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Clinical usability of morning surge blood pressure for predicting future hypertension in a young population

Objective	Early diagnosis of hypertension (HT) is a critical issue for physicians. This study was conducted to determine if morning surge blood pressure (MSBP) could be used to predict future HT. The study also examined which demographic data in a regression model might help to detect future HT without any invasive procedure.
Material and methods	A young population between 18 and 40 yrs of age was included in the study. MSBP and demographic data were used to determine an optimal model for predicting future HT by using Bayesian information criteria and binary logistic regression.
Results	1321 patients with 24 hr ambulatory blood pressure monitoring were included in this study. The odds ratio of 10 units of increase in diastolic MSBP was 1.173511 in the model, which indicates that a 10 mmHg increase in diastolic MSBP increases the odds of future HT in the patient by 17.4%. The odds ratio of age was 1.096365, meaning that at each age above 18 yrs, the patients' odds of future HT rise by 9.6%. The odds ratios for gender (male) and previous HT were 1.656986 and 3.336759, respectively. The odds of future HT in males were 65% higher than for females, and a history of HT implies that the odds of future HT were higher by 230%.
Conclusion	Diastolic MSBP can be used to predict HT in young individuals. In addition, age, male gender, and previous HT add more predictive power to diastolic MSBP. This statistically significant, predictive model could be useful in lessening or preventing future HT.

Keywords	Hypertension; blood pressure; blood pressure monitoring; ambulatory
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Introduction

Hypertension (HT) is one of the leading causes of cardiovascular events. Long-term exposure to HT further increases cardiovascular risks [1–3]. Early onset HT in the young population increases exposure to the disease's negative effects [4]. As a result, early diagnosis of HT is an important issue for physicians [5]. Morning surge blood pressure (MSBP) is a well-known condition that foretellscardiovascular events [6, 7]. Elevated values of MSBP are associated with mortality in elderly patients, however studies in the young population are limited in the literature [8–10]. Therefore, we aimed to investigate whether MSBP can be used to predict future HT in young people. In addition, we also aimed to determine what demographic data and which regression model may best help to detect future HT without any extrainvasive assay being performed in the out-patient clinic.

Material and methods

Study Population

This study was a retrospective cohort study. Inclusion criteria were patients aged between 18 and 40 yrs with 24hr ambulatory blood pressure monitoring (ABPM). ABPM was performed to patients who claimed to have high blood pressure in their daily lives. Pregnancy, severe chronic systematic diseases (except diabetes mellitus), 3 missing consecutivevalues of ABPM, less than 70% correct calculation of blood pressures, and repeated blood pressure values at 5 min intervals were excluded. The patients' demographic data, ambulatory blood pressures, diabetes mellitus status, and blood variable data were also recorded.

Hypertension was determined according to the latest European Society of Cardiology Hypertension Guideline [11]. Diagnostic threshold for HT was ≥130/80 mmHg over 24 hrs according to ABPM. The study population was grouped as Future HT and No Future HT. Future HT was defined as those who were diagnosed with HT after ABPM, those who started to take HT medication after ABPM, or those who had stabile HT under treatment until ABPM and then received an increased dose of medication after ABPM. No Future HT was defined as those who were not diagnosed with HT after ABPM, those who did not start to take HT medication after ABPM, or those who had diagnosis of HT before ABPM and then did not change the dose and type of medication

after ABPM. Hypertension medication included angiotensin converting enzyme inhibitors/angiotensin receptor blockers, calcium channel blockers, diuretics, or their combinations as was appropriate for the patients. The follow-up time was defined as the date of ABMP monitoring to the date of last contact to our medical center. The patients were followed up according to whether they had been diagnosed with HT and whether HT treatment had been started.

ABPM and MSBP

24 hr ABBP (Custo Screen 300, Custo Med, Ottobrunn, Germany) was performed on all patients. Blood pressure was measured at 30-min intervals between 06.00–22.00 hrs and at 1-hr interval between 22.00–06.00 hrs. Participants with 70% or more valid blood pressure values,>20 daytime measurements (with at least 2 valid readings per hr), and >7 night-time measurements (with at least 1 valid reading per hr) were included in the study. MSBPvalues were calculated for all systolic, diastolic, and mean blood pressure values. The MSBP value was calculated by subtracting the lowest blood pressure during sleep from the average of the 4 consecutive values just after awakening. Systolic MSBP (sMSBP), diastolic MSBP (dMSBP) and average MSBP (aMSBP) were obtained for all individuals aMSBP values were obtained from average BP values (Average BP = 2/3xDiastolic BP + 1/3xSystolic BP).

Statistical analyses

The analyses were conducted using SPSS 22.0 (SPSS for Windows 22.0, Chicago, IL, USA) and R (R 4.0.2, Vienna, Austria) [12]. The data consisted of both categorical and continuous variables, which were split into two groups depending on whether the patient exhibited HT and whether the patient's already existing condition worsened after ABPM. Comparison of categorical variables between the groups was performed using the chi square (χ^2) test. The normality of the distribution of all continuous variables was evaluated with the Kolmogorov – Smirnov test and p value bigger than 0.05 was assumed as normal distribution. Normally distributed and non-normally distributed values were shown as mean ± standard deviation (SD) and median (range), respectively. If the continuous variables distributed normally, Independent Samples T-tests were used and if distributed non-normally, Mann-Whitney U tests were used for comparison.

Consequently, the two groups (Future HT and No Future HT) of aMSBP, dMSBP and aMSBP were compared using Independent Samples T tests. The abilities of the morning surge blood pressures (aMSBP, sMSBP, and dMSBP) to detect future HT were analyzed by receiver operating characteristic (ROC) curves. The optimal cut-off value was obtained fromTheClosestto (0, 1) Criteria (ER) in the ROC curve analysis.ER was calculated as $((1\text{-sensitivity})^2 + (1\text{-specifity})^2)^{1/2}$.

Finally, binary logistic regression was employed to model future HT. Eight models were examined where various combinations of morning surge pressure measures were considered in each model. Additionally, age, male gender, and previous history of HT were considered as control variables in each model. Model (1), the first model, included all the MSBP variables, as well as the aforementioned extra control variables. Model (8), the last model, only contained age, gender and HT history.

These models were compared with the Bayesian Information Criterion (BIC) along with various measures of predictive performance. BIC evaluates how well a model fits to the data, or in other words it presents a scale that is useful for determining which model describes better the variation in the dependent variable. BIC is calculated as follows:

$$BIC = (-2 \times LL) + (\log (N) \times k).$$

Where log (N) has the base called the natural logarithm, LL is the log-likelihood of the model, N is the number of examples in the training dataset, and k is the number of parameters in the model. Among the models, the one with the smallest BIC fits the data best. Next the optimal cut-off value for each model was again obtained by the ER. Subsequently, this makes it possible to observe the predictive power of all models, given the optimal cut-off value.

There are many measures to specify the predictive performance of classification methods. The most popular are presented in the caret library of R [13]. We have presented accuracy, no information rate, prevalence, Kappa, sensitivity, specificity, positive predictive value, negative predictive value, detection rate, detection prevalence and balanced accuracy for the eight binary logistic models estimated.

Accuracy is the ratio of correct prediction to overall predictions. The no information rate is a similar measure, however instead of predicting every patient to be positive; the no information rate predicts that all patients belong to group with the most members. The Kappa statistic was initially introduced as a measure of inter-rater reliability, however in this context it measures how far the estimated model varies from a totally random system. In other words, Kappa shows how well the models' predictions match the actual groups to which the observations belong, while controlling for assigning groups randomly to a model. To summarize, we used BIC to identify which models fit the data better, and we used the predictive performance measures (accuracy, kappa, and no information rate) to determine which of the putative models best predicts, for the given optimal cut-off value, future HT. Also, the ROC curve of the preferred model is presented, so that the preferred model can be compared with the individual

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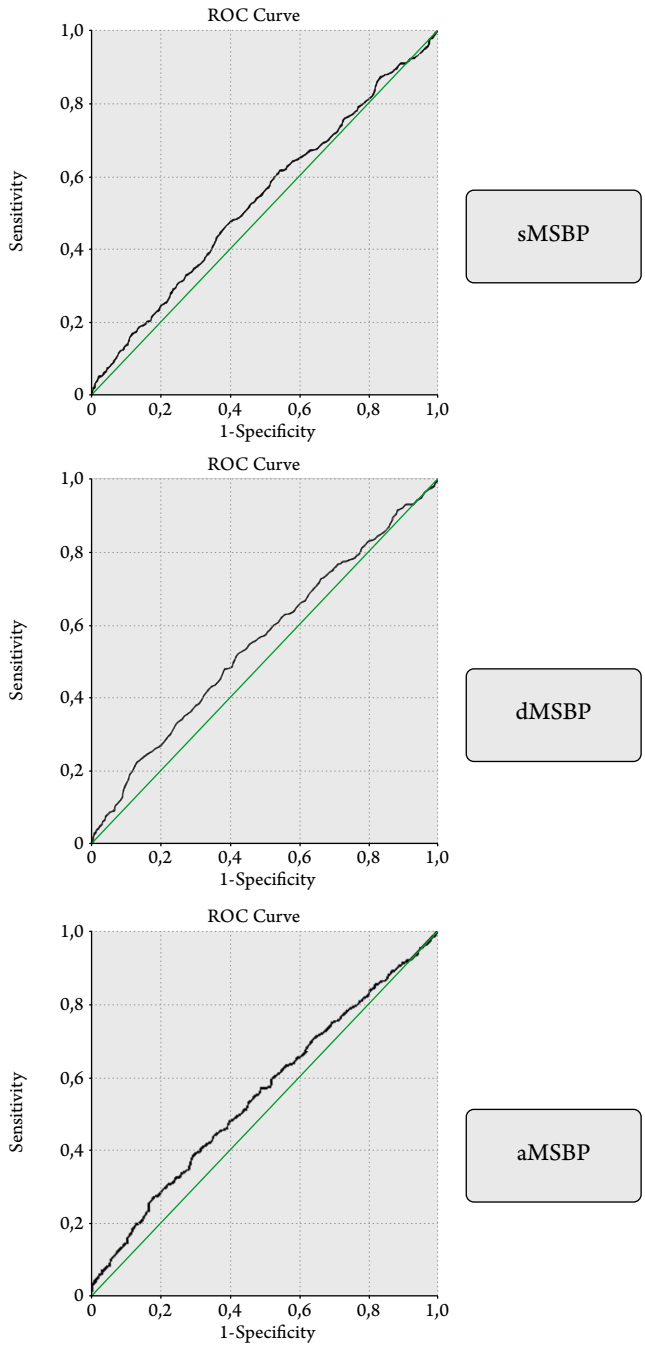
Figure 1. ROC curve analyses of the morning surge blood pressures according to future hypertension



Parameters	Area	Asymptotic Significance	Cut-off	Asymptotic 95% Confidence Interval	
				Lower Limit	Upper Limit
sMSBP	0.536	0.039	30.58	0.501	0.570
dMSBP	0.552	0.002	23.13	0.518	0.587
aMSBP	0.551	0.003	24.41	0.517	0.585

MSBP variables. Statistically significance was assumed as p value smaller than 0.05.

Results

1321 patients with 24 hrABPM were included in this study. 723 (54.7%) patients were female, and the median age was 32 (18-40) yrs. 97 (7.3%) patients were diagnosed with diabetes mellitus. Table 1 shows the demographic data, follow-up time, and blood analysis data grouped according to Future and No Future HT.sMSBP, dMSBP, and aMSBP values were compared according to Future or No Future HT, and their mean values differed significantly (Table 2).

Table 1. Comparison of demographic and blood analysis data according to Future HT and No Future HT

Parameters	Future HT	No Future HT	p
Age (yrs)	36(19-40)	32(18-40)	<0.001
Cholesterol (mg/dl)	196.93±46.15	182.77±37.94	286
Hemoglobin (g/dl)	14.35±1.94	14.05±1.81	399
Creatinine (mg/dl)	0.78±0.13	0.77±0.13	295
Na+ (meq/dl)	138.79±2.1	138.69±2.28	780
K+ (meq/dl)	4.24±0.33	4.24±0.33	200
Gender (female)	255/538	468/783	<0.001
Prev. HT	91/538	55/783	<0.001
Diabetes mellitus	55/538	42/783	0.001
Follow-up time (days)	656.3±213.65	655.03±214.52	0.359

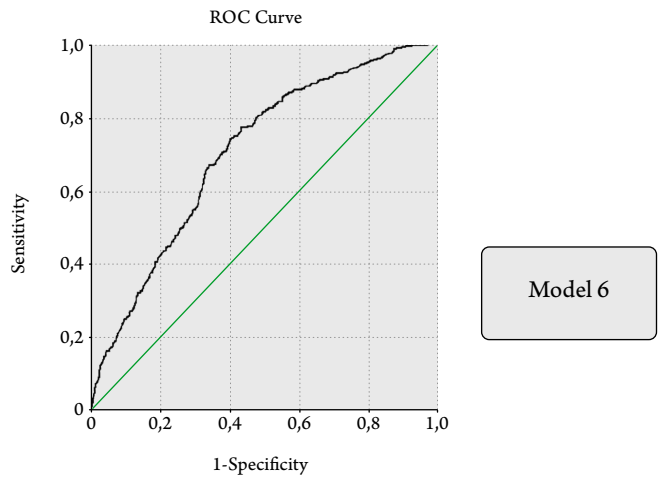
Data are mean (range), ratio, or mean±SD. HT, hypertension; Na,sodium; K, potassium; Prev. HT,previous hypertension.

Table 2. Statistical analyses of morning surge blood pressures according to Future HT

Parameters	Future HT	No Future HT	p
sMSBP (mean±SD)	29.74±13.89	28.11±12.76	0.038
dMSBP (mean±SD)	23.19±10.49	21.41±9.51	0.002
aMSBP (mean±SD)	25.57±11.03	23.66±9.99	0.002

sMSBP,systolic morning surge blood pressure;
dMSBP, diastolic morning surge blood pressure;
aMSBP, average morning surge blood pressure.

Figure 2. ROC curve analysis of Model 6 (best model) according to future HT



Para-meters	Area	Standard Error	Asymptotic Significance	Asymptotic 95% Confidence Interval	
				Lower	Upper
Model 6	0.707	0.015	<0.001	0.678	0.737

Table 3. Models (1-8) of the morning surge blood pressure and demographic variables according to binary logistic regression and Bayesian information criteria

Parameters	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
sMSBP	-0.025	-0.006	-0.021	-	0.007	-	-	-
	(0.014)	(0.008)	(0.011)	-	(0.005)	-	-	-
dMSBP	-0.012	0.022*	-	0.012	-	0.016*	-	-
	(0.024)	(0.01)	-	(0.019)	-	(0.006)	-	-
aMSBP	0.055	-	0.038**	0.004	-	-	0.015**	-
	(0.035)	-	(0.014)	(0.018)	-	-	(0.006)	-
Age	0.092**	0.092**	0.092**	0.092**	0.093**	0.092**	0.092**	0.093**
	(0.011)	(0.011)	(0.011)	(0.011)	(0.011)	(0.011)	(0.011)	(0.011)
Male	0.520**	0.518**	0.521**	0.503**	0.503***	0.505**	0.497**	0.526**
	(0.13)	(0.130)	(0.130)	(0.129)	(0.129)	(0.129)	(0.129)	(0.128)
Prev HT	1.212**	1.209**	1.212**	1.205**	1.205**	1.205**	1.204**	1.212**
	(0.188)	(0.188)	(0.188)	(0.188)	(0.188)	(0.188)	(0.188)	(0.188)
Constant	-4.519**	-4.509**	-4.529**	-4.553**	-4.390**	-4.544**	-4.549**	-4.203**
	(0.408)	(0.407)	(0.408)	(0.407)	(0.402)	(0.405)	(0.407)	(0.378)
Obs.	1321	1321	1321	1321	1321	1321	1321	1321
LL	-735.009	-736.343	-735.149	-736.632	-738.819	-736.656	-736.835	-739.823
BIC.	1520.320	1515.803	1513.415	1516.381	1513.570	1509.243	1509.601	1509.390
Optimal Cutoff	0.29890	0.30303	0.29547	0.30714	0.29762	0.30610	0.30319	0.31169
Accuracy	0.6571	0.6586	0.6518	0.6646	0.6412	0.6654	0.6556	0.6480
Prevalence	0.4625	0.4519	0.4739	0.4391	0.4784	0.4398	0.4489	0.4504
No Inf. Rate	0.5375	0.5481	0.5261	0.5609	0.5216	0.5602	0.5511	0.5496
Kappa	0.2936	0.2907	0.2891	0.2964	0.2701	0.2976	0.2827	0.2678
Sensitivity	0.4599	0.4606	0.4553	0.4664	0.4446	0.4672	0.4570	0.4487
Specificity	0.8268	0.8218	0.8288	0.8205	0.8215	0.8203	0.8173	0.8113
Pos. PredVal.	0.6955	0.6807	0.7054	0.6708	0.6955	0.6708	0.6708	0.6609
Neg. PredVal.	0.6401	0.6489	0.6281	0.6619	0.6172	0.6630	0.6489	0.6423
Det. Rate	0.2127	0.2082	0.2157	0.2051	0.2127	0.2051	0.2051	0.2021
Det. Prev.	0.3058	0.3058	0.3058	0.3058	0.3058	0.3058	0.3058	0.3058
Bal. Accuracy	0.6433	0.6412	0.6420	0.6434	0.6331	0.6439	0.6372	0.6300

*p<0.05, and**p<0.01. sMSBP,systolic morning surge blood pressure;dMSBP, diastolic morning surge blood pressure;aMSBP, average morning surge blood pressure; Prev. HT,previous HT; Obs., number of patients; LL, log-likelihood of the model; BIC, Bayesian information criteria.

The success of predicting Future HT regarding the individual MSBP variables was compared with ROC curve analysis (Figure 1). The optimal cut-off values for the binary classifiers were30.58 for sMSBP, 23.13 for dMSBP, and 24.41 mmHg for aMSBP. Area under the curve values were 0.536, 0.552 and 0.551 for sMSBP, dMSBP and aMSBP, respectively. All off ROC curve analyses were statistically significant (p=0.039, p=0.002 and p=0.003 for sMSBP, dMSBP and aMSBP, respectively).

In Table 3, the estimates of the eight binary logistic regression and relevant statistics are presented. In these binary logistic regression models, eight combinations (all subsets) of MSBP variables were considered. Additionally, age, gender, and previous HT history were also included in each model. Following the model estimates, the number of observations, log likelihood, and BIC are presented. Next, the optimal cut-off values according to the ER are presented, followed by the prediction performance measures of the models depending on the presented cut-off value.

Model (6) fit the data better than the other seven competing models since BIC is lowest for this model. Furthermore, prediction measures also favor this model. Accuracy, sensitivity, negative predictive value and balanced accuracyare highest in model (6). Kappa also supports model (6) in the sense that model (6) is the furthest from a system assigning groups randomly. The only measures that do not favor model (6) are specificity and positive predictive value. Most of the predictive performance measures suggest model (6) as a better classifier. Further more, the ROC curve analysis of the model indicates that the area under the curve is0.707 (p<0.001), which is higher than previous ROC curve analyses of individual morning surge blood pressure indicators (Figure 2). In summary, there is convincing evidence that dMSBP predicts future HT. Additionally, age, gender and previous HT variables increase the predictive power when considered along with dMSBP.

The odds ratio of 10 units of increase in dMSBP was 1.173511in model (6); which indicates that a 10 mmHg increase in diastolic MSBP increases the odds of future HT

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in the patient by 17.4%. The odds ratio of age was 1.096365, meaning of each age above 18 the patients odds of future HT rise by 9.6%. The odds ratios for gender (male) and previous HT were 1.656986 and 3.336759, respectively. The odds of future HT in males are 65% higher than females and a history of HT implies anodds of deterioration, i.e., future HT, by 230%.

Discussion

This study was conducted to determine if which MSBP value (systolic, diastolic, or average) is better for detecting future HT in young people. In addition, we used some basic demographic data to obtain a usable regression model for predicting future HT in clinical practice. dMSBP is the stronger parameter among morning surge blood pressure variables for prediction of future HT. In addition, basic demographic data such as age, male gender, and previous HT strengthen the predictive strength of dMSBP.

Prediction of HT in the young population has always been a matter of interest, and physicians have conducted many studies of the subject up to the present time. Especially important, is the fact that non-invasive and easy accessible methods have been used to address this problem. Kähönen et al. found that an index of systemic vascular resistance predicts the incidence of HT in young patients [14]. Another study found that Body mass index (BMI) was associated with HT prediction in an early adulthood population [15]. The Framingham HT risk prediction model was applied to young populations in another study that found this model a useful tool for HT prediction [16]. MostHT prediction studies comprise metabolic parameters and vascular indices. As previously known, metabolic parameters such as higher weight, BMI, and waist circumference are associated with HT. In this study, we aimed to use more simple parameters like MSBP and demographic parameters to apply a rapid and easy HT prediction model to early adults.

ABPM is a valuable tool to detect HT and HT subtypes (e.g. white-coat, masked, nocturnal HT) in clinical practice [17]. ABPM should be preferred to office blood pressure monitoring for HT tracking from early adulthood to late adulthood [18]. ABPM studies were mainly designed to evaluate dipper/non-dipper and blood pressure variability parameters [18, 19]. MSBP parameter were mainly used for cardiovascular mortality prediction [20, 21]. However, no previous studies on MSBP for prediction of future HT have been found in the literature. Therefore, this study may add valuable information to the literature.

Hypertension is one of the most important chronic diseases that affect cardiovascular risk and events. Aortic stiffness and carotid intima-media thickness reflect the state of the major vessels, and these are predictors of cardiovascular events [22–24]. It is also known that HT and these conditions accompany each other [25]. However, it is not clear whether HT causes these conditions or whether these conditions cause HT [25, 26]. In addition, MSBP was found to be associated with aortic stiffness and carotid intima-media thickness [27, 28]. In the light of these data, prolonged exposure to high MSBP can cause aortic stiffness, which may explain the mechanism of the later development of HT. However, this issue is not clear, and more studies should be performed to explain this mechanism.

In this study, prediction of future HT was best modeled with dMSBP, age, male gender, and previous HT. All these parameters can be obtained easily in out-patient clinics. In this study, we aimed to evaluate our prediction of future HT with basic demographic data and MSBP. Ageing is one of the leading causes of HT. Inflammation, oxidative stress, and endothelial dysfunction have cumulative, negative effects on the arterial vasculature and increase vascular resistance [29]. Although, our study population consisted of young adults, vascular ageing begins from birth. Male gender is a greater risk of developing HT. This is attributed to hormonal differences, and after female post-menopause, the risk is equalized [30]. Importantly, estrogens influence the vascular system by inducing vasodilatation, modulating the renin-angiotensin aldosterone system, inhibiting vascular remodeling processes, and the sympathetic system [31]. In the present study, the study population was under 40 yrs old, and most of the females were of reproductive age. This situation explains the gender differences found in our study.

In conclusion, HT is a disease that progresses insidiously and creates long term exposure to cardiovascular events. Therefore, it is important to make a diagnosis before HT progress. In the young population, early diagnosis of HT is a subject of interest. In the present study, we found that MSBP parameters (especially dMSBP) may be used for predicting HT in young people. In addition, age, male gender, and previous HT add more predictive power to dMSBP.

Limitations

Firstly, this was a retrospective study. In the future, prospective studies are needed to investigate this issue. Secondly, the mean follow-up time was approximately 2 yrs. This is a shorter time compared with other studies, so future studies should follow the patients much longer. Thirdly, our demographic data did not include weight, height, body mass index, waist circumference, and pregnancy status. All these parameters affect blood pressure, so they should be included in future studies. Another limitation was that the patients who had diagnosis of HT after ABPM were not grouped according to different HT medication therefore they were not studied with statistical analyses. Finally, considering the retrospective nature of this study, we could not control daily stressors during ABPM, so we could not standardize this situation.

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No conflict of interest is reported.

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