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New predictors of self-reported adherence measured with Morisky Medication Scale and blood pressure control in Romanian hypertensive patients – SEPHAR IV

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Abstract

This paper aims to find new predictors of poor antihypertensive treatment adherence in the Romanian adult hypertensive population. Six hundred eighty hypertensive subjects identified in the SEPHAR IV survey were evaluated by a study questionnaire, including a 4-item Morisky Medical Adherence Score (MMAS-4), BP and anthropometric measurements, and laboratory workup. BP control was defined as <140/90 mmHg at both study visits (4 days apart). According to the MMAS-4 score, adherence was considered low (3-4p), moderate (1-2p) and high (0p). Statistical analysis was performed with SPSS Statistics 18.0 software at a significance level of p≤0.05. Of the total 680 hypertensive subjects, 461 were receiving antihypertensive treatment. According to BP control, treated hypertensives were further divided into two groups – controlled (181 subjects, 39.2%) and uncontrolled HTN (280 subjects, 60.8%). The mean age was 63.25±11.65 years and the female gender was more prevalent (61.1%). Distribution regarding residence was balanced (urban area – 51.5%). Low antihypertensive treatment adherence was recorded in 46 subjects representing 9.9% of the total group, with a significantly higher rate among uncontrolled hypertensive subjects [35 subjects (12.5%) *vs.* 11 subjects (6.1%); p=0.024]. Total cholesterol (AUC=0.659; CI=95%: 0.557–0.761; p=0.005) and LDL cholesterol (AUC=0.645; CI=95%: 0.537–0754; p=0.011) were statistically significant predictors of low treatment adherence. The MMAS-4 is a readily available tool that can be used in daily clinical practice. The lipid profile can be used to identify less adherent HT patients. Future research should establish a metabolic profile of the nonadherent patient and focus on developing strategies to increase adherence.

Keywords: hypertension, medication adhesion questionnaire, nonadherence, lipid profile.

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Introduction

Despite modern and evolving therapies, hypertension (HTN) still represents a major worldwide health problem and remains a leading cause of ischemic heart disease, heart failure, stroke, chronic kidney disease and vascular dementia [1]. A systematic review of population-based studies from 90 countries evaluated the global prevalence of HTN to be 31.1% among adults over 20 years of age [2], and current projections estimate a 30% increase in its prevalence by 2025 [3]. HTN is more prevalent in low and middle-income countries in which levels of awareness, treatment and control are lower compared to high-income countries [4]. HTN has a complex physiopathology in which old age, genetic factors, unhealthy lifestyles such as lack of physical activity, male gender, excess sodium intake and obesity are primary factors in the development of high blood pressure values [5].

Despite constantly emerging modern therapies, long-term adherence to medication remains a substantial challenge among patients with HTN. This aspect was highlighted in 2003 by the World Health Organization [6], and suboptimal adherence remained constant during the last decade [7]. A persistent gap remains between guideline recommendations *versus* real-world blood pressure (BP) control rates. The National Health and Nutrition Examination Survey (NHANES) conducted between 1999 and 2018 shows that the optimal BP control (defined as resting BP values <140/90 mmHg) increased from 31.8% to 53.8% in 2014 but later declined to 43.7% in 2018 [8]. BP control rates significantly vary with the country's economic status. As such, while high-income countries report BP control in up to 50% of adult hypertensives, low-middle-income countries have a significantly lower BP control rate – 25% [9]. Global adherence to antihypertensive medication is estimated to be between 30% and 50% [10], with significant inter-country variations: 38.8% in the United States *versus* 85% in Australia [11]. Treatment adherence in HTN is extremely challenging partly due to the asymptomatic nature of the disease [12]. However, inadequate BP control leads to potentially severe target organ damage. For this reason, both European and AHA guidelines emphasize the need to address drug adherence as a major issue in HTN management. The 4-item Morisky Medication Adherence Scale (MMAS-4) is a standardized questionnaire that evaluates treatment adherence, initially designed only for HTN subjects [13].

The scope of our study was to evaluate HTN prevalence and BP control in subjects with previously diagnosed HTN, to evaluate medication adherence and to identify predictors of low treatment adherence in order to optimize prevention strategies and HTN management in Romania.

Material and methods

SEPHAR IV is a cross-sectional multicentric survey conducted on a representative sample of the adult Romanian population (1477 subjects, 18 to 80 years). It encompasses two visits with the following components: completing the study questionnaire, BP and anthropometric measurements, and collection of blood and urine samples.

The study protocol and its implementation procedures were supervised by the project reviewers and approved by the Local Ethics Committee. All the participants included in the study signed written informed consent for all elements of the evaluation: questionnaire, BP and anthropometric measurements and laboratory workup.

Statistical analysis

Statistical analysis was performed with SPSS Statistics 18.0 software at a significance level of $p \leq 0.05$. A descriptive analysis (means, medians, standard deviation and range for continuous data and frequency analysis for categorical data) was performed for all the target variables. Primary indicators (minimum, maximum, frequency), mean value indicators (mean, median), and dispersion indicators (standard deviation, standard error, confidence interval for the mean) were used for descriptive statistical analysis. The Skewness test ($-2<p<2$) was used to validate the normality of the value series for continuously examined variables. T-student test and F test (ANOVA) were used for quantitative variables. The chi-square test and Kruskal-Wallis correlation were used for qualitative variables. A receiver operator characteristic (ROC) curve was plotted to analyze the sensitivity/specificity balance.

Study questionnaire

The study questionnaire consisted of 11 items regarding socio-demographic data, 8 items regarding the medical history (including past medical history and family history) and risk factors, 15 items regarding knowledge about cardiovascular disease and prevention, 7 items regarding medication and treatment adherence and 8 items for sleep disorders and sleep apnea. The final part of the questionnaire included items to be completed with the results of anthropometric and BP measurements and the details of blood and urine sample collection.

The measure of adherence was the MMAS-4. It is a questionnaire that helps identify poor adherence to antihypertensive treatment. This method has been validated for several chronic diseases,

although it was initially developed by Morisky, Green and Levine to assess compliance with medication in patients with HTN. It includes four questions, interspersed in a cordial way, during a conversation about the illness: 1. Do you ever forget to take the drugs for your illness?; 2. Are you ever careless regarding to taking your medication?; 3. Do you stop taking your medication when you feel well?; 4. If you ever feel ill, do you quit your treatment [14, 15]. According to MMAS-4 score, adherence was considered low (3-4), moderate (1-2) and high (0).

BP measurements

BP measurements were taken using an automatic BP measuring device certified by e STRIDE BP Scientific Advisory Board. The use of other devices was forbidden. Before performing BP measurements, arm circumference was measured (using a tailor's tape measure with a maximum deviation of 0.5 cm at the widest level of the arm). A standard cuff was used in patients with an arm circumference ≤32 cm, and a larger cuff for patients with an arm circumference >32 cm. BP was initially measured bilaterally. Two additional BP measurements were performed at the arm in which the highest BP was originally recorded, and the average of these two measurements was recorded. All measurements were performed at least 1 minute apart, following current ESC Hypertension guidelines [16]. HTN was defined as SBP ≥140 and/or DBP ≥90 mmHg, previous diagnosis of HTN or current BP lowering treatment. Adequate HTN control was defined as a BP value <140/90 mmHg upon clinical examination.

Anthropometric measurements

The anthropometric measurements were made using the following devices:

- Weight – using an approved electronic scale, with a maximum deviation of 0.1 kg, with the subject wearing light clothes (without outer garments and without shoes);
- Height – using a portable measuring device with a maximum deviation of 0.5 cm;
- Waist circumference, hip circumference, neck circumference and arm circumference – using a tailor's measuring tool, with a maximum deviation of 0.5 cm.

Obesity was defined as body mass index (BMI) ≥30 kg/m^2 [17].

Collection of blood samples

Prior to taking a blood sample, the nurse made sure that the subject had not eaten for the past 8–14h or that he/she had not drunk any sweet drinks or drinks of any caloric value in the past 8–14h. The nurse used a preassembled blood draw kit containing a 22G needle, a vacutainer kit, 8 ml vacuum type tube with separator gel for biochemistry, a 2 ml vacuum type tube with EDTA anticoagulant for glycated hemoglobin and a 6 ml vacuum type tube with sodium fluoride glycolytic inhibitor for blood glucose.

The nurse performed the following actions: confirmed the subject's personal data, took samples of venous blood with the subject in a sitting position with a maximum duration of stasis of 30 seconds, transferred urine from the initial receptacle

Table 1. Descriptive statistics of demographical data in patients with or without HTN.

Parameters	All cases n=1477	HTN n=680	Non HTN n=797	P-value for Chi-Square Tests
Demographical data				
Age years; median/interval	51.67 53/20–95	60.74 63/22–95	43.93 44/20–85	0.001
≥50 y	859 (58.2%)	559 (82.2%)	300 (37.6%)	0.001
Female	885 (59.9%)	379 (55.7%)	506 (63.5%)	0.002
Urban	808 (55.1%)	340 (50.4%)	468 (59.0%)	0.001
Education				
Without studies	16 (1.1%)	8 (1.2%)	8 (1.0%)	0.001
Primary	138 (9.3%)	96 (14.1%)	42 (5.3%)	
Secondary	711 (48.1%)	390 (57.4%)	321 (40.3%)	
High school	612 (41.4%)	186 (27.4%)	426 (53.5%)	

to the vacuum transport tube, filled out the referral form to the laboratory (filling in the time and date of sample collection), marked all the test tubes with stickers containing the subject's individual study code, prepared the material for transportation and transported the material to the central laboratory.

Laboratory testing was carried out after the materials were delivered to the central laboratory. The test results were electronically delivered to the study organizers, who introduced these data into the database.

Results

The study investigators evaluated a total number of 1477 subjects, 797 normotensives and 680 with newly diagnosed or previously known HTN, which shows an HTN prevalence of 46% (Table 1). The mean age was significantly higher in HTN patients compared to the non-HTN group (60.74 *vs.* 43.93 years; p=0.001) (Table 1). 59.9% of the subjects were represented by female gender (55.7% *vs.* 63.5%; p=0.002), and 55.1% had a residence in urban areas (50.4% *vs.* 59.0%; p=0.001).

The HTN group included 680 subjects, with 461 receiving medical treatment. According to BP control, treated patients with a prior diagnosis of HTN were further divided into two groups – controlled (181 subjects, 39.2%) and uncontrolled HTN (280 subjects, 60.8%).

The mean age was 63.25±11.65 years old, and the female gender was more prevalent (61.1%). Distribution regarding residence was balanced (urban area 51.5%). Most participants had secondary education, most of the studied group had medical insurance (more than 98%), and more than half knew the normal BP range. 43.2% of the patients were smokers, and the mean family income was 482.70±75.38 Euro (Table 2).

Table 3 illustrates adherence rates in patients with current antihypertensive treatment in the uncontrolled and controlled subgroups. High adherence was significantly associated with controlled HTN and low adherence with uncontrolled HTN.

The vast majority of the studied group was represented by subjects >50 years old (88.2%). Although adherence scores were higher in older adults,

Table 2. Descriptive statistics data in patients with uncontrolled status of HTN.

Parameters	Status HTN		P-value for Chi-Square Tests
	Uncontrolled (n=280)	Controlled (n=181)	
Demographical data			
Gender			
Male	116 (41.5%)	77 (42.5%)	0.256
Female	164 (58.5%)	104 (57.5%)	
Residence			
Rural	97 (50.8%)	109 (46.8%)	0.336
Urban	93 (49.2%)	124 (53.2%)	
Education			
No education/primary	48 (17.1%)	23 (12.7%)	
Secondary	156 (55.7%)	109 (60.2%)	0.894
High school	76 (27.1%)	49(27.1%)	
Smoker status			
Smoker	53 (18.9%)	26 (14.4%)	0.643
Non smoker	227 (81.1%)	155 (85.6%)	
Medical status			
Knows the normal values of BP	188 (67.1%)	117.13 (64.6%)	0.497
Medical insurance	265 (94.6%)	179 (98.9%)	0.876

Table 2. Continued.

Parameters	Status HTN		P-value for Chi-Square Tests
	Uncontrolled (n=280)	Controlled (n=181)	
Treatment			
ACE inhibitors	60 (21.4%)	36 (19.8%)	0.634
ARBs	55 (19.8%)	28 (15.1%)	0.140
B-blockers	124 (45.2%)	92 (50.0%)	0.245
CCBs	43 (15.3%)	24 (13.1%)	0.440
Fixed dose combination	54 (19.4%)	26 (21.2%)	0.578
Diuretics	72 (25.8%)	43 (23.8%)	0.584

ACE – angiotensin-converting enzyme; ARBs – angiotensin receptor blockers; CCBs – calcium channel blockers.

Table 3. Adherence rates in treated HTN patients.

Morisky score	All cases (n=461)	Uncontrolled (n=280)	Controlled (n=181)	P-value
High adherence	246 (53.4%)	141 (50.4%)	105 (58%)	
Moderate adherence	169 (36.7%)	104 (37.1%)	65 (35.9%)	**0.024**
Low adherence	46 (9.9%)	35 (12.5%)	11 (6.1%)	

the association did not reach statistical significance (p=0.231) (Figure 1).

More than half of the study group was obese (56.9%). Weight and BMI were higher in HTN subjects with moderate adherence scores (Table 4).

Total cholesterol (p=0.024) and low-density lipoprotein cholesterol (LDL cholesterol) (p=0.01) were significantly higher in patients with low adherence to antihypertensive treatment (Table 5).

Total cholesterol (AUC=0.659; CI=95%: 0.557–0.761; p=0.005) and LDL cholesterol (AUC=0.645; CI=95%: 0.537–0754; p=0.011) were statistically significant predictors of low treatment adherence (Figure 2, Table 6).

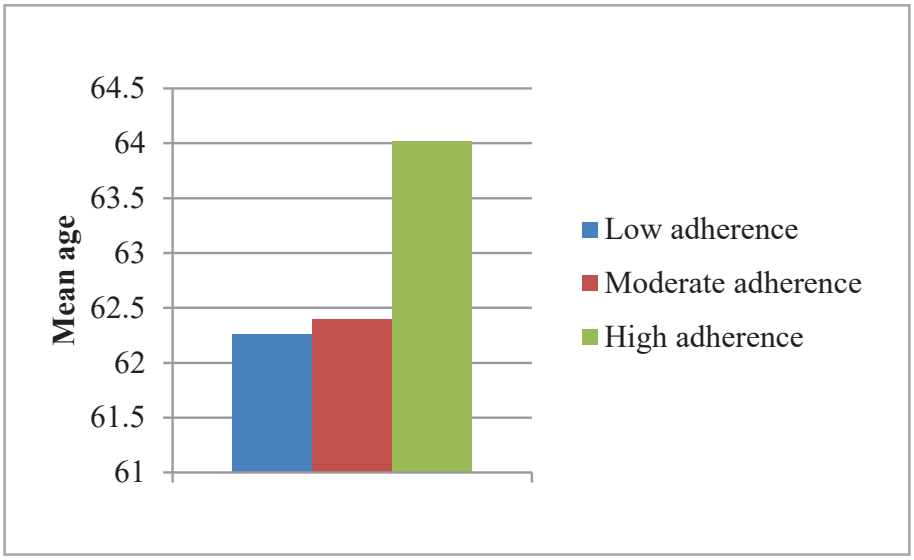

Figure 1. Mean age by Morisky score in HTN patients.

Table 4. Descriptive statistics of anthropometric data in patients with treated HTN by Morisky score.

Anthopometric Parameters	Adherence			F ANOVA test
	High	Moderate	Low	
Weight (cm)	83.49±16.09	87.72±16.72	81.09±14.33	**0.003**
Height (kg)	165.13±9.93	166.34±9.70	162.78±9.69	0.050
BMI (kg/m²)	30.60±5.26	31.76±5.66	30.62±4.97	**0.047**
Waist circumference (cm)	103.52±14.20	105.40±12.77	104.87±13.79	0.284
Hip circumference (cm)	110.01±10.84	110.49±10.21	109.77±13.41	0.869
Neck circumference (cm)	39.18±5.14	39.82±4.93	39.02±3.99	0.293
Arm circumference (cm)	31.27±4.64	31.36±4.15	31.06±3.63	0.912

BMI – body mass index.

Discussion

The main results of our study are that the prevalence of HTN is high and HTN control in Romania still needs to be improved. A major cause of failing to achieve guideline-recommended BP targets in Romania is poor patient adherence, as shown by Morisky questionnaire results.

Adherence to BP-lowering drugs varies widely between different countries due to differences in study design, target population subsets and methods of evaluating medication adherence [18, 19]. More than half of our study group presented a high level of adherence (54.7%), which is quite low compared to other reports in high-income countries [20]. Nonetheless, other studies reported even lower adherence rates [21, 22].

A study that included 89 countries in 2018 showed that 60% of treated HTN subjects had controlled BP [23]. These results are similar to our investigation, where 58.1% of the studied population were controlled HTN patients. A previous study reported that high adherence subjects are more likely, with 45%, to achieve BP control when compared to those with low or medium adherence [24]. Our analysis supports these results, as high treatment adherence scores were associated with better BP control. Also, the link between adherence and outcomes was proved in many pieces of research [25, 26].

Gender can cause, in many situations, inequities regarding health [27]. The impact of gender on treatment adherence is insufficiently studied. A previous study conducted in the United States shows that male subjects present higher adherence rates to HTN treatment than female patients [28]. However, in our analysis, gender did not significantly influence adherence scores or HTN status (controlled or uncontrolled). However, a previous analysis of 1406 subjects showed that HTN control was significantly associated with old age and female gender

Table 5. Descriptive statistics of laboratory parameters in patients with treated HTN by Morisky score.

Laboratory Parameters	Adherence			F ANOVA test
	High	Moderate	Low	
Cholesterol (mg/dl)	198.23±50.54	194.71±43.75	220.18±44.49	**0.024**
Triglycerides (mg/dl)	133.77±70.41	134.33±89.19	137.32±55.62	0.974
HDL (mg/dl)	52.22±13.47	52.92±13.24	49.82±11.78	0.491
LDL (mg/dl)	128.76±45.48	124.90±44.64	151.88±49.52	**0.010**
Creatinine (mg/dl)	0.83±0.24	0.80±0.17	0.80±0.27	0.449
Uric acid (mg/dl)	6.05±1.63	5.87±1.48	5.57±1.70	0.573
Potassium (mmol/l)	4.56±0.54	4.58±0.51	4.85±0.57	**0.050**
HbA1c (%)	6.06±1.04	5.89±0.90	5.81±0.63	0.189
Glucose (mg/dl)	111.82±29.58	107.48±30.81	102.03±12.85	0.157

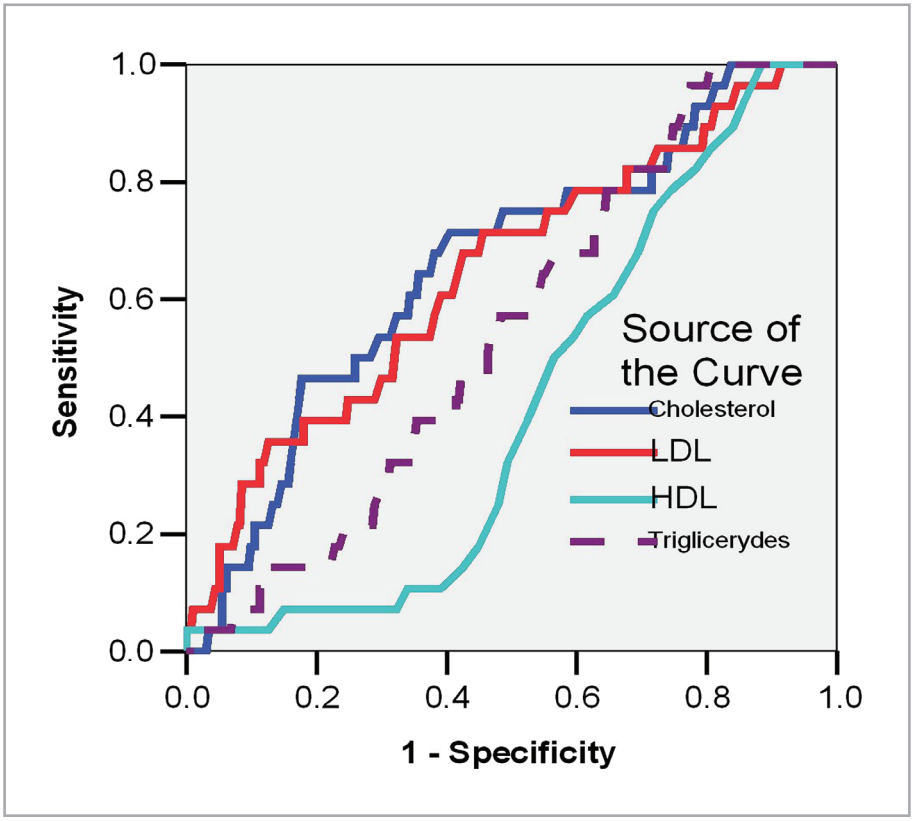

Figure 2. ROC curve. Biological predictors of low adherence.

[29]; in our analysis, age did not influence BP control rates. Similar to our findings, a previous meta-analysis suggested that the relationship between gender, age and level of adherence is weak [30].

Patient education is an important step in HTN treatment. Subjects living in rural areas tend to have lower income, a lower education level and more difficulties accessing healthcare services, which significantly decreases treatment adherence rates [31]. Contrary to previous reports [32, 33], our analysis showed no significant association between treatment adherence and place of residence, which could suggest that the health-related urban-rural gaps have gradually narrowed.

BMI is associated with increased mortality and higher cardiovascular risk [34]. Obesity can also influence drug pharmacodynamics. Lifestyle modifications such as a healthy diet, weight reduction and regular physical activity reduce not only systolic and diastolic BP but also prevent HTN-associated cardiovascular complications [6, 35]. Care providers should be focused on educating the patient and encouraging lifestyle changes, in which weight reduction must be a specific target. Although in our study, HTN subjects with moderate adherence presented slightly higher BMI values compared to high adherence patients, this finding has a little clinical impact as both values correspond to grade I obesity.

Table 6. Biological predictors of low adherence.

The result variable	AUC	Standard error	Sig.	Confidence Interval 95%
Cholesterol	0.659	0.052	**0.005**	0.557–0.761
LDL-cholesterol	0.645	0.055	**0.011**	0.537–0.754
HDL-cholesterol	0.423	0.044	0.180	0.337–0.510
Triglycerides	0.547	0.047	0.410	0.455–0.640

The test result variable(s): Cholesterol, LDL, HDL, Triglicerydes have at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased. a – Under the non-parametric assumption; b – Null hypothesis: true area=0.5.

Previous studies that addressed the issue of treatment adherence focused on demographic characteristics, the number of drugs prescribed, self-regulation theories, educational level, and drug-related adverse effects. To the best of our knowledge, this is the first study that showed an association between low treatment adherence and lipid profile in HTN patients. The close correlation between low adherence to HTN treatment and atherogenic dyslipidemia can be interpreted as a lack of regularity and consistency in terms of compliance with the recommended medical treatment. The same inconsistency probably occurs in the situation of treating dyslipidemia or HTN-associated dyslipidemia. In addition, a lack of adherence can also be manifested in non-compliance regarding lifestyle modifications, such as a healthy diet, constant physical effort, and maintaining adequate body weight, all of these creating a healthy lifestyle. Patients who suffer from obesity and dyslipidemia are also less likely to have high adherence rates to pharmaceutical and non-pharmaceutical treatment options. On the other hand, low adherence to HTN treatment in dyslipidemic subjects could be due to a higher degree of cerebral lacunarism, an HTN-related cognitive impairment, which could impact treatment adherence.

The MMAS-4 is a readily available tool that can be used in daily clinical practice to assess adherence to an antihypertensive regimen in a patient with poorly controlled BP values. In patients with poor adherence scores, physicians should focus more on patient education, lifestyle changes and increasing treatment adherence before deciding to change BP treatment. The use of single-pill combinations of BP-lowering drugs is associated with better adherence. According to our results, patients with poor adherence have higher total cholesterol and LDL cholesterol values. A polypill of a statin and a BP-lowering agent could be useful in increasing individual compliance and improving long-term cardiovascular prognosis.

The results of our research underline the clear need for new interventions in order to improve HTN adherence in Romania and show that the lipid profile can be used to identify specific groups of HTN patients who are likely to have low compliance. Therefore, future research should focus on defining the clinical and biological profile of the nonadherent subject and the development of strategies that increase adherence.

One of the limitations of our study is represented by the indirect method for the evaluation of medication adherence.

However, MMAS-4 is a validated questionnaire, and it was applied in a standardized way by trained medical staff.

In Romania, BP control is still far from adequate, regardless of lifestyle changes or effective medications. As HTN control requires a special multimodality approach, healthcare providers should improve communication and should include it in clinical practice adherence assessment.

Conclusion

This is the first study in which lipid profile is proven to be a predictor for adherence to antihypertensive treatment. The MMAS-4 is a readily available tool that can be used in daily clinical practice. The lipid profile can be used to identify less adherent HTN patients. Future research should establish a metabolic profile of the nonadherent patient and focus on developing strategies to increase adherence.

Conflict of interest

The authors declare no conflict of interest.

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