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Machine Learning Methods in Assessing the Risks of Target Organ Damage in Masked Hypertension

Aim	To develop models for predicting the risk of target organs damage (TOD) in different phenotypes of "masked" arterial hypertension (MAH) based on methods of machine learning (ML).
Material and methods	A retrospective cohort analysis was performed for 284 clinical records of patients (261 males, 23 females; median age, 38 years). Group 1 included 125 patients with grade 1-2 arterial hypertension (AH) and low or moderate risk; group 2 included 159 subjects with normal "office" blood pressure (BP) exposed to chronic professional stress. The 24-h BP monitoring (24-h BPM) and ultrasound examination of the heart and carotid arteries were performed; glomerular filtration rate (GFR) was estimated using the CKD-EPI formula. MAH was phenotyped by clustering 24-h BPM data, and the risk of TOD was predicted by analysis of odd ratios (OR) and with the ML methods, random forest (RF) and artificial neural networks (ANN). Data were analyzed using the R language in the RStudio environment.
Results	According to results of the 24-h BPM and cluster analysis, 121 (76.1%) subjects of group 2 had MAH. The MAH phenotypes were identified as follows: systolic-diastolic (SDMAH) (43.8%); isolated systolic (ISMAH) (35.5%), and isolated diastolic (IDMAH) (20.7%). As compared to stable AH, subjects with different MAH phenotypes showed both increases and decreases in individual 24-h BPM indexes. Thus, in subjects with IDMAH, mean 24-h values of systolic and diastolic BP were significantly lower than with AH while in SDMAH, they were considerably higher. The OR analysis demonstrated that odds of differently located TOD were associated with definite MAH phenotypes. With that, ISMAH was associated with the highest risk of glomerular hyperfiltration; IDMAH was associated with reduced GFR and vascular remodeling; and SDMAH was associated with left ventricular myocardial hypertrophy. The developed models for predicting the risk of TOD based on the RF and ANN methods showed a high accuracy, which was provided by multistep procedures of selecting the predictors and cross-validation.
Conclusion	Modern ML technologies enhance the risk stratification of patients with different clinical variants of AH.

Keywords	"Masked" arterial hypertension; target organ damage; prediction; machine learning methods
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Hypertension is one of the most relevant healthcare problems today due to its increasing prevalence and the severity of its economic burden on the state and society. That is why the scientific community focuses on early diagnosis and minimization of the risk of developing associated cardiovascular complications (CVCs). Masked hypertension (MH) is a type of essential hypertension defined as mean 24-hr ambulatory blood pressure (BP) ≥130/80 mm Hg and/or mean daytime BP ≥135/85 mm Hg and/or mean night-time BP ≥120/70 mm Hg with normal clinic BP [1, 2]. Several studies have used different synonyms of MH to specify the characteristics of this clinical condition: hidden hypertension, home hypertension, inverse white coat hypertension, etc. [3]. The prevalence of MH in different studies varied significantly, but most often, the range was 10–30%, depending on sex, age, anthropometric characteristics, race, socioeconomic status of subjects, and other characteristics [2–4].

Recently there has been an increasing number of studies designed to assess various aspects of MH, including the risk of target organ damage (TOD) [5]. Left ventricular mass index (LVMI) and relative thickness (RWT) of the left ventricular posterior wall (LVPW) were shown to be significantly higher in patients with MH than in individuals with normal BP. Pulse wave velocity (PWV) and central BP corresponded to normal rates [6, 7]. Other studies demonstrated increased intima-media thickness (IMT) and greater arterial stiffness in combination with left ventricular hypertrophy (LVH) in patients with MH [7, 8]. Individual patterns of 24-hr BP profiles were studied in patients with MH, and the findings were compared with the signs of TOD of different localizations [9, 10]. For example, nocturnal phenotype MH was more often associated with increased risk of TOD and a higher probability of CVCs, compared to the morning or daytime phenotypes. IMT was significantly higher in patients with isolated systolic MH (ISMH) and systolic/diastolic MH (SDMH) than in those with isolated diastolic MH (IDMH) [7]. The workplace MH phenotype was associated with the type of professional activities, the intensity of the impact of various stress factors, and individual psychophysiological status [2]. The severity of stress factors in such cases directly correlated with diastolic blood pressure (DBP) and with LVMI.

However, there is not adequate data in the literature about the association of MH phenotypes with TOD of different localization and with prediction of TOD risks, taking into account the 24-hr BP profile. Several studies showed that the use of machine learning methods increases the accuracy of calculations and their predictive significance. Thus, multinomial logistic regression was used to find associations between MH, «white coat» hypertension, and stable hypertension with LVH, carotid atherosclerosis, and microalbuminuria [5, 8]. At the same time, continuous improvement of artificial intelligence technologies improves the quality of clinical data analysis and the accuracy of predicting CVCs. Thus, the objective of the study was to develop models for predicting TOD risks in different MH phenotypes using machine learning methods.

Material and Methods

A cohort retrospective study was conducted based on the analysis of 284 medical records (261 male and 23 female patients) aged 18–55 yr (median age 38 yr with 95% confidence interval [CI] from 36 to 39 yr) who underwent inpatient examination and treatment in Naval Clinical Hospital #1477 during 2015–2018. The study was performed according to good clinical practice and the principles of the Helsinki Declaration. The study protocol was approved by the local ethic committee of the School of Biomedicine of the Far Eastern Federal University. All subjects signed informed consent to be included in the study.

Group 1 included 125 patients with previously diagnosed grade 1–2 hypertension with low and moderate cardiovascular risk, and Group 2 included 159 patients with normal or high normal «office blood pressure» who were chronically exposed to occupational stress factors and underwent a routine annual physical examination. In Group 2, there were no recorded episodes of increased BP, clinical, functional, or laboratory signs of endocrine and cerebrovascular pathologies, coronary artery disease, acute infectious/inflammatory diseases, and exacerbation of chronic diseases.

At admission to the hospital, all subjects underwent 24-hr blood pressure monitoring (24hBPM) using a BPlab v. 05.02.00 recorder (Russia) with oscillometric measurements in the decompression phase. Monitoring started at 9–10 am with 15-min intervals between measurements during the day and 30-min intervals at night. The following parameters were analyzed: mean 24-hr night-time and daytime systolic blood pressure (SBP) and DBP, variability of SBP and DBP, SBP and DBP area index, mean 24-hr pulse pressure (PP), night-time dipping, morning surge (MS) and its rate. Data from healthy individuals were used as normal values [3]. Ultrasound examination of the heart and carotid arteries (CA) was performed with a Vivid-9 device. LV end-diastolic dimension (EDD), left ventricular, diastolic posterior wall thickness (LVPWT), interventricular septal thickness, and IMT at the level of carotid bifurcation were estimated. IMT > 0.9 mm was considered a sign of arterial remodeling. LVPW RWT was calculated as:

$$(2 \times LVPWT)/LVEDD.$$

For calculation of relative LVMI, LVMI was normalized to the upper limit of its reference values associated with the respective sex to exclude the influence of the sex-associated factors on the calculation of LV remodeling risks: 115 g/m^2 for male patients, 95 g/m^2 for female patients. The ratio of relative LVMI and LVPW RWT was used to identify individuals with normal heart geometry, concentric remodeling, and concentric and eccentric hypertrophy. Glomerular filtration rate (GFR) was calculated using the CKD-EPI

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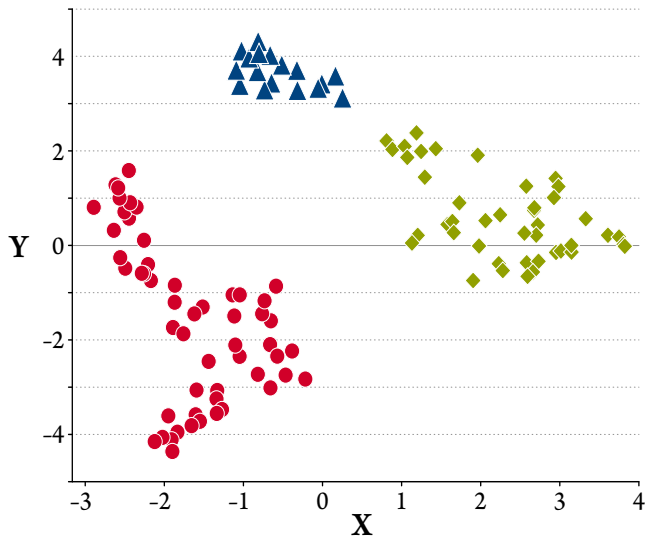
formula. Individuals with glomerular hyperfiltration (GFR >120 ml/min/1.73 m^2) and hypofiltration (GFR < 80 ml/min/1.73 m^2) were identified.

Data processing and analysis were performed in several steps. In the first step, persons with normal BP (n = 38) and MH (n = 121) were selected, based on 24hBPM results, from the group of patients with normal and high normal office blood pressure. To verify hemodynamic phenotypes of MH, we used four criterion factors of 24hBPM (mean daytime and night-time values of SBP and DBP), which were subjected to density-based spatial clustering of applications with noise (DBSCAN) after a preliminary dimensionality reduction using the Uniform Manifold Approximation and Projection (UMAP) method [11, 12]. The Davies-Bouldin index was used to assess the quality of clustering. A value less than 1 indicated that the results were acceptable [11]. The Mann-Whitney U-test was used to analyze differences in 24hBPM values and TOD signs of the compared groups. In the next step of the study, Fisher's exact test and the odds ratio (OR) were used to assess the risk of TOD in various phenotypes of MH and stable hypertension. The Pearson correlation coefficient was used to evaluate linear associations of 24hBPM and TOD. The presence of non-linear correlations was determined by machine learning methods, i.e., random forest [RF] and artificial neural networks [ANN], which were used to develop prediction models. ANN networks were built using a multi-layered architecture with1–6 hidden layers, each containing 7–25 neurons. Models were developed on a training sample containing 75% of all data and verified on a test sample containing 25% of all data). Two metrics were used to assess the accuracy of the models: average relative approximation error (ARAE; if >15% the model was excluded from further analysis) and the coefficient of multiple determination (R2). The latter characterized the informative significance of predictors and its tendency to indicate the increasing accuracy of models. The data were analyzed using R language in RStudio v. 1.0.153. The Neuralnet library was used to build the ANN network [13, 14].

Figure 1. Figure 1. Geometrical clustering in the indicative space of daytime and night-time SBP and DBP in individuals with MH.



The x- and y- axes: complex non-linear transformations of the combination of modern methods of biomedical data processing in units; 1 — systolic/diastolic MH; 2 — isolated systolic MH; 3 — isolated diastolic MH. SBP, systolic blood pressure; DBP, diastolic blood pressure; MH, masked hypertension.

Results

According to the results of 24hBPM, 38 (23.9%) individuals with «true» normotension and 121 (76.1%) patients with MH were identified among subjects with normal office blood pressure. Hemodynamic phenotypes of MH were verified with the use of a combination of modern methods of biomedical data processing (UMAP and DBSCAN), which allowed identifying three clusters with high accuracy (Davies – Bouldin index = 0.72): SDMH – 53 (43.8%) subjects, ISMH – 43 (35.5%), and IDMH – 25 (20.7%) (Figure 1).

The majority of 24hBPM findings in individual MH clusters differed significantly from the control values except for night-time SBP in IDMH, which corresponded to the values in individuals with normal BP (Table 1). Unlike patients with stable hypertension, subjects with different MH phenotypes had both increases and decreases in individual 24hBPM parameters. For example, in individuals with IDMH, the mean 24-hr values of SBP and DBP were significantly lower than in those with stable hypertension, whereas in SDMH these values were significantly higher, except for daytime SBP and DBP. In individuals with ISMH, SBP corresponded to the values of SBP in patients with hypertension, but the DBP values were lower. The findings showed that the SDMH phenotype differs from other subject groups by higher rates of night-time hyperbaric load.

In the second stage of the study, a comparative assessment of the TOD signs was performed in individuals with normal BP, patients with stable hypertension, in the MH group as a whole, and its phenotypes (Table 2). Before the clustering procedures, the MH group significantly differed from the hypertension group in all signs of TOD, but individuals with normal BP differed only in LVPW

Table 1. 24hBPM in individuals with normal BP, MH, and hypertension

Parameter	Normal BP (n=38)	Hypertension (n=125)	MH (n=121)		
			SDMH (n=53)	ISMH(n=43)	IDMH (n=25)
SBP daytime, mm Hg	124 (120–127)	138 (136–141)	143.5 (139–147) p_0<0.0001 p_1=0.051	139 (136–141) p_0<0.0001 p_1=0.83	119 (117–122) p_0<0.01 p_1<0.0001
SBP night-time, mm Hg	106.5 (104–109)	120 (119–123)	126 (122–129) p_0<0.0001 p_1=0.025	119 (117–121) p0<0.0001 p_1=0.23	106 (104–109) p_0=0.86 p_1<0.0001
DBP daytime, mm Hg	75 (71–77)	89 (87–91)	90 (89–92) p_0<0.0001 p_1=0.15	79 (78–81) p_0<0.001 p_1<0.0001	83 (80–86) p_0<0.0001 p_1<0.001
DBP night-time, mm Hg	63 (59–65)	76 (75–78)	79 (77–82) p_0<0.0001 p_1=0.016	66 (63–68) p_0<0.01 p_1<0.0001	70 (68–74) p_0<0.0001 p_1<0.01

Data are expressed as the median and a 95% confidence interval. p_0 corresponds to differences between the MH and normal BP groups, p_1 to differences between the MH and hypertension groups. 24hBPM, 24-hour blood pressure monitoring; BP, blood pressure; MH, masked hypertension; SDMH, systolic/diastolic masked hypertension; ISMH, isolated systolic masked hypertension; IDMH, isolated diastolic masked hypertension.

Table 2. Signs of target organ lesions in individuals with normal BP, MH, and hypertension

Parameter	Normal BP (n=38)	MH (n=159)	SDMH (n=53)	ISMH (n=43)	IDMH (n=25)	Hypertension (n=125)
Relative LVMI, units	0.77 (0.73–0.81)	0.8 (0.77–0.81) p_0=0.035 p_1<0.0001	0.81 (0.79–0.83) p_0=0.0044 p_1=0.005	0.78 (0.73–0.8) p_0=0.54 p_1<0.00001	0.79 (0.73–0.89) p_0=0.19 p_1=0.03	0.88 (0.83–0.91) p_0<0.0001
LVPW RWT, units	0.36 (0.35–0.363)	0.377 (0.36–0.38) p_0=0.008 p_1=0.0044	0.38 (0.36–0.39) p_0=0.009 p_1=0.09	0.375 (0.36–0.39) p_0=0.045 p_1=0.014	0.367 (0.35–0.38) p_0=0.18 p_1=0.034	0.384 (0.383–0.39) p_0<0.0001
GFR, ml/min/1.73 m^2	94.6 (89–100.1)	96.9 (92.25–102.5) p_0=0.43 p_1=0.004	96.93 (86.77–104.8) p_0=0.54 p_1=0.027	109.4 (97.5–111.5) p_0=0.02 p_1<0.0001	87.9 (74.3–94.3) p_0=0.0496 p_1=0.18	88.8 (84.4–95.1) p_0=0.25
IMT, mm	0.78 (0.74–0.83)	0.82 (0.79–0.86) p_0=0.14 p_1=0.005	0.84 (0.8–0.88) p_0=0.06 p_1=0.1	0.775 (0.72–0.83) p_0=0.82 p_1=0.0005	0.9 (0.8–1) p_0=0.03 p_1=0.78	0.9 (0.86 –0.92) p_0=0.0004

Data are expressed as the median and a 95% confidence interval. p_0 corresponds to differences between the MH and normal BP groups, p_1 to differences between the MH and hypertension groups. 24hBPM, 24-hour blood pressure monitoring; BP, blood pressure; MH, masked hypertension; SDMH, systolic/diastolic masked hypertension; ISMH, isolated systolic masked hypertension; IDMH, isolated diastolic masked hypertension; LVMI, left ventricular mass index; LVPW RWT, a relative wall thickness of the left ventricular posterior wall; GFR, glomerular filtration rate; IMT, intima-media thickness.

RWT. The findings suggest that patients with MH are comparable in those indicators to the subjects with normal BP to a greater extent than to patients with stable hypertension. However, comparison of the TOD signs with particular MH phenotypes made it possible to parse these correlations. Thus, the SDMH phenotype differed significantly from individuals with normal BP in relative LVMI and LVPW RWT and corresponded to the individuals with normal BP in GFR and IMT. The comparison of SDMH to stable hypertension revealed that GFR significantly increased, the rate of LV remodeling was lower, and IMT did not change significantly. In the ISMH group, only LVPW RWT and GFR rates were higher than in individuals

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Table 3. Odds ratio target organ damage in patients with hypertension and MH

Parameter	SDMH	ISMH	IDMH	Hypertension
Relative LVMI >1.0 unit	1.8 (0.33–9.7)	1.8 (0.31–10.4)	1.1 (0.1–13)	3.6* (1–25.2)
LVPW RWT >0.42 unit	5.5 (0.93–144)	4.2 (0.6–115.6)	4.4 (0.3–145)	7.7** (1.5–188.3)
GFR, ml/min/1.73 m²				
<80	3.2 (0.8–24.5)	1.5 (0.3–12.7)	6.7* (1.3–57.2)	5.1* (1.4–35.8)
>120	0.4 (0–2.7)	1.5 (0.4–8.3)	0	0.16 (0–1.1)
IMT > 0.9 mm	5.9 (1–152.2)*	3.2 (0.44–88)	8.3 (1–251.4)*	7.1 (1.4–176)*

Data are expressed as odds ratio and 95% confidence interval. *, p<0.05; **, p<0.01. SDMH, systolic/diastolic masked hypertension; ISMH, isolated systolic masked hypertension; IDMH, isolated diastolic masked hypertension; LVMI, left ventricular mass index; LVPW RWT, a relative wall thickness of the left ventricular posterior wall; GFR, glomerular filtration rate; IMT, intima-media thickness.

with normal BP, while the levels of relative LVMI and IMT corresponded to those in individuals with normal BP. Compared to the hypertension group, the subjects with ISMH showed a significant increase in GFR, while the other parameters were significantly lower. In individuals with IDMH, IMT exceeded the control level, and the GFR was below it. In this phenotype, the values of GFR and IMT did not differ from those in stable hypertension, and the rates of relative LVMI and LVPW RWT were significantly lower. Thus, the analysis of quantitative values of TOD in the individual MH groups showed that individuals with normal BP are mostly comparable to those with the ISMH phenotype, and patients with stable hypertension to individuals with the IDMH and SDMH phenotypes.

In the next step of the study, the probability of TOD in various phenotypes of MH was analyzed (Table 3). It was found that patients with hypertension are exposed to a significantly higher risk of TOD than individuals with normal BP. Thus, in this group, the risk of developing eccentric LV hypertrophy increased up to 3.6 times, concentric LV remodeling up to 7.7 times, arterial remodeling up to 7.1 times, and decrease in GFR up to 5.1 times the corresponding parameters in individuals with normal BP. In the group of patients with MH, the risk of TOD was the highest in individuals with IDMH and SDMH. Thus, the maximum risk in patients with IDMH is associated with the development of renal dysfunction (GFR less than 80 ml/min/1.73 m^2; OR 6.7; $p < 0.05$) and arterial atherosclerosis (OR 8.3; $p < 0.05$). With SDMH, the probability of cardiovascular remodeling increases, and the risk of kidney disease decreases versus the IDMH phenotype. Individuals with ISMH are exposed to a higher risk of cardiovascular remodeling and lower risk of developing kidney dysfunction. However, it should be noted that the maximum risk of glomerular hyperfiltration was found in the ISMH group.

Correlation analysis showed that age was associated with TOD more closely than with 24hBPM parameters in all clinical forms of hypertension. For example, significant but low correlations were established only between DBP, DBP area index, SBP, SBP area index, and relative LVMI, as well as, PP and GFR (Table 4). In other cases, no reliable correlations were found, which indicated that most of the correlations were non-linear. Thus, preliminary analysis showed that the patient's age is the basic predictor for the calculation of predicted values of TOD. Machine learning methods (RF, ANN) were used to search for non-linear associations of 24hBPM and TOD, and additional predictors for these models were selected based on the results of OR analysis (see Table 3). Thus, the highest probability of glomerular hypofiltration in IDMH and hyperfiltration in ISMH as established by OR estimation suggested that the mean 24-hr PP could be used as a predictor of GFR. It was the lowest in the first case and the highest in the second case.

This hypothesis was confirmed in the modeling process, during which an increasing accuracy of the models was established when the combination of other factors, such as age and PP, were used (Table 5). The RF model demonstrated a higher accuracy of calculations versus the ANN model. This was confirmed by the values of ARAE in the test sample (7 and 11%, respectively) and by the increase in RF R2 from 0.49 to 0.76 compared to the increase in ANN R2 from 0.33 to 0.42.

The highest IMT rate was found in individuals with IDMH, and the lowest in individuals with ISMH, which

suggested a correlation between this parameter and the levels of DBP. This hypothesis was tested using the RF and ANN models, which showed the highest accuracy of IMT prediction when factors describing age, daytime DBP, and night-time DBP were combined in one model. A two-fold increase in R2 with combination of these factors confirmed their predictive significance. The analysis of OR associated with relative LVMI showed the most significant probability of LV remodeling in patients with stable hypertension, which was characterized by hyperbaric deviations of the 24-hr BP profile with simultaneous increases in SBP and DBP. For this reason, in addition to age, SBP and DBP were used as predictors in the relative LVMI prediction models for different periods of the day. This made it possible to increase R2 from 0.26 to 0.66 in the RF model and from 0.16 to 0.48 in the ANN model. At the same time in the test sample, ARAE did not exceed 9% in these models. Testing of potential predictors in the modeling of LVPW RWT showed that night-time DBP, SBP MS, and DBP MS had the highest informative significance, and their combination of the RF and ANN models increased R2 up to 3.5 times.

Discussion

MH appears to be a poorly diagnosed, latent clinical condition that predisposes patients to subclinical TOD and increased risk of CVCs [5]. In patients with MH, CVCs are reported up to 2.5 times more often than in individuals with normal BP and almost as often as in patients with stable hypertension [6]. The rate of transformation of MH into stable hypertension within 5 yr is 35–75% [3]. These data strongly argue the benefits of active identification of patients with MH, especially in the high-risk population that also includes individuals who are exposed to chronic occupational stress. In our study, the high prevalence of MH among the subjects (76.1%) showed that adverse factors of the work environment have a significant impact on the development of this clinical condition. Several studies showed that stress-induced MH involves a prolonged response of BP regulatory systems, such that the effects persist for a long time and are characterized by the hyperbaric load on the target organs [8].

The MH phenotypes were identified based on the results of the clustering of 24hBPM rates to assess the similarities and differences of particular phenotypes with stable hypertension and normal BP. The higher levels of SBP and DBP in 24hBPM at bedtime and their comparable values during waking hours in patients with hypertension indicated a relative nature of the categorization of subjects and a possibility of similar

Table 4. Correlation of age and 24hBPM with signs of TOD

Parameter	Relative LVMI	LVPW RWT	GFR	IMT
Age	0.41***	0.25***	-0.58***	0.5***
SBP, daytime	0.18**	0.07	0.2**	0
SBP, night-time	0.21***	0.12*	0.13*	0.09
SBP, daytime	0.31***	0.15*	-0.116	0.18**
DBP, night-time	0.33***	0.23***	-0.14*	0.23***
PP, daytime	-0.09	-0.07	0.38***	-0.2**
SBP MS	0.03	-0.08	0.1	-0.03
DBP MS	0	-0.12	0.12	0

Other parameters of 24hBPM are not specified due to near-zero correlations. *, p<0.05; **, p<0.01; ***, p<0.001. 24hBPM, 24-hour blood pressure monitoring; TOD, target organ damage; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; SBP MS, morning surge in systolic blood pressure; DBP MS, morning surge in diastolic blood pressure; PAD–the amount of morning increase in diastolic blood pressure; LVMI, left ventricular mass index; LVPW RWT, a relative wall thickness of the left ventricular posterior wall; GFR, glomerular filtration rate; IMT, intima-media thickness.

Table 5. Comparative analysis of the accuracy of the target organ damage prediction models using the coefficient of multiple determination, R2

Parameter	Predictor	RF	ANN
GFR	Age	0.49	0.33
	PP	0.25	0.146
	Age + PP	0.76	0.42
IMT	Age	0.34	0.25
	SBP, daytime	0.21	0.1
	DBP, night-time	0.28	0.05
	Age + daytime DBP	0.63	0.41
	Age + night-time DBP	0.56	0.36
	Age + daytime DBP + night-time DBP	0.65	0.5
Relative LVMI	Age	0.26	0.16
	SBP, daytime	0.28	0.29
	DBP, night-time	0.23	0.24
	Age + SBP daytime	0.61	0.4
	Age + daytime DBP	0.54	0.3
	Age + night-time DBP	0.57	0.3
	Age + DBP night-time + SBP daytime	0.66	0.48
LVPW RWT	Age	0.15	0.067
	DBP, night-time	0.18	0.057
	Age + night-time DBP	0.41	0.104
	Age + night-time DBP + SBP MS + DBP MS	0.53	0.21

RF, random forest; ANN, artificial neural networks; GFR, glomerular filtration rate; TIM - intima-media thickness; LVMI, left ventricular mass index; LVPW RWT, a relative wall thickness of the left ventricular posterior wall; PP, pulse pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure; SBP MS, morning surge in systolic blood pressure; DBP MS, morning surge in diastolic blood pressure.

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risks of TOD. However, the results of OR analysis showed that MH phenotypes are differentiated by the probability of TOD. Thus, IDMH was more aggressive than other phenotypes in terms of vascular remodeling and kidney dysfunction, and SDMH was more aggressive in terms of LV remodeling. At the same time, ISMH was characterized by the highest risk of glomerular hyperfiltration. Data on the association of hemodynamic MH phenotypes and severity of TOD presented in the scientific literature are contradictory. For example, the increase in carotid IMT was shown to be more pronounced in ISMH than in IDMH [5]. In another study, the increase in IMT was more associated with an isolated increase in DBP [7]. At the same time, our study showed that the risk of kidney disease and arterial atherosclerosis was higher in individuals with IDMH than in patients with stable hypertension. These data confirm the findings of other studies on the increasing prevalence of subclinical TOD in a long history of MH and its higher levels in comparison to stable hypertension [4, 10].

Machine learning methods are some of the most used technologies of artificial intelligence, with a steadily increasing role in clinical medicine and healthcare [14]. Over the past decade, various machine learning technologies were used to predict the development and outcomes of CVCs: support vector machines, decision trees, RF, adaptive boosting, naive Bayes classifier, ANN, and others. [15, 16]. The accuracy of prediction in these cases depended on the modeling methods, the set of input data, quality of predictors, and hypotheses. In this paper, we chose RF and ANN for the prediction of TOD based on the results of previous studies showing the acceptable accuracy of these methods in various areas of clinical cardiology [12]. The highest quality of the selection of a predictor used in the construction of models was insured by a multi-step procedure of identifying primary (age) and additional (24hBPM parameters) predictors and by the results of OR analysis. Thus, the highest rates of glomerular hyper- and hypofiltration in ISMH and IDMH were associated with the levels of PP, which was used as a predictor and significantly improved the accuracy of modeling. Similar approaches were employed in the prediction models for TOD of different localization. The highest accuracy of the RF and ANN models was insured by cross-validation in the test sample, which allowed selecting only variants with ARAE <15%. Thus, the use of machine learning methods makes it possible to optimize risk stratification in patients with various clinical variants of hypertension and correspondingly develop personalized prevention and treatment programs.

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