NON-COMUNICABLE DISEASES

Longitudinal machine learning model for predicting systolic blood pressure in patients with heart failure

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Keywords

Systolic Blood Pressure • Heart Failure • Least Squares Support Vector Regression • Longitudinal data

Summary

Objective. *Systolic blood pressure (SBP) strongly indicates the prognosis of heart failure (HF) patients, as it is closely linked to the risk of death and readmission. Hence, maintaining control over blood pressure is a vital factor in the management of these patients. In order to determine significant variables associated with changes in SBP over time and assess the effectiveness of classical and machine learning models in predicting SBP, this study aimed to conduct a comparative analysis between the two.*
Methods. *This retrospective cohort study involved the analysis of data from 483 patients with HF who were admitted to Farshchian Heart Center located in Hamadan in the west of Iran, and hospitalized at least two times between October 2015 and July 2019. To predict SBP, we utilized a linear mixed-effects model (LMM) and mixed-effects least-square support vector regression (MLS-SVR). The effectiveness of both models was evaluated based on the mean absolute error and root mean squared error.*
Results. *The LMM analysis revealed that changes in SBP over time were significantly associated with sex, body mass index (BMI), sodium, time, and history of hypertension (P-value < 0.05). Furthermore, according to the MLS-SVR analysis, the four most important variables in predicting SBP were identified as history of hypertension, sodium, BMI, and triglyceride. In both the training and testing datasets, MLS-SVR outperformed LMM in terms of performance.*
Conclusions. *Based on our results, it appears that MLS-SVR has the potential to serve as a viable alternative to classical longitudinal models for predicting SBP in patients with HF.*

Introduction

Heart failure (HF) is a common, chronic, and complex clinical syndrome [1, 2]. The incidence and prevalence of HF are increasing with aging [3, 4]. The lifetime risk of HF is about 20% [5]. More than 37 million people are suffering from HF worldwide [6]. World Health Organization (WHO) reported that the annual incidence of HF is estimated to be 660,000 per year worldwide. It is expected to be doubled in the next 30 years [7]. About 3.5 % of the Iranian adult population is estimated to be suffering from HF in the future [8].
Blood pressure is a key factor for prognosis in HF patients, easily measured in the patient's examination [9, 10]. Abnormal blood pressure may lead to a worse prognosis in these patients. Several studies have shown that having low or high blood pressure can increase mortality in HF patients [10-14]. Hence, maintaining control over blood pressure is a vital factor in the management of these patients [15]. The reported prevalence of high blood pressure in HF patients was between 25% to 70% in Europe [16] and about 44% in Iran [17]. Furthermore, clinical trials indicate that the risk of HF reduce to nearly 50% by hypertension treatment [18].
Systolic blood pressure (SBP) is strongly indicative of the prognosis of HF patients [19, 20]. Several studies have shown an association between SBP values with hospitalization and death [10, 21, 22]. Therefore predicting SBP values as a prognostic factor can help reduce readmission and mortality [22]. According to previous studies, SBP values can be changed between visits [23-25]. Therefore, using a longitudinal set of SBP values compared to a single SBP value may increase prognostication accuracy in HF patients [10, 26-28].
There are several models for analyzing data, which are measured at several time points. Linear mixed-effects models (LMM) are common classical models that have been widely used for analyzing these data. However, these models are only able to account for linear relationships between variables [29]. Accordingly, if the relationships between variables are nonlinear, classical models such as LMM may not be useful for data analysis. [30]. To overcome the problem of LMM can be applied to machine learning models [30, 31]. Among them, mixed-effects least-squares support vector regression (MLS-SVR) has been proved to be a very appealing and promising model [32].
In some studies, machine learning models have been used to predict hospitalization and mortality in HF patients [2, 33-35]. However, based on our knowledge,

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no studies have assessed longitudinal changes in SBP by machine learning models. Furthermore, evidence on the association of different variables on SBP changes over time in HF patients is still limited. In order to determine significant variables associated with changes in SBP over time and assess the effectiveness of classical and machine learning models in predicting SBP, the objective of this study was to conduct a comparative analysis between the two.

Methods

Data collection

This retrospective cohort study involved the analysis of data from 541 patients with HF who were admitted to Farshchian Heart Center located in Hamadan in the west of Iran, and hospitalized at least two times between October 2015 and July 2019. From the initial 541 patients, 58 patients were excluded due to missing at least one of the study variables. Therefore, the analyzes were performed based on a sample of 483 patients. Informed consent was obtained from all patients included in the study. This study was submitted to and approved by the Ethical Committee of Hamadan University of Medical Science (IR.UMSHA.REC.1398.276).

Some of the information regarding patients such as age, sex, body mass index (BMI), history of hypertension (HTN), cholesterol, triglyceride, high-density lipoprotein (HDL), low-density lipoprotein (LDL), sodium (Na), and baseline SBP were extracted from medical records. The baseline SBP in each hospitalization was the response variable.

Linear mixed-effects models (LMM)

The LMM is one of the popular classical models for analyzing continuous longitudinal data. Suppose the denote the longitudinal response of interest, that measured for subject i at time j . An LMM can be expressed as:

$$y_{ij} = \mathbf{w}'\mathbf{x}_{ij} + \mathbf{b}_i{}'\mathbf{z}_{ij} + \varepsilon_{ij}$$

Here, is a vector of parameters that are associated with fixed effects covariates, is a vector of random effects associated with covariates, and is errors vector from. The are assumed normally distributed with zero mean and covariance matrix and are independent of [29].

Mixed-effects least-squares support vector regression (MLS-SVR)

The MLS-SVR is one of the appealing machine learning models for analyzing longitudinal data. Let the training dataset be $D=\{(x_{ij},y_{ij})\}_{ij=1}^{N,n_i}$, where is the *j*-th response variable of the *i*-th subject corresponding to fixed-effects covariates. The regression function can be expressed as:

$$y_{ij} = b_0 + \mathbf{w}'\varphi(\mathbf{x}_{ij}) + \mathbf{b}_i'\mathbf{z}_{ij} + \varepsilon_{ij}$$

Here, is a nonlinear feature mapping function, is the bias term, is a vector of random effects covariates with the random effects parameter, and error vector. For known **B** and the optimization problem of the nonlinear MLS-SVR can be defined as:

$$\min \ \frac{1}{2}\mathbf{w}'\mathbf{w} + \frac{\lambda_1}{2}\sum_{i=1}^{N}\mathbf{b}_i'\mathbf{B}^{-1}\mathbf{b}_i + \frac{\lambda_2}{2}\sum_{i=1}^{N}\sum_{j,k=1}^{n_i}\varepsilon_{ij}\mathbf{R}_{i\ jk}^{-1}\varepsilon_{ik}$$

subject to equality constraints

$$y_{ij} = b_0 + \mathbf{w}'\varphi(\mathbf{x}_{ij}) + \mathbf{b}_i'\mathbf{z}_{ij} + \varepsilon_{ij}$$

Here, and are tuning or regularization parameters, and is the (j,k) th element of the inverse matrix of, $\mathbf{R}_i$, $i=1,\dots,N$, $j,k=1,\dots,n_i$.

The expression (3) is optimized using the Lagrange function and solving linear equations. Finally, the optimal regression function for a given, expressed as:

$$\hat{y}(\mathbf{x_0},\mathbf{z_0}) = \hat{b}_0 + \sum_{i=1}^{N}\sum_{j=1}^{n_i}\hat{\alpha}_{ij}K(\mathbf{x_{ij}},\mathbf{x_0}) + \hat{\mathbf{b}}_i'\mathbf{z_0}$$

where are the Lagrange multiplier, and is the kernel function. The Gaussian RBF function is one of the common kernels utilized in this study [32, 36].

Variable Importance (VIMP)

In the present study, each variable's importance in predicting SBP was evaluated by a permutation approach with 100 iterations [37]. In each iteration, values of one variable were randomly permuted, and values of other variables were considered constant. Then MAE was calculated for each permutation and the main dataset. Eventually, the mean of differences between MAE for the main dataset and MAE for each permutation was considered as the variable importance (VIMP)[30].

Performance criteria

The performance of both LMM and LS-SVR models was assessed in the testing and training dataset. The data were randomly divided into training and testing set with an 70:30 ratio. This procedure was repeated 100 times. The performance of MLS-SVR was compared to LMM via two criteria, which are mean absolute error (MAE) and root mean squared error (RMSE).

Results

This study consisted of 483 HF patients, with 1320 SBP measurements. During the follow-up period, the frequency of hospitalization for these patients was varied between 2 to 5 times. The mean (standard deviation) age of patients at the first hospitalization was 72.06 (13.42) years, majority of the patients were male 318 (65.8 %), and with a history of HTN 276 (57.1 %). The characteristics of the HF patients are given in Table I.

The results of the LMM are presented in Table II. According to the results, sex was significantly related to SBP changes (P = 0.012), which were higher in women. There was a strong association between SBP changes and the history of HTN (P < 0.001). So that the SBP changes were greater in HF patients with a history of

Tab. I. Characteristics of heart failure patients.

Variables	Median	Mean	SD
Age (Year)	73	71.63	13.49
BMI (kg/m²)	28.72	25.92	4.94
Cholesterol (mgr/dl)	163	138.36	40.31
HDL (mgr/dl)	42	36.62	9.55
LDL (mgr/dl)	98	82.10	31.41
Triglyceride (mgr/dl)	131	109.97	40.31
Na (mgr/dl)	141.5	138.77	3.95

BMI: Body mass index, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, Na: Sodium, SD: standard deviation.

Tab. II. Linear mixed-effects model analysis for SBP in heart failure patients.

Variables	Coefficient (Standard Error)	P-value
Intercept	-56.05 (22.74)	0.013
Time (Month)	-0.14 (0.06)	0.015
Sex (Female)	4.13 (1.68)	0.014
History of HTN (Yes)	7.68 (1.51)	< 0.001
Age (Year)	0.06 (0.05)	0.286
BMI (kg/m²)	0.40 (0.15)	0.009
Cholesterol (mgr/dl)	0.03 (0.03)	0.220
HDL (mgr/dl)	-0.06 (0.05)	0.245
LDL (mgr/dl)	0.03 (0.03)	0.358
Triglyceride (mgr/dl)	0.01 (0.01)	0.218
Na (mgr/dl)	1.07 (0.16)	< 0.001

SBP: systolic blood pressure, HTN: Hypertension, BMI: Body mass index, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, Na: Sodium.

Tab. III. The performance criteria of the models.

Models	Dataset	MAE	RMSE
		Mean (SD)	Mean (SD)
LMM	Training	12.44 (0.28)	16.01 (0.35)
	Testing	17.92 (0.79)	22.79 (0.71)
MLS-SVR	Training	2.21 (0.07)	2.81 (0.10)
	Testing	17.36 (0.56)	22.07 (0.74)

LMM: Linear mixed-effects model, MLS-SVR: Mixed-effects least-squares support-vector regression, MAE: mean absolute error, RMSE: Root mean squared error, SD: standard deviation.

HTN. Also, the variables of BMI and Na were positively associated with the SBP changes, while time was negatively associated with the SBP changes.

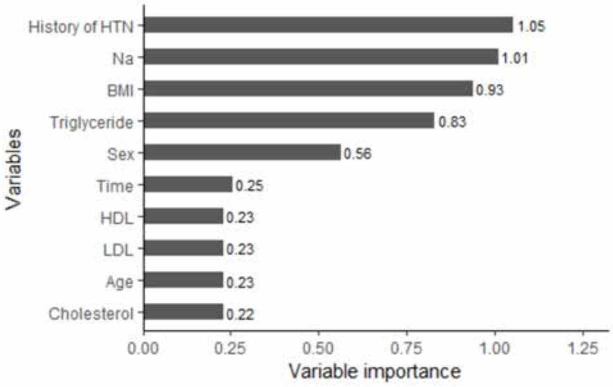
The VIMP of the variables obtained from MLS-SVR is shown in Figure 1. According to the MLS-SVR analysis, the four most important variables in predicting SBP were identified as history of HTN, Na, BMI, and triglyceride.

Table III shows the performance of LMM and MLS-SVR models to predict SBP in training and testing datasets. As seen, the performance of MLS-SVR compared to LMM was better in both training and testing datasets.

Discussion

One of the important goals for managing HF patients is to control and achieve appropriate blood pressure to reduce mortality and readmission. In the current study, the effects of several variables on SBP changes over time were assessed using classical and machine learning models. The LMM analysis revealed that changes in SBP over time were significantly associated with sex, BMI, Na, time, and history of HTN. Furthermore, according to the MLS-SVR analysis, the four most important variables in predicting SBP were identified as history of HTN, Na, BMI, and triglyceride.

Fig. 1. VIMP for predicting SBP in heart failure patients.
SBP: Systolic blood pressure, VIMP: Variable importance, HTN: Hypertension, BMI: Body mass index, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, Na: Sodium.



We found a strong association between SBP changes and the history of HTN. So that the SBP changes were greater in HF patients with a history of HTN, the reason may be that these patients might have had a lack of adherence to the use of blood pressure-lowering medicines or an unhealthy diet [38]. Svetkey et al. [39] reported that BP changes were consistently higher in hypertensive than in non-hypertensives.

According to previous studies, there is a close relationship between dietary Na intake and the incidence of hypertension. The reduction in daily Na intake is associated with decreased incidence of hypertension and its morbidity and mortality. A modest reduction in Na intake will cause a fall in blood pressure in a hypertensive and normotensive population. [40]. Also, it has been shown that higher dietary Na intake is strongly related to hospitalization and readmission in patients with chronic HF [41]. The results of our study are in agreement with previous studies because they showed a positive and significant relationship between Na and SBP.

Based on our findings, increased BMI was associated with increased SBP changes. Previous cross-sectional studies have confirmed this result [42, 43]. Ji et al. [44] indicated a greater SBP changes in women compared to men. These findings are also consistent with our results, indicating sex difference in SBP changes over time.

In this study, MLS-SVR identified triglyceride as the fourth important variable for SBP changes in HF patients. However, no significant effect was detected for triglyceride in the LMM model. This may be due to a nonlinear relationship between triglyceride and SBP changes. Previous studies have reported triglyceride as a factor associated with blood pressure [45, 46]. The association of high triglyceride and systemic HTN has been shown as components of metabolic syndrome and an important contributor to cardiovascular disease in many studies [47].

In the current study, we also compared the performance of classical and machine learning models using cross-validation. According to the results, in both the training and testing datasets, MLS-SVR outperformed LMM in terms of performance. This can be attributed to considering nonlinear and complex relationships between variables by the MLS-SVR model. Therefore, MLS-SVR may be a useful model for predicting SBP in HF patients. Seok et al. [36], in their study, showed that their proposed MLS-SVR model was better than standard models for longitudinal data. In another study, the performance of MLS-SVR was better than LMM, based on two real data and simulation [48]. The results of these two studies were in agreement with our study. In addition, Moghadasi Amiri et al. [30] conducted a comparative study of classical and machine learning models for longitudinal data. They used these models to predict serum creatinine. According to their results, MLS-SVR had the best performance compared to other models, which is consistent with our results.

There are two limitations in this study. First, this was a retrospective study in which some information was missing from patients' records. Second, information regarding the use of HF drugs was not collected. Despite these limitations, this study identified some important variables on SBP changes in HF patients. The results can help cardiologists better control and treat abnormal blood pressure for preventing death and readmission in these patients.

Conclusions

The findings suggest that BMI, Na, and history of HTN were the most important predictors of changes in SBP, as identified by both LMM and MLS-SVR models. Based on our results, it appears that MLS- has the potential to serve as a viable alternative to classical longitudinal models for predicting SBP in HF patients. However, further research is required.

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Conflict of interest statement

The authors declare that they have no conflicts of interest.

Authors' contributions

RNV and HM contributed to the study design, analysis, and interpretation of data. SKH participated in data collection, data analysis, and writing. JF and AM participated in the interpretations and drafting of the manuscript. All authors read and approved the final manuscript.

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