Naive Bayesian-based nomogram for identification of early asymptomatic Dilated Cardiomyopathy

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Abstract

Dilated cardiomyopathy (DCM) is one of the leading causes of heart failure. The most used parameter for measuring heart function and predicting outcomes in DCM patients is the left ventricular ejection fraction (LVEF). However, it has some inherent drawbacks. Recent studies have reported that left ventricular global longitudinal strain (GLS) and heart rate variability (HRV) can be used for the prediction of DCM. Therefore, we aimed to investigate a Naive Bayesian-based nomogram produced on clinical and instrumental features, which can be used to support the diagnosis of early asymptomatic DCM. The study encompassed 49 DCM and 50 healthy subjects (HC). The models were produced by naive Bayes algorithms considering the set of selected HRV features, LVEF, GLS, age, and sex. The results showed that the most informative parameters were: GLS, LVEF, meanRR, SD2 age, and sex, listed in order of importance. The obtained classification accuracy was 80%. A naive Bayesian-based nomogram highlighted that GLS brings more information than LVEF, followed by HRV features, age and sex. In conclusion, this study demonstrates that a Naive Bayesian-based nomogram is a powerful tool for the prediction of early asymptomatic DCM and that allows detailed clinical interpretation of the produced model.

1. Introduction

Dilated cardiomyopathy (DCM) is one of the leading causes of heart failure [1]. The most used feature for measuring heart function and predicting outcomes in DCM patients is the left ventricular ejection fraction (LVEF) [2]. However, it has some inherent drawbacks. One of them is that the LVEF cut-off has not yet been clearly defined, yielding diagnosis in the so-called «grey zone» (LVEF: 41%-49%) challenging [3], especially in the early asymptomatic phase.

Diagnosis of DCM, particularly in the early stages of the disease, can often be difficult and rely on advanced echocardiography (speckle tracking analysis), cardiac magnetic resonance imaging, comprehensive tissue characterization analysis, and genetic testing that often are not available or difficult to deliver to patients. Recent studies have reported that left ventricular global longitudinal strain (GLS) [4] and heart rate variability (HRV), as supplementary features to the LVEF, can be used for better prediction of DCM [5].

GLS is a newly emerging topic which has a significant role in predicting cardiovascular outcomes [6]. GLS has shown greater effectiveness in identifying the overall deterioration of the left ventricle when compared to the LVEF measurement alone [4].

On the other hand, heart disease-related pathophysiological changes and subsequent alteration of Heart Rate Variability (HRV) can provide additional important prognostic information [7], which might not be contained within GLS and LVEF. Nevertheless, to the present day, there is a lack of work that uses GLS and HRV with the LVEF to differentiate DCM patients, especially in the early phase.

A naive Bayes classifier is a basic probabilistic classifier that uses the Bayes theorem (from Bayesian statistics) and has the benefit of requiring a modest quantity of training data to estimate the classification parameters, and frequently outperforms more advanced algorithms [8].

The biggest advantage of the naive Bayes classifier is that the produced model can be interpreted using nomograms. A nomogram is a basic and self-explanatory visualization that is both helpful and powerful in the diagnostic guidance between groups, and it is a graphical representation of numerical relationships. Besides allowing the prediction, naive Bayesian nomograms reveal the structure of the model and the relative influences of the features on the class probability. In particular, the lengths of the lines correlate to the spans of odds ratios, implying that variables are important. In addition, nomograms allow the calculation of the scores for each feature, and such scores may be utilized not only to obtain the classification outcome, but also the probability of having a specific disease [9]. This is particularly important for examining the thresholds of GLS, HRV and LVEF in order to introduce new aids for DCM diagnosis, especially when the research is still in its early stage.

Therefore, in the present work, we aimed to investigate the performance Naive Bayesian-based model produced on HRV features, GLS and LVEF, age and sex and how a such model with its nomograms can be used to support a diagnosis of early asymptomatic DCM.

2. Methods

The study encompassed 49 DCM (27M/22F, aged 59± 16 y) and 50 healthy subjects (HC, 23M/27F, aged 55±21 y). The DCM patients were enrolled after clinical assessment and only early asymptomatic DCM patients were included in the study (patients without cardiac insufficiency symptoms and with cardiac insufficiency symptoms classified by New York Heart Association NYHA scale as class 1). The mean±SD of LVEF in DCM group was 51.2±10.8%. Coronary angiography was systematically performed in patients older than 35 and with cardiovascular risk factors and/or without a familial history of DCM. Patients with known trigger factors, such as toxic insults from alcohol or drug abuse, and tachyarrhythmias were excluded from the study.

All subjects underwent a 24h Holter ECG recording using the ambulatory electrocardiographic recorder SpiderView (Sorin Group, Italy) with a sampling rate of 200Hz. The RR intervals were extracted and labelled by using SyneScope analysis software (Sorin Group, Italy). The RR interval records were cut into 5 min segments without overlap. Each RR 5-minutes segment was included in the analysis only if the longest ectopic beats subsequence (labelled with “ectopic” by the ECG Holter) or the longest artefact subsequence does not exceed 10s (so-called Hearth rate Total variability [5]) The segments were interpolated with cubic spline and resampled at 2 Hz, producing two different HRV signals. Subsequently, for each signal, and in each segment, linear and non-linear HRV features were extracted.

In particular, the linear parameters MeanRR, SDNN, RMSSD, NN50 and pNN50 evaluating the RR variability were calculated directly from the RR sequence, whilst in the frequency domain, the absolute powers in Low (LF=0.04-0.15Hz) and High (HF=0.15-0.40Hz) frequency bands, related to the vagal and sympathetic nerve control on the heart rhythm, were estimated from the interpolated HRV signal. Moreover, the normalized low and high-frequency powers (LFn, HFn) and their ratio (LF/HF) were calculated from the latter parameters. The non-linear analysis was carried out by calculating Poincaré plot parameters (SD1, SD2) reflecting the short and long-term variability. In addition, the Fractal Dimension (FD) using Higuschi’s algorithm has been extracted.

In addition to the HRV features, LVEF and GLS were added as promising discriminatory features. The LVEF has been obtained by the Simpson biplane method [10] and the GLS has been obtained for the speckle tracking echocardiography. The measurement of GLS was performed offline using dedicated software (TomTec Arena v2.0, TomTec Imaging Systems, Unterschleißheim, Germany). The investigators visually assessed the detected endocardial border and, if necessary, manually adapted the tracing to ensure the correct tracing of the contours.

For feature selection we used ReliefF [11] method, which has been widely applied in machine learning tasks to improve classification performance. The cut-off of ReliefF’s estimates of the informative attribute was set to 0.08.

The models were produced by naive Bayes algorithms considering the set of selected HRV features, LVEF, GLS, age, and sex. The classification accuracy, F1, precession and recall of the dataset were estimated using 5-fold cross-validation. Finally, the nomogram has been created and used as an aid to interpret and validate the obtained model.

The study was conducted according to the principles of the Declaration of Helsinki. All participants released their written informed consent.

3. Results

The results in Table 1 showed that the most informative features (exceeding the threshold ReliefF’s estimates of informative attribute) for classification between early asymptomatic DCM and HC were: GLS, LVEF, meanRR, SD2 age, and sex, listed in order of importance.

Table 1. Features with corresponding ReliefF’s estimates of the informative attribute. The selected features are marked with asterisks.

#	**Feature**	**ReliefF**	#	**Feature**	**ReliefF**
1	GLS*	0.064	7	SDNN	0.007
2	Sex*	0.058	8	FD	0.006
3	LVEF*	0.051	9	HFn	0.003
4	Age*	0.022	10	LFn	0.003
5	meanRR*	0.008	11	SD1	0.002
6	SD2*	0.008	12	LF/HF	-0.006

The obtained classification accuracy of the produced Naive bayesian model was 0.80 (80%) and the area under the ROC curve was 0.84, while the F1 was 0.79, precision 0.82 and recall 0.80. The confusion matrix Figure 1. is used to calculate the performance indicators described above.

The produced nomogram of the Bayesian model is reported in Figure 2.

Table 2. Confusion matrix of the produced model

		predicted		
		DCM	HC	Σ
actual	DCM	65.3%	34.7%	49
	HC	6.0%	94.0%	50
	Σ	35	64	99

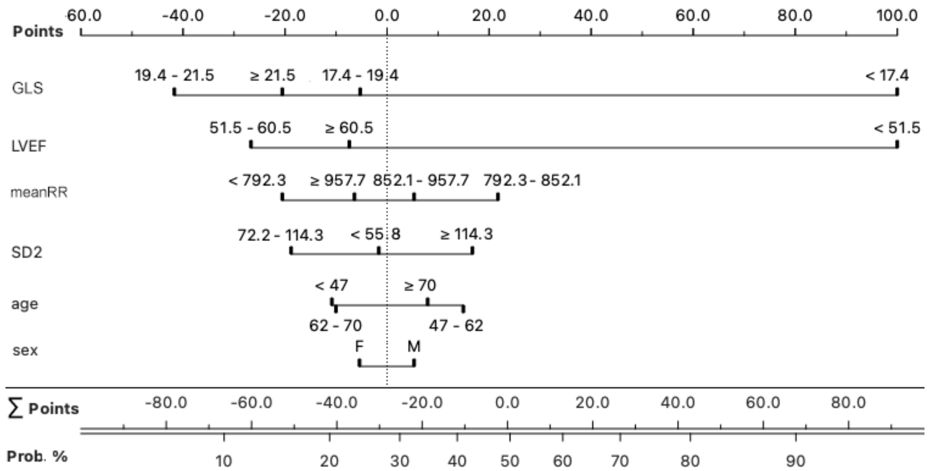

Figure 2. Nomogram for naive Bayes classifier for the DCM patients. The scoring can be obtained as a sum of the score of each individual parameter.

4. Discussion

Dilated cardiomyopathy (DCM), a progressive cardiac muscle disease, is a leading cause of heart failure [1]. The most often used variable for measuring heart function and predicting outcomes in DCM patients is LVEF. However, it has some inherent drawbacks, including late reduction only in patients with advanced cardiac disease, low reliability in patients with left ventricular hypertrophy and volume reduction, very poor inter- and intra-observer variability, and problematic endocardial boundary identification [2]. On the other hand, many authors use GLS [12] and heart rate variability (HRV) for the prediction of various heart diseases [13–16].

There is growing research interest in the development of machine learning models for computer-aided diagnosis that exploits HRV, GLS and LVEF extracted parameters in combination with other available clinical data [17].

Despite the importance of model interpretability, the majority of existing models focus only on accurate prediction and seldom provide a relevant clinical explanation for their outcomes [18]. Interpretability approaches are unquestionably a key issue that must be considered while developing prediction models for healthcare [19], such as naive Bayes with nomograms. Hence, the production of clinically plausible machine learning models that can guide diagnosis and can provide information on the feature relevance is desired. We aimed to investigate the performance Naive Bayesian-based model produced on HRV features, GLS and LVEF, age and sex and how a such model with its nomograms can be used to support a diagnosis of early asymptomatic DCM. We demonstrated that GLS, LVEF, meanRR, SD2 age, and sex are the most informative features for differentiations of DCM from HC. The model accuracy was 80% and the investigation of nomograms further shows empirical thresholds obtained from the DCM patients.

The importance of GLS, LVEF, meanRR, SD2, age and sex has been confirmed yet again by the nomograms. We can observe that GLS has greater importance in comparison to the LVEF, especially when the LVEF is in the range from 51.5 to 60.5. This is in the line with the works that demonstrate the superiority of GLS over the LVEF, where the first is available. Furthermore, the model empirically identified two thresholds, 51.5 for LVEF and 17.4 for GLS for the diagnosis of DCM, which is in line with thresholds reported in the literature [12, 20]. Such information helps us to examine the physiological plausibility of the model, and in combination with the classical performance measures evaluate its power as a diagnostic aid. Through the nomogram, the model also identifies two important ranges for GLS, 19.5 - 21.5 and 17.5 - 19.4, whose clinical importance should be further investigated in the larger study population. The nomogram also reveals the importance of the HRV features, especially of the meanRR and SD2, which can play an important role in the differentiation of other heart diseases from the DCM as recently shown by Accardo et al. 2022 [5]. Finally, age and sex appear to be the least significant in all of the six selected features, even though the DCM seems to affect equally both males and females. The age parameter introduces four distinctive ranges (<47, 47-62,62-70 and ≥70 y). The highest occurrence of the asymptomatic DCM appears to be in the range 47-62 y, followed by the patients above 70. Interestingly, patients in the range of 62-70 y have a lower probability of asymptomatic DCM, which can be explained by the progression of DCM [21].

Furthermore, nomograms can be printed on paper and utilized by clinicians to determine the likelihood of being in the DCM or HC group. The scoring is performed for each of the features and then summed up to obtain the final probability.

In conclusion, this study demonstrates the power and importance of interpretable machine learning models and in particular how Naive Bayesian-based nomogram tools can be used for the prediction of early asymptomatic DCM.

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