longer than 120 ms have a three-fold greater risk of death or heart transplantation than the patients whose QRS duration is smaller than 120 ms [22]. Regarding chamber remodelling, left atrial dilation frequently occurs in patients with DCM as a predictor of adverse outcomes. Gulati et al reported that, the risk of cardiovascular death or heart transplantation increased from 8% to 24% if the left atrial volume index is larger than 72 mL/m^2 in patients with DCM [23]. Left atrial dilation is a consequence of mitral regurgitation and left ventricular cavity enlargement [21]. Regarding tissue characteristics, focal fibrosis can be non-invasively detected using LGE-CMR, and the quantification of LGE was independently associated with the risk of mortality and heart failure morbidity in DCM. Indeed, the presence and quantification of LGE could indicate the risk of sudden cardiac death, and it has been used to guide clinician in their choice of device implantation. Gulati et al reported that the 5-year risk of death was 19.9% in patients with DCM who had an LVEF = 35% with LGE, while it was 9.4% in a cohort of patients without LGE [24].

After selecting the significant features, model building is another key procedure. To assess whether the model is suitable for predicting cardiovascular events in patients with severe DCM, AUC in 10-fold cross-validation was an effective metric in binary classification problems. It turned out that it performed well using naive Bayes classifier in the present study (AUC, 0.887 [95% confidence interval, 0.813–0.961]), which had significantly higher AUC than MAGGIC score (0.887 vs 0.599, $P < 0.01$) and LVEF (0.887 vs 0.504, $P < 0.01$). Furthermore, a simple, transparent, and easy-to-understand model that may fit well is recommended as the first choice, such a model is helpful for clinicians when analysing the generated knowledge and the final results [10]. The naive Bayes classifier is an easy-understanding classifier, it calculates the probability of each class given the values of the feature vector. A table of conditional probabilities between features and predictive results will be generated after training, which may help clinicians to understand the risk stratification results and explain the results to patients. Although a recent study recommended using ML algorithms without any prior assumption [9,25], because the simplified ML model with a strong assumption probably had a reduced accuracy or AUC. However, a suitable assumption may greatly simplify processing and demonstrate excellent performance in practice. In the present study, the features were not truly independent; however, the experimental results showed that this assumption of the naive Bayes classifier was not detrimental in practice. A similar conclusion had been reported previously [26].

5. Limitation

This was a double-centre study involving a relatively limited sample of patients with severe DCM. Thus, it might be subject to referral bias, and further multi-centre studies with larger samples of patients are warranted.

6. Conclusions

In the present study, ML provided an effective way to predict the risk of cardiovascular events in patients with severe DCM during 1-year follow-up. ML may help clinicians with risk stratification and individual patient management for in the future.

Author contribution

Rui Chen and Aijia Lu drafted the manuscript; Aijia Lu, Jingjing Wang, Lei Zhao and Wanjia Wu acquired the data; Hongwen Fei and Xiaohai Ma revised the manuscript; Rui Chen, Zhicheng Du and Zhuliang Yu provided the analysis method. Hui Liu and Xiaohai Ma provided the conception and design of the study.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ejrad.2019.06.004.

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