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A simple score to screen for isolated ambulatory hypertension in older adults. Development and validation

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ABSTRACT

Introduction and objectives: Masked or isolated ambulatory hypertension (IAH), a poor-prognosis condition, can be diagnosed with ambulatory blood pressure monitoring (ABPM), but ABPM is not available in many clinical practices. We developed and validated a score to screen for IAH among older adults, where limited information is available.

Methods: A total of 645 community-dwelling adults ≥ 65 years from the Seniors-ENRICA-2 cohort (derivation sample) and 327 from the Seniors-ENRICA-1 cohort (external-validation sample), with untreated casual BP < 140/90 mmHg (mean of the last 2 of 3 BP) were examined. Probabilities of having IAH (mean 24-h ambulatory BP ≥ 130/80 mmHg) were calculated with a multivariable model (with sex, age, and clinical variables). Beta coefficients were used to allocate points to each variable in an IAH score (range, 0–12).

Results: Participants' mean age was 70.8 years (46.7% men); 19.7% had IAH. Allocated score-points were: male sex (1 point), age ≥ 80 (2 points), body-mass index (2 points if 25–29; 3 if ≥30 kg/m^2), the first BP measurement (2 points if ≥140/90 mmHg), and the mean of the second and third BP (2 points if 120–129/80–84; 4 if 130–139/85–89). Probabilities of having IAH for scores of 6, 7, 8, 9, or ≥10 points were 25%, 35%, 47%, 59%, and 72%, respectively. Area-under-the-ROC curve was 0.80 for the derivation and 0.73 for the validation-sample. Two subjects at high risk of IAH (>8 points) and 3 at middle risk (≥6) needed to undergo ABPM to detect 1 IAH case.

Abbreviations: MH, masked hypertension; IAH, isolated ambulatory hypertension; BP, blood pressure; ABPM, ambulatory blood pressure monitoring; NND, number needed to detect.

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Conclusions: A simple score with 4 routine variables performed well identifying IAH in older adults. For high scores, using ABPM for diagnosing IAH was very size-efficient.

Una escala sencilla para identificar la hipertensión ambulatoria aislada en adultos mayores. Desarrollo y validación

Palabras clave:
Hipertensión
Monitorización ambulatoria de la presión arterial
Hipertensión enmascarada
Predicción
Personas mayores

RESUMEN

Introducción y objetivos: La hipertensión enmascarada o ambulatoria aislada (HAA) se puede diagnosticar con monitorización ambulatoria de presión arterial (MAPA), pero no está disponible en muchas clínicas. Desarrollamos una puntuación sencilla para detectar HAA en adultos mayores donde la información es limitada.

Métodos: Se examinó a 645 adultos ≥ 65 años de la cohorte poblacional Seniors-ENRICA-2 (muestra de derivación) y 365 de la cohorte Seniors-ENRICA-1 (validación externa), con presión arterial (PA) casual no tratada < 140/90 mmHg (media de las últimas 2 de 3 mediciones). Se calcularon las probabilidades de tener HAA (PA media de 24 h ≥ 130/80) con un modelo multivariable, cuyos coeficientes beta se usaron para asignar puntos a cada variable en una escala de puntuación (rango, 0-12).

Resultados: Muestra con edad media de 70,8 años (46,7% varones); 19,7% tenían HAA. Los puntos asignados fueron: varón (1 punto), edad ≥ 80 (2 puntos), índice de masa corporal (2 puntos si 25-29; 3 si ≥ 30 kg/m^2), primera medición de PA (2 puntos si ≥ 140/90 mmHg), media de segunda y tercera PA (2 puntos si 120-129/80-84; 4 si 130-139/85-89). Las probabilidades de tener HAA para puntuaciones de 6, 7, 8, 9 o ≥10 puntos fueron 25, 35, 47, 59 y 72%, respectivamente. El área bajo la curva ROC fue 0,80 para la muestra de derivación y 0,73 para la de validación. Para detectar un aso de HAA se necesitaría examinar con MAPA a 2 personas con alto riesgo (>8 puntos).

Conclusiones: Una puntuación simple con 4 variables rutinarias tuvo buen rendimiento para identificar HAA en adultos mayores. Para puntuaciones altas, usar MAPA para diagnosticar HAA resultó muy eficiente clínicamente.

Introduction

Masked hypertension (MH), i.e., elevated blood pressure (BP) when measured outside but not inside clinic, is rather frequent and with ominous prognosis.[1–6] Detection of this condition can be done by self-measured BP monitoring at home during several days, or ambulatory BP monitoring (ABPM), typically for 24 h/day and, thus, including such an important BP indicator as nighttime BP.[1–4,7,8]

ABPM is not available in many clinical practices, even in high-income countries.[9] Therefore, identification of factors associated with MH is important to select those individuals at higher risk for this condition. Sociodemographic characteristics (sex, age), morbidities (diabetes, obesity, depression, insomnia), clinic BP, and unhealthy behaviors (smoking, sedentariness) have been shown associated with MH.[1–4,6,10–17] However, only a few studies have estimated the probability of having MH based on simple, easy-to-use in practice, predictors. One study suggested that adding some variables (sex and work outside the home) to office BP at the prehypertensive range did not improve identification of MH,[13] and another study found that a clinic BP index provides a useful approach to identifying candidates for MH.[17]

In this study we use the term "isolated ambulatory hypertension" (IAH) as a proxy for MH, since casual clinic BP was unavailable in our cohort, instead we used observer-measured casual BP at home; home BP levels are similar to office BP in the lower BP range (both 120 and 130 mmHg),[18] and by definition MH patients are not hypertensive on casual BP. We use IAH as a more restrictive concept than MH, since it would include those subjects who are masked of their ambulatory hypertension at home, and perhaps some of them also in office. Therefore, we aimed to (a) develop and validate a score based on simple clinical variables, including BP, to identify patients most likely to have IAH and, thus, most suitable for undergoing ABPM; and (b) calculate the size-efficiency of performing ABPM according to the subjects IAH score, i.e., the number of subjects at a given risk score needed to be examined with ABPM to diagnose 1 case of IAH. We focused specifically on older people living in the community, a population group where MH is frequent, at high risk of hypertension-related vascular events, and clinically challenging (e.g., may have important therapeutic implications).[1,19]

Methods

Study design and population

Seniors-ENRICA-2is a cohort of 3273 community-dwelling individuals, aged 65–94 years, residing in Madrid, selected in January 2016–December 2017 by sex- and district-stratified random sampling of all individuals holding a national healthcare card. Since all people residing in Spain are entitled to free healthcare, the list of cardholders closely approximates the entire resident population of Madrid.[20] Data were collected in 3 stages by personnel trained in the study procedures: a phone interview to obtain sociodemographic, lifestyle, and morbidity data; a home visit to collect blood samples; and another home visit to perform physical examination (including BP measurements).

As derivation sample to calculate the IAH score, we used data from 2394 subjects who accepted to undergo ABPM and had successful readings. As external-validation sample we used data from the Seniors-ENRICA-1 cohort, comprising 1047 community-dwelling participants aged ≥ 60 years across Spain, assessed in October 2012 to October 2013 following similar data collection to Seniors-ENRICA-2 cohort, and with valid ABPM as done by other studies.[2,21,22]

Study participants provided written informed consent, and the Clinical Research Ethics Committee of Hospital Universitario La Paz, Madrid, approved the Seniors-ENRICA-2 and Seniors- ENRICA-1 cohort-studies. This manuscript follows the recommendations of the TRIPOD statement (Table 1 of the supplementary data).[23]

Study variables

We used available data on a number of variables associated with MH,[1–4,6,10,11,17] and also used opinion of experts in MH in our research team. First, we considered sex, age, and self-reported health behaviors, including tobacco smoking (current-, ex- or never-smokers), sleep quality (considering "poor sleep" if reporting "almost always or sometimes difficulty falling asleep or awakening during the night" or "very bad, bad or regular sleep quality"), sleep duration ("how many hours do you usually sleep per day including both nighttime and daytime?"), physical activity (time in hours per week that they spend walking, including commuting), and sedentary behavior (being seated more than 8 h a day, including sitting time watching TV, on the computer, listening to music, reading, during meals or during transportation). Diabetes was approached as a physician diagnosis, current use of glucose-lowering drugs, or fasting serum glucose >125 mg/dL; chronic kidney disease as glomerular filtration rate <60 mL/min/1.73 m^2 as per Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Sleep apnea syndrome and depression requiring treatment were also considered, based on self-report of a physician diagnosis. Body mass index (BMI) was calculated as measured weight in kilograms divided by squared measured height in meters (overweight, BMI 25–29.9 kg/m^2; obesity, ≥30 kg/m^2).

Blood pressure measurement

Single-point casual BP was measured 3 times (at 2-min intervals, after resting 5 min in a seated position) at 1 visit, by certified examiners, following standardized conditions,[8,22] using a validated oscillometric device (Mobil-O-Graph 24 h PWA monitor, I.E.M., Germany; Mediscan, Spain) and appropriate-size cuffs.

Thereafter, 24-h ABPM was performed using the Mobil-O-Graph device, which registers BP at 20-min intervals for the 24-h period. The ABPM recordings were performed on working days and the participants were instructed to maintain their usual activities, and to keep the arm extended and immobile at the time of each cuff inflation (appropriate-size cuffs were used). ABPM recordings were considered valid if ≥70% BP measurements were successful during both the daytime and nocturnal periods, defined individually according to the patient's self-reported time of going to bed and getting up.[7]

IAH was defined as casual home BP < 140/90 mmHg (mean of the second and third measurements) and mean 24-h ABPM ≥ 130/80 mmHg in the absence of antihypertensive drug treatment.[7,8]

Statistical analysis

For the derivation sample, 1331 participants were excluded for being on antihypertensive treatment, 375 for having elevated casual BP and 43 for lacking data for variables; thus, the analyses were performed with 645 untreated subjects with casual BP (mean of the last 2 readings) <140/90 mmHg. For the external validation sample, after applying the same exclusion criteria, the analyses were performed with 356 untreated subjects with casual BP <140/90 mmHg (mean of the last 2 BP). Between-group differences in clinical characteristics were assessed with the Chi-square test for categorical variables and the Student *t* test for continuous variables.

For the derivation sample, the association between each clinical characteristic and the presence of IAH was summarized with odds ratios (OR), and 95% confidence intervals (95%CI), obtained from logistic regression. Variables that attained univariate statistical significance ($P < .1$), were included in a multivariable model, and a forward stepwise selection procedure was used. The final model also included sex and age. As sensitivity analysis, we built a model adding interactions of sex and age with the other covariates and tested if model prediction based on the Akaike information criterion and the area under the receiver operating characteristic curve (AUC) was improved. Beta coefficients from the multivariable model were used to assign points to each variable in a score (range, 0–12) created to estimate the probability of having IAH. Variables that were associated with IAH were usually assigned 1 point for simplicity of use of the score, while those with stronger association were given 2–4 points, according to widely used procedures.[24,25] We stratified the risk of having IAH into 3 categories: high (risk > 50%), middle (risk > 25%), and low (<25%).

Table 1 – Characteristics of the participants, according to cohort and blood pressure status.

Characteristic	Derivation cohort		P-value	Validation cohort		P-value
	Normotension	IAH		Normotension	IAH	
N (%)	518 (80.3)	127 (19.7)		294 (89.9)	33 (10.1)	
Sociodemographic						
Men	233 (45.0)	68 (53.5)	.08	140 (47.6)	17 (51.5)	.67
Age, mean	7.6 (4.1)	71.3 (4.2)	.13	70.3 (5.7)	71.7 (6.8)	.21
Age ≥ 80 years	13 (2.5)	7 (5.5)	.08	26 (8.8)	4 (12.1)	.52
Morbidities						
Body mass index, kg/m²						
<25	220 (42.5)	22 (17.3)		95 (32.3)	8 (24.2)	
25–29.9	238 (46.0)	75 (59.1)		134 (45.6)	15 (45.5)	
≥30	60 (11.5)	30 (23.6)	<.001	65 (22.1)	10 (30.3)	.48
Body mass index, kg/m², mean	25.9 (3.6)	27.6 (4.0)	<.001	27.0 (3.7)	28.6 (5.0)	.03
Diabetes	58 (11.2)	15 (11.8)	.85	34 (11.6)	4 (12.1)	1.00
Sleep apnea syndrome	24 (4.6)	7 (5.6)	.66	7 (2.4)	2 (6.1)	.23
Depression	49 (9.5)	7 (5.5)	.16	28 (9.5)	6 (18.2)	.13
Chronic kidney disease	17 (3.4)	2 (1.6)	.31	10 (3.4)	1 (3.0)	1.00
Blood pressure measurement						
1st casual SBP, mmHg, mean	122.7 (13.9)	135.4 (12.6)	<.001	127.2 (13.0)	137.1 (10.6)	<.001
1st casual DBP, mmHg, mean	73.9 (9.3)	80.4 (7.8)	<.001	70.4 (8.1)	76.2 (8.5)	<.001
2nd and 3rd casual SBP, mmHg, mean	121.3 (1.8)	128.9 (8.0)	<.001	123.3 (9.7)	131.3 (6.6)	<.001
2nd and 3rd casual DBP, mmHg, mean	74.1 (7.7)	78.8 (7.3)	<.001	69.7 (8.1)	73.5 (8.6)	.01
24-h ambulatory SBP, mmHg, mean	116.7 (7.1)	132.8 (6.7)	<.001	119.4 (7.8)	133.0 (4.3)	<.001
24-h ambulatory DBP, mmHg, mean	69.5 (6.3)	78.7 (5.8)	<.001	68.2 (5.9)	74.9 (7.5)	<.001
1st casual BP categories						
<140 and 90 mmHg	453 (87.5)	73 (57.5)		243 (82.7)	17 (51.5)	
≥140 and/or 90 mmHg	65 (12.5)	54 (42.5)	<.001	51 (17.4)	16 (48.5)	<.001
2nd and 3rd casual BP[a]						
<120 and <80 mmHg	194 (37.5)	10 (7.9)		103 (35.0)	2 (6.1)	
120–129 and/or 80–84 mmHg	171 (33.0)	27 (21.3)		106 (36.1)	10 (30.3)	
130–139 and/or 85–89 mmHg	153 (29.5)	90 (70.9)	<.001	85 (28.9)	21 (63.6)	<.001
Health behaviors						
Tobacco smoking						
Never smoker	264 (51.0)	62 (48.8)		171 (58.2)	21 (63.6)	
Former smoker	207 (4.0)	52 (40.9)		96 (32.7)	9 (27.3)	
Current smoker	47 (9.0)	13 (10.2)	.88	27 (9.2)	3 (9.1)	.81
Sleep duration (h/day), mean	7.1 (1.5)	7.0 (1.5)	.43	13.2 (3.6)	14.0 (3.2)	.23
Poor sleep quality	401 (77.4)	105 (82.7)	.20	241 (82.0)	28 (85.0)	.68
Walking (h/day), mean	1.2 (.8)	1.3 (1.0)	.47	1.0 (0.7)	1.1 (0.8)	.44
Sedentary behavior	459 (88.6)	108 (85.0)	.27	250 (85.0)	32 (97.0)	.06

Data are expressed as means (SD) or *n* (%). Isolated ambulatory hypertension (IAH): normal casual blood pressure (BP) (average of the second and third BP measurements <140/<90 mmHg) and high mean 24-h ambulatory BP (≥130 and/or 80 mmHg) in untreated individuals. Normotension: normal casual BP (<140/<90 mmHg) and normal 24-h BP (<130/<80 mmHg). SD: standard deviation. SBP: systolic blood pressure; DBP: diastolic blood pressure.

[a] Average of the second and third blood pressure measurements.

To assess the extent to which the IAH score discriminated between individuals with and without IAH, we calculated and plotted the AUC (and 95%CI). To assess the model calibration, we plotted the estimated and observed probability of IAH for each score point and used the Hosmer–Lemeshow's goodness-of-fit test (built on each risk-point) to statistically assess the differences between such probabilities. Since the cut-off points defining categories in the IAH score were somewhat arbitrary and can result in loss of information, we conducted a sensitivity analysis by replicating the IAH model using continuous categories of the same covariates, and again we estimated the AUC and used the Hosmer–Lemeshow test. Lastly, the diagnostic ability and calibration of the score developed from the derivation sample were assessed in the external-validation sample.

The size-efficiency of performing ABPM according to the subjects' IAH score, i.e., the number of subjects at a given risk (or threshold) score needed to be examined with ABPM to diagnose 1 case of IAH (NND), was calculated as follows: 1/probability of IAH at each risk point (IAH_i) or at and above each risk point (IAH_{i+}). Probability of IAH_{i+} was calculated as $\Sigma_i([N_i/N_{i+}]^*$probability of $IAH_i)$, where N_i and N_{i+} stand for the number of individuals at each point and at and above each point, respectively. By convention, we rounded any decimal NND upwards to the next whole number.[25] Confidence intervals were corrected for small samples where appropriate.

Table 2 – Factors associated with isolated ambulatory hypertension based on multiple logistic regression modeling, in normotensive adults aged 65 and over.

Variables	β coefficient	Odds ratio (95%CI)	P-value
Sex, men	0.26	1.30 (0.83–2.03)	.20
Age ≥ 80 years	1.09	2.98 (0.97–9.17)	.05
Body mass index categories, kg/m²			
25–29	0.95	2.58 (1.49–4.45)	.001
≥30	1.26	3.53 (1.79–6.95)	<.001
Casual blood pressure (1st measurement), mmHg			
≥140 and/or 90	0.91	2.49 (1.53–4.04)	<.001
Casual blood pressure, mmHg (average of 2nd and 3rd measurements)			
120–129 and/or 80–84	0.93	2.52 (1.16–5.51)	.02
130–139 and/or 85–89	2.04	7.70 (3.71–15.99)	<.001

95%CI: 95% confidence interval.

Variable	Values	Points
Sex	Men	1
Age	≥ 80 years	2
Body mass index	25-29 kg/m²	2
	≥ 30 kg/m²	3
Casual blood pressure	1st measurement of ≥ 140 and/or 90 mmHg	2
	Average of 2nd and 3rd measurements of 120-129 and/or 80-84 mmHg	2
	Average of 2nd and 3rd measurements of 130-139 and/or 85-89 mmHg	4
	Isolated ambulatory hypertension score	Sum (0-12)

N	59	30	87	82	80	80	60	87	30	39	9	1	1
Total points	0	1	2	3	4	5	6	7	8	9	10	11	12
Probability of isolated ambulatory hypertension	0.02	0.03	0.05	0.08	0.12	0.18	0.25	0.35	0.47	0.59	0.70	0.79	0.86

Fig. 1 – Probability of having isolated ambulatory hypertension based on the score estimated from the multivariable logistic model, among normotensive subjects aged 65 and over.

Analyses were conducted in April–September 2020, using Stata/SE version 13 (Stata Corp, United States), SPSS version 24 (IBM, United States), and R version 3.0.2 (R Foundation for Statistical Computing, Austria).

Results

In the derivation sample, participants' mean age was 70.8 years (46.7% men), and 127 (19.7%) had IAH. Subjects with IAH were more frequently men, very old, and with excess weight, and had higher mean BMI, casual- and 24-h-BP than normotensive individuals (Table 1). They also had a higher frequency of elevated first BP measurement and of the "130–9/85–9 mmHg" category. In the external validation sample, IAH patients had higher mean age, BMI, and casual- and 24-h-BP, and higher frequency of elevated first-casual-BP and of the "130–9/85–9 mmHg" category than normotensive individuals, and 10.1% had IAH (Table 1).

Variables associated with isolated ambulatory hypertension

In the multivariable analysis, the variables significantly associated with IAH were: BMI 25–29 kg/m² (OR, 2.58; 95%CI, 1.49–4.45), BMI ≥ 30 kg/m² (OR, 3.53; 95%CI, 1.79–6.95), the first casual BP ≥ 140/90 mmHg (OR 2.49; 95%CI, 1.53–4.04), and the mean of the second and third casual BPs within the "120–9/80–4 mmHg" category (OR, 2.52; 95%CI, 1.16–5.51) or within the "130–9/85–9 mmHg" category (OR, 7.70; 95%CI, 3.71–15.99) (Table 2). OR for age ≥ 80 years was 2.98 (95%CI, 0.97–9.17; P = .05), and 1.30 for male sex (95%CI, 0.83–2.03; P = .2).

Score to screen for isolated ambulatory hypertension. Discrimination and calibration

Score points assigned to the variables associated with IAH were as follows: men, 1 point; age ≥ 80 years, 2 points; BMI of 25–29, 2 points; BMI ≥ 30 kg/m², 3 points; first BP measurement ≥ 140/90, 2 points; mean of the second and third BP measurements of 120–9/80–4, 2 points; and 4 points if this mean was 130–9/85–9 mmHg (Fig. 1). The probability of IAH was 0.02, 0.03, 0.05, 0.08, 0.12, 0.18, 0.25, 0.35, 0.47, 0.59, and 0.72 for scores of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and ≥10, respectively (Fig. 1).

The AUC for the score was 0.80; 95%CI, 0.77–0.84 (Fig. 1A of the supplementary data), and the Hosmer–Lemeshow test P value was 0.18 for the observed vs predicted IAH probabilities, indicating support for a properly calibrated model (Fig. 2A).

Sensitivity analyses

Figs. 2 and 3 of the supplementary data show the AUC of models without and with only the variable most strongly

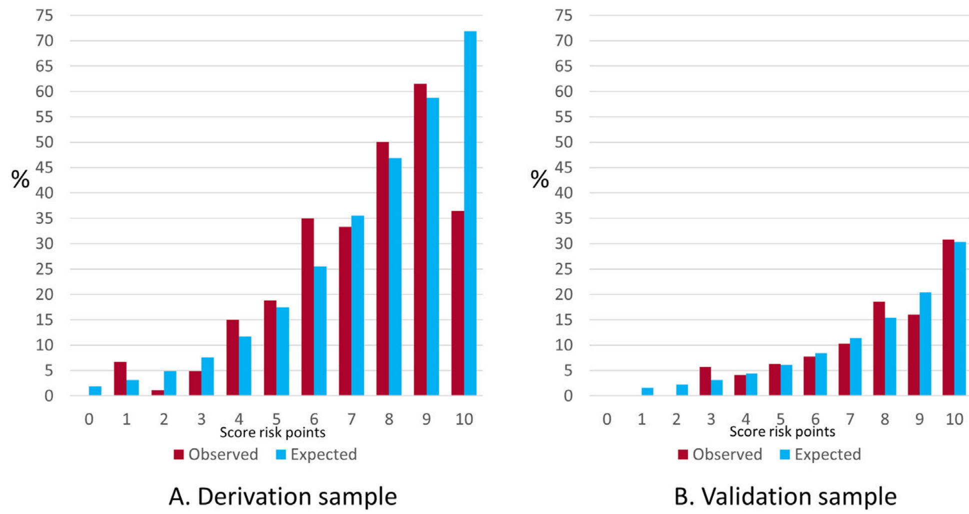

Fig. 2 – Calibration of the isolated ambulatory hypertension (IAH) score. Observed (A) and expects (B): observed and model predicted prevalence of isolated ambulatory hypertension, respectively. *X* axis: risk-score points of IAH; *Y* axis: percentage of individuals with IAH.

Specific risk-point metrics (for the physician)				Cumulative risk-threshold metrics (for the healthcare manager)			
Risk Score	Population	Probability of IAH	NND_i	Risk Score	Population	Probability of IAH	NND_{i+}
Points	N (%)	% (95%CI)	No. (95%CI)	Points	N (%)	% (95%CI)	No. (95%CI)
0	59 (9.1)	1.9 (0.04-9.1)	53 (11-2331)	≥ 0	645 (100)	19.6 (16.5-22.7)	5 (5-7)
1	30 (4.7)	3.1 (0.1-17.2)	33 (6-1185)	≥ 1	588 (90.9)	21.6 (18.3-24.9)	5 (4-6)
2	87 (13.5)	4.9 (1.3-11.4)	21 (9-79)	≥ 2	558 (86.2)	22.6 (19.1-26.1)	5 (4-6)
3	82 (12.7)	7.6 (2.7-15.2)	14 (7-37)	≥ 3	471 (72.7)	25.8 (21.8-29.7)	4 (4-5)
4	80 (12.4)	11.7 (5.3-20.3)	9 (5-19)	≥ 4	388 (60.0)	29.6 (25.1-34.1)	4 (3-4)
5	80 (12.4)	17.5 (9.9-27.6)	6 (4-11)	≥ 5	308 (47.6)	34.2 (28.9-39.5)	3 (3-4)
6	60 (9.3)	25.5 (14.7-37.9)	4 (3-7)	≥ 6	228 (35.2)	39.9 (33.5-46.3)	3 (3-3)
7	87 (13.5)	35.5 (25.6-46.6)	3 (3-4)	≥ 7	168 (25.9)	45.2 (37.7-52.7)	3 (2-3)
8	30 (4.6)	46.9 (28.3-65.7)	3 (2-4)	≥ 8	80 (12.4)	56.3 (44.7-67.3)	2 (2-3)
9	39 (6.0)	58.7 (42.1-74.4)	2 (2-3)	≥ 9	50 (7.8)	61.9 (47.2-75.3)	2 (2-3)
10+	11 (1.7)	72.3 (39.0-94.0)	2 (2-3)	10+	11 (1.7)	72.3 (39.0-94.0)	2 (2-3)

Fig. 3 – Probability of having IAH and number of subjects needed to be examined with ambulatory blood-pressure monitoring to detect one with IAH, according to the risk score of IAH. Untreated normotensive subjects aged 65 and over. NNDi: NND at each risk point (i). NNDi+: NND at (i) and above a given risk point (i+). Specific risk-point metrics for physicians: high-risk status of having IAH (red) defined as probability >50% (≥9 points); middle-risk status (orange) defined as risk >25% (≥6 points). Cumulative risk-threshold metrics for healthcare managers: high-risk status (red) set at a risk threshold of 50% (≥8 risk points); middle-risk status (orange) set at a threshold of 25% (≥3 risk points). By convention, any decimal NND is rounded upwards to the next whole number. IAH, isolated ambulatory hypertension; NND; number needed to detect.

associated with IAH ("mean of the last 2 BP"; AUC, 0.75 and 0.73, respectively). Model prediction based on the AIC slightly improved after consideration of interaction of sex and age with other covariates, from 127 to 115 (Table 2 of the supplementary data). Likewise, model's AUC was only slightly higher when interaction terms were added (0.81–0.83). Lastly, when all variables in the multivariable model were modeled as continuous, the AUC was 0.80 (0.76–0.84) (Fig. 4 of the supplementary data), practically the same as the AUC of the main model.

Validation of the score

In the external validation sample, probabilities of IAH were 0.02–0.36 for scores of 0–≥10 (Fig. 5 of the supplementary data). The AUC for the score was 0.73; 95%CI, 0.64–0.82 (Fig. 1B of the supplementary data), and the Hosmer–Lemeshow's *P*-value was .93 for the observed vs predicted IAH probabilities (Fig. 2B).

Number needed to detect one case of isolated ambulatory hypertension

The NNDs for a score of 6, 7, 8, 9, and ≥10 points were 4, 3, 3, 2, and 2, respectively (Fig. 3, column 4, orange for the 3 first NNDs and green for the last 2).

In cumulative terms, 12.4% of all the subjects were at high risk of having IAH (≥8 points; Fig. 3, column 6), and 60.3% were at middle risk (>2 and <8 points). The NNDs for a score of ≥8 points (high probability of IAH, Fig. 3, column 7 in red) and ≥3 points (middle risk, orange) were 2 (Fig. 3, column 8 in green) and 3–4 (orange), respectively.

In the external validation sample, NNDs for scores of 0–≥10 were 50, 50, 34, 25, 17, 13, 10, 7, 5, 4, and 3, respectively (Fig. 5 of the supplementary data). NNDs for middle-risk score (≥6 points) was 6, and it was 4 for high-risk subjects (>8 points).

Discussion

This study shows the usefulness of a score as a screening tool for IAH in older adults, developed from the combination of simple demographics, anthropometrics and 3 BP measurements at one visit. This combination could aid to select older patients at higher risk of IAH, who can get more benefit from ABPM if this cannot be offered to all patients. In addition, the clinical effort needed (number of subjects to be examined with ABPM) to detect one subject with IAH was only 2 among high-risk subjects.

In our study, the prevalence of IAH in the derivation sample, was higher than in the external validation sample, which may partly be explained by the joint effect of higher levels of known determinants of MH in the former (e.g., higher frequency of men, overweight, high-normal BP – and mean first casual BP –, and smoking, see Table 1).[1–4,6,10,14,16] The higher risk profile of the derivation- compared with the validation cohort can also contribute to explain the higher discriminative power in the former, which was additionally a more recent cohort.

Consistent with previous studies on MH, BMI and casual BP were significantly associated with IAH.[1,4–6,10,12,14,16] Nevertheless, our study specifically examined the single contribution of the first vs the second and third BP measurement at 1 visit in older adults. Although we used the mean of the last 2 casual BP < 140/90 mmHg for defining IAH, 42% of the IAH subjects had the first casual BP elevated, suggesting a white-coat effect at the first measurement that can "mask" a potential case of IAH if only 1 BP measurement is taken. Most importantly, that a first elevated BP measurement is predictive of IAH is one additional reason to perform ABPM to confirm this condition in older patients. This is important since a white-coat effect is more frequent in older people.[26,27]

Our results are also consistent with the indications of ABPM for detecting MH in people with "high-normal BP" in the office according to the European guidelines (clinic systolic BP 130–9) and also in people with "elevated BP" in the office according to American guidelines (clinic systolic BP, 120–9).[8,27,28]

Clinical and policy implications

The screening score may help the physician and the healthcare manager to decide on the appropriate use of ABPM. For the physician, individual risk of having IAH (or MH) would be easy to calculate, and ABPM could be a size-efficient strategy to detect IAH based on the score. In an individual with low probability of IAH (<25% or <6 points), avoiding ABPM could be a reasonable choice as it is low-risk for the patient and size-inefficient (Fig. 3, column 4, red). Conversely, reserving ABPM to patients with a high probability of IAH (>50% or >8 points), would be very size-efficient (only 2 patients would need ABPM to diagnose 1 with IAH).

For the healthcare manager, a policy oriented to considering ABPM in subjects with a probability of IAH > 50% (at least 8 points) entails a population burden probably assumable by the health system, involving only 12% of all subjects in the population (Fig. 3, column 6) and being very size-efficient (only 2 subjects would need to be examined with ABPM to detect 1 with IAH; Fig. 3, column 8, green). The issue of a wider use of ABPM, including patients at middle risk of IAH (>25%), is one of affordability and would involve a burden of 60% of all the patients in our study population; nevertheless, only 3–4 of these subjects are needed to undergo ABPM to detect one with IAH.

Limitations

This study presents some limitations. First, casual BP was not measured in the clinic but in subjects' homes. Nevertheless, unlike self-measured home BP along several days, only 3 BP readings were taken on a single occasion by trained observers unfamiliar to the subjects, thus an observer effect and white-coat effect was present.[29] These observer-measured home BP measurements have also been used in other studies to estimate MH and its consequences,[21,29,30] and are increasingly used in clinical practice with many patients providing their doctors with BP taken at home either by the patient or another person. However, observer-measured home-BP may still be somewhat lower than in office where a clinical effect (setting) is added to the observer effect (staff),[29] which could lead to some overestimation of the prevalence of MH on clinic BP. Nevertheless, BP-thresholds based on office-BP and home-BP measurement are similar in the lower BP range (including both 120/80 and 130/80 mmHg),[28] so the magnitude of the bias should be small. Also, IAH only include real (ambulatory) hypertension masked at home, thus likely losing some non-hypertensive patients in the clinic with ambulatory hypertension.

Second, ABPM data were obtained from a single ABPM recording, and reproducibility of MH is fair only in the short-term.[1,13,31,32] Nevertheless, we only aimed to estimate the probability of having IAH at a moment in time – a single entire day-, and only 1 24-h ABPM is common clinical practice.[1,17]

Conclusions

A simple score based on 4 variables easily available in routine practice (sex, age, BMI, and 3 casual-BP measurements in one visit) reliably identified IAH in older adults. A ≥8-point score identified IAH with a probability >50%, so that only an average of two patients should undergo ABPM to diagnose one case of IAH. Although the score may be applicable to similar settings, recalibration to the local environment may be necessary.

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Authors' contribution

Concept and design: J.R. Banegas, A. Hernández-Aceituno, J.J. Cruz, and F. Rodríguez-Artalejo. Drafting of the manuscript: A. Hernández-Aceituno, J.R. Banegas. Statistical analysis:

What is known about the subject?

- Few studies have estimated the probability of having masked or isolated ambulatory hypertension (IAH) based on predictors, and none has calculated the clinical effort (number of ABPM) needed to detect one case of this condition in older patients living in the community.

Does it contribute anything new?

- A simple score with 4 variables (sex, age, body-mass index, and 3 casual BP measurements at a single visit) performed well and served to estimate the probability of having IAH (mean 24-h ambulatory BP ≥ 130/80 mmHg).
- Only 2 subjects at high risk of IAH (>50% probability or >8-point score) need to be examined with 24-h ABPM to detect 1 case of IAH.
- An easy-to-use clinical score may be useful and size-efficient for identifying IAH in older adults if ABPM cannot be offered to all patients.

A. Hernández-Aceituno, J.J. Cruz. Supervision; obtention of funding: J.R. Banegas. Administrative, technical, or material support: J.R. Banegas, A. Graciani. Acquisition, analysis, or interpretation of data; critical revision of the manuscript for important intellectual content: all authors. A. Hernández-Aceituno, J.J. Cruz, and J.R. Banegas had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflicts of interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.rccl.2021.07.003

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