# Morning blood pressure surge as a predictor of cardiovascular events in patients with hypertension

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***Background*** **The prognostic value of ambulatory blood pressure (BP) monitoring (ABPM) is poorly understood in Latin American populations.**

***Methods*** **A prospective observational study was conducted on 1339 patients with hypertension who underwent 24-h BP monitoring between 2015 and 2019. The incidence of serious adverse cardiovascular events (MACE) was analysed using a Cox proportional hazards model adjusted for potential confounders. Three previously reported morning surge definitions were evaluated for SBP and DBP using different ABPM components: sleep-through morning surge, pre-awakening, and morning night-time difference.**

***Results*** **The mean age was 62 years, 52% were female, 32.8% had dyslipidaemia, 27.2% were smokers, and 7.8% had diabetes. During a median follow-up period of 32 months, 197 MACE occurred. In men, the adjusted hazard ratio (HR) was 1.84 [95% confidence interval (CI), 1.35–2.49; *P*<0.001). The HR increased to 2.03 (95% CI, 1.89–2.17; *P*<0.001) with a cut-off value of 35 mmHg for a 10 mmHg increase in sleep-through morning surge. The increased adjusted HR associated with the morning rise persisted for each secondary endpoint, including 21 cardiovascular deaths [HR: 2.70 (95% CI, 2.03–3.60; *P*<0.001)], 78 myocardial infarctions [HR: 1.92 (95% CI, 1.72–2.15; *P*<0.001)], 24 hospitalisations for heart failure [HR: 1.77 (95% CI, 1.48–2.12; *P*<0.001)], 22 strokes [HR: 2.32 (95% CI, 1.85–2.91; *P*<0.001)], and 52 atrial fibrillations [HR: 1.94 (95% CI, 1.71–2.20; *P*<0.001)].**

***Conclusion*** **The morning BP rise was the most important circadian prognostic factor for MACE in patients with hypertension, which deserves more attention. *Blood Press Monit* 28: 149–157** 

**Blood Pressure Monitoring** 2023, **28**:149–157

**Keywords: ambulatory blood pressure monitoring, circadian rhythm, hypertension, morning surge, night-time hypertension, prognosis**

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**Received** 14 September 2022 **Accepted** 27 November 2022.

## Introduction

Hypertension is the leading cause of cardiovascular disease and death worldwide. Disparities in the prevalence, diagnosis, and treatment of hypertension suggest that health systems in low- and middle-income countries face a rapidly increasing burden of cardiovascular diseases relationship with hypertension complications [1,2].

The diagnostic and prognostic value of ambulatory blood pressure monitoring (ABPM) is well established in several regions of the world, but evidence is low in Latin America [1,3–6]. The absence of nocturnal BP reduction and the rise in morning BP influence the development of targeted organ damage and increased cardiovascular risk; however [7]. Few centres in Argentina have validated ABPM devices, and the prognostic ability of AMBP needs to be confirmed in our population.

BP oscillates according to a circadian pattern with lows during sleep and highs during wakefulness [8–11]. An elevated BP in the morning is a physiological response. Exacerbation of physiological responses can be considered a risk factor for cardiovascular events. Kario *et al.* coined the term morning BP rise as a rise after waking [12]. Using ABPM measurements, several definitions of morning surge have been explored using ABPM measurements, including morning rise during sleep, morning rise before waking, pre-awakening morning surge, and rising morning surge. The most widely used method is the sleep-through morning surge as the morning systolic rise BP (SBP) (i.e. the 2-h average of six 20-min BP readings immediately after awakening) minus the lowest

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website, www.bpmonitoring.com.

 DOI: 10.1097/MBP.0000000000000641

nocturnal SBP (i.e. the average of the three readings the lowest nocturnal reading) [8]. There is no consensus on the best definition and thresholds for the morning rise. Some previous studies associated higher morning peaks with increased risk of cardiovascular events and all-cause mortality [6,8,13–18]. The only study describing the prognostic value of morning peaks for cardiovascular disease was conducted in Uruguay as part of the multicentre International Database of Ambulatory BP in relation to Cardiovascular Outcome (IDACO) study [19].

The morning increase in BP currently poses three major questions: 1 – prognostic role of MS and its association with cardiovascular events, 2 – reproducibility of the technique in non-Asian populations and identification of the cut-point that predicts the largest number of events, and 3 – the best method to predict major cardiovascular events.

The aim of this study was to evaluate the prognostic value of ABPM and circadian patterns, including three types of morning BP elevations, in patients with a recent diagnosis of hypertension referred to the Hypertension Unit of Hospital Español de Mendoza (Mendoza, Argentina) between 2015 and 2019.

## Methods

### Study design and participants

This prospective observational blinded-endpoint study included hypertensive patients followed and recruited in the Hypertension Unit of the Hospital Español de Mendoza (Mendoza, Argentina) who underwent ABPM between 1 January 2015 and 31 December 2019. The calculation of the sample size was carried out according to those published at the time of the study design [7–9]. Patients were eligible if they were Argentine residents, aged at least 18 years, with diagnosed hypertension. People should be able to self-reported awake and asleep times and, a completely acceptable ABPM record with at least three SBP and DBP measurements within 2 h after awakening for the assessment of circadian patterns, and morning surge evaluations were included. The Ethics Committee of the Hospital Español de Mendoza approved the protocol, informed consent was obtained from Resolution No. 67, and all participants provided written informed consent. Patients will be excluded from the study if: they are pregnant, under 18 years of age, do not meet the specific inclusion criteria for ambulatory monitoring, it was not possible to obtain data on cardiovascular events, and patients with chronic atrial fibrillation.

At the beginning of the study, information on health behaviours and previously diagnosed concomitant diseases were collected by trained personnel. Height and weight were measured during the study period. Smokers were defined as those who had smoked 100 cigarettes in their lifetime or who were current smokers. Dyslipidaemia and diabetes were defined according to the presence or absence of pharmacological treatment, as indicated by the treating physician. Pharmacological treatment for hypertension was categorised as no treatment, monotherapy, or treatment with more than two medications at baseline.

The follow-up was carried out through telephone calls every 3 months and an annual face-to-face consultation to update their clinical situation. Questions related to cardiovascular events were asked. The information on the major cardiovascular events and hospitalisation was obtained from the review of digital medical records.

### Ambulatory blood pressure monitoring

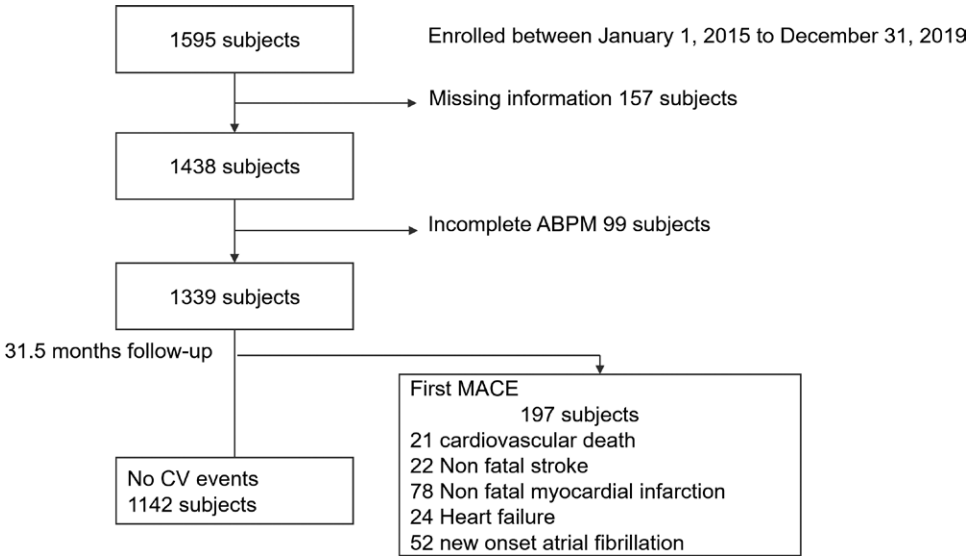
The Meditech AMBP04 CardioTens device (validated according to British Hypertension Society and Association for the Advancement of Medical Instrumentation accuracy criteria and recommended by disease management systems) was applied to the nondominant arm of participants between 9:00 and 11:00 am and removed 24 h later [20]. The cuff size was selected according to the measured arm circumference. The device measured BP every 20 min from 6:00 am to midnight and every 30 min from midnight until 6:00 am. The awake and sleep periods corresponded to patients' diary entries. The ambulatory monitoring were considered complete if >had 10 SBP and DBP values during awake and five during sleep [21–23]. Riser, non-dipper, dipper, and extreme dipper were defined as percent SBP reductions during sleep periods of <0%, 0%–10%, 10%–20%, and >20%, respectively. Satisfactory monitoring was considered when 90% of the measurements were correct.

Independently, three previously reported morning surge definitions were calculated for SBP and DBP using different ABPM components. Sleep-through morning surge was calculated as the mean BP 2 h after awakening minus the mean around the lowest nocturnal BP measurement (the mean of the lower and the measurements before and after the lowest reading). Pre-awakening was calculated as the mean BP at 2 h post-awakening minus the mean BP at 2 h pre-awakening. The morning night-time difference (MND) was calculated as two morning BP readings minus the average night-time BP.

### Outcomes

The primary endpoint was the occurrence of serious adverse cardiovascular events (MACE) including cardiovascular mortality, nonfatal ischaemic heart disease, nonfatal stroke, hospitalisation for heart failure, and atrial fibrillation. In each case, secondary outcomes were part of the primary outcome. Atrial fibrillation events were assigned after confirmation by 24-h Holter recording. Events were assigned by non-medical personnel by coding medical records.

**Fig. 1**




Flow diagram of the study.

### Statistical analysis

The analyses described below for systolic values were also performed for diastolic values. The distributions of participants' sleep-through surge, pre-awakening surge, and MND were plotted against age and partitioned according to the occurrence of MACE using locally estimated scatterplot smoothing (Loess). The Cox proportional hazard regression method was used to calculate hazard ratios (HRs) for MACE, considering the competing risk of death.

The HRs for MACE were determined for the sleep-through morning surge, pre-awakening surge, and MND as continuous variables. After collinearity detection, six models were developed for the systolic and diastolic values of the rising variables. All models included adjustments for age (in 1-year and 10-year increments), sex, BMI, dyslipidaemia, smoking status, diabetes, antihypertensive treatment, 24-h BP values, and chronotypes. All analyses were repeated for each secondary endpoint. In addition, cut-point values were estimated using the surv_cutpoint function from the Maxstat package for R. Smooth HRs for MACE components of each type of systolic and diastolic morning surge were also determined in adjusted models using the smoothHR package for R. Analyses were performed with Jamovi 2.2 and R version 4.0 [24,25].

## Results

A total of 1595 subjects were consecutively included. Figure 1 illustrates the flow of the study. Complete information was available for 1438 subjects. After excluding 99 subjects with incomplete ABPM, 1339 subjects remained available for the analysis. No missed follow-up data are recorded. The median follow-up time was 31.5 months (27.1–35.6 months). These 197 events included 21 cardiovascular deaths (CVDs), 78 myocardial infarctions (MIs), 24 episodes of heart failure, 22 strokes, and 52 new-onset atrial fibrillation.

Table 1 lists the baseline data of the patients. The mean age was 59.6 years, and females accounted for 52.4%. According to BMI values, 72% were overweight and 34% were obese. The prevalence rates of dyslipidaemia were 32.8%, 27.2%, and 7.8%, respectively. The average office, 24-h, daytime, and night-time BP values were within the range of controlled hypertension, according to practice guidelines for office and out-of-office BP measurement [21]. However, uncontrolled hypertension occurred in 22% of patients when daytime SBP and DBP were considered in 15% of the patients. Nocturnal uncontrolled values were higher for both SBP and DBP (42% and 39%, respectively). The average morning BP values were closer to the nocturnal values.

Both SBP and DBP values of sleep-through morning surge, pre-awakening surge, and MND were higher in patients who experienced MACE, regardless of age (Fig. 2).

### Univariable analysis

Weight had a low-predictive power for MACE, heart failure, and atrial fibrillation, but it did not reach statistical significance for CVD, MI, or stroke. Height was not associated with any of the primary or secondary endpoints. The HR for height was 1.01 [95% confidence interval (CI), 0.99–1.02; p = 0.489). BMI increased the HR for atrial fibrillation and heart failure, but not for MACE. Both overweight and obesity did not increase HR for

**Table 1 Demographic data and baseline characteristics**

| | Overall (*N*=1339) |
|---|---|
| Gender, male (%) | 651 (48.6) |
| Age, years | 59.6 (16.2) |
| Weight, kg | 79.7 (18.7) |
| BMI, kg/m$^2$ | 28.4 (5.5) |
| Dyslipidemia (%) | 439 (32.8) |
| Tobacco (%) | 364 (27.2) |
| Diabetes (%) | 105 (7.8) |
| Antihypertensive treatment | |
| No treatment (%) | 215 (16.1) |
| Monotherapy (%) | 649 (48.5) |
| >2 drugs (%) | 475 (32.8) |
| Office blood pressure | |
| SBP, mmHg | 137.2 (12.6) |
| DBP, mmHg | 84.7(11.1) |
| Office heart rate, bpm | 78.4 (11.3) |
| Diurnal blood pressure | |
| SBP, mmHg | 125.8 (13.3) |
| DBP, mmHg | 74.4 (10.7) |
| Mean, mmHg | 89.1 (10.7) |
| Diurnal heart rate, bpm | 75.3 (10.5) |
| Nocturnal blood pressure | |
| SBP, mmHg | 118.3 (15.1) |
| DBP, mmHg | 67.9 (11.4) |
| Mean, mmHg | 82.1 (11.9) |
| Nocturnal heart rate, bpm | 69.4 (10.4) |
| Morning blood pressure | |
| SBP, mmHg | 118.9 (18.1) |
| DBP, mmHg | 69.1 (13.9) |
| Mean, mmHg | 82.8 (15.0) |
| Morning heart rate, bmp | 68.4 (12.1) |
| 24-h blood pressure | |
| SBP, mmHg | 123.5 (12.3) |
| DBP, mmHg | 72.4 (13.2) |
| Mean, mmHg | 88.3 (14.5) |
| 24-h heart rate, bmp | 72.8 (13.1) |
| Circadian pattern | |
| Dipper, *n* (%) | 431 (32.2) |
| Non-dipper, *n* (%) | 489 (36.5) |
| Riser, *n* (%) | 284 (21.2) |
| Extreme dipper, *n* (%) | 135 (10.1) |
| Sleep-through blood pressure surge | |
| SBP, mmHg | 20.9 (15.5) |
| DBP, mmHg | 17.3 (14.1) |
| Prewakening blood pressure surge | |
| SBP, mmHg | −2.9 (18.3) |
| Diastolic, mmHg | −0.1 (14.3) |
| Morning night-time blood pressure difference | |
| SBP, mmHg | 0.6 (16.4) |
| Diastolic, mmHg | 1.2 (13.5) |

Values correspond to mean (SD).
BP, blood pressure; bpm, beat per minute.

MACE by 0.77 (95% CI, 0.55–1.07; $P=0.116$) and 0.80 (95% CI, 0.60–1.06; $P=0.124$), respectively. Increasing age was associated with the occurrence of MACE and each secondary endpoint, both per year and per decade (Table 2). Men had a higher HR for the occurrence of primary and secondary endpoints. Among those treated for dyslipidaemia, MACE HR decreased to 0.71 (95% CI, 0.52–0.98; $P=0.035$), mainly due to the HR decrease in HR from MI to 0.54 (95% CI, 0.31–0.94; $P=0.029$), while the other endpoints showed no significant differences. Smoking was not associated with an increased HR for MACE or any secondary endpoint. Patients with diabetes had a higher risk of MACE and MI than those without diabetes. The other secondary endpoints did not increase in the patients with diabetes. When the 24-h average SBP increased by 1 mmHg and 10 mmHg, the HR for MACE increased 1.02-fold (95% CI, 1.01–1.03, $P<0.001$) and 1.24-fold (95% CI, 1.12–1.37, $P<0.001$), respectively. Most secondary endpoints had higher HR, with the exception of stroke and atrial fibrillation. None of the endpoints were related to the 24-h average diastolic values. Antihypertensive treatments did not reduce the HR of MACE or their individual components. Considering dipper as the reference, circadian pattern riser, non-dipper, and extreme dipper did not increase the HR for MACE or the secondary endpoints, except for CVD which was higher in extreme dipper and heart failure was higher in non-dippers.

The HR of MACE increased by 1 mmHg with an increase in the sleep-through surge of SBP, and DBP increased by 1 mmHg. All secondary endpoints had higher HR for systolic and diastolic values. The values for each 10-mmHg increase in sleep-through surge SBP were higher for the primary and secondary endpoints.

The pre-wake systolic value increased HR to 1.06 (95% CI, 1.06–1.07, $P<0.001$), and for each 10-mmHg increase HR increased to 1.83 (95% CI, 1.73–1.95, $P<0.001$). All secondary endpoints increased the HR to similar levels when both 1 and 10 mmHg changes in pre-awakening values were considered. Additionally, diastolic values increased HR to 1.05 (95% CI, 1.05–1.06, $P<0.001$) for MACE and 1.69 (95% CI, 1.57–1.83, $P<0.001$) for a 10 mmHg increase, consistently increasing all individual endpoints.

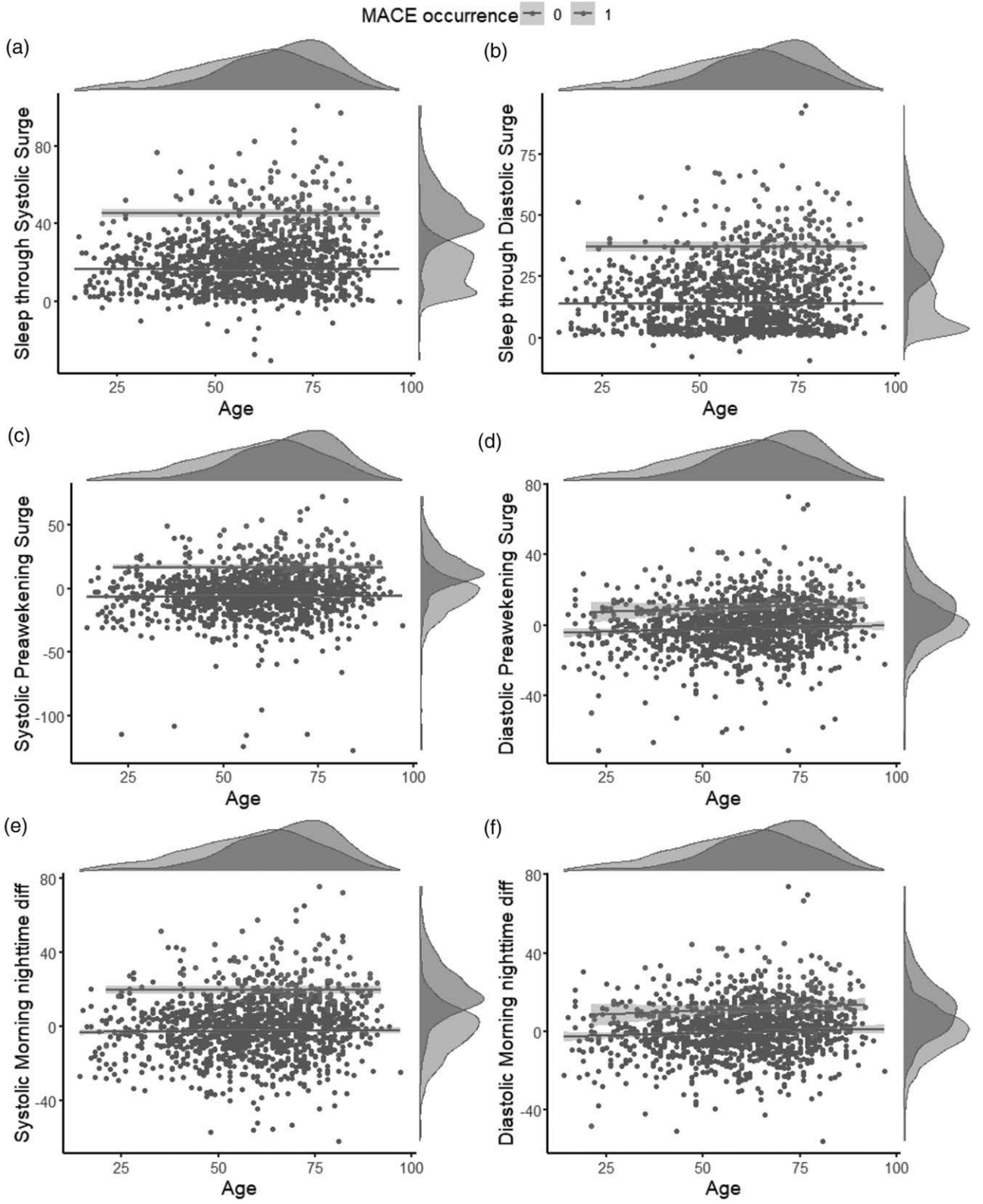
The MND of SBP and DBP increased the HR of MACE. A systolic increase of 1 mmHg in MND increased CVD, MI, heart failure, stroke, and atrial fibrillation. A similar increase was associated with diastolic MND levels at the secondary endpoints. The increase in HR for a 10 mmHg increase in diastolic sleep-through surge, as well as for systolic and diastolic MND, was also consistently higher for the primary and secondary endpoints.

The systolic and diastolic values of the three measures of morning surge were correlated within and between each definition (Supplementary Table 1, Supplemental Digital Content 1). Therefore, multivariate analysis was performed for each form of morning rise.

### Multivariable analysis

Primary and secondary outcomes were assessed for circadian patterns, 1- and 10-mmHg increases in the systolic and diastolic values of sleep-through surge, pre-awakening rise, and MND (see Supplementary Table 2, Supplemental Digital Content 1, *http://links.lww.com/BPMJ/A187*). Multivariate analysis was adjusted for age, sex, dyslipidaemia, smoking habits, diabetes, BMI, antihypertensive treatment, and 24-h BP. The HR for the covariates remained in the ranges described in the univariate analysis, but BMI and diabetes had values of 1.01 (95% CI, 0.99–1.04; $P=0.322$) and 1.17 (95% CI, 0.76–1.78;

**Fig. 2**




MACE events regarding morning surge definitions across subjects' age. (a) Sleep-through surge for SBP in function of age for patients that suffered MACE (black dots and black Loess regression line) or remained healthy during follow-up (grey dots, and grey Loess regression line). (b) Diastolic sleep-through surge. (c) Systolic pre-awakening surge. (d) Diastolic pre-awakening surge. (e) Systolic morning night-time difference (diff). (f) Diastolic morning night-time difference (diff).

**Table 2 Prognostic value of circadian patterns and morning surge for the primary and the secondary outcomes using multivariate analysis adjusted for covariates age, gender, smoking, dyslipidemia, diabetes, antihypertensive treatment, 24-h blood pressure and BMI**

| | | HR multivariable | | | | | |
|---|---|---|---|---|---|---|---|
| Covariate | Comparison | MACE | Cardiovascular death | Myocardial infarction | Stroke | Heart failure | Atrial fibrillation |
| Circadian pattern | Dipper | 1 | 1 | 1 | 1 | 1 | 1 |
| | Non-dipper | 1.16 (0.72–1.86, $P$=0.540) | 1.61 (0.39–6.62, $P$=0.511) | 1.26 (0.43–3.68, $P$=0.675) | 1.19 (0.30–4.69, $P$=0.807) | 1.99 (0.46–8.62, $P$=0.358) | 1.77 (0.49–6.40, $P$=0.386) |
| | Riser | 0.98 (0.67–1.43, $P$=0.923) | 1.10 (0.27–4.42, $P$=0.893) | 0.77 (0.44–1.35, $P$=0.359) | 0.74 (0.23–2.33, $P$=0.603) | 2.13 (0.69–6.56, $P$=0.186) | 1.28 (0.63–2.61, $P$=0.489) |
| | Extreme dipper | 1.33 (0.90–1.96, $P$=0.152) | 3.17 (0.91–11.04, $P$=0.070) | 1.51 (0.79–2.90, $P$=0.215) | 0.88 (0.25–3.11, $P$=0.847) | 1.45 (0.40–5.22, $P$=0.572) | 1.49 (0.61–3.66, $P$=0.380) |
| STS SBP | 1 mmHg | 1.07 (1.06–1.07, $P$<0.001) | 1.10 (1.07–1.14, $P$<0.001) | 1.07 (1.06–1.08, $P$<0.001) | 1.09 (1.06–1.11, $P$<0.001) | 1.06 (1.04–1.08, $P$<0.001) | 1.07 (1.06–1.08, $P$<0.001) |
| | 10 mmHg | 2.03 (1.89–2.17, $P$<0.001) | 2.70 (2.03–3.60, $P$<0.001) | 1.92 (1.72–2.15, $P$<0.001) | 2.32 (1.85–2.91, $P$<0.001) | 1.77 (1.48–2.12, $P$<0.001) | 1.94 (1.71–2.20, $P$<0.001) |
| STS diastolic | 1 mmHg | 1.08 (1.07–1.09, $P$<0.001) | 1.11 (1.08–1.14, $P$<0.001) | 1.07 (1.06–1.08, $P$<0.001) | 1.10 (1.07–1.13, $P$<0.001) | 1.09 (1.07–1.12, $P$<0.001) | 1.07 (1.06–1.09, $P$<0.001) |
| | 10 mmHg | 2.16 (2.00–2.34, $P$<0.001) | 2.80 (2.08–3.78, $P$<0.001) | 1.93 (1.72–2.18, $P$<0.001) | 2.64 (2.00–3.47, $P$<0.001) | 2.41 (1.88–3.09, $P$<0.001) | 2.00 (1.71–2.34, $P$<0.001) |
| MND SBP | 1 mmHg | 1.06 (1.06–1.07, $P$<0.001) | 1.07 (1.05–1.10, $P$<0.001) | 1.06 (1.05–1.07, $P$<0.001) | 1.08 (1.05–1.10, $P$<0.001) | 1.05 (1.03–1.07, $P$<0.001) | 1.06 (1.05–1.08, $P$<0.001) |
| | 10 mmHg | 1.87 (1.74–2.00, $P$<0.001) | 2.03 (1.56–2.63, $P$<0.001) | 1.80 (1.60–2.02, $P$<0.001) | 2.13 (1.68–2.70, $P$<0.001) | 1.66 (1.36–2.02, $P$<0.001) | 1.85 (1.62–2.11, $P$<0.001) |
| MND Diastolic | 1 mmHg | 1.06 (1.05–1.07, $P$<0.001) | 1.07 (1.03–1.10, $P$<0.001) | 1.06 (1.04–1.07, $P$<0.001) | 1.09 (1.06–1.12, $P$<0.001) | 1.08 (1.05–1.11, $P$<0.001) | 1.06 (1.04–1.08, $P$<0.001) |
| | 10 mmHg | 1.77 (1.62–1.93, $P$<0.001) | 1.90 (1.39–2.59, $P$<0.001) | 1.76 (1.53–2.03, $P$<0.001) | 2.34 (1.75–3.14, $P$<0.001) | 2.11 (1.61–2.75, $P$<0.001) | 1.81 (1.49–2.20, $P$<0.001) |
| PreAwa SBP | 1 mmHg | 1.06 (1.05–1.07, $P$<0.001) | 1.07 (1.05–1.10, $P$<0.001) | 1.06 (1.05–1.07, $P$<0.001) | 1.08 (1.05–1.10, $P$<0.001) | 1.06 (1.04–1.08, $P$<0.001) | 1.06 (1.05–1.08, $P$<0.001) |
| | 10 mmHg | 1.82 (1.70–1.95, $P$<0.001) | 2.01 (1.57–2.59, $P$<0.001) | 1.76 (1.58–1.96, $P$<0.001) | 2.10 (1.68–2.62, $P$<0.001) | 1.74 (1.44–2.11, $P$<0.001) | 1.84 (1.62–2.09, $P$<0.001) |
| PreAwa diastolic | 1 mmHg | 1.05 (1.05–1.06, $P$<0.001) | 1.06 (1.03–1.09, $P$<0.001) | 1.05 (1.04–1.07, $P$<0.001) | 1.08 (1.05–1.11, $P$<0.001) | 1.07 (1.04–1.09, $P$<0.001) | 1.06 (1.04–1.08, $P$<0.001) |
| | 10 mmHg | 1.71 (1.57–1.85, $P$<0.001) | 1.82 (1.36–2.43, $P$<0.001) | 1.66 (1.46–1.89, $P$<0.001) | 2.19 (1.69–2.84, $P$<0.001) | 1.89 (1.50–2.38, $P$<0.001) | 1.83 (1.51–2.22, $P$<0.001) |

BP, blood pressure; MND, morning night-time differences; PreAwa, pre-awakening; STS, sleep-through surge.

$P$=0.478), respectively. The multivariate analysis of the main predictive variables for cardiovascular events, highlighting in A, the role of systolic sleep-through surge and in B, the role of the diastolic sleep-through surge is shown in Fig. 3. In both analyses, males and riser circadian pattern presented a higher risk. Age and 24 h mean values also were associated with increased risk of MACE.

The cut-off value that maximised the differences for MACE was 35 mmHg for sleep-through systolic surge. The adjusted HR was 47.94 (95% CI, 29.73–77.31; $P$<0.001). This extreme value is supported by the fact that 166 MACE occurred among the 273 patients classified as >35 mmHg and only 31 MACE among the remaining 1132 subjects. In patients who exceeded the cut-off, the median survival was 17.7 (95% CI, 15–22.6) months. The cut-off value for diastolic sleep-through surge was 31 mmHg and the adjusted HR was 17.87 (95% CI, 13.03–24.52; $P$<0.001) with a median survival of 22.1 (95% CI, 17.7–25.9) months. The cut-off values for systolic and diastolic pre-awakening were 9.7 and 14.4 mmHg, and median survival was 30.5 (95% CI, 24.6–39) and 37.8 (95% CI, 23.9–42.3) months, respectively. The adjusted HR for systolic and diastolic rise before awakening above the calculated cut-off were 12.96 (95% CI, 9.36–17.96; $P$<0.001) and 6.74 (95% CI, 4.94–9.20; $P$<0.001), respectively. The cut-off values for systolic and diastolic MND were 1 and 2 mmHg, respectively. Adjusted HR were 15.40 (95% CI, 8.90–26.64; $P$<0.001) and 3.25 (95% CI, 2.35–4.51; $P$<0.001) with median survival of 28.2 (95% CI, 23.3–37.3) and 37.8 (95% CI, 25.5–48.0) months, respectively.

The Ln HR curve of the dependence of the overall risk of MACE on the systolic and diastolic sleep-through values shows that the reference value for these variables is 2.1 mmHg and 6.4 mmHg, respectively, with a progressive increase in risk until the respective threshold value is reached (Fig. 4). After the threshold value, the Ln HR stabilised at approximately 7 mmHg and 5 mmHg, respectively.

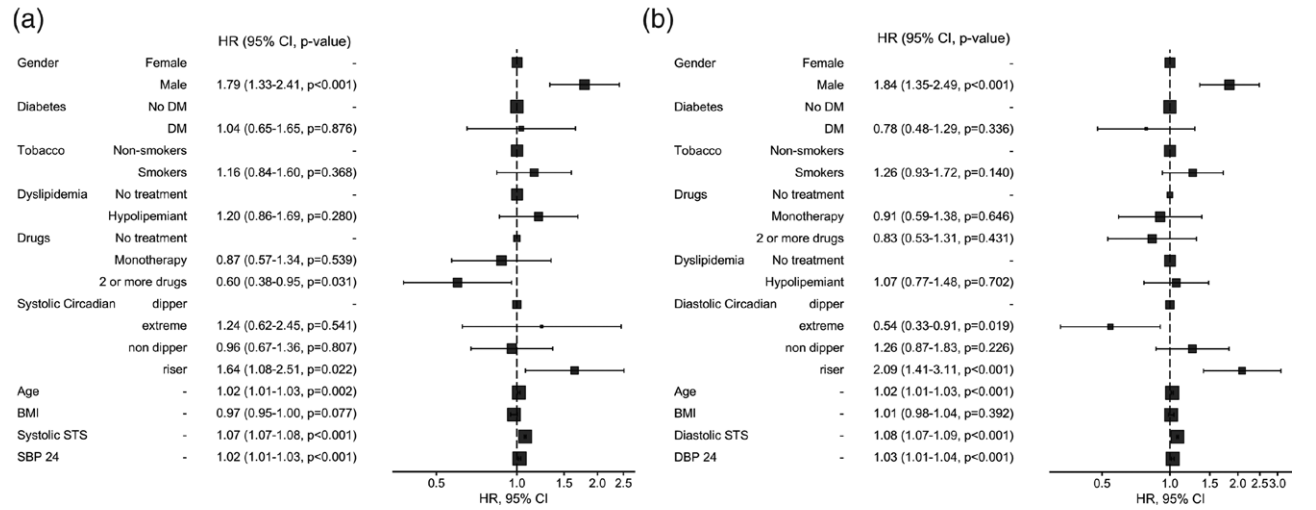
## Discussion

In this study, the relationship between the circadian pattern of BP variation and the occurrence of MACE was investigated in a representative sample of the general population of a cohort in western Argentina. The results show that patterns of morning pressure rise are associated with MACE and each component of the primary endpoint.

Examining morning BP surge types has no unique approach; however, sleep-through is the most frequent. Additionally, the cut-off points used to define high morning surges were diverse. Among the study participants, 21% had a high systolic sleep-through morning surge. Compared to prior studies that used other forms of classification, our results can be considered

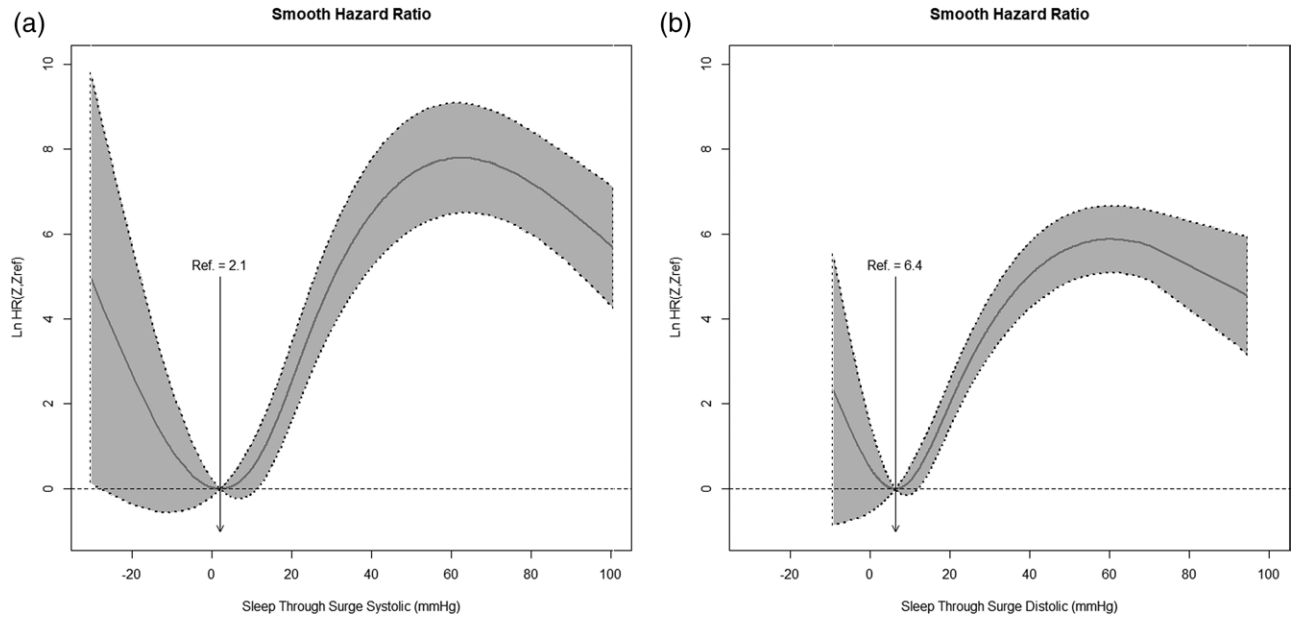
an appropriate percentage because all studies found high systolic morning surges between 10% and 33% of the sample [12,18,19,26,27]. However, only 3% of participants in the present study achieved a threshold of >55 mmHg, as reported by Kario *et al.* in 2003 [12]. Considering another cut-off point, similar to the one reported by Metoki (>40 mmHg) determined by quintile segmentation, 10% of our participants were above this value [27]. Additionally, for similar cut-off points around 34 mmHg and 37 mmHg, the percentages were defined by the segmentation method as deciles in the IDACO study, quartiles by Verdecchia *et al.*, and tertiles by Amici *et al* [18,19,26]. Finally, the lowest cut-off point of 21 mmHg reported by Booth *et al.* would have included

**Fig. 3**




The multivariate analysis of the main predictive variables for cardiovascular events, highlighting in (a) the role of systolic sleep-through surge and in (b) the role of the diastolic sleep-through surge.

**Fig. 4**




Smooth HR for MACE across the systolic (a) and diastolic (b) values of the sleep-through surge. The red lines correspond to the predicted Ln HR values after adjusting the covariates age, gender, smoking, dyslipidemia, diabetes, antihypertensive treatment, 24-h blood pressure and BMI. The 95% confidence intervals are indicated in grey. HR, hazard ratio.

45.7% of our population. Therefore, we agree with previous reports that cut-off points should be taken with caution because they are highly variable and have questionable out-of-sample performance [28].

Our sleep-through morning surge and MACE results add complexity to the previously reported results. The IDACO study that included 5645 Europeans, Asians, and South Americans (899 from Montevideo, Uruguay) reported an adjusted HR for cardiovascular events of 1.30 (95% CI, 1.06–1.60) in those with a systolic sleep-through surge of ≥37 mmHg versus <37 mmHg [19]. Among 716 black adults in the Jackson Heart Study, sleep-through morning surges were not associated with an increased cardiovascular risk. In contrast, among 3012 Italian adults, increased systolic sleep-through morning surge presented an HR for cardiovascular events of 0.60 (95% CI, 0.41–0.88), lower for those >36 mmHg versus ≤19.5 mmHg [18]. Furthermore, a systematic review and meta-analysis demonstrated that a systolic sleep-through morning surge of >36 mmHg vs. ≤36 mmHg was not associated with cardiovascular events [HR: 0.90 (95% CI, 0.42–1.91)] [7]. An update including our results considering the systolic sleep-through morning surge as dichotomic will probably change the meta-analysed HR for cardiovascular events.

Sleep-through has been more commonly investigated in prior studies, but MND has not been associated with cardiovascular events. The prognostic values of both systolic and diastolic MND were less than those found with sleep-through; however, MND is easier to measure and should be further studied.

Interestingly, here, we report a smooth HR for the systolic and diastolic sleep-through morning surge and offer potential reference values for both variables. This approach is gaining popularity owing to the better description of the hazards associated with the range of variables under study [29].

Some authors have revealed that a higher morning BP surge in older patients is independently associated with the stroke risk of ambulatory BP, nocturnal BP falls, and silent infarcts [30]. In this study, an increased risk of stroke was observed, regardless of age. This could have an important impact, particularly on the prevalence of dementia and long-term disability. On the other hand, the JAMP study, the largest study to date on the association between morning surge (MS) and stroke, suggests that MS is linearly associated with stroke risk, especially in dipper-status patients [31]. This analysis could not be done in our study as it was not designed to answer this hypothesis, but it will be an interesting question about the role of MS and BP variability.

The pathophysiological mechanism is thought to be the release of catecholamines and angiotensin in the early morning hours. Increased sympathetic activity, particularly the α-adrenergic component, increases vascular tone in the small resistance arteries and may contribute to increased morning BP [32].

### Limitations

This study is limited because the data belong to a single centre; however, the evaluation of circadian patterns and morning surge is within the range of the sample size of other similar studies and adds valuable information from Latin America. Some participants may have misreported sleep and wake times, resulting in potential errors in morning surge estimation. However, our results were consistent and could diminish the risk of misreporting by using the three forms to estimate the morning surge. The latter should be interpreted with caution due to the previously reported morning surge's limited reproducibility but was not tested in the current study.

### Conclusion

Three-morning surge estimations as continuous variables increased the HR for MACE and CVD, MI, heart failure, stroke, and atrial fibrillation in our single-centre cohort. The estimated cut-off points significantly increased the HR for those with higher values. The calculated reference and its corresponding increases in HR for the studied range of values are of additional interest to our population and future studies. Among the ABPM measures, morning surge deserves more attention.

### Perspectives

The three different definitions of morning BP surge predicted higher rates of cardiovascular events in a Latin American population with extensive follow-up. The cut-off points had sufficient accuracy in estimating clinically relevant increases in cardiovascular HR. Additionally, morning BP surge in this population was an independent variable of cardiovascular risk after adjusting for usual covariates. These findings may contribute to the prognostic value of BP monitoring, as well as for chronotherapy.

## Acknowledgements

This work was supported by Grant Research Projects of the National University of Cuyo N° 06/J089 and 06/J494.

### Conflicts of interest

There are no conflicts of interest.

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